Université de Montréal

L'usage secondaire des données médico-administratives afin d'optimiser l'usage des médicaments chez les patients atteints de maladies respiratoires chroniques :

Adhésion aux médicaments, identification de cas et intensification du traitement

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Résumé

L'adhésion aux médicaments chez les patients présentant un asthme ou une maladie pulmonaire obstructive chronique (MPOC) est reconnue pour être faible. Pour intervenir efficacement, les médecins de famille doivent évaluer de manière précise l'adhésion aux médicaments. Ne pas détecter la non-adhésion peut réduire davantage la maîtrise de la maladie, entraîner une intensification non-nécessaire du traitement, mener à des schémas pharmacologiques plus complexes et coûteux et par conséquent, augmenter le risque d'événements indésirables. La présente thèse vise à approfondir les connaissances sur l'usage secondaire des données médico-administratives afin d'optimiser l'adhésion et l'usage des médicaments chez les patients atteints de maladies respiratoires chronique, au moyen d'une approche méthodologique mixte de recherche. Plusieurs questions méthodologiques cruciales concernant l'étude de l'intensification du traitement en asthme ont également été abordées.

Le premier axe porte sur le développement de l'outil e-MEDRESP, qui s'appuie sur les renouvellements d'ordonnances et qui est conçu pour donner rapidement accès aux médecins de famille à une mesure objective et facilement interprétable de l'adhésion aux médicaments utilisés dans le traitement de l'asthme et de la MPOC. L'outil a été développé en collaboration avec des médecins de famille et des patients à l'aide de groupes de discussion et d'entrevues individuelles. Dans le cadre d'une étude de faisabilité, l'outil e-MEDRESP a été par la suite implanté dans les dossiers médicaux électroniques de plusieurs cliniques de médecine familiale au Québec (346 patients, 19 médecins). Les résultats ont montré que l'intégration de d'e-MEDRESP dans le flux de travail des médecins était faisable. Les médecins ont indiqué que l'outil leur a permis de : 1) mieux évaluer l'adhésion aux médicaments de leurs patients (cote moyenne et écart-type sur une échelle de Likert à 5 points [perception d'accord] de 4,8±0,7); et 2) ajuster les traitements prescrits (4,8±0,7 et 4.3±0,9). Une analyse pré-post n'a pas révélé d'amélioration au niveau de l'adhésion aux médicaments chez les patients dont le médecin a consulté e-MEDRESP lors d'une visite médicale. Toutefois, une amélioration statistiquement significative a été observée chez les patients dont le niveau d'adhésion était inférieur à 80 % au cours de la période de six mois précédant la visite et qui étaient traités par des corticostéroïdes inhalés (Proportion of days covered (PDC) = 26,4 % (IC à 95 % : 14,3-39,3 %) ou des antagonistes muscariniques à action prolongée (PDC = 26,9 % (IC à 95 % : 12,4-40,2 %)).

Le deuxième axe présente des travaux préparatoires à la conduite d'une cohorte qui sera réalisée à partir de bases de données médico-administratives et qui aura comme objectif d'estimer

l'association entre l'adhésion aux médicaments et l'intensification du traitement de l'asthme, une question peu explorée à ce jour. Avant de débuter une telle étude, il est important de s'assurer que les bases de données médico-administratives peuvent être utilisées pour identifier de manière adéquate les patients asthmatiques et l'intensification du traitement. Dans un premier temps, une revue systématique a été effectuée pour identifier les données probantes disponibles concernant la validité des algorithmes permettant d'identifier les patients asthmatiques dans les bases de données médico-administratives. L'algorithme qui a été développé par Gershon et coll. (*Revue canadienne de pneumologie*, 2009; vol. 16, no 6, p. 183-188), qui comprenait deux visites médicales ambulatoires ou une hospitalisation pour asthme sur deux ans, présentait le meilleur compromis entre la sensibilité (84 %) et la spécificité (77 %). Dans un second temps, une définition opérationnelle de l'intensification du traitement a été élaborée dans le cadre d'une étude Delphi qui incorporait un processus consensuel d'experts. Cette définition comprend sept étapes et s'inspire des lignes directrices 2020 de l'initiative mondiale de lutte contre l'asthme. Les définitions obtenues à partir de ces deux études seront intégrées dans l'étude de cohorte.

Les études constituant cette thèse démontrent l'importance de développer des outils qui permettent aux médecins d'évaluer l'adhésion aux médicaments dans leur pratique clinique, en plus d'enrichir la littérature scientifique médicale sur l'intensification du traitement chez les patients asthmatiques.

Mots clés : Adhésion aux médicaments, asthme, MPOC, dossiers médicaux électroniques, intensification du traitement, recherche sur les méthodologiques mixtes

Abstract

Medication adherence in patients with asthma and chronic obstructive pulmonary disease (COPD) is notoriously low and is associated with suboptimal therapeutic outcomes. To intervene effectively, family physicians need to assess medication adherence efficiently and accurately. Otherwise, failure to detect nonadherence may further reduce patient disease control and result in unnecessary treatment escalation that can increase the risk of adverse events and lead to more complex and costly drug regimens. The overarching goal of this thesis was to investigate how the use of secondary healthcare data can be leveraged to optimize medication adherence in clinical practice. Methodological considerations to facilitate our understanding of treatment escalation in asthma using secondary healthcare data were also examined.

In the first part of my doctoral research program, I led a project which aimed at developing e-MEDRESP, a novel web-based tool built from pharmacy claims data that provides to family physicians with objective and easily interpretable information on patient adherence to asthma/COPD medications. This tool was developed in collaboration with family physicians and patients using a framework inspired by user-centered design principles. As part of a feasibility study, e-MEDRESP was subsequently implemented in electronic medical records across several family medicine clinics in Quebec (346 patients, 19 physicians). Findings showed that its integration within physician workflow was feasible. Physicians reported that the tool helped to: 1) better evaluate their patients' medication adherence; and 2) adjust prescribed therapies, with mean ± sd ratings (5-point Likert scale) of 4.8±0.7 and 4.3±0.9, respectively. A pre-post analysis did not reveal improvement in adherence among patients whose physician consulted e-MEDRESP during a medical visit. However, significant improvements in adherence for inhaled corticosteroids (Proportion of days covered (PDC): 26.4% (95% CI: 14.3-39.3%)) and long-acting muscarinic agents (PDC: 26.4% (95% CI: 12.4-40.2%)) were observed among patients whose adherence level was less than 80% in the 6-month period prior to the medical visit.

The second part of this research program consisted of two studies which laid the groundwork to estimate the association between medication adherence and treatment escalation in asthma using Canadian healthcare administrative data, a phenomenon that is currently under-explored in the literature. Prior to embarking in this study, it is important to ensure that healthcare administrative databases can be used to identify asthma patients and treatment escalations in an adequate manner. First, a systematic review was conducted to obtain an overview of the available evidence supporting

the validity of algorithms to identify asthma patients in healthcare administrative databases. The algorithm developed by Gershon et al. (*Canadian Respiratory Journal*, 2009;16(6):183-188) comprising ≥2 ambulatory medical visits or ≥1 hospitalization for asthma over two years had the best trade-off between sensitivity (84 %) and specificity (77%). Second, an operational definition of treatment escalation was developed through a Delphi study that incorporated an expert consensus process. This definition includes 7 steps and was inspired by the 2020 Global for Initiative for Asthma treatment guidelines. I plan to integrate the definitions obtained from these two studies in a future cohort study which aims to examine the association between medication adherence and treatment escalation in asthma.

My research provides compelling evidence on the importance of developing and evaluating the feasibility of implementing tools which can aid physicians in assessing medication adherence in clinical practice and extends the literature on treatment escalation in asthma.

Keywords: Medication adherence, asthma, COPD, electronic medical records, pharmacy claims database, Treatment escalation, mixed-methods research

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List of Abbreviations

Anti-IgE: Anti-immunoglobin E
COPD: Chronic obstructive pulmonary disease
OCS: Oral corticosteroids
CDSS: Clinical decision support systems
CMG: Continuous measure of medication gaps
CR: Compliance ratio
CTS: Canadian Thoracic society
DSQ: Dossier Santé Québec
EHR: Electronic health records
EMR: Electronic medical record
FEV_1: Forced expiratory volume in 1 second
FG: Focus group
GBD: Global burden of disease
GINA: Global Initiative for Asthma
GOLD: Global Initiative for COPD
HIS: Health information systems
ICS: Inhaled corticosteroids
LAAC: Long-acting muscarinic agonists
LAMA: Long-acting muscarinic agents
LTRA: Leukotriene receptor antagonists
MDI: Metered dose inhaler
MOXXI: Medical office of the 21st century
MPR: Medication possession ratio
MPRm: Medication possession ratio (modified)
NPMG: New prescription medication gaps
MITT: Multiple inhaler triple therapy
MRA: Medication refill adherence
NPV: Negative predictive value
PDC: Proportion of days covered
PPDC: Proportion of prescribed days covered
PPV: Positive predictive value
QHR: Quebec Health Record
SABA: Short-acting $beta_2$-agonists
SAMA: Short-acting muscarinic antagonists
UCD: User-centered design

To Jay & Triton

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CHAPTER 1: INTRODUCTION

"*Drugs don't work in patients who don't take them.*"

C. Everett Koop, Former US Surgeon General

Asthma and chronic obstructive pulmonary disease (COPD) are leading causes of chronic morbidity and mortality that pose substantial economic and social burdens worldwide.[1] Globally, asthma affects over 350 million people[2] and approximately 174 million people have moderate-to-severe COPD.[3] In Canada, nearly 9.5% of the total population is living with asthma[4] and it is estimated that between 10-25% of Canadians over 35 years old will develop COPD in their lifetime.[5,6] Despite a plethora of effective treatments, the **medication adherence** level[1] in patients with asthma and COPD is notoriously low, often falling below 50%.[7-10] Nonadherence is associated with low disease control, increases in emergency department (ED) visits, and hospitalizations, as well as rising healthcare costs.[1,11,12] Although medication adherence is a complex and multifaceted issue, its detrimental public health effects are preventable.

A large majority of asthma and COPD patients are treated in primary care.[13,14] As the front-line healthcare providers, family physicians have an important impact on patients' perception of prescribed therapy. Yet to intervene effectively, family physicians need to *first* assess adherence accurately and in a timely manner—a challenging aspect of care in routine clinical practice. Physicians often rely on patient self-report;[15] however, studies have shown that patients tend to overestimate their adherence to their prescribed therapy.[16-18] Alternatively, pharmacy claims, which are generated whenever a prescription at a community pharmacy is filled,[19] can be used to obtain more objective and non-invasive measures of medication adherence.[20] In addition, a downside of this approach is that these data are not consistently available in clinical practice. Indeed, only a few medication adherence assessment tools based on pharmacy claims data have been structured to fit around the daily practice of family physicians.[21-25] As a prime example, physicians in the US can request pharmacy claim histories through e-prescribing platforms integrated in their electronic health records for patients who provided prior consent.[26] Since 2013, healthcare professionals in the Canadian province of Quebec can access pharmacy claims through the

[1] Unless otherwise specified, the adherence level refers to the proportion of patients who are not adherent to their prescribed treatment. This term will be used throughout this thesis.

Quebec Health Record (QHR) [*Dossier Santé Québec* (DSQ)], which is a data repository that allows physicians, pharmacists, and other healthcare professionals to access health information on their patients, including medication data.[27]One major drawback, however, is that it provides raw and unprocessed pharmacy data. When it was initially available to healthcare professionals, information on filled prescriptions, regardless of reimbursement status, was available. Now, it also includes all medications entered in the pharmacy system, including those that were not dispensed by the patient. Nevertheless, little effort was made to aggregate and process the medication data, which can be hard for healthcare professionals to interpret and integrate in their workflow, especially for polymedicated patients.

Broadly speaking, many of these platforms and tools have the potential to help physicians in monitoring medication adherence in a timely manner. In this context, family physicians could benefit from innovative tools that will better assist them in detecting their non-adherent patients. Ideally, these tools should display easily interpretable medication adherence information and be seamlessly integrated within the physician workflow. To the best of our knowledge, very few tools have been developed in Canada. In recent years, healthcare institutions have increasingly leveraged clinical data captured in electronic health records and clinical decision support systems (CDSS) to enhance patient care and help bridge the gap between optimal practice and actual clinical care. CDSS are computer applications that analyze and process clinical data (laboratory results, prescription data) to assist clinicians in making diagnostic and therapeutic decisions and implementing evidence-based clinical guidelines at point of care.[28] To the best of our knowledge, there is a lack of CDSS that have incorporated medication adherence assessment tools within their digital platforms. Most of CDSS that were developed for asthma or COPD focused on guidelines decision supports, self-management plans, and patient advice sheets/information sheets.[29-31] While these aspects are crucial to enhance patient care, prescribers should also have access to tools that will help them monitor medication use and identify their non-adherent patients in a timely manner.

The consequences of undetected nonadherence go beyond unfavourable therapeutic outcomes—it may also directly impede physician prescribing practices, especially in asthma. According to clinical guidelines, asthma patients are treated with a step-care approach, whereby controller medication doses are gradually increased, or medications are added when disease control is not achieved.[2,32] Due to this incremental approach to therapy, failure to detect nonadherence may result in **unnecessary treatment escalation** that can in turn increase the risk of adverse events, lead to more complex and costly drug regimens, and further reduce medication adherence. In fact, unnecessary treatment escalation stems from the difficulties in distinguishing nonadherent patients form those who are truly refractory to

treatment, among patients who have uncontrolled disease. Since objective measurements of medication adherence are not easily accessible in routine clinical practice, physicians' decision to escalate treatment is most often based on disease control, even when nonadherence may be the underlying reason behind uncontrolled disease. Thus, in addition to better equipping family physicians in assessing patient medication adherence, it is crucial to understand how patterns of treatment escalation in the real-world setting are affected by medication adherence as well as disease control. Due to the complex therapeutic landscape in asthma, it is important to be able to first identify treatment escalation patterns at a population-level. These notions appear to be under-explored in the literature.

To fill these important research gaps, this doctoral thesis was conducted in two parts. The overarching goal of this thesis was to investigate how the secondary use of healthcare data (e.g. administrative claims, prescription refills) can be leveraged to optimize medication adherence and support clinical decision-making in routine clinical practice. Methodological considerations to facilitate our understanding of treatment escalation in asthma patients, which can be unintended consequence of undetected medication non-adherence, will also be examined. In the first part of this thesis, I led a multi-phase study which aimed at: 1) developing **e-MEDRESP**, a novel web-based tool built from **pharmacy claims data** that allows family physicians to monitor adherence to respiratory medications; and 2) evaluating the feasibility of implementing e-MEDRESP in family physician's electronic medical records (EMR) across several family medicine clinics in Quebec. The second part laid the groundwork for a population-based cohort study which aims to estimate the **association between medication adherence** and subsequent **treatment escalation in asthma** using healthcare administrative data. Of note, COPD patients were not considered, as the notion of disease control in COPD cannot be well studied using administrative databases alone. Due to time constraints, the cohort study was unfortunately beyond the scope of this dissertation. However, two separate studies were conducted to: 1) select a valid operational definition to identify asthma patients in healthcare administrative database; and 2) develop a treatment escalation definition in asthma that can be applied to healthcare administrative databases. The definitions obtained from these studies will be subsequently used in the cohort study, which I will perform, within the next year, in collaboration with Lucie Blais, the principal investigator of this doctoral research program, and her research team.

For the e-MEDRESP study, we used a two-phase exploratory design.[33] In Phase I, focus groups and individual interviews were conducted with family physicians and asthma/COPD patients to: 1) identify the barriers and facilitators of assessing medication adherence in routine clinical practice; and 2) develop an e-MEDRESP prototype using a framework inspired by user-centered design (UCD) principles.[34] e-MEDRESP

was subsequently constructed by applying algorithms to pharmacy claims data that reflected end users' recommendations using the reMed claims database. Its web-based format allowed us to seamlessly integrate it in electronic medical records (EMR). In Phase II, e-MEDRESP was available for a 16-month period following its implementation in participating clinics, during which the feasibility of integrating this tool in routine clinical practice was comprehensively assessed. Results of the e-MEDRESP study were reported in two separate articles. The development process of e-MEDRESP was published in *Respiratory Care* [2020, 65(9); 1355-1366],[15] whereas the feasibility study was submitted to the *International Journal of Clinical Practice*.

For the second part of the thesis, a systematic literature review was first conducted to identify studies that have validated asthma case-finding algorithms applied to health administrative data. A Delphi study was subsequently conducted to develop an operational definition of treatment escalation adapted to asthma in collaboration with experts in pulmonology, pharmacy, and epidemiology. Indeed, identifying treatment escalation in asthma using claims data can be challenging owing to the complexity of the asthma therapeutic landscape. Although the literature on this topic is limited, the most commonly reported method of studying asthma treatment escalation patterns is through the identification of step-up episodes that correspond to clinical practice guidelines.[35-41] However, claims-based treatment escalation definitions that have been reported so far in the literature are variable, mainly due to differing interpretations of asthma treatment guidelines. Importantly, these definitions were not established through a validated or rigorous process. Given the gap between treatment guidelines and the real-world practice, this inconsistency underscores the need to establish an operational treatment escalation definition adapted to asthma patients, through an expert consensus process. Results of the systematic literature review were published in *The journal of Asthma* [2020, epub ahead of print],[42] whereas the Delphi study was submitted to *Respiratory Medicine*. As mentioned previously, the definitions obtained from these studies will ultimately lay the groundwork for a population-based cohort study which aims to evaluate the association between medication adherence and treatment escalation in asthma.

This article-based thesis comprises seven chapters. The upcoming chapter presents a literature review covering the main themes of my doctoral thesis, which ultimately allowed me to identify the research gaps and strengthen the rationale of my research program. An overview of the research objectives is found in the third chapter, and the four manuscripts are presented in the fourth chapter. It is to be noted that research methods are presented within each manuscript and their respective supplementary materials. Finally, an in-depth discussion of my research projects and conclusions are presented in the fifth chapter, along with clinical implications and perspectives on future research.

CHAPTER 2: LITERATURE REVIEW

The objective of this literature review was three-fold. The first part aimed to summarize the literature encompassing the clinical definitions, disease burden, disease management, and pharmacological therapy of asthma and COPD, with a focus on adult populations. In addition to assessing current research trends, the following treatment guidelines were consulted: 1) Guide for asthma management and prevention by the Global Initiative for Asthma (GINA);[2] 2) Global Strategy for the Diagnosis, Management and Prevention of COPD by the Global Initiative for Chronic Obstructive Lung Disease (GOLD);[32] and 3) Position statements from the Canadian Thoracic Society (CTS).[43,44] The second part pertains to medication adherence, the different methods to assess it in clinical practice, as well as the currently published studies on medication adherence assessment tools based on pharmacy claims data across different therapeutic fields, with a focus on asthma and COPD. Specific challenges associated with integrating structured electronic medication data within physician workflow will also be discussed. The last part of this chapter will explore how the secondary use of healthcare data can help us understand the consequences of medication non-adherence and prescribing practices (treatment escalation) at a population-level. The following topics will be specifically explored: 1) claims-based algorithms to identify asthma patients; and 2) treatment escalation patterns in asthma in the real-world setting. Studies which have evaluated the relationship between medication adherence and subsequent treatment escalation were evaluated and critically assessed.

2.1 Asthma

2.1.1 Definition, Prevalence, and Burden of Illness

The GINA guidelines define asthma as a "heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by a history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and intensity, together with variable expiratory airflow limitation."[2] Symptoms and airflow limitation may resolve spontaneously or through pharmacological therapy.[2] Additionally, patients may be asymptomatic for several consecutive weeks or months. Notwithstanding, when disease is uncontrolled, patients may experience exacerbations, consisting of potentially life-threatening acute or subacute flare-ups.

With over 350 million individuals affected worldwide, asthma has become an important public health issue and a leading cause of chronic morbidity.[2] According to Statistics Canada, 8.1% of Canadians

aged 12 and older reported having been diagnosed with asthma by a healthcare professional in 2014, representing approximately 2.4 million people.[45] In 2013, Ismaila *et al.* conducted a systematic review of the burden of asthma in Canada, including the direct and indirect costs, the key drivers of healthcare resource utilization, and the impact of asthma on patients' quality of life.[11] The review found a substantial clinical burden, reflected by high rates of hospitalizations (1.43-63 hospitalizations per 1000 patients per year), as well as ED and physician visits (1.1-14.9 physician visits for asthma per year). The economic burden is also considerable, with direct costs ranging from an average annual cost of $336 to $657 per patient. Indirect costs due to time loss from work, productivity loss, and functional impairment also increase the overall burden. Studies in the review highlighted a high prevalence of psychological distress (31%-50%) and the diminished quality of life among asthma patients compared with individuals without asthma.

Due to the increase in effective treatments and advances in asthma management in recent years, asthma mortality and morbidity has been on the decline since the late 1990s.[46] Nevertheless, the majority of asthma-related hospitalizations and deaths are preventable with proper treatment.

2.1.2 Disease Management and Pharmacological Therapy

According to the GINA guidelines, the hallmarks of optimal asthma control include minimal respiratory symptom burden, no activity limitation, normal respiratory function, and absence of the need for rescue bronchodilator medications.[2] Additional criteria for assessing disease control include nocturnal symptoms, occurrence of asthma exacerbations, physical activity, absenteeism, and forced expiratory volume in 1 second (FEV_1) or peak expiratory flow values.[2] Pharmacological treatment aims at preventing symptoms by reducing airway inflammation and hyperactivity.

Asthma treatment should be tailored to each patient and take into account the level of symptom control, risk factors of exacerbations, phenotypic characteristics, treatment effectiveness, patient preference, treatment cost, and **medication adherence**. There are two main types of treatments: 1) quick relief (or rescue) medications, which are taken on an as-needed basis for short-term relief of symptom; and 2) controller medications, which are taken regularly to control chronic symptoms and prevent asthma exacerbations.

In clinical practice, asthma patients are treated with a step-care approach, which entails gradually increasing controller medication doses or adding controller medications when disease control is not achieved with the current treatment regimen.[47] Patients may be prescribed treatment on an as-needed basis for quick relief of symptoms or take a controller medication on a daily basis. Prior to 2019, GINA

recommended as-needed rescue short-acting beta2-agonists (SABA) to treat symptoms in patients with intermittent asthma (step 1). However, since April 2019, GINA no longer recommends as-needed SABA as the preferred reliever therapy. Instead, the current guidelines encourage the use of as-needed low dose Budesonide (ICS)-Formeterol (LABA) (Symbicort®) or low dose ICS whenever a SABA is taken, as the preferred reliever therapy. These recommendations are regarded as the most critical change in asthma management in 30 years, which stemmed from safety concerns of initiating asthma therapy with SABA alone.[48] Indeed, several studies have suggested an increased risk of adverse effects of short-term regular use of SABA alone, including reduced bronchoprotection and bronchodilator response, increased airway hyperresponsiveness, exercise-induced bronchoconstriction and allergic responses, and increased eosinophilic inflammation and mast cell mediator release.[49-51] In 2018, a large double-blind clinical trial found a 64% reduction in severe exacerbations in patients with mild asthma treated with as-needed low dose budesonide-formoterol compared with SABA only.[52]

For patients with mild persistent asthma, low dose ICS plus as-needed reliever medication are recommended. Other less effective controller medications include leukotriene receptor antagonists (LTRA) and theophylline, although the latter treatment is no longer found in recent guidelines. Subsequent steps for uncontrolled asthma include adding other controller medications or increasing the dose of ICS controller medications. For adults, the preferred step-up treatment is combination of ICS/LABA. For patients with persistent symptoms or severe exacerbations, add-on treatments include long-acting anticholinergics (LAAC), anti-immunoglobin E (anti-IgE), and anti-interleukin 5 treatment. It is to be noted that LAAC are also referred to as long-acting muscarinic agents (LAMA).

In case of acute exacerbation, a short course of oral corticosteroids is prescribed. Maintenance oral corticosteroid therapy could be prescribed in patients with severe asthma, although side effects are common (cataract, glaucoma, hypertension, diabetes, adrenal suppression, osteoporosis, etc.).

Prior to considering treatment escalation, guidelines recommend that physicians verify for common problems such as inhaler technique, **medication adherence**, persistent allergen exposure, and comorbidities. Treatment step-down should be considered once good control has been achieved and maintained for 3 months. Asthma patients may be given a written asthma action plan tailored to their level of asthma and health literacy and that will allow them to recognize and respond to worsening asthma control. The action plan typically includes the patient's usual asthma medications, instructions on when and how to increase medications and initiate oral corticosteroids, and how to access appropriate medical care in case of worsening symptoms.

2.2 Chronic Obstructive Pulmonary Disease

2.2.1 Definition, Prevalence, and Burden of Illness

Although asthma is rarely life-threatening, COPD is a progressive, debilitating, and often fatal disease.[32] Treatment options can improve quality of life and reduce the risk of having an exacerbation but cannot fully reverse lung function decline. The GOLD guidelines define COPD as a "common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway or alveolar abnormalities usually caused by significant exposure to noxious particles or gases."[32] COPD is an umbrella term encompassing two clinical manifestations: 1) obstructive chronic bronchitis (mixture of small airways disease); and 2) emphysema (parenchymal destruction), of which the relative contributions vary from person to person. It was estimated that cigarette smoking is the principal underlying cause in 80% to 90% of COPD cases.[53] COPD may also be caused by long-term cumulative exposure to noxious gases and particles, as well as genetics (alpha-1 Antitrypsin deficiency), airway hyper-responsiveness, and poor lung growth during childhood. In clinical practice, spirometry is required to make the diagnosis of COPD and the presence of a post-bronchodilator FEV1/FVC < 0.7 confirms the presence of persistent airflow limitation, which is the hallmark of COPD.[32]

The reported prevalence rates of COPD among individuals over 35 years are highly variable, ranging between 4-25%.[5,6,54] The discrepancy between these estimates is partly due to the different methods used to estimate prevalence. Namely, studies based on self-reported diagnosis may underestimate the true prevalence of COPD in the population, as many individuals with COPD are unaware that they have this condition. For example, a Canadian study revealed that the prevalence of measured airflow obstruction compatible with COPD was 16.6% (95% CI: 14.3%-18.9%), which was two to six times greater than estimates based on self-reported diagnosis.[5] Along similar lines, an administrative database study estimated that one in four Canadians over 35 years old will develop the disease in their lifetime.[55] More recently, Adeloye *et al.*[54] published a systematic review and meta-analysis on the global and regional estimates of COPD prevalence, as part of the Lancet Global Burden Study (GBD), which is the most comprehensive worldwide observational epidemiological study to date.[3] From a meta–regression epidemiological model, it was estimated that there were about 227.3 million COPD cases in the year 1990 among people aged 30 years or more, corresponding to a global prevalence of 10.7% (95% CI: 7.3%–14.0%) in this age group. The prevalence and burden of COPD are projected to increase over the coming decades due to continued exposure to COPD risk factors, coupled with the aging of the world's population.

The number of COPD cases increased to 384 million in 2010, with a global prevalence of 11.7% (95% CI: 8.4%–15.0%). According to the GBD,[3] mortality due to COPD is eight times higher than asthma-related mortality.

In 2015, Dang-Tan *et al.*[12] conducted a systematic review which aimed at providing a holistic overview of the burden of COPD in Canada, including the direct and indirect costs, the key drivers of healthcare resource utilization, and the impact of COPD on patients' quality of life. On average, COPD patients were found to have 0 to 4 annual emergency department visits, 0.3 to 1.5 annual hospital visits, and 0.7 to 5 annual physician visits. Moreover, 60 to 68% of COPD patients were found to be inactive and 60 to 72% reported activity restriction. The economic burden is also substantial, with average annual total cost per patient ranging between CAN $2,444-4,391 from a patient perspective to CAN $3,910-6,693 from a societal perspective. Although COPD is the fourth leading cause of death in Canada, proper medical treatment, integrated care, and self-care management programs may reduce the overall burden to Canadian patients and society.

It is to be noted that some patients may have concurrent diagnosis of asthma and COPD. This condition is sometimes referred to asthma and COPD overlap (ACO). To this day, no consensus regarding the definition of ACO exists.[56,57] Despite the lack of a universal definition for ACO, there is emerging agreement that some of the key features of this condition include: 1) persistent airflow limitation in symptomatic individuals of at least 40 years of age; 2) a well-documented history of asthma in childhood or early adulthood; and 3) a significant exposure history to cigarette or biomass smoke.[58]

2.2.2 Disease Management and Pharmacological Therapy

Similar to asthma, an incremental approach to COPD treatment and management is recommended. According to GOLD[32] and the Canadian Thoracic society (CTS) guidelines recommendations,[43] each treatment regimen should be tailored to the patient's symptom burden, risk of exacerbations, drug availability, and treatment response. Non-pharmacological management of COPD include smoking cessation strategies, vaccination, self-management education, pulmonary rehabilitation, and supplemental oxygen. For patients who have a few symptoms and a low exacerbation risk, short-acting bronchodilators used on an "as needed" basis are recommended.[59] These include SABA or short-acting muscarinic agents (SAMA). Long-acting bronchodilators, such as LABA or LAMA, are considered the first-line maintenance therapy in patients with more severe airflow limitation. When disease control is sub-optimal, the addition of another long-acting bronchodilator as a subsequent step is recommended; as a result, combined inhalers containing a LABA and a LAMA are often used in patients with moderate to

severe COPD.[59,60] Long-term treatment with ICS added to long-acting bronchodilators is further recommended for patients at high risk of exacerbations.

Oral corticosteroids are used to treat acute exacerbations in hospitalized patients, or during emergency department visits, and were shown to reduce the likelihood of treatment failure and relapse and improve lung function and breathlessless.[61] Similarly, antibiotics, when indicated, can shorten recovery time, reduce the risk of early relapse, treatment failure and hospitalization duration.[32] Continuous prophylactic use of some antibiotics, including macrolides, may reduce the risk of exacerbations.[62] Similar to asthma, guidelines recommend that physicians assess common problems such as inhaler technique, **medication adherence**, and comorbidities prior to considering treatment escalation.

2.3 Medication Adherence

2.3.1 Definition

Medication adherence is essential to optimize therapeutic outcomes and reducing the overall disease burden. The World Health Organization defines medication adherence as "the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider."[7] The Respiratory Effectiveness Group further defines medication adherence as a "multi-phased temporal process" that involves: 1) initiation of prescribed therapy (primary adherence); 2) implementation of therapy as prescribed (correct dose, inhalation technique, and frequency); persistence ("duration of the time from initiation to discontinuation of therapy"[63]).

Of note, studies which use healthcare data (pharmacy claims, EMR data) to estimate adherence often make the distinction between primary and secondary adherence. **Primary nonadherence** is a discrete event that denotes whether or not a patient redeemed a prescribed medication or an appropriate alternative within an acceptable period of time after it has been initially prescribed.[64] **Secondary adherence** is an ongoing process measuring prescription refills among patients who previously filled their first prescriptions. [64]

2.3.1.1 Inhaler Techniques – A crucial Dimension of Medication Adherence in Asthma And COPD

Broadly speaking, medication adherence results in improved clinical outcomes for chronic disease management, as well as reduced mortality from chronic conditions.[65] It is important to note that in asthma and COPD, inhaler technique is also a crucial dimension of treatment adherence. Inhaler technique mistakes are common in these patients, and include failure to coordinate actuation with inhalation and failure to achieve sufficient inspiratory flow to actuate certain types of inhalers.[66,67]A recent systematic review revealed that the rate of critical inhaler handling errors, defined as errors that may impact the effectiveness of the delivered drug and thereby lead to the inadequate disease control, was high in asthma and COPD patients, ranging from 14% to 90%.[68] Along the same lines, device-handling errors and their association with poor disease control in asthma and COPD are also well documented in the literature.[69 70-74]

2.3.2 Methods to Assess Medication Adherence in Clinical Practice

Given that adherence to controller medications is a key determinant of treatment success, it is crucial that physicians recognize non-adherent patients and actively engage in interventions which aim at enhancing patient treatment adherence. Yet, assessment of medication adherence in clinical practice can be challenging. Methods to assess adherence can be classified as **direct** or **indirect** and are presented in

Table 1. Of note, patient self-report, electronic measures and pharmacy claims data are the most widely used measures of adherence in observational studies and interventional studies. Since each method to measure adherence has its strengths and limitations, it is generally acknowledged that no gold standard exists for measuring medication adherence. Alternatively, combining different methods may enhance the validity of the data collected.[75]

Table 1. Summary of different measures to assess medication adherence

Method	Type of Measure	Advantages	Disadvantages
Direct	**Biochemical testing** e.g. Measurement of drug/metabolite in blood or urine	-Accurate -Provides physical evidence that the patient took the medication	-Expensive -Intrusive -Ill-adapted to inhaler devices -Not possible to verify inhaler technique -Complicated to implement in clinical practice
Indirect	**Physician assessment** Based on patients' accounts during medical visits	-Simple -Inexpensive	-Subjective -Patient incorrect recall -Patient social desirability bias -Depends on patient-physician relationship
	Patient self-report From validated questionnaires or patient diaries	-Simple -Inexpensive	-Subjective -Patient incorrect recall -Patient social desirability bias
	Canister weighing	-Simple -Inexpensive	-Requires digital scale and qualified personnel -Not possible to verify inhaler technique -Hawthorn effect
	Pill count	-Simple -Inexpensive	-Hawthorn effect -Not possible to verify inhaler technique
	Electronic monitoring	-Can assess timing of ingested or inhaled doses -Objective measure -Prospectively collected data	-Expensive -Intrusive -Complicated to implement in clinical practice -Hawthorn effect
	Pharmacy claims data (available in administrative claims data, drug information systems, and pharmacy management systems)	-Objective -Relatively inexpensive to obtain -Prospectively collected data	-Medicine purchase does not guarantee consumption -Pharmacy claims databases may be incomplete, e.g. data availability may depend on patient drug insurance coverage -Not possible to verify inhaler technique -Not always available in routine clinical practice

The following sections **2.3.2.1** and **2.3.2.2** provide a more detailed description of all these methods. Please refer to section **2.3.3** for adherence estimates to asthma controller medications (and psychometric properties), according to these different methods.

2.3.2.1 Direct Measures

Direct measures include measurements of the drug or its metabolite in blood or urine.[76] These biochemical tests can be taken randomly or at specific intervals, and are considered to be among the most accurate methods to measure adherence as they provide physical evidence that the patient took the medication. However, biochemical testing can be expensive, intrusive, ill-adapted to inhaler devices, and complicated to implement in clinical practice.

2.3.2.2 Indirect Measures

The following section presents details on **indirect measures**: 1) physician assessment; 2) patient self-report; 3) canister weighting; 4) pill counts; 5) electronic monitoring; and 6) pharmacy claims data.

1) Physician Assessment

For physicians, the most practical method of evaluating medication adherence is through patient or caregiver interviews during medical visits. It is generally acknowledged that using open-ended, non-threatening and non-judgmental questions may help physicians in detecting their non-adherent patients more easily.[77,78] However, reliance on their intuition is not foolproof. In a cohort study conducted by Sherman *et al.,*[79] adherence was determined using pharmacy claims data in 116 asthma patients and was compared with physician adherence assessments. Physicians were able to identify 21 (49%) of 43 patients who refilled ≤ 50% of prescribed doses of long-term controllers and only 3 (27%) of 11 patients who overused their rescue medications.

2) Patient self-report

Patient-self report measures can also be obtained via structured questionnaires. Several validated standardized questionnaires have been developed to assist physicians and researchers in detecting nonadherence. The most frequently used include the 8-item Morisky Medication Adherence Scale (MMAS-8)[80], Brief Medication Adherence Questionnaire,[81] and the Medication adherence report scale (MARS).[82] In recent years, a few medication adherence assessment questionnaires have been developed and validated for patients with chronic respiratory diseases. These include the MARS-A,[83] a modified Medication Adherence Report Scale for asthma, the 'Test of the Adherence to Inhalers' (TAI),[84] and the Medication Intake Survey-Asthma.[85] More details on the **validity and psychometric properties** of these questionnaires are presented in Section **2.3.3**. Although self-report measures are simple and inexpensive to obtain, studies have shown that they are particularly prone to inaccuracies, since patients have a

tendency to over-estimate their degree of adherence due to patients' incorrect recalls or attempts to fulfill treating physicians' expectations (social desirability bias).[86-89] In the same vein, Gamble *et al.*[18] revealed that asthmatic patients who initially denied nonadherence only admitted not following treatment recommendations of their physicians when presented with objective measurements of their medication adherence, such as pharmacy claims data.[16]

3) Canister Weighing

Canister weighing is a simple, albeit relatively costly method, in which adherence is estimated by successive determinations of canister weight.[90] A limitation of this approach is that it requires a digital scale and qualified personnel to handle it and perform the calculations. In addition, patients can intentionally actuate the inhaler device without consuming the medicine, in an attempt to appear adherent to treatment. A possible "Hawthorn effect" may also result from such interventions, whereby a patient's behavior may change, as a consequence of being monitored during a study.[91,92]

4) Pill counts

Pill counts assess adherence by comparing the number of doses remaining in a container with the number of doses that should remain, if a patient has perfect adherence.[76] Typically, the number of dosage units that have been taken between two scheduled appointments or clinic visits are calculated. An example of a formula that can be used to assess adherence based on pill counts is found below:[76]

$$\frac{\text{(Number of dosage units dispensed - number of dosage units remained)}}{\text{Prescribed number of dosage unit per day} \times \text{number of days between 2 visits}}$$

This method is considered simple and inexpensive, although the manual counting of pills is not a procedure that can be implemented on a large-scale. Similar to canister weighing, a Hawthorn effect may come into play. It is also not possible to verify that a dose removed from a container was actually consumed or whether it was consumed under the correct dosing schedule.[76]

5) Electronic monitoring

In electronic monitoring, electronic data capture devices are attached to the drug dispensing device and data on medication use are prospectively collected.[75] These devices can save the date and time of each inhalation device actuation, and in some cases, may assess the quality of inhalation.[93] In asthma and COPD, inhalation devices include metered-dose inhalers (pMDIs), dry powder inhalers or nebulizers. Thus, a key advantage of this method is that it can assess the timing of the ingested or inhaled doses. However,

this method of assessment can be complicated, intrusive, and expensive to implement in clinical practice. Like canister weighing and pill counts, it is also susceptible to the Hawthorn effect.[92,94,95]

6) Pharmacy claims data

Pharmacy claims data (prescription refills; dispensing data) can be useful to assess adherence, as they provide information on prescriptions dispensed in community pharmacies. These prospectively collected data are housed by pharmacy management systems and are populated in large databases of structured data pertaining to medication services delivered in community pharmacies. They provide evidence regarding prescriptions that have been filled by the patient, as well as the frequency of refill.[75]Pharmacy claims data are typically available in administrative claims databases, and drug information systems.

Despite their usefulness, these data have some limitations. Namely, prescriptions filled in hospitals, speciality pharmacies, and long-term care facilities are not typically captured by pharmacy claims. In addition, they do not contain information on prescriptions which were written by the physician but not filled by the patient. Another downside is that these data often incomplete and only cover certain segments of the population or specific medication insurance programs. Thus, it is important to make the distinction between prescriptions dispensed in pharmacies and those that are reimbursed by payers; not all medications can be reimbursed, and patients are not all covered by the same drug insurer.[96]

Moreover, purchasing medicine does not guarantee consumption. Information on inhaler technique, which is a critical aspect for respiratory medications, are also not captured in these data. Nonetheless, they offer more objective measures of medication adherence than patient self-report/physician assessments and may be easier to implement in clinical practice than electronic monitoring.[43] They also eliminate the possibility of recall bias, as they have been collected prospectively. Pharmacists often rely of pharmacy claims data to assess patient medication adherence; however, only a few tools based on pharmacy claims data have been structured to fit around the daily practice of physicians (please refer to section **2.6** for details).

Despite their limitations, pharmacy claims data have been widely used in pharmacoepidemiologic studies to assess adherence across various therapeutic fields. Over the years, different metrics based on pharmacy claims data have been developed to evaluate medication adherence. Some of the most used are summarized in **Table 2**.

Table 2. Summary of different measures to assess medication adherence using pharmacy claims data

Metric	Formula	Key features and advantages	Disadvantages
Proportion of days covered (PDC)[97]	$\frac{\text{Total day's supply}}{\text{Number of days in evaluation period}} x\ 100$ ⇒ capped at 100	-Simple, based upon medication availability	-Assumes that the medications were prescribed for daily chronic use -Excess medication is not considered
Proportion of Prescribed Days Covered (PPDC)[8]	$\frac{\text{Total day's supply}}{\text{Number of days prescribed in evaluation period}} x\ 100$	-Based upon medication availability but takes into account the quantity of drug prescribed	Requires the number of remaining refills for each prescription (not available in all claims databases)
Medication possession ratio (MPR) [98]	$\frac{\text{Total day's supply}}{\text{Number of days in evaluation period}}$	-Simple, based upon medication availability -Allows values greater than 1, which would indicate "oversupply"	-Assumes that the medications were prescribed for daily chronic use
The medication possession ratio [modified] (MPRm)[98]	$\frac{\text{Total day's supply}}{\text{Last Fill date- First fill date + days' supply of last fill}}$	-Based on medication availability but adjusted to include the final refill period. -Uses the dispensing dates to calculate the denominator; avoids arbitrary definition of the end of the observation period	-Assumes that the medications were prescribed for daily chronic use -May overestimate adherence in patients who stopped their therapy prematurely
Continuous measure of medication gaps (CMG)[20]	$\frac{\text{Total day of treatment gaps}}{\text{Last fill date-first fill date}}$	-Provides a measure of nonadherence -Uses the dispensing dates to calculate the denominator; avoids arbitrary definition of the end of the observation period	-Excess medication on hand is not considered
New prescription medication Gaps (NPMG)[99]	Same as CMG, but the denominator corresponds to the time between the date the provider first prescribes the medication until whichever of the following events come first: 1) end of follow-up; 2) censoring due to the patient being switched to an alternate therapy; or 3) the doctor orders the medication to be stopped	-Takes into consideration treatment switches or cessations	-Requires physician prescription data (not available in all claims databases)
Compliance ratio (CR)[100]	$\frac{\text{(Total days' supply - days' supply of last fill)/ last claims date}}{\text{Last fill date- first fill date}}$	-Provides adherence value for the periods between refills -Uses the dispensing dates to calculate the denominator; avoids arbitrary definition of the end of the observation period	-May overestimate adherence in patients who stopped their therapy prematurely without physician recommendation

2.3.3 Prevalence of Medication Nonadherence and Persistence

The following sub-sections outline medication adherence and persistence estimates reported in the literature, according to the methods used (direct vs. indirect). As was previous described in sections **2.1.2** and **2.2.2**, there are two main types of treatments in asthma and COPD: 1) quick relief (or rescue) medications, which are taken on an as-needed basis for short-term relief of symptom; and 2) controller medications, which are taken regularly to control chronic symptoms and prevent exacerbations. This section will focus on the adherence to **respiratory controller medications**, since many studies in the broader literature have suggested that poor adherence to controller therapy is associated with sub-optimal treatment outcomes.[1,11,12] The overuse of rescue medications is also an important barrier to effective treatment management. Indeed, these agents do not resolve the underlying inflammatory pathology that gives rise to worsening symptoms and may even increase the risk of exacerbations.[101] Although the overuse of rescue medications is often correlated with low treatment adherence to controller medications,[102] it is considered a proxy of worsening symptoms and inadequate disease control, not a measure of non-adherence *per se*.

Apart from studies which based adherence estimates on self-report measures, most of the studies in the literature appear to show evidence of a sub-optimal level of medication adherence in asthma and COPD patients (often below 50%). Generally, studies using electronic monitoring, self-report measures, and canister weighting were conducted within small populations, which limits their applicability to routine clinical practice. In contrast, studies which have used pharmacy claims data to estimate adherence were conducted in larger and more diverse populations, which enhances their generalizability and offers the possibility of assessing several dimensions of adherence and medication use, such as primary adherence, secondary adherence and persistence. However, the operational definitions to estimate adherence and patient selection were not consistent throughout the studies, which may have introduced sources of variability. Specific strengths and weaknesses of individual studies will be further elaborated in the following sections. Notwithstanding their methodological strengths and limitations, all these studies collectively provide valuable insight on adherence patterns in individuals with asthma or COPD.

2.3.3.1 Medication Adherence Estimates in Asthma

Adherence Estimates from Blood Plasma Levels

In the 1970s and 1980s, blood and saliva measures of theophylline (oral bronchodilator) were commonly used to examine patient medication use before inhaled anti-inflammatory medication became the standard of care.[103] However, published studies which have used this approach were conducted in small populations and did not specifically assess medication adherence *per se* but rather aimed at assessing pharmacokinetics properties of theophylline.[104,105] Moreover, a case-series study advised to use this method with caution, as pharmacokinetic variations and anomalies among some patients may provide inaccurate estimates of medication adherence.[106]

In 2009, Gamble *et al.* obtained blood plasma prednisolone levels and cortisol levels (oral corticosteroids) in 51 patients with difficult refractory asthma who were prescribed oral corticosteroids as maintenance therapy.[18] The investigative team found that 23 patients (45%) were non-adherent according to the blood plasma prednisolone and cortisol assays. The article did not provide the specific criteria that was used to define non-adherence.

To best of our knowledge, no direct measures of adherence are currently available for any of the inhaled controller medications.

Adherence Estimates from Patient Self-Report

Table 3 presents different studies which have compared adherence estimates derived from patient self-report instruments (e.g., diaries, standardized questionnaires) with more objective measures, such as electronic monitoring and pharmacy claims data.

Despite their ease of use, self-report measures have several limitations. All studies cited in **Table 3** suggest that patients tend to over-estimate their medication use, compared to more objective measures, such as electronic monitoring methods and pharmacy claims data (see columns highlighted in blue). It also appears that these medication adherence questionnaires have not been implemented in the routine clinical care setting. As shown in **Table 3**, many have been assessed and validated within small cohorts, thereby limiting their applicability in routine clinical practice. Of note, the time frame to assess adherence were relatively short (often less than 6 months), further reinforcing the notion that these instruments are not adapted to assess long-term medication use.

ence Estimates Derived from Patient Self-Report Instruments with Other Measures of Adherence

tudy esign	**Sample characteristics and size**	**Drugs under study**	**Follow-up duration** (Time frame to assess adherence)	**Reference standard or other methods used**	**Adherence or inhaler use, according to reference standard**	**Self-report inhaler use or adherence**	**Psychometric or predictive properties**
omized olled	n=19 ≥18 y with asthma	Inhaled controller medications (Cromolyn-like agents)	-Could not obtain full-text article, so information could not be found	Electronic monitoring	10 of 19 subjects (52.6%) used their inhaled medication appropriately during the study period	All subjects reported using appropriately their controller medication for more than half of the study days	N/A
omized olled	n=55 ≥18 y with asthma	Inhaled controller medications	-6 months (electronic monitoring) -1 week (diary)	Electronic monitoring	37.5%	92.8%	Weak correlation r=0.44
pective rt	n=27 Children with asthma	Inhaled controller medications	6 months	-Electronic monitoring -Canister weight	-Electronic monitoring: 50% -Canister weighing: 69%	Children and mothers: ≥80%	N/A
-section y	n=100 ≥18 y with asthma	Mast Cell Stabilizers, ICS, LABA	3 months	Pharmacy claims	Compliance ratio: 0.52 ± 0.27	Mean score: 4.07 ± 1.0 ⇒Mean score of 5=perfect adherence	*Weak correlation* % agreement: 75.5% r = 0.348, p = 0.01
center, pective rt study	n=55 ≥18 y, with persistent asthma	ICS	3 months	Electronic monitoring	Patients used their ICS on 55% of days prescribed and 38% of doses prescribed.	4.3 ± 0.8 at baseline; 4.1± 0.8 at 1 month; 4.3 ±0.8 at 3 months ⇒equivalent to skipping ICS rarely or never.	*Moderate to weak correlation* r=0.42, P<0.001

Study, country	Self-report method or instrument	Study design	Sample characteristics and size	Drugs under study	Follow-up duration (Time frame to assess adherence)	Reference standard or other methods used	Adherence or inhaler use, according to reference standard	Self-report inhaler use or adherence	Psychometric or predictive properties
Jentzsch et al., 2009[110] Brazil	Patient diary (patient/child self-report)	Prospective cohort study	n= 102 3-14 y with asthma	ICS (beclome-thasone Dipropionate)	12 months	-Pharmacy claims -Electronic monitoring -Canister weight	Pharmacy claims: PDC 70% Electronic monitoring: 51.5% Canister weight: 46.3%	97.9%	Agreement between electronic and canister weight: kappa= 0.76 (95% CI 0.65–0.87). *Agreements between the other measures were not obtained.*
Patel *et al*., 2013[111] New Zealand	Self-report questionnaire (no name)	Randomized controlled trial	n=51 16–65 y, stable asthma	ICS/LABA	24 weeks	Electronic monitoring	Mean number of actuations: 18.7-22.0	Mean number of actuations: 26.4-27.1	Limits of agreement ranging from ±15.8-25.6 actuations (obtained from Bland–Altman-like plots)
Plaza et al., 2016[84] Spain	Test of the Adherence to Inhalers' (TAI)	Cross-sectional multicenter	n=99 ≥18 y, with asthma	Inhaled controller medications	14 days	Electronic monitoring	46.5% patients were classified as adherents	49.5% patients were classified as adherents	*Weak correlation* ρ=0.293, p=0.01
Dima *et al*., 2017[85] France	Medication Intake Survey-Asthma (MIS-A)	Prospective cohort study	n=902 6–40 y with asthma	Inhaled controller medications	4 months	Pharmacy claims	CMA (mean ± sd): 60 ± 35 %	MIS score (mean ± sd): 75 ± 29 %	*Moderate to strong correlation* ρ = 0.51-0.85, p ≤ .001

Abbreviations: CMA: Continuous Medication Availability; ICS: Inhaled corticosteroids; LABA: Long-acting β2-agonists, y: years old

Adherence Estimates from Electronic Monitoring Devices

Spector *et al.*[107] was one of the first research team to examine the use of electronic devices to monitor medication adherence in asthma patients. A total of 19 adult asthmatic patients were followed for 12 weeks during a clinical trial. The study reported a mean adherence level to inhaled controller medications (cromolyn-like agents) of 47%. Other studies which examined adherence to asthma controller medications using monitoring devices reported estimates ranging from 37 to 50%.[17,83,84,108] As shown in **Table 3**, these estimates were obtained from small patient cohorts or RCTs, thus limiting their generalizability to the real-world setting. Duration of follow-up ranged between 12 weeks and 12 months; therefore, time frame to assess medication adherence varied considerably across studies and may explain the discrepancy in the estimates obtained.

Adherence Estimates From Canister Weighing

Like patient self-report, adherence estimation from canister weighing tends to generally over-estimate adherence, compared to other more objective methods. As a prime example, Bender *et al.* compared four adherence assessment methods—child report, mother report, canister weight, and electronic measurements of metered dose inhaler (MDI)— in 27 children with mild-to-moderate asthma who were followed prospectively for 6 months. Children and mothers reported, on average, over 80% adherence to prescribed inhaled controller therapy. Canister weight revealed, on average, adherence of 69%, which was considerably lower than self-report (p-values not provided). On the other hand, electronic monitoring revealed an average adherence of 50%, suggesting that electronic adherence monitoring might be more accurate than self-report or canister weight measures. In contrast, a later study conducted by Jentzsch *et al*. revealed a strong agreement between canister weight measures and electronic monitoring [weighted kappa= 0.76 (95% CI 0.65–0.87)].[110] Notwithstanding, the "canister dumping phenomenon", whereby patients intentionally actuate the inhaler device without consuming the medicine, in an attempt to appear adherent to treatment has been documented in the literature.[89,112]

Adherence and Persistence Estimates from Pharmacy Claims Data

Pharmacy claims data can be used to examine patterns of medication use in large populations with a large follow-up period, and thus offer the possibility to study different aspects of adherence, including primary and secondary adherence, as well as persistence to therapy. Of note, studies on primary adherence typically involve linking pharmacy claims databases to other prescription databases to obtain information on initial written prescriptions by physicians.

In the literature, **primary adherence** to asthma controller medications estimates range from 65 to 94%.[113-123] Studies on **secondary adherence** to asthma controller medications reported estimates ranging from 22 to 66 %.[8,121,124-130] In these studies, the most common metric to measure adherence was the PDC, usually measured over a 12-month period. **Persistence** to asthma therapy is also generally sub-optimal, with results indicating that between 10 to 40% of asthma patients are persistent to inhaled controller therapy one year following treatment initiation.[121,128,131,132]

A comprehensive portrait of asthma medication use was provided more recently in a US study conducted by Wu *et al*.,[121] which assessed primary/secondary medication adherence and persistence to the most common controller medications among a large (n=69,652) and diverse population using prescription and pharmacy claims data. This study found that 14–20% of subjects who were prescribed controller medications for the first time did not fill their prescriptions. Secondary adherence was assessed using an adjusted PDC, which uses an index date based on the date of the first prescription rather than the date of the fill. The mean adjusted 1-year PDC was 19% for ICS, 30% for LTRA, and 25% for ICS/LABA. Additionally, between 64-76% of subjects filled their prescription within 30 days and again between 31 and 180 days after the initial prescription; the authors referred this behaviour as “early-stage persistence”. Thus, results from this study contribute to the growing evidence in the literature regarding the sub-optimal use of medications among asthma patients.

The posology and number of inhaler devices may also have an influence on medication adherence. Marceau *et al.* revealed that among ICS/LABA users, persistence is higher in patients on combination therapy, compared to concurrent ICS/LABA users, i.e. ICS and LABA in two different inhalers.[132] In particular, combination users were found to be 17% less likely to stop their treatment (adjusted hazard ratio, 0.83; 95% CI, 0.78-0.88) and filled on average 0.9 more prescriptions per year than concurrent users (p=0.0001).[132] In addition, Averell *et al.* compared once-daily (ICS/LABA) fluticasone furoate/vilanterol (FF/VI) versus the twice-daily ICS/LABA budesonide/formoterol (B/F) and

fluticasone propionate/salmeterol (FP/SAL).[128] The study reported a significantly higher mean PDC for FF/VI versus B/F (0.453 vs 0.345; adjusted $p < 0.001$) and FP/SAL (0.446 vs 0.341; adjusted $p < 0.001$). These results therefore suggest that once-daily ICS/LABA treatment might result in improved adherence compared with twice-daily alternatives.

2.3.3.2 Medication Adherence in COPD

Adherence Estimates from Blood Plasma Levels

To best of our knowledge, no direct measures of adherence have been evaluated for COPD medications.

Adherence Estimates from Patient Self-Report

Studies examining adherence to COPD patients using validated questionnaires, such as the Morisky or the MARS scale, reported nonadherence estimates to COPD controller medications ranging between 30 and 65%.[133-138] In these studies, non-adherence was identified using pre-defined thresholds. For example, one study summed the total scores from each of item the Morisky questionnaire (6-point Likert scale) and classified non-adherence by score score ≤5, after dividing the total score by the number of questions.[137]

Unlike asthma, there is a paucity of studies comparing the accuracy and validity of self-report measures with more objective measures of adherence in COPD patients. In 2014, Tommelin *et al.* compared the accuracy of the MARS-5 scale for identifying nonadherent users of inhalation medication among patients with COPD, compared with medication refill adherence (MRA) as the reference standard.[139] The study reported a mean adherence score of 23.5 ± 2.6 and 83.4% ± 23.8%, using the MARS-5 and MRA scores, respectively. Of note, the MARS-5 scores can range from 5-25, with higher scores indicating higher adherence. The investigative team reported a poor correlation between continuous MRA and MARS-5 scores ($\rho = 0.10$; $P = 0.011$). Sensitivity, specificity and PPV values were subsequently obtained by dichotomizing MRA adherence score (MRA ≥80% = adherent) and varying the non-adherence threshold of the MARS-5 scores from 5 to 20. Even with varying thresholds, MARS-5 did not reach sufficient sensitivity (53% to 13%), specificity (57% to 94%), and PPV (42% to 57%) to detect nonadherence compared with dichotomized MRA. In light of these findings, it was concluded that self-reported adherence measured by MARS-5 is inaccurate in identifying nonadherence to COPD inhaled controlled medications. An Important strength of this study was that it was conducted in a

relatively large sample size (n=613) and various measures of accuracy were obtained. However, adherence was only measured over a 3-month period, which is not ideal, as patients' medication-taking behaviour may vary over time. In addition, patients included in the study were part of a randomized clinical trial, which may not reflect medication use in the real-world setting.

Adherence Estimates from Electronic Monitoring Devices

Studies which examined adherence to COPD medications using monitoring devices are scarce, especially in the real-world setting. In 2017, Sulaiman *et al.* published a prospective observational study which examined the adherence level to salmeterol/fluticasone, a commonly prescribed combination ICS/LABA, using electronic monitoring devices, in patients who were discharged from hospital. [140] The study reported a mean adherence to salmeterol/fluticasone of 22.6% if the doses were taken correctly and on time. Due to the novel nature of the electronic monitoring device used in this study, the investigative team was able to successfully evaluate all aspects of inhaler use, including time of use, the interval between doses, and even the proficiency of inhaler use. As a result, the study highlighted the extent to which correct inhaler technique is a barrier to optimal medication use in COPD patients using objective measures and state-of-the-art technology. Another strength of this study was that it was conducted in a real-world population. However, adherence was only assessed over a 1-month period within a small sample size, rendering the analysis of adherence patterns over time not possible.

Adherence and Persistence Estimates from Pharmacy Claims Data

There is evidence to suggest that COPD patients display more adherent behaviours than asthma patients.[84] Nevertheless, current evidence reveals that adherence to COPD therapy is dismal. Studies evaluating adherence to COPD monotherapy treatment (LAMA or LABA) from pharmacy claims data reported estimates ranging from 38 to 63%.[10,141-146] In these studies, the most common metric of adherence used was the PDC and MPR. One study use the compliance rate, which represents the percentage of days with doses available divided by days to last refill.[147] A recent administrative claims database study reported a mean PDC to maintenance COPD controller therapy (including monotherapy and combination therapy) of 47%.[148] Additionally, reported estimates of persistence of COPD maintenance therapy were low, often falling between 9 and 57%.[141,149-152]

It is to be noted that adherence and persistence to triple therapy (ICS/LAAC/LABA) have been less explored in the literature. Because triple therapy in a single inhaler is a relatively new therapeutic

option for COPD, studies examining treatment patterns in COPD triple therapy included patients on multiple inhaler triple therapy (MITT), (e.g., adding a LAMA to an ICS/LABA fixed dose combination). For instance, a recent administrative database cohort study conducted in a US commercially insured population revealed that patients on MITT have a mean PDC of 37%.[153] The research team also found that adherence for each single inhaler was higher than adherence to MITT. These results support the notion that adherence could be improved by reducing the number of inhalers in patients with triple therapy. To the best of our knowledge, this hypothesis has not been fully tested in the literature yet. Indeed, the Trelegy Ellipta (fluticasone furoate/umeclidinium/vilanterol) is the only single inhaler triple therapy currently available and gained its marketing authorizations in 2017 in USA and Europe and 2018 in Canada. Due to this recent approval, evaluating adherence to this drug using administrative databases may be too premature.

2.3.4 Discrepancy in Adherence Estimates Across Administrative Database Studies

There is a large variability in adherence and persistence estimates across many of the studies using pharmacy claims data. This inconsistency can be explained by differences in the operational definitions of adherence and persistence, including the time frame to allow patients to fill the initial prescription and whether or not the following elements were considered in the adherence calculations: 1) distinction between controller medications and as-needed rescue medications; 2) inclusion of new users of the medications; and 3) representativity of patient sample.[154] For persistence measures, there is an inconsistency in the definition of the threshold used (grace period), which corresponds to the number of days allowed between refills to determine whether or not a patient is persistent to treatment. Despite these inconsistencies, the literature pertaining to medication adherence in individuals with asthma and COPD suggests that adherence to controller therapy is considerably low.

2.3.5 Predictors of Medication Adherence in Asthma and COPD

Overall, medication adherence is a complex issue woven into a myriad of factors related to patients, physicians, and healthcare systems. A systematic review of observational studies identified factors related to adherence to inhaled medications in adults with asthma and found that stronger beliefs in inhaler medication benefits and older age were good predictors of medication adherence.[155] Other factors identified in the review include **social and economic factors** (cost of treatment, prescription coverage, income); **therapy-related factors** (reliever prescription, number of drugs, number of daily dose); **condition-related factors** (asthma exacerbations, asthma duration, asthma severity, presence

of symptoms, pulmonary function); and **patient-related factors** (age, sex, ethnicity, education, medication knowledge, illness beliefs, comorbidity, healthcare utilization, quality of life).[155] According to the literature, predictors of adherence in COPD patients are similar to those of asthma patients; however, COPD patients are often faced with additional problems related to comorbidities, complex treatment regimens, and polytherapy—all which can contribute to sub-optimal adherence.[93] Moreover, many organizational factors related to the healthcare system can have an influence on adherence outcomes. Factors associated with improved adherence include fewer patients seen per hour, longer appointment length, evening consultation hours, multilingual staff, consistency of care, ease of making appointments, ease and effectiveness of telephone communication, and use of telephone calls for reminders and follow-up.[156]

2.3.6 Supporting Medication Adherence in Primary Care

2.3.6.1 The Role of Healthcare Professionals

Healthcare providers have an important impact on patients' perception of prescribed therapy. Since most asthma and COPD patients are managed in primary care, healthcare providers, such as community pharmacists, family physicians, and nurses, can play a prominent role in educating and engaging asthma/COPD patients on potential treatment benefits. They also have the unique opportunity to monitor adherence and disease control and to provide ongoing counselling and inhaler technique training. In the last decades, healthcare professional-led interventions aimed at supporting medication adherence have become increasingly popular, especially among community pharmacists. A review conducted by Wilhelmsen and Eriksoon suggested that interventions delivered by pharmacists and nurses showed better result in improving adherence and disease control than interventions delivered by general practitioners.[157] Thus, further research is warranted to gain a greater understanding on how to leverage interprofessional-collaboration to better support patient medication adherence. Indeed, understanding and resolving adherence problems should be an ongoing process that requires continuous efforts from healthcare professionals and patients. The following subsections present examples of healthcare provider-led interventions that aimed at improving patient adherence, as well as some of the barriers and facilitators that healthcare professionals face when tackling non-adherence in routine clinical practice.

2.3.6.1.1 Pharmacists

Community pharmacists frequently interact with patients and have direct access to prescription refill information. Therefore, they are important influencers of patient adherence since they can easily monitor medication adherence and identify drug-related problems. As a result, many adherence interventions in the literature have been structured to fit around the daily practice of community pharmacists. A recent systematic review and meta-analysis evaluated the effect of pharmacist-led interventions on asthma and COPD management, focusing mainly on inhalation technique and medication adherence. Interventions varied across studies and included patient education and counselling, medication review, assessing adherence based on prescription refills, lifestyle modification, medication management, as well as cognitive behavioral therapies, such as prescribing, adjusting, monitoring, and identifying drug-related problems.[158] According to the meta-analysis, pharmacist-led interventions showed a positive effect on medication adherence (1.34 [95% CI 1.18-1.53], P < .0001) and inhalation technique (1.85 [95% CI 1.57-2.17], P < .00001) in COPD and asthma patients. However, when results were stratified according to patient diagnosis, results were not statistically significant for COPD patients. Other interesting strategies that can better support pharmacists' patient care process include the appointment-based model (ABM), whereby patients have a designated appointment day to pick up all medications.[159] Prior to the appointment, pharmacy staff call patients to identify any changes to their medications and confirm that each prescription should be refilled. This process can also help pharmacists to identify, prevent or resolve medication-related problems. This patient-centered model is clinically appealing; it diverts the pharmacy staff's focus from passively filling prescriptions to having a more proactive role in the patient care process.

2.3.6.1.2 Primary Care Physicians

Although the literature on physician-led interventions to support medication adherence is expanding, these interventions are not as common as pharmacist-led interventions. A qualitative study conducted by Tarn *et al.* revealed that only a minority of physicians asked patients detailed questions about medication adherence during medical visits, although most physicians generally agreed on the importance on assessing it.[160] It was suggested that time constraints that physicians face when trying to address numerous health issues during short office visits may impede their ability to efficiently assess and address adherence. According to the Respiratory Effectiveness group, shared decision-making and successful clinical management can be achieved when patients and providers have a shared

understanding and common perception of symptoms and clinical problems.[156] This situation, referred to as "concordance", allows physicians to tailor treatment regimens to patients' needs and preferences, monitor disease, and identify nonadherence more easily. Furthermore, concordance encourages patients to increase their engagement and to willingly adhere to their prescribed treatment plan. Generally, successful primary care-based adherence interventions in asthma and COPD aimed at enhancing patient-physician communication skills in the context of shared decision-making. Other successful strategies include patient/physician education, patient counselling, and simplifying therapy regimens.[156] **In addition, providing physicians with adherence information feedback has the potential to support and improve medication adherence** (see section Integration of Pharmacy Claims Data in EMRs**2.6** for more details).

2.3.6.1.3 Nurses

Although nurses are well positioned to support patient medication adherence, nurse-led interventions are less common in the literature. Nonetheless, several nurse-led interventions were shown to improve adherence and patient outcomes; these include counseling, comprehensive assessments of medication during home visits, medication education and written factsheets, care plans and medication schedules, and verbal and written reminders by telephone or using electronic devices.[161,162]

2.3.7 Consequences of Medication Nonadherence

A large body of evidence points to the detrimental effects of medication nonadherence on therapeutic outcomes among asthma and COPD patients. A systematic review conducted by Barnes *et al.* showed that good adherence was associated with higher FEV1, a lower percentage of eosinophils in sputum, reduction in hospitalizations, reduced use of oral corticosteroids, and lower mortality rate in asthma patients. In fact, the study suggested that 24% of exacerbations and 60% of asthma-related hospitalizations could be attributed to poor adherence.[163] Along similar lines, another systematic review conducted by Van Boven *et al.*[164] indicated a clear association between adherence and both clinical and economic outcomes, with evidence from studies revealing increased hospitalizations, mortality, decreasing quality of life, and loss of productivity among non-adherent patients.

Not surprisingly, medication nonadherence places an important cost burden on patients and healthcare systems. A US study revealed that for 1000 COPD patients, a 5% point increase in PDC

reduced the annual number of inpatient visits (-2.5%) and emergency room visits (-1.8%) and slightly increased outpatient visits (+0.2%); the net reduction in annual cost was approximately $300,000.[143] These findings were echoed by a US cohort study which revealed that adherence versus nonadherence to ICS/LABA combination therapy or LAMA monotherapy in COPD patients was associated with 37.1% lower overall medical costs (95% CI: 0.43-0.91) and 53.4% lower inpatient costs (95% CI: 0.30-0.72).[145] However, adherence was associated with 46.9% higher (95% CI: 1.13-1.91) respiratory-related healthcare (medical + outpatient pharmacy) costs, compared to nonadherence.

Similarly, healthcare costs and loss of productivity are markedly higher in non-adherent asthma patients, compared to adherent patients.[165] Nevertheless, a large retrospective claims US database study reported that savings generated by reductions in high-cost events (i.e. hospitalizations, ER visits) did not compensate for the increased drug costs for adherent vs. non-adherent asthma patients.[130] When comparing the lowest and highest adherence quartile, costs related to asthma care per person per month increased significantly from $65.11 (95% CI = $57.02-$73.20) to $147.46 (95% CI = $139.48-$155.44) for patients on LTRA and from $38.71 (95% CI = $29.52-$47.90) to 93.13 (95% CI = $83.70-$102.56) for patients on ICS. However, in patients with more severe asthma, the study revealed that higher medication adherence leads to lower health care use and costs despite increased drug spending (specific numbers were not provided but were graphically summarized). These results suggest that the cost-benefit balance of improved adherence may be more favourable in patients with more severe forms of asthma.

2.4 Clinical Decision Support Systems

In recent years, healthcare institutions have increasingly leveraged clinical data captured in EMR and **clinical decision support systems** (CDSS) to enhance healthcare and help bridge the gap between optimal practice and actual clinical care. CDSS are computer applications that analyze and process clinical data (e.g. laboratory results, prescription data) to assist clinicians in making diagnostic and therapeutic decisions and implementing evidence-based clinical guidelines at point of care.[28] CDSS are typically integrated in EMR and can simplify access to critical data needed to make decisions, provide reminders and alerts during medical visits, assist in establishing a diagnoses, or flag inappropriate prescribing behaviors.[28] Although this dissertation focusses on the development medication adherence assessment tools, it is worth mentioning that these tools are a type of CDSS. That is, through the innovation of healthcare technology**, they assist clinicians in providing personalized treatments and**

optimizing prescribing decisions based on patient healthcare data. When designed properly, medication adherence assessment tools can provide physicians with objective and easily interpretable information on medication adherence assessment, which is the first step in optimizing prescribing decisions and improving patient medication adherence. The following subsections summarizes the literature encompassing CDSS and some of the common challenges of adopting them in clinical practice.

2.4.1 Clinical Decision Support Systems for Asthma and COPD

The literature reveals a paucity of CDSS for COPD; however, the number of CDSS for asthma are on the rise. In 2014, Matui *et al.*[166] published a systematic review that aimed at synthesizing the evidence for the use of CDSS by healthcare professional treating asthma patients. The review identified 8 CDSS that were evaluated in clinical trials. Six of the systems were integrated into an EMR,[167-172] one was partly integrated,[31] and one was a stand-alone system.[29] Most of these CDSS provided patient-tailored recommendations based on treatment guidelines. In addition, the CDSS comprised a wide array of clinical tools, including data entry sheets, standardized documentation for asthma severity classification, standardized drug and spirometry order sets and asthma action plans. Despite their great potential, the review revealed that these CDSS were not frequently used during the study evaluation periods and concluded that the current generation of CDSS is unlikely to result in improvements in outcomes for patients with asthma. In 2018, McKibben *et al*.[173] published a systematic review that gathered evidence on the use of computerized alerts that identify excessive prescribing of SABAs to improve asthma management. A total of four CDSS were identified. [29,31,174,175] In addition to alerts, the interventions also provided guidelines decision supports,[29-31] allergy specialist referrals,[175]self-management plans,[29] patient advice sheets,[29,31] and patient information letters.[174] The authors concluded that there is some evidence that electronic alerts can reduce excessive prescribing of SABAs, when delivered as part of a multicomponent intervention in an integrated health care system. Further research is required to establish optimal design of such systems. In addition, heterogeneity across healthcare systems may be present interoperability challenges.

More recently in 2019, Gupta *et al.*[176] developed a computerized clinical decision support system (the Electronic Asthma Management System (eAMS)) to address major care gaps and sought to measure its impact on care in adults with asthma. The eAMS consisted of a touch tablet patient questionnaire completed in the waiting room, with real-time data processing producing EMR-

integrated clinician decision support. The eAMS improved asthma quality of care in real-world primary care settings, as evidenced by an increase in asthma action plan delivery by (from 0% at baseline to 17.8% of patients and 30.5% of visits with the intervention). Nevertheless, authors acknowledged that even when CDSS improve care, time constraints are a critical barrier to their usage. They also pointed that system improvements may be considered to further enhance uptake of the tool.

2.5 Clinical Adoption of New Health Information Systems: Conceptual Frameworks

It is beyond doubt that CDSS have become increasingly relevant and hold the potential to transform health care, while optimizing prescribing practices and enhancing quality of patient care in a timely manner. However, most studies which have evaluated the implementation of CDSS in clinical practice have concluded that their uptake in clinical practice need to be enhanced. **Similar usability challenges have also been observed with medication adherence assessment tools** (section **2.6.2**). Indeed, the deployment of health information systems, such as CDSS, around the world continues to turn in mixed performances: from benchmark successful implementations resulting in transformations in patient care to never being implemented in a clinical setting. The evidence supporting the key features that improve their performance in routine clinical practice is well documented in the literature. [177-179] In general, successful CDSS have the following three characteristics: (1) decision support integrated into the workflow; (2) decision support delivered at the time and place of decision making; (3) actionable recommendations are provided; (4) recommendations are based on validated and accurate data; (5) information is presented in a user-friendly and easily interpretable format.

To gain a better understanding of the processes and possible challenges with clinical adoption of health information systems, including CDSS, several adoption models have been developed, including the Fit between Individuals, Task and Technology (FITT) framework,[180] the Clinical Adoption Framework,[181] and the Design-Reality Gap Model from Heeks.[182] Price and Lau[183] have highlighted that while these models are useful in gauging the clinical relevance of new health information systems, they are not sufficiently contextualized in a manner that can be accessible to key stakeholder audiences such as clinicians and administrators. Furthermore, they fail to generate a seamless link between health information technology adoption and clinical benefit over time.

To fill this research gap, Price and Lau[183] developed the "**clinical adoption meta-model**", which describes the clinical adoption of health information systems based on **four dimensions** related to post-deployment adoption: (1) availability; (2) use; (3) behavior changes; and (4) outcome change.

Table 4 provides a summary of the key features of this model, along with examples of indicators that can help stakeholders to better evaluate the development and deployment of new technologies in clinical practice. In addition, the model puts forth seven **archetypes** to describe the typical adoption trajectories for clinical information systems; these are summarized in **Table 5**.

For researchers and implementers of new health information systems, this model can: (1) help link implementation goals to the expected behavioral changes of end-users; (2) optimize the study design of implementation/feasibility studies and determine the most appropriate study outcomes; (3) provide valuable insights that can help better understand challenged implementations. For this reason, **the clinical adoption meta-model will be revisited throughout this thesis and will be used to better conceptualize the adoption of e-MEDRESP into clinical practice.**

Table 4. Clinical Adoption Meta-Model: Key features and Dimensions Assessed

Dimension	**Definition and key aspects**	**Aspects and examples of indicators**
AVAILABILITY	Ability for the end users to access and interact with a HIS	• User access: percentage of uptime of an EMR • System availability: Number of users with accounts to access
SYSTEM USE	Interactions with the HIS by intended end-users	• Use: Number of logins/user/month • User experience: Survey of user experience
CLINICAL BEHAVIOUR	Meaningful adaptation of clinical workflows or health behaviors that are facilitated by the HIS	• General capacity: Number of patients seen per day in the office • Specific behaviours: Rate of blood pressure screening
CLINICAL OUTCOMES	Impacts attributable to the adoption of the HIS	• Patient outcomes: Increase in medication adherence

		• Provider outcomes: Decrease in inappropriate prescribing in elderly patients

Abbreviations: HIS: Health information system

Table 5. Archetypes that Describe the Typical Adoption Trajectories for Health Information Systems (HIS), based on the Clinical Adoption Meta-Model

Archetype	Description	Contribution factors (examples)
No Deployment	• HIS is not released to its users	• Development is not completed • A technical flaw prevents deployment
Low Adoption	• Use of HIS initially increases but is not sustained • No behavior changes or outcome benefits are seen that can be attributed to the new HIS	• Misalignments between new HIS and clinical practice • After initial use, value is not perceived by users or new HIS may be too cumbersome
Adoption without Benefit (behaviour and outcome)	• HIS is available and uptake by end-users is high and sustained over time • Changes in behaviours and outcomes, do not occur	• An existing process is simply replicated by the HIS • End-users chose not to incorporate the features of the new HIS • Good practice was already present • The duration of evaluation is not sufficient to see changes.
Behaviour Change without Outcome Benefit	• HIS is being used • Intended behaviour change occurs • Expected outcomes are not realized	• Outcomes are already good • A longer time is required to see the clinical outcome • Behaviours supported are not linked to the outcome
Adoption with Outcome Benefits	• Most desirable archetype • There is a correlation between HIS availability, use, behaviour, and the expected outcomes.	• Seamless integration of HIS into clinical workflow • Good alignment between HIS features and unmet clinical needs
Adoption with Harm	• Least desirable archetype • Unintended consequence(s) occur after the deployment and adoption of the HIS resulting in a measured harm	• Misalignment between HIS features and unmet clinical needs
Benefit without Use	• One or more confounding interventions have occurred to achieve the expected improvements.	• Patients may undergo multiple interventions that aim to improve the same outcome as the HIS, rendering the assessment of the clinical relevance of the tool more difficult.

Abbreviations: HIS: Health information system

2.6 Integration of Pharmacy Claims Data in EMRs

It is beyond doubt that the digitization of healthcare practices has become a game changer for patient care improvement. Over the years, structured electronic medication data are no longer being solely used for administrative and billing purposes, they now have the potential to enhance clinical activities in the entire medication management cycle. Notwithstanding this ongoing healthcare revolution, integrating electronic medication data within the clinical workflow is a complex endeavor. Sections **2.6.1** and **2.6.2** will present examples of medication adherence assessment tools that have been implemented in clinical practice. Their key features will be described, as well as the barriers and facilitators that were encountered during their implementation process.

2.6.1 Quebec Context

Quebec Health Record (*Dossier Santé Québec*)

In the Quebec province, there is a lack of medication adherence tools that are adapted to clinical practice. Since 2013, physicians in the Canadian province of Quebec can access pharmacy claims through the Quebec Health Record (QHR), which is a **data repository** that allows physicians, pharmacists, and other healthcare professionals to access health information on their patients.[27]All Quebec-based EMR providers provide direct access to the QHR via their EMR. Of note, the QHR is not to be confused with EMRs. An EMR is an "electronic record of health-related information on an individual that can be created, gathered, managed, and consulted by authorized clinicians and staff within *one health care organizatio*n,"[184] whereas the QHR is a data warehouse that regroups patient health data across *various healthcare organizations*, including hospitals (mostly laboratory and imagery tests) and pharmacies. As such, the QHR is not a medication adherence tool *per se*; it is a data repository that stores medication lists, among other types of patient health data.

In 2018, Motulsky *et al.* published a comprehensive report on the clinical usefulness of the QHR using a mixed-methods research approach.[185] The aim of the study was to identify the benefits and usability challenges associated with the three QHR clinical domains—medication, laboratory, and medical imaging–that are currently available to QHR users. Findings revealed that the medication domain was the most widely used among the three domains in many primary and tertiary healthcare settings, with family physicians being the most frequent users. The main advantage of the medication domain is that it paints a more complete profile of patient medication use than EMRs, since patient

information comes from various prescribers in different healthcare settings, and over prolonged periods of time. One major drawback, however, is that it provides raw and unprocessed pharmacy data. When it was initially available to healthcare professionals, information on filled prescriptions, regardless of reimbursement status, was available. Now, it also includes all medications entered in the pharmacy system, including those that were not dispensed by the patient. Nevertheless, little effort was made to aggregate and process the medication data (i.e., one line per prescription), which can be hard for healthcare professionals to interpret and integrate in their workflow, especially for polymedicated patients. Many redundancies and duplicated records in the medication domain were reported, as well as a lack of standardization of the fields that were used to describe prescription refills. Thus, it appears that QHR developers have not performed analysis on the pharmacy data prior to making them available to physicians—an approach that could facilitate data interpretation. To overcome these challenges, the report recommended to develop tools integrated within the QHR that could classify medications according to generic names, dosage, date of dispensing's, type of prescriber, and pharmacy.

2.6.2 Medication Adherence Assessment Tools Based on Pharmacy Claims Data

Only a few tools based on pharmacy claims data have been structured to fit around the daily practice of family physicians. This section provides an overview of these tools, which were identified through the MEDLINE and EMBASE bibliographic databases using a search strategy validated by a librarian. For this narrative literature review, only tools designed for physicians were retained. A total of 8 tools were identified, 4 of which were not disease specific, 2 which were adapted for asthma, and 2 which were adapted for diabetes. Medication adherence assessment tools adapted to COPD were not found. The lack of tools may be due to the fact that smoking cessation programs are the main area of behavioral research well tested with COPD patients.[186] **Table 7** provides a summary of studies on medication adherence assessment tools, based on pharmacy claims data, which were developed for physicians. Further details on each tool are provided in section **2.6.2**

A summary of the clinical usefulness of each tool, assessed based on specific pre-determined criteria that were inspired by the literature, is presented in **Table 8.** Some of the criteria were also obtained from the Clinical Adoption Meta-Model that was discussed in the previous section (section **2.5**). Broadly speaking, several criteria and factors will facilitate physician adoption of new healthcare information technology in clinical practice.[187] First, the ideal e-health tool should be **seamlessly integrated in clinical practice** and not result in loss of productivity or increased clinician burden.[188,189] Second, the tool should be **user-friendly** and **intuitive**.[190-192] Moreover, prior data processing should be

carried out to allow physicians to efficiently assimilate a large amount of clinical information in a timely manner.[193,194] In this context, tools based on pharmacy claims data should contain **easily accessible and interpretable information** on medication adherence and use, as opposed to raw data (one line per filled prescription). Third, it is important to consider the **physician and patient perspective** to ensure the effective uptake of e-health technologies throughout the design, development, and testing process.[187] Alongside these factors, the extent to which the tools were rigorously evaluated in clinical practice was also assessed. Outcomes of interest include physician uptake of tools in clinical practice, user feedback on tool, and capacity of tool to improve medication adherence. Many of these outcomes are captured by the Clinical Adoption Meta-Model, as shown in **Table 6**. Collectively, these components will ultimately allow identify the research gaps, which will be presented later in section 2.6.3**.**

Table 6. Using the Clinical Adoption Meta-Model to Assess the Clinical Usefulness of Medication Adherence Assessment Tools.

Dimension	Definition	Examples of indicators
AVAILABILITY	Ability for the end users to access and interact with a HIS	• Was the tool integrated in an EMR?
SYSTEM USE	Interactions with the HIS by intended end-users	• Was use of the tool monitored in clinical practice? • Was user experience captured through questionnaires/surveys or interviews?
CLINICAL BEHAVIOUR	Meaningful adaptation of clinical workflows or health behaviors that are facilitated by the HIS	• Did the tool optimize prescribing behaviours of physicians? • Did the tool reduce unnecessary treatment escalation or result in a simplification of the therapeutic regimen? • Were physicians more proactive in tackling medication adherence in clinical practice?
CLINICAL OUTCOMES	Impacts attributable to the adoption of the HIS	• Did the tool result in improved patient medication adherence?

Abbreviations: EMR: Electronic Medical Record; HIS: Health information system

Table 7. Medication Adherence Assessment Tools Based on Pharmacy Claims data That Were Designed for Physicians

Study/Tool, Country, year	Study Design	Number of patients/ Physicians	Study population	Description of Tool and physician use	Method/metric for assessing adherence	Physician use, patient/physician feedback	Adherence improvement
TOOLS THAT ARE NOT DISEASE-SPECIFIC							
Surescripts™ Medication Management for Adherence[195,196] USA 2011-present	N/A	N/A	N/A	Clinicians can request aggregated pharmacy claims data in real time within their EMR via Surescripts, an e-prescribing network.	PDC Clinicians can see the past 12 months of a patient's prescription history to help determine medication adherence	NOT EVALUATED	NOT EVALUATED
Personal medicine profile (PEM)[21] DENMARK 2012	N/A	The PEM has been evaluated in 583 patients, but tool appears to be available nationwide	Tool has been evaluated in elderly patients ≥ 65 years old, taking more than 4 drugs per day	Web-based tool for electronic prescription and monitoring of purchased medicine.	Graphical presentation of adherence over a 15-month period, calculated by daily dosages, number of tablets purchased per month, and expected time to refill	NOT EVALUATED	NOT EVALUATED
Veterans Affairs Electronic Medical Record System[22] USA 2006-present	N/A	Tool has been evaluated in 38 327 patients, total number of patients for whom tool is available is not indicated in the literature	U.S. Veteran population	Algorithms integrated within EMR System to measure drug adherence.	Graphical display of patients' medication refill gaps for each prescribed medication in a visually accessible, clear, graphical format	NOT EVALUATED	NOT EVALUATED

Study/Tool, Country, year	Study Design	Number of patients/ Physicians	Study population	Description of Tool and physician use	Method/metric for assessing adherence	Physician use, patient/physician feedback	Adherence improvement
Medical office of the 21st century (MOXXI)[197,198] Canada (QC) 2006 Nb. Many articles on MOXXI were published; two of these studies were retained for the purpose of this literature review	**1) Implementation follow-up study,** which aimed to develop and evaluate the acceptability and use of MOXXI[197] **2) RCT** which aimed at evaluating the capacity of MOXXI to enhance adherence among patients taking antihypertensive and lipid-lowering drugs[198]	**Implementation follow-up study**: -28 family physicians -13,515 patients **RCT**: -2,293 patients		Portable electronic prescribing and integrated drug management system (via a tablet) that allowed physicians to write and transmit prescriptions from any location	Graphical display of adherence: -The medication profile displays days of drug supply, available by calendar time, based on the date the drug was dispensed and the duration of the prescription. -Drugs prescribed by the physician are displayed as blue bars, those prescribed by other physicians as red bars. Drugs that are prescribed electronically but are not yet dispensed are shown as grey bars	**Implementation study** -Biweekly use rate of physician use of medication profile: 12.6/100 visits. -Mean (sd) rating of medication adherence assessment tool (physician satisfaction): 3.5 (0.98) *Based on five-category Likert scale*	**RCT** ADHERENCE DID NOT IMPROVE Adherence was defined as the proportion of days in which an individual had a supply of prescribed medication on the basis of prescription refills and was calculated for each active drug at the index visit. Adherence was estimated in the 3 months prior to the index visit and the 6 months after.
TOOLS ADAPTED FOR ASTHMA							
Med-Resp[199] Canada (QC) 2019	Sequential exploratory pilot study	Physicians= 6 (pulmonologists) Patients= 23	Adults with moderate-to-severe asthma	Paper-based graphical tool was given to the pulmonolgist prior to the medical visit	-Calendar showing monthly dispensing of asthma controller and SABA medications, as well as oral corticosteroids. -Bar charts illustrating the daily dose of ICS, number of oral corticosteroids, and weekly doses of SABA on a quarterly and annual basis.	PHYSICIAN USE Not evaluated USER FEEDBACK Tool was highly appreciated by pulmonologists and patients following completion of feedback questionnaire/ phone interview	ADHERENCE DID NOT IMPROVE Adherence was measured 6 months before and after index visit (via PDC), according to each controller medication .

Study/Tool, Country, year	Study Design	Number of patients/ Physicians	Study population	Description of Tool and physician use	Method/metric for assessing adherence	Physician use, patient/physician feedback	Adherence improvement
Williams *et al.*, 2010[23] USA	Clustered RCT	Providers n=188 (n=88 intervention; n=105 control) Patients n=2,698 (n=1335 intervention; 1363 control)	Adults with asthma	Physicians could view updated ICS adherence information on their patients referred to as general adherence information via electronic prescription software (ePrescribing)	General adherence information: CMA Details on patient ICS adherence: 1-year graphic representation of the time of prescription, time of fill and day's supply	General adherence information: viewed in 70% of patients Detailed adherence information : viewed in 2.6% patients	IMPROVEMENT IN ADHERENCE REPORTED Adherence was significantly higher in the intervention group when the patient's physician chose to view detailed adherence information compared with patients in the control arm (35.7% vs. 23.3%; p=0.026) and patients from the intervention arm whose physician did not view adherence information (35.7% vs. 12.3%; p=0.002). Adherence was assessed in the last 3 months of the intervention via CMA
TOOLS ADAPATED FOR DIABETES							
Schectman *et al.*, 2004[200] USA	Prospective cohort	83 physicians 340 diabetic patients	Adults patients with type 2 diabetes	Physicians were provided with a feedback report on the most recent date and result of diabetes care measures and recent diabetes medication refills AND An educational session on intervention was provided to the physicians	-Refill adherence (for oral agents): Number of days of therapy dispensed on all but the last prescription in interval/ total number of days in interval. -Average daily dose (for oral agents and insulin): dispensed amount/ refill interval Also available: One line per filled prescription of insulin or oral agent (with date of refill, strength, and dose)	-65% physicians perceived the intervention favorably. -77% of physicians stated that the adherence feedback was moderately to very easy to understand -92% stated that it was moderately to very useful.	IMPROVEMENT IN ADHERENCE REPORTED Adherence improved among patients of physicians attending the educational session. Mean absolute increase: 95% CI: +1.8% to +6.6% (P=0.009) Adherence was assessed in the pre- (June to November 2001) and post intervention (January to June 2002) periods

Study/Tool, Country, year	Study Design	Number of patients/ Physicians	Study population	Description of Tool and physician use	Method/metric for assessing adherence	Physician use, patient/physician feedback	Adherence improvement
Dixon *et al.*, 2016[25] USA	Before-After Pilot Study	15 family physicians 96 patients with diabetes	Adult patients with type 2 diabetes	Web-based module for an EMR system to electronically integrate the capture and presentation of information regarding patients' disease management, medication adherence, and perceived barriers to adherence	PDC	Only half of the providers believed that the tool was useful to patient-provider conversations on adherence; the remaining physicians responded negatively or were neutral.	IMPROVEMENT IN ADHERENCE REPORTED Adherence significantly and meaningfully improved (improvements ranged from 6% to 20%) consistently across diabetes as well as cardiovascular drug classes. PDC was assessed over the 12-month period prior to the intervention period and over 9 months after the intervention period

Abbreviations: CI: Confidence interval; CMA: Continuous medical availability HIT: Health information technology; ICS: Inhaled corticosteroids; PDC: Proportion of days covered; MPR: Medication possession ratio; RCT: Randomized clinical trial; SE=Standard Error; VA=Veterans affairs

Table 8. Evaluation of Clinical Usefulness of Medication Adherence Assessment Tools Based on Pharmacy Claims Data

✓ advantages ✗ limits ✓ element is available, but only partially ? unable to verify in the literature

	Physician workflow and Evaluation of tool in clinical practice			Tool Development	Tool components			Current availability in clinical practice	
Study/Tool, Country, year	**Integration in an EMR**	**Evaluation in routine clinical practice and RCT**	**Monitoring of physician use in clinical practice**	**Involvement of primary end-users and user feedback**	**Graphical display or calendar of drug dispensing**	**Medication dosages, name, potency**	**Adherence evaluation period and metric**	**Patient population coverage**	**Currently available in clinical practice**
TOOLS THAT ARE NOT DISEASE SPECIFIC									
Surescripts™ Medication Management for Adherence[195,196] USA 2011-present	YES ✓	WAS NOT EVALUATED ✗	WAS NOT EVALUATED ✗	Unknown ?	YES ✓	YES ✓	12 months Metric: PDC ✓	Nationwide ✓	Available to 6300 providers ✓
Personal medicine profile (PEM)[21] Denmark 2012	NO Web-based tool ✓	WAS NOT EVALUATED ✗	WAS NOT EVALUATED ✗	Unknown ?	Individual graph per drug, showing prescription duration refill gaps ✓	YES But system is unable to capture all dispensed medications ✓	15 months Metric: PDD ✓	National ✓	Unknown ?
Veterans Affairs Electronic Medical Record System[22] USA 2006-present	YES ✓	WAS NOT EVALUATED ✗	WAS NOT EVALUATED ✗	Unknown ?	Individual graph per drug, showing prescription duration refill gaps ✓	YES ✗	12 months ✓	Only available for US veterans ✗	YES ✓
Medical office of the 21st century (MOXXI)[197,198] Canada (QC) 2006	NO Separate electronic prescribing and drug management system, available via hand-held device ✗	YES Evaluated in a large feasibility study and RCT (n=13,515) ✓	YES Low use of the medication profile (15/100 medical visits) ✓	Physician feedback was obtained during feasibility study ✓	Graphical display of all prescribed drugs, along with day's supply ✓	YES ✓	6 months ✓	Only available for patients with public drug insurance ✗	Unknown ?

	Physician workflow and evaluation in clinical practice			Tool Development	Tool components			Current availability in clinical practice	
Study/Tool, Country, year	**Integration in an EMR**	**Evaluation in routine clinical practice**	**Monitoring of physician use in clinical practice**	**Involvement of primary end-users**	**Graphical display or calendar of drug dispensing**	**Medication dosages, name, potency**	**Adherence evaluation period and metric**	**Patient population coverage**	**Currently available in clinical practice**
TOOLS ADAPTED FOR ASTHMA									
Williams *et al.*, 2010[23] USA	YES ✓	Assessed via cluster RCT Large sample size (n=1,335) ✓	YES Moderate to low use ✓	Unknown ?	Graphical display of all prescribed drugs, along with day's supply ✓	YES ✓	12 months CMA ✓	Unknown ?	Unknown ?
Med-Resp[199] Canada (QC) 2019	NO Paper-based ✗	YES Small sample size (n=23) ✗	NO PRIOR EVALUATION ✗	Development with physicians and patients, user feedback obtained ✓	Graphical display of all prescribed drugs, along with day's supply ✓	YES Medication name not available; adherence information is summarized by pharmacologic class ✓	12 months ✓	Only individuals with private drug insurance ✗	NO ✗
TOOL ADAPTED FOR DIABIATES									
Schectman *et al.*, 2004[200] USA	NO Paper-based ✗	YES small sample size (n=343) ✓	NO ✗	Physician feedback was obtained ✓	NO One line per filled prescription ✗	YES ✓	Refill adherence Average daily dose ✓	Unknown ?	Unknown ?
Dixon *et al.*, 2016[25]	YES ✓	YES, pilot study, small sample size (n =99) ✓	NO ✗	Physician feedback was obtained ✓	No detailed information on medication use ✗	YES Medication name not available; adherence information is summarized by pharmacologic class ✓	12 months PDC ✓	Unknown ?	Unknown ?

2.6.2.1 Non Disease-Specific Adherence Assessment Tools Based on Pharmacy Claims Data

Surescripts™ Medication Management for Adherence – USA

Physicians in the US can request pharmacy claims data in real time within their EMR via Surescripts, a nation-wide health information network that connects virtually all EMR vendors, pharmacy benefit managers (PBMs), pharmacies, and clinicians.[195,196] An increasing number of health plans, along with long-term and post-acute care organizations, specialty hubs and specialty pharmacy organizations are also connected to Surescripts. For patients who provided prior consent, physicians can view the past 12 months of their prescription history to help determine medication adherence. Available data include pharmacy claims from retail and mail-order pharmacies, and from pharmacy benefit managers for private and public insurers. A key advantage of the Surescripts medication history module is that it is directly integrated within the EMR workflow. In other words, no connection to an outside portal or additional login credentials are required to access Surescripts. For each medication dispensed, the generic drug name, dosage, days' supply, quantity dispensed, prescription date, as well as the National Drug Code, are provided. Colour codes are also applied to designate adherence levels (green: optimal; yellow: medium; red: sub-optimal). Furthermore, clinicians can receive medication-specific messages based on each patient's diagnosis and PDC score. They can also document reasons behind nonadherence and may send the information to payers. For example, if medication cost is an issue for the patient, physicians can directly communicate this information to the payer through the portal.

To the best of our knowledge, no study has evaluated the rate of physician use of this tool or its capacity to improve medication adherence, which makes it difficult to assess its clinical usefulness. However, Comer *et al.* have used Surescripts to identify the prevalence and predictors of 1) medication discrepancies between pharmacy claims data and the medication list in a primary care EMR;[201] 2) primary nonadherence to antihypertensive therapy in primary care practice.[26] To the best of our knowledge, Surescripts™ does not appear to have been developed in collaboration with the primary end-users (not reported in the literature).

Personal electronic medicine profile (PEM) – Denmark

The personal electronic medicine profile (PEM) is a web-based tool for electronic prescription and monitoring of purchased medicine in Denmark.[21] It can provide patients, physicians, and pharmacists with an individually based overview of all prescribed and dispensed drugs in Denmark, including information on time of drug purchase, number of tablets, and daily dosage. Moreover, the PEM contains a graphical display of adherence, calculated by daily dosages, number of tablets purchased, and expected time to refill. The medication information presented in PEM is extracted from Denmark's National Prescription (NDP) database. In 2012, Harbig *et al.* evaluated the accuracy of the PEM as a tool for monitoring drug nonadherence as compared with pill counts.[21] The study found that PEM could not accurately process nonadherence in 44% of all drugs. The major sources of error included incomplete prescription information (34%) and inaccurate dosage registration (10%), which occurred due to data extraction errors between the NDP and the PEM. Although the authors concluded that the PEM is inferior to pill counting methods in terms of accuracy of drug nonadherence monitoring, they highlighted that the PEM could be a powerful tool for electronic monitoring of drug nonadherence if prescription information was recorded uniformly and correctly. Therefore, further work is needed to enhance the accuracy of this tool and to validate its use in routine clinical practice. To the best of our knowledge, no studies on the PEM have been published since, which makes it difficult to assess its clinical usefulness. Its capacity to improve adherence has not yet been assessed. From the published literature, we cannot establish whether PEM has been developed with the primary end-users.

Veterans Affair Electronic Medical Record System – USA

Since 2006, the Veterans Affairs electronic medical record has begun to display patients' medication refill gaps for each prescribed medication in a more visually accessible, clear, graphical format.[22] Although this information does not account for hospitalizations or prior overstocks due to dosage changes, this type of easily accessible, objective information at the time of prescribing or renewing prescriptions is an important first step in ensuring that assessment of current adherence becomes an integral part of outpatient clinical decision making. To our knowledge, however, the accuracy and usefulness of this tool to monitor and improve adherence has not been reported in the literature. It has been previously used to assess the prevalence of nonadherence and relationship between patient adherence and treatment escalation among patients with poorly controlled hypertension. To the best of our knowledge, this tool does not appear to have been developed with primary end-users (not reported in the literature).

Medical Office of the XXIst Century (MOXXI) – Québec, Canada

A McGill-based research team led by Robyn Tamblyn developed and evaluated the acceptability and use of an integrated electronic prescribing and drug management system (MOXXI) for primary care physicians.[197] Specifically, MOXXI is a portable electronic prescribing and integrated drug management system that enables physicians to write and transmit prescriptions using a handheld personal digital assistant. Among its many features, MOXXI has a medication profile dashboard and medication adherence monitoring tool which provides a calendar summary of the patient's current medication therapy. Medications prescribed or dispensed in the past six months are shown with a color legend corresponding to: 1) whether a medication that was prescribed has been dispensed; 2) medications prescribed by other physicians; 3) lapses in treatment as calculated by drug by day exposure; and 4) therapy overlap days. MOXXI is only available for patients with public drug insurance (RAMQ).

During an implementation study, physicians were asked to rate the ease of use, intent to use, actual use, expected impact, and perceived value of the MOXXI system, through questionnaires with five-category Likert scales.[197] According to respondents, the medication profile was the most useful and highly rated aspects of the system. The list of prescribed medications and list of medication dispensed had a mean ± sd rating of 4.13 ±0.74. On the other hand, the medication adherence assessment tool had a mean rating of 3.5 ± 0.98. In the first 20 months following implementation, the biweekly use rate of the medication profile was 12.6/100 visits. To explain this low use, authors suggested that the handheld devices in which MOXXI could be accessed were "barely adequate" to handle the complexity of this system. Limited screen size, memory, and battery life were some of the constraints encountered by users. Authors also indicated that the small sample size limited the ability to assess physician-level determinants of use.

During a subsequent RCT, the capacity of MOXXI to enhance patient adherence was evaluated among patients taking antihypertensive and lipid-lowering drugs (n=2293).[198] On average, physicians reviewed the drug profile in 15 per 100 visits, and access was greater for patients on multiple medications. No significant change in refill adherence was observed after 6 months of follow-up. The study authors found that patients whose physician accessed the adherence monitoring tools were more likely to have their drug profile reviewed. However, when adherence problems were detected, authors indicated that physicians may not have had the capacity to intervene when the reasons for nonadherence related to a patient's medication beliefs and motivational issues rather than therapy-related problems such as side effects, complexity, or cost. Thus, it was concluded that the capacity of MOXXI to result in increased

adherence could be enhanced if it were part of a multi-factorial intervention involving a multi-disciplinary care team that could provide counseling to non-adherent patients.

The MOXXI system has many clinically appealing and notable features. First, the tool was evaluated using rigorous research methods. Second, detailed information on medication use is presented in a user-friendly format and physicians can also identify prescriptions which were never filled, thereby them allowing them to evaluate both primary and secondary adherence at a glance. Third, the tool also serves as an e-prescribing platform and a drug management platform and collects data on healthcare utilisation (hospitalizations, ER visits), which may better inform physicians on patient therapeutic outcomes. It is thus no surprise that the tool was highly rated among physicians. However, at the time of its conception and implementation, EMR were not available in any of the participating clinics. Integrating the MOXXI system within an EMR system, rather than a handheld device, may have enhanced its interoperability and maximized its implementation and use in clinical practice.

2.6.2.2 Adherence Assessment Tools Based on Pharmacy Claims Data for Asthma

Med-Resp – Québec, Canada

The research team of Lucie Blais undertook a pilot project at the asthma outpatient clinic of the *Hôpital du Sacré-Coeur de Montréal* which aimed at developing Med-Resp, a paper-based medication adherence assessment tool for asthma patients.[202] Med-Resp was designed in collaboration with pulmonologists and patients. Pulmonologists had access to this tool during their outpatient consults, as part of a pilot study. Med-Resp includes two components. The first component presents the monthly dispensing of asthma controller and SABA medications, as well as oral corticosteroids. The second component presents bar charts illustrating the daily dose of ICS, number of oral corticosteroids prescriptions, and weekly doses of SABA on a quarterly and annual basis. The estimate of the mean daily ICS dose was calculated by using an algorithm that takes into account the following parameters: potency of different ICS; medication form; quantity dispensed; and medication dispensing dates. Data on pharmacy claims were obtained via the reMed drug claims database. reMed is a computerized claims database which collects information on prescribed medications dispensed in community pharmacies for a sample of Quebec residents. reMed is developed based upon data purchased from community pharmacies' computer services providers, which transfer medication data required for reimbursement. The link between the providers and reMed is established by way of a dynamic, computerized, and confidential list which contains the identity of enrolled participants.[203]

Although Med-Resp was highly appreciated by the physicians and patients, the evaluation of its effectiveness to improve prescribing and patients' adherence was compromised due to important limitations of the research infrastructure. First, only patients with private drug insurance could participate in the study since reMed, at the time of the study, did not record complete drug data for patients with public drug insurance. Second, physicians did not have access to an EMR and the graphical tool had to be printed and dragged in the paper medical record by a research assistant before the patient's medical visit, which is not an efficient and a large scale implementable procedure.

Of note, the e-MEDRESP project presented in this doctoral thesis builds upon this research. Indeed, the Med-Resp study allowed Professor Blais' team to confirm the need to further develop medication adherence assessment tools adapted to routine clinical practice. Importantly, the Med-Resp study confirmed the eagerness of physicians to have access to an objective measure of patients' adherence to prescribed medications and the necessity that such tools be integrated in an EMR and available for all patients, regardless of their drug insurance plan, to be effectively used in routine clinical practice. Thus, important distinctions between the Med-RESP and e-MEDRESP is that the latter was: 1) adapted to asthma and COPD medications; 2) available for patients with public or private drug insurance; 3) integrated in EMRs via its web-based format; and 4) implemented within a multicentric clinical setting. Prior to initiating the study, we hypothesized that this enhanced research infrastructure could result in a more efficient data collection process on feasibility outcomes. This hypothesis is further elaborated and confirmed in the feasibility study presented in section **4.2** of the results section. Indeed, because e-MEDRESP is web-based, it was possible to track physician use of e-MEDRESP throughout the feasibility study. The tool was also seamlessly integrated into the physicians' workflow, as confirmed by physician questionnaires. Specifically, the tool was easily accessible within their EMR and we did not require additional staff to facilitate the access of the tool the physicians.

Asthma Adherence Assessment Tool (Williams *et al.*, 2010) – USA

Williams *et al.* conducted a clustered RCT to assess the effect of providing to primary care physicians information on patient adherence to ICS controller medications.[23] Through an electronic prescription software (ePrescribing), physicians in the intervention group could view updated **general ICS adherence information**, which consisted of a summary of overall adherence using the CMA metric), and **detailed information on ICS adherence**, which comprised a 1-year graphic representation of the time of

prescription, time of fill and day's supply. Frequency of SABA use and ICS daily dose were also calculated via algorithms that take into consideration the total day's supply, dosage, and potency information.

Adherence was assessed in the last 3 months of the intervention via the CMA metric. The investigative team found that there was no statistically significant improvement in ICS adherence in patients in the intervention arm (n=1335) compared with those in the usual care arm (n=1363). However, adherence was significantly higher in the intervention group when the patient's physician opted to view **detailed adherence information**, compared with patients in the control arm (35.7% vs. 23.3%; p=0.026) and patients from the intervention arm whose physician did not view adherence information (35.7% vs. 12.3%; p=0.002). Of note, among patients in the intervention group, the **general adherence information** was viewed at least once during the study period in 939 (70%) patients among patients in the intervention arm. In contrast, physicians viewed the **detailed adherence information** in only 52 (2.6%) of these patients. Although the tool does not appear to have been developed in collaboration with physicians, the study authors explained that the intervention was explicitly designed to be feasible and minimally obtrusive in the clinical setting. As a result, the low rate of physician use indicates that not all clinicians were sufficiently motivated to review the details of their patients' medication use. The authors suggested that "further inducements" may be required to encourage clinicians to use this information as intended. Nevertheless, these findings show that asthmatic patients are more likely to routinely take ICS when physicians closely monitored their medication use and reviewed electronic prescription information.

An important advantage of this tool was that it was integrated in the physician EMR. Moreover, it was evaluated in a cluster RCT, which allowed the authors to adequately evaluate the effectiveness of the tool to improve adherence. The low physician consultation of the detailed adherence information is a drawback and highlights the need to investigate further the determinants which would encourage physicians to closely monitor the medication adherence of their patients.

2.6.2.3 Adherence Assessment Tools based on Pharmacy Claims Data for Other Diseases

DIABETES - Schectman *et al.* 2004 – USA

Schectman *et al.* conducted a prospective cohort study to determine whether providing physicians with prescription refill feedback would improve adherence among diabetic patients.[204] 83 physicians were provided with a paper report summarizing refill-based adherence data for diabetes medications (including percentage adherence for oral agents and average daily dose of anti-diabetic medications (oral and insulin) on each of their 340 patients. To the best of our knowledge, this tool does not appear to have

been developed in collaboration with physicians (not reported in the literature). Adherence was calculated using the refill adherence metric that was obtained by dividing the number of days of therapy dispensed on all but the last prescription in index period by the total number of days in the index period. The index period was not clearly defined, but authors mentioned that it corresponded to the refill interval from the health system pharmacy. Adherence was not calculated for insulin, although the strength, dose, and date of refill was provided for this medication.

Additionally, an educational session on adherence assessment and improvement techniques was held, and all physicians received a written outline on this topic. 6-month change in refill adherence (doses filled/doses prescribed) of their patient were assessed. The mean absolute increase in adherence for patients whose physician did not attend the educational session was 0.2% (95% CI, -2.0% to +2.4%; p=0.85) versus, a significant mean increase of 4.2% (95% CI: 1.8% to 6.6%; p=0.0009) for patients whose physician attended the educational program. Restricting the analysis to the 106 patients with baseline level of adherence <80%, patients of physicians attending the educational session showed greater improvement in adherence than patients of non-attendees (17% vs 10%, p= 0.09). Physician feedback questionnaire revealed that the majority of physicians (65%) perceived the intervention favorably. Additionally, 77% of physicians stated that the adherence feedback was moderately easy to understand.

This study had many strengths. Namely, it was conducted in routine clinical practice; an educational session on adherence was provided to physicians; and the adherence feedback reports were detailed. However, the study was conducted in a small population and the feedback adherence report was paper-based. Due to these limitations, use of the tool by physicians could not be monitored and the capacity to implement this tool on a wider scale was compromised.

DIABETES - Dixon *et al.*, 2016 – USA

In 2016, Dixon *et al.* conducted a pre-post pilot study which aimed at evaluating the feasibility of implementing a web-based module for an EMR system which electronically integrated the capture and presentation of information regarding patients' disease management, medication adherence and patient-reported perceived barriers to adherence.[25] A total of 15 family physicians and 96 patients with diabetes were enrolled. In the web-based module, adherence to Type 2 diabetes medications and related medications was displayed as a percentage that was calculated using the PDC. The web-based module was available for 9 months (intervention period) and adherence was measured using the PDC over the 12-month period prior to the intervention period and over 9 months after the intervention period. Although adherence significantly and meaningfully improved consistently across diabetes as well as cardiovascular

medications (improvements ranged from 6%-20%), the use of the web-based tool by the physicians did not appear to be monitored in the study, thereby making it difficult to isolate the effect of providing physicians with prescription refill data on their patients' medication adherence. To the best of our knowledge, the tool does not appear to have been developed in collaboration with the primary-end users (not reported in the literature).

User feedback revealed that only half of the providers believed that the tool was useful to patient-provider conversations on adherence; the remaining physicians responded negatively or were neutral. In particular, providers were not confident with the quality or completeness of the medication information presented and were unsure that data from all pharmacies were collected.

A key strength of this tool was that it was seamlessly integrated in EMR and that it collected patient reported outcomes. Limitations of the study was its relatively small sample size and the fact that only the PDC of medication classes was presented. Detailed information on medication use (drug name, dosage, dates of prescription refills) may have enhanced the clinical usefulness of this tool.

2.6.3 EMR Medication Adherence Assessment Tools –Features Critical to Successful Implementation

Section **2.6.2** presented an overview of medication adherence assessment tools that were constructed using pharmacy claims data and that were designed for physicians. Overall, the literature regarding the implementation of these types of tools is less elaborated than that the broader field of CDSS (section 2.4). However, similar usability and implementation challenges can be observed between these two types of tools. Consistent with the clinical adoption meta-model,[181] the success of implementation of a medication adherence assessment tool depends on the ability for the end-users to access and interact with the tool (i.e. via an EMR) and whether meaningful adaptations of clinical workflows and healthcare behaviors can be facilitated by the tool. When analyzing the clinical adoption trajectories of these tools, most tools had a low user adoption. Thus, it is possible that the tools were used frequently in the beginning but was not sustained throughout the study. It is also possible that there was a misalignment between the tools and clinical practice. Of note, most of the studies evaluating the implementation of medication adherence assessment tools were conducted within small prospective cohorts. Another critical issue is that most studies were not sufficiently powered or adequately designed to assess the impacts attributable to the adoption of the new tools in clinical practice (i.e. improvement in patient medication adherence or improvement in disease control). Physician behavioral changes, such as reduction in unnecessary treatment escalation or improvement in prescribing practices, were also not assessed in these studies.

Nevertheless, the evidence gathered in this review provides useful insights on the key features of the ideal medication adherence assessment tool and the factors that could ensure its seamless integration within physician workflow. These insights are further elaborated in the next sections.

2.6.3.1 Information Technology Infrastructure Required to Ensure Large-Scale Implementation

Many of the studies were conducted using small sample sizes or within limited research infrastructures. To be efficiently integrated within physician workflow, these tools need to be seamlessly integrated in EMR. In contrast, CDSS are typically integrated within EMR. Among the medication adherence assessment tools identified in this chapter, Surescripts appears to be the only tool which currently has the potential to be implementable on a large scale, due to its direct integration in EMR.[195,196] However, no study has yet evaluated its clinical usefulness or its capacity to enhance medication adherence.

2.6.3.2 Factors to Maximize Physician Use of Medication Adherence Assessment Tool

Although many of the tools appeared to be useful in assessing medication adherence, their use in clinical practice was not as high as expected. In the study conducted by Williams *et al.*, the **general adherence information** was viewed at least once during the study period in 939 (70%) patients among patients in the intervention arm. However, the **detailed information** on adherence to asthma medications was only accessed in 2.4% of the enrolled patients and the study authors highlighted the need to further encourage physicians to monitor medication adherence.[114] In the MOXXI feasibility study, the rate of physician use of the medication profile was 12.6/100 visits.[197] The MOXXI team indicated that the relatively small sample size of the feasibility study limited the ability to assess physician-level determinants of use. They also mentioned the disadvantages of providing MOXXI through hand-held devices which could have affected physician use, such as limited screen size, memory, and battery life. Thus, it could be argued that integrating the MOXXI system within an existing EMR system may enhance its uptake in clinical practice.

On a broader level, further research is required to determine the barriers and facilitators of implementation of such tools. It can also be hypothesized that the higher the rate of physician use, the higher the likelihood that physicians will intervene among their non-adherent patients, which could ultimately help improve patient adherence to prescribed therapy in the long run. However, for this to occur, these tools must result in meaningful adaptions of the clinical workflows, as well was patient/physician behaviours. The comprehensiveness, quality, and reliability of medication-related data are also important factors to consider. This point is further elaborated in **section 2.6.3.4**.

Schectman *et al*. reported that patient adherence was improved in patients whose physician attended the optional education session on adherence that was provided as part of the study.[204] Although

physician use of the tool was not monitored in this study, it can be speculated that physicians who attended the educational session were more likely to consult the medication adherence report and intervene to improve their patients' adherence. Williams *et al*. revealed that adherence was improved in patients whose physician opted to view more detailed information on their adherence, compared to physicians who only viewed general adherence information that was presented as a percentage.[114] These findings suggest that the effectiveness of a tool to improve medication adherence could be influenced by the physician's perception on the importance of assessing medication adherence or the quality of the tool.

2.6.3.3 Importance of Developing Tools in Collaboration with Primary end-users

Another point worth mentioning is that it does not appear that many tools were developed in collaboration with primary end users. It is possible that end-users were involved to some extent in the development process of these tools; however, this methodological aspect was seldom reported in the published studies, possibly due to lack of writing space. Indeed, it was previously suggested that the way in which a health information product is designed and implemented has a significant impact on the usability and overall user experience.[205] Such an approach may help design and develop tools that are adapted to physicians' needs and reduce clinician burden.[205] It may also help determine the ideal tool format and content, as well as the most appropriate metrics to describe medication adherence and use. The ideal tool should be able to provide a holistic picture on patient medication use and adherence in a way that is easily and quickly interpretable by the physician. Graphical summaries of patient adherence may ultimately allow physicians to assimilate an enormous amount of information on medication adherence in a timely manner, thereby facilitating decision-making. The involvement of primary end-users in the development process of such medication adherence assessment tools needs to be further explored.

2.6.3.4 Complexity of Medication Data

In the studies identified in this review, the complexity of integrating electronic medication data within physician data was seldom discussed. In her recent book chapter "*Big Data Challenges from a Pharmacy Perspective,*" Motulsky highlighted medication data challenges in the clinical setting.[96] First, it is important to realized that medication data are overly complicated because they are constantly in flux; new medications enter the market while others are withdrawn on a monthly basis and these trends differ across jurisdictions. For example, a drug may be coded differently within a given time for reasons related to billing purposes or drug approval; this coding mechanism is useful for inventory and billing purposes, but its relevance is limited when it comes to clinical activities and can complexify underlying algorithms

that were designed to process the electronic medication data for use by providers in the clinical practice. Second, not all medication data sources are equivalent. There is a lack of harmony and standards, both in terms of practices and terminologies, that are inherent to medication-related data. For example, if a medication adherence assessment tool based on pharmacy claims data has been developed within a specific jurisdiction, it may not be easily transposable to other healthcare settings, as medication data are governed by local rules, practices, and particularities.

Even within a given jurisdiction, many medication data sources may exist. Indeed, as was mentioned in section **2.3.2.2**, pharmacy claims databases are often incomplete and only cover certain segments of the population or specific medication insurance programs. Ideally, we should have in place independent infrastructures that: 1) can link all medication data sources; 2) standardize medication data in a cohesive manner across the various data sources. These concerns regarding the reconciliation between different sources of medication-related data were echoed by the findings of Dixon *et al*., who reported that providers did not completely trust the reliability and completeness of the pharmacy claims data that were integrated in their EMR web-based module.[25] Additionally, Tamblyn *et al.* highlighted the need to establish an independent infrastructure to link each pharmacy in order to retrieve a complete medication list.[197] It is a costly, yet necessary endeavour, to ensure a successful implementation in clinical practice.

2.6.3.5 Patient-Related Data and Consent

Motulsky has argued that, when it comes to medication data, patient-related data is where the "core of the analytic potential resides."[96] This information can provide valuable insights on the consequences of medication exposure, including side effects, patient preferences, and behavioral aspects (e.g. medication adherence, inhaler technique). It can also help us to determine whether the real-world effectiveness of medications can be aligned with prescriber practices and patients. Yet, patient-related data is seldom available in electronic medication data, including pharmacy claims data. Thus, future health information systems should find ways to incorporate patient-related data into their platforms in order to support clinical decision-making at the point of care. For instance, patient-generated health data that can be collected from patient mobile apps and devices are interesting avenues to explore, although such information technology endeavors are still at their infancy. [206] Furthermore, obtaining patients' consent to share their medication-related data is imperative. However, it is important to consider how the patient-physician relationship may be affected in a context when physicians can have access to information regarding their patients' medication use.

2.6.3.6 Other considerations

Medication adherence is a complex and multi-faceted aspect intermingled with numerous factors related to the patient, healthcare providers, and healthcare system. As was mentioned in section **2.3.6**, patient education and counselling showed some positive effects on medication adherence and that interventions delivered by pharmacists and nurses showed a better result in improving adherence and outcomes than interventions led by general practitioners.[157] However, study authors pointed out that no single strategy showed improvement in all settings and emphasized the need to better screen patients for non-adherence. Therefore, it can be hypothesized that the clinical usefulness of medication adherence assessment tools could be enhanced if they became part of a multi-factorial intervention which focuses on physician and patient education, patient-physician communication, patient counseling, as well as inter-professional collaboration. Along the same lines, integrating medication adherence assessment tools in existing CDSS has the potential to enhance their potential in clinical practice.

2.7 The Use of Healthcare Administrative Databases to Identify Asthma Patients and Treatment Escalation Patterns

As was shown in the beginning of this chapter, administrative healthcare data can be leveraged to optimize medication use and support clinical decision-making in routine clinical practice. Further, these data can also help us understand the consequences of medication non-adherence and prescribing practices at a population-level. This brings us to the second part of this thesis, which aims to lay the groundwork for a population-based study which aims to evaluate the relationship between nonadherence to asthma controller medications and unnecessary treatment escalation in the real-world setting, using healthcare administrative databases.

Prior to embarking in this study, it is important to ensure that healthcare administrative databases can be used to identify asthma patients and treatment escalation patterns in an adequate manner. To address this important research question, a systematic review was conducted to review the available evidence supporting the validity of algorithms to identify asthma patients in healthcare administrative databases. Results of this review are presented in the third article of this thesis (**Section 4.3**). In addition, it is also important to evaluate whether healthcare administrative databases are an adequate source to identify treatment escalation in asthma. This latter notion is further explored in the Delphi study are

presented in the fourth and final article of this thesis (**Section 4.4**). The following subsections provide background research and methodological considerations for these two topics.

2.7.1 The Use of Healthcare Administrative Database to Conduct Epidemiologic Data

Healthcare administrative data, which are collected every time a patient has an encounter with the healthcare system, were developed primarily for reimbursement purposes. Specifically, they comprise a myriad of clinical variables pertaining to health service use, including diagnoses, medical procedures, healthcare resource utilization, and drug dispensing data (pharmacy claims). They are often used by health care providers, payers, and policy makers in order to conduct operations, evaluate population outcomes, and measure the quality of care.[207] Notably, **diagnosis data** can be useful to conduct numerous healthcare activities, including health outcome assessment, quality of care performance, case mix and risk adjustment, reimbursement, payments, and contracting of payment systems, and health system performance and policy analysis.[207] Of note, administrative health data are relatively inexpensive to obtain and contain prospectively collected data on health service use at a population level that can span multiple decades. As such, they have been widely used in epidemiologic studies to inform health policy and advance therapeutic research in various diseases and conditions, including asthma.[41,208-211] However, since these data are a by-product of constantly evolving and heterogenous healthcare systems, it is important to ensure that these data are valid for research.

It is equally important to consider the critical differences in terms of database structure, content, and quality that can exist between different healthcare administrative databases. Even within the same country, administrative data collected separately in different regions and jurisdictions can vary in content and quality.[212] In Canada, for instance, population and drugs covered by provincial programs vary across provinces and over time. This heterogeneity can potentially contribute and lead to interprovincial differences in study populations and accrual periods. Further, the version and precision of the ICD coding system used in physician claims data is variable across jurisdictions. Indeed, each coding system has its own ontology and specific codes based on an established hierarchy. Additionally, the coding systems are updated periodically to reflect healthcare practice changes, as well as to incorporate new therapies and processes.[213] The precision and quality of coding systems are further exacerbated by errors that can be made by providers who incorrectly diagnose patients or who fill incorrectly patient encounter forms.[207] Similarly, variations in the content and completeness of hospital discharge abstracts, drug indication and formulary restrictions across provinces further contribute to inter-database heterogeneity.[212] All these

aspects need to be considered when selecting a healthcare administrative database for research purposes.

2.7.1.1 Validity of Diagnosis Codes for Asthma

The first critical step in constructing a population-based cohort using administrative data is to identify, as accurately as possible, patients with the disease of interest. In healthcare administrative databases, variables defined by diagnostic or procedural codes are considered proxy measures of the disease or procedure that they represent. Thus, the validity of a proxy variable depends on whether it is statistically associated with the entity it represents.[214] Statistical measures to assess the validity of a diagnostic codes include sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Validity and completeness are determined by comparing the database information with other data reference standards that can be used to ascertain patient diagnosis, such as comparison with paper medical records or EMRs or patient self-reported data collected in surveys or interviews. The choice of an appropriate reference varies by study question, variables used for the research study, as well as availability of other data sources.[213]

In recent years, the literature on the validity of claims-based case definitions for asthma has grown exponentially. Therefore, conducting a systematic literature review is a useful approach to confirm and ascertain the validity of healthcare administrative databases for asthma research. In the context of this thesis, the systematic review was conducted for two reasons:

1. To confirm that healthcare administrative are valid for asthma research;
2. To select the optimal asthma case-finding algorithm for population-based cohort study which aims to assess the association between mediation adherence and subsequent treatment escalation in asthma.

However, prior to initiating an administrative database study and selecting the best case-finding algorithm, it is imperative to assess the relative importance of sensitivity, specificity, PPV, and NPV, and prioritize the diagnostic accuracy measure most relevant to the research question.[215] Thus, the relevance and choice of a specific algorithm should not be made arbitrarily, but rather be based on the research question and availability of data elements in the administrative database of interest. As a prime example, it is desirable to select algorithms having higher sensitivities for surveillance studies, since this approach minimizes the number of missed cases.[215,216] On the other hand, a high PPV is important when identifying a cohort defined by disease status. High PPVs and NPVs ensure that only persons who truly have the condition of interest are included in the study, [215] and are desirable in studies seeking to examine causal

or association relationships. Indeed, identifying a sample of patients in whom asthma has been diagnosed as accurately as possible is arguably one of the most important first steps in conducting rigorous epidemiologic research.[217] In this context, when assessing the association between medication adherence and treatment escalation, we need to select an algorithm that fulfills the following criteria:

1. Provides a good trade-off between sensitivity and specificity
2. Has a relatively high PPV
3. Has been tested in adult populations
4. Has been tested in Canadian administrative databases

When conducting systematic reviews of diagnostic accuracy studies, is it imperative to consider the heterogeneity originating from differences in the design and conduct of included studies and to assess their methodological quality, risk of bias, and generalizability. Ideally, the optimal algorithm should be obtained from a study that used rigorous research methods. To this end, a critical appraisal of the methodological quality of included studies was included in the systematic review of this thesis. Specifically, quality assessment was performed using the **Qu**ality **A**ssessment of **D**iagnostic **A**ccuracy **S**tudies revised tool (QUADAS-2)[218], which is the tool recommended for use in systematic reviews of diagnostic accuracy by the Agency for Healthcare Research and Quality of the Cochrane Collaboration.[219] The QUADAS tool consists of 4 key domains that discuss patient selection, index test, reference standard, as well as the flow of patients through the study and timing of the index tests and reference standard (flow and timing). Details of this tool are elaborated in the supplementary materials of the systematic review (Section **4.3.1**).

The selection of the optimal asthma case-finding algorithm for the population-based cohort study will be based on the results of this systematic review and will be further presented and elaborated in the final discussion chapter of this thesis (**Chapter 5).**

2.7.2 Treatment Escalation in Asthma in the Real-World Setting

Healthcare administrative claims databases, including pharmacy claims data, can be used to efficiently identify treatment escalation in asthma. However, it is challenging to identify treatment escalation using these data because of the complex therapeutic landscape for asthma. Although the literature on this topic is limited, the most widely used method to study treatment escalation in healthcare administrative databases involves the identification of step-up episodes that correspond to clinical practice guidelines. At first glance, it appears that the claims-based treatment escalation definitions reported in the literature

are variable, mainly due to differing interpretations of the asthma treatment guidelines.[35,37,39,41] In addition, different terms in the literature can be used to designate treatment escalation, including "treatment intensification," and "treatment step-up". Thus, it would be relevant to conduct a systematic review to explore and build upon existing definitions of treatment escalation in the literature.

Another critical issue is that, while the current treatment guidelines provide a framework that physicians can use to tailor the patient's therapy according to their disease severity and level of disease control, they were not designed to identify treatment escalation at a population level. Therefore, it is crucial to pinpoint the different treatment possibilities in clinical practice and ascertain all clinical scenarios for which the prescriber's original therapeutic intent was to escalate therapy. Ideally, this undertaking can be achieved through expert consensus, and the Delphi method is an approach that can be used to build and achieve consensus among experts. It consists of a flexible group facilitation technique that can be used to determine consensus for a defined clinical problem for which little or no evidence exists or for which there is contradictory information.[220,221] Specifically, consensus can be achieved through an iterative process that employs a systematic progression of repeated rounds of voting among an expert panel through online questionnaires. In addition, the starting point of Delphi study usually consists of a systematic review that aims to identify the various criteria that can be used to define the clinical problem under study. Such an approach will facilitate consistent and effective approaches to identify treatment escalation in healthcare administrative databases. This point will be further explored in the Delphi study (section 4.4).

2.7.2.1 Association Between Medication Adherence and Treatment Escalation

The last part of this chapter aims to explore the extent to which the relationship between treatment escalation and medication adherence to controller medications has been explored in the literature. To the best of our knowledge, Van Boven *et al.* published in 2019 the first and only study that evaluated this association.[39] The study population consisted of patients who initiated ICS/LABA FDC and adherence was assessed in the year prior to treatment initiation using trajectory-based modeling. Patients receiving additional GINA step 5 therapy were identified during a maximum follow-up time of 2 years. GINA step 5 was defined as any dispensing of either: 1) low dose maintenance OCS: 1 or 5 mg prednisone or prednisolone; 2) biologics: omalizumab, mepolizumab, benralizumab; or 3) LAMA.

In total, 3062 new ICS/LABA FDC users were identified, of whom 120 (3.9%) received additional GINA-5 therapy. In total, 4 adherence trajectories were identified: 1) "nonpersistent users" (20.4% of

patients); 2) seasonal users or reinitiators, termed “seasonal users” (8.3% of patients); 3) persistent users with sub-optimal medication use, termed “poor adherers” (58.1%); 4) persistent users with optimal drug use, termed “good adherers” (13.2% of patients). Reported results appeared contradictory: poor adherence was associated with longer time to additional GINA-5 (adjusted hazard ratio: 0.58; 95% CI 0.35-0.95); yet, over 80% of additional GINA-5 therapy was initiated in poorly adherent patients.

In the discussion, the authors pointed out that the finding that the likelihood of receiving additional GINA step 5 therapies is lower in poorly adherent patients was contrary to their hypothesis. Instead, they expected that non-adherent patients would be more likely to have their treatment escalated, since it can be challenging for physicians to assess medication adherence objectively and rapidly during routine consultations. Therefore, among patients who have uncontrolled disease, it could be difficult for physicians to distinguish non-adherent patients from those who have optimal adherence but who are refractory to treatment. To explain this unexpected finding, they suggested that reverse causality may have come into play: individuals who have a more severe form of asthma may be more symptomatic and consult their physicians more frequently, thereby making them more susceptible to treatment escalation, regardless of their adherence level. Nevertheless, the authors highlighted that it is crucial to equip physicians with more objective and validated adherence measurements in daily practice, given that most patients who received GINA Step-5 therapy were non-adherent to their treatment.

A key strength of this study is the use of trajectory modeling to describe adherence patterns, which is an approach that has not been used in previous studies. Indeed, trajectory modeling appears to be a more clinically intuitive method to describe adherence behaviours in the population, compared to the more common way of classifying patients as either adherent or non-adherent based on a pre-defined threshold (e.g. <80% of medication refill to define nonadherence). However, trajectory modeling analysis requires an adequate follow-up time. In the study, patients had to have a minimum post-index period of 1 year, which obliged the authors to only include treatment escalation episodes beyond that period. Yet it is possible that patients had their treatment escalated within that 1-year period, which was not considered in the analysis. In addition, under these circumstances, patients who had a treatment escalation in the first year were probably classified as being non-adherent since their prescribed therapy changed, thus increasing the measurement error for the adherence; this may also have caused a reverse causality bias. Another limitation of this study is its relatively small sample size. Though findings were statistically significant, a larger sample size may have allowed the authors to describe the adherence patterns more accurately in the population. Finally, since secondary healthcare data was used (pharmacy

prescription refills) to assess adherence, inhaler technique was not considered in the analysis. This limitation highlights the downside of using secondary healthcare data to assess medication adherence.

To the best of our knowledge, this study is the first to evaluate the association between medication adherence and treatment escalation in asthma. However, it was only assessed in patients with moderate-to-severe asthma and may have serious methodological problems. To build upon this research, the Delphi study conducted in this thesis aimed to develop a method to identify treatment escalation in all asthma patients, regardless of disease severity or initial treatment prescribed. Furthermore, treatment escalation rates were calculated in a population-based cohort of asthma patients.

CHAPTER 3: THESIS OBJECTIVES

An overview of the research program is presented in **Figure 1**. In total, this doctoral dissertation comprised four studies. The fifth study (cohort study) was beyond the scope of this dissertation. However, I plan on conducting this study within the next year in collaboration with Lucie Blais' research team.

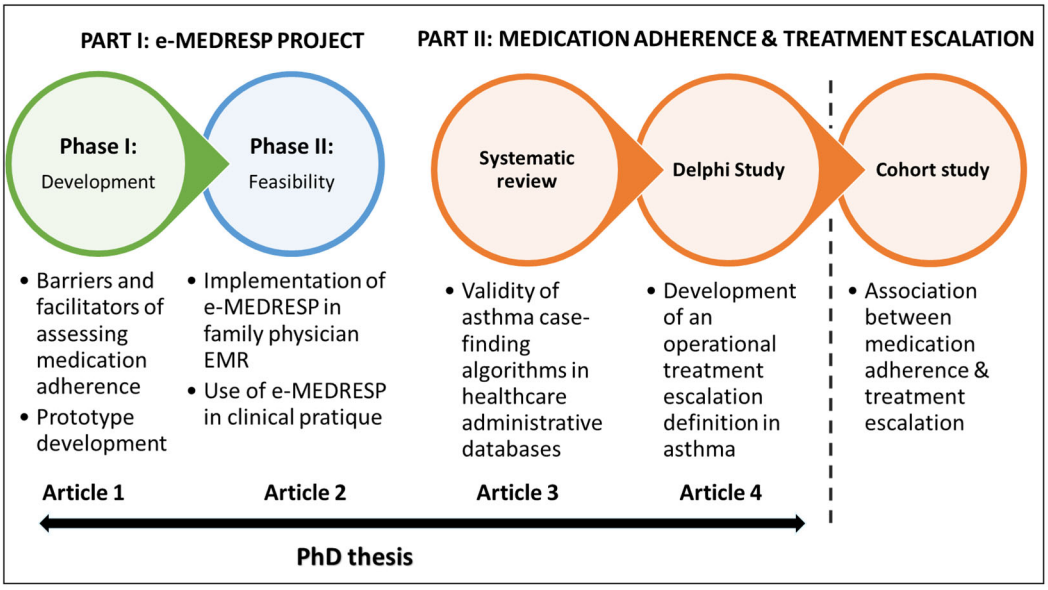

Figure 1. Overview of Doctoral research program

Rationale of Research Program: The overarching goal of this thesis was to investigate how the secondary use of healthcare data can be leveraged to optimize patient medication adherence and support clinical decision-making in routine clinical practice. Because these healthcare data are generated each time a patient has an encounter with the healthcare system, they can serve as powerful tools to better understand patient medication-taking behaviours and physician prescribing practices. **Figure 2** illustrates the underlying concepts that form the basis of this research program. In **PART I**, the e-MEDRESP project aimed to explore how pharmacy claims data and health information technology can be used to help physicians monitor and identify their non-adherent patients in a timely manner. Thus, it can be hypothesized that developing a tool based on pharmacy claims data has the potential to facilitate clinical decision-making at the point of care and positively influence prescriber and patient behaviour. In **PART II**, methodological considerations to facilitate our understanding of the consequences of undetected medication adherence were also investigated. Specifically, healthcare administrative data can be used to explore the hypothesis that undetected non-adherence can lead to unnecessary treatment escalation.

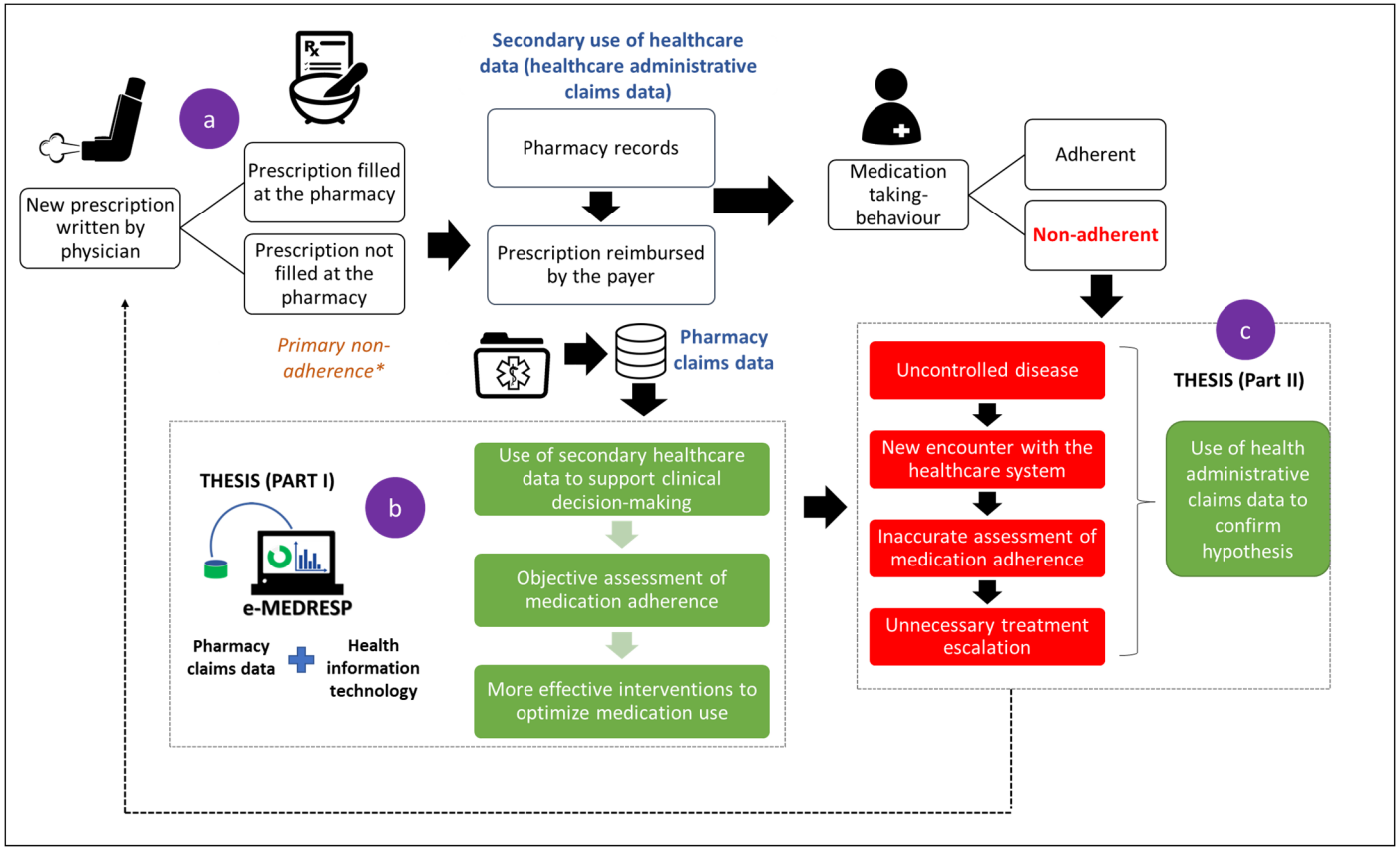

Figure 2. Rationale of Research Program and Underlying Concepts

a. Each time a patient has an encounter with the healthcare system, whether it is at the pharmacy or at the doctor's office, healthcare administrative data are generated. **b.** Healthcare administrative data (pharmacy claims) can be leveraged to better support clinical decision-making in routine clinical practice using health information technology (Part I). **c.** Healthcare data can be used to understand the unintended consequences of undetected medication nonadherence, including unnecessary treatment escalation (Part II). Unnecessary treatment escalation can further exacerbate non-adherence problems and lead to costly and complex therapeutic regimens.

*Pharmacy claims data do not capture prescriptions that were written by physicians but not dispensed at pharmacies by the patients (primary non-adherence). Due to this limitation, this dimension of medication non-adherence was not explored in this thesis.

Part I: e-MEDRESP Project

An overview of the e-MEDRESP study is presented in

Figure 3 below.

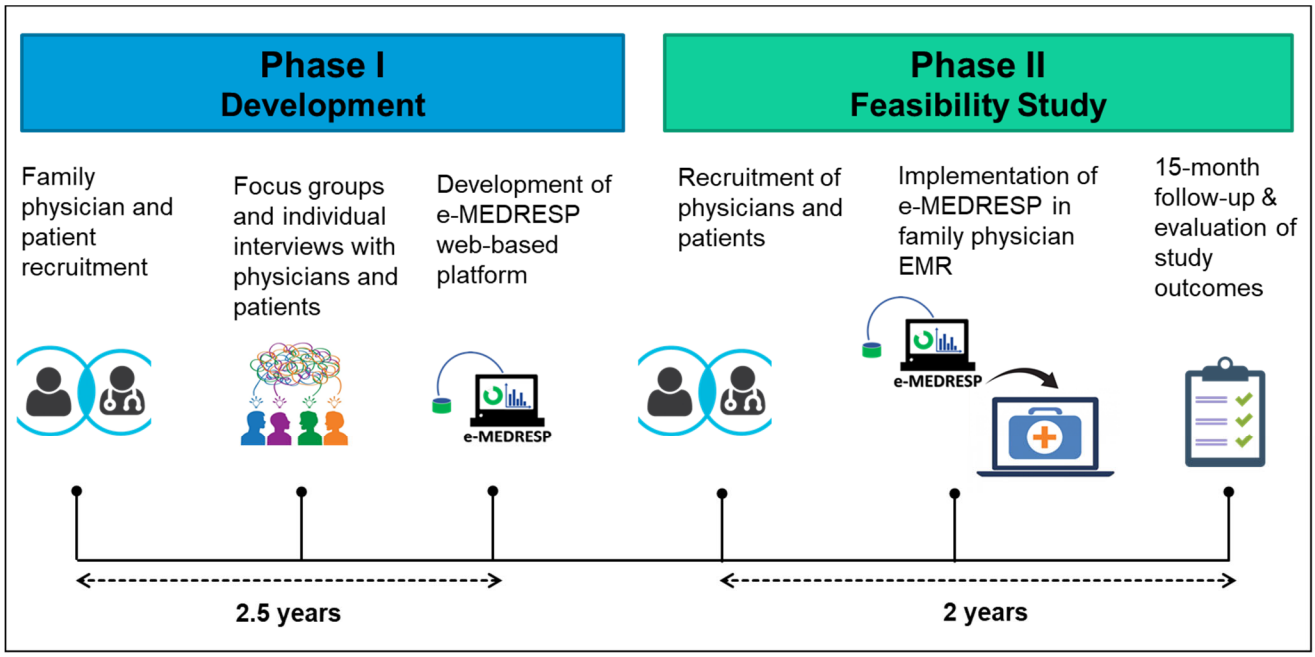

Figure 3. Overview of the e-MEDRESP study

3.1 Phase I: Development of e-MEDRESP

3.1.1 Exploratory Phase

Primary objective: To identify the **barriers** and **facilitators** of assessing medication adherence in patients with chronic respiratory diseases in routine clinical practice, from the perspective of family physicians and patients.

3.1.2 Development Phase

Primary objective: To develop **e-MEDRESP**, a web-based tool that will allow family physicians to monitor adherence to respiratory medications using pharmacy claims data in routine clinical practice.

Specific objectives:

a. To design an **e-MEDRESP prototype** in collaboration with family physicians and patients;

b. To construct the e-MEDRESP **web-based module** using an integrated health informatics approach specifically designed for OMNIMED, a leading EMR system provider in the Canadian province of Quebec.

3.2 PHASE II: Feasibility of Implementing e-MEDRESP in Clinical Practice

Primary objective: To test the feasibility of implementing e-MEDRESP in routine clinical practice

Specific objectives:

a. To evaluate the **uptake of e-MEDRESP** by patients and physicians in routine clinical practice;
b. To evaluate **patients' and physicians' satisfaction** with e-MEDRESP.

Secondary objectives

a. To explore the capacity of e-MEDRESP to **improve medication adherence** following its implementation in participating clinics;
b. To explore the capacity of e-MEDRESP to **improve disease control** following its implementation in participating clinics;
c. To explore how e-MEDRESP affects **prescription changes** following its implementation in participating clinics.

To gain a better understanding of the processes and possible challenges with the clinical adoption e-MEDRESP, the "clinical adoption meta-model" was used. **Table 9** presents the dimensions of the model, along with the indicators that will be used to evaluate each dimension. Each indictor is related to one of the objectives listed above.

Table 9. Clinical Adoption Meta-Model: Key features and Dimensions Assessed

Dimension	Definition	Aspects	Indicators
AVAILABILITY	Ability for the end users to access and interact with e-MEDRESP	System availability	• Number of physicians with access to e-MEDRESP
SYSTEM USE	Interactions e-MEDRESP by intended end-users	Use	• Number of times e-MEDRESP was consulted during a medical visit
		User experience	• Electronic questionnaire of physician experience • Phone interviews with patient after e-MEDRESP was consulted by a treating physician
CLINICAL BEHAVIOUR	Meaningful adaptation of clinical workflows or health behaviors that are facilitated by the HIS	Specific behaviours	• Prescription changes following consultation of e-MEDRESP (exploratory outcome)
CLINICAL OUTCOMES	Impacts attributable to the adoption of the HIS	Patient outcomes	• Improvement in medication adherence (exploratory outcome) • Improvement in disease control (exploratory outcome)

3.3 Part II: Medication Adherence and Treatment Escalation

Two separate studies were conducted, as starting points for a future study which aims to assess the relationship between medication non-adherence and treatment escalation in asthma. The Canadian healthcare system was targeted.

SYSTEMATIC REVIEW: Diagnostic algorithms to identify asthma patients in healthcare administrative databases

Primary objectives:

- To review the available evidence supporting the **validity of algorithms** to identify asthma patients in healthcare administrative databases;
- To select the **best case-finding algorithms** that can be use in the population-based study aiming to assess the association between medication non-adherence and treatment escalation.

DELPHI STUDY: Development of an asthma treatment escalation definition adapted to Canadian healthcare administrative databases

Primary objective: To develop an operational definition of treatment escalation that can be applied in healthcare administrative databases, based on consensus among key experts in the fields of pulmonology, clinical pharmacy, family medicine, and pharmacoepidemiology.

Secondary objective: To estimate the rate of treatment escalation within a population-based cohort of asthma patients that was constructed using Quebec administrative databases.

CHAPTER 4: RESULTS

4.1 First Article: Development of e-MEDRESP

Development of a web-based tool built from pharmacy claims data to assess adherence to respiratory medications in primary care

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Author contributions: AY designed the study and main conceptual ideas, under the supervision and guidance of LB and SP. AY wrote the first draft of the manuscript with support from LB and SP. MKT and AY organized the FGs, whereas SP moderated the FGs. AY conducted the individual interviews. AY, CD, and MKT transcribed the FG and interview data and performed the network thematic analysis which was discussed with SP. AF and AY developed the algorithms underlying the e-MEDRESP web-based tool. AY, CL, MFB, LB, AF revised and approved the final e-MEDRESP prototype. LB, AY, SP, AF, CD, MKT, CL, and MFB interpreted the data, revised the manuscript, had access to complete study data, and had authority over manuscript preparation as well as approval of the final version and the decision to submit for publication.

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Name and location of the institution where the study was performed: *Centre Intégré Universitaire de santé et de services sociaux du Nord-de-l'île-de-Montréal*, Montréal, QC, Canada

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QUICK LOOK

Current knowledge

Medication adherence in individuals with asthma and COPD is notoriously low and is associated with suboptimal therapeutic outcomes. The majority of these patients are treated in primary care and family physicians need to assess adherence accurately and work closely with other healthcare professionals to intervene effectively. In clinical practice, family physicians could benefit from tools that will better assist them in detecting their non-adherent patients in a timely manner.

What this paper contributes to our knowledge

The timely assessment of medication adherence in clinical practice is impeded by many barriers, including short duration of medical visits, limited healthcare accessibility, and lack of objective and easily interpretable information on medication adherence. To alleviate some of these barriers, we developed e-MEDRESP, a novel web-based tool based on pharmacy claims data that will allow family physicians to rapidly assess adherence to respiratory medications. The clinical usefulness of e-MEDRESP may be enhanced if it becomes part of a multi-factorial intervention which focus on patient education, patient-physician communication, and inter-professional collaboration between family physicians, pharmacists, respiratory therapists, and nurses.

Useful links

Link to e-MEDRESP tutorial
Example of an e-MEDRESP report of an asthma patient (fictious patient)
Example of an e-MEDRESP report of a COPD patient (fictious patient)

ABSTRACT

Background: Medication adherence in asthma and chronic obstructive pulmonary disease (COPD) is notoriously low. To intervene effectively, family physicians need to assess adherence accurately—a challenging endeavour.

Objectives: In collaboration family physicians and patients with asthma or COPD, we aimed to: 1) explore the barriers and facilitators of assessing medication adherence in clinical practice (exploratory phase); 2) develop e-MEDRESP*,* a novel web-based tool that will allow physicians to monitor adherence using pharmacy claims data (development phase).

Methods: We used qualitative research methods and a framework inspired by user-centered design principles. Five focus groups were held [two with patients (n=15) and three with physicians (n=20)], and ten individual interviews with physicians. In the exploratory phase, data were analyzed using thematic networks. In the development phase, we identified components to be included in an e-MEDRESP prototype through an iterative approach. The e-MEDRESP web-based tool was constructed by applying algorithms to pharmacy claims data that reflected end-users' recommendations, through a health informatics approach designed for electronic medical records.

Results: Main barriers to assessing medication adherence included lack of objective information regarding medication use and short duration of medical visits. Physicians emphasized that identifying patients at risk for non-adherence requires a team effort with pharmacists, respiratory therapists, and nurses. Participants also agreed that the use of easily interpretable pharmacy claims data could be an important facilitator. To this end, they contributed to the development of the e-MEDRESP prototype, which contains graphical representations of the adherence to respiratory controller medications and dispensing of rescue medications.

Conclusions: e-MEDRESP has the potential to allow physicians to assess adherence objectively and facilitate patient-physician communication concerning medication use. Future studies aim to evaluate the feasibility of implementing e-MEDRESP in clinical practice. It would be relevant to develop strategies that could facilitate the sharing of information presented in e-MEDRESP among primary care health professionals.

Key words: Treatment adherence, qualitative research, asthma, COPD, electronic medical records, medical informatics

INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are leading causes of chronic morbidity and mortality that pose substantial economic and social burdens worldwide.[1] Globally, asthma affects over 300 million people[2] and approximately 65 million have moderate-to-severe COPD.[3] Although adherence to long-term therapy is essential to optimize treatment effectiveness, a significant portion of these individuals do not take medications as prescribed.[4] Indeed, adherence in individuals with asthma and COPD is notoriously low, often falling below 50%.[5-7] Medication nonadherence has detrimental effects on therapeutic outcomes and leads to increases in emergency department visits, hospitalizations, and healthcare-related costs.[1, 8, 9]

In asthma, reasons behind sub-optimal medication adherence include issues pertaining to age, medication costs, adverse effects, inhaler device convenience, limited health literacy, patients' knowledge and illness beliefs, as well as limited patient involvement in the medical decision-making process.[4, 10, 11] Predictors of adherence in patients with COPD are similar; however, they are often faced with additional problems related to comorbidities, complex treatment regimens, and polytherapy—all which can contribute to sub-optimal medication use.[12] Research has shown that successful interventions to promote optimal medication use should be seamlessly integrated within clinical practice and be based on enhanced patient-physician communication and patient education.[13]

A large majority of individuals with asthma or COPD are treated in primary care.[14, 15] Prior to prescribing appropriate therapy, clinical guidelines recommend that physicians assess disease control and verify for common problems such as inhaler technique, comorbidities, and medication adherence.[2, 16] Yet, assessing medication adherence accurately in routine clinical practice can be a challenging endeavour. In practice, physicians commonly assess adherence through patient self-report. Yet, this method is prone to inaccuracies, since patients have a tendency to over-estimate their adherence level due to incorrect recall or attempts to fulfill treating physicians' expectations.[17, 18] Accordingly, physicians may have difficulties detecting non-adherence and reliance upon their intuition was shown to be inaccurate.[19, 20]

Alternatively, pharmacy claims data, which are generated whenever a prescription at a community pharmacy is filled,[21] may offer a more objective measurement of medication adherence,[13] and have been used in many population-based studies to assess medication adherence.[5-7] To the best of our knowledge, few studies have evaluated the use of tools based on pharmacy claims data to assess medication adherence in clinical practice.[22-26] As a prime example, physicians in the US can request pharmacy claim histories through e-prescribing platforms integrated in their electronic health

records.[27]Additionally, since 2013, physicians in the Canadian province of Quebec may access pharmacy claims through the Quebec Health Record (QHR), which is a data repository that allows healthcare professionals to access health information on their patients.[28] One major drawback of the QHR, however, is that it provides raw and unprocessed pharmacy claims data (i.e. one line per filled prescription), which can be hard for physicians to summarize and interpret efficiently in their workflow. Broadly speaking, these tools and platforms have the potential to enhance physicians' ability to monitor medication adherence in a timely manner; however, none were developed in collaboration with end-users, which might explain why the uptake of some of these tools was not as high as expected.

The purpose of this study is to better understand the problems that revolve around the assessment of medication adherence in routine clinical practice. We believe that the use of healthcare technology may help alleviate some of the challenges physicians face when assessing medication adherence. Specifically, we aimed to gain greater understanding on the barriers and facilitators of assessing adherence to respiratory medications, from the perspective of family physicians and patients with asthma or COPD, through a qualitative study (exploratory phase). Taking inspiration from user-centered design principles, we subsequently developed e-MEDRESP, a web-based tool built from pharmacy claims data that will allow family physicians to monitor adherence to respiratory medications in routine clinical practice (development phase). This phase was conducted in two steps: 1) design of e-MEDRESP in collaboration with family physicians and patients with asthma or COPD; and 2) construction of the e-MEDRESP web-based tool using an integrated health informatics approach designed for electronic medical records (EMRs).

METHODS

Study design

We used a qualitative research methodology and a framework inspired by user-centered design principles. For the exploratory phase, we conducted a qualitative descriptive study, an approach based on the general principles of naturalistic inquiry, which aims to acquire greater insight into a specific phenomenon or human experience.[29] For the development phase, a framework inspired by the user-centered design principles was adopted, which is an iterative design process in which we focus on user needs in each phase of the design and development processes.[30] Participants included patients with asthma or COPD treated in family medicine clinics and family physicians, recruited between January 2017 and March 2018 in the Canadian province of Quebec.

Participants and procedures

Participants were recruited from family medicine clinics which subscribed to the OMNIMED, a leading EMR provider in Quebec. Patients were eligible if they: 1) had a diagnosis of asthma or COPD recorded in their EMR; 2) were treated by a family physician; and 3) were 18 years or older. Eligible family physicians must have treated patients diagnosed with asthma or COPD in the last year prior to recruitment. In keeping with the research design adopted, purposive sampling[31] was used, with the aim of obtaining maximal variation in key characteristics among participants, including age, sex, region of residence, number of years since diagnosis of asthma or COPD (for patients), and number of years of practice in family medicine (for physicians). Emails and faxes were sent to physicians to invite them to participate in the study. Patient recruitment was then performed in collaboration with the medical director of one of the participating clinics. Specifically, the clinic appointed a research assistant to contact eligible patients by phone and invite them to participate in the study. Patients and physicians received a compensation for the time incurred due to study participation.

Data collection

Data for the exploratory phase and the first step of the development phase were collected through five focus groups (FGs) [two with asthma or COPD patients (n = 15) and three with family physicians (n = 20)]. To enhance the data collection strategy without compromising the project timeline, ten individual telephone interviews were subsequently conducted with physicians unable to attend FGs. Each FG ran between 50-120 minutes, whereas interviews lasted between 30-45 minutes. FGs were led by a moderator (SP) and two research assistants (AY, MKT), while interviews were conducted by a research assistant (AY). All FGs and interviews were conducted in French using a semi-structured interview guide. The complete translated interview guides are available in the electronic supplementary files (S1-S2).

In the exploratory phase of the FGs and interviews, we identified the barriers and facilitators of assessing medication adherence in clinical practice. Topics of discussion included: 1) methods of assessing medication adherence; 2) patient-physician communication concerning medication use; 3) practical and ethical implications of using pharmacy claims data to measure medication adherence; and 4) role of other primary care health professionals, including pharmacists, respiratory therapists, and nurses. The second part of each FG and interview was devoted to the design of e-MEDRESP (development phase). Topics of discussion included format and content of e-MEDRESP, as well as the most appropriate metrics to assess medication adherence and use. Specifically, we identified components to be included in a prototype of e-MEDRESP. Of note, since our aim was to develop a tool that could be seamlessly integrated within

physician workflow, physicians mostly contributed to the development phase. Data collection thus prioritized the physician perspective but was completed with patients' accounts. An iterative approach was used to design e-MEDRESP, whereby results of the first FG informed changes to the interview guide for subsequent FG and interviews. Feedback on the prototype was also gathered through informal review by two members of the research team: a pulmonologist (CL) and a clinical pharmacist specialized in respiratory diseases (MFB).

Data analysis

All discussions were audio-recorded, transcribed verbatim, and verified for accuracy.[32] Transcripts were analyzed and coded independently by three investigators (AY, CD, MKT). Data analysis began with data familiarization, in which transcripts and field notes were carefully re-read.

Exploratory phase – Barriers and facilitators of assessing medication adherence

To identify the barriers and facilitators of assessing medication adherence, we used the thematic network technique,[33] a theoretically-flexible analytical tool used to explore the understanding of an issue by identifying the main themes constituting a piece of text. Transcripts were first dissected using a coding framework that was devised using ideas coming from the literature review, topics in the interview guides, and concepts identified during the discussions. This coding framework was developed through an iterative process whereby codes were continuously refined as clearer insight was gained on the collected data. Once consensus on the coding framework was reached, overarching themes were identified by grouping codes that unify a common idea.[34, 35] Themes were subsequently clustered into basic themes (i.e., lowest order premises of evidence), then into organizing themes (i.e., middle-order themes), and finally into global themes (i.e., macro super-ordinate themes). Web-like illustrations (networks) were developed to depict the salient themes and the relationships between them. Interviews were conducted until data saturation was reached, which is the point in which no new codes emerged from the data and themes were considered to be adequately specified.[36, 37] The Dedoose software[38] (version 8.0.42) was used to assist in data analysis.

Development Phase - Creation of the e-MEDRESP web-based module

For the development phase, opinions and user preferences regarding tool content and format were identified. Once the paper-based prototype was finalized and no additional suggestions were given by the participants, an interactive web-based module was built in the Visual Studio 2017 community software

(version 15.9). e-MEDRESP was constructed by developing algorithms of medication adherence which reflect the end-user recommendations identified during the discussions. These algorithms were subsequently applied to pharmacy claims data recorded in the reMed database.[39] reMed is a computerized claims database which collects information on prescribed medications dispensed in community pharmacies for a sample of Quebec residents. reMed is developed based upon data purchased from community pharmacies' computer services providers, which transfer medication data required for reimbursement. The link between the providers and reMed is established by way of a dynamic, computerized, and confidential list which contains the identity of enrolled participants.

Research ethics

This study was approved by the research ethics committee of the *Centre Intégré Universitaire de santé et de services sociaux du Nord-de-l'île-de-Montréal.* All participants signed an information and consent form.

RESULTS

Participant characteristics

The characteristics of patients (n=15) and family physicians (n=30) are presented in Table 1 and Table 2, respectively. Patients were on average 63 years old, were mostly male (60%), and have been diagnosed with their respiratory disease for nearly 11 years, on average. Although the FGs were conducted separately with patients with asthma (n=6) and COPD (n=6), some participants reported having both respiratory diseases (n=3). Physicians were on average 41 years old, 59% were women, and have been practicing family medicine for 12 years, on average.

Exploratory phase – Barriers and facilitators of assessing medication adherence

Consistent with our research purpose, we grouped participants' discussions into two global themes, namely the barriers and facilitators of assessing medication adherence in primary care. Figure 1 presents the thematic network illustrating the global, organizing, and basic themes. Excerpts from the transcripts are herein presented to support the identified themes. For indicative purposes, additional excerpts are available in the supplementary file (S3-S4).

Barriers to assessing medication adherence

Patient beliefs related to medication use and disease

Physicians explained that prior to properly assessing medication adherence, they must establish a treatment regimen that their patient is willing and able to follow. However, they raised the issue that some patients showed reluctance to take medications on a regular basis. According to them, discussing medication adherence was especially challenging with COPD patients, who appear to have adapted, over the years, to a limited quality of life and suboptimal respiratory function due to the insidious nature of the disease. As explained by a physician with 40 years of experience in family medicine, COPD patients often "*trivialize their symptoms*". Because asthma patients commonly seen in their practice are usually younger and more adaptive to change, physicians reported having fewer difficulties initiating discussions regarding medication adherence with them.

In contrast, most asthma and COPD patients in the study mentioned that they usually follow their physician's treatment recommendations. Yet, a small proportion reported either adjusting the doses of their prescribed therapeutic regimen or not taking their prescribed medications altogether. Some COPD patients also confused natural disease progression with treatment effects, claiming that respiratory controller medications can lead to lung collapse. In this respect, patients' illness and treatment perceptions corroborate to some extent with the discussions that were held with physicians and may add a layer of complexity to the discussion on medication adherence with their physician.

Lack of objective and easily interpretable information on medication use

The most salient discussions among family physicians revolved around their desire to have access to easily interpretable and objective information on medication adherence. Physicians also acknowledged that patient self-report measures of adherence were often inaccurate: "*We directly ask patients knowing full well that patient reliability is mediocre. We know that adherence in patients with COPD is about 40% and relying on patients' accounts can be misleading*" (26-year-old physician, recent medical graduate).

To obtain more objective information on medication adherence, most physicians reported accessing the data repository of the QHR to access pharmacy claims data. Although the QHR provides valuable information that allows them to optimize patient care, physicians voiced their concern about the prescription module of the QHR. Physicians emphasized the need to make the data in the QHR more easily interpretable, especially for diseases with complex therapeutic regimens, such as asthma and COPD. Indeed, the prescription module is neither clinically intuitive nor user-friendly, as was explained by a 57-

year old physician with over 27 years of experience: "*When it comes to the QHR, there is no organization! It's a jumble of information. […] Sometimes I have to go through 2-3 pages to find the drug I am looking for.*"

Disease management and physician practices

Some physician practices might directly hinder the assessment of adherence. In particular, some physicians admitted to not prioritize adherence to respiratory medications in their approach to disease management. Moreover, some physicians reported difficulties in keeping up with the evolving therapeutic landscape of asthma and COPD, as various respiratory therapeutic agents have been entering the market in the last few years,[40] many of which the comparative safety/effectiveness profiles are not well understood to them. Accordingly, some physicians acknowledged that it was difficult to establish an optimal therapeutic regimen that is adapted to their patients' needs.

Organization of healthcare services

Issues related to the organization of healthcare services, such as short duration of medical visits and limited healthcare accessibility, also represented significant barriers. Physicians consistently reported not having enough time to comprehensively assess adherence. Furthermore, physicians struggle to obtain accurate information on medications dispensed in hospital pharmacies or to know the medication history of patients that have been followed by other physicians. In fact, access to complete health information on patients is often spread over many medical records kept by different health structures or healthcare professionals in many healthcare settings.[41] Moreover, asthma and COPD patients complained about how the difficult transition of care between their pulmonologist and family physician affected their access to vital healthcare: "*When my pulmonologist retired, I was told that I was going to be followed by a family doctor. I waited three and a half years for a family doctor. I recently met her, so she obviously doesn't know me very well.*" (81-year-old asthma patient, diagnosed for 35 years).

Thus, some patients reported having little opportunities to discuss their medication adherence with the same provider. This lack of continuity of care with the same provider may thus be problematic, especially given that not all physicians integrate the assessment of medication adherence in their approach to disease management.

Facilitators to assessing medication adherence

Patient-physician relationship

When discussing medication adherence, participants agreed on the importance of having a trusting relationship between the patient and physician, built over time. Moreover, to foster patient empowerment, physicians stressed the need to work collaboratively with their patients, adapt to their knowledge level, ask open-ended questions, and use language that is non-patronizing. In a similar vein, a 58-year old asthma patient said: *"I think it's important that our doctor respects us. My doctor told me to stop smoking, but he knows I am not at this stage yet. He respects me and gives suggestions, without forcing me. He communicates with me."*

Inter-professional collaboration

Physicians reported that collaboration with other healthcare professionals greatly facilitated the assessment of medication adherence. They highlighted the role of respiratory therapists, who conduct spirometry tests, verify inhaler device techniques, and patient adherence to treatment recommendations. Physicians also mentioned directly calling pharmacists to obtain information on prescription refills, and some reported that pharmacists send them faxes to notify them that their patient has not filled his/her prescription. Indeed, physicians explained that medication adherence monitoring is a team effort with other healthcare professionals, as such collaboration allows them to determine whether sub-optimal disease control is due to inadequate therapeutic regimen, low medication adherence, or incorrect use of inhaler device.

Use of pharmacy claims data

Physicians and patients reported that the use of pharmacy claims data may facilitate discussions on medication adherence. Such information could provide an objective measure of medication use, even though filling a prescription does not necessarily guarantee its consumption. Generally, patients believed that physicians' access to pharmacy claims could help initiate discussion concerning their medication use and agreed that physicians should have access to this information: *"If doctors prescribe us medications, they assume that we take them. I agree that physicians should have access [to our prescription refill data]. I would even be okay with physicians knowing exactly if I took all the doses... that I didn't just hide my inhalers in a cupboard at home."* (38-year-old asthma patient, diagnosed for 22 years).

However, some patients described physicians' access to such information as a "*double-edged sword*": on one hand, physicians may be able to rapidly detect non-adherent patients; however, if they know that patients do not follow treatment recommendations, the patient-physician relationship may be strained. Some physicians shared a similar opinion: "*I think this is a delicate issue… the patient can ask himself: "What? You have access to all this information? You even know when I [purchased my medicine]? It's unpleasant to feel like you are under the radar."* (39-year-old physician, 6 years of clinical experience).

Development phase – Creation of the e-MEDRESP web-based module

Despite the limitations of pharmacy claims data, physicians pointed out that such data may help them detect non-adherent patients more easily if information on medication use is seamlessly integrated in EMRs and is presented in a user-friendly manner. Thus, physicians expressed their eagerness to contribute to the development of e-MEDRESP. The final version of the e-MEDRESP web-based module is presented in Figure 2 and includes three distinctive sections.

Section 1: One-year medication adherence

Physicians agreed that presenting medication adherence as a percentage and applying color codes would allow them to easily flag their non-adherent patients. Therefore, the first section of e-MEDRESP that was developed displays the adherence level to controller medications filled in the prior year, presented as a percentage in a doughnut chart. For patients filling several controller medications in the 1-year period, the global adherence to controller medications is shown, which represents the average percentage adherence to all controller medications dispensed in the prior year. A collapsible section underneath the global adherence doughnut chart was created to show detailed information on the percentage adherence to controller medications dispensed in the prior year, according to medication class. The proportion of days covered (PDC)[42] was the metric chosen to assess adherence over a one-year period. The PDC is defined as the total days' supply divided by the number of days of study period.[42] For medications initiated in the prior six months, it was decided that adherence would be calculated starting from the date of the first dispensing. The following color code scheme was selected to designate adherence levels: green for an optimal adherence (≥80%); yellow for a medium-level adherence (50-79%), and red for a sub-optimal adherence (<50%).

For patients filling medications containing inhaled corticosteroids (ICS) in the prior year, physicians deemed it was appropriate to illustrate the mean daily ICS dose, on a quarterly and annual basis, using a bar chart. In e-MEDRESP, the mean daily ICS dose is thus calculated via an algorithm which

we developed in previous studies[43, 44] that takes into account the following parameters: potency of different ICS; medication form; quantity dispensed (taking into account number of doses per device); and medication dispensing date. By using the equivalency table published in the Canadian asthma consensus report,[45] the mean daily ICS dose is converted to the equivalent of the fluticasone propionate HFA medication.

Section 2: List of respiratory medications dispensed in the prior year

Physicians wished to include in e-MEDRESP a component that could help them to rapidly identify, over a one-year period, important refill gaps. To satisfy this requirement, we built a comprehensive table of all controller and rescue medications, as well as oral corticosteroids and antibiotics, dispensed in the prior year. Generic names and type of device, along with prescription durations, are provided in the table.

Section 3: Rescue medications, oral corticosteroids and antibiotics dispensed per trimester

Physicians felt that it was pertinent to include in e-MEDRESP a section that could: 1) allow them to assess disease control based on their patients' use of rescue medications; and 2) identify potential markers of disease exacerbations. To this end, the third section included in e-MEDRESP presents several bar charts illustrating the days' supply of oral corticosteroids and antibiotics, as well as the weekly doses of rescue medications, per trimester. For short-acting β2-agonists (SABA), the average weekly number of doses is estimated using an algorithm which we developed in a previous study[46] that incorporates the following parameters: dose per inhalation, pharmaceutical form, quantity dispensed (taking into account number of doses per device), and dates of prescription dispensing. If a SABA other than salbutamol is dispensed, the mean number of doses is converted to a salbutamol equivalent. For short-acting anticholinergics, the mean weekly number of doses is estimated using an algorithm that incorporates the following parameters: dose per inhalation, pharmaceutical form, quantity dispensed (taking into account number of doses per device), and dates of prescription dispensing.

Other salient features of e-MEDRESP

Upon the request of several physicians, an explanatory document presenting the list of inhaled respiratory medications, along with photos of inhaler devices, was integrated in e-MEDRESP. Physicians mentioned that having access to this document could be useful if they wanted to further discuss medication use with their patients or adjust their treatment. Additionally, a video tutorial and an explanatory document were created to introduce physicians to e-MEDRESP. An automated data extraction procedure was established

to update the information presented in e-MEDRESP every two weeks. Ultimately, physicians felt that e-MEDRESP could help them provide more personalized treatments based on their patients' medication adherence. After each FG and interview, most physicians expressed their eagerness to have access to such a tool in their EMR. As one physician with 15 years of clinical experience exclaimed: "*Now that we know that such a tool could exist, we expect it will be available to us very soon!*"

DISCUSSION

Our study has highlighted important barriers of assessing and monitoring adherence to respiratory medications, from the perspective of family physicians and asthma and COPD patients. These included short duration of medical visits, limited healthcare accessibility, and patient understanding of treatment recommendations. Importantly, the lack of objective, rapidly accessible, and easily interpretable information on medication use constitutes an important barrier to monitoring adherence. To overcome this barrier, physicians contributed to the development of e-MEDRESP, a novel web-based tool for assessing adherence to respiratory medications, constructed from pharmacy claims data. Furthermore, a good patient-physician relationship coupled with a strong inter-professional collaboration are crucial in helping physicians to identify non-adherent patients.

It is beyond doubt that medication adherence monitoring should be an integral component of disease management and patient care. With increasingly evolving healthcare models in recent years, primary care professionals now have a proactive, continuous, and multidisciplinary approach to disease management which is also leveraged by the innovation of EMRs.[15] In the last decade, treatment guidelines, including the Global Initiative for Asthma (GINA) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD), began to encourage physicians to address medication adherence with their patients on a regular basis.[2, 16, 47, 48] Yet, our findings suggest that physicians may not always have time to comprehensively assess it. Consistent with previous findings in the literature,[49-51] study participants explained that a strong patient-physician relationship enables physicians to detect non-adherent patients more easily as it fosters more open and honest communication, in addition to promoting patient-centered care. Furthermore, having information from past health care events (e.g. prescriptions dispensed in hospitals, acute exacerbation occurrences), otherwise called 'informational continuity',[52] and having a long-term patient-provider relationship, might also be important facilitators to the timely monitoring of adherence. Working closely with other healthcare professionals such as pharmacists and respiratory therapists may also help mitigate some of these time-related constraints and promote informational continuity.

We believe that e-MEDRESP may help alleviate some of the barriers that physicians face when discussing medication use with their patients, as it provides objective information on medication adherence. Our results support the idea that pharmacy claims data, when processed into a user-friendly format, can enhance communication regarding medication use and promote adherence, but only when used in a context in which the patient feels empowered and is involved in the decision-making process. Importantly, patients must provide consent to their physicians having access to their detailed pharmacy refill histories, which may not always be easy to obtain. In a study we conducted in an outpatient asthma clinic,[53] only 40% of eligible patients with moderate-to-severe asthma accepted to provide such consent. This low acceptance rate could be partly explained by some patients' reluctance to share detailed information on their medication use with their pulmonologist. Although patients and physicians in the present study acknowledged these ethical implications, they remained optimistic and emphasized the need to develop tools based on pharmacy claims that can empower patients and facilitate communication on medication use.

Our findings should be interpreted in the light of some limitations. Because participation was on a voluntary basis, physicians as well as asthma and COPD patients included in our study may not be fully representative of the primary care setting. For example, patients may have been more adherent to their medications compared to the general population of patients with chronic respiratory diseases and therefore be more at ease to discuss their medication use in a group setting. Some of our findings, such as those pertaining to the QHR, are more applicable to the Quebec primary care setting and may not be generalizable to other clinical settings. Limitations of e-MEDRESP include those which are inherent to pharmacy claims data. Namely, pharmacy claims data in reMed only include prescriptions dispensed in community pharmacies. Thus, prescriptions filled in hospital pharmacies or prescriptions which were written by the treating physician but not filled by the patient are not captured by the tool. Moreover, filling prescriptions does not guarantee that the medication will be taken by the patient. Nevertheless, e-MEDRESP can serve as communication aid and help physicians identify non-adherent patients more easily, which will ultimately allow them to counsel and support their patients in a timely manner.

Overall, our study has many strengths and extends the literature on the practical and logistic issues regarding the assessment of adherence to respiratory medications in clinical practice. Of note, combining FG and interview data resulted in a nuanced and richer analysis and provided an opportunity to achieve data saturation more rapidly, although this methodological approach was initially adopted to ensure the timeliness of data collection. The analysis of the transcripts by three independent investigators, coupled with our iterative approach to qualitative inquiry, ensured congruence between

the research purpose, literature review, data collection strategies, participant sampling, and analysis, which ultimately conferred validity and reliability to our findings.[54]Although physicians play an important role in assessing and promoting medication adherence, integrating the patient perspective into our analysis allowed us to gain further insight on illness beliefs and treatment perceptions among patients, as well as patient-physician communication barriers. Finally, developing e-MEDRESP in collaboration with physicians allowed us to better understand the unmet needs of the primary-end users and ensured that the tool can be easily integrated within physician workflow.

Clinical implications and future work

We are currently integrating e-MEDRESP in the EMRs of several clinics in the Canadian province of Quebec. A feasibility study will be conducted to evaluate physicians' use of e-MEDRESP, physician and patient satisfaction with the tool, and its capacity to enhance patient medication adherence and physician prescribing practices. A cluster randomized clinical trial is also envisaged to evaluate the effectiveness of e-MEDRESP to improve medication adherence and disease control. The clinical usefulness of e-MEDRESP may be enhanced if it becomes part of a multi-factorial intervention which focus on patient education, and patient-physician communication. As there is an emerging trend for interdisciplinary teams to provide primary health care, it would be relevant to develop strategies that could facilitate the sharing of information presented in e-MEDRESP among primary care health professionals, including pharmacists, respiratory therapists, and nurses. Ultimately, the integration of easily interpretable pharmacy claims data in EMRs may serve as the basis for monitoring adherence and improving prescribing practices.

CONCLUSIONS

In routine clinical practice, the accurate assessment of medication adherence in asthma and COPD patients may be hindered by several barriers, including time-related constraints and lack of objective and easily interpretable information on medication use. e-MEDRESP has the potential to allow physicians to measure adherence objectively and facilitate patient-physician communication concerning medication use. Future studies are required to evaluate the feasibility of implementation, as well as patient and physician satisfaction of e-MEDRESP in clinical practice.

REFERENCES

1. Soriano JB, Abajobir AA, Abate KH, Abera SF, Agrawal A, Ahmed MB, et al. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. 2017;5(9):691-706.
2. Global Initiative for Asthma. Pocket Guide for Asthma Management and Prevention
3. World Health Organisation. Burden of COPD
4. George M. Adherence in Asthma and COPD: New Strategies for an Old Problem. Respiratory care 2018;63(6):818-831.
5. Blais L, Kettani FZ, Forget A, Beauchesne MF, Lemiere C, Ducharme FM. Assessing adherence to inhaled corticosteroids in asthma patients using an integrated measure based on primary and secondary adherence. European journal of clinical pharmacology 2017;73(1):91-97.
6. Humenberger M, Horner A, Labek A, Kaiser B, Frechinger R, Brock C, et al. Adherence to inhaled therapy and its impact on chronic obstructive pulmonary disease (COPD). BMC Pulmonary Medicine 2018;18(1):163.
7. Savaria F, Beauchesne MF, Forget A, Blais L. Adherence and Persistence to Long-Acting Anticholinergics Treatment Episodes in Patients With Chronic Obstructive Pulmonary Disease. The Annals of pharmacotherapy 2017;51(12):1063-1068.
8. Ismaila AS, Sayani AP, Marin M, Su Z. Clinical, economic, and humanistic burden of asthma in Canada: a systematic review. BMC pulmonary medicine 2013;13:70-70.
9. Dang-Tan T, Ismaila A, Zhang S, Zarotsky V, Bernauer M. Clinical, humanistic, and economic burden of chronic obstructive pulmonary disease (COPD) in Canada: a systematic review. BMC research notes 2015;8:464-464.
10. Dima AL, Hernandez G, Cunillera O, Ferrer M, de Bruin M. Asthma inhaler adherence determinants in adults: systematic review of observational data. European Respiratory Journal 2015;45(4):994.
11. Pollard S, Bansback N, FitzGerld JM, Bryan S. The burden of nonadherence among adults with asthma: a role for shared decision-making. Allergy 2017;72(5):705-712.
12. Bourbeau J, Bartlett SJ. Patient adherence in COPD. Thorax 2008;63(9):831-838.
13. Kini V, Ho PM. Interventions to Improve Medication Adherence: A Review. Jama 2018;320(23):2461-2473.
14. Wechsler ME. Managing asthma in primary care: putting new guideline recommendations into context, Mayo Clinic Proceedings, 2009. Vol. 84. Elsevier.
15. Broekhuizen BD, Sachs AP, Verheij TJ. COPD in primary care: from episodic to continual management
16. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of COPD
17. Jimmy B, Jose J. Patient Medication Adherence: Measures in Daily Practice. Oman Medical Journal 2011;26(3):155-159.
18. Lim KG, Rank MA, Li JT, Patel A, Volcheck GW, Branda ME, et al. How well does patient self-report predict asthma medication possession? Implications for medication reconciliation and adherence assessment. Journal of Asthma 2010;47(8):878-882.
19. Martin LR, Williams SL, Haskard KB, DiMatteo MR. The challenge of patient adherence. Therapeutics and Clinical Risk Management 2005;1(3):189-199.
20. Sherman J, Hutson A, Baumstein S, Hendeles L. Telephoning the patient's pharmacy to assess adherence with asthma medications by measuring refill rate for prescriptions. The Journal of Pediatrics 2000;136(4):532-536.

21. Cadarette SM, Wong L. An Introduction to Health Care Administrative Data. The Canadian journal of hospital pharmacy 2015;68(3):232-237.
22. Harbig P, Barat I, Lund Nielsen P, Damsgaard EM. Instantaneous detection of nonadherence: quality, strength, and weakness of an electronic prescription database. Pharmacoepidemiology and drug safety 2012;21(3):323-328.
23. Heisler M, Hogan MM, Hofer TP, Schmittdiel JA, Pladevall M, Kerr EA. When more is not better: treatment intensification among hypertensive patients with poor medication adherence. Circulation 2008;117(22):2884-2892.
24. Williams LK, Peterson EL, Wells K, Campbell J, Wang M, Chowdhry VK, et al. A cluster-randomized trial to provide clinicians inhaled corticosteroid adherence information for their patients with asthma. JAllergy ClinImmunol 2010;126(2):225-231, 231.
25. Vollmer WM, Feldstein A, Smith DH, Dubanoski JP, Waterbury A, Schneider JL, et al. Use of health information technology to improve medication adherence. The American journal of managed care 2011;17(12 Spec No.):Sp79-87.
26. Dixon BE, Alzeer AH, Phillips EO, Marrero DG. Integration of Provider, Pharmacy, and Patient-Reported Data to Improve Medication Adherence for Type 2 Diabetes: A Controlled Before-After Pilot Study. JMIR medical informatics 2016;4(1):e4.
27. Comer D, Couto J, Aguiar R, Wu P, Elliott D. Using aggregated pharmacy claims to identify primary nonadherence. The American journal of managed care 2015;21(12):e655-660.
28. DSQ. Dossier Santé Québec
29. Colorafi KJ, Evans B. Qualitative Descriptive Methods in Health Science Research. HERD: Health Environments Research & Design Journal 2016;9(4):16-25.
30. Garrett JJ. Elements of user experience, the: user-centered design for the web and beyond. Pearson Education; 2010.
31. Green J, Thorogood N. Qualitative methods for health research. Sage; 2014.
32. Poland BD. Transcription quality. In: Gubrium JF, Holstein JA, editors. Handbook of interview research. Thousand Oaks, CA: Sage, 2002:629-650.
33. Attride-Stirling J. Thematic networks: an analytic tool for qualitative research. Qualitative research 2001;1(3):385-405.
34. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology 2006;3(2):77-101.
35. Vaismoradi M, Jones J, Turunen H, Snelgrove S. Theme development in qualitative content analysis and thematic analysis. Journal of Nursing Education and Practice 2016;6(5):100.
36. Saunders B, Sim J, Kingstone T, Baker S, Waterfield J, Bartlam B, et al. Saturation in qualitative research: exploring its conceptualization and operationalization. Quality & Quantity 2018;52(4):1893-1907.
37. Guest G, Bunce A, Johnson L. How many interviews are enough? An experiment with data saturation and variability. Field methods 2006;18(1):59-82.
38. Dedoose.
39. RQRM. reMed : Data Registry for Prescribed Medications / Banque de données sur les médicaments d'ordonnance
40. Gross NJ, Barnes PJJAjor, medicine cc. New therapies for asthma and chronic obstructive pulmonary disease. 2017;195(2):159-166.
41. Quantin C, Coatrieux G, Fassa M, Breton V, Jaquet-Chiffelle DO, de Vlieger P, et al. Centralised versus decentralised management of patients' medical records. Studies in health technology and informatics 2009;150:700-704.

42. Nau DP. Proportion of days covered (PDC) as a preferred method of measuring medication adherence. Springfield, VA: Pharmacy Quality Alliance 2012.
43. Blais L, Beauchesne MF, Rey E, Malo JL, Forget A. Use of inhaled corticosteroids during the first trimester of pregnancy and the risk of congenital malformations among women with asthma. Thorax 2007;62(4):320-328.
44. Martel M-J, Rey É, Beauchesne M-F, Perreault S, Lefebvre G, Forget A, et al. Use of inhaled corticosteroids during pregnancy and risk of pregnancy induced hypertension: nested case-control study. BMJ 2005;330(7485):230.
45. Boulet L-P, Becker A, Bérubé D, Beveridge R, Ernst P. Summary of recommendations from the Canadian asthma consensus report, 1999. Canadian Medical Association Journal 1999;161(11 suppl 2):S1-S12.
46. Blais L, Beauchesne M-F, Lévesque S. Socioeconomic status and medication prescription patterns in pediatric asthma in Canada. Journal of Adolescent Health 2006;38(5):607.e609-607.e616.
47. Reddel HK, Bateman ED, Becker A, Boulet L-P, Cruz AA, Drazen JM, et al. A summary of the new GINA strategy: a roadmap to asthma control. European Respiratory Journal 2015;46(3):622-639.
48. Lareau SC, Yawn BP. Improving adherence with inhaler therapy in COPD. International journal of chronic obstructive pulmonary disease 2010;5:401.
49. Kerse N, Buetow S, Mainous AG, 3rd, Young G, Coster G, Arroll B. Physician-patient relationship and medication compliance: a primary care investigation. Annals of family medicine 2004;2(5):455-461.
50. Stavropoulou C. Non-adherence to medication and doctor-patient relationship: Evidence from a European survey. Patient education and counseling 2011;83(1):7-13.
51. Tarn DM, Mattimore TJ, Bell DS, Kravitz RL, Wenger NS. Provider views about responsibility for medication adherence and content of physician-older patient discussions. J Am Geriatr Soc 2012;60(6):1019-1026.
52. McKendry R, Haggerty J. Defusing the confusion: concepts and measures of continuity of health care. Canadian Health Services Research Foundation= Fondation canadienne de la recherche sur les services de santé; 2002.
53. Yousif A, Lemière C, Cartier A, Forget A, Blais L. Development of a graphical tool to measure medication adherence in asthma patients: A mixed-methods pilot study. Journal of Asthma 2019;56(5):543-552.
54. Morse JM, Barrett M, Mayan M, Olson K, Spiers J. Verification strategies for establishing reliability and validity in qualitative research. International journal of qualitative methods 2002;1(2):13-22.

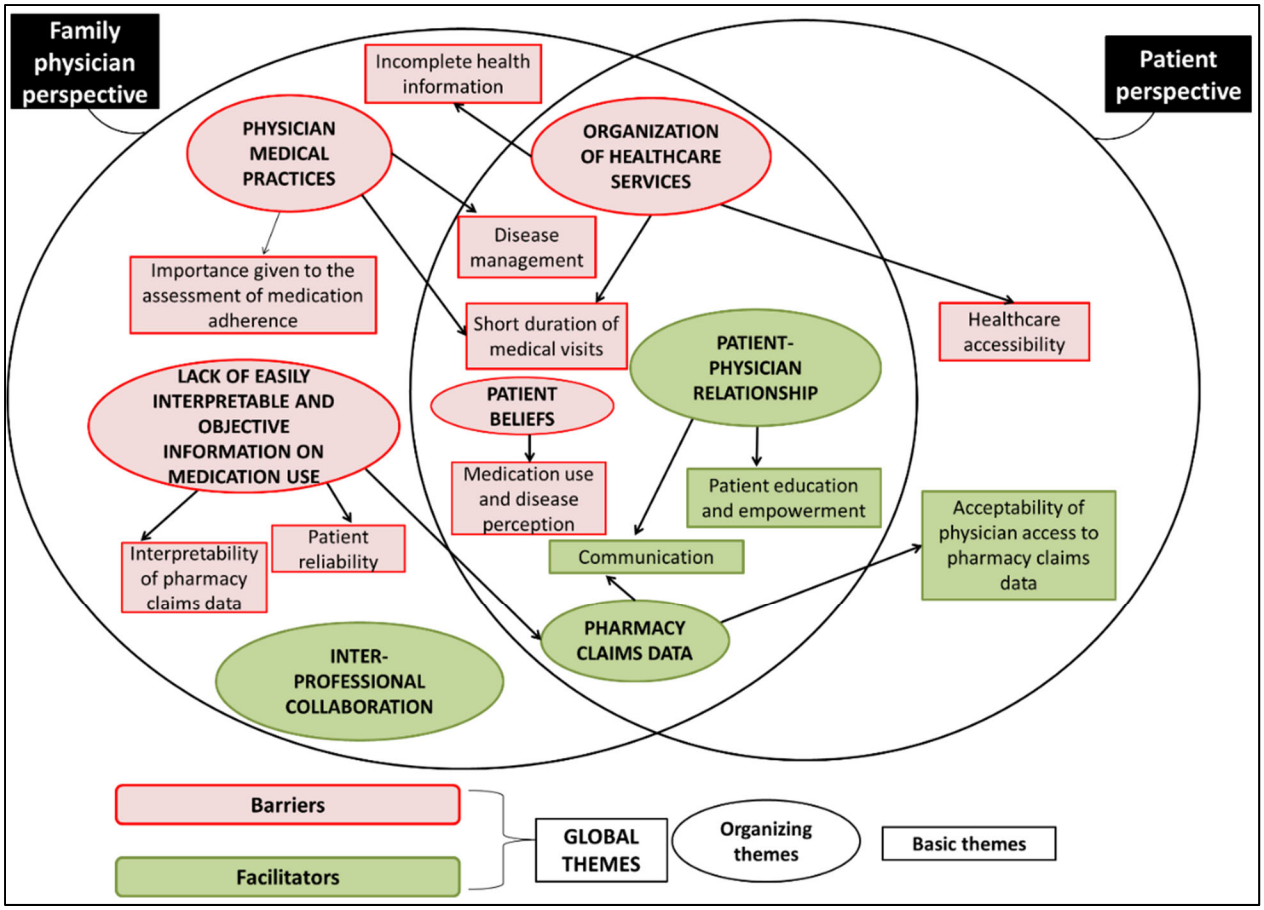

Figure 1. Thematic network depicting barriers and facilitators of assessing and monitoring medication adherence in primary care

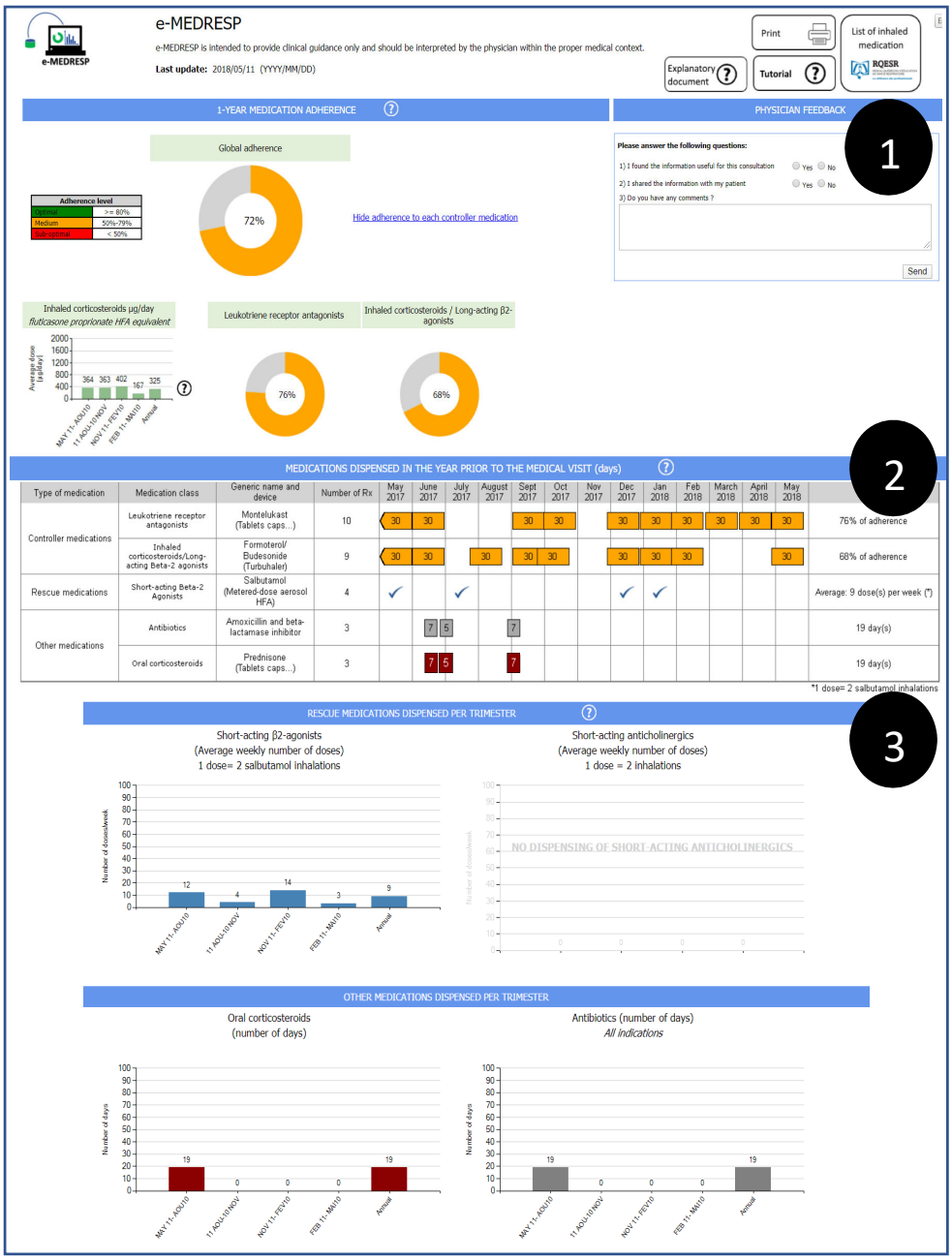

Figure 2. e-MEDRESP prototype

Example of an e-MEDREP report of an asthma patient. The web-based format of e-MEDRESP is compatible with electronic medical records, thus ensuring its seamless integration within physicians' workflow. All information on medication adherence is calculated from pharmacy claims data. **Section 1** displays the adherence to all controller medications dispensed in community pharmacies in the year prior to the medical visit, presented as a percentage. Information on adherence to controller medications, according to medication class is also available. Colour codes are used to designate different adherence levels. **Section 2** shows an overview of all respiratory medications dispensed in community pharmacies in the prior year. Dates and duration of refills, as well as generic names of medications, are provided. **Section 3** presents the use of rescue medications, oral corticosteroids, and antibiotics dispensed in the prior year, per trimester. Of note, e-MEDRESP is available in English and French.

Table 1. Subject characteristics (n=15)

	n (%)*
Age (mean ± standard deviation)	63.3 ± 12.8
Men	9 (60.0)
Diagnosis, as reported by subject	
Asthma	6 (40.0)
COPD	6 (40.0)
Concomitant diagnosis of asthma and COPD*	3 (20.0)
Number of years since diagnosis	
<5	6 (40.0)
5-10	5 (33.3)
≥10	4 (27.7)
Mean (standard deviation)	10.5 (10.0)
Smoking status	
Non-smoker	9 (60.0)
Level of physical activity	
None	5 (33.3)
Low	5 (33.3)
Moderate	4 (26.7)
High	1 (6.7)

COPD: Chronic obstructive pulmonary disease

*Unless otherwise specified

Table 2. Family physician characteristics (n=30)

	n (%)*
Age (Mean ± standard deviation)	41.0 ± 3.9
Women	17 (58.6)
Number of years of practice in family medicine	
<10	17 (56.7)
10-19	4 (13.3)
20-29	3 (10.0)
≥30	6 (20.0)
Mean (standard deviation)	12 (11.5)
Practice region	
Urban	17 (56.7)
Rural	13 (43.3)
Approximate number of patients with chronic respiratory diseases seen per month	
<20	9 (30.0)
20-39	13 (43.3)
≥40	8 (26.7)
Patients with respiratory diseases most commonly seen in clinical practice	
COPD	21 (70)
Asthma	4 (13.3)
Equal number of asthma and COPD patients	5 (16.7)

COPD: Chronic obstructive pulmonary disease

* Unless otherwise specified

4.1.1 First Article: Supplementary materials

Article: Development of a web-based tool for assessing adherence to respiratory medications using pharmacy claims data in primary care

Electronic supplementary material

S1: Interview guide - Patients with asthma or COPD

S2: Interview guide - family physicians

S3: Barriers to assessing and monitoring medication adherence, key quotes

S4: Facilitators of assessing medication adherence, key quotes

S1: INTERVIEW GUIDE - PATIENTS WITH ASTHMA OR COPD

A. Disease experience

1. For how long have you been diagnosed with your respiratory disease (asthma or COPD)?
2. Who established the diagnosis? In which place?

B. Medication adherence and use

1. To you, what does it mean to take your medications correctly?
    - Have you heard of the term medication adherence?
2. Do you sometimes modify the prescribed doses of your respiratory medications? Why?
3. What strategies do you use to remember to take your medications? Do you sometimes forget to take your medications?
4. Do you notice a relationship between your respiratory medication use, your disease symptoms and your exacerbations?
5. Do you take medications to treat conditions other than your respiratory disease?

C. Patient-Physician relationship and communication

According to the scientific literature, the physician-patient relationship plays a vital role in promoting medication adherence.

1. How would you describe your relationship with your family doctor?
2. What is the nature of the communication with your doctor concerning your disease (medical explanations, medication use, side effects)?
3. Do you discuss your medication use with your doctor? If yes, what subjects are discussed?

D. Use of pharmacy claims data to assess and monitor medication adherence

Suppose your physician can have access to information on all the medications you purchased at your pharmacy. Would you be comfortable with your physician having access to this kind of information?

- How would such information affect your relationship with your family physician?

S2: INTERVIEW GUIDE - FAMILY PHYSICIANS

A. Patient-physician relationship and communication concerning medication use

1. What is your definition of medication adherence?
2. How do you address medication adherence in your practice?
    - Do you discuss medication adherence with your patients?
    - Which strategies do you use to verify medication adherence?
3. Is communication concerning medication use different in patients with chronic respiratory diseases (asthma, COPD), compared to patients with other chronic diseases?

B. Development of e-MEDRESP and use of pharmacy claims data to measure adherence

1. Do you access the prescription refill data found in the Quebec Health Record[2] to verify medication adherence with your patients?
    - What is your opinion on the ease of interpretability of this data?
2. Would a tool based on prescription refills (otherwise known as pharmacy claims data) be relevant in clinical practice? Would it help you assess medication adherence and use?
3. If we were to develop an electronic tool based on pharmacy claims data[3], what kind of information would like to see?
    - What would be the most appropriate metric to describe medication adherence and use (percentages, graphics, etc.)?
    - How would you like the medications to be categorized?
4. What additional information would you require to monitor your patients' medication adherence and use in a more adequate manner?
5. At which frequency would you like to receive updated information on your patients' medication use?
6. How would having access to an objective and easily interpretable information on your patients' medication use affect your relationship with your patient?

Brainstorming and presentation of various prototypes.

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[2] Quebec Health Record (QHR): Electronic data repository in the Canadian province of Quebec that allows doctors, pharmacists, and other healthcare professionals to access health information on their patients (medical results, pharmacy prescription information

[3] Our definition of an electronic tool is a tool that is integrated in electronic medical records.

S3: BARRIERS TO ASSESSING AND MONITORING MEDICATION ADHERENCE

(First global theme)

Key quotes (translated from French), classified according to organizing and basic themes

Organizing Theme	Basic theme	Transcript excerpt	Participant characteristics
Patient beliefs	Disease perception	Patients with COPD never complain and always trivialize their symptoms. It's incredible how their disease worsened with time! So, we as physicians, come up with treatment plans, but what's the use? Compared to asthma patients, COPD patients do not realize the severity of their disease.	Dr, male, 64 years old, 40 years of experience in family medicine
	Disease perception	It seems that [COPD patients] have adapted to an inferior quality of life. So we see them, they are exhausted, they suffer from sleep apnea and when we ask them the question [on their general health], they respond " Oh no, I feel well."	Dr, female, 34 years old, 8 years of experience in family medicine
	Disease perception	Most patients say: "Oh I feel so much better, doctor!" And then you listen to their lungs and realize that they are not well at all. It's probably the only objective measure of compliance that I have, at least according to my short medical experience. So I tell myself, either compliance is the problem… or the drug is not effective. And to know which of these two is the problem can be quite obscure.	Dr, male, 26 years old, recent medical graduate
	Disease/Treatment perception	There is a lot of education that needs to be done with patients with COPD. I have a lot of patients who do not believe they have a disease, so whenever I prescribe them an inhaler, I often sense a feeling of mistrust from them. There is a lot of education to do in this respect. Indeed, respiratory therapists can be very useful but some patients do not even show up to their appointments with the therapists.	Dr, female, 34 years old, 8 years of experience in family medicine
	Treatment perception	P7: I do not feel the need [to take my respiratory medication]. That's the thing. In my everyday life. P11: But if the doctor prescribed it, it's because you need it. P7: I am not sure that I need it that much. That's the thing.	P7: Male patient, 40 years old, diagnosed with COPD for 14 years P11: Patient, 68 years old, diagnosed with COPD for 4 years
	Treatment perception	I heard that prolonged inhaler use can cause your lungs to dry up. Is this true?	Patient, male, 56 years old, diagnosed with COPD for 4 years

Organizing Theme	Basic theme	Transcript excerpt	Participant characteristics
Lack of objective information regarding medication use	Patient reliability	We would like something more objective. Maybe not perfect, but at least objective so that we do not solely rely on what patients tell us.	Dr, female, 34 years old, 4 years of experience in family medicine
	Patient reliability	We need to rely on the patient, and the patients often do not want to tell their doctor that they didn't exactly do what we told them to do (laughs). Or it could be that the patient himself makes suggestions and says: "I forget to take my medication… I would like it to be more simple... or could we change the medication?" It is the patient who is in charge of his health.	Dr, female, 57 years old, 32 years of experience in family medicine
	Patient reliability	We directly ask patients whether they took their medication, knowing full well that patient reliability is mediocre. We know that adherence in patients with COPD is about 40%. So there are two points here: does the patient take the medication and does he/she take it well? And relying on patients' accounts can be quite misleading.	Dr, male, 26 years old, recent medical graduate
	Patient reliability	It's not always easy [to assess adherence] because we rely on [patients]. Sometimes, the pharmacist communicates with us and tells that the [patients] did not renew their prescription, so that can help us. Otherwise, there isn't really a method to verify whether what they tell us is true. But they often end up telling us because we end up increasing doses, or changing inhaler and they know that it's because they didn't take it... they end up telling us.	Dr, female, 55 years old, 28 years of experience in family medicine
	Interpretability of pharmacy claims data	When it comes to the QHR, there is no organization! It's a jumble of information. There is no categorization; there is a lot of redundancy […] It's one line per medication, but sometimes I have to go through 2-3 pages to find the drug I am looking for. It's really not user-friendly! The information is there, but you need to look for it. For a patient who takes 2-3 medications, it is relatively simple, but for a lot of patients who take more than 7 medications, it becomes problematic. There is no order in the QHR... it was just given to us like that… ok well there is the name of the prescriber, the date of prescription, but there are no subcategories. There is no work that has been done within the QHR to make it more easily accessible. We need to reason from this data... the QHR is still at its preliminary phases.	Dr, male, 57 years old, 27 years of experience in family medicine

Organizing Theme	Basic theme	Transcript excerpt	Participant characteristics
	Interpretability of pharmacy claims data	The QHR helps us, but you need to dig into the information. You need to play close attention, as if you were a detective!	Dr, female, 35 years, 10 years of experience in family medicine
Physician medical practices	Disease management	What is also complicated is that I often go to conferences on COPD and learn about available treatments and there seems to be uncertainty regarding the efficacy of inhalers on survival and morbidity. What they say [at the conferences] is that the inhalers will only help relieve the symptoms but then the patient tells me: "These inhalers are not helping me". So I don't have arguments to convince them, to insist that they take their medications. Maybe I am party to blame. So maybe I put less pressure on my patients to take their inhalers because I myself am not sure which medication has a better efficacy relative to another one. [...] What is also complicated is that there are always new COPD drugs entering the market each week!	Dr, female, 39 years old, 2 years of experience in family medicine
	Importance given to assessment and monitoring of medication adherence	I must admit that I do not exert as much effort when reinforcing the adherence to an anticoagulant than to a COPD medication. I noticed that's the same problem with other doctors like me who do not have much experience. So sometimes we realize that the patient does not take his [COPD] medication. Is the COPD medication just as important as other medications to treat other diseases? Probably. [...] I don't systematically monitor the adherence to all medications.	Dr, male, 30 years old, 3 years of experience in family medicine
	Disease management	When I check their prescriptions and verify the technique of utilization, I sometimes look as lost as they are. So I can imagine why they do not always have trust in their prescribed therapeutic regimen. If I am lost, I can only imagine that they are too.	Dr, female, 35 years old, 10 years of experience in family medicine
Organization of healthcare services	Short duration of medical visits	[Medical visit durations] vary from doctor to doctor. I take about 15-20 minute during patients' annual visits, but other doctors take a lot less time. And COPD patients have a lot of other health problems, so I don't always have time to verify compliance. We must choose our battles.	Dr, female, 29 years old, 2 years of experience in family medicine
	Incomplete health information	When patients are hospitalized… often the hospital pharmacy does not have all the inhalers available... So doctors modify the prescriptions and often patients end up with many different inhalers.	Dr, male, 37 years old, 11 years of experience in family medicine

Organizing Theme	Basic theme	Transcript excerpt	Participant characteristics
	Incomplete health information	The reality is that… especially when we take on new patients who have been previously followed by the same doctor for 30 years and I am not able to read previous doctors' handwriting [in paper medical records], I tell my patient " I am sorry, I will start my recipes all over again, and we will redo all the medical tests together. I am sorry, but there is no easy way for me to find out which drugs you have already tried" This is the reality of the disease management and care of an elderly patient.	Dr, male, 26 years old, recent medical graduate
	Healthcare accessibility	When my respiratory physician retired, I was told that I was going to be followed by a family doctor. I waited for three and a half years for a family doctor. I recently met her, so she obviously doesn't know me very well.	Patient, female, 81 years old, diagnosed with COPD for 35 years
	Healthcare accessibility	Medical visits. With respiratory physicians. It's been 25 years I haven't seen a respiratory physician. I am about to die. I only have 30% of my lungs left. So it would be the least of things to have a medical visit every 6 months. Patients are left on their own because some doctor retired. What's the deal?	Patient, male, 70 years, diagnosed with asthma/COPD overlap for 25 years

S4: FACILITATORS OF ASSESSING AND MONITORING MEDICATION ADHERENCE

(Second global theme)

Key quotes (translated from French), organized by theme

Organizing theme	Basic theme	Transcript excerpt	Participant characteristics
Patient-physician relationship	Communication	We should accompany patients rather than reprimand them.	MD, female, 50 years old, 17 years of experience in family medicine
	Patient empowerment	I always try to work in collaboration with the patient. Like I always say, I work WITH the patient, not above the patient. I am not a teacher, I am not the one who will scold them […] It's really to try to show that the patient is responsible for his own health and that I am not there to shove medications in their mouths.	MD, female, 57 years old, 32 years of experience in family medicine
	Communication	I think it's important that our doctor respects us. My doctor told me to stop smoking, but he knows I am not at this stage yet. He respects me and gives suggestions, without forcing his recommendations on me. He communicates with me.	Patient, male, 58 years old, diagnosed with asthma for 4 years
	Communication	One of the first questions I ask them is: "Do you take your medication regularly?" It's very simple, but if we do not ask, they may hide the truth from us and we lose them. So if I am open, they are open. So it will be easy to understand why they only take their medication at specific times during the year, or as needed... As long as we show that we are open, there won't be any secrets. Or sometimes, I reformulate my question: "Do you sometimes forget to take your medication?" And my patient says "yes". So finally I get an answer. So I continue" How often do you forget? Once every week? Once every month? Do you regularly get your prescription at the pharmacy? Do you sometimes prolong your prescription at the pharmacy? Do you get your prescription every month and a half?" Small questions like that...	MD, male, 32 years old, 2 years of experience in family medicine
Physician access to pharmacy claims data	Relevance of having access to pharmacy claims data	[Opinion on pharmacy claims data]: It's not perfect, but it's fine. It opens up new lines of inquiry for me. I think it would… it would satisfy an existing need.	MD, female, 57 years old, 32 years of experience in family medicine
	Relevance of having access to pharmacy claims data	Patients don't take their medications… they only wait until they have an exacerbation to take action. Then pharmacists send us a fax, indicating that the situation is critical.	MD, female, 35 years old, 10 years of experience in family medicine
	Relevance of having access to pharmacy claims data	It would be nice to have a history of medication adherence every year. To see which inhaler or medication worked, see if medication compliance changed after increasing a dose or after I changed their prescriptions. If would be nice to see if our interventions really have an impact on patient compliance.	MD, male, 65 years old, 42 years of experience in family medicine

Organizing theme	Basic theme	Transcript excerpt	Participant characteristics
	Patient acceptability	If doctors prescribe us medications, they assume that we take them. And they prescribe them because we need them. So yes, I very much agree that physicians should have access [to our prescription refill data]. I would even be okay with physicians knowing exactly if I took all the doses... that I didn't just hide my inhalers in a cupboard at home and use only use them when I need them. *Did I really use them?*	Patient, female, 38 years old, diagnosed with asthma for 22 years
	Patient acceptability	I believe it's a good idea. The doctor will be able to better understand the situation. The pharmacist knows which medication you took, but the doctor cannot exactly know which medication was purchased.	Patient, female, 37 years old, diagnosed with asthma for 8 years
	Patient acceptability	It's for sure a double-edged sword… for sure. At any given time, this is what happens: you see your doctor, you don't feel well. He gave you drugs but then he realizes that you only took half of them. What's the point of going back to the doctor?	Patient, male, 65 years old, diagnosed with COPD for 3 years
	Patient acceptability	I think this is a delicate issue… in the sense that the patient can ask himself: "What? You have access to all this information? You even know when I [purchased my medicine]" It's not really cool to feel like you are under the radar.	MD, female, 39 years old, 6 years of experience in family medicine
Inter-professional collaboration	Inter-professional collaboration - *respiratory therapists*	I often request pulmonary function tests and at the same time, respiratory technicians often check how the medications are taken. And then they send us a report. It's super useful.	MD, female, 57 years old, 32 years of experience in family medicine
	Inter-professional collaboration - *respiratory therapists*	Sometimes, they use their inhaler incorrectly so then they say that their medication doesn't work. So one strategy is to get help from the respiratory therapist […] that's when we realize that the medications are not taken correctly.	Dr, male, 37 years old, 11 years of experience in family medicine
	Inter-professional collaboration - *respiratory therapists*	We have a respiratory therapist who started to work with us at the clinic. She gives us a great service; we are very lucky. So I have a few patients who have been recently diagnosed, we start a new medication, and the therapist does a spirometry test. So that gives an objective measure to the patient. Maybe the patient does not feel any improvements, but clinically, objectively, the patients gained back 20% of his pulmonary function with the use of the inhaler.	MD, female, 50 years old, 17 years of experience in family medicine
	Inter-professional collaboration - *pharmacists*	Sometimes, the pharmacist communicates with us and informs us that the patient did not come fill their prescriptions. Otherwise, we don't really have a way of knowing that what patients tell us is true.	MD, female, 55 years old, 28 years of experience in family medicine

4.2 Second Article: Feasibility of Implementing e-MEDRESP in Clinical Practice

Feasibility of Implementing a Web-based Tool Built from Pharmacy Claims Data (e-MEDRESP) to Monitor Adherence to Asthma/COPD Medications in Primary Care

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Author contributions

AY wrote the first draft of the manuscript. AY, LB, and CL devised the project and the main conceptual ideas. MFB provided clinical expertise to support the development e-MEDRESP. AY and AF conducted the statistical analyses. Finally, all authors interpreted the data, revised the manuscript, had access to complete study data, and had authority over manuscript preparation as well as approval of the final version and the decision to submit for publication.

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ABSTRACT

Objectives: e-MEDRESP is a novel web-based tool built from pharmacy claims data that provides objective and easily interpretable information regarding adherence to asthma/COPD medications. The aim of this study was to assess the feasibility of implementing e-MEDRESP in primary care.

Methods: As part of prospective cohort study, e-MEDRESP was integrated in electronic medical records and was available for 19 family physicians and 346 of their adult patients between July 2019 and November 2020. Counters were embedded in the tool to track physician use of the tool throughout the study. Patient and physician satisfaction with e-MEDRESP were collected via phone interviews and online questionnaires. The capacity of e-MEDRESP to improve adherence was explored using the reMed drug claims database.

Results: 252 patients had at least one medical visit during the study. e-MEDRESP was consulted by 15 (79%) physicians for 85 (34%) of these patients during a medical visit. 73 patients underwent a phone interview; 84% reported discussing their medication use with their physician; 33% confirmed seeing their e-MEDRESP report on the physician's computer and indicated that it was easy to interpret. Physicians reported that the tool helped to better evaluate their patients' medication use, with a mean rating (out of 5) of 4.8 ± 0.7. When we assessed the adherence to controller medications in the 6 months before and after the first physician consultation of e-MEDRESP during a medical visit, no improvement in adherence was observed. However, among patients whose adherence level was less than 80% upon the consultation, improvement in adherence was observed in those who filled inhaled corticosteroids or long-acting muscarinic agents [respectively, PDC: 26.4% (95% CI: 14.3-39.3%) and 26.9% (95% CI: 12.4-40.2%)].

Conclusions: The integration of e-MEDRESP within physician workflow is feasible. e-MEDRESP can serve as a powerful tool to assist physicians in monitoring medication adherence and improving patient care.

Key words: Medication adherence, electronic medical records, e-health tools, asthma, COPD

INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are major causes of chronic morbidity and mortality worldwide. Globally, asthma affects over 350 million people[1] and approximately 174 million have been diagnosed with COPD.[2] Despite a plethora of effective treatments, medication adherence in individuals with asthma or COPD is dismal, often falling below 50%.[3-6] Consequences of nonadherence include inadequate disease control and worsening symptoms, as well as increased healthcare costs.[7-9]

A wealth of evidence from the literature highlights the detrimental effects of medication nonadherence on therapeutic outcomes. In asthma, nonadherence generally results in decreased pulmonary function, as well as an increase in hospitalizations and emergency department visits.[10] In fact, 24% of exacerbations and 60% of asthma-related hospitalizations could be attributed to poor adherence.[10] Along similar lines, a US study revealed that for 1000 COPD patients, a 5% point increase in adherence reduced the annual number of inpatient visits (-2.5%) and emergency room visits (-1.8%); further, the net reduction in annual cost was approximately $300,000.[11] Although adherence to prescribed therapy is a complex issue, its detrimental public health effects are preventable.

A large majority of asthma and COPD patients are treated in primary care.[12,13] As the front-line healthcare providers, family physicians have an important impact on patients' perception of prescribed therapy. To propose effective interventions, family physicians need to first assess adherence accurately and in a timely manner—a challenging aspect of patient care. In practice, physicians often rely on patient self-report;[14] however, studies have shown that patients often overestimate their medication adherence.[15-17] Notably, one study reported an average adherence to asthma controller therapy of over 80% based on patient self-report, while electronic monitoring of metered dose inhaler actuation revealed an average adherence of 50% for the same patients.[16] Alternatively, pharmacy claims data can be used to obtain objective and non-invasive measures of medication adherence.[18] They provide information on medications filled by patients, as well as frequency of refills.[19] A downside of this approach is that these data are not systematically available in clinical practice. Only a few medication adherence assessment tools based on pharmacy claims data have been structured to fit around the daily practice of family physicians.[20-26] Most of these tools were not disease-specific, although some were adapted to diabetes[24,25] and asthma.[22,26] To the best of our knowledge, none were specifically developed for COPD patients. Additionally, many of the existing tools were paper-based or not integrated in electronic medical records (EMRs), which may have presented usability challenges among physicians. Furthermore, only one tool was developed in collaboration with the primary end-users.[26] Yet previous research suggests that integrating

the physician and patient perspectives at the design, development, and testing process can help ensure the effective uptake of new tools, including e-health technologies, in clinical practice.[27]

In collaboration with family physicians and patients with asthma or COPD, we previously developed e-MEDRESP, a novel web-based tool built from pharmacy claims data that provides to family physicians with objective, continuously updated, and easily accessible and interpretable information on adherence to asthma and COPD medications.[14] To ensure the seamless integration of e-MEDRESP within physician workflow, our research team formed a partnership with OMNIMED, a leading EMR vendor in Quebec, Canada. As part of a 16-month feasibility study, e-MEDRESP was integrated in the EMR of participating clinics which subscribe to OMNIMED.

The purpose of this study was to assess the feasibility of implementing e-MEDRESP in family medicine clinics. Specifically, we aimed to: 1) evaluate physician use of e-MEDRESP in routine clinical practice; 2) evaluate physician and patient satisfaction with e-MEDRESP; and 3) explore the capacity of e-MEDRESP to improve patient adherence and disease control, as well as prescription changes, 6 months before and after the first consultation of e-MEDRESP by the treating physician.

BACKGROUND AND SIGNIFICANCE

e-MEDRESP was developed using a framework inspired by user-centered design principles and an integrated health technology approach.[14] This tool provides graphical and tabular representations of medication adherence to asthma and COPD controller medications and reliever medication use, through algorithms based on physician preferences. Within e-MEDRESP, these algorithms are computed using pharmacy claims data recorded in reMed,[28] a drug claims database which routinely collects information on prescribed medications dispensed in community pharmacies for registered patients. An automated data extraction procedure was established to update the information presented in e-MEDRESP every two weeks. Moreover, physicians are not required to input any data to access the tool. An overview of e-MEDRESP's development process and underlying algorithms have been previously published.[14]

An example of an e-MEDRESP report is presented in Figure 1. Briefly, e-MEDRESP comprises three sections that allow physicians to simultaneously identify important refill gaps and easily flag non-adherent patients based on color codes. The first section of e-MEDRESP displays the percentage adherence to all asthma and COPD controller medications dispensed in community pharmacies in the prior year. Information on adherence to controller medications, according to medication class, is also available. For patients who filled medications containing inhaled corticosteroids (ICS), the mean daily ICS dose is presented on a quarterly and annual basis, using a bar chart. The second section provides an overview of

all asthma and COPD medications dispensed in community pharmacies in the prior year. Dates and frequency of refills, as well as generic names of medications, are provided. The third section presents the use of reliever medications, oral corticosteroids, and antibiotics dispensed in the prior year, per trimester. Other salient features of e-MEDRESP include a video tutorial, the option to print individual patient reports, as well as an explanatory document presenting the list of inhaled respiratory medications with photos of inhaler devices.

MATERIALS AND METHODS

Design

We conducted a feasibility study in 10 family medicine clinics in the Quebec province. A prospective cohort using a convergent mixed-method design was used,[29] whereby quantitative and qualitative data were collected concomitantly over a 16-month period (July 2019 – November 2020), and then merged, with the aim of evaluating the feasibility of implementing e-MEDRESP in clinical practice, from the perspective of family physicians and patients with asthma/COPD. To ensure the timeliness of data collection, e-MEDRESP was progressively deployed in clinics while patient recruitment was ongoing. In total, there were 7 phases of implementation between July 2019 and June 2020, with each physician taking part in a single implementation phase. Cohort entry corresponded to the date of implementation of e-MEDRESP in the EMR. Of note, 21 patients were recruited after the tool was available in their physician's EMR; for these patients, cohort entry corresponded to the date of study enrollment. Follow-up ended on November 20, 2020 for all participants.

Setting and participants

Participants were recruited from all the family medicine clinics which subscribed to the OMNIMED EMR in the Quebec province. To be eligible, family physicians must have treated patients diagnosed with asthma or COPD in the prior year. Eligible patients were required to: be at least 18 years old; have an asthma or COPD diagnosis recorded in the EMR; be treated by a participating family physician; and have been prescribed at least one asthma or COPD controller medication in the previous year. Email and fax correspondence were sent to clinics of potentially eligible physicians inviting them to participate in the study. Within a week of contact, research team members contacted the clinics by phone to provide an overview of the study objectives. Physicians interested in participating were subsequently required to complete an information and consent form and return it to the research team to confirm their study

enrollment. Patient recruitment was conducted in collaboration with recruited physicians. Specifically, participating clinics appointed a research assistant to contact eligible patients by phone to explain the project and invite them to participate. To confirm their participation, patients were required to complete an information and consent form and return it to the research team via email or mail. Enrolled patients were also registered in the reMed database, which allowed us to obtain their prescription refill data from community pharmacies. Patients and physicians received compensation for time incurred due to study participation.

Intervention

The e-MEDRESP web-based module was accessible through the homepage of the EMR of enrolled patients (patient file). Following each implementation phase, the list of enrolled patients was faxed to the participating clinics and each participating physician was contacted by a member of the research team to schedule an in-person or telephone meeting. The purpose of the meeting was to remind the physicians of the study objectives, to demonstrate the location of the tool within their EMR system, and to provide training on how to use e-MEDRESP. Physicians were also invited to view a video tutorial that presented the notable features of e-MEDRESP and were given an accompanying explanatory document.

Feasibility Outcomes

Use of e-MEDRESP in routine clinical practice

Physician use of e-MEDRESP was monitored following cohort entry, using hit counters that were integrated in the tool. Through unique identifiers, these counters allowed us to identify the date when e-MEDRESP was consulted, according to enrolled patients and physicians. Throughout the study, we determined the number physicians who used e-MEDRESP at least once, as well as the number of patients for which e-MEDRESP was consulted by the treating physician at least once, during and outside medical visits. Moreover, the number of medical visits per patient (all causes) and the number of medical visits in which e-MEDRESP was consulted by a treating physician was calculated. We also determined the time that elapsed between the date of cohort entry and each consultation of e-MEDRESP, as well as the season in which the tool was consulted. When available, information on the type of clinical encounter (annual, emergency, in-person appointment, telehealth, etc.) was also obtained.

Clinical usefulness of e-MEDRESP

Following the first physician consultation of e-MEDRESP during a medical visit, patient satisfaction with e-MEDRESP was assessed via a telephone interview. Specifically, patients were asked if physicians discussed with them their adherence to their asthma or COPD controller medications and if the information presented in e-MEDRESP was shared with them during the visit. If the treating physician shared the information presented in e-MEDRESP, patients were asked their opinion on the ease of interpretability of e-MEDRESP and the extent to which e-MEDRESP facilitates patient-physician communication concerning medication use. Physicians' feedback regarding e-MEDRESP, as well as suggestions to further improve it, were assessed via two online questionnaires. The first questionnaire was administered after the first use of e-MEDRESP during a medical visit with an enrolled patient and the second questionnaire was administered at the end of study. Two main domains were assessed in the questionnaires: 1) perceived clinical usefulness of e-MEDRESP; and 2) ease of use and interpretability of information presented in e-MEDRESP. Formats of questions included 5-point Likert scales, as well as dichotomous and open-ended questions. Finally, to better understand the clinical relevance of e-MEDRESP during the COVID-19 pandemic, a post hoc survey was sent out to physicians.

Capacity of e-MEDRESP to improve medication adherence and disease control (secondary outcomes)

Patients' adherence to controller medications was calculated via a modified version of the proportion of days covered (PDC)[30] and was evaluated 6 months before (pre-evaluation period) and after (post-evaluation period) e-MEDRESP was consulted by the treating physician for the first time during a medical visit, using pharmacy claims data recorded in reMed. Details on the PDC calculations are presented in the supplementary materials (S1). A PDC below 80% was indicative of sub-optimal adherence, as clinical evidence suggests that this threshold is the level above which the medication has a reasonable likelihood of achieving the most clinical benefit.[31] Additionally, the mean weekly number doses of short-acting β2-agonists (SABA) and occurrence of exacerbations were also assessed within these two periods and were used as proxies for disease control. Specifically, exacerbations were defined as a filled prescription for oral corticosteroids of a duration of less than 14 days and the mean weekly number of doses of SABA was estimated using an algorithm which we developed in a previous study[32] that incorporates the following parameters: dose per inhalation, pharmaceutical form, quantity dispensed, and dates of prescription dispensing. If a SABA other than salbutamol is dispensed, the mean number of doses is converted to a salbutamol equivalent. A mean weekly number of doses greater than 4 was considered a marker of

uncontrolled disease, as per clinical guidelines.[33] Finally, to explore how e-MEDRESP affected prescribing practices, we identified the number of medical visits which resulted in controller prescription changes within the 6-month period following the first physician consultation of e-MEDRESP during a medical visit. Prescription changes included any controller treatment add-on or ICS dose change. The mean daily prescribed ICS dose was calculated via an algorithm which we developed in previous studies[34,35] that takes into account the following parameters: potency of different ICS; medication form; quantity dispensed; and medication dispensing date. By using the equivalency table published in the Canadian asthma consensus report,[36] the mean daily ICS dose was converted to the equivalent of the fluticasone propionate.

Statistical and data analysis

Patients' and physicians' sociodemographic characteristics upon recruitment, as well as asthma and COPD medication adherence and use in the year prior to cohort entry, were analyzed using descriptive statistics. Medication adherence was calculated using a modified version of the PDC (see supplementary file (S1) for details). Proportions were calculated for categorical variables and means and standard deviations were calculated for continuous ones.

Use of e-MEDRESP during the study period was analyzed descriptively. The proportion and 95% confidence intervals (CI) of the following variables were computed: 1) physicians who used e-MEDRESP at least once; 2) patients who had at least one medical visit; 3) patients for which e-MEDRESP was consulted by the treating physician at least once, during and outside medical visits; 4) medical visits in which e-MEDRESP was consulted by a physician for each type of clinical encounter as well as season and month of consultation. The mean time and standard deviation between each consultation of e-MEDRESP and the date of cohort entry were also assessed. Further, to evaluate patient and physician satisfaction with e-MEDRESP, descriptive analyses were conducted on the answers obtained from telephone interviews and online questionnaires; means and standard deviations were computed for Likert-Scale questions and proportions and 95% CI for dichotomous questions. Specific comments on the clinical usefulness of e-MEDRESP were qualitatively described.

For the secondary analyses, the following variables were compared in the 6-month period prior and after e-MEDRESP was consulted by the treating physician for the first time during a medical visit using paired t-tests: 1) PDC of controller medications and 95% CI; 2) mean weekly number of doses of SABAs and 95% CI; 3) number of OCS prescriptions of less than 14 days. Sub-analyses were also conducted in: 1) patients for which the mean PDC of controller medications was less than 80% during the first consultation

of e-MEDRESP; and 2) patient who had uncontrolled disease, defined by the presence of at least one OCS prescription or mean weekly number of doses of SABA of at least 4. Furthermore, the proportion of patients and 95% CI who had a prescription change within 6 months following a physician consultation of e-MEDRESP during a medical visit were computed. The secondary analyses were executed in patients for whom the treating physician has consulted e-MEDRESP at least once during a medical visit and for which a 6-month follow-up period was available. All statistical analyses were performed with SAS 9.4® (SAS Institute, Cary NC).

Research ethics

This study was approved by the research ethics committee of the *Centre Intégré Universitaire de santé et de services sociaux du Nord-de-l'île-de-Montréal.*

RESULTS

Description of e-MEDRESP cohort

A total of 19 family physicians and 346 of their patients were enrolled in the study. The patient cohort comprised 188 asthma patients, 131 COPD patients, and 27 patients with concomitant asthma and COPD diagnoses (Table 1). The median follow-up duration of patients was 416.0 days (IQR: 399.0-461.0). Patients were on average 59 years old and were mostly female. Upon cohort entry, the most prescribed controller medications were ICS/long-acting β2-agonists (LABA), ICS monotherapy, and long-acting muscarinic agents (LAMA), with average one-year adherence PDC levels of 51.6% ± 28.3%, 36.1% ± 26.5%, and 68.0% ± 28.5%, respectively. Physicians were on average 47 years old and the majority were female and practiced in rural settings (Table 2). The median duration in which e-MEDRESP was available in the EMR of physicians was 438.5 days (IQR: 416.0-461.0). The recruitment flow charts are available in the supplementary file (S2). Recruitment rates for patients and physicians were 38% and 5%, respectively.

Use of e-MEDRESP in routine clinical practice

Out of the 19 recruited physicians, 15 (79.0% [95% CI: 54.4%-94.0%]) used e-MEDRESP at least once during the study. Out of the 346 patients enrolled, physicians viewed the e-MEDRESP reports of 133 patients, and these occurred during or outside medical visits. Throughout the study, 252 patients (38.4% [95% CI: 33.2%-43.8%]) had at least one medical visit with one of the enrolled physicians (Table 1). The e-MEDRESP report of 85 (33.7%; CI: 27.9%-39.9%) of these patients was consulted by a physician during a medical visit.

Consultations of e-MEDRESP by physicians since cohort entry

Throughout the study, the tool was consulted by physicians 202 times (Table 3). Among these consultations, 102 (50.5%; 95% CI: 43.4%-57.6%) occurred during medical visits. Further, the majority occurred during in-person scheduled medical visits, while a minority took place in telehealth visits. Most consultations occurred in the fall season and within the first 60 days following cohort entry. Of note, some physicians had a small number of patients enrolled in the study, thus providing them with less opportunities to view the tool throughout the study (details are presented in the S3 supplementary material).

Use of e-MEDRESP by physicians since the first implementation

The rate of physician use of e-MEDRESP was higher in the first 5 months following the start of the study (July 2019) and peaked in October and November 2019, which coincided with the largest implementation phase of the tool in the EMR of participating clinics (Figure 2). A decrease in use was noticed during the COVID-19 pandemic, although the rate of use started to rise again in fall 2020. Physician use of e-MEDRESP according to patient diagnosis did not reveal any specific trends (supplementary material; figure S3). The post hoc survey results are presented in the supplementary material (S5). Although many physicians reported that their use of e-MEDRESP did not drastically change during the pandemic, some indicated that they did not use the tool frequently because they had to modify their practice to adapt to the unusual circumstances surrounding the public health crisis. Namely, they frequently carried out emergency and mental-health teleconsultations; as a result, medication adherence assessment was not prioritized.

Clinical usefulness of e-MEDRESP

Overall, the tool appeared to be greatly appreciated by users. Patient and physician testimonies are presented in Figure 3. Among patients whose physician consulted the tool during a medical visit (n=85), we were able to reach 73 patients for a phone interview; 83.6% (95% CI: 73.1%-91.2%) reported discussing their medication use with their physician; and among them, 32.8% (95% CI: 21.3%-46.0%) confirmed seeing their e-MEDRESP report on the physician's computer. Using a 5-point Likert scale, patients indicated that their e-MEDRESP report was easy to interpret (mean rating ±sd: 4.1 ± 1.0). Furthermore, patients reported that e-MEDRESP facilitated patient-physician communication on medication (mean rating: 3.8 ± 0.9).

Table 4 provides an overview of physicians' evaluation of e-MEDRESP. Following their first use of e-MEDRESP, physicians conveyed that the tool helped to better evaluate their patients' medication use

(mean rating: 4.7 ± 0.6). They also felt that the tool facilitated communication on medication adherence and helped them adjust the prescribed therapy, with mean ratings of 4.3 ± 0.9 and 4.8 ± 0.6, respectively. Upon the first use of e-MEDRESP, physicians unanimously reported that they intended to continue to use this tool and appreciated its seamless integration in the EMR. The questionnaire that was administered at the end of the study revealed similar results, although the ratings were slightly lower.

Throughout the study, physicians provided many suggestions to further improve e-MEDRESP. Specifically, it was suggested to add a functionality that will allow them to distinguish prescriptions that were written by other healthcare providers and to ensure that percentage adherence calculations consider prescription switches or cessations. As asthma clinical guidelines began to recently encourage the use of as-needed low dose Budesonide (ICS)-Formeterol (LABA) (Symbicort®) as the preferred reliever therapy,[1] it was suggested remove percentage adherence calculations for this medication when patients use it on an as-needed basis, but to still provide information on the frequency of refills. Moreover, most physicians were interested in having access to medication adherence assessment tools that are adapted to other diseases, including diabetes, hypertension, and mental health disorders.

Capacity of e-MEDRESP to improve adherence

Among the 85 patients who had a consultation of e-MEDRESP during a medical visit, 79 had at least 6 months of follow-up data after the first consultation; therefore, the secondary analyses were conducted on these patients. When we assessed the adherence to controller medications 6 months before and after e-MEDRESP was first consulted by a physician, no improvement in adherence or disease control was observed (Table 5). However, among patients whose PDC was less than 80% (n=36) in the 6-months prior to the first consultation of e-MEDRESP, statistically significant improvement in mean PDC were observed in patients who filled either an ICS or a LAMA [respectively, 26.9% (95% CI: 12.6%-40.2%) and 26.4% (95% CI: 14.3%-39.3%)]. In the 6 months following the first consultation of e-MEDRESP during a medical visit, 12 patients(16.7 %; 95% CI: 8.9%-27.3%) had a treatment switch or add-on and 13 patients (18.1%; 95% CI: 10.0%-29.0%) had an ICS dose increase.

DISCUSSION

In this study, family physicians were provided with e-MEDRESP, an innovative electronic tool based on pharmacy claims data that allowed them to obtain objective and easily interpretable information on medication adherence and use for their patients with asthma or COPD. The study findings are encouraging: feasibility was demonstrated; e-MEDRESP was greatly appreciated by users; and

improvement in adherence was observed among patients taking some of the most commonly prescribed medications to treat moderate-to-severe asthma or COPD.

Our assessment revealed that e-MEDRESP was widely used in the beginning of the study. In fact, 74% of physician consultations of the tool occurred within the first 180 days following cohort entry. A decrease in use was observed towards the end of the study, which may be explained by several factors. The post hoc survey suggested that the COVID-19 pandemic may have affected the use of e-MEDRESP, since some physicians modified their practices to better adapt to the circumstances surrounding the public health crisis. Additionally, some of the enrolled patients had several medical visits throughout the study; thus, a physician may not necessarily use e-MEDRESP at every encounter, especially if the reason for the visit is not respiratory-related. Finally, some patients may have moved, changed family practices or died during follow-up, although this information was not accessible to the research team.

On an encouraging note, positive feedback on the clinical usefulness of e-MEDRESP was gathered from physicians and patients. Questionnaires, telephone interviews, and testimonies collectively showed that e-MEDRESP facilitated patient-physician communication and helped them to provide a more personalized treatment based on their patients' medication adherence. Although the prototype of this tool was extensively developed in collaboration with patients and physicians in a previous study,[14] physicians provided feedback on how to further improve it, including modifications to the adherence calculations that could better reflect recent changes in clinical guidelines. In contrast, patients did not provide specific negative feedback on the tool. Telephone interviews revealed that only 33% of patients had the opportunity to view their e-MEDRESP report during medical visits, indicating that the tool may have been more adapted to physicians' needs. Therefore, new strategies are required to better ensure patient engagement. Given the growing popularity of mobile phone apps targeting medication adherence,[37] we believe that linking e-MEDRESP to a mobile phone app that offers educational materials may provide more personalized and interesting avenues for patients to optimize their medication-taking behaviour, though further studies are required to confirm this hypothesis. At a broader level, our findings underscore the importance of iteratively developing e-health technologies that are tailored to end-user needs, from prototype development to the implementation process.

When we assessed the medication adherence in the 6 months before and after the first physician consultation of e-MEDRESP during a medical visit, no improvement in adherence was observed. However, among patients whose mean adherence level was less than 80% upon the consultation, subsequent statistically significant improvement in adherence was observed among patients who took ICS monotherapy or LAMAs. Although these results are promising, these improvement in adherence may be

partially explained by the fact that most physician consultations took place in fall; as a result, adherence was often assessed in the fall and winter seasons in the post-evaluation period. It was previously shown that ICS use is highly seasonal and peaks in winter;[38] thus, adherence improvements observed in our analysis may be partly due to this phenomenon. Additionally, improvement in adherence was not observed in other medication classes, possibly due to inadequate sample sizes. It can also be argued that physicians may not have been always equipped to address medication adherence, even if they were able to detect non-adherent patients using e-MEDRESP. Indeed, adherence is a complex phenomenon entrenched in a myriad of factors, including social and economic factors (cost of treatment, prescription coverage); therapy-related factors (number of drugs, number of doses); condition-related factors (disease severity/control); and patient-related factors (age, illness beliefs, comorbidity, healthcare utilization).[39,40] It was also previously shown that patient education and counselling showed some positive effects on medication adherence and that interventions delivered by pharmacists and nurses showed a better result in improving adherence and outcomes than interventions led by general practitioners.[41] Thus, we believe that the effectiveness of e-MEDRESP could be enhanced if it became an integral part of multi-layered interventions which focus on strengthening patient and physician education, patient-physician relationship, and inter-professional collaboration.

Above all, this study extends the literature on the development of e-health technology tools aimed at enhancing healthcare quality. From its inception, e-MEDRESP was designed using several criteria that were previously shown in the literature to facilitate physician adoption of new healthcare information technology in clinical practice.[27] First, physicians and patients were consulted throughout the development and feasibility assessment process to ensure that e-MEDRESP was user-friendly and clinically intuitive.[42-44] Second, e-MEDRESP was implemented in EMRs to ensure that the tool was efficiently integrated within physician workflow. Such an approach ensured that the tool did not result in loss of productivity or increased clinician burden.[45,46] Among the existing medication adherence assessment tools reported in the literature,[20-26] physician uptake of the tool in clinical practice was not always closely monitored and patient and physician feedback were seldom collected. Moreover, capacity of these tools to improve adherence was not always assessed, and when they were, the periods in which adherence was assessed were not always clearly defined. Yet such methodological considerations should be embedded in the design and implementation of new e-health technologies and are important steppingstones to large-scale implementation. These factors may collectedly explain why the uptake of some of these tools in clinical practice was not as high as expected.

The results of this study should be interpreted in the lights of some limitations. Drawbacks of e-MEDRESP include those that are inherent to pharmacy claims data. Namely, purchase at the pharmacy does not necessarily mean that the patient consumed the medicine. Nevertheless, pharmacy claims data are considered a more objective and accurate measures of adherence, and were shown to be correlated with treatment outcomes.[47] Limitations related to sample size should also be noted: patient and physician recruitment rates were low and some physicians had a low number of patients recruited, thus providing them with less opportunities to use the tool and share feedback. It may also have been easier to recruit physicians who were already proactive in promoting medication adherence in their practice. In a similar vein, enrolled patients appeared to have, on average, higher level of medication adherence than the general population.[3-6] Therefore, our sampling strategy may not have entirely reflected the complexities of the real-world clinical setting.

Clinical implications and recommendations for large-scale implementation

Although feasibility was demonstrated, we identified several strategies that should be considered prior to large-scale implementation. First, it is important to integrate the suggestions put forth by the participants of this study in order to further improve e-MEDRESP. Second, we recommend continuing to further engage patients in the shared-decision making process and conduct feasibility studies with other healthcare professionals, such as pulmonologists, nurses, and pharmacists to gauge the clinical relevance of e-MEDRESP in different healthcare settings. Cluster randomized clinical trials are ultimately required to evaluate the effectiveness of e-MEDRESP to improve adherence and enhancing prescribing practices. Third, physician recruitment methods need to be modified, given our low recruitment rate. Although the level of participation in research by general practitioners is generally low,[48] we believe that recruiting physicians solely by phone, email or fax was not ideal. Instead, in-person visits may help to better elicit their interest. Using promotional materials that present physician and patient testimonies on e-MEDRESP could also boost participant engagement.

CONCLUSIONS

We successfully implemented the e-MEDRESP web-based tool in primary care. The key strengths of this tool lie in its ease of accessibility and user-friendly format. Larger studies are required to evaluate the effectiveness of e-MEDRESP to improve medication adherence and prescribing practices. Ideally, e-MEDRESP should be integrated in multi-focal interventions which aim to foster patient and physician education and stronger patient-physician relationship, as well as inter-professional collaboration.

REFERENCES

1. Global Initiative for Asthma. Pocket Guide for Asthma Management and Prevention. 2020; https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_-final-_wms.pdf.
2. World Health Organisation. Burden of COPD. 2018; http://www.who.int/respiratory/copd/burden/en/.
3. World Health Organization. Adherence to Long-Term Therapies: Evidence for Action. 2003; http://www.who.int/chp/knowledge/publications/adherence_full_report.pdf.
4. Blais L, Kettani FZ, Beauchesne MF, Lemiere C, Perreault S, Forget A. New measure of adherence adjusted for prescription patterns: the case of adults with asthma treated with inhaled corticosteroid monotherapy. *The Annals of pharmacotherapy.* 2011;45(3):335-341.
5. Cyr MC, Beauchense MF, Lemiere C, Blais L. Comparison of the adherence and persistence to inhaled corticosteroids among adult patients with public and private drug insurance plans. *Journal of population therapeutics and clinical pharmacology = Journal de la therapeutique des populations et de la pharamcologie clinique.* 2013;20(1):e26-41.
6. Savaria F, Beauchesne MF, Forget A, Blais L. Adherence and Persistence to Long-Acting Anticholinergics Treatment Episodes in Patients With Chronic Obstructive Pulmonary Disease. *The Annals of pharmacotherapy.* 2017;51(12):1063-1068.
7. Ismaila AS, Sayani AP, Marin M, Su Z. Clinical, economic, and humanistic burden of asthma in Canada: a systematic review. *BMC pulmonary medicine.* 2013;13:70-70.
8. Soriano JB, Abajobir AA, Abate KH, et al. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. 2017;5(9):691-706.
9. Dang-Tan T, Ismaila A, Zhang S, Zarotsky V, Bernauer M. Clinical, humanistic, and economic burden of chronic obstructive pulmonary disease (COPD) in Canada: a systematic review. *BMC research notes.* 2015;8:464-464.
10. Bårnes CB, Ulrik CS. Asthma and Adherence to Inhaled Corticosteroids: Current Status and Future Perspectives. 2015;60(3):455-468.
11. Toy EL, Beaulieu NU, McHale JM, et al. Treatment of COPD: relationships between daily dosing frequency, adherence, resource use, and costs. 2011;105(3):435-441.
12. Wechsler ME. Managing asthma in primary care: putting new guideline recommendations into context. Paper presented at: Mayo Clinic Proceedings2009.
13. Broekhuizen BD, Sachs AP, Verheij TJ. COPD in primary care: from episodic to continual management. In: British Journal of General Practice; 2012.
14. Yousif A, Pelaez S, Lemiere C, et al. Development of a Web-Based Tool Built From Pharmacy Claims Data to Assess Adherence to Respiratory Medications in Primary Care. *Respiratory care.* 2020.
15. Lim KG, Rank MA, Li JT, et al. How well does patient self-report predict asthma medication possession? Implications for medication reconciliation and adherence assessment. *Journal of Asthma.* 2010;47(8):878-882.
16. Bender B, Wamboldt F, O'Connor SL, et al. Measurement of children's asthma medication adherence by self report, mother report, canister weight, and Doser CT. *Annals of Allergy, Asthma & Immunology.* 2000;85(5):416-421.
17. Gamble J, Stevenson M, McClean E, Heaney LG. The prevalence of nonadherence in difficult asthma. *American journal of respiratory and critical care medicine.* 2009;180(9):817-822.

18. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. *Journal of clinical epidemiology.* 1997;50(1):105-116.
19. Lehmann A, Aslani P, Ahmed R, et al. Assessing medication adherence: options to consider. *International Journal of Clinical Pharmacy.* 2014;36(1):55-69.
20. Harbig P, Barat I, Lund Nielsen P, Damsgaard EM. Instantaneous detection of nonadherence: quality, strength, and weakness of an electronic prescription database. *Pharmacoepidemiology and drug safety.* 2012;21(3):323-328.
21. Heisler M, Hogan MM, Hofer TP, Schmittdiel JA, Pladevall M, Kerr EA. When more is not better: treatment intensification among hypertensive patients with poor medication adherence. *Circulation.* 2008;117(22):2884-2892.
22. Williams LK, Peterson EL, Wells K, et al. A cluster-randomized trial to provide clinicians inhaled corticosteroid adherence information for their patients with asthma. *JAllergy ClinImmunol.* 2010;126(2):225-231, 231.
23. Vollmer WM, Feldstein A, Smith DH, et al. Use of health information technology to improve medication adherence. *The American journal of managed care.* 2011;17(12 Spec No.):Sp79-87.
24. Dixon BE, Alzeer AH, Phillips EO, Marrero DG. Integration of Provider, Pharmacy, and Patient-Reported Data to Improve Medication Adherence for Type 2 Diabetes: A Controlled Before-After Pilot Study. *JMIR medical informatics.* 2016;4(1):e4.
25. Schectman JM, Schorling JB, Nadkarni MM, Voss JD. Can prescription refill feedback to physicians improve patient adherence? *Am J Med Sci.* 2004;327(1):19-24.
26. Yousif A, Lemière C, Cartier A, Forget A, Blais L. Development of a graphical tool to measure medication adherence in asthma patients: A mixed-methods pilot study. *Journal of Asthma.* 2019;56(5):543-552.
27. de Grood C, Raissi A, Kwon Y, Santana MJ. Adoption of e-health technology by physicians: a scoping review. *J Multidiscip Healthc.* 2016;9:335-344.
28. RQRM. reMed : Data Registry for Prescribed Medications / Banque de données sur les médicaments d'ordonnance. www.rqrm.ca/plateformes/optimisation-de-l-usage/64-4-remed-data-registry-for-prescribed-medications-banque-de-donnees-sur-les-medicaments-d-ordonnance.html.
29. Kroll T, Neri M. Designs for mixed methods research. *Mixed methods research for nursing and the health sciences.* 2009;31.
30. Nau DP. Proportion of days covered (PDC) as a preferred method of measuring medication adherence. *Springfield, VA: Pharmacy Quality Alliance.* 2012.
31. Karve S, Cleves MA, Helm M, Hudson TJ, West DS, Martin BC. Good and poor adherence: optimal cut-point for adherence measures using administrative claims data. *Current medical research and opinion.* 2009;25(9):2303-2310.
32. Blais L, Beauchesne M-F, Lévesque S. Socioeconomic status and medication prescription patterns in pediatric asthma in Canada. *Journal of Adolescent Health.* 2006;38(5):607.e609-607.e616.
33. Global Initiative for Asthma. Pocket Guide for Asthma Management and Prevention. 2018; https://ginasthma.org/wp-content/uploads/2018/03/wms-GINA-main-pocket-guide_2018-v1.0.pdf.
34. Blais L, Beauchesne MF, Rey E, Malo JL, Forget A. Use of inhaled corticosteroids during the first trimester of pregnancy and the risk of congenital malformations among women with asthma. *Thorax.* 2007;62(4):320-328.
35. Martel M-J, Rey É, Beauchesne M-F, et al. Use of inhaled corticosteroids during pregnancy and risk of pregnancy induced hypertension: nested case-control study. *BMJ.* 2005;330(7485):230.

36. Boulet L-P, Becker A, Bérubé D, Beveridge R, Ernst P. Summary of recommendations from the Canadian asthma consensus report, 1999. *Canadian Medical Association Journal.* 1999;161(11 suppl 2):S1-S12.
37. Park JYE, Li J, Howren A, Tsao NW, De Vera M. Mobile Phone Apps Targeting Medication Adherence: Quality Assessment and Content Analysis of User Reviews. *JMIR Mhealth Uhealth.* 2019;7(1):e11919-e11919.
38. Sloan CD, Gebretsadik T, Wu P, Mitchel EF, Hartert TV. Reactive versus proactive patterns of inhaled corticosteroid use. *Annals of the American Thoracic Society.* 2013;10(2):131-134.
39. Dima AL, Hernandez G, Cunillera O, Ferrer M, de Bruin M. Asthma inhaler adherence determinants in adults: systematic review of observational data. *European Respiratory Journal.* 2015;45(4):994.
40. Bourbeau J, Bartlett SJ. Patient adherence in COPD. *Thorax.* 2008;63(9):831-838.
41. Wilhelmsen NC, Eriksson T. Medication adherence interventions and outcomes: an overview of systematic reviews. *European Journal of Hospital Pharmacy.* 2019;26(4):187.
42. Stream GR. Trends in adoption of electronic health records by family physicians in Washington State. *Informatics in primary care.* 2009;17(3):145-152.
43. Kaushal R, Bates DW, Jenter CA, et al. Imminent adopters of electronic health records in ambulatory care. *Informatics in primary care.* 2009;17(1):7-15.
44. Thorn SA, Carter MA, Bailey JE. Emergency physicians' perspectives on their use of health information exchange. *Ann Emerg Med.* 2014;63(3):329-337.
45. Valdes I, Kibbe DC, Tolleson G, Kunik ME, Petersen LA. Barriers to proliferation of electronic medical records. *Informatics in primary care.* 2004;12(1):3-9.
46. Leu MG, O'Connor KG, Marshall R, Price DT, Klein JD. Pediatricians' use of health information technology: a national survey. *Pediatrics.* 2012;130(6):e1441-1446.
47. Engelkes M, Janssens HM, de Jongste JC, Sturkenboom MC, Verhamme KM. Medication adherence and the risk of severe asthma exacerbations: a systematic review. *The European respiratory journal.* 2015;45(2):396-407.
48. Salmon P, Peters S, Rogers A, et al. Peering through the barriers in GPs' explanations for declining to participate in research: the role of professional autonomy and the economy of time. *Family practice.* 2007;24(3):269-275.

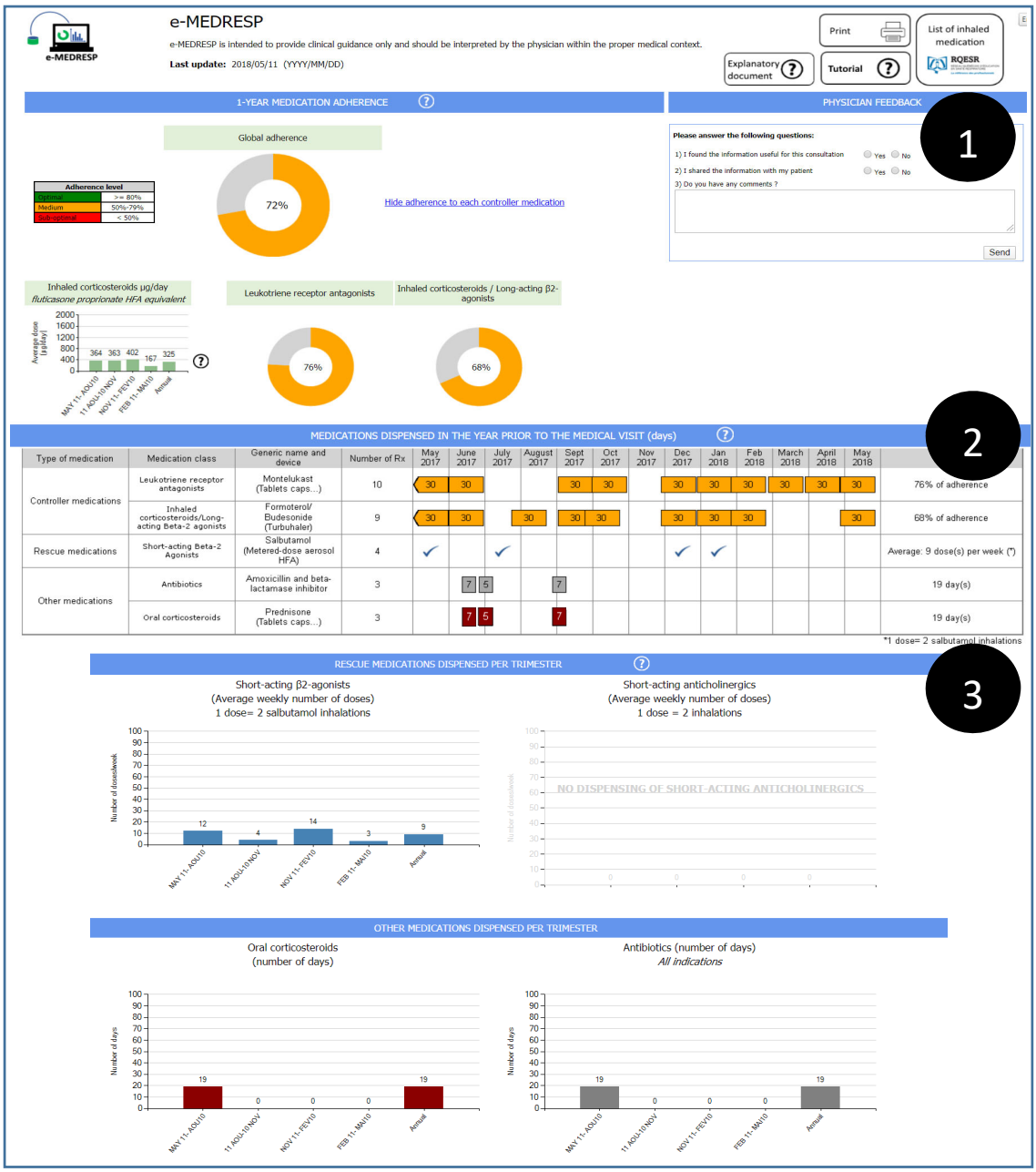


Figure 1. Example of an e-MEDREP report for an asthma patient.

Section 1 displays the adherence to all asthma and COPD controller medications dispensed in community pharmacies in the year prior to the medical visit, presented as a percentage. **Section 2** provides an overview of all asthma and COPD medications dispensed in community pharmacies in the prior year. Dates and duration of refills, as well as generic names of medications, are provided. **Section 3** presents the use of rescue medications, oral corticosteroids, and antibiotics dispensed in the prior year, per trimester.

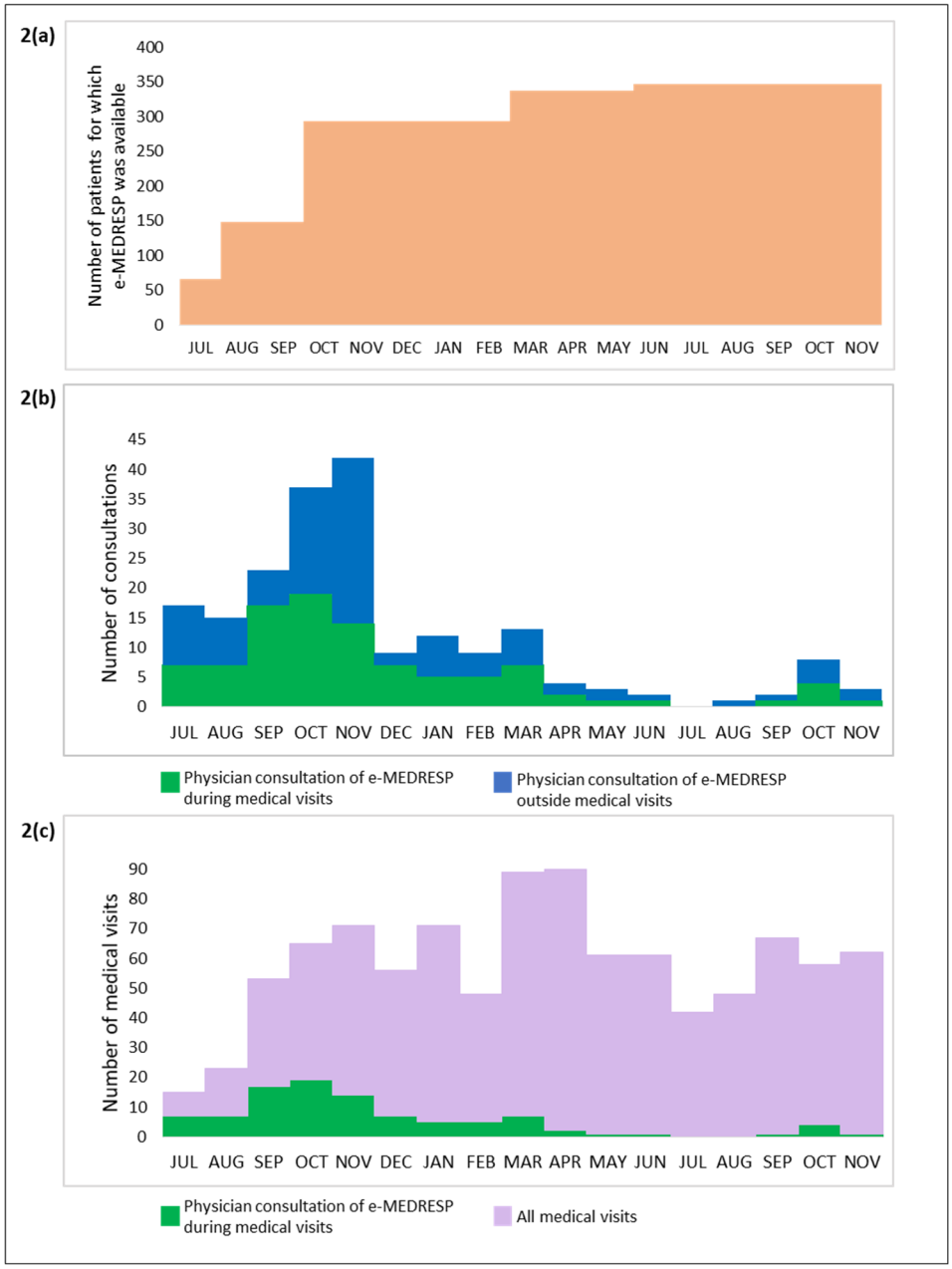


Figure 2. Physician use of e-MEDRESP throughout the study period

2a. Progressive implementation of e-MEDRESP in the EMR. In total there were 7 phases of implementation which occurred between July 2019 and June 2020. **2b. Physician use of e-MEDRESP throughout the study.** Graphical representation of number of consultations of e-MEDRESP on a monthly basis, during or outside medical visits. **2c. Medical visits in which e-MEDRESP was consulted.** Graphical representation of number of consultations of e-MEDRESP during medical visits on a monthly basis. Of note, medical visits displayed in (2b) and (2c) corresponded to clinical encounters for any cause.

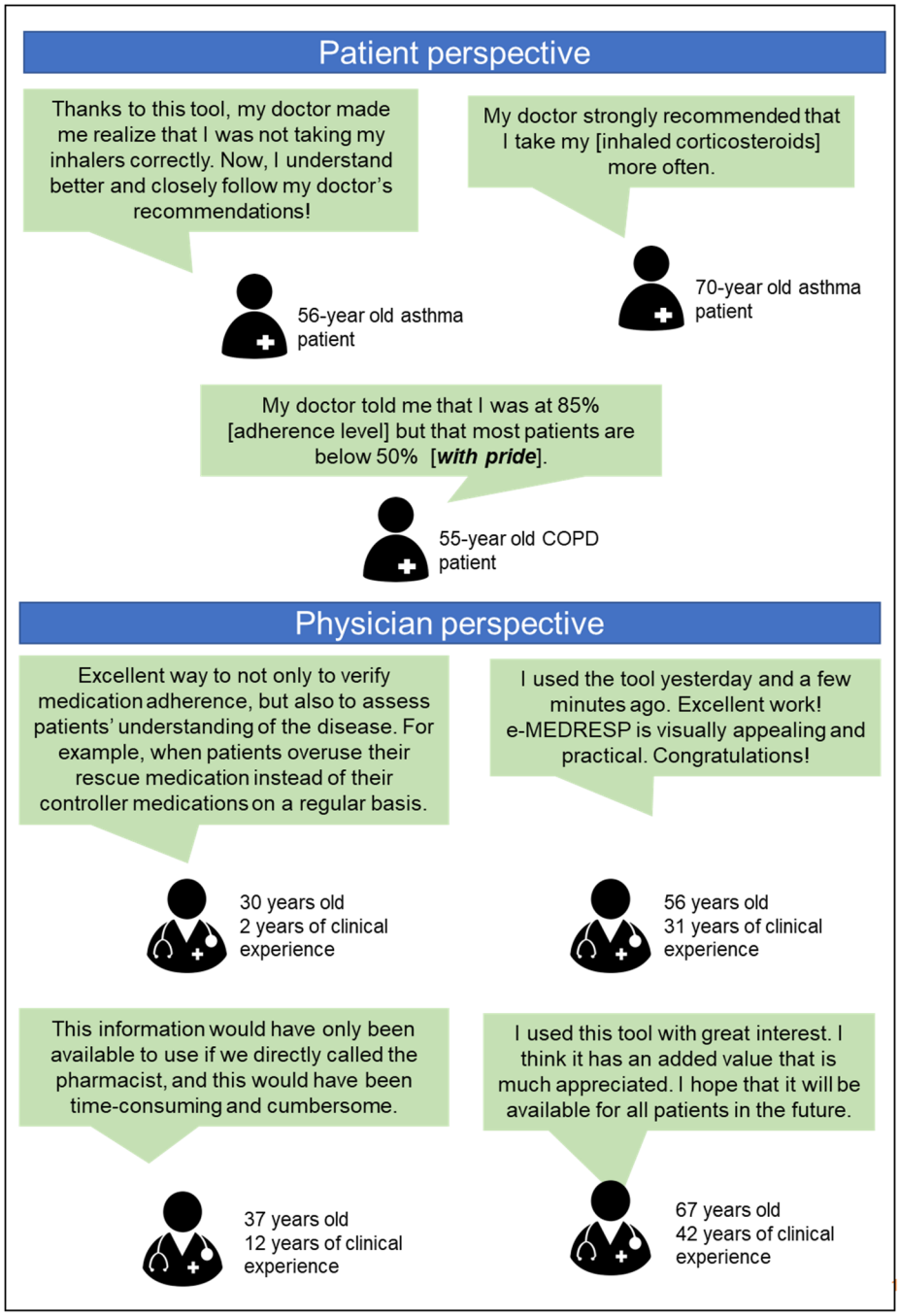


Figure 3. Physician and patient testimonies on e-MEDRESP

Table 1. Patient characteristics upon recruitment and medication use in the year prior to cohort entry (n=346)

Characteristics	All (n=346)	Asthma (n=188)	COPD (n=131)	Concurrent asthma/COPD (n=27)
Characteristics upon recruitment, as recorded in the reMed database n (%)				
Age in years, mean ± sd	59.2 ± 16.8	50.8 ± 17.08	69.6 ± 9.5	67.3 ± 10.8
Female	205 (59.2)	121 (64.4)	66 (50.4)	18 (66.7)
Smoking status				
Non-smoker	103 (29.8)	87 (46.3)	13 (9.2)	3 (11.1)
Previous smoker	161 (46.5)	71 (37.8)	75 (57.3)	15 (55.6)
Smoker	76 (22.0)	26 (13.8)	41 (31.3)	9 (33.3)
Missing values	6 (1.7)	4 (2.1)	2 (1.5)	0
Level of physical activity				
None	104 (30.1)	44 (23.3)	51 (38.9)	9 (33.3)
Low	146 (42.2)	89 (47.3)	50 (38.2)	7 (25.9)
Moderate	47 (13.6)	25 (13.3)	18 (13.7)	4 (14.8)
High	22 (6.4)	19 (10.1)	2 (1.5)	1 (3.7)
Missing	27 (7.8)	11 (5.9)	10 (7.6)	6 (22.2)
Variables related to implementation of e-MEDRESP in EMR, n (%)				
Duration of follow-up in days				
90-179	9 (2.6)	7 (3.7)	1 (0.8)	1 (3.7)
180-364	44 (12.7)	28 (14.9)	15 (11.5)	1 (3.7)
≥365	293 (84.7)	153 (81.4)	115 (87.8)	25 (92.6)
Median (Interquartile range)	416.0 (399.0-461.0)	399.0 (399.0-461.0)	461.0 (399.0-461.0)	461.0 (399.0-503.0)4
Number of medical visits during study follow-up				
None	94 (27.2)	60 (31.9)	30 (22.9)	4 (14.8)
1	69 (19.9)	41 (21.8)	22 (16.8)	6 (22.2)
2-4	112 (32.4)	55 (29.3)	46 (35.1)	11 (40.8)
5-8	42 (12.1)	15 (8.0)	22 (16.8)	5 (18.5)
>8	29 (8.4)	17 (9.0)	11 (8.4)	1 (3.7)
Mean ± sd (among patients who had at least one visit)	2.6 ± 2.9	2.6 ± 3.0	3.0 ± 3.0	2.7±2.0
Adherence to controller medications among users, one year prior to cohort entry* n (%), Mean PDC** **±** sd				
Inhaled corticosteroids + long-acting β2-agonists	154 (44.5) 51.6 ± 28.3	99 (52.7) 45.7 ± 27.1	41 (31.3) 60.4 ± 28.3	14 (51.9) 66.6 ± 26.1
Inhaled corticosteroids	115 (33.2) 36.1 ± 26.5	74 (39.3) 38.3 ± 28.3	31 (23.7) 32.6 ± 24.9	10 (37.0) 30.8 ± 15.3
Long-acting muscarinic agents	94 (27.2) 68.0 ± 28.5	8 (4.3) 50.5 ± 30.8	76 (58.0) 69 ± 28	10 (41.7) 74.3 ± 28.3

Characteristics	All (n=346)	Asthma (n=188)	COPD (n=131)	Concurrent asthma/COPD (n=27)
Leukotriene antagonist receptors	37 (10.7) 76.2 ± 25.9	30 (16.0) 76.3 ± 26.7	6 (4.6) 74.7 ± 25.9	1 (3.7) 83 ± -
Long-acting muscarinic agents + long-acting β2 agonists	32 (9.2) 81.1 ± 23	-	32 (24.4) 81.1 ± 23	-
Long-acting β2-agonists	14 (9.2) 52.6 ± 36.7	4 (21.3) 73.5 ± 32.7	8 (6.1) 47.1 ± 39.6	2 (7.4) 33 ± 24
Inhaled corticosteroids + long-acting muscarinic agents + long-acting β2-agonists	55 (15.9) 89.6 ± 14	-	55 (42.0) 89.6 ± 14	-
Use of inhaled corticosteroids (ICS), one year prior to cohort entry*				
Patients with at least one ICS prescription (alone or in combination), n (%)	234 (67.6)	148 (78.7)	66 (50.4)	20 (74.0)
Mean daily ICS dose (µg/day[†]) ± sd	226.5 ± 185	191.1 ± 174.1	287 ± 201.3	289.1 ± 140.8
Use of rescue medications and oral corticosteroids, one year prior to cohort entry*				
Mean weekly doses of short-acting β2-agonists (salbutamol eq.), n (%)				
None	187 (54.0)	107 (56.9)	70 (53.4)	10 (37.0)
<4	54 (15.6)	30 (16.0)	15 (11.4)	9 (33.3)
≥4	105 (30.3)	51 (27.1)	46 (33.6)	8 (29.7)
Patients with at least one oral corticosteroid prescription	64 (18.5)	22 (11.7)	31 (23.6)	14 (51.9)

* Cohort entry corresponded to the date of implementation of e-MEDRESP in EMR

** A modified version of the PDC, which takes into consideration treatment initiation was used. Adherence calculation details are presented in the supplementary materials (S1).

[†] When applicable, inhaled corticosteroid doses were converted to fluticasone propionate HFA equivalent. Doses were calculated for all patients who were taking at least one ICS-containing medication.

Table 2. Characteristics of family physicians who used e-MEDRESP at least once during the study (n=15)

Physician characteristics after first use of e-MEDRESP	**n (%)***
Age in years, mean ± standard deviation	47.4 + 15.9
Women	9 (60.0)
Number of years of practice in family medicine	
<5	5 (33.3)
5-14	3 (20.0)
15-34	2 (13.3)
≥35	5 (33.3)
Practice region	
Urban	6 (40.0)
Rural	9 (60.0)
Approximate number of patients with asthma or COPD seen per month	
<10	4 (26.7)
10-20	7 (46.7)
>20	1 (6.7)
Missing	3 (20.0)
Patients with respiratory diseases most commonly seen in clinical practice	
COPD	6 (40.0)
Asthma	1 (7.1)
Equal number of asthma and COPD patients	5 (33.3)
Missing	3 (20.0)
Number of patients enrolled in the study	
<10	5 (33.3)
10-20	3 (20.0)
21-30	4 (26.7)
>30	3 (20.0)
Duration of study follow-up in days **	
Median (interquartile range)	438.5 (416.0-461.0)

Abbreviations: COPD: Chronic obstructive pulmonary disease

* Unless otherwise specified

**This period corresponds to the time between the time of implementation (first time e-MEDRESP was available in EMR) to end of study (November 2020).

Table 3. Consultations of e-MEDRESP by physicians since cohort entry

Variables related to medical visits	**First consultation of e-MEDRESP* (n=133)** n (%)	**Consultations of e-MEDRESP throughout the study follow-up* (n=202)** n (%)
Number of days since cohort entry**		
<60	93 (69.9)	120 (59.4)
61-180	18 (13.5)	48 (23.8)
181-365	12 (9.0)	23 (11.4)
≥ 365	10 (7.5)	11 (5.5)
Mean ± sd	78.3 ± 113.3	78.3 ± 113.3
Type of clinical encounter		
Annual exam	7 (5.3)	7 (3.5)
Urgent/walk-in visit	14 (10.7)	19 (9.4)
Telehealth	6 (4.5)	7 (3.5)
Appointment at the clinic	43 (32.3)	50 (24.8)
Type of clinical encounter unknown	15 (11.3)	17 (8.4)
Outside a medical visit	48 (36.0)	102 (50.5)
Reason for clinical encounter		
Respiratory-Related	5 (3.8)	6 (3.0)
Other	19 (14.3)	23 (11.4)
Not available	61 (45.9)	71 (35.1)
Outside a medical visit	48 (36.1)	100 (49.5)
Season		
Winter	18 (13.7)	33 (16.3)
Spring	2 (1.5)	10 (5.0)
Summer	35 (26.7)	49 (24.3)
Fall	78 (58.7)	110 (54.5)

* Per patient

** Cohort entry corresponds to the date of implementation of e-MEDRESP in EMR

Table 4 Physician baseline evaluation of e-MEDRESP: Perceived usefulness & usability

Items evaluated	BASELINE (n=12)		END OF STUDY (n=13)	
	Physician rating Mean ± Sd	**% Agree or strongly agree,** n (%)	Physician rating Mean (Sd)	**% Agree or strongly agree,** n (%)
Perceived usefulness (1=Strongly disagree, 5=Strongly agree)				
1. e-MEDRESP is generally useful to your clinical practice.	4.8 ± 0.5	12 (100.0)	4.4 ± 0.8	11 (84.6)
2. e-MEDRESP helps you better evaluate your patients' respiratory medication use.	4.8 ± 0.6	11 (91.7)	4.5 ± 0.7	12 (92.3)
3. e-MEDRESP helps you better adjust the doses of the prescribed respiratory medications.	4.3 ± 0.9	9 (75.0)	3.9 ± 0.6	10 (76.9)
4. e-MEDRESP facilitates the communication with your patient concerning his/her use of respiratory medications.	4.8 ± 0.5	9 (75.0)	4.3 ± 0.5	11 (84.6)
5. e-MEDRESP helps you save time.	4.0 ±0.9	8 (66.7)	3.7 ± 0.9	7 (53.8)
6. You intend to continue to use e-MEDRESP.	4.8 ± 0.4	12 (100.0)	N/A	N/A
7. You intend to recommend e-MEDRESP to your colleagues.	4.6 ± 0.8	10 (83.3)	4.3 ± 0.8	11 (84.6)
Usability scale – Content and format of e-MEDRESP (1=Strongly disagree, 5=Strongly agree)				
8. The use of color facilitates the interpretation of the information presented in e-MEDRESP.	4.7 ± 0.7	11 (91.7)	4.7 ± 0.5	13 (100.0)
9. The section presenting the adherence level to controller medication is easy to interpret.	4.8 ± 0.5	12 (100.0)	4.7 ± 0.5	13 (100.0)
10. The calendar which provides an overview of the respiratory medications dispensed in the prior year is easy to interpret.	4.7 ± 0.7	11 (91.7)	4.0 ± 0.8	11(84.6)
11. The bar chart illustrating the pattern of dispensing of rescue medications is easy to interpret.	4.5 ± 0.7	11 (91.7)	4.5 ± 0.7	12 (92.3)
12. The bar chart presenting the pattern of dispensing of oral corticosteroids per trimester is easy to interpret.	4.5 ± 0.8	10 (83.3)	4.6 ± 0.5	13 (100.0)
13. The bar chart presenting the pattern of dispensing of antibiotics per trimester is easy to interpret.	4.6 ± 0.7	11 (91.7)	4.5 ± 0.7	12 (92.3)

Table 5. Assessment of differences in medication adherence and disease control over a six-month period after first consultation of e-MEDRESP by a physician during a medical visit

Asthma/COPD respiratory medications	**n**	**6 months prior to consultation**	**6 months after consultation**	**Mean Difference (post-pre) (95% CI)**
		Mean ± sd	Mean ± sd	
Adherence to controller medications (PDC) among patients who took at least one controller medication (n=63)*				
Inhaled corticosteroids + long-acting β2 agonists combination therapy	32	69.3 ± 24.5	69.7 ± 28.3	0.3 (-8.7 to 9.3)
Inhaled corticosteroids monotherapy	10	56.7 ± 29.5	67.9 ± 14.9	11.2 (-8.7 to 31.1)
Leukotriene receptor antagonists	13	88.9 ± 13.1	80.8 ± 23.7	-8.2 (-21.5 to 5.3)
Long-acting muscarinic agents	19	78.4 ± 25.5	80.8± 24.1	2.4 (-12.4 to 17.3)
Long-acting β2-agonists + Long-acting muscarinic agents	8	88.4 ± 13.5	84.5 ± 25.1	-3.9 (-19.8 to 11.9)
Adherence to controller medications, among patients whose PDC was less than 80% during first consultation of e-MEDRESP (PDC)* (n=36)				
Inhaled corticosteroids + long-acting β2 agonists combination therapy	21	56.0 ± 18.8	62.3 ± 29.5	6.3 (-5.2 to 17.9)
Inhaled corticosteroids monotherapy	7	41.7 ± 20.2	68.6 ± 16.4	26.9 (14.3 to 39.3)[†**]
Long-acting muscarinic agents	8	52.8 ± 18.5	79.1 ± 21.9	26.4 (12.6 to 40.2)[†]
Leukotriene receptor antagonists	2	63.5 ± 0.7	69.0 ± 25.5	5.5 (-216.9 to 227.9)
Long-acting β2-agonists + Long-acting muscarinic agents	3	72.3 ± 2.9	66.0 ± 35.7	-6.3 (-87.8 to 75.2)
Proxies of disease control: use of rescue medications or oral corticosteroids (n=79)				
Mean weekly short-acting β2-agonist dose (salbutamol eq.), n (%)				
None		39 (49.4)	32 (40.5)	
<4		15 (19.0)	23 (29.1)	
≥4		25 (31.7)	24 (30.4)	
Mean ± sd		4.7 ± 7.3	4.7 ± 7.2	0.0 (-0.9 to 0.9)
Oral corticosteroids, number of prescriptions less than 14 days				
None		68 (86.1)	70 (88.6)	
1		7 (8.9)	4 (5.06)	
>1		4 (5.1)	5 (6.3)	0.0 (-0.6 to 0.6)
Mean ± sd		0.2± 0.6	0.2 ± 0.5	
Use of rescue medications or oral corticosteroids, among patients with uncontrolled disease during first consultation of e-MEDRESP (n=30) [††]				
Mean weekly short-acting β2-agonist dose (salbutamol eq.), n (%)				
None		19 (63.3)	25 (83.3)	
<4		7 (23.3)	2 (6.7)	
≥4		4 (13.3)	3 (10.0)	
Mean ± sd		11.7 ± 7.9	10.3 ± 9.0	-1.4 (-3.6 to 0.9)
Oral corticosteroids, number of prescriptions less than 14 days				

None	18 (64.3)	22 (78.6)	
1	6 (21.4)	2 (7.1)	
>1	4 (14.3)	4 (14.2)	
Mean ± sd	0.4 ± 0.8	0.5 ± 0.7	-0.2 (-0.5 to 0.14)

*Adherence was assessed for medications that were prescribed both before and after the visit with access to e-MEDRESP. A modified version of the PDC, which takes into consideration treatment initiation was used. Details on PDC calculations are presented in the supplementary materials. Therefore, the analysis was only conducted in patients who took the same controller medication in both evaluation periods

** *p-value* < 0.05

†*p*-value < 0.01

†† Patients were considered uncontrolled if they had a mean weekly short-acting β2-agonist dose (salbutamol eq.) greater than 4 or at least 1 prescription filled of oral corticosteroids in the 6 months prior to the consultation of e-MEDRESP

4.2.1 Second Article: Supplementary Materials

Feasibility of Implementing a Web-based Tool Built from Pharmacy Claims Data (e-MEDRESP) to Monitor Adherence to Asthma/COPD Medications in Primary Care

Electronic supplementary material

S1: Adherence calculations – Explanations

S2: Participant recruitment flow chart

S3: Medical visits in which e-MEDRESP was accessible to participating physicians (n=19)

S4. Physician use of e-MEDRESP since beginning of study, according to patient diagnosis

S5. Post hoc survey to better understand the clinical relevance of e-MEDRESP during the COVID-19 pandemic

S1. Adherence calculations – Explanations

Adherence calculation for the baseline characteristics (Table 1)

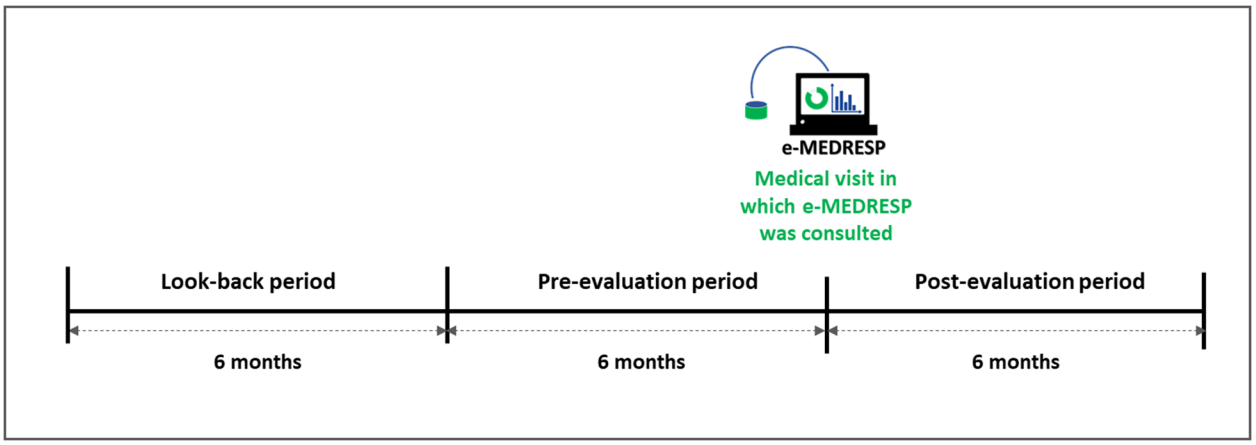
- Adherence was calculated for each medication class, using a modified PDC that took into consideration treatment initiation.
- Since all participants were prevalent users and details on physician prescriptions were not available, it was assumed that patients newly initiated their treatment if the first fill occurred within the 6 months prior to cohort entry (implementation of e-MEDRESP in EMR)
- Thus, if the first fill was within the six months period prior to cohort entry, then the PDC corresponded to the total days' supply divided by the date of cohort entry minus the date of the first filling. Otherwise, the PDC corresponded to the total days' supply divided by 365 days.

Adherence calculation in the exploratory pre-post analyses (Table 5)

Similar to Table 1, adherence was calculated for each medication class, using a modified PDC that took into consideration treatment initiation. In contrast, the PDC corresponded to the total days' supply divided by a denominator that was determined by the treatment initiation, as explained below.

For simplification purposes, the following variables denote the periods which were considered in the calculations:

- **Pre-evaluation period:** 6 months prior the date of the first medical visit in which e-MEDRESP was consulted;
- **Post-evaluation period:** 6 months following to date of the first medical visit in which e-MEDRESP was consulted;
- **Look-back period**: 6 months prior to the pre-evaluation period.



1. In our analysis, we only included patients for whom medications belonging to the same class were filled at least once in the **pre-evaluation period** and in the **post-evaluation.**
2. If there was at least one fill in the **look-back period** and in **pre-evaluation period,** then the denominator of the PDC of the pre-evaluation period corresponded to 6 months.
3. If there was no dispensing in the **look-back period**, then it was assumed that a new treatment was initiated in the **pre-evaluation period**. For those cases, the denominator corresponded to the date of the **medical visit** minus the date of the first filling in the **pre-evaluation period**. In our analysis which included 79 patients, only one patient initiated the treatment in the pre-evaluation period. The mean duration of the pre-evaluation period was 179.6 ± 12.5.
4. The denominator in the post-evaluation period corresponded to 6 months for all patients.

S2. Participant recruitment flow chart

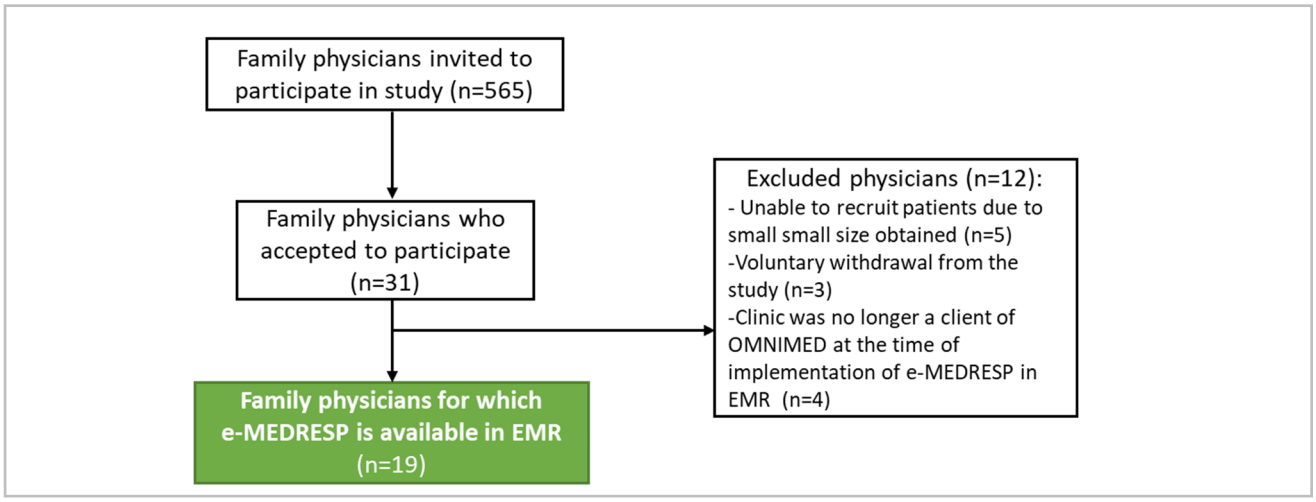


Figure S1.1 Family physician recruitment

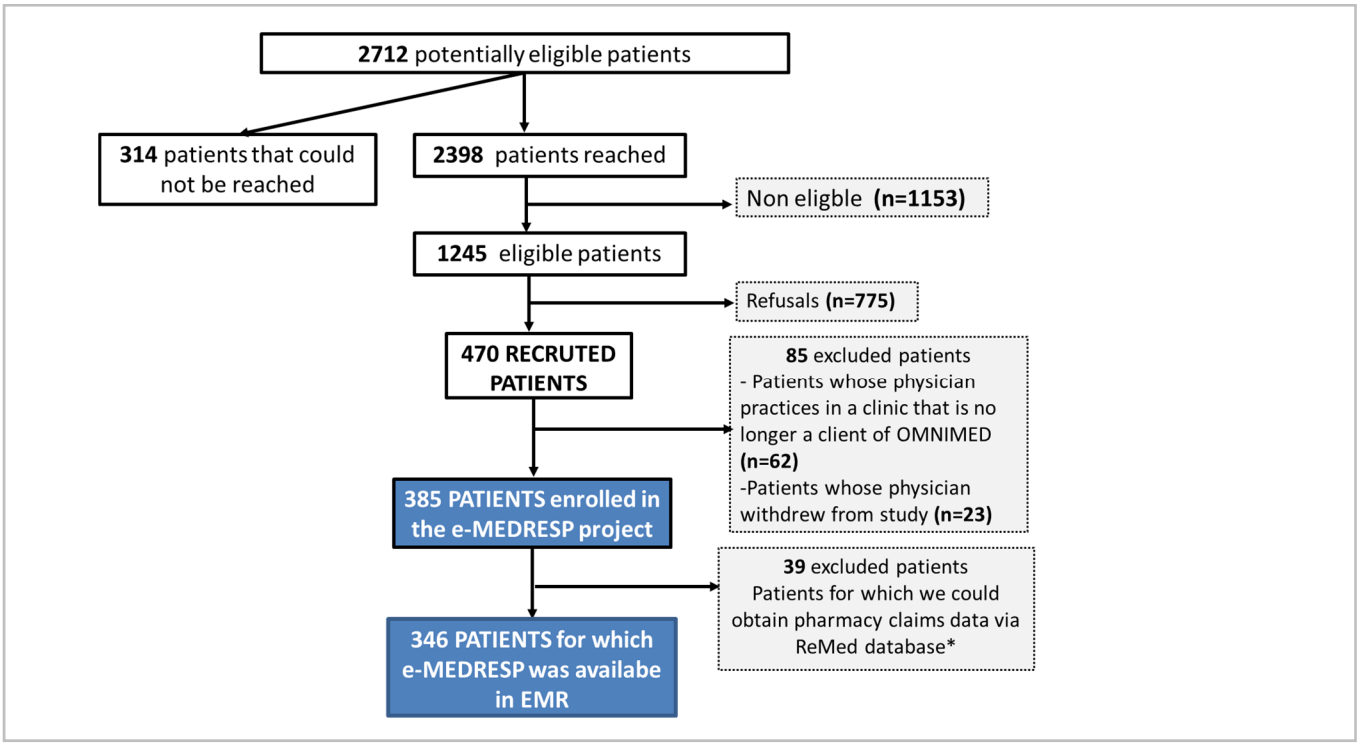


Figure S1.2 Patient recruitment

*Patients had to be excluded because we could not obtain their pharmacy claims data via the reMed database. Possible reasons for this occurrence include:

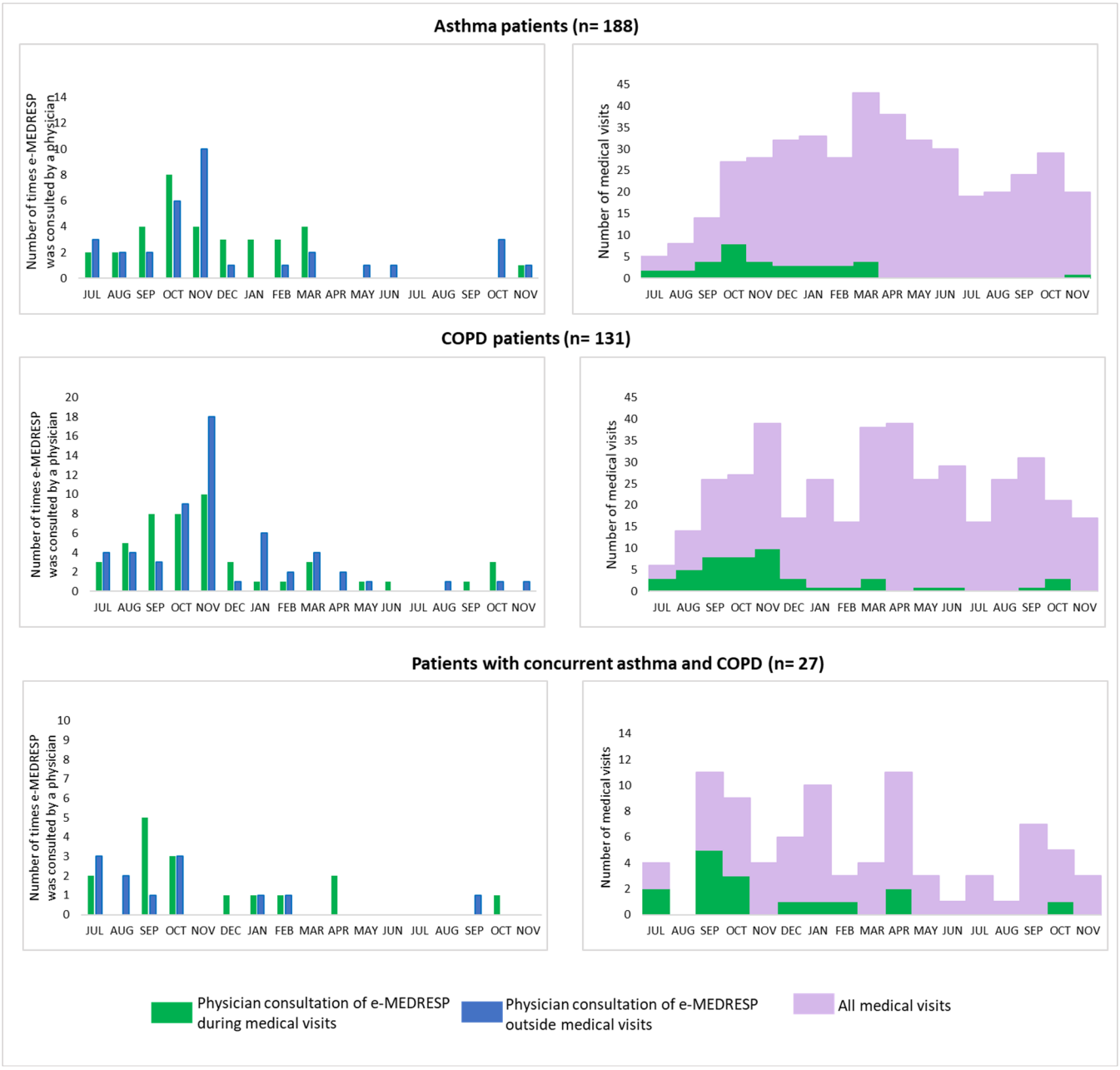
- Death of patient prior to cohort entry
- Non-eligible pharmacy reMed obtains data on prescriptions refills from the IT service providers of the pharmacies. At the moment, there are two IT providers (namely PrioRx and ReFlex Rx) that do not participate in the reMed database.
- IT logistical problems, e. g. the link between reMed and the IT service provider of pharmacies for some patients could not be made. For example, this problem could occur if the patient does not provide the right medical insurance number upon registration in reMed.

S3. Medical visits in which e-MEDRESP was accessible to participating physicians (n=19)

	Participating physicians n (%)
Number of medical visits in which the physician had the opportunity to access e-MEDRESP*	
Less than 10	4 (21.1)
10-19	6 (31.6)
20-49	2 (10.5)
≥ 50	7 (36.8)
Number of patients who had at least one medical visit during the study	
Less than 10	11 (57.9)
10-19	4 (21.1)
20-49	3 (15.8)
≥ 50	1 (5.3)

* A patient can have more than one medical visit

S4. Physician use of e-MEDRESP since beginning of study, according to patient diagnosis



S5. Post hoc survey to better understand the clinical relevance of e-MEDRESP during the COVID-19 pandemic

Survey was distributed in May 2020. 14/19 (74%) physicians completed the questionnaire.

Table S3.1 Questions regarding consults conducted since the beginning of the pandemic

		% time devoted in clinical practice, n (%)					
		0%	**1-24%**	**25-49%**	**50-74%**	**75-99%**	**100%**
Since March 14 2020, what modalities to do you use to perform medical consults with your patients?	Telephone consults	0 (0.0)	0 (0.0)	1 (7.1)	7 (50.0)	4 (28.6)	2 (14.3)
	Videoconference consults	14 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	In-person visits at the clinic	3 (21.4)	5 (35.7)	6 (42.9)	0 (0.0)	0 (0.0)	0 (0.0)
Do you currently have access to the OMNIMED EMR, as well as all its functionalities during your consults? *	During telephone consults	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	13
	During videoconference consults	12 (85.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (14.3)
	In-person visits at the clinic	2 (14.3)	0 (0.0)	1 (7.1)	0 (0.0)	0 (0.0)	11 (78.6)
What types of medical consults do you do with your patients? **	Consults without appointments (emergency)	4 (28.6)	6 (42.9)	2 (14.3)	1 (7.1)	0 (0.0)	0 (0.0)
	Consults with appointment	0 (0.0)	2 (14.3)	3 ()	6 (42.9)	3 (21.4)	0 (0.0)
	Annual exams	3 (21.4)	10 (7.1)	1 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Follow-up of tests and lab results	1 (7.1)	9	3 (21.4)	0 (0.0)	1 (7.1)	0 (0.0)

* 3 physicians reported doing home visits (5% of the time); 1 physician reported only doing teleconsultations since she was at her third pregnancy trimester

**One physician reported doing more consults related to mental health care

Table S3.2 General questions on use of e-MEDRESP during the COVID-19 pandemic and future intent to use tool

	n (%)
Please describe your use of the e-MEDRESP tool since the beginning of the pandemic Increase in use Decrease in use* No change in use	 1 (7.1) 3 (21.4) 10 (71.5)
In the next few weeks, do you intend on using the e-MEDRESP tool if you have a consult with one of the participating patients of the e-MEDRESP project? Yes No	 12 (85.7) 2 (14.3)

*Two physicians reported that they had to modify their practice to adapt to the unusual circumstances surrounding the pandemic (emergency and mental-health related consults) and one physician reported that he did not have medical consults in which he felt the need to use the tool.

Key take-aways

- All physicians had access to e-MEDRESP during the pandemic, including during telephone consults.
- The majority of physicians intended to continue to use e-MEDRESP after completing the survey.
- Reasons which may explain decrease of use of e-MEDRESP during the COVID-19 pandemic:
  - A decrease number of respiratory-related medical visits (more emergencies, mental health-related consults)
  - Modification of practice to better adapt to circumstances surrounding the public health practice (more telehealth consultations, shorter duration of consults, less medical visits overall, etc.)
  - Personal circumstances which may decrease the number of consults done overall (e.g. pregnancy

4.3 Third Article: Systematic Review of Diagnostic Algorithms to Identify Asthma Patients in Healthcare Administrative Databases

The Validity of Diagnostic Algorithms to Identify Asthma Patients in Healthcare Administrative Databases: A Systematic Literature Review

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Declaration of interest

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Abstract

Objectives: To review the available evidence supporting the validity of algorithms to identify asthma patients in healthcare administrative databases.

Methods: A systematic literature search was conducted on multiple databases from inception to March 2020 to identify studies that reported the validity of case-finding asthma algorithms applied to healthcare administrative data. Following an initial screening of abstracts, two investigators independently assessed the full text of studies which met the pre-determined eligibility criteria. Data on study population and algorithm characteristics were extracted. A revised version of the **Qu**ality **A**ssessment of **D**iagnostic **A**ccuracy **S**tudies tool was used to evaluate the risk of bias and generalizability of studies.

Results: Twenty studies met the eligibility criteria. Algorithms which incorporated ≥1 diagnostic code for asthma over a one-year period appeared to be valid in both adult and pediatric populations; (sensitivity≥85%; specificity≥89%; PPV≥70%). The validity was enhanced when: 1) the time frame to capture asthma cases was increased to two years; 2) ≥2 asthma diagnoses were considered; and 3) when diagnoses were recorded by a pulmonologist. Algorithms which integrated pharmacy claims data appeared to correctly identify asthma patients; however, the extent to which asthma medications can improve the validity remains unclear. The quality of several studies was high, although disease progression bias and biases related to self-reported data was observed in some studies.

Conclusions: Healthcare administrative databases are adequate sources to identify asthma patients. More restrictive definitions based on both asthma diagnoses and asthma medications may enhance validity, although further research is required to confirm this hypothesis.

Key words: asthma, validation, diagnostic algorithms, administrative databases.

INTRODUCTION

Asthma is a major non-communicable disease characterized by variable symptoms of wheezing, breathlessness, chest tightness or cough, and by reversible expiratory airflow limitation (1, 2). With over 334 million individuals affected worldwide, asthma has become an important public health issue and a leading cause of chronic morbidity, especially among children (2).

To inform health policy and advance therapeutic research in asthma and other chronic diseases, healthcare administrative databases have been widely used in epidemiologic studies and post-marketing drug safety and effectiveness research (3-7). These data sources are preferred over more traditional methods of data collection such as questionnaires, as they provide the opportunity to study disease burden and trajectories in large populations, as well as study rare outcomes, including mortality and hospitalizations, using real-world data (8, 9). Additionally, information in administrative databases do not rely on patient self-report, thereby eliminating the possibility of recall bias (10). However, since these data are primarily used for billing purposes and are a by-product of complex and evolving healthcare systems, there is a concern that misclassification of clinical information may introduce bias. In this context, it is crucial to assess the validity of these data sources for research (11).

Identifying a sample of patients in whom asthma has been diagnosed as accurately as possible is arguably one of the most important first steps in conducting rigorous epidemiologic research (12). In an effort to assess the value of healthcare data for secondary research on asthma, Nissen *et al.* conducted a systematic review on the current methods used to validate asthma diagnoses in electronic health records (EHR) (13), while Sharifi *et al.* reviewed validation methods to capture asthma exacerbations in administrative data (14). To the best of our knowledge, the validity of the existing asthma diagnosis case definitions applied to healthcare administrative data have not yet been synthesized. Indeed, the past two decades have witnessed an explosion in asthma research conducted using healthcare administrative data and it is crucial to identify the case-finding algorithms which have a better overall performance in terms of distinguishing individuals who actually have asthma and those who do not. The aim of this study was thus to conduct a systematic literature review to identify studies that have validated asthma case-finding algorithms applied to healthcare administrative data. A critical appraisal of each study was conducted alongside to assess potential sources of bias and generalizability of findings. Our hypothesis is that healthcare administrative databases are an adequate source to capture asthma cases.

METHODS

This study is among a series of systematic reviews of validated methods for identifying various chronic diseases using healthcare administrative data that have been conducted by the Quebec Strategy for Patient-Oriented Research (SPOR) Support Unit, as part of its mandate to implement strategies to facilitate access and use of health data.

Search strategy and selection criteria

To identify relevant articles, we searched the following databases from their inception to November 8, 2018: Medline; PubMed; Embase; CINAHL; AgeLine; PsycINFO; Abstracts in social gerontology; and all Evidence-Based Medicine Reviews (EBM) Reviews. The search strategy encompassed the following concepts: 1) asthma (and related terms such as bronchospasms); 2) validity (specificity, sensitivity, positive predictive value (PPV), negative predictive value (NPV), and receiver operating characteristic (ROC) curves); and 3) healthcare administrative data. Search strategies were developed in collaboration with a librarian and were adapted to each database. The Scopus database was used to update the search on March 2020 through a similar search strategy that was validated by a librarian. A complete list of search terms is found in the electronic supplementary files (Table S1).

For this systematic review, we included studies which: 1) applied at least one asthma diagnostic algorithm to healthcare administrative data; 2) validated the algorithm definition(s) against a reference standard; 3) reported at least one of the following key measures of diagnostic accuracy: sensitivity, specificity, PPV or NPV. Studies were excluded if only kappa values were reported or if regression models were used to identify asthmatic patients. Studies which only reported algorithms that combined asthma and chronic obstructive pulmonary disease (COPD) codes were excluded.

All titles and abstracts were independently screened by two investigators, with the aim of identifying original research papers which fit the pre-specified eligibility criteria. All abstracts identified by either reviewer in the abstract screening phase were then assessed in full text. Disagreements of eligibility were resolved by a third reviewer. As a complement to the systematic review, bibliographies of included articles were manually searched for additional pertinent articles, and those articles were subsequently screened and reviewed using the same method (snowballing) (15). The grey literature was also searched to broaden the scope to more relevant studies and provide a more complete view of available evidence.

Data Extraction

For each retained study, a reviewer extracted the relevant information using a standardized data abstraction form. A second reviewer validated the extracted information by the first reviewer and disagreements were resolved by consensus or by a third reviewer, when necessary. Data elements of interest included: 1) study characteristics (author, year, country); 2) population characteristics (sample size, eligibility criteria); 3) name of administrative database; 4) diagnostic algorithm; 5) reference standard used to identify asthma cases and non-cases; and 6) measures of diagnostic accuracy.

Quality assessment

The **Qu**ality **A**ssessment of **D**iagnostic **A**ccuracy **S**tudies revised tool (QUADAS-2) (16) was used to assess risks of bias and generalisability for each eligible study. Based on the recommendations of Whiting *et al.* (2011) (16) and taking inspiration from the systematic reviews on validated algorithms conducted by Woodfield *et al.* (17), Tan *et al.,* (18) and Van Mourik *et al.* (19), the QUADAS-2 was specifically adapted for case identification algorithms in healthcare administrative databases. Details of the quality assessment domains and criteria are presented in the supplemental file.

RESULTS

The literature search yielded 1019 citations. The number of references assessed and reasons for exclusion are shown in Figure 1. After excluding duplicates, 645 abstracts were reviewed and 62 articles were selected for full-text review. The literature review update resulted in 95 additional citations, of which three were retained for analysis. In total, twenty articles met the eligibility criteria and were retained for analysis; fourteen of which were identified through the electronic database search, and six of which were identified via snowballing (n=5) or the grey literature (n=1).

Table 1 provides an overview of the characteristics of the retained studies. The majority were conducted in Canada (n=8) (12, 20-26) and in the United States (n=6) (27-32); other studies were performed in Italy (33-35), Australia (36), Denmark (37), and the United Kingdom (38). A total of five studies were conducted in pediatric populations (22, 25, 27, 31, 37), seven in adult populations (20, 21, 26, 29, 32, 36, 38), and the other studies included pediatric, adolescent or adult populations (12, 23, 24, 28, 30, 33-35). Among studies which restricted their populations to adults, some studies focused on specific population segments, including women delivering live born infants (32), geriatric individuals (26), patients with multimorbidity (36), and patients who underwent a colectomy (38). The studies were published between 2000 and 2019 and reported on study populations identified between 1994 and 2017.

Quality assessment

Several studies had a good methodological quality. However, studies which used surveys, questionnaires or interviews as the basis for the reference standard (n=7) have potentially introduced bias related to self-reported data, including misclassification bias. Moreover, the validity of several algorithms tested in pediatric populations may have been hampered by the disease progression bias (22, 23, 25, 28, 31, 33-35), which arise when the patient condition changes between administering the index and reference test (39). The quality assessment domains, criteria and results are shown in the supplementary files (Table S2; Figure S1).

Reference standards

In adult populations, reference standards used to distinguish asthma cases from non-cases consisted of clinical case definitions involving: 1) documentation of diagnoses in medical charts, reviewed by either trained chart abstractors or research nurses (12, 30, 32, 38); 2) adjudication of asthma by a physician using the criteria specified in the Expert Panel Report of Guidelines on Asthma (29) or clinical criteria involving a combination of documented diagnoses as well as patient history of wheezing and shortness of breath (33); and 3) patient self-reported data from surveys (21, 23, 36). For pediatric asthma, reference standards included:1) review of diagnoses documented in medical records by trained chart abstractors or research nurses (12, 27, 35); 2) pediatric allergist-diagnosed asthma (22); 3) review of medical charts by a general pediatrician and a pediatric respirologist using clinical criteria based on documented episodes of wheezing and response to asthma medication (24, 35); and 4) parent report of a physician diagnosis of asthma, wheezy cough or reactive airway disease through telephone interviews or questionnaires (25, 28, 34). Furthermore, one study sent out, for each child with no discharge diagnosis of asthma recorded in their medical chart, a questionnaire to the general practice clinic where the child was registered at the time of the study to further confirm absence or presence of asthma diagnosis (37).

Summary of algorithms and validity

Table 2 and 3 provide details of the algorithms reported in each publication, according to whether studies used, respectively, clinical/chart review (n=13) or self-reported data (n=7), as the basis for the reference standard. Of note, meta-analysis was not conducted due to substantial heterogeneity found in the studies with respect to study characteristics, types of reference standards used, and diagnostic accuracy measures reported.

The majority of studies developed and tested asthma diagnostic algorithms as the primary research question, while eight reported on the validity of other diagnoses as well, most commonly COPD (22, 23, 26, 29, 32, 33, 36, 38). Most studies constructed their algorithms using either a combination of pharmacy claims and healthcare utilization data (ambulatory medical visits, emergency department visits or hospitalizations) (22, 23, 28, 30-33, 36), or only healthcare utilization data (12, 20, 21, 24-27, 29, 38). Three studies developed algorithms based exclusively on pharmacy claims data (34, 35, 37). Nearly all publications used ICD-9-CM or ICD-9 codes to identify asthma patients, and consistently used the 493.X (asthma) code (Table 4), although two studies did not provide the specific codes used (22, 38). The majority of studies reported sensitivity, specificity or PPV values, whereas six studies reported all four key diagnostic measures of accuracy (20, 23, 25, 31, 36, 38).

Pediatric populations

Among studies conducted in pediatric populations, PPV ranged from 41 to 92%, NPV from 85 to 99%, sensitivity from 31 to 96%, and specificity from 27 to 99%. Of these, three studies provided evidence that one asthma diagnosis from an ambulatory medical visit over a one-year period was adequate to identify pediatric asthma cases (sensitivity ≥85%, PPV ≥75%) (12, 24, 27). In contrast, Lix *et al.*, which used self-reported data as the basis for their reference standard, reported a sensitivity of 30% (23). Additionally, Korzyrskyj *et al.* showed that the accuracy was enhanced when a combination of asthma medications and ambulatory medical visits were considered in the algorithms (sensitivity ≥ 80% and PPV ≥ 90%) (22), although the authors did not provide the list of respiratory medications considered. The study by Moth *et al.* (37) developed and validated several algorithms exclusively on pharmacy claims data and the highest sensitivity (63%) and specificity (86%) were reported in the operational definition which included, over a one-year period, at least one respiratory medication, and required inhaled beta2-agonists or inhaled corticosteroids (ICS) to be filled at least twice and excluded SABA in liquid form. Bechtold *et al*. also validated a medication-based algorithm and observed that the sensitivity increased when the time frame used to identify asthma cases was lengthened to four years (34).

Adolescent/Adult populations

Among studies conducted in adult or adolescent populations, PPV ranged from 35 to 100%, NPV from 82 to 100%, sensitivity from 7 to 96%, and specificity from 27 to 99%. Similar to pediatric populations, the validity of theses algorithms were reasonably good when at least one ambulatory medical visit, emergency department visit, or hospitalization for asthma was identified over a one-year period (PPV: 70-90%;

specificity: 89-100%) (12, 21, 23). However, reported sensitivity values were fairly low. For example, Lix *et al*.(23) and Huzel *et al.* (21) reported sensitivity values ranging between 13 to 60%, although their reference standard consisted of self-reported data. Additionally, Biffi *et al.* (33) reported sensitivity values which ranged between 39 and 64% but the algorithms included only hospitalizations and pharmacy claims data and omitted ambulatory medical encounters. Although authors explained that they selected their algorithms to avoid detecting false disease cases, specificity values were not reported. As exemplified by Lujiic *et al*. (36) and Hajibandeh *et al*. (38), specificity values were particularly high when algorithms were constructed using solely hospitalization data (93-100%), at the expense of much lower sensitivity values (7-18%). Of note, Gershon *et al.* (20) showed that the validity was increased when two or more ambulatory medical visits or one hospitalization (or both criteria) were identified over a two-year period (sensitivity: 84%; specificity: 77%). Similarly, Vollmer *et al.* (30) reported that increasing the time frame of asthma outpatient encounters to two years resulted in an enhanced capacity to capture prevalent asthma cases, although they did not report any diagnostic accuracy measure for this operational definition. Another strategy to enhance diagnostic accuracy was suggested by Blais *et al.* (12) who showed that the PPV increased when the diagnosis was made by a pulmonologist. For example, for patients aged between 16-44 years old, the PPV was found to be 75% for pulmonologists and 67% for family physicians when at least one asthma diagnosis was recorded over a 1-year period. Additionally, Dore *et al.* (29) focused on the identification of prevalent asthma cases and reported a PPV of 74% when at least one asthma diagnosis was identified in the 6-month period prior to initiating a long-acting beta-2 agonist, although the PPV decreased with age. Authors of this study also reported PPVs according to sex, although they did not observe any statistically significant differences.

DISCUSSION

Overall, findings from this review suggest that healthcare administrative data are adequate to capture asthma cases. Several high-quality studies were identified, although significant heterogeneity was observed across studies in terms of patient characteristics, types of reference standards used, and diagnostic accuracy measures reported. Definitions which included at least one diagnosis from health service utilisation data over a one-year period were the most commonly reported algorithms and were generally valid across different age groups. For this review, several strategies that can increase the validity of the algorithms have emerged, including: 1) lengthening the time frame used to capture asthma cases; 2) requiring at least two asthma diagnoses; 3) including diagnoses recorded by a pulmonologist.

A number of valid asthma algorithms have been reported in the literature, suggesting that healthcare administrative databases can provide a vast arena to conduct population-based asthma research. However, prior to embarking in an administrative database study and selecting the best case-finding algorithm, researchers must assess the relative importance of sensitivity, specificity, PPV, and NPV, and prioritize the accuracy measure that is most relevant to the research question (40). As a prime example, it is desirable to select algorithms that have higher sensitivities for surveillance studies, since this approach minimizes the number of missed cases (40, 41). Most studies in this review tested multiple algorithms to identify the one which has the best trade-off between sensitivity and specificity. Generally, lengthening the time frame to capture asthma cases or increasing the number of diagnoses increased the specificity, at the cost of a lower sensitivity. Operational definitions based solely on hospitalization data were not sensitive, albeit highly specific, since this approach tends to capture more moderate-to-severe asthma patients. On the other hand, a significant number of studies chose the PPV as their main measure of validity, which is important when identifying a cohort defined by disease status. High PPVs and NPVs ensure that only persons who truly have the condition of interest are captured (40), and are desirable in studies seeking to examine causal or association relationships. Studies which used a combination of pharmacy claims data and healthcare utilization data generally had favourable PPV values.

Pharmacy claims data were incorporated in many of the algorithms identified in this review, although many studies conducted in the US and in Canada did not use this approach. A reason for this may be explained by the paucity of databases which comprehensively link all pharmacies to a central data system in these countries. For example, several Canadian databases such as the *Régie de l'assurance de maladie du Québec* only provide prescription medication data for the elderly, recipients of social assistance, and individuals who do not have access to a private drug insurance program through their employer. On the other hand, many US databases only cover commercially insured individuals (via private insurance). Along the same lines, depending on the data sources and local organization and processes, medications dispensed in the hospital setting (emergency department, inpatient wards, same-day surgery clinics) are not always captured in administrative databases. Thus, diagnostic algorithms based on pharmacy claims data may exclude certain segments of the population, which may in turn reduce their generalizability and usefulness for population-based studies, including disease surveillance projects. Additionally, pharmacy claims data typically include prescriptions dispensed in community pharmacies. Therefore, prescriptions which were written by the physician but not filled by the patient will not be captured. It is also possible that some epidemiologists who conducted these studies did not have access to medication data, which are more commonly used by pharmacoepidemiologists. Although findings from

this review suggest that algorithms using pharmacy claims data were generally valid, it is unclear which asthma medications can optimize the diagnostic accuracy. It is also unclear to which extent pharmacy claims data can enhance the capacity to capture asthma cases, since the validity of medication-based algorithms were not drastically different from those which used exclusively diagnostic codes. Moreover, the few studies that evaluated the change in validity of adding medications to healthcare utilization data did not report important changes in the diagnostic accuracy measures (10, 22, 23, 29, 33, 36). Thus, further research is warranted to explore the relevance of incorporating medication data into case-finding asthma algorithms. We hypothesize that pharmacy claims data can be used to efficiently identify asthma patients who have low rates of health services utilization or who appear to have a better level of disease control or a milder form of the disease. Due to the step-care approach to asthma therapy (2), whereby treatments are prescribed or adjusted based on a patient's level of disease severity and control, it may be possible to tailor algorithms to different levels of disease severity, although further studies are required to substantiate this concept.

It was difficult to compare the validity of algorithms between pediatric and adult populations, since only three studies stratified their validity statistics according to different age groups (12, 23, 29). However, the disease progression bias may have affected several pediatric studies, since it has been estimated that less than 50% of children with early-onset wheezing will go on to develop asthma during adolescence (42). Not only it is not possible to routinely assess airflow limitation in this age group, episodic respiratory symptoms such as wheezing, and cough are also common in children without asthma (2). This difficulty in making confident diagnosis of asthma in children 5 years and younger further highlights the necessity to ensure that the time gap between the index and reference test is as small as possible.

Broadly speaking, it is easier to assess the clinical usefulness of algorithms in studies in which authors report disease prevalence, as well as multiple measures of diagnostic accuracy (sensitivity, specificity, and predictive values) for several different algorithms (43), and across various age groups. However, few studies in this review delved into this level of detail due to methodological constraints. Some studies also failed to provide sufficient details on patient selection procedures and choice of reference standards, thus limiting our capacity to comprehensively evaluate their usefulness. Although several studies were methodologically sound, the majority of studies used medical chart review as the reference standard for the asthma diagnosis. However, such an approach is not optimal, as getting a definitive diagnosis of asthma would require pulmonary function tests in addition to symptom assessment – information that is not consistently recorded in medical charts (12). In addition, a recent study by Aaron *et al.* (44) found that a diagnosis of asthma could not be established in 33% of adults with physician-

diagnosed asthma, following a medical assessment consisting of home peak flow and symptom monitoring, spirometry, and serial bronchial challenge tests. Hence, absence of an asthma diagnosis in the medical chart does not automatically imply that a patient does not have asthma, and vice-versa. The majority of studies acknowledged this limitation but explained that this methodological choice was made due to feasibility and practical reasons. Yet, when an appropriate reference standard is selected and patients are randomly sampled from the general population, the disease prevalence approximates the population prevalence and provides unbiased estimates of sensitivity, specificity, PPV, and NPV (43). This approach, though ideal, may not always be feasible in all research settings.

All in all, this review demonstrated that the validity of healthcare administrative data for asthma research is adequate, since misclassification of clinical information appears to be minimal. Because administrative claims data are generated primarily for reimbursement purposes, data on health service use and charges are relatively complete for services covered by the health plan of the database (45). Nevertheless, in systems which do not cover universal coverage, healthcare delivery system coverage for an individual can change over time; thus, the possibility for extended longitudinal analyses may be compromised. This limitation highlights the necessity to ensure that the time frame to capture asthma cases is not too long—we recommend that it should preferably not exceed two years. Further, the incorporation of EHR data may be beneficial, since they contain a wealth of clinical information, such as reason for medication prescription, laboratory tests results, and patient vitals. However, issues related to data completeness, coupled with their lack of interoperability across health systems, add another layer of complexity for conducting longitudinal studies using EHR data, especially if an individual seeks care from more than one provider (45). In theory, linkage of EHRs and administrative claims may drive the development of better performing asthma case-finding algorithms and merits further investigation; however, such an endeavor may be complex and resource intensive.

The results presented in this review should be interpreted in the light of some limitations. Namely, articles whose full texts were not available in English or French were excluded, which may have introduced a language bias. There was also a possibility of missing articles that were not indexed in the bibliographic databases under terms related to administrative data or validation. Nonetheless, our rigorous systematic research methods combined with the grey literature search, ensured that our search strategy was optimized. Furthermore, potential limitations concerning the data extraction procedure remain. Ideally, two reviewers should have each conducted the data extraction independently. Yet in this review, one reviewer extracted the relevant information, whereas a second reviewer validated the extracted information by the first reviewer and disagreements were resolved by consensus or by a third reviewer.

This methodological approach, though not optimal, was chosen to ensure the timeliness of data collection. In an effort to maximize the accuracy of collected data, several quality control checks were conducted by a third reviewer. Finally, publication bias cannot be ruled out, whereby asthma diagnostic algorithms with poor validity may have been withheld from publication.

CONCLUSIONS

Healthcare administrative databases appear to adequately identify asthma patients. Algorithms that included at least one diagnostic code for asthma or that required a diagnosis by a respiratory physician appeared to be highly valid. Further research is required to confirm if algorithms based on both asthma diagnoses and asthma medications can result in a more enhanced validity. The relevance and choice of a specific algorithm should not be made arbitrarily, but rather be based on the research question and availability of data elements in the administrative database of interest.

REFERENCES

1. Holgate ST, Thomas M. Chapter 7 - Asthma. In: O'Hehir RE, Holgate ST, Sheikh A, editors. Middleton's Allergy Essentials: Elsevier; 2017. p. 151-204.
2. Global Initiative for Asthma. Pocket Guide for Asthma Management and Prevention 2018 [Available from: https://ginasthma.org/2018-pocket-guide-for-asthma-management-and-prevention/.
3. Blais L, Salah Ahmed SI, Beauchesne MF, Forget A, Kettani FZ, Lavoie K. Risk of postpartum depression among women with asthma. The journal of allergy and clinical immunology In practice. 2018.
4. Kaiser SV, Rodean J, Bekmezian A, Hall M, Shah SS, Mahant S, et al. Effectiveness of Pediatric Asthma Pathways for Hospitalized Children: A Multicenter, National Analysis. J Pediatr. 2018;197:165-71.e2.
5. Hamada S, Tokumasu H, Sato A, Iwasaku M, Kawakami K. Asthma Controller Medications for Children in Japan: Analysis of an Administrative Claims Database. Global pediatric health. 2015;2:2333794x15577790.
6. Bengtson LGS, Yu Y, Wang W, Cao F, Hulbert EM, Wolbeck R, et al. Inhaled Corticosteroid-Containing Treatment Escalation and Outcomes for Patients with Asthma in a U.S. Health Care Organization. Journal of managed care & specialty pharmacy. 2017;23(11):1149-59.
7. Jeffery MM, Shah ND, Karaca-Mandic P, Ross JS, Rank MA. Trends in Omalizumab Utilization for Asthma: Evidence of Suboptimal Patient Selection. The journal of allergy and clinical immunology In practice. 2018;6(5):1568-77.e4.
8. Kemppainen M, Lahesmaa-Korpinen AM, Kauppi P, Virtanen M, Virtanen SM, Karikoski R, et al. Maternal asthma is associated with increased risk of perinatal mortality. PLoS One. 2018;13(5):e0197593.
9. Tse SM, Samson C. Time to Asthma-Related Readmission in Children Admitted to the ICU for Asthma. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2017;18(12):1099-105.
10. Funk MJ, Landi SN. Misclassification in administrative claims data: quantifying the impact on treatment effect estimates. Current epidemiology reports. 2014;1(4):175-85.
11. van Walraven C, Austin PJJoce. Administrative database research has unique characteristics that can risk biased results. 2012;65(2):126-31.
12. Blais L, Lemiere C, Menzies D, Berbiche D. Validity of asthma diagnoses recorded in the Medical Services database of Quebec. Pharmacoepidemiology and drug safety. 2006;15(4):245-52.
13. Nissen F, Quint JK, Wilkinson S, Mullerova H, Smeeth L, Douglas IJJCe. Validation of asthma recording in electronic health records: a systematic review. 2017;9:643.
14. Sharifi M, Krishanswami S, McPheeters MLJV. A systematic review of validated methods to capture acute bronchospasm using administrative or claims data. 2013;31:K12-K20.
15. Sayers A. Tips and tricks in performing a systematic review. The British Journal of General Practice. 2007;57(542):759-.
16. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Annals of internal medicine. 2011;155(8):529-36.
17. Woodfield R, Grant I, Sudlow CL. Accuracy of Electronic Health Record Data for Identifying Stroke Cases in Large-Scale Epidemiological Studies: A Systematic Review from the UK Biobank Stroke Outcomes Group. PLoS One. 2015;10(10):e0140533.
18. Tan EH, Low EXS, Dan YY, Tai BC. Systematic review and meta-analysis of algorithms used to identify drug-induced liver injury (DILI) in health record databases. Liver international : official journal of the International Association for the Study of the Liver. 2018;38(4):742-53.

19. van Mourik MS, van Duijn PJ, Moons KG, Bonten MJ, Lee GM. Accuracy of administrative data for surveillance of healthcare-associated infections: a systematic review. BMJ Open. 2015;5(8):e008424.
20. Gershon AS, Wang C, Guan J, Vasilevska-Ristovska J, Cicutto L, To T. Identifying patients with physician-diagnosed asthma in health administrative databases. Canadian respiratory journal. 2009;16(6):183-8.
21. Huzel L, Roos LL, Anthonisen NR, Manfreda J. Diagnosing asthma: the fit between survey and administrative database. Canadian Respiratory Journal. 2002;9(6):407-12.
22. Kozyrskyj A, HayGlass K, Sandford A, Pare P, Chan-Yeung M, Becker A. A novel study design to investigate the early-life origins of asthma in children (SAGE study). Allergy. 2009;64(8):1185-93.
23. Lix L, Yogendran M, Burchill C, Metge C, McKeen N, Moore D, et al. Defining and validating chronic diseases: an administrative data approach. Winnipeg: Manitoba Centre for Health Policy. 2006.
24. To T, Dell S, Dick PT, Cicutto L, Harris JK, MacLusky IB, et al. Case verification of children with asthma in Ontario. Pediatric allergy and immunology. 2006;17(1):69-76.
25. Omand JA, Maguire JL, O'Connor DL, Parkin PC, Birken CS, Thorpe KE, et al. Agreement between a health claims algorithm and parent-reported asthma in young children. Pediatric Pulmonology. 2019;54(10):1547-56.
26. Wilchesky M, Tamblyn RM, Huang A. Validation of diagnostic codes within medical services claims. Journal of clinical epidemiology. 2004;57(2):131-41.
27. Bronstein JM, Santer L, Johnson V. The use of Medicaid claims as a supplementary source of information on quality of asthma care. Journal for Healthcare Quality. 2000;22(6):13-8.
28. Dombkowski KJ, Lamarand K, Dong S, Perng W, Clark SJ. Using Medicaid claims to identify children with asthma. Journal of Public Health Management and Practice. 2012;18(3):196-203.
29. Dore DD, Ziyadeh N, Cai B, Clifford CR, Norman H, Seeger JD. A cross-sectional study of the identification of prevalent asthma and chronic obstructive pulmonary disease among initiators of long-acting β-agonists in health insurance claims data. BMC pulmonary medicine. 2014;14(1):47.
30. Vollmer WM, O'Connor EA, Heumann M, Frazier EA, Breen V, Villnave J, et al. Searching multiple clinical information systems for longer time periods found more prevalent cases of asthma. Journal of clinical epidemiology. 2004;57(4):392-7.
31. Wakefield DB, Cloutier MM. Modifications to HEDIS and CSTE algorithms improve case recognition of pediatric asthma. Pediatric pulmonology. 2006;41(10):962-71.
32. Andrade SE, Scott PE, Davis RL, Li D-K, Getahun D, Cheetham TC, et al. Validity of health plan and birth certificate data for pregnancy research. Pharmacoepidemiology and drug safety. 2013;22(1):7-15.
33. Biffi A, Comoretto R, Arfè A, Scotti L, Merlino L, Vaghi A, et al. Can healthcare utilization data reliably capture cases of chronic respiratory diseases? a cross-sectional investigation in Italy. BMC pulmonary medicine. 2017;17(1):20.
34. Bechtold P, Ranzi A, Gambini M, Capelli O, Magrini N, Cavallini R, et al. Assessing Paediatric Asthma Occurrence through Dispensed Prescription Data and Questionnaires. European Journal of Public Health. 2012;23(5):873-8.
35. Bianchi M, Clavenna A, Sequi M, Bonati M. Asthma diagnosis vs. analysis of anti-asthmatic prescriptions to identify asthma in children. European journal of clinical pharmacology. 2011;67(9):967-8.
36. Lujic S, Simpson JM, Zwar N, Hosseinzadeh H, Jorm L. Multimorbidity in Australia: Comparing estimates derived using administrative data sources and survey data. PLOS ONE. 2017;12(8):e0183817.
37. Moth G, Vedsted P, Schiotz P. Identification of asthmatic children using prescription data and diagnosis. European journal of clinical pharmacology. 2007;63(6):605-11.

38. Hajibandeh S, Hajibandeh S, Deering R, McEleney D, Guirguis J, Dix S, et al. Accuracy of routinely collected comorbidity data in patients undergoing colectomy: a retrospective study. International journal of colorectal disease. 2017;32(9):1341-4.
39. Whiting P, Rutjes AWS, Reitsma JB, Bossuyt PMM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC medical research methodology. 2003;3:25-.
40. Chubak J, Pocobelli G, Weiss NS. Tradeoffs between accuracy measures for electronic health care data algorithms. Journal of clinical epidemiology. 2012;65(3):343-9.e2.
41. Pekkanen J, Pearce N. Defining asthma in epidemiological studies. The European respiratory journal. 1999;14(4):951-7.
42. Spahn JD, Covar R. Clinical assessment of asthma progression in children and adults. Journal of Allergy and Clinical Immunology. 2008;121(3):548-57.
43. Widdifield J, Labrecque J, Lix L, Paterson JM, Bernatsky S, Tu K, et al. Systematic review and critical appraisal of validation studies to identify rheumatic diseases in health administrative databases. Arthritis care & research. 2013;65(9):1490-503.
44. Aaron SD, Vandemheen KL, FitzGerald JM, Ainslie M, Gupta S, Lemière C, et al. Reevaluation of Diagnosis in Adults With Physician-Diagnosed AsthmaReevaluation of Asthma Diagnosis in Adults With Previously Diagnosed AsthmaReevaluation of Asthma Diagnosis in Adults With Previously Diagnosed Asthma. JAMA. 2017;317(3):269-79.
45. Mary Elizabeth Ritchey; Suzanne L. West; George Maldonado. Validity of Drug and Diagnosis Data in Pharmacoepidemiology. In: Brian L Strom, editor. Pharmacoepidemiology. 6 ed: Hoboken, NJ : Wiley-Blackwell; 2020.

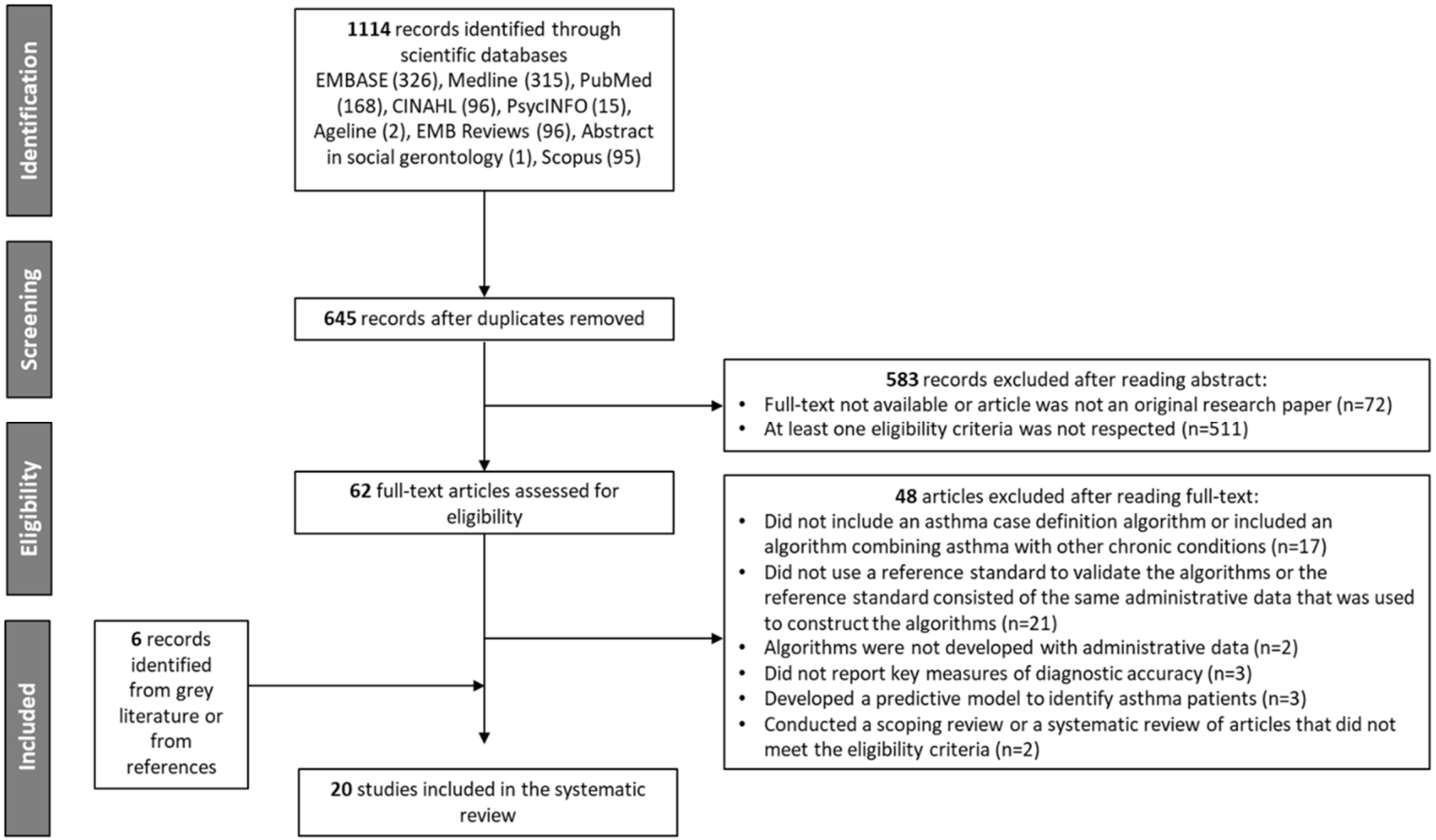


Figure 1. PRISMA-style flow chart of study selection and review

Table 1. Study characteristics (n=20)

Authors, year, Country	Primary validation study?	Sample characteristics (validation sample size), study period	Healthcare Administrative data source	Administrative data type	Reference standard
Andrade *et al.*, 2013 (32) United States	No	Women delivering a live born infant (n=133) 2001-2007	The Medication Exposure in Pregnancy Risk Evaluation Program database	Ambulatory medical visits ED visits Hospitalizations Pharmacy claims	Chart review
Bechtold *et al.,* 2012 (34) Italy	Yes	Pediatric/adolescent population 6-7 y (n=7,014) 13 y (n=3,232) 2000-2003	Italian Public Health Service Database	Pharmacy claims	Self-report (parent)
Biffi *et al.*, 2017 (33) Italy	No	Pediatric and adult populations 0-39 y (validation *n* unclear) 2010	Lombardy Healthcare Utilization databases	Hospitalizations Pharmacy claims	Chart review
Bianchi *et al*., 2011 (35) Italy	Yes	Pediatric/adolescent population 6-17 y (n=244) 2008	Lombardy National Health Service database	Pharmacy claims	Chart review
Blais *et al.*, 2006 (12) Canada	Yes	Adolescent and adult populations 16-44 y (n=359) 45-80 y (n=367) 2000-2002	*Régie de l'assurance maladie du Québec* (Medical Services database)	Ambulatory medical visits	Chart review
Bronstein *et al.,* 2000 (27) United States	Yes	Pediatric/adolescent population 2-13 y (n=98) 1994-1995	Medicaid claims database	Ambulatory medical visits Medical procedures	Chart review
Dombkowski *et al.* 2012 (28) United States	Yes	Pediatric/adolescent population 2-18 y (n=440) 2005-2006	Medicaid database and Children's Special Health Care Services database	ED visits Ambulatory medical visits Hospitalizations Pharmacy claims Medical procedures	Self-report (parent)
Dore *et al.*, 2014 (29) United States	No	Adult population ≥20 y, LABA and LABA/ICS initiators or switchers (n=370) 2005-2008	Normative Health Information Database, a claims database of a large US commercial health plan (UnitedHealth Care).	Ambulatory medical visits Hospitalizations	Chart review
Gershon *et al.*, 2009 (20) Canada	Yes	Adult population 19-80 y (n=518) 2003	Ontario Health Insurance Plan database	Ambulatory medical visits Hospitalizations	Chart review
Hajibandeh *et al.,* 2017 (38) United Kingdom	No	Adult population > 18 y who underwent any types of colectomy (n=267) 2015-2016	Hospital Episodes Statistics (HES)	Hospitalizations	Chart review

Authors, year, Country	Primary validation study?	Sample characteristics (validation sample size), study period	Healthcare Administrative data source	Administrative data type	Reference standard
Huzel *et al.*, 2002 (21) Canada	Yes	Adult population 20-44 y (n=2,479) 1993-1994	The Manitoba Population Health Research Repository	Ambulatory medical visits	Self-report
Kozyrskyj *et al.* (2009)(22) Canada	No	Pediatric population 7-8 y (n=723) 2002-2005	Manitoba's Healthcare databases	Ambulatory medical visits Hospitalizations Pharmacy claims	Clinical test
Lix *et al.*, 2006 (23) Canada	No	Adolescent/adult populations 12-18 y (n=833) ≥19 y (n=5,589) 2000-2001	Population Health Research Data Repository housed at the Manitoba Centre for Health Policy	Ambulatory medical visits Hospitalizations Pharmacy claims	Self-report
Lujic *et al.*, 2017 (36) Australia	No	Adult population with multimorbidity ≥45 y (n= 11,384) 2007-2009	-New South Wales admitted patient data collection -Pharmaceutical Benefits Scheme	Hospitalizations Pharmacy claims	Self-report
Moth *et al.*, 2007 (37) Denmark	Yes	Pediatric population 6-14 y (n=6,352) 2000-2003	The regional Health Service Register and the Odense Pharmacoepidemiologic Database	Pharmacy claims	Chart review
Omand *et al*., 2019 (25) Canada	Yes	Pediatric population 1-5 y (n=3,642) 2008-2013	Canadian Institute for Health Information, Discharge Abstract Database, Ontario Health Insurance Plan	Ambulatory medical visits Hospitalizations	Self-report (parent)
To *et al.*, 2006 (24) Canada	Yes	Pediatric/adolescent populations 0-18 y (n=630) 2000-2001	Ontario Health Insurance Plan database	Ambulatory medical visits	Chart review
Vollmer *et al.*, 2004 (30) United States	Yes	Adolescent/adult populations 15-55 y (n=132) 1999	Kaiser Permanente Northwest Division databases	ED visits Ambulatory medical visits Hospitalizations Pharmacy claims	Chart review
Wakefield *et al.*, 2006 (31) United States	Yes	Pediatric population 6 months-18 y Medicaid:1998-2001 (n=3,905) ConnectiCare: 2001-2004 (n=1,458)	Medicaid and ConnectiCare databases	ED visits Ambulatory medical visits Hospitalizations Pharmacy claims	Self-report (parent)
Wilchesky *et al.*, 2004 (26) Canada	No	Geriatric population ≥66 y (n= 1,099) 1995-1996	*Régie de l'assurance maladie du Québec* (Medical Services database)	Ambulatory medical visits	Chart review

Abbreviations: ED: Emergency department; ICS: Inhaled corticosteroids; LABA: Long-acting beta2-agonists; n: number, y: years old.

Table 2. Chart review or clinical test as reference-standard (n=13)

Author, year	Algorithm case definitions*	Se (95% CI)**	Sp (95% CI)**	PPV (95% CI)**	NPV (95% CI)**
Andrade *et al.*, 2013 (32)	(≥2 ambulatory medical visits at least 30 days apart) OR (≥1 hospitalization) OR (≥1 ambulatory medical visit and ≥1 pharmacy claim) over 1 year prior to pregnancy through the date of delivery. Medications: SABA, LABA, ICS, LTRA, mast cell stabilizer, methylxanthine	-	-	95 (91-99)	-
Biffi *et al.*, 2017 (33)	<40 y and ≥1 of the following criteria, over 1 year: Benefitted of exemption for asthma; ≥1 hospitalization; ≥2 pharmacy claims of any of the following drugs: LTRA, chromones; ≥2 pharmacy claims of any of the following drugs: SABA, LABA/ICS fixed combinations (only 0-19 y); ≥2 pharmacy claims of ICS AND ≥1 pharmacy claim of SABA; ≥2 pharmacy claims of ICS in addition to ≥2 pharmacy claims of ipratropium, oxitropium or theophylline (only 0-19 y); ≥1 pharmacy claim of antibiotics (ATC: J01; only 20-39 y); AND ≥1 of the following criteria: ≥2 pharmacy claims of theophylline and ≥2 pharmacy claims of any of the following drugs: beta-agonist, ipratropium, oxitropium, ICS; ≥2 pharmacy claims of SABA or LABA/ICS fixed combinations; ≥ 2 pharmacy claims of ICS AND ≥2 pharmacy claims of ipratropium or oxitropium	39 (-)	-	-	-
	<40 y and ≥1 of the following criteria, over 1 year: ≥1 pharmacy claim of one of the following drugs: SABA, LABA, LABA/ICS, ICS, chromones, LAAC, theophylline; ≥1 pharmacy claim of LTRA and ≥1 pharmacy claim of any other respiratory drug; ≥1 pharmacy claim of OCS and ≥1 pharmacy claim for any respiratory drug	63 (-)	-	-	-
	<40 y and ≥1 of the following criteria, over 1 year: ≥2 pharmacy claims of one of the following drugs: SABA, LABA, LABA/ICS, ICS, chromones, LAAC, theophylline; ≥2 pharmacy claims of LTRA and ≥2 pharmacy claims of any other drug for chronic respiratory diseases; ≥2 pharmacy claims of OCS and ≥2 pharmacy claims of any other respiratory drug	31 (-)	-	-	-
Bianchi et al., 2011 (35)	6-17 y, ≥1 pharmacy claim of one of the following drugs: SABA, non-SABA, or OCS over 1 year	90 (-)	98 (-)	32 (-)	10 (-)
Blais *et al.*, 2006 (12)	≥1 ambulatory medical visit over 1 year:				
	16-44 y, seen by a family physician	-	-	67 (58-75)	99 (97-100)
	16-44 y, seen by a pulmonologist	97 (94-100)	85 (78-94)	75 (68-85)	96 (92-100)
	45-80 y, seen by a family physician	-	-	60 (50-70)	100 (96-100)
	45-80 y, seen by a pulmonologist	94 (92-96)	65 (56-75)	78 (69-87)	93 (87-98)
	≥2 ambulatory medical visits over 1 year:				
	16-44 y, seen by a family physician	-	-	78 (65-90)	-
	16-44 y, seen by a pulmonologist	87 (80-94)	94 (89-99)	77 (64-90)	-
	45-80 y, seen by a family physician	-	-	68 (56-80)	-
	45-80 y, seen by a pulmonologist	84 (77-91)	83 (75-90)	87 (78-96)	-

Author, year	Algorithm case definitions*	Se (95% CI)**	Sp (95% CI)**	PPV (95% CI)**	NPV (95% CI)**
Bronstein *et al.*, 2000 (27)	2-13 y, ≥1 ambulatory medical visit over 1 year	-	-	88 (-)	85 (-)
	2-13 y, ≥1 medical procedure corresponding to a nebulizer treatment over 1 year			88 (-)	97 (-)
Dore *et al.*, 2014 (29)	≥1 hospitalization or ≥1 ambulatory medical visit, 6 months before initiating a LABA:				
	All population	-	-	74 (63-82)	-
	20-39 y	-	-	79 (58-93)	-
	40-64 y	-	-	73 (60-83)	-
	≥65 y	-	-	60 (15-95)	-
	Men only	-	-	74 (56-87)	-
	Women only	-	-	74 (60-85)	-
Gershon *et al.*, 2009 (20)	19-80 y, ≥1 ambulatory medical visit OR ≥1 hospitalization over unspecified period (or both criteria):				
	Against expert panel dx	95 (90-98)	59 (54-64)	51 (45-57)	96 (93-98)
	Against practitioner chart dx	92 (88-96)	64 (58-68)	61 (55-66)	93 (89-96)
	19-80 y, ≥2 ambulatory medical visits OR ≥1 hospitalization over 2 years (or both criteria):				
	Against expert panel dx	84 (77-89)	77 (72-81)	62 (54-68)	91 (88-94)
	Against practitioner chart dx	81 (74-86)	82 (77-86)	73 (66-78)	87 (83-91)
	19-80 y, ≥2 ambulatory medical visits OR ≥1 hospitalization over 3 years (or both criteria):				
	Against expert panel dx	85 (79-90)	75 (70-79)	60 (54-67)	92 (88-95)
	Against practitioner chart dx	82 (76-87)	79 (75-84)	71 (65-77)	88 (83-91)
	19-80 y, ≥3 ambulatory medical visits OR ≥1 hospitalization over 2 years (or both criteria):				
	Ref. standard: expert panel dx	74 (67-81)	87 (83-90)	72 (64-78)	88 (85-92)
	Ref. standard: practitioner chart dx	68 (61-74)	90 (86-93)	80 (73-86)	82 (78-86)
	19-80 y ≥3 ambulatory medical visits OR ≥1 hospitalization over 3 years (or both criteria):				
	Ref. standard: expert panel dx	76 (68-82)	85 (81-88)	69 (61-76)	89 (85-92)
	Ref. standard: practitioner chart dx	70 (64-77)	88 (84-92)	78 (72-84)	83 (79-87)
Hajibandeh *et al.*, 2017 (38)	>18 y, ≥1 hospitalization over unspecified period	18 (-)	100 (-)	100 (-)	81 (-)
Kozyrskyj *et al.*, 2009 (22)	7-8 y, ≥1 hospitalization OR ≥2 ambulatory medical visits OR ≥4 pharmacy claims over 1 year	47 (35-60)	92 (78-98)	91 (76-98)	-
	7-8 y, ≥1 hospitalization OR ≥2 ambulatory medical visits OR ≥2 pharmacy claims over 1 year	67 (54-78)	92 (78-98)	94 (82-99)	-
	7-8 y, ≥1 hospitalization OR ≥1 ambulatory medical visit OR 2 pharmacy claims over 1 year	77 (65-78)	92 (78-98)	94 (82-99)	-
	7-8 y, ≥1 hospitalization OR ≥1 ambulatory medical visit OR ≥2 bronchodilators OR ≥1 controller medication over 1 year	80 (69-89)	89 (74-97)	93 (83-98)	-
	7-8 y, ≥ 1 hospitalization OR ≥1 ambulatory medical visit OR ≥2 bronchodilators OR (≥1 bronchodilator and ketotifen or oral steroid) OR ≥1 controller medication over 1 year	82 (70-90)	83 (67-94)	90 (79-96)	-
Moth *et al.*, 2007(37)	6-14 y, ≥1 pharmacy claim, excluding beta2-agonists in liquid form, over 1 year	96 (95-96)	43 (41-45)	-	-
	6-14 y, ≥1 pharmacy claim, excluding beta2-agonists in liquid form or if an inhaled beta2-agonist was filled only once, over 1 year	83 (81-84)	73 (71-75)	-	-
	6-14 y, ≥1 pharmacy claim, excluding beta2-agonists in liquid form or if an inhaled beta2=agonist or ICS was filled only once, over 1 year	63 (62-65)	86 (84-87)	-	-

Author, year	Algorithm case definitions*		Se (95% CI)**	Sp (95% CI)**	PPV (95% CI)**	NPV (95% CI)**
	6-14 y, ≥1 pharmacy claim, excluding beta2-agonists in liquid form or if an inhaled beta2-agonist or an ICS was filled only once, over a 6-month capture period and a 1-year observation window†		78 (76-79)	81 (79-83)	-	-
	6-14 y, ≥1 pharmacy claim, excluding beta2-agonists in liquid form or if an inhaled beta2-agonist or an ICS was filled only once, over a 1-year capture period and a 6-month observation window†		59 (58-60)	87 (85-88)	-	-
	6-14 y, ≥1 pharmacy claim, excluding beta2-agonists in liquid form or if an inhaled beta2-agonist or an ICS was filled only once, over a 9-month capture period and observation window†		70 (69-71)	83 (81-85)	-	-
To *et al.*, 2006 (24)	0-18 y, 1 ambulatory medical visit		91 (-)	83 (-)	-	-
Vollmer *et al.*, 2004 (30)	*Medication dispensing criteria*	15-55 y, (≥2 ambulatory medical visits) OR (1 ambulatory medical visit and ≥2 ED visit or hospitalizations) OR (any industrial medicine visit) OR (any visit and either one of two medication dispensing criteria) in the past year	-	-	95 (-)	-
	1) (≥1 dispensing of either an ICS or of cromolyn AND ≥1 dispensing of beta-agonist inhaler); 2) ≥4 dispensings of beta-agonist inhalers; 3) ≥1 order for nebulizer treatment in the outpatient setting.	15-55 y, 1 ambulatory medical visit in the past year	-	-	90 (-)	-
		15-55 y, ≥4 beta-agonists with or without a nebulizer treatment order, but no asthma visits and no ICS in the past year	-	-	70 (-)	-
		15-55 y, 1 ED visit for asthma and nebulizer treatment order, but no other asthma medication dispensing criteria met and no other types of asthma visits in the past year	-	-	100 (-)	-
		15-55 y, 1 hospitalization, but neither medication dispensing criterion met and no ambulatory visits of any kind in the past year	-	-	50 (-)	-
		15-55 y, 1 ED visit or urgent care visit, but no other types of asthma visits and no medication dispensing criteria met in the past year	-	-	80 (-)	-
		15-55 y, 1 nebulizer treatment but no asthma visits of any kind and no other medication dispensing criteria in the past year	-	-	27 (-)	-
Wilchesky *et al.*, 2004 (26)	≥66 y, 1 ambulatory medical visit in the year prior the start of the MOXXI study:					
	Ref. standard: dx recorded by MOXXI physicians only (primary care physicians)		30 (27-33)	99 (99-99)	-	-
	Ref standard: dx recorded by all billing physicians		43 (40-46)	97 (97-97)	-	-

Abbreviations: ED: Emergency department; ICS: Inhaled corticosteroids; LAAC: Long-acting anticholinergics; LABA: Long-acting beta2-agonists; LTRA: Leukotriene receptor antagonists; SABA: Short-acting beta2-agonists; y: years old.

*Ambulatory medical visits, ED visits and hospitalizations refer to medical encounters that have an asthma diagnosis.

**When applicable, validity statistics were rounded to the nearest integer.

†Capture period: period in which children were identified by their first prescription of anti-asthmatic medication succeeded by an observation period in which the children's subsequent prescriptions were registered.

Table 3. Self-report as reference standard (n=7)

Author, year	Algorithm case definitions	Se (95% CI)*	Sp (95% CI)*	PPV (95% CI)*	NPV (95% CI)*
Bechtold *et al.,* 2012 (34)	≥1 pharmacy claim of an inhaled bronchodilator (LABA, SABA) over 1 year:				
	Ref. standard: wheezing symptoms in past year; Age groups 6-7 y & 13 y	32 (31-33)	98 (98-98)	-	-
	Ref. standard: wheezing symptoms in past year; Age group 6-7 y	34 (32-35)	98 (97-98)	-	-
	Ref. standard: wheezing symptoms in past year; Age group 13 y	28 (26-29)	99 (98-99)	-	-
	≥1 pharmacy claim of an inhaled bronchodilator (LABA, SABA) over 2 years:				
	Ref. standard: wheezing symptoms in past year; Age groups 6-7 y & 13 y	56 (54-56)	94 (93-94)	-	-
	Ref. standard: wheezing symptoms in past year; Age group 6-7 y	61 (60-62)	92 (92-93)	-	-
	Ref. standard: wheezing symptoms in past year; Age group 13 y	44 (42-45)	97 (96-97)	-	-
	≥1 pharmacy claim of an inhaled bronchodilator (LABA, SABA) over 4 years:				
	Ref. standard: wheezing symptoms in past year; Age groups 6-7 y & 13 y	70 (69-71)	83 (83-84)	-	-
	Ref. standard: wheezing symptoms in past year; Age group 6-7 y	76 (75-77)	79 (78-80)	-	-
	Ref. standard: wheezing symptoms in past year; Age group 13 y	57 (56-59)	93 (92-94)	-	-
	≥1 pharmacy claim of an inhaled bronchodilator (LABA, SABA) over 4 years:				
	Ref. standard: physician diagnosis of asthma; Age groups 6-7 y & 13 y	61 (60–62)	84 (84-85)	-	-
	Ref. standard: physician diagnosis of asthma; Age group 6-7 y	68 (67–69)	80 (79-81)	-	-
	Ref. standard: physician diagnosis of asthma Age group 13 y	50 (48–51)	94 (94-95)	-	-
Dombkowski *et al.*, 2012 (28)	Children with asthma dx (2-18 y): ≥1 pharmacy claim AND ≥1 any other combination of health services utilization over 2 years	-	-	89 (-)	-
	≥6 SABA/year AND ≥1 any other combination of health services health utilization over 2 years	-	-	93 (-)	-
	≥1 hospitalization OR ≥1 ED visit AND ≥1 any other combination of services utilization over 2 years	-	-	100 (-)	-
	≥1 hospitalization OR ≥1 ED visit for asthma only over 2 years	-	-	73 (-)	-
	≥1 ambulatory medical visit AND ≥1 any other combination of services utilization over 2 years	- -	-	65 (-)	-
	≥1 ambulatory medical visit over 2 years	-	-	69 (-)	-
	≥1 procedure or durable medical equipment claim AND ≥1 any other combination of health services utilization over 2 years	-	-	71 (-)	-
	≥1 procedure or durable medical equipment claim over 2 years	-	-	67 (-)	-
Huzel *et al.*, 2002 (21)	20-44 y, ≥1 ambulatory medical visit over 1 year before the survey:				
	Ref. standard: Asthma attack	38 (-)	98 (-)	-	-
	Ref. standard: Asthma medication	41 (-)	99 (-)	-	-
	Ref. standard: Attack or medication	38 (-)	99 (-)	-	-
	Ref. standard: Attack and medication	43 (-)	98 (-)	-	-
	Ref. standard: Attack, medication or symptoms	8 (-)	100 (-)	-	-
	20-44 y, ≥1 ambulatory medical visit over 2 years before the survey:				
	Ref. standard: Asthma attack	51 (-)	98 (-)	-	-

Author, year	Algorithm case definitions	Se (95% CI)*	Sp (95% CI)*	PPV (95% CI)*	NPV (95% CI)*
	Ref. standard: Asthma medication	54 (-)	98 (-)	-	-
	Ref. standard: Attack or medication	50 (-)	99 (-)	-	-
	Ref. standard: Attack and medication	57 (-)	98 (-)	-	-
	Ref. standard: Attack, medication or symptoms	10 (-)	100 (-)	-	-
	20-44 y, ≥1 ambulatory medical visit over 5 years before the survey:				
	Ref. standard: Asthma attack	63 (-)	97 (-)	-	-
	Ref. standard: Asthma medication	65 (-)	97 (-)	-	-
	Ref. standard: Attack or medication	61 (-)	98 (-)	-	-
	Ref. standard: Attack and medication	70 (-)	96 (-)	-	-
	Ref. standard: Attack, medication or symptoms	14 (-)	99 (-)	-	-
Lix *et al.*, 2006 (23)	≥1 ambulatory medical visit over 1 year:				
	≥12 y	31 (27-35)	99 (99-99)	70 (64-76)	94 (94-95)
	12-18 y	30 (21-38)	98 (97-99)	70 (57-83)	90 (88-92)
	19-49 y	30 (24-36)	99 (99-99)	72 (63-81)	95 (94-95)
	≥50 y	33 (26-39)	99 (98-99)	69 (59-79)	95 (94-96)
	≥2 ambulatory medical visits over 1 year:				
	≥12 y	18 (15-21)	100 (99-100)	77 (70-85)	93 (93-94)
	12-18 y	16 (9-23)	99 (99-100)	82 (66-98)	89 (86-91)
	19-49 y	17 (12-22)	100 (99-100)	74 (62-86)	94 (93-95)
	≥50 y	21 (15-26)	100 (99-100)	80 (68-91)	94 (93-95)
	≥1 pharmacy claim over 1 year:				
	≥12+ y	55 (51-60)	96 (95-96)	55 (50-59)	96 (96-97)
	12-18 y	43 (34-53)	97 (96-98)	71 (60-81)	92 (90-94)
	19-49 y	50 (44-57)	98 (97-98)	62 (55-69)	96 (95-97)
	≥50 y	69 (62-76)	94 (93-95)	46 (40-52)	97 (97-98)
	≥1 hospitalization OR ≥1 ambulatory medical visit over 1 year:				
	≥12 y	31 (27-35)	99 (99-99)	70 (65-76)	94 (94-95)
	12-18 y	30 (21-38)	98 (97-99)	70 (57-83)	90 (88-92)
	19-49 y	30 (24-36)	99 (99-99)	72 (63-81)	95 (94-95)
	≥50 y	34 (27-40)	99 (98-99)	69 (59-78)	95 (94-96)
	≥1 hospitalization OR ≥2 ambulatory medical visits over 1 year:				
	≥12 y	19 (16-22)	100 (99-100)	78 (70-85)	93 (93-94)
	12-18 y	16 (9-23)	99 (99-100)	82 (66-98)	89 (86-91)
	19-49 y	18 (13-23)	100 (99-100)	75 (63-86)	94 (93-95)
	≥50 y	22 (16-27)	100 (99-100)	79 (68-90)	94 (93-95)
	≥1 hospitalization OR ≥1 ambulatory medical visit OR ≥1 pharmacy claim over 1 year:				
	≥12 y				
	12-18 y	58 (54-63)	96 (95-96)	54 (50-58)	96 (96-97)
	19-49 y	49 (39-58)	97 (96-98)	70 (60-80)	93 (91-94)

Author, year	Algorithm case definitions	Se (95% CI)*	Sp (95% CI)*	PPV (95% CI)*	NPV (95% CI)*
	≥50 y	54 (47-60)	97 (97-98)	60 (53-67)	96 (96-97)
		70 (64-77)	93 (92-94)	45 (39-51)	98 (97-98)
	≥1 hospitalization OR ≥2 ambulatory medical visits OR ≥2 pharmacy claims over 1 year:				
	≥12 y	47 (43-51)	98 (97-98)	64 (60-69)	95 (95-96)
	12-18 y	33 (25-42)	99 (98-100)	79 (67-90)	91 (89-93)
	19-49 y	42 (35-48)	99 (99-99)	78 (71-85)	95 (95-96)
	≥50 y	61 (54-68)	96 (95-97)	54 (47-60)	97 (96-98)
	≥1 ambulatory medical visit over 2 years:				
	≥12 y	44 (40-48)	98 (98-98)	66 (61-71)	95 (95-96)
	12-18 y	46 (37-55)	97 (95-98)	67 (57-78)	92 (90-94)
	19-49 y	43 (36-49)	99 (98-99)	69 (62-77)	95 (95-96)
	≥50 y	44 (37-51)	98 (97-98)	62 (54-70)	96 (95-97)
	≥2 ambulatory medical visits over 2 years:				
	≥12 y	30 (26-34)	99 (99-99)	74 (68-80)	94 (93-95)
	12-18 y	33 (25-42)	99 (98-100)	84 (73-95)	91 (89-93)
	19-49 y	29 (23-35)	99 (99-100)	73 (64-83)	94 (94-95)
	≥50 y	30 (23-36)	99 (99-99)	70 (60-80)	95 (94-96)
	≥1 pharmacy claim over 2 years:				
	≥12 y	70 (66-74)	94 (93-94)	50 (46-54)	97 (97-98)
	12-18 y	68 (59-76)	95 (94-97)	69 (61-78)	95 (94-97)
	19-49 y	65 (59-72)	96 (95-97)	56 (50-62)	97 (97-98)
	≥50 y	76 (70-82)	91 (90-92)	40 (35-45)	98 (97-99)
	≥1 hospitalization OR ≥1 ambulatory medical visit over 2 years:				
	≥12 y	45 (41-49)	98 (98-98)	66 (61-71)	95 (95-96)
	12-18 y	46 (37-55)	97 (95-98)	67 (57-78)	92 (90-94)
	19-49 y	43 (37-49)	98 (98-99)	69 (61-77)	96 (95-96)
	≥50 y	46 (39-53)	98 (97-98)	63 (55-71)	96 (95-97)
	≥1 hospitalization OR ≥2 ambulatory medical visits over 2 years:				
	≥12 y	31 (27-35)	99 (99-99)	74 (69-80)	94 (94-95)
	12-18 y	33 (25-42)	99 (98-100)	84 (73-95)	91 (89-93)
	19-49 y	30 (24-36)	99 (99-100)	73 (64-82)	95 (94-95)
	≥50 y	32 (25-38)	99 (99-99)	71 (61-80)	95 (94-96)
	≥1 hospitalization OR ≥1 ambulatory medical visit OR ≥1 pharmacy claim over 2 years:				
	≥12 y	73 (69-76)	93 (92-94)	48 (45-52)	97 (97-98)
	12-18 y	69 (61-78)	95 (93-96)	66 (57-74)	95 (94-97)
	19-49 y	70 (64-76)	95 (94-96)	54 (48-59)	98 (97-98)
	≥50 y	77 (71-83)	90 (89-92)	39 (33-44)	98 (98-99)

Author, year	Algorithm case definitions	Se (95% CI)*	Sp (95% CI)*	PPV (95% CI)*	NPV (95% CI)*
	≥1 hospitalization OR ≥2 ambulatory medical visits OR ≥2 pharmacy claims over 2 years:				
	≥12 y	58 (53-62)	97 (96-97)	61 (57-65)	96 (96-97)
	12-18 y	49 (39-58)	98 (97-99)	81 (71-90)	93 (91-94)
	≥19-49 y	54 (47-60)	98 (98-99)	73 (66-79)	96 (96-97)
	≥50 y	67 (61-74)	94 (93-95)	48 (42-54)	97 (97-98)
	≥1 ambulatory medical visit over 3 years:				
	≥12 y	53 (49-57)	97 (97-97)	61 (56-65)	96 (95-96)
	12-18 y	62 (53-71)	95 (94-97)	66 (57-75)	94 (93-96)
	19-49 y	49 (42-55)	98 (97-98)	62 (55-69)	96 (95-97)
	≥50 y	53 (46-60)	97 (96-97)	56 (49-64)	96 (96-97)
	≥2 ambulatory medical visits over 3 years:				
	≥12y	38 (34-42)	99 (98-99)	71 (66-77)	95 (94-95)
	12-18 y	48 (39-57)	98 (97-99)	82 (72-91)	93 (91-94)
	19-49 y	34 (28-40)	99 (99-99)	71 (62-79)	95 (94-96)
	≥50 y	36 (29-43)	99 (98-99)	65 (56-74)	95 (94-96)
	≥1 pharmacy claim over 3 years:				
	≥12 y	75 (71-78)	92 (92-93)	47 (43-50)	98 (97-98)
	12-18 y	77 (69-85)	94 (92-96)	66 (58-74)	96 (95-98)
	19-49 y	70 (64-76)	94 (94-95)	51 (45-56)	98 (97-98)
	≥50 y	79 (73-85)	89 (88-91)	37 (32-42)	98 (98-99)
	≥1 hospitalization OR ≥1 ambulatory medical visit over 3 years:				
	≥12 y	54 (49-58)	97 (96-97)	61 (56-65)	96 (95-96)
	12-18 y	62 (53-71)	95 (94-97)	66 (57-75)	94 (93-96)
	19-49 y	49 (43-56)	98 (97-98)	62 (55-69)	96 (95-97)
	≥50 y	54 (47-61)	97 (96-97)	57 (49-64)	96 (96-97)
	≥ 1 hospitalization OR ≥2 ambulatory medical visits over 3 years:				
	≥12 y	38 (34-43)	99 (98-99)	71 (66-76)	95 (94-95)
	12-18 y	48 (39-57)	98 (97-99)	82 (72-91)	92 (91-94)
	19-49 y	35 (29-41)	99 (98-99)	71 (62-79)	95 (94-96)
	≥50 y	37 (31-44)	98 (98-99)	65 (56-74)	95 (94-96)
	≥1 hospitalization OR ≥1 ambulatory medical visit OR ≥1 pharmacy claim over 3 years:				
	≥12 y	78 (74-81)	91 (91-92)	44 (41-47)	98 (98-98)
	12-18 y	78 (71-86)	92 (90-94)	61 (53-69)	97 (95-98)
	19-49 y	75 (69-80)	93 (92-94)	48 (43-53)	98 (97-98)
	≥50 y	81 (76-87)	88 (87-90)	36 (31-40)	98 (98-99)
	≥1 hospitalization OR ≥2 ambulatory medical visits OR ≥2 pharmacy claims over 3 years:				

Author, year	Algorithm case definitions	Se (95% CI)*	Sp (95% CI)*	PPV (95% CI)*	NPV (95% CI)*
	≥12 y	66 (62-70)	96 (95-96)	58 (54-62)	97 (97-97)
	12-18 y	69 (61-78)	97 (96-98)	77 (69-85)	95 (94-97)
	19-49 y	60 (54-66)	98 (97-98)	68 (61-74)	97 (96-97)
	≥50 y	72 (65-78)	93 (92-94)	45 (39-51)	98 (97-98)
	≥1 ambulatory medical visit over 5 years:				
	≥12 y	64 (59-68)	95 (95-96)	55 (51-59)	97 (96-97)
	12-18 y	75 (67-83)	92 (90-94)	59 (51-67)	96 (95-97)
	19-49 y	61 (54-67)	96 (95-97)	55 (49-61)	97 (96-97)
	≥50 y	61 (54-68)	96 (95-97)	53 (46-59)	97 (96-98)
	≥2 ambulatory medical visits over 5 years:				
	≥12 y	50 (46-55)	98 (97-98)	66 (62-71)	96 (95-96)
	12-18 y	60 (51-70)	97 (95-98)	74 (65-83)	94 (92-96)
	19-49 y	50 (44-57)	98 (97-98)	65 (58-72)	96 (95-97)
	≥50 y	44 (37-51)	98 (97-99)	63 (55-71)	96 (95-97)
	≥1 pharmacy claim over 5 years:				
	≥12 y	82 (78-84)	90 (89-91)	43 (40-46)	98 (98-99)
	12-18 y	87 (80-93)	91 (89-93)	59 (51-66)	98 (97-99)
	19-49 y	78 (73-83)	92 (91-93)	45 (40-50)	98 (98-99)
	≥50 y	83 (77-88)	88 (86-89)	35 (30-39)	98 (98-99)
	≥1 hospitalization OR ≥1 ambulatory medical visit over 5 years:				
	≥12 y	64 (60-68)	95 (95-96)	55 (51-59)	97 (96-97)
	12-18 y	75 (67-83)	92 (90-94)	59 (51-67)	96 (95-97)
	19-49 y	61 (54-67)	96 (95-97)	55 (48-61)	97 (96-97)
	≥50 y	61 (54-68)	96 (95-97)	53 (46-59)	97 (96-98)
	≥1 hospitalization OR ≥2 ambulatory medical visits over 5 years:				
	≥12 y	51 (46-55)	98 (97-98)	66 (61-70)	96 (95-96)
	12-18 y	60 (51-70)	97 (95-98)	74 (65-83)	94 (92-96)
	19-49 y	50 (44-57)	98 (97-98)	65 (58-72)	96 (95-97)
	≥50 y	45 (38-52)	98 (97-98)	62 (54-70)	96 (95-97)
	≥1 hospitalization OR ≥ ambulatory medical visit OR ≥1 pharmacy claim over 5 years:				
	≥12 y				
	12-18 y	84 (81-87)	89 (88-89)	40 (37-43)	98 (98-99)
	19-49 y	87 (81-94)	89 (86-91)	54 (47-61)	98 (97-99)
	≥50 y	82 (77-87)	91 (89-92)	41 (37-46)	98 (98-99)
		85 (80-90)	86 (85-88)	33 (29-38)	99 (98-99)
	≥1 hospitalization OR ≥2 ambulatory medical visits OR ≥2 pharmacy claims over 5 years:				
	≥12 y	75 (72-79)	94 (94-95)	54 (50-57)	98 (97-98)
	12-18 y	80 (73-88)	95 (93-96)	70 (62-78)	97 (96-98)

Author, year	Algorithm case definitions		Se (95% CI)*	Sp (95% CI)*	PPV (95% CI)*	NPV (95% CI)*
	19-49 y		71 (65-77)	96 (95-97)	59 (53-55)	98 (97-98)
	≥50 y		78 (72-84)	92 (91-93)	43 (38-49)	98 (98-99)
Lujic *et al.*, 2017 (36)	≥45 y, ≥1 hospitalization over 2 years		7 (6-8)	100 (100-100)	81 (77-84)	87 (87- 87)
	≥45 y, ≥2 pharmacy claims over 2 years		65 (65-66)	93 (93-93)	57 (57-58)	95 (95-95)
	≥45 y, ≥1 hospitalization over 2 years OR ≥2 pharmacy claims over 2 years		66 (65-67)	93 (93-93)	57 (57-58)	95 (95-95)
Omand et *al*., 2019 (25)	≥1 hospitalization for asthma OR ≥ two separate ambulatory or ED visits over 2 years:					
	1-5 y		81 (75-86)	90 (89-91)	34 (30-38)	99 (98-99)
	1-3 y		68 (49-83)	91 (89-92)	16 (10-23)	99 (98-100)
	3-5 y		83 (77-88)	89 (88-90)	41 (36-46)	98 (98-99)
Wakefield *et al.*, 2006 (31)	Probable asthma†: 6 months-18 y	≥1 hospitalization with a primary discharge dx OR ≥1 ED visit OR ≥1 ambulatory medical visit, over 1 year*: -Medicaid children	61 (59-64)	98 (98-99)	97 (96-98)	74 (72-75)
		(≥1 hospitalization or ≥1 ED visit or ≥1 ambulatory medical visit) OR (≥2 pharmacy claims), over 1 year: -Medicaid children	77 (75-79)	98 (97-98)	97 (96-98)	82 (81-84)
		(≥1 hospitalization or ≥1 ED visit or ≥1 ambulatory medical visit) OR (≥1 pharmacy claim), over 1 year: -Medicaid children	90 (89-92)	95 (94-96)	94 (93-95)	92 (90-93)
		-ConnectiCare children	80 (-)	93 (-)	75 (-)	95 (-)
	Persistent asthma‡: 6 months-18 y	(≥4 pharmacy claims) OR (≥1 hospitalization or ≥1 ED visit) OR (≥4 ambulatory medical visits and ≥2 pharmacy claims), over 1 year: -Medicaid children	44 (41-47)	94 (93-94)	69 (65-73)	85 (84-86)
		(≥4 pharmacy claims) OR (≥1 hospitalization or ≥1 ED visit) OR (≥1 ambulatory medical visit and ≥1 anti-inflammatory drug), over 1 year: -Medicaid children	67 (64-70)	93 (92-94)	75 (72-78)	90 (89-91)
	Medications used in all algorithms: Bronchodilators (including theophylline and salmeterol), ICS, OCS, and anti-inflammatory drugs (including LTRA)	(≥4 pharmacy claims) OR (≥1 hospitalization or ≥1 ED visit) OR (≥2 anti-inflammatory drugs), over 1 year: -Medicaid children	58 (54-61)	94 (93-95)	74 (71-77)	88 (87-89)
		(≥4 pharmacy claims) OR (≥1 hospitalization or ≥1 ED visit) OR (≥1 ambulatory medical visit and ≥ 1 anti-inflammatory drug) OR (≥2 anti-inflammatory drugs), over 1 year: -Medicaid children	72 (69-75)	93 (92-94)	76 (73-79)	92 (91-93)
		(≥4 pharmacy claims) OR (≥1 hospitalization or ≥1 ED visit) OR (≥1 ambulatory medical visit) OR (≥1 anti-inflammatory drug), over 1 year: -Medicaid children	92 (90-94)	80 (79-82)	59 (56-61)	97 (96-98)

Author, year	Algorithm case definitions	Se (95% CI)*	Sp (95% CI)*	PPV (95% CI)*	NPV (95% CI)*
	(≥4 pharmacy claims) OR (≥1 hospitalization or ED visit) OR (≥2 ambulatory medical visits) OR (≥1 anti-inflammatory drug), over 1 year:				
	-Medicaid children	87 (85-89)	89 (88-90)	70 (67-73)	96 (95-96)
	-ConnectiCare children	84 (-)	92 (-)	38 (-)	99 (-)
	(≥1 hospitalization or ≥1 ED visit) OR (≥2 ambulatory medical visits) OR (≥1 anti-inflammatory drug), over 1 year:				
	-Medicaid children	86 (84-88)	90 (89-91)	72 (70-75)	96 (95-96)
	(≥1 hospitalization or ≥1 ED visit) OR (≥3 ambulatory medical visits) OR (≥1 anti-inflammatory drug), over 1 year:				
	-Medicaid children	84 (81-86)	93 (92-94)	79 (76-81)	95 (94-96)
	-ConnectiCare children	78 (-)	93 (-)	41 (-)	99 (-)

Abbreviations: ATC: Anatomical Therapeutic Chemical Classification System; dx: diagnosis; ED: Emergency department; ICS: Inhaled corticosteroids; LABA: Long-acting beta2-agonists; LTRA: leukotriene antagonist receptors; OCS: Oral corticosteroids; SABA: Short-acting beta2-agonists; y: years old.

*Ambulatory medical visits, ED visits and hospitalizations refer to medical encounters that have an asthma diagnosis

**When applicable, validity statistics were rounded to the nearest integer

†The first algorithm of the "probable asthma" category correspond to the definition of the Council of State and Territorial Epidemiologists; the other two algorithms correspond to variations of this definition.

‡The first algorithm of the "persistent asthma" category correspond to the definition of the Health Plan Employer Data and Information Set; the other seven algorithms correspond to variations of this definition

Table 4. Diagnostic codes and medications used in algorithms of retained studies

Author, year	Codes used and medications (if applicable)
Andrade *et al.*, 2013 (32)	-ICD-9-CM: 493-493.92
Bechtold *et al.*, 2012 (34)	-Selective beta2-adrenergic agonists (ATC: R03AC) and adrenergics in fixed combination (ATC: R03AK)
Bianchi *et al.*, 2011 (35)	-Drugs belonging to the R03 main therapeutic group of the ATC
Biffi *et al.*, 2017 (33)	For the first operational definition in Table 1: -ICD-9-CM: 493; Exemption code: 007.493 -ATC: R03AK07, R03AK06, R03AC02. R03CC02, R03AC04, R03CC04, R03BA01, R03BA05, R03BA03, R03BA02, R03BA08, R03BC01, R03BC03, R03DA04, R03DC03 For the second and third operational definitions in Table 1: -ICD-9-CM: 493 -ATC: R03AC12, R03AC13, R03AK07, R03AK06, R03AC02, R03CC02, R03AC04, R03CC04, R03BA01, R03BA05, R03BA03, R03BA02, R03BC01, R03BC03, R03BB01, R03BB02, R03DA04, R03DC01, R03DC03, H02
Blais *et al.*, 2006 (12)	-ICD-9: 493.0; 493.1; 493.9
Bronstein *et al.*, 2000 (27)	-ICD-9: 493 -CPT-4: 94640; 94650; 94651; 94664; 94655
Dore *et al.*, 2014 (29)	-ICD-9: 493.xx
Dombkowski *et al.*, 2012 (28)	-ICD-9-CM: 493.0, 493.1, 493.2, 493.8, 493.9
Gershon *et al.*, 2009 (20)	-OHIP: 493
Hajibandeh *et al.*, 2017 (38)	-HES comorbidity codes: Not specified
Huzel *et al.*, 2002(21)	-ICD-9: 490, 491, 492, 493, 496
Kozyrskyj *et al.*, 2009 (22)	-ICD-9-CM; Controller medications: Not specified
Lix *et al.*, 2006 (23)	-ICD-9-CM: 493, -ATC: M02AA, M02AB01, M02AC, M02AX03, M04AA, R03AA01, R03AB02, R03AB03, R03AC02, R03AC03, R03AC04, R03AC08, R03AC12, R03AC13, R03AK01, R03AK03, R03AK04, R03AK06, R03BA01, R03BA02, R03BA03, R03BA05, R03BA06, R03BB01, R03BC01, R03BC03, R03CB01, R03CB03, R03CC02, R03CC03, R03CC07, R03CC53, R03CK, R03DA02, R03DA04, R03DA05, R03DA43, R03DA53, R03DA54, R03DA55, R03DA74, R03DB05, R03DC01, R03DC03, R06AX17, M02AA, M02AB01, M02AC, M02AX03, M04AA
Lujic *et al.*, 2017(36)	-ICD-10-AM: J45, J46 -ATC: R03AC02, R03AC03, R03AC12, R03AC13, R03AK06, R03BA01, R03BA02, R03BA05, R03BB01, R03BC01, R03BC03, R03CC02, R03CC03, R03DA04, R03DC03
Moth *et al.*, 2007(37)	-ATC: R03BA01, R03BA02, R03BA05, R03AC02, R03AC03, R03AC04, R03CC02, R03CC03, R03AC12, R03AC13, R03CC12, R03AK06, R03AK07, R03DC03, R03BC01, R03AK03 R03AK04, R03BB01, R03BB04, R03DA04
Omand et *al.*, 2019 (25)	-ICD-10: J45, J46 -OHIP: 493
To *et al.*, 2006 (24)	-OHIP: 493
Vollmer *et al.*, 2004 (30)	-ICD-9: Not specified
Wakefield *et al.*, 2006 (31)	-ICD-9: 493
Wilchesky *et al.*, 2004 (26)	-ICD-9: 493.0-493.9

Abbreviations: ATC: Anatomical Therapeutic Chemical Classification System; CPT-4: Current Procedures Terminology, 4th Edition; HES: Hospital Episode Statistics; ICD-9: International Statistical Classification of Diseases and Related Health Problems, Ninth Revision; ICD-9-CM; International Statistical Classification of Diseases and Related Health Problems, Ninth Revision, Clinical Modification; ICD-10: International Statistical Classification of Diseases and Related Health Problems, Tenth Revision; ICD-10-AM: International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification

4.3.1 Third Article: Supplementary Materials

The Validity of Diagnostic Algorithms to Identify Asthma Patients in Healthcare Administrative Databases: A Systematic Literature Review

Electronic supplementary material

S1: Bibliographic search strategy

S2: Quality assessment

TABLE S1: BIBLIOGRAPHIC SEARCH STRATEGY

Medline
(MH "Asthma") OR asthma* OR bronchospasm*
AND
(MH "Sensitivity and Specificity") OR specificit* OR sensitivit* OR "predictive value*" OR "positive predictive value*" OR "ppv" OR "negative predictive value*" OR "npv" OR valid* OR "roc curve*" OR "roc" OR "receiver operating characteristic*" OR "auc" OR "area under curve*" OR kappa*
AND
(MH "Health Information Systems") OR (MH "Billing and Claims") OR (MH "Coding") OR (MH "Databases, Factual") OR "administrative data*" OR "medico-administrative data*" OR "administrative register data*" OR "health* administrative data*" OR "administrative code*" OR "medico-administrative code*" OR "health* administrative code*" OR "health* data*" OR "billing data*" OR "billing code*" OR claim*

CINAHL, PsycINFO, Abstract in Social Gerontology, Ageline, All EBM Reviews
asthma* OR bronchospasm*
AND
specificit* OR sensitivit* OR "predictive value*" OR "positive predictive value*" OR "ppv" OR "negative predictive value*" OR "npv" OR valid* OR "roc curve*" OR "roc" OR "receiver operating characteristic*" OR "auc" OR "area under curve*" OR kappa*
AND
"administrative data*" OR "medico-administrative data*" OR "administrative register data*" OR "health* administrative data*" OR "administrative code*" OR "medico-administrative code*" OR "health* administrative code*" OR "health* data*" OR "billing data*" OR "billing code*" OR claim*

PubMed
asthma OR asthmas OR asthmatic OR bronchospasm OR bronchospasms
AND
specificity OR sensitivity OR "predictive value" OR "predictive values" OR "positive predictive value" OR "positive predictive values" OR "ppv" OR "negative predictive value" OR "negative predictive values" OR "npv" OR validation OR validity OR "roc curve" OR "roc curves" OR "roc" OR "receiver operating characteristic" OR "receiver operating characteristics" OR "auc" OR "area under curve" OR "area under curves" OR kappa OR kappas
AND
"administrative data" OR "administrative database" OR "medico-administrative data" OR "medico-administrative database" OR "administrative register data" OR "administrative register database" OR "health administrative data" OR "health administrative database" OR "healthcare administrative data" OR "healthcare administrative database" OR "administrative code" OR "administrative codes" OR "medico-administrative code" OR "medico-administrative codes" OR "health administrative code" OR "health administrative codes" OR "healthcare administrative code" OR "healthcare administrative codes" OR "health data" OR "health database" OR "healthcare data" OR "healthcare database" OR "billing data" OR "billing database" OR "billing code" OR "billing codes" OR claim OR claims

Embase
"asthma"/exp OR "bronchospasm"/exp OR "bronchospasm*":ti,ab,kw OR "asthma*":ti,ab,kw
AND
"sensitivity and specificity"/exp OR "predictive value"/exp OR "validity"/exp OR "receiver operating characteristic"/exp OR "area under the curve"/exp OR ("predictive*" NEXT/1 "value*"):ti,ab,kw OR "ppv":ti,ab,kw OR "npv":ti,ab,kw OR "sensitivity":ti,ab,kw OR "specificit*":ti,ab,kw OR "valid*":ti,ab,kw OR "receiver operat* characteristic*":ti,ab,kw OR "roc":ti,ab,kw OR "auc":ti,ab,kw OR "area under curve*":ti,ab,kw OR "kappa*":ti,ab,kw
AND
"administrative database"/exp OR "administrative data"/exp OR "billing and claims"/exp OR "medical information system"/exp OR 'factual database'/exp OR ("administrative*" NEAR/2 "data*"):ti,ab,kw OR ("administrative*" NEAR/2 "code*"):ti,ab,kw OR ("health*" NEAR/2 "data*"):ti,ab,kw OR ("billing*" NEAR/2 "data*"):ti,ab,kw OR ("billing*" NEAR/2 "code*"):ti,ab,kw OR ("billing*" NEAR/2 "billing*"):ti,ab,kw OR claim:ti,ab,kw OR claims:ti,ab,kw

Grey literature search:

We focused our grey literature search in the websites of Canadian health policy units: Health Canada, Canadian Institute for Health information, Health Canada, Institut national de santé publique du Québec, Régie de l'assurance maladie du Québec, and Institut de la statistique du Québec.

S2: QUALITY ASSESSMENT

The quality assessment is adapted from the Quality Assessment of Diagnostic Accuracy Studies revised tool (QUADAS-2)

Table S2: Evaluation results of risk of bias and generalisability domains (low, high, unclear or not applicable)

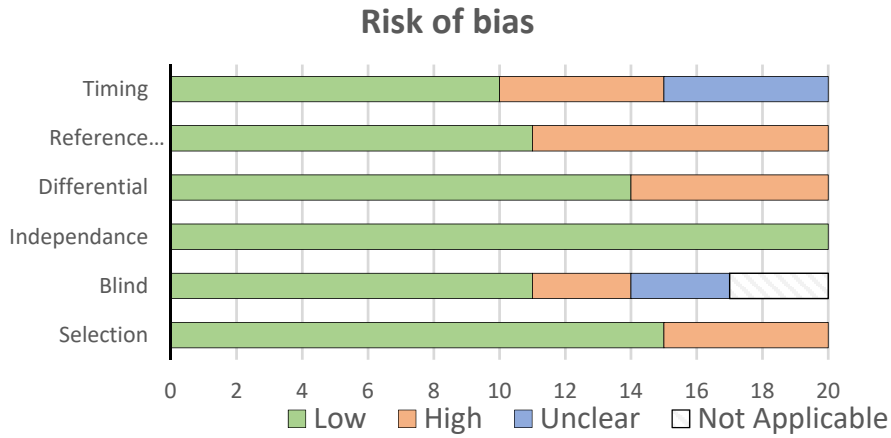
Studies (n=20)	Risk of bias							Generalisability		
	Patient selection	Blinding	Indepen-dence	Differential and/or partial	Reference standard*	Timing	**Score (1-6)†**	Patient spectrum§	Reference standard*	**Score (1-2)†**
Andrade, 2013	L	U	L	H	L	L	4	L	H	**1**
Bechtold, 2012	H	L	L	L	H	L	4	H	L	**1**
Bianchi, 2011	H	H	L	H	L	L	3	H	H	**2**
Biffi, 2017	L	L	L	H	H	U	3	H	H	**2**
Blais, 2006	L	L	L	L	L	L	6	H	H	**2**
Bronstein, 2000	H	L	L	L	L	L	5	H	H	**2**
Dore, 2014	L	L	L	L	H	L	5	L	H	**1**
Dombkowski, 2012	L	H	L	H	H	U	2	H	L	**1**
Gershon, 2009	L	L	L	L	L	U	5	H	H	**2**
Hajibandeh, 2017	L	H	L	H	L	U	3	L	L	**0**
Huzel, 2002	H	NA	L	L	H	H	2	L	L	**0**
Kozyrskyj, 2009	H	U	L	L	L	H	3	H	H	**2**
Lix, 2006	L	NA	L	L	H	H	3	H	L	**1**
Lujic, 2017	L	NA	L	L	H	L	4	L	L	**0**
Moth, 2007	L	U	L	H	L	L	4	H	H	**2**
Omand, 2019	L	L	L	L	H	U	4	H	L	**1**
To, 2006	L	L	L	L	L	L	6	L	H	**1**
Vollmer, 2004	L	L	L	L	L	L	6	H	H	**2**
Wakefield, 2006	L	L	L	L	H	H	4	L	L	**0**
Wilchesky, 2004	L	L	L	L	L	H	5	L	H	**1**
Total Low	15	11	20	14	11	10		8	8	
Total High	5	3	0	6	9	5		12	12	
Total Unclear	0	3	0	0	0	5		0	0	
Total NA	0	3	0	0	0	0		0	0	

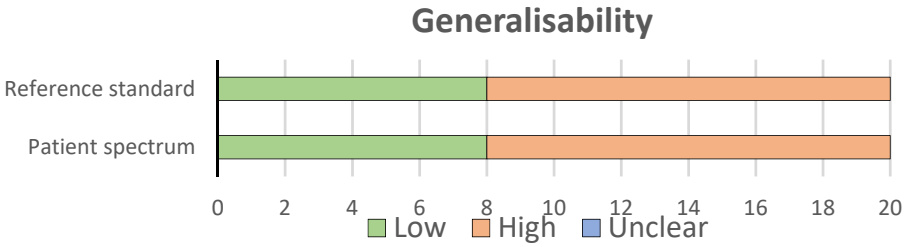
§ Studies combining adult and pediatric populations were considered highly generalizable

* For studies using self-reported data such as surveys, interviews and questionnaires (Dombkowski, Wakefield, Lix, Huzel, Bechtold, Omand): Due to bias associated with self-reported data, such as social desirability, recall period, sampling approach, or selective recall, the risk of bias and applicability of reference standards of these studies were rated high and low respectively.

† For the risk of bias domain, the total score for each study corresponds to the number of 'low' ratings. For the generalisability domain, the total score for each study corresponds to the number of 'high' ratings.

Figure S1: Summary of risk of bias and generalisability (low, high, unclear or not applicable)





Section 2: Signaling questions and rating criteria

RISKS OF BIAS

Patient selection: Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?

- Low: The whole sample/random selection of the sample received verification using medical records/physician questionnaire; case–control design avoided; inappropriate exclusions avoided
- High: some of the sample did not receive verification because reference standard data were missing (missing records/unreturned questionnaires); case–control design; inappropriate exclusions

Blinding: Were the reference standard results interpreted without knowledge of the results of the index test (data algorithm)?

- Low: blinding present, or the reference standard diagnosis was made prior to the study (eg., the reference standard was a prospectively generated register); codes assigned without knowledge of reference standard;
- High: blinding not present, or not reported
- Unclear: insufficient published data
- Not applicable: the results (of index test and/or ref standard) are objective, i.e. are not "interpretable". For instance, review of full medical records to confirm diagnostics is "interpreted" by the abstractor, but a direct result, such as a diagnostic code or a self-reported condition, is not.

Independence: Was the reference standard independent of the index test (i.e. index test did not form part of the reference standard)?

- Low: the reference standard was independent of the index test
- High: the index test formed part of the reference standard (eg., coded diagnoses were used to identify disease cases, and there was no further confirmation)

Differential and/or partial: Did all patients receive the same reference standard regardless of the index test result?

- Low: yes
- High: some/all code positive cases received different reference standards from code negative cases eg., disease code positive cases not present in a disease register (potential false positive cases) were selected for subsequent medical record review, but disease code negative cases present in asthma register (potential false negative cases) did not have subsequent medical record review; not all patients who were evaluated with the index test received the same reference standard; If only assessing patients with positive reference – or do not receive the same RS.

Reference standard: Is the reference standard likely to correctly classify the patient?

- Low: the reference standard was likely to identify all cases (hospitals, primary care, community), AND was either based on an expert reviewing the full medical record or was based on a non-expert (eg., research assistant, research nurse, or 'adjudicator') following clearly described rules
- High: the reference standard diagnosis was made by a non-expert and there was not a clear protocol to exclude differential diagnoses (or other conditions that could be confused with the

target condition), and/or the reference standard used self-reported data such as questionnaires, interviews or surveys.

<u>Flow & timing</u>: Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?

- Low: The information used to make the reference standard diagnosis was the same as the information used at the time of coding, or the time period between the reference standard and the index test is short enough to be reasonably sure that the target condition did not change between the two tests.
- High: The information used to make the reference standard diagnosis was not the same as the information used at the time of coding
- Unclear: insufficient published data

GENERALISABILITY

<u>Patient selection</u>: Was the patient spectrum representative of the patients who will receive the test in practice?

- Low: the study was performed in a more selected population (eg., restricted to patients admitted to medical specialties, where coding performance might be higher)
- High: the study included patients diagnosed and treated in a representative mixture of specialist and non-specialist settings, and the population was otherwise relatively unselected.
- Unclear: insufficient published data

<u>Reference standard</u>: Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?

- Low: data specific of asthma such as lung function tests results not available
- High: medical record data (extracts or full record) including data specific of asthma that would be used in current practice to exclude other pulmonary conditions
- Unclear: insufficient published data

Reference:

Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Annals of internal medicine. 2011;155(8):529-536.

4.4 Fourth Article: Delphi Study – Treatment Escalation in Asthma

Development of Treatment Escalation Operational Definition for Asthma Adapted to Healthcare Administrative Databases: A Delphi Study

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Author contributions

AY wrote the first draft of the manuscript. AY and RFB conducted the literature review and extracted the data. AF and AY conducted the cohort study. ND, CL, MFB, LB, and AY contributed to the recruitment of experts. AF, MBF, CL, ND, LB, and LB contributed to the development of the Delphi questionnaires. All authors interpreted the data, revised the manuscript, had access to the complete study data, and had authority for manuscript preparation, approval of the final version, and the decision to submit for publication.

Declaration of competing interest

AY received a doctoral training award from the *Fonds de Recherche du Québec – Santé*. LB has received research grants and professional fees from AstraZeneca, GlaxoSmithKline, and Genentech for studies unrelated to this work. MFB has received speaker fees and research grants from AstraZeneca, Boehringer-Ingelheim, and Novartis for studies unrelated to this work. CL is a consultant for AstraZeneca, GlaxoSmithKline, Sanofi Genzyme, and TEVA Innovation, and has received research grants from AstraZeneca and TEVA Innovation for studies unrelated to this work. AF, ND, and RFB have no conflicts of interest to disclose, financial or otherwise.

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ABSTRACT

Background: A growing interest to study asthma treatment escalation patterns in the real-world has recently emerged, notably with the marketing of novel and expensive biologic therapies in severe asthma. Healthcare administrative claims databases can serve as a useful tool to study treatment escalation patterns at a population-level; however, claims-based asthma treatment escalation definitions reported in the literature are variable. The aim of this study was to develop an operational definition of treatment escalation in adults with asthma that can be applied to healthcare administrative data, through a rigorous expert consensus.

Methods: A mixed-methods research design incorporating a Delphi process was used to build consensus regarding the treatment escalation definition. A multi-disciplinary expert panel participated in three iterative rounds of structured online questionnaires, which were based on treatment escalation criteria that were inspired from a systematic review that was conducted as part of this study. The final definition was constructed using criteria for which a 75% level of agreement was achieved among experts. The applicability of the definition was tested in a population-based cohort of asthma patients.

Results: We developed a claims-based treatment escalation definition that was adapted from the Global Initiative for Asthma treatment guidelines. Its salient features include seven treatment steps, as well as escalation options for treatments that are not typically found in clinical guidelines. Additionally, the definition provides methods to identify treatments in severe asthma, such as oral corticosteroid maintenance therapy and chronic azithromycin use.

Conclusions: The operational definition of treatment escalation presented in this study bridges the gap between clinical guidelines and the real-world practice setting and lays the groundwork for future observational studies on treatment escalation patterns among individuals with asthma.

Key words: Asthma, treatment escalation, healthcare administrative databases, Delphi, expert consensus

INTRODUCTION

As a leading cause of chronic morbidity, asthma imposes an enormous societal and economic burden worldwide, affecting over 334 million people.[1] Although there is no cure, a plethora of effective treatments exist, of which inhaled corticosteroids (ICS), alone or in combination with long-acting beta2-agonists (LABA), are the most commonly prescribed. The Global Initiative for Asthma (GINA)[2] recommend to treat asthma patients with a step-care approach, whereby ICS doses are gradually increased, or other controller medications are added when disease control is unachieved. In recent years, there has been growing interest to study treatment escalation in the clinical practice setting, especially with the advent of novel therapies indicated in patients with severe asthma.

Treatment decision-making in asthma is complex and relies on assessment of common problems, such as inhaler technique, environmental control, disease control, and medication adherence.[2] An area in the literature that remains underexplored is the relationship between medication adherence and treatment escalation. Indeed, medication adherence in asthma patients often falls below 50%,[3,4] and is associated with sub-optimal treatment outcomes, including inadequate disease control and increases in healthcare utilization.[5,6] Medication adherence problems are further exacerbated by physicians' struggle to measure adherence accurately in clinical practice. Indeed, physicians commonly rely on patient self-report; yet this method is prone to inaccuracies since patients often over-estimate their adherence due to incorrect recall or social desirability bias.[7-9] Most often, physicians' decision to intensify treatment is mainly based on disease control, even when non-adherence may be the underlying reason behind uncontrolled disease. Due to the incremental approach to therapy, failure to detect non-adherence in asthma patients may result in unnecessary treatment escalation that can increase the risk of adverse events and lead to higher level of non-adherence due to more complex and costly drug regimens.

Healthcare administrative claims databases, including pharmacy claims, can be used to efficiently study the association between medication adherence and treatment escalation. However, identifying treatment escalation using these data is challenging owing to the complexity of the asthma therapeutic landscape. Although the literature on this topic is limited, the most reported method of studying treatment escalation in healthcare administrative databases is through the identification of step-up episodes that correspond to clinical practice guidelines.[10-15] However, claims-based treatment escalation definitions reported in the literature are variable, mainly due to differing interpretations of asthma treatment guidelines. Another critical issue to keep in mind is that current treatment guidelines provide a framework that physicians can use to tailor their patient's therapy to their disease severity and level of disease control; they were not designed to identify treatment escalation at a population-level. In this

context, it is crucial to pinpoint the different treatment possibilities in clinical practice and ascertain all clinical scenarios for which the prescriber's original therapeutic intent was to escalate therapy. Ideally, such an undertaking can be achieved through expert consensus.

The aim of this study was to develop an operational definition of treatment escalation in asthma that can be applied to healthcare administrative data, through a Delphi process based on expert consensus. Since treatment recommendations differ in pediatric populations, this study focused on asthma in adult populations. This study will form the basis of a future cohort study aiming to evaluate the association between medication adherence and treatment escalation in the real-world setting.

METHODS

Study Design

A mixed-methods research design incorporating a Delphi process was used to build consensus regarding the treatment escalation definition. The Delphi method is a flexible group facilitation technique that can be used to determine consensus for a defined clinical problem for which little or no evidence exists or for which there is contradictory information.[16,17] Specifically, consensus was achieved through an iterative process that employs a systematic progression of repeated rounds of voting among an expert panel through online questionnaires. We formed a multi-disciplinary expert panel which included 4 pulmonologists, 3 hospital pharmacists, 3 community pharmacists, 2 family physicians, and 2 epidemiologists. Panel members were recruited by email and came from major metropolitan areas in Canada, including Montreal, Toronto, and Quebec City. Participants had at least 10 years of clinical and/or research experience in epidemiology. Consultation rounds took place between March and September 2020.

The starting point of the Delphi process consisted of a systematic review aiming to identify the different criteria and clinical scenarios that can be used to ascertain asthma treatment escalation using routinely collected electronic healthcare data. Using Canadian healthcare administrative databases, we subsequently constructed the claims-based algorithm that reflected the operational treatment escalation definition that was proposed by the expert panel during the Delphi process and applied it to a population-based cohort of asthma patients.

Systematic literature review

We identified observational studies examining asthma treatment escalation using routinely collected electronic healthcare data, including healthcare administrative claims and electronic health record (EHR)

data. To identify relevant articles, we searched the following databases from January 1996 to March 2020: Medline, Embase, CINAHL, Global Health, and all Evidence-Based Medicine Reviews. Search strategies were developed in collaboration with a librarian. The screening and data extraction process was conducted according to PRISMA guidelines. A complete list of search terms and details on screening/data extraction methods are found in the electronic supplementary files (S1). Based on the review literature findings, knowledge gaps were identified and were used to develop the Delphi questionnaires.

Delphi process

1. Development of questionnaires and consensus process

Consensus among the 15 experts was achieved via an iterative process consisting of three rounds of structured online questionnaires. In round 1, experts were asked to rate the clinical relevance of different criteria that can be used to identify treatment escalation in asthma, based on the literature review findings and treatment guidelines. They were also presented with various clinical scenarios and requested to identify the ones for which the prescriber's therapeutic intent was the mostly likely to escalate therapy. In round 2, a treatment escalation definition based on the criteria for which there was the highest level of agreement among the experts in round 1 was presented. Experts were required to further refine the criteria presented in the definition. Round 3 was conducted for confirmatory purposes and experts were requested to validate and refine the definition of treatment escalation developed in round 2. In all rounds, percent agreement was the metric used to identify expert consensus. Retained criteria were those for which there was at least a 75% agreement among experts, a threshold based on previous literature.[18] Prior to each round, the questionnaires were pilot tested with healthcare researchers unfamiliar with the project to evaluate content validity and to ensure that questions were clearly written. Study data were collected using REDCap, an electronic data capture tools.[19,20]

2. Application of the treatment escalation definition in a population-based cohort

The applicability of the definition proposed during the Delphi process was tested within a cohort of asthma patients through two phases. In Phase I, all treatment possibilities in the cohort were identified and subsequently compared to the definition proposed by the experts at each round to ensure that the definition captured all relevant clinical scenarios. In Phase II, treatment escalation rates were estimated once the definition obtained from the Delphi process was finalized.

Data source

A cohort of 90, 567 individuals with asthma was constructed. Subjects were selected from the Asthma and COPD patients with Public drug Insurance (ACPI) database, which was formed by linking two Quebec (Canada) administrative databases. 1) The *Régie d'assurance maladie du Québec* (RAMQ) medical service and drug claims database; and 2) *Maintenance et exploitation des données pour l'étude de la clientèle hospitalière* (MED-ECHO) hospitalization database. Eligible subjects had an asthma diagnosis, defined by at least one hospitalization with a diagnosis of asthma in the MED-ECHO database or two ambulatory medical visits with a diagnosis of asthma within two consecutive years recorded in the RAMQ database between January 1, 2002 and December 31, 2015. This definition was shown to have a high sensitivity (83.8%) and specificity (76.5%) in Canadian administrative databases.[21,22] Cohort entry (CE) corresponded to the date of a new prescription for an asthma controller medication following asthma diagnosis and subjects were followed until the earliest occurrence of one of the following events: treatment escalation as defined by experts; end of coverage of the RAMQ drug insurance; date of death; 2 years of follow-up or December 31, 2016. Details on cohort eligibility criteria, flow chart of cohort selection, and subject baseline characteristics are presented in the supplementary file (S2).

Phase I: Identification of treatment possibilities during the Delphi process

Prior to the first round and developing the first questionnaire, treatments at CE were identified to obtain an overview of treatment possibilities in clinical practice. In subsequent rounds, treatment escalation definitions proposed by experts were tested within the cohort. Treatments at CE and treatment escalation identified at follow-up were manually reviewed by the research team to ensure they were all captured by the escalation definition proposed at each round and that treatment escalation events were clinically coherent. This treatment identification process was repeated between each round, until all treatment possibilities were captured by the definition proposed by the experts. Treatment ascertainment methods at baseline and during follow-up are presented in the supplementary file (S2).

Phase II: Estimation of treatment escalation rates using the final definition of the Delphi panel

Once the treatment escalation definition was finalized, treatment escalation rates and corresponding 95% confidence intervals (CI) at 6, 12, and 24 months post CE were estimated. Among patients whose treatment was escalated, we also summarized, using propositions, the treatment steps that they transitioned to, according to treatment step at CE.

Ethics approval

This study was approved by the research ethics committee of the *Centre Intégré Universitaire de santé et de services sociaux du Nord-de-l'île-de-Montréal.*

RESULTS

Systematic literature review

A total of 7 studies, mostly published in the last 5 years, met the eligibility criteria (Figure 1). The majority of studies were conducted in the United States (n=4)[10-12,15] and the remainder were conducted in the United Kingdom[14,23] and Australia.[13]

Operational definitions used to describe treatment escalation

The definitions of treatment escalation differed widely across studies (Table 1). Of note, none of the studies have used rigorous methods or expert opinion to establish the definitions. The most common definitions entailed a transition to a higher step, defined in accordance with treatment guidelines, with GINA being the most used guidelines. One study defined treatment escalation as evidence of either inhaled corticosteroids (ICS) dose increase, or add-on/switch from another controller medication [LABA, leukotriene receptor antagonists (LTRA) or long-acting muscarinic agents (LAMA)] to an existing ICS-containing treatment.[14,15]

Methods to identify long-term OCS therapy differed greatly across studies. Two studies required continuous use of OCS for a minimum time period, ranging between 14 to 60 days,[11,12] whereas one study defined OCS maintenance therapy as any dispensing of low dose prednisone or prednisolone (1-5 mg), without specifying the time frame.[13] In three studies, patient EHR were reviewed to determine whether the OCS was dispensed for maintenance therapy and not for acute use only.[10,14,23] Finally, one study did not consider OCS maintenance therapy as a treatment escalation possibility.[15]

Rates of treatment escalation obtained from literature review

Reported proportions of treatment escalation ranged from 0.7 to 30%, depending on the study population, disease severity, follow-up duration and treatment escalation definition. As a prime example, Zeiger *et al*.[24] found that 30% of patients with uncontrolled disease had their treatment stepped up within 3 months. On the other hand, Bengtson *et al.*[15] found that among asthma patients who initiated a long-term ICS-containing regimen, approximately 14% escalated therapy within a year of initiation. Van Boven *et al*.[24] and Buhl *et al.*[14] both studied treatment escalation in asthma patients with moderate-to-severe

asthma who initiated ICS/LABA combination, but reported drastically different rates over a 1-year period (3.9-15.2%).

Development of Delphi questionnaires

The literature review identified several discrepancies regarding the asthma treatment escalation definitions used across studies. Thus, the questionnaires that were administered in the Delphi rounds aimed at harmonizing these findings. As previously mentioned, the cohort study that was conducted alongside the Delphi process (Phase I) provided insights on real-world treatment patterns and helped develop the round-specific questionnaires. All questionnaires are presented in the supplemental materials (S3).

Delphi process

Summary of first round

In round 1, most of the questions evaluated the experts' preferences with the different criteria that can be used to identify asthma treatment escalation and OCS maintenance therapy, based on the literature review findings. To identify treatment escalation, the participants preferred the definition which entailed a transition to a higher treatment step, defined in congruence with the GINA guidelines. Other criteria having a high level of agreement among experts included evidence of either ICS or ICS-containing therapy dose increase and add-on of another controller medication to the existing therapy. Experts highlighted that a definition based on treatment guidelines was clinically intuitive and adapted to the patients' level of disease control. However, many experts pointed out that treatment steps are not always followed in clinical practice. To address this limitation, we retained the definition based on the GINA 2020 treatment steps, but adaptations were made in subsequent rounds to ensure that all treatment possibilities were considered.

Second and third rounds: Development of treatment escalation operational definition

The operational definition of asthma treatment escalation that was developed in rounds 2 and 3 is presented in Figure 2. This definition can be applied in any cohort in which: i) a treatment has been identified at CE, hereafter referred to as "baseline treatment"; ii) a new treatment has been identified during follow-up, hereafter referred to as "new treatment". The first part of the definition requires to categorize the "baseline treatment" and "new treatment" based on a modified version of the GINA 2020 guidelines (Figure 2, Part A). The most significant changes proposed by the panel consisted of splitting

steps 4 and 5 into two parts each to consider the different possibilities of treatment add-ons and to distinguish patients with more severe forms of asthma. In light of recent findings which provide evidence that chronic macrolide therapy could reduce the number of exacerbations in severe uncontrolled asthma,[25] the panel also recommended to add low-dose azithromycin in step 5b. Additionally, treatments that do not fit the GINA 2020 treatment guidelines were referred to as "other treatments".

Once the treatment baseline categorization in Part A is completed, then treatment escalation can be identified using three different options (Part B, Figure 2). These options consider transitions to higher treatment steps, ICS dose increases, and controller medication add-on.

Considerations for severe asthma

Other than biologic therapy, patients with severe asthma can be treated with chronic OCS or azithromycin use. The experts acknowledged the challenges of identifying these treatments using healthcare administrative databases, since information on drug indication or complete information on posology is not typically available in pharmacy claims data. To this end, the experts put forth several definitions to ascertain these treatments (Figure 3). To identify chronic OCS, the experts agreed that individuals should have a total days' supply of OCS of at least 90 days over a 180-day evaluation period. They also agreed that excluding individuals with asthma who have other concomitant conditions for which long-term use of OCS is common or is the mainstay therapy was an appropriate method to isolate individuals who use OCS exclusively to treat their asthma. The experts proposed a list of these conditions, which was inspired and adapted from a list obtained from the literature.[26] Alternatively, to avoid excluding patients unnecessarily based on their comorbidities, it was suggested to take into account these comorbidities during the identification of treatment escalation. Specifically, if a person is prescribed OCS maintenance therapy as a treatment add-on, this treatment change would constitute an escalation only if the individual does not have any prior comorbidities for which chronic use of OCS is the mainstay therapy. Lastly, the experts suggested that an individual with asthma can be considered on chronic azithromycin if at least 3 prescriptions were filled within a 6-month period, with each prescription lasting at least 28 days.

Application of treatment escalation operational definition in the population-based cohort

Upon CE, 4.5% of asthma subjects had a treatment that corresponded to "other treatments", i.e. treatments that do not follow practice guidelines. After applying the treatment escalation definition in the cohort, the overall rate of treatment escalation was 16.7 (95% CI: 16.5-17.0) and 11.0 (95% CI: 10.8-11.3) cases per 100 person-years, respectively, in the first and second year following the dispensing of a

new prescription of a controller medication. Of note, these new prescriptions do not necessarily coincide with a new treatment initiation. Among subjects whose treatment was escalated, most patients with moderate asthma (steps 3-4b) transitioned to the consecutively higher treatment step (Table 2). In contrast, most individuals in steps 5a or 5b whose treatment was escalated remained in their respective step but received either an ICS dose increase or a treatment add-on (Table 2). As shown in Table 3, rates of treatment escalation were consistently higher in the first 6 months of follow-up across all treatment steps and were higher in patients with milder forms of asthma (step 2 and 3). The complete list of treatments identified at CE and during follow-up are presented in the supplementary material (Tables S2.8-S2.9).

DISCUSSION

Through rigorous research methods that were supported by an expert panel, we developed a treatment escalation definition that was adapted from the GINA guidelines. This definition comprises three options and takes into account transition to higher treatment steps, inhaled corticosteroid dose increases, and controller treatment add-on, as well as treatments that are not typically included in clinical guidelines. Furthermore, the applicability of this operational definition was successfully tested in a population-based cohort of adults with asthma.

The systematic review that was conducted as the starting point for the Delphi process revealed that operational definitions of asthma treatment escalation are highly variable across the literature. Additionally, none of the definitions appeared to have been established through a rigorous expert consensus. These differences were further reflected by the discrepancies in the treatment escalation rates reported in the retained studies. Although these studies collectively provided valuable insight on treatment escalation patterns in the real-world setting, some of the approaches used to identify treatment escalation failed to include all treatment possibilities in clinical practice, particularly in severe asthma. As a prime example, definitions of OCS maintenance therapy were inconsistent throughout the studies and were at times too simplistic. Additionally, most definitions in the studies entailed transitions to higher treatment steps based on clinical guidelines; however, our experts pointed out that treatment escalation can still occur if an individual remains on the same step after a treatment change. Overall, the Delphi process was a successful approach in harmonizing the findings from the literature review and proved to be a useful method to identify treatment escalation patterns in population-based observational studies.

In the cohort analysis, 4.5% of the identified treatments did not fit clinical guidelines, echoing findings from studies in the review. For instance, Zeiger *et al.*[10] and Broder *et al.*[11] reported, respectively, that 2.5 and 15% of patients with uncontrolled asthma had treatments that could not be classified according to the NHLBI Expert Panel Report 3 guidelines. Although the definition proposed in our study is based on treatment guidelines, it also includes treatments that are not typically found in guidelines and presents clinical scenarios for which the prescriber's therapeutic intent was most likely to escalate treatment.

In recent years, the arsenal of asthma treatment options has broadened with the advent of novel agents, particularly monoclonal antibody therapies targeting IgE, interleukin (IL)-4/IL-13 and IL-5 cytokine pathways. With the expected rise in the use of expensive biologics and increasing evidence on the impact of OCS adverse effects, understanding how prescribing patterns compare with clinical treatment guidelines will help us gain insight on the key aspects that prevent optimal pharmacological treatment. Given the complex therapeutic landscape of asthma, the necessity to adequately identify treatment escalation in asthma at a population level is relevant. Furthermore, the findings of this study can form the basis of future studies which aim to evaluate the relationship between asthma control, medication adherence, and treatment escalation. Such studies could provide insight on physician prescribing practices and could ultimately help determine whether patients' treatment escalation was an appropriate treatment decision.

To the best of our knowledge, this study is the first to develop an operational definition of treatment escalation that is based on expert consensus. An important strength of the Delphi process is the incorporation of a systematic literature review, which provided valuable guidance for the development of the questionnaires that were administered in the consultation rounds. Another salient feature is the iterative process that was used to develop the treatment escalation definition, which was informed by the expert opinion and the cohort analysis. Despite these methodological strengths, the results of this study should be interpreted in the light of some limitations. Namely, the participants of the Delphi process only included Canadian experts; yet a multi-national panel would have enhanced the generalizability of study findings. However, since our definition was based on international guidelines, we believe that it could easily be applied or adapted to different healthcare settings. Moreover, future studies are required to ensure the applicability of the treatment escalation definition across various databases. Lastly, the cohort study used to test the definition was based on administrative data that were retrospectively collected between 2002 and 2016, which prevented us from ascertaining treatments that appeared in more recent treatment guidelines, such as chronic azithromycin use.

CONCLUSIONS

This study provided an expert consensus on an operational definition of treatment escalation adapted to healthcare administrative database using rigorous mixed research methods. Given its broad clinical implications, this definition of treatment escalation lays the groundwork for future real-world observational studies on treatment escalation patterns among asthma patients.

REFERENCES

1. Global Asthma Network. The Global Asthma Report; 2014. *Auckland, New Zealand.* 2014.
2. Global Initiative for Asthma. Pocket Guide for Asthma Management and Prevention. 2020; https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_-final-_wms.pdf.
3. Blais L, Kettani FZ, Beauchesne MF, Lemiere C, Perreault S, Forget A. New measure of adherence adjusted for prescription patterns: the case of adults with asthma treated with inhaled corticosteroid monotherapy. *The Annals of pharmacotherapy.* 2011;45(3):335-341.
4. Wu AC, Butler MG, Li L, et al. Primary adherence to controller medications for asthma is poor. *Annals of the American Thoracic Society.* 2015;12(2):161-166.
5. Dima AL, Hernandez G, Cunillera O, Ferrer M, de Bruin M. Asthma inhaler adherence determinants in adults: systematic review of observational data. *European Respiratory Journal.* 2015;45(4):994.
6. Mäkelä MJ, Backer V, Hedegaard M, Larsson K. Adherence to inhaled therapies, health outcomes and costs in patients with asthma and COPD. *Respiratory Medicine.* 2013;107(10):1481-1490.
7. Lim KG, Rank MA, Li JT, et al. How well does patient self-report predict asthma medication possession? Implications for medication reconciliation and adherence assessment. *Journal of Asthma.* 2010;47(8):878-882.
8. Bender B, Wamboldt F, O'Connor SL, et al. Measurement of children's asthma medication adherence by self report, mother report, canister weight, and Doser CT. *Annals of Allergy, Asthma & Immunology.* 2000;85(5):416-421.
9. Gamble J, Stevenson M, McClean E, Heaney LG. The prevalence of nonadherence in difficult asthma. *American journal of respiratory and critical care medicine.* 2009;180(9):817-822.
10. Zeiger RS, Schatz M, Li Q, Zhang F, Purdum AS, Chen W. Step-up care improves impairment in uncontrolled asthma: an administrative data study. *The American journal of managed care.* 2010;16(12):897-906.
11. Broder MS, Chang EY, Sapra S. Care of asthma patients in relation to guidelines. *Allergy and asthma proceedings : the official journal of regional and state allergy societies.* 2010;31(6):452-460.
12. Dilokthornsakul P, Thompson AM, Campbell JD. Treatment patterns and related clinical consequences in adults with asthma. *The Journal of asthma : official journal of the Association for the Care of Asthma.* 2019;56(7):739-747.
13. van Boven JFM, Koponen M, Lalic S, et al. Trajectory Analyses of Adherence Patterns in a Real-Life Moderate to Severe Asthma Population. *The Journal of Allergy and Clinical Immunology: In Practice.* 2019.
14. Buhl R, Heaney LG, Loefroth E, et al. One-year follow up of asthmatic patients newly initiated on treatment with medium- or high-dose inhaled corticosteroid-long-acting β(2)-agonist in UK primary care settings. *Respir Med.* 2020;162:105859.
15. Bengtson LGS, Yu Y, Wang W, et al. Inhaled Corticosteroid-Containing Treatment Escalation and Outcomes for Patients with Asthma in a U.S. Health Care Organization. *Journal of managed care & specialty pharmacy.* 2017;23(11):1149-1159.
16. Jones J, Hunter D. Consensus methods for medical and health services research. *Bmj.* 1995;311(7001):376-380.
17. Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. *Journal of Advanced Nursing.* 2000;32(4):1008-1015.

18. Diamond IR, Grant RC, Feldman BM, et al. Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. *Journal of clinical epidemiology.* 2014;67(4):401-409.
19. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. A metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of biomedical informatics.* 2009;42(2):377-381.
20. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international community of software platform partners. *Journal of biomedical informatics.* 2019;95:103208.
21. Gershon AS, Wang C, Guan J, Vasilevska-Ristovska J, Cicutto L, To T. Identifying patients with physician-diagnosed asthma in health administrative databases. *Canadian respiratory journal : journal of the Canadian Thoracic Society.* 2009;16(6):183-188.
22. Yousif A, Dault R, Courteau M, et al. The validity of diagnostic algorithms to identify asthma patients in healthcare administrative databases: a systematic literature review. *Journal of Asthma.* 2020:1-17.
23. Gayle A, Tebboth A, Pang M, et al. Real-life prescribing of asthmatic treatments in UK general practice over time using 2014 BTS/SIGN steps. *NPJ Prim Care Respir Med.* 2019;29(1):25.
24. Stone B, Davis JR, Trudo F, et al. Characterizing patients with asthma who received Global Initiative for Asthma steps 4-5 therapy and managed in a specialty care setting. *Allergy and asthma proceedings : the official journal of regional and state allergy societies.* 2018;39(1):27-35.
25. Gibson PG, Yang IA, Upham JW, et al. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial. *The Lancet.* 2017;390(10095):659-668.
26. Liu D, Ahmet A, Ward L, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. *Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology.* 2013;9(1):30.

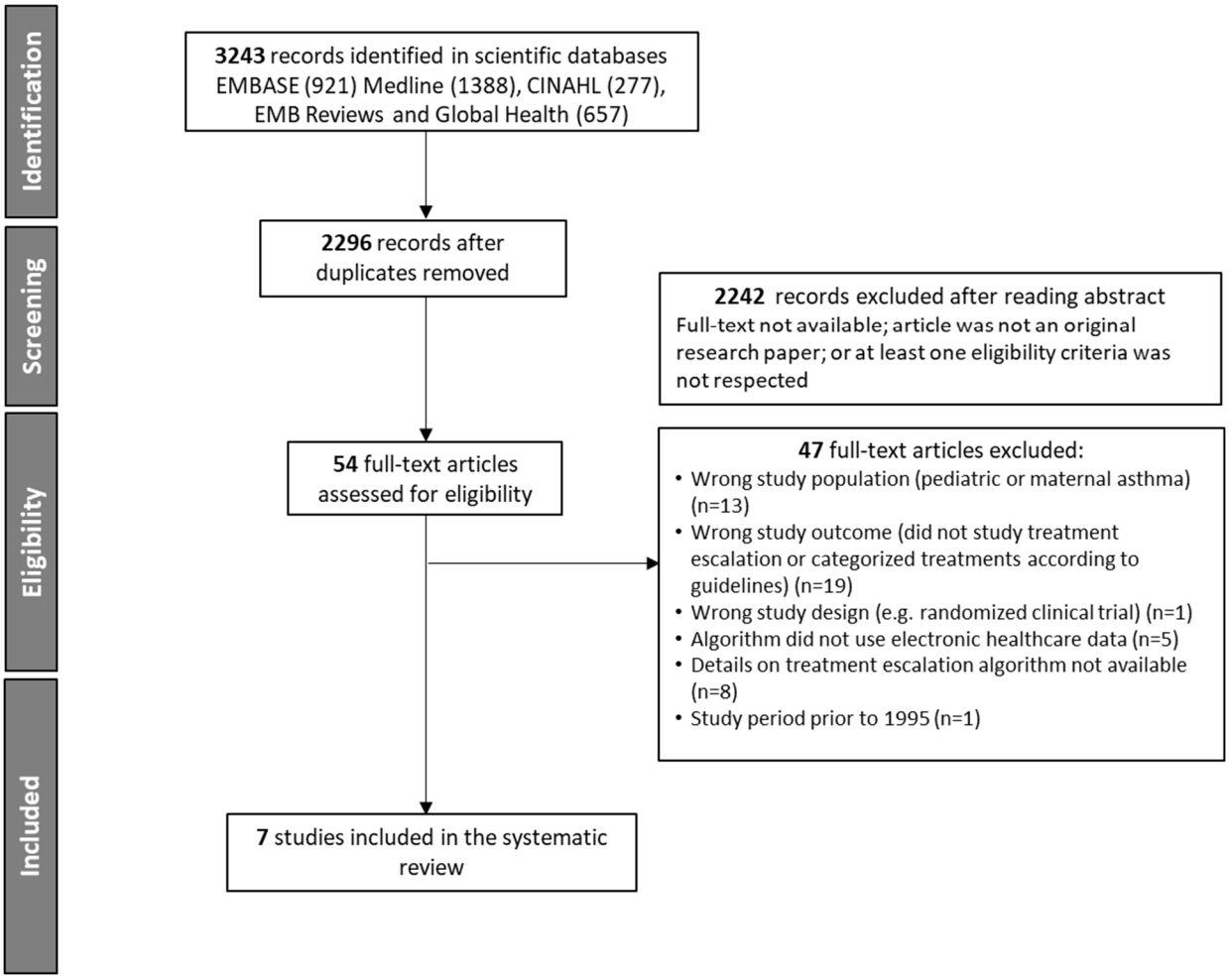
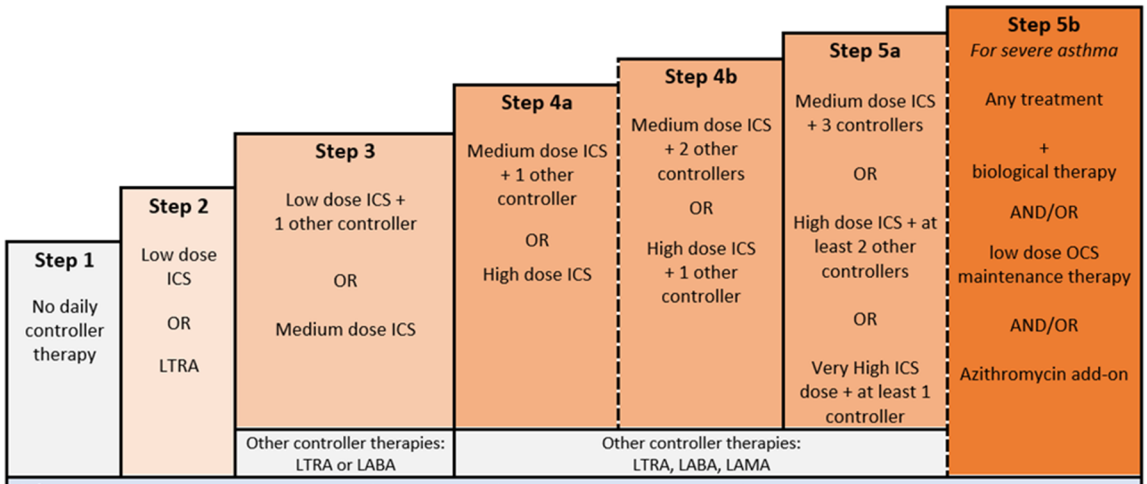


Figure 1. PRISMA-style flow chart of study selection and review

PART A: TREATMENT IDENTIFICATION

Baseline and new treatments are categorized in accordance with a modified version of GINA 2020 treatment steps:



Other treatments —Treatments that are less frequently prescribed. Examples are presented below:

- Any theophylline-containing therapy
- LTRA + at least 1 other controller therapy (besides ICS)
- Low dose ICS + at least 2 other controller therapies (e.g. Low dose ICS + LABA + LTRA)
- Very dose high ICS monotherapy

ICS dose:
Low: < 250 mcg/day; Medium: 250-499 mcg/day; High: 500-1000 mcg/day; Very high: >1000 mcg/day; *Fluticasone propionate HFA equivalent*

PART B: APPLICATION OF TREATMENT ESCALATION ALGORITHM

Treatment escalation option	Explanation	Examples
Option 1: Treatment escalation based on a transition to a higher treatment step	When the baseline and new treatment both correspond to one of the treatment steps that were adapted from the GINA 2020 guidelines, treatment escalation will be defined as a transition to a higher treatment step.	Baseline treatment: Medium dose ICS + LABA (step 4a) New treatment: **High dose ICS** + LABA (step 4b)
Option 2: Treatment escalation based on add-on of another controller therapy in individuals whose baseline treatment belongs to steps 5a or 5b	Among individuals who remain in steps 5a or 5b after an add-on of a new controller therapy, such prescription change will constitute a treatment escalation.	Baseline treatment: High dose ICS/LABA + tiotropium + low dose OCS maintenance therapy (step 5b) New treatment: High dose ICS/LABA + tiotropium + low dose OCS maintenance therapy **+ biologic therapy** (step 5b)
Option 3: Treatment escalation based on an ICS dose increase or add-on of another controller therapy when either the baseline or new treatment belongs to the "Other treatments" category in PART A	If either the baseline or new treatment does not correspond to any of the treatment steps that were adapted from the GINA 2020 guidelines (see "other treatments" in PART A), treatment escalation will be defined as any evidence of an ICS-dose increase or an add-on of another controller therapy.	Baseline treatment: Low dose ICS/LABA (step 3) New treatment: Low dose ICS/LABA **+ LTRA** (defined as "other treatments")

Figure 2. Asthma treatment escalation algorithm developed in collaboration with the multidisciplinary expert panel.

Abbreviations: ICS: Inhaled corticosteroids; LABA: Long-acting beta2-agonists; LAMA: Long-acting muscarinic agents; LTRA: Leukotriene receptor antagonist; OCS: Oral corticosteroids

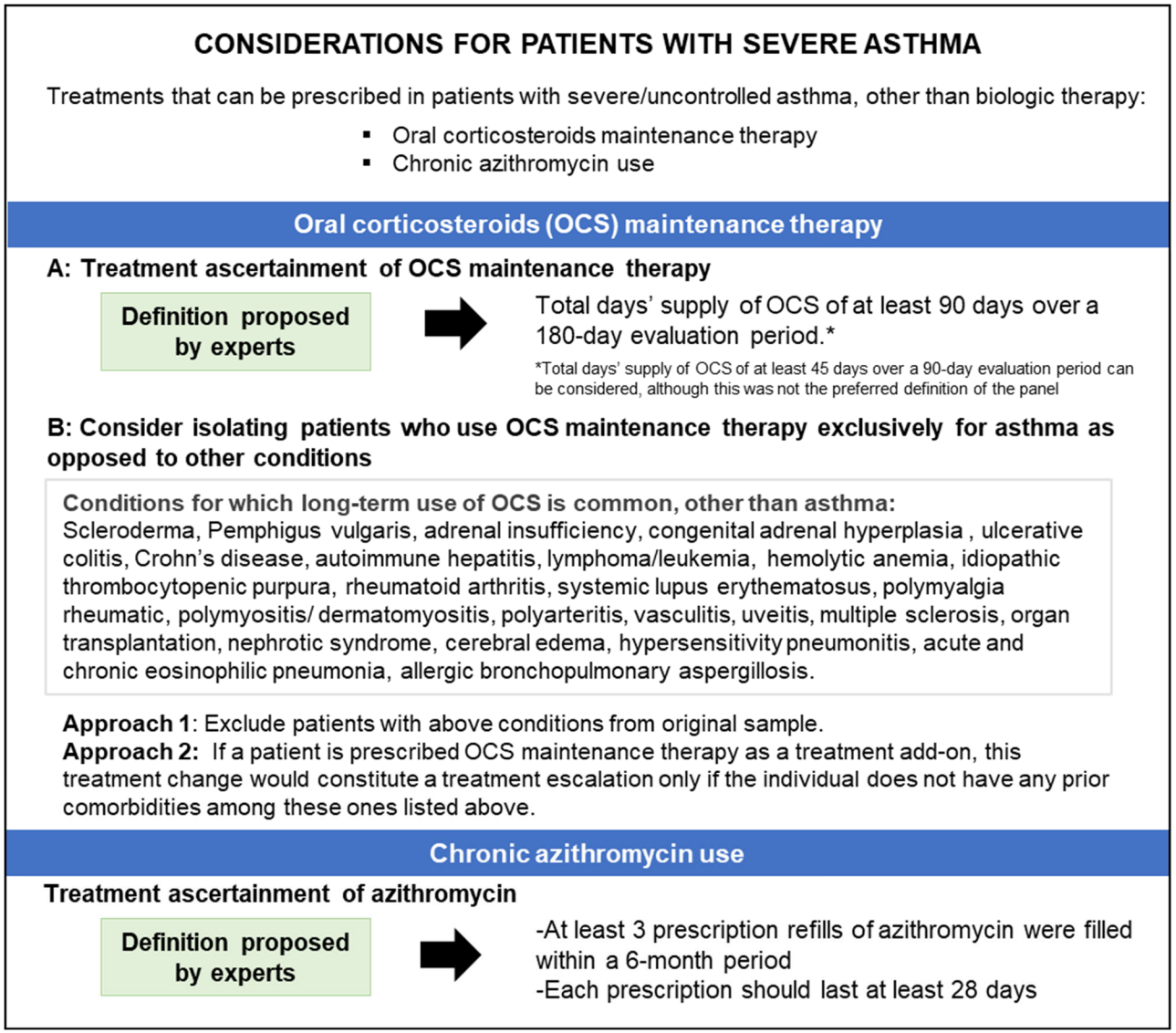


Figure 3. Special considerations when identifying patients with severe asthma

Table 1. Studies examining treatment escalation in asthma using healthcare administrative or electronic healthcare data

Author, year, country	Database, electronic health data type	Study period, Patient sample size & characteristics	Treatment guidelines	Operational definition of treatment escalation or step-assignment algorithm	Treatment escalation rates
Broder *et al.*, 2010[11] United States	Ingenix i3 LabRx database Administrative claims data	2005-2006 n=18,343 12-64 years old with evidence of uncontrolled asthma No diagnosis of COPD, emphysema, cystic fibrosis, bronchopulmonary dysplasia	Expert Panel Report 3, National Heart, Lung, and Blood Institute (2007)	**Transition to higher treatment step** **Step 1:** SABA only **Step 2:** No LABA; any of the following: low dose ICS, cromolyn sodium, LTRA, nedocromil, and/or theophylline **Step 3:** Medium dose ICS and LABA; Medium dose ICS + either LTRA; theophylline, or zileuton **Step 4:** Medium dose ICS and LABA; Medium dose ICS and either LTRA, theophylline, or zileuton **Step 5:** High dose ICS, LABA, and long-term use of OCS (Total supply of ≥ 60 days in a 6-month period); and omalizumab if evidence of allergy **No asthma treatment:** No use of any asthma medication **Undefined:** Asthma treatment not fitting any aforementioned step 1-6	**Treatment escalation rate**: Step 1: 41.3% Step 5: 12.4% Escalation rates for steps 2-4 were not provided. **CE:** Date of marker of uncontrolled disease **Maximum follow-up**: 12 months
Zeiger *et al.*, 2010[10] United States	Kaiser Permanente Southern California Region Administrative claims data	2005-2008 n = 7 694 ≥12 years old individuals with uncontrolled asthma No cystic fibrosis, COPD, emphysema, chronic bronchitis, Churg-Strauss syndrome, Wegener granulomatosis, sarcoidosis, immune deficiencies, pulmonary hypertension, bronchiectasis	Expert Panel Report 3, National Heart, Lung, and Blood Institute (2007)	**Transition to higher treatment step** **Step 1:** SABA only **Step 2:** Monotherapy low-dose ICS, LTRA, Mast-cell stabilizer or theophylline **Step 3:** Low dose ICS + either LABA, LTRA, mast-cell stabilizer or theophylline OR monotherapy high-dose ICS **Step 4:** Medium dose ICS + either LABA, LTRA, mast-cell stabilizer or theophylline OR Monotherapy high dose ICS **Step 5:** High dose ICS + LABA with or without Omalizumab **Step 6:** High dose ICS +LABA with or without Omalizumab + OCS maintenance dose therapy (EMRs of patients in step 6 were reviewed to determine that the OCS dispensed for maintenance therapy and not for acute use only)	**Treatment escalation rate:** 30.1% **CE:** Date of uncontrolled disease **Maximum follow-up**: 3 months

Author, year, country	Database, electronic health data type	Study period, Patient sample size & characteristics	Treatment guidelines	Operational definition of treatment escalation or step-assignment algorithm	Treatment escalation rates
Bengston *et al.*, 2017[15] United States	Optum Research database Administrative claims data	Optum Research database 2008-2015 n = 35,126 ≥12 years old with asthma who initiated a long-term ICS or ICS-containing regimen	Global Initiative for Asthma (2017) National Heart, Lung, and Blood Institute (2017)	**Baseline treatment:** ICS or ICS-containing regimen. Patients who filled, in addition to their ICS-containing regimen, Mast cell stabilizers, theophylline, or Omalizumab were also included. **Treatment escalation algorithm:** 1) Evidence of an ICS dose increase 2) Switch among ICS, LABA, or LTRA 3) Add-on of another controller medication (Mast cell stabilizer, theophylline, Omalizumab, LABA)	**Treatment escalation rate:** 14.6% **Index date**: Date of treatment initiation **Maximum follow-up**: 12 months
Dilokthonrsakul *et al.*, 2019[12] United States	PharmMetrics Administrative claims data	2006-2014 n=12,049 ≥ 12 years with mild (step 1) or severe (step 2)	Global Initiative for Asthma (2014)	**Transition to higher treatment step** **Step 1:** SABA only **Step 2:** Low-dose ICS OR LTRA OR Theophylline OR Mast cell stabilizer **Step 3:** Low dose ICS+LABA or Medium/high dose OR Low-dose ICS +LTRA OR Low-dose ICS + Theophylline **Step 4:** Medium/high-dose ICS +LABA OR Medium/High-dose ICS+LABA OR Medium/high-dose ICS + Theo **Step 5:** Omalizumab or OCS maintenance therapy (defined as > 14 days' supply/claim of OCS, exclusion of patients with conditions for which long-term use of OCS is the mainstay therapy)	**Rates according to baseline treatment step**: Step 1: 11.2% Step 4: 1.6%; **Index date**: First date of asthma diagnosis **Maximum follow-up**: 3 months
Gayle *et al.*, 2019[23] United Kingdom	Clinical Practice Research Datalink HER data	2006-2016 n=607,212 12-89 years old, with active asthma diagnosis	British Thoracic Society, Scottish Intercollegiate Guideline Network (2014)	**Transition to higher treatment step** **Step 1:** SABA only **Step 2:** Low-medium dose ICS only (no use of LABA, LAMA, LTRA, theophylline, chromones) **Step 3:** Low-medium dose ICS plus LABA (ICS/LABA fixed- or free-dose combination), or Low-medium dose ICS plus LTRA or theophylline **Step 4:** High dose ICS plus 1 or more of: LABA, LAMA, LTRA theophylline, chromones **Step 5:** Long-term/frequent use of OCS, defined as at least 5 consecutive prescriptions of rescue OCS over 6 months or at least one prescription of a non-rescue OCS	**Rates according to baseline treatment step:** Step 1: 11.9% Step 2: 2.4% Step 3: 2.5% Step 4: 0.7% Step 5: N/A **Index date:** Date of uncontrolled disease **Maximum follow-up**: 2 months

Author, year, country	Database, electronic health data type	Study period, Patient sample size & characteristics	Treatment guidelines	Operational definition of treatment escalation or step-assignment algorithm	Treatment escalation rates
Van Boven et *al.*, 2019[13] Australia	Australian Pharmaceutical Benefits scheme Administrative claims data	2013-2017 n=3,062 12-44 years old with asthma, new users initiating ICS/LABA FDC, no COPD diagnosis	Global Initiative for Asthma (2019)	**First GINA Step 5 add-on therapy, defined as dispensing as either:** -Monoclonal antibody therapy (omalizumab, mepolizumab, benralizumab) -OCS maintenance therapy, defined as 1 or 5 mg prednisone or prednisolone -LAMA	**Treatment escalation rate**: 3.9% **CE:** Date of treatment initiation **Maximum follow-up**: 12 months
Buhl *et al.*, 2020[14] United Kingdom	Clinical Practice Research Datalink HER data	2006-2016 Asthma patients on GINA steps 4/5, newly initiated with medium dose ICS/LABA (n=22,229) or high dose ICS/LABA (n=16,575), no diagnosis of COPD or Cystic fibrosis	Global Initiative for Asthma (2019)	Addition of one or more asthma controllers, including LAMA, LTRA, theophylline, or maintenance OCS in patients of both ICS-LABA cohorts, and increase in ICS dose only in the medium-dose ICS-LABA cohort.	**Rates according to baseline treatment**: -Medium ICS/LABA: 19.0% -High ICS/LABA: 26.1% Overall rate: 15.2% **CE:** Date of treatment initiation **Maximum follow-up**: 12 months

BTS: British Thoracic society; ICS: Inhaled corticosteroids; CE: Cohort entry; FDC: Fixed dose combinations; LABA: Long-acting beta2-agonists; LAMA: Long-acting muscarinic agents; LTRA: Leukotriene Receptor Antagonists; NHLBI: National Heart, Lung, and Blood Institute; SABA: Short-acting Beta2-agonists; SIGN: Scottish Intercollegiate Guideline Network

*For this study, rates were recalculated since results in article described how patients transitioned from one treatment step to another within 6-month intervals. The results presented in the above table describe the overall rate of patients whose treatment was escalated, according to initial treatment step

Table 2. Rate of treatment escalation, according to treatment step at cohort entry

	Rate of treatment escalation per 100 person-years (95% confidence interval)		
	Follow-up period		
Treatment at baseline	**0 to 6 months**	**7 to 12 months**	**13 to 24 months**
2	56.1 (51.3 - 60.8)	35.34 (31.07 - 39.61)	25.0 (22.0 - 27.9)
3	21.9 (21.1 - 22.8)	17.81 (17.02 - 18.6)	15.7 (15.1 - 16.3)
4a	16.2 (15.6 - 16.8)	10.8 (10.3 - 11.4)	8.7 (8.3 - 9.1)
4b	18.0 (16.9 - 19.0)	11.9 (11.0 - 12.8)	8.6 (8.0 - 9.2)
5a	10.9 (9.8 - 12.1)	8.8 (7.7 - 9.9)	5.8 (5.1 - 6.5)
5b	15.2 (12.8 - 17.6)	9.4 (7.4 - 11.4)	7.3 (6.0 - 8.7)
Other treatments	31.7 (29.1 - 34.3)	21.6 (19.3 - 23.9)	14.6 (13.2 - 16.1)

Table 3. Transition of treatment steps, among individuals whose asthma treatment was escalated in the two years following cohort entry

		Treatment escalated: number of patients (%)						
		2	**3**	**4a**	**4b**	**5a***	**5b***	**Other treatments**
Treatment at baseline	**2**		342 (32.6)	398 (37.3)	252 (23.6)	23 (2.2)	6 (0.6)	39 (3.7)
	3			5811 (77.8)	1136 (15.2)	252 (3.4)	113 (1.5)	154 (2.1)
	4a				4715 (74.5)	1132 (17.9)	249 (3.9)	232 (3.7)
	4b					2147 (85.0)	224 (8.9)	155 (6.1)
	5a					492 (59.1)	210 (25.2)	130 (15.6)
	5b						317 (88.8)	40 (11.2)
	Other treatments		5 (0.4)	119 (9.1)	225 (17.2)	217 (16.6)	22 (1.7)	718 (55.0)

*Patients who remained in steps 5a or 5b, but whose treatment was escalated

4.4.1 Fourth Article: Supplementary Materials

Development of an Asthma Treatment Escalation Operational Definition Adapted to Healthcare Administrative Databases: A Delphi Study

Electronic supplementary materials

S1. Literature review

S1.1 Electronic search strategy

MEDLINE

CONCEPTS		
Treatment escalation	**Electronic healthcare data**	**Asthma**
("Dose-Response Relationship, Drug"/ or ((treatment? or dose? Or dosage? Or care) adj1 (modif* or intensif* or escalat* or step* or pattern? Or regimen?)).tw,kw.) or (ICS adj3 (dose? Or dosage?)).tw,kw. or (Drug Dose-Response?).tw,kw. or (step* ADJ (up or down or wise or level?)).tw,kw.) or (((BTS adj SIGN) or GINA or ATS or CTS or JSA or NHLBI or "Japanese Society of Allergology" or "national heart lung and blood institute" or "British thoracic society" or "Global initiative for asthma") ADJ5 (guideline? Or guidance? Or step* OR Best Practice?)).tw,kw)	(Health Information Systems/ or exp Medical Records Systems, Computerized/ or exp Medical Records/ or Insurance, Pharmaceutical Services/ or Health Expenditures/ or exp Asthma/ec, ep, sn or exp Economics/) OR (cohort analysis/ or cohort studies/ or longitudinal studies/ or follow-up studies/ or retrospective studies/ or "Observational Studies as Topic"/ or Observational Study.pt.) or (((administrative or medico-administrative or health or medical or pharmaceutical or drug or insurance) ADJ1 (data or code? or coding or codif* or claim? or study or studies)).tw,kw. or (pharmacy claim?).tw,kw.) ((EMR or ((Medical or patient or health or pharmaceutical) adj (Record? Or data)) or ((Health or medical) adj Information System?)).tw,kw. Medicare or ((drug or medication or Pharmac* Service? Or Prescription) adj1 (claim? Or plan? Or insurance?)).tw,kw.) OR (((insurance or claim?) Adj database?).tw,kw.) OR ((cohort or longitudinal or retrospective or incidence or "real-life" or "real-world" or reallife or realword or ((Follow-Up or FollowUp) adj (study or studies))).tw,kw.) OR ((((Health or healthcare or Medical Care or Treatment or drug) adj (Expenditure? Or spending or cost?)) or economics).tw,kw.)	(exp Asthma/ OR (Asthma* OR Bronchospasm* OR Bronchial Spasm?) or (bronch* adj3 spasm*).tw,kw.) or (asthma* or antiasthma* or anti-asthma* or wheez* or bronchospas* or bronchoconstrict*).tw,kw.) or (((Respiratory ADJ (Sound? OR Hypersensitivit*)) or (bronch* adj3 spasm*) or (bronch* adj3 constrict*) or ((bronchial* or respiratory or airway* or lung*) adj3 (hypersensitiv* or hyperreactiv* or allerg* or insufficienc*)) or ((dust or mite*) adj3 (allerg* or hypersensitiv*))).tw,kw.)

EMBASE

CONCEPTS		
Treatment escalation	**Electronic healthcare data**	**Asthma**
((treatment? or dose? Or dosage?) adj1 (modif* or intensif* or escalat* or step* or pattern? Or regimen?).tw,kw.) Or ((ICS adj3 (dose? Or dosage?)).tw,kw.) Or ((Drug Dose-Response?).tw,kw.) OR ((step* ADJ (up or down or wise or level?)).tw,kw.) OR (((BTS adj SIGN) or GINA or JSA or NHLBI or "Japanese Society of Allergology" or "National Heart Lung and Blood institute" or "British Thoracic Society" or "Global Initiative for Asthma") ADJ5 (guideline? Or guidance? Or step*)).tw,kw.	(exp "billing and claims"/ OR medical information system/) or (cohort analysis/ or longitudinal study/ or follow-up/ or retrospective study/ or observational study) or (((administrative or medico-administrative or health or medical or pharmaceutical or drug or insurance) ADJ1 (data or code? or coding or codif* or claim? or study or studies)).tw,kw. or (pharmacy claim?).tw,kw.) or ((EMR or ((Medical or patient or health or pharmaceutical) adj (Record? Or data)) or ((Health or medical) adj Information System?)).tw,kw.)) or (Medicare or ((drug or medication or Pharmac* Service? Or Prescription) adj1 (claim? Or plan? Or insurance?)).tw,kw.) or (((insurance or claim?) Adj database?).tw,kw.) or ((cohort or longitudinal or retrospective or incidence or "real-life" or "real-world" or reallife or realword or ((Follow-Up or FollowUp) adj (study or studies))).tw,kw.) or ((((Health or healthcare or Medical Care or Treatment or drug) adj (Expenditure? Or spending or cost?)) or economics).tw,kw.)	(asthma*.tw, kw.or bronchospas*.tw,kw. or (bronch* adj3 spasm*).tw,kw.) OR ((asthma* or antiasthma* or anti-asthma* or wheez* or bronchospas* or bronchoconstrict*).tw,kw.)) OR (((Respiratory ADJ (Sound? OR Hypersensitivit*)) or (bronch* adj3 spasm*) or (bronch* adj3 constrict*) or ((bronchial* or respiratory or airway* or lung*) adj3 (hypersensitiv* or hyperreactiv* or allerg* or insufficienc*)) or ((dust or mite*) adj3 (allerg* or hypersensitiv*))).tw,kw.)

All EMB reviews and Global Health

CONCEPTS		
Treatment escalation	**Electronic healthcare data**	**Asthma**
((treatment? or dose? or dosage?) adj1 (modif* or intensif* or escalat* or step* or pattern? Or regimen?).tw,kw.) or ((ICS adj3 (dose? Or dosage?)).tw,kw.) or ((Drug Dose-Response?).tw,kw.) or ((step* ADJ (down or wise or level?)).tw,kw.) or ((((BTS adj SIGN) or GINA or JSA or NHLBI or "Japanese Society of Allergology" or "National Heart Lung and Blood Institute" or "British Thoracic Society" or "Global Initiative for Asthma") ADJ5 (guideline? Or guidance? Or step*)).tw,kw.)	(((administrative or medico-administrative or health or medical or pharmaceutical or drug or insurance) ADJ1 (data or code? or coding or codif* or claim? or study or studies)).tw,kw. or (pharmacy claim?).tw,kw.) or ((EMR or ((Medical or patient or health or pharmaceutical) adj (Record? Or data)) or ((Health or medical) adj Information System?)).tw,kw.) or (Medicare or ((drug or medication or Pharmac* Service? Or Prescription) adj1 (claim? Or plan? Or insurance?)).tw,kw.) or (((insurance or claim?) Adj database?).tw,kw. (cohort or longitudinal or retrospective or incidence or "real-life" or "real-world" or reallife or realword or ((Follow-Up or FollowUp) adj (study or studies))).tw,kw.) or ((((Health or healthcare or Medical Care or Treatment or drug) adj (Expenditure? Or spending or cost?)) or economics).tw,kw.)	(asthma*.tw,kw.or bronchospas*.tw,kw. or (bronch* adj3 spasm*).tw,kw.) or ((asthma* or antiasthma* or anti-asthma* or wheez* or bronchospas* or bronchoconstrict*).tw,kw.) oR (((Respiratory ADJ (Sound? oR Hypersensitivit*)) or (bronch* adj3 spasm*) or (bronch* adj3 constrict*) or ((bronchial* or respiratory or airway* or lung*) adj3 (hypersensitiv* or hyperreactiv* or allerg* or insufficienc*)) or ((dust or mite*) adj3 (allerg* or hypersensitiv*))).tw,kw.)

CINHAL

CONCEPTS		
Treatment escalation	**Electronic healthcare data**	**Asthma**
TX ((("treatment" or “dose” or “dosage”) N1 ("modif*" or "step" or "escalat*" or "pattern*" or "regimen*")))) OR AB (("ICS" N3 ("dose*" or "dosage*"))) OR TX (("step" N1 ("down" or "wise" or "level*"))) OR TX ("BTS" N1 "SIGN" OR "GINA" or "JSA" OR "NHLBI" OR "Japanese Society of Allergology" OR "National Heart Lung and Blood Institute" OR "British Thoracic Society" OR (("Global Initiative for Asthma") N5 ("guideline*" or "guidance*" or "step*")))	TX ((MH "Epidemiological Research") OR (MH "Retrospective Design")) OR TX (((“administrative” or “medico-administrative” or “health” or “medical” or “pharmaceutical” or “drug” or “insurance”) N1 (“data” or “code*” or “coding” or “codif*” or “claim*” or “study” or “studies”)) Or “pharmacy claims”) OR TX (“EMR” OR ((“medical” or “pharmaceutical” or “patient”) N1 (“Record*” OR “data”)) OR (“(health” or “medical”) N1 “information system*”))) OR TX (“Medicare” OR ((“drug” or “medication” or “pharmac* service*” or “prescription”) N1 (“claim*” Or “plan*” Or “insurance*”))) OR TX (“insurance” N1 “database” OR “claim*” N1 “database”) OR TX (“cohort” or “longitudinal” or “retrospective” or “incidence” or "real-life" or "real-world" or “reallife” or “realworld” OR ((“follow-up”or "followup") N1 (“study” or “studies”)))	AB (“asthma*” or “broncospas*” Or “bronch* N3 “spasm*” OR (MH "Asthma+")) OR AB (“asthma*” or “antiasthma*” or “anti-asthma*” or “wheez*” or “bronchospas*” or “bronchoconstrict*”) OR AB (“Respiratory” N1 (“sound*” OR “hypersensitivit*”) OR (“bronch*” N3 “constrict”) OR ((“bronchial*” or “respiratory” or “airway*” or “lung”) N3 (“hypersensitiv*” or “hyperreactiv*” or “allerg*” or “insufficienc*”)) OR ((“dust” or mite”) N3 (“allerg*” or “hypersensitiv*”)))

S1.2 Systematic review methods

Eligibility criteria:

- **Study population:** Adults with asthma
- **Design**: Observational studies which used electronic health data (administrative databases or electronic health records databases)
- **Outcome of interest**: Treatment escalation for asthma definitions and treatment escalation rates.
    - Studies categorizing therapies according to treatment guidelines (treatment steps) without providing a definition of treatment escalation were excluded. This is because we were interested in examining which transitions between treatment steps constituted a treatment escalation; further, treatment escalation rates were an outcome of interest in this review.
- Time frame: 1996 - present

Screening

- All titles and abstracts were independently screened by two investigators (AY, RFD).
- Original research papers which fit the pre-specified eligibility criteria identified by either reviewer were then assessed in full text.
- For each retained study, two reviewers (AY, RFD) independently extracted the relevant information using a standardized data abstraction form and disagreements were resolved by consensus or by a third reviewer (AF), when necessary.
- Data elements of interest included study and population characteristics, as well as treatment escalation definition and rates. The Covidence systematic review software was used to assist in the screening and data extraction processes.

S2 Asthma population-based cohort study

S2.1 Information on healthcare claims database used in analysis

The Asthma and COPD patients with Public drug Insurance (ACPI) database

The ACPI database was formed by linking two administrative databases from the Canadian province of Quebec: 1) The *Régie de l'assurance maladie du Québec* (RAMQ) medical service database; and 2) *Maintenance et exploitation des données pour l'étude de la clientèle hospitalière* (MED-ECHO) hospitalization database.

The RAMQ database collects data on medical services provided by physicians in private clinics, outpatient clinics, ED or hospitals for all Quebecers (fee for service) and medications dispensed in community pharmacies for Quebecers who are covered by the RAMQ Drug Insurance Plan, which represents 90% of elderly, 1.8 million people ≤65 years old with no access to a drug insurance plan at work, and individuals receiving social assistance.
(ref: https://www.ramq.gouv.qc.ca/en/citizens/prescription-drug-insurance)

The MED-ECHO database covers all residents of Quebec and records data on acute care hospitalizations. The ACPI database contains detailed information on prescribed medications filled at community pharmacies, ambulatory medical visits, ED visits, hospitalizations, date of death (when applicable), age and sex for all asthma and COPD patients covered by the RAMQ Drug Insurance Plan.

S2.3 Eligibility criteria

- To have an asthma diagnosis, defined by at least one hospitalization with a diagnosis of asthma in the MED-ECHO database or two ambulatory medical visits with a diagnosis of asthma within two consecutive years recorded in the RAMQ database between January 1, 2002 and December 31, 2015.
- To have a dispensed new prescription for a controller medication. The date of dispensing of this controller medication will be referred hereafter as AsthmaRx.
- The date of cohort entry (CE) corresponds to the date of dispensing of the earliest new prescription for a controller medication that meets the following criteria:
    - No COPD diagnosis in the two years prior to AsthmaRx
    - To be covered by the RAMQ drug insurance in the year prior to AsthmaRx
    - To be ≥18 years old at AsthmaRx
    - No dispensing of a long-acting muscarinic agents (LAMA) or on LAMA/Long-acting beta2-agonist dual therapy (LAMA-LABA) in the 90 days prior to AsthmaRx, as these treatments are typically given to COPD patients.
    - No filled controller medications in the year prior to AsthmaRx other than the ones filled at AsthmaRx and in the 90 days prior to this date.

S2.4 Treatment ascertainment at baseline (cohort entry)

Figure 1 presents the method used to ascertain treatment at cohort entry (CE). Two pre-index periods were considered: 1) 90 days prior to CE (**pre-index period 1**); 2) period spanning between 365 days prior to CE and pre-index period 1 (**pre-index period 2**).

A subject's baseline treatment corresponded to all treatments dispensed at CE, in addition to all prescriptions of other controller medications that were dispensed in pre-index period 1. This approach was used for patients who were on multiple controller therapy, but who may not necessarily fill all their prescriptions on the same day.

In addition, to minimize misclassification with respect to treatment, patients were required to not have controller medications in pre-index period 2, other than the ones dispensed at CE and on pre-index period 1.

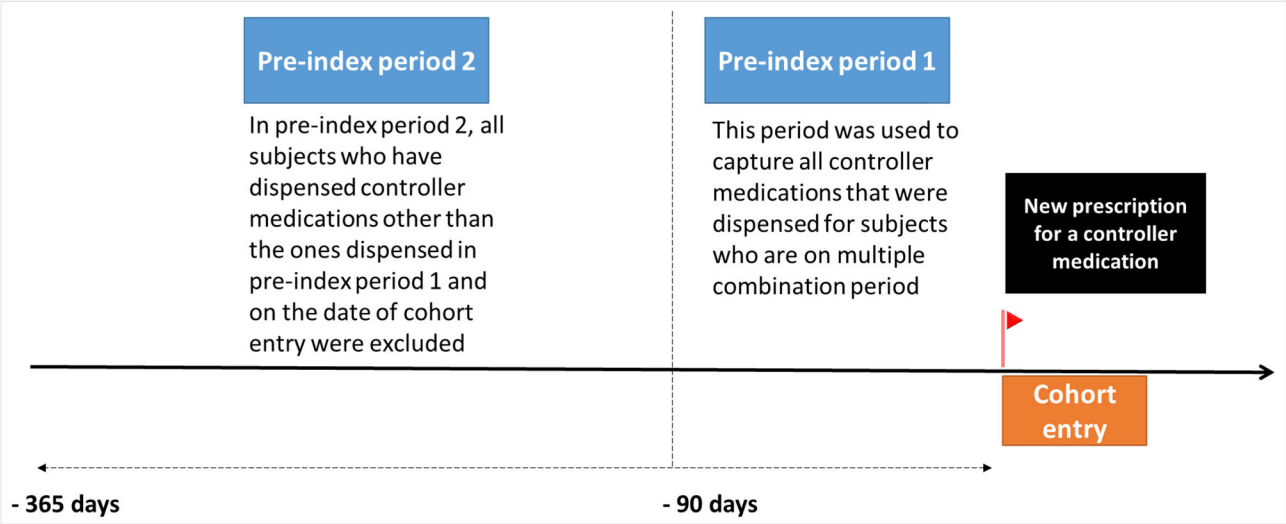


Figure S2.1. Treatment ascertainment at cohort entry

S2.5 Identification of treatment escalation episodes

Figure 2 below illustrates how treatment escalation episodes were identified. Each time a patient fills a prescription for a controller medication during follow-up, a period of 90 days was applied following the date of this prescription to ascertain new treatment. A subjects' treatment on this date will correspond to all controller medications filled on this date, as well as all other controller medications dispensed in the 90-days period after this date. If the treatment change did not result in a treatment escalation, then follow-up will resume.

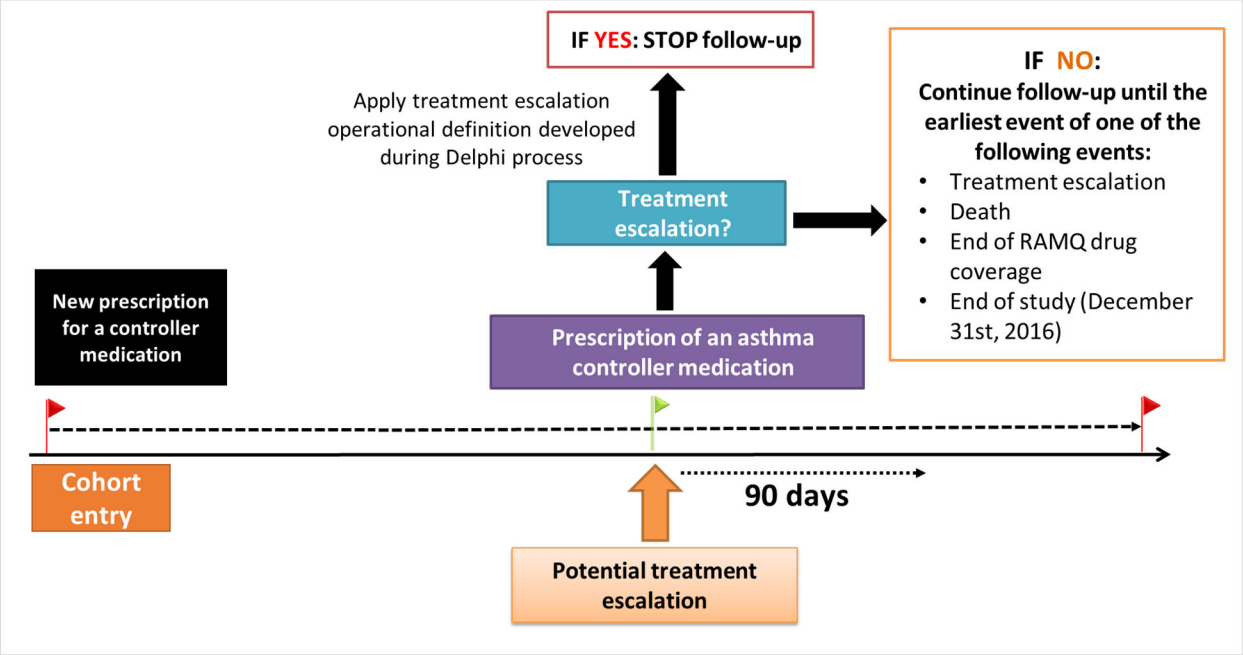


Figure S2.2. Identification of treatment escalation during follow-up

S2.6 Flow diagram of cohort selection

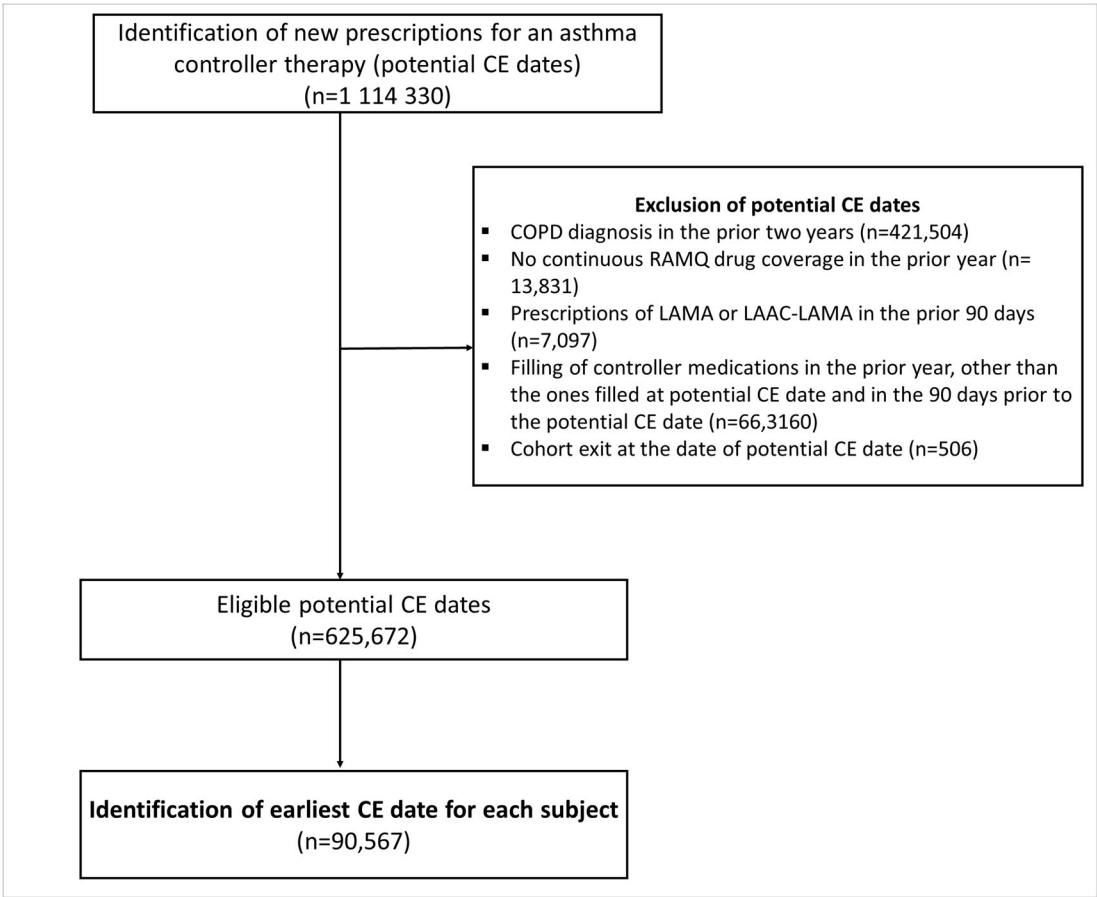


Figure S2.3. Flow diagram of cohort selection

Abbreviations: CE: Cohort Entry; LABA: Long-acting beta2-agonists; LAMA: Long-acting muscarinic agents; RAMQ: *Régie d'assurance maladie du Québec*

S2.7 Baseline characteristics of cohort subjects

Table S2.7 Baseline characteristics of cohort subjects

Characteristics	No treatment escalation (n=70 410)	Treatment escalation (n=20 157)
Patient characteristics, n(%)*		
Age (years)		
≥18-40	17 246 (24.5)	4 078 (20.2)
>40-65	27 082 (38.5)	8 078 (40.1)
>65-80	21 007 (29.8)	6 495 (32.2)
>80	5 065 (7.9)	1 506 (7.5)
Female	46 071 (65.4)	13 225 (65.6)
Atopy	7057 (10.0)	2 156 (10.7)
Presence of comorbidity, other than asthma, for which OCS maintenance therapy is common	3 992 (5.7)	1323 (6.6)
Follow-up duration, mean ± sd	641.6 ± 189.5	693.3 ± 114.9
Asthma-related variables		
Treatment at cohort entry		
ICS monotherapy	36 203 (51.4)	10 331 (51.3)
ICS/LABA	14 589 (20.7)	3 530 (17.5)
ICS + ICS/LABA	4 067 (5.8)	1 165 (5.8)
ICS/LABA + LAMA	2 827 (4.0)	471 (2.3)
ICS/LABA + LTRA	2 637 (3.8)	779 (3.9)
ICS +LTRA	2760 (3.9)	965 (4.8)
LTRA	806 (1.1)	672 (3.3)
ICS + LAAC	922 (1.3)	428 (2.1)
ICS + ICS/LABA + LTRA	792 (1.1)	241 (1.2)
Other treatment combinations**	4807 (6.9)	1575 (7.8)
Prescribed ICS daily dose at cohort entry		
Low	1 007 (1.5)	893 (4.6)
Medium	37 146 (53.6)	12 394 (64.4)
High	27 810 (40.1)	5 152 (26.8)
Very high	3 360 (4.9)	805 (4.2)
Specialty of prescriber at cohort entry		
General practitioner	49 693 (70.6)	13 553 (67.2)
Pulmonologist	16 704 (23.7)	5 393 (26.8)
Other	4 013 (5.7)	1 211 (6.0)

*unless otherwise specified

** Each other treatment combination represents <1%

Abbreviations: ICS: Inhaled corticosteroids; LABA: Long-acting beta2-agonists; LAMA: Long-acting muscarinic agents; LTRA: Leukotriene receptor antagonist; OCS: Oral corticosteroids; Theo: Theophylline

S2.8 Cohort Analysis: List of treatments identified at baseline

Table S2.8 Treatments identified at baseline

Treatment step*	Cumulative prescribed daily ICS dose**	Treatment at baseline	n	%
3	Medium	ICS	26 441	29.2
4a	High	ICS	18 154	20.0
4a	Medium	ICS-LABA	11 949	13.2
4b	High	ICS-LABA	5 120	5.7
4a	Medium	ICS+ICS-LABA	2 195	2.4
4b	Medium	ICS-LABA+LTRA	1 970	2.2
4b	High	ICS+ICS-LABA	1 913	2.1
4a	Medium	ICS+LTRA	1 901	2.1
4b	Medium	ICS-LABA+LAMA	1 637	1.8
4b	High	ICS+LTRA	1 589	1.8
2	-	LTRA	1 478	1.6
5a	High	ICS-LABA+LAMA	1 381	1.5
5a	High	ICS-LABA+LTRA	1 236	1.4
9	Very high	ICS	1 101	1.2
5a	Very high	ICS+ICS-LABA	1 013	1.1
2	Low	ICS	838	0.9
4a	Medium	ICS+LAMA	700	0.8
3	Low	ICS-LABA	611	0.7
4b	High	ICS+LAMA	573	0.6
5a	V. High	ICS-LABA	439	0.5
Other	High	ICS+THEO	409	0.5
5a	Medium	ICS+ICS-LABA+LTRA	401	0.4
5b	Medium	ICS+OCS	369	0.4
9	Medium	ICS+THEO	359	0.4
4b	Medium	ICS+ICS-LABA+LTRA	313	0.4
5b	High	ICS+OCS	321	0.4
Other	-	THEO	303	0.3
Other	V. High	ICS+ICS-LABA+LTRA	303	0.3
5b	Medium	ICS-LABA+OCS	263	0.3
5a	High	ICS-LABA+LAMA+LTRA	257	0.3
5a	Medium	ICS-LABA+LAMA+LTRA	234	0.3
Other	V. High	ICS-LABA+LAMA	232	0.3

... Each remaining treatment not listed above represent ≤ 0.25%

*ICS dose (mcg/day, fluticasone propionate HFA equivalent): Low: ≤250; Medium: >250-500; High: >500-1000; Very high: > 1000. Cumulative prescribed ICS dose was measured within the 90 days prior to cohort entry.

** Step according to the treatment escalation definition developed in Delphi study

Abbreviations: ICS: Inhaled corticosteroids; LABA: Long-acting beta2-agonists; LAMA: Long-acting muscarinic agents; LTRA: Leukotriene receptor antagonist; OCS: Oral corticosteroids; Theo: Theophylline

S2.9 Cohort Analysis: List of treatment escalation episodes identified at follow-up

Table S2.9 Treatment escalation events identified during follow-up (95% of cohort)

Treatment step	Cumulative prescribed daily ICS dose**	Treatment at escalation event	n	%
4a	High	ICS	3 292	16.3
4b	High	ICS+ICS-LABA	1 814	9.0
4a	Medium	ICS-LABA	1 552	7.7
4b	High	ICS-LABA	1 421	7.1
5a	Very high	ICS+ICS-LABA	1 284	6.4
4b	Medium	ICS-LABA+LTRA	901	4.5
4a	Medium	ICS+LTRA	777	3.9
4b	Medium	ICS-LABA+LAAC	740	3.7
4b	High	ICS+LTRA	737	3.7
5a	High	ICS-LABA+LAAC	659	3.3
5a	High	ICS-LABA+LTRA	621	3.1
4b	High	ICS+LAAC	461	2.3
5a	High	ICS+ICS-LABA+LTRA	441	2.2
4a	Medium	ICS+LAAC	369	1.8
3	Medium	ICS	354	1.8
9	Very high	ICS+ICS-LABA+LTRA	331	1.6
5a	High	ICS+ICS-LABA+LAAC	299	1.5
4a	Medium	ICS+ICS-LABA	284	1.4
Other	Very high	ICS+ICS-LABA+LAAC	281	1.4
5a	Medium	ICS-LABA+LAAC+LTRA	274	1.4
5b	Medium	ICS-LABA+ OCS maintenance therapy	163	0.8
5a	High	ICS-LABA+LAAC+LTRA	157	0.8
Other	High	ICS+THEO	138	0.7
Other	Medium	ICS+THEO	138	0.7
5b	Medium	ICS+ OCS maintenance therapy	128	0.6
Other	Medium	ICS-LABA+THEO	96	0.5
4b	Medium	ICS+ICS-LABA+LTRA	92	0.5
4b	Medium	ICS+ICS-LABA+LAAC	88	0.4
5b	High	ICS+ OCS maintenance therapy	88	0.4
5b	Medium	ICS-LABA+LAAC+ OCS maintenance therapy	72	0.4
5b	Medium	ICS-LABA+LTRA+ OCS maintenance therapy	72	0.4
5a	High	ICS+LAAC+LTRA	71	0.4
5b	High	ICS-LABA+ OCS maintenance therapy	63	0.3
5b	High	ICS-LABA+LAAC+ OCS maintenance therapy	62	0.3

Treatment step	Cumulative prescribed daily ICS dose**	Treatment at escalation event	n	%
Other	Medium	ICS-LABA+LTRA+THEO	61	0.3
Other	High	ICS+LTRA+THEO	59	0.3
Other	Medium	ICS-LABA+LAAC+THEO	55	0.3

… Each remaining treatment not listed above represent ≤ 0.25%

*ICS dose (mcg/day, fluticasone propionate HFA equivalent): Low: ≤250; Medium: >250-500; High: >500-1000; Very high: > 1000

** Step according to the treatment escalation definition developed in Delphi study

Abbreviations: ICS: Inhaled corticosteroids; LABA: Long-acting beta2-agonists; LAMA: Long-acting muscarinic agents; LTRA: Leukotriene receptor antagonist; OCS: Oral corticosteroids; Theo: Theophylline

S2.10 Distribution of steps, according to developed treatment escalation definition during Delphi study, at baseline and at follow-up

Table S2.10.1 Distribution of treatment steps at baseline

Treatment step	n	%
2	2316	2.6
3	27254	30.1
4a	34899	38.5
4b	13335	14.7
5a	6441	7.1
5b	2234	2.5
Other	4088	4.5

Table S2.10.1 Distribution of treatment steps among subjects whose treatment was escalated

Treatment step	n	%
3	353	1.8
4a	6328	31.8
4b	6328	31.8
5a	4263	21.4
5b	1141	5.7
Other	1468	7.4

S3 Delphi Structured Questionnaires

S3.1 Questionnaire Round 1

Instructions

Thank you for your participation in this first round of the Delphi study which aims to develop an **operational definition** of **treatment escalation** (intensification) in **asthma** that can be applied to **healthcare administrative data**, including data on prescriptions filled in community pharmacies (**pharmacy claims data**).

Consensus among experts on the treatment escalation definitions will be achieved via an iterative process consisting of three rounds of structured online questionnaires. During each round of consultation, experts will be requested to rate different criteria that could be relevant to this definition.

In the first round, you will be asked **general questions** regarding the optimal definition of treatment escalation that can be applied to healthcare administrative data. In the subsequent rounds, specific criteria will be established and the definition will be refined until a consensus among experts will be achieved. Definitions will only be constructed for **adult populations**.

Please note that the questionnaire has 6 questions.

Background and Research Context

The following variables are typically found in healthcare administrative databases. **These variables are thus available to establish the definition**:

- Generic name of the medication and device
- Medication class
- Medication form
- Quantity dispensed (including number of doses per device)
- Medication dispensing date
- Medication potency

A systematic literature review was previously conducted to identify how treatment escalation in asthma was defined in studies which used healthcare administrative data. Most studies were published in the last five years, indicating that there is an emergent trend to study treatment escalation and related outcomes in asthma patients in the real-world setting. Of note, the definitions of treatment escalation in asthma **differed widely from one study to another**.

Specifically, **two main types** of definitions were used:

1. **FIRST DEFINITION: Transition to a higher step**, defined in accordance to clinical treatment guidelines (link to guidelines was provided)

2. **SECOND DEFINITION:** Evidence of either:
    i. Inhaled corticosteroids (ICS) or ICS-containing **therapy dose increase**;
    ii. **Treatment switch (interclass and intraclass)**;
    iii. **Add-on** of another controller medication.

When completing the questionnaire, please bear in mind the important distinctions between these two definitions. The majority of the questions will evaluate the expert panel's preferences and level of agreement with these two definitions.

Questions on the optimal asthma treatment escalation definition

1) To which extent do you agree with the **first definition** to identify treatment escalation, i.e. **Transition to a higher step**, defined in accordance to clinical treatment guidelines.

   ☐ Strongly agree

   ☐ Agree

   ☐ Neither agree or disagree

   ☐ Disagree

   ☐ Completely disagree

   If you have answered strongly agree or agree, which **treatment guideline(s)** (and **year**) should be used to reflect today's clinical practice in the Canadian population?

   _____

   If you did not answer "**strongly disagree**" or "**agree**", please justify your choice.

2) For the **second definition** to identify treatment escalation, please indicate your **level of agreement** with each of the following criteria:

	Strongly agree	**Agree**	**Neither agree or disagree**	**Disagree**	**Completely disagree**
Evidence of either ICS or ICS-containing therapy dose increase					
A treatment switch between medications belonging to the same pharmacological class (e.g. a switch from fluticasone propionate HFA to budenoside or a switch from mepolizumab to dupilumab)					
A treatment switch between medications belonging to different classes (e.g. switch from an ICS/long-acting β2 agonist combination therapy.					
Add-on of another controller medication to the existing therapy, i.e. the number of controller medications increases overall for a patient.					

3) Which definition is the most **appropriate** to use in **healthcare administrative databases**?

o First definition, presented in question1

o Second definition, presented in question 2:

o None of the above (please provide an alternate definition): _____

4) Is there a possibility of **treatment escalation** in patients who are on **a biologic therapy (e.g. omalizumab, dupilumab)**?

o Yes

o No

If you answered yes, please provide details on therapy:

_____

Oral corticosteroids as maintenance therapy for severe asthma

5) Identifying **oral corticosteroid maintenance therapy** for severe asthma can be challenging, since we do not have access to drug indication in healthcare administrative databases. Indeed, oral corticosteroids may be used to treat acute exacerbations or to treat conditions other than asthma.

Given these limitations, what would be the **most appropriate method** to identify patients on oral corticosteroid **maintenance therapy** for asthma in healthcare administrative databases? *More than one option can apply.*

A) Require a regular use of low-dose oral corticosteroids for a specific time period.

☐ B) Exclude individuals who have conditions for which long-term use of oral corticosteroids is common or is the mainstay therapy (e.g. scleroderma, systemic vasculitis, multiple sclerosis, Crohn's disease, rheumatoid arthritis, organ transplantation)

☐ C) Other (please specify):

_____

If you answered A, please propose a definition on how we could identify oral corticosteroid maintenance therapy for severe asthma in administrative databases. For example, one study in the literature required that a patient dispenses at least one 30-day prescription of an oral corticosteroid

over a one-year period whereas another study required a total supply of at least 60 days within a 6-month period.

If you answered B, please answer the question below:

Table 1 presents a **list of diseases and disorders** for which long-term use of oral corticosteroids is common or is the mainstay therapy. This list was obtained from a literature review: Please select all the diseases/disorders for which oral corticosteroids are the mainstay therapy, to the best of your knowledge.

Table 1. List of diseases for which long-term use of oral corticosteroid is common

Field of medicine	Diseases/disorders	
Allergy and pulmonology	Severe asthma	☐
	Interstitial lung disease	☐
	Atopic dermatitis	☐
	Urticaria/angioedema	☐
	Anaphylaxis	☐
	Nasal polyps	☐
	Hypersensitivity pneumonitis	☐
	Sarcoidosis	☐
	Acute and chronic eosinophilic pneumonia	☐
Dermatology	Scleroderma	☐
	Pemphigus vulgaris	☐
	Contact dermatitis	☐
Endocrinology	Adrenal insufficiency	☐
	Congenital adrenal hyperplasia	☐
Gastroenterology	Ulcerative colitis	☐
	Crohn's disease	☐
	Autoimmune hepatitis	☐
	Lymphoma/leukemia	☐
	Hemolytic anemia	☐
	Idiopathic thrombocytopenic purpura	☐
Rheumatology/immunology	Rheumatoid arthritis	☐
	Systemic lupus erythematosus	☐
	Polymyalgia rheumatica	☐
	Polymyositis/dermatomyositis	☐
	Polyarteritis	☐
	Vasculitis	☐
Ophthalmology	Uveitis	☐
	Keratoconjunctivitis	☐
Other	Multiple sclerosis	☐
	Organ transplantation	☐
	Nephrotic syndrome	☐
	Chronic active hepatitis	☐
	Cerebral edema	☐

To your knowledge, are there any diseases in **Table 1** for which oral corticosteroid is **not** the mainstay therapy?

- Yes
- No

If you answered No, please indicate the disease(s) in **Table 1** for which oral corticosteroid use is **not** common or is not the mainstay therapy:

_____

To your knowledge, are there **other diseases** for which long-term use of oral corticosteroids is common or is the mainstay therapy that are **not** listed in Table 1?

_____

Events attributable to treatment escalation

6) Seasonal fluctuations may lead to treatment escalation to prevent or treat uncontrolled asthma.

Using healthcare administrative data, how would you identify treatment escalation due to seasonal fluctuations of asthma?

_____

Is there any other context in which treatment escalation should be considered, other than uncontrolled asthma (high use of short-acting beta2-agonists, exacerbations) and seasonal fluctuations?

_____

S3.2 Questionnaire Round 2

PART I: ASTHMA TREATMENT ESCALATION

In the previous round of consultations, two main definitions were proposed to identify asthma treatment escalation:

The **FIRST DEFINITION** was **Transition to a higher step**, defined in accordance to clinical treatment guidelines [such as Global Initiative for Asthma (GINA)];

70% of participants preferred this definition, with a level of agreement of 4.2 ± 0.6 (5=completely agree; 1= completely disagree).

For the **SECOND DEFINITION**, the following two criteria had the highest level of agreement among participants:

- Evidence of either **ICS or ICS-containing** therapy **dose increase**; mean rating: **4.7 ± 0.5**
- **Add-on of another controller medication** to the existing therapy (of different pharmacological classes); mean rating: **4.6 ± 0.7**

Indeed, participants generally preferred the first definition because it is clinically intuitive and adapted to the patients' level of disease control. However, many experts pointed out the limitations of this definition. Namely, steps are not always followed in clinical practice and developing a claims-based algorithm that takes into consideration GINA guidelines may be challenging due to the limitations of pharmacy claims data. Accordingly, **we propose to combine the first and second definitions, but to adapt them to ensure to that all treatment possibilities are considered.**

Development of Treatment Escalation Algorithm

To identify all treatment possibilities, we constructed a cohort of over 80, 000 individuals with **asthma** who were **prescribed at least one respiratory controller medication** using Quebec **healthcare administrative databases**. Over 250 different treatments were identified between 2006 and 2016.

The next two sections present the proposed treatment escalation algorithm.

CATEGORIZATION OF TREATMENTS

Treatments will be categorized in accordance with a **modified version of GINA 2019 treatment steps**, as presented in Figure 1 below. Treatments that do not fit these steps will be referred to as "**other treatments"**; these treatments are less common and represent less than 5% of our cohort.

All treatments outlined in Figure 1, including "other treatments", will be taken into account in the proposed treatment escalation algorithm presented in the next section.

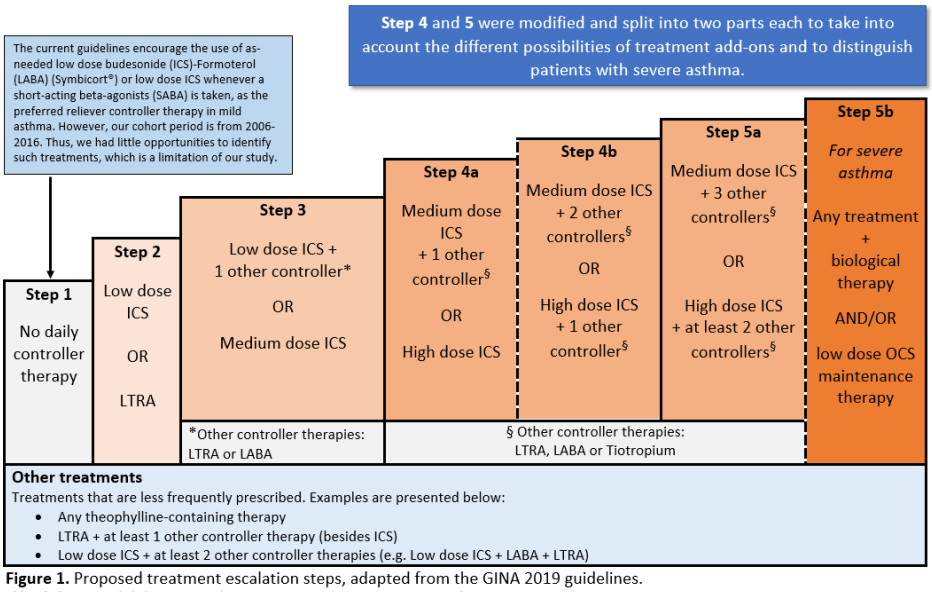


Figure 1. Proposed treatment escalation steps, adapted from the GINA 2019 guidelines.
Abbreviations: ICS: Inhaled corticosteroids; LABA: Long-acting beta2-agonist; LTRA: Leukotriene receptor antagonist

PROPOSED TREATMENT ESCALATION ALGORITHM

Treatment escalation will be identified by comparing the **initial treatment** at baseline and the subsequent **new treatment** and will be defined according to **three different options** presented below.
In these options, **treatment steps** correspond to those that were **adapted from the GINA 2019 guidelines** (Figure 1).

1. **Treatment escalation based on a transition to a higher treatment step**

   When the initial treatment and the new treatment both correspond to one of the treatment steps that were adapted from the GINA 2019 guidelines, treatment escalation will be defined as a transition to a higher treatment step. See example 1 below.

2. **Treatment escalation based on add-on of another controller therapy in individuals on steps 5a or 5b**

   Among individuals who remain in steps 5a or 5b after an add-on of a new controller therapy, such prescription change will constitute a treatment escalation. See example 2 below.

3. **Treatment escalation based on an ICS dosage increase or add-on of another controller therapy when at least one of the treatments do not correspond to any of the treatment steps**

   If either the initial treatment or the new treatment does not correspond to any of the treatment steps that were adapted from the GINA 2019 guidelines (see "other treatments" in Figure 1), treatment escalation will be defined as any evidence of an ICS-dose increase or an add-on of another controller therapy. See example 3 below.

Table 1. Examples of treatment escalation scenarios

Example	Initial treatment	New Treatment	Treatment escalation?
1	Medium dose ICS + LABA (step 4a)	**High dose ICS** + LABA (step 4b)	YES
2	High dose ICS/LABA + tiotropium + low dose OCS maintenance therapy (step 5b)	High dose ICS/LABA + tiotropium + low dose OCS maintenance therapy **+ biologic therapy** (step 5b)	YES
3	Low dose ICS/LABA (step 3)	Low dose ICS/LABA **+ LTRA** (defined as "other treatments")	YES
	Low-dose ICS + Theophylline (defined as "other treatments")	**Medium dose ICS +** Theophylline (defined as "other treatments")	YES

1. **Do you agree with this proposed treatment escalation algorithm?**

   ☐ YES

   ☐ NO

   Please provide any comments you may have:

   _____

ORAL CORTICOSTEROIDS AS MAINTENANCE THERAPY FOR SEVERE ASTHMA

In the first round of consultations, the following definitions were proposed to identify oral corticosteroid (OCS) maintenance therapy for severe asthma in the first round of consultations:

- **PART A**: Require a regular use of low-dose OCS for a specific time period.
- **PART B**: Exclude individuals who have conditions for which long-term use of OCS is common or is the mainstay therapy. In the first round, we provided a list of these conditions that was obtained from the literature (Liu et al. (2013) AACI, 9(1), 30).

Over 60% and 90% of respondents agreed with PARTS A and B, respectively.

PART A: The method that was most commonly proposed required that the patient has a total supply of oral corticosteroids for at least 50% of the study period (or evaluation period). Therefore, we will retain this definition for our treatment escalation algorithm.

We now have to determine a **minimum threshold for the evaluation period**. This period needs to be short enough to be clinically significant and it cannot be too long because of the limitations of our database. Specifically, medication dispending data may not be available for patients who have switched to a medical drug regime that is not covered by our database.

2. Would a period of **90 days** be **clinically acceptable**, as the **minimum threshold** for an evaluation period? **For example, if an individual with asthma has a total days' supply of OCS of at least 45 days over a 90-day period, would you consider this person to be on OCS-maintenance therapy?**

☐ YES

☐ NO

If you answered No, please justify your answer and provide the minimum duration of the evaluation period that is clinically significant.

_____

PART B: The panel corroborated the list of diseases that we provided in the first round for which long-term use of OCS could be prescribed (other than severe asthma).

Therefore, it could be appropriate to exclude asthma subjects who have at least one concomitant condition for which OCS use is common or is the main stay therapy (eg. Crohn's disease).

However, it was pointed out that some of the diseases presented in the list may **be a comorbidity of severe asthma** (e.g. interstitial lung disease (ILD), vasculitis with ILD), and it is therefore not advisable to exclude subjects who have such conditions. Alternately, we could conduct statistical analyses that allows to control for the presence of such diseases (**statistical adjustment**).

We thus propose the methods outlined below.

Table 2. Methods to control for the presence of concomitant conditions in which long-term use of OCS is common

Exclusion of subjects who have <u>at least one</u> of the following conditions	**Statistical adjustment in subjects who have <u>at least one</u> of the following conditions**
Conditions that are unlikely to be a comorbidity related to severe asthma -Scleroderma -Pemphigus vulgaris -Adrenal insufficiency -Congenital adrenal hyperplasia -Ulcerative colitis -Crohn's disease -Autoimmune hepatitis -Lymphoma/leukemia -Hemolytic anemia -Idiopathic thrombocytopenic purpura -Rheumatoid arthritis -Systemic lupus erythematosus -Polymyalgia rheumatica -Polymyositis/ dermatomyositis -Polyarteritis -Vasculitis -Uveitis -Multiple sclerosis -Organ transplantation -Nephrotic syndrome -Cerebral edema	**Conditions that that are comorbidities potentially associated with asthma** -Interstitial lung disease -Vasculitis -Nasal polyps -Hypersensitivity pneumonitis -Acute and chronic eosinophilic pneumonia -Atopic or contact dermatitis

3. **Do you agree with the methods presented in Table 1?**
   - ☐ YES
   - ☐ NO

   Please provide any comments you may have:

   _____

EVENTS ATTRIBUTABLE TO TREATMENT ESCALATION

4. Seasonal fluctuations may lead to treatment escalation to prevent or treat uncontrolled asthma. In the previous round of consultations, the panel proposed several methods to **identify treatment escalation** due to **seasonal fluctuations** of asthma.

Although these methods could represent plausible clinical scenarios, we propose the following definition due to the limitations of our database:

Creation of a variable that indicates whether a medication for allergic rhinitis (e.g. nasal corticosteroids) has been dispensed at cohort entry and during a treatment escalation event in the follow-up.

Although this definition is limited, it will be tested in our databases in order to assess its clinical usefulness.

Of note, it may be difficult to develop a claims-based algorithm from the other definitions proposed by the panel. Indeed, most of these definitions require that cohort subjects have at least 2 years of medication drug insurance coverage. This may be a limiting factor, as not all individuals in our database have 2 years of medical drug insurance coverage, namely due the occurrence of switches to drug medical coverage regimes that are not covered by our database.

Methods proposed by the panel

1) Escalation according to the chosen definition that is not maintained all year but is recurrent for more than 2 consecutive years
2) Use the same definition for treatment escalation (ex the GINA steps), but consider a seasonal fluctuation escalation if the increase in treatment is over a minimum of 60 days. Specific time periods could also be used, fall-winter vs summer;
3) Stratify data by seasons especially months where seasonal flu is common. If more medications are used only in those months, they may not be strong indicator for severe asthma needing medication escalation;

4) This would need to be assessed over more than 1 year (i.e. at least 2 years with the same pattern for a given patient). Specific periods could be identified such as the winter season and spring. The escalation in a season would have to be followed by de-escalation in the following season. We could also use a definition which combines the use of medications for allergic rhinitis.
5) Dispensing of antibiotics for infections or the presence of nasal corticosteroids or anti H1 due to seasonal allergies.

Do you agree with this definition, given the limitations of our database?

☐ YES

☐ NO

Please provide any comments or suggestions you may have:

_____

S3.3 Questionnaire Round 3

TREATMENT ESCALATION IN ASTHMA - Round 3

In the second round of consultations, consensus was almost achieved for the proposed definitions. Therefore, this will be the **final round** of consultations.

Following this round, you **may be contacted individually** to confirm some aspects of the algorithm, if necessary.

Of note, the last component of the questionnaire regarding **treatment escalation due to seasonal fluctuations** will be eliminated, due to the difficulties in addressing this occurrence using data recorded in administrative databases. For the definition of this type of treatment escalation, all the suggestions provided by the panel will be considered and we will attempt to conduct exploratory analyses on our end to determine which definition can be applied to our database.

Your input and feedback are greatly appreciated!

Development of Asthma Treatment Escalation Algorithm

In the second round of consultations, we proposed a treatment escalation algorithm that was adapted from the GINA 2019/2020 guidelines, in an effort to include all treatment possibilities in the real-world setting.

Click here to view the proposed algorithm.

92% of the participants agreed with the proposed algorithm. However, three additional suggestions were provided to consider all treatment possibilities:

1. Addition of **azithromycin** in step 5b
2. Replace Tiotropium by any **long-acting muscarinic agents**
3. Consider **any ICS dose increase** as a treatment step-up, even if the patient is already on a high dose

For example, patients with severe uncontrolled asthma despite being on high ICS/LABA therapy can be prescribed an additional ICS.

In the previous rounds, we suggested **three levels** of ICS daily dose, in accordance with current clinical guidelines. To take into account higher doses, we suggest adding a **fourth level**, as presented below:

Low: < 250 mcg/day
Medium: 250-499 mcg/day
High: 500-1000 mcg/day
Very high: >1000 mcg/day

Fluticasone propionate HFA equivalent

The modified version of the GINA 2019 treatment steps is presented below (see changes highlighted in blue)

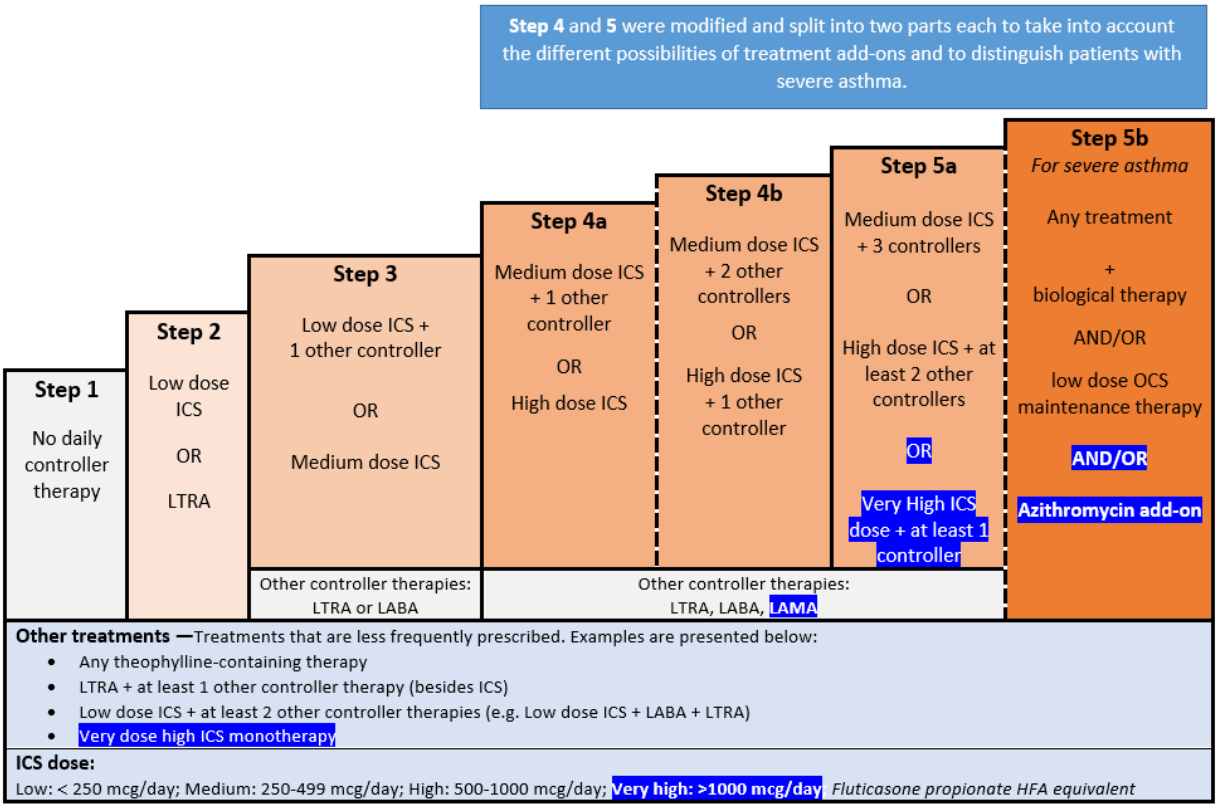


Figure 1. Proposed treatment escalation steps, adapted from the GINA 2019 guidelines.
Abbreviations: ICS: Inhaled corticosteroids; LABA: Long-acting beta2-agonist; LAMA: Long-acting muscarinic agents; LTRA: Leukotriene receptor antagonist

1. Do you agree with the changes highlighted in blue?

- YES
- NO

2. Identifying **chronic azithromycin use** in severe asthma using healthcare administrative databases is not straightforward, as we do not have information on drug indication or complete information on posology. Given these definitions, we propose the following operational definition:

- At least **3 prescription refills** of azithromycin within a 6-month period
- Each prescription should last **at least 28 days (duration provided by the pharmacist during prescription fill process)**

Do you agree with the proposed definition?

- YES
- NO

Additional comments (optional):

_____

ORAL CORTICOSTEROIDS AS MAINTENANCE THERAPY FOR SEVERE ASTHMA

To identify asthma patients on oral corticosteroid (OCS) maintenance therapy, it was agreed that: Individuals should regularly **use low-dose OCS** for a given time period (**at least 50% of total day supply** of the **evaluation period**)

In the second round of consultations, we asked what would be the **minimum threshold for an evaluation period**.

We proposed a period of 90 days (i.e. if an individual with asthma has a total days' supply of OCS of at least 45 days over a 90-day period, then this person would be considered on OCS maintenance therapy).

72% of the panel responded that 90 days was a sufficient period. However, many respondents indicated that this was not an ideal approach, since 45 days of treatment with OCS is too short to ensure that an asthma patient is on a chronic dose of OCS. Therefore, we propose to extend this period to 180 days.

In other words, if a person has a total days' supply of at least 90 days over a 180-day period, then we would consider this person on OCS maintenance therapy. If it is not possible to use a 180-day period, a 90-day period could be acceptable.

Do you agree with the proposed definition?

- Yes
- No

Comments:

_____

In the second round of consultations, we proposed two methods to control for the presence of concomitant conditions for which long-term use of OCS is common, which involved exclusion and statistical adjustments.

Click here to view these methods

86% of the panel agreed with these methods. However, some minor changes were proposed by the panel, as shown below.

Table 1. Methods to control for the presence of concomitant conditions in which long-term use of OCS is common

Exclusion of subjects who have at least one of the following conditions	**Statistical adjustment in subjects who have at least one of the following conditions**
Conditions that are unlikely to be a comorbidity related to severe asthma -Scleroderma -Pemphigus vulgaris -Adrenal insufficiency -Congenital adrenal hyperplasia -Ulcerative colitis -Crohn's disease -Autoimmune hepatitis -Lymphoma/leukemia -Hemolytic anemia -Idiopathic thrombocytopenic purpura -Rheumatoid arthritis -Systemic lupus erythematosus -Polymyalgia rheumatica -Polymyositis/ dermatomyositis -Polyarteritis -Vasculitis -Uveitis -Multiple sclerosis -Organ transplantation -Nephrotic syndrome -Cerebral edema **-Hypersensitivity pneumonitis** [a] **-Interstitial lung disease** [a] **-Acute and chronic eosinophilic pneumonia** [a] **-Allergic bronchopulmonary aspergillosis** [b]	**Conditions that that are comorbidities potentially associated with asthma** ~~**Nasal polyps**~~ [c] -Atopic or contact dermatitis

a. Reason for excluding individuals with hypersensitivity pneumonitis, acute/chronic eosinophilic pneumonia, and interstitial lung disease, instead of conducting statistical adjustment.

These conditions are not either necessarily severe comorbidity in asthma. Furthermore, these conditions are rare.

b. Reason for excluding patients with concurrent allergic bronchopulmonary aspergillosis (ABPA)

ABPA is a rare disease for which OCS chronic use may be prescribed. Although this disease is common in people with asthma or cystic fibrosis, we recommend to exclude these patients instead of conducting statistical adjustment since this disease is a rare cause of poorly controlled asthma, occurring in less than 1% of asthma patients.

c. Reason for not conducting statistical analysis in individuals with nasal polyps.

OCS maintenance therapy is not usually indicated for this condition.

Do you agree with the proposed changes?

- o Yes
- o No

Comments:

_____

Alternative method:

Alternatively, to avoid excluding patients unnecessarily, it was suggested **to not exclude patients based on these comorbidities**, but rather take into account these comorbidities during the identification of treatment escalation episodes, as explained below:

Alternative method: If a person is prescribed OCS maintenance therapy, this change would constitute a treatment escalation **only** if the individual does not have concomitant conditions in which long-term use of OCS is common (Table 1).

This alternative approach may also be useful in individuals with mild asthma who have a comorbidity for which chronic OCS use is the mainstay therapy. As a prime example, an asthma subject on low ICS daily dose with one of these comorbidities may have a treatment escalation episode that does not involve OCS maintenance therapy. Thus, this subject would have been unnecessarily excluded from the sample using the approach proposed in previous rounds.

Which method do you prefer?

- Excluding or conducting statistical adjustments for individuals who have comorbidities for which chronic use of OCS is the mainstay therapy (method suggested in round 1 and 2).
- The alternative method, as described above in blue.
- Both methods are acceptable and should be chosen on a case-by-case basis

Comments:

_____

CHAPTER 5: DISCUSSION

The digitization of healthcare practices holds many promises for patient care improvement, notably through constantly evolving technology and sophisticated analytics capabilities. Electronic medication data are no longer being solely used for administrative and billing purposes; they now have the potential to enhance clinical activities at the point of care and during the entire medication management cycle. Notwithstanding this ongoing data-driven revolution, integrating structured electronic medication data within the clinical workflow is a complex endeavor. This thesis sought to investigate how the secondary use of healthcare data can be leveraged to optimize medication use and support clinical decision-making in routine clinical practice, with a focus on the problems revolving around medication adherence in asthma and COPD patients. Specifically, my research shows how tools based on pharmacy claims data can be used to aid physicians in assessing medication adherence in clinical practice. Indeed, without accurate information on their patients' adherence, physicians may not always be able to identify their non-adherent asthma/COPD patients in a timely manner. This situation can in turn reduce patient disease control and result in unnecessary treatment escalation that can increase the risk of adverse events and lead to more complex and costly drug regimens. Along these lines, this thesis also sought to examine methodological considerations when using administrative healthcare data to facilitate our understanding of the consequences of medication nonadherence at a population level, including unnecessary treatment escalation. As will be discussed in this chapter, the four studies forming the basis of this doctoral thesis each resulted in unique contributions to the scientific literature on medication adherence in asthma/COPD and pave the way for future research that is clinically meaningful and that leverages on the innovation of EMRs and healthcare technology.

5.1 e-MEDRESP Project

The first part of this thesis aimed to develop e-MEDRESP, a novel electronic medication adherence assessment tool based on pharmacy claims data that provides to family physicians with objective and easily interpretable information on medication adherence of their patients with asthma or COPD. To ensure its seamless integration in clinical practice, e-MEDRESP was developed in collaboration with family physicians and patients using a framework inspired by user-centered principles and was subsequently integrated in the EMR of many clinics in Quebec as part of a successful feasibility study.

5.1.1 Development of e-MEDRESP (Article 1) – Key Findings

The first study of this dissertation highlighted some of the most important barriers and facilitators of assessing medication adherence in clinical practice, from the perspective of the family physicians and patients with asthma/COPD. Broadly speaking, this study extends the literature on the role of healthcare professionals in supporting medication adherence in primary care. Specifically, the study aimed to better understand the problems that revolve around the *assessment of medication adherence* in routine clinical practice. We also investigated how the use of healthcare technology and administrative healthcare data can help alleviate some of the challenges physicians face when assessing medication adherence. Several focus groups and interviews were held, and the qualitative analysis revealed that main barriers to assessing medication adherence included lack of objective information regarding medication use and short duration of medical visits. Physicians also emphasized that identifying patients at risk for non-adherence requires a team effort with pharmacists, respiratory therapists, and nurses. Physicians and patients also agreed that the use of easily interpretable pharmacy claims data could be an important facilitator.

Importantly, it was in this study that an e-MEDRESP prototype was developed in collaboration with these primary end-users using an iterative process. Once the paper-based prototype was finalized and no additional suggestions were given by the participants, an interactive web-based module was built in the Visual Studio 2017 community software. Specifically, e-MEDRESP was constructed by developing algorithms of medication adherence which reflected the end-user recommendations identified during the discussions. Of note, the development of the web-based version of the tool was complex and necessitated a close collaboration with several external programmers and the biostatistician of our research lab. In total, the development process, from prototype elaboration to implementation in the EMR, took nearly 2.5 years.

5.1.1.1 Strengths and Limitations

Several rigorous qualitative research methods were applied. In particular, focus groups and interview data were combined, which resulted in a nuanced and richer analysis and provided an opportunity to achieve data saturation more rapidly. The analysis of the transcripts by three independent investigators, coupled with our iterative approach to qualitative inquiry, ensured congruence between the research purpose, literature review, data collection strategies, participant sampling, and analysis, which ultimately conferred validity and reliability to our findings. Finally, developing e-MEDRESP in collaboration with physicians and patients allowed us to better understand the unmet needs of the primary-end users and ensured that the tool can be easily integrated within physician workflow.

However, the study had several methodological drawbacks. The first concerns the sampling approach. We originally planned to recruit participants using purposive sampling.[31] This would have allowed us to obtain maximal variation in key characteristics among participants, including age, sex, region of residence, number of years since diagnosis of asthma or COPD (for patients), and number of years of practice in family medicine (for physicians). However, due to time constraints and the significant recruitment difficulties, this approach was unfortunately not possible. Instead, convenience sampling was used, whereby research participants were selected based on their ease of availability and willingness to participate.[222] In this context, it can be speculated that it was easier to recruit physicians who were already proactive supporting patient medication adherence. In addition, enrolled patients may have been more adherent to their medications compared to the general population of subjects with chronic respiratory diseases and therefore be more at ease to discuss their medication use in a group setting. In contrast, purposive sampling would have allowed us to search for participants who covered the spectrum of positions and perspectives in relation to the phenomenon that we were studying (i.e. medication adherence in clinical practice).[222]

Another limitation of the study relates to the extent of the involvement of the users in the development process of e-MEDRESP. In principle, every stage of the user-centered design includes testing and analysis, and these activities require looping back to earlier stages; as a result, development occurs in iterative cycles of assessing-designing-testing-analyzing-refining-testing-analyzing-refining.[223,224] In the study, participants' comments were used to refine the prototype after each interview and the improved prototype was presented to new participants in subsequent interviews. Moreover, the electronic prototype of the tool was thoroughly tested and revised by a pulmonologist and two clinical pharmacists who were not involved in the interviews at the end of the study. Indeed, it was our aim to reach as many new potential users as possible to maximize feedback and obtain various clinical perspectives. With

hindsight, it would have been useful and relevant to present the finalized prototype to all the participants who took part in the study—or at least a sample of the participants—and conduct further testing with them prior to initiating the feasibility study. Due to timing and logistic constraints, this approach was unfortunately not possible.

Furthermore, limitations of e-MEDRESP include those which are inherent to pharmacy claims data. Namely, pharmacy claims data in reMed only include prescriptions dispensed in community pharmacies. Thus, prescriptions filled in hospital pharmacies or prescriptions which were written by the treating physician but not filled by the patient are not captured by the tool. In addition, they do not capture the medications that are given directly to patients by physicians. Not to mention that filling prescriptions does not guarantee that the medication will be taken by the patient. Because written physician prescriptions are not available in claims data, it is also difficult to identify treatment switches and to make the distinction between physician-prescribed treatment cessation and non-adherence. Nevertheless, participants in the study confirmed that e-MEDRESP could serve has a useful communication aid and could help physicians better counsel their patients on the importance of optimizing medication adherence.

5.1.2 Feasibility of Implementing e-MEDRESP in Clinical Practice (Article 2) – Key Findings

The e-MEDRESP feasibility study extended the literature on the implementation of e-health technology tools aimed at enhancing the quality of healthcare. Out the 346 patients enrolled, 252 patients had at least one medical visit during the study. e-MEDRESP was consulted by 15 physicians for 85 (34%) of these patients during a medical visit. 84% of patients reported discussing their medication use with their physicians; additionally, 33% confirmed seeing their e-MEDRESP report on the physician's computer and indicated that it was easy to interpret.

Encouragingly, positive feedback on the clinical usefulness of e-MEDRESP was gathered from physicians and patients. Questionnaires, telephone interviews, and testimonies collectively showed that e-MEDRESP facilitated patient-physician communication; allowed physicians to rapidly detect their non-adherent patients; and helped them to provide a more personalized treatment based on their patients' adherence to controller medications. Not to mention that improvement in adherence was observed among patients taking some of the most commonly prescribed medications to treat moderate-to-severe asthma or COPD.

5.1.2.1 Study Findings in the Context of the Clinical Adoption Meta-Model

Consistent with the clinical adoption meta-model,[181] the success of implementation of a medication adherence assessment tool depends on the ability for the end-users to access and interact with the tool (i.e. via an EMR) and whether meaningful adaptations of clinical workflows and healthcare behaviors are facilitated by the tool. The four dimensions stipulated by the model were integrated in the methodological framework of the study. First, **availability** of the tool was facilitated by e-MEDRESP's seamless integration in physicians' EMR. Second, **system use** was monitored using hit counters embedded in the tool and was further assessed with physician surveys and patient phone interviews. The last two dimensions of the clinical adoption model, **clinical behaviors and outcomes**, were considered in the study, but only in the exploratory analyses. Specifically, prescription changes following consultation of e-MEDRESP were described, but due to the limited sample size, trends could not be observed. The capacity of e-MEDRESP to improve patient medication adherence was investigated and although improvement in adherence was observed in some of the most commonly prescribed medications in asthma/COPD, it cannot be ascertained that these improvements were attributable solely to e-MEDRESP. As well, the study was not sufficiently powered to detect clinically significant improvement in adherence or disease control, nor was the design the most appropriate to study this outcome. To investigate the impacts that are solely attributable to the adoption of e-MEDRESP in clinical practice, it would have been necessary to conduct a cluster-randomized clinical trial which would have allowed us to compare the effect of e-MEDRESP on medication adherence, compared with usual care practices.

When analyzing its clinical adoption trajectory, e-MEDRESP appeared to have a low user adoption. Thus, it is possible that the tools were used frequently in the beginning but was not sustained throughout the study. It is also possible that there was a misalignment between e-MEDRESP and clinical practice. Despite the positive feedback obtained from users, e-MEDRESP was not used as widely as anticipated, although the rate of use (34%) was higher than similar studies in the literature.[23,175] As was previously mentioned in the literature review (Chapter 2), studies in the literature which have evaluated the feasibility of implementing medication adherence assessment tools in clinical practice have not always rigorously evaluated their use by physicians; [21,22,24,25,199,204] therefore, the mere fact that we closely monitored the use of e-MEDRESP in clinical practice is a methodological strength in itself. In addition, medical visits included in our analysis comprised consults that were not necessarily specific to asthma or COPD (all-cause). As such, physicians may not have felt the need to access e-MEDRESP at every available opportunity, especially if the medical visit was not respiratory-related. It would have been relevant to calculate the rate of use among medical visits for asthma or COPD care; however, accurate information

on the diagnosis associated with medical visits was not available. As confirmed by the Post hoc survey, the COVID-19 pandemic may have affected the use of e-MEDRESP in routine clinical practice, as physicians were compelled to modify their practice to better adapt to the exceptional circumstances of the public health crisis. They were less concerned with medication adherence and focused on more urgent care, such as psychological problems. Finally, the study sample was not sufficiently powered to allow us to determine patient- or physician-level determinants of use, nor did we have access to detailed patient and physician characteristics. Instead of conducting a Post hoc survey to better understand the clinical relevance of e-MEDRESP, it would have been interesting to conduct short interviews with the participating physicians at the end of the study. However, due to time constraints, this was not possible.

5.1.2.2 Other Strengths and Limitations

From its inception, e-MEDRESP was designed using several criteria that were previously shown in the literature to facilitate physician adoption of new healthcare information technology in clinical practice.[187] First, e-MEDRESP was implemented in EMRs to ensure that the tool was efficiently integrated within physician workflow. Such an approach ensured that the tool did not result in loss of productivity or increased clinician burden.[188,189] Second, physicians and patients were consulted throughout the development and feasibility assessment process to ensure that e-MEDRESP was user-friendly and clinically intuitive.[190-192] Finally, prior to embarking on a large-scale implementation of an e-health technology, it is imperative to rigorously assess its clinical usefulness. Among the existing medical assessment tools reported in the literature,[21-25,199,204] physician uptake of the tool in clinical practice was not always closely monitored and patient and physician feedback were seldom collected. Moreover, capacity of these tools to improve medication adherence was not always assessed or the periods in which adherence was assessed were not always clearly defined. Yet such methodological considerations should be embedded in the design and implementation of new e-health technologies. These factors may collectively explain why the uptake of some of these tools in clinical practice was not as high as expected. This thesis resolved these important methodological limitations.

The results of the feasibility study should be considered in the light of some limitations. Participant recruitment proved to be a monumental task, and the logistics of the recruitment process required several months of planning. Despite the great efforts exerted by the research team, recruitment rate was low, especially among family physicians. Furthermore, since physicians were recruited by email and fax, documenting reasons for refusal was challenging, although lack of interest or time was the most common reason reported. It was also difficult to determine the proportion of invitations that truly reached the

targeted physicians or to compare the characteristics of participants and non-participants, since the medical secretaries were the main point of contact during the follow-up phone calls. Recruitment challenges were further exacerbated by the low number of patients recruited for several enrolled physicians. As a result, these physicians had fewer opportunities to use the tool and share their feedback during the feasibility study.

Another methodological drawback concerns the method used to identify non-adherent patients. A PDC below 80% was used, since clinical evidence suggests that this threshold is the level above which the medication has a reasonable likelihood of achieving the most clinical benefit.[31] However, this threshold is not specific to asthma and COPD. Although it is unclear from the literature what the optimal threshold is for these two diseases, we could have contacted clinical experts to determine this threshold or at least, conduct sensitivity analyses with different adherence levels to test the robustness of our analysis. Alternatively, we could have used trajectory modeling to describe adherence patterns and to identify non-adherent patients.[39] Trajectory modeling is a more clinically intuitive method to describe adherence behaviours in the population, compared to the common way of classifying patients as either adherent or non-adherent based on pre-defined levels. Notwithstanding its clinical appeal, trajectory modeling requires a long follow-up period and a large sample size; thus, this approach merits to be explored in future studies.

Finally, it may have been easier to recruit physicians who were already proactive in promoting optimal medication adherence of their patients. In a similar vein, patients in the e-MEDRESP cohort appeared to have, on average, higher level of medication adherence than the general population.[7-10] The patient recruitment was also relatively low (38%). Thus, our sampling strategy may not have entirely reflected the complexities and nuances of the real-world clinical practice setting.

5.1.2.3 The e-MEDRESP project: Clinical Implications and Future Work

Although a prototype of e-MEDRESP was extensively developed in collaboration with patients and physicians in the first study of this research program, family physicians provided feedback on how to further improve it throughout the feasibility study, including modifications to the adherence calculations that better reflect recent changes in clinical guidelines. At a broader level, these suggestions underscore the importance of iteratively developing e-health technologies, from prototype development to the implementation process. The e-MEDRESP feasibility study highlighted the need to continue to conduct feasibility studies with other healthcare professionals, such as pulmonologists, nurses, and pharmacists in

order to gauge the clinical relevance of this tool in different healthcare settings. Furthermore, most physicians were recruited from family medicine groups (FMG), which is a group of physicians working closely with other healthcare professionals, including nurses, pharmacists and respiratory therapists, in the provision of services to enrolled patients on a non-geographic basis.[225] Thus, widening the access of e-MEDRESP to different healthcare professionals and adapting it to other chronic diseases may also enhance of the uptake of the tool in clinical practice. Another potential strategy to enhance the use of e-MEDRESP in clinical practice is to incorporate it within an existing clinical decision support system. This approach could ultimately help physicians provide personalized recommendations for care, based on patient-level clinical data and medication adherence (including inhaler technique).

Of note, patients did not provide detailed feedback on the tool. Yet, telephone interviews revealed that only 33% of patients had the opportunity to view their e-MEDRESP report during medical visits, indicating that the tool may have been more adapted to physicians' needs. Therefore, new strategies are required to better ensure patient engagement. Given the growing popularity of mobile phone apps targeting medication adherence,[37] we believe that linking e-MEDRESP to a mobile phone app that offers educational materials may provide more personalized avenues for patients to optimize their medication-taking behaviour, though further studies are required to confirm this hypothesis.

One of the biggest challenges faced in this project was related to family physician recruitment. Although the level of participation in research by general practitioners is notoriously low,[226] we believe that recruiting physicians solely by phone, email or fax was not ideal. Due to logistical constraints, physician recruitment was initiated before the development of e-MEDRESP was finalized. This approach was not optimal, since physicians did not have the opportunity to view the tool and gauge its clinical relevance upon recruitment. Thus, for future projects, physician recruitment methods need to be modified, given our low recruitment rate. Instead, in-person visits offering demos of the tool may help to better elicit interest of physicians. Using promotional materials that present physician and patient testimonies on e-MEDRESP could also boost participant engagement.

As previously mentioned, cluster randomized clinical trials are required to evaluate the effectiveness of e-MEDRESP to improve adherence. Given that medication adherence is a complex phenomenon entrenched in a myriad of factors related to the patient, healthcare provider, and healthcare system, e-MEDRESP should be integrated in multi-focal interventions which aim to foster patient and physician education and stronger patient-physician relationship, as well as inter-professional collaboration. Integrating patient-generated health data in the tool (side effects, illness beliefs, ease of

use of inhaler, etc.) could also enhance its clinical relevance, as it would allow physicians to tailor treatment decisions to each patients' individual preferences and health states.

5.1.2.3.1 Large-Scale Implementation of e-MEDRESP – Challenges and Pitfalls

To ensure the seamless integration of e-MEDRESP in clinical practice, we formed a partnership with OMNIMED, a leading EMR provider in Quebec. Given that the e-MEDRESP tool is web-based and is housed in an independent server at the Université de Montréal, it can technically be transposable to other EMR systems. Notwithstanding this appealing feature, the road to the large-scale implementation of e-MEDRESP in clinical practice is paved with many challenges. Namely, obtaining patient consent and registering patients to the reMed dug claims database to retrieve their medication data is a time-consuming process. In Quebec, the ideal scenario would be to integrate e-MEDRESP within the Quebec Health Record (*Dossier Santé Québec*). Unfortunately, the Quebec Health Record cannot be currently used for research proposes. Thus, for now, we need to continue to rely on reMed to manually register patients.

Beyond Quebec, the e-MEDRESP algorithms would need to be adapted to individual pharmacy databases and pharmacy management systems. As was mentioned in the introduction, medication-related data is complex and not all medication data sources are equivalent across jurisdictions. There is a lack of harmony and standards, both in terms of practices and terminologies, that are inherent to medication-related data. As for reMed, several mechanisms and quality control procedures were established over the years to take into consideration billing-specific drug coding mechanisms that can affect and hinder the interpretability of medication data in the clinical setting. There is also a dictionary specific to asthma and COPD medications that can be linked to reMed data which considers the coding changes and particularities of drugs entering the market and those that are withdrawn or temporarily discontinued. This dictionary is maintained and periodically updated by our research lab. Yet, extending e-MEDRESP to other healthcare systems beyond Quebec would require the establishment of mechanisms that can facilitate the data processing of the medication data and translate them into a format that is useful and relevant for clinicians, while taking into consideration local rules, practices, and particularities.

5.2 Medication Adherence and Treatment Escalation in Asthma

The second part of this thesis consisted of two studies which laid the groundwork for a population-based cohort study which aims to estimate the association between medication adherence and subsequent treatment escalation in asthma using healthcare administrative data. Accordingly, healthcare administrative data can provide an interesting avenue to further our understanding on the consequences of medication nonadherence at a population level. However, since these data are a by-product of constantly evolving and heterogenous healthcare systems, it is important to ensure that these data are valid for research.

In the first study, a systematic literature review was conducted to select optimal asthma case-finding algorithms that can be used in administrative database research. In the second study, an operational definition of treatment escalation was developed, using the Delphi consensus process. This definition was inspired by the 2020 Global for Initiative for Asthma treatment guidelines. Although the final cohort study which aims to examine the association between treatment escalation and medication adherence is beyond the scope of this doctoral thesis, I plan to conduct, within the next year, this study in collaboration with Lucie Blais and her research team using the definitions obtained from the studies. At a broader level, these two studies highlight important methodological issues that should be considered when conducting this future cohort study.

5.2.1 Systematic Review on the Validity of Asthma Case-Finding Algorithms in Healthcare Administrative Databases (Article 3) – Key findings and Implications for Future Research

The systematic review showed that healthcare administrative databases appear to adequately identify asthma patients. The next step would be select the algorithm that is the most appropriate to use in the future cohort study that aims to assess the association between medication adherence and treatment escalation. As mentioned in the literature review of this thesis (section **2.7.2.1)**, prior to embarking in this study and selecting the best case-finding algorithm, we must assess the relative importance of sensitivity, specificity, PPV, and, NPV, and prioritize the accuracy measure that is most relevant to the research question.[215] For instance, it is desirable to select algorithms that have higher sensitivities for surveillance studies, since this approach minimizes the number of missed cases.[215,216] Most studies in this review tested multiple algorithms to identify the one which has the best trade-off between sensitivity and specificity. Generally, lengthening the time frame to capture asthma cases or increasing the number of diagnoses increased the specificity, at the cost of a lower sensitivity. Operational definitions based solely on

hospitalization data were not sensitive, albeit highly specific since this approach tends to capture more moderate-to-severe asthma patients. On the other hand, a significant number of studies included in the review chose the PPV as their main measure of validity, which is important when identifying a cohort defined by disease status. High PPVs and NPVs ensure that only persons who truly have the condition of interest are captured,[215] and are desirable in studies seeking to examine causal relationships or associations.

For the population-based cohort study which aims to study the **association** between **medication adherence** and **treatment escalation**, we need to select an algorithm that fulfills the following criteria:

- Provides a good trade-off between sensitivity and specificity;
- Has a relatively high PPV;
- Has been tested in adult populations;
- Has been tested in Canadian administrative databases;

Among the 20 studies retained in this review, the studies conducted by Blais *et al.*[217] and Gershon *et al.* [227] fulfill the above criteria. For the Blais *et al.* study, the algorithms which required two asthma diagnosis to be made by a pulmonologist over a 1-year period had the highest validity (sensitivity: 87%, specificity: 94%, PPV: 77%). However, such a strategy may exclude an important segment of the population, given that most asthma patients are treated in primary care. Alternatively, the following algorithm proposed by Gershon *et al.* appeared to have the best trade-off between sensitivity (84%) and specificity (77%) and yielded a reasonably high PPV (62%):

> **Two or more ambulatory medical visits** for asthma or **one hospitalization** for asthma over two years, among individuals aged 19-80 years old

Based on the literature review, I recommend selecting this algorithm for the population-based cohort study that aims to assess the association between medication adherence and treatment escalation. Of note, this study was conducted using Ontario healthcare administrative databases. As was discussed in the introduction of this thesis (section **2.7.1**), there are differences in terms of content, coding, and completeness across Canadian administrative healthcare databases. Thus, further research is required to validate this algorithm across different Canadian jurisdictions.

5.2.1.1 Strengths and limitations

Overall, the study was conducted using rigorous research standards and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This study was among a series of systematic reviews of validated methods for identifying various chronic diseases using healthcare administrative data that have been conducted by the Quebec Support for People and Patient-Oriented Research and Trials (SUPPORT Unit), as part of its mandate to implement strategies to facilitate access and use of health research data.

The review presented some limitations. Namely, articles whose full texts were not available in English or French were excluded, which may have introduced a language bias. There was also a possibility of missing articles that were not indexed in the bibliographic databases under terms related to administrative data or validation. Nonetheless, our rigorous systematic research methods combined with the grey literature search, ensured that our search strategy was optimized. Lastly, publication bias cannot be ruled out, whereby asthma diagnostic algorithms with poor validity may have been withheld from publication.

5.2.2 Development of an Asthma Treatment Escalation Definition Adapted to Healthcare Administrative Databases (Article 4): Key Findings

Through rigorous research methods that were supported by an expert panel, we developed a treatment escalation definition that was adapted from the 2020 GINA guidelines. This definition comprises three options and takes into account transition to higher treatment steps, inhaled corticosteroid dose increases, and controller treatment add-on, as well as treatments that are not typically included in clinical guidelines. Furthermore, the applicability of this operational definition was also successfully tested in a population-based cohort of adults with asthma selected from administrative databases.

The systematic review that was conducted as the starting point for the Delphi process revealed that operational definitions of asthma treatment escalation are highly variable across the literature. Additionally, none of the definitions appeared to have been validated or established through a rigorous expert consensus. These differences were further reflected by the discrepancies in the treatment escalation rates reported in the retained studies. Although these studies collectively provided valuable insight on treatment escalation patterns in the real-world setting, some of the approaches used to identify treatment escalation failed to include all treatment possibilities in the real-world setting, particularly in severe asthma. Overall, the Delphi process was a successful approach in harmonizing the findings from

the literature review and proved to be a useful method to identify treatment escalation patterns in population-based observational studies.

5.2.2.1 Strengths and Limitations

To the best of our knowledge, this study is the first to develop an operational definition of treatment escalation that is based on expert consensus and rigorous mixed-methods research. An important strength of the Delphi process is the incorporation of a systematic literature review, which provided valuable guidance for the development of the questionnaires that were administered in the consultation rounds. Another salient feature is the iterative process that was used to develop the treatment escalation definition, which was informed by expert opinion and the cohort study findings.

Despite these methodological strengths, the results of this study should be interpreted in the light of some limitations. Namely, the participants of the Delphi process only included 15 Canadian experts, whereas a larger multi-national panel would have enhanced the generalizability of study findings. However, since our definition was based on international guidelines, we believe that it could easily be applied or adapted to different healthcare settings. Given the heterogeneity in terms of content and validity across different databases, future validation studies are required to ensure the applicability of the treatment escalation definition across different jurisdictions. Another point to consider is that pharmacy claims data do not typically record medications dispensed in hospital pharmacies. Yet, a prescription change leading to a treatment escalation can occur during an inpatient stay, especially if the patient was hospitalized after an asthma exacerbation. The treatment escalation algorithm that was developed in this study will eventually capture this treatment escalation, if the patient dispenses the new prescription in a community pharmacy after hospital discharge. Nevertheless, the algorithm may under-estimate the timing of the treatment escalation or fail to identify the treatment escalation event altogether if the patient does not fill his prescription in a community pharmacy after hospital discharge.

Lastly, the cohort study used to test the definition was based on administrative data that were retrospectively collected between 2002 and 2016, which prevented us from ascertaining treatments that appeared in more recent treatment guidelines, such as chronic azithromycin use. Along similar lines, the Delphi questionnaires were developed using criteria that were obtained from a literature review on treatment escalation definitions published between 1996 and 2020, a period during which physician prescribing practices and the availability of different asthma medications may have evolved. However, treatment guidelines have not significantly changed over the last 30 years, other than the fact that as-

needed SABA is no longer the preferred reliever therapy for patients with mid asthma since 2019. Since the treatment escalation definition was based on controller medications and not reliever therapies, we believe that this change in treatment guidelines does not have a major impact on the applicability of the treatment escalation definition developed. Notwithstanding, it is always important to take into consideration changes in treatment practices over time. In future cohort studies which apply this definition, it would be thus appropriate to select recent study periods or adjust for the year of cohort entry in statistical analyses.

5.2.2.2 Clinical Implications and Future Work

In recent years, the arsenal of asthma treatment options has broadened with the advent of novel agents, particularly monoclonal antibody therapies targeting IgE, interleukin (IL)-4/IL-13 and IL-5 cytokine pathways. With the expected rise in the use of expensive biologics and increasing evidence on the impact of oral corticosteroids adverse effects, understanding how prescribing patterns compare with clinical treatment guidelines will help us gain insight on the key aspects that prevent optimal pharmacological treatment. Given the complex therapeutic landscape of asthma, the necessity to adequately identify treatment escalation in asthma at a population level has become increasingly relevant. Treatment decision-making in the context of asthma is complex and relies on careful assessment of common problems, such as inhaler technique, disease control, and medication adherence.[47] Yet, accurately assessing medication in clinical practice is challenging; thus, physicians may prescribe expensive biologic therapy to patients with severe asthma, even though the reason behind disease non-control is medication non-adherence. Thus, the findings of this study can form the basis of future studies which aim to evaluate the relationship between asthma control, medication adherence, and treatment escalation. Such studies could provide insight on physician prescribing practices and could ultimately help determine whether patients' treatment escalation was an appropriate treatment decision.

5.3 Conclusions

The digitization of healthcare practices, coupled with the increasing availability and use of secondary healthcare data, holds the promise to revolutionize patient care. Using a rigorous mixed-methods research approach, this thesis examined how administrative healthcare data can be leveraged to: 1) optimize medication adherence in routine clinical practice in patients with chronic respiratory diseases; and 2) gain a greater understanding on prescribing practices that can lead to unnecessary treatment escalation in asthma, which is an unintended consequence of patient medication nonadherence.

In the e-MEDRESP project, structured electronic medication data was successfully integrated within the workflow of family physicians. To the best of our knowledge, the e-MEDRESP medication adherence assessment tool is among few of its kind in Canada. e-MEDRESP has the potential to allow physicians to assess adherence objectively and to facilitate patient-physician communication concerning medication use. Further research is required to evaluate the effectiveness of e-MEDRESP to improve medication adherence, to enhance its clinical adoption in clinical practice, and to boost physician and patient engagement. Additional work to ensure a large-scale implementation of e-MEDRESP is also warranted.

In the second part of this thesis, two distinct studies were conducted to lay the groundwork for a future cohort study which aims to assess the association between medication adherence and subsequent treatment escalation. Healthcare administrative data can help elucidate this phenomenon, which is currently under-explored in the literature. However, given that these data are a by-product of constantly evolving and heterogenous healthcare systems, several methodological issues need to be considered prior to conducting this study; this thesis has provided practical solutions for a number of these methodological considerations.

Overall, medication adherence is a complex phenomenon that results in sub-optimal therapeutic outcomes. As well, it can inadvertently affect prescribing practices and treatment decisions. Administrative healthcare data can help alleviate some of these problems that revolve around medication adherence. Given that medication adherence will continue to persistently affect patients living with chronic diseases, the methodology that was implemented in this research program can also be used as a model for chronic diseases other than asthma and COPD.

BIBLIOGRAPHY

1. Soriano JB, Abajobir AA, Abate KH, et al. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. 2017;5(9):691-706.
2. Global Initiative for Asthma. Pocket Guide for Asthma Management and Prevention. 2019; https://ginasthma.org/2018-pocket-guide-for-asthma-management-and-prevention/.
3. The Lancet. Global Burden Disease (GBD) 2015; https://www.thelancet.com/gbd.
4. Breathe - The Lung Association. https://www.lungsask.ca/about-us/news-room/backgrounders-and-information-sheets/asthma-fact-sheet. Accessed May 4, 2020.
5. Evans J, Chen Y, Camp PG, Bowie DM, McRae L. Estimating the prevalence of COPD in Canada: Reported diagnosis versus measured airflow obstruction. *Health reports.* 2014;25(3):3-11.
6. Gershon AS, Warner L, Cascagnette P, Victor JC, To T. Lifetime risk of developing chronic obstructive pulmonary disease: a longitudinal population study. *Lancet (London, England).* 2011;378(9795):991-996.
7. World Health Organization. Adherence to Long-Term Therapies: Evidence for Action. 2003; http://www.who.int/chp/knowledge/publications/adherence_full_report.pdf.
8. Blais L, Kettani FZ, Beauchesne MF, Lemiere C, Perreault S, Forget A. New measure of adherence adjusted for prescription patterns: the case of adults with asthma treated with inhaled corticosteroid monotherapy. *The Annals of pharmacotherapy.* 2011;45(3):335-341.
9. Cyr MC, Beauchense MF, Lemiere C, Blais L. Comparison of the adherence and persistence to inhaled corticosteroids among adult patients with public and private drug insurance plans. *Journal of population therapeutics and clinical pharmacology = Journal de la therapeutique des populations et de la pharamcologie clinique.* 2013;20(1):e26-41.
10. Savaria F, Beauchesne MF, Forget A, Blais L. Adherence and Persistence to Long-Acting Anticholinergics Treatment Episodes in Patients With Chronic Obstructive Pulmonary Disease. *The Annals of pharmacotherapy.* 2017;51(12):1063-1068.
11. Ismaila AS, Sayani AP, Marin M, Su Z. Clinical, economic, and humanistic burden of asthma in Canada: a systematic review. *BMC pulmonary medicine.* 2013;13:70-70.
12. Dang-Tan T, Ismaila A, Zhang S, Zarotsky V, Bernauer M. Clinical, humanistic, and economic burden of chronic obstructive pulmonary disease (COPD) in Canada: a systematic review. *BMC research notes.* 2015;8:464-464.
13. Wechsler ME. Managing asthma in primary care: putting new guideline recommendations into context. Paper presented at: Mayo Clinic Proceedings2009.
14. Broekhuizen BD, Sachs AP, Verheij TJ. COPD in primary care: from episodic to continual management. In: British Journal of General Practice; 2012.
15. Yousif A, Pelaez S, Lemiere C, et al. Development of a Web-Based Tool Built From Pharmacy Claims Data to Assess Adherence to Respiratory Medications in Primary Care. *Respiratory care.* 2020.
16. Lim KG, Rank MA, Li JT, et al. How well does patient self-report predict asthma medication possession? Implications for medication reconciliation and adherence assessment. *Journal of Asthma.* 2010;47(8):878-882.
17. Bender B, Wamboldt F, O'Connor SL, et al. Measurement of children's asthma medication adherence by self report, mother report, canister weight, and Doser CT. *Annals of Allergy, Asthma & Immunology.* 2000;85(5):416-421.

18. Gamble J, Stevenson M, McClean E, Heaney LG. The prevalence of nonadherence in difficult asthma. *American journal of respiratory and critical care medicine.* 2009;180(9):817-822.
19. Cadarette SM, Wong L. An Introduction to Health Care Administrative Data. *The Canadian journal of hospital pharmacy.* 2015;68(3):232-237.
20. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. *Journal of clinical epidemiology.* 1997;50(1):105-116.
21. Harbig P, Barat I, Lund Nielsen P, Damsgaard EM. Instantaneous detection of nonadherence: quality, strength, and weakness of an electronic prescription database. *Pharmacoepidemiology and drug safety.* 2012;21(3):323-328.
22. Heisler M, Hogan MM, Hofer TP, Schmittdiel JA, Pladevall M, Kerr EA. When more is not better: treatment intensification among hypertensive patients with poor medication adherence. *Circulation.* 2008;117(22):2884-2892.
23. Williams LK, Peterson EL, Wells K, et al. A cluster-randomized trial to provide clinicians inhaled corticosteroid adherence information for their patients with asthma. *The Journal of Allergy and Clinical Immunology: In Practice.* 2010;126(2):225-231, 231.
24. Vollmer WM, Feldstein A, Smith DH, et al. Use of health information technology to improve medication adherence. *The American journal of managed care.* 2011;17(12 Spec No.):Sp79-87.
25. Dixon BE, Alzeer AH, Phillips EO, Marrero DG. Integration of Provider, Pharmacy, and Patient-Reported Data to Improve Medication Adherence for Type 2 Diabetes: A Controlled Before-After Pilot Study. *JMIR medical informatics.* 2016;4(1):e4.
26. Comer D, Couto J, Aguiar R, Wu P, Elliott D. Using aggregated pharmacy claims to identify primary nonadherence. *The American journal of managed care.* 2015;21(12):e655-660.
27. DSQ. Dossier Santé Québec. 2018; http://dossierdesante.gouv.qc.ca/.
28. Payne TH. Computer decision support systems. *Chest.* 2000;118(2 Suppl):47s-52s.
29. McCowan RN, IW Ricketts, FC Warner, G. Hoskins, GE Thomas, C %J Medical informatics, medicine tIi. Lessons from a randomized controlled trial designed to evaluate computer decision support software to improve the management of asthma. 2001;26(3):191-201.
30. Tamblyn R, Ernst P, Winslade N, et al. Evaluating the impact of an integrated computer-based decision support with person-centered analytics for the management of asthma in primary care: a randomized controlled trial. *The Journal of the American Medical Informatics Association.* 2015;22(4):773-783.
31. Eccles M, McColl E, Steen N, et al. Effect of computerised evidence based guidelines on management of asthma and angina in adults in primary care: cluster randomised controlled trial. *British Medical Journal.* 2002;325(7370):941.
32. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of COPD. 2019; http://www.goldcopd.org/.
33. Cameron R. A sequential mixed model research design: Design, analytical and display issues. *International Journal of Multiple Research Approaches.* 2009;3(2):140-152.
34. Garrett JJ. *Elements of user experience, the: user-centered design for the web and beyond.* Pearson Education; 2010.
35. Zeiger RS, Schatz M, Li Q, Zhang F, Purdum AS, Chen W. Step-up care improves impairment in uncontrolled asthma: an administrative data study. *The American journal of managed care.* 2010;16(12):897-906.
36. Broder MS, Chang EY, Sapra S. Care of asthma patients in relation to guidelines. *Allergy and asthma proceedings : the official journal of regional and state allergy societies.* 2010;31(6):452-460.

37. Dilokthornsakul P, Thompson AM, Campbell JD. Treatment patterns and related clinical consequences in adults with asthma. *The Journal of asthma : official journal of the Association for the Care of Asthma.* 2019;56(7):739-747.
38. Gayle A, Tebboth A, Pang M, et al. Real-life prescribing of asthmatic treatments in UK general practice over time using 2014 BTS/SIGN steps. *Primary care respiratory medicine.* 2019;29(1):25.
39. van Boven JFM, Koponen M, Lalic S, et al. Trajectory Analyses of Adherence Patterns in a Real-Life Moderate to Severe Asthma Population. *The Journal of Allergy and Clinical Immunology: In Practice.* 2019;8(6):1961-1969.
40. Buhl R, Heaney LG, Loefroth E, et al. One-year follow up of asthmatic patients newly initiated on treatment with medium- or high-dose inhaled corticosteroid-long-acting β(2)-agonist in UK primary care settings. *Respir Med.* 2020;162:105859.
41. Bengtson LGS, Yu Y, Wang W, et al. Inhaled Corticosteroid-Containing Treatment Escalation and Outcomes for Patients with Asthma in a U.S. Health Care Organization. *Journal of managed care & specialty pharmacy.* 2017;23(11):1149-1159.
42. Yousif A, Dault R, Courteau M, et al. The validity of diagnostic algorithms to identify asthma patients in healthcare administrative databases: a systematic literature review. *Journal of Asthma.* 2020:1-17.
43. Bourbeau J, Bhutani M, Hernandez P, et al. CTS position statement: Pharmacotherapy in patients with COPD—An update. In: Taylor & Francis; 2017.
44. Canadian Thoracic Society. 10 CTS Guideline - Asthma Management Continuum – Consensus Summary for children six years of age and over, and adults. 2010; http://www.lignesdirectricesrespiratoires.ca/node/287. Accessed November 30, 2015.
45. Statistics Canada. Asthma. 2014; https://www150.statcan.gc.ca/n1/pub/82-625-x/2015001/article/14179-eng.htm. Accessed April 23 2019.
46. To T, Simatovic J, Zhu J, et al. Asthma deaths in a large provincial health system. A 10-year population-based study. *Annals of the American Thoracic Society.* 2014;11(8):1210-1217.
47. Global Initiative for Asthma. Pocket Guide for Asthma Management and Prevention. 2020; https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_-final-_wms.pdf.
48. Reddel HK, FitzGerald JM, Bateman ED, et al. GINA 2019: a fundamental change in asthma management. *Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents.* 2019;53(6):1901046.
49. Dusser D, Montani D, Chanez P, et al. Mild asthma: an expert review on epidemiology, clinical characteristics and treatment recommendations. *Allergy.* 2007;62(6):591-604.
50. Taylor DR, Sears MR, Cockcroft DWJMC. The beta-agonist controversy. *Medical Clinics.* 1996;80(4):719-748.
51. Hancox RJ. Concluding remarks: can we explain the association of beta-agonists with asthma mortality? A hypothesis. *Clinical reviews in allergy & immunology.* 2006;31(2-3):279-288.
52. O'Byrne PM, FitzGerald JM, Bateman ED, et al. Inhaled Combined Budesonide–Formoterol as Needed in Mild Asthma. *New England Journal of Medicine.* 2018;378(20):1865-1876.
53. Government of Canada. Chronic Obstructive Pulmonary Disease (COPD). 2019; https://www.canada.ca/en/public-health/services/chronic-diseases/chronic-respiratory-diseases/chronic-obstructive-pulmonary-disease-copd.html. Accessed December 29, 2020.
54. Adeloye D, Chua S, Lee C, et al. Global and regional estimates of COPD prevalence: Systematic review and meta-analysis. *J Glob Health.* 2015;5(2):020415.
55. Gershon AS, Guan J, Victor JC, Goldstein R, To T. Quantifying health services use for chronic obstructive pulmonary disease. *American journal of respiratory and critical care medicine.* 2013;187(6):596-601.

56. Postma DS, Rabe KF. The asthma–COPD overlap syndrome. *New England Journal of Medicine.* 2015;373(13):1241-1249.
57. Bateman ED, Reddel HK, van Zyl-Smit RN, Agusti A. The asthma–COPD overlap syndrome: towards a revised taxonomy of chronic airways diseases? *The Lancet Respiratory Medicine.* 2015;3(9):719-728.
58. Sin DD, Miravitlles M, Mannino DM, et al. What is asthma− COPD overlap syndrome? Towards a consensus definition from a round table discussion. *European Respiratory Journal.* 2016;48(3):664-673.
59. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of COPD. 2015; http://www.goldcopd.org/. Accessed 30 November 2015.
60. Suissa S, Dell'Aniello S, Ernst P. Concurrent use of long-acting bronchodilators in COPD and the risk of adverse cardiovascular events. *European Respiratory Journal.* 2017;49(5).
61. Walters JA, Tan DJ, White CJ, Gibson PG, Wood-Baker R, Walters EH. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews.* 2014(9).
62. Herath SC, Normansell R, Maisey S, Poole P. Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD). *The Cochrane database of systematic reviews.* 2018;10(10):CD009764-CD009764.
63. Cramer JA, Roy A, Burrell A, et al. Medication compliance and persistence: terminology and definitions. *Value in health.* 2008;11(1):44-47.
64. Adams AJ, Stolpe SF. Defining and Measuring Primary Medication Nonadherence: Development of a Quality Measure. *Journal of managed care & specialty pharmacy.* 2016;22(5):516-523.
65. Neiman AB, Ruppar T, Ho M, et al. CDC grand rounds: improving medication adherence for chronic disease management—innovations and opportunities. *Morbidity mortality weekly report* 2017;66(45):1248.
66. Virchow JC, Crompton GK, Dal Negro R, et al. Importance of inhaler devices in the management of airway disease. *Respir Med.* 2008;102(1):10-19.
67. Haughney J, Price D, Barnes NC, Virchow JC, Roche N, Chrystyn H. Choosing inhaler devices for people with asthma: current knowledge and outstanding research needs. *Respir Med.* 2010;104(9):1237-1245.
68. Chrystyn H, van der Palen J, Sharma R, et al. Device errors in asthma and COPD: systematic literature review and meta-analysis. *NPJ primary care respiratory medicine.* 2017;27(1):22-22.
69. Price D, Haughney J, Sims E, et al. Effectiveness of inhaler types for real-world asthma management: retrospective observational study using the GPRD. *Journal of asthma and allergy.* 2011;4:37-47.
70. Molimard M, Raherison C, Lignot S, et al. Chronic obstructive pulmonary disease exacerbation and inhaler device handling: real-life assessment of 2935 patients. *European Respiratory Journal.* 2017;49(2).
71. Chogtu B, Holla S, Magazine R, Kamath A. Evaluation of relationship of inhaler technique with asthma control and quality of life. *Indian J Pharmacol.* 2017;49(1):110-115.
72. Harnett CM, Hunt EB, Bowen BR, et al. A study to assess inhaler technique and its potential impact on asthma control in patients attending an asthma clinic. *The Journal of asthma : official journal of the Association for the Care of Asthma.* 2014;51(4):440-445.
73. Kebede B, Mamo G, Molla A. Association of Asthma Control and Metered-Dose Inhaler Use Technique among Adult Asthmatic Patients Attending Outpatient Clinic, in Resource-Limited Country: A Prospective Study. *Canadian respiratory journal.* 2019;2019:6934040-6934040.

74. Price D, Thomas M, Mitchell G, Niziol C, Featherstone R. Improvement of asthma control with a breath-actuated pressurised metred dose inhaler (BAI): a prescribing claims study of 5556 patients using a traditional pressurised metred dose inhaler (MDI) or a breath-actuated device. *Respir Med.* 2003;97(1):12-19.
75. Lehmann A, Aslani P, Ahmed R, et al. Assessing medication adherence: options to consider. *International Journal of Clinical Pharmacy.* 2014;36(1):55-69.
76. Lam WY, Fresco P. Medication Adherence Measures: An Overview. *BioMed research international.* 2015;2015:217047.
77. Kleinsinger F. Working with the noncompliant patient. *Perm J.* 2010;14(1):54-60.
78. Brown MT, Bussell JK. Medication Adherence: WHO Cares? *Mayo Clinic Proceedings.* 2011;86(4):304-314.
79. Sherman J, Hutson A, Baumstein S, Hendeles L. Telephoning the patient's pharmacy to assess adherence with asthma medications by measuring refill rate for prescriptions. *The Journal of Pediatrics.* 2000;136(4):532-536.
80. Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive Validity of a Medication Adherence Measure in an Outpatient Setting. 2008;10(5):348-354.
81. Svarstad BL, Chewning BA, Sleath BL, Claesson C. The Brief Medication Questionnaire: a tool for screening patient adherence and barriers to adherence. *Patient education and counseling.* 1999;37(2):113-124.
82. Chan AHY, Horne R, Hankins M, Chisari C. The Medication Adherence Report Scale: A measurement tool for eliciting patients' reports of nonadherence. 2020;86(7):1281-1288.
83. Cohen JL, Mann DM, Wisnivesky JP, et al. Assessing the validity of self-reported medication adherence among inner-city asthmatic adults: the Medication Adherence Report Scale for Asthma. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology.* 2009;103(4):325-331.
84. Plaza V, Fernández-Rodríguez C, Melero C, et al. Validation of the 'Test of the Adherence to Inhalers' (TAI) for Asthma and COPD Patients. *J Aerosol Med Pulm Drug Deliv.* 2016;29(2):142-152.
85. Dima AL, van Ganse E, Laforest L, Texier N, de Bruin M, the A-LABg. Measuring medication adherence in asthma: Development of a novel self-report tool. *Psychology & Health.* 2017;32(10):1288-1307.
86. Jimmy B, Jose J. Patient Medication Adherence: Measures in Daily Practice. *Oman Medical Journal.* 2011;26(3):155-159.
87. Wilson IB, Carter AE, Berg KM. Improving the self-report of HIV antiretroviral medication adherence: is the glass half full or half empty? *Current HIV/AIDS reports.* 2009;6(4):177-186.
88. George J, Kong DCM, Stewart K. Adherence to disease management programs in patients with COPD. *International journal of chronic obstructive pulmonary disease.* 2007;2(3):253-262.
89. Rand CS, Wise RA, Nides M, et al. Metered-dose inhaler adherence in a clinical trial. *The American review of respiratory disease.* 1992;146(6):1559-1564.
90. Jentzsch NS, Camargos PAMJJBdP. Methods of assessing adherence to inhaled corticosteroid therapy in children and adolescents: adherence rates and their implications for clinical practice. 2008;34(8):614-621.
91. Chuenjit W, Engchuan V, Yuenyongviwat A, Sangsupawanich P. Achieving good adherence to inhaled corticosteroids after weighing canisters of asthmatic children. *F1000Res.* 2017;6:266-266.
92. Wickstrom G, Bendix T. The "Hawthorne effect"--what did the original Hawthorne studies actually show? *Scandinavian journal of work, environment & health.* 2000;26(4):363-367.
93. Bourbeau J, Bartlett SJ. Patient adherence in COPD. *Thorax.* 2008;63(9):831-838.

94. Gregoriano C, Dieterle T, Dürr S, Arnet I, Hersberger KE, Leuppi JD. Impact of an Electronic Monitoring Intervention to Improve Adherence to Inhaled Medication in Patients with Asthma and Chronic Obstructive Pulmonary Disease: Study Protocol for a Randomized Controlled Trial. *JMIR research protocols.* 2017;6(10):e204-e204.
95. Apter AJ, Wang X, Bogen DK, et al. Problem solving to improve adherence and asthma outcomes in urban adults with moderate or severe asthma: a randomized controlled trial. *The Journal of allergy and clinical immunology.* 2011;128(3):516-523.e235.
96. Motulsky A. Big Data Challenges from a Pharmacy Perspective. In: Househ M, Kushniruk AW, Borycki EM, eds. *Big Data, Big Challenges: A Healthcare Perspective: Background, Issues, Solutions and Research Directions.* Cham: Springer International Publishing; 2019:33-44.
97. Nau DP. Proportion of days covered (PDC) as a preferred method of measuring medication adherence. *Springfield, VA: Pharmacy Quality Alliance.* 2012.
98. Vanderpoel DR, Hussein MA, Watson-Heidari T, Perry A. Adherence to a fixed-dose combination of rosiglitazone maleate/metformin hydrochloride in subjects with type 2 diabetes mellitus: a retrospective database analysis. *Clinical therapeutics.* 2004;26(12):2066-2075.
99. Karter AJ, Parker MM, Moffet HH, Ahmed AT, Schmittdiel JA, Selby JV. New prescription medication gaps: a comprehensive measure of adherence to new prescriptions. *Health services research.* 2009;44(5 Pt 1):1640-1661.
100. Ren XS, Kazis LE, Lee A, Zhang H, Miller DR. Identifying patient and physician characteristics that affect compliance with antihypertensive medications. *Journal of Clinical Pharmacy and Therapeutics.* 2002;27(1):47-56.
101. Nwaru BI, Ekström M, Hasvold P, Wiklund F, Telg G, Janson C. Overuse of short-acting β2-agonists in asthma is associated with increased risk of exacerbation and mortality: a nationwide cohort study of the global SABINA programme. *European Respiratory Journal.* 2020;55(4):1901872.
102. Makhinova T, Barner JC, Richards KM, Rascati KL. Asthma Controller Medication Adherence, Risk of Exacerbation, and Use of Rescue Agents Among Texas Medicaid Patients with Persistent Asthma. 2015;21(12):1124-1132.
103. Weinstein AG. Asthma Adherence Management for the Clinician. *The Journal of Allergy and Clinical Immunology: In Practice.* 2013;1(2):123-128.
104. Aviram M, Tal A, Ben-Zvi Z, Gorodischer R. Monitoring Theophylline Therapy Using Citric Acid-Stimulated Saliva in Infants and Children With Asthma. *Pediatrics.* 1987;80(6):894-897.
105. Tal A, Aviram M, Gorodischer R. Variations in theophylline concentrations detected by 24-hour saliva concentration profiles in ambulatory children with asthma. *The Journal of allergy and clinical immunology.* 1990;86(2):238-243.
106. Kossoy AF, Hill M, Lin FL, Szefler SJ. Are theophylline "levels" a reliable indicator of compliance? *The Journal of allergy and clinical immunology.* 1989;84(1):60-65.
107. Spector SL, Kinsman R, Mawhinney H, et al. Compliance of patients with asthma with an experimental aerosolized medication: implications for controlled clinical trials. *The Journal of allergy and clinical immunology.* 1986;77(1 Pt 1):65-70.
108. Berg J, Dunbar-Jacob J, Rohay JM. Compliance with inhaled medications: the relationship between diary and electronic monitor. *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine.* 1998;20(1):36-38.
109. Erickson SR, Coombs JH, Kirking DM, Azimi AR. Compliance from self-reported versus pharmacy claims data with metered-dose inhalers. *The Annals of pharmacotherapy.* 2001;35(9):997-1003.
110. Jentzsch NS, Camargos PA, Colosimo EA, Bousquet J. Monitoring adherence to beclomethasone in asthmatic children and adolescents through four different methods. *Allergy.* 2009;64(10):1458-1462.

111. Patel M, Perrin K, Pritchard A, et al. Accuracy of patient self-report as a measure of inhaled asthma medication use. *Respirology.* 2013;18(3):546-552.
112. Tashkin DP, Rand C, Nides M, et al. A nebulizer chronolog to monitor compliance with inhaler use. *Am J Med.* 1991;91(4a):33s-36s.
113. Watts RW, McLennan G, Bassham I, El-Saadi O. Do patients with asthma fill their prescriptions? A primary compliance study. *Australian family physician.* 1997;26:S4-6.
114. Williams LK, Joseph CL, Peterson EL, et al. Patients with asthma who do not fill their inhaled corticosteroids: a study of primary nonadherence. *Journal of Allergy and Clinical Immunology.* 2007;120(5):1153-1159.
115. Berger Z, Kimbrough W, Gillespie C, et al. Lower copay and oral administration: predictors of first-fill adherence to new asthma prescriptions. *Am Health Drug Benefits.* 2009;2(4):174-180.
116. Liberman JN, Hutchins DS, Popiel RG, Patel MH, Jan SA, Berger JE. Determinants of primary nonadherence in asthma-controller and dyslipidemia pharmacotherapy. *American Journal of Pharmacy Benefits.* 2010;2(2):111-118.
117. Fischer MA, Stedman MR, Lii J, et al. Primary medication non-adherence: analysis of 195,930 electronic prescriptions. *Journal of general internal medicine.* 2010;25(4):284-290.
118. Fischer MA, Choudhry NK, Brill G, et al. Trouble getting started: predictors of primary medication nonadherence. *The American journal of medicine.* 2011;124(11):1081. e1089-1081. e1022.
119. Shin J, McCombs JS, Sanchez RJ, Udall M, Deminski MC, Cheetham TC. Primary nonadherence to medications in an integrated healthcare setting. *The American journal of managed care.* 2012;18(8):426-434.
120. Pottegard A, Christensen R, Houji A, et al. Primary non-adherence in general practice: a Danish register study. *European journal of clinical pharmacology.* 2014;70(6):757-763.
121. Wu AC, Butler MG, Li L, et al. Primary adherence to controller medications for asthma is poor. *Annals of the American Thoracic Society.* 2015;12(2):161-166.
122. Bronstein JM, Santer L, Johnson V. The use of Medicaid claims as a supplementary source of information on quality of asthma care. *Journal for healthcare quality : official publication of the National Association for Healthcare Quality.* 2000;22(6):13-18.
123. Ducharme FM, Noya FJ, Allen-Ramey FC, Maiese EM, Gingras J, Blais L. Clinical effectiveness of inhaled corticosteroids versus montelukast in children with asthma: prescription patterns and patient adherence as key factors. *Current medical research and opinion.* 2012;28(1):111-119.
124. Bender BG, Pedan A, Varasteh LT. Adherence and persistence with fluticasone propionate/salmeterol combination therapy. *The Journal of allergy and clinical immunology.* 2006;118(4):899-904.
125. Navaratnam P, Friedman HS, Urdaneta E. Mometasone furoate vs fluticasone propionate with salmeterol: multivariate analysis of resource use and asthma-related charges. *Current medical research and opinion.* 2009;25(12):2895-2901.
126. Broder MS, Chang EY, Ory C, Kamath T, Sapra S. Adherence and persistence with omalizumab and fluticasone/salmeterol within a managed care population. *Allergy and asthma proceedings : the official journal of regional and state allergy societies.* 2009;30(2):148-157.
127. Delea TE, Hagiwara M, Stanford RH, Stempel DA. Effects of fluticasone propionate/salmeterol combination on asthma-related health care resource utilization and costs and adherence in children and adults with asthma. *Clinical therapeutics.* 2008;30(3):560-571.
128. Averell CM, Stanford RH, Laliberté F, Wu JW, Germain G, Duh MS. Medication adherence in patients with asthma using once-daily versus twice-daily ICS/LABAs. *Journal of Asthma.* 2019:1-10.

129. Makhinova T, Barner JC, Richards KM, Rascati KL. Asthma Controller Medication Adherence, Risk of Exacerbation, and Use of Rescue Agents Among Texas Medicaid Patients with Persistent Asthma. *Journal of managed care & specialty pharmacy.* 2015;21(12):1124-1132.
130. Mattke S, Martorell F, Hong SY, Sharma P, Cuellar A, Lurie N. Anti-inflammatory medication adherence and cost and utilization of asthma care in a commercially insured population. *J Asthma.* 2010;47(3):323-329.
131. Dorais M, Blais L, Chabot I, LeLorier J. Treatment persistence with leukotriene receptor antagonists and inhaled corticosteroids. *Journal of Asthma.* 2005;42(5):385-393.
132. Marceau C, Lemiere C, Berbiche D, Perreault S, Blais L. Persistence, adherence, and effectiveness of combination therapy among adult patients with asthma. *The Journal of allergy and clinical immunology.* 2006;118(3):574-581.
133. Krauskopf K, Federman AD, Kale MS, et al. Chronic Obstructive Pulmonary Disease Illness and Medication Beliefs are Associated with Medication Adherence. *Copd.* 2015;12(2):151-164.
134. Stafyla E, Kotsiou OS, Deskata K, Gourgoulianis KI. Missed diagnosis and overtreatment of COPD among smoking primary care population in Central Greece: old problems persist. *International journal of chronic obstructive pulmonary disease.* 2018;13:487-498.
135. Shrestha R, Pant A, Shakya Shrestha S, Shrestha B, Gurung RB, Karmacharya BM. A Cross-Sectional Study of Medication Adherence Pattern and Factors Affecting the Adherence in Chronic Obstructive Pulmonary Disease. *Kathmandu University medical journal (KUMJ).* 2015;13(49):64-70.
136. Sriram KB, Percival M. Suboptimal inhaler medication adherence and incorrect technique are common among chronic obstructive pulmonary disease patients. *Chron Respir Dis.* 2016;13(1):13-22.
137. Duarte-de-Araujo A, Teixeira P, Hespanhol V, Correia-de-Sousa J. COPD: understanding patients' adherence to inhaled medications. *International journal of chronic obstructive pulmonary disease.* 2018;13:2767-2773.
138. Pierobon A, Sini Bottelli E, Ranzini L, et al. COPD patients' self-reported adherence, psychosocial factors and mild cognitive impairment in pulmonary rehabilitation. *International journal of chronic obstructive pulmonary disease.* 2017;12:2059-2067.
139. Tommelein E, Mehuys E, Van Tongelen I, Brusselle G, Boussery K. Accuracy of the Medication Adherence Report Scale (MARS-5) as a quantitative measure of adherence to inhalation medication in patients with COPD. *Annals of Pharmacotherapy.* 2014;48(5):589-595.
140. Sulaiman I, Cushen B, Greene G, et al. Objective Assessment of Adherence to Inhalers by Patients with Chronic Obstructive Pulmonary Disease. *American journal of respiratory and critical care medicine.* 2017;195(10):1333-1343.
141. Wurst KE, St Laurent S, Mullerova H, Davis KJJIjocopd. Characteristics of patients with COPD newly prescribed a long-acting bronchodilator: a retrospective cohort study. 2014;9:1021.
142. Breekveldt-Postma NS, Koerselman J, Erkens JA, Lammers J-WJ, Herings RMJRm. Enhanced persistence with tiotropium compared with other respiratory drugs in COPD. 2007;101(7):1398-1405.
143. Toy EL, Beaulieu NU, McHale JM, et al. Treatment of COPD: relationships between daily dosing frequency, adherence, resource use, and costs. 2011;105(3):435-441.
144. Cramer JA, Bradley-Kennedy C, Scalera AJCrj. Treatment persistence and compliance with medications for chronic obstructive pulmonary disease. 2007;14(1):25-29.
145. Halpern R, Baker CL, Su J, et al. Outcomes associated with initiation of tiotropium or fluticasone/salmeterol in patients with chronic obstructive pulmonary disease. 2011;5:375.

146. Albrecht JS, Park Y, Hur P, et al. Adherence to Maintenance Medications among Older Adults with Chronic Obstructive Pulmonary Disease. The Role of Depression. *Annals of the American Thoracic Society.* 2016;13(9):1497-1504.
147. Toy EL, Beaulieu NU, McHale JM, et al. Treatment of COPD: relationships between daily dosing frequency, adherence, resource use, and costs. *Respiratory Medicine.* 2011;105(3):435-441.
148. Dhamane AD, Schwab P, Hopson S, et al. Association between adherence to medications for COPD and medications for other chronic conditions in COPD patients. *International journal of chronic obstructive pulmonary disease.* 2017;12:115.
149. Mueller S, Wilke T, Bechtel B, Punekar YS, Mitzner K, Virchow JC. Non-persistence and non-adherence to long-acting COPD medication therapy: A retrospective cohort study based on a large German claims dataset. *Respiratory Medicine.* 2017;122:1-11.
150. Breekveldt-Postma NS, Koerselman J, Erkens JA, Lammers JW, Herings RM. Enhanced persistence with tiotropium compared with other respiratory drugs in COPD. *Respiratory Medicine.* 2007;101(7):1398-1405.
151. Penning-van Beest F, van Herk-Sukel M, Gale R, Lammers JW, Herings R. Three-year dispensing patterns with long-acting inhaled drugs in COPD: a database analysis. *Respir Med.* 2011;105(2):259-265.
152. Dalon F, Devouassoux G, Belhassen M, et al. Persistence to COPD therapies and impact on exacerbations: a French claims data study. *European Respiratory Journal.* 2018;52(suppl 62):PA2273.
153. Bogart M, Stanford RH, Laliberté F, Germain G, Wu JW, Duh MS. Medication adherence and persistence in chronic obstructive pulmonary disease patients receiving triple therapy in a USA commercially insured population. *International journal of chronic obstructive pulmonary disease.* 2019;14:343-352.
154. Blais L, Kettani FZ, Forget A, Beauchesne MF, Lemiere C, Ducharme FM. Assessing adherence to inhaled corticosteroids in asthma patients using an integrated measure based on primary and secondary adherence. *European journal of clinical pharmacology.* 2017;73(1):91-97.
155. Dima AL, Hernandez G, Cunillera O, Ferrer M, de Bruin M. Asthma inhaler adherence determinants in adults: systematic review of observational data. *European Respiratory Journal.* 2015;45(4):994.
156. van Boven JFM, Ryan D, Eakin MN, Canonica GW, Barot A, Foster JM. Enhancing Respiratory Medication Adherence: The Role of Health Care Professionals and Cost-Effectiveness Considerations. *The Journal of Allergy and Clinical Immunology: In Practice.* 2016;4(5):835-846.
157. Wilhelmsen NC, Eriksson T. Medication adherence interventions and outcomes: an overview of systematic reviews. *European Journal of Hospital Pharmacy.* 2019;26(4):187.
158. Jia X, Zhou S, Luo D, Zhao X, Zhou Y, Cui YM. Effect of pharmacist-led interventions on medication adherence and inhalation technique in adult patients with asthma or COPD: A systematic review and meta-analysis. *J Clin Pharm Ther.* 2020;45(5):904-917.
159. Centers for Disease Control and Prevention. Tailored Pharmacy-Based Interventions to Improve Medication Adherence. https://www.cdc.gov/dhdsp/pubs/medication-adherence.htm. Accessed March 24, 2021.
160. Tarn DM, Mattimore TJ, Bell DS, Kravitz RL, Wenger NS. Provider views about responsibility for medication adherence and content of physician-older patient discussions. *J Am Geriatr Soc.* 2012;60(6):1019-1026.
161. Verloo H, Chiolero A, Kiszio B, Kampel T, Santschi V. Nurse interventions to improve medication adherence among discharged older adults: a systematic review. *Age and Ageing.* 2017;46(5):747-754.

162. Van Camp YP, Van Rompaey B, Elseviers MM. Nurse-led interventions to enhance adherence to chronic medication: systematic review and meta-analysis of randomised controlled trials. *European journal of clinical pharmacology.* 2013;69(4):761-770.
163. Bårnes CB, Ulrik CS. Asthma and Adherence to Inhaled Corticosteroids: Current Status and Future Perspectives. 2015;60(3):455-468.
164. van Boven JFM, Chavannes NH, van der Molen T, Rutten-van Mölken MPMH, Postma MJ, Vegter S. Clinical and economic impact of non-adherence in COPD: A systematic review. *Respiratory Medicine.* 2014;108(1):103-113.
165. Joshi AV, Madhavan SS, Ambegaonkar A, Smith M, Scott VG, Dedhia H. Association of medication adherence with workplace productivity and health-related quality of life in patients with asthma. *The Journal of asthma : official journal of the Association for the Care of Asthma.* 2006;43(7):521-526.
166. Matui P, Wyatt JC, Pinnock H, Sheikh A, McLean S. Computer decision support systems for asthma: a systematic review. *NPJ Prim Care Respir Med.* 2014;24:14005.
167. Bell LM, Grundmeier R, Localio R, et al. Electronic health record-based decision support to improve asthma care: a cluster-randomized trial. *Pediatrics.* 2010;125(4):e770-777.
168. Fiks AG, Hunter KF, Localio AR, et al. Impact of electronic health record-based alerts on influenza vaccination for children with asthma. 2009;124(1):159-169.
169. Kuilboer M, Van Wijk M, Mosseveld M, et al. Computed critiquing integrated into daily clinical practice affects physicians' behavior. 2006;45(04):447-454.
170. Martens JD, van der Weijden T, Severens JL, et al. The effect of computer reminders on GPs' prescribing behaviour: a cluster-randomised trial. 2007;76:S403-S416.
171. Plaza V, Cobos A, Ignacio-García JM, et al. Cost-effectiveness of an intervention based on the Global INitiative for Asthma (GINA) recommendations using a computerized clinical decision support system: a physicians randomized trial. 2005;124(6):201-206.
172. Tierney WM, Overhage JM, Murray MD, et al. Can computer-generated evidence-based care suggestions enhance evidence-based management of asthma and chronic obstructive pulmonary disease? A randomized, controlled trial. 2005;40(2):477-498.
173. McKibben S, Bush A, Thomas M, Griffiths C. The use of electronic alerts in primary care computer systems to identify the over-prescription of short-acting beta(2)-agonists in people with asthma: a protocol for a systematic review. *NPJ primary care respiratory medicine.* 2017;27(1):30-30.
174. Zeiger RS, Schatz M, Li Q, et al. Real-time asthma outreach reduces excessive short-acting β2-agonist use: a randomized study. 2014;2(4):445-456. e445.
175. Tamblyn R, Ernst P, Winslade N, et al. Evaluating the impact of an integrated computer-based decision support with person-centered analytics for the management of asthma in primary care: a randomized controlled trial. *Journal of the American Medical Informatics Association : JAMIA.* 2015;22(4):773-783.
176. Gupta S, Price C, Agarwal G, et al. The Electronic Asthma Management System (eAMS) improves primary care asthma management. 2019;53(4).
177. Kawamoto K, Houlihan CA, Balas EA, Lobach DFJB. Improving clinical practice using clinical decision support systems: a systematic review of trials to identify features critical to success. 2005;330(7494):765.
178. Gupta S, Price C, Agarwal G, et al. The Electronic Asthma Management System (eAMS) improves primary care asthma management. *The European respiratory journal.* 2019;53(4):1802241.
179. Gardner RM. Computerized clinical decision-support in respiratory care. *Respiratory care.* 2004;49(4):378-386; discussion 386-378.

180. Ammenwerth E, Iller C, Mahler CJBmi, making d. IT-adoption and the interaction of task, technology and individuals: a fit framework and a case study. 2006;6(1):1-13.
181. Lau F, Price M, Keshavjee KJHQ. Making sense of health information system success in Canada. 2011;14(1):39-46.
182. Heeks RJIjomi. Health information systems: Failure, success and improvisation. 2006;75(2):125-137.
183. Price M, Lau F. The clinical adoption meta-model: a temporal meta-model describing the clinical adoption of health information systems. *BMC Medical Informatics and Decision Making.* 2014;14(1):43.
184. Health UDo, Services H. The National Alliance for Health Information Technology report to the Office of the National Coordinator for Health Information Technology on defining key health information technology terms. In:2008.
185. Motulsky A, Sicotte C, Gagnon M-P, et al. Le DSQ-Dossier santé du Québec, un système de partage des données cliniques à l'échelle du Québec: Analyse de l'utilisation et des bénéfices. 2018.
186. Bender BG. Nonadherence in chronic obstructive pulmonary disease patients: what do we know and what should we do next? *Current opinion in pulmonary medicine.* 2014;20(2):132-137.
187. de Grood C, Raissi A, Kwon Y, Santana MJ. Adoption of e-health technology by physicians: a scoping review. *J Multidiscip Healthc.* 2016;9:335-344.
188. Valdes I, Kibbe DC, Tolleson G, Kunik ME, Petersen LA. Barriers to proliferation of electronic medical records. *Informatics in primary care.* 2004;12(1):3-9.
189. Leu MG, O'Connor KG, Marshall R, Price DT, Klein JD. Pediatricians' use of health information technology: a national survey. *Pediatrics.* 2012;130(6):e1441-1446.
190. Stream GR. Trends in adoption of electronic health records by family physicians in Washington State. *Informatics in primary care.* 2009;17(3):145-152.
191. Kaushal R, Bates DW, Jenter CA, et al. Imminent adopters of electronic health records in ambulatory care. *Informatics in primary care.* 2009;17(1):7-15.
192. Thorn SA, Carter MA, Bailey JE. Emergency physicians' perspectives on their use of health information exchange. *Ann Emerg Med.* 2014;63(3):329-337.
193. Ajami S, Bagheri-Tadi T. Barriers for Adopting Electronic Health Records (EHRs) by Physicians. *Acta Inform Med.* 2013;21(2):129-134.
194. Levine M, Richardson JE, Granieri E, Reid MC. Novel telemedicine technologies in geriatric chronic non-cancer pain: primary care providers' perspectives. *Pain medicine.* 2014;15(2):206-213.
195. Surescripts. Medication history for reconciliation. 2019; https://surescripts.com/inform-care-decisions/medication-history/. Accessed December 2nd, 2019.
196. Surescripts. Demo: Surescripts Insights for Medication Adherence. 2017; https://www.youtube.com/watch?v=wK4F2gzcBPQ. Accessed December 2nd, 2019.
197. Tamblyn R, Huang A, Kawasumi Y, et al. The development and evaluation of an integrated electronic prescribing and drug management system for primary care. *Journal of the American Medical Informatics Association : JAMIA.* 2006;13(2):148-159.
198. Tamblyn R, Reidel K, Huang A, et al. Increasing the detection and response to adherence problems with cardiovascular medication in primary care through computerized drug management systems: a randomized controlled trial. *Medical decision making : an international journal of the Society for Medical Decision Making.* 2010;30(2):176-188.
199. Yousif A, Lemière C, Cartier A, Forget A, Blais L. Development of a graphical tool to measure medication adherence in asthma patients: A mixed-methods pilot study. *Journal of Asthma.* 2019;56(5):543-552.

200. Schectman JM, Schorling JB, Nadkarni MM, Lyman JA, Siadaty MS, Voss JD. The effect of physician feedback and an action checklist on diabetes care measures. *American journal of medical quality : the official journal of the American College of Medical Quality.* 2004;19(5):207-213.
201. Comer D, Couto J, Aguiar R, Wu P, Elliott DJ. Usefulness of pharmacy claims for medication reconciliation in primary care. *The American journal of managed care.* 2015;21(7):486-493.
202. Baribeau V LC, Cartier A, Forget A, Kettani FZ, Blais L.,. Évaluation électronique de l'adhésion des patients au traitement d'entretien de l'asthme: étude de faisabilité. 4ième Colloque annuel du Réseau québécois de recherche sur les médicaments. *Journal of Population Therapeutics and Clinical Pharmacology* 2014;21(2):A6, p.e312.
203. RQRM. reMed : Data Registry for Prescribed Medications / Banque de données sur les médicaments d'ordonnance. www.rqrm.ca/plateformes/optimisation-de-l-usage/64-4-remed-data-registry-for-prescribed-medications-banque-de-donnees-sur-les-medicaments-d-ordonnance.html.
204. Schectman JM, Schorling JB, Nadkarni MM, Voss JD. Can prescription refill feedback to physicians improve patient adherence? *Am J Med Sci.* 2004;327(1):19-24.
205. Teague R. Reducing clinician burden with user-centered design. 2019; https://www.allscripts.com/wp-content/uploads/2019/08/WhitePaper_ClinicianBurden-1.pdf. Accessed December 3rd, 2019.
206. Genes N, Violante S, Cetrangol C, Rogers L, Schadt EE, Chan Y-FY. From smartphone to EHR: a case report on integrating patient-generated health data. *Digital Medicine,.* 2018;1(1):23.
207. Peabody JW, Luck J, Jain S, Bertenthal D, Glassman P. Assessing the Accuracy of Administrative Data in Health Information Systems. 2004;42(11):1066-1072.
208. Blais L, Salah Ahmed SI, Beauchesne MF, Forget A, Kettani FZ, Lavoie K. Risk of postpartum depression among women with asthma. *The journal of allergy and clinical immunology In practice.* 2018.
209. Kaiser SV, Rodean J, Bekmezian A, et al. Effectiveness of Pediatric Asthma Pathways for Hospitalized Children: A Multicenter, National Analysis. *J Pediatr.* 2018;197:165-171.e162.
210. Hamada S, Tokumasu H, Sato A, Iwasaku M, Kawakami K. Asthma Controller Medications for Children in Japan: Analysis of an Administrative Claims Database. *Global pediatric health.* 2015;2:2333794x15577790.
211. Jeffery MM, Shah ND, Karaca-Mandic P, Ross JS, Rank MA. Trends in Omalizumab Utilization for Asthma: Evidence of Suboptimal Patient Selection. *The journal of allergy and clinical immunology In practice.* 2018;6(5):1568-1577.e1564.
212. Doyle CM, Lix LM, Hemmelgarn BR, Paterson JM, Renoux C. Data variability across Canadian administrative health databases: Differences in content, coding, and completeness. 2020;29(S1):68-77.
213. Ritchey ME, West SL, Maldonado G. Validity of Drug and Diagnosis Data in Pharmacoepidemiology. In: *Pharmacoepidemiology.*2019:948-990.
214. van Walraven C, Bennett C, Forster AJ. Administrative database research infrequently used validated diagnostic or procedural codes. *Journal of clinical epidemiology.* 2011;64(10):1054-1059.
215. Chubak J, Pocobelli G, Weiss NS. Tradeoffs between accuracy measures for electronic health care data algorithms. *Journal of clinical epidemiology.* 2012;65(3):343-349.e342.
216. Pekkanen J, Pearce N. Defining asthma in epidemiological studies. *The European respiratory journal.* 1999;14(4):951-957.
217. Blais L, Lemiere C, Menzies D, Berbiche D. Validity of asthma diagnoses recorded in the Medical Services database of Quebec. *Pharmacoepidemiology and drug safety.* 2006;15(4):245-252.

218. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Annals of internal medicine.* 2011;155(8):529-536.
219. Cochrane. Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy. 2021; https://training.cochrane.org/resource/cochrane-handbook-systematic-reviews-diagnostic-test-accuracy. Accessed April 2, 2021.
220. Jones J, Hunter D. Consensus methods for medical and health services research. *Bmj.* 1995;311(7001):376-380.
221. Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. *Journal of Advanced Nursing.* 2000;32(4):1008-1015.
222. The SAGE Encyclopedia of Qualitative Research Methods. 2008.
223. Nielsen J. *Usability engineering.* Morgan Kaufmann; 1994.
224. De Vito Dabbs A, Myers BA, Mc Curry KR, et al. User-centered design and interactive health technologies for patients. *Comput Inform Nurs.* 2009;27(3):175-183.
225. Breton M, Lévesque J-F, Pineault R, Hogg W. Primary Care Reform: Can Quebec's Family Medicine Group Model Benefit from the Experience of Ontario's Family Health Teams? *Healthcare policy.* 2011;7(2):e122-e135.
226. Salmon P, Peters S, Rogers A, et al. Peering through the barriers in GPs' explanations for declining to participate in research: the role of professional autonomy and the economy of time. *Family practice.* 2007;24(3):269-275.
227. Gershon AS, Wang C, Guan J, Vasilevska-Ristovska J, Cicutto L, To T. Identifying patients with physician-diagnosed asthma in health administrative databases. *Canadian respiratory journal.* 2009;16(6):183-188.