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Persistence and adherence of combination therapy among adult asthmatic patients

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Persistence and adherence of combination therapy among adult asthmatic patients

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RÉSUMÉ

Introduction : La persistance et l'adhésion aux traitements de l'asthme combinant les corticosteroïdes inhalés (CSI) et les béta2-agonistes à longue action (BALA) dans le même inhalateur (traitement de combinaisons) comparativement aux thérapies concommitantes avec les deux médicaments inhalés séparément (traitement concommittant) sont peu documentées.

Objectif : Comparer la persistance et l'adhésion entre les patients asthmatiques âgés entre 16 et 44 ans débutant un traitement combiné de BALA et de CSI et ceux débutant une thérapie concommitante des deux médicaments.

Méthode : Étude rétrospective de cohorte appariée, reconstruite à partir des banques de données de la Régie de l'assurance-maladie du Québec en sélectionnant des patients débutant l'une des deux thérapies entre janvier 1999 et décembre 2002. Les patients sous combinaisons ont été appariés un à un aux patients sous traitement concommitant en fonction de marqueurs de contrôle et de sévérité de l'asthme dans l'année précédant le début du traitement. La persistance est déterminée par des analyses Kaplan-Meier et par un modèle de régression de Cox ajusté (variables socio-démographiques et marqueurs de sévérité et de contrôle) alors que l'adhésion est évaluée chez les patients persistants selon le pourcentage de jours sous traitement en relation avec la quantité de médicament dispensée, en comparant les deux traitements à l'aide d'un modèle de régression linéaire.

Résultats : La persistance diminue à 10% et 5% 12 mois après l'initiation du traitement, puis à 5% et 2% sur une période de 24 mois chez les utilisateurs de produits de combinaisons et de traitement concommitant, respectivement. Les utilisateurs d'une thérapie combinée ont 17% moins de chance de cesser leur traitement (taux relatif : 0,83; 95%CI: 0,78-0,88) et comptent en moyenne 0,9 plus de prescriptions renouvelées par année que les utilisateurs d'une thérapie concommitante (p=0,0001). Les

utilisateurs de thérapie concommitante cessaient leur traitement au BALA sensiblement plus que les CSI (p <0,0001). Le nombre de jours sous traitement pendant la première année était significativement supérieur chez les utilisateurs d'une thérapie combinée (90,4 vs. 73,1; p<0,0001). L'adhésion au traitement était sensiblement inférieure chez les patients sous thérapie combinée comparativement à celle des patients sous thérapie concommittante (55% vs. 58%; p=0,0031).

Conclusion : Les patients sous thérapie combinée étaient sensiblement plus persistants que les utilisateurs de thérapie concommittante, mais relativement moins adhérants. La persistance aux traitements inhalés de maintenance est très faible chez les patients asthmatiques d'âge adulte.

Mots clés : Asthme, corticostéroïdes inhalés, béta2-agonistes à longue durée d'action, base de données administratives, pharmaco-épidémiologie, produits de combinaison, cohorte.

ABSTRACT

Background: Limited evidence exists on persistence and adherence with asthma combination regimens including both inhaled corticosteroids (ICS) and long-acting β_2-agonists (LABA) within the same inhaler (combinations) compared to these medications inhaled separately (concurrents).

Objective: To compare persistence and adherence between 16-44 years old asthmatic patients, starting a single-inhaler combination of ICS and LABA or a concurrent regimen of both medications.

Methodology: This retrospective one-to-one matched cohort is based upon claims data. Newly treated asthmatics with either a combination or concurrent therapy were selected from the *Régie de l'assurance maladie du Québec* (RAMQ) database between January 1999 and December 2002. Combinations were one-to-one matched to concurrents using markers of asthma severity and control in the year prior to treatment initiation. Persistence was determined by a Kaplan-Meier analysis and a Cox Regression model, adjusting for socio-demographics and markers of asthma severity and control. Adherence was estimated according to the number of filled prescriptions in relation to the time patients persisted on the prescribed therapy and compared between the two drug regimens using a linear regression model.

Results: Persistence fell to 10% and 5% 12 months after treatment initiation, and to 5% and below 2% over 24 months for combination and concurrent users, respectively. Overall, 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 prescription per year than concurrent users (p-value=0.0001). Concurrent users ceased their LABA treatment slightly more than ICS (p-value <0.0001). Average days under treatment during the first year was significantly higher with combinations (90.4 vs. 73.1;

p<0.0001). Treatment adherence was slightly lower for patients taking combinations vs. concurrents (55% vs. 58%; p=0.0031).

Conclusion: Combination users were slightly more persistent than concurrent therapy users, but relatively less adherent. Persistence to inhaled controller therapies is very low among adult asthmatic patients.

Key words : Asthma, inhaled corticosteroids, long-acting beta2-agonists, administrative database, pharmacoepidemiology, combination, cohort.

TABLE DES MATIÈRES

LISTE DES TABLEAUX

MÉMOIRE

ARTICLE

LISTE DES FIGURES

MÉMOIRE

ARTICLE

LISTE DES ABBRÉVIATIONS

FEV_1	Forced Expiratory Volume
GINA	Global Initiative for Asthma
ICS	Inhaled Corticosteroids
LABA	Long-Acting Beta 2 (β_2)-Agonists
MEF	Maximum Expiratory Flow
MPR	Medication Possession Ratios
NAEPP	National Asthma Education and Prevention Program
PASS	Power Analysis and Sample Size (NCSS Statistical Software)
PEF	Peak Expiratory Flow
PEFR	Peak Expiratory Flow rate
PEF_1	Peak Expiratory Flow in one second
PEFam	Morning Peak Expiratory Flow
PEVF	Peak Expiratory Volume Flow
RAMQ	*Régie de l'assurance maladie du Québec*
RCT	Randomized Controlled Trial
SABA	Short-Acting Beta 2 (β_2)-Agonists
SAS	Statistical Analysis System Software
US	United States (of America)

INTRODUCTION

The international guidelines (GINA)[1] and latest Canadian consensus[2] uphold the concept of asthma management as a continuum, contingent on underlying symptoms severity and pulmonary tests results. When asthma is not optimally controlled with inhaled corticosteroids (ICS) alone, the addition of long-acting β_2-agonists (LABA) to ICS is accepted as the most effective therapy to control moderate to severe asthma.[3] This therapeutic approach is also supported by NAEPP guidelines[4] for the treatment of uncontrolled persistent asthma. ICS and LABA have a complementary effect,[5,6,7,8] treating both components of asthma: underlying airway inflammation and obstruction, respectively [3,9,10]. It has been shown that this regimen provides greater asthma control than increasing the dose of ICS [11,12] and may also improve outcomes (lung function, exacerbation rates, and quality of life) in asthmatics who remain symptomatic on ICS.[13]

The administration of both ICS and LABA concurrently with different inhalers or using a single inhaler combining both medications may not be equivalent. 'Concurrent' administration entails the manipulation of two different inhaling devices (one for each drug) whereas 'combination' involves a single inhaling device which contains both agents.[14] Two combination products are presently available in Canada: one combining fluticasone (ICS) and salmeterol (LABA) into the same inhaler, known as Advair/Seretide, and another combining budesonide (ICS) and formoterol (LABA) into the same inhaler, known as Symbicort.

Average medication compliance, an essential component of a successful health outcome, has been shown to be lower in patients with respiratory disorders, most of which require inhaled medications.[15] Although inhaled corticosteroids are the most effective treatment for asthma, historically they have elicited poor compliance, likely because patients may not perceive the medication to be working.[15] It has been shown that adherence to asthma treatments declines as the regime becomes more

complicated, either by increasing the number of medications and/or the number of daily doses.[16,17]

Systematic reviews of compliance literature[18,19] have shown that simpler, less frequent dosing regimens resulted in better compliance across a variety of therapeutic classes. Intuitively, a combination regimen of corticosteroid/beta2-agonist in one inhaler is likely to improve patient compliance by simplifying the treatment regimen and providing noticeable symptom relief while alleviating the underlying inflammation. Consequently, it has been hypothesized[20,21] that the use of combination inhalers can improve patient's adherence and consequently overall asthma control.[22,23,24] However, limited evidence exists on persistence and adherence with asthma combination regimen including both ICS and LABA within the same inhaler compared to these medications inhaled separately. So far, we found two published studies[25,26] in which this hypothesis was tested in usual care clinical practice settings in the US. We thus performed a population-based cohort study to compare treatment persistence and adherence between 16-44 years old asthmatic patients starting a combination and a concurrent therapy, using data collected in the *Régie de l'assurance maladie du Québec* database.

OBJECTIVES

The objectives of this study were the following:

1. To estimate treatment persistence and adherence with combination therapy (LABA plus ICS in one device) among asthmatic patients aged between 16-44 years old;
2. To estimate treatment persistence and adherence with LABA prescribed concurrently with ICS (in two devices) among asthmatic patients aged between 16-44 years old;
3. To compare treatment persistence and adherence between the two drug regimens.

This study was conducted to provide significant real-life information for asthma patients and their treating physicians on the hypothesized adherence and persistence benefits that would be expected from the ease of administration of combination therapy regimens.

LITERATURE REVIEW

Asthma definition

Inflammation and its resultant effects on airway structure are considered to be the main mechanisms leading to the development and maintenance of asthma.[27] In the recent Global Initiative for Asthma (GINA) Guidelines[1], asthma is defined as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation causes an associated increase in airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment.[1]

Burden of Asthma

Despite advances in understanding the disease and the availability of more effective treatments, asthma still places a heavy burden on the quality of life of those suffering from it. This is often a result of under-diagnosis, under-treatment, lack of understanding and knowledge about the disease, and inadequate asthma supervision.[28]

Asthma Worldwide

Worldwide, the rate of asthma is increasing significantly, rising by 50 percent every decade.[29] Currently, approximately 300 million people (or about 5% of the global population) suffer from asthma and this figure is expected to increase by an additional 100 million people by 2025.[29] It is estimated that asthma accounts for about one in every 250 deaths worldwide.[29]

Asthma in the US

A 1998 document from the United States Department of Health and Human Services reported a sharp increase in the rate of self-reported asthma among all age groups between the years 1980 and 1994, from 30.7 to 53.8 per 1,000 (3.1% to 5.4%).[30]

In 2003 it was estimated that 20 million Americans had asthma. Of these, 11 million Americans had an asthma attack and it is estimated that about 30 million Americans or about 10 percent of the U.S. population, have been diagnosed with asthma in their lifetime, according to the American Lung Association and the National Center for Health Statistics.[4] In the United States alone, asthma was estimated to result in 10 million missed school days, over 1.5 million emergency department visits, approximately 500,000 hospitalizations, and over 5,000 death annually.[31,32,33,34]

Asthma in Canada

In Canada, the number of people with asthma has been increasing over the last 15 years.[35] Currently, Canada has one of the highest incidences of asthma in the world, with an estimated 2.2 million Canadians (8.4 per cent of the population) over the age of 12 currently diagnosed with asthma.[36] As of March 2005, an estimated five per cent of adults have taken medications for asthma or have experienced symptoms in the past 12 months.[37] According to the 1996-1997 National Population Health Survey (NPHS) Asthma Supplement, 35% of individuals with current asthma have been restricted in their daily activities by asthma; 22% for one to five days and 13% for more than five days in the previous year. The number of hospitalizations due to asthma may be a more serious sign of poor disease control; 5.3% of those diagnosed with asthma in Canada require hospitalization each year.[38] In Canada, direct costs of asthma, which include medical/nursing care and medication, are estimated at $600 million per year[39]. In 1994, the cost of hospitalization as a result of asthma was $135 million in Canada.[37] Visits to emergency rooms may also be a sign of poorly controlled asthma. The NPHS Asthma Supplement survey found that 18% of individuals with active asthma had visited an emergency department at least once in the previous 12 months.[38] With 146,000 emergency room visits every year due to asthma attacks[40], asthma is the leading cause of emergency room visits[29] and the third leading cause of work loss in Canada.[41]

Asthma mortality rates in Canada increased from 1970 to the mid-1980s; however by 1995 they had decreased to below the 1970 level, except in young adults where increases had been more important in the 1970s.[35] While the death rate from asthma has slowly decreased since 1990, there are still approximately 10 asthma deaths per week in Canada; asthma is the cause of deaths of 20 children and 500 adults each year.[40] It is estimated that more than 80 per cent of deaths due to asthma could be prevented with proper education.[41]

Asthma disease management and treatment goal

It has been shown that an underassessment of asthma severity results in ineffective treatment and suboptimal outcomes.[42,43] In Canada, clinical practice guidelines to diagnose and establish treatment plans for patients with asthma are provided by the Canadian Asthma Consensus Guidelines[27]. According to the Canadian Consensus, the primary goal of asthma therapy is to obtain the best possible results for each patient, which include: fewest symptoms, least interference with daily living, least need for "rescue medications" and best lung function test of forced expiratory volume (FEV) or peak expiratory flow, and fewest side effects from medications. Overall, the therapy should lead to adequate control of the disease in order to reduce the consequences of asthma and, ideally, its severity over time.[27,32] However, a conceptual concern about the different approaches to asthma severity categorization is that these methods are based on the concept of asthma control rather than asthma severity.[44] We need to distinguish underlying severity from current control severity.

Canadian Consensus

The overall approach advocated by the Canadian Consensus[27] for the management of asthma clearly distinguishes asthma control and asthma severity assessments. Asthma severity is more difficult to assess and may only be determined after asthma control is achieved.[2]

Optimal control of asthma is characterized by the absence of respiratory symptoms and of the need for rescue bronchodilator, as well as normal pulmonary function[27]. This is difficult to achieve in all patients with asthma, so treatment needs are based on 'acceptable' asthma control, defined using clinical and physiologic parameters (Table 2 – page 81)[27]. Optimal management of asthma requires adequate evaluation of the patient and his or her environment; a clinician should also evaluate new patients' asthma using the asthma control criteria (Table 2).[2] Asthma control may be achieved through appropriate environmental measures, adequate patient education and pharmacotherapy tailored to the individual. Once control of asthma has been maintained for at least several months, an attempt should be made to reduce medication within the bounds of acceptable control[27].

The severity of asthma in a patient is judged by the frequency and duration of respiratory symptoms, the presence of persistent airflow limitation and the medication required to maintain control.[27] Signs of severe or poorly controlled asthma combine features of: lung functions (forced expiratory volume in one second (FEV_1) or peak expiratory flow (PEF) below 60% of predicted values); symptoms control (limitation of daily activities, night-time symptoms; need for an inhaled β2-agonist several times a day or at night); history of hospital admissions or emergency department visit(s); and the occurrence of a prior near-fatal episode (loss of consciousness, need for intubations). [27]

The latest issue of the Canadian guidelines[2] uphold the concept of asthma management based on a stepwise continuum (Figure 1 – page 84), commensurate with underlying symptoms and pulmonary function tests results, to determine the appropriate therapeutic regimen which are listed in Table 3 on page 81. If control is inadequate, the reason(s) should be identified and maintenance therapy modified according to the continuum[2] (Figure 1). When asthma is well controlled, one of the best ways to judge severity is to determine the level of treatment needed to maintain acceptable control.[27]

Moreover, since asthma severity is likely to vary over time,[27] any new treatment should be considered a therapeutic trial and its effectiveness should be re-evaluated after 4–6 weeks according to the asthma management continuum.[2]

In a recent 3-year observational database study of asthmatic patients, Stempel et al.[45] documented that asthma control - on the basis of medical and pharmacy claims - might change over time, irrespective of age, sex, and prior asthma control status. That study emphasized the need to address asthma control both in patients with initially well-controlled disease and in those patients who present with evidence of uncontrolled asthma since both groups continue to be at risk for asthma symptoms as well as for asthma exacerbations. This finding is of particular relevance to highlight the value of using database to monitor asthma control variations from the pre-initiation period, at index date, as well as throughout the analysis of prescribing trends and medication refill rates used as a proxy for drug utilization over time.

Other Asthma Guidelines

The asthma severity and control assessments proposed by the Canadian Consensus[27] combine features that are also supported by other widely known guidelines. For instance, the American guidelines (NAEPP Expert Panel Report 2)[32] also recommend an assessment of asthma based on symptoms (diurnal and nocturnal) as well as lung function prior to the initiation of a treatment. Within each of these three variables, levels of gradation in severity established by the NAEPP lead the physician to classify a patient's asthma into one of four separate categories, and overall asthma severity is then determined according to the worst individual variable. The British Guidelines on the Management of Asthma[46], also recommend an individual assessment of severity based on diurnal and nocturnal symptoms, and include physical activity limits, exacerbations, absence from school or work, use of rescue SABA, and lung function. The National Asthma Campaign in Australia[47] stipulates that asthma severity

should be assessed while the patient is clinically stable, and that severity categorization would rest on a history of either hospitalization or near-fatal asthma attacks. The inclusion of historical features differs from the NAEPP approach to severity categorization in that aspect; the US recommendations concentrate on current symptoms and lung function abnormalities. As shown in Table 4 on page 82, the Canadian Consensus guidelines[2] combine aspects from both the British and the Australian methods: five disease severity categories like the British Guidelines, and three separate categories of control based on symptoms as defined above, similar to the Australian guidelines.

Asthma treatments

There are several types of current therapies in asthma, which could mainly be grouped as either bronchodilators or anti-inflammatory therapies (Table 3 – page 81), also referred to as relievers or controllers respectively. Bronchodilators relax airway smooth muscles and provide immediate relief from asthma symptoms such as wheezing and shortness of breath, whereas anti-inflammatory therapies are used as a maintenance treatment of the underlying inflammation which characterizes asthma. The bronchodilators consist of inhaled short-acting β2-agonists (SABA), inhaled long-acting β2-agonists (LABA), inhaled anticholinergics, and theophyline. In the Canadian Consensus[2], anti-inflammatory therapies include inhaled corticosteroids (ICS), antileukotrienes and cromones.

Recommendation ICS first-line

'Reliever' medications such as SABAs provide rapid relief of acute bronchoconstriction and it has been shown that patients tend to take more as-needed medication as their asthma control declines.[48] Based upon the recognition that asthma is primarily an inflammatory condition, the Canadian Consensus[27] advises that the major

thrust of therapy should be controlled using anti-inflammatory therapy. Inhaled beta2-agonists may therefore only be used infrequently; SABAs are only recommended for use as-needed.

It has been well established that inhaled corticosteroids (ICS) relieve persistent symptoms very effectively, improve lung function, decrease bronchial hyperresponsiveness and reduce morbidity caused by asthma.[49,50,51,52,53,54] Several randomized clinical trials in adults with asthma concurred that ICS might be the most effective available medication in improving forced expiratory volume in one second (FEV_1).[55,56] Observational study results showed that regular use of low dose ICS could reduce asthma hospitalizations by as much as 80%, both early and later on in the course of the disease.[54,57,58] In addition, it had previously been shown that compliance with ICS therapy reduces the risk of asthma exacerbations as well as the risk of death from asthma by 21% for each additional ICS canister used.[59] Not surprisingly, ICS constitute the preferred controller medication in the treatment of persistent asthma because they are the most effective with the least side effects anti-inflammatory medications available for treating the underlying inflammation.[2,60] This is reflected in current practice, where the use of controller medication increased 8-fold between 1978 and 2002, inhaled corticosteroids (ICS) manifesting the biggest increase.[61]

Therefore, on the basis of substantive Level 1 evidence - defined as randomized controlled trials (RCTs) or meta-analysis of RCTs of adequate size to ensure a low risk of incorporating false-positive or false-negative results[2] - several guidelines, including the Canadian Consensus, recommend ICS as first-line agents in the treatment of patients with persistent asthma.[4,62] Studies have shown that the early initiation of anti-inflammatory therapy (i.e. within 2 years of the onset of symptoms) with ICS is believed to improve the prospects of achieving good long-term asthma control[63,64,65]. In addition,

there is evidence to suggest that this approach may reduce airway remodelling[66]. In previous reports, the Canadian Consensus positioned ICS as the mainstay of asthma therapy and as clearly indicated in all but the mildest cases.[27] The latest update of the Consensus recommend ICS as the optimal intervention even for patients with mild persistent asthma.[2] Inhaled corticosteroids (ICS) should therefore be introduced as the initial maintenance treatment for asthma, even in subjects who report asthma symptoms less than three times per week.[2] Daily long-term control with ICS is therefore recommended to prevent exacerbations and chronic symptoms for all patients with persistent asthma, whether the persistent asthma is mild, moderate, or severe.

Recommendations ICS/LABA

However, when a patient's asthma is not well controlled with first-line inhaled corticosteroids therapy alone, the use of both ICS and long-acting β-agonist (LABA) therapy is accepted as the most effective treatment regimen to control moderate and severe asthma.[3] As part of their stepwise approach for asthma management, both International (GINA)[1] and Canadian guidelines[2,27,62] recommend the use of low dose ICS coupled with inhaled LABA, based on the physician's assessment of the patient's underlying severity of asthma symptoms. This therapeutic approach is also supported by NAEPP[4] guidelines as the most convenient and effective regimen for uncontrolled persistent asthma.

ICS/LABA - Improved Outcomes

ICS and LABA have a complementary effect,[5,6,7,8] treating both components of asthma: underlying airway inflammation and airway obstruction, respectively.[3,9,10] In an earlier landmark trial, Greening et al. demonstrated that treatment with both ICS and LABA provides greater asthma control for patients not optimally controlled on a moderate-dose ICS.[11] It has also been shown that the maximal effect of this regimen could be obtained when the added LABA (salmeterol) dose was 50ug twice daily.[67] The

lesser effect of higher dose ICS on lung function is likely to be a reflection of the plateauing dose-response curve of ICS, particularly when responses such as PEFR, FEV_1, and bronchial responsiveness are measured.[68,69]

ICS/LABA vs. Increased dose of ICS

In an extensive meta-analysis including several clinical trials, the addition of LABA to low-dose fluticasone was superior to increasing the dose of fluticasone in patients with moderate to severe persistent asthma.[12] This regimen lead to improvements in spirometry, and in symptoms score as well as to a decreased number of exacerbations.[70] Other trials involving the ICS/LABA combination also confirmed that LABA plus low-dose ICS (88ug twice daily) was more effective than higher-dose ICS alone in reducing asthma exacerbations in patients with persistent asthma,[71] in improving morning peak expiratory flow, and in leading to a 26% decrease in symptom-free days[72]. The Gaining Optimal Asthma ControL (GOAL) study has also shown the superiority of a combination of salmeterol/fluticasone propionate (SFC) compared with fluticasone propionate alone (FP) in terms of improving guideline-defined asthma control.[73]

The FACET trial showed reduction in asthma exacerbations and increase in morning PEF with the addition of formoterol irrespective of the budesonide dose. The addition of formoterol to low dose budesonide was more effective than a fourfold higher dose of budesonide alone.[74] Similar conclusions could also be reached according to the results of the OPTIMA trial[75]. In that study, a first group of 698 patients was randomly assigned to receive a low dose ICS (100 µg budesonide twice daily) and a LABA (6 µg formoterol twice daily), an ICS alone (100 µg budesonide twice daily) or placebo. The addition of 6 µg of formoterol to the ICS resulted in improved lung function. However, no additional benefit was found with this combined regimen when compared with budesonide alone (100 µg twice daily) in that mild asthma patients group. Compared

with placebo, even in patients with mild asthma, the addition of an ICS resulted in a 68% reduction in severe exacerbations. In the second OPTIMA study group (n = 1272) composed of patients previously been treated with ICS and having slightly worse lung function (mean FEV_1 predicted value 86% compared with 90%), the addition of formoterol did provide additional benefit compared with placebo and, more importantly, compared with doubling of the dose of the ICS.

Overall, there does not appear to be any difference between the use of ICS alone or in combination for patients with mild asthma who have never received an ICS, while it is clear that the combined ICS/LABA regimen provides benefits for patients with moderate to severe asthma. The Canadian Consensus[27] reviewed other available data[76] and concluded that there is insufficient evidence of additional benefit for the initial use of combination inhaler therapy in patients with mild persistent asthma who have not been treated previously with ICS.

ICS/LABA – Synergy

In summary, clinical trials evaluating the effect of adding LABA therapy to 'low dose' ICS demonstrated improvements in asthma outcomes in terms of both lung function and exacerbation rates, in asthmatic patients who remain symptomatic on low-dose ICS alone. Moreover, it has been shown that LABA added to ICS therapy provides superior asthma control compared with the addition of leukotriene modifiers[77,78] or theophylline.[79] Earlier findings concluded that the superior control obtained with the LABA/ICS combination is likely a consequence of the complementary actions of the drugs when taken together, potentially the activation of the glucocorticoid receptor by salmeterol.[80] Myo et al. have recently documented that a synergistic/additive effect of the ICS/LABA combination might be on molecular pathways that are not typically considered steroid sensitive, i.e. the cascade of inflammatory mediators deriving from membrane phospholipid metabolism.[5] Another recent publication assessing the synergy

of LABA/ICS regimens stated that molecular interactions between corticosteroids and beta2-adrenoceptors may underlie the clinical added benefits of combination therapy[81]. The combination of corticosteroids and LABA potentiates inhibition of interleukin-8 and eotaxin release from human airway smooth muscle cells and granulocyte-macrophage colony-stimulating factor release from epithelial cells, and also the inhibition of airway smooth muscle cell proliferation.[81]

Concurrent vs. Combination

The use of LABA plus ICS in a concurrent (or concomitant) use versus a combination technique may not be equivalent. 'Concurrent' entails the manipulation of two different breath-activated devices (one for each drug) and 'combination' denotes a single inhaling device which contains both agents. Therefore, combination therapy implies only one inhalation maneuver per dose, whereas concurrent therapy implies two.[14] There are two commercial products that combine a LABA (formoterol or salmeterol) and an ICS (budesonide or fluticasone). These two combination products are presently available in Canada: (1) GlaxoSmithKline markets Advair® as 100/50 micrograms, 250/50 micrograms or 500/50 micrograms dry powder inhalers of fluticasone propionate (ICS) / salmeterol xinafoate (LABA) into the same inhaler (Diskus®), with each inhalation providing 50 µg of salmeterol and 125/25 and 250/25 fluticasone/salmeterol in metered dose inhalers. The unit cost for these products varies from $77.80 to $132.16, depending on the strength. The supply is expected to last for an average of one month. (2) AstraZeneca markets Symbicort® as 100/6 micrograms or 200/6 micrograms of budesonide/formoterol dry powder inhaler (Turbuhaler®). Unit costs for these products are $65.10 and $84.63 respectively. The supply is expected to last for an average of one or two months.[82]

Improved Safety with combined inhalers

Short-acting β2-agonists have been used for symptom relief for many years.[83] However, it has been shown that SABAs are overused and that this inappropriate use, particularly among ICS users, might be explained by undertreatment or poor compliance with ICS.[84] Inhaled beta-agonists may be associated with excessive and inappropriate reliance on symptomatic treatment in poorly controlled asthma.[85] The inappropriate use of LABA as monotherapy without ICS also raises safety concerns and this practice does not hold with international guidelines[1,] nor with the Canadian Consensus recommendations.[27] Combination inhalers ensure that patients cannot neglect their ICS maintenance therapy in favor of the LABA,[82] because patients may perceive the benefits of bronchodilation more easily, which may improve adherence and overall asthma control.[22] Recently, a long- but also fast-acting agent, formoterol, has been approved for symptom relief.[86] It is important to reiterate that based on current evidence fast-acting bronchodilators may be used to relieve acute intermittent asthma symptoms, but only *on demand* and at the minimum dose and frequency required. When a reliever is needed for more than 3 times a week (aside from a pre-exercise dose), it suggests suboptimal asthma control and indicates the need to re-assess treatment. [87]

Safety Issues with LABA Monotherapy

Several studies have shown the detrimental effect of using LABA as monotherapy. In a randomized, double-blind, placebo-controlled, parallel-group study with salmeterol, Lazarus and al.[88] showed that despite reasonable control of symptoms and lung function, treatment failure and asthma exacerbations occurred more often in the salmeterol-treated group (42 µg twice daily) compared to patients treated with triamcinolone (400 µg twice daily). Another study evaluating the corticosteroid-sparing effect of LABA noted a large increase in asthma exacerbations (46.3% of patients) after

complete elimination of triamcinolone compared with subjects taking both trimaciolone (400 µg twice daily) and salmeterol (13.7% of patients).[89] Furthermore, this has recently been confirmed with the interim analysis of the recently discontinued SMART study, which demonstrated that salmeterol was associated with a significantly higher prevalence of adverse events, including death, than a placebo in the approximately 50% of 26,000 subjects who were not on ICS.[90] Although effective when given with an ICS, it has been suggested that a reduced effect over time and receptor desensitization, not at the bronchial smooth muscle level but on the mast cells and lymphocytes, may account for the relative lack of evidence of an effect of the LABAs on airway inflammation.[85] By combining anti-inflammatory treatment with a LABA in a single inhaler, both the inflammatory and bronchoconstrictive aspects of asthma can be covered without introducing any new or unexpected adverse consequences. The most common drug-related adverse events with the LABA/ICS combination were those known to be attributable to the constituent medications (ICS therapy and/or LABA therapy).[9]

Better outcomes with Combined Inhalers vs. Low Dose ICS

The benefits of combination therapy include better day-to-day control and a reduction in exacerbations compared with monotherapy with ICS at a lower dose.[23] Total control of asthma - defined as no daytime or night-time symptoms, no use of rescue SABAs, no exacerbations and a peak flow rate of >80% predicted - may be achieved with the use of combined salmeterol/fluticasone in a single inhaler in up to 41% of patients with moderate to severe asthma, compared with only 28% of patients treated with fluticasone alone. Superior asthma control and improved patient quality of life were subsequently demonstrated in favor of the combination therapy in studies comparing the budesonide/formoterol combination with budesonide alone.[91,92] Furthermore, there is evidence suggesting that ICS and LABA administered in a single

inhaler may be superior in reducing asthma exacerbations than the administration of the same products in two separate inhalers.[93]

Combination fluticasone/salmeterol

The first trial comparing the combination and concurrent use of fluticasone/salmeterol conducted by Aubier et al.[94] showed that both combination and concurrent therapies achieved significantly greater improvement in morning and evening PEFR compared to fluticasone alone. Both combination and concurrent therapies improved PEFR by 10% whereas fluticasone alone improved morning PEFR by 4%. Further studies also demonstrated that combination treatment with both LABA and ICS in the same inhaler was as effective as using two separate inhalers to deliver LABA and ICS.[95,96,97,98,99] The EDICT trial by Ringdal et al. showed that in symptomatic patients with moderate-to-severe asthma, fluticasone/salmeterol (50/250 microg bd), administered in a single device (Diskus), was at least as effective as an approximately three-fold higher microgram corticosteroid dose of budesonide (800 microg bd) given concurrently with formoterol (12 microg bd) in terms of improvement in PEFam, and superior at reducing exacerbations and nights symptoms or awakenings. Fluticasone/salmeterol was also the less costly treatment due primarily to lower hospitalization and drug costs according to that study.[16]

Combination budesonide/formoterol

The first trial using budesonide/formoterol in a single inhaler was conducted by Zetterstrom et al.[91] In patients with persistent asthma symptoms despite treatment with ICS, budesonide/formoterol administered via a single dry powder Turbuhaler device

appears to be as effective as treatment with the constituent medications administered via separate inhalers in improving PEF, controlling symptoms and preventing mild exacerbations. Adjustable maintenance dosing with budesonide/formoterol is associated with a lower overall dosage and appears to maintain control as effectively as fixed dosing.[24,100] Another study comparing self-guided adjustable maintenance dosing with budesonide/formoterol in a single inhaler with fixed dosing showed that asthma patients on adjustable maintenance dosing with budesonide/formoterol maintained control of symptoms using significantly less medication overall than fixed dosing. Adjustable maintenance dosing achieved guideline goals of effective asthma control at an appropriately low maintenance dose.[101]

Bronchodilating action

A recent double-blind, placebo-controlled, cross-over study [102] involving twenty subjects with mild to moderate asthma showed that the bronchodilating action of the long-acting beta-agonist formoterol administered as a single evening dose from the combination budesonide/formoterol Turbuhaler (2x100/6mug) attenuated the biphasic pattern of the circadian rhythm in airway tone, resulting in a bronchodilation of at least 24h. Lung function measurements were assessed at baseline, at 1h and subsequently every 4h post-dose for 24h. The results of that study showed that compared with placebo, the combination budesonide/formoterol Turbuhaler significantly improved the three measures of airways function (FEV_1), specific airways conductance (sGaw) and maximum expiratory flow at 25-75% of vital capacity (MEF(25-75%))) throughout the 24h period, with a difference in FEV_1 at 24h of 0.20L (0.04-0.35L).

Combination fluticasone/salmeterol versus Combination budesonide/formoterol

More recent literature report on findings from head-to-head assessments of both combination regimens, however the focus was mainly on fixed versus adjustable dosage which extend beyond the scope of this research study. A recent review[103] of the publications on the clinical evidence of budesonide/formoterol and salmeterol/fluticasone regimens concluded that both are effective and well-tolerated asthma treatments.

Reduced complexity

Adherence to medical therapy (the extent to which recommendations are followed as defined) is a complex and dynamic behavioral process that is strongly influenced by the patient, his or her support environment, practices of health care providers, and the characteristics of care delivery systems.[104] Moreover, it has been shown that adherence to treatment in asthma declines as the regime becomes more complicated, either by increasing the number of medications and/or the number of daily doses.[16,17] Therefore, complexity of drug regimen is a well-established contributor to poor compliance and simplified regimens are associated with better compliance.[19,105,106,107,108] As a result, more convenient treatments may represent an important benefit for patients with asthma, and an effort to simplify the complexity of the therapy could also result in improved adherence, potentially leading to better disease control.[24] For example, results of a recent RCT suggest that not only is the combination of budesonide/formoterol in a single inhaler as safe and effective in the long-term treatment of asthma as its constituent agents taken concurrently, but also that the lower number of withdrawals (frequency of discontinuation due to asthma deterioration from recorded adverse events) with this combination therapy may reflect better adherence to treatment compared with both agents taken via separate inhalers.[109] With its fast onset

of action (due to the bronchodilating effect of formoterol), this combination therapy may help patients feel more in control of their condition and improve adherence to their medication.[24]

Effectiveness vs. Efficacy

The relative effectiveness of combined vs. separate delivery modes in actual clinical practice may be different. Clinical studies used to support the guidelines are not indicative of 'real life', where patients frequently cannot use their inhaler correctly.[110] Differences in adherence to recommended therapies between real world and clinical trials may contribute to the differences in results from these two distinct environments. In clinical trials, patients are carefully selected and supervised for their adherence to recommended therapies and meticulously trained on the use of their inhalers. In clinical practice, the most effective treatments require the utilization of inhalers, such as ICS which are used with inadequate technique by a significant numbers of patients.[111,112,113] The fact that asthma is a chronic illness involving long-term therapy combined to the difficulty for patients to adequately manipulate their inhaler may lead to poor persistence, consequently reducing the effectiveness of asthma therapy in clinical practice.

Although the benefits of combined ICS plus LABA therapy can be achieved with separate inhalers, the convenience of combination regimens may improve patient adherence and may therefore reduce the morbidity of asthma.[24,81] However, there is limited evidence demonstrating that improved adherence in current practice results from the use of combination therapy of LABA and ICS instead of the concurrent therapy. Two retrospective cohort studies measured treatment adherence using the number of prescriptions recorded in a United States claims database over a 12-month period.

Stoloff et al. published the first study[25] testing this hypothesis. Prescription refill rates for asthma medications were determined for a cohort of 2511 patients aged 12 years or older who had been seen for asthma. The primary analysis was the comparison of the adherence measures across five study cohorts composed of patients selected on the basis of one asthma medical claim and one pharmacy claim: LABA/ICS in combination (n=563), LABA/ICS concurrent (n=224), LABA/anti-leukotriene combination (n=75), ICS alone (n=798), and anti-leukotrienes alone (n=776). The differences in medication possession ratios (MPR) - defined as the number or days supplied (from first to last prescription) divided by the treatment duration period (from index date to the exhaustion of the last prescription) - and refill rates - defined as the number of monthly (30-day supply) prescription claims for the cohort regimens over the 12-month follow-up period, including the index claim - were reported, and ANOVAs adjusting for potential differences in demographic and baseline measures models were used to statistically test the differences in treatment days, MPRs, refill rates, and mean short-acting β2-agonist use across cohorts. All analyses controlled for cohort demographics, physician specialty at index, pre-index total health care costs, and pre-index asthma medication use which contributed to minimize the risk of confounding. Patients who were prescribed combination LABA/ICS obtained significantly more refills (4.06) compared to fluticasone prescribed with salmeterol concurrently (2.35). Findings from Stoloff et al.[25] confirm that subjects refilled their ICS almost twice as often if it was combined in the same device with a LABA rather than the two being prescribed in separate devices. Therefore, the utilization of a single inhaler containing both an ICS and a LABA may increase the likelihood that patients would not only obtain optimal ICS therapy, but also benefit from the additive effects of the LABA.

More recently, a similar study by Stempel et al.[26] confirmed the results from the Stoloff study, documenting that adherence profiles of ICS/LABA in a single inhaler are significantly better when compared to ICS and LABA in separate inhalers, and compared to the other regimens. The methodology was similar to the one in the Stoloff study, except for the addition of an inclusion criteria (at least one SABA claim) by Stempel et al. and a slightly higher number of subjects (n=3503). In both studies, the cohorts were similarly identified on the basis of the index medication with unequal numbers of patients between groups. Stempel et al.[26] found that the mean number of prescription refills for ICS/LABA combination (3.98) was significantly higher than ICS (2.29) and the ICS component of ICS/LABA (2.36) and ICS/anti-leukotrienes (2.15). No significant differences were observed between combination and anti-leukotrienes refill rates (4.33). The mean number of treatment days was greater for combinations compared to ICS, ICS/LABA concurrent, and ICS/anti-leukotrienes.

The strengths and weaknesses are similar in both studies. The use of refill rates from a large database is particularly important to assess prescribing and utilization trends in clinical practice. It is important however to ensure that the cohorts are homogeneous for comparison purposes. The selection of patients on the basis of having a prescription of one of the various regimen types at index date may have introduced a potential selection bias where patients could experience different levels of severity across cohorts; patients may not be newly treated with a combination or a concurrent therapy at the beginning of the follow-up period. In both the Stoloff et al. and the Stempel et al. studies,[25,26] patients on concurrent therapy might have been treated for a longer period of time than patients on combination therapy at the beginning of the 12-month observation period, since LABA arrived on the market a few years before the combination therapy. Furthermore, the tendency for persistence to decrease over time[45]

might result in a bias when comparing adherence between patients using combination or concurrent therapy.

Adherence and persistence to treatment

Suboptimal adherence and poor persistence to treatment are widely spread across all major diseases, and it has been shown that 'survival' on the prescribed medication decreases sharply in the first six months of treatment.[114] In Canada, the economic consequence of non-persistence (direct and indirect costs) in terms of preventable negative outcomes attributed to the premature treatment discontinuation, have been estimated around $7-9 billion per year.[115]

Non compliance is particularly critical in chronic disease and has been qualified as a major therapeutic challenge.[15] The complexity of the regimen is inversely related to compliance across a spectrum of therapeutic classes.[15] Furthermore, decreased medication compliance is observed with extended duration of treatment,[116,117] while other factors such as level of education, IQ, social status, and other demographic variables have not been found to correlate with medication compliance rates.[18] Adherence, formerly referred to as compliance, is a patient-centered term. It suggests that patients carry out and maintain certain behaviors, such as taking medications, after making an informed choice in a supportive environment.[118] Persistence, or continuing to take a prescribed regimen over a period of time, is also critical for chronic disease therapies.[116,119] Poor persistence is reflected in the finding that on average 30-50% of patients with chronic diseases will not continue to follow drug treatments, as prescribed by their doctor, over time.[120,121] Some examples of factors related to noncompliance and inhaled drugs include patients taking long-term medication who stop treatment if they have not experienced an attack for an extended period.[122] The degree of suboptimal

adherence is also documented in the literature, with up to 80% of patients expected to be non-adherent to their treatment regimen at a given time.[120,121,123]

A review of published electronic monitoring data of compliance – defined by most publications as the proportion of days with the appropriate number of doses taken – showed that the mean dose taking compliance rate similarly ranged from 70% to 80% across all therapeutic areas, except for respiratory diseases where the rate was closer to 50%.[15]

The documented relationship of poor adherence to increased morbidity and even mortality further highlights the importance of patient adherence to prescribed asthma medication therapy.[54,57,58,59,124] A literature review by Cochrane et al.[111] found that asthma patients took the recommended ICS doses of inhaled medication on 20% to 73% of days and that the frequency of efficient inhalation technique ranged from 46% to 59% of patients. Overall, Cochrane et al. concluded that only a small percentage of the prescribed dose of an ICS is likely to reach the target organ, the lung, because of patient noncompliance with the prescribed dose, difficulty in correct use of the inhaler, and the ability of a properly used inhaler to essentially deliver the drug to the lung.

Compliance with ICS therapy is often thought to be poor, and worse than with bronchodilators, probably due to the absence of immediate relief or perceptible effect from ICS compare to short-acting β2 agonists.[125] At least two studies[126,127] support the view that inhaled corticosteroid adherence appears to be worse than adherence with inhaled β2 agonists. However in both studies,[126,127] the β2 agonists were probably short-acting, and it was not clear if similar results would be found if adherence with ICS is compared to long-acting β2 agonists.[128] Compliance with ICS was subsequently shown to improve with concomitant use of long-acting beta2-agonists.[129] Another prescription analysis later showed that mean adherence to new start monotherapy to

ICS was 33.8% and to inhaled long-acting β2 agonists was 40%, with adherence increasing along with the use of short acting β2 agonists,[130] hence perpetuating the view that persistence appears to be lower with ICS than with β2 agonists and that adherence to inhaled asthma therapies is generally low whether ICS are taken alone or in concomitant use with β2 agonists.

Although routine use of ICS can markedly improve symptoms and reduce asthma complications,[65,51,131] the contribution of an overall less than perfect adherence to ICS (approximately 50%)[113,124] among adult patients with asthma could still be correlated with several poor asthma-related outcomes. Williams et al.[124] found that adherence to ICS was significantly and negatively correlated with the number of emergency department visits (correlation coefficient [R] = -0.159), the number of fills of an oral steroid (R = -0.179), and the total days' supply of oral steroid (R = -0.154). After adjusting for potential confounders, including the prescribed amount of ICS, each 25% increase in the proportion of time without ICS medication resulted in a doubling of the rate of asthma-related hospitalization (relative rate, 2.01; 95% CI, 1.06-3.79). In a more recent study using electronic devices to measure compliance to ICS in patients with asthma, it was found that on average, patients took 72% +/- 24% of their prescription. Among the potential predictors of noncompliance to ICS in adults with asthma, age was the only significant predictor (compliance increased with increasing age).[132] A recent review of the literature[128] summarized the determinants of patient adherence to an aerosol regimen for the treatment of asthma as follows: complexity of the inhalation regimen (dosing frequency, number of drugs), route of administration (oral vs. inhaled), type of inhaled agent (corticosteroid adherence is worse than with short-acting β2 agonists), patient awareness of monitoring, as well as a variety of patient beliefs and socio-cultural and psychological factors. In a study specifically assessing

these determinants,[133] favorable attitude toward ICS was associated with greater adherence.

Measures of persistence and adherence in asthma

Most of the earlier compliance research has evaluated measures of medication consumption for randomized clinical trials of drug therapy.[134] The measures of persistence and adherence in asthma vary according to the different studies or interventions. A clear distinction must be drawn between medications that are prescribed, medications that are dispensed, and medications that are actually taken. About one in seven prescriptions are not cashed in and dispensed[135], and nonadherence to prescription instructions, both intentional and nonintentional, is widespread.[136,137] Accurate data on both what is prescribed and what is taken is required, as well as information about individual beliefs and behaviors around medication taking.[138] The relationship between the duration of drug action and timing of doses, which has a critical impact on the efficacy of treatment, can only be assessed by measures of dose-timing such as electronic medication monitors.[139] Covert electronic monitoring of inhalers is the gold standard, but this approach has been utilized in only a few small studies because it requires specialized electronic devices.[140,141] Other methods for assessing adherence or persistence to asthma inhaler include patient self-reporting in diaries and weighing of used canisters, but these methods may be respectively subjective or inaccurate. MacDonald and colleagues[142] have identified several different approaches for measuring adherence or persistence (see Table 5 on page 83), ranging from more subjective techniques such as health care scales, 10-item checklist for inhaler use, and self-report scales, to objective claims database analyses. Results of a systematic review showed that few articles described the development or use of self-report methods to measure change in medication over time. No questionnaire that was commonly used for this purpose could be found, nor one that

had been evaluated and published. Considerable work has been undertaken to develop questionnaires or diaries for individual projects, but because these tools and their validation are rarely published, they are not available for other researchers to use, and comparison across studies is difficult.[138] Overestimation of people's accounts in self-reports might bias the results of medication adherence studies; patients may be affected by the context of the interview or questionnaire, such as a desire to please or to be seen as "good patients"[138] by giving a socially acceptable response. Moreover, a questionnaire such as The Monash Respiratory Questionnaire[143] includes lists of possible asthma medication and two columns of tick-boxes to check for regular use or use during an asthma attack, but the validation of this format is not clearly described and it has not specifically been developed to measure adherence to treatment. Physician reports in medical charts might be biased by unawareness of patient behavior, provider self-presentation, or liability concerns, although data on the accuracy of chart entries remains fairly sparse.[144] Collateral ratings (eg, by spouses or health professionals) can be useful but may vary in accuracy given the distance from the patient's daily activities.[145] For instance, electronic monitoring of nebulizer use provides a more precise measure of long-term medication use than does self-report on diary cards.[146] Pill counts and tests such as blood assay can be useful as long as patients do not dispose of or consume medication just before it to appear compliant.[147]

Overall, there seems to be no one adherence measure against which to calibrate others, making concurrent validation difficult. Adherence research in clinical settings is limited by challenges; respondent burden can be a concern and certain measurement strategies are limited to certain regimens (eg, pill counts for medication) or have different meaning with different regimens.[148] Pharmacy refill data is likely to be an accurate representation of what is actually taken, especially for long-term medication that is measured over many months.[138] Refill compliance studies using databases could

be characterized by three attributes: (1) the distribution of the compliance variable (continuous or dichotomous); (2) the number of refill intervals evaluated (single or multiple); (3) the use of the measure to assess either the time period over which medications were available to the patient or the time intervals during which gaps in therapy occurred.[149] Refill compliance measures have a major role in population-based studies that must assess drug exposure retrospectively, or that cannot employ more precise measures of medication consumption.[149] Other measures of compliance, in particular electronic monitoring, are more suitable for clinical trials of drug therapy and for evaluation of drug efficacy when the timing of drug doses is likely to affect patient outcomes.[149]

Patients' satisfaction with their medication predicts continuance of pharmaceutical treatment, correct medication use and compliance with medication regimens.[150,151] Observational studies of outcomes of asthma therapy are needed to understand the implications of choice of controller in different populations.[152] It has been demonstrated that ICS adherence can be estimated by using prescription refill information, and that these measures are independently associated with important asthma outcomes.[124] Previous studies evaluated the adherence and/or persistence of patients using asthma treatment inhalers and showed that compliance to ICS in patients with asthma is often known to be suboptimal and difficult to predict.[132]

It is proposed that patients' decision to continue, alter, or discontinue medical treatments are influenced by a variety of characteristics, including real or anticipated beliefs regarding the effectiveness or harms of treatment.[153,154] Therefore, it is reasonable to suggest that a less complex treatment regimen, with a faster onset of action would enhance compliance. Hence, the objective of our population-based cohort study was to compare both persistence and adherence to treatment between 16-44 years old asthmatic patients starting a combination and a concurrent therapy, using data

collected in a large health care insurance database in Canada. The larger sample in our study compared to similar studies adds statistical power. The drug utilization comparison between groups was characterized by three different measures to evaluate persistence and adherence. The use of a one-to-one matching cohort methodology mitigated the risk for potential confounding; and assessing medication use as an indicator of severity before including the patients in the cohort contributed to the homogeneity of our treatment groups at baseline. To further minimize the potential for confounding variables, we selected covariates in our Cox regression analysis based on an assessment of the most recent or widely used variables in the literature to date. Since persistence and adherence tend to vary according to treatment duration, the main strength of our study compared to the two other published cohort studies[25,26] is that patients needed to be new users of combination or concurrent therapy to enter in our study cohort.

In this section, we have reviewed the background and rationale that lead to recommendations of ICS and LABA therapy for moderate to severe asthma patients. This combination has proven better efficacy than ICS alone, considering that LABA monotherapy is not a recommended therapeutic option. However, persistence and adherence to concomitant ICS and LABA therapy are generally poor and the literature particularly underlines the sub-optimal use of ICS. Data have indicated that simplified treatment regimen may improve persistence and adherence, and this constitutes the rationale for combining both ICS and LABA in a single inhaler. The scarcity of data to demonstrate persistence and adherence to this simplified LABA/ICS inhaler regimen compared to both medication taken concomitantly has prompted the necessity to conduct further research in that area.

METHODS

Sources of Data

This population-based study required access to claims data from the *Régie de l'assurance maladie du Québec* (RAMQ) databases. The RAMQ is the government body responsible for the administration of health care services in the Canadian province of Quebec. These databases contain administrative data files with information on medical services dispensed to Quebec residents, and on prescriptions filled by the residents of Quebec insured by the RAMQ for their medications. At the time of the study, 43% of the total population of the province of Quebec, Canada[155] was insured by the RAMQ for their medications. In 1999, the RAMQ drug plan covered over 3,000,000 people classified into three groups: welfare recipients (640,895 individuals), seniors of 65 years old or more (874,204 individuals), and people from the general population, aged under 65 years old who do not have access to a private group insurance (1,609,848 individuals). This last group of beneficiaries had been covered by the RAMQ Drug Insurance Plan since January 1st, 1997. The computerized RAMQ data is separated into demographics, medical services, and pharmaceutical files, each containing the individual's health insurance number, which is the link between them. Because the RAMQ plan offers universal medical coverage, both demographic data and information on medical services are available in the RAMQ databases for all the residents of the province of Quebec, representing approximately 7.3 million individuals.

The demographic file lists age, gender, postal code and year of death. The medical services file includes claims data on inpatient or ambulatory medical services such as: site of medical practice (outpatient clinic, emergency department, hospitalization); nature of the medical act, date, diagnosis (ICD-9 codes); as well as the encrypted identification and physician's specialty.[156] The pharmaceutical file, which has

been validated for research and previously used for peer-reviewed publications of pharmacoepidemiologic research studies,[157,158] contains data on prescriptions filled at community pharmacies: drug name, date, dose, quantity, dosage form, and duration as indicated by the pharmacist, as well as the encrypted identification and prescribing physician's specialty. The different RAMQ drug codes for anti-asthmatic medications appear in Table 1 on page 74.

Study Population

A retrospective study looks backwards and examines exposures to suspected risk or protection factors in relation to an outcome that is established at the start of the study. This retrospective, observational, drug utilization study is based upon a cohort of patients with known exposures to combination (LABA and ICS in the same inhaler) or concurrent therapy (LABA and ICS prescribed in two different devices, within a plus or minus 15-day interval), who are followed over a period of time. Advair™ (salmeterol xinafoate/ fluticasone propionate) was the first combination therapy approved by Health Canada in November 1999 and the second combination therapy Symbicort® Turbuhaler® (budesonide/eformoterol) was granted approval in February 2002. The cohort was established by selecting asthma patients who were beneficiaries of the RAMQ Prescription Drug Insurance Plan. New users of combination therapy and new users of LABA and ICS concurrently were selected from the RAMQ database between January 1, 1999 and September 30, 2002. New users were defined as patients who had not received a combination therapy or a LABA for at least one year before the date of the first prescription of a combination therapy or the date of the first prescription of concurrent therapy of both LABA and ICS filled on or after January 1, 1999.

A cohort of 12,386 patients was identified on the basis of eligibility criteria : at the time of inclusion in the cohort - which corresponded to the date of the beginning of a

combination or a concurrent therapy - subjects were required to be: (1) Aged between 16 and 44 years old inclusively; (2) Insured under the Quebec drug plan in the preceding year and at least 30 days following cohort entry; and (3) Exempt of any recorded prescription for a combination therapy, a concurrent ICS and LABA therapy, or a LABA monotherapy in the preceding year. This latter exclusion criteria ensures that patients selected in the cohort are really new users of either the combined or concurrent LABA/ICS regimen. Patients could have been on ICS alone since this is the first-line therapy for asthmatic patients and in the Canadian guidelines LABA is only recommended as an add-on therapy for those patients who cannot achieve asthma control on ICS alone.[2] If patients had used a LABA in the year preceding their entry in the cohort, they could likely have been on concurrent therapy and would therefore not correspond to the definition of new users. The lower limit of our selected age group in the first eligibility criteria is determined in line with the RAMQ categorization for adults. The higher limit ensures that chronic obstructive pulmonary disease patients are excluded from the cohort as the onset of that disease typically occurs in individuals in their mid-40s, and distinguishing between asthma and COPD is difficult and may be impossible in some older patients.[159] For each patient included in the cohort, we obtained from RAMQ socio-demographics data, physician characteristics, and data on all filled prescriptions and medical services dispensed between January 1, 1998 and December 31, 2002.

From the 12,386 individuals who met the eligibility criteria, a final one-to-one matched cohort was formed (n=5,118). The one-to-one combination to concurrent matching was based upon: (1) markers of asthma severity: number of prescriptions of ICS filled in the year preceding cohort entry, and daily dose of ICS prescribed at cohort entry (i.e. first prescription of the combination or concurrent therapy) and (2) markers of asthma control: number of prescriptions of oral corticosteroids and short-acting β2-

agonists filled in the year prior to cohort entry. Matching on ICS prescriptions refills and selecting patients who have already consumed ICS in the year preceding their entry in the cohort would not affect the primary outcome measure of the study because persistence and adherence are assessed for patients who start a new regimen consisting of both LABA and ICS taken together, whether the regimen is administered with a single inhaler or with two inhaling devices. Unmatched users of concurrent or combination therapy were not included in the study. The one-to-one matching was aimed at ensuring equal distribution of confounders amongst both study groups, more specifically in terms of asthma control and severity.

Subjects were followed until the earliest of these events: December 31, 2002, death, a switch between a concurrent and a combination therapy, or loss of coverage under the drug insurance plan.

Drug Exposure and Persistence

The concurrent therapy was reconstructed by using an algorithm based on the dispensing date, amount dispensed, duration of treatment, and the name of the medication. Patients considered in the concurrent group had refilled prescriptions of ICS (beclomethasone, fluticasone propionate, budesonide) and LABA (salmeterol, formoterol) within an interval of 15 days between the dispensing dates. Patients considered in the combination group were simply identified if they had one filled prescription for that treatment (fluticasone propionate/salmeterol or budesonide/formoterol) since a single inhaling device combines both agents. The rationale behind selecting new users is based on the knowledge that persistence and adherence tend to vary over time[160]; if patients would already be treated with one of the regimen under study before entering the cohort, it may have an influence on the study outcome. All new users of combination therapy were included in the study with the

consideration that this regimen only became available in the market as of November 1999. Consequently, new users of concurrent therapy may have been on their treatment regimen for a longer duration during the study period, prompting the necessity to adjust for previous adherence in a multivariate model.

Assessing failure to refill prescriptions constitutes a reliable and objective measure of persistence in large patient groups.[149] The primary outcome of persistence was defined as having prescriptions of the ongoing therapy continuously renewed within a pre-specified grace period (time window). This grace period for renewal was defined as the sum of three times the duration of the current prescription (in days) plus all overlaps accumulated since the beginning of the therapy. An overlap was considered when a patient refilled a prescription before its end; for example, a 30-day prescription dispensed on January 1st (end date equal to January 30) and refilled on January 15, would generate a 15-day overlap. For patients who did not persist on treatment, the discontinuation date was the last day of drug supply, that is the end date of the last filled prescription plus all overlaps since the beginning of the therapy. For concurrent patients, a discontinuation was observed if they ceased either both prescriptions of LABA and ICS, LABA alone, or ICS alone.

Determinants of Persistence

Potential determinants of persistence pertaining to the patients' characteristics included age (5-year differential), gender (male versus female), receipt of social assistance (yes/no), area of residency (urban versus rural), and the average number of different medications at cohort entry. Markers of asthma severity and control were also considered as potential determinants of persistence: prescribed daily dose of ICS ($\leq$ 250, $>$ 250 - 500 and $>$ 500 mcg of fluticasone or equivalent) at cohort entry, number of prescriptions filled in the year preceding cohort entry for ICS, oral

corticosteroids, and short-acting β_2-agonists; hospitalization for asthma (yes/no); visit to an emergency room for asthma (yes/no), and medical visits to a respiratory physician for asthma (yes/no), all in the year prior to cohort entry. As potential determinants of treatment persistence, we also identified the prescribing physician's specialty (general practitioner, respiratory physician, or other specialist) at cohort entry; and assessed whether individuals had records for at least one prescription of anti-leukotrienes (yes/no) or theophylline (yes/no) in the year prior to cohort entry.

Patient's Adherence

Three indicators of patient's adherence were calculated and compared between users of each therapy group using t-tests.

First, the average number of prescriptions of combination or concurrent therapy filled per patient during the year following cohort entry. For patients under concurrent therapy, adherence is calculated as the average adherence for the LABA and ICS, in line with the definition of concurrent (prescribed within +/- 15 days). This calculation indicates in which treatment group, combination or concurrent, patients have the most refills.

Second, the average number of days under either therapy with the prescribed dose during the year following cohort entry (i.e. sum of drug supply days of all prescriptions filled during that year, with censoring of the last prescription if it crosses the end of the year). This measure provides a gross indicator of the drug utilization pattern during the first year of treatment, indicating in which groups patients have more days of treatment under the prescribed medication. These two measures were calculated among patients who were followed for at least one year

Third, as the main measure of adherence, we calculated the percentage of time patients took the prescribed dose, while persistent to the therapy under study (sum of

drug supply days between the first and last fill dates divided by length of drug therapy)[161]. This measure of adherence was calculated among patients who filled at least two prescriptions of either combination or concurrent therapy during the study period. This constituted our main measure of adherence because it considered the time during which patients had persisted on treatment during the study period. In contrast with the two first measures which were performed on individuals who had been followed up for at least one year, it was important to evaluate adherence in the context of persistence, to have a measure of adherence that was independent of the persistence. Thus, this third measure reflects both persistence over time and adherence to the prescribed medication.

Statistical Analysis

Statistical power and sample size

At the design stage of any investigation, it is common practice to minimize the probability of failing to detect a real effect (type II error, false negative). The probability of type II error is equal to one minus the power of a study (probability of detecting a true effect). In order to do so, our study protocol included a selected power level for our study, along with the two-sided significance level at which we intended to accept or reject null hypotheses of our statistical tests. The significance level (5%) is the probability of type I error (incorrectly rejecting the null hypothesis, false positive).

Before selecting patients from the cohort, we used the PASS statistical and power analysis software[162] to perform a Two Proportions Power Analysis to estimate the required sample size. The type I error α was set to 0.05, the power of the bilateral test was set to 0.90 and we estimated that the proportion of patients who refilled their prescription at least once within the year following the index date would be of 40% for the concurrent therapy (LABA + ICS) patients, based on the compliance range found in the literature. More specifically, this estimated proportion of patients who refill their prescription was based on previous asthma study with similar methodology in which it was found that 38% of ICS patients renewed their prescription at least once within the year following the initiation of the ICS therapy.[113] The output generated by the PASS software indicated that group sample size of n = 831 would be required to detect a difference of 20% between the concurrent therapy and the combination therapy, that is a net difference of 8% between the estimated proportion of patients that would persist in their concurrent therapy vs. combination therapy. PASS was also used to estimate the sample size required in each group to demonstrate a difference in the probability to remain on the medication regimen under study. A Log-Rank Survival Power Analysis

was performed assuming that 75% of patients will be censored, at a power of 0.90, and an alpha error of 0.05. The output of PASS showed that group sample size in both groups should be of n = 2100 to be able to show an absolute difference of 5% one year after the initiation of the compared therapies.

Estimation and comparison of treatment persistence

Treatment persistence between concurrent and combination groups was compared using three analyses.

Firstly, we estimated the proportion of patients without prescription refill during the year following the beginning of therapy, and compared these proportions with a khi-square test. This analysis was restricted to patients who had at least one year of follow-up.

Secondly, the cumulative persistence rate was estimated using the Kaplan-Meier failure time analysis.[163] This method estimates survival rates, expressed as the survivor function (S), which corresponds to the number of individuals surviving longer than time (t), divided by the total number of individuals studied. Time (t) can be the survival time, time-to-event or time to failure such as treatment discontinuation in our study. Kaplan-Meier curves plot percent survival as a function of time.

Survival analysis methodology, such as the Kaplan Meier analysis, consists of a set of procedures useful for analyzing experiments where the response variable is the time until the occurrence of an event of interest (discontinuation of treatments under study). The main characteristic of survival data is the presence of censoring, which is a partial observation of the response, where some individuals are free from the event due to the end of the study, or due to being withdrawn according to censoring criteria. This method automatically accounts for censored patients, as both the numerator and denominator are reduced on the day a patient is censored. Day I is the first day of the

study for each subject. As the event of interest is usually not observed for all subjects due to, amongst other reasons, the end of the study, a corresponding censoring indicator is defined to indicate whether the event has occurred or not. It is usual to assume the value 1 when an event has occurred within the follow up period and 0 otherwise[164]. Censored subjects contribute to the data up until the time of censoring, but contribute no data after that. This method assumes that censored individuals have the same prospect of survival as those who continue to be followed.

In our study, non-persistence was considered if there was no renewal within a pre-defined grace period following the date of the latest prescription. The Kaplan-Meier curves were compared between both regimens using log-rank tests[165]. For patients using the concurrent therapy, we also estimated Kaplan-Meier curves for ICS and LABA separately and then, compared these curves with the log-rank test. It is common to compare two survival curves between two treatments using log-rank tests. The log-rank test function provides methods for comparing survival curves where some of the observations may be censored and where the overall grouping may be stratified. These methods are nonparametric in that they do not make assumptions about the distributions of survival estimates or hazard curves. The null hypothesis tested here is that the risk of treatment discontinuation is the same in both groups. For each time interval, the observed number of discontinuation in each group is compared with the expected number of discontinuations if the null hypothesis were true. All the observed and expected values are combined into one khi-square statistic and the p-value is determined from that.

Thirdly, the Cox Regression Model was used to further compare the probability of non-persistence between both drug regimens (combination versus concurrent therapy), while adjusting for the potential determinants described above. Cox

regression model (Cox, 1972) is without any doubt the most popular model used for lifetime data analysis[164]. When the hazard function depends on time, hazard ratios can be estimated after fitting a Cox's proportional hazards model which assumes that for each group the hazard functions or failure rates are proportional at each time (no particular distribution function assumed for the hazard function). In other words, if an individual shows a risk of failure equal to three times the risk of failure of another individual in the beginning of the study, then this ratio will be the same for any other time t during the follow-up period[164]. The purpose of using the Cox regression model is to estimate the survival curves and assess the importance of these predictors upon the response variable; namely time until discontinuation in our study (modeling predictors' effects on survival data via the hazard function). Predictors can be a number of factors that are thought to be related to the event under study. The number of factors to be considered depends on the purpose of the study and they can be qualitative (sex, place of residence, gender, etc.) or quantitative (age, drug utilization, etc.).[166] The hazards ratio associated with a predictor variable is generated; along with a confidence interval. The hazards ratio may also be thought of as the relative discontinuation rate. If the ratio value is inferior to 1, the likelihood of treatment discontinuation for the patients exposed to the combination therapy is inferior to the likelihood of discontinuation for patients in the other group (concurrent therapy); the exposure to combination therapy is then found to be a protective factor of treatment discontinuation. For example, with a hazard ratio of 0.83 (adjusted for all the variables considered in the regression analysis), combination users would be 17% less likely to stop their treatment as compared to concurrent users (adjusted hazard ratio= 0.83; 95%CI: 0.78-0.88). Conversely, if the value of the ratio would be superior to 1, there would be a higher risk of discontinuation for patients in the combination therapy group than for those in the concurrent therapy group; exposure to combination therapy would have been considered as a factor that

may increase the outcome of treatment discontinuation. If the ratio would be equal to 1, the interpretation would be that there is no significant association between exposure to the combination therapy and treatment discontinuation. If the value 1 is not in the range of the confidence intervals that are also generated with the Cox regression analysis, then it can be concluded that the proportions are significantly different in the two groups, and there is an increased risk in one group compared to the other.

In order to determine the predictors of treatment discontinuation, the hazard ratios in our Cox regression model adjusted for all the co-variables included in the model, on the basis of the first variable (treatment under study). Four categories of co-variables considered as potential determinants for treatment discontinuation were included in the model: (1) socio-demographics (age 5-year difference, gender, socio-economic status as defined by access to social assistance from the Quebec government, place of residence (urban or rural), (2) initial prescription of combination or concurrent therapy (prescribing physician's specialty for the first intention of treatment by which cohort entry was determined and initial average daily dose ICS in micrograms of fluticasone equivalent $\leq$250, >250-500, >500), (3) drug utilization (for each additional prescription of ICS, oral corticosteroids and short-acting β2 agonists; prescription of theophylline and anti-leukotrienes (yes/no); and number of different medications expressed for each additional prescription in the year preceding cohort entry), (4) health care services utilization (hospitalizations, emergency, due to asthma, or GP or respirologist visits for asthma) in the year preceding cohort entry. Health services utilization was measured by calculating the number of prescribing physicians and medical visits recorded during the year preceding cohort entry; except for the number of hospitalizations which was restricted to the year preceding index date.

Sensitivity analysis to test the grace period

We performed a sensitivity analysis to test the impact of the pre-defined grace period, by re-estimating persistence for both therapy groups using different grace periods, defined as two and four times the duration of the latest prescription plus all overlap periods accumulated since the index date. For example, if the duration of the prescription recorded in the drug database was of 30 days and the patient had accumulated 15 days of overlap since the index date, then the grace period would be of 75 days ((30 x 2) + 15). We performed a Kaplan-Meier analysis with these alternative grace periods for treatment renewal to assess their impact on persistence and the log-rank test was used to compare persistence on LABAs and ICSs used concurrently with persistence to combination therapy based on these longer and shorter grace periods for treatment renewal.

Estimation and comparison of treatment adherence

Adherence to the prescribed therapy – namely the average number of prescriptions filled per patient, the average number of days under therapy during the first year of follow-up, and the average percentage of time patients took the prescribed dose while persistent to the therapy – was compared between users of each therapy group using t-tests. Among concurrent users, measures of adherence were also estimated for ICS and LABA separately. Based on the number of patients followed for at least one year, we determined for each treatment group the mean number of filled prescriptions per patient and the mean number of days on prescribed medications during the first year of treatment and determined the p-value for each comparison between the two groups. Treatment adherence to the prescribed therapy while persistent was calculated in each group based on the number of patients with at least two filled prescriptions. The mean

percentage of days with the prescribed dose was determined for each group and the p-value was generated to assess the statistical significance between the two groups.

All analyses were performed on Statistical Analysis System Software (8; SAS Institute, Cary, North Carolina).

Persistence and adherence to combination therapy among adult asthmatic patients

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ABSTRACT

Background: Limited evidence exists on persistence and adherence with asthma combination regimens including both inhaled corticosteroids (ICS) and long-acting β_2-agonists (LABA) within the same inhaler (combinations) compared to these medications inhaled separately (concurrents).

Objective: To compare persistence and adherence between 16-44 years old asthmatic patients, starting combination or concurrent therapies.

Methodology: This retrospective one-to-one matched cohort is based upon claims data. Newly treated asthmatics with either a combination or concurrent therapy were selected from the *Régie de l'assurance maladie du Québec* (RAMQ) database between January 1999 and December 2002. Combinations were one-to-one matched to concurrents using control and severity markers in the year prior to cohort entry. Persistence was determined by a Kaplan-Meier analysis. Cessation probability between groups was assessed using a Cox Regression model, adjusting for socio-demographics and markers of asthma control and severity. Adherence was estimated by the time patients were on the prescribed therapy.

Results: Persistence with combinations fell to 10% 12 months after initiation, down to 5% over 2 years while concurrents' rates declined from 5% to below 2%. Persistence was better with combinations (adjusted hazard ratio for discontinuation (0.83; 95%CI: 0.78-0.88). Concurrents stopped LABA slightly more than ICS (p-value <0.0001). Average days under treatment during the first year was significantly higher with combinations (90.4 vs. 73.1; p<0.0001). Treatment adherence was slightly lower in combinations vs. concurrents (55% vs. 58%; p=0.0031).

Conclusion: Combinations were slightly more persistent than concurrents, but slightly less adherent. Persistence to inhaled controller therapies is very low among adult asthmatic patients.

INTRODUCTION

The international guidelines (GINA)[1] and latest Canadian consensus[2] uphold the concept of asthma management as a continuum, contingent on underlying symptoms severity and pulmonary tests results. When asthma is not optimally controlled with inhaled corticosteroids (ICS) alone, the addition of long-acting β_2-agonists (LABA) to ICS is accepted as the most effective therapy to control moderate to severe asthma.[3] This therapeutic approach is also supported by NAEPP guidelines[4].

ICS and LABA have a complementary effect,[5,6,7,8] treating both underlying airway inflammation and obstruction, respectively [3,9,10]. It has been shown that this regimen provides greater control than increasing the dose of ICS[11,12] and may also improve outcomes (lung function, exacerbation rates, and quality of life) in asthmatics who remain symptomatic on ICS.[13]

Concurrent or combined administration of ICS and LABA may not be equivalent. 'Concurrent' entails the manipulation of two different inhalers (one for each drug) whereas 'combination' involves a single inhaler (containing both agents).[14] Moreover, evidence suggest that ICS and LABA in a single inhaler may be superior in reducing asthma exacerbations than the administration of the same products in two separate inhalers.[15]

Furthermore, adherence to asthma treatments declines as the regimen becomes more complicated, either by increasing the number of medications and/or the number of daily doses.[16,17] Consequently, it has been hypothesized[18,19] that the use of combination inhalers can improve patient's adherence, which may lead to overall asthma control.[20,21,22] Only one published study[23] so far has tested this hypothesis in usual care clinical practice in the US.

Therefore, we performed a population-based cohort study to compare treatment persistence and adherence among asthmatic patients between the ages of 16 and 44, who were starting a combination or a concurrent therapy. The data was obtained from a large health care insurance database in Canada.

METHODS

Sources of Data

This population-based study required access to claims data from the *Régie de l'assurance maladie du Québec* (RAMQ) databases. These contain administrative data files on residents covered by the provincial health care and by the public drug insurance plans, including about 43% of the total population of the province of Quebec, Canada.[24] The computerized data is separated into demographics, medical services, and pharmaceutical files, each containing the individual's health insurance number, which is the link between them.

The demographic file lists age, gender, postal code and year of death. The medical services file includes claims data on inpatient or ambulatory medical services such as: site of medical practice (outpatient clinic, emergency department, hospitalization); nature of the medical act, date, diagnostic (ICD-9 codes); as well as the encrypted identification and physician's specialty.[25] The pharmaceutical file, which has been validated for research and previously used for pharmacoepidemiologic research studies,[26,27] contains data on prescriptions filled at community pharmacies: drug name, date, dose, quantity, and duration as indicated by the pharmacist, as well as the encrypted identification and prescribing physician's specialty.

Study Population

A cohort of 12,386 patients was identified from the RAMQ database between January 1, 1999 and September 30, 2002 on the basis of eligibility criteria. At the time of inclusion in the cohort - which corresponded to the date of the beginning of a combination (LABA and ICS in the same inhaler) or a concurrent therapy (LABA and ICS prescribed in two different devices within a plus or minus 15-day interval) - subjects were required to be: (1) Aged between 16 and 44 years old inclusively; (2) Insured under the Quebec drug plan in the preceding year and at least 30 days following cohort entry; and (3) Exempt of any recorded prescription for a combination or a concurrent ICS and LABA therapy in the preceding year. For each patient included in the

cohort, we obtained from RAMQ socio-demographics data, physician characteristics, and data on all filled prescriptions and medical services dispensed between January 1, 1998 and December 31, 2002.

From the 12,386 individuals who met the eligibility criteria, the final one-to-one matched cohort was formed (n=5,118). The one-to-one combination to concurrent matching was based upon: (1) markers of asthma severity: number of prescription of ICS filled in the year preceding cohort entry and daily dose of ICS prescribed at cohort entry (i.e. first prescription of the combination or concurrent therapy) and (2) markers of asthma control: number of prescriptions of oral corticosteroids and short-acting β_2-agonists filled in the year prior to cohort entry. Subjects were followed until the earliest of these events: December 31, 2002, death, a switch between a concurrent and a combination therapy, or loss of coverage under the drug insurance plan.

Drug Exposure and Persistence

The concurrent therapy was reconstructed by using an algorithm based on the dispensing date, amount dispensed, duration of treatment, and the name of the medication. Patients considered in the concurrent group had refilled prescriptions of ICS (fluticasone, budesonide, beclomethasone) and LABA (salmeterol, formoterol) within an interval of 15 days between the dispensing dates. Patients considered in the combination group were simply identified if they had one filled prescription for that treatment (fluticasone propionate/salmeterol or budesonide/formoterol) since a single inhaling device combines both agents.

Assessing failure to refill prescriptions constitutes a reliable and objective measure of persistence in large patient groups.[28] The primary outcome of persistence was defined as having prescriptions of the ongoing therapy continuously renewed within a pre-specified grace period. This grace period for renewal was defined as the sum of three times the duration of the current prescription (in days) plus all overlaps accumulated since the beginning of the therapy. An overlap was considered when a patient refilled a prescription before its end; for example, a 30-day prescription dispensed on January 1st (end date equal to January 30) and refilled on

January 15, would generate a 15-day overlap. For patients who did not persist on treatment, the discontinuation date was the last day of drug supply, that is the end date of the last filled prescription plus all overlaps since the beginning of the therapy. For concurrent patients, a discontinuation was observed if they ceased either both prescriptions of LABA and ICS, LABA alone, or ICS alone.

We examined the impact of the selected grace period by reiterating the persistence analysis using grace periods based on two and four times the duration of the last prescription plus any accumulated days of overlaps.

Determinants of Persistence

Potential determinants of persistence included age (5-year differential), gender (male versus female), receipt of social assistance (yes/no), area of residency (urban versus rural), and the average number of different medications at cohort entry. Markers of asthma severity and control were also considered as potential determinants of persistence: prescribed daily dose of ICS ($\leq$ 250, > 250 - 500 and > 500 mcg of fluticasone or equivalent) at cohort entry, number of prescriptions filled in the year preceding cohort entry for ICS, oral corticosteroids, and short-acting β_2-agonists; hospitalization for asthma (yes/no); visit to an emergency room for asthma (yes/no), and medical visits to a respiratory physician for asthma (yes/no) in the year prior to cohort entry. We also considered the prescribing physician's specialty (general practitioner, respiratory physician, or other specialist) at cohort entry; as well as records for at least one prescription of anti-leukotrienes (yes/no) or theophylline (yes/no) in the year prior to cohort entry as potential determinants of treatment persistence.

Patient's Adherence

Three indicators of patient's adherence were calculated. First, the average number of prescriptions of combination or concurrent therapy filled per patient during the year following cohort entry. Second, the number of days under either therapy with the prescribed dose during

the year following cohort entry (i.e. sum of drug supply days of all prescriptions filled during that year, with censoring of the last prescription if it crosses the end of the year). These two measures were calculated among patients who were followed for at least one year. Third, as the main measure of adherence, we calculated the percentage of time patients took the prescribed dose, while persistent to the therapy under study (sum of drug supply days between the first and last fill dates divided by length of drug therapy)[29]. This measure of adherence was calculated among patients who filled at least two prescriptions of either combination or concurrent therapy during the study period.

Statistical Analysis

Treatment persistence between concurrent and combination groups was compared using three analyses. Firstly, we estimated the proportion of patients without prescription refill during the year following the beginning of therapy, and compared these proportions with a khi-square test. This analysis was restricted to patients who had at least one year of follow-up.

Secondly, the cumulative persistence rate was estimated using the Kaplan-Meier failure time analysis.[30] Non-persistence was considered if there was no renewal within the pre-defined grace period following the date of the latest prescription. The Kaplan-Meier curves were compared between both regimens using log-rank tests[31]. For patients using the concurrent therapy, we also estimated Kaplan-Meier curves for ICS and LABA separately and then, compared these curves with the log-rank test. We performed a sensitivity analysis to test the impact of the pre-defined grace period by re-estimating persistence for both therapy groups using different grace periods, defined as two and four times the duration of the latest prescription plus overlaps.

Thirdly, the Cox Regression Model was used to further compare the probability of non-persistence between both regimens, while adjusting for the potential determinants described above, and to obtain crude and adjusted hazard ratios of discontinuation.

We also estimated the proportion of patients reinitiating a treatment in the year following the end of their therapy and compared that proportion between users of the combination and concurrent therapy with a khi-square test.

Adherence to the prescribed therapy – namely the average number of prescriptions filled per patient, the average number of days under therapy during the first year of follow-up, and the average percentage of time patients took the prescribed dose while persistent to the therapy – was compared between users of each therapy group using t-tests. Among concurrent users, measures of adherence were also estimated for ICS and LABA separately.

All analyses were performed on Statistical Analysis System Software (8; SAS Institute, Cary, North Carolina).

RESULTS

The matched cohort consisted of 5118 patients: 2,259 new users of a combination therapy were one-to-one matched to new users of concurrent therapy based on the markers of asthma severity and control (as described under Study Population). The remaining unmatched patients (7,268/12,386) were excluded from the analyses.

Patient Characteristics

Table 1 presents the characteristics of the matched combination and concurrent therapy users. Mean age was comparable between groups while the proportion of men was slightly higher in the combination group (38.4% versus 35.0%). The number of combination users receiving social assistance was slightly lower (41.5% versus 47.3%), and fewer of them lived in a rural area (21.8% versus 24.0%) than concurrent users. The number of different medications recorded in the year preceding cohort entry was similar in both groups. During the year preceding cohort entry, the percentage of patients who had at least one emergency visit (11.1% versus 15.3%) and hospitalization (2.1% versus 4.3%) for asthma were lower in the combination group than in the concurrent group. The same trend was observed for the percentage of patients with at least one visit for asthma with a respiratory physician in the year preceding

cohort entry (7.7% for combination versus 16.2% for concurrent) and for the percentage of patients for whom the first prescription was written by a respiratory physician (7.8% for combination versus 18.9% for concurrent). By design, patients from both groups had no prescription of LABA filled in the year preceding cohort entry and in both groups, the average number of prescriptions filled by patients was 1.4 for ICS, 0.3 for oral corticosteroids and 2.7 for short-acting β_2-agonists in the year preceding cohort entry. In both groups, at cohort entry, 61.8% of patients had a prescription of ICS of more than 500 mcg per day in fluticasone equivalent.

Treatment Persistence

As a crude measure of non-persistence to treatment, we estimated that 44.2% of the patients who started a combination therapy and 51.5% of patients who started a concurrent therapy did not renew their prescription during the first year (p-value= 0.0001).

Figure 1 presents the Kaplan-Meier curves representing the cumulative percentages of patients persisting on therapy at different points in time comparing combination (n=2,259) and concurrent (n=2,259) users, using the pre-specified grace period. The graph shows that combination users tended to be more persistent on treatment than concurrent users (p-value for log rank-test < 0.0001). We found that 10% of combination users were still persistent one year after the initiation of therapy, while this percentage was slightly below 5% for concurrent users. The corresponding figures at two years for each regimen were 5% and below 2% respectively. The sensitivity analyses based on two and four times the duration of the latest prescription plus overlaps showed that regardless of the grace period definition, patients on combination therapy were found to be slightly more persistent than patients on concurrent therapy (p-value for log-rank test < 0.0001 for both grace periods).

We also looked at the persistence on LABA and ICS separately among concurrent therapy users. This analysis indicates a slightly better persistence rate for ICS as compared with LABA (p-value for log-rank test < 0.0001). One year after the initiation of the concurrent therapy,

approximately 11% of the patients were still using their LABA and 13% were still using their ICS. These figures were close to 5% for both agents after two years (Kaplan-Meier graph can be viewed at the Online Repository).

Table 2 lists the crude and adjusted hazard ratios for discontinuation as determined by the Cox Regression Model. After adjusting for all potential determinants of discontinuation, we found that combination users were 17% less likely to discontinue their treatment (rate ratio [RR] = 0.83; 95% confidence interval [CI]: 0.78-0.88) than concurrent users. This model also showed that older patients, men, patients receiving social assistance, and patients taking a greater number of different medications were significantly less likely to discontinue their treatment. We also found that patients with markers of asthma severity and lack of control, patients using anti-leukotrienes in the year preceding cohort entry, and patients who had their therapy initially prescribed by a respiratory physician were significantly less likely to discontinue their treatment. On the other hand, patients who received more than 500 mcg of ICS in fluticasone equivalent at cohort entry were found to be more likely to discontinue than patients receiving lower doses. Finally, among patients who stopped their initial therapy according to our definition, we found that 52% (601/1162) of combination users and 34% (555/1609) of concurrent users re-initiated their therapy in the year following discontinuation (p-value < 0.0001).

Treatment Adherence

Results for treatment adherence analyses are presented in Table 3. We found that during the first year, the average number of prescriptions filled was 3.5 for combinations and 2.7 for concurrents (p-value <0.003). We also found that combination users had, on average, more days of drug supply during the first year than concurrent users (90.5 versus 73.1 days; p-value < 0.003). However, treatment adherence was found to be slightly lower for combination than for concurrent therapy users (55% versus 58%; p-value < 0.003).

In the concurrent group, we found that the average prescriptions filled during the first year was 3.5 for ICS and 3.4 for LABA (p-value <0.05). We also found a higher number of average drug supply days for ICS than for LABA during the first year (100.9 versus 89.8 days; p-value < 0.05). However, adherence was found to be slightly lower for ICS therapy than for LABA therapy (53% versus 55%; p-value = 0.1238).

DISCUSSION

Patients on a combination therapy were found to be slightly more persistent than patients treated with ICS and LABA taken in two different inhalers. Persistence with combinations fell to 10% 12 months after initiation and declined to 5% over 2 years. For the same time periods, persistence in the concurrent group decreased from 5% to below 2%. The Cox Regression Model showed that combination users were 17% less likely to stop their treatment than concurrent users. Adherence was also found to be low for both regimens: users of combination and concurrent therapy took on average 55% and 58% of their prescribed doses, respectively.

Our findings are consistent with those of a retrospective cohort study where Stoloff et al. measured treatment adherence for patients aged 12 years or older, using the number of prescriptions recorded in a United States claims database over a 12-month period. They observed that patients who were prescribed LABA/ICS combination obtained significantly more refills (4.06) compared with patients prescribed fluticasone and salmeterol concurrently (2.35). Their study included a smaller number of patients (2511 patients) in a wider range of age groups than in ours. Still, the outcome in terms of persistence with combined inhalers was in the same direction as ours, but the observed difference was larger. One major methodological difference between that study and ours is that their patients were not newly treated with a combination or a concurrent therapy at the beginning of the study. In the Stoloff et al. study, patients on concurrent therapy might have been treated for a longer period of time than patients on combination therapy at the beginning of the 12-month observation period, since long-acting β_2-

agonists arrived on the market a few years before the combination therapy. As we observed in our study, persistence tends to decrease over time, and this phenomenon might explain why in the Stoloff et al. study, combination patients were found to be more adherent while concurrent patients were found to be less adherent than in our study, leading to a larger between-group difference.

In our study, through the Cox Regression Model, we also found that older patients, men, patients receiving social assistance, and patients taking a larger number of different medications, were less likely to discontinue their treatment. Markers of uncontrolled and severe asthma were found to be significant predictors of higher persistence to treatment. However, patients with a dosage higher than 500 mcg of ICS in fluticasone equivalent at cohort entry were found to be significantly more likely to discontinue their treatment.

Although using one inhaler instead of two could likely be easier to manage for patients, it is worthy, as in any observational study, to review the biases that might have distorted the magnitude of our results. Disease severity and degree of asthma control could affect persistence on therapy. One may speculate that sicker patients might be more likely to perceive a benefit from their asthma preventive therapy and thus, be more likely to be persistent. Consequently and with respect to our study, all efforts were made to control differences between treatment groups by matching patients on well known markers of disease severity and control (short-acting β_2-agonists, inhaled and oral corticosteroids utilization in the year prior to cohort entry, and on the prescribed dose of ICS at cohort entry)[32,33,34]. In order to adjust for any remaining differences even after matching, we performed a regression analysis including several potential confounders, such as ED visits and hospitalizations for asthma. Despite matching and adjustment for potential confounders in the regression model, we cannot completely rule out the possibility of residual confounding. Therefore, the study results could be considered as conservative given that the higher level of severity and lack of control seen in the concurrent group – based on higher frequency of ED visits and hospitalizations for asthma prior to cohort

entry and on higher number of different medications at cohort entry – is likely to minimize differences between the two groups.

One frequent argument in favor of combination therapy instead of ICS and LABA in separate inhalers is that patients might be more likely to stop their ICS and continue their LABA, since they might perceive more easily the benefit of the LABA. However, in our study we found the opposite: patients who started a concurrent therapy were slightly more likely to stop LABA than ICS.

Persistence on LABA/ICS therapy is essential to prevent exacerbations in patients suffering from persistent asthma. However, a LABA/ICS regimen could also likely be prescribed to treat other conditions; for example, chronic obstructive pulmonary disease (COPD). Therefore, this issue was minimized in our study by including patients only if they were less than 45 years old at cohort entry; thereby excluding those COPD patients and considering only persistent asthma sufferers.

The main strength of this study is that the analyses were performed on a large population-based administrative database and thus, represent the real-life use of these drugs in clinical practice, with a large sample size providing high statistical power to the analyses. The use of an administrative database to measure drug exposure also eliminates the potential of recall bias[35]. Moreover, our sensibility analyses results showed that the Kaplan-Meier estimators were not influenced by the duration of the selected grace period for treatment renewal; differences of similar magnitude in the persistence rate could still be observed between groups, regardless of the grace period.

One weakness of this study is the absence of clinical measures of asthma severity and control, such as pulmonary function tests and symptoms scores. However, extremely useful markers of disease severity and control allowed us to match and adjust for the potential confounding effects of disease severity and control. In addition, because the study was based

entirely on computerized data of dispensed medications, data may not coincide exactly with the actual intake of the medications, potentially resulting in drug use misclassification.[35]

Our results demonstrate that persistence on LABA/ICS controller therapies presently used in the prophylaxis of asthma remains very poor among adult asthmatic patients. Clearly, many patients take their controller medication sporadically and we should question the impact of this phenomenon on a patient's health, as well as on the use and cost of health care services. Overall, the trivial magnitude of the difference in persistence observed in our study with combination therapy compared to LABA/ICS in separate inhalers reinforces the importance of addressing the issue of asthma management beyond merely reducing the complexity of drug regimens. Whether this slight difference leads to better clinical outcome needs to be investigated.

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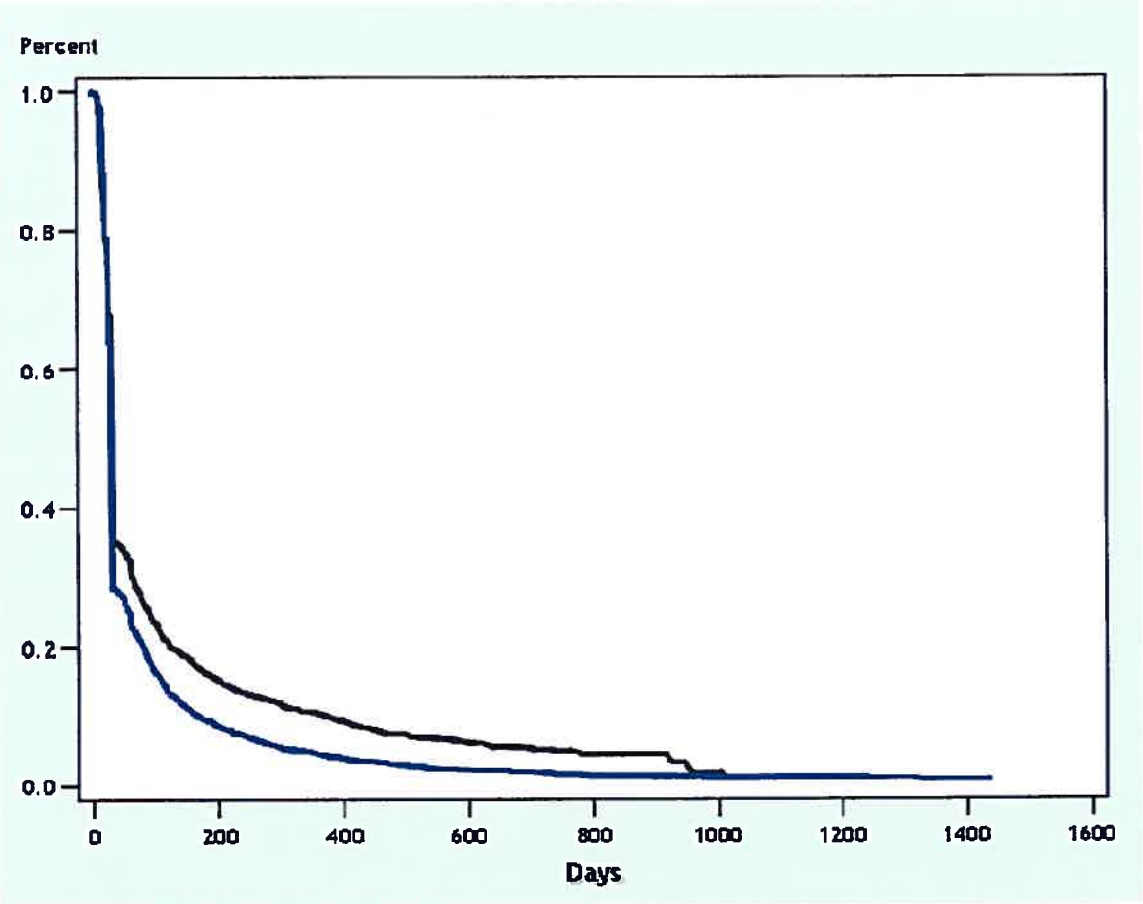
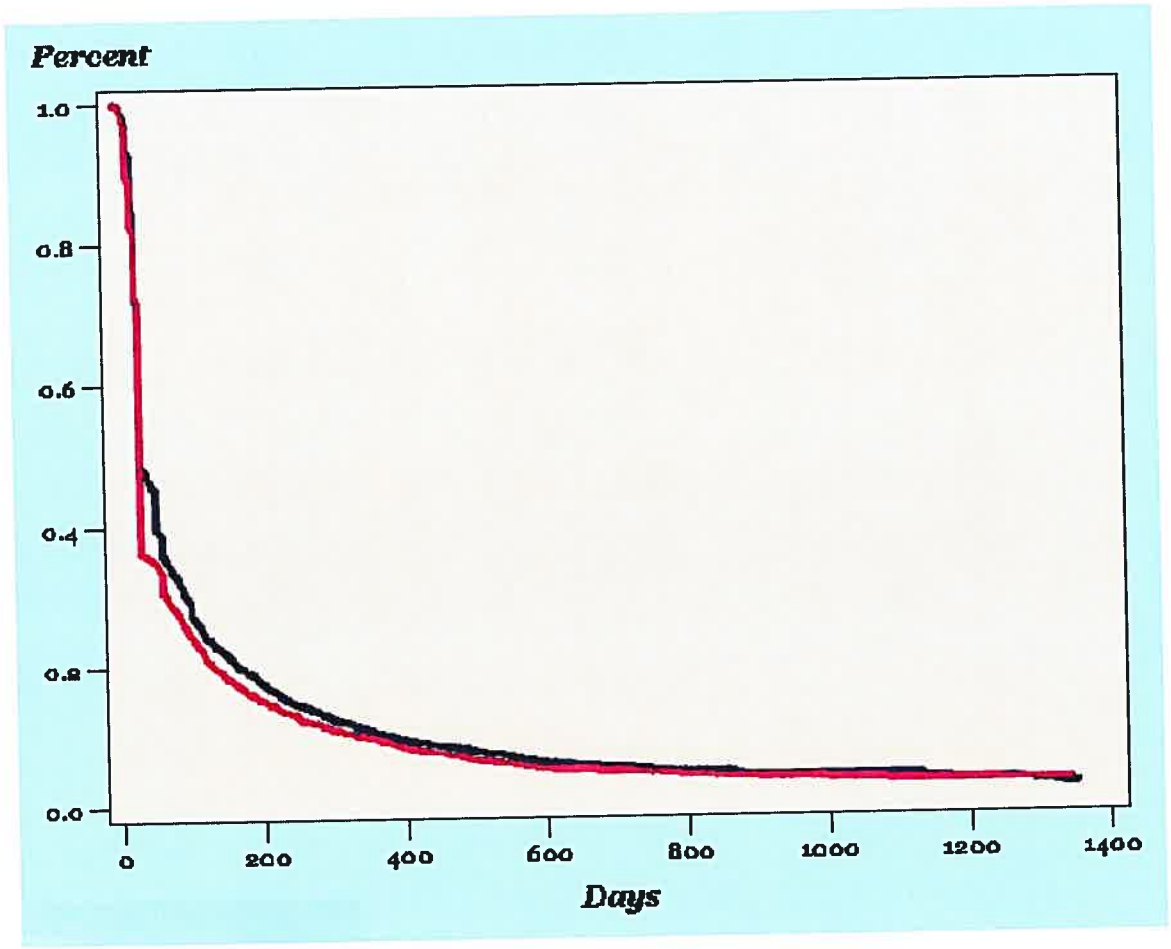
Figure 1. Kaplan-Meier curves comparing persistence over time* between both study groups



Legend for Figure 1
Black – new users combination therapy
Blue – new users concurrent therapy
*grace period of three times the duration of the latest prescription plus overlaps

E Figure 1. Kaplan-Meier curves : persistence over time* for ICS and LABA separately among concurrent users.



Legend for E Figure 1
Black – ICS
Red – LABA
*grace period of three times the duration of the latest prescription plus overlaps

Table 1. Patient's characteristics for new users of a combination or a concurrent therapy.

	Combination (n=2559)	Concurrent (n=2559)
Socio-demographic characteristics		
Age (in years), mean ± s. d.	32.5 ± 8.2	32.7 ± 8.2
Gender, % men	38.4	35.0
Receipt of social assistance, %	41.5	47.3
Living in a rural area, %	21.8	24.0
Number of different medications	6.5 ± 5.6	6.7 ± 5.9
Initial prescription of combination or concurrent therapy		
Prescribed daily dose of inhaled corticosteroid * ‡, mcg		
mean ± s.d.	761.4 ± 363.7	858.7 ± 467.2
% users		
(250	4.3	
> 250 – 500	33.8	
> 500	61.8	
Prescribing physician, %		
Family physician	87.1	74.4
Respiratory physician	7.8	18.9
Other specialists	5.1	6.6
Use of health care services in the year preceding cohort entry		
(1 ED visit for asthma, %	11.1	15.3
(1 hospitalization for asthma, %	2.1	4.3
(1 visit to a respiratory physician for asthma, %	7.7	16.2
Visits to a family physician, mean number per patient ± s.d.	6.7 ± 7.9	7.2 ± 8.2
Visits to a family physician for asthma, mean number per patient ± s.d.	0.8 ± 1.3	1.0 ± 1.7
Prescriptions dispensed in the year preceding cohort entry		
Inhaled corticosteroids*		
% users	51.5	
mean number of filled prescriptions per patient ± s.d.	1.4 ± 2.2	
Short-acting β_2-agonists*		
% users	58.8	
mean number of filled prescriptions per patient ± s.d.	2.7 ± 4.0	
Oral corticosteroids*		
% users	18.9	
mean number of filled prescriptions per patient ± s.d.	0.3 ± 0.8	
Theophyllin, % users	1.8	3.2
Anti-leukotriene, % users	5.0	4.5

‡ Daily dose calculated on the basis of fluticasone equivalent

* The distribution of these variables is identical in both groups since patients were matched on these variables

Table 2. Crude and adjusted hazard ratios of treatment discontinuation comparing new users of combination (n=2559) and concurrent therapy (n=2559).

	Crude HR 95% CI	*Adjusted HR* 95% CI*
Combination versus concurrent therapy	0.83 (0.79-0.88)	0.83 (0.78-0.88)
Socio-demographic characteristics		
Age (5 years difference)	0.96 (0.95-0.98)	0.96 (0.94-0.97)
Male versus female	0.90 (0.85-0.95)	0.92 (0.86-0.98)
Social assistance (yes/no)	0.84 (0.79-0.89)	0.87 (0.82-0.93)
Living in rural versus urban area	0.98 (0.91-1.04)	0.94 (0.87-1.00)
Initial prescription of combination or concurrent therapy		
Daily dose of inhaled corticosteroid (fluticasone equivalent) prescribed, mcg		
≤ 250	Reference	Reference
> 250 – 500	0.85 (0.74-0.98)	1.00 (0.87-1.16)
> 500	1.34 (1.16-1.54)	1.60 (1.39-1.84)
Specialty of the prescribing physician		
General practitioner	Reference	Reference
Respiratory physician	0.78 (0.72-0.86)	0.78 (0.70-0.86)
Other specialist	0.92 (0.83-1.03)	0.87 (0.78-0.97)
Prescriptions filled in the year preceding cohort entry		
Inhaled corticosteroids (each additional prescription)	0.85 (0.84-0.87)	0.90 (0.89-0.92)
Corticosteroids (each additional prescription)	0.96 (0.92-0.99)	1.00 (0.97-1.04)
Short-acting β_2-agonists (each additional prescription)	0.92 (0.91-0.93)	0.96 (0.95-0.96)
Anti-leukotriene (yes/no)	0.71 (0.62-0.82)	0.85 (0.73-0.98)
Theophylline (yes/no)	0.71 (0.59-0.85)	0.98 (0.81-1.18)
Number of different medications (each additional prescription)	0.976 (0.97-0.981)	0.993 (0.987-0.999)
Health care services for asthma in the year prior to cohort entry (yes/no)		
Hospitalization	0.94 (0.80-1.11)	1.06 (0.88-1.27)
Visit to an emergency department	0.82 (0.76-0.89)	0.85 (0.77-0.93)
Medical visit to a respiratory physician	0.85(0.78-0.93)	0.95 (0.86-1.06)

* Hazard ratios adjusted for all variables included in the table

Table 3. Treatment adherence for new users - combination or concurrent therapy.

	Combination	Concurrent		
		ICS and LABA	LABA	ICS
Number of patients followed for one year or more	1368	1739	1739	1739
Number of filled prescriptions per patient during the first year of treatment				
Mean ± s.d.	3.5 ± 3.4	2.7 ± 2.6*	3.37 ± 3.20	3.47 ± 3.08¶
Median	2	2	1	1
Range	1-21	1-14	1-19	1-21
Number of days on prescribed medications during the first year of treatment				
Mean ± s.d.	90.5 ± 90.7	73.1± 73.3*	89.8 ± 87.0	100.9 ± 87.9¶
Median	50	40	55	60
Range	7-393	1-448	4-433	5-511
Treatment adherence to the prescribed therapy while persistent				
Number of patients with ≥ 2 filled prescriptions	879	685	859	913
Percentage of days with the prescribed dose				
Mean ± s.d.	55 ± 19	58 ± 21*	55 ± 19	53 ± 19**
Median	53	55	50	50
Range	4-100	14-100	3-100	3-100

*p-value comparing combination and concurrent users < 0.003
¶ p-value < 0.05 comparing the use of LABA and ICS
** p-value = 0.1238 comparing the use of LABA and ICS

[1] **Global Initiative for Asthma.** National Institute of Health. National Heart, Lung and Blood Institute, WHO. **2003 GINA Report** (available at www.ginasthma.com)

[2] **C Lemière,** T Bai, M Balter et al. on behalf of the Canadian Adult Consensus Group of the Canadian Thoracic Society. **Adult Asthma Consensus Guidelines Update 2003**. Can Respir J 2004; 11 (Suppl A): 9A-18A.

[3] **Barnes P.J. Scientific rationale for inhaled combination therapy with long acting B2-agonists and corticosteroids.** Eur Respir J 2002; 19: 182-191.

[4]**NAEPP Coordinating Committee.** National Asthma Education and Prevention Program Expert Panel Report: **Guidelines for the Diagnosis and Management of Asthma Update on Selected Topics – 2002.** J Allergy Clin Immunol. November 2002. Vol. 11 No.5 pp. S141-S219.

[5]**Myo S**, Zhu X, Myou S, et al. **Additive blockade of b2-integrin adhesion of eosinophils by salmeterol and fluticasone.** Eur Respir J 2004; 23: 511–517.

[6] **Roth M**, Johnson PR, Rudiger JJ, et al. **Interaction between glucocorticoids and beta2 agonists on bronchial airway smooth muscle cells through synchronised cellular signalling.** Lancet 2002; 360: 1293–1299.

[7] **Mak JC**, Hisada T, Salmon M, Barnes PJ, Chung KF. **Glucocorticoids reverse IL-1beta-induced impairment of beta-adrenoceptor-mediated relaxation and up-regulation of G-protein-coupled receptor kinases**. Br J Pharmacol 2002; 135: 987–996.

[8] **Pang L**, Knox AJ. **Synergistic inhibition by b2-adrenoceptor agonists and corticosteroids on tumor necrosis factor-□–induced interleukin-8 release from cultured human airway smooth-muscle cells.** Am J Respir Cell Mol Biol 2000;23:79-85.

[9] **Nelson HS et al. Enhanced synergy between fluticasone propionate and salmeterol inhaled from a single inhaler versus separate inhalers.** J Allergy Clin Immunol 2003, 112: 29-36.

[10] **Remington et al. Long-acting beta-agonists: anti-inflammatory properties and synergy with corticosteroids in asthma.** Current opinion in pulmonary medicine. 2005 Vol 1, No. 1 p.74-8.

[11] **Greening AP**, Ind PW, Northfield M, Shaw G. **Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid.** Allen & Hanburys Limited UK Study Group. *Lancet* 1994;344:219–224

[12] **Shrewsbury S**, Pyke S, Britton M. **Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA).** *Br Med J* 2000;320:1368–1373

[13] **Campbell DA,** Robinson DS. **Cost advantages of combination asthma therapy.** Treat Respir Med. 2004;3(3):133-7.

[14] **Garcia-Marcos L et al. Inhaled corticosteroids plus long-acting B2-agonists as a combined therapy in asthma**. Expert Opin. Pharmacother. 2003. 4 (1). p. 23-39.

[15] **Ringdal et al. Evaluation of different inhaled combination therapies (EDICT): a randomised, double-blind comparison of Seretide (50/250 microg bd Diskus vs. formoterol (12 microg bd) and budesonide (800 microg bd) given concurrently (both via Turbuhaler) in patients with moderate-to-severe asthma.** Respir Med. 2002 Nov;96(11):851-61.

[16] **Coutts JAP,** Gibson NA, Paton JY. **Measuring compliance with inhaled medication in asthma**. Arch Dis Child 1992;67:332-3.

[17] **Chapman KR**, Walker L, Cluley S, Fabbri L. **Improving patient compliance with asthma therapy.** Respir Med 2000;94:2-9.

[18] **Kelloway JS** et al. **Effect of salmeterol on patients' adherence to their prescribed refills for inhaled corticosteroids.** Ann Allergy Asthma Immunol 2000;84:324-328.

[19] **Holt S** et al. **Increasing compliance with inhaled corticosteroids through the use of combination therapy.** J Allergy Clin Immunol February 2004

[20] **Lotvall J. Combination therapy in asthma - fixed or variable dosing in different patients?** Curr Med Res Opin. 2004 Nov;20(11):1711-27.

[21] **Nelson HS. Advair: Combination treatment with fluticasone propionate/salmeterol in the treatment of asthma.** J Allergy Clin Immunol. Vol. 107. No. 2. February 2001.

[22] **Kuna P.** Kuprys I. **Symbicort Turbuhaler: a new concept in asthma management.** Int J Clin Pract. 2002 Dec;56(10):797-803.

[23] **Stoloff SW**, Stempel DA, Meyer J, Stanford RH, Carranza Rosenzweig JR. **Improved refill persistence with fluticasone propionate and salmeterol in a single inhaler compared with other controller therapies.** J Allergy Clin Immunol. 2004 Feb;113(2):245-51

[24] **Régie de l'assurance maladie du Québec.** Health Ministry, Goverment of Québec, Québec: Régie de l'assurance maladie du Québec; 1997

[25] **World Health Organization. International classification of diseases. Manual of the international statistical classification of diseases, injuries, and cause of death. 9th revision.** Geneva, Switzerland: World Health Organization, 1977 (Publication no. PHS 80-1260).

[26] **Blais L**, Beauchesne M-F. **Use of inhaled corticosteroids following discharge from an emergency department for an acute exacerbation of asthma**, Thorax 2004; 59(11): 943-947.

[27] **Tamblyn R**, Lavoie G, Petrella L et al. **The use of prescription claims database in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Quebec.** J Clin Epidemiol 1995;48:999-1009.

[28] **Steiner JF**, Prochazka AV. **The assessment of refill compliance using pharmacy records: methods, validity, and applications**. J Clin Epidemiol 1997;50:105-116.

[29] **Jones C et al. Adherence to Prescribed Treatment for Asthma: Evidence from Pharmacy Benefits Data**. J of Asthma. Vol. 40, No. 1, 2003, pp. 93-101.

[30] **Kalbfleisch JP**, Prentice RL (Eds). **The Statistical Analysis of Failure Time Data.** John Wiley & Sons, 1980.

[31] **Lee, E.T. Nonparametric methods for comparing survival distributions. Statistical methods for survival data analysis; 2nd Ed.**; Wiley Series in Probability and Mathematical Statistics: A probability and Statistics Section, John Wiley & Sons: New York, 1992; 482 pages.

[32] **Boulet, L.P.;** Bai, T.R.; Becker, A.; Bérubé, D.; Beveridge, R.; Bowie, D.M.; Chapman, K.R.; Côté, J.; Cockcroft, D.; Ducharme, F.M.; Ernst, P.; FitzGerald, J.M.; Kovesi, T.; Hodder, R.V.; O'Byrne, P.; Rowe, B.; Sears, M.R.; Simons, E.R.; Spier, S. **What is new since the last (1999) Canadian Asthma Consensus Guidelines?** Can. Respir. J. **2001**, *8* Suppl A, 5A-27A.

[33] **Bukstein, D.A.;** Henk, H.J.; Luskin, A.T. **A comparison of asthma-related expenditures for patients started on montelukast versus fluticasone propionate as monotherapy.** Clin. Ther. 2001, 23(9), 1589-1600.

[34] **Stempel, D.A.**; Mauskopf, J.; McLaughlin, T.; Yazdani, C.; Stanford, R.H. **Comparison of asthma costs in patients starting fluticasone propionate compared to patients starting montelukast.** Respir. Med. 2001, 95(3), 227-234.

[35] **Lynd LD et al. Patterns of Inhaled Asthma Medication Use. A 3-year longitudinal analysis of prescription claims data from British Columbia, Canada.** Chest December 2002; 122:6, 1973-1981.

DISCUSSION

Brief summary of results

Patients on a combination therapy were found to be slightly more persistent than patients treated with concurrent ICS and LABA from two different inhalers. Persistence with combinations fell to 10% 12 months after initiation and declined to 5% over 2 years. In the concurrent group, persistence decreased from 5% at 12 months to below 2% after 2 years. The Cox regression model showed that users of a combination therapy were 17% less likely to stop their treatment than users of a concurrent therapy. Adherence during treatment persistence was also found to be low for both regimens: users of combination and concurrent therapy took on average 55% and 58% of the prescribed doses, respectively. This result is slightly higher than in the published literature where compliance with inhaled medication is reported to be often less than 50%.[140,160,167,168]

Comparability/Consistency with similar studies

Our findings are also consistent with two retrospective cohort studies[25,26] in which adherence to treatment was measured in patients aged 12 years and over on the basis of the number of prescriptions recorded in a United States claims database during a 12-month period. Stoloff et al. were the first to observe that patients who were prescribed LABA/ICS in combination obtained significantly more refills (4.06) compared with patients prescribed fluticasone and salmeterol concurrently (2.35). Their study included a smaller number of patients (2511 patients) in a wider range of age groups than in ours. Still, the outcome in terms of persistence with combined inhalers was in the same direction as ours, but the observed difference was larger. Stempel et al. similarly identified a cohort (n=3503) on the basis of the index medication, with unequal numbers of patients between groups. The mean number of prescription refills for ICS/LABA

combination (3.98) was significantly higher than ICS (2.29) and the ICS component of ICS/LABA (2.36) and ICS/anti-leukotrienes (2.15). The mean number of treatment days was greater for combinations compared to ICS, ICS/LABA concurrently, and ICS/anti-leukotrienes. One major methodological difference between those two studies and ours is that their patients were not newly treated with a combination or a concurrent therapy at the beginning of the study. At the beginning of the 12-month observation period, patients on concurrent therapy in these two studies might have been treated for a longer period of time than patients on combination therapy considering that long-acting β_2-agonists arrived on the market a few years before the combination therapy. Since patients might have been treated with combination or concurrent therapy for different lengths of time at the beginning of the 12-month observation period, they may therefore not be comparable in terms of the likelihood to be persistent or adherent to their therapy considering that persistence and adherence are known to vary considerably over time.[63,169,170] A tendency for persistence to decrease over time was also observed in our study. This phenomenon might explain why in the Stoloff et al. and in the Stempel et al. studies, patients on combination therapy were found to be more adherent while patients in the concurrent group were found to be less adherent than in our study, leading to a larger difference between the two treatment groups.

Predictors of Persistence

In our study, through the Cox regression model, we also found that older patients, men, patients receiving social assistance and patients taking a larger number of different medications were less likely to discontinue their treatment. Markers of uncontrolled and severe asthma such as the average dose of ICS at cohort entry; at least one visit to an emergency department for asthma or to asthma specialists; as well as asthma drug utilization in the year prior to the entry in the cohort, were found to be

significant predictors of higher persistence to the asthma treatments under study. This finding suggests that patients with more severe asthma may tend to be more persistent on their controller medication. However, patients with a dosage higher than 500 mcg of ICS in fluticasone equivalent at cohort entry were found to be significantly more likely to discontinue their treatment. This may be because more inhalations need to be performed every time patients need to reach that dose, and this additional complexity in taking their medications may be perceived as a burden for some patients and eventually drive them to cease their treatment. In our study, we found that 10% of combination users were still persistent one year after the initiation of therapy, while this percentage was slightly below 5% for concurrent users. The corresponding figures at two years for each regimen were 5% and below 2% respectively, showing that treatment simplification with the single inhaler may have some impact on the rate of persistence. When assessing the persistence on ICS and on LABA medications separately, rates yield slightly better persistence for ICS as compared with LABA (p-value for log-rank test < 0.0001). One year after the initiation of the concurrent therapy, approximately 11% of the patients were still using their LABA and 13% were still using their ICS. Over time the persistence rate converged as these figures were close to 5% after two years, a rate that is similar to what we found for combination users. Overall, the relevance of these results from a clinical standpoint is of considerable magnitude considering that each 25% increase in the proportion of time without ICS medication results in doubling of the rate of asthma-related hospitalizations.[124]

Biaises - Confounding

In a recent database study, it was found that the addition of salmeterol as an additional controller was associated with a significant decrease in inhaled corticosteroid use, suggesting decreased adherence in patients on the concomitant

regimen.[140] Although, as shown by this study, it can be expected that the reduced complexity of using one inhaler instead of two could be easier to manage for patients, it is worthy as in any observational study, to review the biases that might have distorted the magnitude of our results. Biases are systematic errors that lead to an incorrect estimate of effect or association; several factors could bias the study results such that they would cancel out, reduce or amplify the real effect. It is important to recognize those variables that are not part of the real association between exposure and disease, that predict the disease, and that are unequally distributed between exposure groups, because they could confound our thinking about the relationship between drug regimen and treatment persistence. For example, studies have shown that asthma is more prevalent in urban areas than in less polluted areas,[171] and worldwide asthma prevalence is expected to increase further, due in part to growing urbanization and pollution.[29] Asthma is indeed more prevalent in urban regions, yet living in the city is not really the cause of asthma. The prevalence of asthma is also apparently higher in lower social classes[172,173]. In our study, the place of residence (rural/urban) and the social assistance beneficiary status were assessed in the patient's socio-demographic characteristics of our study groups and also included in the Cox regression model, but found to be similar in both treatment groups. Moreover, the place of residence may be associated with higher asthma prevalence, but in our study, all the patients were already asthmatics. Living in an urban environment could be a confounder in our study if found to be a determinant of persistence and if the percentage of urban inhabitants differed between our treatment groups. In our Cox regression model, the place of residence was not found to be a strong predictor of persistence to asthma treatment (adjusted hazard ratio= 0.94; 95%CI: 0.88-1.00).

Indication bias and adjustment for asthma control and severity

Our study adjusted for patients' characteristics between groups to also account for a potential bias by indication, whereby characteristics (age, for instance) that have led the physician to choose certain drug may be important determinants of persistence in addition to the characteristics of the drug itself.

One may speculate that sicker patients might be more likely to perceive a benefit from their asthma controller therapy and thus, more likely to be persistent. Consequently, and with respect to our study, all efforts were made to control for these differences between treatment groups by matching patients one-to-one on the basis of the number of filled prescriptions of short-acting β2-agonists, ICS, and oral corticosteroids in the year prior to cohort entry, and on the prescribed dose of ICS at cohort entry, all of which are well known markers of disease severity and control.[62,174,175] Physicians may be inclined to prescribe certain types of medication depending on the level of asthma control or severity. A potential bias from our study consists of confounding induced by the lack of random allocation of patients to treatment with the controllers under study. Such bias is expected as patients with more severe asthma are more likely to be prescribed and dispensed the existing concurrent treatment. Adjusting for asthma control and severity mitigates for this potential bias by indication. Our study was therefore designed to avoid this bias by matching patients in both groups with respect to markers of asthma severity and control. Despite such tight matching, the concurrent still appeared to have slightly more severe asthma than the combination therapy patients. In order to control for this residual confounding by adjusting for these differences that may still exist between the two treatment groups, even after matching according to asthma severity and control, we performed a regression analysis including variables such as asthma-related ED visits and hospitalizations.

Moreover, we cannot completely rule out the possibility of residual confounding in the association between treatment regimen and persistence rate; variables would undoubtedly have to be known or measurable in order to be controlled. Therefore, some confounding by indication may remain. Despite matching, the fact that concurrent users appeared to be slightly more severe than combination users at cohort entry, is likely to under estimate the true difference in persistence. Therefore, our study results could be considered as conservative given that the higher level of severity and lack of control seen in the concurrent group – based on higher frequency of asthma-related ED visits and hospitalizations prior to cohort entry and on the higher number of different medications at cohort entry – is likely to minimize the difference in persistence observed between the two groups..

In our study, drug exposure is assessed by the dispensing of a prescription within a specified time period, prior to the outcome of interest: refill or discontinuation[176]. The drug supply for the most recent fill is used to determine whether the renewal of the prescription occurred within a specified grace period. Although cumulative dosage and duration of drug exposure may not be precisely determined with the refill information, the persistence provides an estimate of the duration of treatment. However, in our study we performed sensitivity analyses with Kaplan-Meier estimates and found that the relationship between the curves indicating persistence for each group were not influenced by the choice of the grace period duration for treatment renewal; differences of similar magnitude in the persistence rate could still be observed between groups, regardless of the grace period.

One argument that is often put forward in favor of using a combination therapy instead of ICS and LABA in separate inhalers is that patients might be more likely to stop their ICS and continue their LABA since they might perceive more easily the benefit

of the LABA. It is important to re-emphasize that the use of LABA without ICS is not a recommended therapeutic option in Canada, and may result in safety issues, including higher risk of morbidity and mortality.[177] Our study findings showed the opposite: patients who started a concurrent therapy were slightly more likely to stop LABA than ICS.

Selection

Persistence on LABA/ICS therapy is essential to prevent exacerbations in patients suffering from persistent asthma. Based on the combination or concurrent LABA/ICS regimens indicated for asthma at the time of the study, we assumed that patients treated with those regimens were treated for asthma because there is no information available in the database on the clinical indication for a drug prescription. The diagnosis registered in the database was assumed to be correct for the purpose of our study although it was not confirmed with medical charts. However, a subsequent study recently confirmed that diagnoses recorded in the Medical Services database of Quebec are valid to identify patients with asthma.[178]

Nevertheless, given the likelihood that LABA/ICS could possibly have been prescribed in the treatment of other conditions; for example, chronic obstructive pulmonary disease (COPD), it was important that our study excludes those COPD patients and considers only patients suffering from asthma. To minimize this issue, patients included in our study had to be less than 45 years old at cohort entry.

Another important inclusion criteria in our study to minimize the between-group differences in severity for the evaluation of persistence and adherence was that patients needed to be exempt from having any recorded prescription of the regimens under study in the year prior to their entry in the cohort. The objective of this selection criteria

was to ensure that the selected patients were really new users, beginning either combination or concurrent LABA/ICS therapy at the time of inclusion in the cohort. Yet, there is still a potential for off-label prescription, as has likely occurred in Quebec with these ICS/LABA combination inhalers becoming a panacea for patients with symptoms of cough, dyspnea, or chest tightness.[82] This phenomenon might distort the result by increasing the rate of discontinuation since these patients would not necessarily be non-persistent if they were actually prescribed the medication for acute utilization. In our study this was not the case as the majority of patients were apparently found to be moderate to severe asthmatics as indicated in Table 1 of the article.

Source data – Administrative database studies

Administrative health-care claims databases offer a number of attractive features from which to form the evidence-base for conducting pharmacoecoepidemiologic studies; these features include the ready availability of data, real-world health-care practice patterns, potentially large sample sizes, and longer follow-up periods.[179] In Canada, the RAMQ and the Saskatchewan Health databases are widely used for pharmacoepidemiologic research. In the US, administrative databases from different health maintenance or managed care organization (Medicaid, for example) are used for the same purpose. In the UK, the General Research Practice Database (GPRD) has resulted in over 400 clinical reviews and papers[180]. In addition, administrative databases have been used specifically in asthma to address the issue of consistency in results from basic science, clinical trials, and observational experience, more specifically to validate observations from clinical trials, confirming that initial treatment with ICS and combined ICS/LABA treatment are the most effective stepwise approaches to the treatment of asthma.[181]

Some prescription claims databases may not contain all the required data to perform a prescription refill analysis. However, the accuracy, quality and comprehensiveness of the drug information contained in the provincial prescription claims database in Quebec (RAMQ) used for our study was assessed, analyzed and validated specifically so that it may be used to monitor drug exposure and physician prescribing. In the published validation study of the RAMQ database, it was concluded that the prescription claims database in Québec may represent one of the most accurate means of determining drugs dispensed to individuals.[158]

Prescription analyses compared to other measures

Previous compliance research in the field of asthma - assessing whether patients are taking their medication as prescribed - was based on different techniques, including blood-level monitoring (biochemical measures of theophylline), patient diaries (self-reported), physician opinion, measuring of the amount of drug used (weighing canisters), or electronic-device measures like a Turbuhaler Inhalation Computer or Nebulizer Chronolog.[140,182,183] It has been reported that self reports, patient diaries, and physician opinion tend to overestimate compliance.[167,183,184] In itself, eliminating the potential of recall bias for drug consumption constitutes a considerable advantage of using an administrative database to measure drug exposure[185]. In epidemiology, the recall bias is categorized as an observation bias whereby individuals may under-report their conditions or over-report utilization behaviors during questionnaire-based studies. In our study, we were able to follow patients for a duration of up to three years. In other types of study designs, losses to follow-up may occur as patients become too ill and interrupt their participation, while healthier individuals remain in the study, hence skewing the results.

Compliance measures using canister weight can be distorted by episodes of canister dumping, or expelling medication into the air before evaluation, as evidenced in the study by Rand et al.[182] A study by Braunstein et al.[183] measuring compliance report, physician rating, and canister weight, all gave significantly higher estimates of patient compliance than the Nebulizer Chronolog electronic method. Finally, assessing adherence through medical charts also has limitations since these may not always be complete in terms of information on prescribed medication, and prescribing behavior may vary due to the particularity of medical practice by physicians participating to research studies. The currently available electronic measure devices offer the most accurate and valid measurement of patient compliance[140,182,183,186], but that technology has been used only in a few studies.

Benefits of using an administrative database in our study

This study was designed and conducted to provide significant real-life information for asthma patients and their treating physicians in terms of adherence and persistence, which would stem from the reduced complexity offered by combination therapy regimens. Overall, these results help inform clinical practice about the utilization patterns of combination therapy, and highlight the unmet medical need in terms of persistence and adherence on controller asthma medication. On that basis, the main strength of this study is that our analyses were performed on a large population-based administrative database, with a large sample size, providing high statistical power to the analyses as well as population-based information that is highly representative of the real-life drug utilization for treating asthma in clinical practice.

Limitations of our study

One limitation of this study, inherent to claims database analyses, is the absence of clinical markers of asthma severity and control such as pulmonary function tests and symptoms scores. However, in our study, extremely useful markers of disease severity and control allowed us to match and adjust for the potential confounding effects of asthma severity and control. According to the Canadian Consensus[2] guidelines, disease severity must be evaluated prior to treatment initiation and monitored subsequently through regular follow-up visits once patients are under treatment. Assessing the dose of inhaled corticosteroids needed to provide control of symptoms may also be an indicator of severity, except in patients with very severe asthma who cannot be controlled with corticosteroids. The level of asthma control achieved by a patient is acknowledged to be a key clinical outcome measure in asthma management, and should also be assessed regularly once the patient is already under treatment. In pharmacy databases such as the RAMQ, the quantity of medication dispensed by the pharmacist has been used to impute a daily dose; drug refills are used as a proxy for drug consumption, which in turn approximates asthma severity and control. In our study, surrogate markers for both asthma severity and asthma control were used to define the study group at the one-to-one matching stage. Our surrogate markers of asthma severity consisted of the number of prescriptions of ICS filled in the year preceding cohort entry and the daily dose of ICS prescribed at cohort entry. We also assessed the number of prescriptions of oral corticosteroids and short-acting β_2-agonists as surrogate markers of asthma control. These markers were also included in our adjusted Cox regression model, along with patient's socio-demographic characteristics as well as health care resource utilization, such as ED visits and hospitalisations for asthma.

In addition, because the study was based entirely on computerized data of dispensed medications to estimate physician prescribing, the actual prescribing could be underestimated because not all prescriptions written for patient use are presented to the pharmacy[187] and the medicine supplied to the patient through pharmaceutical samples are not recorded either. Furthermore, dispensed prescriptions may not coincide exactly with the actual intake of medications (dose-timing, taking the medication within the prescribed time frame); patients may request refills regularly, even if they have not run out of drug, whereas others may stockpile medications or hold quantities of medications for their convenience[188]. This could potentially result in some misclassification of drug use[185] which, if present, might to some extent dilute the association between drug regimen and persistence. It is assumed by design that treatment gaps are due to noncompliance by the patient rather than drug discontinuation by the clinician. The use of administrative pharmacy claims data to analyze adherence and persistence is limited in that without additional clinical data from medical records, we are unable to determine either the medical reason for the start of a new asthma controller or the reason for non-adherence or non-persistence to the therapy.[161]

Linking a claims data analysis to medical records could further strengthen the study by providing indications on worsening factors such as smoking, exercising heavily, cold temperature and perhaps the level of allergens in each patient's environment. The source database used in our study had previously been validated[158] to mitigate the potential of inaccurate data recording and used in similar peer-reviewed published research studies.[189,190] This also ensures that the target population of patients starting a new treatment could accurately be identified in the database.

Study relevance and future research topics

Our results demonstrate that persistence and adherence on LABA/ICS controller therapies presently used in the prophylaxis of asthma remains very poor among adult asthmatic patients. The implication of our results for the treatment of asthma is important and this finding may even curtail the conclusions from the Stempel et al. and Stoloff et al. studies.[25,26] The latter was published earlier and recognized as the first substantive evidence that the use of ICS/LABA therapy in a combination inhaler improves compliance, and that this may contribute to the improved asthma control obtained with combination therapy in general practice.[191] Our results appear to be more in line with previous suggestions that compliance with inhalers dramatically diminish over time on treatment suggesting that long-term compliance or persistence to prescribed therapy is hard to attain.[192] It has been shown that non-compliance in asthma might contribute to its morbidity.[193] Clearly, our study showed that many patients still take their controller medication sporadically (even with the single-inhaler combination regimen) and we should question the impact of this phenomenon in relation to a patient's health, as well as on the use and cost of health care services. Although previous research had shown that simpler, less frequent dosing regimens resulted in better compliance across a variety of therapeutic classes[15], further research involving structured electronic monitoring of inhalers combined with pulmonary function measures may help elucidating the implications of the observed irregular use and discontinuation of combination drugs. Such measurements would clarify the question if it accurately measured the magnitude of compliance improvement and related benefits in terms of asthma outcomes. It is however reasonable to assume that sporadic asthma controller utilization behaviors may result in suboptimal clinical outcomes as evaluated in a real-life setting (effectiveness) and associated opportunity losses in terms of quality of life

and productivity. Still, additional research is needed to estimate the impact of sub-optimal use of controller therapy on asthma morbidity and use of health care services. Moreover, additional research linking patients' behavioral patterns to persistence and adherence might assist physicians in optimizing the asthma management of their patients. Amongst the strategies to ensure that the potential benefits suggested by clinical trials and observational studies can be translated into benefits at the clinical and population level[192], a stronger emphasis on the importance of regular treatment through patient education or interventions involving the assistance of pharmacists[170] might be considered.

CONCLUSION

Overall, combination therapy patients were found to be slightly more persistent than patients treated with ICS and LABA taken in two different inhalers. Adherence to the prescribed regimen during treatment persistence was slightly lower among users of combination than concurrent therapy. According to the results of our study, there is still very low persistence to inhaled controller therapies among adult asthmatic patients. This finding is important in that it reinforces the importance of addressing the issue of asthma management beyond merely reducing the complexity of drug regimens or administration. It suggests that patients are less likely to benefit from the clinically-proven efficacy of drugs due to non-persistence and non-adherence, however further research is needed to assess whether this difference in persistence in favor of combination therapy leads to better clinical outcome and effectiveness.

Table 1 . RAMQ anti-asthmatic medications list with drug codes

Common Coding	Drug Name	
364	aminophylline	
780	beclomethasone (dipropionate)	Inhaled only
45499	budesonide	Inhaled only
39419	cromoglicate sodique	
3380	epinephrine (bitartrate)	
3406	epinephrine (chlorhydrate)	
3419	epinephrine racemique (chlorhydrate)	
38548	fenoterol (bromhydrate)	
38730	flunisolide	Inhaled only
47050	fluticasone (propionate	Inhaled only
47231	formoterol (fumarate)	
47271	formoterol (fumarate dihydrate)	
43124	ipratropium (bromure)	
47186	ipratropium (bromure)/ salbutamol (sulfate)	
5083	isoproterenol (chlorhydrate)	
5096	isoproterenol (chlorhydrate)/ phenylephrine (bitartrate)	
5109	isoproterenol (chlorhydrate)/ phenylephrine (chlorhydrate)	
5070	isoproterenol (sulfate)	
45555	ketotifene (fumarate)	
47303	montelukast sodium	
47033	nedocromil sodium	
6721	orciprenaline (sulfate)	
43475	oxtriphylline	
47153	pirbuterol (acetate)	
45547	procaterol hemihydrate (chlorhydrate)	
10530	salbutamol	
33634	salbutamol (sulfate)	
47335	salmeterol (xinafoate) / fluticasone (propionate)	
47112	salmeterol (xinafoate)	
34180	terbutaline (sulfate)	
9464	theophylline	
9490	theophylline (aminoacetate calcium)	
9737	triamcinolone (acetonide)	Inhaled only
47266	zafirlukast	

Table 2. Canadian Consensus: Asthma Control Criteria

Daytime symptoms less than four days per week
Nightime symptoms less than one night per week
Normal physical activity
Mild, infrequent exacerbations
No absenteeism due to asthma
Fewer than four doses per week of a fast-acting beta2-agonist needed*
Forced expiratory volume in 1 second or peak expiratory flow at 90% of their personal best or greater
Diurnal variability in peak expiratory flow of less than 10% to 15%

Source: Can Respir J Vol 11 Suppl A May/June 2004[2]

Table 3. Canadian Consensus: Therapies currently used in asthma

Bronchodilators	**Anti-inflammatory therapies**
Inhaled short-acting β2-agonists: salbutamol, terbutaline, and fenoterol	Inhaled corticosteroids: budesonide, fluticasone proprionate, beclomethasone dipropionate
Inhaled long-acting β2-agonists: salmeterol and formoterol	Antileukotrienes: montelukast and zafirlucast
Inhaled anticholinergics: ipratropium bromide and tiotropium bromide	Cromones: disodium cromoglycate and nedocromil sodium
Theophylline: slow-release theophylline and aminophylline	Anti-immunoglobulin E: omalizumab

Data adapted from Canadian Consensus.
Source: Can Respir J Vol 11 Suppl A May/June 2004[2]

Table 4. Canadian Consensus: Classification of Asthma Severity

Severity	Symptoms	Treatment
Very severe	May be controlled or not well controlled	Short-acting beta-agonist use High doses of inhaled corticosteroids Additional therapy Oral corticosteroids
Severe	Well controlled	Short-acting beta-agonist use High doses of inhaled corticosteroids Additional therapy
Moderate	Well controlled	Short-acting beta-agonist use Low-to-moderate doses of inhaled corticosteroids ± Additional therapy
Mild	Well controlled	Short-acting beta-agonist use occasionally Low doses of inhaled corticosteroids
Very mild	Mild-infrequent	Short-acting beta-agonist use rarely

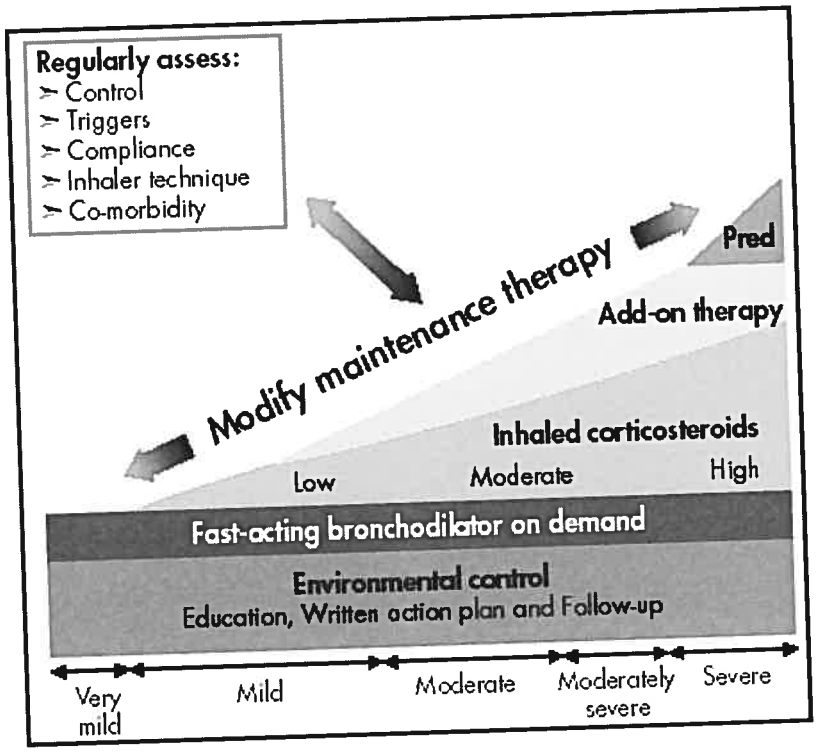
Source: Canadian Asthma Consensus Report, CMAJ 1999.[27]

Table 5. Asthma Interventions and Adherence Outcome*

	Intervention	Control	Adherence outcome
Bailey et al. 1990	Pamphlet, workbook, counseling, telephone, follow-up, support group	Severity of asthma symptoms Bothered by asthma Respiratory problems Impact on life	10-item checklist for inhaler use Self-Report scales Subjective health care scales
Cote et al. 1997	Asthma education program , Written self-management action plan, Symptom monitoring	Missed work Hospitalization ED visits Steroid Use	Weight of used canister
Gallefoss and Bakke 1999	Patient brochure, 2 group sessions (2h) 1 or 2 individual sessions (40 min) from both a nurse and a physiotherapist, individual treatment plan on the basis of the acquired personal information and 2 week of peak flow monitoring	Forced expiratory volume in 1 s Peak expiratory flow	Percentage dispensed divided by prescribed
Levy et al. 2000	Asthma consultation (1h) with study nurse, followed up by > 2 consultations (30 min) at 6 week intervals	Peak flow Symptoms scores Severe attacks Days off work Use of medical services	Adherence to self-management or moderate attacks Adherence to self-management of severe attacks
Van Es et al. 2001	Discussion of asthma management zone systems with pediatricians 4 individual sessions with asthma nurse 3 educational group sessions with asthma nurse	Force expiratory volume in 1 s Symptoms severity Hospital admissions Oral steroids	Self-report Physician estimate

* Adapted from MacDonald H. et al.[142]

Figure 1. Continuum of treatments for asthma management



Continuum of asthma management. Very mild asthma is treated with short-acting beta$_2$-agonists, taken as needed. Inhaled corticosteroids (ICSs) may be introduced as the initial maintenance treatment for asthma, even in subjects who report asthma symptoms less than three times per week. For patients who cannot or will not use ICSs, leukotriene receptor antagonist are an alternative, although they are less effective than low doses of ICSs. If asthma is not adequately controlled by low doses of ICSs, additional therapy should be considered. Addition of long-acting beta$_2$-agonist should be considered as the first option. As an alternative, addition of leukotriene receptor antagonitst or increasing ICSs to a moderate dose may be considered. Theophylline may be considered as a third therapeutic option. Severe asthma may require additional treatment with prednisone. Asthma control should be assessed at each visit, and maintenance therapy should be altered if necessary. Any alteration in medication therapy should be considered a trial, and effectiveness should be re-evaluated after a reasonable period of time. After achieving full control, the medication should be reduced to the minimum necessary to maintain control.

Source: Can Respir J Vol 11 Suppl A May/June 2004[2]

BIBLIOGRAPHIE (MEMOIRE)

[1] **Global Initiative for Asthma.** National Institute of Health. National Heart, Lung and Blood Institute, WHO. **2003 GINA Report** (available at www.ginasthma.com)

[2] **Lemière C,** Bai T, Balter M, et al. on behalf of the Canadian Adult Consensus Group of the Canadian Thoracic Society. **Adult Asthma Consensus Guidelines Update 2003.** Can Respir J 2004; 11 (Suppl A): 9A-18A.

[3] **Barnes PJ. Scientific rationale for inhaled combination therapy with long acting B2-agonists and corticosteroids.** Eur Respir J 2002; 19: 182-191.

[4] **NAEPP Coordinating Committee.** National Asthma Education and Prevention Program Expert Panel Report: **Guidelines for the Diagnosis and Management of Asthma Update on Selected Topics – 2002.** J Allergy Clin Immunol. November 2002. Vol. 11 No.5 pp. S141-S219.

[5] **Myo S**, Zhu X, Myou S, et al. **Additive blockade of b2-integrin adhesion of eosinophils by salmeterol and fluticasone.** Eur Respir J 2004; 23: 511–517.

[6] **Roth M**, Johnson PR, Rudiger JJ, et al. **Interaction between glucocorticoids and beta2 agonists on bronchial airway smooth muscle cells through synchronised cellular signalling.** Lancet 2002; 360: 1293–1299.

[7] **Mak JC**, Hisada T, Salmon M, Barnes PJ, Chung KF. **Glucocorticoids reverse IL-1beta-induced impairment of beta-adrenoceptor-mediated relaxation and up-regulation of G-protein-coupled receptor kinases**. Br J Pharmacol 2002; 135: 987–996.

[8] **Pang L**, Knox AJ. **Synergistic inhibition by b2-adrenoceptor agonists and corticosteroids on tumor necrosis factor- induced interleukin-8 release from cultured human airway smooth-muscle cells.** Am J Respir Cell Mol Biol 2000;23:79-85.

[9] **Nelson HS** et al. **Enhanced synergy between fluticasone propionate and salmeterol inhaled from a single inhaler versus separate inhalers.** J Allergy Clin Immunol 2003, 112: 29-36.

[10] **Remington** et al. **Long-acting beta-agonists: anti-inflammatory properties and synergy with corticosteroids in asthma.** Current opinion in pulmonary medicine. 2005 Vol 1, No. 1 p.74-8.

[11] **Greening AP**, Ind PW, Northfield M, Shaw G. **Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid.** Allen & Hanburys Limited UK Study Group. *Lancet* 1994;344:219–224

[12] **Shrewsbury S**, Pyke S, Britton M. **Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA).** *Br Med J* 2000;320:1368–1373

[13] **Campbell DA,** Robinson DS. **Cost advantages of combination asthma therapy.** Treat Respir Med. 2004;3(3):133-7.

[14] **Garcia-Marcos L** et al. **Inhaled corticosteroids plus long-acting B2-agonists as a combined therapy in asthma**. Expert Opin. Pharmacother. 2003. 4 (1). p. 23-39.

[15] **Claxton A.,** Cramer J, Pierce C. **A systematic review of the associations between dose regimens and medication compliance.** Clin Ther 2001;23(8). 1296-1310.

[16] **Coutts JAP,** Gibson NA, Paton JY. **Measuring compliance with inhaled medication in asthma**. Arch Dis Child 1992;67:332-3.

[17] **Chapman KR**, Walker L, Cluley S, Fabbri L. **Improving patient compliance with asthma therapy.** Respir Med 2000;94:2-9.

[18] **Cramer JA**, Mattson RH, Prevey ML, et al. **How often is medication taken as prescribed?** JAMA. 1989;261:3273-3277.

[19] **Greenberg RN. Overview of patient compliance with medication dosing: a literature review.** Clinical Therapeutics 1984;6(5):592-9.

[20] **Kelloway JS** et al. **Effect of salmeterol on patients' adherence to their prescribed refills for inhaled corticosteroids.** Ann Allergy Asthma Immunol 2000;84:324-328.

[21] **Holt S** et al. **Increasing compliance with inhaled corticosteroids through the use of combination therapy.** J Allergy Clin Immunol February 2004

[22] **Lotvall J. Combination therapy in asthma - fixed or variable dosing in different patients?** Curr Med Res Opin. 2004 Nov;20(11):1711-27.

[23] **Nelson HS. Advair: Combination treatment with fluticasone propionate/salmeterol in the treatment of asthma.** J Allergy Clin Immunol. Vol. 107. No. 2. February 2001.

[24] **Kuna P.** Kuprys I. **Symbicort Turbuhaler: a new concept in asthma management.** Int J Clin Pract. 2002 Dec;56(10):797-803.

[25] **Stoloff SW**, Stempel DA, Meyer J, Stanford RH, Carranza Rosenzweig JR. **Improved refill persistence with fluticasone propionate and salmeterol in a single inhaler compared with other controller therapies.** J Allergy Clin Immunol. 2004 Feb;113(2):245-51.

[26] **Stempel DA**, Stoloff SW, et al. **Adherence to asthma controller medication regimens.** Resp. Med. 2005 (99) 1263-1267.

[27] **Boulet LP**, Becker A, Bérubé D, Beveridge R, Ernst P, on behalf of the **Canadian Asthma Consensus Group Canadian asthma consensus report**, 1999 Can. Med. Assoc. J., Nov 1999; 161: (11Suppl):S1- 62.

[28] **Millar WJ**, Hill GB. **Childhood asthma.** Health Rep 1998;10:9-21 (ENG); 9-22 (FRE).

[29] **Masoli M,** Fabian D, Holt S, Beasley R. **The Global Burden of Asthma Report**, 2004

[30] **United States Department of Health and Human Services: Centers for Disease Control and Prevention. Surveillance for Asthma** - United States, 1960-1995, 2.

[31] **Centers for Disease Control and Prevention. Forecasted state-specific estimates of self-reported asthma prevalence- United States, 1998.** MMWR Morb Mortal Wkly Rep 1998; 47:1002-1025.

[32] **National Asthma Education and Prevention Program (NAEPP), Expert Panel Report 2. Guidelines for the Diagnosis and Management of Asthma.** Washington, DC: Dept of Health and Human Services; 1997. NIH Publication No. 97-4051.

[33] **Pew Environmental Health Commission. Attack asthma: why America needs a public health defense system to battle environmental threats.** Available at : http://www.pewtrusts.com/pdf/hhs_asthma.pdf. Accessed March 20, 2004.

[34] **National Institutes of Health. National Heart, Lung, and Blood Institute. Data fact sheet: asthma statistics.** January 1999.
Available at: http://www.nhlbi.nih.gov/health/prof/lung/asthma/asthstat.pdf. Accessed May 11, 2004.

[35] **The National Asthma Control Task Force. The prevention and management of asthma: A major challenge now and in the future.** Public Health Agency of Canada, 2000. **http://www.phac-aspc.gc.ca/publicat/pma-pca00/pdf/asthma00e.pdf.**

[36] **Statistics Canada**, CANSIM, tables 104-0001 and 105-0001 – catalog product number 82-221-XIF. Last modified date: 2005-02-17.
http://www40.statcan.ca/l02/cst01/health50a_f.htm Accessed July 15 2005.

[37] **British Columbia Lung Association. Asthma in Canada.**
http://www.bc.lung.ca/worldasthma/canadianpicture.htm Accessed July 15, 2005.

[38] **Statistics Canada.** National Population Health Survey: Asthma Supplementary Survey, 1996/97.

[39] **The Asthma Help Site.** The History of Asthma.
http://www.asthma-help.co.uk/historypda.htm Accessed March 1, 2005.

[40] **The Lung Association. Lung Facts.** 1994 Update

[41] **Harrison BD**, Pearson MG. Audit in acute severe asthma–who benefits? J R Coll Physicians Lond 1993;27:387-90.

[42] **Braganza S**, Sharif I, Ozuah PO. **Documenting asthma severity: do we get it right?** J Asthma 2003;40:661-665.

[43] **Wolfenden LL**, Diette GB, Krishnan JA, Skinner EA, Steinwachs DM, Wu AW. **Lower physician estimate of underlying asthma severity leads to undertreatment.** Arch Intern Med 2003;163:231-236.

[44] **Cockcroft DW,** Swystun VA. **Asthma control versus asthma severity**. J Allergy Clin Immunol 1996;98(6 pt 1):1016-1018.

[45] **Stempel DA**, McLaughin TP, Stanford RH, Fuhlbrigge AL. **Patterns of asthma control: A 3-year analysis of patient claims.** J Allergy Clin Immunol 2005. 115(5):935-939.

[46] **British Guideline on the Management of Asthma**. Thorax 2003;58(S1):i1-i94.

[47] **Asthma Management Handbook 1998, National Asthma Campaign.** South Melbourne, Australia: National Asthma Council Australia Ltd, ACN 058 044 634; 1998.

[48] **Ganse E**, Mo¨rk A-C, Osman LM, et al. **Factors affecting adherence to asthma treatment: patient and physician perspectives.** Primary Care Respiratory Journal 2003; 12: 46–61.

[49] **Barnes PJ. Inhaled glucocorticosteroids for asthma.** N Engl J Med 1995;332:868-75.

[50] **Barnes PJ**, Pedersen S. **Efficacy and safety of inhaled corticosteroids in asthma.** Am Rev Respir Dis 1993;148(Suppl):S1-26.

[51] **Haahtela T**, Jarvinen M, Kava T, Kiviranta K, Koskinen S, Lehtonen K, et al. **Comparison of β2-agonist, terbutaline, with an inhaled corticosteroid budesonide in newly detected asthma.** N Engl J Med 1991;325:388-92.

[52] **Juniper EF**, Kline PA, Vanzieleghem MA, Ramsdale EH, O'Byrne PM, Hargreave FE. **Effect of long-term treatment with an inhaled corticosteroid (budesonide) on airway hyperresponsiveness and clinical asthma in nonsteroid dependent asthmatics.** Am Rev Respir Dis 1990;142:832-6.

[53] **O'Byrne M**, Cuddy L, Taylor DW, Birch S, Morris J, Syrotuuik J. **Efficacy and cost benefit of inhaled corticosteroids in patients considered to have mild asthma in primary care practice.** Can Respir J 1996;3:169-75.

[54] **Blais L**, Ernst P, Boivin JF, Suissa S. **Inhaled corticosteroids and the prevention of readmission to hospital for asthma.** Am J Respir Crit Care Med 1998;158:126-32.

[55] **Malmstorm, K.;** Rodriguez-Gomez, G.; Guerra, J.; Villaran, C.; Pineiro, A.; Wei, L.X.; Seidenberg, B.C.; Reiss, T.F. **Oral montelukast, inhaled beclomethasone, and placebo for chronic asthma. A randomized controlled trial.** Ann. Intern. Med. 1999, 130, 487-495.

[56] **Busse, W.;** Raphael, G.D.; Galant, S.; Kalberg, C.; Goode-Sellers, S.; Srebro, S.; Edwards, L.; Rickard, K. **Low-dose fluticasone propionate compared with montelukast for first- line treatment of persistent asthma: a randomized clinical trial.** J. Allergy Clin. Immunol. 2001, *107*(3), 461-468.

[57] **Suissa S**, Ernst P, Kezouh A. **Regular use of inhaled corticosteroids and the long term prevention of hospitalisation for asthma**. Thorax. 2002 Oct;57(10):880-4.

[58] **Blais L**, Ernst P, Boivin JF, Suissa S. **First treatment with inhaled corticosteroids and the prevention of admissions to hospital for asthma**. Thorax 1998; 53:1025-1029

[59] **Suissa S et al. Low-dose inhaled corticosterioids and the prevention of death from asthma.** N Engl J Med 2000; 343:332-336.

[60] **Williams SG**, Schmidt DK, Redd, SC et al. **Key clinical activities for quality asthma care. Recommendations of the National Asthma Education and Prevention Program.** MMWR Recomm Rep. 2003 Mar 28;52 RR-6: 1-8.

[61] **Stafford RS et al. Asthma, rhinitis, other respiratory diseases. National trends in asthma visits and asthma pharmacotherapy, 1978-2002**. J Allergy Clin Immunol. April 2003. Volume 111. No. 4 p.729-735.

[62] **Boulet, L.P.;** Bai, T.R.; Becker, A.; Bérubé, D.; Beveridge, R.; Bowie, D.M.; Chapman, K.R.; Côté, J.; Cockcroft, D.; Ducharme, F.M.; Ernst, P.; FitzGerald, J.M.;

Kovesi, T.; Hodder, R.V.; O'Byrne, P.; Rowe, B.; Sears, M.R.; Simons, E.R.; Spier, S. **What is new since the last (1999) Canadian Asthma Consensus Guidelines?** Can. Respir. J. **2001**, *8* Suppl A, 5A-27A.

[63] **Gillissen A. Managing asthma in the real world** Int J Clin Pract, June 2004, 58, 6, 592–603

[64] **Selroos O**, Pietinalho A, Lo¨froos A-B, Riska H. **Effect of early vs late intervention with inhaled corticosteroids in asthma.** Chest 1995; 108: 1228–34.

[65] **Pauwels RA**, Pedersen S, Busse WW et al. **Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial**. Lancet 2003; 361: 1071–6.

[66] **Laitinen A**, Altraja A, Kampe M et al. **Tenascin is increased in airway basement membrane of asthmatics and decreased by an inhaled steroid**. Am J Respir Crit Care Med 1997; 156: 951–8.

[67] **Woolcock A**, Lundback B, Ringdal N, et al. **Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids.** Am J. Respir Crit Care Med 1996; 153:1481-8.

[68] **Busse WW**, Chervinsky P, Condemi J. et al. **Budesonide delivered by Turbuhhaler is effective in a dose-dependent fashion when used in the treatment of adult patients with chronic asthma.** J Allergy Clin Immunol 1998;101:457-63.

[69] **Dahl R,** Lundback B, Malo J, et al. **A dose-ranging study of fluticasone propionate in adult patients with moderate asthma.** Chest 1998; 104:352-8.

[70] **Heyneman CA**, Crafts R, Holland J, et al. **Fluticasone vs. salmeterol/low-dose fluticasone for long-term asthma control.** Ann Pharmacother 2002, 36:1944-1949.

[71] **Matz J**, Emmett A, Rickard K, et al. **Addition of salmeterol to low-dose fluticasone versus higher-dose fluticasone: an analysis of asthma exacerbations**. J Allergy Clin Immunol 2001;107(5):783-9.

[72] **Condemi JJ**, Goldstein S, Kalberg C, et al. **The addition of salmeterol to fluticasone propionate versus increasing the dose of fluticasone propionate in patients with persistent asthma: Salmeterol Study Group.** Ann Asthma Immunol 1999;82(4):383-9.

[73] **Bateman ED**, Boushey HA, Bousquet J, Busse WW, Clark TJH, Pauwels RA et al. **Can guideline-defined asthma control be achieved? The gaining optimal asthma control study.** Am J Respir Crit Care Med 2004;170:836–844.

[74] **Pauwels RA**, Lofdahl CG, Postma DS, et al. **Effect of inhaled formoterol and budesonide on exacerbations of asthma**. N Engl J Med 1997;337:1405-11.

[75] **O'Byrne PM**, Barnes PJ, Rodriguez-Roisin R, et al. **Low dose inhaled budesonide and formoterol in mild persistent asthma. The OPTIMA randomized trial.** Am J Respir Crit Care Med 2001;164:1392-7.

[76] **Baumgarten C**, Geldszus R, Behre U, Peslis N, Trautmann M, Viani-Initial Study Group. **Initial treatment of symptomatic mild to moderate bronchial asthma with the salmeterol/fluticasone propionate (50/250 microg) combination product (SAS 40023)**. Eur J Med Res 2002;7:1-7.

[77] **Nelson HS**, Busse WW, Kerwin E, Church N, Emmett A, Rickard K, et al. **Fluticasone propionate/salmeterol combination provides more effective asthma control than low-dose inhaled corticosteroid plus montelukast**. J Allergy Clin Immunol 2000;106:1088-95.

[78] **Busse W**, Nelson J, Wolfe J, Kalberg C, Yancey SW, Rickard K. **Comparison of inhaled salmeterol and oral zafirlukast in patients with asthma.** J Allergy Clin Immunol 1999;103:1075-80.

[79] **Davies B**, Brooks G, Devoy M. **The efficacy and safety of salmeterol compared with theophylline: meta-analysis of nine controlled studies.** Respir Med 1998;92:256-63.

[80] **Mak JC**, Nishikawa M, Barnes PJ. **Glucocorticoids increase B 2-adrenergic receptor transcription in human lung.** Am J Physiol 1995;268:L41-6

[81] **Chung KF**, Adcock IM. **Combination therapy of long-acting beta2-adrenoceptor agonists and corticosteroids for asthma.** Treat Respir Med. 2004;3(5):279-89.

[82] **Mayers I**, Damant R. **Role of combination inhaled corticosteroids and long acting beta agonists in the treatment of adult asthma** [Issues in emerging health technology issue #68]. Ottawa: Canadian Coordinating Office for Health Technology Assessment; June 2005.

[83] **Boulet LP. Long- versus short-acting beta 2-agonists. Implications for drug therapy.** Drugs 1994;47(2):207-22.

[84] **Labrecque M**, Laurier C, Champagne F, Kennedy W, Pare M, Cartier A. **Effect of age on the conformity rate to short-acting beta-agonist use criteria in asthma.** J Asthma. 2003;40(7):829-35.

[85] **Hardman JG,** Limbird LE. Goodman & Gilman's: **The Pharmacological Basis of Therapeutics.** McGraw-Hill 2001;643–733.

[86] **Tattersfield AE**, Lofdahl CG, Postma DS, Eivindson A, Schreurs AG, Rasidakis A, et al. **Comparison of formoterol and terbutaline for as-needed treatment of asthma: a randomised trial.** Lancet 2001;357(9252):257-61.

[87] **Becker A**, Lemiere C et al., on behalf of the Asthma Guidelines Working Group of the Canadian Network For Asthma Care* and the Canadian Thoracic Society†. **Summary of recommendations from the Canadian Asthma Consensus Guidelines, 2003 and Canadian Pediatric Asthma Consensus Guidelines, 2003 (updated to December 2004)** CMAJ 2005; 173 (6 suppl): S1–S56.

[88] **Lazarus SC**, Boushey HA, Fahy JV, et al. **Long-acting beta2-agonist monotherapy vs continued therapy with inhaled corticosteroids in patients with persistent asthma: A randomized controlled trial.** JAMA 2001;285:2583-93.

[89] **Lemanske RF** Jr, Sorkness CA, Mauger EA, et al. **Inhaled corticosteroid reduction and elimination in patients with persistent asthma receiving salmeterol: A randomized controlled trial.** JAMA 2001;285:2594-603.

[90] **Wooltorton E. Salmeterol (Serevent) asthma trial halted early.** CMAJ 2003;168:738.

[91] **Zetterstrom O**, Buhl R, Mellem H, et al. **Improved asthma control with budesonide/formoterol in a single inhaler, compared with budesonide alone.** Eur Respir J 2001; 18(2):262-8.

[92] **Lalloo UG**, Malolepszy J, Kozma D, et al. **Budesonide and formoterol in a single inhaler improves asthma control compared with increasing the dose of corticosteroid in adults with mild-to-moderate asthma**. Chest 2003; 123(5):1480-7.

[93] **Ringdal** et al. **Evaluation of different inhaled combination therapies (EDICT): a randomised, double-blind comparison of Seretide (50/250 microg bd Diskus vs. formoterol (12 microg bd) and budesonide (800 microg bd) given concurrently (both via Turbuhaler) in patients with moderate-to-severe asthma.** Respir Med. 2002 Nov;96(11):851-61.

[94] **Aubier M**, Pieters WR, Schlosser NJ, Steinmetz KO. **Salmeterol/fluticasone proprionate (59/500g) in combination in a Diskus inhaler (Seretide) is effective and safe in the treatment of steroid-dependent asthma.** Respir. Med. 1999. 93:876-884.

[95] **Kavuru M**, Melamed J, Gross G, et al. **Salmeterol and fluticasone proprionate combined in a new powder inhalation for the treatment of asthma: a randomized, double-blind, placebo-controlled trial.** J Allergy Clin Immmunol 2000; 105(1):1108-16.

[96] **Shapiro G**, Lumry W, Wolfe J, et al. **Combined salmeterol 50ug and fluticasone propionate 250ug in the discus device for the treatment of asthma.** Am J Respir Crit Care Med 2000; 161:527-34.

[97] **Jenkins C**, Woolcock AJ, Saarelainen P, et al. **Salmeterol/fluticasone propionate combination therapy 50/250ug twice daily in treating moderate to severe asthma.** Respir Med 2000;94:715-23.

[98] **Chapman KR**, Ringdal N, Backer V, et al. **Salmeterol and fluticasone propionate (50/250 microg) administered via combination Diskus inhaler: as effective as when given via separate Diskus inhalers.** Can Respir J 1999; 6 (!)45-51.

[99] **Pearlman DS**, Stricker W, Weinstein S, et al. **Inhaled salmeterol and fluticasone: a study comparing monotherapy and combination therapy in asthma.** Ann Allergy Asthma Immunol 1999; 82(3):257-65.

[100] **Goldsmith DR**, Keating GM **Budesonide/formoterol: a review of its use in asthma.** Drugs. 2004;64(14):1597-618.

[101] **Leuppi JD et al. An individualized, adjustable maintenance regimen of budesonide/formoterol provides effective asthma symptom control at a lower overall dose than fixed dosing**. Swiss Med Wkly 2003; 133: 302-309.

[102] **Masoli M**, Williams M, Weatherall M, Beasley R. **The 24h duration of bronchodilator action of the budesonide/formoterol combination inhaler.** Respir Med. 2005 Jun 2; [Epub ahead of print]

[103] **Ankerst J. Combination inhalers containing inhaled corticosteroids and long-acting beta(2)-agonists : Improved Clinical Efficacy and Dosing Options in Patients with Asthma.** J Asthma. 2005 Dec; 42 (9):715-24.

[104] **Miller NH et al.** Expert Panel on Compliance. **The multi-level compliance challenge : Recommendations for a call to action. A Statement for Health Care Professionals.** Circulation 1997; 95: 1085-1090.

[105] **Col N**, Fanale JE, Kronholm P. **The role of medication non-compliance and adverse drug reactions in hospitalizations of the elderly.** Archives of Internal Medicine 1990;150(4):841-5.

[106] **Balkrishnan R. Predictors of medication adherence in the elderly.** Clinical Therapeutics 1998;20(4):764-71.

[107] **Lau HS**, Beuning KS, Postma-Lim E, et al. **Non-compliance in elderly people: evaluation of risk factors by longitudinal data analysis.** Pharmacy World Science 1996;18:63-8.

[108] **Eisen SA**, Miller DK, Woodward RS, et al. The **effect of prescribed daily dose frequency on patient medication compliance.** Archives of Internal Medicine 1990;150:1881-4.

[109] **Rosenhall L,** Elvstrand A, Tilling B, Vinge I, Jemsby P, Stahl E, Jerre F, Bergqvist PB. **One-year safety and efficacy of budesonide/formoterol in a single inhaler (Symbicort Turbuhaler) for the treatment of asthma.** Respir Med. 2003 Jun;97(6):702-8.

[110] **Barnes PJ**. **Asthma guidelines: recommendations versus reality.** Respir Med. 2004 Apr;98 Suppl A:S1-7.

[111] **Cochrane M.G.,** Bala, MV; Downs K.E., Mauskopf J; Ben-Joseph R.H. **Inhaled corticosteroids for asthma therapy. Patient compliance, devices, and inhalation technique.** Chest **2000**, *117*(2), 542-550.

[112] **Blais R,** Gregoire J.P., Rouleau R, Cartier A, Bouchard J, Boulet, L.P., **Ambulatory use of inhaled beta(2)-agonists for the treatment of asthma in Quebec : a population-based utilization review.** Chest 2001, 119(5), 1316-1321.

[113] **Dorais M**, Blais L, Chabot I, LeLorier J. **Treatment persistence with leukotriene-receptor antagonists and inhaled corticosteroids**, Journal of Asthma 2005; 42(5): 385-93.

[114] **Sidel J,** Ryan K, Nemis-White J. **Shaping the healthcare environment through evidence-based medicine: a case study of the ICONS project.** Hosp Q. 1998 Fall;2(1):29-33.

[115] **Coambs RB**, Jensen P, Thao Ther M, Ferguson BS, Lamy JL, Wong JSW, Abrahamson RV. **Review of the scientific literature on the prevalence, consequence and health costs of non-compliance & inappropriate use of prescription medication in Canada.** University of Toronto Press 1995.

[116] **Claesson S**, Morrison A, Wertheimer AI, et al. **Compliance with prescribed drugs: challenges for the elderly population.** Pharmacy World and Science 1999;21(6):256-9.

[117] **JNC VI. The sixth report of the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI).** Archives of Internal Medicine 1997;157:2413-46.

[118] **Vlasnik et al. Medication adherence: Factors influencing compliance with prescribed medication plans.** The Case Manager. Volume 16, Issue 2, March –April 2005. Pages 47-51. Available online 07 April 2005.

[119] **Roter DL**, Hall JA, Merisca R, et al. **Effectiveness of interventions to improve patient compliance – a meta-analysis.** Med. Care 1998;36(8):1138-61.

[120] **Bachman R., Better compliance and medicine use: Making it happen.** Pharm Times. April 1993: 77-83.

[121] **Dunbar-Jacob J,** Erlen JA, Schlenk EA, Ryan CM, Sereika SM, Doswell WM. **Adherence in chronic disease.** Annual Review of Nursing Research 2000, 18:48-90.

[122] **Borgstrom L et al. Lung deposition of budesonide inhaled via Turbuhaler: a comparison with terbutaline sulphate in normal subjects.** Eur Respir J 1994; 7:69–73

[123] **Dunbar-Jacob J**, Burke LE, Puczynski S. **Clinical assessment and management of adherence to medical regimens** In: Managing chronic illness. A biopsychological perspective (Nicassio M, Smith T., eds), American Psychological Association, Washington D.C., 1995: 313-341.

[124] **Williams LK**, Pladevall M, Xi H, Peterson EL, Joseph C, Lafata JE, Ownby DR, Johnson CC. **Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma.** J Allergy Clin Immunol. 2004 Dec;114(6):1288-93.

[125] **Wasserfallen J-B**, Baraniuk JN. **Clinical use of inhaled corticosteroids in asthma.** J Allergy Clin Immunol 1996;97(1 Pt 2):177–182.

[126] **Milgrom H**, Bender B, Ackerson L, Bowry P, Smith B, Rand C. **Noncompliance and treatment failure in children with asthma.** J Allergy Clin Immunol 1996;98(6):1051–1057.

[127] **Bender B**, Milgrom H, Rand C, Ackerson L. **Psychological factors associated with medication nonadherence in asthmatic children.** J Asthma 1998;35(4):347–353.

[128] **Rau JL. Determinants of Patient Adherence to an Aerosol Regimen.** Respir Care 2005;50(10):1346-1356.

[129] **Woude van der et al. Compliance with inhaled glucocorticoids and concomitant use of long-acting b2-agonists.** Respir Medicine (2001) 95, 404–407.

[130] **Jones C** et al. **Adherence to Prescribed Treatment for Ashtma: Evidence form Pharmacy Benefits data.** Journal of asthma. 2003; 40 (1) 93-101.

[131] **Kerstjens HA**, Brand PL, Hughes MD, Robinson NJ, Postma DS, Sluiter HJ, et al. **A comparison of bronchodilator therapy with or without inhaled corticosteroid therapy for obstructive airways disease**. Dutch Chronic Non-Specific Lung Disease Study Group. N Engl J Med 1992; 327:1413-9.

[132] **Lacasse Y**, Archibald H, Ernst P, Boulet LP. **Patterns and determinants of compliance with inhaled steroids in adults with asthma.** Can Respir J. 2005 May-Jun;12(4):211-7.

[133] **Apter AJ et al. Modifiable barriers to adherence to inhaled steroids among adults with asthma: it's not just black and white.** J Allergy Clin Immunol. 2003 Jun;111(6):1219-26.

[134] **Rudd P. In search of the gold standard for compliance measurement.** Arch Intern Med 1979; 139:627-628.

[135] **Beardon PHG**, MgGilchrist MM, McDevitt DG, MacDonald TM. **Primary non-compliance with prescribed medication in primary care**. BMJ 1993;307:846–8.

[136] **Marinker M.** Personal paper: **writing prescriptions is easy**. BMJ 1997;314:747–8.

[137] **Carter S**, Taylor D, Levenson R. **A question of choice—compliance in medicine taking**. 2nd ed. London: Medicines Partnership; 2003.

[138] **Paterson C. et al. A narrative review shows the unvalidated use of self-report questionnaires for individual medication as outcome measures** Journal of Clinical Epidemiology Volume 58, Issue 10 , October 2005, p. 967-973

[139] **Green LW**, Mullen PD, Friedman RB. **Epidemiological and community approaches to patient compliance.** In: Cramer JA, Spilker B, Eds. Patient Compliance in Medical Practice and Clinical Trials. New York: Raven Press; 1991:373-386.

[140] **Bosley CM**, Parry DT, Cochrane GM. **Patient compliance with inhaled medication : does combining beta-agonists with corticosteroids improve compliance?** Eur Respir J 1994;7:504-9.

[141] **Simmons MS**, Nides MA, Kleerup EC, Chapman KR, Milgrom H, Ran CS. Et al. **Validation of the Doser, a new device for monitoring metered-dose inhaled use.** J Allergy Clin Immonuol 1998;102:409-13.

[142] **MacDonald HP**, Garg AX, Haynes BR. **Interventions to enhance patient adherence to medications prescriptions.** JAMA. 2002 288; 2868-2869.

[143] **Morris NV**, Abramson MJ, Rosier MJ, Strasser RP. **Assessment of the severity of asthma in a family practice.** J Asthma 1996;33:425–39.

[144] **DiMatteo MR**, Robinson JD, Heritage J, et al. **Correspondence among patients' self reports, chart records, and audio/videotapes of medical visits.** Health Commun. 2003;15:393–413.

[145] **Hays RD**, DiMatteo MR. **Key issues and suggestions, sources of information, focus of measures, and nature of response options**. Journal of Compliance in Health Care. 1987;2:37–53.

[146] **Butz AM et al. Monitoring nebulizer use in children: comparison of electronic and asthma diary data.** Ann Allergy Asthma Immunol. 2005 Mar;94(3):360-5

[147] **Urquhart J**. Biological measures. In: Burke LE, Ockene IS, eds. **Compliance in Healthcare and Research.** Armonk, NY: Futura; 2001:105–116.

[148] **DiMatteo R. Variations in Patients' Adherence to Medical Recommendations. A quantitative Review of 50 years of Research.** Medical Care. Vol. 42 (3) March 2004

[149] **Steiner JF**, Prochazka AV. **The assessment of refill compliance using pharmacy records: methods, validity, and applications**. J Clin Epidemiol 1997;50:105-116.

[150] **Anderson RB**, Hollenberg NK, Wiliams GH: **Physical Symptoms Distress Index: a sensitvite tool to evaluate the impact of pharmacological agents on quality of life.** Archives of Internal Medicine 1999, 159:693-700.

[151] **Diamond R. Drugs and the quality of life: the patient's point of view.** Journal of Clinical Psychiatry 1985,46: 29-35.

[152] **Balkrishnan R**, Nelsen LM, Kulkarni AS, Pleasants RA, Whitmire JT, Schechter MS. **Outcomes associated with initiation of different controller therapies in a Medicaid asthmatic population: a retrospective data analysis.** J Asthma. 2005 Feb;42(1):35-40.

[153] **Lloyd AJ. The extent of patient' understanding of the risk of treatments.** Quality in Health Care 2001, 10(Suppl 1): i14-i18.

[154] **Bowling A**, Ebrahim S. **Measuring patients' preferences for treatment and perceptions of risk.** Quality in Health Care 2001,10(Suppl 1):i2-i8.

[155] **Régie de l'assurance maladie du Québec.** Health Ministry, Goverment of Québec, Québec: Régie de l'assurance maladie du Québec; 1997.

[156] **World Health Organization. International classification of diseases. Manual of the international statistical classification of diseases, injuries, and cause of death. 9th revision.** Geneva, Switzerland: World Health Organization, 1977 (Publication no. PHS 80-1260).

[157] **Blais L**, Beauchesne M-F. **Use of inhaled corticosteroids following discharge from an emergency department for an acute exacerbation of asthma**, Thorax 2004; 59(11): 943-947.

[158] **Tamblyn R**, Lavoie G, Petrella L et al. **The use of prescription claims database in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Quebec.** J Clin Epidemiol 1995;48:999-1009.

[159] **Sin BA**, Akkoca O, Saryal S, Oner F, Misirligil Z. **Differences between asthma and COPD in the elderly.** J Investig Allergol Clin Immunol. 2006;16(1):44-50.

[160] **Yeung M**, O'Connor SA, Parry DT, Cochrane GM. **Compliance with prescribed drug therapy in asthma.** Respir Med 1994;88:31-5.

[161] **Jones C** et al. **Adherence to Prescribed Treatment for Asthma: Evidence from Pharmacy Benefits Data**. J of Asthma. Vol. 40, No. 1, 2003, pp. 93-101.

[162] http://www.ncss.com/pass.html NCSS Statistical Software. Accessed June 1, 2005.

[163] **Kalbfleisch JP**. Prentice RL (Eds). **The Statistical Analysis of Failure Time Data.** John Wiley & Sons, 1980.

[164] http://www.ceso.duke.edu/servlet/CesoController?actionH=layers&menuNum=1&id=4&layer=layer5 Center for Excellence in Surgical Outcomes© - Duke University Medical Center. Accessed July 10, 2005.

[165] **Lee E.T. Nonparametric methods for comparing survival distributions. Statistical methods for survival data analysis; 2nd Ed.**; Wiley Series in Probability and Mathematical Statistics: A probability and Statistics Section, John Wiley & Sons: New York, 1992; 482 pages.

[166] **Kleinbaum DG**, et al. **Applied Regression Analysis and Other Multivariable Methods (3rd edition).** Duxbury Press 1998.

[167] **Dompeling E**, van Grunsven PM, van Schayck CP, et al. **Treatment with inhaled steroids in asthma and chronic bronchitis: long-term compliance and inhaler technique.** Fam Pract 1992, 9:161-166.

[168] **Chmelik F**, Doughty A. **Objective measurements of compliance in asthma treatment.** Ann Allergy 1994;73:527-32.

[169] **Willey C**, Redding C. Stafford J, et al. **Stages of change for adherence with medication regimens for chronic diseases: Development and validation of a measure** Clin Ther 2000; 22 (7): 858-871.

[170] **Wahl C**, Gregoire JP, Teo K, Beaulieu M, Labelle S, Leduc B, Cochrane B, Lapointe L, Montague T. **Concordance, compliance and adherence in healthcare: closing gaps and improving outcomes** Healthc Q. 2005;8(1):65-70.

[171] **Bates DV**, Sizto R. **Air pollution and hospital admissions in Southern Ontario: the acid summer haze effect.** Environ Res 1987;43:317-31.

[172] **Persky VW**, Slezak J, Contreras A, et al. **Relationship of race and socioeconomic status with prevalence, severity, and symptoms of asthma in Chicago school children.** Ann Allergy Asthma Immunol 1998; 81:266-271.

[173] **Litonjua AA**, Carey Vj, Weiss ST, et al. **Race, socioeconomic factors, and area of residence are associated with asthma prevalence.** Pediatr Pulmonol 1999; 28:394-401.

[174] **Bukstein DA,** Henk, HJ, Luskin, AT. **A comparison of asthma-related expenditures for patients started on montelukast versus fluticasone propionate as monotherapy.** Clin. Ther. 2001, 23(9), 1589-1600.

[175] **Stempel DA**, Mauskopf, J, McLaughlin, T.; Yazdani, C.; Stanford, R.H. **Comparison of asthma costs in patients starting fluticasone propionate compared to patients starting montelukast.** Respir. Med. 2001, 95(3), 227-234.

[176] **Shapiro S. The role of automated record linkage in the post-marketing surveillance of drug safety: A critique.** Clin Pharmacol Ther 1989; 46:371-386.

[177] http://www.gsk.ca/en/health_info/serevent_safety_letter_en.pdf Accessed August 25, 2005.

[178] **Blais L**, Lemiere C, Menzies D, Berbiche D. **Validity of asthma diagnoses recorded in the Medical Services database of Quebec.** Pharmacoepidemiol Drug Saf. 2005 Dec 23.

[179] **Dasbach EJ. The Use of Claims Databases in Pharmacoeconomic Studies** Value in Health, Volume 6, Number 2, 2003.

[180] www.gprd.com Accessed August 25, 2005.

[181] **Spahn J**, Covar R, Stempel DA. **Asthma: addressing consistency in results form basic science, clinical trials, and observational experience.** J Allergy Clin Immunol. 2002 May; 109(5 Suppl):S490-502.

[182] **Rand CS**, Wise RA. **Measuring adherence to asthma medication regimens.** Am J Respir Crit Care Med 1994;149:S69-S76.

[183] **Braunstein GL**, Trinquet G, Harper AE, et al. **Compliance with nedocromil sodium and a nedocromil sodium/salbutamol combination**. Eur Respir j 1996; 9:893-898.

[184] **Mihalko SL et al. Challenges and innovations in enhancing adherence.** Controlled Clinical Trials 25 2004. 447-457.

[185] **Lynd LD et al. Patterns of Inhaled Asthma Medication Use. A 3-year longitudinal analysis of prescription claims data from British Columbia, Canada.** Chest December 2002; 122:6, 1973-1981.

[186] **Coutts JAP**, Gibson Na, Pateon Jy. **Measuring compliance with inhaled medication in asthma**. Arch Dis Child 1991; 67:332-333.

[187] **Allen-Reamey FC**, Samet JM, Rand CS et al. **Trends in use of inhaled-corticosteroids for asthma management: 1994-1998.** Ann Epidemiol 2004, 14: 161-167.

[188] **Cramer JA**, Spilker B, eds. **Patient Compliance in Medical Practice and Clinical Trials**. New York: Raven Press; 1991.

[189] **Blais L**, Beauchesne M-F. **Use of inhaled corticosteroids following discharge from an emergency department for an acute exacerbation of asthma**, Thorax 2004; 59(11): 943-947.

[190] **Blais R**, Grégoire J-P, Rouleau R, et al. **Ambulatory use of inhaled b2-agonists for the treatment of asthma in Quebec. A population-based utilization review.** Chest 2001;119:1316–21.

[191] **Holt S**, Beasley DM. **Increasing compliance with inhaled corticosteroids through the use of combination therapy.** J Allergy Clin Immunol February 2004.

[192] **Cochrane GM**. **Compliance and outcomes in patients with asthma.** Drugs 1996;52:12.

[193] **Horn CR**, Clark TJH, Cohchrane GM. **Compliance with inhaled therapy and morbidity from asthma.** Respir Med 1990;84:67-70.