Inhaled Corticosteroids and the risk of exacerbations in Chronic Obstructive Pulmonary Disease

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfilment of the requirements of the degree of Masters of Science

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covered in the introduction to each paper), a final conclusion and summary, a thorough bibliography, and an appendix containing an ethics certificate in the case of research involving human or animal subjects, microorganisms, living cells, other biohazards and/or radioactive material.

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Abstract

In this thesis, composed of two separate articles, we studied the frequency of COPD exacerbations and assessed the effectiveness of inhaled corticosteroids in preventing a first exacerbation of COPD. We used an inception cohort of COPD patients, formed from the computerised databases of Saskatchewan.

The rate of COPD exacerbations was 11.5 per 100 person-years. It increased with age and was 50% higher in men than women. Use of inhaled corticosteroids in the year prior to the index date and current use were associated with a small increase in the risk of a first exacerbation (adjusted RR=1.27, 95% CI: 1.08-1.48 and 1.51, 95% CI: 1.22-2.87, respectively). The risk increased with increasing daily dose (adjusted RR per 1000 µg=1.83, 95% CI: 1.47-2.28).

We did not find that the use of inhaled corticosteroids reduces the risk of a first exacerbation in patients with COPD.

RESUMÉ

Dans cette thèse, composée de deux articles, nous avons étudié la fréquence d'exacerbations liées à la broncho-pneumopathie chronique obstructive (BPCO), et avons évalué l'efficacité des corticostéroïdes en inhalation dans la prévention d'une première exacerbation de BPCO. Nous avons utilisé une cohorte de patients atteints de BPCO formée à partir des bases de données du Saskatchewan.

Le taux d'exacerbations de BPCO était de 11.5 par 100 années-personnes et croissant avec l'âge. Le taux d'exacerbations était de 50% plus élevé chez les hommes que chez les femmes.
L'utilisation des corticostéroïdes en inhalation dans l'année précédente et l'utilisation courante étaient associées à une légère augmentation du risque relatif d'une première exacerbation (RR ajusté = 1.27, intervalle de confiance de 95%: 1.08-1.48 et 1.51, intervalle de confiance de 95%: 1.22-2.87, respectivement). Le risque augmentait avec la dose moyenne par jour (RR ajusté par 1000 µg = 1.83, intervalle de confiance de 95%: 1.47-2.28.)

Il n'a pas été possible de démontrer que l'utilisation des corticostéroïdes inhalés diminue le risque d'une première exacerbation chez les patients atteints de BPCO.

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My greatest appreciation goes to my family, especially my parents. Their seemingly endless support and beliefs have enabled me to progress through this program with confidence. This thesis is dedicated to them.

Contribution of Authors

The thesis document includes the text of two articles to be submitted for publication.

Dr. Samy Suissa acted as primary thesis supervisor and Dr. Ernst as co-supervisor. Dr. Suissa was responsible for the research question. Both Dr. Suissa and Dr. Ernst were responsible for establishing appropriate measurement procedures and for designing the study. Magda Melo, MSc candidate, was responsible for carrying out the literature review and performing the statistical analysis; interpreting; organising and presenting the results; and writing the manuscript. Dr. Suissa and Ernst reviewed drafts of the articles, as well as the remaining chapters that compose this thesis.

Disclaimer

This study is based in part on non-identifiable data provided by the Saskatchewan Department of Health. The interpretation and conclusions contained herein do not necessarily represent those of the Government of Saskatchewan or the Saskatchewan Department of Health.

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Chapter 1: Introduction

1. Introduction

This thesis consists of two articles, one pertaining to rates of disease exacerbation in chronic obstructive pulmonary disease (COPD), and the other to the effectiveness of inhaled corticosteroids, currently widely used in the treatment of the symptoms of COPD.

The first article is a descriptive study of the rates of exacerbation of COPD patients according to demographic determinants and duration of the disease. The second article describes the effectiveness of inhaled corticosteroids in preventing a first exacerbation of COPD in newly diagnosed patients, in particular those who had never previously experienced a moderate or severe exacerbation of their disease.

This first chapter is divided into four sections. First, a review of what is known about clinical aspects of COPD and, in particular, acute exacerbations and burden of the disease will be presented. This is followed by a section on the pharmacological properties of inhaled corticosteroids, with emphasis on their role in controlling inflammation. The third section is a literature review of published studies that were designed to evaluate the role of inhaled corticosteroids in COPD. Finally, the rationale and objectives of the two studies presented in this thesis will be stated.

1.1. Chronic Obstructive Pulmonary Disease

Chronic Obstructive Pulmonary Disease (COPD) is defined by the American Thoracic Society (ATS) as a condition characterised, clinically, by the presence of airflow obstruction due to chronic bronchitis and/or

emphysema. The airflow obstruction is generally progressive, may be accompanied by airway hyperreactivity, and may be partially reversible. *Chronic bronchitis* is a condition with chronic or recurrent excess mucus secretion into the bronchial tree that occurs on most days during a period of at least 3 months in each of two consecutive years in a patient in whom other causes of cough have been excluded. *Emphysema* is an abnormal permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis (1). It is believed that chronic bronchitis is present in 85% of COPD (2).

COPD symptoms do not usually become apparent until age 50. Individuals with COPD experience a reduced quality of life due to increasing shortness of breath, which causes a limitation in activities. Cigarette smoking is recognised as the underlying cause of COPD in at least 90% of cases, and it is also the major risk factor associated with an accelerated decline of FEV_1 (forced expiratory volume exhaled after 1 second) (3). Moreover, smoking cessation is the only measure that has been shown to slow the progression of the disease (4-7). Other factors which may contribute to the development of COPD include passive smoking, occupational exposure to dust and fumes, air pollution, airways hyperresponsiveness, and α1-antitrypsin deficiency. The last is a rare genetic abnormality that causes panlobular emphysema in younger adults, and which accounts for less than 1% of COPD (1;2). In addition, the role of gender continues to be controversial. Some authors have shown that cigarette smoking is more detrimental in women than men (8;9), while others showed a higher mortality due to COPD in male patients, even after adjusting for disease severity and age (10).

One of the features of COPD is repeated respiratory infections. In the COPD patient this can cause acute exacerbations in respiratory symptoms, and may contribute significantly to accelerating the decline in pulmonary lung function tests due to inflammation-induced fibrosis of bronchi and bronchioles (4). This hypothesis has been challenged by several studies, yielding conflicting results. In 1977, Fletcher and Peto concluded from their 10-year prospective study of early stages of the development of COPD that infective processes and chronic mucus hypersecretion do not cause airflow obstruction to decline more rapidly (11). The fact that this study was performed on young, mild COPD patients, who would not be expected to have frequent bacterial colonization, despite being sputum producers, has been raised to discredit the conclusion of the authors (12). More recently, Donaldson and colleagues showed that the frequency of exacerbations contributes to long term decline in lung function of patients with moderate to severe COPD (13).

The spirometer, invented by Hutchinson in 1846, is still the key instrument for the diagnosis of COPD. Spirometry has been considered essential to determine the degree of airflow obstruction, severity of the disease, and prognosis; it has also been used extensively in clinical trials to assess responses to therapy (14). This is most often measured as the *forced expiratory volume exhaled after 1 second* (FEV_1). It has not proven to be a good predictor of the symptomatic response to treatment (15), however, or to quality of life (16) in COPD patients.

1.1.1. Acute Exacerbations

An acute worsening of respiratory symptoms in COPD patients, such as worsening dyspnea, fatigue, increased sputum volume, or sputum

purulence, is often described as an exacerbation or "flare" of COPD, although the definitions may vary (1;17).

In 1984, Anthonisen and colleagues described criteria to assess the severity of an acute exacerbation based on symptoms (9), in order to determine which patients with exacerbation would benefit from an antibiotic treatment. Briefly, a severe, or type 1, exacerbation, was defined whenever increased dyspnea, sputum volume, and sputum purulence were present. A moderate, or type 2, exacerbation was defined when two of these three symptoms were present. And finally, a mild, or type-3, exacerbation was defined when one of these symptoms was present in addition to at least one of the following findings: upper respiratory infection (sore throat, nasal discharge) within the previous 5 days; fever without other cause; increased wheezing; increased cough; or an increase in respiratory rate or heart rate by 20% as compared to baseline.

In 1999, an international working group of respirologists, proposed the following definition of a COPD exacerbation:

> *a sustained worsening of a patient's condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD.*

Furthermore, three stages of a COPD exacerbation based on healthcare utilisation were described: 1) *mild* severity when there is an increased need for medication that is managed in the patient's own normal environment; 2) *moderate*, when the patient has an increased need for medication and seeks additional medical assistance; and 3) *severe*, when the patient or caregiver recognises obvious and/or rapid deterioration in the condition, requiring hospitalisation (18).

Bacterial tracheobronchial infections are believed to be the most common inciting cause of acute exacerbations of COPD (2). Exacerbations may also be provoked by inhalation of environmental irritants, gastroesophageal reflux or aspiration, viral infections, illness leading to debility and weakness, discontinuation of medications (19), deviation from diet (17;19), and cardiopulmonary events, such as heart failure, arrhythmia, or pulmonary emboli (1;2;19).

It is believed that the frequency with which bacterial infection causes an exacerbation depends on the dominant pathology, patients with chronic bronchitis being more susceptible to bacterial bronchial infections than those with predominant emphysema (20). Repeated injury from inhalation of atmospheric pollutants or tobacco leads to mucus hypersecretion, loss of ciliated cells, an increase in the number of goblet cells, and mucosal gland hypertrophy. These changes in morphology of the airway make it susceptible to bacterial infection. Bacteria are believed to cause at least half of exacerbations (20;21). Sethi and colleagues were able to demonstrate that bacterial infections are responsible for 70-75% of exacerbations, with up to 60% caused by *Streptococcus penumoniae*, *Haemophilus influenzae* or *Moraxella catarrhalis* (19). Atypical organisms are implicated in about 10% of exacerbations, and the remaining 25 to 30% of cases are caused by viruses. Another line of evidence that supports the argument that bacteria are a major cause of acute exacerbations is the fact that bacteria present in airway secretions of exacerbated patients have been associated with increased airway inflammation (22). Furthermore, a study by Anthonisen *et al.* demonstrated that antibiotic treatment in acute exacerbations results in a decrease in the levels of some inflammatory parameters (9).

Potential markers of airway inflammation in acute exacerbations include an increase in neutrophil infiltration in the lung tissue, an increase in urinary excretion of isoprostane $F_{2\alpha}$-III, and, less specifically, an increase in plasma C-reactive protein (17). However, these markers have not been validated, and it is not really known if airway inflammation is a *sine qua non* of acute exacerbations (17). This makes the evaluation of treatment for COPD exacerbations difficult.

Whether the underlying cause of an acute exacerbation is bacterial or not, these episodes have a considerable effect on morbidity and result in a decrease in COPD patients' quality of life (23).

Optimal ambulatory treatment of acute exacerbations of COPD includes use of bronchodilators and systemic corticosteroids, as well as antibiotics if a bacterial infection is suspected (24). Without definite data on the optimal duration of therapy with antibiotics, most clinicians prescribe courses of 5 to 10 days. As for the duration of corticosteroid administration, a recent study supported a course of 5 to 10 days (25). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend oral corticosteroids for outpatients tapering over a course of eight days (beginning with 40 mg a day and decreasing the dose by 10 mg every other day) (26). For patients who are severe enough to be hospitalised, oxygen and mechanical ventilation may also be required (24).

A meta-analysis of randomised trials performed to assess the effectiveness of antibiotic therapy in acute exacerbations of COPD demonstrated a statistically significant difference benefiting antibiotic users (27). The authors based their estimation on units of standard deviation, because of the diversity of outcome measure across the reviewed studies and, therefore, were not able to quantify that benefit. In general, the guidelines suggest that Gram's stain and culture of expectorated sputum

are not cost-effective and, hence, should only be performed in a more complicated subset of patients, such as patients who have not responded to initial therapy, patients residing in nursing homes, and patients who are sufficiently ill to require hospitalisation (28). ATS guidelines recommend antibiotic therapy only if there is evidence of infection, but recognise the fact that the decision needs to be made clinically, because sputum culture is not cost-effective. In general, a change in sputum colour or consistency during an exacerbation is an indication for antibiotic therapy. However, the same symptoms may be present if the causative agent is a virus, in which case treatment with antibiotics is not warranted (21).

Acute exacerbations are often accompanied by hypoxemia and worsened hypercapnia (9;18;29). Results from two recent studies suggest that patients experience exacerbations of the disease regularly, and presented median rates of 2.4 and 3 episodes per year (23;30). Another study suggested that acute exacerbations are more frequent in active smokers than non-smokers, and that stopping smoking can reduce the frequency by approximately one third (31).

According to studies that involved daily assessment of symptom scores by patients, about 50% of acute exacerbations were not reported to physicians (23;30).

1.1.2. Burden of the disease

The World Bank has estimated that COPD is responsible for more than 29 million disability-adjusted life-years, and 1 million years of life lost per

annum around the world (32). In the US, it is estimated that 15 million people have COPD, making it the fourth leading cause of death, exceeded only by heart attacks, cancers, and stroke (6). In 1996, in the US, COPD accounted for over 106,000 deaths (7), and its costs were estimated at more than $14 billion (33). Niederman *et al.* estimated that during 1995, in the US, total direct costs of inpatient and physician services related to the treatment of acute exacerbations accounted for 1.6 billion dollars, of which 1.2 billion dollars were spent for individuals ≥65 years old (34). In 1998, it was estimated that in the US around 662,000 hospitalisations were attributable to COPD (1.9% of total hospitalisations), and in 2,530,000 hospitalisations (7.0% of total hospitalisations) COPD was listed as a contributing cause (35). Furthermore, it has been estimated that by the year 2020, COPD will be the fifth highest burden of disease worldwide and will rank third of the most common causes of death (5;36;37). Reasons for this rise include a reduced mortality from other cause and both an increase in cigarette smoking and environmental pollution in developing countries (5).

In Canada, 1998 statistics show that COPD was the primary cause of death for 9,398 Canadians (4% of all deaths in Canada), although the real mortality rate may be higher as the National Mortality Database does not capture underlying causes of death (38). According to the National Population Health Survey of 1998/99, the estimated number of Canadians diagnosed with COPD was 498,400. In addition, COPD accounted for 2.5% of all male hospitalisations and 2.1% of female hospital separations (38). In 1997, the average length of stay in hospital for COPD was 10.5 days. Respiratory diseases accounted for nearly 3.79 billion dollars of direct health care costs in Canada in 1993. This estimate includes expenditures on drugs, physician care, hospital care and research. Approximately one-third of these costs ($1.33 billion) were spent on chronic bronchitis, emphysema

and asthma. Indirect costs, including mortality and morbidity costs (short and long-term disability) as measured by loss of productivity, were double the direct costs in 1993, with approximately $3 billion attributed to chronic bronchitis, emphysema and asthma (38).

1.2. Inhaled Corticosteroids

Inhaled corticosteroids have been widely used in the treatment of chronic obstructive pulmonary disease (COPD) and asthma, and although their role in asthma therapy is well established (39), their benefit in the management of COPD is still unclear. The recognition that chronic inflammation is also present in COPD provides a rationale for their use in this condition. Guidelines for the management of COPD have been developed over the last decade with the most widely cited being the Consensus Statement of the European Respiratory Society (ERS), the American Thoracic Society (ATS) Standards Statement and the Guidelines of the British Thoracic Society (BTS). All 3 guidelines recommend inhaled bronchodilators (anticholinergics and β_2-agonists) as first-line therapy, but while ERS and BTS suggest that inhaled corticosteroids may be of value in patients documented to respond to corticosteroids, ATS does not recommend their use at all (40).

Table 1 shows all the corticosteroids (inhaled, oral and IV) currently available in Canada. Of the inhaled corticosteroids fluticasone and budesonide have higher affinity for the glucocorticoid receptor than beclomethasone, but in terms of therapeutic index they are similar and their full effect is only attained after several days of therapy (39).

1.2.1. Mechanism of Action

The mode of action of glucocorticosteroids (the group of corticosteroids used in the therapy of asthma and COPD) is not well understood. It is believed that at the cellular level the molecule penetrates the cell wall and binds to the glucocorticoid-receptor present in the cytoplasm. This receptor is normally attached to two heat shock proteins of 90 kDa. each that stabilise the receptor and prevent it from adhering to DNA. Upon binding of the glucocorticoid molecule to the receptor, the receptor-hormone complex undergoes conformational changes that allow dissociation from the heat shock protein. The glucocorticoid molecule is then transported to the cell nucleus where it binds to a specific sequence of DNA called the Glucocorticoid Responsive Element (GRE), which regulates a small set of primary target genes. This, in turn, leads either to increased transcription with formation of new proteins, such as lipocortin-1, or to inhibition of transcription of certain target genes and consequent blockage of the synthesis of several cytokines (41). Lipocortin-1 inhibits phospholipase A_2, which is involved in the production of pro-inflammatory lipid products such as prostaglandins, platelet activating factor and leukotrienes. Cytokines in turn are involved in several inflammatory processes, from exudation at inflammatory sites, through to the cytokine-induced expression of nitric oxide synthase, and the trafficking of inflammatory cells to the site of inflammation. In addition, glucocorticosteroids have also vasoconstrictor properties that reduce the airway mucosal edema and thickening that is present in asthma (42).

Inhaled corticosteroids are not completely deprived of adverse effects although these occur less than with a comparable dose of oral corticosteroids (43). Some portion of the inhaled drug is swallowed, and

can therefore reach the circulation by direct absorption from the gastrointestinal tract. The potential negative effects of inhaled corticosteroids include adrenal suppression, bone loss, skin thinning, dysphonia, candidiasis (39;44), cataracts (45-47), decreased linear growth in children, metabolic changes, and behavioural abnormalities (42;43). In children the effect of inhaled corticosteroids in slowing the growth rate has been difficult to separate from the effect of the disease, as asthma itself is believed to delay puberty (39;46). Moreover, there is no evidence that inhaled corticosteroid therapy influences adult height (46).

In summary, inhaled corticosteroids have a recognised important anti-inflammatory action in asthma, but their benefit in COPD is not well characterised (48-50). Although inhaled corticosteroids are less hazardous than systemic corticosteroids, there is still uncertainty as to adverse effects if used chronically.

1.3. Inhaled corticosteroids in COPD

Several studies have investigated the role of inhaled corticosteroids in the rate of decline in FEV_1 among COPD patients, but the results have been conflicting. Table 2 summarises the principal findings of those studies.

A meta-analysis by Van Grunsven *et al.* (51) showed that the long-term use (at least 2 years) of high doses of inhaled corticosteroids in patients with moderate to severe COPD improved significantly the FEV_1 measurements before bronchodilator administration. The improvement observed in FEV_1 after bronchodilator administration was, however, not significantly different from the one observed with placebo.

In the Lung Health Study (48) the rate of FEV_1 decline after bronchodilator did not differ between the group taking triamcinolone and the placebo group. Follow up at 9 and 33 months showed that patients in the triamcinolone group had significantly fewer respiratory symptoms and fewer visits to a physician due to respiratory symptoms. Nevertheless, the fact that patients with a history of asthma were not excluded may have confounded the results.

Pauwels *et al.* (52) reported a significant improvement in FEV_1 after 6 months of budesonide use and similar trends in the rate of decline in FEV_1 between placebo and active group from 9 months until the end of the study.

The Copenhagen City Lung Study (53) showed no significant effect of budesonide on the rate of FEV_1 decline after 36 months follow up.

The ISOLDE study (Inhaled Corticosteroids in Obstructive Lung Disease in Europe) (54) showed similar annual rate of FEV_1 decline in patients on placebo and patients on fluticasone. However, patients on fluticasone had significantly fewer exacerbations (median exacerbation rate was 0.99 year vs. 1.32 year on placebo, $p=0.026$), and a reduced rate of decline in quality of life.

Conversely, in the study by Paggiaro *et al.* (55) the number of patients who had experienced at least one exacerbation after 6 months did not differ significantly between fluticasone and placebo groups, although in the placebo group more patients had moderate to severe exacerbations.

Bourbeau and colleagues (56) studied the effect of budesonide 1600 µg a day in patients with advance COPD who had not shown an improvement with 40 mg/day prednisone administered for 2 weeks in the run-in phase. By the end of the study, at 6 months, the difference in the change in FEV_1 between the placebo and the budesonide group was not significant.

Renkema *et al.* (57) studied the long-term effect of high dose budesonide in non-allergic patients with COPD in a randomised double blind placebo controlled parallel trial of budesonide and placebo tablet, budesonide and prednisolone 5 mg/d, and a third arm of placebo inhalations and placebo tablet. After 24 months, and taking into account only patients that had at least 3 FEV_1 measurements, median FEV_1 slopes between groups were not significantly different. In this study, symptom scores were significantly different in the two active treatment groups when compared with baseline, but the frequency and duration of exacerbations were similar in the three groups. In addition to these measurements, the authors also analysed plasma cortisol levels and found a significant decrease only in the group taking budesonide and prednisolone. Conclusions that can be drawn from this study are limited by the following: there were only between 18 and 21 patients in each group; there was variability in the frequency of FEV_1 measurements; 11 patients withdrew from the study between 2 and 22 months.

A few small studies using a crossover design that looked at the effect of inhaled corticosteroids on lung function failed to provide significant results (58;59). However, the sample sizes were far too small and the follow-up periods short.

Keatings *et al.* (60) studied the change in inflammatory indices among COPD patients after crossing placebo and inhaled or oral corticosteroids periods. Asthmatic patients were used as positive controls. Results showed a significant reduction in sputum eosinophil number in asthmatic patients with oral corticosteroid, but no significant change in inflammatory cells in COPD patients receiving either inhaled or oral corticosteroids. Nevertheless, the results must be carefully interpreted as the study was only single-blinded and used a small sample size (10 asthma patients and 8 COPD patients). In addition, the period of exposure to the inhaled corticosteroid was only 2 weeks.

Culpitt *et al.* (61) investigated the effect of fluticasone on the change in inflammatory cells, as well as on lung function. Again, no change in the number of inflammatory cells was observed between drug periods, and no significant improvement in daily lung function tests was found. Once more, care should be taken when interpreting these results due to the limited number of patients involved.

A recent systematic review of several of these randomised placebo-controlled trials on the effect of long-term use of inhaled corticosteroids on the frequency of exacerbations of COPD, showed a 30% protective effect of inhaled corticosteroids in reducing the rates of COPD exacerbations (62). Nevertheless, results should be interpreted with caution for several reasons: exacerbations were not an end point in the reviewed studies, the daily dose of inhaled corticosteroid used varied even among studies that used the same inhaled corticosteroid agent, and patients' baseline characteristics varied among studies. Moreover, the definition of acute exacerbation of COPD differed between studies or was not specified. In addition, the time of follow-up varied from 6 to 40 months among studies.

The majority of the studies described above, designed to address the effect of inhaled corticosteroids in COPD, have focused primarily on the decline in lung function (FEV_1), which constitutes only one measure of the disease process. Observations with exacerbations were not planned and should, therefore, be interpreted with caution. Recently, observational studies have focused primarily on COPD outcomes.

The population-based study by Sin and Tu showed that patients receiving inhaled corticosteroids within 90 days post-discharge had a relative risk reduction for repeat hospitalisation of 24% (95% CI: 20-29%) and for all-cause mortality of 29% (95% CI: 22-35%) (63). However, the authors did not exclude patients who could simultaneously have an asthmatic component of their disease, to whom inhaled corticosteroids are known to be beneficial. Moreover, the analysis did not account for time-dependency of exposure. In other words, we don't know whether the patients that were prescribed inhaled corticosteroids within 90 days of discharge continued on that medication or not, nor for how long.

More recently, Soriano and colleagues used the UK General Practice Research Database (GPRD) to compare all-cause mortality, over a three-year period, in COPD patients using regularly fluticasone propionate and/or salmeterol with COPD patients using other bronchodilators (64). Regular use was defined by three or more prescriptions of salmeterol or fluticasone propionate occurring over a six month period. Results showed that the regular use of fluticasone, alone or in combination with salmeterol, was associated with increased survival of COPD patients managed in primary care. Here again, the authors first selected the regular users, and then performed an intention-to-treat analysis, i.e., they did not account for time-dependency of exposure.

1.4. Rationale and Objectives

A cohort study by Seemungal *et al.* showed that declines in lung function after an exacerbation were highly significant, and that on day thirty-five following an exacerbation only 75.2% of the individuals had recovered their peak expiratory flow rate (PEFR) to baseline values (30). Moreover, on day ninety-one, 7.1% of patients had still not recovered their baseline PEFR. In this same cohort it was observed that the median time to a next exacerbation was increased with oral steroid therapy (p=0.037). Blais *et al.* demonstrated that in asthmatic patients inhaled corticosteroids administered regularly in the year following the diagnosis reduce the risk of admission to the hospital for asthma by up to 80% (65). If a similar benefit is shown in COPD patients, there would be great impact in the disease therapeutics. These latter studies argue in favour of the need to assess the role of inhaled corticosteroids in the early stage of COPD. This is the rationale behind the second paper presented in this thesis.

The aim of the first paper is to describe the rate of exacerbations of COPD, according to gender, age at exacerbation, and duration of disease. The aim of the second paper is to determine whether the use of inhaled corticosteroids is associated with the risk of a first exacerbation in COPD patients.

Taken together the first paper describing rates of exacerbation of COPD and the second, exploring the impact of inhaled corticosteroids in a first exacerbation will enhance understanding of this increasingly prevalent disease.

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TABLE 1. CORTICOSTEROIDS THAT CAN BE USED IN COPD.

Pharmaceutical form of Corticosteroid	Corticosteroid
Inhaled	Beclomethasone dipropionate, monopropionate Fluticasone dipropionate Triamcinolone acetonide Budesonide Flunisolide
Oral	Prednisone Triamcinolone Methylprednisolone
Intravenous (IV) - for hospital administration only	Methylprednisolone sodium succinate

TABLE 2. LITERATURE REVIEW

Reference, publication year	Type of Study, sample size, population	Drug	Follow-up	Outcome measure	Findings
Van Grunsven [48] 1999	Meta-analysis of 3 clinical trials Only COPD	Inhaled corticosteroids	24 mo.	FEV1 pre- & post-bronchodilator	Benefit in FEV1 rate pre-bronchodilator after 2 yr.: +0.034L/yr (95% CI:0.005-0.063; p=0.026) Similar FEV1 rate post-bronchodilator (95% CI: 0.006-0.0084, p=0.095)
Lung Health Study Research Group [49] 2000	Multicentre placebo controlled, randomised trial 1,116 patients 40-69 y.o.	Triamcinolone 1200 µg/d	40 mo.	FEV1	Similar rate of FEV1 decline in both groups(p=0.50) Fewer respiratory symptoms (p=0.005) Fewer visits to a GP (p=0.03)
Pauwels [50] 1999	Randomised double-blind, placebo controlled Only COPD 1,277 pts 30-65 y.o.	Budesonide 800 µg/d	36 mo.	FEV1	Improvement after 6 mo.: +17mL/yr vs –18 mL/yr in placebo (p<0.001) Similar slopes from 9mo. until end (p=0.39)
Vestbo [51] 1999	Randomised, double-blind, placebo controlled 290 patients with mild-moderate COPD 30-70 y.o.	Budesonide 1200 µg/d for 6 mo + 800 µg/d for 30 mo.	36 mo.	FEV1	Similar rate of decline (95% CI:-12.8 to 19.0; p=0.9)
Burge [52] 2000	Randomised, double blind, placebo controlled 751 pts with moderate-severe COPD 40-75 y.o.	Fluticasone 1000 µg/d	36 mo.	FEV1	Similar rate of decline (p=0.16) Fewer exacerbations (p=0.026)

Reference, publication year	Type of Study, sample size, population	Drug	Follow-up	Outcome measure	Findings
Paggiaro [53] 1998	Multicentre randomised double blind placebo controlled 281 COPD pts 50-75 y.o.	Fluticasone 1000 µg/d	6 mo.	FEV1 # and severity of exacerbations 6 min.-walking test	Improvement of ≥10% in FEV1 seen in 29% of patients on fluticasone and 18% on placebo (p=0.053) Similar # of exacerbations (p=0.449); less severe exacerbations (p<0.001) Improvement in 6 min walking test (p=0.032)
Bourbeau [54] 1998	Randomised double blind parallel trial Age ≥40 y.o. Non-responders to oral corticosteroids in run-in phase 79 patients (39 in budesonide; 40 in placebo group)	Budesonide 1600 µg/d	6 mo.	FEV1 Secondary outcomes: exercise capacity, dyspnea after exercise and quality of life	Change in FEV1 after 6 mo.: Budesonide: 8 (95% CI: -51 to 68); Placebo: 12 (95% CI: -61 to 85); difference: -4 (95% CI: -95 to 87) Secondary outcomes did not differ between treatment groups.
Renkema [55] 1996	Randomised double-blind, placebo-controlled, parallel trial 58 stable COPD pts < 70 y.o.	1) Budesonide 1600µg/d+ placebo tablet; 2) Budesonide 1600 µg/d + prednisolone 5mg od 3) Placebo inhalations + placebo tablet	24 mo.	FEV1, symptom scores, Frequency and duration of exacerbations, adrenal activity	Median FEV1 slope: Placebo: -60 mL/yr (range:-570 to 140 mL/yr) Budesonide: -30 mL/yr (range: -180 to 870 mL/yr) Combination Tx: -40 mL/yr (range: -340 to 60 mL/yr) Symptom scores significantly lower in both active Tx groups Frequency and duration of exacerbation were not significantly different in the 3 groups Mean plasma cortisol level after 2 yr decreased significantly in the combination group

Reference, publication year	Type of Study, sample size, population	Drug	Follow-up	Outcome measure	Findings
Nishimura [56] 1999	Randomised double blind placebo controlled Crossover trial 34 COPD pts ≥55 y.o.	Beclomethasone 3 mg/d	4 Wks	FEV1	Only 5 patients showed improvement
Weiner [57] 1995	Randomised double blind placebo controlled crossover trial 30 COPD pts: 8 respondents to β2-agonists	Budesonide 800 μg/d	6 Wks	FEV1	Improvement in FEV1 only in respondents to β2-agonists following drug ($p<0.01$)
Keatings [58] 1997	Single blind, crossover design For budesonide: 15 COPD pts aged 45-78 y.o. For prednisolone: 11 asthmatics (positive control) 9 COPD	Budesonide 800 μg/d Prednisolone 30 mg/d	2 Wks	FEV1, FVC, PEFR Concentration of TNF-α, IL-8, ECP, EPO, MPO, HNL in sputum (inflammatory indices)	No significant changes in pulmonary function tests nor inflammatory cells after placebo or budesonide. No significant changes in pulmonary function test nor in inflammatory cells in COPD pts after oral prednisolone
Culpitt [59] 1999	Randomised double blind placebo controlled crossover trial 13 COPD pts 62±2 y.o	Fluticasone 1000 μg/d	4 Wks	PEF Dyspnea scores # inflammatory cells	Similar daily PEF between drug periods ($p>0.05$) No change in # of inflammatory cells, no change in median dyspnea scores
Alsaeedi [60] 2002	Systematic review of randomised placebo controlled trials on the effect of inhaled corticosteroids in COPD 9 studies reviewed (n=3,976) Only COPD	Inhaled corticosteroids	6-40 mo.	Frequency of exacerbations between treated and not treated patients	RR=0.70; 95% CI: 0.58 to 0.84 Significant test of heterogeneity ($p=0.03$)

Reference, publication year	Type of Study, sample size, population	Drug	Follow-up	Outcome measure	Findings
Sin [61] 2001	Nested case-control in administrative databases of Ontario 22,620 pts ≥65 y.o.	Beclomethasone Budesonide Flunisolide Triamcinolone	From 1992-1997	Re-hospitalisation; mortality due to COPD	OR (95% CI): 0.71 (0.65-0.78) for re-hospitalisation; 0.76 (0.71-0.80) for mortality
Soriano [62] 2002	Retrospective cohort of newly diagnosed COPD patients identified in the GPRD during 1990-1999 ≥ 50 yrs 1,045 COPD users of fluticasone and/or salmeterol and 3,620 COPD users of other bronchodilators.	Fluticasone propionate and /or salmeterol	3 yrs	3 year survival (all-cause mortality)	Survival at 3 years in FP and/or salmeterol users (78.6%) greater than in the reference group (63.6%) FP + salmeterol: adjusted HR=0.48; 95% CI: 0.31 to 0.73; FP: adjusted HR=0.62; 95% CI: 0.45-0.85; salmeterol: adjusted HR=0.79; 95% CI: 0.58-1.07)
Seemungal [30] 2000	Cohort study 101 COPD pts	Inhaled corticosteroids	30 mo.	Rates of exacerbation Time to next exacerbation Lung function (PEFR, FEV1, FVC)	Exacerbation rate: 2.4/yr; Median time to next exacerbation increased with oral steroids (p=0.037) Recovery of PEFR to baseline: on day 35 only 75.2% reached baseline; on day 91, still 7.1% had not recovered
Blais [63] 1998	Nested case-control in administrative databases of Saskatchewan 13,563 newly treated asthmatic patients 5-44 y.o.	Inhaled corticosteroids	12 mo. treatment	First admission to hospital for asthma	Patients on inhaled corticosteroids were 40% less likely to be admitted to hospital for asthma (OR=0.6; 95% CI 0.4-1.0). Patients on inhaled corticosteroids and theophylline given subsequently were 80% less likely to be admitted for asthma (OR=0.2; 95% CI 0.1-0.5)

Chapter 2: The Health Databases of Saskatchewan

For the two articles included in this thesis we used as source information, data from the Saskatchewan Health databases. The Prescription Drug database, that includes information on drugs covered by the government and dispensed in community pharmacies, served as the base for construction of the COPD cohort. Linked hospital information was used in both articles to identify severe exacerbations of the disease. This chapter describes the source of information used, and how the COPD cohort was formed.

2. The Health Databases of Saskatchewan

The computerised databases of Saskatchewan Health, a provincial government department, were created to help coordinate province-wide health care programs, which have been publicly funded since 1968. Residents of the province enjoy universal health insurance, except for those whose health care is funded federally, such as members of the Royal Canadian Mounted Police, members of the Canadian Forces, and inmates of federal penitentiaries, which account for less than 1% of the total population (1). More than 2.2 million individuals have been registered for coverage since its initiation. Major databases include the *Population Registry*, the *Prescription Drug Database* and the *Hospital Services Database*.

2.1 The Population Registry

The Population Registry contains demographic and coverage information for all eligible residents, as well as their Health Service Number

(HSN), which is a lifetime number, assigned at registration that uniquely identifies each resident. The HSN enables linkage of the computer databases. In addition, the Population Registry also contains information on the date of coverage initiation and termination.

2.2 The Prescription Drug Database

The Prescription Drug Data contains information on drugs listed in the Saskatchewan Formulary, which are those generally covered and intended for outpatients. This formulary is updated bi-annually and listed drugs are under continuous review. Moreover, in order for a drug to be covered it must be prescribed by a licensed practitioner. When the Prescription Drug Plan began, on September 1st, 1975, the beneficiaries paid a small dispensing fee for each prescription, and Saskatchewan Health paid the pharmacy for the balance of the cost. Currently, a family based deductible system is in place (1).

This database collects information on an individual patient basis and contains information about the patient, drug information, prescribing physician, pharmacy and cost. Patient fields include the HSN, which enables linkage to other databases, sex, year of birth, and designation of special status (e.g., welfare recipient). Drug information consists of drug identification number (DIN), active ingredient number (AIN), generic and brand names, strength and dosage form, manufacturer name, date dispensed, quantity dispensed, and "No substitution" indicator if applicable (1). In addition, it includes the pharmacologic-therapeutic classification, which was adapted from The American Hospital Formulary Service classification system.

The Prescription Drug database is submitted to several validation checks. Checks are done at the pharmacy level at the time a drug is dispensed, as to identification of the claimant, his eligibility, demographic accuracy and whether the drug is covered by the Plan. In addition, submitting pharmacies undergo routine audits (1).

2.3 The Hospital Services Database

The Hospital Services Database contains information on all separations, that is, discharge, transfer, or death, taking place in all hospitals of the province. The file contains the HSN, sex and month and year of birth, as well as discharge diagnosis (up to three) and treatment information (up to three procedures), accident code, and other administrative data. The diagnostic and treatment classification system is the World Health Organisation International Classification of Diseases, Ninth Revision (ICD-9). The procedure classification system is the Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures (CCP). Both codes use four digits. The administrative information consists of the admission and discharge dates, length of stay, admission and separation types, level of care codes, case mix group and resource intensity weight (for estimation of costs associated with a given hospitalisation), information on the attending physician and surgeon (if applicable), and hospital identification number (1).

All hospital data are cross-checked with the population registry for patient eligibility, identification and demographic accuracy. Moreover, computer programs check for illogical entries (1).

2.4 Study Population

To form the COPD cohort the Drug Prescription database of Saskatchewan Health, was restricted to include individuals aged 55 years or older who had been dispensed at least one prescription of any inhaled or oral beta-agonist, xanthine or ipratropium bromide, or any oral corticosteroid between January 1st, 1990, and December 31st, 1997. In order to exclude individuals who might have had only a prescription for occasional treatment, selection was further restricted to subjects who had been dispensed a minimum of 3 prescriptions for a β_2-agonist, ipratropium or xanthine, on 2 different dates in any one year period (from January 1990 to December 1997). Entry to the cohort was the date of the third prescription. Moreover, in order to identify the newly treated COPD patients we further restricted entry into the cohort to subjects who had not received any β_2-agonist, ipratropium bromide, xanthines, asthma medications, nasal corticosteroids or inhaled corticosteroids, during the 5 years pre-study entry. Figure 1 describes the construction of the COPD cohort.

The COPD cohort was then linked to the Hospital database to allow identification of all hospitalisations related to respiratory diseases and to estimate true follow up time, taking into account time spent in hospital during the study period.

The time frame was selected because it was after January 1990 that high dose inhaled corticosteroid therapy became generally available. Figure 2 shows the time frame of the cohort of interest for both studies.

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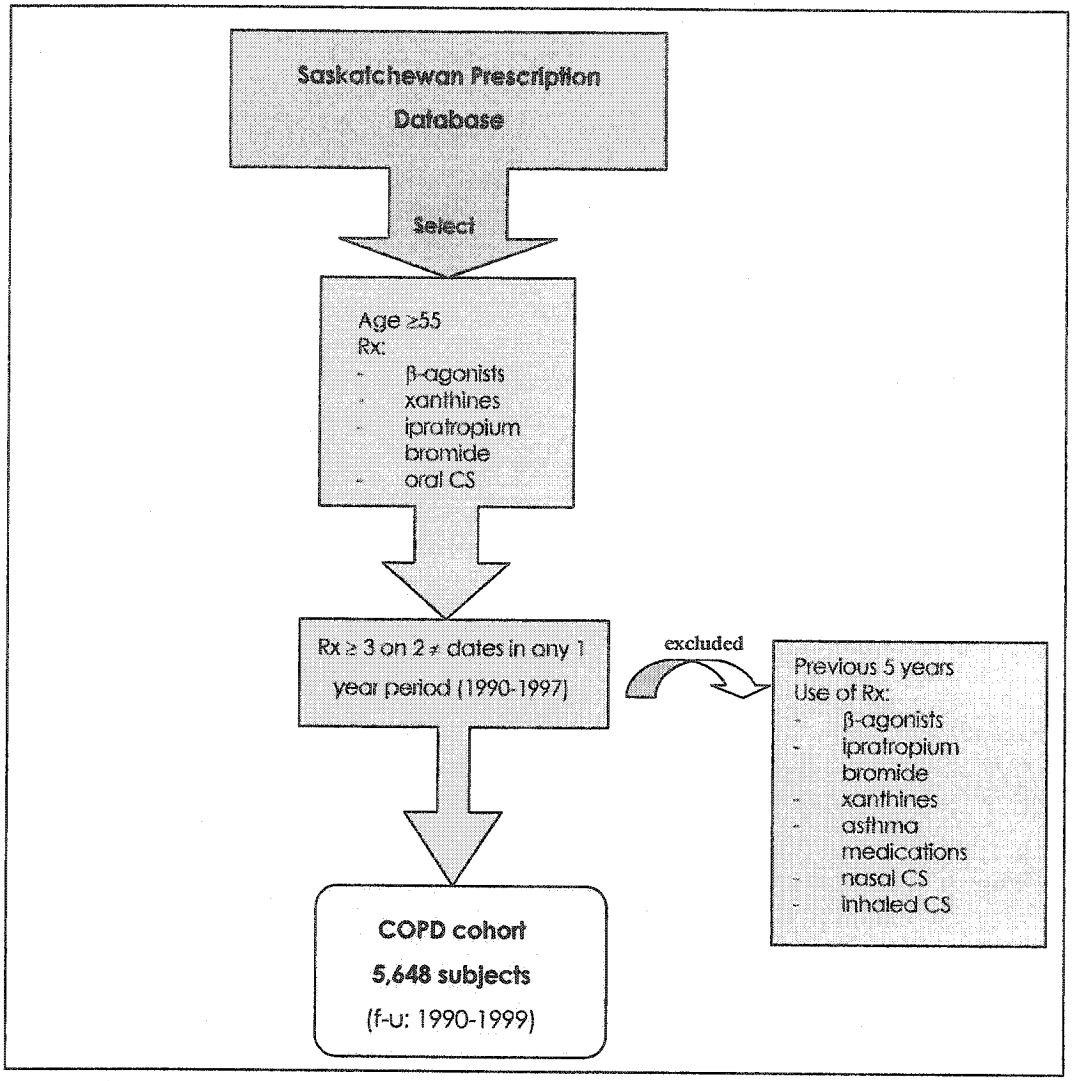
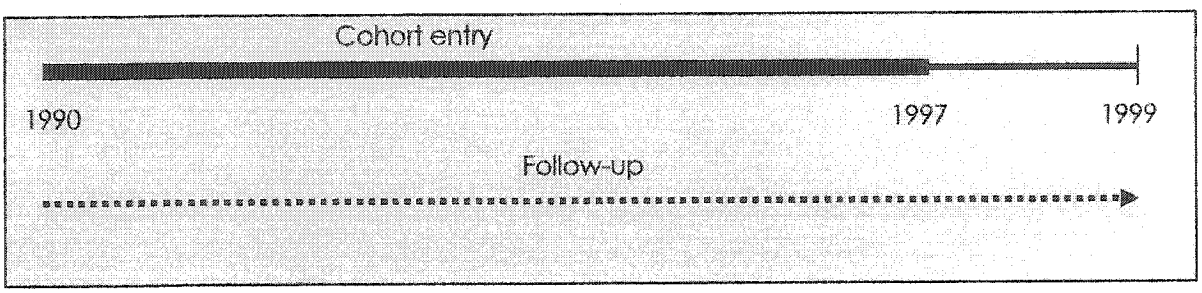
FIGURE 1. CONSTRUCTION OF THE COPD COHORT.



CS:corticosteroids; f-u: follow-up

FIGURE 2. TIME FRAME FOR COHORT ENTRY AND FOLLOW UP.



CHAPTER 3: RATES AND PATTERNS OF COPD EXACERBATIONS

3.1 PREFACE

The following paper is the first descriptive study, to our knowledge, to quantify the rate of treated chronic obstructive pulmonary disease (COPD) exacerbations in a population-based cohort. In addition, the methodology used to determine the outcome of interest has not been tested before. The knowledge that the occurrence of exacerbations in this patient population causes great burden for the individual and the society urges one to determine the frequency and patterns of these events. This would enable the development of preventive measures, as well as, better allocation of health care resources.

The article describes the methodology used and provides rates by gender, age, duration of the disease, and calendar year.

In estimating the rate of exacerbations in a large cohort of COPD patients, the following assumptions were made:

- exacerbations follow a Poisson distribution;
- censored observations have an outcome probability similar to that of individuals remaining under observation;
- losses are uniform during each interval of time;
- and there are no secular trends over the calendar period covered by the accrual (1990-1997).

The use of a Poisson distribution to describe the occurrence of rare events, such as exacerbations in an inception cohort of COPD patients, suggests that the estimated rate is constant in any time unit within a defined interval. That is, n persons followed during t units of time are equivalent to t persons observed during n units of time (1). This notion is

important for the interpretation of the results described in the following paper.

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3.2 Rates and Patterns of COPD Exacerbations

Abstract

Acute exacerbations of COPD are believed to be a common occurrence in COPD patients and are known to be associated with considerable disease deterioration, but their patterns are not well known. Our aim is to describe the frequency of acute exacerbations of COPD in a large population-based cohort.

We used an inception cohort of COPD patients, formed from the Administrative Databases of Saskatchewan. The outcome was the occurrence of all moderate or severe exacerbations from 1990 to 1999. Moderate exacerbations were defined by dispensing of both a prescription for an antibiotic and a prescription for an oral corticosteroid on the same day. Severe exacerbations were defined by a hospitalisation with a primary discharge diagnosis of COPD.

There were 5,645 patients that entered the COPD cohort between 1990 and 1997, of which 1,489 experienced at least one exacerbation requiring treatment during follow-up. The overall rate of acute exacerbations was 11.5 per 100 person-years. It increased with age and was highest in the age group 75-84 years (13.0 exacerbations per 100 person-years). The rate of exacerbations was higher in men than women (13.7 vs. 9.1 per 100 person-years). It was highest in the first trimester of therapy for the disease (13.8 per 100 person-years) and stabilised thereafter around 12.0 exacerbations per 100 person-years.

Our results indicate that men have higher rate of exacerbations than women, and that the rate does not increase with increasing disease duration over the first 10 years of disease.

INTRODUCTION

Acute exacerbations of COPD are known to be associated with considerable morbidity and mortality in patients with chronic obstructive pulmonary disease (COPD) (1;2). They are also associated with important loss of quality of life (3), are a common cause of hospital admission (4), often after failed initial therapy in the community and are a frequent cause of readmission to hospital (5). The following factors are thought to trigger exacerbations of COPD: viral infections, bacterial infections, inhalation of environmental irritants, discontinuation of medications and changes in diet (6).

There is little information on the frequency and pattern of exacerbations in COPD, but economic studies suggest that the burden of these events to society is considerable. US data showed that, in 1995, total direct costs of inpatient and physician services related to the treatment of acute exacerbations were 1.6 billion dollars, of which 1.2 billion were spent on individuals ≥65 years old (7). In 1998, about 2% of hospitalisations were attributed to COPD, and in 7% of all hospitalisations, COPD was listed as a contributing cause (8). It is believed that moderate to severe COPD patients experience 2-3 exacerbations a year (3;9), and that about 50% of exacerbations are not reported. However, this information is derived from studies based on patients' self-reports.

Furthermore, the expression "frequent exacerbations" is sometimes used to endorse the use of certain medications in COPD patients, although it is not defined (10). The lack of a standard definition of acute exacerbation of COPD or of a severity grading system contributes to the difficulty in assessing the real impact of these episodes among COPD

patients, as well as the impact on the health care system. Probably the most commonly used definition clinically involves the combination of the three following clinical findings: worsening of dyspnea, an increase in sputum purulence and increase in sputum volume.

Our study aims to provide detailed information regarding the frequency of treated exacerbations in a large population of COPD patients followed over a prolonged period of time.

METHODS

Source Population

The primary source of data was a COPD cohort that was formed from the computerised databases of Saskatchewan Health. These databases were developed to support the universal health insurance program provided to all residents of the province since 1975 (with the exception of the native population who have their prescription costs paid by a federal government agency, members of the Royal Canadian Mounted Police and Armed Forces). Two million people have been covered by this program since it began. Dispensed prescriptions, use of health care services and vital status information are all recorded, and the information can be linked for each individual through their Health Service Number (HSN). The HSN is a lifetime number that uniquely identifies a person and that is issued at registration (11).

COPD Cohort

The COPD cohort was formed by selecting individuals aged 55 years or older, who had received at least 3 prescriptions for β_2-agonists, ipratropium bromide or xanthines, in any one year period, on two different dates between January 1st, 1990, and December 31st, 1997. Entry into the cohort was the date of the third prescription. In order to include only subjects with new onset of therapy for COPD, we excluded subjects who had used β_2-agonists, ipratropium bromide, xanthines, asthma medications, nasal corticosteroids or inhaled corticosteroids during the 5 years before these three prescriptions.

All patients in the cohort were followed from cohort entry to the earliest of the following dates: December 31, 1999, emigration from the province, or death.

Outcome

The outcome was the occurrence of all moderate or severe exacerbations during follow-up. Moderate exacerbations were defined as dispensing of a prescription for a systemic antibiotic and an oral corticosteroid on the same day. Severe exacerbations were defined by a hospitalisation with a primary discharge diagnosis of COPD (ICD-9 codes 490-492 and 496). If an exacerbation, whether moderate or severe, occurred within 30 days of a previous exacerbation, it was considered as a relapse and not a new exacerbation. A less restrictive definition of moderate exacerbation was also used, namely the dispensing of a prescription for an antibiotic and an oral corticosteroid within seven days of each other.

Statistical Analysis

Crude rates of COPD exacerbations were computed by dividing the number of exacerbations by the person-time of follow-up. These rates were stratified by gender and time-dependent age. We also estimated the overall rate of COPD exacerbations using the less restrictive definition for moderate exacerbation. In order to assess whether the burden of COPD has changed over time, we determined the rate of exacerbations that occurred in each calendar year, i.e., from 1990 to 1999.

We repeated these analyses for the rate of the first exacerbation. We computed this rate over duration of follow-up, using the actuarial method. We excluded from this analysis 1,192 patients that had had at least one exacerbation before cohort entry, otherwise their first exacerbation after cohort entry would not be their first exacerbation of the disease. Time intervals of different length were used to allow examination of longer duration of follow-up, where the number of individuals was small.

In all instances, we assumed that exacerbations follow a Poisson distribution, and that rates were constant within each stratum. Ninety-five percent confidence intervals were computed for all rates. All analyses were performed using SAS software version 8 (1999-2001 by SAS Institute, Cary, NC, USA).

RESULTS

There were 5,648 patients who entered the COPD cohort between 1990 and 1997. Of these, 3 were excluded because they had no follow-up. Of the remaining 5,645 patients, 53.9% were male, and the mean age was 73.5 years. The distribution of the COPD cohort by age groups at cohort entry, by respiratory drugs that defined cohort entry and prescriptions for antibiotics and/or oral corticosteroids during follow-up are shown in table 1.

We identified a total of 3,048 exacerbations, of which 384 were excluded from all subsequent analyses since they occurred within 30 days of a previous one. Thus, there were 2,664 exacerbations that occurred in 1,489 patients, of which 627 were moderate and 2,037 were severe.

The overall rate of exacerbations of COPD during the 10-year follow up period was 11.5 per 100 person-years. Men had a higher overall rate of exacerbations than women (13.7 vs. 9.1 exacerbations per 100 person-years), and this difference was constant across all age groups. In general, rates of exacerbation increased with increasing age and were highest in the 75-84 age group (Table 2). Using the alternative definition of moderate exacerbation, i.e., the dispensing of a prescription for an antibiotic and an oral corticosteroid within seven days of each other, the overall rate of COPD exacerbation was 13.3 per 100 person-years. The rate of COPD exacerbations increased over calendar time from 9.5 exacerbations per 100 person-years in 1990, to 12.7 exacerbations per 100 person-years in 1992, and then decreased, although the accrual of patients continued until the end of 1997. In 1999, the rate of COPD exacerbation was 12.5 exacerbations per 100 person-years. In the first three months from onset of treatment of COPD (cohort entry), the rate of COPD exacerbations was

13.8 per 100 person-years, in the twelfth month it was 8.7 per 100 person-years, and then it stabilised around 11.7 exacerbations per 100 person-years as the duration of the disease increased.

Table 3 shows that the rate of severe exacerbations was higher than that of moderate exacerbations for both genders. In men the rate of severe exacerbations was almost four times that of moderate exacerbations (10.9 vs. 2.8 per 100 person-years, respectively). In addition, the rate of a first exacerbation was also higher for men than women (5.9 vs. 4.4 exacerbations per 100 person-years). The rate of a first severe exacerbation was also higher than the rate of moderate in both genders (3.8 vs. 2.1 per 100 person-years in males and 2.5 vs. 1.8 per 100 person-years in females). Figure 1 shows the hazard curve for the first exacerbation of COPD. The risk of a first exacerbation is higher in individuals that stay in the cohort only one year or less, and then decreases as the time of survival increases. The hazard stabilises around 4.5 per 100 person-years in individuals that are followed for four years or more.

Discussion

The overall rate of an acute exacerbation of COPD in our population-based cohort was 11.5 per 100 person-years, or 0.115 exacerbations per patient per year, which is lower than the rates presented in other studies. Anthonisen *et al.* during a trial designed to assess the role of antibiotics in the treatment of exacerbations in stable COPD patients, with mean age 67.3 years, reported an average of 1.3 ± 1.5 exacerbations per patient per year, of which 40% were severe, as defined by the occurrence of three symptoms: increase in dyspnea, increase in sputum volume and sputum purulence, and 40% were moderate, defined by the presence of two of the previous symptoms (12). However, in their study exacerbations were diagnosed by patients' recall of symptoms. In our study, severe exacerbations accounted for 76% (2,037) of all exacerbations. Seemungal *et al.* followed a cohort of patients with moderate to severe COPD to assess their quality of life during exacerbations and when their condition was stable and found a rate of 2.7 exacerbations per patient per year (3). In this study, exacerbations were defined as an increase in any two "major symptoms" (dyspnea, sputum purulence, sputum volume) and increase in one "major" and one "minor symptom" (wheeze, sore throat, cough, and nasal congestion/discharge) for at least two consecutive days. The information on exacerbations was obtained by self-report and by means of daily diary cards. The authors also found that 50% of exacerbations were not reported and were diagnosed only from the diary cards. A more recent study also by Seemungal and colleagues, where patients with moderate to severe COPD were followed for 2.5 years, suggested a median exacerbation rate of 2.4 exacerbations per patient per year (9). The authors used the same definition as used in the previous study. However, this study included only 101 patients that attended the outpatient clinics of a

reference hospital and who were willing to participate in a long-term study. In addition, only about 250 exacerbations (50%) were reported to the researchers, and only 154 of all exacerbations were treated. Furthermore, in patients with two or more exacerbations and for whom the treatment had been recorded (n=134) only 25% of exacerbations were treated with both an antibiotic and an oral steroid, and 12.1% received no treatment. Another recent cohort study, where a total of 81 patients with moderate-to-severe COPD were followed for 56 months, found a mean rate of 2.1 exacerbations per patient per year (13). In this study, an exacerbation had to be self-reported or caught by the physician at each monthly visit, in order to be identified. It was defined by a substantial worsening of one or more symptoms (dyspnea, cough, sputum production, viscosity, and purulence) as compared to a "usual level", or a minor worsening of two or more symptoms and after excluding other causes of worsening of symptoms, such as pneumonia, upper respiratory infection, and congestive heart failure. The fact that our results are lower than the ones obtained in these studies is not surprising for several reasons: our study was a population-based study that included members of the general population who were being treated for COPD and who contributed with person-time to the cohort; unlike the studies published so far, it was not only restricted to patients with moderate to severe disease; our definition of exacerbation required that a patient sought a physician, and then was prescribed treatment, or was hospitalised. However, our definition of exacerbation assures that they are clinically relevant and associated with morbidity and costs. One limitation of our definition is that we excluded from the numerator patients who might have had an exacerbation and were treated with only an antibiotic or with only an oral corticosteroid. The overall rate of COPD exacerbations using an alternative approach to define a moderate exacerbation, i.e., the dispensing of a prescription for an

antibiotic and an oral corticosteroid within seven days of each other, was not very different from the one obtained by our more strict definition. The overall rate would have been higher (13.2 per 100 patients-year or 0.132 exacerbations per patient per year instead of 0.115 per patient per year) if we had not excluded the 384 relapses that occurred within 30 days of an exacerbation.

In this study we were interested in assessing the effect of gender and age on the risk of acute exacerbations in a population-based cohort of COPD patients. Age is a known risk factor for a more rapid decline of lung function. It is also associated with the number of years of cigarette smoking, which is the major risk factor for COPD (14). The effect of gender in COPD has been disputed by several authors. Chronic obstructive pulmonary disease has historically occurred more frequently in men, which has been attributed to sex-related differences in smoking patterns worldwide. More recently, men were shown to report more respiratory symptoms than women, even after adjusting for smoking (14). Furthermore, men were found to have higher risk for dying of COPD after adjusting for disease severity and age (15). Nevertheless, a few studies on the gender related differences and lung function have suggested that smoking is more detrimental for women than for men (15-17).

Gender differences observed in our results point in the direction of the results of the study by Sunyer and colleagues (15). The authors followed the vital status of a cohort of asthma and COPD patients, who visited the emergency room of four major hospitals in the city of Barcelona, between 1985 and 1989. In their study men had higher risk of dying of all causes of death, for all respiratory causes and for COPD, than women. The risk of

dying of COPD remained higher among men than women even after adjusting for disease severity and for age.

Dissimilar to our findings are the observations that women are more vulnerable to the effect of smoking than men (16;17), which argues against the higher rates of COPD exacerbation observed in men in our study. A recent study on the gender related differences in severe, early-onset COPD suggested that women smokers were more susceptible to severe COPD than men (16). Chen *et al.* studied the interaction between sex and smoking habits on lung function in adults, 25 to 59 years of age, in a rural community in Saskatchewan, and found that cigarette smoking was more detrimental in women than men (17). It is likely that in our COPD cohort, with a mean age of 74 years, the proportion of male smokers is higher than the proportion of female smokers and that this difference is accounting for the difference in the rates of exacerbation observed.

Behind the definition of a severe exacerbation is the assumption that the patient is sick enough, first, to be transported to an emergency unit of a hospital, and then to be admitted. This information depends on the ability of the diagnostic code to properly represent the condition, and also on the validity of the information entered. Rawson and colleague studied the validity of the recording of several conditions, including chronic obstructive pulmonary disease, in the Saskatchewan hospital database, and concluded that for COPD there was exact agreement in 94.2% of the cases between computerised hospital data and discharge diagnosis in medical charts. Furthermore, the authors concluded that the concordance between medical charts and hospital computer data on personal and demographic factors was excellent (≥92%) (18).

The results presented in this study depend also on the accuracy of the information registered in the Prescription Drug database of the Province

of Saskatchewan. The Prescription Drug database is submitted to numerous validation checks, and pharmacies that collect information undergo regular audits (11). Moreover, drug utilisation reviews and program evaluations are ongoing within the Drug Plan, which also serves to validate the system.

One strength of our study is the use of a population-based cohort of COPD patients, which provides a better picture of what happens in the community, away from the artificial and strict environment of clinical trials. However, one can argue that our cohort is not a true COPD cohort, because it was not based on clinical information. By restricting entry into the cohort to individuals 55 years and older who during the previous 5 years did not have any prescription for respiratory drugs, nor had prescriptions for drugs more commonly used in asthma, we believe that we were able to isolate patients who were newly diagnosed COPD patients. Patients entered into the cohort at the same stage of their disease minimising possible selection bias and prevalence bias and, therefore, allowing for a more accurate estimate of the rate of exacerbation by duration of the disease.

In conclusion, our findings suggest that in a population-based cohort of COPD patients only about 23% will experience moderate or severe exacerbations during an average period of 3.7 years of follow-up. The average rate in this population-based study was 11.5 per 100 person-years. This can be interpreted in different ways. It means that among 100 patients followed for 1 year, the probability of occurrence of an acute exacerbation is 0.115, which is the same probability for a cohort of 50 patients followed for 2 years or for one single subject followed for 100 years. Of relevance is the rate of severe exacerbations requiring hospitalisation, which were 0.109

exacerbations per patient per year for men and 0.065 exacerbations per patient per year for women. From a population perspective, this is an important finding as it provides an indication on how resources will be used for COPD patients. The fact that in our study we detected more severe exacerbations than moderate may indicate that COPD patients underestimate their condition, and, therefore, it is not until their condition worsens and they require hospitalisation that patients are treated for an exacerbation. Results from a recent international survey suggest that subjects with COPD underestimate their morbidity and may, therefore, be under treated (19).

Given that the frequency of exacerbations has been shown to be related with a long term decline in lung function in patients with moderate to severe disease (20), efforts should be made to develop new strategies to encourage smoking cessation, the major risk factor for the development of COPD (14), and to develop new ways to stabilise the disease.

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TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF THE COPD COHORT

	N
COHORT SIZE (1990-1999)	5,645
MEAN DURATION OF FOLLOW-UP (YEARS)	3.7
AGE AT ENTRY IN YEARS (%)	
55-64	1,048 (18.6)
65-74	1,939 (34.4)
75-84	1,814 (32.1)
≥ 85	844 (15.0)
MEAN AGE (SD)	73.5 (9.6)
AGE RANGE	55-106
MALE GENDER (%)	3,041 (53.9)
BRONCHODILATORS DEFINING COHORT ENTRY (%)†	
Inhaled β_2-agonists	73.8
Oral β_2-agonists	10.8
Xanthines	25.3
Inhaled ipratropium	32.3
Ipratropium/Salbutamol	2.5
SUBJECTS WHO HAD EXACERBATIONS PRIOR TO COHORT ENTRY (%)	1,192 (21.1)
TOTAL NUMBER OF PRESCRIPTIONS DISPENSED DURING FOLLOW-UP	
Oral corticosteroids	14,288
Antibiotics	31,865
SUBJECTS WHO HAD DURING FOLLOW-UP AT LEAST 1 PRESCRIPTION OF:	
Only oral corticosteroids	164
Only antibiotics	2,825
Both antibiotics and oral corticosteroids	1,783
None of the above	873

†Percentages add up to over 100 because subjects could have used up to three different drugs at cohort entry.

TABLE 2. RATES OF EXACERBATIONS BY AGE GROUP AND BY GENDER

		AGE GROUPS				TOTAL
		55-64	65-74	75-84	≥85	
FEMALE	EVENTS	128	397	389	103	1,017
	PERSON-YEARS	1,821.9	3,944.2	3,654.7	1,694.4	11,115.2
	RATE*	7.0	10.1	10.6	6.1	9.1
	95% CI	5.9-8.4	9.1-11.1	9.6-11.8	5.0-7.4	8.6-9.7
MALE	EVENTS	207	616	606	218	1,647
	PERSON-YEARS	1,991.7	4,641.8	4,026.3	1,399.9	12,059.7
	RATE*	10.4	13.3	15.1	15.6	13.7
	95% CI	9.1-11.9	12.3-14.4	13.9-16.3	13.6-17.8	13.0-14.3
TOTAL	EVENTS	335	1,013	995	321	2,664
	PERSON-YEARS	3,813.6	8,586.0	7,680.9	3,094.2	23,174.9
	RATE*	8.8	11.8	13.0	10.4	11.5
	95% CI	7.9-9.8	11.1-12.5	12.2-13.8	9.3-11.6	11.1-11.9

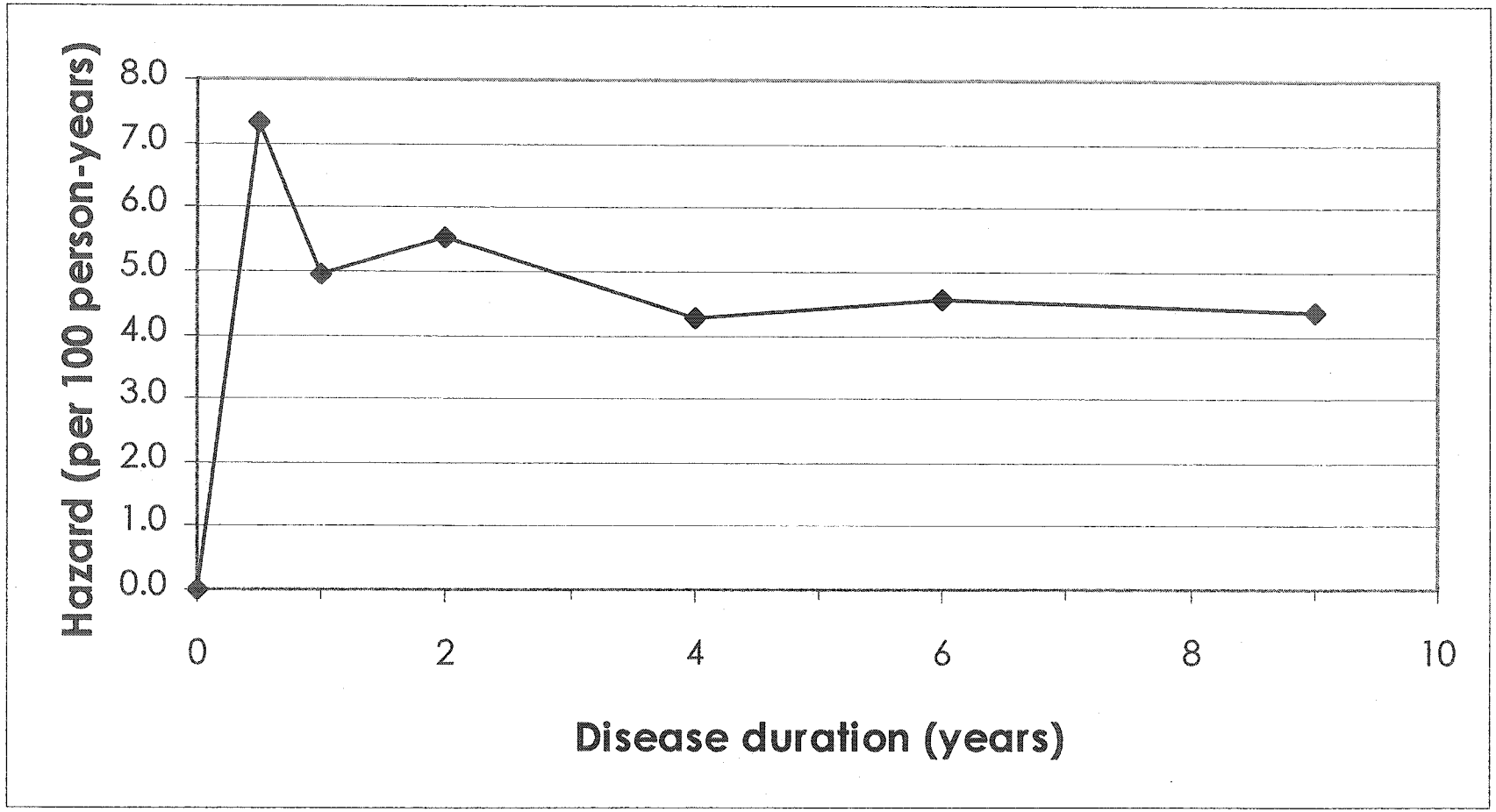
*Rates per 100 person-years

TABLE 3. RATES OF ALL EXACERBATIONS BY TYPE AND GENDER

GENDER	N. EXACERBATIONS BY TYPE PERSON-YEARS		RATE PER 100 PERSON-YEARS	95% CONFIDENCE INTERVALS
ALL EXACERBATIONS				
Females (n=2,604)	Moderate	292	2.6	2.3-2.9
	Severe	725	6.5	6.1-7.0
	Total	1,017	9.1	8.6-9.7
	Person-years	11,115.2		
Males (n=3,041)	Moderate	335	2.8	2.5-3.1
	Severe	1,312	10.9	10.3-11.5
	Total	1,647	13.7	13.0-14.3
	Person-years	12,059.7		
FIRST EXACERBATION†				
Females (n=2,604)	Moderate	174	1.8	1.6-2.1
	Severe	239	2.5	2.2-2.9
	Total	413	4.4	4.0-4.8
	Person-years	9,479.1		
Males (n=3,041)	Moderate	208	2.1	1.8-2.4
	Severe	375	3.8	3.4-4.2
	Total	583	5.9	5.4-6.4
	Person-years	9,864.1		

†Excluded patients who had had an exacerbation before cohort entry (n=1,192)

FIGURE 1. HAZARD CURVE FOR FIRST EXACERBATIONS OF COPD



CHAPTER 4: INHALED CORTICOSTEROIDS AND THE RISK OF A FIRST EXACERBATION IN COPD PATIENTS

4.1 PREFACE

The paper presented in this chapter focuses on the evaluation of some of the possible benefits associated with inhaled corticosteroids in treatment of COPD. In particular, a major question is whether inhaled corticosteroids reduce exacerbations of the disease, thereby delaying the deterioration of lung function.

The results and methodology employed are presented in this paper. Due to space limitations the rationale for assessing certain variables as potential confounders is not presented in the article, but will be discussed in the last section of this chapter.

The strength of this study is the use of a large cohort of newly diagnosed COPD patients. Entry into the cohort was the day of the third prescription (occurring on at least two different days) for COPD treatment occurring within a year of the first prescription of medications commonly used in the treatment of COPD (inhaled β_2-agonist, oral β_2-agonist, xanthine, ipratropium bromide, or a combination of inhaled ipratropium and inhaled β_2-agonist). This method of selecting subjects who reached the three-prescription entry criterion results in minimisation of the possible selection bias. Estimates of rate ratios are, therefore, not biased by left censoring of the data. We identified the first exacerbation, either moderate or severe, occurring after entry into the cohort. The other advantage of using an inception cohort is the fact that patients are at the same stage of the disease when they enter into the cohort, and, therefore, the assessment of exposure is not confounded by prevalence bias.

Confounding by indication is a major problem in pharmacoepidemiology studies because the reason for prescribing a given drug is usually associated with the outcome under study. In the present study we have tried to minimize confounding by indication by adjusting our analysis for the number of prescriptions for respiratory medications that were dispensed in the twelve month period preceding the index date, and by restricting our analysis to patients who had not experienced an exacerbation prior to cohort entry.

4.2 Inhaled Corticosteroids and the Risk of a First Exacerbation in COPD Patients

Abstract

While the role of inhaled corticosteroids in asthma therapy is well established, their benefit in the management of chronic obstructive pulmonary disease (COPD) is still controversial. We assessed whether inhaled corticosteroids were effective in preventing a first exacerbation of COPD.

We used the Saskatchewan Health databases to form a cohort of 5,645 COPD patients, 55 years and older, newly treated for COPD. The patients entered the cohort from 1990-97 and were followed until December 31, 1999, or the occurrence of their first ever exacerbation. Moderate exacerbations involved prescriptions for an antibiotic and oral corticosteroid on the same day. Severe exacerbations were hospitalisations with a primary discharge diagnosis for COPD. We used a nested case-control design and matched on year of birth and cohort entry. Rate ratios were further adjusted for co-medication use and other confounders.

There were 995 exacerbations among the 4,455 subjects who had not had an exacerbation prior to cohort entry. The rate of a first exacerbation was increased with any use of inhaled corticosteroids in the year prior to the index date (rate ratio 1.27; 95% CI: 1.08-1.48) and current use (rate ratio 1.51; 95% CI: 1.22-1.87). The rate of a first exacerbation increased with increasing daily doses; the rate ratios ranged from 1.28 for a daily dose of 500 µg or less to 2.94 for daily doses greater than 1500 µg/day.

Our results suggest that inhaled corticosteroids are not beneficial in reducing the risk of a first ever exacerbation of COPD. The increased risk observed is likely a result of residual confounding by indication.

INTRODUCTION

Inhaled corticosteroids are currently the mainstay of adult asthma management, and although their benefit in chronic obstructive pulmonary disease (COPD) is still disputed (1;2), they are also widely used in patients with COPD (3). Certain similarities between asthma and COPD, for example, the presence of both inflammatory and bronchospastic components, provides a rationale for the use of inhaled corticosteroids in COPD patients. During the second part of the last decade several studies designed to investigate the efficacy of inhaled corticosteroids in the rate of decline of FEV_1 have been published, with most reporting negative results (4-14). A few, however, suggested a beneficial effect of inhaled corticosteroids in reducing the number and severity of exacerbations (4;8;13;14). More recently, a systematic review of randomised clinical trials of inhaled corticosteroids in COPD showed a 30% reduction in the rate of exacerbations with the use of inhaled corticosteroids (15). However, none of the studies in this review had acute exacerbations as their primary end-point, and the definition of an acute exacerbation varied, or was not provided.

An acute exacerbation or "flare" of COPD is a frequent occurrence in COPD patients. It is characterised by any combination of worsening dyspnea, increase in sputum purulence and increase in sputum volume (16). It is believed that bacterial infection is the underlying cause in as many as 70-75% of cases, with the remainder being attributed to viruses (17) and other causes (16;18). Exacerbations have a considerable effect on morbidity and quality of life of COPD patients (19) and constitute an important cause of hospital admission and readmission, with the consequent high burden on the health care system (19;20). In 1995, in the

US, total direct costs of inpatient and physician services for the treatment of acute exacerbations of COPD accounted for about 1.6 billion dollars (21), and in 1998, 662,000 hospitalisations (1.9% of all hospitalisations) were attributed to COPD (22).

In a cohort of COPD patients followed for 2.5 years it was observed that 35 days after an exacerbation about 25% of the cases had not reached their baseline lung function and that by day 91, complete recovery of lung function had still not occurred in 7% of the cases (13). These results suggest a constant deterioration in overall well being with increasing episodes during the course of the disease. Hence, one important goal of treatment is to delay the time to a first exacerbation, as was demonstrated with inhaled corticosteroids in asthma (23). This study assessed the effect of inhaled corticosteroids in preventing a first exacerbation of COPD in a population-based cohort of COPD patients.

METHODS

Source data and population

The primary source of data was the computerised databases of Saskatchewan Health. These data bases were developed to help coordinate the health care services that are provided to all residents of the province since 1975, with the exception of members of the Royal Canadian Mounted Police and Armed Forces. Two million people have been covered by this program since it began. Dispensed prescriptions, use of health care services and vital status information are all recorded and the information can be linked for each individual by means of a unique Health Service Number (HSN) (24).

COPD cohort

The COPD cohort was initially formed from all individuals 55 years or older, who had received at least one bronchodilator (inhaled or beta-agonist, xanthine or ipratropium bromide) between January 1st, 1990, and December 31st, 1997. We restricted the cohort to individuals who had been dispensed at least 3 prescriptions on at least two different dates for these bronchodilators, in any one year period from January 1990, to December 1997. This ensures that treatment was not occasional. Entry into the cohort was the date of the third prescription. Subjects who had received β_2-agonists, ipratropium bromide, xanthines, cromolyn or nedocromil, nasal corticosteroids or inhaled corticosteroids during the 5 years prior to cohort entry were excluded. This was done to eliminate asthma patients and to select subjects with first onset of regular drug therapy for COPD.

All patients in the cohort were followed from the date of cohort entry to the earliest of the following dates: December 31, 1999, occurrence of a first COPD exacerbation, emigration from the province or death.

Outcome

The outcome of interest was the first exacerbation of COPD, moderate or severe, occurring after entry into the cohort. A moderate exacerbation was defined by prescriptions for a systemic antibiotic and an oral corticosteroid on the same day. A severe exacerbation was defined by hospitalisation with a primary discharge diagnosis of COPD (ICD-9 codes 490-492 and 496). The first of these exacerbations to occur was the outcome of interest, and the date of its occurrence was considered the index date. Because we were interested in a first exacerbation, we restricted our cohort to individuals who had never had a recorded exacerbation, either moderate or severe, before entry into the cohort.

Study design

We used a nested case-control design within the cohort. For each case we matched all available controls on the year of birth (±1 year) and the year of entry into the cohort to control for secular trends in medical practice. In addition, controls had to be at risk at the time the case occurred. That date was also the index date for the matched controls.

Exposure to Inhaled Corticosteroids

The exposure of interest was current exposure to inhaled corticosteroids, defined as dispensing of beclomethasone, flunisolide, fluticasone, triamcinolone, or budesonide in the two months prior to the index date. Given that there may be a prodromic phase of a COPD exacerbation, we identified dispensing of inhaled corticosteroids occurring in the 15 days before the index date. Current exposure was then analysed in two different ways: including the period of 15 days prior to the index date and excluding this period. The effect of having a prescription for inhaled corticosteroids in the period 16-60 days before index and at least another one in the period of 61-365 days before index was also analysed. Lastly, past use was considered whenever there was a prescription for an inhaled corticosteroid dispensed in the 61-365 days before index, but not in the 60 days prior to the index date.

In order to ascertain the effect of different doses of inhaled corticosteroids in preventing a first exacerbation of the disease, average daily doses of inhaled corticosteroid over the previous year were calculated. For the calculation of daily dose of inhaled corticosteroids we excluded hospitalisation days, which occurred in the year prior to index date. Because the Saskatchewan Prescription Database does not contain information on drugs used during hospitalisation we cannot exclude the possibility that some individuals might have used corticosteroids, either inhaled, oral or intravenously while in the hospital.

Statistical Analysis

We selected all available controls for each case, and therefore descriptive statistics were weighted by the inverse of the number of controls in each matched set. Conditional logistic regression for matched case-control data was used to obtain crude and adjusted odds ratios as estimates of rate ratios of COPD exacerbations that were associated with the use of inhaled corticosteroids. Adjustment was performed for severity of COPD, believed to be closely related to severe and/or more frequent exacerbations (25), as well as for concurrent diseases.

Severity of COPD was assessed by the following variables: number of prescriptions for oral corticosteroids, antiallergic agents (cromolyn and nedocromil), inhaled, oral or nebulised β_2-agonists, xanthines, ipratropium bromide and for systemic antibiotic dispensed in the 12 months prior to index date. Medications used during the 12 month period before the index date served as proxy measures for chronic disease. Comorbidities of interest were cardiac diseases, cardiovascular diseases, diabetes, neurological disorders, psychiatric diseases and rheumatoid arthritis. Gender was addressed as a possible determinant and effect modifier.

Ninety-five percent confidence intervals were computed for all rate ratios. All analyses were performed in SAS software version 8 (1999-2001 by SAS Institute, Cary, NC, USA).

RESULTS

The inception cohort of COPD patients was composed of 4,455 individuals, after 1,192 subjects were excluded because they had an exacerbation prior to cohort entry. All patients with a first COPD exacerbation after cohort entry were identified and matched with all the available controls. Between January 1st, 1990, and December 31st, 1999, there were 995 patients identified with a first exacerbation, of which 381 patients were identified with a moderate exacerbation and 614 with a severe exacerbation. The majority of the patients were men and mean age was 74.

Table 1 describes the distribution of the study subjects by selected characteristics, study medication, and possible confounding variables. In general, the two groups were well matched, with same mean age and similar follow-up time. Case patients were more likely to be men and had more severe COPD than controls as attesting by the higher mean number of prescriptions for respiratory medications and higher mean number of prescriptions for antibiotics dispensed during the 12 month period that preceded a first exacerbation (mean number of antibiotic prescriptions for cases 1.86 vs. 1.23 for controls). Current use of β-blockers and/or benzodiazepines was similar in cases and controls. In addition, case patients had more cardiac disease and more rheumatoid arthritis than controls.

Table 2 summarises the results of the regression analyses for different time windows of inhaled corticosteroid exposure. The adjusted rate ratio for any use of inhaled corticosteroid in the previous year as compared with no use was 1.27 (95 percent confidence interval, 1.08 to 1.48). Current

exposure, excluding the 15 day-period prior to the index date, as compared to no exposure yielded an adjusted rate ratio of 1.51 and a 95 percent confidence interval ranging from 1.22 to 1.87. When the prodromic period was included, the adjusted rate ratio did not change appreciably (adjusted RR=1.54, 95 percent confidence interval, 1.28 to 1.86). Moreover, past use of inhaled corticosteroids and exposure in both the past and current periods were also associated with the risk of a first exacerbation (adjusted RR for past use=1.40, 95 percent confidence interval, 1.17 to 1.67, and adjusted RR for both current and past periods=1.52, 95 percent confidence interval, 1.21 to 1.92). Furthermore, the risk of current exposure to inhaled corticosteroids in a first exacerbation occurring in the first two years of follow-up was slightly higher than the risk of a first exacerbation occurring after 2 years since cohort entry (Table 2).

Crude and adjusted rate ratios for the effectiveness of various daily doses of beclomethasone or the equivalent are displayed in Table 3. The majority of cases and controls that took inhaled corticosteroids used a daily dose of 500 µg or less. The risk of a first exacerbation increased with increasing daily doses of inhaled corticosteroids, varying from 1.28 for a daily dose of 500 µg or less to 2.94 for a daily dose higher than 1500 µg. It corresponds to an increase of 83% for every additional 1000 µg.

DISCUSSION

In our study we found that the use of inhaled corticosteroids was not associated with a reduction in the risk of a first exacerbation of COPD. In fact, the risk appears to be slightly increased among users of inhaled corticosteroids.

Our results are in accordance with Renkema's *et al.* study, which showed that frequency and duration of exacerbations were not significantly different between the two active treatments (budesonide alone and budesonide and prednisolone) and placebo (14). Paggiaro and colleagues showed similar number of exacerbations between active (fluticasone) and placebo groups administered for 6 months, but less severe exacerbations in the fluticasone group (8). On the other hand, results from the Lung Health Study and from the ISOLDE trial suggested fewer exacerbations (4;7) and fewer visits to general practitioners (4) among those receiving inhaled corticosteroids; these were not the primary endpoints of these studies, however, and patients involved were younger.

Our results were not able to show a benefit of inhaled corticosteroids, which is in opposition to the results of a recent systematic review that showed a 30% protective effect of inhaled corticosteroids in preventing acute exacerbations of COPD (15). However, this systematic review used information from studies where acute exacerbations were either not defined or where definitions varied substantially between studies. Furthermore, the studies combined were heterogeneous in other relevant characteristics, such as dose of inhaled corticosteroids used and duration of follow-up. In particular, the authors did not study the very first

exacerbation as we did to reduce the heterogeneity from varying disease severity and duration.

Confounding by indication is a major concern in observational studies of drug benefit such as this one, because the reason for prescribing a certain medication is often associated with the outcome of interest (26), introducing a bias. Collet and Boivin state that in theory, it would be possible to control for this, if one could measure with sufficient accuracy the estimate of the effect of this confounder (26). In studies using information from large drug databases we rarely have the indication for prescription, which makes it difficult, if not impossible, to control completely for this bias. In our study we used the frequency of prescriptions for respiratory disease dispensed during the year that preceded the exacerbation, as a measure of severity. This assumes that sicker patients are more likely to receive more medications to treat their symptoms. Moreover, we used a matched design to control for effects of age and duration of disease, above and beyond the effect of severity of COPD. We noticed that after controlling for gender and severity of the disease, the association of an increase in the risk was reduced significantly; however, residual confounding was likely present. Furthermore, we minimised confounding by indication by focusing on the first treated exacerbation of COPD after initial treatment in order to select patients at the same stage of the disease. Nevertheless, confounding by indication remains the most likely explanation for the increase in the risk of a first exacerbation observed with increasing daily doses of inhaled corticosteroids. More severe patients are more likely to be prescribed higher doses of inhaled corticosteroids or are more likely to be prescribed these drugs more frequently. Protopathic bias is also a concern in observational studies and is present when one attributes an outcome to an exposure that actually resulted from early signs and symptoms of the outcome under study (26). In our study we tried to avoid this bias by classifying as non-

exposed the individuals who had been dispensed an inhaled corticosteroid only during the prodromic phase, that is, during the 15-day period that preceded an exacerbation. In our study there was no difference in the risk of a first exacerbation in current users of inhaled corticosteroids when we extended the period of exposure to allow exposure during the prodromic phase.

We chose to study a *true* first exacerbation because the period of time between exacerbations is believed to decrease with the progression of the disease, and full recovery after an acute exacerbation may not occur (13). Therefore, if there was a benefit in using inhaled corticosteroids it might be better perceived in the early stage of the disease. Any other exacerbation would be correlated with the preceding ones and the possible benefit of inhaled corticosteroids would be difficult to assess. By excluding subjects who had exacerbations before cohort entry we are only able to generalise our results to patients in an earlier stage of COPD.

We considered an individual to be currently exposed if there was a dispensing of a prescription in the 60-day period prior to an exacerbation. Selection of a 60-day period was based on two factors: 1) inhaled corticosteroids are often prescribed in a high dose (1000 µg/day) for COPD patients; 2) the most commonly prescribed high dose metered-dose-inhaler delivered 200 doses of 250 µg/each. Hence, we estimated that a compliant patient would need to refill a prescription every 50 days. We used a period of 60 days to allow for some non-compliance and to allow for patients who are prescribed less than 1000 µg/day.

This study used information from the Prescription Drug database of the province of Saskatchewan, which is subject to several validation checks

at the time a prescription is dispensed. In addition, submitting pharmacies routinely undergo audits (24). However, in this database, information available represents only dispensed prescriptions and thus may not correspond entirely to medication used. This would result in a non-differential misclassification of exposure with a consequent underestimation of the rate ratio.

Our results depend in part on the definition of a moderate exacerbation. We defined a moderate exacerbation as a same day dispensing of an oral corticosteroid and antibiotic. This definition is based on Canadian guidelines for the management of acute chronic bronchitis (16). However, because there is still a dispute on whether the use of antibiotics in treating exacerbations of COPD is useful (27;28), many physicians may not prescribe antibiotics if they are not certain that the exacerbation has a bacterial etiology. Seemungal *et al.* followed a cohort of COPD patients for 2.5 years, and observed that treatment was started at a median of 3 days after onset of symptoms; prednisolone was administered in 27.3% of exacerbations; antibiotics in 85.6%; and both an antibiotic and a oral corticosteroid were administered in only 25% of patients with an exacerbation (13). Moreover, 12% of exacerbations were left untreated. Hence, it is likely that our cases represent an underestimate of all occurrences of exacerbations, in which case point estimates of rate ratios may be too low. In addition, we did not try to assess mild exacerbations, which the patient usually manages on his own without seeking the assistance of a physician, for instance, by increasing the frequency of administration of his bronchodilator (29). This would have been difficult to capture in a database study. The accuracy of the information on severe exacerbations leading to hospitalisation is dependent on how well the codes of discharge diagnosis are entered. Any error in coding or entering

this information would result in non-differential misclassification, with underestimation of the rate ratio.

In conclusion, our results suggest that inhaled corticosteroids are not efficacious in preventing a first exacerbation of COPD. The small increase in risk is most likely due to residual confounding by indication, but it is unlikely that the remaining unmeasured confounding would account for a significant benefit of inhaled corticosteroids.

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TABLE 1. CHARACTERISTICS OF THE STUDY SUBJECTS.

	Cases (n=995)	Controls (n=5,416)†
Mean Age (sd)	73.9(8.5)	73.9 (8.2)
Male (%)	58.6	51.0
Mean days of follow-up until index	897	921
NUMBER OF PRESCRIPTIONS IN THE PREVIOUS 12 MONTHS* OF:		
Oral corticosteroids	26.0 (0.85±2.14)	8.1 (0.23±1.16)
Nasal corticosteroids	5.4 (0.16±0.90)	5.8 (0.16±0.90)
Inhaled β_2-agonists	74.6 (4.98±5.55)	52.7 (2.53±3.77)
Combivent	8.7 (0.58±2.46)	3.1 (0.17±1.18)
Oral β_2-agonists	6.2 (0.18±1.02)	5.0 (0.17±0.95)
Inhaled ipratropium	38.4 (2.34±4.31)	22.1 (1.17±3.00)
Other asthma drugs	2.1 (0.09±0.81)	1.3 (0.05±0.64)
Xanthines	20.7 (1.01±2.62)	15.7 (0.80±2.38)
Antibiotics	69.1 (1.86±2.11)	54.5 (1.23±1.73)
Use of β-blockers and/or Benzodiazepines‡	14.7	16.6
COMORBIDITIES**		
Cardiac Disease	39.8	34.9
Cardiovascular Disease	52.7	52.7
Diabetes	7.2	9.0
Psychiatric Disease	31.3	32.3
Neurological Disorders	7.1	7.1
Rheumatoid arthritis	1.0	0.7

*Values are percentages (mean ± standard deviation) in the previous 12 months.
**Year before index date; values are percentages.
†To account for case-control matching, all means and percentages for controls were weighted by the inverse of the number of controls in each matched case-control set.
‡Any use during the month before index date.

TABLE 2. MATCHED RATE RATIOS (RR) FOR COPD EXACERBATIONS ACCORDING TO DIFFERENT PATTERNS OF INHALED CORTICOSTEROID USE.

USE IN THE PAST	CASES (N=995)	CONTROLS (N=5,416)	CRUDE RR	ADJUSTED† RR (95% CI)
NO USE	453	3,232	reference	reference
ANY USE‡	542	2,184	1.77	1.27 (1.08-1.48)
CURRENT USE				
Current*	312	928	2.47	1.54 (1.28-1.86)
Current**	198	626	2.33	1.51 (1.22-1.87)
PAST USE ***	359	1,353	2.00	1.40 (1.17-1.67)
PAST + CURRENT§	171	524	2.44	1.52 (1.21-1.92)
CURRENT USE**				
≤ 2 years of FU	528	2,835	2.13	1.50 (1.19-1.90)
> 2 years of FU	467	2,641	2.68	1.25 (0.94-1.67)

‡Any use: any use in the previous 12 months
*Includes the prodromic phase (0-15 days before event)
**Excluding prodromic phase
***Use of IC 61-365 days before index, but not in the 0-60 days before index
§Past + Current: use in the period 16-365 days before index
†Adjusted for gender, number of prescriptions for inhaled β_2-agonist, combination of a β_2-agonist and ipratropium bromide, oral corticosteroids, antibiotics and ipratropium bromide in the previous 12 months.

TABLE 3. MATCHED RATE RATIOS (RR) FOR COPD EXACERBATIONS BY DAILY DOSE OF INHALED CORTICOSTEROIDS.

USE IN PAST YEAR	CASES (N=995)	CONTROLS (N=5,416)	CRUDE RR	ADJUSTED† RR (95% CI)
None	453	3,232	1.00 (reference)	1.00 (reference)
≤500 µg	350	1,755	1.51	1.28 (1.09-1.52)
501-1000 µg	118	328	2.70	1.56 (1.19-2.04)
1001-1500 µg	56	76	5.48	2.32 (1.54-3.48)
> 1500 µg	18	25	6.36	2.94 (1.46-5.89)
MEAN DAILY DOSE IN µg (SD)	258.0 (440.7)	120.9 (258.6)	3.42‡	1.83‡ (1.47-2.28)

†Adjusted for gender, number of prescriptions for inhaled β_2-agonist, combination of a β_2-agonist and ipratropium bromide, oral corticosteroids, antibiotics and ipratropium bromide in the previous 12 months.
‡Increase in risk is per 1000 µg increase in the daily dose of inhaled corticosteroids.

4.3 Additional Comments

Due to space limitations, some issues in the design of our study may not have received sufficient attention in the article presented in this chapter. In particular, the reason behind the selection of the possible confounders for our model was not addressed. In this section, we intend to justify the choice of certain variables.

A confounder is a variable that is associated with both the drug exposure and the outcome, without being in the causal pathway between drug exposure and outcome (1).

Gender is a variable that is usually considered for adjustment, even when the relation of this variable with the exposure or with the outcome is not fully understood, i.e., even if one is not sure that it is a confounder. In our study, literature support the assessment of gender as a possible confounder or effect modifier in our analysis. Men are known to have more respiratory symptoms than women, even when adjusting for smoking (2) and disease severity (3;4), although a recent study on gender related differences in severe, early-onset COPD suggested that women that smoke were more susceptible to severe COPD than male smokers (5). On the other hand, there is a concern that inhaled corticosteroids may have an effect on bone metabolism which would put postmenopausal women at higher risk of developing osteoporosis (6-8) and, therefore, reduce the likelihood that such medications are prescribed.

Use of β-blockers is relatively contraindicated in COPD patients, due to the potential of these drugs to cause bronchoconstriction (2). Similarly, benzodiazepines may have a marked effect on respiration, especially in severe cases and during sleep (2). Hence, the use of β-blockers or benzodiazepines in the month prior to index date, was

considered a risk factor for the occurrence of an acute exacerbation of COPD and its effect as possible confounder was tested in the logistic model. The use of β-blockers or benzodiazepines did not predict a first exacerbation.

In our study we also considered some chronic diseases that are related to either the use of oral corticosteroids (one of the drugs used to define a moderate exacerbation), to a worsening of respiratory function and consequently to COPD, to the exposure of interest (inhaled corticosteroids) or related to all of them. That is, these diseases can act as confounders. In the present study medications served as proxy measures for chronic disease, as proposed in Von Korff's Chronic Disease Score (9) but with a few changes in order to include specific drugs that became available after 1992. The following chronic diseases were evaluated as possible confounders: cardiac and cardiovascular diseases, diabetes, rheumatoid arthritis, neurological disorders and psychiatric disorders.

Cardiac and cardiovascular diseases are related to cigarette smoking, which is clearly a risk factor for more severe pulmonary obstruction (2;10); cardiac diseases, such as heart failure may also mimic an exacerbation of COPD (11).

Diabetes patients are more prone to infectious diseases, a risk factor for acute exacerbations of COPD. In addition, physicians are reluctant to prescribe oral corticosteroids to diabetic patients, due to the known adverse effect of oral corticosteroids to cause hyperglycaemia (12;13). This was the rationale that led us investigate diabetes as a potential confounding variable.

Parkinson's disease, a neurological disorder, is related to COPD because muscular spasticity is an obstacle to coughing, and

consequently an obstacle to the removal of secretions from the lungs. Parkinson's disease also impacts the exposure to inhaled corticosteroids, as these patients have difficulty in administering inhaled corticosteroids by use of available devices.

Rheumatoid arthritis is a condition that may inhibit the patient's ability to administer inhaled corticosteroids. Therefore, it was expected that COPD patients suffering from rheumatoid arthritis would use less inhaled corticosteroids when compared with COPD patients without this condition.

Furthermore, psychiatric patients are believed to be less compliant to therapy in general. Non-compliance to therapy was determined as one of the risk factors for an acute exacerbation of COPD (14). In addition, patients taking antidepressants are at risk of respiratory failure and consequently should be closely monitored. This information supports the need to control for psychiatric disorders in our analysis.

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Chapter 5: Conclusion

In this research, we found that on average the rate of COPD exacerbations in newly treated patients was 11.5 exacerbations per 100 person-years. Men had a higher rate of exacerbations than women across all age groups. The rate was greatest in the first three months of disease, and then stabilized with disease duration. We also found that inhaled corticosteroids do not appear to prevent a first ever exacerbation of the disease. These findings, however, are subject to the merits and drawbacks of observational studies, in particular, with regard to the accuracy and completeness of the Saskatchewan Health databases.

Epidemiological studies are now recognised as an essential research tool to assess beneficial or harmful effects of drugs after marketing. They were introduced to fill a gap left by pre-marketing studies, which due to their short-duration and artificiality of protocol, do not document long-term safety and efficacy, nor safety and efficacy in the context of everyday clinical practice. This is of particular concern whenever a new indication is suggested after marketing, since the requirements that drug manufacturers have to comply with are less strict than when a drug is first introduced in the market, or when the medication is used off-label. Although randomised clinical trials are recognised as the only type of studies that are truly able to control for unknown confounders, due to the process of randomisation, their structure eliminates many "real-life" variables (1). Compliance is likely to be different when patients are not in an experimental setting, and drugs other than those being studied can augment or reduce efficacy or toxicity. Co-morbidities may also alter the bioavailability of the drug under study. Moreover, in experimental studies, both patients' access to standard therapy and the physicians' freedom of therapeutic choice are strictly controlled. Another deficiency of randomised clinical trials is the assessment of long-term efficacy, as high costs and logistic constraints mean these

studies tend to be short in duration. Outside the artificial setting of a clinical trial, persons who might have been excluded from participation in an experimental study are now not only likely to receive the drug, but may also differ as to dosage, adherence, and concomitant drugs, from participants in clinical trials (2).

A major advantage of non-experimental studies is that they do not interfere with the real world of medicine and disease (1) and, therefore, in some situations, are better able to study effectiveness of medications. Each observational study is more likely to include a broad representation of the population at risk. In addition, physicians do not use therapeutic agents in a uniform way, and observational studies usually include subjects with coexisting illnesses and a wide spectrum of disease severity, where treatment is tailored to the individual patient (3). Hence, well-designed non-experimental epidemiological studies may provide a good reflection of clinical practice.

The major criticism made of epidemiological studies of drug effectiveness performed using information from administrative databases is the potential for confounding by indication for treatment. This occurs because there is always a rationale for prescribing, which is related to the clinical outcome, and patients selected for therapy with a given drug may differ from those not receiving the drug, as to their expected clinical course (2). Strom *et al.* advise a "judicious use of non-experimental techniques with due attention to potential confounding by indication" (4). In administrative databases reasons for prescribing a drug are usually not recorded or are incomplete.

Another limitation of pharmacoepidemiology studies performed using information from administrative databases is the inability to adjust for potential confounders not included in the database. This is the case for smoking habits in studies of diseases where smoking is a risk factor.

In this thesis, the source of information was the Saskatchewan Health databases. Information recorded in these databases is accurate and complete. Residents of the province of Saskatchewan enjoy universal health insurance, except for those whose health care is funded federally, such as members of the Royal Canadian Mounted Police, members of the Canadian Forces, and inmates of federal penitentiaries, which account for less than 1% of the total population (5). In addition, the Prescription Drug database is submitted to several validation checks. Checks are done at the pharmacy level when a drug is dispensed to an identified claimant, verifying eligibility, patient demographics, and whether the drug is covered by the Plan. In addition, on a regular basis, a sample of paid claims is selected and sent to the beneficiaries for confirmation that the service paid had been provided, and that all the information on the claim was correct (6).

One important assumption in database studies of dispensed medications is that the prescription dispensed is actually ingested as intended. A common approach to deal with this problem is to restrict entry into the study to patients who have been dispensed two or more prescriptions of the same drug in a defined time interval used to indicate exposure (6).

In the two studies presented in this thesis, we attempted to address all possible biases related to database studies. We used the criterion of "three prescriptions on two different days during a one year-period" to identify treated COPD patients among individuals 55 years or older, who had been dispensed respiratory medications. We used recognized criteria of accurate identification of moderate and severe exacerbations of COPD. Furthermore, in the study presented in the second paper, we also controlled for all available potential confounders and restricted our analyses to the first ever exacerbation.

Our results suggest that the use of inhaled corticosteroids does not reduce the risk of a first exacerbation in patients with COPD. The increased risk observed is likely a result of residual confounding by indication. However, it is unlikely that the extent of the remaining unmeasured confounding conceals a significant benefit of inhaled corticosteroids.

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