THE USE OF ASTHMA MEDICATIONS AMONG ASTHMA CASES IN SASKATCHEWAN FROM JANUARY 1, 1991 TO DECEMBER 31, 2000.

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ABSTRACT

Asthma affects nearly two and a half million people in Canada (1). In Saskatchewan, the prevalence of asthma has increased across all age groups since 1981. Current literature indicates that the purchase of all asthma medications increased in the last 20 years both province and nationwide (2;3). Since the early 1990s, the Canadian Consensus Guidelines (CCG) for the treatment of asthma recommended increasing the use of inhaled corticosteroids as a mainstay for controlling asthma symptoms. The CCG have also encouraged decreasing the use of short-acting, inhaled beta$_2$-agonist medication.

The objective of this descriptive epidemiological study was to investigate asthma medication prescribing at the individual level among physician-diagnosed asthma patients, aged 0 to 64 years, in Saskatchewan from January 1, 1991 to December 31, 2000. Saskatchewan residents covered under the provincial health insurance plan who received a physician's diagnosis of asthma, identified each calendar year, were included in the study (296,430 asthma patients in total).

Nearly 80.0% of this asthma population purchased at least one asthma medication in each calendar year. From 1991 to 2000, users and the mean number of prescriptions of short-acting beta$_2$-agonists decreased slightly. The proportion of users and mean number prescriptions per year of inhaled corticosteroids increased. The highest mean numbers of prescriptions and users of inhaled corticosteroids were among the 0-4 year olds.

Short-acting beta$_2$-agonists, inhaled corticosteroids, and oral corticosteroids were the most popular medications. Users of theophyllines and cromoglycates decreased. The 15-34 year old males showed the greatest "inappropriate" use as high users of short-acting beta$_2$-agonists and low users of inhaled corticosteroids.

There was increasing compliance with the CCG over the ten years. The combination of beta$_2$-agonists with inhaled corticosteroids usurped beta$_2$-agonist monotherapy as the most popular form of asthma therapy by the year 2000. Users of

combination therapy increased from 19% to 38.7%, while users of beta$_2$-agonists alone decreased from 34.5% to 23.1%.

From 1996 to 2000, the monthly number of both short-acting β_2-agonists and inhaled corticosteroids prescriptions decreased for all users in July and August. Peak increases in the number of short-acting beta$_2$-agonist prescriptions, for children under 15, occurred in September. For adults, peak increases occurred in December for both medications.

These study results will enhance the understanding of asthma medication use among children and adults and will help healthcare professionals develop new treatment programs for the management of asthma.

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DEDICATION

For my father, who I not only admire for his intelligence, character, integrity, and dedication, but who I love for his endless generousity, his eccentric sense of humour, his compassion, his steadfast temperament, and his boundless unconditional love.

For my mother who is an inspiration to me as she continues to learn new skills, expand her knowledge base, and travel to new destinations. I am awed by her intelligence, her creativity, her affection, her passion and vitality, her unconditional love, and her ability to be our home.

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BDP-CFC	Beclomethasone-chlorofluorocarbon ……	11
CACG	Canadian Asthma Consensus Group ……	2
CCG	Canadian Consensus Guidelines ……	4
COPD	Chronic obstructive pulmonary disease ……	19
HIRF	Health Insurance Registration File ……	20
HSN	Health services number ……	20
ICD	International Classification of Diseases ……	20
PRS	Person Registry System ……	20
RAMQ	Régie de l'assurance maladie du Québec ……	15

1. INTRODUCTION

1.1 Introduction and Study Rationale

Asthma is a hyper-responsive inflammatory process in which airways are narrowed, through inflammation, bronchoconstriction, and excessive production of mucus. This is usually in response to at least one of many triggering factors. Asthma is a common disease in Canada with nearly 2.5 million affected persons nationwide (1). A definition of asthma established at the Canadian Asthma Consensus Conference in 1999 is as follows:

> "Asthma is characterized by paroxysmal or persistent symptoms such as dyspnea, chest tightness, wheezing, sputum production and cough associated with variable airflow limitation and a variable degree of hyper-responsiveness of airways to endogenous or exogenous stimuli." (4)

During a typical asthma episode the muscles around the bronchi of the lungs contract, the membrane lining the inside of the bronchi becomes inflamed, and excess mucus in the air passages is secreted forming mucus plugs which further restrict air flow (5).

Although asthma occurs in adults, prevalence decreases with age (1). Children and young adults are the principal sufferers of the disease (1). Over the last 20 years the prevalence, incidence, hospitalization rates, and mortality rates for asthma have increased in Canada (3). Nationally, the prevalence of physician-diagnosed asthma among Canadians aged four and older in 1994/95 was 7% (6). In 1996/97 the prevalence was 8%, and in 1998/99 it had increased to 9% (6). Statistics Canada found in 1998/99 that males aged 4 to 14 were more likely to be diagnosed with asthma than females but, for most other age groups, females were more likely to receive an asthma diagnosis (6).

One of the most recent studies of the prevalence of asthma in Saskatchewan in 1998 found that for asthma cases identified by first physician visit each year, the prevalence of asthma in the provincial population was 8.1% among children aged 0 to 4 years, 5.9% for those 5 to 14 years, 3.5% for those 15 to 34 years, and 2.7% for those 35 to 64 years (2;7). For children aged 0 to 14 years, prevalence was greater for males than for females. For those between the ages of 15 and 64, the prevalence was greater for females than for males (7). In Saskatchewan, the prevalence of asthma showed a trend of increase across all age groups from 1981 to 1996 until 1997 and 1998 when there was a period of stability and even decline (2;7).

As well as being indirectly costly and limiting individual quality of life, asthma is also directly expensive to the entire Canadian population. The estimated healthcare cost (including drugs, physician care, hospital care, and research) of chronic bronchitis, emphysema, and asthma in 1993 was $1.33 billion (CAD). It is one of Canada's most costly diseases ranking third after cardiovascular diseases and mental health disorders (1;8).

Although a recent review of economic studies in Canada, Australia, and the U.K. showed that there is wide variation in the measure of the "economic burden" of asthma (9), it can be seen across analyses that the cost of asthma is universally high. In a meta-analysis where the economic burden of asthma was defined as hospitalizations due to non-compliance with prescribed medication regimens, researchers concluded that the cost of asthma was $1,018 million (CAD) per year (10).

The treatment of asthma through drug management is a major component of the direct healthcare costs and management of asthma. The recommended "continuum approach," first established in 1996 by the Canadian Asthma Consensus Group (CACG) (11), as seen in Figure 1-1, states that persons with very mild asthma are typically managed with an "as-needed" β_2-agonist drug for symptom relief or before exercise or other anticipated trigger (12). If the β_2-agonist is needed more than three times per week, or if lung function is abnormal, an inhaled corticosteroid therapy is started. Those with moderate asthma are often prescribed a maintenance therapy that involves inhaled corticosteroids in addition to β_2-agonist rescue medication for symptom relief. An additional controller therapy may be added at the moderate severity level depending on

reassessment. Severe asthma can include daily maintenance therapy with inhaled corticosteroids and daily maintenance with additional controller therapy such as a long-acting, inhaled β_2-agonist or anti-leukotrienes (if the person cannot or will not use the inhaled corticosteroid treatment) or oral glucocorticosteroids or other controller therapies. Again, this is in addition to short-acting β_2-agonist rescue medication for symptom relief (4;12).

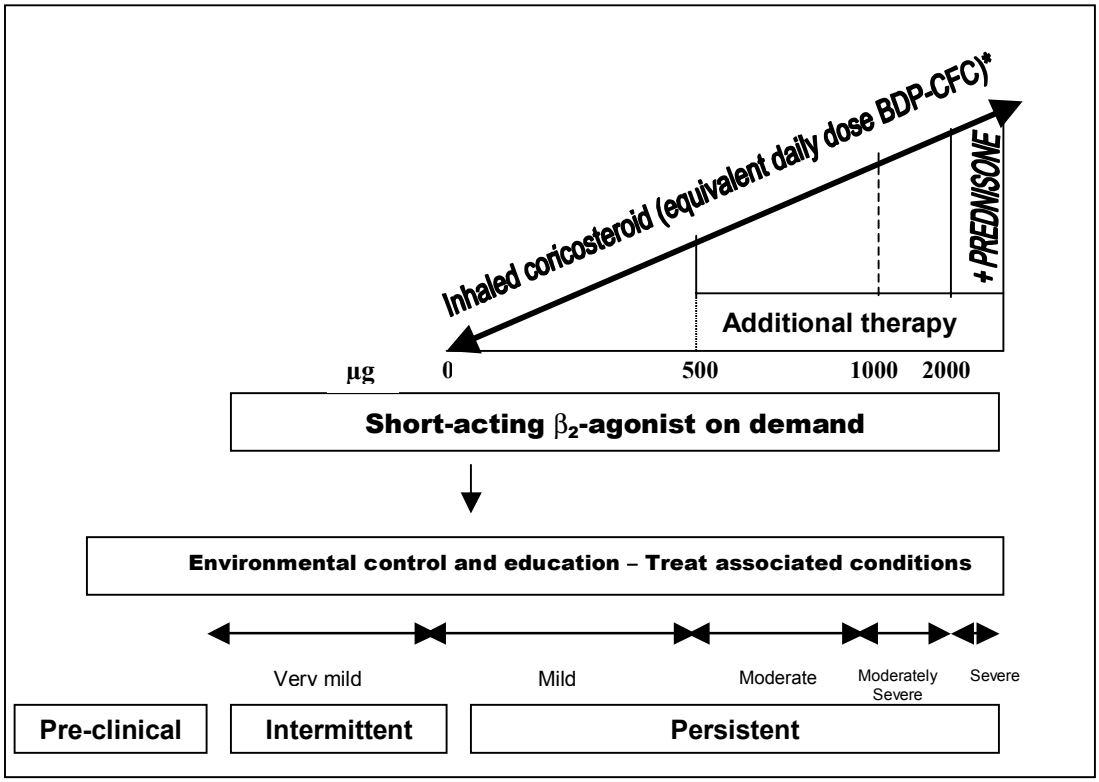

Figure 1-1 Continuum of asthma management. Adapted from Asthma Guidelines Update, 2001 (12)

Research has shown that when short-acting beta$_2$-agonist rescue medication is relied upon, for those with moderate to severe asthma, the condition is worsened [with increased hyperresponsiveness of the airways (13), remodeling of airway smooth muscle, and increased production of mediating cells which motivate an inflammatory response in the airways and mucus production (14)], and the need for rescue medication is increased. Thus begins a negative cycle of worsening asthma with an ever-increasing demand for reliever medication.

To understand the epidemiology of asthma and the health care utilization patterns of persons diagnosed with asthma in Saskatchewan, it is useful to observe and record the drug treatment regimens sought by persons with asthma. It is logical to suppose that an increase in the prevalence of asthma will be followed by an increase in the receipt of treatment and consequent purchase of asthma medications.

An appreciation of the treatment patterns, both real and those recommended by the CACG, will be helpful in managing the role of pharmacotherapy in the treatment of asthma in Saskatchewan. This information may contribute to the determination of appropriate and effective targeted strategies for treatment and asthma education needs in the province.

1.2 Statement of the Problem

The majority of research into asthma treatment has been of an ecological nature. Few studies have examined the development of asthma medication purchasing at the individual level with consideration of the historical context (i.e., $beta_2$-agonist medication having been linked to mortality epidemics in the past) and the Canadian Consensus Guidelines (CCG) for the treatment of asthma (since their inception to the present) that may have influenced medication, research, education, and behaviour changes over time.

1.3 Purpose of the Study

The purpose of this study is to examine the current trends in the use of asthma medication by persons with physician-diagnosed asthma in the Province of Saskatchewan over the last decade. This information provides insight into the prescribing and drug treatment trends associated with national practice and management guidelines for asthma. As pharmacological treatment is used to measure asthma severity, the results of this study may make some inferences about that aspect of the disease, as well as asthma prevalence in Saskatchewan.

The data was collected at the level of the individual which improved the precision of the associations between groups (by age, gender, region, medication group, etc.) to medication purchasing patterns over time. This level of analysis advances our

understanding of the unique characteristics of persons with physician-diagnosed asthma and their medication use.

1.4 Statement of Research Questions

This thesis project is an analysis of data from the Physician Services Database and Saskatchewan Outpatient Prescription Drug Plan Database from January 1, 1991 to December 31, 2000. This analysis addresses the following research questions:

1) What is the variation in proportion of users of each drug for the treatment of asthma by age, sex, and region per year and in the mean number of asthma medications per person by age and sex per year from January 1, 1991 to December 31, 2000?

2) What are the specific combinations of asthma medication used among persons with physician-diagnosed asthma by age and sex for the period of January 1, 1991 to December 31, 2000?

3) What is the variation in the monthly age-sex specific, short-acting inhaled $ß_2$-adrenergic agonist and inhaled corticosteroid use for the years 1996 to 2000?

1.5 Significance of the Study

The results of this study further the understanding of the epidemiology of asthma, provide useful information to health care workers in the treatment of asthma, and assist in the development of public policy related to the provision of health services for the Saskatchewan population.

This project cannot be generalized to populations that are greatly different from the Province of Saskatchewan with its particular set of population characteristics, including the structure of health insurance coverage. The Physician Services and Outpatient Prescription Services databases captured almost all of the information pertinent to this study for the provincially-covered population of Saskatchewan. These databases can be electronically linked using individual Health Services Numbers.

2. BACKGROUND INFORMATION AND LITERATURE REVIEW

An overview of asthma itself (defining characteristics, pathophysiology, and epidemiology), the management of asthma, and the special circumstances surrounding the pharmacological treatment of the disease is presented in this section. The background information will provide a context for this research study in attempting to understand the purchase of asthma medications by particular population characteristics.

2.1 Background Information

2.1.1 Pathophysiology

Asthma is characterized by two major processes: inflammation of the airways, and bronchoconstriction. The mechanisms of an asthma attack include contraction of the bronchi, inflammation of the membrane lining, and overproduction of mucus in the bronchioles. At the cellular level during an asthma attack, mast and eosinophil cells are excited, often in response to a "trigger" or allergen in the system, and substances including histamines and leukotrienes are released into the system (4). This response contributes to the narrowing of the airways. Common triggers include exposure to dust, pollen, cold air, and physical exertion (4). An asthma attack can also occur as a response to an emotional stimulus, aspirin (and other drugs), and certain foods (4).

To date, the pathogenesis of asthma is not entirely understood. While much has been learned about the triggers, outcomes of asthma attacks, and the role that drug treatment plays in the mediation of asthmatic episodes, the specific cause (or causes) of these episodes is not certain. In response to a trigger, excessive mucus accumulates and plugs the airways, inflammation occurs, and the presence of excess blood in the vessels that serve the lungs may also present.

Mediators such as histamines, prostaglandins, leukotrienes, and chemotactic factors are released from lung cells (mast cells, eosinophils, T-lymphocytes, etc.) with an aim to rid the airways of a foreign agent(s). However, for a person with asthma, the response to a trigger or irritant is in excess of what is normally seen and the result is

significantly reduced airflow. These mediators initiate and prolong the asthmatic episode until treatment is applied to halt and reverse the effect of this systemic response.

2.1.2 Symptoms

Wheezing, coughing, chest tightness, shortness of breath, and the coughing of mucus or phlegm are common manifestations of an asthmatic episode (4). Mild attacks may include a chronic dry cough while severe episodes can include fatigue, sudden drops in blood pressure upon inhalation, disappearance of breath sounds, and cyanosis. The frequency of attacks varies widely in the asthmatic population from seldom and brief to chronic and persistent. Asthmatic episodes can occur at night during a period of sleep when bronchial reactivity seems inordinately sensitive. Nocturnal symptoms are often taken as a sign of poor asthma control.

2.1.3 Pharmacological treatment of asthma

The CCG for asthma propose the pharmacological management of asthma follow the algorithm of a continuum as seen in Figure 1-1 (page 3) (12). Medications are to be used at a minimal effective dose only after, and with ongoing consideration of, environmental control of asthma triggers and factors (12). Each asthma patient is to be managed on a individual basis and should be encouraged to monitor and modify their own treatment if, and when, their disease worsens quickly (12). The treatment of asthma is aimed at reducing and/or eliminating the respiratory symptoms of the disease and restoring normal lung function. Through pharmacotherapy this is often achieved through two types of asthma medications: relievers, and controllers (Table 2-1).

Table 2-1 Asthma medications by their generic and brand names

RELIEVERS (for intermittent symptoms)	
GENERIC NAME	**BRAND NAME**
Sympathomimetic (adrenergic) agents (β_2-agonists)	
Fenoterol Hydrobromide	Berotec
Orciprenaline SO4	Alti/Apo-Orciprenaline, Alupent, Orcipren
Salbutamol SO4	Airomir, Alti-Salbutalmol, Apo-Salvent, Asmavent, Dom-Salbutamol, Gen-Salbutamol, Med-Salbutamol, Novo-Salmol, Nu-Salbutamol, Pms-Salbutamol, Rho-Salbutamol,Ventodisk, Ventolin
Terbutaline SO4	Bricanyl
Isoproterenol	Isuprel
Procaterol	Adrenaline
Antispasmolytics	
Ipratroprium Bromide	Atrovent, Apo/Gen-Ipratropium /Novo/Nu/ Pms
CONTROLLERS (for maintenance therapy)	
GENERIC NAME	**BRAND NAME**
Corticosteroids	
Beclomethasone Dipropionate	Beclodisk, Becloforte, Beclovent, Vanceril
Budesonide	Pulmicort
Fluticasone Propionate	Bronalide, Flovent
Flunisolide	Flunisolide
Triamcinolone	Aristocort, Azmacort, Kenalog, Triamcine
Prednisone	Apo-Prednisone, Deltasone, Novo-Prednisone, Prednisone, Winpred
Predinsolone Sodium Phosphate	Pediapred
Long-acting Inhaled β_2-agonists	
Salmeterol Xinafoate	Serevent

Formoterol Fumarate	Foradil, Oxese
Leukotriene Modifiers	
Zafirlukast	Accolate
Montelukast	Singulair
Respiratory Smooth Muscle Relaxants (Spasmolytics)	
Oxtriphylline	Apo-Oxtriphylline, Choledyl, Novo-Triphyl, Rouphylline
Theophylline	Apo-Theo-La, Novo-Theophyl, Slo-Bid, Theolair, Theochron, Theo-Dur, Theo-SR, Uniphyl
Unclassified Therapeutic Agents	
Sodium Cromoglycate	Gen-Cromoglycate, Intal, Nalcrom, Apo/ Novo /Nu-Cromolyn,
Ketotifen Fumarate	Apo/Novo/Nu/Pms-Ketotifen, Zaditen
Nedocromil SO4	Tilade

2.1.3.1 Reliever medication

Reliever medications include the bronchodilators (predominantly short-acting inhaled β_2-agonists) which bring immediate, fast-acting relief from the brochospasm associated with an asthma attack by relaxing the muscles around the bronchi. Their effect is usually of a short duration although some longer acting β_2-agonists can bring relief for up to 12 hours, as they are lipophilic, meaning that the drug with remain in fat tissue for extended periods releasing slowly into the system (15). Other reliever medications include ipratropium bromide, which is considered to be less effective than short-acting β_2-agonists but appropriate for persons showing low tolerance for β_2-agonist drugs (4).

The dilemma regarding the use of short-acting β_2-agonist medication for the control of asthma is that although these medications provide the best (and often only) available treatment for the immediate relief of asthma symptoms, some research suggests they may become ineffective after increased and extended dosing (16). Worse

yet, research also suggests that in some circumstances the use of short-acting β_2-agonists may intensify the disease (17).

2.1.3.2 Controller medication

Both anti-inflammatory medications, steroidal (e.g., oral and inhaled glucocorticosteroids, oral leukotriene-receptor antagonists) and non-steroidal (e.g., inhaled cromoglycate and oral nedocromil), are used to maintain control of asthma. Corticosteroids provide relief from the disease by reducing both the inflammation of the airways, and the production of mucus. The effects of these drugs are gradual and as such they are prescribed for use as long-term maintenance therapy for the control of asthma (4). These medications address airway inflammation but do not relieve the immediate acute symptoms during an asthma attack. Long-acting β_2-agonists also fall into the category of controller medications as they provide prolonged relief from bronchial constriction (up to 12 hours).

A principal side-effect associated with anti-inflammatory drug use is mild fungal infection of the mouth and throat (candidiasis). There is also an additional concern that growth retardation may result as a side effect of the treatment for children using corticosteroid drugs in high doses or in oral form over long periods of time (18). A reduction in bone mineral density is a side-effect associated with oral corticosteroid use that is especially concerning for very old and very young persons with asthma (18).

2.1.4 The management of asthma

The CACG favour the "continuum approach" (Figure 1-1, page 3) (12) for the management of asthma as opposed to the step-wise approach endorsed by the National Institutes of Health in the United States (19). The CCG for the appropriate treatment of asthma aligns a pharmacological regimen with the corresponding symptom characteristics and severity of the individual's disease. It also stresses the importance of education and environmental control in the management of asthma. The CCG proposes an algorithm for the management of asthma that focuses on four main areas: diagnosis; achievement of control; maintenance of control; and, regular follow-up.

Current recommendations state that if a short-acting β_2-agonist is needed more than 3 times a week, 400-1000 μg per day of beclomethasone-chlorofluorocarbon (*BDP-CFC*) or its equivalent should be initiated (4;12), this is 200-1000 μg per day for children (4). For children requiring at least 400μg per day of *BDP-CFC,* a steroid sparing medication such as salmeterol or montelukast should be added (20). This represents the next phase in the continuum where symptom characteristics are considered "persistent" and the severity of asthma is rated "moderate" or worse. When acceptable control is achieved, the goal of management is to establish the minimal amount of medication needed to maintain symptom control.

Regular follow-up and re-evaluation of the treatment regimen is critical to asthma management. This includes the creation of an action plan, ongoing evaluation of environmental control, confirmation that compliance with medication is maintained, continuing education and, if required, specialist referral (4).

2.2 Literature Review

2.2.1 International research history

In the 1960s, 1970s, and 1980s there were epidemics of asthma mortalities reported first in six countries and then specifically in New Zealand (21). In the many studies that followed, the epidemics were found to be most strongly associated with isoprenaline forte and fenoterol (21), which have been described as having "the distinction of being high-dose, poorly selective full agonists with relatively greater cardiac side effects." (22)

Research by Stolley in 1972 attempted to track the time-trend data to better understand the relationship between isoprenaline forte and asthma mortality. In six of the eight countries in which the drug was released there was a strong association between the drug and asthma deaths. In the two remaining countries, the drug was introduced late in the asthma season resulting in low sales; thus, they did not experience the mortality epidemics of the other countries. There were no mortality epidemics in the U.S., Canada, Sweden, or West Germany where isoprenaline forte was not licensed (22).

Studies conducted in Australia and the USA examined trends in the use of asthma medications in the 1970s, early to mid 1980s, and early 1990s (23-25). These

studies indicated that since the 1970s, there has been an overall increase in the proportion of asthma prescriptions purchased. They also show that there is greater use of bronchodilators over inhaled corticosteroids. Although trends in the use of bronchodilators were high in these studies, conclusions regarding the characteristics of users were not possible because of the ecological nature of the data.

2.2.2 Canadian research history

Given the international results, a nested case-control study by Spitzer et al. was conducted from 1978 to 1987 and published in 1992 in Saskatchewan to investigate the relationship between death and the use of fenoterol and salbutamol beta$_2$-agonist brochodilators. The study revealed high odds ratios with mortality and fenoterol use (OR=6.1, 95% C.I. 3.1 to 12.2) and salbutamol use (OR=4.1, 95% C.I. 2.1 to 8.0) (17). The odds ratios increased with additional doses of these medications. The subjects using fenoterol regularly, 4 times daily with additional rescue doses as-needed, had worse outcomes at the end of the trial as compared to those who used the medication on an as-needed basis only. Explanations for the increase in risk included the hypothesis that short-acting β_2-agonists may be responsible for worsening the disease's severity and, therefore, the risk of death and near death.

In a study by Habbick et al. investigating the trends in asthma-related medication use between 1989 and 1993 in the Saskatchewan population aged 5 to 54 years, the mean number of prescriptions per person decreased for all drugs to treat asthma (26). From 1989 to 1993, inhaled β_2-agonists decreased from 4.35 to 3.05 mean prescriptions per year and inhaled corticosteroids decreased from 2.98 to 2.25 (26). The amount of fenoterol and inhaled salbutamol bronchodilators dispensed per person decreased by 40% and 58%, respectively while the amount of inhaled corticosteroid increased by 35% in 1989 to 1992 and then declined slightly in 1993. The authors offered as explanation the possibility that the observed changes in the use of these drugs may have been related to the awareness among health care workers of studies relating use of short-acting β_2-agonists to asthma deaths and near deaths. Since the analysis was based on aggregated data and not on individual level data, the appropriateness of an individual's dosage or coincident drug use could not investigated.

Later, serious criticism was brought against these two Canadian studies because of the disparity in potency between fenoterol, being the much stronger, and salbutamol (albuterol) (21;27). The criticisms of the Spitzer et al. study extended to the methodology, but more importantly evidence that questioned a simple relationship between the use of beta$_2$-agonists and death emerged with the absence of mortality epidemics in countries where short-acting, beta$_2$-agonist purchases (excluding fenoterol and isoprenaline forte) increased rapidly (21). Upon reanalysis of the Spitzer et al. study, it was found that excessive dosing of beta$_2$-agonists was, in fact, the risk associated with death and near-death (27).

2.2.3 Current Canadian research

2.2.3.1 Use of asthma medications

In a recent study by Lynd et al., researchers performed a retrospective longitudinal analysis on three years of prescription claims in British Columbia to identify factors associated with the rising use of short-acting, beta$_2$-agonists in the province (28). Consistent with the recent trend of asthma prevalence reaching a plateau (7), researchers discovered that short-acting beta$_2$-agonists prescription claims did not increase or decrease between 1996 to 1998. They also discovered that inhaled corticosteroids did not increase in use in a trend analysis during that same period.

Additionally, Lynd et al. discovered that adults between the ages of 18 to 34 years were 1.5 times more likely to increase their short-acting beta$_2$-agonist use than those less than 18 years of age. Males were more likely than females to increase their beta$_2$-agonist use by 1.7 times. Persons receiving social assistance were 2.3 times more likely to increase their use of beta$_2$-agonists than those who were not. Finally, a varied dose of inhaled corticosteroids between 1996 and 1998 also affected the increase in short-acting beta$_2$-agonist used (28).

In research by Diette et al., factors associated with the overuse of short-acting beta$_2$-agonists and the under use of inhaled corticosteroids were analysed from a sample of employed 18 to 65 year olds with asthma who were enrolled in managed health care plans (25). Their results showed that inhaled beta$_2$-agonists were the most frequently

used medication in 1993, with 94.4% of moderate or severe asthma patients using these drugs, followed by inhaled corticosteroids (with 66.6% using).

The most common combination used by subjects in this study was inhaled $beta_2$-agonists with inhaled corticosteroids (17.4% of patients) in 1993 (25). The second most popular combination of medications was $beta_2$-agonists, inhaled corticosteroids, and theophyllines (7.6% of patients).

Short-acting β_2-agonists were used excessively by 15.8% of the moderate to severe asthma patients and 3.6% of the mild asthma patients in the Diette et al. study (25). Of the moderate to severe asthma patients who were using $beta_2$-agonists excessively, 10.7% were not using any form of corticosteroid (inhaled or oral corticosteroid), but 42.7% were using only an oral corticosteroid.

The excessive use of short-acting $beta_2$-agonists appeared to be associated with more severe asthma symptoms. Those with moderate to severe asthma who used $beta_2$-agonists excessively were more likely to use inhaled corticosteroids, although in insufficient amounts. Excessive users of inhaled short-acting β_2-agonists were also more likely to have a peak flow meter, have greater asthma knowledge, be more likely to use other asthma medications, be more likely to use heath care services, and have greater satisfaction with their care. Excessive $beta_2$-agonist use was also associated with being a patient of a pulmonologist rather than a general practitioner or allergist (25).

Inhaled corticosteroids were underused by 64% of the moderate to severe asthma patients. Inadequate use of inhaled corticosteroids was associated with using less $beta_2$-agonists, being female, being non-white, being younger (18-34 years old), having fewer asthma symptoms, and working full time (25). It was also associated with not having a peak flow meter, lacking asthma knowledge, being less likely to use other asthma medications, being less likely to use hospital or emergency departments in the last year, and having lower satisfaction with care. Under use of inhaled corticosteroids was also associated with being a patient of generalist rather than a pulmonologist or allergist.

In a recent study by Blais et al. to assess the appropriate use of inhaled short-acting β_2-agonists and inhaled long-acting $beta_2$-agonists in the province of Quebec, researchers found that short-acting $beta_2$-agonists were overused, inhaled corticosteroids were underused, and long-acting $beta_2$-agonists were used inappropriately (according to

the 1996 CCG) (29). The subjects in the study were covered by the Régie de l'assurance maladie du Québec (RAMQ) which covers persons 65 years old and older, welfare recipients, and persons without access to group health insurance. The highest proportion of appropriate use of short-acting beta$_2$-agonists was among the youngest asthma patients in the study (5-18 years old). Appropriate use of medications was greater when prescribed by a specialist, pediatricians (for short-acting beta$_2$-agonists) and respirologists (for long-acting beta$_2$-agonists).

Researchers showed that while appropriate use was best among those aged 5-18 years, the RAMQ drug plan in Quebec provides free prescription medications to children less than 18 years of age. Blais et al. offered that since inhaled corticosteroids are much more expensive than short-acting beta$_2$-agonists, differential costs may help to explain why appropriateness in use declines after the age of eighteen. Adult male patients were of particular concern to researchers in the study because of their high inappropriate use of inhaled short-acting beta$_2$-agonists (29).

In an earlier study by Laurier et al. in the early 1990s in the province of Quebec (using a similar population to the previously mentioned Quebec study), researchers found that those who used theophyllines comprised the largest proportion of users (75.1% in the seniors group and 68.4% in the income security [welfare] recipients group) receiving ambulatory drug reimbursement programs (30). Inhaled beta$_2$-agonist users made up the second most populous group with 60.3% of seniors and 57.6% of welfare recipients. Inhaled corticosteroid users made the third most populous group with 43.2% of seniors and 35.6% of welfare recipients.

Upon sampling these two populations to discover which specific asthma drugs were being utilized, the results were similar for the two groups. That is, both the seniors and the welfare recipients used beta$_2$-agonist inhaled salbutamol 100 μg most commonly (46.1% for seniors and 40.4% for welfare recipients) and both had 4.1 mean prescriptions per year (30). Most of the subjects used at least one form of theophylline. Researchers found that the seniors' mean number of prescriptions per year were slightly greater for all asthma drugs compared to the welfare recipients. The most common combinations of preparations for both seniors and welfare recipients were inhaled beta$_2$-agonists and inhaled corticosteroids (43% for seniors and 34.9% for welfare recipients),

followed by short-acting inhaled beta$_2$-agonists, inhaled corticosteroids, and theophyllines. The third most commonly used combination was beta$_2$-agonists, inhaled corticosteroids, theophyllines, and ipratropium bromide (30).

2.2.3.2 Asthma and seasonality

The literature concerning the relationship between the seasons and asthma focussed mainly on asthma hospitalizations and/or emergency room treatment as the outcome measure. The research is certain and unanimous on one area, that adults and children must be separated in these studies as they are affected by the seasons differently and distinctly (31). The results across the reviewed research showed that pre-school and school age children experienced peak seasonal asthma exacerbations in September, and then had disease lows or seasonal troughs over the summer months, particularly in August (31-33). They then had peak exacerbations in December, secondary to those in September. In January there was a sudden drop in exacerbations that was inconsistent with researcher's expectations, but was not explored (31-33).

In the Crighton et al. study, the most important finding was that seasonal patterns were driven by the youngest (0-4 years) group, in particular by males. This influence was reversed in older groups where females were hospitalized more often. A significant difference was found between males and females in the 0-4 year, and 5-9 year old age groups, wherein males were hospitalized two to three times the rate of females. The older subjects in the study had little change for either sex. The variation for adults that could be observed was for those aged 60 years and older (32).

In the Johnston et al. study, researchers established the association between the presence of rhinoviruses and asthma exacerbation, with some children needing to go to the emergency room (33). Those who did not seek emergency care, the controls, turned out to have more severe asthma than the cases and had controller medication prescribed to them. Controls used environmental control measures such as anti-dust mite bed sheets. Researchers also investigated insurance claims for children's prescriptions for inhaled corticosteroids. They found claims were lowest in August which suggested that children may be using less controller medication immediately before the school year when they were at greatest risk for a virally induced asthma exacerbation. Researchers

also suggested that children may be additionally exposed to a greater allergen load upon return to school in September. Johnston et al. concluded that children using anti-inflammatory medication were less likely to go to the emergency room during the period of expected peak exacerbations (33).

Seasonal variation in asthma among children was shown to be the same in England (from eight years of collected data) as it has been in other similar time-trend studies (31). Children 0-4 years and 5-14 years old had asthma exacerbations, as measured by hospital admissions, peaked 100% above the average in late September, followed by a lesser peak in early December. When measured by general practitioner visits, asthma exacerbations peaked 25% above average in early December followed by late September. Both age groups had minimum values, below average, in August.

For adults in this English study, those aged 15-44 years had peak hospital admissions in late September, and peak general practitioner visits at 30% above average in late June and late September. For adults of 45-64 years of age, hospital admissions were elevated during the winter while general practitioner visits were raised for a short period at the end of June (31).

2.3 Summary and Conclusions

The studies reviewed reveal the trend for a strong reliance on the reliever treatment arm of pharmacological asthma management. Despite recommendations by asthma control experts, asthma patients using medication have continued to favour the use of bronchodilators (short-term inhaled rescue medications) over inhaled corticosteroids (long-term anti-inflammatory medications).

The studies reviewed are based on aggregated data, limiting evaluation of individual drug use patterns associated with prevalence, diagnosis, severity of disease, morbidity and mortality. Also, the studies do not include all age groups which limit knowledge of drug use patterns for the general population and comparability across studies.

Several studies have used the health insurance database alone to investigate the trends in asthma prevalence (34;35). Other studies have used the health insurance database in conjunction with prescription drug databases to validate asthma diagnoses

and examine trends in asthma prevalence and use of asthma-related drugs (2;36). Validation studies have shown that health insurance claims provide a reasonably accurate, reliable and valid representation of health care utilization in the province of Manitoba (37;38). The health insurance claims database was used to develop indicators of health and to predict health outcomes (39;40). In a Saskatchewan based study during the 1980s, over 70% of the asthma patients had at least one asthma related drug prescription in each year of the study period (2).

The reviewed research indicates that there has been an increase in the prevalence of asthma and that prevalence differs by age group and sex. In most studies examining medication use there has been an increase in the prevalent purchase of all asthma medications. Bronchodilators have been favoured over inhaled corticosteroids over the past two decades, although there is some indication that a shift in prescription and drug purchase toward more anti-inflammatory medications may be occurring. This behaviour shift, if real, supports the CCG for the management of asthma.

Continued research and surveillance at the individual level of data analysis is warranted. This information is invaluable for the evaluation of treatment guidelines and practice. It also enhances general understanding of the epidemiology of the disease. Ongoing study of the use patterns of inhaled corticosteroids alone and in combination with bronchodilators in populations of children and adults with moderate to severe asthma would be an important contribution to our understanding of the disease.

3. RESEARCH METHODS AND PROCEDURES

3.1 Introduction

This thesis work is one part of a larger study being conducted by Dr. A. Senthilselvan and Dr. J.A. Dosman entitled Prevalence, Severity and Treatment of Asthma in Saskatchewan, 1989 to 1998. The overall objectives of that study are as follows:

1. [determine] changes and regional variations in period prevalence of physician-diagnosed asthma, chronic obstructive pulmonary disease (COPD), and bronchitis;

2. [determine] changes and regional variations in severity of asthma, COPD, and bronchitis;

3. [determine] period prevalence and severity of asthma, COPD, and bronchitis among the registered Indian population;

4. [determine] changes and regional variations in use of asthma medication among asthma cases.

The purpose of the analysis herein, is to address the fourth objective of the larger study. The larger study received compiled data from The Saskatchewan Health Department to address its research questions. The databases used to compile data for this portion of the research were a demographic information database, The Physician Services Database and the Outpatient Prescription Drug Database.

Information regarding hospital services from the Hospital Services Database was supplied to the primary researchers of the larger study. This information was not necessary to the research questions concerning this particular study.

3.2 International Classification of Disease for Asthma

The International Classification of Diseases (ICD) is an internationally recognized structured coding system published by the World Health Organization and it was used to classify asthma cases in the overall study.

All individuals covered under the provincial health plan that received a coding of 493.0 by a physician for each year of the study, from January 1, 1991 to December 31, 2000, were included in the asthma database. Code 493.0 is extrinsic asthma (asthma without mention of status asthmaticus).

3.3 Data Source

The Outpatient Prescription Drug Database and The Physician Services Database, which were combined for this study's purposes, were originally established for administrative purposes. Their primary function is to record and process services rendered by the health care system so that health care professionals and organizations can be appropriately remunerated. The Physician Services Database consists of a record of persons who have visited their physician at least once in a given calendar year, from January 1, 1991 to December 31, 2000, and received a diagnosis of asthma. The purpose of the visit is recorded according to a fee for service billing schedule by the physician and submitted to Saskatchewan Health.

Saskatchewan Health uses the Person Registry System (PRS) which is a central computer file that contains the unique health services number (HSN), name, address, sex, date of birth, and dates of health coverage initiation and termination of every individual under Saskatchewan Health's jurisdiction. This file is updated daily for name or address changes, births, deaths, and new arrivals and departures from the province (41). Saskatchewan residents are required to obtain a health card to receive health care benefits from the provincial government. The nine-digit HSN on the health card uniquely identifies each eligible client. The HSN and attached information are maintained in the Health Insurance Registration File (HIRF) and are updated regularly by the Health Registration Department.

The Physician Drug Database containing information pertaining to an individual's physician visit is combined with their demographic information as a

healthcare client including: a pseudo-identification number (replacing the HSN); age (in 5-year age categories from 0 to 64 years); sex; health district; service date, and; primary diagnosis.

The Outpatient Prescription Drug Database is a record of Saskatchewan residents who have filled at least one drug prescription in any given year from January 1, 1991 to December 31, 2000. The database provides information regarding the name, dispensing date, drug class and drug category, quantity, strength, and form of any medication purchased by an individual in Saskatchewan covered under the provincial health insurance plan under the control of the Medical Services Branch of Saskatchewan. For the purposes of this study, a pseudo-identification number linked these individuals across all databases under the management of Saskatchewan Health.

3.4 Study Design

This is a descriptive study based on data drawn from the population of all Saskatchewan residents covered under the provincial health insurance plan from January 1, 1991 to December 31, 2000. There is a high level of detailed patient/client information in these databases, which a can be relied upon for a reasonable degree of accuracy. Both this and the larger study are ensured a suitable level of confidence in the identification of nearly all known cases of asthma and the purchase of asthma medications in the Province of Saskatchewan from 1991 to 2000.

3.5 Subjects for Analysis

Health insurance coverage is extended to all residents of the Province of Saskatchewan by the provincial government with the exception of members of the Canadian Armed Forces, members of the Royal Canadian Mounted Police and, inmates of federal prisons (42). These groups are insured under federal government programs. Those persons identified as Metis or First Nations are also often covered under federal health care plans. First Nations persons who were covered under the provincial health care insurance plan for the study period were identified by Saskatchewan Health using the Person Registry System (PRS) and excluded from these analyses. All other Saskatchewan residents who were covered under the provincial health care insurance

plan from January 1, 1991 to December 31, 2000 formed the study population from which subjects were drawn. Figure 3-1 describes the conceptual framework used for asthma subject extraction.

The Outpatient Physician Services database contains information sent by physicians for payment for medical services rendered to patients (fee for service or alternate payment plan). The Outpatient Prescription Drug database includes information of all prescription drugs purchased by Saskatchewan clients. These drugs are listed in the Saskatchewan Formulary which is updated yearly (43).

For each calendar year from January 1, 1991 to December 31, 2000, the study utilized data complied by Saskatchewan Health that electronically linked persons with extrinsic asthma (ICD9: 493.0) between databases. Persons with asthma identified in each calendar year in the Outpatient Physician Services database were joined to their individual purchases of asthma medications in the Outpatient Prescription Drug database.

To maintain confidentiality, 5-digit residence codes were provided only for those subjects living in cities with a population of 10,000 or more. For subjects living in smaller centres (<10,000), identification of those living in townships and rural areas was gathered and provided by Saskatchewan Health with the original data set.
For each year, Saskatchewan Health linked physician-diagnosed asthma cases (ICD9: 493.0) to the individual's use of the Outpatient Prescription Drug database. In addressing the analysis of the proportion of the medication purchases within the first thesis question, all Saskatchewan residents with physician-diagnosed asthma, who were covered under the provincial healthcare insurance plan between 1991 and 2000, were included in the denominator. For the remaining thesis questions, only persons who appeared in the Outpatient Prescription Drug database each year were included in the analyses.

3.5.1 Age categories

The division of age categories was based on the study of the prevalence of asthma in Saskatchewan for the years 1981 to 1990 (2) which served as a parent document for this study.

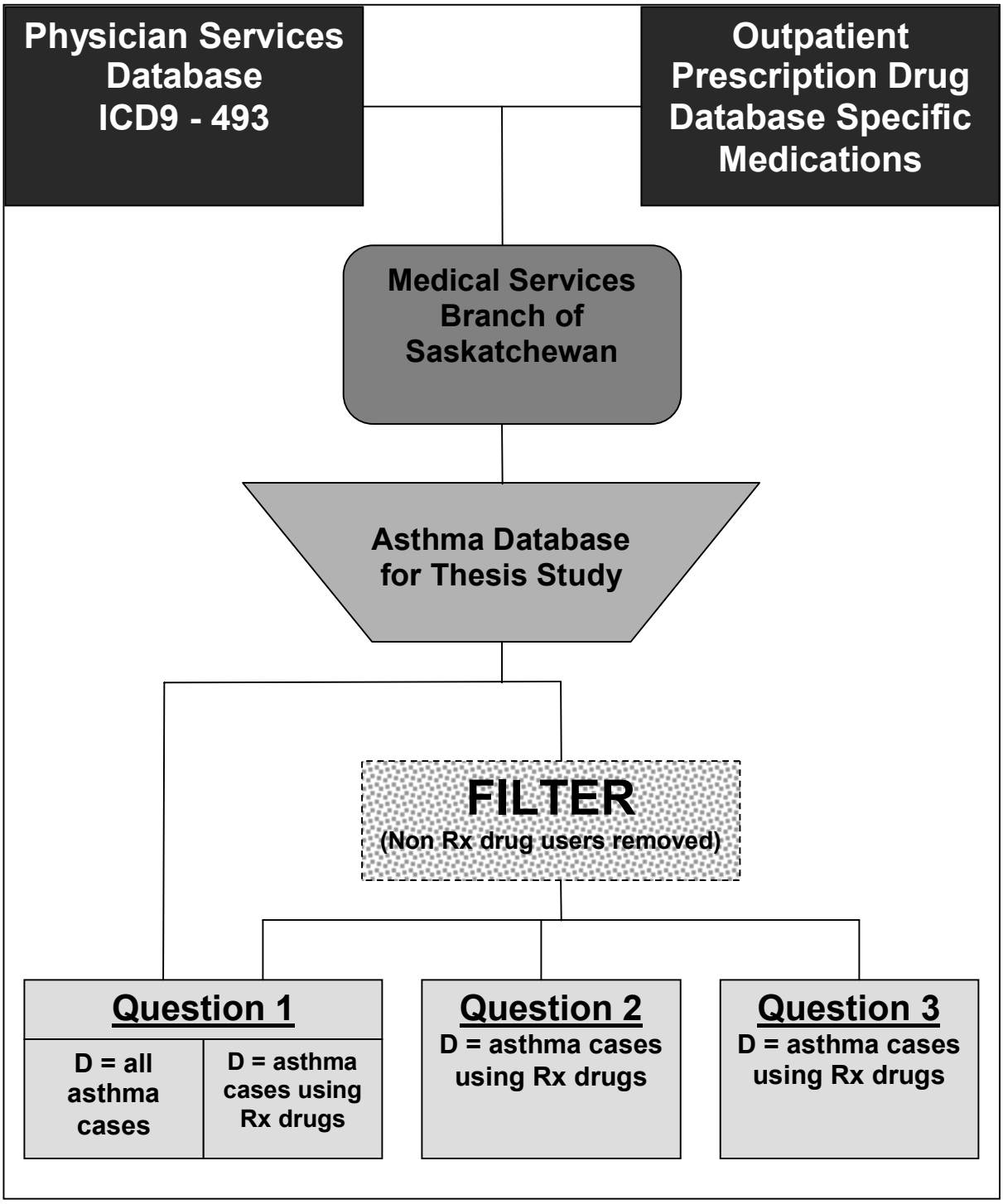

Figure 3-1 Data extraction and analysis conceptual framework.

3.6 Operational Definitions

Asthma: A subject was defined as having asthma by the first visit to a physician in each calendar year, at which time the subject received a diagnosis of ICD9: 493.0.

Purchaser: The terms user and purchaser are used interchangeably.

Use (of medications): The term "use" describes the purchase of one or more asthma prescription medications by persons with physician-diagnosed asthma.

User: A user is defined as a person with physician-diagnosed asthma in each study year that has purchased at least one prescription of asthma medication.

3.7 Ethical Considerations

The anonymity of the subjects in this study was assured by Saskatchewan Health through the replacement of their Health Service Numbers (HSNs) with pseudo-identification numbers. The database consisted of large numbers of cases, an average of 29,643 persons per year for the ten years of the study period.

As indicated on the ethics approval found in Appendix A, the asthma database is accessible only to those persons involved in the larger study, Prevalence, Severity, and Treatment of Asthma in Saskatchewan, 1989 to 1998, under the supervision of Dr. A. Senthilselvan and Dr. D. Rennie. Upon conclusion of the study herein, access to the database will be discontinued, and all working copies of the database will be erased or given to Dr. A. Senthilselvan.

3.8 Data Analysis

Variables were examined by using frequencies and cross tabulations. The linear by linear test for trends was used for examining categorical data over time. Differences were claimed to be statistically significant when the p value was less than 0.05. Statistical computations were performed using SPSS version 11.0 software.

3.8.1 Research question 1:

For each calendar year, the proportion of asthma cases that purchased asthma medication was obtained for age, sex, region, and medication group. There was a change in the health region boundaries in Saskatchewan in 1993 from 33 Health Districts to 13 Regional Health Authorities. The current northernmost health region consisted of three Health Authorities: Athabasca; Keewatin Yatthé; and, Mamawetan Churchill River. For this study, regional health authorities were used to examine proportions of asthma users by region. Changes in the proportion of asthma medication use over time were examined using a linear by linear test for trends analysis. The denominator for this portion of the analysis was all physician-diagnosed cases of asthma that had at least one physician visit for each calendar year.

For each calendar year, the mean (standard deviation, sd) number of asthma medications per person was examined by age, sex, and medication group for all asthma cases that purchased at least one asthma medication. The denominator for these analyses included only those cases where a purchase of at least one asthma medication occurred in a given calendar year. Changes in the mean (sd) number of asthma medications over time were examined by age group, sex, and by sex within age groups. The overall mean number of prescriptions and the proportion of purchasers by drug group for the ten year study period were examined. The mean number of prescriptions per purchaser was examined by sex within age groups for 1991, 1994, 1997, and 2000. Finally, for the year 2000, each medication group was assessed for associations with sex, and sex within age group using chi-square test for proportion.

3.8.2 Research question 2:

The concurrent use of asthma medications was investigated by obtaining the proportions of combinations of prescriptions purchased by asthma cases in each calendar year. Persons who used only short-acting, $beta_2$-agonists or only inhaled corticosteroids were included in these analyses. Persons who used single preparations of oral corticosteroids, antispasmodics, respiratory smooth muscle relaxants, or unclassified therapeutic agents were excluded. The proportion of persons using specific asthma medication combinations was examined over the ten years. The years 1991, 1994, 1997,

and 2000 were highlighted for examination of combination use by age groups. Changes in the proportion of asthma medication use over time were examined using the linear by linear test for trends. The denominator for this portion of analysis was physician-diagnosed cases of asthma that utilized the Outpatient Prescription Drug Plan for the purchase of asthma medications for each given year, excluding those who used only single preparations of medications of the above excluded (single use) drug groups in each calendar year.

3.8.3 Research question 3:

For each calendar year, for the years 1996 to 2000, the numbers of inhaled short-acting β_2-adrenergic agonist and inhaled corticosteroid prescriptions used per month were calculated. The frequencies of monthly prescriptions were examined by age groups, and sex for these years. Trends in the number of prescriptions were tested using linear by linear test for trends. The denominator for this portion of analysis was all physician-diagnosed cases of asthma who utilized the Outpatient Prescription Drug Plan for the purchase of asthma medications at least once in a given calendar year.

4. RESULTS

4.1 Research Question #1:

Is there variation in percentage of users of each drug for the treatment of asthma by age, gender and region per year and in the mean number of asthma medications per person by age, gender per year from January 1, 1991 to December 31, 2000?

4.1.1 Users with asthma by year

Table 4-1 shows the proportion of persons in the asthma population of Saskatchewan for the years 1991 to 2000 who purchased at least one asthma medication in each year. The average number of persons with asthma, between the ages of 0 to 64, in the years 1991 to 2000 was 29,643 persons. The year with the lowest population of persons with asthma was 1991 with 25,277 persons. The highest asthma population year was in 2000, with 32,621 persons.

Table 4-1 Total number of persons with asthma in Saskatchewan aged 0 to 64 and proportion who purchased at least one asthma medication by year, 1991 to 2000*

Year	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	Total
Total population (N)	25277	26058	27562	28825	30234	31048	31461	31071	32273	32621	296430
% purchased one or more prescription	76.1	76.1	74.8	76.1	78.4	78.4	77.7	77.6	79.3	78.8	77.4

*persons received a diagnosis of asthma with their first physician visit for each year

On average, 77.4% of persons between the ages of 0 to 64 years used at least one asthma drug. There was a small increase in the proportion of persons with asthma who purchased asthma medication over the 10 year study period, which was a significant result on a linear by linear test for trend at: $\chi^2 = 214.5$, df 1, $p < 0.001$. The year in which the lowest proportion of the asthma population in Saskatchewan purchased at least one asthma medication was 1993. The greatest proportion of purchasers was in 1999 with 79.3% of the asthma population purchasing at least one asthma medication.

4.1.2 Users with asthma by age and year

For 1991 to 2000, those aged 35 to 64 years were the greatest purchasers of asthma medications (78.2%), followed by 15-34 year old purchasers (77.3%) (Table 4-2). The average proportion of 5-14 year old medication purchasers with asthma was 77.2% and the average proportion of 0-4 year olds was 75.4% over the ten year period of the study.

Children aged 0-4 years had the highest increase in the proportion of users of asthma medication between 1991 and 2000 (6.1%). Users in all age groups decreased in the percentage of persons purchasing asthma medications in 1993. The decrease was small for the 15-34 year old age group in comparison to other age groups. In the last two years of the study period, all of the age groups had similar proportions of asthma medication users, which was slightly less than 80% of the asthma population. The linear by linear test for trends within each age group had significant results (all $p < 0.001$).

Table 4-2 Number of persons with asthma and proportion who purchased an asthma medication by age and year, 1991 to 2000.*

	0-4 years		5-14 years		15-34 years		35-64 years	
Year	%	N†	%	N†	%	N†	%	N†
1991	73.9	3971	77.5	7870	75.5	7013	76.4	6423
1992	73.9	4084	76.1	7836	76.6	7413	76.6	6725
1993	72.1	3973	73.8	8440	76.1	8093	75.8	7056
1994	73.5	3933	75.8	8902	76.8	8574	77.0	7416
1995	75.2	4105	78.6	9460	78.4	8829	79.8	7840
1996	74.7	4228	77.8	9276	79.0	9207	80.2	8337
1997	76.0	4156	76.8	8972	77.8	9344	79.3	8989
1998	75.4	4113	76.6	8336	77.9	9516	79.0	9106
1999	78.8	4122	79.5	8820	77.8	9571	80.6	9760
2000	80.0	3973	79.3	8466	77.5	9978	79.0	10204
Total average	75.4	4066	77.2	8638	77.3	8754	78.2	8186

*NB: persons received a diagnosis of asthma with their first physician visit for each year
†N is the denominator

4.1.3 Users with asthma by sex and year

As observed in Table 4-3 during the ten year study period, there was a greater average proportion of males who purchased at least one asthma medication compared with females (78.1% versus 76.5%). The difference between sexes was approximately 2.0% for most years and was found to be significant ($p < 0.001$). The difference between males and females appeared to decrease by 2000. As the male proportion of medication purchasers increased moderately, from 77.5% to 79.4% over the ten year period, the female proportion of purchasers increased (from 74.4% to 78.1%). As seen previously, in the year 1993 there were fewer purchasers of asthma medication for both sexes.

Table 4-3 Number of persons with asthma and proportion of users, aged 0 to 64, in Saskatchewan by sex and year, 1991 to 2000

Year	Male		Female	
	%	N	%	N
1991	77.5	13509	74.4	11768
1992	77.0	13776	75.0	12282
1993	75.7	14506	73.7	13056
1994	76.8	15017	75.3	13808
1995	78.9	15963	77.9	14271
1996	79.1	16063	77.5	14985
1997	78.0	16212	77.4	15249
1998	77.9	15999	77.2	15072
1999	80.2	16444	78.3	15829
2000	79.4	16733	78.1	15888
Overall	78.1	15422	76.5	14221

4.1.4 Users by health region and year

As Table 4-4 shows, a similar proportion of the population purchased at least one asthma medication within a given year of the study period in all health regions, with the exception of the Northern health region. In contrast to the increases observed in other health regions over the ten year study period, the proportion of users in the Northern health region decreased over time and had almost 11.0% fewer purchasers per region than all other 10 health regions from 1994 onward.

Table 4-4 Total number of persons with asthma and the proportion who purchased an asthma medication, aged 0 to 64, in Saskatchewan by health region and year, 1991 to 2000*

Year	Regina Qu'Appelle		Saskatoon		Sun Country		Five Hills		Cypress		Sunrise		Heartland		Kelsey Trail		Prince Albert Parkland		Prairie North		Northern Health Region	
	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N
1991	77.8	6488	72.7	6702	76.2	1699	79.5	1668	76.4	1290	79.1	1962	76.1	1505	77.3	836	75.2	1826	74.7	1153	70.7	147
1992	78.7	6687	71.5	7060	78.4	1865	80.8	1706	75.4	1306	80.2	2116	76.7	1520	77.1	759	74.9	1631	73.0	1224	68.5	184
1993	78.1	7185	71.1	7810	74.0	1670	77.0	1807	72.3	1336	78.0	2118	76.4	1590	74.7	867	76.6	1700	70.4	1285	67.0	194
1994	77.5	8029	72.9	8074	75.0	1757	80.9	1986	77.6	1337	77.9	1911	77.4	1633	76.5	895	77.3	1759	75.9	1235	61.7	209
1995	78.4	8502	77.0	8594	80.0	1757	79.5	2039	77.5	1411	80.6	1944	80.5	1607	79.1	895	78.9	1917	80.3	1330	66.2	237
1996	78.9	8999	77.0	9028	80.1	1698	79.8	2087	77.2	1336	79.6	1844	80.8	1652	79.5	917	78.9	1864	78.6	1385	56.6	235
1997	78.0	9192	76.4	8912	79.1	1839	80.4	2085	75.8	1384	78.3	1933	79.2	1676	79.2	950	77.9	1929	79.9	1311	58.0	243
1998	76.5	9184	77.1	8656	79.7	1940	79.4	2045	77.7	1397	79.9	1906	79.2	1555	76.6	900	79.8	1853	77.0	1394	61.6	237
1999	78.7	9514	79.4	9062	80.7	2121	80.1	2097	84.6	1534	80.5	2006	80.7	1501	77.1	954	80.5	1857	76.6	1399	68.1	226
2000	78.4	9812	78.1	9281	81.3	1981	78.7	2070	77.4	1298	81.5	2166	79.9	1510	80.7	933	81.9	1913	75.7	1426	58.9	224
Total mean	78.1	8359	75.3	8318	78.5	1833	79.6	1959	77.2	1363	79.6	1991	78.7	1575	77.8	891	78.2	1825	76.2	1314	63.7	214

* Persons received a diagnosis of asthma with their first physician visit for each year, N is the denominator

4.1.5 Distributions of asthma prescriptions by age group and calendar year

The number of asthma prescriptions purchased over the ten year study period increased from 129,763 in 1991 to 139,486 in 2000 (Table 4-5). The smallest number of asthma prescriptions was purchased in 1993 (113,997).

The percentage of the total asthma prescriptions per year increased with successive age groups. The 0-4 and 5-14 year old age groups had the lowest percents of asthma prescriptions in each year of the study.

Table 4-5 Percentage of asthma prescriptions purchased by persons with asthma in Saskatchewan by age and year, 1991 to 2000*

Year	Total	0-4 years		5-14 years		15-34 years		35-64 years	
	N	%	N	%	N	%	N	%	N
1991	129763	10.4	13441	24.3	31554	27.4	35517	38.0	49251
1992	126549	10.6	13436	22.8	28829	28.4	35937	38.2	48347
1993	113997	9.6	10934	21.7	24734	30.0	34150	38.8	44179
1994	119297	9.4	11217	22.3	26620	30.2	36074	38.0	45386
1995	130544	9.6	12574	22.8	29758	29.1	37942	38.5	50270
1996	133388	9.7	12932	21.0	28026	29.6	39485	39.7	52945
1997	131813	9.5	12474	19.4	25602	29.1	38321	42.0	55416
1998	129115	8.9	11440	18.2	23497	29.6	38206	43.4	55972
1999	138975	9.7	13445	19.6	27193	27.6	38302	43.2	60035
2000	139486	9.3	13041	19.0	26481	28.4	39672	43.2	60292
10 year average	129293	9.7	12493	21.1	27229	29.0	37361	40.3	56627

*Persons received a diagnosis of asthma with their first physician visit for each year

The 35-64 year old group was the only group to increase in the percentage of asthma prescriptions over the study period. The 35-64 year old group had the highest percentage of prescriptions in every calendar year and at least 7.0% higher than all other age groups throughout the study period.

4.1.6 Distribution of asthma prescriptions by sex and calendar year

The percentage of prescriptions was consistently greater for males over the ten year period than it was for females (Table 4-6). The proportion of prescriptions for males decreased over the study period while that of females increased. The sex difference was narrowed toward the year 2000.

Table 4-6 Percentage of asthma medication purchased by persons with asthma, aged 0 to 64, in Saskatchewan by sex and year, 1991 to 2000*

Year	Total Prescriptions	Male		Female	
	N	%	N	%	N
1991	129763	56.1	72781	43.9	56982
1992	126549	55.1	69717	44.9	56832
1993	113997	54.4	62043	45.6	51954
1994	119297	54.0	64478	46.0	54819
1995	130544	53.9	70353	46.1	60191
1996	133388	52.9	70563	47.1	62825
1997	131813	51.8	68295	48.2	63518
1998	129115	52.5	67765	47.5	61350
1999	138975	52.0	72258	48.0	66717
2000	139486	51.8	72289	48.2	67197
Total mean	129293	53.5	68874	46.6	60239

*Persons with asthma purchased at least one asthma medication in each year

4.1.7 Mean number of prescription purchases by year

Overall, mean prescription purchases decreased over the ten years of the study (Table 4-7). For each year, from 1991 to 2000, the standard deviation for the mean number of prescription purchases per year was greater than the mean number itself. This indicated large variability in the data.

4.1.8 Mean number of prescription purchases by age group and year

For all age groups, the mean number of prescription purchases decreased from 1991 to 2000 (Table 4-8). Those aged 0-4 years and 5-14 years had the lowest mean prescription purchases. The 35-64 year old group had the highest mean prescription

Table 4-7 Mean number of prescriptions purchased by persons with asthma by year, 1991 to 2000

	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
Mean	6.8	6.4	5.5	5.4	5.5	5.5	5.4	5.4	5.4	5.4
Std. Dev.	8.27	7.78	6.64	6.54	6.52	6.68	6.61	6.54	6.56	6.46

Table 4-8 Mean number of prescriptions purchased by persons with asthma by age group and year, 1991 to 2000

	1991		1992		1993		1994		1995		1996		1997		1998		1999		2000	
Age groups	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.
0-4yrs	4.6	5.14	4.5	4.70	3.8	3.69	3.9	3.74	4.1	3.95	4.1	3.89	4.0	3.81	3.7	3.50	4.1	3.71	4.1	3.16
5-14yrs	5.2	5.99	4.8	5.35	4.0	4.24	4.0	4.04	4.0	4.05	3.9	3.88	3.7	3.80	3.7	3.80	3.9	3.94	4.0	3.86
15-34yrs	6.7	6.71	6.3	7.45	5.6	6.25	5.5	6.22	5.9	6.06	5.4	6.20	5.3	6.02	5.2	5.64	5.1	5.70	5.1	5.67
35-64yrs	10.1	11.17	9.4	10.56	8.3	9.20	8.0	9.11	8.0	9.13	8.0	9.35	7.8	9.14	7.8	9.09	7.6	9.06	7.5	8.82

purchases. The 0-4 year old group had the least change in mean purchases over the ten year study period. The 35-64 year old group had the greatest decrease in the mean number of prescriptions from 1991 to 2000 (2.6%).

4.1.9 Mean number of prescription purchases by sex and year

When mean prescription purchases were examined by sex for the years 1991 to 2000, there were decreases for both males and females (Table 4-9). For all years of the study period, males had more average prescription purchases per year than females. When the mean number of prescription purchases was considered by age and sex (Table 4-10), the greatest differences were found for the 15-34 year old and 35-64 year old groups. Within each age group from 1991 to 2000, males had a larger mean number of prescriptions than females. By 2000, both males and females in the 35-64 year old group had the highest mean number of prescription use, 7.81 and 7.23, respectively.

Tables 4-8 and 4-9 showed that the mean number of prescriptions decreased sharply for both sexes, within and across age groups, from 1991 to 1993 and seemed to plateau or stabilize to 2000.

Table 4-9 Mean number of prescriptions purchased by persons with asthma by sex and year, 1991 to 2000

Year	Male		Female		All	
	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.
1991	7.0	8.44	6.5	8.07	6.8	8.27
1992	6.6	7.79	6.2	7.75	6.4	7.78
1993	5.7	6.55	5.4	6.74	5.5	6.64
1994	5.6	6.55	5.3	6.52	5.4	6.54
1995	5.6	6.44	5.4	6.62	5.5	6.52
1996	5.6	6.51	5.4	6.85	5.5	6.68
1997	5.4	6.44	5.4	6.79	5.4	6.61
1998	5.4	6.34	5.3	6.74	5.4	6.54
1999	5.5	6.29	5.4	6.88	5.4	6.56
2000	5.4	6.12	5.4	6.80	5.4	6.46
Overall	5.7	6.75	5.5	6.96	5.6	6.85

Table 4-10 Mean number of prescriptions purchased by persons with asthma by age group, sex and year, 1991 to 2000

Year	0-4 years				5-14 years				15-34 years				35-64 years			
	Male		Female		Male		Female		Male		Female		Male		Female	
	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.
1991	4.8	5.21	4.3	4.98	5.4	6.08	4.9	5.82	7.3	8.09	6.2	7.57	11.2	12.15	9.1	10.22
1992	4.6	4.81	4.3	5.37	5.0	5.37	4.6	5.31	7.1	7.87	5.6	6.94	10.2	11.03	8.8	10.13
1993	3.9	3.78	3.7	3.53	4.1	4.30	3.8	4.16	6.1	6.52	5.0	5.92	8.9	9.37	7.8	9.05
1994	4.0	3.81	3.6	3.61	4.1	4.27	3.7	3.67	6.0	6.50	5.0	5.89	8.7	9.58	7.4	8.72
1995	4.1	3.97	4.0	3.89	4.1	4.16	3.8	3.87	6.0	6.27	5.0	5.81	8.7	9.47	7.6	8.84
1996	4.2	4.06	3.9	3.57	4.0	3.96	3.6	3.75	5.8	6.31	5.0	6.06	8.4	9.57	7.5	9.17
1997	4.0	4.02	3.8	3.43	3.9	3.86	3.5	3.69	5.6	6.15	4.9	5.87	8.2	9.39	7.5	8.94
1998	3.9	3.68	3.4	3.16	3.8	3.68	3.5	3.96	5.6	5.74	4.7	5.52	8.3	9.29	7.4	8.93
1999	4.3	3.85	3.8	3.43	4.1	4.01	3.6	3.81	5.5	5.61	4.9	5.77	8.1	9.20	7.3	8.94
2000	4.2	3.64	3.9	3.56	4.1	3.92	3.8	3.75	5.4	5.55	4.8	5.76	7.8	8.77	7.2	8.86
Total Mean	4.2	4.12	3.9	3.79	4.2	4.41	3.9	4.22	6.0	6.45	5.1	6.08	8.7	9.76	7.7	9.15

4.1.10 Proportion of users and mean number of prescriptions by drug groups

The drug groups selected for this portion of the analysis were the major medications used by persons with asthma over the ten year study period. Separated into medication groups according to the Saskatchewan Health Prescription Drug Plan Formulary (43), we observed which asthma medications increased and decreased over the ten years of the study period (Table 4-11).

4.1.10.1 Short-acting inhaled beta$_2$-agonists

Short-acting, inhaled beta$_2$–agonists were the predominant asthma medication used by persons with asthma in this study. This was reflected both in the proportion of persons purchasing the medication and within their mean number of prescriptions. Over the study period the proportion of persons purchasing inhaled short-acting beta$_2$–agonists remained relatively steady, but the mean number of prescriptions gradually decreased.

Between 1991 and 1993 there was a significant decline in the purchasing of inhaled beta$_2$-agonists, from 79.7% in 1991 to 75.9% in 1993. After 1993, the proportion purchased increased gradually to the end of the study period to maintain a percentage in the upper seventies.

4.1.10.2 Inhaled corticosteroids

The greatest increase in use over the ten year study period was in the inhaled corticosteroid medication group, from 41.5% in 1991 to 70.4% in 2000. Mean prescription drug purchases nearly doubled by 2000 but were still much lower than the mean number of prescriptions of inhaled short-acting beta$_2$-agonists.

4.1.10.3 Oral corticosteroids

The proportion of persons purchasing oral corticosteroids increased over the ten year study period. However, the mean number of prescriptions per person remained relatively constant throughout the study period.

Table 4-11 Proportion of asthma medications purchased by persons with asthma and mean number of prescriptions per purchaser by year, 1991 to 2000

Medication	1991		1992		1993		1994		1995		1996		1997		1998		1999		2000	
	User %	Mean x	User %	Mean x	User %	Mean x	User %	Mean x	User %	Mean x	User %	Mean x	User %	Mean x	User %	Mean x	User %	Mean x	User %	Mean x
Short-acting β_2	79.7	3.5	78.5	3.2	75.9	2.8	76.3	2.7	76.8	2.6	77.1	2.6	77.6	2.6	79.3	2.6	78.3	2.6	78.9	2.5
Inhaled Corticosteroids	41.5	1.2	48.5	1.4	54.9	1.4	58.1	1.5	64.3	1.7	66.4	1.8	66.8	1.8	65.9	1.8	69.9	1.9	70.4	2.0
Oral Corticosteroids	14.4	0.3	14.9	0.3	16.9	0.3	18.8	0.4	18.5	0.4	17.2	0.3	17.3	0.3	18.3	0.3	18.9	0.3	18.0	0.3
Oral β_2	16.2	0.3	14.0	0.2	10.9	0.2	9.6	0.1	8.4	0.1	6.1	0.1	5.8	0.1	6.0	0.1	5.0	0.1	4.3	0.1
Theophyllines	15.1	0.6	10.5	0.4	8.0	0.3	5.7	0.3	4.6	0.2	3.9	0.2	3.5	0.2	3.0	0.1	2.6	0.1	2.0	0.1
Sodium Cromoglycates	25.4	0.8	22.3	0.7	16.3	0.4	13.6	0.4	10.8	0.3	7.9	0.2	5.5	0.2	3.4	0.1	2.0	0.1	1.0	0.0
Inhaled Ipratropium Bromide	3.5	0.1	3.1	0.1	3.0	0.1	3.2	0.1	4.1	0.1	4.8	0.2	6.1	0.2	6.3	0.2	7.2	0.2	6.9	0.2
Long-acting β_2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.0	0.4	0.0	0.5	0.0	0.9	0.0	1.2	0.1	1.7	0.1
Nedocromil	0.0	0.0	0.2	0.0	0.2	0.0	0.2	0.0	0.2	0.0	2.0	0.1	1.3	0.0	0.9	0.0	0.6	0.0	0.4	0.0
Ketotifen	0.0	0.0	0.7	0.0	0.6	0.0	0.5	0.0	0.3	0.0	0.3	0.0	0.2	0.0	0.1	0.0	0.1	0.0	0.1	0.0
Combined (Salmeterol & Fluticasone)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.8	0.0	3.1	0.0
Leukotrienes	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.8	0.1	0.1	0.2

4.1.10.4 Oral $beta_2$-agonists

In 1991, 16.2 percent of the population of persons with asthma was taking oral $beta_2$-adrenergic agonists. Over the ten years of the study period that number decreased steadily to 4.3 percent in 2000.

4.1.10.5 Theophyllines

In the early years of the study there was a sizable proportion of persons purchasing theophyllines (15.1%) and a notable mean number of theophylline prescriptions purchased per user (0.60%). Both of these measures decreased markedly by the year 2000.

4.1.10.6 Sodium cromoglycates

At 25.4% in 1991, sodium cromoglycates were purchased by a large percent of persons with asthma. This percentage decreased rapidly over the ten years of the study ending with 1.0% prescriptions purchased per year in 2000. The mean number of prescriptions also decreased quickly from 0.79 in 1991 to 0.03 in 2000. By the end of the study, sodium cromoglycates seemed to disappear from use by persons with asthma.

4.1.10.7 Inhaled ipratropium bromide

Relative to some of the other asthma medications used during the study period, the proportion of purchasers and mean number of prescriptions for inhaled ipratropium bromide was low. However, from 1991 to 2000 the proportion of persons purchasing inhaled ipratropium bromide doubled, as did the mean number of prescriptions. Although the mean prescriptions for inhaled ipratropium bromide decreased from 0.12 in 1991 to 0.09 in 1993, the mean number of prescriptions increased from 1993 to the end of the study period.

4.1.10.8 Long-acting $beta_2$-agonists

Long-acting $beta_2$-agonists were not purchased by persons in the asthma population until 1995. By 2000 the proportion of purchasers was 1.7%.

4.1.10.9 Nedocromil and ketotifen

Nedocromil and Ketotifen were used by a small percentage of the population, at most 2.0% of users, and in very small quantities, at most 0.06 mean prescriptions. Both medication groups showed a decline in use during the study period.

4.1.10.10 Combination medication (salmeterol and fluticasone)

The combination drug of the long-acting $beta_2$-agonist, Salmeterol, and the inhaled corticosteroid, Fluticasone, was not purchased by persons with asthma until the year 2000.

4.1.10.11 Anti-leukotrienes

As a new class of medication, the anti-leukotrienes provided only two years of data. In 1999 the percent of anti-leukotrienes purchased by persons with asthma was 1.8%, and the mean was 0.08 prescriptions per year. In 2000, the proportion of purchasers was 3.1% and the mean number of prescriptions had increased to 0.18.

4.1.11 Mean number of prescriptions for 1991, 1994, 1997, and 2000

Four years of data (1991, 1994, 1997, and 2000) were examined to compare the prescription purchasing behaviour of persons with asthma by class of asthma medication. Each year was compared to the next in chronological order and an overall comment was made after all four years were reviewed individually.

4.1.11.1 Mean number of prescriptions for 1991

Inhaled short-acting $beta_2$-agonists had the greatest mean number of prescriptions compared to all other drugs for the treatment of asthma in 1991 (Table 4-12). This mean increased with successive age groups, with the 35-64 year old age group having the greatest mean number of prescriptions. In all of the age groups, males had a greater mean than females. The difference in the mean number of prescriptions between males and females increased within increasing successive age groups.

Table 4-12 Mean number of prescriptions purchased per purchaser by sex and age for the year 1991

Medication	0-4 years			5-14 years			15-34 years			35-64 years		
	Male Mean	Female Mean	Total Mean	Male Mean	Female Mean	Total Mean	Male Mean	Female Mean	Total Mean	Male Mean	Female Mean	Total Mean
Short-acting β_2	1.7	1.4	1.6	2.6	2.4	2.5	5.1	4.0	4.5	5.5	4.1	4.8
Inhaled Corticosteroids	0.3	0.4	0.4	0.9	0.9	0.9	1.0	1.0	1.0	2.3	2.0	2.1
Oral Corticosteroids	0.2	0.1	0.2	0.1	0.1	0.1	0.2	0.2	0.2	0.7	0.7	0.7
Oral β_2	0.8	0.8	0.8	0.3	0.3	0.3	0.1	0.1	0.1	0.2	0.2	0.2
Theophyllines	0.2	0.2	0.2	0.2	0.2	0.2	0.5	0.5	0.5	1.6	1.4	1.5
Sodium Cromoglycates	1.5	1.4	1.5	1.2	1.0	1.1	0.3	0.3	0.3	0.5	0.5	0.5
Inhaled Ipratropium Bromide	0.1	0.1	0.1	0.0	0.1	0.1	0.0	0.1	0.1	0.4	0.3	0.3
Long-acting β_2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Nedocromil	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Ketotifen	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Combined (Salmeterol & Fluticasone)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Leukotrienes	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

With inhaled corticosteroids in 1991, the mean number of prescriptions increased with successive age groups, from 0.35 for 0-4 year olds, to 2.12 for the 35-64 year olds. There appeared to be little difference between the 5-14 year olds, at 0.91 mean prescriptions per year, and the 15-34 year olds at 1.00 mean prescriptions. The difference between males and females was small for all age groups, except the 35-64 year old group, which had a difference of 0.32.

Oral corticosteroids had the greatest mean number of prescriptions among the 35-64 year old group, 0.69 mean prescriptions per year, though again, the mean prescriptions increased with age groups. The smallest mean number of prescriptions was among the 5-14 year old group with 0.12 mean prescriptions per year, followed by the 0-4 year old group with 0.14 mean prescriptions per year. The difference between males and females was small for all age groups.

In 1991, oral $beta_2$-agonists were utilized most by younger children. The 0-4 year old age group had the highest mean number of prescriptions, at 0.78, followed by 5-14 year olds at 0.29. The difference between males and females was small for all age groups.

In 1991, the mean number of prescriptions for theophyllines per year increased with age from 0.18 for 0-4 year olds to 1.50 for 35-64 year olds. The difference between males and females was small for all age groups except for the 35-64 year old group, which had a difference of 0.21.

Sodium cromoglycates seemed to be used for children, since the mean number of prescriptions per year decreased with decreasing age groups for the year. Those aged 0-4 had the greatest mean at 1.47 prescriptions per year in 1991, and those aged 5-14 had 1.11 mean prescriptions per year. The two older age groups (15-34 years and 35-64 years old) had much smaller means, and the difference between males and females was smaller within the older age groups. In the two younger age groups, males had much higher mean prescriptions of sodium cromoglycates than females.

Inhaled ipratropium bromide seemed to be a drug purchased mainly by the 35-64 year old age group with a mean number of 0.31 prescriptions per year. Other age group's means were 0.50, for 5-14 year and 15-34 year olds, and 0.70 for 0-4 year olds.

The difference between males and females was small for all age groups except for the 35-64 year old group, which had a difference of 0.10.

4.1.11.2 Mean number of prescriptions for 1994

In 1994, short-acting inhaled $beta_2$-agonists had the greatest mean number of prescriptions compared to all other drugs for the treatment of asthma, except for the 0-4 year old age group for whom inhaled corticosteroids were highest (Table 4-13). As in 1991, the mean number of inhaled $beta_2$-agonist prescriptions increased with increasing age. For all age groups, males had a greater mean than females. The sex difference was much greater within the two older age groups (15-34 years and 35-64 years old) than within the two younger age groups. From 1991 to 1994, the mean number of inhaled $beta_2$-agonist prescriptions decreased for all groups.

From 1991 to 1994, the mean number of inhaled corticosteroid prescriptions increased for all groups. The 35-64 year old group still had the largest mean number, with 2.09 prescriptions per year, while the 0-4 year old group had the smallest, with 1.25 inhaled corticosteroid prescriptions per year. In all age groups but the 0-4 year olds, males had moderately greater mean prescriptions than females.

Oral corticosteroids had the same pattern in 1994 as in 1991. The mean number of prescriptions increased slightly, from 1991 to 1994, for all but the 35-64 year old group, which remained the same. The difference between males and females was small within all age groups.

Oral $beta_2$-agonists had greater mean numbers of prescriptions in the younger two age groups (0-4 year and 5-14 year olds) than the older groups, this was the same pattern found in 1991. The difference between males and females was small for all age groups. From 1991 to 1994, the mean number of oral $beta_2$-agonist prescriptions decreased for all groups. Mean theophylline prescriptions were low in all age groups except the 35-64 year old group in 1994. From 1991 to 1994, the mean number of theophylline prescriptions decreased in all groups, especially in the two younger age groups (0-4 year and 5-14 year olds). The difference between males and females was small within all age groups except the 35-64 year old group, which had a difference of 0.10.

Table 4-13 Mean number of prescriptions purchased per purchaser by sex and age for the year 1994

Medication	0-4 years			5-14 years			15-34 years			35-64 years		
	Male Mean	Female Mean	Total Mean	Male Mean	Female Mean	Total Mean	Male Mean	Female Mean	Total Mean	Male Mean	Female Mean	Total Mean
Short-acting β_2	1.1	1.0	1.1	1.6	1.5	1.6	4.1	3.1	3.6	4.5	3.3	3.8
Inhaled Corticosteroids	1.3	1.2	1.3	1.5	1.3	1.4	1.3	1.2	1.2	2.2	2.0	2.1
Oral Corticosteroids	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.3	0.3	0.7	0.7	0.7
Oral β_2	0.4	0.4	0.4	0.2	0.2	0.2	0.0	0.1	0.0	0.1	0.1	0.1
Theophyllines	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.2	0.2	0.8	0.7	0.7
Sodium Cromoglycates	0.8	0.7	0.8	0.6	0.5	0.5	0.1	0.1	0.1	0.2	0.2	0.2
Inhaled Ipratropium Bromide	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.3	0.3	0.3
Long-acting β_2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Nedocromil	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Ketotifen	0.1	0.1	0.1	0.1	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0
Combined (Salmeterol & Fluticasone)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Leukotrienes	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Though the mean number of prescriptions per year was lower in 1994 than 1991 for sodium cromoglycates, the pattern was the same. The two younger age groups (0-4 year and 5-14 year olds), had greater mean prescriptions and greater differences between the means of males and females than the two older age groups (15-34 year and 35 to 64 year olds).

The mean number of prescriptions of inhaled ipratropium bromide per year for 35-64 year olds was the same in 1991 and 1994. Mean prescriptions were low in all age groups except the 35-64 year old group. The difference between males and females was small for all age groups.

In 1994 the mean numbers of prescriptions per year for Nedocromil and Ketotifen were very low. The means seemed to increase with successive age groups and the difference between males and females was small for all age groups.

4.1.11.3 Mean number of prescriptions for 1997

In some user groups in 1997, short-acting inhaled $beta_2$-agonists no longer had the greatest mean number of prescriptions compared to all other drugs for the treatment of asthma (Table 4-14). Since the early 1990s, the mean number of short-acting inhaled $beta_2$-agonists decreased while that of the inhaled corticosteroids increased. As in previous years, the mean number of short-acting $beta_2$-agonist prescriptions increased with increasing successive age groups. Males were more frequent users than females and the difference between the means for sex appeared to be much greater within the older two age groups (15-34 year and 35-64 year olds) than within younger two age groups (0-4 year and 5-14 year olds). From 1994 to 1997, the mean number of inhaled short-acting $beta_2$-agonist prescriptions decreased for all groups.

In 1997, inhaled corticosteroids had the highest mean number of prescriptions in the 0-4 year old and 5-14 year old age groups. The same distribution of the mean number of inhaled corticosteroids prescriptions over age and sex in 1994, was found in 1997 but the values were greater in 1997. The mean prescriptions increased most for the 0-4 year old group from 1994 to 1997 (1.25 to 1.71). The difference between males and females was small for all age groups except the 5-14 year old group, which had a mean difference of 0.20 mean prescriptions per year.

Table 4-14 Mean number of prescriptions purchased per purchaser by sex and age for the year 1997

Medication	0-4 years			5-14 years			15-34 years			35-64 years		
	Male Mean	Female Mean	Total Mean	Male Mean	Female Mean	Total Mean	Male Mean	Female Mean	Total Mean	Male Mean	Female Mean	Total Mean
Short-acting β_2	1.3	1.2	1.3	1.6	1.4	1.5	3.8	3.0	3.4	3.9	3.1	3.4
Inhaled Corticosteroids	1.7	1.7	1.7	1.7	1.5	1.7	1.4	1.4	1.4	2.4	2.4	2.4
Oral Corticosteroids	0.3	0.2	0.2	0.2	0.2	0.2	0.2	0.3	0.2	0.6	0.6	0.6
Oral β_2	0.3	0.3	0.3	0.1	0.1	0.1	0.0	0.0	0.0	0.1	0.1	0.1
Theophyllines	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.5	0.5	0.5
Sodium Cromoglycates	0.4	0.4	0.4	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.1
Inhaled Ipratropium Bromide	0.1	0.1	0.1	0.0	0.0	0.0	0.1	0.1	0.1	0.6	0.6	0.6
Long-acting β_2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1
Nedocromil	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1
Ketotifen	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Combined (Salmeterol & Fluticasone)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Leukotrienes	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

The mean number of oral corticosteroid prescriptions appeared mainly unchanged from 1994 to 1997 for all the age groups except for the 35-64 year old group, which decreased from 0.69 to 0.58 mean prescriptions. The same basic pattern existed for oral corticosteroids between 1994 and 1997. Males had higher mean prescriptions than females in the 0-4 year old group and females had higher mean prescriptions in the 15-34 year old group.

For oral $beta_2$-agonists the same distribution of mean prescriptions over age and sex found in 1994, was found in 1997 but the mean numbers were lower in 1997. The difference between males and females was small to nil for all age groups.

The theophyllines group appeared to have the same pattern of mean prescriptions purchased in 1997 as was found in 1994 and 1991. The mean numbers of prescriptions themselves were lower than in previous years. There was little difference between males and females in all age groups.

Compared to 1994, the mean number of prescriptions per year was lower in 1997 for sodium cromoglycates across all age groups, for both sexes. As in 1994, in 1997, the two younger age groups had greater mean prescriptions than the 15-34 year old, and 35-64 year old age groups.

In 1997, the inhaled ipratropium bromide drug group increased the mean number of prescriptions in all age groups from 1994, most notably for the 35-64 year old group. The 35-64 year old group increased from 0.31 to 0.57 mean number of prescriptions purchased from 1994 to 1997. Inhaled ipratropium bromide's mean prescription purchases were very low for those under 35 years of age. The difference between males and females was small to nil for all age groups.

4.1.11.4 Mean number of prescriptions for 2000

In 2000, inhaled short-acting $beta_2$-agonists had a high mean number of prescriptions compared to all other drugs for the treatment of asthma (Table 4-15). Short-acting inhaled $beta_2$-agonists had the highest mean number of prescriptions in the 15-34 year old, and 35-64 year old groups. As observed in the previous three examined years, the mean number of prescriptions increased with successive increasing age groups. In all age groups, males had greater means than females and the differences

Table 4-15 Mean number of prescriptions purchased per purchaser by sex and age for the year 2000

Medication	0-4 years			5-14 years			15-34 years			35-64 years		
	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total
	Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean
Short-acting β_2	1.3	1.2	1.3	1.5	1.4	1.5	3.5	2.8	3.1	3.6	2.8	3.1
Inhaled Corticosteroids	2.2	2.1	2.2	2.0	1.8	1.9	1.4	1.4	1.4	2.5	2.5	2.5
Oral Corticosteroids	0.4	0.2	0.3	0.2	0.2	0.2	0.2	0.3	0.2	0.4	0.5	0.5
Oral β_2	0.2	0.2	0.2	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0
Theophylline	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.3	0.3
Sodium Cromoglycates	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Inhaled Ipratropium Bromide	0.1	0.1	0.1	0.1	0.0	0.1	0.1	0.1	0.1	0.6	0.5	0.6
Long-acting β_2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.2
Nedocromil	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Ketotifen	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Combined (Salmeterol & Fluticasone)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1
Leukotrienes	0.0	0.0	0.0	0.2	0.2	0.2	0.1	0.2	0.1	0.2	0.3	0.3

between the means were greater within the older two age groups (15-34 years and 35-64 years old) than within the two younger age groups (0-4 years and 5-14 years old).

From 1997 to 2000, the mean number of inhaled short-acting $beta_2$-agonist prescriptions decreased for the two older age groups while the two younger age groups changed very little. The mean number of prescriptions decreased most for the 35-64 year old group from 1997 to 2000 (3.44 to 3.11). The 0-4 year old group increased, from 1997 at 1.25 to 2000 at 1.26 mean prescriptions per year.

Inhaled corticosteroids had the same distribution of mean number of prescriptions over age and sex in 2000 as was found in 1997, but the mean number of prescriptions had increased in 2000. The mean number of prescriptions increased most for the 0-4 year old group from 1997 to 2000 (1.71 to 2.16). The 15-34 year old group increased the least, from 1997 at 1.40 to 2000 at 1.42 mean prescriptions per year. The difference between males and females was small (for the two older age groups), to moderate (for the two younger age groups).

The mean number of oral corticosteroid prescriptions appeared unchanged from 1997 to 2000 for the 5-14 year old and 15-34 year old groups. From 1997 to 2000 the mean number of prescriptions decreased moderately for the 35-64 year old group while they increased moderately for the 0-4 year old group. There was a modest difference between males and females in all age groups, except within the 5-14 year old group.

Oral $beta_2$-agonists had the same distribution of mean number of prescriptions over age and sex in 2000 as was found in 1997. The mean numbers of prescriptions were lower in 2000 than in 1997. The differences between males and females were small within all age groups. The mean number of theophylline prescriptions decreased very little for all age groups except for the 35-64 year old group from 1997 to 2000, which decreased notably from 0.47 to 0.26. There was very little to no difference between males and females for all age groups in 2000.

In 2000, the sodium cromoglycate drug group had all but disappeared from asthma medication usage. From 1997 to 2000 the mean number of prescriptions decreased most for the two younger age groups (0-4 years and 5-14 years old) and decreased a little for the 15-34 year old and 35-64 year old age groups. The mean number of prescriptions purchased decreased most for the 0-4 age group from 0.36 in

1997, to 0.03 in 2000. There was very little to no difference between males and females for all age groups in 2000.

The mean number of inhaled ipratropium bromide prescription purchases did not increase appreciably from 1997 to 2000 for all age groups. There was very little difference between males and females groups except within the 35-64 year old group, wherein the mean for males was moderately greater than that for females.

The mean number of long-acting $beta_2$-agonist prescriptions increased very little for all except for the 35-64 year old group, which decreased from 1997 to 2000. There was also very little difference between males and females for all age groups except within the 35-64 year old group.

The mean number of prescriptions purchased for the Nedocromil drug group decreased in 2000 from 1997 across all age groups except in the 0-4 year old group. The 0-4 age group had zero prescriptions in 2000, as it did in 1997. There was very little to no difference between males and females for all age groups in 2000.

The mean number of prescriptions purchased for the Ketotifen drug group decreased in 2000 from 1997 across all age groups except in the 15-34 year old group. The 15-34 age group had zero prescriptions in 2000, as it did in 1997. There was very little to no difference between males and females for all age groups in 2000.

4.1.11.5 Summary of mean number of prescriptions

In summary, there was a pattern of steady decline the in mean number of short-acting inhaled $beta_2$-agonist use across all ages, in both sexes over time. Short-acting $beta_2$-agonist prescriptions were highest in the two older age groups (15-34 years and 35-64 years) for both sexes, with males having a consistently greater mean number of prescriptions than females. There were few differences by sex for all the drug groups. Most sex differences were within the oldest group, 35-64 year olds, where there is generally more diversity in the population.

The highest mean inhaled corticosteroid prescription use was among the youngest, 0-4 year olds, and the oldest, 35-64 year old age groups, in both males and females.

Most importantly, there was a trend over time for the mean number of short-acting beta$_2$-agonist prescriptions to decrease and for the mean number of inhaled corticosteroid prescriptions to increase. This trend was most predominant in children.

4.1.12 Characteristics of users by medication group in 2000

To further explore the characteristics of users for the type of medication being prescribed, data from the final year of the study was analyzed. Significant differences between the proportion of medication purchased by male and female users in 2000 were found for several medication groups (Table 4-16). More males purchased inhaled short-acting beta$_2$-agonists and theophyllines than females. More females than males purchased oral corticosteroids, long-acting beta$_2$-agonists, inhaled ipratropium bromide and anti-leukotriene medications.

Table 4-16 Distribution of persons with asthma who purchased specific asthma medication by sex and medication group, 2000

Medication	Total	Male	Female	
	%	%	%	*p value*
Short-acting β_2	78.9	79.8	77.9	<0.001
Inhaled Corticosteroids	70.4	70.6	70.2	0.435
Oral Corticosteroids	18.0	16.8	19.2	<0.001
Oral β_2	4.3	4.5	4.2	0.230
Theophyllines	2.0	2.3	1.7	<0.001
Sodium Cromoglycates	1.0	1.0	1.0	0.734
Inhaled Ipratropium Bromide	6.9	6.2	7.6	<0.001
Long-acting β_2	1.7	1.2	2.3	<0.001
Nedocromil	0.4	0.4	0.4	0.939
Ketotifen	0.1	0.1	0.1	0.525
Combined Medication (Fluticasone & Salmeterol)	0.8	0.7	0.9	0.049
Leukotrienes	3.1	2.7	3.5	<0.001

There were very few significant differences between males and females in the purchase of specific medications in 2000. While more males than females purchased oral corticosteroids in the 0-4 year old age group and inhaled corticosteroids in the 5-14 year old age group, the pattern was reversed for the adult age groups.

When medication groups were further stratified by age as well as sex, significant differences were found between male and female groups within some age groups (Table 4-17). The three dominant medication groups, for all ages and both sexes, were short-acting inhaled $beta_2$-adrenergic agonists, inhaled corticosteroids, and oral corticosteroids.

There were no differences between the proportion of male and female users under 15 years of age in the short-acting inhaled $beta_2$-agonist medication group. Short-acting $beta_2$-agonist medication was purchased more by persons in the 15-34 year old group than by those in any other age group. Males purchased significantly more $beta_2$-agonists in the 15-34 year and the 35-64 year old age groups.

Inhaled corticosteroids were purchased most by 0-4 year olds (82.1%) and the least in the 15-34 year old group, particularly by males (57.9%). All age groups, except the 0-4 year old group, had significant differences between males and females. In the 5-14 year old group, males purchased significantly more inhaled corticosteroids than females. In the two older age groups (15-34 year and 35-64 year olds), the medication was purchased more by females.

Oral corticosteroids were purchased most frequently by the 0-4 year and 35-64 year old age groups in 2000, both being just over 22.0%. Males and females were significantly different in all age groups, except in the 5-14 year old age group for oral corticosteroids. In the 0-4 year old group, males purchased more than females. In the two older groups (15-34 year and 35-64 year olds) females purchased more oral corticosteroids than males.

Oral $beta_2$-agonists were purchased most by the 0-4 year old group (15.2%). The proportion of males and females did not differ significantly in all age groups, except within the 5-14 year old group, wherein more females purchased the medication.

Table 4-17 Distribution of persons with asthma who purchased a specific asthma medication by sex, age, and medication group, 2000

Medication	0-4 years				5-14 years				15-34 years				35-64 years			
	Male	Female	Total		Male	Female	Total		Male	Female	Total		Male	Female	Total	
	%	%	%	*p*-value	%	%	%	*p*-value	%	%	%	*p*-value	%	%	%	*p*-value
Short-acting β_2	71.5	69.6	70.8	0.243	74.5	73.3	74.0	0.299	89.8	85.2	87.4	<0.001	80.0	76.4	77.9	<0.001
Inhaled Corticosteroids	82.6	81.2	82.1	0.311	77.2	73.5	75.8	<0.001	57.9	62.2	60.1	<0.001	69.6	72.4	71.2	0.006
Oral Corticosteroids	25.3	16.5	22.1	<0.001	14.1	12.9	13.6	0.180	12.5	17.4	15.1	<0.001	19.8	24.8	22.7	<0.001
Oral β_2	14.3	16.6	15.2	0.086	4.7	6.1	5.2	0.014	1.5	1.6	1.6	0.620	1.8	2.2	2.0	0.185
Theophyllines	0.6	0.6	0.6	0.990	0.2	0.4	0.3	0.087	0.8	1.1	1.0	0.211	4.9	4.8	4.8	0.728
Sodium Cromoglycates	1.0	0.8	0.9	0.505	1.5	1.7	1.6	0.510	0.8	0.6	0.7	0.231	0.7	1.0	0.9	0.200
Inhaled Ipratropium Bromide	6.7	7.3	6.9	0.537	3.2	2.4	2.9	0.075	3.0	4.9	4.0	<0.001	13.0	12.8	12.9	0.751
Long-acting β_2	0.0	0.3	0.1	0.019	0.5	0.5	0.5	0.840	1.0	1.4	1.2	0.137	2.7	4.5	3.8	<0.001
Nedocromil	0.0	0.0	0.0	- -	0.3	0.2	0.3	0.196	0.5	0.5	0.5	0.987	0.6	0.5	0.5	0.707
Ketotifen	0.0	0.3	0.2	0.046	0.1	0.1	0.1	0.956	0.1	0.0	0.0	0.529	0.0	0.0	0.0	0.751
Combined (Salmeterol & Fluticasone)	0.0	0.0	0.0	- -	0.5	0.2	0.4	0.990	0.7	0.8	0.8	0.682	1.2	1.5	1.4	0.229
Leukotrienes	0.6	0.7	0.7	0.915	3.7	3.4	3.6	0.459	2.1	2.8	2.5	0.039	3.2	4.9	4.2	<0.001

In 2000, there was no significant difference between males and females in any age group for those with asthma who purchased theophylline medication. There were no significant differences between males and females for the medication group inhaled ipratropium bromide, except in the 15-34 year old group, wherein more females than males purchased the medication.

In 2000, the proportion of persons with asthma who purchased long-acting $beta_2$-adrenergic agonists increased with successive age groups. Males and females differed only in the 0-4 year old and 35-64 year old groups, with more females than males having purchased the medication.

For the drug groups Sodium Cromoglycates, Nedocromil, Ketotifen, and the combination drug containing Salmeterol and Fluticasone, in 2000 these drugs were used very little or not at all across all age groups. There were no significant differences between males and females for these medication groups.

Anti-leukotrienes were purchased most by those in the 35-64 year old group (4.2%). They were purchased least by those in the 0-4 year old group. There were significant differences between males and females in the two older age groups, with more females having purchased the medication than males.

4.1.12.1 Summary of characteristics of users by medication group in 2000

In summary, the three dominant medication groups in the year 2000 were inhaled short-acting $beta_2$-agonists, inhaled corticosteroids, and oral corticosteroids. Males in the 15-34 year old age group were the most frequent users of short-acting $beta_2$-agonist medication. Inhaled corticosteroids were purchased most by 0-4 year olds, and least by 15-34 year old males. In the two older age groups (15-34 year and 35-64 year olds), inhaled and oral corticosteroids were purchased most by females. Oral corticosteroids were purchased most by the youngest and oldest age groups. The 0-4 year old age group had the highest use of oral $beta_2$-agonists, which did not include nebulized medication, at 15.2%. Long-acting $beta_2$-agonists and anti-leukotriene medication were more often purchased by women, 35-64 years of age.

4.2 Research Question #2:

What is the distribution of specific combinations of asthma medication use among persons with physician-diagnosed asthma by age and sex for the period of January 1, 1991 to December 31, 2000.

The CCG of 1996 and 1999 (4;11) provided information on recommended and potential combinations of medications suitable for asthma management. In conjunction with the guidelines, the data was examined for the frequency of use of specific combinations of medications over the ten years of the study.

Several permutations were made to identify the most frequently purchased medication combinations. The six most frequently identified combinations are presented in Table 4-18. These combinations happened to coincide with those suggested by the CCG.

Where the frequency, and contribution, of a combination was very small it was excluded from the analysis as a distinct combination and instead joined the group "All other medications" (used in combinations). In the final assessment, the "All other medications" category contained all the combinations of asthma medications not specified as being the top six most frequently purchased by persons using asthma medication.

4.2.1 Proportion of users of asthma medication combinations by year

Short-acting inhaled beta$_2$-adrenergic agonist medication used alone had the largest proportion of purchasers from 1991 to 1993 (Table 4-18). From 1994 to 2000, beta$_2$-agonists were second most popular to the combination of inhaled short-acting beta$_2$-agonists and inhaled corticosteroids to an increasing degree (as the combined medications increased in proportion and the single preparation received a decreasing share).

Inhaled corticosteroids had only 3.9% of purchasers in 1991, but from 1992 to 1996 this proportion increased to 13.8% to become the third largest group that year. From 1996 to 1998, the number of purchasers of inhaled corticosteroids dropped to 12.0% in 1998. In 1999 and 2000, their number recovered to 13.2% in 2000. Overall,

Table 4-18 Percentage of purchasers of most frequently used asthma medication combinations, for those aged 0-64, including only inhaled beta$_2$-agonists and inhaled corticosteroids in their single preparations, 1991 to 2000

Medication(s)	1991 %	1992 %	1993 %	1994 %	1995 %	1996 %	1997 %	1998 %	1999 %	2000 %
All other medications (used in combinations)	15.1	13.5	12.9	13.0	12.3	11.6	12.3	12.7	14.4	15.3
Short-acting β_2-agonists (used alone in year)	34.5	31.9	29.7	28.1	25.0	23.8	24.1	25.9	23.1	23.1
Inhaled corticosteroids (used alone in year)	3.9	6.3	9.9	10.9	12.5	13.8	13.4	12.0	13.2	13.1
Short-acting β_2-agonists + Inhaled corticosteroids	19.0	23.8	27.1	29.7	33.2	35.1	36.7	37.0	37.8	38.7
Short-acting β_2-agonists + Inhaled corticosteroids + Oral corticosteroids	4.1	5.0	6.9	8.0	8.9	8.5	8.5	9.0	9.3	8.6
Short-acting β_2-agonists + Inhaled corticosteroids + Smooth muscle relaxants	3.4	2.7	2.0	1.4	1.2	1.1	0.9	0.8	0.7	0.5
Short-acting β_2-agonists + Inhaled corticosteroids + Unclassified agents	5.3	5.7	4.2	3.4	3.0	2.8	2.0	1.2	0.8	0.4
Short-acting β_2-agonists + Smooth muscle relaxants	3.3	1.9	1.2	0.8	0.5	0.4	0.4	0.3	0.2	0.2
Short-acting β_2-agonists + Unclassified therapeutic agents	11.4	9.3	6.0	4.6	3.4	2.9	1.8	1.1	0.6	0.3
TOTAL N	18091	18686	19490	20831	22825	23373	23573	23350	24881	25102

purchasers of inhaled corticosteroids increased steadily over the ten year study period.

The drug combination of inhaled short-acting beta$_2$-adrenergic agonists and inhaled corticosteroids was the primary combination used in all years. By 2000, 38.7% of users were purchasing this combination. The drug combination of inhaled short-acting beta$_2$-adrenergic agonists, inhaled corticosteroids, and oral corticosteroids had 4.1% purchasers in 1991. By 2000, this combination had doubled to 8.6%.

The medication combination of short-acting inhaled beta$_2$-adrenergic agonists, inhaled corticosteroids, and respiratory smooth muscle relaxants (including theophyllines), had a relatively low percentage of purchasers at the beginning of the study in 1991 with 3.4%. The percentage for this combination gradually and steadily declined every year of the study period to 0.5% by the year 2000.

The medication combination of inhaled short-acting beta$_2$-adrenergic agonists, inhaled corticosteroids and unclassified therapeutic agents (including sodium cromoglycates) had 5.3% purchasers in 1991. By the end of the study period, 0.4% of asthma medication purchasers were using this combination of medications.

A more popular combination of short-acting beta$_2$-adrenergic agonists and smooth muscle relaxants had 11.4% of purchasers in 1991. The proportion of purchasers of this combination decreased sharply every year of the ten year period of the study to 0.3% of purchasers in 2000. The "All other medications" group accounted for about 15.0% of users throughout the study period.

4.2.2 Proportion of users of asthma medication combinations by age for 1991, 1994, 1997, and 2000

There was gradual change in the use of medication(s) over all ten years of the study that was shown to be far more dramatic when viewed using only four index years, 1991, 1994, 1997 and 2000 (Figure 4-1 or Appendix D). When a linear by linear test for trends was performed for the medication combinations for the selected four years, the result was significant at $\chi^2 = 1905.35$, df 1, $p < 0.001$. Over the study period, the difference in the proportion of specific combinations use between males and females was minimal (Appendix B).

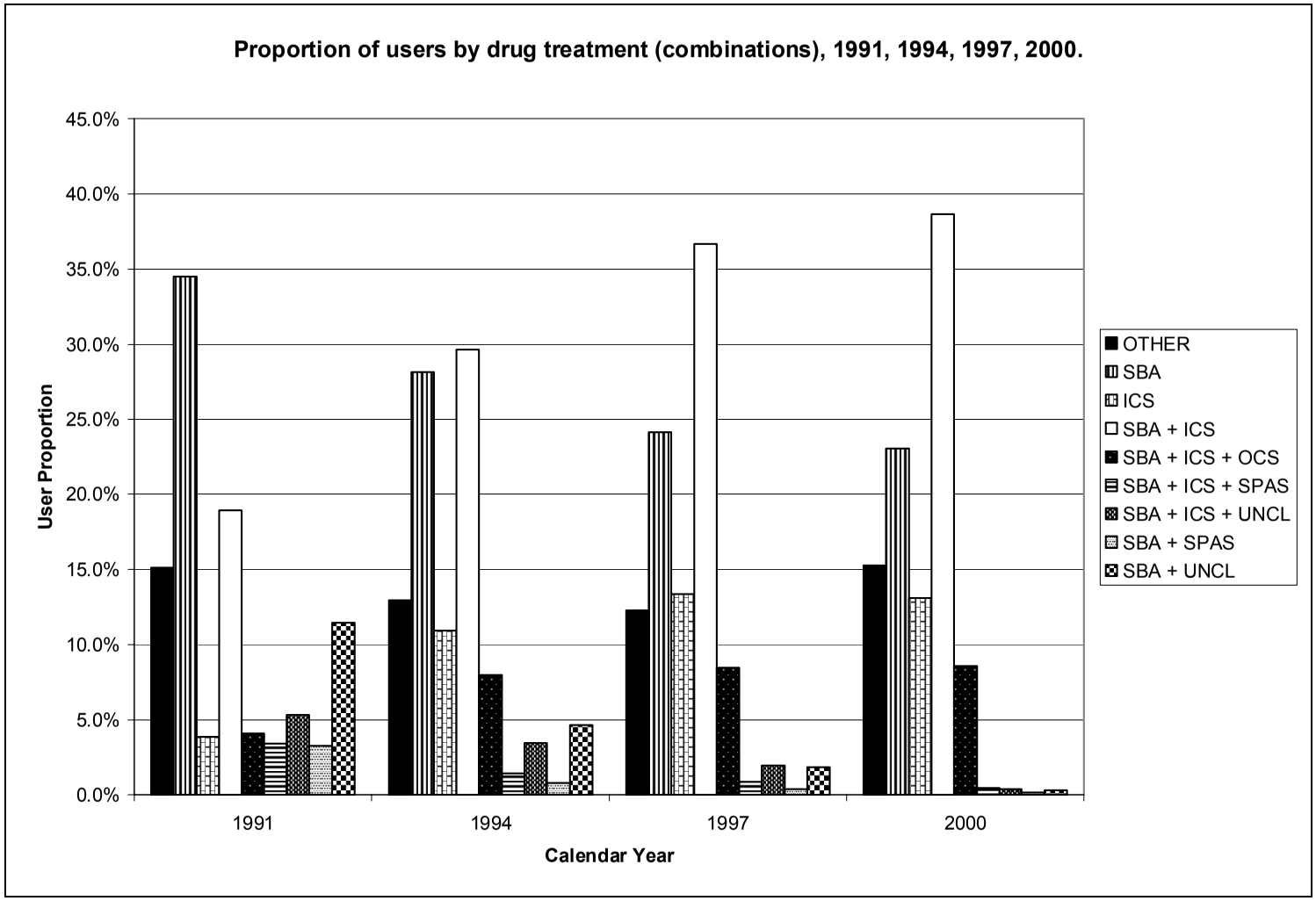

Figure 4-1 Proportion of users by medication treatment for 1991, 1994, 1997, 2000

While the proportional use of the preferred combination of inhaled short-acting beta$_2$-adrenergic agonists and inhaled steroids increased in each age group over time, the most dramatic increases were seen for children in the 0-4 year old age group (Tables 4-19 and 4-20). In 1991, only 4.5% of the 0-4 year olds purchased this combination. Instead, most 0-4 year old combination drug users were purchasing short-acting beta$_2$-adrenergic agonists with unclassified agents (including sodium cromoglycates) at 28.3%. By 2000, 41.4% of 0-4 year olds, purchased the short-acting beta$_2$-adrenergic agonist and inhaled corticosteroid combination. The use of the inhaled short-acting beta$_2$-adrenergic agonists and unclassified agents combination was virtually undetectable.

Children in the 5-14 year old group doubled their purchase of inhaled short-acting beta$_2$-adrenergic agonists with inhaled corticosteroids from 1991 to 2000. They also reduced their use of inhaled short-acting beta$_2$-adrenergic agonists with unclassified agents from 16.7% to 0.3%.

There was an increase in the proportion of both 0-4 year old and 5-14 year old users in the purchase of the inhaled short-acting beta$_2$-adrenergic agonists, inhaled corticosteroid, and oral corticosteroid combination. From 1991 to 2000, the 0-4 year olds increased from 1.2% to 15.6%, and the 5-14 year olds increased from 2.2% to 7.7%.

4.2.3 Summary of research question #2

In summary, there was a change in the distribution of medication combinations from 1991 to 2000. The use of short-acting beta$_2$-agonist medication, used alone, decreased over time, while the use of inhaled corticosteroids (monotherapy) increased. Inhaled corticosteroids and inhaled short-acting beta$_2$-agonists, in combination, increased from 20.0% in 1991 to 40.0% of medications dispensed in 2000. Similarly, there was an increase in the combined use of inhaled corticosteroids, short-acting beta$_2$-agonists, and oral corticosteroids, which more than doubled from 4.0% in 1991 to 9.0% in 2000.

Reductions in the use of both smooth muscle relaxants and unclassified agents, each in their respective combination with inhaled corticosteroids and short-acting beta$_2$-agonists, were observed over the study period. The largest change in the use of inhaled corticosteroids and short-acting beta$_2$-agonists in combination, was seen

Table 4-19 Proportion of drug treatment users by age group, 1991 and 1994

	Age Groups			
	0-4yrs	5-14yrs	15-34yrs	35-64yrs
Calendar year - 1991				
Medication(s)	%	%	%	%
All other medications (used in combinations)	16.2	11.6	11.8	22.7
Short-acting β_2-agonists (used alone in year)	38.9	33.1	43.4	23.8
Inhaled corticosteroids (used alone in year)	1.0	4.0	3.8	5.4
Short-acting β_2-agonists + Inhaled corticosteroids	4.5	19.9	22.2	22.7
Short-acting β_2-agonists + Inhaled corticosteroids + Oral corticosteroids	1.2	2.2	4.5	7.6
Short-acting β_2-agonists + Inhaled corticosteroids + Smooth muscle relaxants	0.4	1.2	3.4	7.9
Short-acting β_2-agonists + Inhaled corticosteroids + Unclassified agents	6.1	9.4	2.8	2.6
Short-acting β_2-agonists + Smooth muscle relaxants	3.4	2.0	3.1	5.0
Short-acting β_2-agonists + Unclassified agents	28.3	16.7	5.0	2.2
TOTAL	2699	5719	5065	4608
Calendar year - 1994				
All other medications (used in combinations)	14.1	10.0	9.5	20.1
Short-acting β_2-agonists (used alone in year)	28.1	24.6	37.0	21.8
Inhaled corticosteroids (used alone in year)	10.3	15.7	7.5	9.8
Short-acting β_2-agonists + Inhaled corticosteroids	21.3	30.6	32.0	30.0
Short-acting β_2-agonists + Inhaled corticosteroids + Oral corticosteroids	6.8	6.0	7.7	11.2
Short-acting β_2-agonists + Inhaled corticosteroids + Smooth muscle relaxants	0.2	0.3	1.5	3.2
Short-acting β_2-agonists + Inhaled corticosteroids + Unclassified agents	6.7	5.8	1.5	1.3
Short-acting β_2-agonists + Smooth muscle relaxants	0.4	0.3	0.7	1.6
Short-acting β_2-agonists + Unclassified agents	12.1	6.8	2.4	1.1
TOTAL	2656	6357	6405	5413

Table 4-20 Proportion of drug treatment users by age group, 1997 and 2000

	Age Groups			
	0-4	5-14	15-34	35-64
Calendar year - 1997				
Medication(s)	%	%	%	%
All other medications (used in combinations)	12.5	7.1	8.3	21.4
Short-acting β_2-agonists (used alone in year)	19.6	21.9	33.6	18.5
Inhaled corticosteroids (used alone in year)	14.9	20.1	8.6	11.1
Short-acting β_2-agonists + Inhaled corticosteroids	34.9	37.3	38.5	34.9
Short-acting β_2-agonists + Inhaled corticosteroids + Oral corticosteroids	9.8	7.5	7.5	9.8
Short-acting β_2-agonists + Inhaled corticosteroids + Smooth muscle relaxants	0.2	0.1	0.8	1.9
Short-acting β_2-agonists + Inhaled corticosteroids + Unclassified agents	3.5	3.1	1.1	1.0
Short-acting β_2-agonists + Smooth muscle relaxants	0.3	0.0	0.4	0.8
Short-acting β_2-agonists + Unclassified agents	4.3	2.8	1.1	0.6
TOTAL	3022	6652	7090	6809
Calendar year - 2000				
All other medications (used in combinations)	11.4	10.2	11.9	24.4
Short-acting β_2-agonists (used alone in year)	13.5	19.7	33.5	19.6
Inhaled corticosteroids (used alone in year)	17.3	18.5	8.2	11.7
Short-acting β_2-agonists + Inhaled corticosteroids	41.4	42.8	38.5	34.2
Short-acting β_2-agonists + Inhaled corticosteroids + Oral corticosteroids	15.6	7.7	6.8	8.3
Short-acting β_2-agonists + Inhaled corticosteroids + Smooth muscle relaxants	0.1	0.1	0.3	1.1
Short-acting β_2-agonists + Inhaled corticosteroids + Unclassified agents	0.4	0.6	0.3	0.3
Short-acting β_2-agonists + Smooth muscle relaxants	0.1	0.0	0.1	0.3
Short-acting β_2-agonists + Unclassified agents	0.2	0.3	0.3	0.2
TOTAL	3100	6592	7600	7810

between the years 1991 and 1994.

While the proportional use of the most preferred combination of inhaled short-acting beta$_2$-adrenergic agonists and inhaled corticosteroids increased over time in each age group, the most dramatic increases were seen in the 0-4 year age group. There were no changes between males and females in the use of selected combinations during the study period.

4.3 Research Question #3:

What is the variation in the monthly age-sex specific, short-acting inhaled ß$_2$-adrenergic agonist and inhaled corticosteroid use for the years 1996 to 2000?

In order to identify seasonal variation in the use of short-acting beta$_2$-agonist and inhaled corticosteroid medication, data from the years 1996 to 2000 were examined. As seen in Figures 4-2 and 4-3, there was limited variation between the years in the number of prescriptions purchased by month for either inhaled corticosteroids or short-acting beta$_2$-agonists.

From 1996 to 2000, within each year, the number of short-acting beta$_2$-agonist prescriptions increased from around 5000 prescriptions at the beginning of the year to 6000 prescriptions at the end of the year. All five years showed a similar pattern with a gradual increase in the number of prescriptions from January to December, and peak increases occurring in May, September and December (Figure 4-3). There were also shared low points across the five years, in the months of February, July, and November.

On a linear by linear test for trends for the year 2000, the result for trend by month was significant ($\chi^2 = 25.97$, df 1, $p < 0.001$), demonstrating that as time passed by month, the number of inhaled short-acting beta$_2$-agonist prescriptions increased significantly. Similar significant trends were found for 1999 ($p < 0.001$) and 1996 ($p < 0.001$). The lowest number of prescriptions in the year 2000 was 4460 (February) and the highest was 5978 (December). The lowest number of prescriptions of beta$_2$-agonists in 1999 was 4872 (February) and the highest was 6621 (December). In 1996, the lowest number of prescriptions was 4753 in February, and the highest number was 6049 in

December. Although similar patterns were seen for 1997 and 1998, the results of the linear by linear test for trends for those years were not significant.

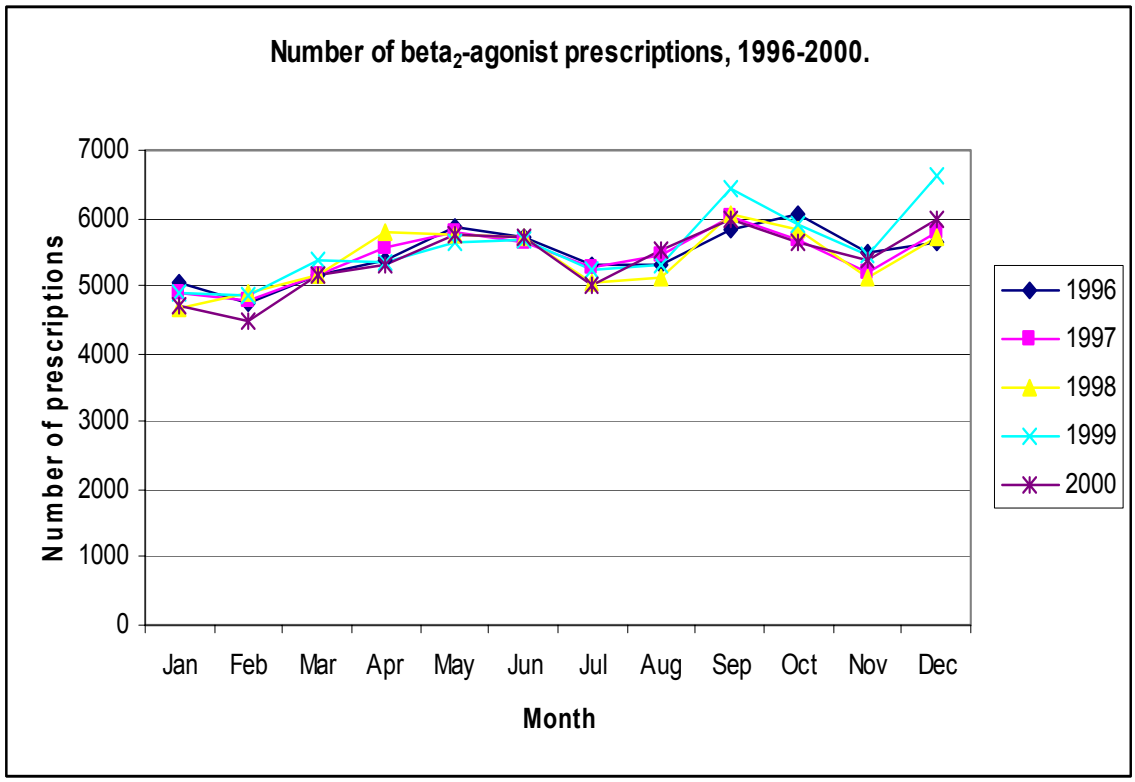

Figure 4-2 Number of short-acting β_2-agonist prescriptions purchased, 1996 to 2000

From 1996 to 1998, within each year, the number of inhaled corticosteroids increased from around 3100 prescriptions at the beginning of the year to 4200 prescriptions at the end of the year. For the years 1999 and 2000, the number of inhaled corticosteroid prescriptions increased from around 3500 at the beginning of the year to 5300 at the end of the year. In all five years there was an increase from January to December, with peak increases occurring during the same months: May and June, September and October, and December. The shared trough period was during July and August, with another small dip occurring in November.

The year 1999 was significant in a linear by linear test for trends at ($\chi^2 = 55.47$, df 1, $p < 0.001$), meaning that inhaled corticosteroid prescriptions increased significantly over the year. Other years significant for the linear by linear test were:

1998 ($\chi^2 = 12.10$, df 1, $p < 0.00$); 1997 ($\chi^2 = 10.38$, df 1, $p < 0.001$); and, 1996 ($\chi^2 = 45.46$, df 1, $p < 0.001$). The only year that was not significant for the linear by linear test for trends was the year 2000, meaning that the number of prescriptions neither increased nor decreased significantly over the year.

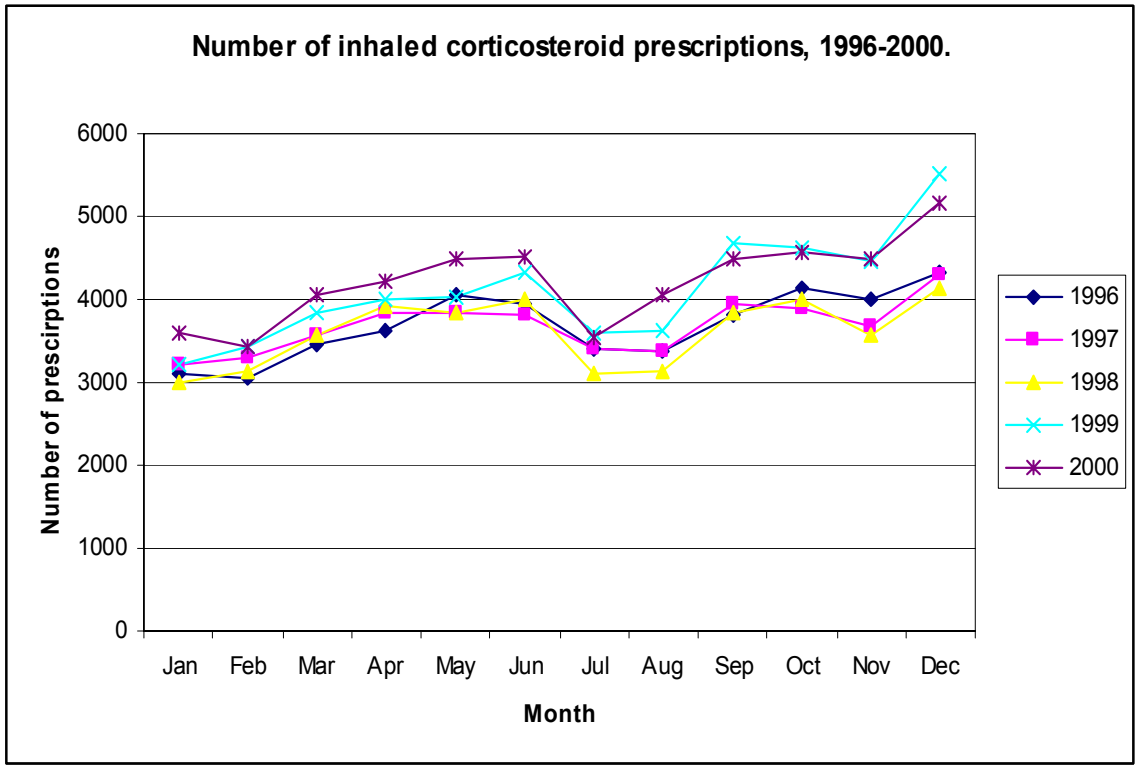

Figure 4-3 Number of inhaled corticosteroid prescriptions purchased, 1996 to 2000

4.3.1 Monthly distribution of short-acting β_2-agonist prescriptions by age group and calendar year

The patterns of monthly use of short-acting inhaled beta$_2$-agonists and inhaled corticosteroids, by age groups, were generally consistent over the five years that were chosen for review.

4.3.1.1 Short-acting β_2-agonist prescriptions by age group and month, 1996

Among all the age groups, the number of short-acting inhaled beta$_2$-agonist prescriptions was highest in the 15-34 year old group (Figure 4-4).

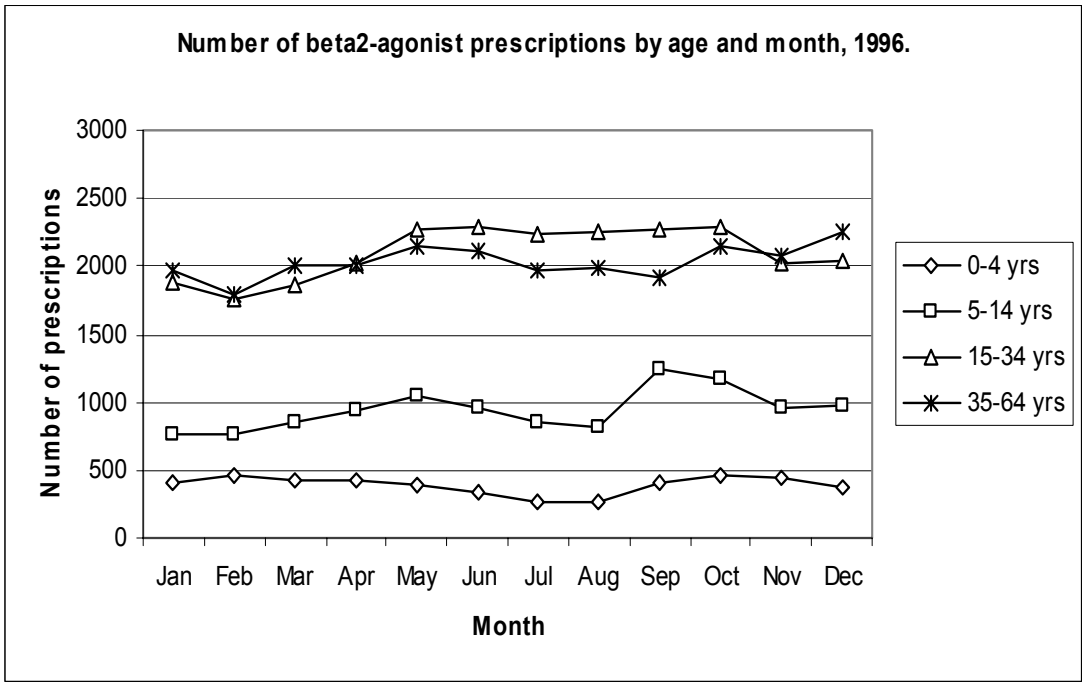

Figure 4-4 Number of beta$_2$-agonist prescriptions by age group and month, 1996

The two older age groups shared a low in the number of prescriptions in February, followed by a steady increase to a peak in May. The 15-34 year old group maintained this peak until October when there was a decrease in the number of prescriptions to December. The 35-64 year old group decreased their number of beta$_2$-agonist prescriptions after May to a low in September then the number was increased gradually to a final peak in December, the opposite direction of the 15-34 year old group.

The peak increase for the 5-14 year olds occurred in September, with a smaller peak in May. The peak increases for the 0-4 year old group were small by comparison, but seemed to occur in February and October. The two younger age groups shared a dip in the number of β_2-agonist prescriptions during the July and August period.

All the age groups had significant results for the linear by linear test for trends. All the age groups, except the 0-4 year olds, appeared to increase in the number of short-acting inhaled beta$_2$-agonist prescriptions over the year. The linear by linear trends were as follows: 0-4 year old group: $\chi^2 = 9.84$, df 1, $p < 0.01$; 5-14 year old group: $\chi^2 =$

12.52, df 1, $p < 0.001$; 15-34 year old group: $\chi^2 = 17.07$, df 1, $p < 0.001$; and, 35-64 year old group: $\chi^2 = 27.74$, df 1, $p < 0.001$.

4.3.1.2 Short-acting β_2-agonist prescriptions by age group and month, 1997

In 1997, the highest monthly use occurred with the 15–34 year old group, and the 35-64 year old group. The 0-4 year old group had the lowest number of prescriptions, between 270 (August) and 482 (April) (Figure 4-5).

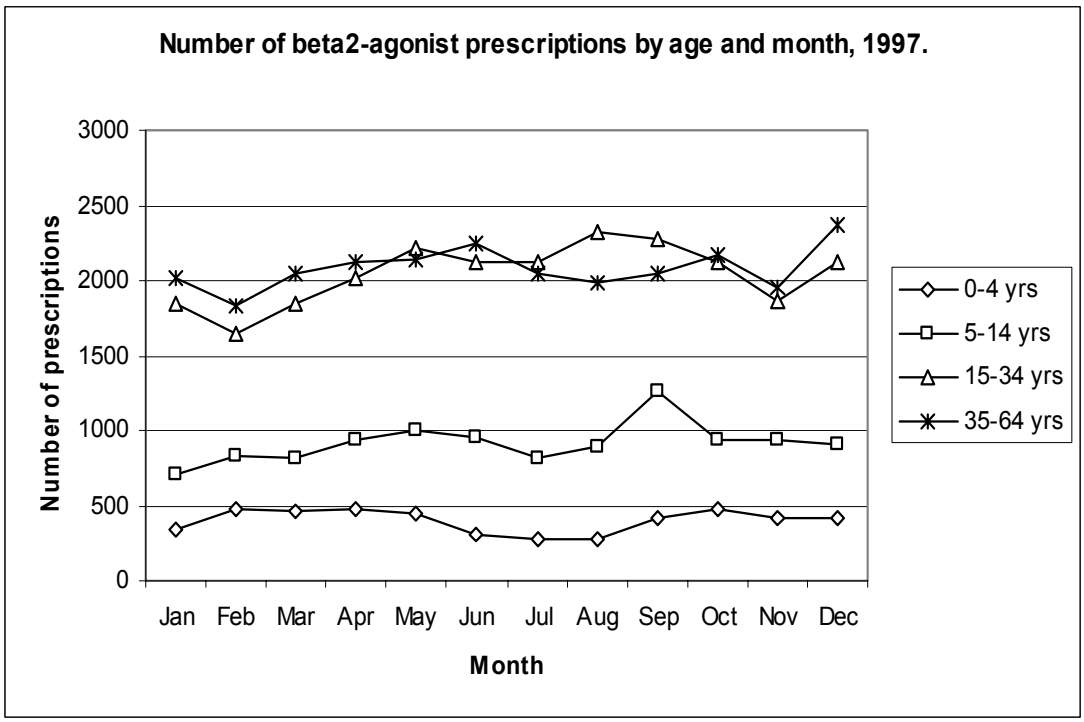

Figure 4-5 Number of beta$_2$-agonist prescriptions by age group and month, 1997

The 35-64 year old age group had significant results for the linear by linear test for trends ($\chi^2 = 8.25$, df 1, $p < 0.01$), indicating an increase in prescriptions over the year in 1997. Where the 35-64 year old group had a dip in the number of beta$_2$-agonist prescriptions, the 15-34 year olds had a peak. Other than this divergence, the two older age groups shared similar patterns of increase and decrease in the number of prescriptions.

In 1997, the 5-14 year old age group had significant results for the linear by linear test for trends, $\chi^2 = 17.61$, df 1, $p < 0.001$, indicating an increase in prescriptions

over the year in 1997, as was the case in 1996. The 5-14 year old group had a large peak in the number of prescriptions in September that the 0-4 year old group did not. Both groups had a dip in the number of prescriptions in July.

4.3.1.3 Short-acting β_2-agonist prescriptions by age group and month, 1998

Though the numbers of prescriptions between the two older groups were similar and in a much higher range than the two younger groups, it was shown in 1998, as not seen previously, that the 15-34 year old group shared a pattern of peak increases and decreases with the 5-14 year old group (Figure 4-6). The peak increases for the 5-14 year olds and the 15-34 year olds were in May and September. The important summer trough was shared among all four age groups in 1998. The 35-64 year old age group was the only group in 1998 with significant results for linear by linear test for trends, $\chi^2 = 7.80$, df 1, $p < 0.01$, indicating an increase in beta$_2$-agonist prescriptions.

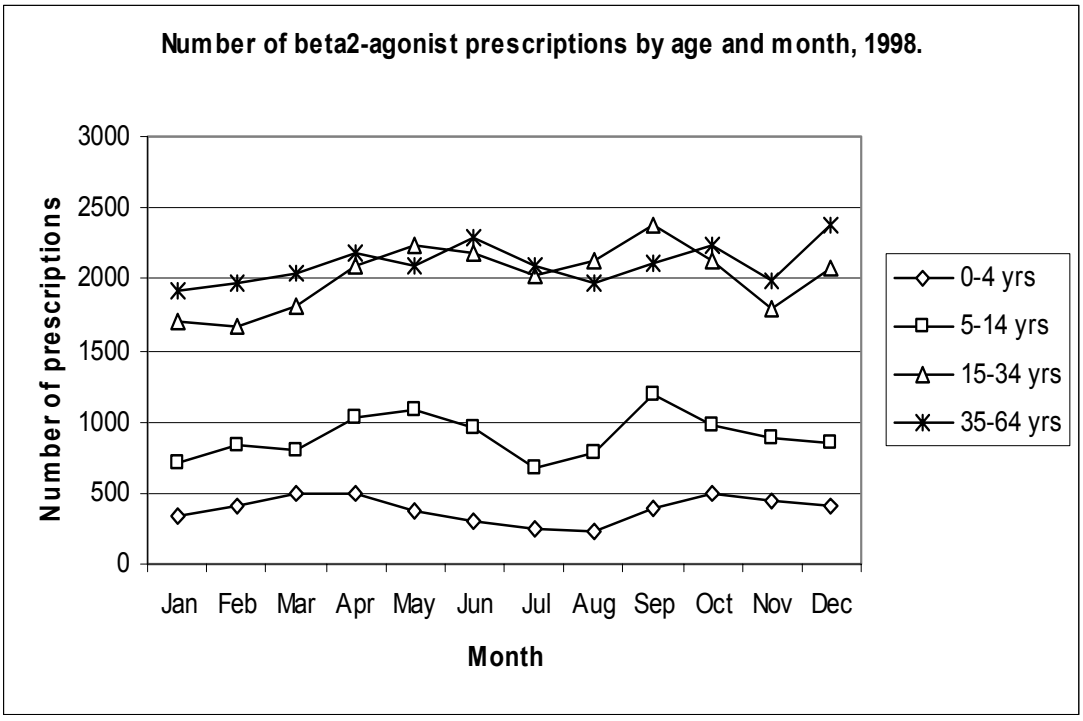

Figure 4-6 Number of beta$_2$-agonist prescriptions by age group and month, 1998

4.3.1.4 Short-acting β_2-agonist prescriptions by age group and month, 1999

All age groups, except for the 0-4 year olds, appeared to increase in the number of short-acting inhaled beta$_2$-agonist prescriptions over the year (Figure 4-7). All of the

age groups had significant results for the linear by linear test for trends. For the 0-4 year old group the linear by linear result was $\chi^2 = 28.91$, df 1, $p < 0.001$. For this group, the number of prescriptions appeared to decrease notably from March to August, and also greatly increase from August to December. For the 5-14 year old group the linear by linear result was $\chi^2 = 8.78$, df 1, $p < 0.01$. The linear by linear result for the 15-34 year old group was $\chi^2 = 12.14$, df = 1, $p < 0.001$, and for the 35-64 year old group it was $\chi^2 = 41.31$, df 1, $p < 0.001$. As in 1998, the 5-14 year old group and the 15-34 year old group had similar patterns of peak increases and decreases during the year of 1999.

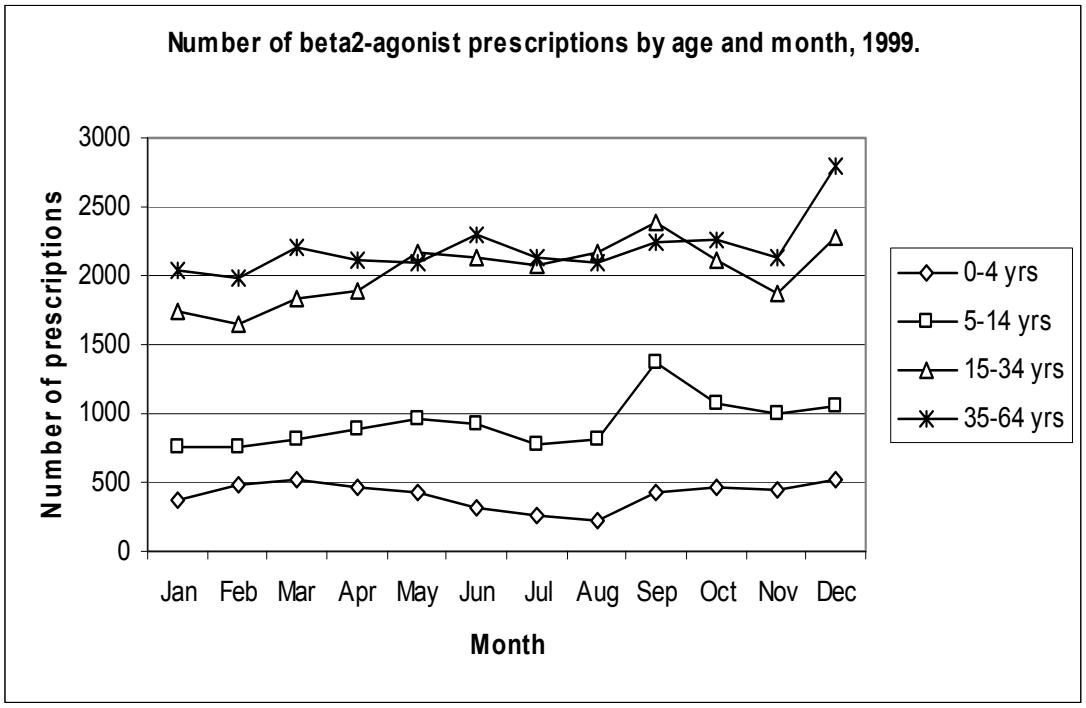

Figure 4-7 Number of beta$_2$-agonist prescriptions by age group and month, 1999

All four age groups shared a dip in July and August, but for the two older age groups it was a more subtle decrease. September continued to be the most important month of increase in the number of prescriptions for the 5-14 year old age group. December was again, an important peak for the two older groups since 1997.

4.3.1.5 Short-acting β_2-agonist prescriptions by age group and month, 2000

In 2000, all four age groups seemed to share a pattern of peak increase in May followed by a drop in the number of beta$_2$-agonist prescriptions in July (Figure 4-8).

The 5-14 year old and 15-34 year old groups showed peak increases in September. All age groups except the 15-34 year olds showed an increase in prescriptions in December. The 35-64 year old age group had significant results for the linear by linear test for trends, $\chi^2 = 21.58$, df 1, $p < 0.001$, indicating an increase in prescriptions in 2000. The 15-34 year old age group also had significant results for the linear by linear test for trends, $\chi^2 = 9.10$, df 1, $p < 0.01$, which indicated an increase in the number of prescriptions over the year.

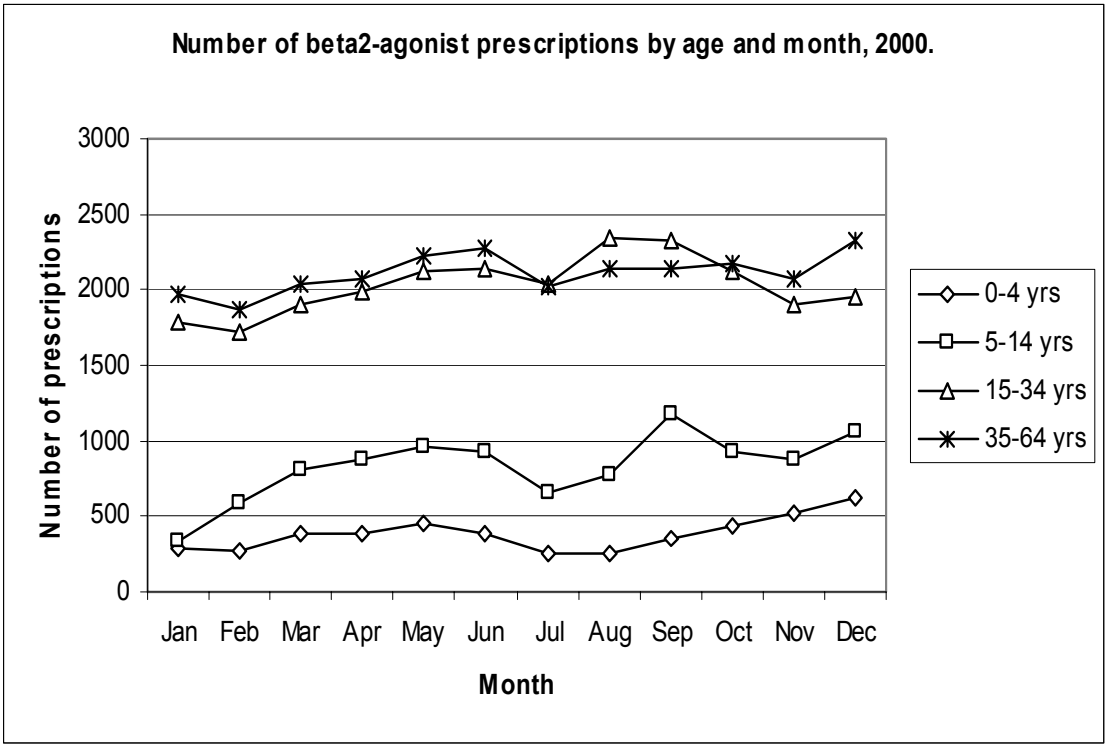

Figure 4-8 Number of beta$_2$-agonist prescriptions by age group and month, 2000

4.3.2 Monthly inhaled corticosteroid prescriptions by age group and calendar year

4.3.2.1 Inhaled corticosteroid prescriptions by age group and month, 1996

Among all four age groups, the number of inhaled corticosteroid prescriptions was highest for the 35-64 year old group (Figure 4-9).

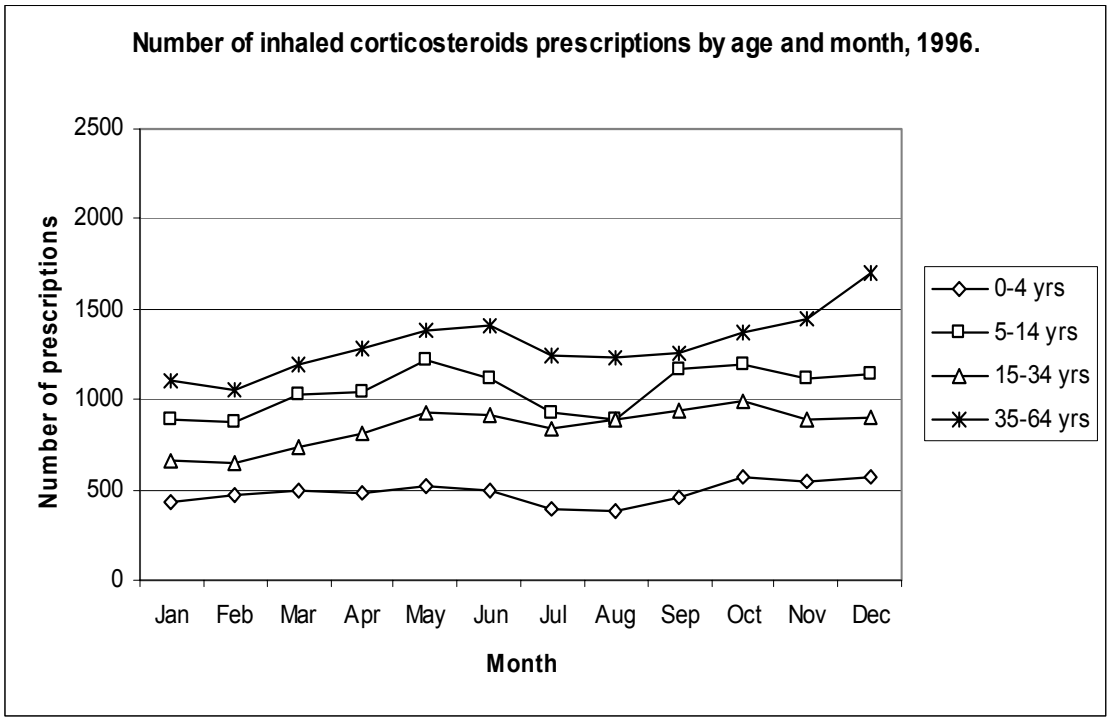

Figure 4-9 Number of inhaled corticosteroid prescriptions by age group and month, 1996

All four age groups appeared to have peak increases in May, followed by a sharp decrease in the number of inhaled corticosteroid prescriptions in July and August. For the 15-34 year old age group the July decrease was subtle. The 5-14 year old group had an increase in prescriptions in September, while for the 0-4 year and 15-34 year old groups this increase occurred in October. For the 35-64 year old group, from the summer trough, there was a steady increase in the number of inhaled corticosteroid prescriptions to December. All age groups, except for the 5-14 year old age group, had significant results for the linear by linear test for trends ($p < 0.001$), indicating an increase in prescriptions over time.

4.3.2.2 Inhaled corticosteroid prescriptions by age group and month, 1997

The age groups over five years old appeared to increase in their number of prescriptions over the year (Figure 4-10). All the age groups, except the 15-34 year old group, shared a notable decrease in prescriptions in August. The 35-64 year olds seemed to share a peak increase in prescriptions in June with the 5-14 year old group.

The two younger age groups showed an increase in prescriptions in September, though the peak was more extreme for the 5-14 year old group. The most striking peak increase was for the 35-64 year old group in their number of inhaled corticosteroid prescriptions in December of 1997. All age groups, except for the 0-4 year old age group, had significant results for the linear by linear test for trends ($p < 0.001$).

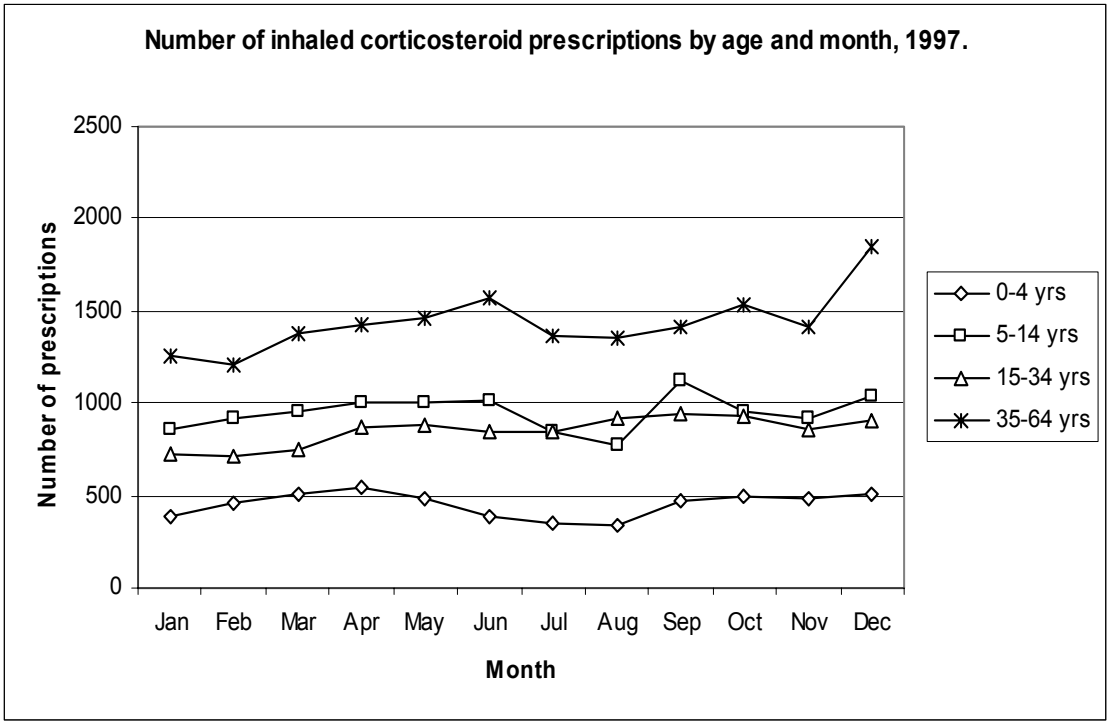

Figure 4-10 Number of inhaled corticosteroid prescriptions by age group and month, 1997

4.3.2.3 Inhaled corticosteroid prescriptions by age group and month, 1998

In 1998 only one age group, the 35-64 year old group, had a significant result for the linear by linear test for trends, $\chi^2 = 13.03$, df 1, $p < 0.01$. All four age groups shared a low in the number of inhaled corticosteroid prescriptions in July and August followed by an increase in the fall (Figure 4-11). The 5-14 year olds and 15-34 year old group also shared a peak increase in May. The most notable peak for the 35-64 year old group remained that of December's, but in 1998 there was a secondary peak in June.

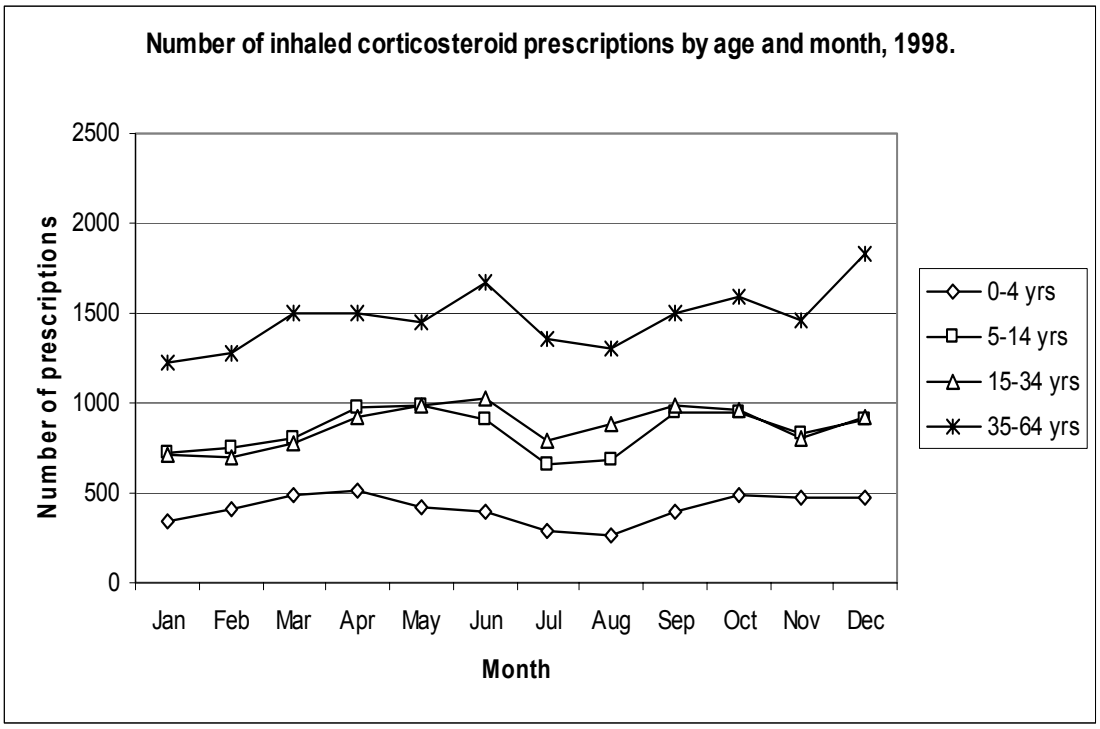

Figure 4-11 Number of inhaled corticosteroid prescriptions by age group and month, 1998

4.3.2.4 Inhaled corticosteroid prescriptions by age group and month, 1999

In 1999, the 0-4 year old age group and the 35-64 year old age group had significant results for the linear by linear test for trends ($p < 0.001$). As in previous years, all four age groups shared a low in the number of inhaled corticosteroid prescriptions in July and August followed by an increase in the fall (Figure 4-12). The peak increase in prescriptions in September was mainly shared between the 5-14 year old group and the 15-34 year old group. In 1999, the three oldest groups had an increase in prescriptions in June, while the 0-4 year old group had an increase earlier in March. As seen previously, the most notable peak for the 35-64 year old group was in December.

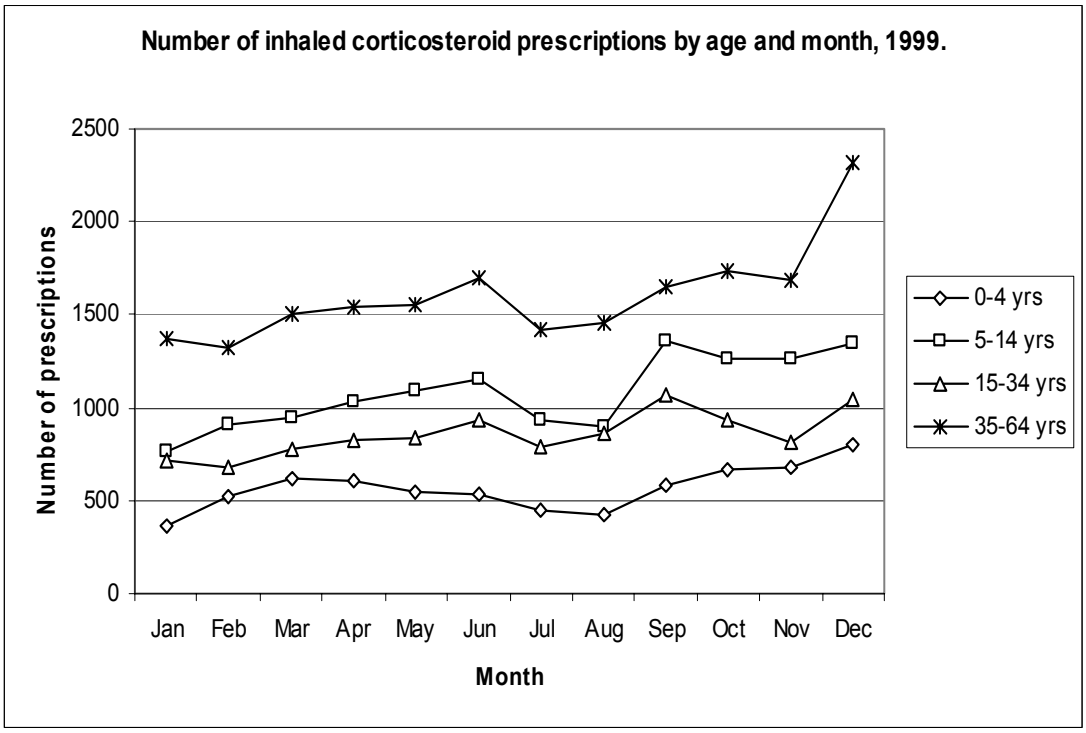

Figure 4-12 Number of inhaled corticosteroid prescriptions by age group and month, 1999

4.3.2.5 Inhaled corticosteroid prescriptions by age group and month, 2000

In 2000, only one age group, the 5-14 year old group, had a significant result for the linear by linear test for trends, $\chi^2 = 10.61$, df 1, $p < 0.001$. All four age groups shared a low in the number of inhaled corticosteroid prescriptions in July increase in the fall (Figure 4-13). Once again, the peak increase in prescriptions in September was mainly shared by the 5-14 year old and the 15-34 year old groups. The three oldest groups, as in 1999, had an increase in prescriptions in June while the 0-4 year old group had an increase earlier in May (it was March in 1999). As seen previously, the most notable peak for the 35-64 year old group was in December. In 2000, it appeared that all four age groups increased in the number of inhaled corticosteroid prescriptions in December.

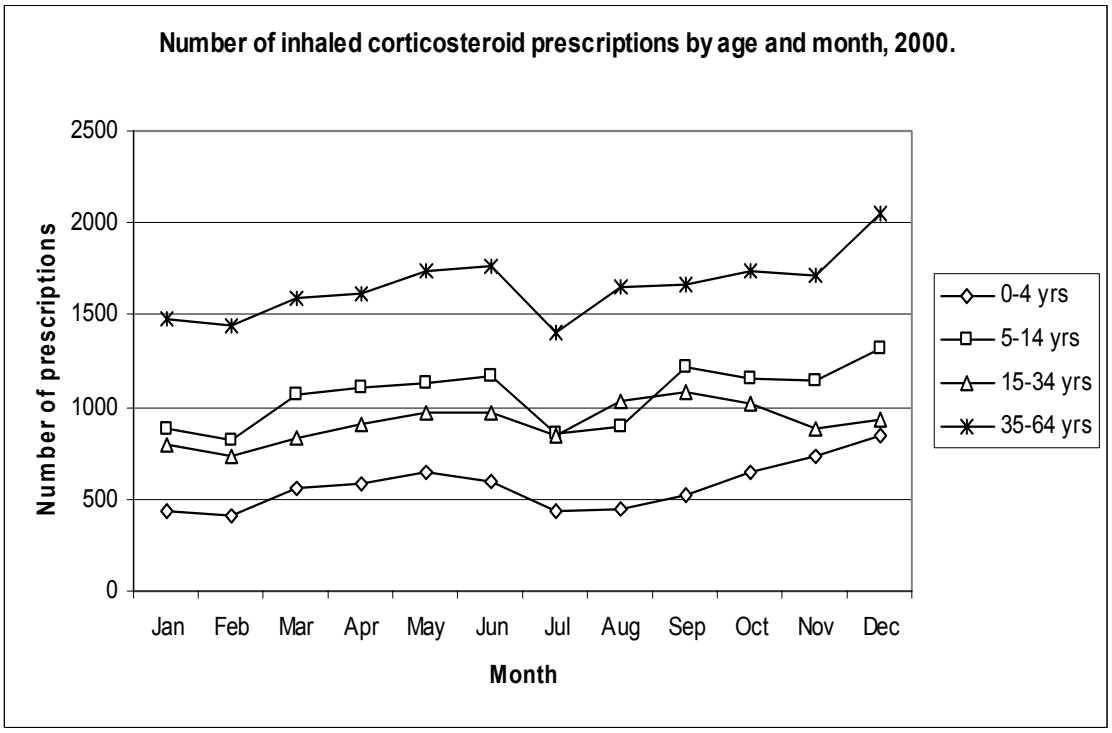

Figure 4-13 Number of inhaled corticosteroid prescriptions by age group and month, 2000

4.3.3 Monthly distribution of β_2-agonist prescriptions by sex and calendar year

For each of the five years, the difference between the numbers of short-acting beta$_2$-agonist prescriptions for males and females was minimal, and remained around 500 prescriptions. Males and females shared the same pattern of increases and decreases, which was similar to that of the number of beta$_2$-agonist prescriptions by age and month showing all years, 1996 to 2000 (Figure 4-2). In all sex comparisons, males had a greater number of prescriptions for each month, for all years.

When short-acting inhaled beta$_2$-agonist prescriptions were examined by age, sex, and month, it was found that 35-64 year old females had a greater number of prescriptions than males of this age group in all months, for all the years, from 1996 to 2000 (except for February and August of 1998 when males had a few more prescriptions than females). The 35-64 year old female group often had the greatest number of prescriptions of all age and sex groups during the year, except when superseded by the 15-34 year old males. The 15-35 year old male group had the greatest number of

prescriptions for every May and from the beginning of summer to the end of fall, from 1996 to 2000.

4.3.4 Monthly distribution of inhaled corticosteroid prescriptions by sex and calendar year

For each of the five years, the difference between the numbers of inhaled corticosteroid prescriptions for males and females was minimal and closer in number than those of beta$_2$-agonist prescriptions. Males and females shared the same pattern of increases and decreases as the number of inhaled corticosteroid prescriptions by age and month showing all years, 1996 to 2000 (Figure 4-3).

In most comparisons by sex, males had a greater number of prescriptions, with the exception of the year 1998 when in July, females had 1556 prescriptions and males had 1549 prescriptions. The 35-64 year old females were also found to consistently have the highest number of prescriptions of all sex and age groups, for all months, and all years from 1996 to 2000.

4.3.5 Summary of research question #3 results

In summary, there was little change between the five years in the patterns of each medication purchased by month for both inhaled short-acting beta$_2$-agonists and inhaled corticosteroids, respectively. There was peak use for inhaled beta$_2$-agonists in the spring and fall in all years. There was a decrease in the use of both medications during the summer months. There was a marked increase for both short-acting beta$_2$-agonists and inhaled corticosteroids in December.

When monthly purchases of short-acting beta$_2$-agonists were examined by age, there was an increase in September for the 5-14 year olds, and in December for the 35-64 year olds. These patterns were consistent for all years.

There was a decrease in the purchase of inhaled corticosteroids in the summer months for the 5-14 year old group, and a marked increase in inhaled corticosteroid purchases by the 35-64 year old age group in December. Again, these patterns were consistent for all years. The largest decreases in inhaled corticosteroid prescriptions occurred in the summer, and in January for the 5-14 year and 35-64 year old age groups.

4.4 Summary of Results

The results of this thesis provide some important information regarding asthma prescription purchases by Saskatchewan residents from 1991 to 2000.

Question 1

- Over the ten years, the proportion of persons with asthma who purchased at least one asthma prescription increased slightly, but significantly.
- There were more males with asthma, and more male users of asthma medications throughout the study period. Male users increased to a lesser degree than female users from 1991 to 2000.
- All age groups increased in the proportion of users between 1991 and 2000. The highest increase in use over time was for the 0-4 year old age group (6.1%). There was a particular decrease in the proportion of persons in all age groups in 1993.
- Excluding the northern health region, there was little variation in the proportion of persons with asthma per region who purchased asthma medication, 75.3% to 79.6%. The northern health region had the lowest proportion of asthma medication users per health region (63.7%).
- Over the ten years, the share of total yearly asthma prescriptions for the 5-14 year old group decreased 5.3%, and the 35-64 year old group increased 5.2%.
- Of total asthma prescriptions, the 0-4 year old group purchased only a 10.0% share between age groups. The 35-64 year old age group had the greatest share of total prescriptions (40.3%). Not surprisingly, males had a greater share of total prescriptions between the sexes.
- Mean prescription purchases of all asthma medications decreased from 1991 to 2000. The lowest mean prescriptions were among the 0-4 year, and 5-14 year old age groups. The highest mean prescriptions were in the 35-64 year old groups.
- Means decreased across all age groups and for both sexes over time. The greatest sex differences were found within the 15-34 year and 35-64 year old age groups. Within each age group from 1991 to 2000, males had a higher mean number of prescriptions than females.

- Over the ten years, more users with asthma purchased inhaled short-acting beta$_2$-agonists, followed by inhaled corticosteroids, then oral corticosteroids.
- There was a trend over time for the mean number of beta$_2$-agonist prescriptions to decrease, and for the mean number of inhaled corticosteroid prescriptions to increase. This trend was most notable in children.
- There was a pattern of steady decline, across all ages and in both sexes, in mean short-acting beta$_2$-agonist prescriptions over time. Short-acting inhaled beta$_2$-agonist mean prescriptions were highest in the two oldest age groups (15-34 years and 35-64 years) for both sexes, with males having the consistently greater mean.
- The highest mean inhaled corticosteroid prescription use was among the 0-4 year, and 35-64 year old groups, for both males and females.
- Males in the 15-34 year old age group had the greatest proportion of short-acting inhaled beta$_2$-agonist medication of all age/sex user groups in the year 2000. They were also the lowest users of inhaled corticosteroid medication.
- At the end of the study period, 0-4 year olds had the greatest proportion of inhaled corticosteroids. In the two older age groups (15-34 year and 35-64 year olds), inhaled and oral corticosteroids had more female purchasers in 2000.
- In 2000, the 0-4 year old age group had the largest proportion of users of oral beta$_2$-agonists (15.2%), a medication group that excluded the nebulized form of the medication.

When specific combination therapies for asthma were examined, the following findings were observed:

<u>Question 2</u>

- Over the ten year period, the use of short-acting inhaled beta$_2$-agonist medication (alone) decreased over time while the use of inhaled corticosteroids (alone) increased.
- There was a two-fold increase in the combined use of inhaled corticosteroids and beta$_2$-agonists from 1991 to 2000. The greatest change in use of this combination occurred between 1991 and 1994.
- The differences between males and females were minimal.

- The 0-4 year old age group had the most dramatic increase in the inhaled corticosteroid and short-acting β_2-agonist combination from 1991 to 2000.
- There was a marked reduction in the use of smooth muscle relaxants and unclassified medications, each used in combination with inhaled corticosteroids and short-acting $beta_2$-agonists by the end of 2000.

When seasonal patterns of prescriptions for inhaled short-acting $beta_2$-agonist and inhaled corticosteroid purchases from 1996 to 2000 were examined the following observations were made:

Question 3

- There was little change between the five years in the patterns of medication purchased by month for both inhaled short-acting $beta_2$-agonists and inhaled corticosteroids.
- There was a sharp decline in the number of prescriptions filled, for both medications, during the summer months and in mid-winter (January and February).
- There was a marked increase in prescription filling for 5-14 year olds in September. For 35-64 year olds an increase occurred in December. These patterns of purchase increases were consistent for all years examined.
- There was no noticeable difference in the patterns of monthly purchasing of prescriptions for either $beta_2$-agonists or inhaled corticosteroids between men and women.

5. DISCUSSION

The main objectives of this study were to describe the characteristics of persons with asthma in a general population who use asthma medications, the manner in which asthma medication is used, and the seasonal variation in the purchase of the most common asthma medications.

5.1 Use of Asthma Medication by Persons with Asthma

The first important finding in this study was that nearly 80% of persons diagnosed with asthma in Saskatchewan from 1991 to 2000 purchased at least one asthma medication. Over time, the proportion of medication users increased gradually. The purchase of asthma-related drugs by asthmatics was reported by Senthilselvan for the years 1981 to 1990 in Saskatchewan, and in that period the proportion of purchasers rose from an average of 65.0%, for all age groups, to 75.0% (2). Changes in recommended asthma medication, delivery systems, and attitudes toward pharmacological treatment of asthma, may be explanations for the continued steady increase in the proportion of persons with asthma using medication that was observed in this 1991 to 2000 study. Improved education and dissemination of national guidelines for the treatment of asthma (first published in 1996) to healthcare workers, and persons with asthma, could also partially explain improved "appropriateness" in asthma treatment. Just over 20 percent of persons who received an asthma diagnosis did not pursue a pharmacologic treatment regimen and could be presumed to be cases of very mild severity, or (more likely) of non-compliance. Senthilselvan suggested that overcoding of asthma and low socioeconomic status, where purchasing of medication may be a problem, could explain the non-purchasing behaviour of some persons with asthma (2).

5.1.1 Asthma medication users by age

Subjects were separated into four physiologically meaningful (i.e., homogeneous) age groups, and it was found that the oldest group (35-64 year olds) maintained the greatest proportion of medication purchasers for almost the entire ten year study period. It was the youngest age group (0-4 year olds) that had the greatest increase in users over the ten year period with a rise of 6.1%. This youngest age group had the greatest proportion of users in 2000 (Table 4-2). This was later shown to be due to more users purchasing inhaled corticosteroid medication (as a monotherapy and/or in combination with short-acting beta$_2$-agonists (Tables 4-19 and 4-20).

In 1992, an article by Spitzer et al. raised alarm throughout the asthma community about the elevated risk of near-death and death related to the use of short-acting beta$_2$-agonists (17). In Table 4-1 it was shown that although the population of persons with asthma continued to increase, in 1993 the proportion of persons who purchased asthma medication in that year decreased. Again, in Table 4-2, it was shown that in 1993 in all age groups, except the 15-34 year old group, there was a small decrease in the proportion of medication users. When the proportion of asthma medication users was stratified by region, a decrease in 1993 was not seen in this data (Table 4-4).

A decrease in the mean number of prescriptions was seen for all medications, except inhaled and oral corticosteroids, over the ten year period (Table 4-11). Events that may have influenced the decrease in the mean use of short-acting beta$_2$-agonists include research from New Zealand that showed a relationship between increased beta$_2$-agonist use and death (44;45), the Spitzer et al. article of 1992, and the publication of Canadian national asthma treatment guidelines.

5.1.2 Asthma medication users by sex

In every year of the study period, male asthmatics had a greater proportion of purchasers; and male users maintained higher mean prescription purchases of asthma medications. Toward the end of the study period, the differences between the sexes narrowed on both measures. The mean numbers of prescriptions for medication users 15 years and older were greater compared to users less than 15 years of age. The mean

number of prescriptions per year was particularly high for the oldest age group (35-64 years old).

5.2 Asthma Medication Users and Their Mean Use of Single Preparations

The overall mean number of asthma prescriptions for users with asthma decreased over the ten year period. The three leading single medications used throughout the ten year period of this study were short-acting beta$_2$-agonists, inhaled corticosteroids, and oral corticosteroids. From 1991 to 2000, the proportion of persons purchasing inhaled corticosteroids increased, as did the mean number of inhaled corticosteroid prescriptions (Table 4-11). The users and mean use of inhaled corticosteroids increased for all ages and both sexes, as seen in Tables 4-18 and 4-10. This finding is consistent with the CCG, which have recommended the progressively earlier introduction of inhaled corticosteroids with every new publication (4;11;12;46). However, current research suggests that fear and misunderstanding about the role and potential side effects of inhaled corticosteroids could be interfering with their use by asthmatic patients (47).

5.2.1 Short-acting beta$_2$-agonists

The purchasing of only short-acting beta$_2$-agonists persisted in the asthma population from 1991 to 2000, despite the CCG that recommended that this medication should only be used alone in very mild cases of asthma, or only occasionally, in adulthood (Figure 1-1) (11). Although the proportion of persons using beta$_2$-agonists alone did decrease slightly from 1991 to 2000 (79.7% to 78.9%, Table 4-11), it was still far too high to be in compliance with consensus guidelines. By the year 2000, it seems unlikely that a quarter of the medication-purchasing asthma population, including those who did not purchase any asthma medication, had pre-clinical (or sub-clinical) to very mild asthma (4;11).

Short-acting beta$_2$-agonist mean prescriptions were greater for males in all age groups throughout the study period. This result is supported by research by Schatz et al. who found that all males in their study (aged 2 to 64 years) had significantly greater mean beta$_2$-agonist prescriptions than their female counterparts ($p < 0.001$) (48). In the

current study, particularly high users in the year 2000 were the 15-34 year old males with 3.53 mean prescriptions and 35-64 year old males with 3.56 mean prescriptions (Table 4-15). The mean overall prescription use of the 15-34 year old males in 2000 was 5.44 (Table 4-9); of this number, 3.53 mean prescriptions (approximately 65.0% of this group's total medications) were devoted to short-acting $beta_2$-agonist medication use. Schatz et al. also found high short-acting, $beta_2$-agonist medication use with the highest mean prescriptions among males 14-22 years and 23-64 years old, 7.9 to 7.7 mean prescriptions per year, respectively (48). Blais et al. also found high inappropriate use of short-acting $beta_2$-agonists among their adult male patients (29).

Unlike the younger adult males, in this study, 35-64 years old males who also had high $beta_2$-agonist use, had a relatively high mean number of inhaled corticosteroid prescriptions; 2.45 mean prescriptions in 2000, which accounted for approximately 32.0% of the group's total medications. Both males and females in this oldest age group frequently used, and were high users of, all asthma medications in general (Table 4-15). Schatz et al. also saw increased medication dispensings in their oldest age group (23-64 years) (48). Females of this age group used more inhaled and oral corticosteroid medications than males; and males used more short-acting $beta_2$-agonists than females (48).

5.2.2 Inhaled corticosteroids

The increases observed in inhaled corticosteroid users and numbers of mean prescriptions during the study period were congruent with that recommended as first-line therapy for asthma by the CCG. The 0-4 year old age group's mean prescription use in this study was increasingly dominated by inhaled corticosteroid medication (2.16 mean prescriptions representing approximately 53.0% of this group's total medications) and less by short-acting $beta_2$-agonist mean number of purchases (1.26 mean prescriptions representing approximately 30.0%) in the year 2000 (Table 4-15). One possible explanation for better adherence to the CCG in the very young children in this study is in the increased interest and control parents, physicians, and other interested parties (for example, schools) have over persons under 15 years of age. The increase in inhaled corticosteroid users in the 0-4 year group over time, may be explained by the availability

of improved, appropriate delivery devices (diskhalers, aerochambers) and/or the development of nebulized Budesonide in the later years of the study. Prior to these developments it would have been difficult to administer inhaled corticosteroids to children less than five years of age.

The 15-34 year old males had the lowest mean number of inhaled corticosteroid prescriptions, 1.42 (approximately 26.0% of the group's total medications), in the year 2000 (Table 4-15). The 15-35 year old females had a similarly low mean number of inhaled corticosteroid prescriptions, but had a much lower mean number of $beta_2$-agonist prescriptions compared to their male counterparts (Table 4-15). Schatz et al. found that mean prescriptions for inhaled corticosteroids were lowest for their middle age group (14-22 year olds), though the mean prescriptions for males were significantly greater than those for females ($p < 0.01$) (48).

Overall, the biggest users of inhaled corticosteroids, in proportion and mean number of prescriptions in this study, were the 35-64 year old group. This is similar to the increased inhaled corticosteroids use found by Schatz et al. for the 23-64 year old age group (48).

The length of time with the disease could be important in understanding the pattern of use by males and females in this study. Lindberg et al. found in their study of asthma medication compliance in Swedish subjects that increasing age and female sex were significant factors in patients taking their prescribed medication (49). However, Lindberg et al. also found that increasing length of the disease decreased the odds of patient compliance with their prescribed medication (49).

5.2.3 Other medications

The decreases in users and mean number of prescriptions for sodium cromoglycate and theophylline medications over time were also consistent with the CCG. New treatments such as anti-leukotrienes, the pre-combined medication (Fluticasone and Salmeterol), and long acting $beta_2$-agonists were too "newly emerged" in the study period to be observed for their true role and impact on the asthma population in Saskatchewan.

Oral corticosteroids, the third most often purchased medication, were first used mainly in 0-4 year old children, but later established a hold in the oldest age group (35-64 year olds). Schatz et al. found that females in the 23-64 year old age group were more likely than men to require oral steroids (48). Oral corticosteroids and long-acting $beta_2$-agonists appeared to have been used as supportive medication, presumably (as CCG indicated) where asthma cases were resistant to treatment and/or disease severity increased for all ages(4).

5.3 Asthma Medication Users of Preparations in Combination

The largest change in the number of users of inhaled corticosteroids and short-acting $beta_2$-agonists, as can be seen in Figures 4-1 and 4-2, occurred between 1991 and 1994 when the Spitzer et al. article was published (17). It can be seen in Figures 4-3 and 4-4, that there were gradual increases in both the inhaled corticosteroid monotherapy group and the short-acting $beta_2$-agonists/inhaled corticosteroid combination group, with a corresponding decrease in the short-acting $beta_2$-agonist monotherapy group, which continued to the end of the study period. As these results are consistent with the CCG recommendations of both 1996 and 1999, it is postulated that physician and patient education were partly responsible for these changes despite the concern of the CACG that dissemination and implementation of the guidelines had not been wholly successful (4;12;46).

Users of both the inhaled corticosteroids and inhaled short-acting $beta_2$-agonists combination, and the inhaled corticosteroids, short-acting $beta_2$-agonists, and oral corticosteroids combination doubled over the study period. Users of inhaled corticosteroids (monotherapy) more than tripled from 1991 to 2000. A short course of oral corticosteroids for very young children was recommended in the 1996 CCG for severe exacerbations, which may explain the increase in users from 1991 to 2000 (11). Again, these results of increased users of inhaled corticosteroids singly and in combination are reassuring. These results do not contradict existing research that found under use of inhaled corticosteroids and over use of short-acting $beta_2$-agonists (25), but they have provided a long-term view of an encouraging trend.

A reduction in the use of smooth muscle relaxants and unclassified agents, each in respective combination with inhaled corticosteroids, and short-acting beta$_2$-agonists, was in accordance with the CCG recommendations. This may be taken as further evidence that dissemination and implementation of the guidelines occurred during the study period (4).

While the proportional use of the inhaled short-acting beta$_2$-adrenergic agonists, inhaled corticosteroids combination increased over time in all age groups, the largest increase was in the 0-4 year old group (see Appendix C). Again, this may be due to the increased influence over this age group by parents who monitored their children's treatment recommendations. There were no changes between males and females in the use of selected combinations during the study period.

5.4 Seasonal Variation of Prescription Purchases

Between 1996 and 2000, short-acting beta$_2$-agonist and inhaled corticosteroid medication monthly purchases were similar within medication type for each calendar year. Purchases of both types of medications decreased every year during the summer months. Similar results were also reported by Crighton et al. (32), Johnston et al.(33), and Fleming et al. (31) who encountered the same "summer trough" before an autumn peak in asthma exacerbations and/or hospital admissions. As in the case of the current findings, the reported patterns appeared to be heavily influenced by children. The peak purchase of beta$_2$-agonists in the spring, fall, and winter from 1996 to 2000 is supported by existing research where large peaks have been reported in the autumn with minor peaks in December, January, and April (32). Existing research has also shown age dependent results in seasonal asthma exacerbations, with children experiencing more episodes in September, and older subjects having increases with the approach of winter (31). In this study there was a marked increase for both beta$_2$-agonists and inhaled corticosteroids in December for the 35-64 year old age group. This finding of a winter increase in prescriptions in older adults could be related to influenza occurrences, or it may be an artifact of prescription purchasing practices. It is possible that prescription purchasers who have paid their prescription deductible for the year wished to take advantage of the province's drug plan, which would pay for medications over the

deductible, before the beginning of a new year. Purchasers may also have been motivated by private or alternative insurance provisions for prescription purchases that ended in December. These incentives might help to explain the observation of lower prescription numbers in January of each examined year, relative to the preceding December.

Short-acting beta$_2$-agonist prescriptions increased in September for the 5-14 year old group. Johnston et al. explored asthma exacerbations in Canadian school children and found decreased purchases of inhaled corticosteroids in the summer months for the 5-15 year old group (33). Researchers also found that children were using less controller medication prior to returning to school in the fall, and may have been subjected to an elevated risk of a viral-induced asthma exacerbation (33). Since rhinoviruses have been shown to have some association with the fall asthma epidemic in children (33), it would seem prudent to begin prophylactic treatment earlier in the summer, before their return to school, to see if this measure can remedy the fall exposure.

5.5 Study Strengths

This study was different from previous research in asthma pharmacological treatment because it drew from a combined patient and prescription database for the province of Saskatchewan that included almost every member of the population who received an asthma diagnosis, and then purchased a pharmacological treatment for that condition. A study of this scale would not be possible by means of a self-report survey method, for example, as accuracy and response rate would be greatly decreased. In addition, because Saskatchewan Health provided this study with pseudo-numbers to identify individuals, it was possible to calculate the mean use of medications by individuals over the ten year study period. This was a significant improvement over previous (ecological) research.

The assumption tentatively used in this study is that the frequency with which one fills prescriptions is a proxy variable for both use and severity. Because short-acting beta$_2$-agonist medications are inexpensive, it is possible that asthma patients purchased them just to have them on-hand, thereby inflating the appearance of beta$_2$-agonist medication overuse. Supporting this assumption are the four years of elevated beta$_2$-

agonist prescriptions found each December, which were followed by four comparatively low prescription numbers in January.

Having ten years of data provided a heightened level of assurance that the observed trends and patterns in asthma care and treatment in Saskatchewan were genuine. The extended period, and provision of individual data, allowed for a level of scrutiny that has not yet been fully explored.

5.6 Study Limitations

Descriptive studies are designed to "…describe the existing distribution of variables, without regard to causal or other hypotheses." (50) They are often used to analyze registry data, measure risks, and generate hypotheses. As these studies are frequently retrospective, certain biases and limitations inject variability into the collected data. These may include one or more of the following: diagnostic shift (the disease is diagnosed by evolving criteria over time); a change in the units of measurement in the diagnosis and/or treatment of the disease over time or a change in diagnostic tests over time.

As the physician-billing database was used to determine the prevalence of asthma (using the ICD-9 three-digit code), the primary function of the database was physician remuneration, and the potential for a misclassification bias was present. Though an asthma related medication purchase was used to validate the diagnosis, the possibility of a bias persists as similar conditions require similar pharmacologic treatments (e.g., chronic obstructive pulmonary disease and short-acting beta$_2$-agonists for first-line treatment) (51).

The most important limitation of this study was that the prescription purchase does not connote the actual use of the medication. Further, it does not ensure appropriate delivery of the medication is being practiced.

In this study's analyses, not all users/purchasers could be considered the same users for each year of this study, and therefore the results did not reflect individual change but rather, population change. As such, we were unable to discern if, for example, the greatest short-acting beta$_2$-agonist users were indeed the most severe

asthmatics. With the addition of the hospitalization data to which this study's data is linked, our understanding of asthma severity in Saskatchewan will improve.

As mentioned previously, it is not possible to discern if the CCG influenced the changes in the purchasing behaviour of the asthma population and/or the behaviour of parents, educators, and physicians who care for asthmatic patients. The results of these ten years of data imply that the CCG have made a real impact.

6. RECOMMENDATIONS FOR FUTURE RESEARCH

As a descriptive epidemiologic study, there are countless opportunities to generate new hypotheses and research from this study. The surveillance of those who consume asthma medications and the manner in which they use their medications should continue, with particular focus on short-acting beta$_2$-agonists, inhaled corticosteroids, and new emerging medications, such as anti-leukotrienes.

This thesis study showed that the proportion of users and their mean number of short-acting beta$_2$-agonist prescriptions were much higher than acceptable, according to national guidelines. Monitoring of the continued decrease in both of these measures could serve as both an indication that the disease is reaching a suitable level of control (and severity is decreasing), and that the CCG are having an impact on asthma treatment. Complimentary surveillance of the increase in inhaled corticosteroid users and their mean number of prescriptions would also support an impression of improved asthma control.

Short-acting beta$_2$-agonist users and mean number of prescriptions were particularly high among 15-34 year old males, and all 35-64 year old adults. Further study of high risk and/or low-compliance groups would be warranted. To address the issue of the large population of short-acting beta$_2$-agonist monotherapy users, it may be useful to study special groups such as occasional users, and exercise induced users. In addition, some means of understanding pre- and post-deductible prescription filling in Saskatchewan may be helpful in adjusting a potentially inflated number of certain medication purchases.

The elevated use of oral beta$_2$-agonist medication in the last year of the study was of concern, particularly for the 0-4 year old age group, as this medication group did not include a nebulized route of delivery. Future research may wish to investigate reasons for this unexpected finding.

Validation of the relationship between the purchase of asthma medications and actual use is an enduring problem that requires further research. Thus far, self-reported use of medications is often biased and insufficient as a measure of patient compliance (48;49). Length of time since the onset of the disease may be a factor in determining patient compliance (48;49). A longitudinal study of medication use that follows patients from their initial diagnosis of asthma into adulthood could add new information to the understanding of patient compliance.

In future research regarding the seasonal variation of asthma exacerbations in school children, it might be useful to apply a case-control model to the problem, following through on recommendation of existing research (33). As increased exposure to rhino-viruses is suspected in combination with observed summer decreases in asthma medication, cases could begin their prophylactic inhaled corticosteroid treatment before returning to school. The controls in the trial would continue to refrain from taking their inhaled corticosteroid medication as usual.

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APPENDIX A
COPY OF ETHICS APPROVAL

UNIVERSITY ADVISORY COMMITTEE
ON ETHICS IN BEHAVIOURAL SCIENCE RESEARCH

NAME: D. Rennie (N. White) **BSC#:** 01-44
Agricultural Medicine/Nursing/Community Health & Epidemiology

DATE: March 8, 2001

The University Advisory Committee on Ethics in Behavioural Science Research has reviewed the Application for Ethics Approval for your study "Variations in the Use of Asthma Medications among Physician-Diagnosed Asthma Cases from January 1, 1989 to December 31, 1998" (01-44).

1. Your study has been APPROVED.
2. Any significant changes to your proposed study should be reported to the Chair for Committee consideration in advance of its implementation.
3. The term of this approval is for 5 years.

I wish you a successful and informative study.

Valerie Thompson, Chair
University Advisory Committee
on Ethics in Behavioural Science Research

VT/bk

Office of Research Services, Ethics Committees, University of Saskatchewan
Kirk Hall Room 207, 117 Science Place, Saskatoon SK S7N 5C8 CANADA
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APPENDIX B
PROPORTION OF DRUG TREATMENT USERS BY SEX, 1991, 1994, 1997, AND 2000.

Number of purchasers of most frequently used asthma medication combinations, for those aged 0-64, including inhaled beta$_2$-agonists and inhaled corticosteroids in their single preparations by sex for the years, 1991, 1994, 1997 and 2000

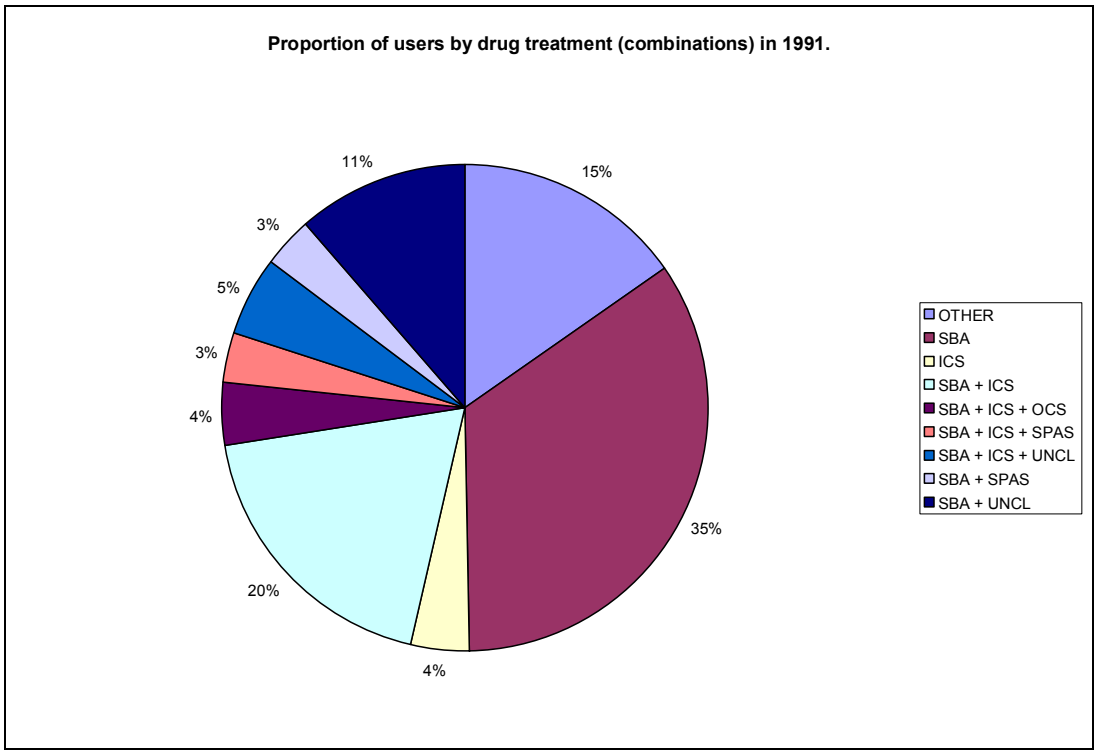
Medication(s)	1991		1994		1997		2000	
	Male %	Female %	Male %	Female %	Male %	Female %	Male %	Female %
All other medications (used in combinations)	14.6	15.8	12.1	14.0	11.3	13.4	13.6	17.1
Short-acting β_2-agonists (used alone in year)	35.0	33.9	28.2	28.0	24.6	23.6	23.3	22.8
Inhaled corticosteroids (used alone in year)	3.0	4.9	10.5	11.4	13.2	13.5	12.7	13.5
Short-acting β_2-agonists + Inhaled corticosteroids	18.7	19.3	30.1	29.2	37.4	35.9	40.2	37.0
Short-acting β_2-agonists + Inhaled corticosteroids + Oral corticosteroids	3.6	4.6	7.9	8.1	8.1	8.9	8.9	8.3
Short-acting β_2-agonists + Inhaled corticosteroids + Smooth muscle relaxants	3.3	3.5	1.4	1.4	0.8	0.9	0.4	0.5
Short-acting β_2-agonists + Inhaled corticosteroids + Unclassified agents	5.8	4.7	3.8	3.0	2.3	1.6	0.4	0.4
Short-acting β_2-agonists + Smooth muscle relaxants	3.2	3.4	0.7	0.9	0.4	0.4	0.2	0.2
Short-acting β_2-agonists + Unclassified therapeutic agents	12.8	9.8	5.3	3.9	1.9	1.7	0.4	0.2
TOTAL N	9911	8180	10979	9852	12211	11362	13008	12094

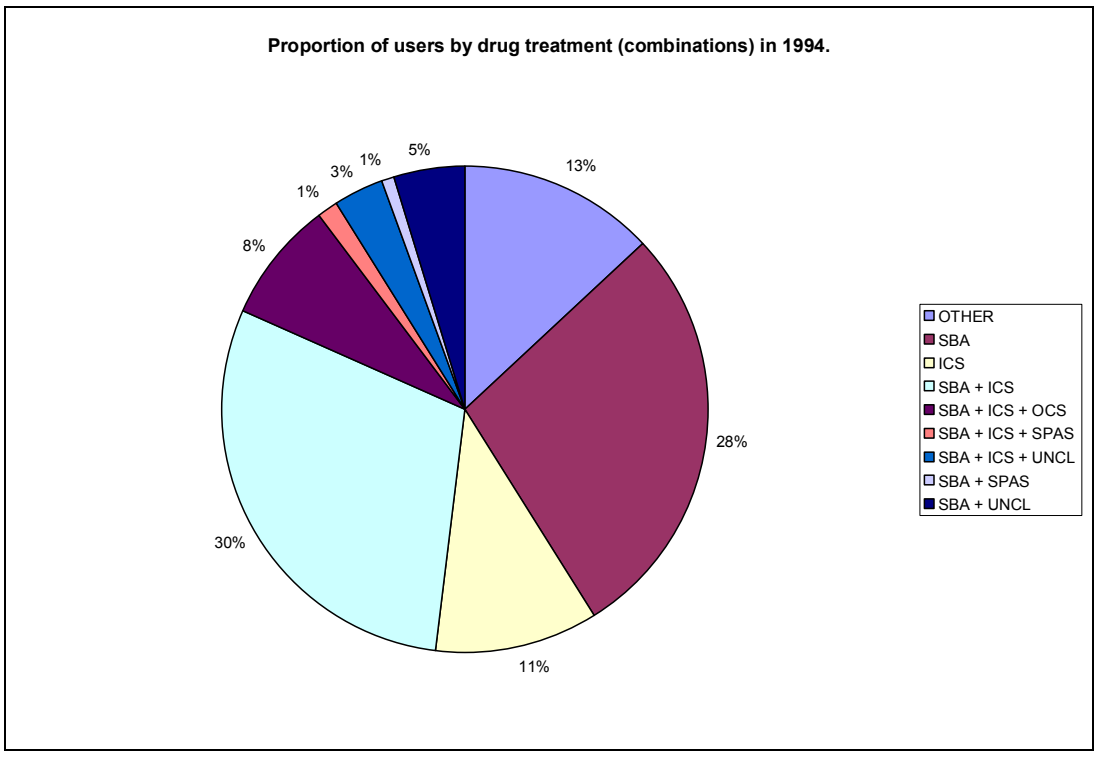
APPENDIX C
PROPORTION OF DRUG TREATMENT USERS BY AGE GROUP, 1991 AND 2000.

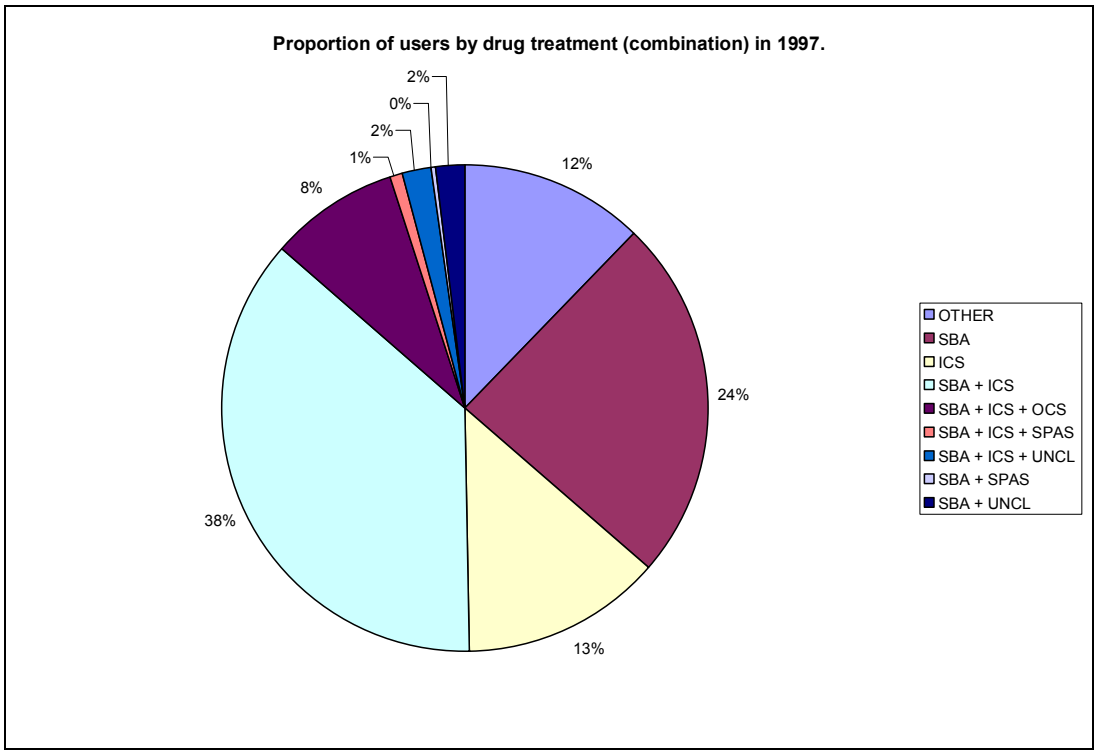
Proportion of purchasers by medication treatment and age group, 1991 and 2000

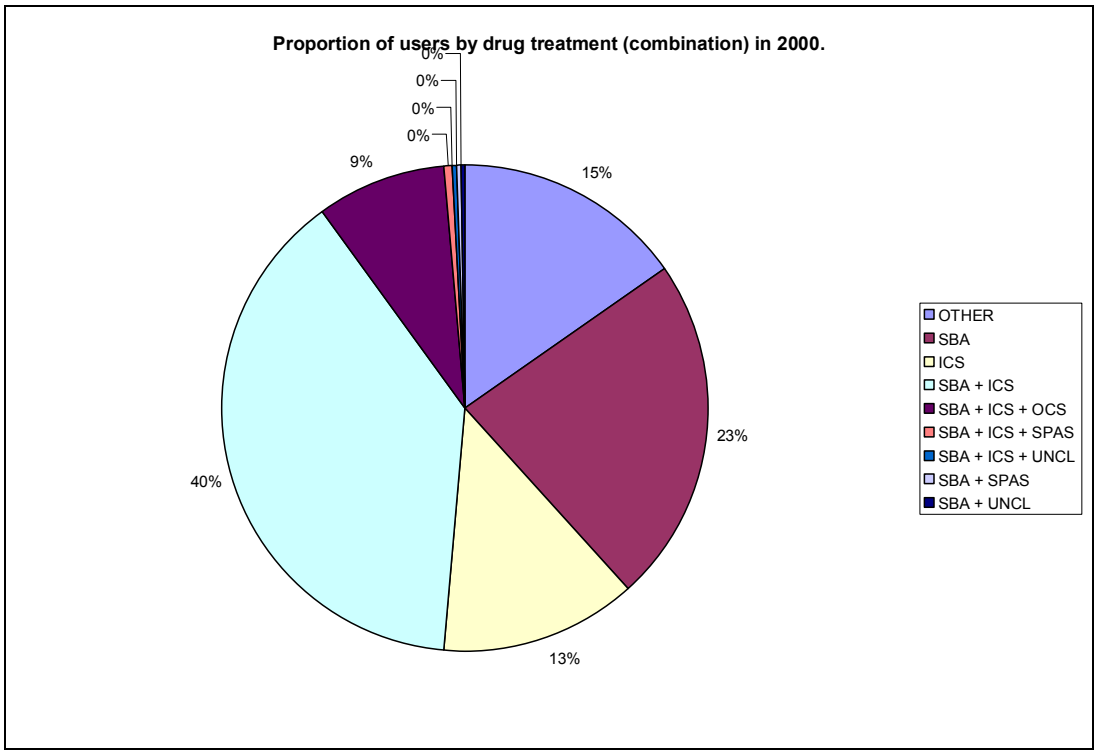
Medication(s)	0-4 years		5-14 years		15-34 years		35-64 years	
	1991	2000	1991	2000	1991	2000	1991	2000
	%	%	%	%	%	%	%	%
All other medications (used in combinations)	16.2	11.4	11.6	10.2	11.8	11.9	22.7	24.4
Short-acting β_2-agonists (used alone in year)	38.9	13.5	33.1	19.7	43.4	33.5	23.8	19.6
Inhaled corticosteroids (used alone in year)	1.0	17.3	4.0	18.5	3.8	8.2	5.4	11.7
Short-acting β_2-agonists + Inhaled corticosteroids	4.5	41.4	19.9	42.8	22.2	38.5	22.7	34.2
Short-acting β_2-agonists + Inhaled corticosteroids + Oral corticosteroids	1.2	15.6	2.2	7.7	4.5	6.8	7.6	8.3
Short-acting β_2-agonists + Inhaled corticosteroids + Smooth muscle relaxants	0.4	0.1	1.2	0.1	3.4	0.3	7.9	1.1
Short-acting β_2-agonists + Inhaled corticosteroids + Unclassified agents	6.1	0.4	9.4	0.6	2.8	0.3	2.6	0.3
Short-acting β_2-agonists + Smooth muscle relaxants	3.4	0.1	2.0	0.0	3.1	0.1	5	0.3
Short-acting β_2-agonists + Unclassified agents	28.3	0.2	16.7	0.3	0.5	0.3	2.2	0.2
TOTAL (N)	2699	3100	5719	6592	5065	7600	4608	7810

APPENDIX D
PROPORTION OF PURCHASERS BY MEDICATION TREATMENT, 1991, 1994, 1997, AND 2000.






Proportion of users by drug treatment (combination) in 1997.
2%
0%
2%
1%
8%
12%
24%
38%
13%
OTHER
SBA
ICS
SBA + ICS
SBA + ICS + OCS
SBA + ICS + SPAS
SBA + ICS + UNCL
SBA + SPAS
SBA + UNCL


Proportion of users by drug treatment (combination) in 2000.
0%
0%
0%
0%
9%
15%
23%
40%
13%
OTHER
SBA
ICS
SBA + ICS
SBA + ICS + OCS
SBA + ICS + SPAS
SBA + ICS + UNCL
SBA + SPAS
SBA + UNCL