PHARMACEUTICAL USE IN MANITOBA: Opportunities to Optimize Use

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Community Health Sciences

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About the Manitoba Centre For Health Policy

The Manitoba Centre for Health Policy (MCHP) is located within the Department of Community Health Sciences, Faculty of Medicine, University of Manitoba. The mission of MCHP is to provide accurate and timely information to health care decision-makers, analysts and providers, so they can offer services which are effective and efficient in maintaining and improving the health of Manitobans. Our researchers rely upon the unique Population Health Research Data Repository (Repository) to describe and explain patterns of care and profiles of illness, and to explore other factors that influence health, including income, education, employment and social status. This Repository is unique in terms of its comprehensiveness, degree of integration, and orientation around an anonymized population registry.

Members of MCHP consult extensively with government officials, health care administrators, and clinicians to develop a research agenda that is topical and relevant. This strength, along with its rigorous academic standards, enables MCHP to contribute to the health policy process. MCHP undertakes several major research projects, such as this one, every year under contract to Manitoba Health (MB Health). In addition, our researchers secure external funding by competing for research grants. We are widely published and internationally recognized. Further, our researchers collaborate with a number of highly respected scientists from Canada, the United States, Europe and Australia.

We thank the University of Manitoba, Faculty of Medicine, Health Research Ethics Board for their review of this project. MCHP complies with all legislative acts and regulations governing the protection and use of sensitive information. We implement strict policies and procedures to protect the privacy and security of anonymized data used to produce this report and we keep the provincial Health Information Privacy Committee informed of all work undertaken for MB Health.

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Executive Summary

Introduction

This report provides a snapshot of prescribing across several categories of medications for all Manitobans over an 11–year period (1997/98–2008/09). It describes a population–based profile of utilization for antipsychotics and benzodiazepines and the related medications in older adults, medications and glucose test strips for diabetes mellitus, inhalers for asthma and chronic obstructive lung disease, and biologic agents to treat rheumatoid arthritis, inflammatory bowel disease, ankylosing spondylitis, and psoriasis. The report assesses a range of influences on medication utilization, such as patient sociodemographic factors and prescriber characteristics. Some literature suggests that, for a variety of reasons, these groups of medications are not always prescribed optimally. The report evaluates the impact of patient and prescriber characteristics on measures of optimal medication use based on recent literature and guidelines including: the use of inhaled or oral corticosteroids prior to the use of inhaled long acting beta agonists (LABA) for asthma, the use of LABA with concomitant inhaled or oral corticosteroids, avoiding the use of high dose second generation antipsychotics (SGAs) in older adults, and reserving higher cost new medications for diabetes mellitus as second line therapy.

Study Methods

Overall study methods

This report captures all Manitoba residents who had coverage by Manitoba Health and filled prescriptions in Manitoba from 1997/98 through the end of 2008/09. The following databases were accessed: the population registry, prescription medication records, physician reimbursement claims, hospital files, personal care home (PCH) files, vital statistics, and Statistics Canada census files.

Measures of use and determinants of use

Prevalent users and incident users were determined for each quarter from 1997/98 through the end of 2008/09. Incident (or new) users were defined by those who had not received a prescription for one year for each medication or medication group. Both prevalent and incident utilization is expressed as users per 1,000 residents per quarter. The influence of sociodemographic characteristics (age, sex, region of residence, and socioeconomic status) on medication utilization over time were evaluated with generalized estimating equation (GEE) modeling to determine if individuals in one group were more likely to receive a prescription than those in another group, while controlling for other factors.

Optimal use analysis

For several medication categories, a measure of potentially optimal or less than optimal utilization was created. For incident users of the medication of interest, the variables of sociodemographic characteristics, prescriber characteristics, time, and measures of health services utilization in the period immediately preceding the new prescription were evaluated to determine factors predictive of this potentially less than optimal use. These analyses were performed with logistic regression modeling.

Key Findings

Antipsychotics, benzodiazepines and related medications in older adults

The use of second generation antipsychotics (i.e., risperidone, olanzapine, quetiapine), benzodiazepines, and related medications in older adults in Manitoba is increasing; and it is especially high in residents of personal care homes, despite recommendations to avoid these agents, whenever possible, in older adults with dementia. By 2008/09, 27% of older adults residing in personal care homes received a prescription for a second generation antipsychotic (the most commonly used agent was risperidone). Use of high dose second generation antipsychotics is less then optimal due to an increased risk for dose related adverse effects, such as falls and movement disorders. It is good news that from 2002/03–2007/08, only 10.2% of new users of second generation antipsychotics received high doses of these agents within the first year of therapy. Users of high dose second generation antipsychotics were younger and more likely to be male, have psychosis or dementia (taking medications to treat dementia), and be taking fewer other medications. No prescriber or environment characteristics (including PCH environment and type of PCH) predicted this less than optimal prescribing.

Medications and test strips for diabetes mellitus

The use of metformin, the most appropriate first line agent for the treatment of type 2 diabetes mellitus, has increased dramatically over time, consistent with guidelines and recommendations. By 2008/09, metformin accounted for more than 82% of first prescriptions for medications to treat diabetes. The use of test strips for self monitoring of blood glucose has also increased dramatically over time. Recent (2009) recommendations suggest that individuals receiving no oral anti–diabetic agents, or anti–diabetic agents that do not cause hypoglycemia, should not monitor blood glucose regularly (rather, only under special circumstances such as when they are ill or changing their medication regimen). This suggests that up to 40% of all Manitobans using test strips and that up to 24–27% of test strips used in Manitoba may have been in excess of what recent evidence and recommendations support. The use of more costly newer agents as the first prescription for the treatment of diabetes was minimal (3.5%), as these agents are generally not covered by Manitoba Pharmacare, or are used only for specific patient circumstances. Individuals were more likely to receive a new medication for diabetes as a first prescription for a diabetes medication if they lived in a rural location; were younger; had more ambulatory physician visits and hospitalizations; or saw a specialist, a fee–for–service physician, or a longer practicing physician. These findings suggest that the Manitoba Pharmacare criteria for the new agents for diabetes were adhered to.

Inhaled medications for the treatment of asthma and chronic lung disease

Current asthma guidelines recommend the use of corticosteroids prior to the use of LABA, and they do not recommend LABA without the use of corticosteroids due to concern for increased asthma morbidity with LABA. The use of LABA without prior corticosteroids in Manitobans with asthma is increasing, despite asthma guidelines. Similarly, the use of LABA without corticosteroids in Manitobans with asthma is increasing. Persons with asthma are more likely to be prescribed asthma medications not according to guidelines if they have less severe asthma or see general practitioners. Challenges to the interpretation of this data include the difficulty of using administrative data to assign a diagnosis of asthma. Further education for patients and physicians about the role of LABA in the treatment of asthma, especially in light of recent warnings about use of LABAs, is required.

Biologic agents

In Manitoba, the utilization of biologic agents for treatment of rheumatoid arthritis, inflammatory bowel disease, ankylosing spondylitis, and psoriasis, has increased with time. By 2008/09, 0.15% of the adult population had received prescriptions for these medications. This increase in utilization reflects an increase in randomized controlled trial evidence for the efficacy of these agents. More than 95% of users of the biologic agents had a diagnosis of one of the approved indications for use. A patient specific prior approval process for coverage of these medications by the Manitoba Drug Benefits and Interchangeability Formulary likely serves to encourage evidence–informed prescribing of these biologic agents.

Conclusions and Recommendations

This study describes incident and prevalent utilization of antipsychotics and benzodiazepines/related medications in older adults; medications and glucose test strips for diabetes mellitus; inhalers for asthma and chronic obstructive lung disease; and biologic agents by patient sociodemographic characteristics and region of residence within the province of Manitoba. Eleven years of prescription drug data (1997/98–2008/09) have been employed, using previously developed population–based indicators of medication utilization. Possible excessive use of second generation antipsychotics (SGAs) in older adults, particularly those residing in personal care homes, has been observed despite warnings issued by Health Canada regarding risks associated with this class of medications in individuals with dementia; however, the percentage of new users of SGAs receiving high doses of these agents appears to be small (approximately 10%). The undesirable concomitant use of antipsychotics and benzodiazepines was also limited. Anti–diabetic medications appeared to be used optimally with metformin being the most prescribed first line agent; however, the use of glucose test strips may be more than what is supported by the most recent recommendations. Pharmacare policies appeared to be effective in limiting the use of the more expensive, newer anti–diabetic agents. Some use of LABA in Manitoba appeared not to be in line with current guidelines for the treatment of asthma, with many individuals receiving LABA or LABA/corticosteroid inhalers without an adequate trial of corticosteroid therapy; implementation of policies to promote optimal use of this class of medications might be considered. Due to the nature of the agents and the patient-specific coverage policy, biologic medications used for the treatment of rheumatoid arthritis, inflammatory bowel disease, ankylosing spondylitis, and psoriasis seem to be prescribed for these indicators appropriately despite a significant increase observed in their utilization.

Chapter 1: Introduction and Methods

This MCHP deliverable evaluates the influence of several factors on the utilization of a select group of prescription medications in Manitoba from 1997/98–2008/09. It includes an in–depth exploration of the usage and prescribing patterns of several classes of medication with a view to understanding the potential factors influencing use.

In general, these chapters address factors impacting usage including patient demographics and measures of health service use, provider (initial prescriber) characteristics, and time. Medications of interest include:

- Psychoactive medication used in older adults, with a focus on **Second Generation Antipsychotics (SGAs)**[1] and other antipsychotics, benzodiazepines (and the related medications zopiclone and zaleplon), particularly in older adults residing in personal care homes (PCHs)
- Medications used to treat **diabetes mellitus** (type 1 and type 2), with a focus on newer medications and test strips to test serum blood glucose
- Inhaled medications used to treat **asthma and chronic obstructive pulmonary disease**, with a focus on combination long acting beta agonists (LABA)/inhaled corticosteroids to treat asthma
- Biologic agents used to treat rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, and psoriasis

Many of the proposed medications for analysis were identified in the 2005 MCHP report on "High Cost Users of Pharmaceuticals" and in the 2009 MCHP report "Effects of Manitoba Pharmacare Formulary Policy on Utilization of Prescription Medications". Medications included in the analysis are important to study due to concerns about adverse effects (SGAs in older Manitobans, long acting beta agonists (LABAs)/inhaled corticosteroids without concurrent inhaled corticosteroids), new guidelines (medications and test strips for diabetes mellitus), increasing utilization in the population over time (all medications) and the need to explore opportunities to optimize use.

Research questions in conjunction with Manitoba Pharmacare were operationalized within the data available in MCHP's prescription and health care databases.

Specific research objectives include:

- To describe the utilization of each category of medications according to patient characteristics including: age, sex, socioeconomic status (SES), and region of residence over time
- To explore opportunities for optimal prescribing by determining the proportion of users of medications with potentially optimal or less than optimal prescribing patterns
- To explore opportunities for optimal prescribing by determining factors (patient or prescriber) predictive of potentially optimal or less than optimal prescriptions

1 Throughout this report, terms in bold typeface are defined in the Glossary at the end of the report.

Methods

Scope

This report focuses on all Manitobans with provincial health cards from Manitoba Health who filled prescriptions in Manitoba from 1997/98–2008/09. Individuals had to be in the Manitoba Health registry for at least 365 days in the year of analysis plus the 365 days prior to the year of analysis to be included in the study population.

Data sources

Data for this report were derived from anonymized (no identifying information) health care administrative data contained in the Population Health Research Data Repository, which is housed at the Manitoba Centre for Health Policy and includes virtually all Manitobans. We used the following databases: the population registry, prescription dispensation records from outpatient dispensaries through Manitoba Health's **Drug Programs Information Network (DPIN)**, physician reimbursement claims, hospital files, personal care home files, vital statistics and Statistics Canada Census public use files, as well as the Manitoba Physician Practice database files. Records from these files were linked through the use of a scrambled health identification number. Data from the fiscal years (April 1–March 31) of 1997/98 through 2008/09 were used.

Categorization of medications

The **Anatomical Therapeutic Chemical (ATC)** classification system for medications was used to define categories of medications. This classification system divides medications into different groups according to the organ or system on which they act and the therapeutic or chemical characteristics of the medication. There are five levels of classification for this system (World Health Organization, 2009). A list of all the medications with ATC codes used in this analysis is included in Appendix Table 1.1.

Measures of utilization

Pharmaceutical use is expressed as prevalent users, intensity of use for these prevalent users, and incident users.

Prevalent users

Prevalent users were Manitobans registered for 365 days in a fiscal year of interest, plus the 365 days prior to the year of analysis, who had filled at least one prescription for the medication of interest (in a particular quarter). In order to calculate prevalence for each quarter, the total count of prevalent users was divided by the population of Manitobans registered for 365 days in a fiscal year (resident). For this analysis, the first quarter (Q1) of each year was April–June, the second quarter (Q2) was July–September, the third quarter (Q3) was October–December and the fourth quarter (Q4) was January–March.

Intensity of use

Prevalent use was also expressed as **defined daily dose (DDD)** per 1,000 residents per day as a measure of intensity of use. The DDD is a technical unit of measurement that was developed to overcome the limitations of counting prescriptions, which can vary and be for any quantity of medication (Merlo, Wessling, & Melander, 1996). The DDD standardizes the measure of medication utilization with and between medications and is useful to quantify medication use in a population. The DDD is the average daily dose per day for a medication dispensed for the main indication in usual practice. For each medication, a DDD is calculated by the World Health Organization Collaborating Centre for Drug Statistics Methodology (World Health Organization, 2009). The DDD is only calculated for oral solid dosage forms. The number of DDDs per 1,000 residents was calculated for this analysis.

Incident users

Incident users were Manitobans registered for 365 days in a fiscal year, plus the 365 days prior to the year of analysis, who had not filled a prescription for the medication of interest for at least one year and then filled a first prescription for the medication of interest in a particular quarter. Incident users per population for each medication were described by sociodemographic characteristics. In order to calculate incidence rates for each quarter, total count of incident users was divided by the population of Manitobans registered for days in a fiscal year, plus the 365 days prior to the year of analysis. For this analysis, the first quarter (Q1) of each year was April–June, the second quarter (Q2) was July–September, the third quarter (Q3) was October–December and the fourth quarter (Q4) was January–March.

Sociodemographic characteristics

Sociodemographic characteristics of prescription medication users were defined as follows:

- Age groups (18 and younger, 19–44, 45–64, 65–84, 85 and older). For the analysis of inhaled medications for asthma analysis in children only, the age groups were as follows: up to four, five to eight, nine to 12, and 13 to 18 years. Age calculation was based as of December 31 of the fiscal year of interest (the year of first prescription). Age was a continuous variable for the logistic regression analyses.
- Sex: male versus female.
- Region of residence was defined in two ways. Medication users were categorized as being rural or urban as determined by the postal code registered with Manitoba Health**. Those who were registered in Winnipeg or Brandon were categorized as urban, while the rest of Manitoba was considered to be rural. Some analyses categorized Manitoba residents as being part of five regions by Regional Health Authority (RHA) as follows:** Rural South (South Eastman, Central, and Assiniboine RHAs); Mid (North Eastman, Interlake, and Parkland RHAs); North (NOR–MAN, Burntwood, and Churchill RHAs); Brandon; and Winnipeg (see Figure 1.1).
- Socioeconomic status: As Manitoba has an income based deductible for the provincial Pharmacare program, prescription medication users were divided into three groups, based on out of pocket expenses for prescription medications and median neighbourhood income quintile (from Statistics Canada 2006 census files) as follows (see Figure 1.2):
    - Lower income: individuals in the lowest and second lowest median neighbourhood income quintile
    - Higher income: individuals residing in the neighbourhoods with the three highest median neighbourhood income quintiles.
    - Income unknown: individuals who cannot be assigned a neighbourhood income from the census data. This category includes individuals residing in facilities such as psychiatric facilities, prisons, wards of the Public Trustee and Child and Family services, and personal care homes.
- Death in first year: For older adults (older than 65) receiving antipsychotics, new users of antipsychotics who died in the first year of therapy were identified. This variable was included as a covariate in the logistic regression. Deaths were identified through Vital Statistics data and through hospital abstracts.

Figure 1.1: Regional Health Authorities (RHAs) of Manitoba

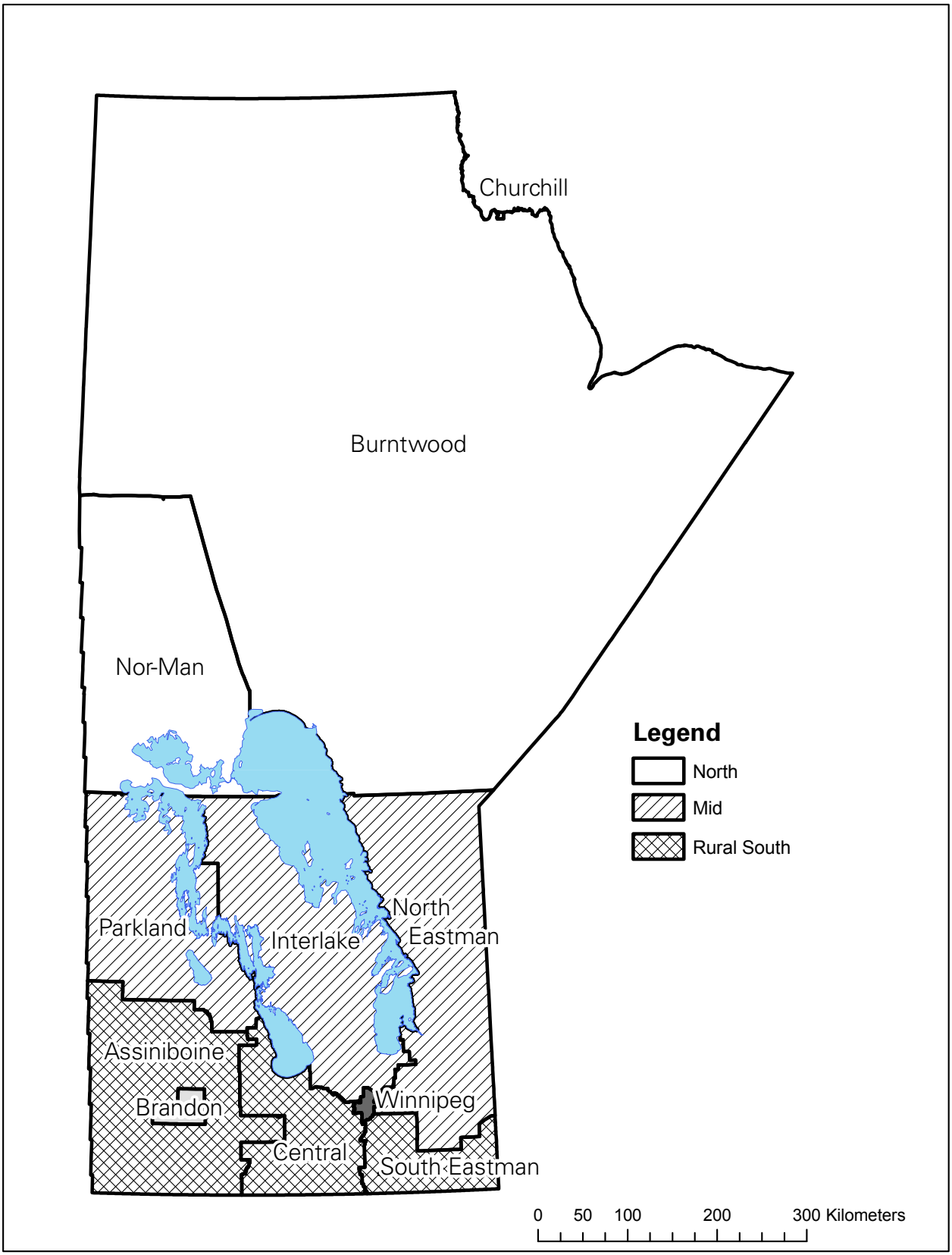
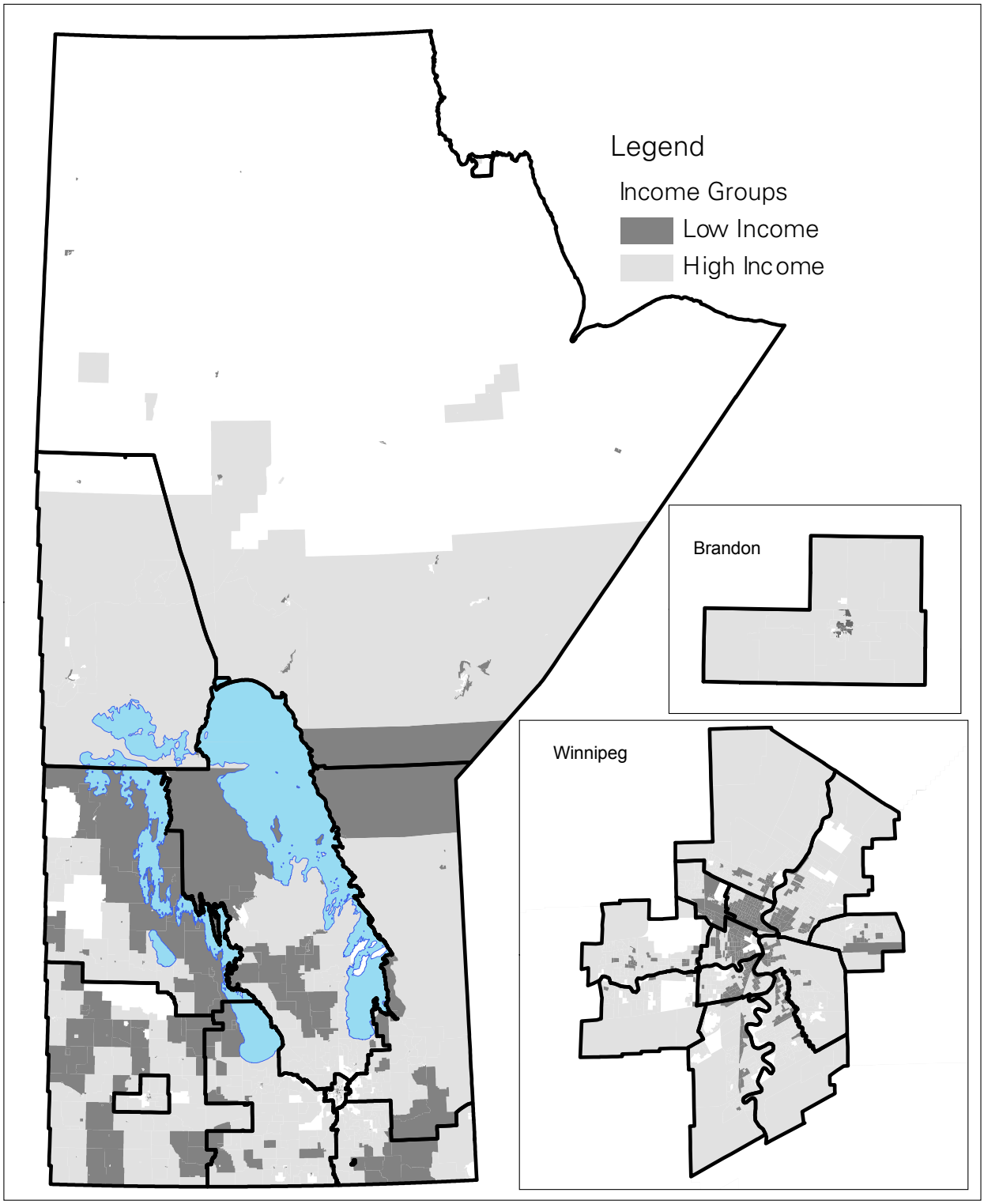


Figure 1.2: Distribution of Rural and Urban Income Groups 2006 Census Data Dissemination Areas



Charles Burchill, Manitoba Centre for Health Policy.
September 2010 Based on 20% Population groups of
Average Household Income by Census Dissemenination Areas.
Census of Canada 2006.

Note: White areas in map indicate census areas which are not enumerated (such as park areas).

- Medical services utilization for the year prior to the incident prescription of a medication of interest (physician and hospital claims) were evaluated to determine the following variables, which were included as covariates in logistic regression models:
    - Number of ambulatory physician visits (continuous variable).
    - Number of inpatient hospitalizations (overnight stays) for any reason (continuous variable).
    - Number of major **Aggregated Diagnosis Groups (ADGs)**, the number of conditions that involve significant resource use and clinical outcomes (continuous variable) used as a measure of total morbidity. Formerly known as Ambulatory Diagnostic Groups, ADGs continue to be part of the Adjusted Clinical Group (ACG) case–mix system. The ACG method groups every ICD–9/ICD–9–CM medical diagnosis codes assigned to a patient into one of 32 different ADGs based on five clinical and expected utilization criteria:
        a. duration of the condition (acute, recurrent, or chronic)
        b. severity of the condition (e.g., minor and stable versus major and unstable)
        c. diagnostic certainty (symptoms focusing on diagnostic evaluation versus documented disease focusing on treatment services)
        d. etiology of the condition (infectious, injury, or other)
        e. specialty care involvement (medical, surgical, obstetric, haematology, etc.) (Johns Hopkins University Bloomberg School of Public Health, 2001; Johns Hopkins University Bloomberg School of Public Health, 2003; Martens et al., 2008; Martens et al., 20010; Reid, Roos, MacWilliam, Frohlich, & Black, 2002)
    - Hospitalization immediately before incident prescription (within three days).
    - For adults older than 65 receiving antipsychotics, diagnosis of **psychosis** (present or absent). Psychosis was defined as any claim for a psychotic (ICD–9–CM: 295–299, ICD–10–CA: F2, F3, F84, R410) in any diagnosis field for MD or hospital claims in one year prior to the prescription of interest (Daumit et al., 2003).
    - For adults receiving a prescription for medication to treat diabetes mellitus, a separate analysis was conducted for individuals with a diagnosis of type 1 or 2 diabetes mellitus, rather than the entire population. Diabetes mellitus was defined as either a) two or more physician visits or one hospitalization with a diagnosis of diabetes (ICD–9–CM: 250, ICD–10–CA: E10–E14) or b) one or more prescriptions to treat diabetes (Fransoo et al., 2009).
    - For children receiving a prescription for inhaled medications to treat asthma and chronic lung disease, a separate analysis was conducted for individuals with a diagnosis of asthma, rather than the entire population. Asthma was defined as one physician claim, one hospital claim for ICD–9–CM: 464, 466, 490, 491, 493 or ICD–10–CA: J04, J05, J20, J21, J40, J41, J42, J45, J441, J448, or one prescription for an asthma medication (listed in Appendix Table 1.1) in a three–year period (Lix et al., 2006).
- Prescription medication utilization–for the year prior to the incident prescription of a medication of interest, DPIN claims were evaluated to determine the following variables which were included as covariates in logistic regression models:
    - Number of different medications (WHO ATC category 4th level chemical subgroup, e.g., N06AB selective serotonin reuptake inhibitors) (continuous variable)
    - For older adults receiving antipsychotics, use of an acetylcholinesterase inhibitor (donepezil, galantamine, rivastigmine) (present or absent)

- For adults and children receiving prescriptions for inhaled medications used to treat asthma, the number of prescriptions for systemic antibiotics (see Appendix Table 1.1) (continuous variable)
- For adults and children receiving prescriptions for inhaled medications used to treat asthma, the number of prescriptions for other asthma medications (except the leukotriene receptor antagonists monteleukast and zafirlukast) (see Appendix Table 1.1) (continuous variable)
- For adults and children receiving prescriptions for inhaled medications used to treat asthma, use of leukotriene receptor antagonists (present or absent)

Prescriber characteristics

Based on the work of others which have evaluated prescriber characteristics and prescribing practices (Baker, Hayes, Massie, & Craig, 1999; Cadieux, Tamblyn, Dauphinee, & Libman, 2007; Chin, Friedmann, Cassel, & Lang, 1997; Kozyrskyj, Raymond, & Racher, 2007; Mosca et al., 2005; Steinman, Landefeld, & Gonzales, 2003; Tamblyn, McLeod, Hanley, Girard, & Hurley, 2003), characteristics of prescribers (of incident prescriptions of the medication of interest and at the time of the incident prescription) were defined from the Manitoba Physician Practice database. Non–medical professionals are not included. The following variables were included as covariates in logistic regression models:

- Location of training (North America versus other)
- Years since licensure in Manitoba (continuous variable)
- Hospital affiliation (treating physician has hospital privileges)
- Type of physician reimbursement (fee for service or other)
- Specialist (psychiatrist, pediatrician, medical specialist, surgeon, anesthetist) or general practitioner.

Other factors

Other factors which may have influenced utilization of medications were defined as follows:

- Pharmaceutical policy. Medications or groups of medications were categorized according to their coverage by the Manitoba Drug Benefits and Interchangeability Formulary. Manitoba Health offers a province–wide drug insurance program to all Manitobans, according to a published list of benefits in its Manitoba Drug Benefits and Interchangeability Formulary and under conditions of an income–based deductible. Prescription medications are given Part 1, Part 2, or Part 3 status on the Manitoba Drug Benefits and Interchangeability Formulary. Part 1 provides open listing, whereas Part 2 and 3 designations limit access according to pre–determined criteria. Part 2 listings may be second–line therapeutic agents or agents to be used only in specific clinical situations. They require notification by physicians or pharmacists that the medication meets Exception Drug Status (EDS). Part 3 status is reserved for products that require physicians to contact Pharmacare to obtain special approval for use (by telephone or in writing). For this group, EDS is granted on a case by case basis for specific criteria for use of the medication and is generally for one or three years coverage, which can be renewed. It is important to note that there are numerous other formularies in Manitoba (First Nations and Inuit Health Branch, private insurance, Department of Veterans Affairs) that might impact Manitoba residents covered by these formularies.

The following variables were included as covariates in logistic regression models:

- Year of incident prescription (calendar year).

- Personal care home (PCH) environment was characterized for users of antipsychotics or benzodiazepines (and related medications). PCHs in Manitoba are typically referred to as proprietary (i.e., for profit) and non–proprietary (i.e., not–for–profit) facilities. All proprietary PCHs in Manitoba are free–standing facilities; non–proprietary PCHs are either free–standing or juxtaposed to another healthcare facility (Doupe et al., 2006). For the analysis of antipsychotics or benzodiazepines (and related medications), users were categorized as:
    - recent admissions to PCH (less than 30 days) from home
    - recent admissions to PCH (less than 30 days) from hospital
    - residing in a PCH for more than 30 days, admitted from home
    - residing in a PCH for more than 30 days, admitted from hospital, for both proprietary and non–proprietary PCH

  Because proprietary and non–proprietary PCH status has previously shown to impact the use of psychotropic medications in older adults (Doupe et al., 2006), we included this covariate. It should be noted that only approximately 73% of PCHs fill prescriptions at community pharmacies (and are therefore included in the DPIN system). Medication use for PCHs where prescriptions are filled through hospitals is not known (Doupe et al., 2006).

How This Report is Organized

The findings of this report are divided into chapters, each representing a group of medications selected for analysis. Each chapter includes an introduction, methods, analyses and discussion. For each chapter, the analyses are presented in the order of descriptive analysis (including influence of sociodemographic variables on utilization), regional analysis, and lastly, an analysis of patterns of optimal use.

Descriptive analysis

Prevalent and incident utilization and intensity of use (users per population and DDDs per population and per user per day) are presented for each quarter of every fiscal year from 1997/98–2008/09. Users per population are presented per 1,000 residents registered in Manitoba for 365 days in a fiscal year, plus the 365 days prior to the year of analysis. All years are fiscal years.

Influence of sociodemographic variables on utilization

Generalized Estimating Equation modeling (GEE) was used to determine the impact of sociodemographic characteristics on medication utilization over time. Variables in these general models included were age, gender, socioeconomic status, region of residence, and time.

Regional analysis

Regional analysis of prevalent medication utilization for the fiscal years 1998/99, 2003/04, and 2008/09 compares prevalent users (annual rates, adjusted for age, sex, and socioeconomic status) across five regions of Manitoba (Rural South, Mid, North, Winnipeg and Brandon) and Manitoba overall. Prevalent medication utilization (presented as users per 1,000 residents), was adjusted to the 2003/04 Manitoba population. Prevalent users were counted as being users if they filled at least one prescription for a medication of interest in the whole fiscal year.

Optimal use analysis

For several medication categories, a measure of potentially optimal or less than optimal utilization was created. For incident users of the medication of interest, sociodemographic, prescriber, time, and measures of health services utilization in the period immediately preceding the new prescription were evaluated to determine factors predictive of this potentially less than optimal utilization. These analyses were performed with logistic regression modeling. As time effects were likely important for several aspects of these analyses, only incident

users of the medication of interest who initiated therapy in 2002/03 through 2008/09 were included in these analyses. Details about the specific optimal prescribing criteria for each medication appear in the methods section for each chapter. The optimal use models explored:

- What factors predict incident utilization of *high dose SGAs* amongst older adults from 2002/03 through 2007/08?
- What factors predict incident utilization (first use of a prescription) for any medication for diabetes mellitus being a new medication for diabetes mellitus (new insulins or new oral anti–diabetic agent) among adult Manitobans from 2002/03 through 2008/09?
- What factors predict incident use of LABA or LABA/inhaled corticosteroid combination with no prescriptions for oral or inhaled corticosteroids in the year prior to the first prescription among either adults or children with asthma from 2002/03 through 2008/09?
- What factors predict incident use of LABA therapy alone with no prescriptions for oral or inhaled corticosteroids 90 days before or after the first prescription among either adults or children with asthma from 2002/03 through 2008/09?

Data analysis

The data analysis for this deliverable was generated using SAS software, Version 9.2 of the SAS System for Sun or Solaris Operating System, Copyright 2002–2008, SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

Data Limitations

All data included in this report are derived from contact with the healthcare system. Because not everybody who seeks medical attention and receives a prescription for a medication actually fills the prescription, this may underestimate the number of prescriptions written for medications of interest in Manitoba. Medication use not captured within the DPIN system includes physician samples which may be possible, most notably for the newer agents for diabetes mellitus or for inhalers for chronic lung disease. As costs are a consideration in the decision to fill a prescription, this phenomenon may occur across a socioeconomic gradient. Some individuals are not included in the DPIN system, namely those incarcerated or who have prescriptions covered through the Royal Canadian Mounted Police. Some individuals receiving prescriptions at remote nursing stations may not be included in the DPIN system. These individuals make up a very small proportion of the Manitoba population, as most prescriptions for remote Manitoba communities are filled in Winnipeg and flown in. Finally, it should be noted that only approximately 73% of PCHs fill prescriptions at community pharmacies (and are therefore included in the DPIN system). Medication use for PCHs where prescriptions are filled through hospitals is not known (Doupe et al., 2006).

Similarly, for several analyses, we evaluated medical diagnoses through administrative data. The use of administrative data may underestimate the prevalence of a given condition in the population, because these definitions require individuals to seek contact with the health care system. In primary care, the use of administrative data may underestimate the prevalence of a disease in the population because most ambulatory physician visits can only result in a single billing code, therefore a single diagnosis. This may be particularly common with individuals with multiple or complex medical conditions. There is also potential for the use of administrative data to overestimate the prevalence of a given condition in the population due to misclassification. Additionally, the administrative data does not include individuals without Manitoba Health cards.

Chapter 2: Antipsychotics, Benzodiazepines and Related Medication Use in Older Manitobans

Antipsychotics are a broad class of medications used to treat a variety of psychiatric conditions. The class consists of newer or second generation antipsychotics (SGAs), also named "atypical" antipsychotics, which include risperidone, olanzapine, and quetiapine and the older or first generation antipsychotics, also indentified as "typical" antipsychotics, which include haloperidol and phenothiazines. During the study period (1997/98–2008/09), almost all antipsychotics on the Pharmacare formulary were Part 1(open listing) on the Manitoba Drug Benefits and Interchangeability Formulary, except long acting risperidone (Risperdal Consta®) injection and zuclopenthixol (Clopixol®) injection. Both first and second generation antipsychotics have been used in older adults to treat behavioural disturbances associated with dementia; however, only risperidone has been approved in Canada for this indication (Risperdal Product Monograph, 2008).

Mounting evidence suggests harm with the use of antipsychotics in older adults (Health Canada, 2005a; Rochon et al., 2008). In 2002, Health Canada issued a warning about the association between the utilization of risperidone and cerebrovascular accidents in individuals with dementia (Health Canada, 2002). In early 2004, Health Canada issued a similar warning about olanzapine, which advised physicians to reassess the risk and benefits of prescribing these medications to older adults with dementia (Health Canada, 2004). Several studies have demonstrated an increased risk of mortality with the use of first and second generation antipychotics for individuals with dementia (Ballard et al., 2009; Ray, Chung, Murray, Hall, & Stein, 2009; Schneider, Dagerman, & Insel, 2005; Wang et al., 2005). In 2005, Health Canada issued a third warning against the use of SGAs in the individuals with dementia. Harm has been demonstrated for antipsychotic use in individuals with dementia within 30 days of a new prescription and any use could be considered undesirable in this patient population (Gill et al., 2007; Rochon et al., 2008; Salzman et al., 2008). Antipsychotics are also associated with dose–related adverse effects, such as movement disorders, delirium, and decreased blood pressure. In addition, the use of a wide range of psychotropic medications has been associated with an increased risk for falls. In a meta–analysis, the odds ratio for any psychotropic use was 1.73 (95% CI 1.52–1.97) in individuals aged 60 and older who had experienced one or more falls (Leipzig, Cumming, & Tinetti, 1999). It has also been suggested that antipsychotics may be overprescribed in Canadian nursing homes (Hagen et al., 2005). In order to minimize the dose related adverse effects of antipsychotics, it is recommended that the lowest possible effective dose of antipsychotics be used when prescribing antipsychotics for the treatment of dementia and other behavioural disorders in older adults (Hanlon et al., 2009; Jeste et al., 2008; Rochon, 2010).

Benzodiazepines are a class of medications used for the treatment of anxiety and the short–term management of insomnia, as well as other conditions such as panic disorder and seizures. The related medications, zopiclone and zaleplon, are used primarily for the management of insomnia. Evidence of an association between use of benzodiazepines and harm in older adults has been identified (Bartlett, Abrahamowicz, Grad, Sylvestre, & Tamblyn, 2009; French et al., 2005; Tamblyn, Abrahamowicz, du, McLeod, & Bartlett, 2005), and these agents are considered to be potentially inappropriate for prescription in older adults (Fick et al., 2003). Benzodiazepines can be classified according to their pharmacokinetic properties into short–acting or long–acting agents; however, because of an inconsistent association between duration of action and risk of injury associated with benzodiazepines, we considered these medications together as a group (Tamblyn et al., 2005). Zopiclone and zaleplon were grouped together.

Since benzodiazepines and antipsychotics are both associated with harm in older adults, we sought to describe the utilization of these groups of medications within older adults, both in community– and PCH–dwelling individuals.

Methods

We evaluated the utilization of antipsychotics, benzodiazepines and the related medications, zopiclone and zaleplon, in the older (over 65) Manitoba population over time. These evaluations were also conducted in specific populations according to place of residence. For several analyses, we excluded individuals residing in a PCH in order to compare utilization of medications amongst individuals residing in a PCH to those residing in the community. Excluded from the population were individuals less than 65 years of age receiving antipsychotics in PCH and in the community. For the PCH population, individuals who did not spend at least one day in a PCH during the fiscal year of interest were excluded. For the community dwelling older adult population, individuals who spent at least one day in a PCH during the fiscal year of interest were excluded. It should be noted that only approximately 73% of PCHs fill prescriptions at community pharmacies (and are therefore included in the DPIN system). Medication use for PCHs where prescriptions are filled through hospitals is not known (Doupe et al., 2006).

Prevalent and incident utilization of antipsychotics for the population of Manitoba over age 65 was determined for the following medications: olanzapine, risperidone, and quetiapine. First generation antipsychotics were all members of the ATC class N05A (excluding lithium carbonate). Prevalent and incident use of benzodiazepines (alprazolam, bromazepam, clonazepam, clobazam, chlordiazepoxide, diazepam, flurazepam, lorazepam, nitrazopam, oxazepam, temazepam, and triazolam) and related medications (zopiclone and zaleplon) were also determined. Due to the additive potential for adverse effects, the prevalent and incident use of SGA in combination with benzodiazepines, zopiclone or zaleplon were also determined; this was defined as at least one prescription for each category within the same quarter. Details about the medications included in these categories are presented in Appendix Table 1.1.

Incident users were those users of an antipsychotic who had not received an antipsychotic (first or second generation agent) in the one year prior to the year of interest. Similarly, incident users of benzodiazepines had no use of a benzodiazepine and new users of zopiclone or zapleplon had no use of either medication in the one year prior to their first prescription.

Prevalent and incident utilization is presented as prevalent and incident users per 1,000 Manitoba population older than 65, and then divided as those residing in the community and in PCH.

Prevalent use was also expressed as defined daily dose (DDD) per 1,000 residents per day as a measure of intensity of use. The DDD is a technical unit of measurement that was developed to overcome the limitations of counting prescriptions, which can vary and be for any quantity of medication (Merlo et al., 1996). The DDD standardizes the measure of medication utilization with and between medications and is useful to quantify medication use in a population. The DDD is the average daily dose per day for a medication dispensed for the main indication in usual practice. For each medication a DDD is calculated by the World Health Organization Collaborating Centre for Drug Statistics Methodology (World Health Organization, 2009). The DDD is only calculated for oral solid dosage forms. The intensity of use is presented as DDDs per 1,000 population per day and as DDDs per user per day. The DDDs for the oral medications evaluated are included in Appendix Table 1.1.

The influence of sociodemographic characteristics on prescribing over the entire study period (1997/98–2008/09) was determined with generalized estimating equations. Regional analysis of medication utilization for the fiscal years 1998/99, 2003/04, and 2008/09 compares prevalent users (annual rates, adjusted for age, sex, and socioeconomic status) across five regions of Manitoba (Rural South, Mid, North, Winnipeg, and Brandon) and Manitoba overall.

Optimal use evaluation

For incident utilization of SGAs among older adults, we evaluated the following criteria (note: as time effects were likely important in changing prescribing patterns, only incident users of the medication of interest who initiated therapy in 2002/03 through 2008/09 were included in these analyses):

- Number of DDDs per user per year over time (from 2002/03 through 2008/09) in order to evaluate the changes in dose intensity over time. A reduction in dose intensity over time would indicate optimal prescribing.
- Proportion (from 2002/03 through 2008/09) of individuals who were i) recent admissions to PCH (less than 30 days) from home, ii) recent admissions to PCH (less than 30 days) from hospital, iii) residing in a PCH for more than 30 days, admitted from home, and iv) residing in a PCH for more than 30 days, admitted from hospital, over time in order to determine when SGAs are initiated.
- Proportion of PCH (from 1998/99 through 2008/09) residents who received a SGA and who were also prescribed (in the same year) an acetylcholinesterase inhibitor (donepezil, galantamine, rivastigmine) which would imply a diagnosis of dementia over time. This population is at particularly high risk of adverse effects of SGAs. A reduction in the proportion of PCH residents who received a SGA and who were also prescribed an acetylcholinesterase inhibitor would be optimal.
- Proportion of older adult Manitobans (from 1997/98 through 2007/08) who received a high dose SGA, as recommendations would suggest that the lowest possible effective dose of antipsychotics be used when using antipsychotics for the treatment of dementia, and other behavioural disorders in older adults (Hanlon et al., 2009; Jeste et al., 2008; Rochon, 2010). A reduction in the proportion of older Manitobans who received a high dose SGA over time would be optimal.
- Proportion of older Manitobans who were users of SGAs (from 2002/03 through 2007/08) who received a high dose SGA.
- We evaluated factors predictive of incident utilization of high dose SGAs (less than optimal) amongst older Manitobans from 2002/03 through 2007/08.
    - Sociodemographic factors included: age; sex; region of residence; socioeconomic status; being hospitalized within three days of the incident prescription; number of different medications; and diagnosis of a psychosis (defined as any claim for a psychotic (ICD–9–CM: 295–299, ICD–10–CA: F2, F3, F84, R410) in any diagnosis field for physician or hospital claims in one year prior to the prescription of interest (Daumit et al., 2003).
    - Other factors included: dementia as suggested by the use of an acetylcholinesterase inhibitor (donepezil, galantamine, rivastigmine); number of major ADGs; and the number of ambulatory visits and hospitalizations for any reason in the year prior to the first prescription.
    - Prescriber characteristics included: hospital affiliation, location of training, years since licensure in Manitoba, type of reimbursement, and specialist status.
    - Other characteristics included: PCH type (propietary vs not) and year of first prescription.

- *High dose second generation antipsychotic (SGA) use* was defined as any one prescription for a SGA within the first year of incident SGA use where the number of days supplied divided by the total quantity of tablets was greater than or equal to 1.5 mg/day of risperidone, 10 mg/day of olanzapine, or 200 mg/day of quetiapine (Alexopoulos, Schultz, & Lebowitz, 2005; De Deyn et al., 2005; Jeste et al., 1999a; Jeste et al., 2008; Jeste, Rockwell, Harris, Lohr, & Lacro, 1999b; Katz et al., 1999; Street et al., 2000; Tariot et al., 2006; Zhong, Tariot, Mintzer, Minkwitz, & Devine, 2007).

Results

Community–dwelling older adults

A total of 143,491 community–dwelling older adult Manitobans were included as the denominator in this analysis in the analysis of antipsychotics, benzodiazepines, and related medications in 1997/98, and 153,189 in 2008/09.

Community–dwelling older adults: Prevalence

Prevalent utilization of olanzapine, risperidone, and quetiapine increased from 1997/98 to 2008/09 among both older adults residing in the community and in PCH (see Figure 2.1). The SGA risperidone was prescribed most often. For community–dwelling older adults, prevalent utilization of SGAs increased from 0.6 to 13.5 users per 1,000 community–dwelling older adults, while prevalent utilization of first generation antipsychotics in this population declined from 12.8 to 5.9 users per 1,000 by the end of the study period. Users of risperidone increased from 0.6 to 6.5 per 1,000 community–dwelling older adults, olanzapine increased from 0.05 to 3.7 per 1,000, and quetiapine increased from 0.07 to 3.9 per 1,000.

For community–dwelling older adults, the use of benzodiazepines was much greater than antipsychotics, although prevalent users changed only slightly from 108.6 to 109.1 users per 1,000 community–dwelling older adults over the study period; however, the use of the related medications, zopiclone and zaleplon, increased from 13.6 to 53.0 users per 1,000 over the study period (see Figure 2.2).

For SGAs, there was greater prevalent utilization in community–dwelling older adults amongst females as compared to males and the oldest age group (85 and older) as compared to those aged 65–84, following adjustment for other factors (see Table 2.1).

Community–dwelling older adults: Dose intensity

The dose intensity of SGAs in the population of community–dwelling older adults increased over the study period, from 0.2 DDDs per 1,000 community–dwelling older adults per day at the beginning of the study to peak at 6.5 at the end of 2004/05 (see Figure 2.3). Then it declined to 4.9 by the end of the study period.

Dose intensity of benzodiazepines changed slightly from 65.2 to 68.6 DDDs per 1,000 community–dwelling older adults over the study period, while that of zopiclone and zaleplon increased from 9.5 to 49.6 per 1,000 (see Figure 2.4).

Community–dwelling older adults: Incidence

For community–dwelling older adults, new users of SGAs increased from 0.2 to 1.6 users per 1,000 community–dwelling older adults per quarter, while that for first generation agents decreased from 1.9 to 1.0 users per 1,000 per quarter over the same period (see Figure 2.5). Risperidone utilization (0.2 to 1.0 users per 1,000 per quarter) was followed by olanzapine (0.1 to 0.3 users per 1,000 per quarter) and

quetiapine (0.04 to 0.4 users per 1,000 per quarter). New users of benzodiazepines decreased from 12.2 to 10.7 users per 1,000 community–dwelling older adults per quarter, while new users of zopiclone and zaleplon increased from 3.0 to 7.2 users per 1,000 per quarter (see Figure 2.6).

Community–dwelling older adults: Sociodemographic characteristics

For all agents studied, there was greater incident utilization in community–dwelling older adults amongst females (except quetiapine and combination SGAs with benzodiazepines and the related medications) and the very old as compared to those aged 65–84 (except benzodiazepines and related medications), following adjustment for other factors (see Table 2.2). There were inconsistent effects of rural or urban location; but there was greater incident utilization of first generation antipsychotics in rural community–dwelling older adults as compared to urban. Greater utilization of first and second generation antipsychotics occurred amongst older adults with low socioeconomic status as compared to high socioeconomic status.

Community–dwelling older adults: Regional variation

When adjusted for age, sex, and socioeconomic status, the prevalent utilization of all SGAs increased for community–dwelling older adults over the time period evaluated (1998/99 to 2008/09) across all regions of Manitoba (see Figure 2.7). Prevalent use for SGAs in the Rural South were significantly lower than the Manitoba average at 2003/04 and 2008/09, whereas Mid was significantly lower than the Manitoba average for 2003/04 only.

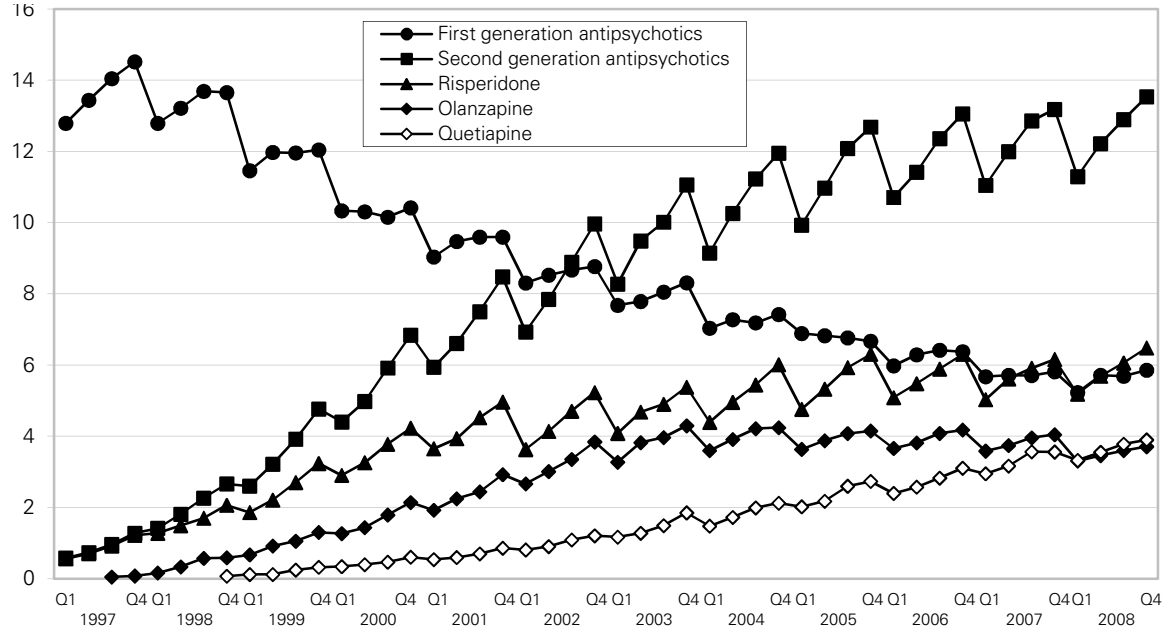
When adjusted for age, sex, and socioeconomic status, the prevalent utilization of first generation antipsychotics decreased for community–dwelling older adults over the study period across all regions of Manitoba (see Figure 2.8). Prevalent use of first generation antipsychotics in Winnipeg was significantly lower than the Manitoba average in 1998/99 and 2003/04. Prevalent use of first generation antipsychotics in Brandon was significantly lower than the Manitoba average in 1998/99.

When adjusted for age, sex, and socioeconomic status, the prevalent utilization of benzodiazepines and related medications increased for community–dwelling older adults (1998/99–2008/09) across all regions of Manitoba, except Winnipeg (see Figure 2.9). Prevalent utilization of benzodiazepines and related medications in the Rural South was significantly higher than the Manitoba average over the study period, and rates in Brandon were higher than the Manitoba average for 2003/04 and 2008/09. Prevalent utilization of benzodiazepines and related medications in the North was significantly lower than the Manitoba average over the study period.

When adjusted for age, sex, and socioeconomic status, the prevalent utilization of all SGAs used in combination with benzodiazepines or related medications increased for community–dwelling older adults (1998/99–2008/09) across all regions of Manitoba (see Figure 2.10). No significant regional variation was observed.

For all antipsychotics, individuals in the "public trustee/unknown" category had greater utilization than the Manitoba average in 1998/99, 2003/04, and 2008/09.

Figure 2.1: Antipsychotics, Quarterly Prevalence
Crude user rates per 1,000 adults in the community aged 65+, Q1 1997-Q4 2008

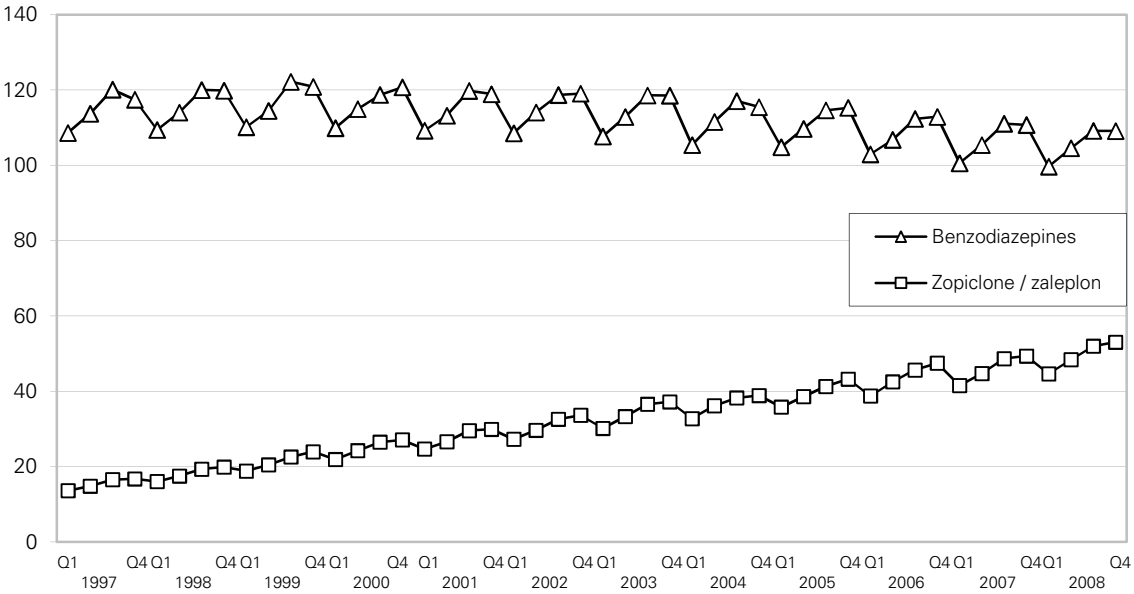


'Q1' indicates rates for the 1st quarter (April to June)
'Q4' indicates rates for the 4th quarter (January to March)
'Q2' and 'Q3' data points are displayed, but not labeled

Note:
Health Canada warning Risperidone 2002Q3
Health Canada warning Olanzapine 2003Q4
Health Canada warning all SGA 2005Q2

Source: Manitoba Centre for Health Policy, 2010

Figure 2.2: Benzodiazepines and Related Medications, Quarterly Prevalence
Crude user rates per 1,000 adults in the community aged 65+, Q1 1997-Q4 2008



'Q1' indicates rates for the 1st quarter (April to June)
'Q4' indicates rates for the 4th quarter (January to March)
'Q2' and 'Q3' data points are displayed, but not labeled

Note:
Health Canada warning Risperidone 2002Q3
Health Canada warning Olanzapine 2003Q4
Health Canada warning all SGA 2005Q2

Source: Manitoba Centre for Health Policy, 2010

Table 2.1: Prevalent Use (Users per 1,000 Residents) of Antipsychotics, Benzodiazepines, and Related Medications in Community Dwelling Older Adults (65 and Older), 1997/98 to 2008/09

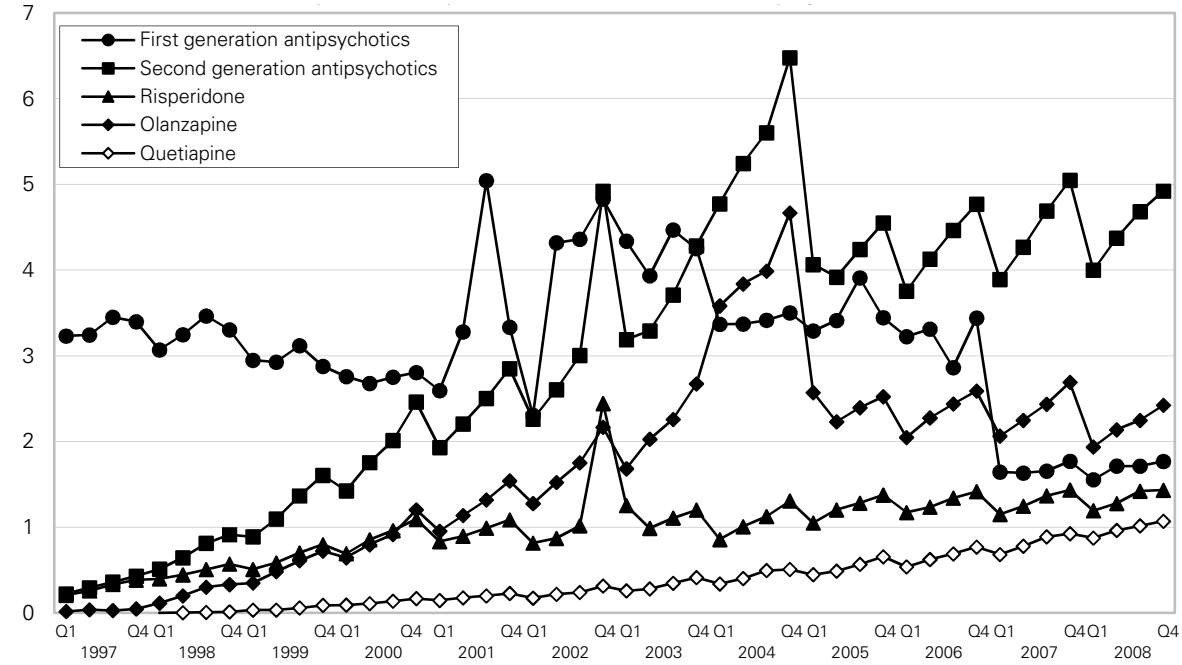
Medication or group of medications	1997Q1 users/1,000	2008Q4 users/1,000	Change in rate per quarter	Age effect 65-84 vs 85+	Socioeconomic status Low vs High	Region effect Rural vs Urban	Sex effect Male vs Female
Second generation antipsychotics	0.58	13.53	1.05 5% increase*	0.65 35% lower*	1.05 NS	0.89 NS	0.75 25% lower*
First generation antipsychotics	12.79	5.86	0.98 2% decrease*	1.28 28% higher*	1.34 34% higher*	1.09 NS	0.62 38% lower*
Benzodiazepines/ zopiclone and zaleplon	118.96	150.97	1 slight increase*	0.81 19% lower*	1.12 12% higher*	1.09 9% higher*	0.6 40% lower*
Risperidone	0.56	6.48	1.03 3% increase*	0.52 48% lower*	1.05 NS	0.91 NS	0.76 24% lower*
Olanzapine	0.05 1997Q3	3.71	1.05 5% increase*	0.79 21% lower*	1.13 NS	0.95 NS	0.63 37% lower*
Quetiapine	0.07 1998Q4	3.9	1.07 7% increase*	1.05 NS	1.2 NS	0.81 19% lower*	0.8 20% lower*
Combination of Second generation antipsychotics + Benzodiazepines or Related Medications	0.2	5.61	1.05 5% increase*	0.9 NS	1.12 NS	0.94 NS	0.54 46% lower*

*Indicates a statistically significant effect ($p<0.05$)

Note: Results for change in rate per quarter, age, socioeconomic status (SES), region, and sex effect are presented as relative rates (adjusted for age, SES, region, sex and time).

Source: Manitoba Centre for Health Policy, 2010

Figure 2.3: Dose Intensity Antipsychotics by Quarter
Crude Defined Daily Dose rates per 1,000 adults in the community aged 65+, Q1 1997-Q4 2008

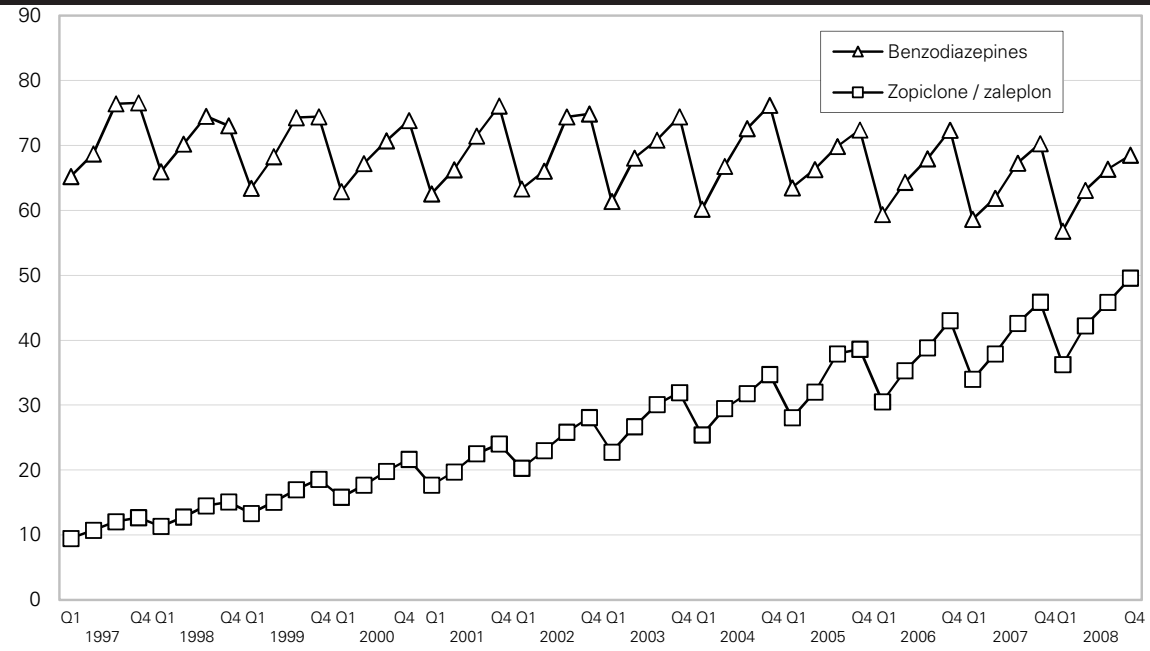


'Q1' indicates rates for the 1st quarter (April to June)
'Q4' indicates rates for the 4th quarter (January to March)
'Q2' and 'Q3' data points are displayed, but not labeled

Health Canada warning Risperidone 2002Q3
Health Canada warning Olanzapine 2003Q4
Health Canada warning all SGA 2005Q2

Source: Manitoba Centre for Health Policy, 2010

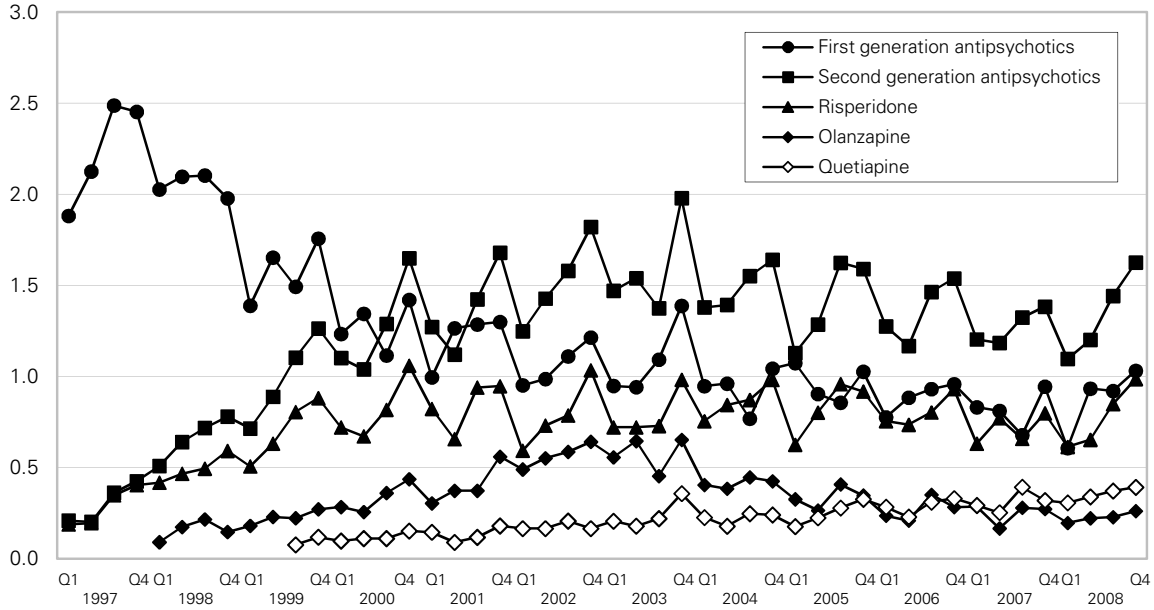
Figure 2.4: Dose Intensity Benzodiazepines and Related Medications by Quarter
Crude Defined Daily Dose rates per 1,000 adults in the community aged 65+, Q1 1997- Q4 2008



'Q1' indicates rates for the 1st quarter (April to June)
'Q4' indicates rates for the 4th quarter (January to March)
'Q2' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2010

Figure 2.5: Antipsychotics, Quarterly Incidence
Crude rates of new users with no use of antipsychotics in prior year per 1,000 adults in the community aged 65+, Q1 1997-Q4 2008

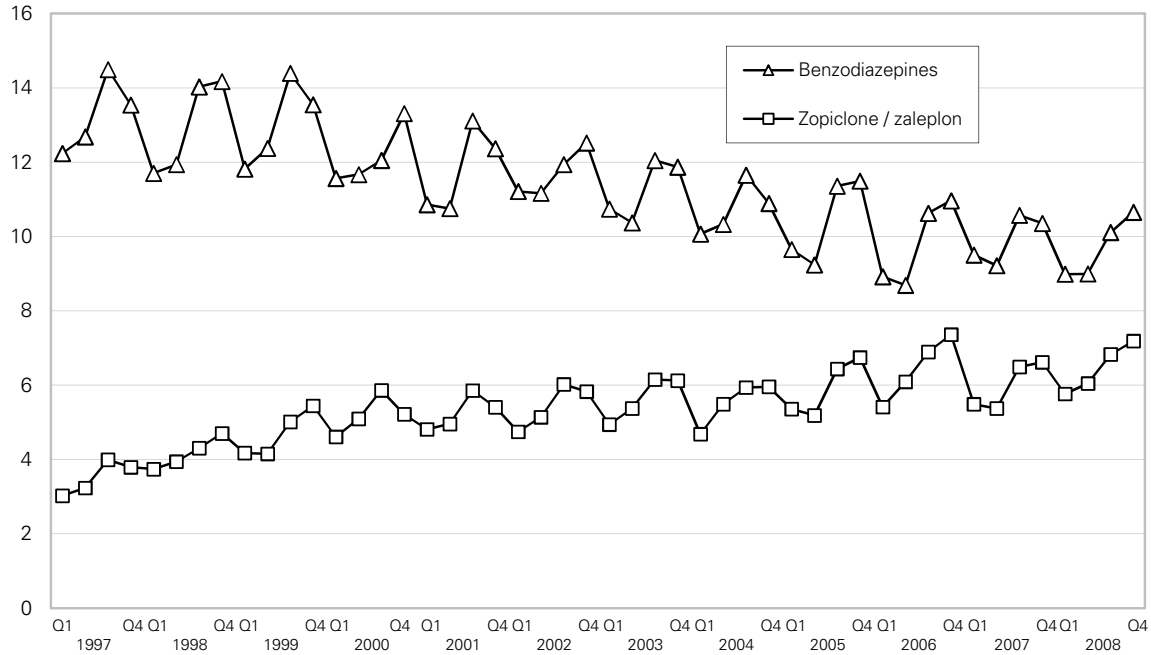


'Q1' indicates rates for the 1st quarter (April to June)
'Q4' indicates rates for the 4th quarter (January to March)
'Q2' and 'Q3' data points are displayed, but not labeled

Health Canada warning Risperidone 2002Q3
Health Canada warning Olanzapine 2003Q4
Health Canada warning all SGA 2005Q2

Source: Manitoba Centre for Health Policy, 2010

Figure 2.6: Benzodiazepines and Related Medications, Quarterly Incidence
Crude rates of new users with no use of antipsychotics in prior year per 1,000 adults in the community aged 65+, Q1 1997-Q4 2008



'Q1' indicates rates for the 1st quarter (April to June)
'Q4' indicates rates for the 4th quarter (January to March)
'Q2' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2010

Table 2.2: Incident Use (Users per 1,000 Residents) of Antipsychotics, Benzodiazepines, and Related Medications in Community Dwelling Older Adults (65+), 1997/98 to 2008/09

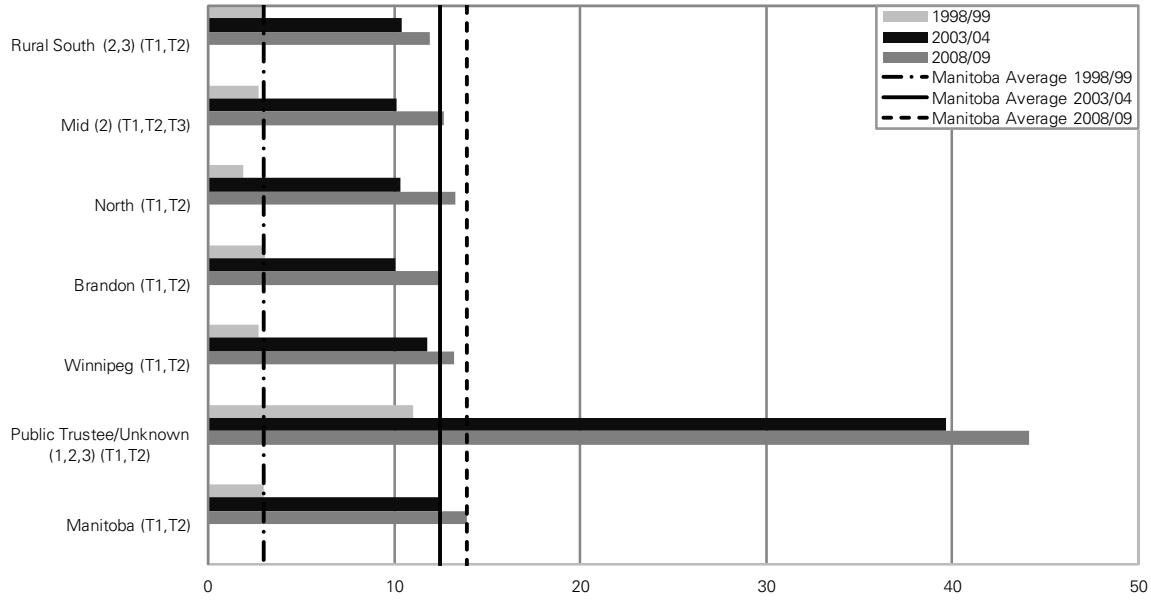
Medication or Group of Medications	1997Q1 users/1,000	2008Q4 users/1,000	Change in rate per quarter	Age effect 65-84 vs 85+	Socioeconomic status Low vs High	Region effect Rural vs Urban	Sex effect Male vs Female
Second generation antipsychotics	0.21	1.63	1.02 2% increase*	0.44 66% lower*	1.1 10% higher*	0.88 12% lower*	0.91 9% lower*
First generation antipsychotics	1.89	1.03	0.98 2% decrease*	0.85 15% lower*	1.14 14% higher*	1.51 51% higher*	0.86 14% lower*
Benzodiazepines/ zopiclone and zaleplon	13.14	13.66	1 slight decrease*	1.08 8% higher*	1 NS	1.01 NS	0.73 27% lower*
Risperidone	0.19	0.99	1.01 1% increase*	0.37 63% lower*	1.1 NS	0.87 13% lower*	0.88 12% lower*
Olanzapine	0.09 1997Q1	0.26	1.01 1% increase*	0.54 46% lower*	1.16 16% higher*	0.9 10% lower*	0.89 11% lower*
Quetipine	0.04 1998Q4	0.39	1.04 4% increase*	0.77 23% lower*	1.12 NS	0.9 NS	1.07 NS
Combination of Second generation antipsychotics + Benzodiazepines or Related Medications	0.06 1997Q3	0.15	1.01 1% increase*	0.6 40% lower*	1.09 NS	1.02 NS	1.17 17% higher*

*Indicates a statistically significant effect ($p<0.05$)

Note: Results for change in rate per quarter, age, socioeconomic status (SES), region, and sex effect are presented as relative rates (adjusted for age, SES, region, sex and time).

Source: Manitoba Centre for Health Policy, 2010

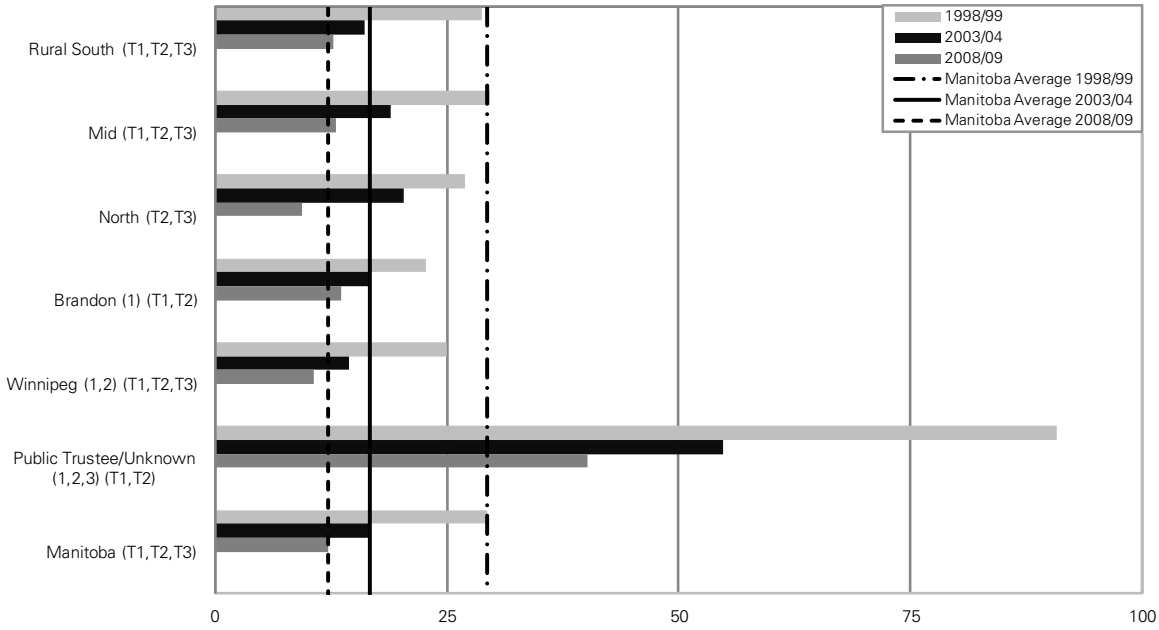
Figure 2.7: Second Generation Antipsychotics, Users per 1,000 Community Dwelling Older Adults by Region
Adjusted by (2003/04) age, sex, and SES per 1,000 residents aged 65+



'1'- indicates area's rate was statistically different from Manitoba average in 1998/99.
'2'- indicates area's rate was statistically different from Manitoba average in 2003/04.
'3'- indicates area's rate was statistically different from Manitoba average in 2008/09.
'T1'- indicates change over time (1998/99 versus 2003/04) was statistically different for that area.
'T2'- indicates change over time (1998/99 versus 2008/09) was statistically different for that area.
'T3'- indicates change over time (2003/04 versus 2008/09) was statistically different for that area.

Source: Manitoba Centre for Health Policy, 2010

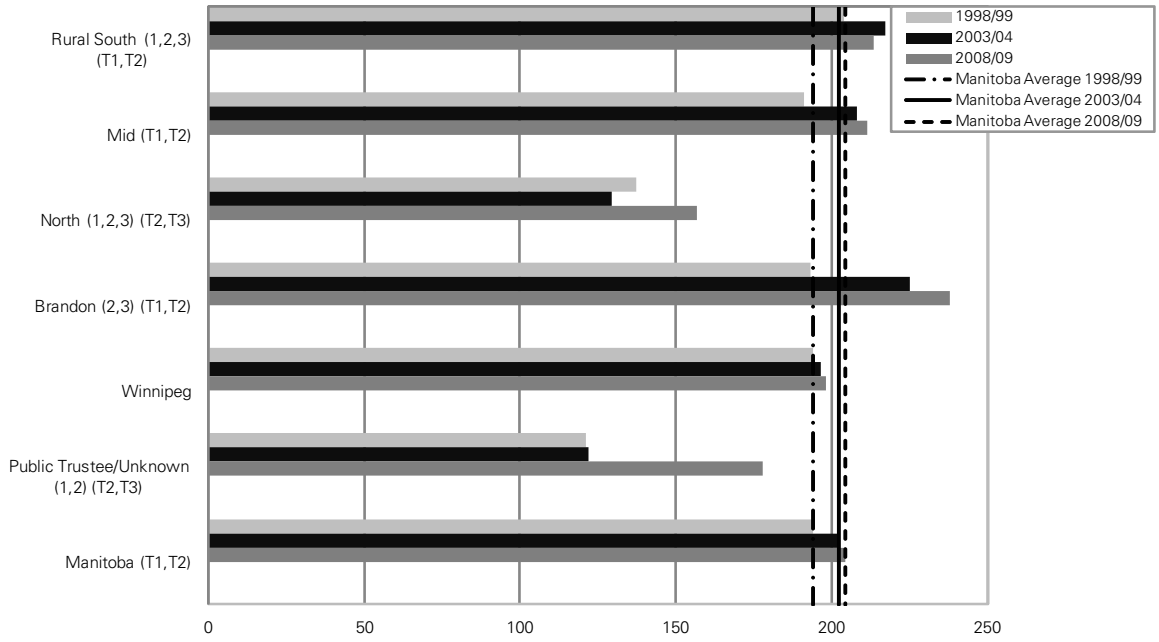
Figure 2.8: First Generation Antipsychotics, Users per 1,000 Community Dwelling Older Adults by Region
Adjusted by (2003/04) age, sex, and SES per 1,000 residents aged 65+



'1'- indicates area's rate was statistically different from Manitoba average in 1998/99.
'2'- indicates area's rate was statistically different from Manitoba average in 2003/04.
'3'- indicates area's rate was statistically different from Manitoba average in 2008/09.
'T1'- indicates change over time (1998/99 versus 2003/04) was statistically different for that area.
'T2'- indicates change over time (1998/99 versus 2008/09) was statistically different for that area.
'T3'- indicates change over time (2003/04 versus 2008/09) was statistically different for that area.

Source: Manitoba Centre for Health Policy, 2010

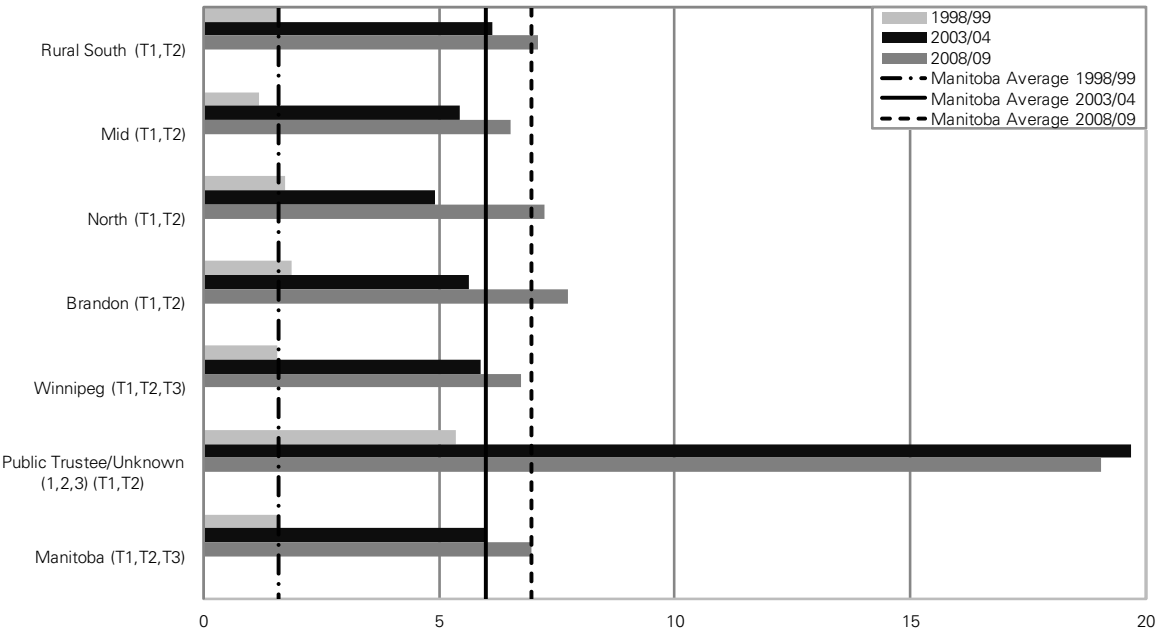
Figure 2.9: Benzodiazepines and Related Medications, Users per 1,000 Community Dwelling Older Adults by Region
Adjusted by (2003/04) Age, Sex, and SES per 1,000 residents aged 65+



'1'- indicates area's rate was statistically different from Manitoba average in 1998/99.
'2'- indicates area's rate was statistically different from Manitoba average in 2003/04.
'3'- indicates area's rate was statistically different from Manitoba average in 2008/09.
'T1'- indicates change over time (1998/99 versus 2003/04) was statistically different for that area.
'T2'- indicates change over time (1998/99 versus 2008/09) was statistically different for that area.
'T3'- indicates change over time (2003/04 versus 2008/09) was statistically different for that area.

Source: Manitoba Centre for Health Policy, 2010

Figure 2.10: Second Generation Antipsychotics in Combination with Benzodiazepines or Related Medications, Users per 1,000 Community Dwelling Older Adults by Region
Adjusted by (2003/04) age, sex, and SES per 1,000 residents aged 65+



'1'- indicates area's rate was statistically different from Manitoba average in 1998/99.
'2'- indicates area's rate was statistically different from Manitoba average in 2003/04.
'3'- indicates area's rate was statistically different from Manitoba average in 2008/09.
'T1'- indicates change over time (1998/99 versus 2003/04) was statistically different for that area.
'T2'- indicates change over time (1998/99 versus 2008/09) was statistically different for that area.
'T3'- indicates change over time (2003/04 versus 2008/09) was statistically different for that area.

Source: Manitoba Centre for Health Policy, 2010

PCH–dwelling older adults

A total of 8,516 PCH–dwelling older adults were included as the denominator in the analysis of antipsychotics, benzodiazepines, and related medications in 1997/98 and 8,818 in 2008/09.

PCH–dwelling older adults: Prevalence

For older adults residing in a PCH, prevalent utilization of SGAs increased from 15.0 to 268.5 users per 1,000 PCH–dwelling older adults, while prevalent utilization of first generation antipsychotics in this population declined from 169.3 to 47.7 users per 1,000 by the end of the study period (see Figure 2.11). Risperidone was the most commonly prescribed SGA, and quetiapine became the second most utilized by the end of the study period. Users of risperidone increased from 15.0 to 167.0 per 1,000 PCH–dwelling older adults, quetiapine increased from 0.9 to 67.6 per 1,000, and olanzapine increased from 0.8 to 49.1 per 1,000.

For older adults residing in a PCHs, the prevalent use of benzodiazepines declined from 170.7 to 161.3 users per 1,000 PCH–dwelling older adults over the study period (see Figure 2.12). The use of zopiclone and zaleplon increased dramatically from 15.0 to 102.6 users per 1,000 over the study period.

Generally, there was greater prevalent utilization in PCH–dwelling older adults amongst those aged 65–84 (compared to those aged 85 and older) and lower utilization amongst PCH residents in rural regions (compared to urban), following adjustment for other factors (see Table 2.3).

PCH–dwelling older adults: Dose intensity

The dose intensity of SGAs in the population of PCH–dwelling older adults increased over the study period, from 5.5 DDDs per 1,000 PCH–dwelling older adults per day at the beginning of the study to peak at 85.5 at the end of 2003/04, and then decline to 70.7 by the end of the study period (see Figure 2.13).

Dose intensity of benzodiazepines increased from 82.1 to 84.9 DDDs per 1,000 PCH–dwelling older adults by the third quarter of 2003 and then declined to 67.0 over the study period, while that of zopiclone and zaleplon increased from 11.7 to 76.5 over the study period (see Figure 2.14).

PCH–dwelling older adults: Incidence

For older adults residing in a PCH, new users of SGAs increased from 3.8 to 21.1 users per 1,000 per quarter, while first generation agents decreased from 19.6 to 8.6 users per 1,000 per quarter over the same time period (see Figure 2.15). Risperidone utilization (3.8 to 15.9 users per 1,000 per quarter) was followed by quetiapine (0.8 to 4.2 users per 1,000 per quarter) and olanzapine (0.7 to 1.4 users per 1,000 per quarter). New users of benzodiazepines decreased from 25.8 to 17.1 users per 1,000 per quarter, while new users of zopiclone and zaleplon increased from 2.8 to 13.6 users per 1,000 per quarter (see Figure 2.16).

PCH–dwelling older adults: Sociodemographic characteristics

Generally, there was greater incident utilization in PCH–dwelling older adults amongst males (versus females) and those aged 65–84 (compared to those aged 85 and older), following adjustment for other factors (see Table 2.4). There was lower incident antipsychotic and benzodiazepine utilization (except quetiapine) in PCH residents of rural areas as compared to urban areas.

PCH–dwelling older adults: Regional variation

When adjusted for age and sex, the prevalent utilization of all SGAs used alone increased for older adults residing in a PCH across all regions of Manitoba over the time period evaluated (see Figure 2.17). Prevalent utilization for SGAs in the North was significantly lower than the Manitoba average in 1998/99

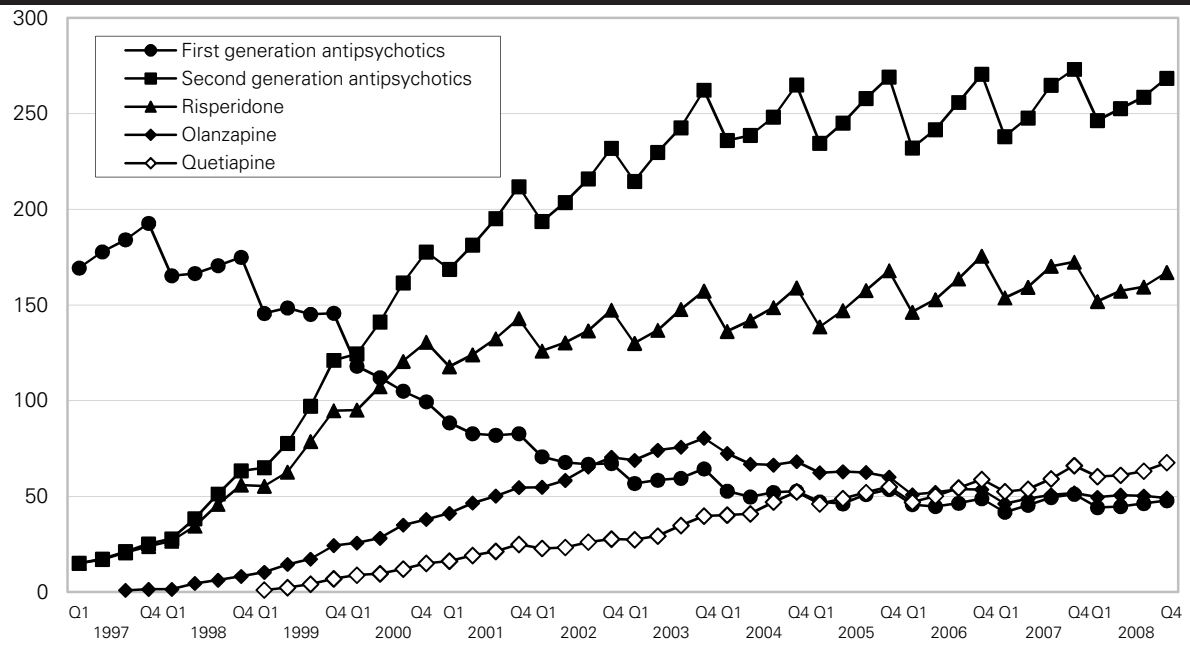
and 2003/04, whereas the Rural South was significantly lower than the Manitoba average for 2003/04 and 2008/09. Utilization in Brandon was significantly lower than the Manitoba average for 1998/99 and 2008/09. Use by individuals including "public trustee/unknown" was greater than the Manitoba average in 1998/99 and 2003/04

Prevalent utilization of first generation antipsychotics in Winnipeg was significantly lower than the Manitoba average in 2003/04 and 2008/09, whereas the Rural South utilization was significantly lower than that of the Manitoba average for 1998/99 and 2003/04 (see Figure 2.18). Prevalent utilization in Brandon was lower than the Manitoba average in 1998/99 and 2008/09.

Prevalent utilization of benzodiazepines and related medications in Brandon was significantly higher than the Manitoba average for 2003/04 and 2008/09 (see Figure 2.19). Prevalent utilization of benzodiazepines and related medications in the Mid and North was significantly lower than the Manitoba average for 1998/99 and 2003/04; however, use in the Mid area was greater than the Manitoba average in 2008/09.

When adjusted for age and sex, the prevalent utilization of all SGAs used in combination with benzodiazepines or related medications increased since 1998/99 for older adults residing in a PCH across all regions of Manitoba (see Figure 2.20). Prevalence of combinations of SGAs with benzodiazepines or related medications in Mid and North Manitoba were significantly lower than the Manitoba average for 2003/04 while the rate for Winnipeg was significantly higher than the Manitoba average for 2003/04 only.

Figure 2.11: Antipsychotics, PCH Residents Quarterly Prevalence
Crude user rates per 1,000 residents in personal care homes aged 65+, Q1 1997-Q4 2008

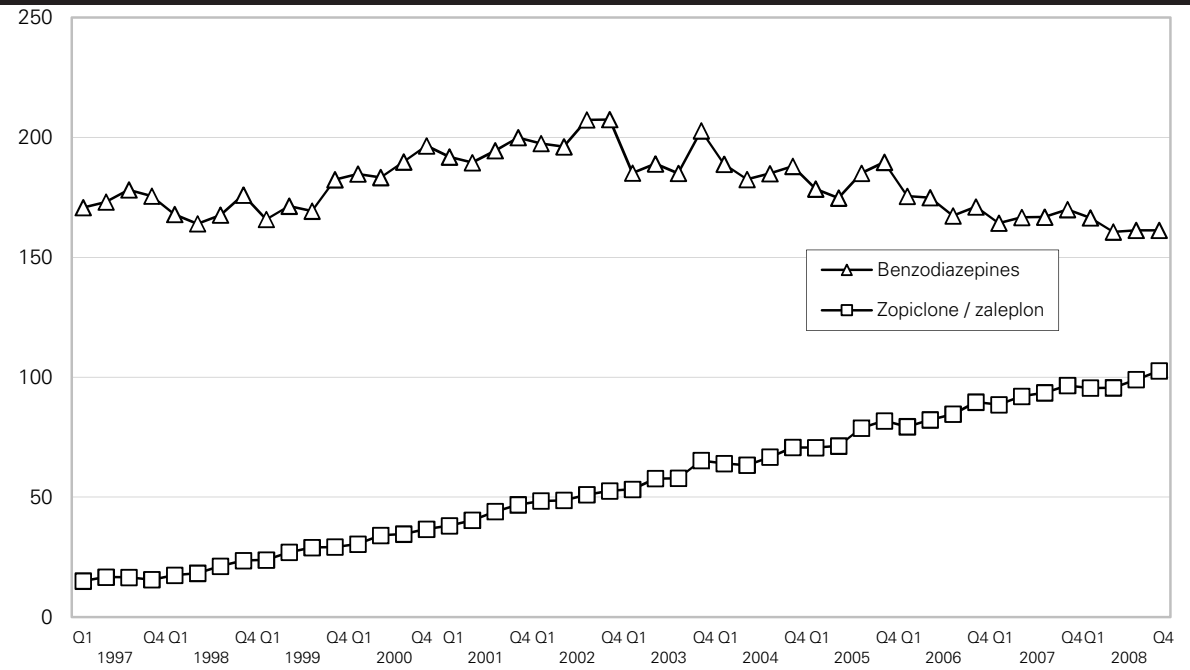


'Q1' indicates rates for the 1st quarter (April to June)
'Q4' indicates rates for the 4th quarter (January to March)
'Q2' and 'Q3' data points are displayed, but not labeled

Health Canada warning Risperidone 2002Q3
Health Canada warning Olanzapine 2003Q4
Health Canada warning all SGA 2005Q2

Source: Manitoba Centre for Health Policy, 2010

Figure 2.12: Benzodiazepines and Related Medications, PCH Residents Quarterly Prevalence
Crude user rates per 1,000 residents in personal care homes aged 65+, Q1 1997-Q4 2008



'Q1' indicates rates for the 1st quarter (April to June)
'Q4' indicates rates for the 4th quarter (January to March)
'Q2' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2010

Table 2.3: Prevalent Use (Users per 1,000 Residents) of Antipsychotics, Benzodiazepines, and Related Medications in PCH Dwelling Older Adults (65+), 1997/98 to 2008/09

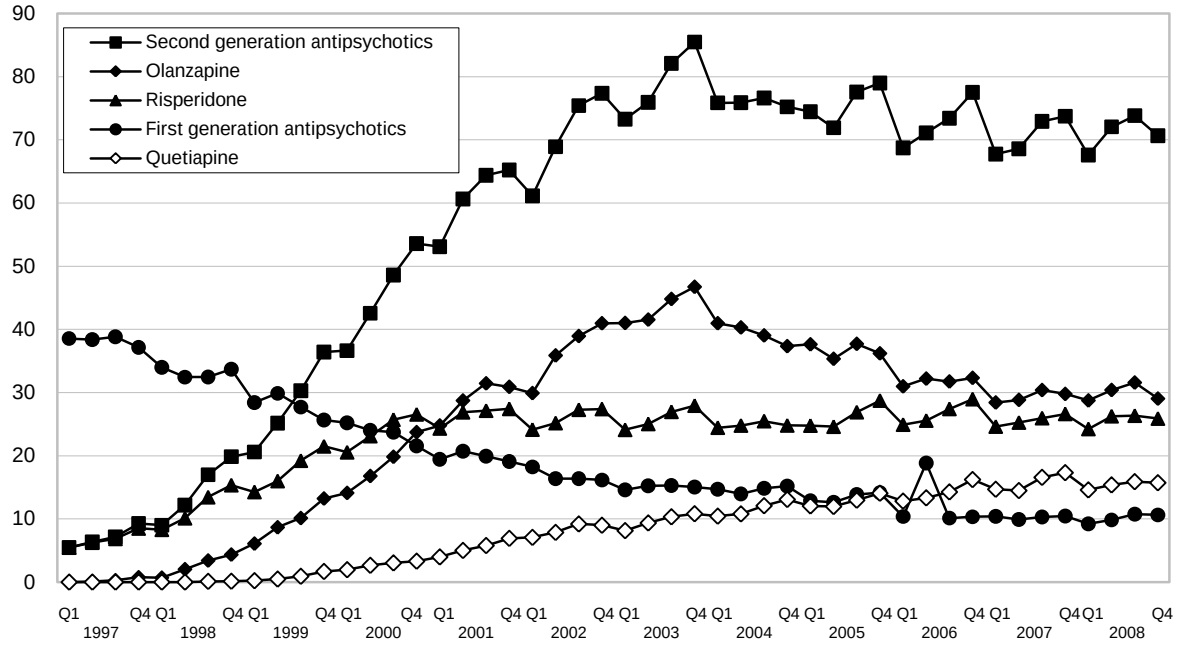
Medication or Group of Medications	1997Q1 users/1,000	2008Q4 users/1,000	Change in rate per quarter	Age effect 65-84 vs 85+	Region effect Rural vs Urban	Sex effect Male vs Female
Second generation antipsychotics	15.03	268.54	1.04 4% increase*	1.39 39% higher*	0.76 24% lower*	1.01 NS
First generation antipsychotics	169.34	47.74	0.97 3% decrease*	1.63 63% higher*	0.9 10% lower*	1.02 NS
Benzodiazepines/ zopiclone and zaleplon	181.31	241.32	1.01 1% increase*	1.2 20% higher*	0.87 13% lower*	0.81 19% lower*
Risperidone	15.03	167.04	1.03 3% increase*	1.26 26% higher*	0.76 24% lower*	1 NS
Olanzapine	0.82 1997Q3	49.1	1.05 5% increase*	1.76 76% higher*	0.68 32% lower*	0.9 10% lower*
Quetiapine	0.92 1999Q1	67.59	1.06 6% increase*	1.79 79% higher*	0.96 NS	1.22 22% higher*
Combination of Second generation antipsychotics + Benzodiazepines or Related Medications	4.81	90.84	1.04 4% increase*	1.65 65% higher*	0.8 20% lower*	0.93 NS

*Indicates a statistically significant effect ($p<0.05$)

Source: Manitoba Centre for Health Policy, 2010

Note: Results for change in rate per quarter, age, region, and sex effect are presented as relative rates (adjusted for age, region, sex and time).

Figure 2.13: Dose Intensity Antipsychotics by Quarter, PCH Residents
Crude Defined Daily Dose rates per 1,000 residents in personal care homes aged 65+, Q1 1997-Q4 2008

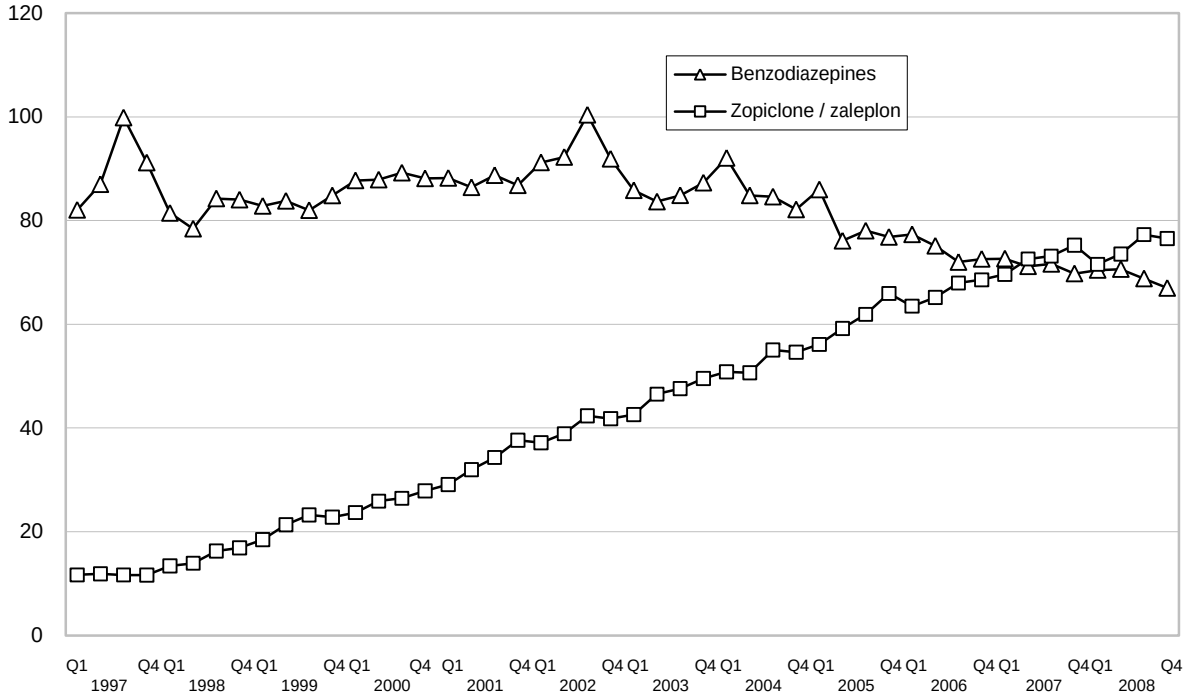


'Q1' indicates rates for the 1st quarter (April to June)
'Q4' indicates rates for the 4th quarter (January to March)
'Q2' and 'Q3' data points are displayed, but not labeled

Health Canada warning Risperidone 2002Q3
Health Canada warning Olanzapine 2003Q4
Health Canada warning all SGA 2005Q2

Source: Manitoba Centre for Health Policy, 2010

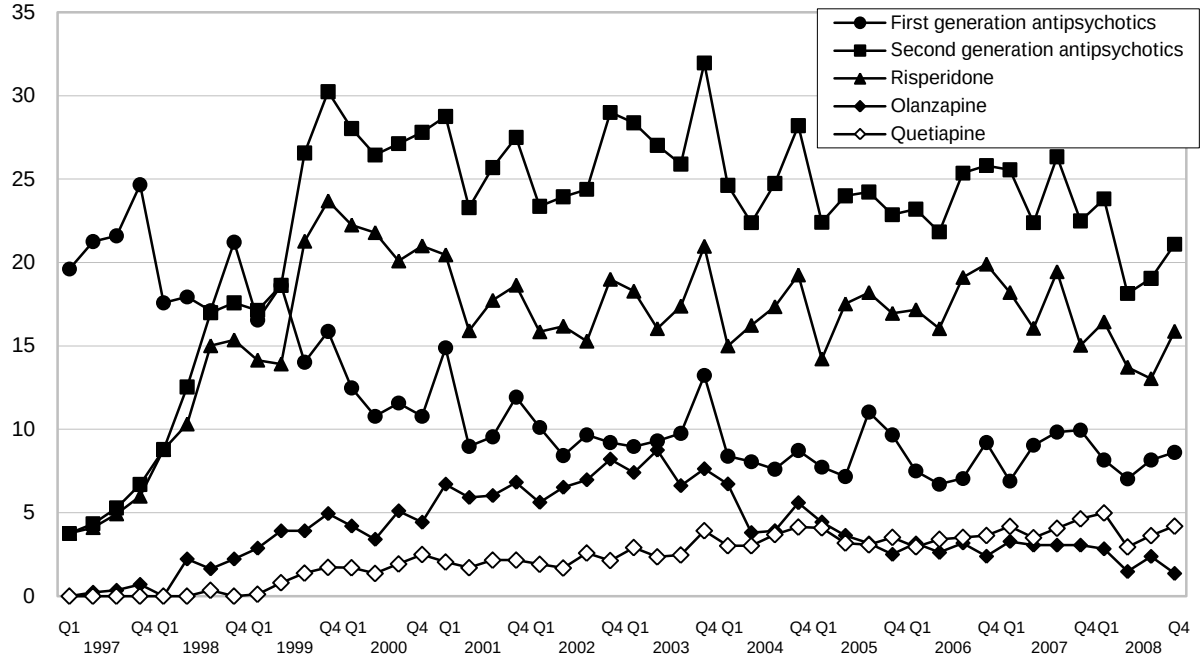
Figure 2.14: Dose Intensity Benzodiazepines and Related Medications by Quarter, PCH Residents
Crude Defined Daily Dose rates per 1,000 residents in personal care homes aged 65+, Q1 1997-Q4 2008



'Q1' indicates rates for the 1st quarter (April to June)
'Q4' indicates rates for the 4th quarter (January to March)
'Q2' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2010

Figure 2.15: Antipsychotics, PCH Residents Quarterly Incidence
Crude rates of new users with no use of antipsychotics in prior year per 1,000 residents in personal care homes aged 65+, Q1 1997-Q4 2008

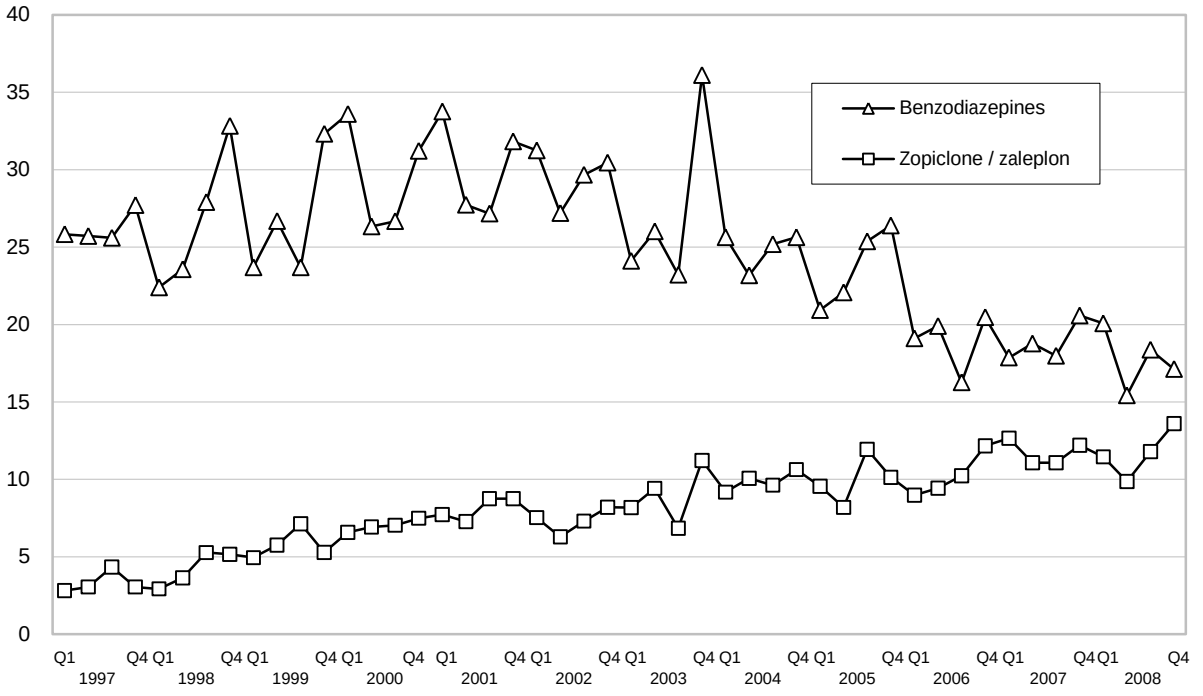


'Q1' indicates rates for the 1st quarter (April to June)
'Q4' indicates rates for the 4th quarter (January to March)
'Q2' and 'Q3' data points are displayed, but not labeled

Health Canada warning Risperidone 2002Q3
Health Canada warning Olanzapine 2003Q4
Health Canada warning all SGA 2005Q2

Source: Manitoba Centre for Health Policy, 2010

Figure 2.16: Benzodiazepines and Related Medications, PCH Residents Quarterly Incidence
Crude rates of new users with no use of antipsychotics in prior year per 1,000 residents in personal care homes aged 65+, Q1 1997-Q4 2008



'Q1' indicates rates for the 1st quarter (April to June)
'Q4' indicates rates for the 4th quarter (January to March)
'Q2' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2010

Table 2.4: Incident Use (Users per 1,000 Residents) of Antipsychotics, Benzodiazepines, and Related Medications in PCH Dwelling Older Adults (65+), 1997/98 to 2008/09

Medication or Group of Medications	1997Q1 users/1,000	2008Q4 users/1,000	Change in rate per quarter	Age effect 65-84 vs 85+	Region effect Rural vs Urban	Sex effect Male vs Female
Second generation antipsychotics	3.76	21.09	1.01 1% increase*	1.21 21% higher*	0.78 22% lower*	1.22 22% higher*
First generation antipsychotics	19.61	8.62	0.98 2% decrease*	1.36 36% higher*	0.85 15% lower*	1.38 38% higher*
Benzodiazepines/ zopiclone and zaleplon	26.66	22.91	1 slight decrease*	1.13 13% higher*	0.79 21% lower*	1.09 9% higher*
Risperidone	3.76	15.88	1.01 1% increase*	1.13 13% higher*	0.74 26% lower*	1.17 17% higher*
Olanzapine	0.23 1997Q4	1.36	1.01 1% increase*	1.44 44% higher*	0.83 17% lower*	1.25 25% higher*
Quetiapine	0.81 1999Q2	4.2	1.03 3% increase*	1.56 56% higher*	1.02 NS	1.53 53% higher*
Combination of Second generation antipsychotics + Benzodiazepines or Related Medications	0.7 1997Q2	3.05	1.01 1% increase*	1.4 40% higher*	0.74 26% lower*	1.48 48% higher*

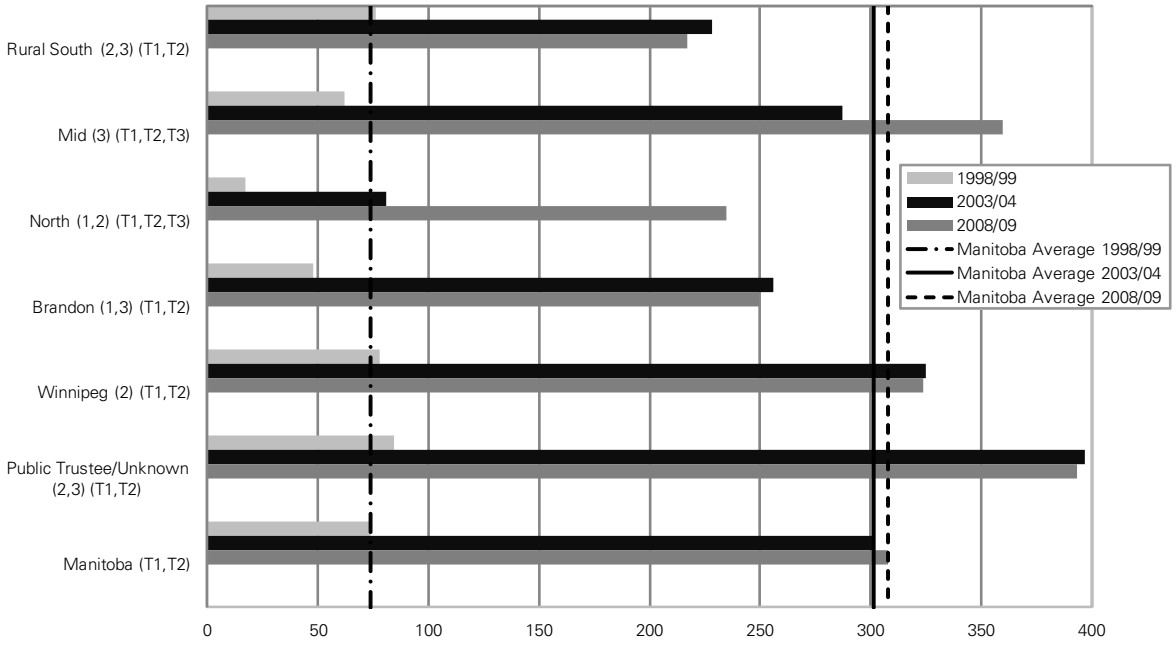
*Indicates a statistically significant effect ($p<0.05$)

Note: Results for change in rate per quarter, age, region, and sex effect are presented as relative rates (adjusted for age, region, sex and time).

Source: Manitoba Centre for Health Policy, 2010

Figure 2.17: Second Generation Antipsychotics, Users per 1,000 PCH Residents by Region

Adjusted by (2003/04) age and sex per 1,000 PCH residents aged 65+

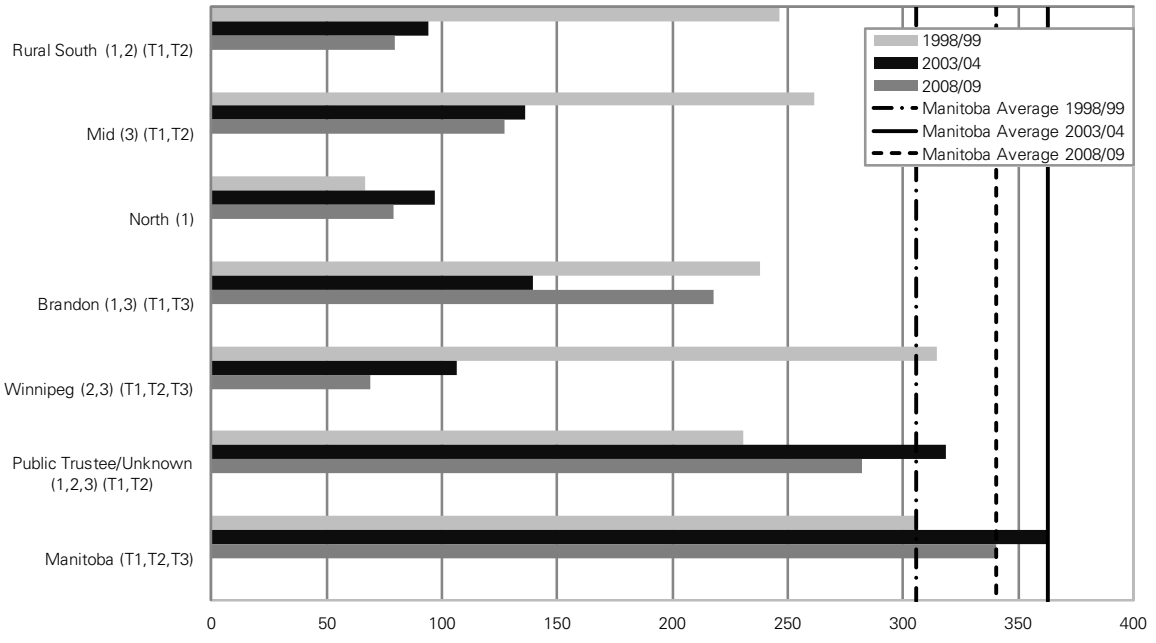


'1'- indicates area's rate was statistically different from Manitoba average in 1998/99.
'2'- indicates area's rate was statistically different from Manitoba average in 2003/04.
'3'- indicates area's rate was statistically different from Manitoba average in 2008/09.
'T1'- indicates change over time (1998/99 versus 2003/04) was statistically different for that area.
'T2'- indicates change over time (1998/99 versus 2008/09) was statistically different for that area.
'T3'- indicates change over time (2003/04 versus 2008/09) was statistically different for that area.

Source: Manitoba Centre for Health Policy, 2010

Figure 2.18: First Generation Antipsychotics, Users per 1,000 PCH Residents by Region

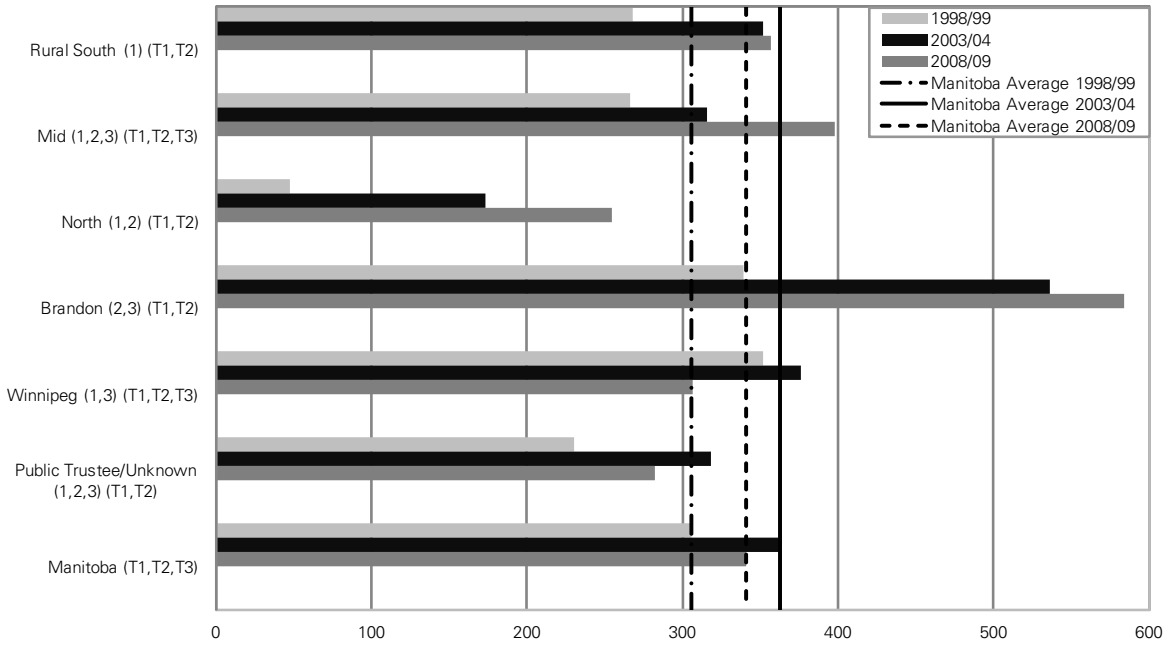
Adjusted by (2003/04) age and sex per 1,000 PCH residents aged 65



'1'- indicates area's rate was statistically different from Manitoba average in 1998/99.
'2'- indicates area's rate was statistically different from Manitoba average in 2003/04.
'3'- indicates area's rate was statistically different from Manitoba average in 2008/09.
'T1'- indicates change over time (1998/99 versus 2003/04) was statistically different for that area.
'T2'- indicates change over time (1998/99 versus 2008/09) was statistically different for that area.
'T3'- indicates change over time (2003/04 versus 2008/09) was statistically different for that area.

Source: Manitoba Centre for Health Policy, 2010

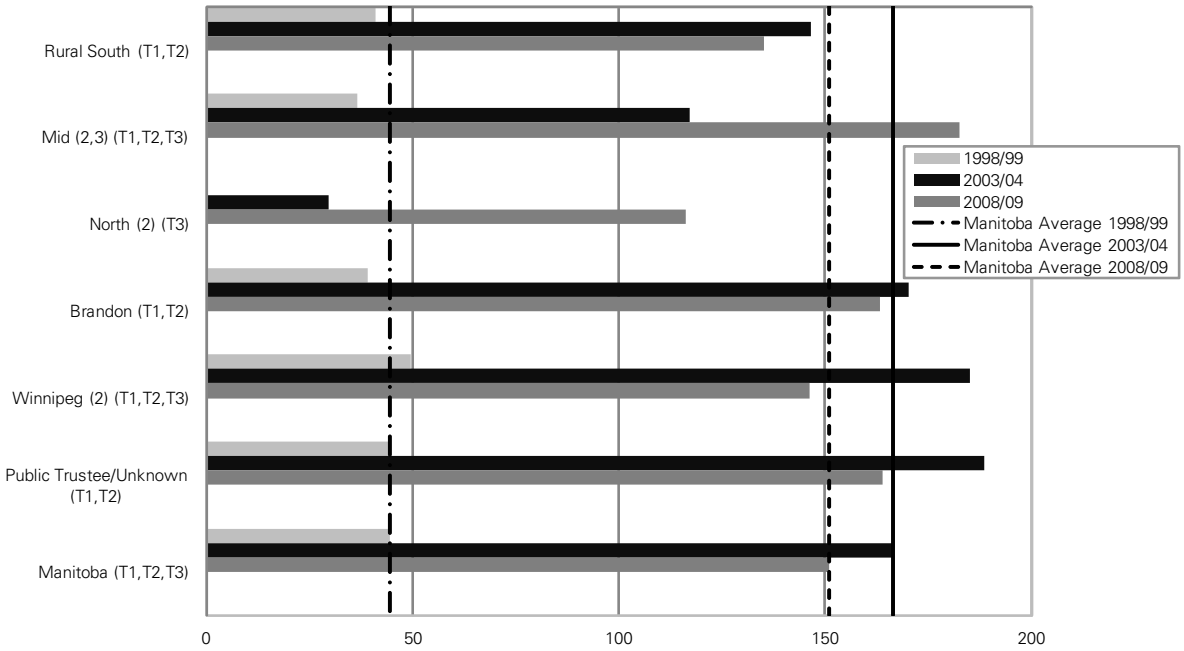
Figure 2.19: Benzodiazepines and Related Medications, Users per 1,000 PCH Residents by Region
Adjusted by (2003/04) age and sex, per 1,000 PCH residents aged 65+



'1'- indicates area's rate was statistically different from Manitoba average in 1998/99.
'2'- indicates area's rate was statistically different from Manitoba average in 2003/04.
'3'- indicates area's rate was statistically different from Manitoba average in 2008/09.
'T1'- indicates change over time (1998/99 versus 2003/04) was statistically different for that area.
'T2'- indicates change over time (1998/99 versus 2008/09) was statistically different for that area.
'T3'- indicates change over time (2003/04 versus 2008/09) was statistically different for that area.

Source: Manitoba Centre for Health Policy, 2010

Figure 2.20: Second Generation Antipsychotics in Combination with Benzodiazepines or Related Medications, Users per 1,000 PCH Residents by Region
Adjusted by (2003/04) age and sex, per 1,000 PCH residents aged 65+



'1'- indicates area's rate was statistically different from Manitoba average in 1998/99.
'2'- indicates area's rate was statistically different from Manitoba average in 2003/04.
'3'- indicates area's rate was statistically different from Manitoba average in 2008/09.
'T1'- indicates change over time (1998/99 versus 2003/04) was statistically different for that area.
'T2'- indicates change over time (1998/99 versus 2008/09) was statistically different for that area.
'T3'- indicates change over time (2003/04 versus 2008/09) was statistically different for that area.

Source: Manitoba Centre for Health Policy, 2010

Table 2.5: Incident Second Generation Antipsychotic Users in PCH
Percent of PCH residents aged 65+

Fiscal Year	Sample Size	Incident Prescription				
		Between 0-29 Days After PCH Admission, PCH Admission from Hospital	Between 0-29 Days After PCH Admission, PCH Admission from Home	Over 29 Days After PCH Admission, PCH Admission from Hospital	Over 29 Days After PCH Admission, PCH Admission from Home	Before PCH Admission
1997/98	(s)	9.9%	2.3%	11.1%	67.3%	9.4%
1998/99	477	10.7%	3.6%	27.0%	48.4%	10.3%
1999/2000	806	16.3%	3.3%	24.6%	45.4%	10.4%
2000/01	964	17.4%	5.8%	28.2%	36.6%	11.9%
2001/02	926	18.9%	6.4%	24.8%	36.8%	13.1%
2002/03	896	23.1%	7.8%	25.3%	28.2%	15.5%
2003/04	1010	22.1%	7.4%	26.1%	30.7%	13.7%
2004/05	893	25.1%	7.1%	26.5%	27.7%	13.7%
2005/06	822	24.9%	6.9%	23.8%	30.9%	13.4%
2006/07	846	21.9%	9.3%	23.9%	28.4%	16.5%
2007/08	856	21.7%	8.6%	27.9%	28.3%	13.4%
2008/09	724	19.1%	11.2%	23.3%	32.2%	14.2%

(s) = Suppressed

Source: Manitoba Centre for Health Policy, 2010

Optimal use evaluation

Over time the DDDs per incident user of SGAs residing in a PCH decreased. In 2003/04 the mean DDDs per user per year was 78.2. This declined to 52.8 in 2008/09 ($p<0.05$).

For new users of SGAs residing in a PCH, most of SGAs were started in PCH; however, the majority of SGA prescriptions began 30 days or more after PCH admission (see Table 2.5).

The proportion of PCH residents who received a SGA and were also prescribed (in the same year) an acetylcholinesterase inhibitor (donepezil, galantamine, or rivastigmine) to treat dementia increased over time from 0.6% in 1997/98 and then peaked at 17.8% in 2003/04 with a slight decline to 16.9% in 2008/09 (see Figure 2.21).

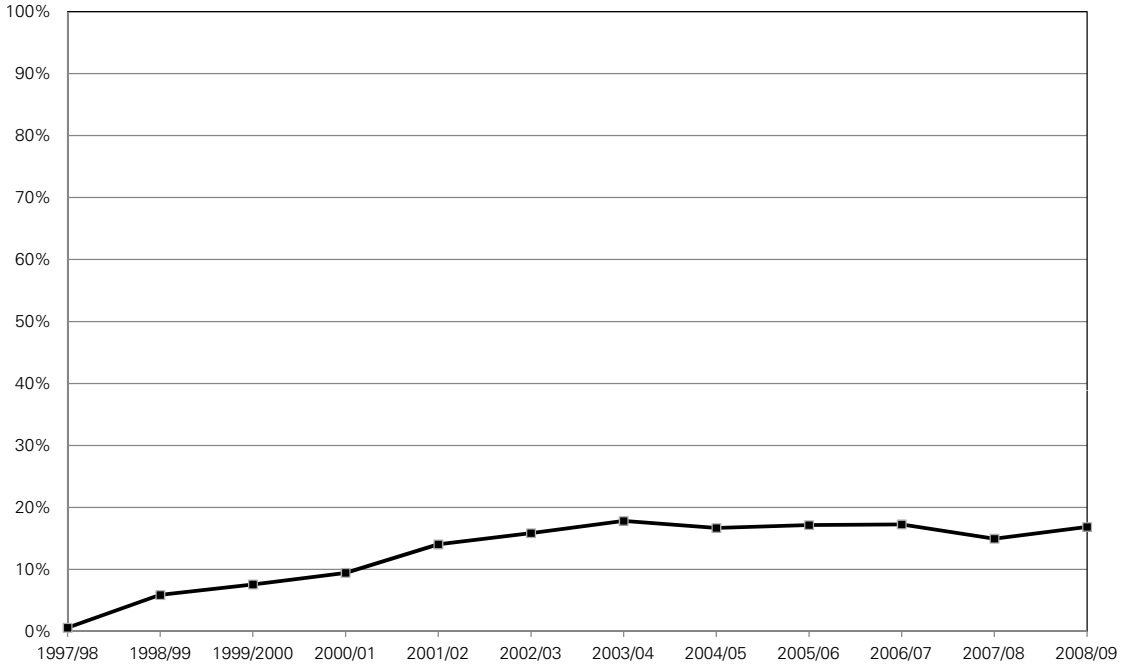
The rate of older adults who received a high dose SGA within the first year of being prescribed an SGA increased from 0.2 to 0.8 per 1,000 older adults by the fourth quarter of 1999 and then declined to 0.4 per 1,000 older adults in the fourth quarter of 2007 (see Figure 2.22). We defined high dose use of SGA use where the number of days supplied divided by the total quantity of tablets was greater than or equal to 1.5 mg/day of risperidone, 10 mg/day of olanzapine, or 200 mg/day of quetiapine (Alexopoulos et al., 2005; De Deyn et al., 2005; Jeste et al., 1999a; Jeste et al., 1999b; Jeste et al., 2008; Katz et al., 1999; Street et al., 2000; Tariot et al., 2006; Zhong et al., 2007;.

Among all older adults who used antipsychotics, the utilization of high dose SGAs declined from 112 to 94 per 1,000 older adult users from the first quarter of 2002 to the fourth quarter of 2007/08 (see Figure 2.23).

Amongst older adults, the use of high dose SGAs is considered less than optimal. From 2002/03 through 2007/08, there were 12,878 incident users of antipsychotics (first and SGAs) among older adults in Manitobans (community–dwelling and PCH–dwelling) who were included in the model. Of these, 1,319 (10.2%) went on to use a high dose of a SGA within the first year of therapy (outcome variable). There were 2.54% missing from the model due to missing variables.

Age, sex, number of different medications, use of an acetylcholinesterase inhibitor, and a psychosis diagnosis significantly influenced the likelihood of receiving a high dose SGA in the first year of therapy (see Table 2.6). Older adults were more likely to receive a high dose SGA within the first year of therapy if they were male, had received a medication for Alzheimer's dementia (acetylcholinesterase inhibitor), or had a diagnosis of psychosis (within the year prior to the first prescription for a SGA) as compared to other incident users of antipsychotics (first or second generation agents). As age increased, older Manitobans and those with a greater number of different medications were less likely to receive a high dose SGA. Prescriber and PCH characteristics were not significant, nor were other measures of health service utilization.

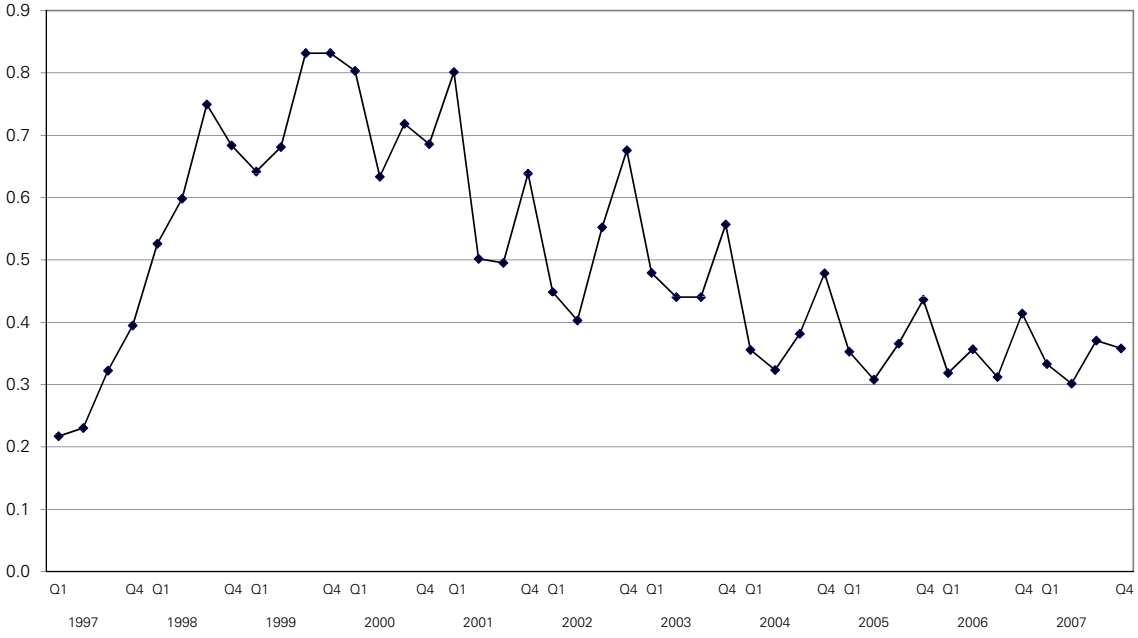
Figure 2.21: Incident Use of Second Generation Antipsychotics with Acetylcholinesterase Inhibitors in the Same Year
Percent of PCH residents aged 65+



Health Canada warning Risperidone 2002Q3
Health Canada warning Olanzapine 2003Q4
Health Canada warning all SGA 2005Q2

Source: Manitoba Centre for Health Policy, 2010

Figure 2.22: High Dose Second Generation Atypical Antipsychotics, Quarterly Incidence
Crude rates of new users with no use of antipsychotics in prior year per 1,000 adults aged 65+, Q1 1997-Q4 2007

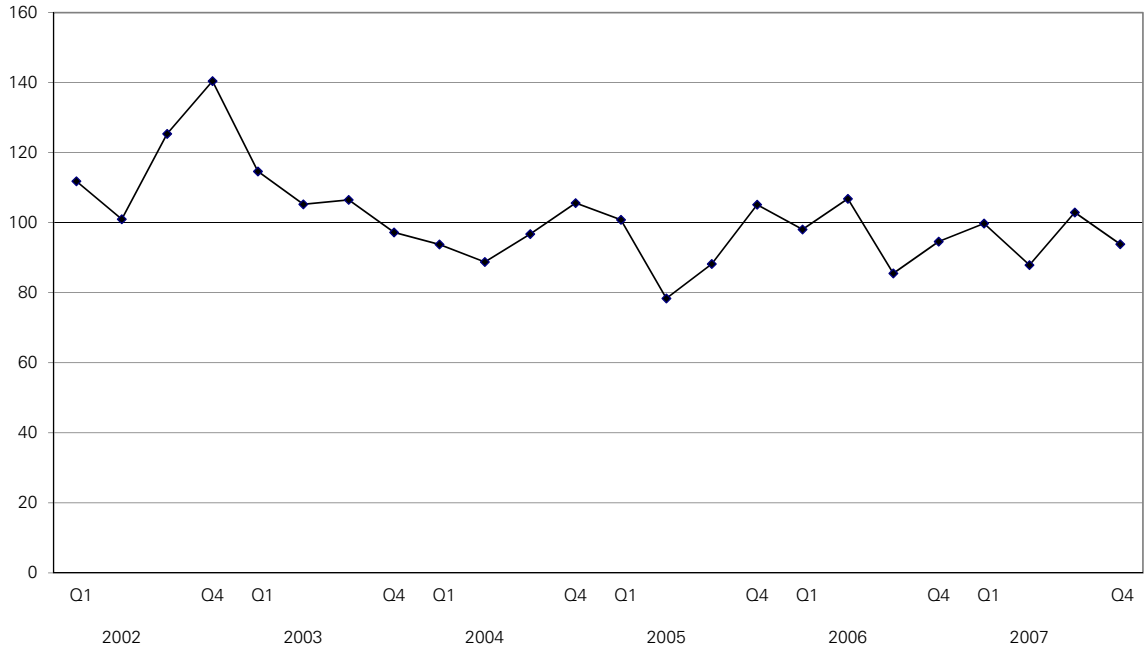


'Q1' indicates rates for the 1st quarter (April to June)
'Q4' indicates rates for the 4th quarter (January to March)
'Q2' and 'Q3' data points are displayed, but not labeled
Note: High dose second generation atypical antipsychotic use is identified if the number of days supplied divided by the total quantity of tablets equaled to greater than 1.5mg/day of risperidone, > 10 mg/day of olanzapine, or > 200mg/day of quetiapine.

Health Canada warning Risperidone 2002Q3
Health Canada warning Olanzapine 2003Q4
Health Canada warning all SGA 2005Q2

Source: Manitoba Centre for Health Policy, 2010

Figure 2.23: High Dose Second Generation Atypical Antipsychotics, Quarterly Incidence Among Users of Antipsychotics
Crude rates of new users year per 1,000 users of antipsychotics aged 65+, Q1 2002-Q4 2007



'Q1' indicates rates for the 1st quarter (April to June)
'Q4' indicates rates for the 4th quarter (January to March)
'Q2' and 'Q3' data points are displayed, but not labeled
Note: High dose second generation atypical antipsychotic use is identified if the number of days supplied divided by the total quantity of tablets equaled to greater than 1.5mg/day of risperidone, > 10 mg/day of olanzapine, or > 200mg/day of quetiapine.

Health Canada warning Risperidone 2002Q3
Health Canada warning Olanzapine 2003Q4
Health Canada warning all SGA 2005Q2

Source: Manitoba Centre for Health Policy, 2010

Table 2.6: Factors Predictive of High Dose Second Generation Antipsychotics within First Year
Adjusted odds ratio estimates for incident older adults (aged 65+) antipsychotic users 2002/03-2007/08

Variable	Odds Ratio	95% Confidence Interval
Age (years, continuous)	0.979	(0.971, 0.987)
Sex (male vs female)	1.177	(1.041, 1.331)
Number of other medications (continuous)	0.967	(0.955, 0.979)
Acetylcholinesterase inhibitor in prior year (yes vs no)	1.278	(1.081, 1.511)
Psychosis in prior year (yes vs no)	1.519	(1.338, 1.726)

Bold = statistically significant p<0.05
Note: Model adjusted for all the variables listed above as well as patient characteristics (region of residence, socioeconomic status, being hospitalized within three days of incident prescription, number of major ADGs, number of physician visits and hospitalizations in the year prior to the first prescription, death within one year); prescriber characteristics (hospital affiliation, location of training, years since licensure in Manitoba, type of reimbursement, specialist status); and environment characteristics (PCH environment, year of first prescription). Individuals were included in the model only once. They were also included if they had one incident prescription for an antipsychotic from 2002/03 through 2007/08 and if they had a value for all of the other variables included in the model.

Source: Manitoba Centre for Health Policy, 2010

Discussion

There was an increase in utilization of SGAs in older Manitobans over time, with SGAs largely replacing first generation agents. We also observed much greater prevalent utilization (20 times) of these agents in PCH–dwelling older adults, so that by the end of the study period, more than 25% of PCH–dwelling older adults had used a SGA. Factors that could contribute to this increase in antipsychotic prescribing include the increasing complexity of individuals residing in a PCH over time (Menec, MacWilliam, Soodeen, & Mitchell, 2002), the approved indication for risperidone to treat behavioural disturbances in dementia, and the perception that the SGAs were safer than the first generation antipsychotics (Defilippi & Crismon, 2000). Prevalent use of benzodiazepines in community–dwelling older adults decreased slightly with time but still remained above 10%, with an increase in use of zopiclone and zaleplon over time. Similarly, prevalent utilization of benzodiazepines declined with time, while utilization of zopiclone and zalaplon (approximately 10% of prevalent PCH–dwelling older adults) increased in PCH–dwelling older adults. Numerous other studies have described these patterns in utilization of psychotropic medications in older adults (Alessi–Severini et al., 2008; Dewa, Remington, Herrmann, Fearnley, & Goering, 2002; Domino & Swartz, 2008; Hagen et al., 2005; Percudani, Barbui, Fortino, & Petrovich, 2005; Trifiro et al., 2005).

Like others (Hagen et al., 2005), we observed greater utilization of psychotropic medications in urban older adults, particularly in PCH residents.

Few well designed randomized controlled trials clearly demonstrate a benefit to using antipsychotics in older adults, particularly those with dementia. Some randomized controlled trials of generally short duration demonstrate evidence for efficacy of low–dose SGAs for aggression, agitation, and psychosis associated with dementia (Brodaty et al., 2003; Katz et al., 1999; Street et al., 2000; Tariot et al., 2006; Zhong et al., 2007); however, numerous studies describe harm for older adults exposed to these medications (Ballard et al., 2009; Schneider et al., 2005; Wang et al., 2005). Common adverse effects of antipsychotics include akathisia, parkinsonism, sedation, anticholinergic effects (e.g., urinary retention, delirium), postural hypotension, cardiac conduction defects, gait abnormalities, incontinence, and falls (APA Practice Guidelines, 2009).

Clinicians caring for such patients must balance the challenge of treating individuals with psychosis or behavioural symptoms associated with dementia and the safety of the patient and caregivers. Numerous studies have demonstrated that the warnings about strokes associated with olanzapine and risperidone did impact utilization of these agents in older adults, yet the impact of these warnings has been small; and numerous older persons continue to be prescribed these medications (Canadian Institute for Health Information, 2009; Dorsey, Rabbani, Gallagher, Conti, & Alexander, 2010; Kozyrskyj et al., 2009; Valiyeva, Herrmann, Rochon, Gill, & Anderson, 2008).

It is recommended that pharmacotherapy be used only when psychotic symptoms or agitation are persistent, recurrent, or cause clinically significant functional disruption (Jeste et al., 2008). In order to minimize adverse effects, it is recommended that the lowest possible effective dose of antipsychotics be use in conjunction with regular monitoring of efficacy, tolerability, and education of patients and caregivers (Gill et al., 2007; Jeste et al., 2008; Rochon, 2010; Schneider et al., 2005). The findings in this report suggest that prescribers in Manitoba are responding to warnings and are prescribing antipsychotics cautiously to their older patients. Only a minority (10.2%) of new users of antipsychotics were prescribed high doses within the first year of therapy. The dose intensity (DDDs per 1,000) of SGAs declined in community–dwelling and reached a plateau in PCH–dwelling residents after warnings about

their potential harm. We also noted that the proportion of new users of antipsychotics who were also prescribed acetylcholinesterase inhibitors (to treat Alzheimer's dementia) reached a plateau after Health Canada warnings were issued. The majority of PCH–dwelling older adults who were started on SGAs were initiated on these therapies after 29 days in the PCH, which suggests that prescriptions followed the assessment of patients' conditions after admission. Older adults were more likely to receive a high dose SGA within a year if they had dementia (use of an acetylcholinesterase inhibitor) or a diagnosis of psychosis, but less likely to receive a high dose SGA as age increased or if they had a greater number of different medications. This suggests that prescribers were less likely to use high dose SGA for more frail patients prone to drug interactions, but that they were likely to use high doses for individuals with more severe symptoms. This is consistent with literature which would suggest that advanced age (85 and older), polypharmacy, and multiple comorbidities can contribute to an increased likelihood of medication related adverse effects (Page, Linnebur, Bryant, & Ruscin, 2010), but that antipsychotics are frequently prescribed for older adults with psychosis or dementia symptoms (Hagen et al., 2005; Rochon, 2010).

The use of antipsychotics and benzodiazepines amongst older Manitobans, particularly those residing in a PCH, is not without concern. Numerous authors have called for caution in prescribing these agents to older adults (APA Practice Guidelines, 2009; Jeste et al., 2008; Rochon et al., 2007; Rochon et al., 2008; Rochon, 2010). It is likely that there are many older adults receiving these medications for good clinical reasons. It is also possible that there are many who are not. Without individual level clinical data, the appropriateness of the use of SGAs in older adults with and without dementia remains uncertain.

Strategies to encourage safer prescribing include medication reviews for important medication related issues such as: adverse effects; opportunities to decrease doses; use of safer alternatives; discontinuation of medications that are ineffective, unnecessary, or causing adverse effects; and using non–drug therapy wherever possible. Educating prescribers, caregivers, and patients is also recommended (Chen, Wynia, Moloney, & Alexander, 2009; Page et al., 2010; Rochon, 2010). Pharmacists can play an active role in the monitoring of individuals receiving these medications through conducting medication reviews and following patients for evidence of efficacy and toxicity (Castelino, Bajorek, & Chen, 2009; Marcum, Handler, Wright, & Hanlon, 2010; Verrue, Petrovic, Mehuys, Remon, & Vander, 2009). The ongoing utilization of antipsychotics in older adults, particularly those residing in personal care homes, is a subject worthy of further study.

Limitations to measures of optimal use of prescription medications using administrative data are important to consider. Limitations to this analysis include the fact that in Manitoba, up to 27% of PCHs do not have medications filled through community pharmacies (Doupe et al., 2006) and are, therefore, not captured in the DPIN system. This limits the generalizability of the results for PCH–dwelling Manitobans. Numerous clinical characteristics may indicate that medications such as high dose SGAs may be optimal therapy for a particular patient at a particular time with the appropriate monitoring and follow up. These clinical characteristics are not available through the type of administrative data used in this analysis. Formulary restrictions in various facilities or PCHs may have also influenced the prescribing of these agents. Other relevant factors to adverse effects experienced by older adults with prescriptions for psychotropic medications, such as over the counter antihistamines or alcohol use, are not captured with administrative data.

In summary, the use of SGAs and benzodiazepines/related medications in older adults in Manitoba is increasing; and it is especially high in residents of personal care homes despite recommendations to avoid these agents in individuals with dementia, whenever possible. By 2008/09, 25% of older adult PCH

residents received a prescription for a second generation antipsychotic (the most commonly used agent was risperidone). High dose SGAs are less than optimal due to an increased risk for dose related adverse effects, such as falls and movement disorders. From 2002/03–2007/08, only 10.2% of new users of SGAs received high doses of these agents. Within the first year of therapy users of high dose SGAs were younger, more likely to be male, have psychosis or dementia, and be taking fewer other medications. No prescriber or environment characteristics (including PCH environment and type of PCH) predicted this less than optimal prescribing.

Chapter 3: Medications for Diabetes Mellitus

Medications for the management of diabetes mellitus include insulin and oral anti–diabetic agents: metformin, sulfonylureas, the newer agents thiazolidenediones (hereafter, glitazones), meglitinides, and acarbose. Insulins are used to treat type 1 diabetes mellitus and both oral agents and insulins are used to treat type 2 diabetes mellitus (Canadian Diabetes Association, 2008). In Manitoba, the newer anti–diabetic agents (glitazones, meglitinides, and acarbose) were generally listed as Part 3 of the Manitoba Drug Benefits and Interchangeability Formulary (prior approval for specific prescribing criteria required for use) when they were first approved for reimbursement by Pharmacare. By the end of the study period (1997/98–2008/09), only pioglitazone and glimeperide remained as Part 3 benefits. The majority of other oral anti–diabetic agents were listed in the Part 1 (open listing) on the Manitoba Drug Benefits and Interchangeability Formulary. Of the newer long acting (basal) insulins, insulin glargine was listed as Part 3, and insulin detemir was not approved for listing. Both agents were not recommended for listing by the Common Drug Review of the Canadian Agency for Drugs and Technologies in Health (CADTH) (Canadian Agency for Drugs and Technologies in Health, 2009b; Canadian Agency for Drugs and Technologies in Health, 2006b). In 2008, criteria for use of insulin glargine per the Manitoba Drug Benefits and Interchangeability Formulary were "as an alternative agent (secondary to NPH and/or premix insulin at daily optimal dose) for individuals who have experienced unexplained nocturnal hypoglycemia at least once a month despite optimal management or who have documented severe or continuing systemic or local allergic reaction to existing insulin" (Manitoba Health, 2008). New rapid acting insulin analogues (lispro and aspart) were placed on Part 1 (open listing) of the Manitoba Pharmacare formulary after market launch. All other agents for the management of diabetes mellitus and blood glucose test strips were Part 1 (open listing) on the Manitoba Drug Benefits and Interchangeability Formulary.

Over the past decade, the treatment of diabetes mellitus has changed. Many new agents and medication classes have been marketed: glitazones, meglitinides, acarbose, long acting sulfonylureas, and new rapid and long acting (basal) insulins. The Canadian Diabetes Association guidelines in 2003 (and subsequent guidelines from 2008) recommended a practice shift away from a stepwise approach, towards a more aggressive treatment approach. These guidelines recommended that in individuals with poor control of diabetes mellitus, as indicated by a hemoglobin A_{1C} greater than 9%, two agents should be initiated (Canadian Diabetes Association, 2008). Both guidelines (2003 and 2008) aim for treatment goals of hemoglobin A_{1C} less than 7% within six to twelve months of diagnosis. In addition, metformin is recommended as a medication of first choice, particularly for obese individuals with type 2 diabetes mellitus, because evidence has demonstrated that treatment with this agent reduces diabetes mellitus related morbidity and mortality (Canadian Diabetes Association, 2008; UK Prospective Diabetes Study Group, 1998).

The evaluation of effectiveness of the new insulins has been surrounded by controversy (Canadian Diabetes Association, 2008). These agents were marketed as producing fewer adverse events, such as hypoglycemia, and allowing for better glucose control compared to the regular insulins. However, a recent CADTH's review of all the available literature concluded that the newer insulins, including basal and rapid acting insulins, should be considered as second line therapy based on minimal benefit and increased cost (Cameron & Bennett, 2009; Canadian Agency for Drugs and Technologies in Health, 2009d; Shea, 2009; Singh et al., 2009).

Recent literature has also evaluated the need for and cost–effectiveness of self–monitoring of blood glucose in individuals with diabetes mellitus managed with and without insulin (Cameron, Coyle, Ur, & Klarenbach, 2010a; Gomes, Juurlink, Shah, Paterson, & Mamdani, 2010; Shea, 2009). The necessity of ongoing self–monitoring of blood glucose also has been debated (Davidson, 2005; Ipp, Aquino, & Christenson, 2005; Rabi, Johnson, & Edwards, 2010; Woo, Cheng, Hanna, & Berard, 2010). CADTH recently recommended that the frequency of self–monitoring of blood glucose be individualized for individuals with type 1 diabetes mellitus, and that the maximum frequency of self–monitoring of blood glucose for most adults with type 2 diabetes mellitus be 14 times per week. The exceptions to these recommendations are individuals with multiple daily insulin injections, those newly initiated on insulin, those with a history of hypoglycemia, other individuals at increased risk of hypoglycemia, those experiencing acute illness or undergoing changes in pharmacotherapy or routine, those with poorly controlled or unstable blood glucose, or those who are pregnant. Additionally, CADTH suggested that for most adults with type 2 diabetes mellitus using either no medications or only oral anti–diabetic agents, the routine use of self–monitoring of blood glucose is not recommended. The exceptions to these recommendations are individuals receiving anti–diabetic agents associated with hypoglycemia (e.g., insulins or sulfonylureas), at increased risk of hypoglycemia, experiencing acute illness or undergoing changes in pharmacotherapy or routine, with poorly controlled or unstable blood glucose, and who are pregnant (Canadian Agency for Drugs and Technologies in Health, 2009c; Shea, 2009).

Since the use of more costly newer agents for diabetes mellitus (both oral anti–diabetic agents and insulins) and the use of test strips for self–monitoring of blood glucose have been the focus of recent controversy in the literature, we sought to describe utilization of these groups of medications and test strips among Manitobans.

Methods

Prevalent and incident utilization for the population of Manitoba was determined for the following medications: insulins, sulfonylureas, glitazones, metformin, meglitinides, and acarbose. Insulins were categorized as new (lispro, aspart, glargine, and detemir) or old (other). Oral anti–diabetic agents were categorized as new (glitazones, meglitinides, acarbose, and the new sulfonylureas (glimeperide)) or old (metformin and other sulfonylureas). Details about the medications included in these categories are presented in Appendix Table 1.1.

We also determined prevalent users and the utilization rates of test strips for diabetes mellitus.

Incident users were those users of a medication for diabetes mellitus who had not received any medication for diabetes mellitus in the one year prior to the year of interest. Incident users of diabetes test strips were those new users who had not received any test strips in the one year prior to their first prescription.

Prevalent and incident utilization is presented as prevalent and incident users per 1,000 for the overall adult population of Manitoba. Prevalent use was also expressed as defined daily dose (DDD) per 1,000 residents per day as a measure of intensity of use. The DDD is a technical unit of measurement that was developed to overcome the limitations of counting prescriptions, which can vary in quantity of medication per prescription (Merlo et al., 1996). The DDD standardizes the measure of medication utilization with and between medications and is useful to quantify medication use in a population. The DDD is the average daily dose per day for a medication dispensed for the main indication in usual practice. For each medication, a DDD is calculated by the World Health Organization Collaborating

Centre for Drug Statistics Methodology (World Health Organization, 2009). The DDD is only calculated for oral solid dosage forms. The intensity of use is presented as DDD per 1,000 population per day and as DDDs per user per day. The DDDs for the oral anti–diabetic agents evaluated are included in Appendix Table 1.1.

The influence of sociodemographic characteristics on prescribing over the entire study period (1997/98–2008/09) was conducted with generalized estimating equations. Regional analysis of medication utilization for the fiscal years 1998/99, 2003/04, and 2008/09 compared prevalent users (annual rates, adjusted for age, sex, and socioeconomic status) across five regions of Manitoba (Rural South, Mid, North, Winnipeg, and Brandon) and Manitoba overall.

Additionally, a separate analysis to examine the influence of sociodemographic characteristics on prescribing over the entire study period (1997/98–2008/09) was conducted with generalized estimating equation for the population of Manitoba with a diagnosis of diabetes mellitus. Diabetes mellitus was defined as either a) two or more physician visits or one hospitalization with a diagnosis of diabetes (ICD–9–CM: 250, ICD–10–CA: E10–E14) or b) one or more prescriptions to treat diabetes (Fransoo et al., 2009).

Optimal Use Evaluation

For incident utilization of medications for diabetes mellitus among adult Manitobans, we evaluated the following criteria:

- Proportion of incident users of medications for diabetes mellitus within each medication category and how this pattern of utilization changed over time (from 1997/98 through 2008/09). The use of metformin as the first medication for type 2 diabetes mellitus is considered optimal.
- For the prevalent utilization of test strips, we evaluated the number of test strips per person (test strip user) per day according to the type of medication for diabetes mellitus (from 1997/98 through 2008/09) including: insulin alone, insulin in combination with an oral anti–diabetic agent, anti–diabetic agents associated with hypoglycemia (meglitinides and sulfonylureas), other oral anti–diabetic agents (metformin, glitazones, and acarbose), and no medications for diabetes mellitus, for two age groups: 19–64 and 65 and older (Gomes et al., 2010). The use of fewer test strips in individuals taking no therapy or taking anti–diabetic agents not associated with hypoglycemia than in individuals receiving prescriptions for anti–diabetic agents associated with hypoglycemia would be optimal.
- We evaluated factors predictive of incident utilization (from 2002/03 through 2008/09) of a first prescription for any medication for diabetes mellitus being a new medication for diabetes mellitus (new insulins or new oral anti–diabetic agents) among adult Manitobans. The use of a first prescription for a new medication for diabetes mellitus is likely less than optimal for most individuals, as these medications are typically second line therapy. Sociodemographic factors included in the model were age, sex, region of residence, socioeconomic status, and being hospitalized within three days of the incident prescription. The number of different medications, number of major ADGs, and the number of ambulatory visits and hospitalizations for any reason in the year prior to the first prescription were also included. Prescriber characteristics included in the model were: hospital affiliation, location of training, years since licensure in Manitoba, type of reimbursement, and specialist status. We also included year of first prescription in the model. As time effects were likely important in changing prescribing patterns, only incident users of the medication of interest who initiated therapy in 2002/03 through 2008/09 were included in this model.

Results

A total of 802,794 Manitoba adults in 1997/98 and 859,108 in 2008/09 formed the denominator for this analysis.

Prevalence

Prevalent utilization of the older medications (metformin and the older sulfonylureas) was greatest over the study period (see Figure 3.1). At the beginning of the study period, metformin utilization was low (7.9 users per 1,000 residents); however, metformin was the most commonly utilized medication for diabetes mellitus by the end of the study period (44.6 users per 1,000 residents). Metformin was followed by sulfonylureas (increase from 18.0 to 25.5 users per 1,000 residents throughout the study period) and insulins (7.4 to 13.8 users per 1,000 residents). Despite initial Part 3 formulary listing (prior approval for specific prescribing criteria required for use), the utilization of glitazones increased from 0.4 users per 1,000 residents in mid 2000 to 10.2 users per 1,000 residents by the end of the 2006, but declined through 2009 to 6.1 users per 1,000 residents by the end of the study period. Utilization of other medications was minimal.

Prevalent utilization of diabetic test strips increased from 8.4 to 30.1 users per 1,000 residents by the end of the study period (see Figure 3.2).

The prevalent use of both older and newer agents increased over time: the prevalent use of older agents increased from 27.3 to 56.3 users per 1,000 residents while new agents increased from 0.7 to 18.2 users per 1,000 residents (see Figure 3.3).

A closer look at prevalent insulin utilization reveals that over the study period, prevalent use of older insulins increased from 7.4 to 10.5 users per 1,000 residents, while prevalent users of new insulins increased from 0.2 to 6.2 users per 1,000 residents (see Figure 3.4).

For all agents studied except newer insulins, there was greater prevalent utilization among those with lower as compared to higher socioeconomic status, rural as compared to urban location, and those aged 65–84 as compared to those aged 19–44, after adjustment for other factors (see Table 3.1).

Dose intensity

The dose intensity of metformin in the population of Manitoba adults increased over the study period, from 6.1 to 39.2 DDDs per 1,000 residents per day; while dose intensity of the sulfonylureas increased from 18.5 to 26.2 DDDs per 1,000 residents per day (see Figure 3.5).

Incidence

New prescribing of metformin increased from 0.3 to 1.9 users per 1,000 residents per quarter (see Figure 3.7). Incident use of suphonlyureas decreased from 1.1 to 0.4 users per 1,000 residents per quarter over the same period.

Incident utilization of blood glucose test strips increased from 2.0 to 6.0 users per 1,000 residents per quarter by the end of the study period (see Figure 3.8).

A closer look at incident insulin utilization reveals that over the study period, new use of older insulins decreased slightly from 0.13 to 0.11 new users per 1,000 residents per quarter, while that of new insulins increased from 0.01 to 0.06 new users per 1,000 residents per quarter (see Figure 3.9).

Sociodemographic characteristics

In analyses which control for other factors, we made some significant observations (see Table 3.2). For all agents studied, there was greater incident utilization among those with lower as compared to higher

socioeconomic status. There was greater incident utilization of all agents except newer insulin and meglitinides for rural locations as compared to urban locations. For all agents, except for insulin and combination insulin with oral therapy, there was greater incident utilization among individuals 65–84 than 19–44.

Regional Variation

When adjusted for age, sex, and socioeconomic status, the prevalent utilization of sulfonylureas in adults increased over the time period in the North, Winnipeg, and Manitoba overall (see Figure 3.10). Prevalent sulfonylureas use in the Mid and North regions were significantly greater than the Manitoba average at all three time periods.

When adjusted for age, sex, and socioeconomic status, the prevalent utilization of glitazones in adults demonstrated inconsistent regional variation (see Figure 3.11). Prevalent glitazone utilization in the Mid and North regions were significantly greater than the Manitoba average in 2003/04 and 2008/09. Prevalent glitazone utilization in Winnipeg was significantly lower than the Manitoba average in 2003/04 and 2008/09.

When adjusted for age, sex, and socioeconomic status, the prevalent utilization of metformin in adults increased over time in all regions of Manitoba (see Figure 3.12). Prevalent utilization of metformin in the North was significantly greater than the Manitoba average in all three years, and utilization in the Mid region was significantly greater than the Manitoba average in 1998/99 and 2008/09. Winnipeg demonstrated significantly lower utilization than the Manitoba average in 2003/04 and 2008/09.

When adjusted for age, sex, and socioeconomic status, the prevalent utilization of all insulins in adults increased over time in all regions of Manitoba (see Figure 3.13). Prevalent insulin use in Mid and North regions was significantly greater than the Manitoba average in all three years. Prevalent utilization of insulin in the Rural South was significantly lower than the Manitoba average in 2003/04 and 2008/09.

When adjusted for age, sex, and socioeconomic status, the prevalent utilization of all oral anti–diabetic agents in adults increased over the time period evaluated in all regions of Manitoba (see Figure 3.14). Prevalent utilization of all oral anti–diabetic agents in the North was significantly greater than the Manitoba average in all three years. Prevalent utilization of all oral anti–diabetic agents in the Rural South was significantly lower than the Manitoba average in 2003/04 and 2008/09.

When adjusted for age, sex, and socioeconomic status, the prevalent utilization of diabetic test strips in adults increased over the time period evaluated in all regions of Manitoba (see Figure 3.15). Prevalent utilization of diabetic test strips in the North and Mid regions of Manitoba was significantly greater than the Manitoba average in all three years. Prevalent utilization of diabetic test strips in Winnipeg was significantly lower than the Manitoba average in 2003/04 and 2008/09.

Manitobans with diabetes: Sociodemographic characteristics

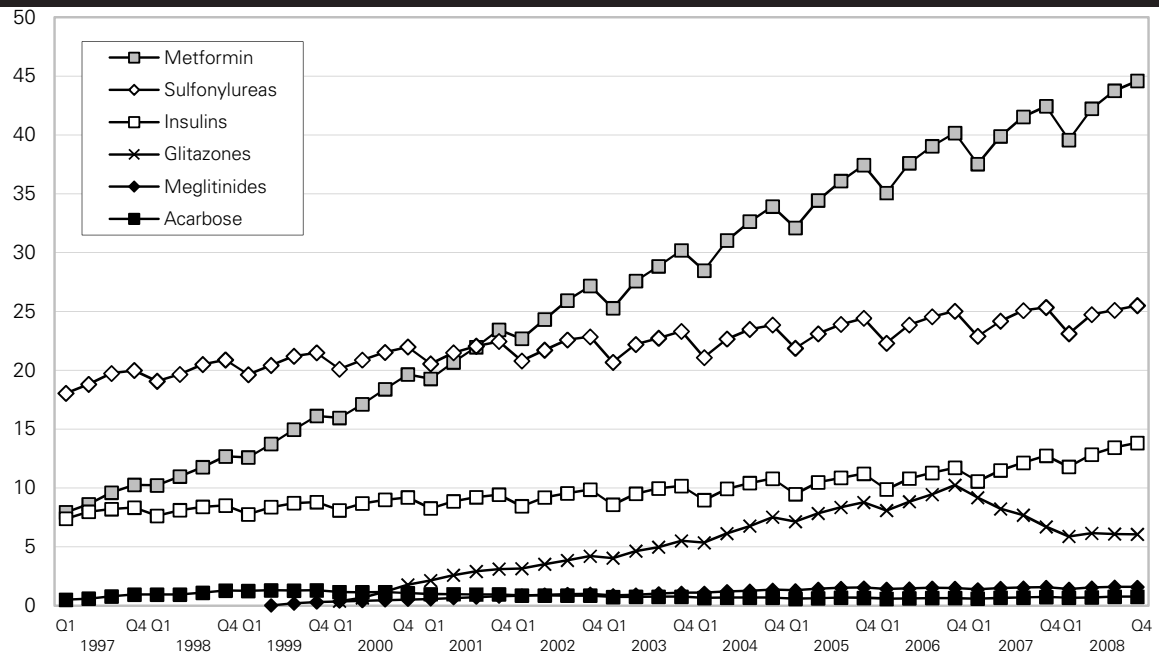
When the analysis of the effect of sociodemographic characteristics on utilization was restricted to individuals with a diagnosis of diabetes mellitus, which was defined as either a) two or more physician visits or one hospitalization with a diagnosis of diabetes (ICD–9–CM: 250, ICD–10–CA: E10–E14) or b) one or more prescriptions to treat diabetes (Fransoo et al., 2009), a total of 40,871 Manitoba adults in 1997/98 and 74,157 in 2008/09 formed the denominator for this analysis.

There was no large effect of socioeconomic status or region of residence on the prevalent utilization of most medications for diabetes mellitus (see Table 3.3). When other factors were controlled for, people with lower socioeconomic status had greater prevalent utilization of metformin, sulfonylureas, acarbose,

and insulin/oral agent combinations, but a lower use of newer insulins and diabetic test strips, than those with higher socioeconomic status. Except for insulins, there was greater prevalent utilization of medications for diabetes mellitus among individuals with diabetes mellitus aged 65–84 when compared to 19–44, when controlling for other factors. We did not observe a consistent effect for rural/urban location or sex.

When this analysis, which controls for other factors, was restricted to individuals with a diagnosis of diabetes mellitus, we did not see a significant effect of socioeconomic status on the incident utilization of most medications for diabetes mellitus, but there was greater incident utilization of sulfonylureas, older insulins, and insulin/oral agent combinations in those with lower socioeconomic status as compared to higher socioeconomic status (see Table 3.4). There was greater incident utilization of sulfonylureas, older insulins, glitazones, acarbose, and test strips in those residing in rural areas as compared to their urban counterparts. We also observed lower incident utilization of all medications and diabetic test strips among individuals with diabetes mellitus aged 65–84 when compared to 19–44.

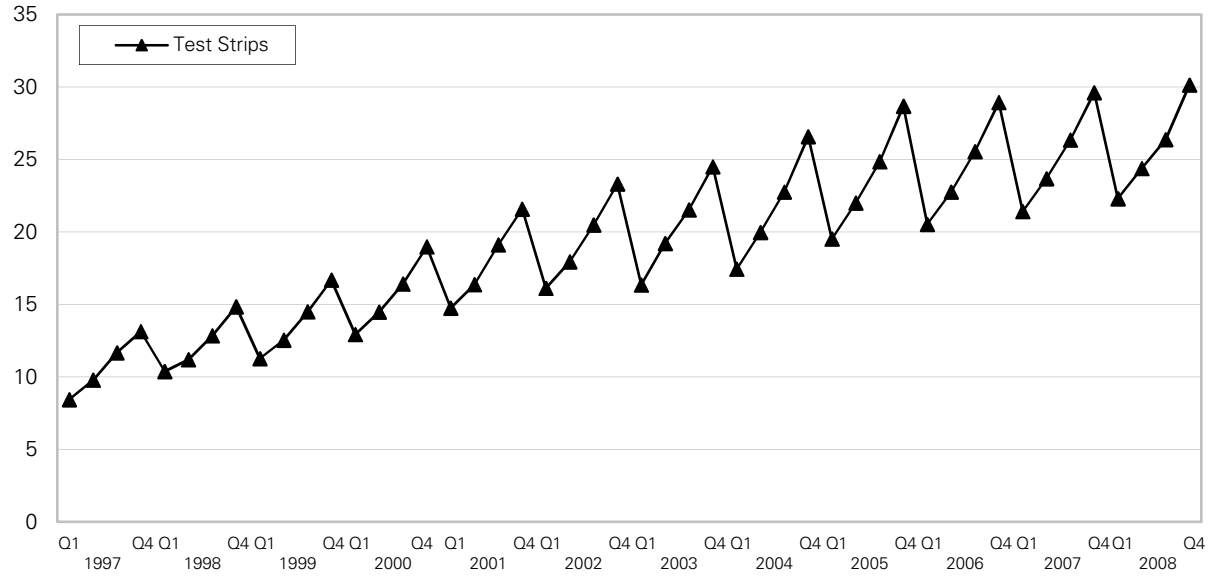
Figure 3.1: Medications for Diabetes Mellitus Quarterly Prevalence, Adults
Crude user rates per 1,000 adults, Q1 1997-Q4 2008



'Q1' indicates rates for the 1st quarter (April to June)
'Q4' indicates rates for the 4th quarter (January to March)
'Q2' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2010

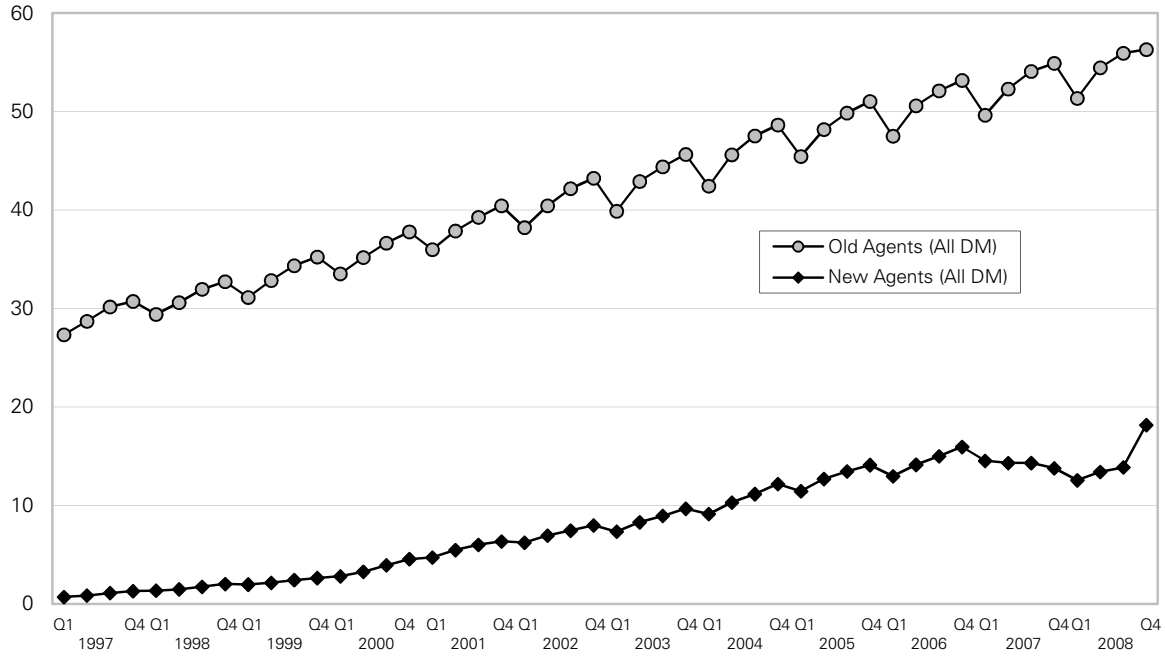
Figure 3.2: Test Strips for Diabetes Mellitus Quarterly Prevalence, Adults
Crude user rates per 1,000 adults, Q1 1997-Q4 2008



'Q1' indicates rates for the 1st quarter (April to June)
'Q4' indicates rates for the 4th quarter (January to March)
'Q2' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2010

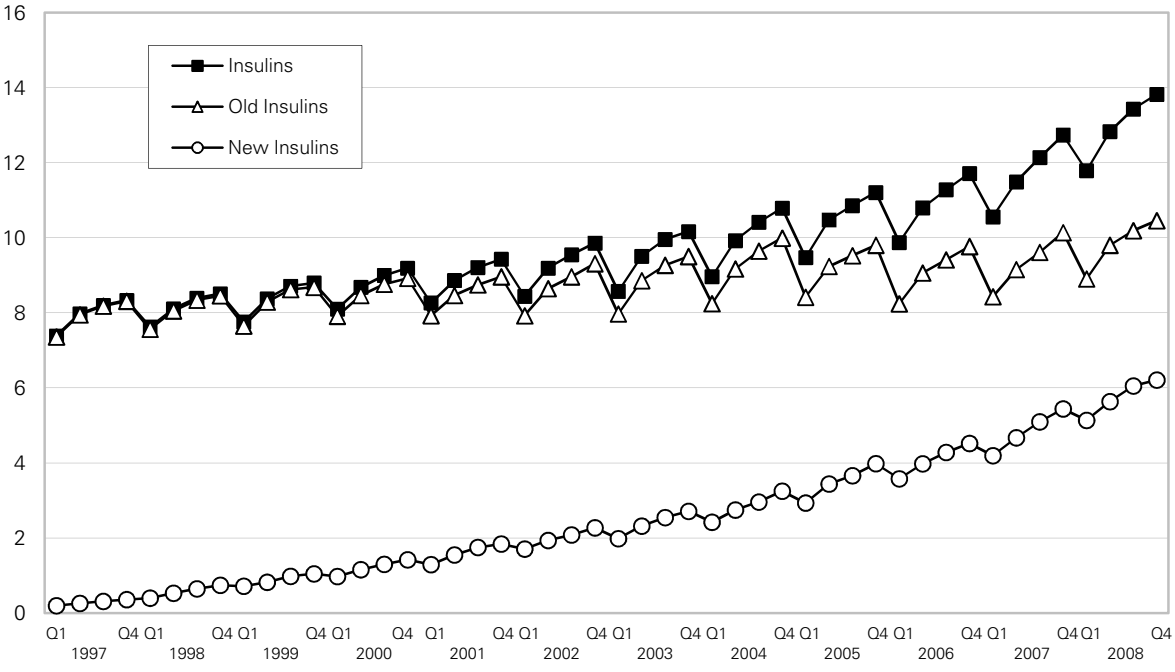
Figure 3.3: Medications for Diabetes Mellitus Quarterly Prevalence, Adults
Crude user rates per 1,000 adults, Q1 1997-Q4 2008



'Q1' indicates rates for the 1st quarter (April to June)
'Q4' indicates irates for the 4th quarter (January to March)
'Q2' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2010

Figure 3.4: Medications for Diabetes Mellitus Quarterly Prevalence, Adults
Crude user rates per 1,000 adults, Q1 1997-Q4 2008



'Q1' indicates rates for the 1st quarter (April to June)
'Q4' indicates rates for the 4th quarter (January to March)
'Q2' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2010

Table 3.1: Prevalent Use (Users/1,000 Residents) of Medications for Diabetes Among Adults, 1997/98 to 2008/09

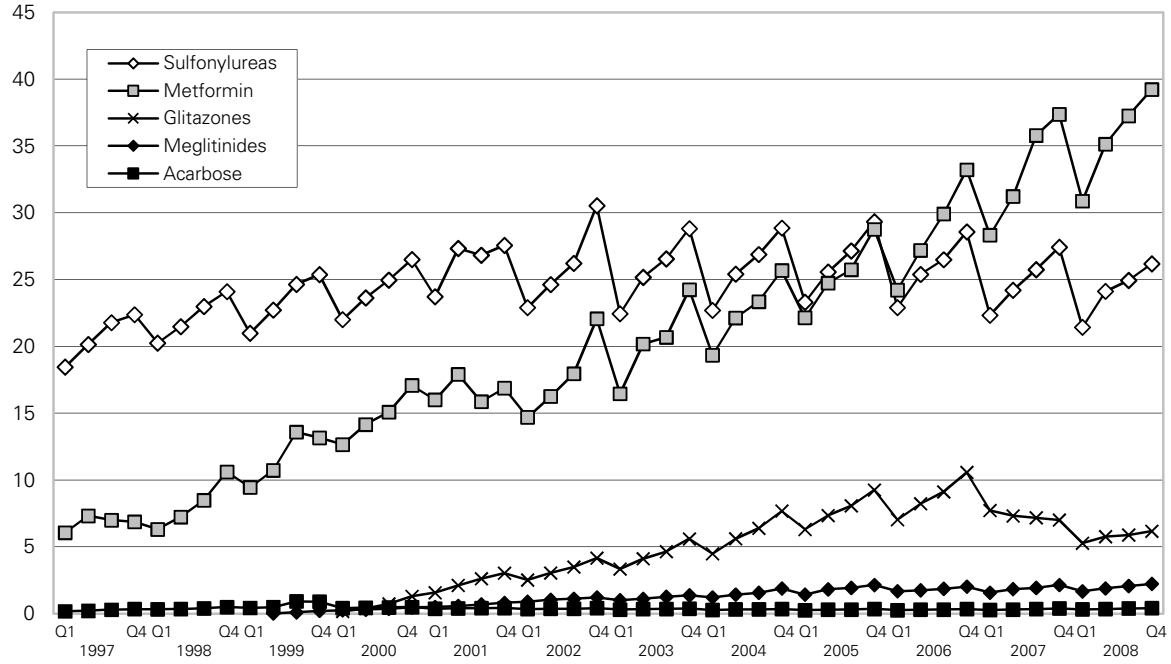
Medication or Group of Medications	1997Q1 users/1,000	2008Q4 users/1,000	Change in rate per quarter	Age effect 65-84 vs 19-44	Socioeconomic status Low vs High	Region effect Rural vs Urban	Sex effect Male vs Female
Metformin	7.93	44.59	1.04 4% increase*	10.21 1021% higher*	1.49 49% higher*	1.23 23% higher*	1.05 NS
Sulfonylureas	18.05	25.5	1 Slight increase*	15.3 1530% higher*	1.69 69% higher*	1.26 26% higher*	1.18 18% higher*
Insulins - older agents	7.36	10.46	1 Slight increase*	4.27 427% higher*	1.39 39% higher*	1.15 15% higher*	1.05 NS
Insulins - newer agents	0.2	6.21	1.07 7% increase*	0.87 NS	0.97 NS	1.1 NS	1.05 NS
Glitazones	0.38 2000Q1	6.06	1.05 5% increase*	9.93 993% higher*	1.53 53% higher*	1.57 57% higher*	1.1 NS
Meglitinides	0.03 1999Q2	1.58	1.04 4% increase*	11.74 1174% higher*	1.39 39% higher*	1.21 21% higher*	1 NS
Acarbose	0.51	0.76	0.99 1% decrease*	14.7 1470% higher*	1.77 77% higher*	1.24 24% higher*	1.02 NS
Combination - Insulin + oral	0.67	6.46	1.04 4% increase*	11.1 1110% higher*	1.65 65% higher*	1.17 17% higher	0.89 NS
Test strips	8.43	30.13	1.02 2% increase*	5.45 545% higher*	1.33 33% higher*	1.3 24% higher*	1 NS

*Indicates a statistically significant effect ($p<0.05$)

Note: Results for change in rate per quarter, age, socioeconomic status (SES), region, and sex effect are presented as relative rates (adjusted for age, SES, region, sex and time).

Source: Manitoba Centre for Health Policy 2010

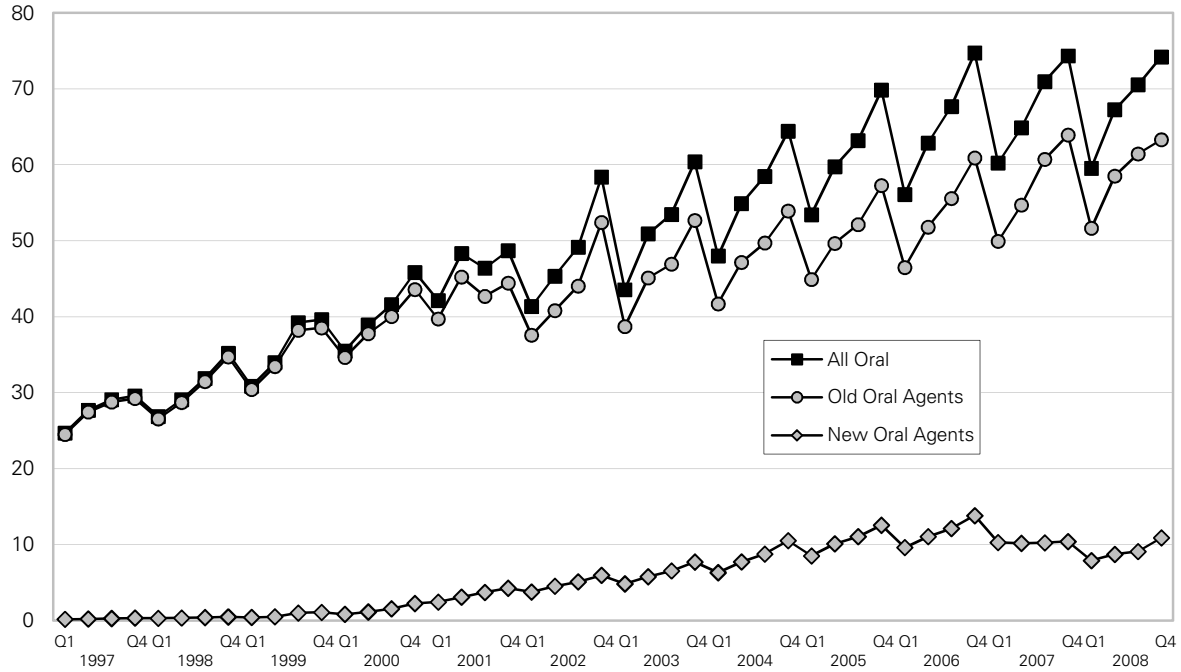
Figure 3.5: Dose Intensity of Medications for Diabetes by Quarter, Adults
Crude Defined Daily Dose rates per 1,000 adults, Q1 1997-Q4 2008



'Q1' indicates rates for the 1st quarter (April to June)
'Q4' indicates rates for the 4th quarter (January to March)
'Q2' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2010

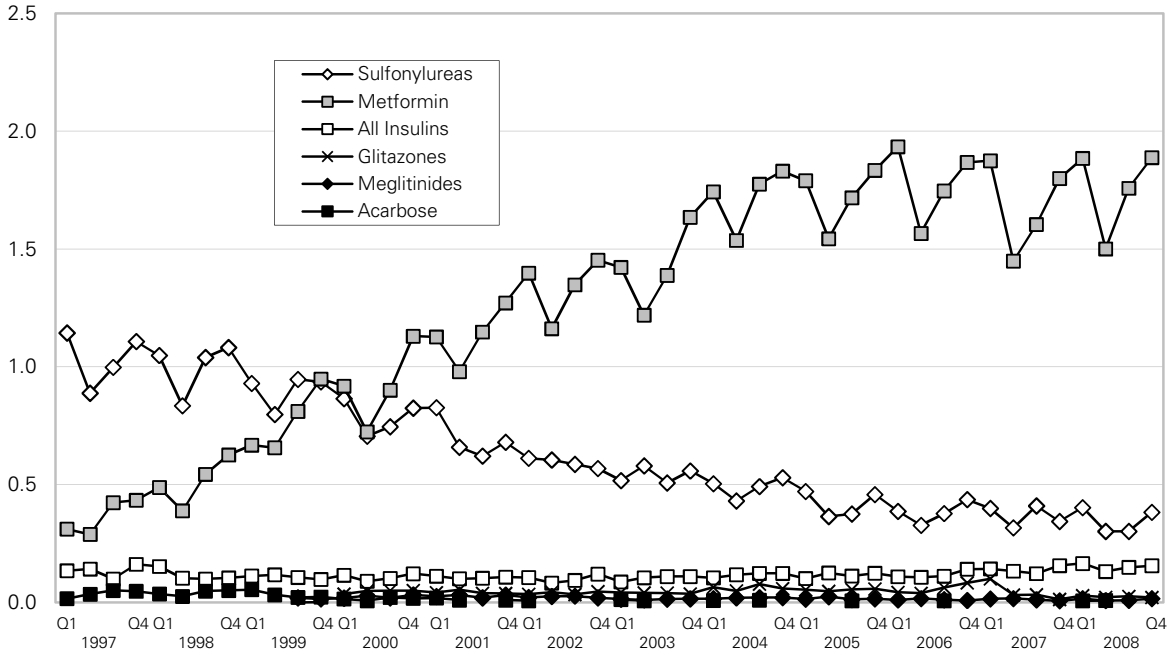
Figure 3.6: Dose Intensity of Medications for Diabetes by Quarter, Adults
Crude Defined Daily Dose rates per 1,000 adults, Q1 1997-Q4 2008



'Q1' indicates rates for the 1st quarter (April to June)
'Q4' indicates rates for the 4th quarter (January to March)
'Q2' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2010

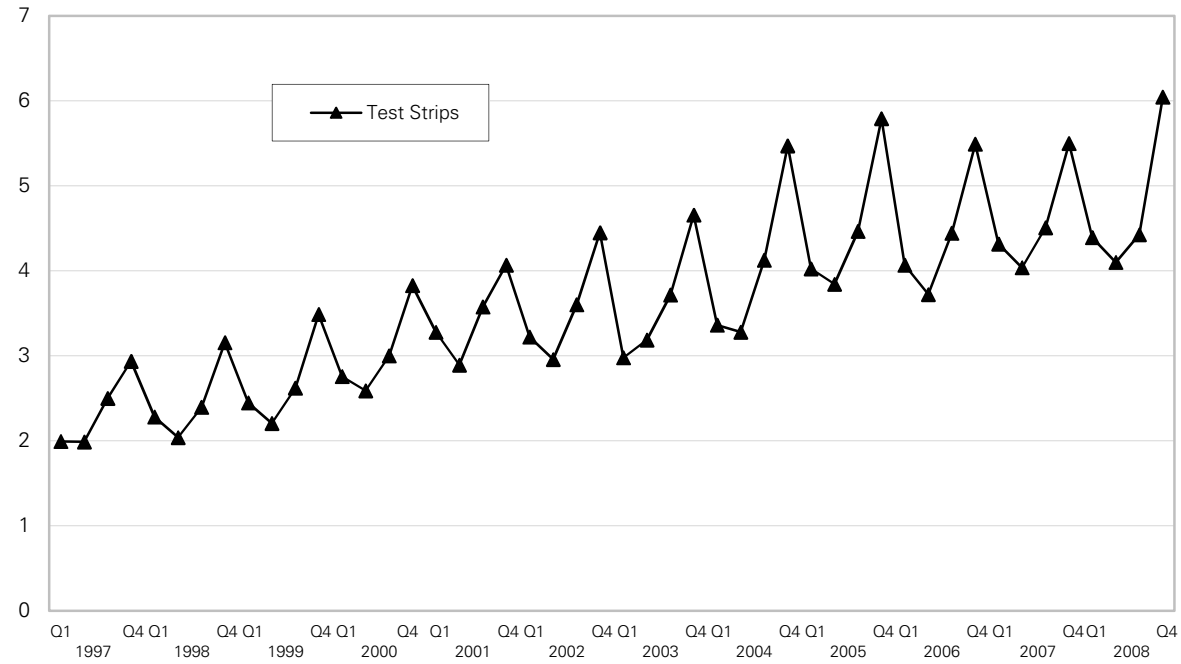
Figure 3.7: Medications for Diabetes Mellitus Quarterly Incidence, Adults
Crude rates of new users with no use of diabetes medications in prior year per 1,000 adults, Q1 1997-Q4 2008



'Q1' indicates rates for the 1st quarter (April to June)
'Q4' indicates rates for the 4th quarter (January to March)
'Q2' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2010

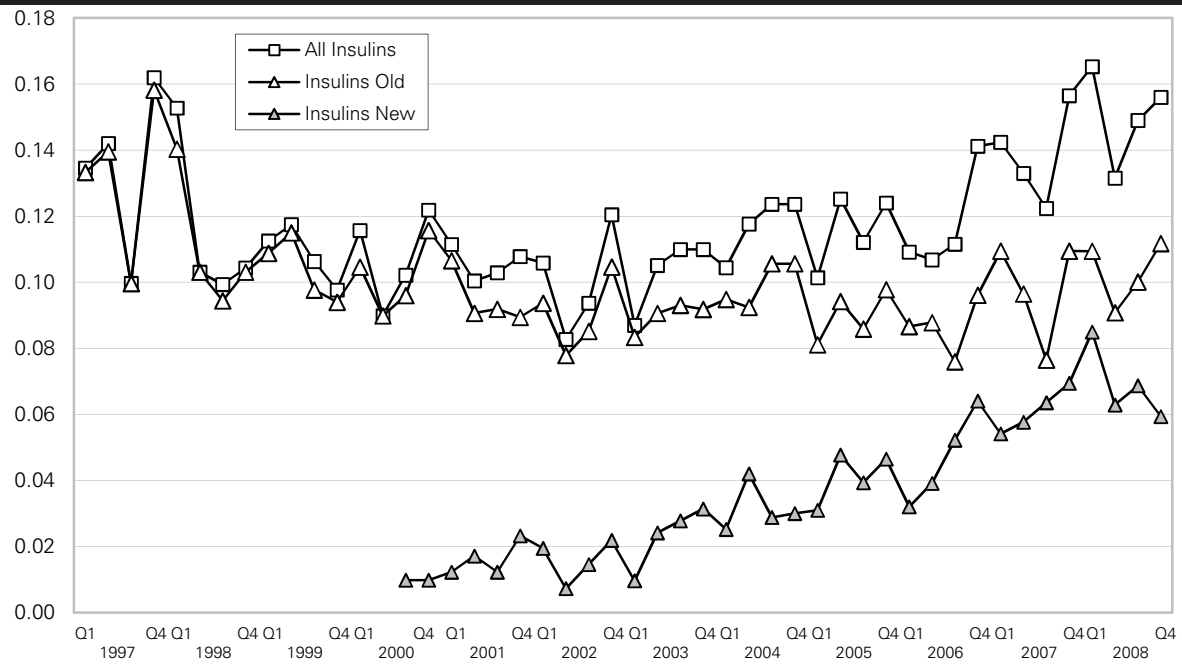
Figure 3.8: Test Strips for Diabetes Mellitus Quarterly Incidence, Adults
Crude rates of new users with no use of test strips in prior year per 1,000 adults, Q1 1997-Q4 2008



'Q1' indicates rates for the 1st quarter (April to June)
'Q4' indicates rates for the 4th quarter (January to March)
'Q2' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2010

Figure 3.9: Medications for Diabetes Mellitus Quarterly Incidence, Adults
Crude rates of new users with no use of diabetes medications in prior year per 1,000 adults, Q1 1997-Q4 2008



'Q1' indicates rates for the 1st quarter (April to June)
'Q4' indicates rates for the 4th quarter (January to March)
'Q2' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2010

Table 3.2: Incident Use (Users/1,000 Residents) of Medications for Diabetes among Adults, 1997/98 to 2008/09

Medication or Group of Medications	1997Q1 users/1,000	2008Q4 users/1,000	Change in rate per quarter	Age effect 65-84 vs 19-44	Socioeconomic status Low vs High	Region effect Rural vs Urban	Sex effect Male vs Female
Metformin	0.31	1.89	1.03 3% increase*	2.96 296% higher*	1.44 44% higher*	1.23 23% higher*	1.02 NS
Sulfonylureas	1.14	0.38	0.97 3% decrease*	4.96 496% higher*	1.86 86% higher*	1.31 31% higher*	1.38 38% higher*
Insulins - older agents	0.13	0.11	0.99 1% decrease*	0.82 NS	2.25 225% higher*	1.7 70% higher*	0.78 NS
Insulins - newer agents	0.01 1999Q3	0.06	1.07 7% increase*	0.26 74% lower*	1.54 54% higher*	1.04 NS	0.49 51% lower*
Glitazones	0.04 2000Q1	0.02	0.99 1% decrease*	3.21 321% higher*	1.4 40% higher	1.67 67% higher*	1.26 26% higher*
Meglitinides	0.02 1999Q3	0.02	0.98 2% decrease*	4.26 426% higher*	1.59 59% higher*	1.15 NS	1.21 NS
Acarbose	0.02	<0.01	0.93 7% decrease*	3.99 399% higher*	1.67 67% higher*	1.82 82% higher*	0.9 NS
Combination - Insulin + oral	0.01	0.05	1.03 3% increase*	1.12 NS	2.23 233% higher*	1.39 39% higher*	1.28 28% higher*
Test strips	1.99	6.04	1.02 2% increase*	4.88 488% higher*	1.37 37% higher*	1.33 33% higher%	1.08 NS

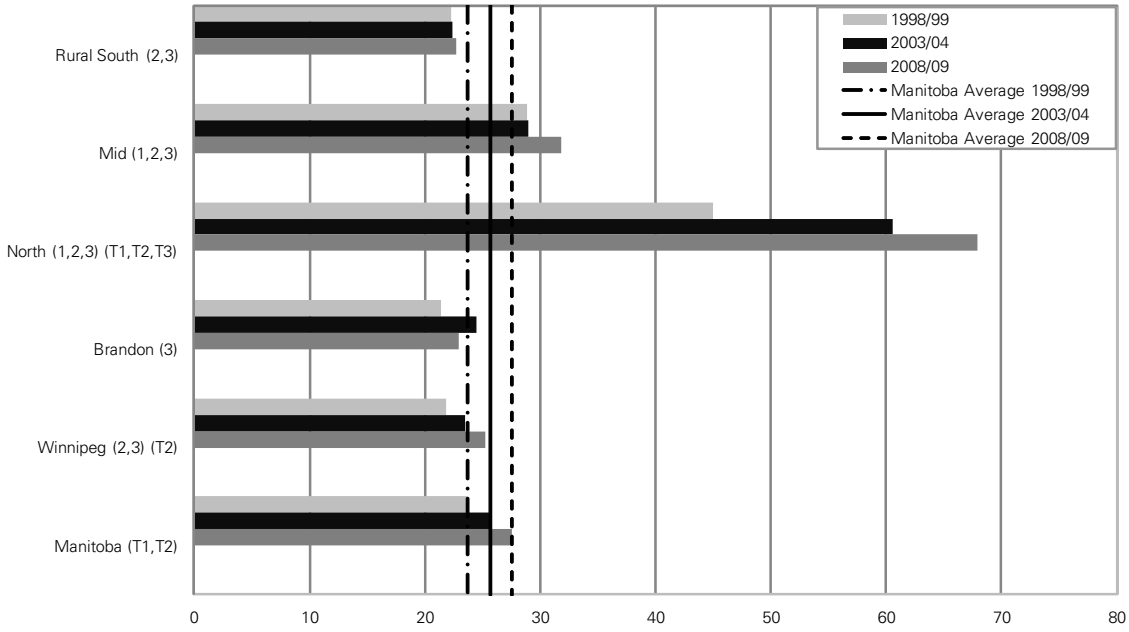
*Indicates a statistically significant effect ($p<0.05$)

Note: Results for change in rate per quarter, age, socioeconomic status (SES), region, and sex effect are presented as relative rates (adjusted for age, SES, region, sex and time).

Source: Manitoba Centre for Health Policy, 2010

Figure 3.10: Sulfonylureas Users per 1,000 Adults by Region

Adjusted by (2003/04) age, sex, and SES per 1,000 residents aged 18+

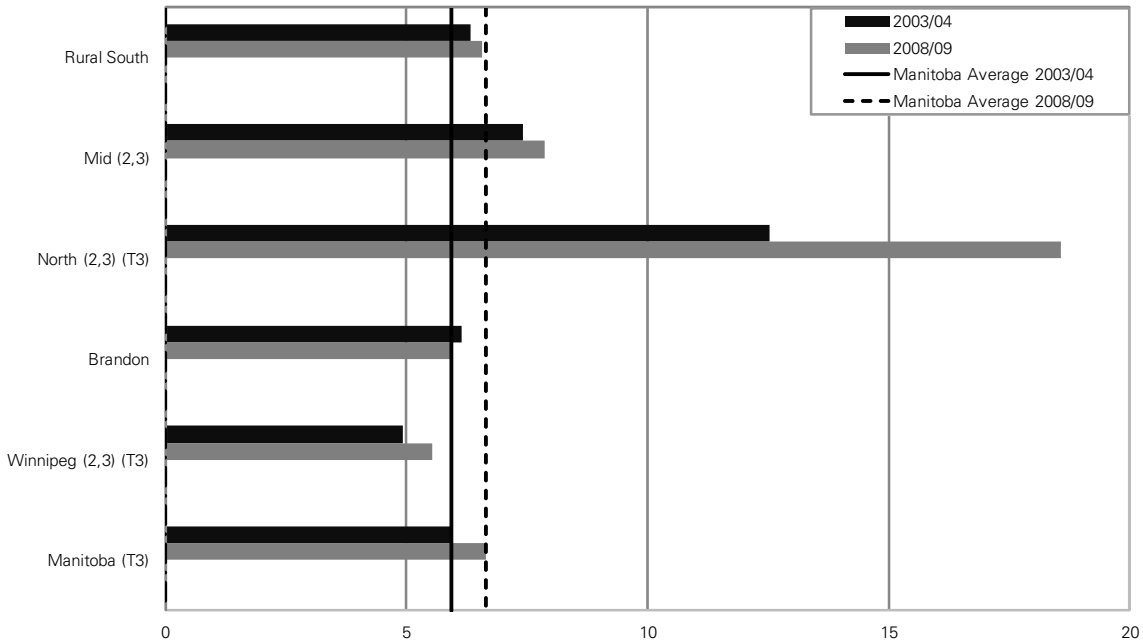


'1'- indicates area's rate was statistically different from Manitoba average in 1998/99.
'2'- indicates area's rate was statistically different from Manitoba average in 2003/04.
'3'- indicates area's rate was statistically different from Manitoba average in 2008/09.
'T1'- indicates change over time (1998/99 versus 2003/04) was statistically different for that area.
'T2'- indicates change over time (1998/99 versus 2008/09) was statistically different for that area.
'T3'- indicates change over time (2003/04 versus 2008/09) was statistically different for that area.

Source: Manitoba Centre for Health Policy, 2010

Figure 3.11: Glitazones Users per 1,000 Adults by Region

Adjusted by (2003/04) age, sex, and SES per 1,000 residents aged 18+

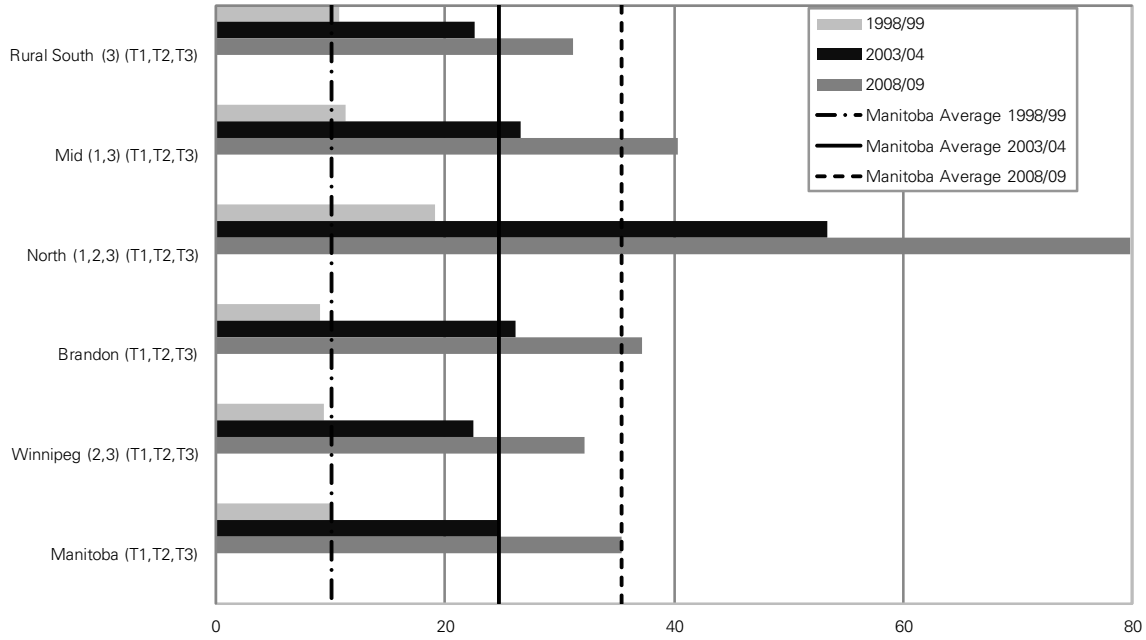


'1'- indicates area's rate was statistically different from Manitoba average in 1998/99.
'2'- indicates area's rate was statistically different from Manitoba average in 2003/04.
'3'- indicates area's rate was statistically different from Manitoba average in 2008/09.
'T1'- indicates change over time (1998/99 versus 2003/04) was statistically different for that area.
'T2'- indicates change over time (1998/99 versus 2008/09) was statistically different for that area.
'T3'- indicates change over time (2003/04 versus 2008/09) was statistically different for that area.

Source: Manitoba Centre for Health Policy, 2010

Figure 3.12: Metformin Users per 1,000 Adults by Region

Adjusted by (2003/04) age, sex, and SES per 1,000 residents aged 18+

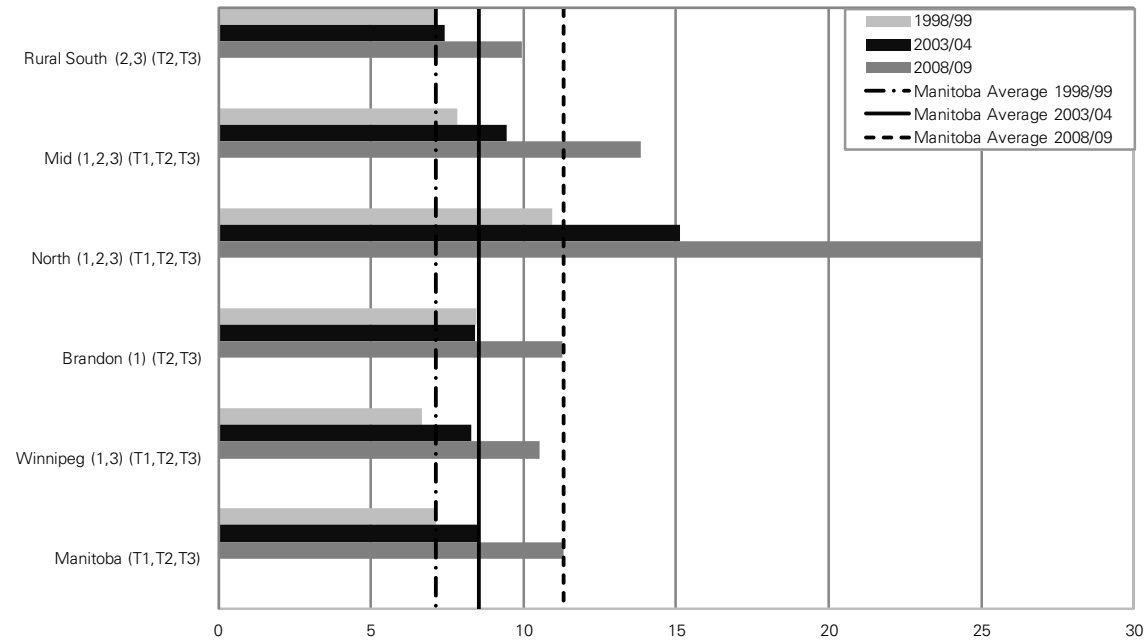


'1'- indicates area's rate was statistically different from Manitoba average in 1998/99.
'2'- indicates area's rate was statistically different from Manitoba average in 2003/04.
'3'- indicates area's rate was statistically different from Manitoba average in 2008/09.
'T1'- indicates change over time (1998/99 versus 2003/04) was statistically different for that area.
'T2'- indicates change over time (1998/99 versus 2008/09) was statistically different for that area.
'T3'- indicates change over time (2003/04 versus 2008/09) was statistically different for that area.

Source: Manitoba Centre for Health Policy, 2010

Figure 3.13: All Insulin Users per 1,000 Adults by Region

Adjusted by (2003/04) age, sex, and SES per 1,000 residents aged 18+

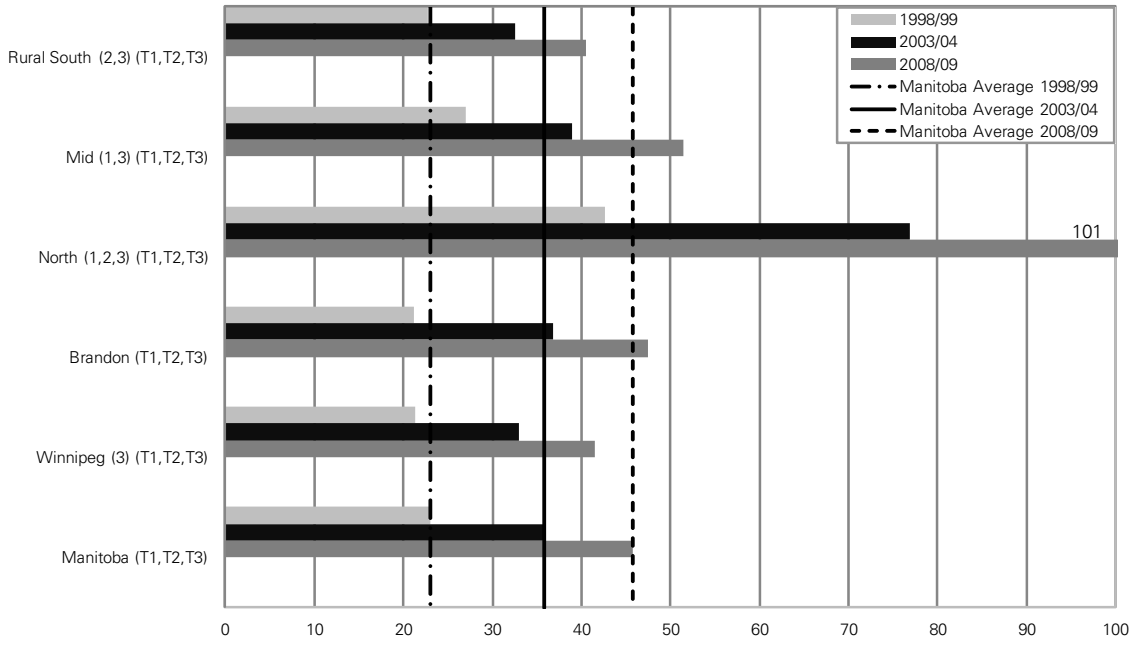


'1'- indicates area's rate was statistically different from Manitoba average in 1998/99.
'2'- indicates area's rate was statistically different from Manitoba average in 2003/04.
'3'- indicates area's rate was statistically different from Manitoba average in 2008/09.
'T1'- indicates change over time (1998/99 versus 2003/04) was statistically different for that area.
'T2'- indicates change over time (1998/99 versus 2008/09) was statistically different for that area.
'T3'- indicates change over time (2003/04 versus 2008/09) was statistically different for that area.

Source: Manitoba Centre for Health Policy, 2010

Figure 3.14: All Oral Drugs for Diabetes Users per 1,000 Adults by Region

Adjusted by (2003/04) age, sex, and SES per 1,000 residents aged 18+

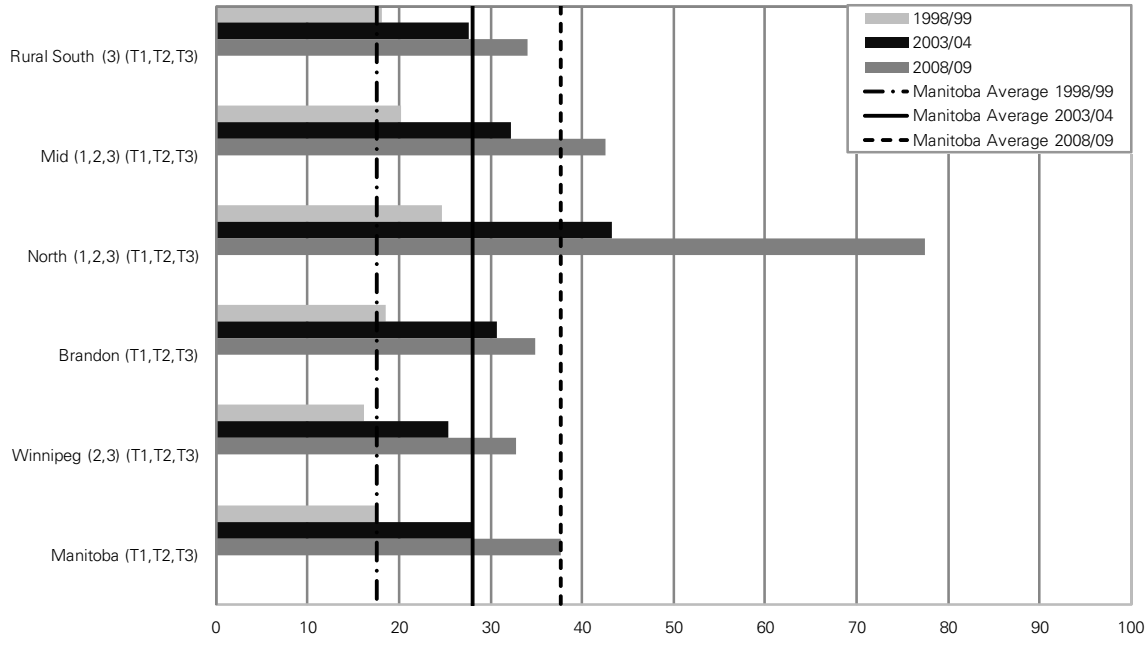


'1'- indicates area's rate was statistically different from Manitoba average in 1998/99.
'2'- indicates area's rate was statistically different from Manitoba average in 2003/04.
'3'- indicates area's rate was statistically different from Manitoba average in 2008/09.
'T1'- indicates change over time (1998/99 versus 2003/04) was statistically different for that area.
'T2'- indicates change over time (1998/99 versus 2008/09) was statistically different for that area.
'T3'- indicates change over time (2003/04 versus 2008/09) was statistically different for that area.

Source: Manitoba Centre for Health Policy, 2010

Figure 3.15: Test Strips Users per 1,000 Adults by Region

Adjusted by (2003/04) age, sex, and SES per 1,000 residents aged 18+



'1'- indicates area's rate was statistically different from Manitoba average in 1998/99.
'2'- indicates area's rate was statistically different from Manitoba average in 2003/04.
'3'- indicates area's rate was statistically different from Manitoba average in 2008/09.
'T1'- indicates change over time (1998/99 versus 2003/04) was statistically different for that area.
'T2'- indicates change over time (1998/99 versus 2008/09) was statistically different for that area.
'T3'- indicates change over time (2003/04 versus 2008/09) was statistically different for that area.

Source: Manitoba Centre for Health Policy, 2010

Table 3.3: Prevalent Use (Users/1,000 Residents) of Medications for Diabetes Among Adults with Diabetes 1997/98 to 2008/09

Medication or Group of Medications	1997Q1 users/1,000	2008Q4 users/1,000	Change in rate per quarter	Age effect 65-84 vs 19-44	Socioeconomic status Low vs High	Region effect Rural vs Urban	Sex effect Male vs Female
Metformin	154.78	512.72	1.02 2% increase*	1.41 41% higher*	1.05 5% higher*	1.05 5% higher*	0.97 NS
Sulfonylureas	352.16	293.49	0.99 1% decrease*	2.2 220% higher*	1.19 19% higher*	1.08 8% higher*	1.1 10% higher*
Insulins - older agents	143.3	120.47	0.99 1% decrease*	0.58 42% lower*	0.93 NS	0.98 NS	1 NS
Insulins - newer agents	3.72	71.48	1.06 6% increase*	0.12 88% lower*	0.63 37% lower*	0.92 NS	1.03 NS
Glitazones	6.31 2000Q1	69.87	1.04 4% higher*	1.43 43% higher*	1.06 NS	1.37 37% higher*	1.03 NS
Meglitinides	0.48 1999Q2	18.25	1.03 3% increase*	1.69 69% higher*	0.96 NS	1.06 NS	0.92 8% lower*
Acarbose	9.88	8.75	0.98 2% decrease*	2.03 202% higher*	1.22 22% higher*	1.06 NS	0.93 NS
Combination - Insulin + oral	12.94	74.42	1.03 3% increase*	1.58 58% higher*	1.12 12% higher*	1 NS	0.83 17% lower*
Test strips	157.91	327.06	1.01 1% Increase*	1.0915 NS	0.92 8% lower*	1.02 NS	0.97 NS

*Indicates a statistically significant effect ($p<0.05$)

Note: In this report, diabetes mellitus was defined as either a) two or more physician visits or one hospitalization with a diagnosis of diabetes (ICD-9-CM: 250, ICD-10-CA: E10-E14); or b) one or more prescriptions to treat diabetes

Note: Results for change in rate per quarter, age, socioeconomic status (SES), region, and sex effect are presented as relative rates (adjusted for age, SES, region, sex and time).

Source: Manitoba Centre for Health Policy 2010

Table 3.4: Incident Use (Users/1,000 Residents) of Medications for Diabetes among Adults with Diabetes 1997/98 to 2008/09

Medication or Group of Medications	1997Q1 users/1,000	2008Q4 users/1,000	Change in rate per quarter	Age effect 65-84 vs 19-44	Socioeconomic status Low vs High	Region effect Rural vs Urban	Sex effect Male vs Female
Metformin	6.12	24.47	1.02 2% increase*	0.42 58% lower*	0.96 NS	1.04 NS	0.98 NS
Sulfonylureas	22.24	4.38	0.96 4% decrease*	0.66 34% lower*	1.27 27% higher*	1.12 12* higher*	1.28 28% higher*
Insulins - older agents	2.57	1.28	0.98 2% decrease*	0.12 88% lower*	1.38 38% higher*	1.37 37% higher*	0.79 21% lower*
Insulins - newer agents	0.15 1999Q3	0.69	1.05 5% increase	0.04 96% lower	0.89 NS	0.80 NS	0.61 39% lower*
Glitazones	0.57 2000Q1	0.24	0.98 2% decrease*	0.45 55% lower*	0.91 NS	1.44 44% higher*	1.17 17% higher*
Meglitinides	0.35 1999Q3	0.19	0.97 3% decrease*	0.60 40% lower	1.08 NS	1.00 NS	1.11 NS
Acarbose	0.32	0.09	0.92 8% decrease*	0.57 43% lower*	1.08 NS	1.53 53% higher*	0.85 NS
Combination - Insulin + oral	0.20	0.53	1.02 2% increase*	0.16 84% lower*	1.40 40% higher*	1.14 NS	1.31 31% higher*
Test strips	35.21	59.78	1.00 Slight increase*	0.83 17% lower*	0.97 NS	1.07 7% higher*	1.07 7% higher*

*Indicates a statistically significant effect ($p<0.05$)

Note: In this report, diabetes mellitus was defined as either a) two or more physician visits or one hospitalization with a diagnosis of diabetes (ICD-9-CM: 250, ICD-10-CA: E10-E14); or b) one or more prescriptions to treat diabetes

Note: Results for change in rate per quarter, age, socioeconomic status (SES), region, and sex effect are presented as relative rates (adjusted for age, SES, region, sex and time).

Source: Manitoba Centre for Health Policy, 2010

Optimal Use Evaluation

The optimal first medication for type 2 diabetes mellitus is metformin (Canadian Diabetes Association, 2008). The proportion of incident users of medications for diabetes mellitus initiated on metformin increased dramatically over the study period, from 23.9% in 1997/98 to 82.2% in 2008/09 (see Figure 3.16).

The mean number of test strips per test strip user increased in each category of user over time (see Tables 3.5 and 3.6). As the likelihood of hypoglycemia increased, the number of test strips per user per day increased.

The distribution of test strips per test strip user in each year increased across each category of user over time; however, more than 25% of strip users used fewer than 100 strips per year, and fewer than 10% of strip users used more than 1,000 strips per year (see Figures 3.17 and 3.18).

For the population of test strip users who used only insulin, over 30% of those aged 19–64 in 2003/04 and 2008/09 used more than 1,000 strips per year, whereas over 20% of those aged 65 and older used more than 1,000 strips per year in those years (see Figures 3.19 and 3.20).

For the population of test strip users who used insulin in combination with other medications for diabetes mellitus, more than 10% in both age categories in 2003/04 and 2008/09 used more than 1,000 strips per year (see Figures 3.21 and 3.22).

For the population of test strip users who used anti–diabetic agents associated with hypoglycemia for diabetes mellitus, over 30% of those aged 19–64 and over 20% of those aged 65 and older used fewer than 100 strips per year (see Figure 3.23 and 3.24).

For the population of test strip users who used other oral anti–diabetic agents not associated with hypoglycemia, over 30% used fewer than 100 strips per year (see Figure 3.25 and 3.26).

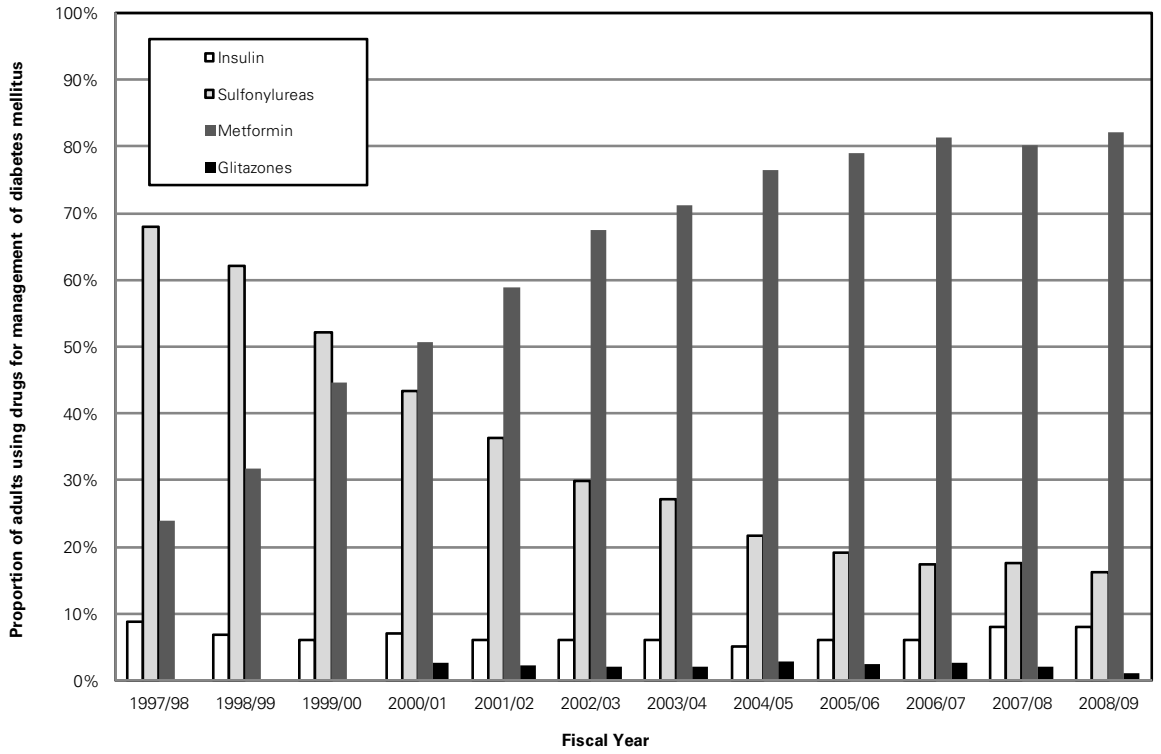
For the population of test strip users who only used test strips but no medications (diet controlled), over 40% used fewer than 100 strips per year (see Figure 3.27 and 3.28).

From 2002/03 through 2008/09, there were 42,586 incident users of medications for diabetes mellitus among adult Manitobans, and they were included in the model. Of these, 1,485 (3.5%) were started on a new anti–diabetic agent (glitazones, meglitinides, glimeperide, or acarbose) or a new insulin (lispro, aspart, glargine, or detemir) as a first prescription for the treatment of diabetes mellitus (outcome variable). A total of 2.75% were excluded from the model because missing values for some variable.

Age, region of residence, number of ambulatory visits, number of hospitalizations for any reason, and being hospitalized for any reason within three days of the incident prescription influenced the likelihood of receiving a new anti–diabetic agents as a first prescription (see Table 3.7). Adult Manitobans were more likely to receive a new anti–diabetic agents as a first prescription if they lived in a rural location or had more ambulatory visits and hospitalizations as compared to incident users of older medication. Adult Manitobans were less likely to receive a new anti–diabetic agents as a first prescription as age increased or if they were hospitalized just before the incident prescription.

Type of physician reimbursement, specialist status, and years since licensure in Manitoba significantly influenced the likelihood of receiving a new anti–diabetic agent as a first prescription for a diabetes mellitus medication. Fee–for–services physicians were more likely to initiate a new medication for diabetes mellitus as a first prescription for a diabetes mellitus medication. As the number of years since licensure in Manitoba increased, a prescriber was more likely to initiate a new medication as a first prescription for a diabetes medication; but general practitioner status resulted in less likelihood to prescribe a new anti–diabetic agent.

Figure 3.16: Proportion of New Users of Drugs for Diabetes Management by Type of Therapy and Year
Crude proportion among adults using drugs for management of diabetes mellitus, 1997/98-2008/09



Source: Manitoba Centre for Health Policy, 2010

Table 3.5: Use of Blood Glucose Test Strips by Medication for Management of Diabetes, Aged 19-64
Crude counts of test strip use for adults aged 19-64

Medication category	Fiscal year	Medication users	% of total users	Medication users with test strips	% of medication users with test strips	% of total test strip users	Total test strips dispensed	% of total test strips dispensed	Significant change (2008/07 vs 1997/98)	Test strips per day (for test strip users) user per day Mean (95% CI)
Insulin	1997/98	3,937	22.6	2,749	69.8	28.5	1,461,525	51.9	p<0.05	1.46 (1.39, 1.52)
	2008/09	4,402	11.6	3,650	82.9	15.1	3,331,208	33.3		2.50 (2.42, 2.58)
Insulin / oral combination	1997/98	746	4.3	619	83.0	6.4	244,927	8.7	p<0.05	1.08 (0.99, 1.18)
	2008/09	4,669	12.3	3,928	84.1	16.3	2,201,800	22.0		1.54 (1.49, 1.58)
Anti-diabetic agents associated with Hypoglycemia	1997/98	9,251	53.2	3,726	40.3	38.6	725,650	25.8	p<0.05	0.53 (0.51, 0.56)
	2008/09	12,429	32.6	6,903	55.5	28.6	2,084,255	20.8		0.83 (0.81, 0.85)
Other anti-diabetic agents	1997/98	1,480	8.5	578	39.1	6.0	106,075	3.8	p<0.05	0.50 (0.45, 0.56)
	2008/09	12,755	33.5	5,830	45.7	24.2	1,570,058	15.7		0.74 (0.72, 0.76)
Only test strip user	1997/98	1,986	11.4	1,986	100.0	20.6	278,175	9.9	p<0.05	0.38 (0.36, 0.41)
	2008/09	3,821	10.0	3,821	100.0	15.8	824,500	8.2		0.59 (0.57, 0.61)
Total	1997/98	17,400	100.0	9,658	55.5	100.0	2,816,352	100.0	p<0.05	0.80 (0.78, 0.82)
	2008/09	38,076	100.0	24,132	63.4	100.0	10,011,821	100.0		1.14 (1.12, 1.15)

*Insulin = at least 1 prescription for insulin with no other drug for diabetes
Insulin combo = at least 1 rx for insulin plus at least 1 rx for another drug for diabetes
Anti-diabetic agents associated with Hypoglycemia = at least 1 rx for meglitindes or sulfonylureas but no insulin
Other anti-diabetic agents = metformin, thiazolidenediones, acarbose but no insulin or other anti-diabetic agents associated with Hypoglycemia
Only test strip user = No glucose lowering drug therapy

Source: Manitoba Centre for Health Policy, 2010

Table 3.6: Use of Blood Glucose Test Strips by Medication for Management of Diabetes, Aged 65+

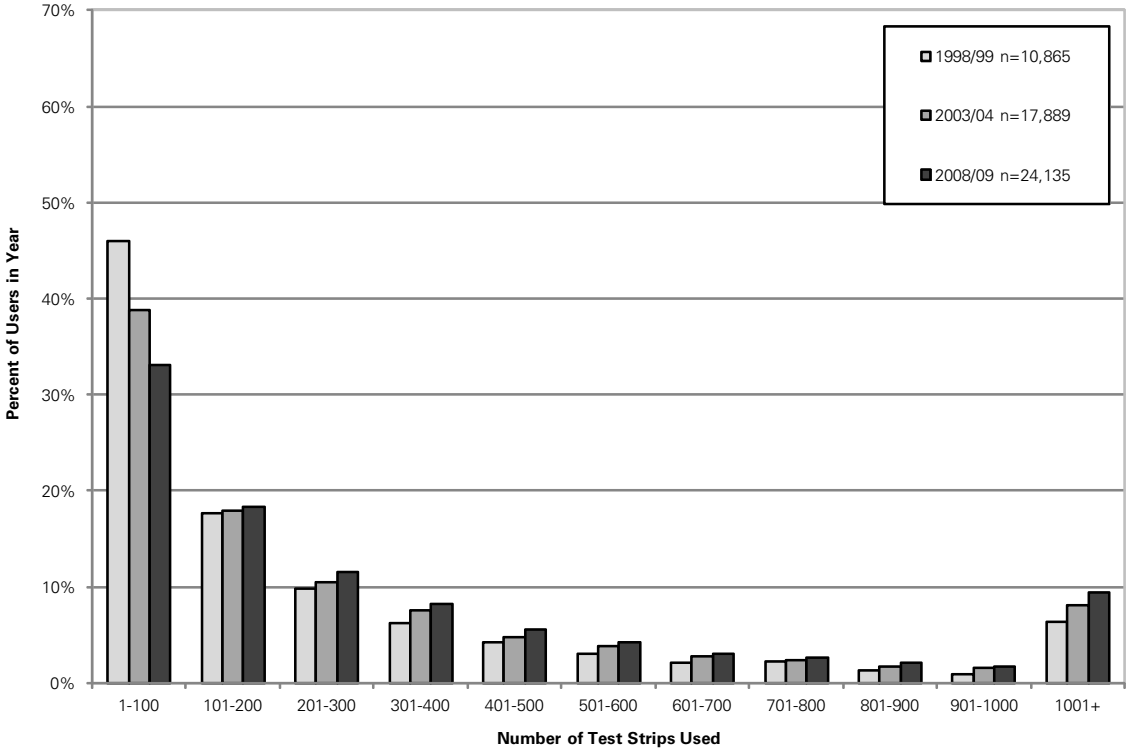
Crude counts of test strip use for adults aged 65 and older

Medication category	Fiscal year	Medication users	% of total users	Medication users with test strips	% of medication users with test strips	% of total test strip users	Total test strips dispensed	% of total test strips dispensed	Significant change (2008/07 vs 1997/98)	Test Strips per day (for test strip users) user per day Mean (95% CI)
Insulin	1997/98	2,104	15.0	1,552	73.8	22.8	680,900	38.3	p<0.05	1.20 (1.14, 1.26)
	2008/09	1,859	7.1	1,568	84.4	9.1	1,326,073	19.1		2.32 (2.23, 2.40)
Insulin / oral combination	1997/98	581	4.2	485	83.5	7.1	207,275	11.7	p<0.05	1.17 (1.08, 1.26)
	2008/09	2,655	10.1	2,306	86.9	13.4	1,477,876	21.2		1.76 (1.70, 1.81)
Anti-diabetic agents associated with Hypoglycemia	1997/98	9,301	66.4	3,341	35.9	49.2	671,400	37.8	p<0.05	0.55 (0.53, 0.57)
	2008/09	10,398	39.7	6,319	60.8	36.8	2,255,664	32.4		0.98 (0.96, 1.00)
Other anti-diabetic agents	1997/98	906	6.5	300	33.1	4.4	54,126	3.0	p<0.05	0.49 (0.42, 0.57)
	2008/09	8,619	32.9	4,292	49.8	25.0	1,260,180	18.1		0.80 (0.78, 0.83)
Only test strip user	1997/98	1,120	8.0	1,120	100.0	16.5	163,925	9.2	p<0.05	0.40 (0.37, 0.43)
	2008/09	2,670	10.2	2,670	100.0	15.6	642,375	9.2		0.66 (0.63, 0.68)
Total	1997/98	14,012	100.0	6,798	48.5	100.0	1,777,626	100.0	p<0.05	0.72 (0.69, 0.74)
	2008/09	26,201	100.0	17,155	65.5	100.0	6,962,168	100.0		1.11 (1.10, 1.13)

*Insulin = at least 1 prescription for insulin with no other drug for diabetes
Insulin combo = at least 1 rx for insulin plus at least 1 rx for another drug for diabetes
Anti-diabetic agents associated with Hypoglycemia = at least 1 rx for meglitindes or sulfonylureas but no insulin
Other anti-diabetic agents = metformin, thiazolidenediones, acarbose but no insulin or other anti-diabetic agents associated with Hypoglycemia
Only test strip user = No glucose lowering drug therapy

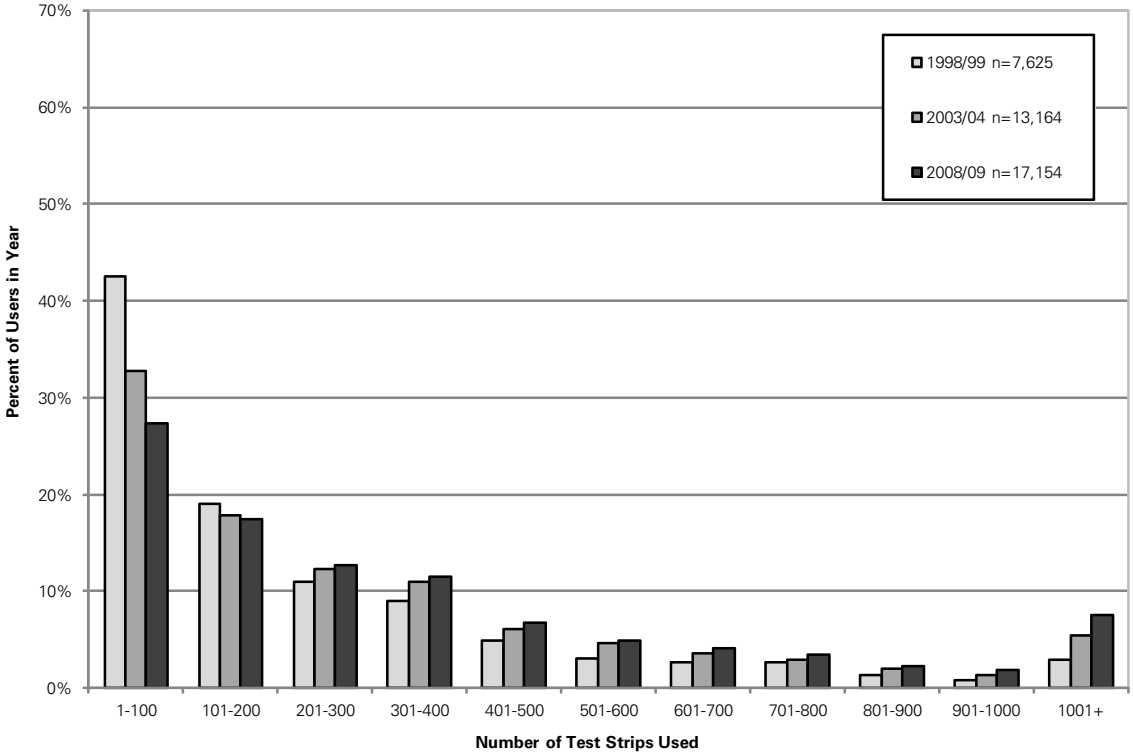
Source: Manitoba Centre for Health Policy, 2010

Figure 3.17: Frequency of Test Strips per Year for All Test Strip Users, Aged 19-64
Crude percent of users by number of test strips used



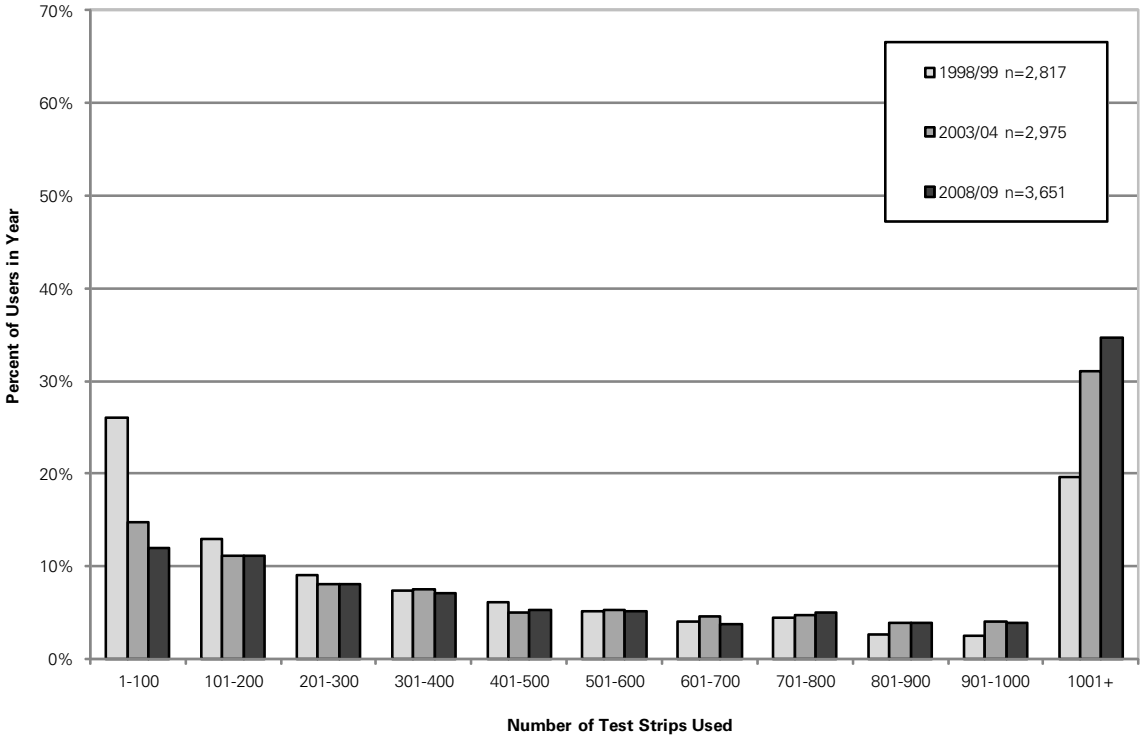
Source: Manitoba Centre for Health Policy, 2010

Figure 3.18: Frequency of Test Strips per Year for All Test Strip Users, Aged 65+
Crude percent of users by number of test strips used



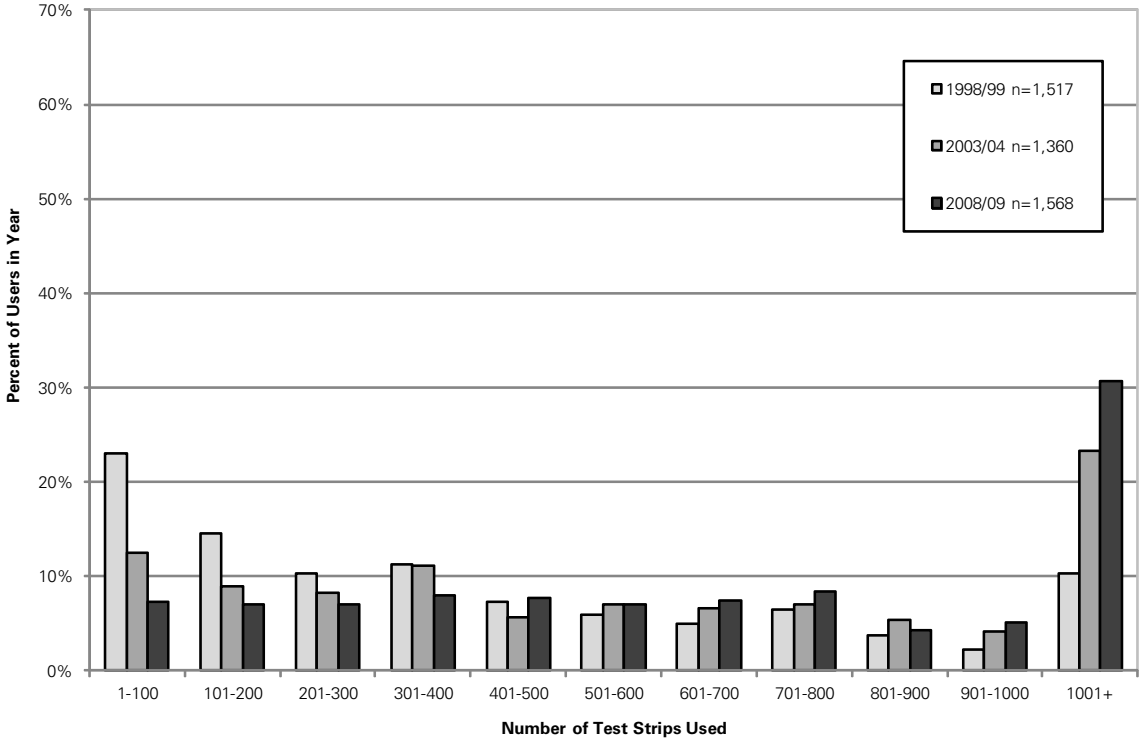
Source: Manitoba Centre for Health Policy, 2010

Figure 3.19: Frequency of Test Strips per Year for Insulin Users With No Other Diabetes Management Drug, Aged 19-64
Crude percent of users by number of test strips used



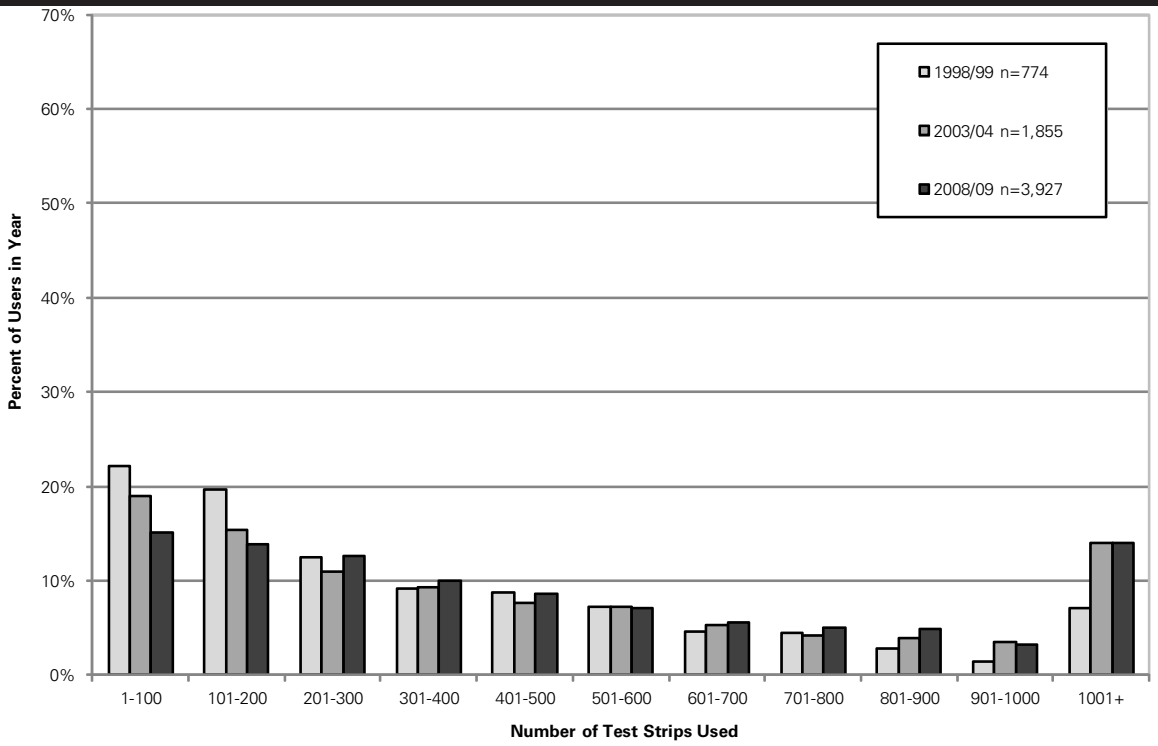
Source: Manitoba Centre for Health Policy, 2010

Figure 3.20: Frequency of Test Strips per Year for Insulin Users With No Other Diabetes Management Drug, Aged 65+
Crude percent of users by number of test strips used



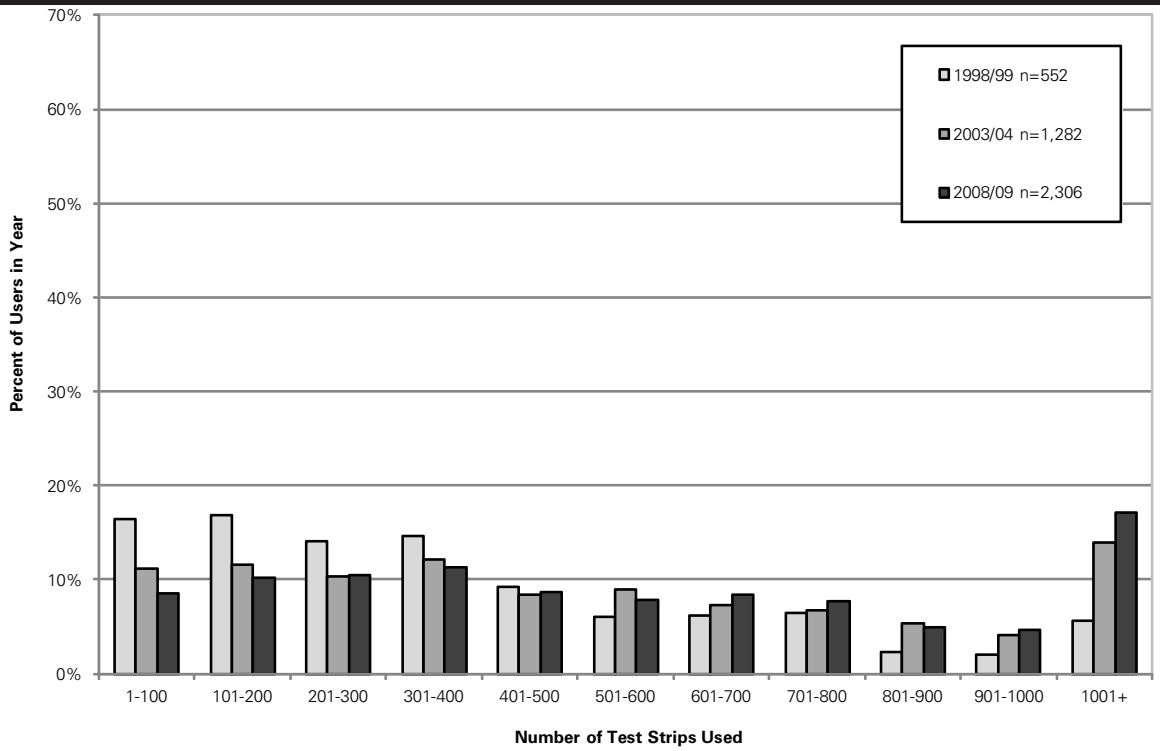
Source: Manitoba Centre for Health Policy, 2010

Figure 3.21: Frequency of Test Strips per Year for Insulin Users With Other Medications for Diabetes, Aged 19-64
Crude percent of users by number of test strips used



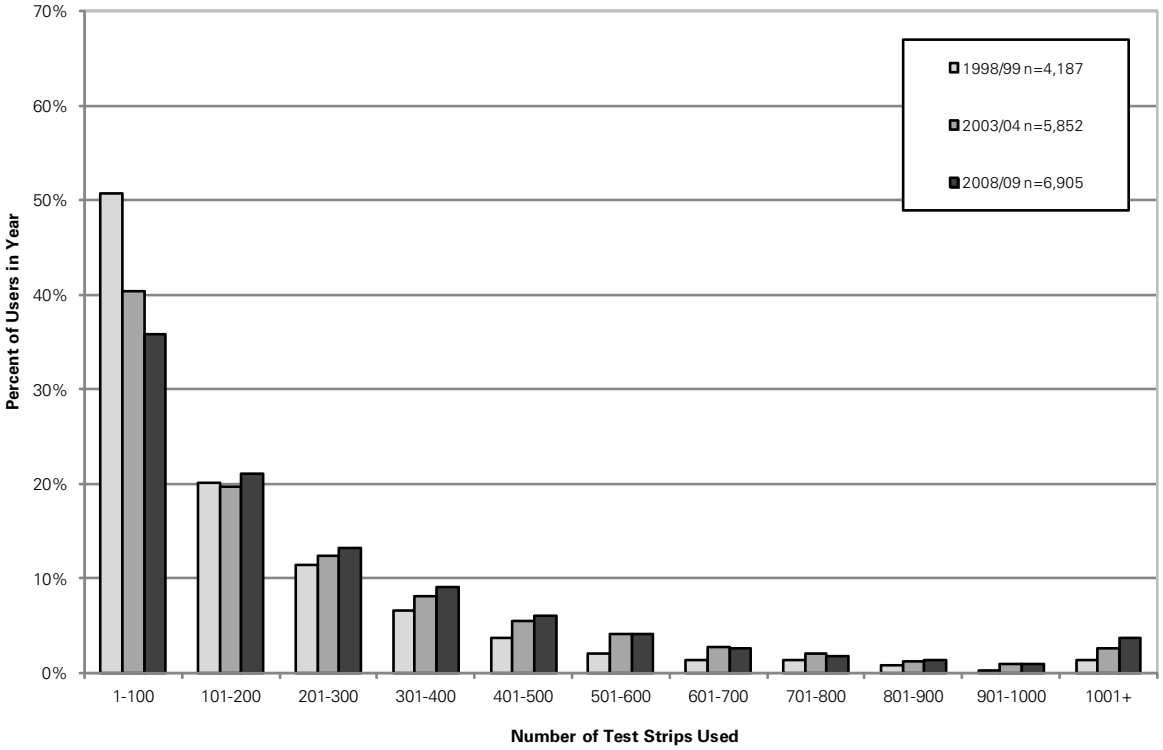
Source: Manitoba Centre for Health Policy, 2010

Figure 3.22: Frequency of Test Strips per Year for Insulin Users With Other Medications for Diabetes, Aged 65+
Crude percent of users by number of test strips used



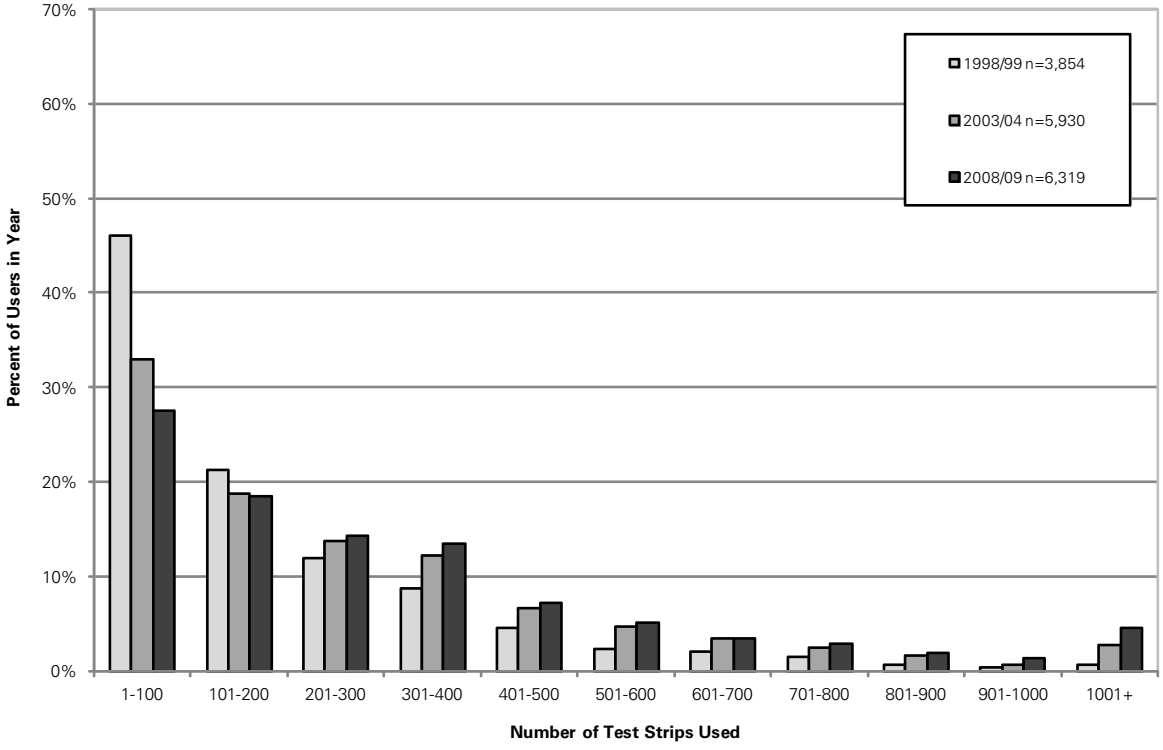
Source: Manitoba Centre for Health Policy, 2010

Figure 3.23: Frequency of Test Strips per Year for Users of Anti-Diabetic Agents Associated with Hypoglycemia (meglitinide or sulfonylurea, no insulin), Aged 19-64
Crude percent of users by number of test strips used



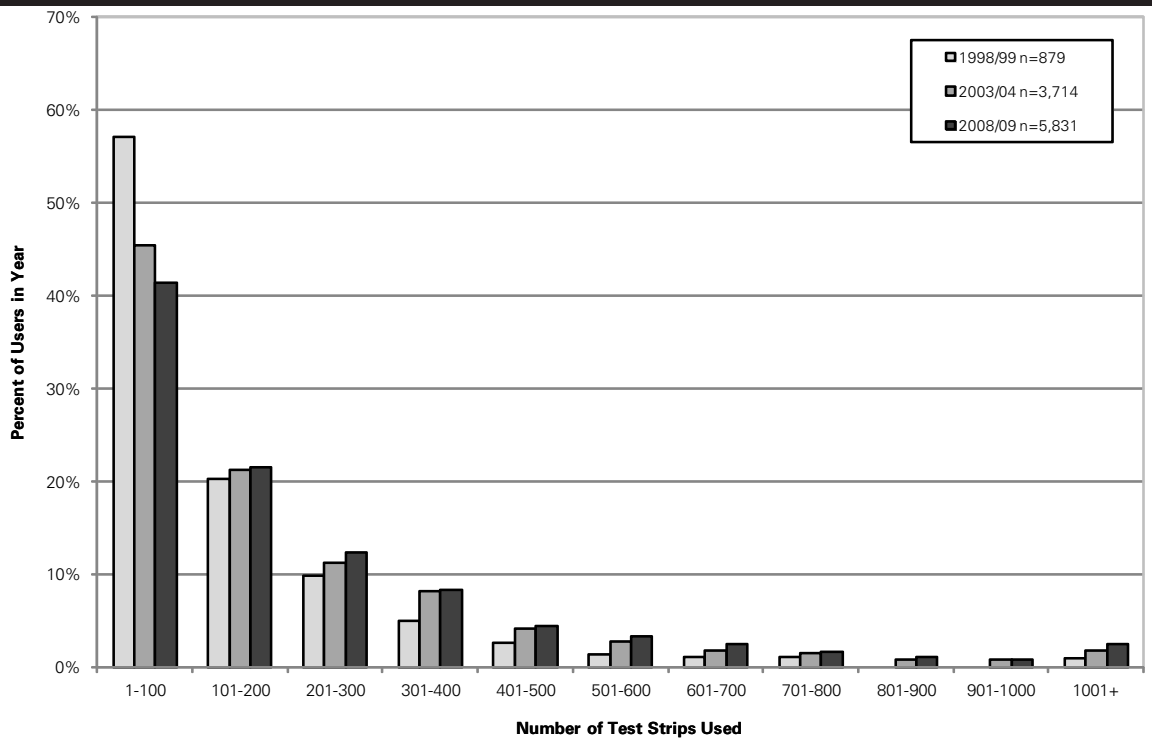
Source: Manitoba Centre for Health Policy, 2010

Figure 3.24: Frequency of Test Strips per Year for Users of Anti-Diabetic Agents Associated with Hypoglycemia (meglitinide or sulfonylurea, no insulin), Aged 65+
Crude percent of users by number of test strips used



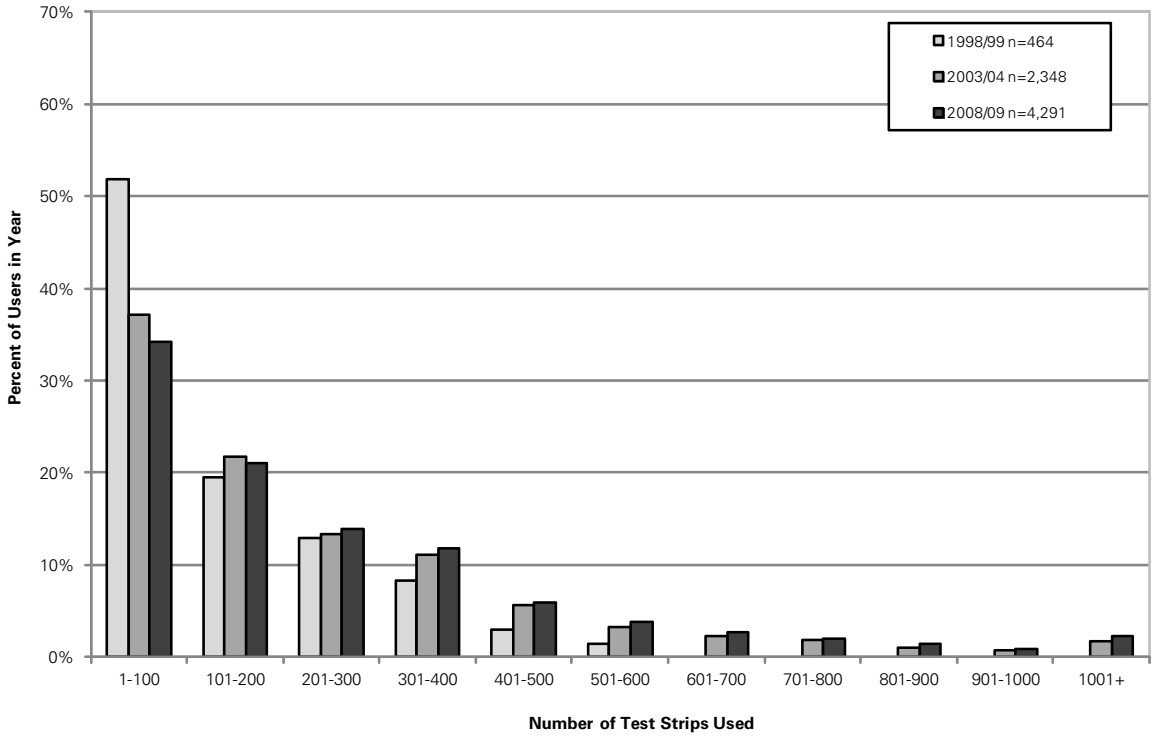
Source: Manitoba Centre for Health Policy, 2010

Figure 3.25: Frequency of Test Strips per Year for Users of Other Anti-Diabetic Agents (metformin, glitazones acarbose), Aged 19-64
Crude percent of users by number of test strips used



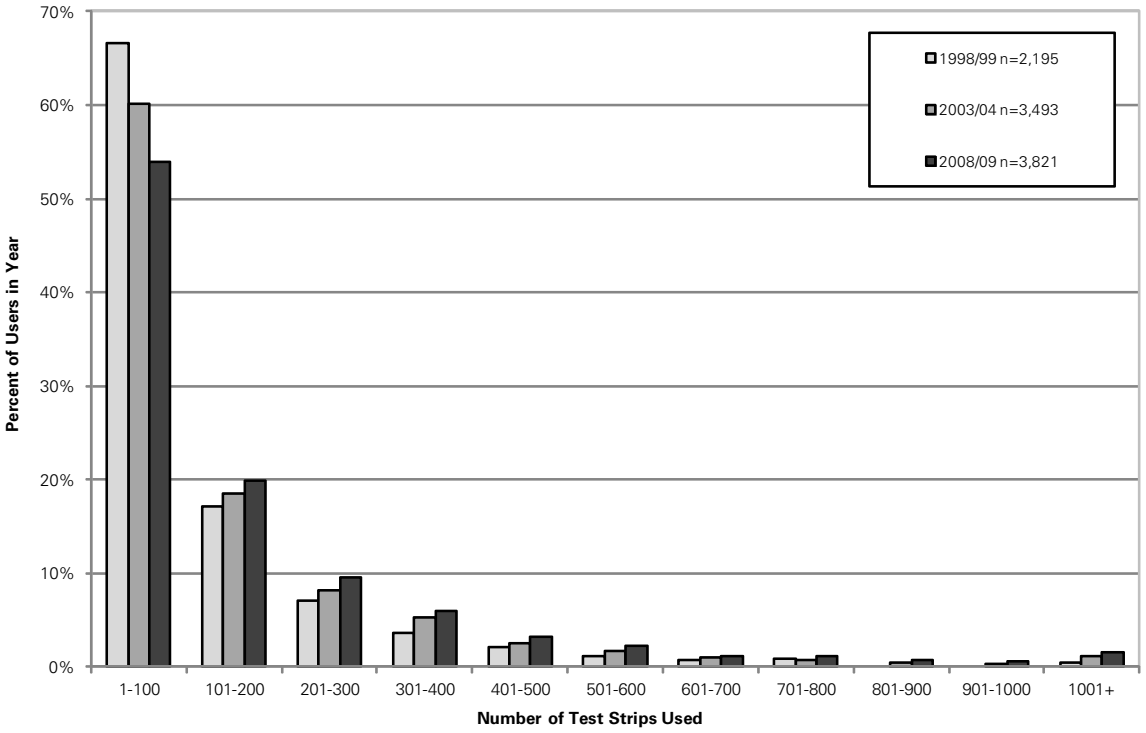
Source: Manitoba Centre for Health Policy, 2010

Figure 3.26: Frequency of Test Strips per Year for Users of Other Anti-Diabetic Agents (metformin, glitazones, acarbose), Aged 65+
Crude percent of users by number of test strips used



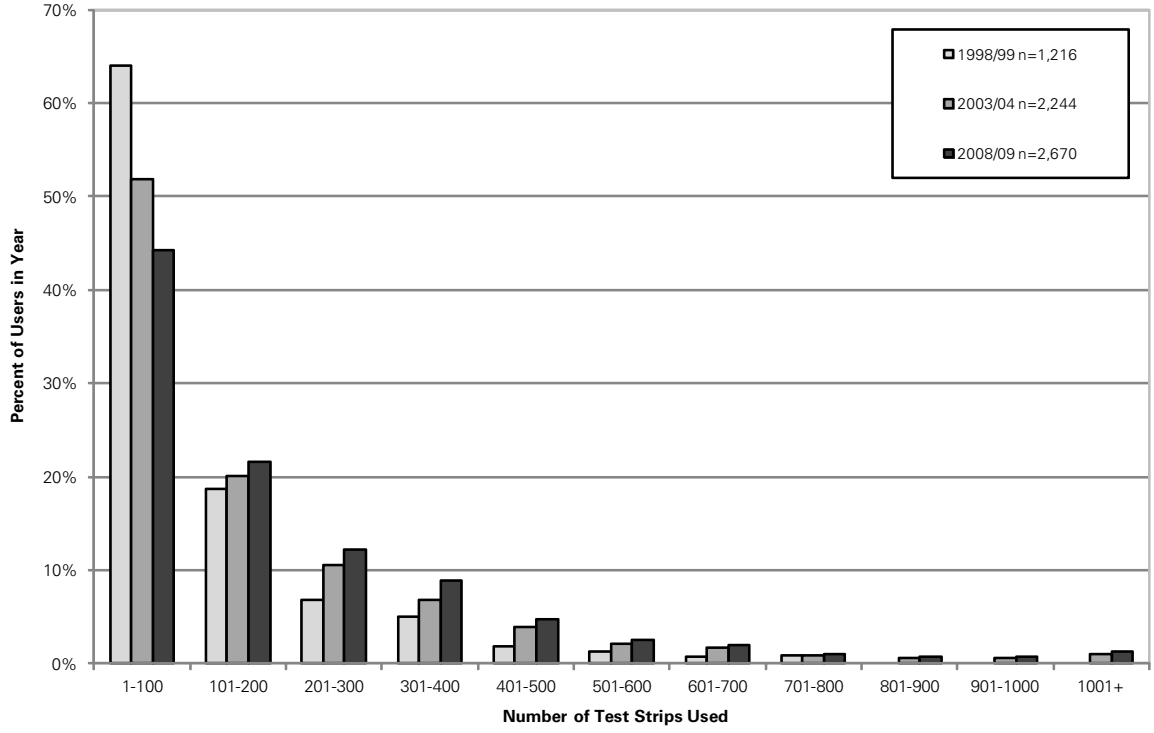
Source: Manitoba Centre for Health Policy, 2010

Figure 3.27: Frequency of Test Strips per Year for Test Strip Users Only (No Medications for Diabetes), Aged 19-64
Crude percent of users by number of test strips used



Source: Manitoba Centre for Health Policy, 2010

Figure 3.28: Frequency of Test Strips per Year for Test Strip Users Only (No Medications for Diabetes), Aged 65+
Crude percent of users by number of test strips used



Source: Manitoba Centre for Health Policy, 2010

Table 3.7: Factors Predictive of Receiving a New Anti-Diabetic Agent as a First Medication for Diabetes
Adjusted odds ratio estimates for incident users of drugs for diabetes, 2002/03-2008/09

Variable	Odds Ratio (95% Confidence Interval)
Age (years, continuous)	0.990 (0.987, 0.994)
Region (missing data vs urban)	0.563 (0.167, 1.900)
Region (rural vs urban)	1.319 (1.169, 1.488)
Number of ambulatory visits in prior year (continuous)	1.022 (1.014, 1.031)
Number of hospitalizations in prior year (continuous)	1.187 (1.088, 1.295)
Hospitalization before treatment (yes vs no)	0.698 (0.549, 0.888)
Physician (general practitioner vs. specialist)	0.418 (0.362, 0.482)
Physician payment (fee for service vs other)	1.289 (1.046, 1.015)
Number of years since physician licensure in MB	1.031 (1.018, 1.589)

Bold = statistically significant effect ($p<0.05$)

Note: Model adjusted for all the variables listed above as well as patient characteristics (sex, socioeconomic status, number of other medications and number of major ADGs in the year prior to the first prescription); prescriber characteristics (hospital affiliation, location of training); and year of first prescription.

New anti-diabetic agents include: glitazones, meglitinides, glimeperide, or acarbose.

Source: Manitoba Centre for Health Policy, 2010

Discussion

There was an increase in prevalent and incident metformin utilization, with a subsequent decline in utilization of sulfonylureas in Manitoba over the study period (1997/98–2008/09). The observed increase in metformin, and the increase in the proportion of incident use of metformin (up to 82% by the end of the study), is appropriate due to the fact that it is first line therapy for diabetes mellitus and, since the publication of the United Kingdom Prospective Diabetes Study (UKPDS) trial in 1998, the only medication for diabetes that has been shown to reduce diabetes mellitus related complications, diabetes related deaths, and all cause mortality (UK Prospective Diabetes Study Group, 1998). Several other studies have described the increase in utilization of metformin and newer agents over time (Alexander, Sehgal, Moloney, & Stafford, 2008; Boyc, Yurgin, & Lage, 2007; Chiang, Chiu, Chen, Wu, & Yang, 2006; Cohen, Neslusan, Conklin, & Song, 2003; Doro et al., 2005; Lusignan et al., 2005; Morgan, Raymond, Mooney, & Martin, 2008; Patel, Srishanmuganathan, Car, & Majeed, 2007; Skaer, Sclar, & Robison, 2006; Stalhammar, Berne, & Svardsudd, 2001; Walley, Hughes, & Kendall, 2005; Wysowski, Armstrong, & Governale, 2003). Other factors which could contribute to the overall increase in utilization of metformin include an increase in diagnosis of diabetes mellitus, response to new treatment guidelines, or increased intensity of therapy for individuals with existing diabetes mellitus (Kozyrskyj et al., 2009).

We observed large differences in the impact of sociodemographic characteristics in the utilization of medications for diabetes mellitus in the general population—namely, increased use among those with lower socioeconomic status and who resided in rural areas. These differences were far less pronounced when the analysis was limited to individuals with a diagnosis of diabetes. A greater prevalence of diabetes mellitus among individuals with lower socioeconomic status, and among rural Manitobans, may explain these results (Dyck, Osgood, Lin, Gao, & Stang, 2010; Fransoo et al., 2009; Green, Blanchard, Young, & Griffith, 2003).

Use of the new medications for diabetes mellitus remained low throughout Manitoba during the study period, likely due to the Part 3 formulary listing on the Manitoba Drug Benefits and Interchangeability Formulary (prior approval for specific prescribing criteria required for use) for the newer agents, which was in place when these medications were marketed. Only 3.5% of incident users of medications for diabetes mellitus were initiated on new medications. Individuals with more physician and hospital visits were more likely to be initiated on newer medications, consistent with prescribers following the Part 3 guidelines and prescribing to those with contraindications to conventional medications. Individuals recently hospitalized were less likely to receive new medications as their first medication for diabetes mellitus, likely reflecting hospital formularies mirroring Pharmacare coverage. Rural individuals were more likely to receive new medications for diabetes mellitus as compared to their urban counterparts, which could reflect differences in diabetes mellitus related complications (Martens et al., 2008) or medical co–morbidities, which would guide treatment decisions (Fransoo et al., 2009). Specialists, fee–for–service prescribers, and those who had practiced for more years since licensure were more likely to initiate new medications for diabetes mellitus, which suggests that some factors such as marketing or education may influence the prescribing of these medications. It is also very likely that several unmeasured factors also had an influential role on use of medications. These include, but are not limited to: physician access, distance of prescriber from academic centres, group or solo prescriber practice, continuing professional development activities, other unmeasured prescriber characteristics, prescriber–patient interactions, pharmaceutical marketing, change and dissemination of clinical practice guidelines, physician sampling of newly marketed medications, and patient perception of benefits and safety of medications.

Despite initial Part 3 listing, the glitazones had the highest rate change of all medication categories evaluated. After evidence of increased risk of cardiac adverse events for rosiglitazone was published in 2007 by Health Canada, utilization of this class of medications decreased, as other authors have observed (Alexander et al., 2008; Cohen, Rabbani, Shah, & Alexander, 2010).

For Manitobans receiving oral medications, insulin, or no therapy, the mean number of test strips per user suggests that testing occurs more frequently than the new CADTH recommendation would support (Canadian Agency for Drugs and Technologies in Health, 2009c; Shea, 2009). However, the number of test strips dispensed increased with the propensity of the medication to cause hypoglycemia; and generally, older test strip users used more test strips than those aged 19–64 (except for those receiving insulin alone, consistent with the recommendation that those with type 1 diabetes mellitus require individualized self–blood glucose monitoring). More test strip utilization was observed amongst individuals with medication for diabetes mellitus than those without medications, consistent with the findings of a study of Ontarians over 65 in 2008 (Gomes et al., 2010). However, the majority of test strip users in Manitoba were individuals not using insulin, where the benefits of self–monitoring of blood glucose are controversial (Davidson, 2005; Ipp et al., 2005; Rabi et al., 2010; Woo et al., 2010). Meta–analyses of randomized controlled trials of self monitoring of blood glucose demonstrated a reduction of 0.17–0.42% in hemoglobin A_{1C}; a value with minimal clinical significance (Rabi et al., 2010). Studies of self–monitoring of blood glucose have been criticized for poor design (Rabi et al., 2010; Woo et al., 2010); however, self–monitoring has been demonstrated to have inconsistent effects on glycemic control and hypoglycemia (Barnett et al., 2008; Farmer et al., 2007; Guerci et al., 2003; Kibriya, Ali, Banik, & Khan, 1999; O'Kane, Bunting, Copeland, & Coates, 2008; Scherbaum, Ohmann, Abholz, Dragano, & Lankisch, 2008) and it may increase anxiety and depression (Franciosi et al., 2001; Peel, Douglas, & Lawton, 2007). For the majority of individuals with no opportunity to experience hypoglycemia (such as those on no anti–diabetic agent or those taking anti–diabetic agents which do not cause hypoglycemia), it is very likely that self monitoring of blood glucose has no benefit, may cause harm, and certainly increases health care costs (Cameron et al., 2010a; Cameron et al., 2010b; Franciosi et al., 2001; Peel et al., 2007; Rabi et al., 2010). Individuals taking no anti–diabetic agents, or taking anti–diabetic agents that do not cause hypoglycemia represented 40% of all Manitobans using test strips by 2008–09. Policy interventions that provide test strips to individuals using insulin and limiting test strips to individuals not receiving insulin have been proposed to reduce use and costs associated with self–monitoring of blood glucose (Gomes et al., 2010).

The potential overuse of strips (for individuals not at risk for hypoglycemia) after the publication of the CADTH recommendation is an area for further research. The role of the pharmacist has been well established in diabetes mellitus management (Jameson & Baty, 2010; Rochester, Leon, Dombrowski, & Haines, 2010). An important role for pharmacists could be patient and prescriber education about the current CADTH recommendation for self–monitoring of blood glucose. Additionally, the changing pattern of medications for diabetes mellitus with the launch of new classes of medications (e.g., sitagliptin) which have increased expenditures on medications for diabetes mellitus in the United States (Alexander et al., 2008) is also an area for future study.

In summary, the use of metformin, the most appropriate first line agent for the treatment of type 2 diabetes mellitus has increased dramatically over time, consistent with guidelines and recommendations. By 2008/09, metformin accounted for more than 82% of first prescriptions for medications to treat diabetes. The use of test strips for self monitoring of blood glucose has also increased dramatically over time. Recent (2009) recommendations suggest that individuals receiving no oral anti–diabetic agents, or anti–diabetic agents that do not cause hypogylcemia should not monitor

blood glucose regularly (rather, only under special circumstances such as when they are ill or changing their medication regimen). This suggests that up to 40% of all Manitobans using test strips and 24–27% of test strips used in Manitoba may have been in excess of what recent evidence and recommendations support. The use of more costly newer agents as the first prescription for the treatment of diabetes mellitus was minimal (3.5%), as these agents are generally not covered by Manitoba Pharmacare or are used for specific patient circumstances. Individuals were more likely to receive a new medication for diabetes mellitus as a first prescription for a diabetes mellitus medication if they lived in a rural location; were younger; had more ambulatory physician visits and hospitalizations; and saw a specialist, a fee for service physician, or a longer practicing physician. These findings suggest that the Manitoba Pharmacare criteria for the new agents for diabetes mellitus were adhered to.

Chapter 4: Inhaled Medications for Asthma and Chronic Obstructive Pulmonary Disease

Inhaled medications used to treat asthma and chronic obstructive pulmonary disease are a diverse group of medications that includes short–acting beta agonists (SABA) such as salbutamol, which are designed to relieve symptoms; long–acting medications designed to prevent symptoms, such (inhaled corticosteroids) and long–acting beta agonists (LABA), which includes salmeterol or formoterol. Other medications included in this category are the anticholinergics (ipratropium and tiatropium), for maintenance treatment of symptoms associated with chronic obstructive pulmonary disease.

The focus of this analysis is the long–acting beta–agonist (LABA)/inhaled corticosteroid combination inhalers and the optimal use of these agents for the treatment of asthma. The first LABA/inhaled corticosteroid combination Advair® (fluticasone/salmeterol) was added to Part 1 (open listing) of the Manitoba Drug Benefits and Interchangeability Formulary in the first quarter of 2000. This was followed by the addition of Symbicort® (budesonide/formoterol). With the exception of the oral agents ketotifen, montelukast, and zafirlukast, which are listed under Part 2 (utilization for established criteria), all other medications for asthma and chronic lung disease in the Pharmacare formulary are Part 1. Due to the rapid increase in prescribing of the LABA/inhaled corticosteroid combination inhalers (Kozyrskyj et al., 2009), the focus of this analysis is the inhaled agents, although there is a role for oral agents in the treatment of asthma and chronic obstructive lung disease. Similarly, although inhaled medications are used for both asthma and chronic obstructive lung disease, this report focuses on the use of LABA/inhaled corticosteroid combinations and the use of these agents in asthma. The epidemiology and sociodemographic characteristics associated with the use of the inhaled medications for asthma and chronic lung disease is performed without reference to what condition the medication is being used for.

Asthma is an inflammatory obstructive pulmonary disorder characterized by symptoms of breathlessness, chest tightness, wheezing, or cough that are often worse at night and in the early morning. Current asthma treatment guidelines emphasize the use of inhaled corticosteroids as first–line therapy for long–term control of persistent asthma symptoms in both children and adults (Fanta, 2009; Lougheed et al., 2010). Asthma guidelines recommend that LABA/inhaled corticosteroid combinations be used as step–up therapy for patients whose asthma is not optimally controlled with inhaled corticosteroids alone (Fanta, 2009; Lougheed et al., 2010). Asthma guidelines do not support the routine use of LABA or LABA/inhaled corticosteroid combination therapy as initial therapy in steroid–naive adults or children (Lemiere et al., 2002; Lougheed et al., 2010; Ni, Greenstone, Lasserson, & Ducharme, 2009). LABAs are not recommended without the use of concomitant oral or inhaled corticosteroids because they do not have sufficient anti–inflammatory properties when used alone (Kuehn, 2010; Chowdhury & Dal Pan, 2010; Lougheed et al., 2010; Martinez, 2005). When used without inhaled corticosteroids, LABAs have been associated with an increased risk of death and hospitalization (Ernst et al., 2006; Lougheed et al., 2010; Nelson, Weiss, Bleecker, Yancey, & Dorinsky, 2006; Salpeter, Buckley, Ormiston, & Salpeter, 2006; Salpeter, Wall, & Buckley, 2010). Health Canada updated safety information for LABAs in 2005 to emphasize the importance of using LABA together with inhaled corticosteroids (Health Canada, 2005b).

The Food and Drug Administration has reviewed the evidence for efficacy and safety of LABAs in 2005, 2007, and 2008; and in 2010, they required label changes for LABAs to reflect this increased risk (Chowdhury & Dal Pan, 2010).

Specific label changes:

- The use of LABA alone without use of a long–term asthma control medication such as an inhaled corticosteroid is contraindicated in the treatment of asthma.
- LABAs should not be used in patients whose asthma is adequately controlled with low or medium dose inhaled corticosteroids.
- LABAs should be used only as additional therapy for patients with asthma who are currently taking but are not adequately controlled with long term asthma control medication, such as inhaled corticosteroids.
- Once asthma control is achieved and maintained, patients should be assessed at regular intervals and step–down therapy should begin (e.g., discontinue LABA).
- Pediatric and adolescent patients who require the addition of a LABA to an inhaled corticosteroid should use a combination product (Robinson, 2010).

The controversy over LABA continues, as recent data suggest that LABA increases the risk for asthma related intubations and deaths, even when used with concomitant inhaled corticosteroids (Salpeter et al., 2010).

Chronic obstructive pulmonary disease is an obstructive pulmonary disorder usually caused by smoking; characterized by progressive, partially reversible airway obstruction and lung hyperinflation; exertional dyspnea; cough and/or sputum production; and frequent respiratory tract infections (O'Donnell et al., 2007). First line therapy for chronic obstructive pulmonary disease includes anticholinergic medications and SABA, although either agent may be used as monotherapy (O'Donnell et al., 2007; O'Donnell et al., 2008). Inhaled corticosteroids and LABA/inhaled corticosteroid combinations are indicated for maintenance treatment and to reduce exacerbations. The combined use of LABA/inhaled corticosteroid combinations can improve pulmonary function, reduce exacerbations, and improve survival in individuals with chronic obstructive pulmonary disease (Hanania et al., 2003; Kardos, Wencker, Glaab, & Vogelmeier, 2007; Kliber, Lynd, & Sin, 2010). LABAs are indicated for individuals with moderate to severe chronic obstructive pulmonary disease with persistent dyspnea with use of SABA or anticholinergics (O'Donnell et al., 2007).

We sought to evaluate the utilization patterns of inhaled medications used to treat asthma and chronic obstructive pulmonary disease in both adults and children in Manitoba. We also explored opportunities to optimize pharmacotherapy for asthma by evaluating the use of LABA and combination LABA/inhaled corticosteroids more closely.

Methods

We evaluated the utilization of inhaled medications used to treat asthma and chronic obstructive pulmonary disease in the Manitoba population (adults and children separately) over time.

Prevalent and incident utilization for the population of Manitoba was determined for the following medications: inhaled corticosteroids (beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, and triamcinolone), SABA (salbutamol, fenoterol, terbulatine), LABA (salmeterol and fomoterol), LABA/inhaled corticosteroid combinations (fluticasone/salmeterol and budesonide/formoterol), and anticholinergic medications (ipraropium [alone and in combination with SABA] and tiatropium). Details about the medications included in these categories are presented in Appendix 1.1.

In Manitoba, all inhaled medications for asthma and chronic pulmonary disease in the Pharmacare formulary are Part1 (open listing) except for tiatropium, which is Part 3 (prior approval for specific criteria required before utilization) of the Manitoba Drug Benefits and Interchangeability Formulary.

Incident users were those users of a medication for asthma or chronic obstructive pulmonary disease who had not received any prescriptions for the medication group of interest in the one year prior to the year of interest.

Prevalent and incident utilization is presented as prevalent and incident users per 1,000 for the overall adult and overall pediatric population of Manitoba. The influence of sociodemographic characteristics on prescribing over the entire study period (1997/98–2008/09) was determined using generalized estimating equations. Regional analysis of medication utilization for the fiscal years 1998/99, 2003/04, and 2008/09 compares prevalent users (annual rates, adjusted for age, sex, and socioeconomic status) across five regions of Manitoba (Rural South, Mid, North, Winnipeg, and Brandon) and Manitoba overall.

Optimal Use Evaluation

We evaluated factors predictive of the following types of incident utilization (from 2002/03 through 2008/09) among both adults and children with asthma (note: as time effects were likely important in changing prescribing patterns, only incident users of the medication of interest who initiated therapy in 2002/03 through 2008/09 were included in these analyses):

- LABA or LABA/inhaled corticosteroid combination with no prescriptions for oral or inhaled corticosteroids in the year prior to the first prescription (less than optimal).
- LABA therapy alone with no prescriptions for oral or inhaled corticosteroids 90 days before or after the first prescription (less than optimal).
- For both of these models, we attempted to exclude individuals with chronic obstructive pulmonary disease who would usually be treated with anticholinergics (whereas other individuals with asthma would not usually be treated with anticholinergics). We did this by excluding all new users of LABA or LABA/inhaled corticosteroid combination who had ever filled a prescription for anticholinergics (Breton, Lelorier, Forget, & Blais, 2007) and those who had a diagnosis of cystic fibrosis (ICD–9: 277). Asthma was defined as one physician claim, one hospital claim or one prescription for an asthma medication (as outlined in Appendix Table 1.1) in the three years prior to the incident prescription (sensitivity 77.7%, specificity 91.2%, Youden's index 0.69, Kappa agreement between administrative data and survey data other studies 0.52) (Chen, Johansen, Thillaiampalam, & Sambell, 2005; Dey & Bloom, 2005; Lix et al., 2006; National Asthma Control Task Force, 2000; Rhodes, Moorman, Reed, & Mannino, 2003).
- Sociodemographic factors included in the models were: age, sex, region of residence, socioeconomic status, and being hospitalized within three days of the incident prescription. The number of different non–asthma medications, number of prescriptions for asthma medications, number of prescriptions for antibiotics (as outlined in Appendix Table 1.1), use of the leukotriene receptor antagonists (monteleukast and zafirlukast), number of major ADGs, and the number of ambulatory visits and hospitalizations for any reason in the year prior to the first prescription were also included. Prescriber characteristics included in the model were: hospital affiliation, location of training, years since licensure in Manitoba, type of reimbursement, and specialist status. Also included in the model was year of first prescription. Individuals were included in the model if they had one incident prescription for a LABA or LABA/inhaled corticosteroid combination or LABA from 2002/03 through 2008/09 and if they had a value for all of the other variables included in the model. Each person was only included once.

Results

Adults

A total of 802,794 adults in 1997/98, up to 859,108 adults in 2008/09 formed the denominator for this analysis.

Adults: Prevalence

Prevalent utilization of the inhaled medications for asthma and chronic obstructive pulmonary disease among adults was greatest for SABA, as prevalent use of these agents increased from 25.0 to 32.4 per 1,000 adult residents over the study period (see Figure 4.1). This was followed by single–agent inhaled corticosteroids; however, the use of this category increased from the beginning of the study from 15.2 to 20.3 by the third quarter of 1999 and then fell to 10.7 users per 1,000 adult residents by the end of the study period. This decline was mirrored by an increase in the use of LABA/inhaled corticosteroid combinations which increased from 0.03 to 16.8 users per 1,000 adult residents. Use of anticholinergics increased from 5.4 to 9.8 per 1,000 adult residents over the study period while use of single–agent LABA increased from 0.4 to 3.5 and then declined to 1.2 users per 1,000 adult residents by the end of the study period.

Adults: Sociodemographic characterstics

For SABA, inhaled corticosteroids, and anticholinerigics, there was greater prevalent utilization among adults for those with low socioeconomic status as compared to higher socioeconomic status, after adjustment for other factors (see Table 4.1). For all agents, there was higher utilization among those aged 65–84 as compared to those aged 19–44, after adjustment for other factors. The most rapid increase over time was the LABA/inhaled corticosteroid combinations; prevalent utilization of these agents increased 9% per quarter.

Adults: Incidence

Incident utilization of the inhaled medications for asthma and chronic obstructive pulmonary disease among adults was greatest for SABA, as new use of these agents increased from 5.8 to 8.8 per 1,000 adult residents per quarter over the study period. This was followed by single agent inhaled corticosteroids; however, the new use of this category increased in the beginning of the study period from 3.7 to 4.6 per 1,000 adult residents per quarter by the third quarter of 1999 and then fell to 2.6 users per 1,000 adult residents per quarter by the end of the study period. This decline was mirrored by an increase in the new use of LABA/inhaled corticosteroid combinations, which increased from 0.03 to 2.6 new users per 1,000 adult residents per quarter. New use of anticholinergics increased from 1.2 to 1.5 per 1,000 adult residents per quarter while new use of single–agent LABA remained low.

Adults: Sociodemographic characterstics

For all agents studied except LABA/inhaled corticosteroid combinations, there was greater incident utilization among adults for those with low as compared to high socioeconomic status, following adjustment for other factors (see Table 4.2). For all agents, there was higher utilization among those aged 65–84 as compared to those aged 19–44, following adjustment for other factors. There was lower incident utilization use amongst males for all agents except LABA and anticholinergics, following adjustment for other factors.

Adults: Regional Variation

When adjusted for age, sex, and socioeconomic status, the prevalent utilization of SABAs in adults increased over the time period evaluated in all regions (see Figure 4.3). Prevalent SABA use in the Rural South region was significantly lower than the Manitoba average at all three time periods. Prevalent SABA use in the Brandon was significantly higher than the Manitoba average at all three time periods.

Prevalent SABA use in the North was greater than the Manitoba average in 2008/09 only.

When adjusted for age, sex, and socioeconomic status, the prevalent utilization of inhaled corticosteroids in adults decreased over the time period evaluated in all regions except for the North (see Figure 4.4). Prevalent use of inhaled corticosteroid in the Rural South region was significantly lower than the Manitoba average in 2003/04 and 2008/09. Prevalent use of inhaled corticosteroids in the North was lower than the Manitoba average in 1998/99 but higher than the Manitoba average in 2008/09.

When adjusted for age, sex, and socioeconomic status, the prevalent utilization of LABAs in adults increased from 1998/99 to 2003/04 but then decreased from 2003/04 to 2008/09 in all regions (see Figure 4.5). Prevalent LABA use in the North was significantly lower than the Manitoba average in 2003/04 and 2008/09.

When adjusted for age, sex, and socioeconomic status, the prevalent utilization of LABA/inhaled corticosteroids in adults increased over the time period evaluated in all regions (see Figure 4.6). Prevalent use of LABA/inhaled corticosteroid in the North region was significantly lower than the Manitoba average in 2008/09, but higher in 2003/04.

When adjusted for age, sex, and socioeconomic status, the prevalent utilization of anticholinergics in adults increased from 1998/99 to 2003/04 but then decreased from 2003/04 to 2008/09 in Manitoba, although these differences were not significant for all regions (see Figure 4.7). Prevalent anticholinergic use in Brandon and the Mid region was significantly higher than the Manitoba average in 1998/99 and 2008/09.

Adults: Optimal use evaluation

Optimal prescribing of LABA/inhaled corticosteroids or LABA for asthma includes use of oral or inhaled corticosteroids prior to the LABA or LABA/corticosteroid combination (Fanta, 2009; Lougheed et al., 2010). For 30,421 adult Manitobans with an incident prescription for a LABA or LABA/inhaled corticosteroid combination from 2002/03 through 2008/09 without prescriptions for anticholinergic inhalers or a diagnosis of cystic fibrosis and a diagnosis of asthma (one physician claim, one hospital claim or one prescription for an asthma medication in three years prior to the incident prescription (Lix et al., 2006)) in the year prior to the incident LABA or LABA/inhaled corticosteroid combination prescription, only 35.7% had been prescribed an oral or inhaled corticosteroid (see Table 4.3). This proportion decreased from 50.2% in 2002/03 to 29.4% in 2008/09.

Optimal prescribing of LABA for asthma includes co–prescription of inhaled corticosteroids (Chowdhury & Dal Pan, 2010; Martinez, 2005; Kuehn, 2010; Lougheed et al., 2010). For 3,214 adult Manitobans with an incident prescription for a LABA from 2002/03 through 2008/09 and a diagnosis of asthma, only 54.0% were prescribed an oral or inhaled corticosteroid within 90 days of this first prescription (see Table 4.4). This proportion decreased from 64.9% in 2002/03 to 42.0% in 2008/09.

Optimal prescribing of LABA/inhaled corticosteroids or LABA for asthma includes use of oral or inhaled corticosteroids prior to the LABA or LABA/corticosteroid combination (Fanta, 2009; Lougheed et al., 2010). From 2002/03 through 2008/09, there were 23,309 incident users of LABA or LABA/inhaled corticosteroid combination among adult Manitobans (without prescriptions for anticholinergic inhalers or a diagnosis of cystic fibrosis and with a diagnosis of asthma in the three years prior to the incident LABA or LABA/corticosteroid prescription) included in the model. Of these, only 7,148 (30.7%) received a prescription for oral or inhaled corticosteroids in the year prior to the first prescription (the outcome variable was not receiving a prescription for oral or inhaled corticosteroids 90 days before or after the

first prescription). A total of 2.31% were missing from the model because of missing values for some variables.

Age, sex, number of different medications, number of hospitalizations for any reason, number of major ADGs, the number of prescriptions for antibiotics, number of prescriptions for other asthma medications, use of leukotriene receptor antagonists, and year of first prescription influenced the likelihood of receiving a LABA or LABA/inhaled corticosteroid combination without previous use of oral or inhaled corticosteroids (see Table 4.5). Adult Manitobans were more likely to receive an incident LABA or LABA/inhaled corticosteroid combination without previous use of oral or inhaled corticosteroids if they were male or had more hospitalizations. With each year after 2002/03, adult Manitobans were more likely to receive an incident LABA or LABA/inhaled corticosteroid combination without previous use of oral or inhaled corticosteroids as compared to 2002/03. Adult Manitobans were less likely to receive an incident LABA or LABA/inhaled corticosteroid combination without previous use of oral or inhaled corticosteroids as age increased, as they had more different medications, major ADGs, more prescriptions for antibiotics or other asthma medications, or had received prescriptions for leukotriene receptor antagonists.

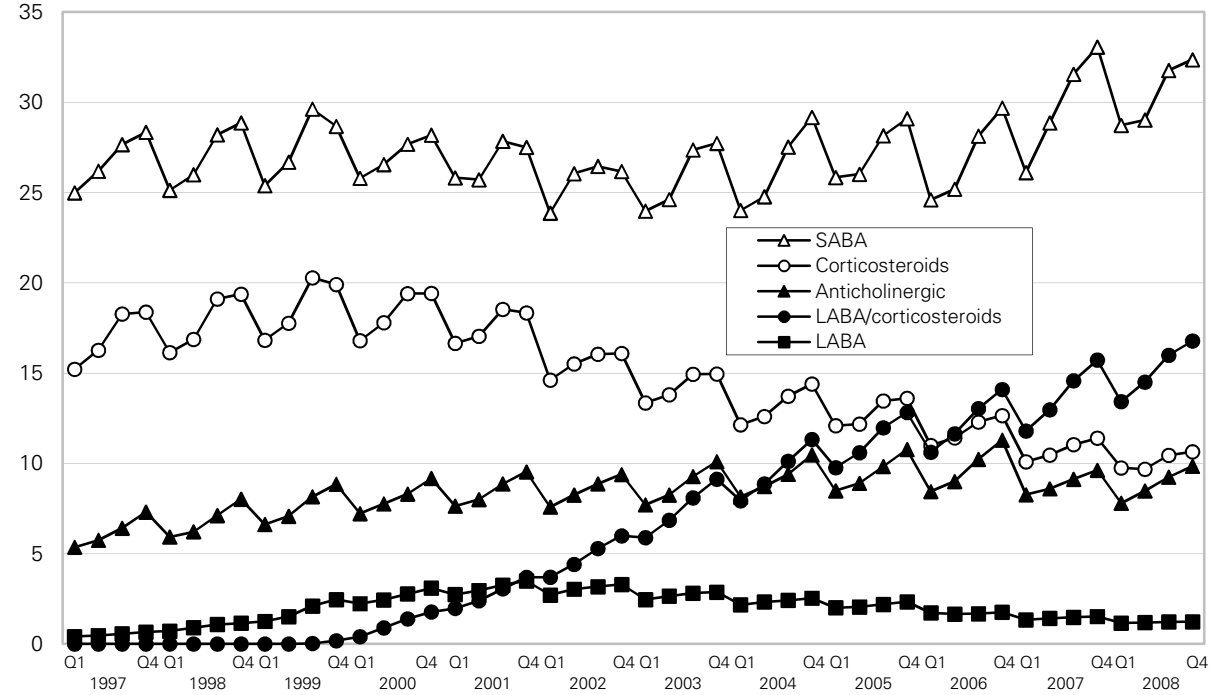
Prescriber specialist status, location of training, type of physician reimbursement, and years since licensure in Manitoba significantly influenced the likelihood of receiving a LABA or LABA/inhaled corticosteroid combination without previous use of oral or inhaled corticosteroids. Prescribers trained in North America were less likely than other prescribers to initiate LABA or LABA/inhaled corticosteroid combination without previous use of oral or inhaled corticosteroids. General practitioners, fee–for–services physicians, and prescribers with more years since licensure in Manitoba were more likely than other prescribers to initiate LABA or LABA/inhaled corticosteroid combination without previous use of oral or inhaled corticosteroids.

Optimal prescribing of single entity LABA for asthma includes co–prescription of inhaled corticosteroids (Chowdhury & Dal Pan, 2010; Kuehn, 2010; Lougheed et al., 2010; Martinez, 2005). From 2002/03 through 2008/09, there were 2,306 incident users of LABA therapy among adult Manitobans (without prescriptions for anticholinergic inhalers or a diagnosis of cystic fibrosis and with a diagnosis of asthma in the three years prior to the incident LABA prescription) included in the model. Of these, only 1,241 (53.8%) received a prescription for oral or inhaled corticosteroids 90 days before or after the first prescription (the outcome variable was not receiving a prescription for oral or inhaled corticosteroids 90 days before or after the first prescription). A total of 2.37% were excluded because of missing values for some variables.

Sex, number of different medications, the number of prescriptions for antibiotics, number of prescriptions for other asthma medications, and year of first prescription influenced the likelihood of receiving a LABA without co–prescribed corticosteroids (see Table 4.6). Adult Manitobans were more likely to receive an incident LABA without co–prescribed corticosteroids if they were male. With each year after 2002/03, adult Manitobans were more likely to receive an incident LABA without co–prescribed corticosteroids as compared to 2002/03. Adult Manitobans were less likely to receive an incident LABA without co–prescribed corticosteroids if they had a greater number of different medications or had received more prescriptions for antibiotics or other asthma medications in the year prior to the incident LABA prescription.

Prescriber specialist status significantly influenced the likelihood of receiving a LABA without co–prescribed corticosteroids. General practitioners were more likely than other prescribers to initiate LABA without co–prescribed corticosteroids.

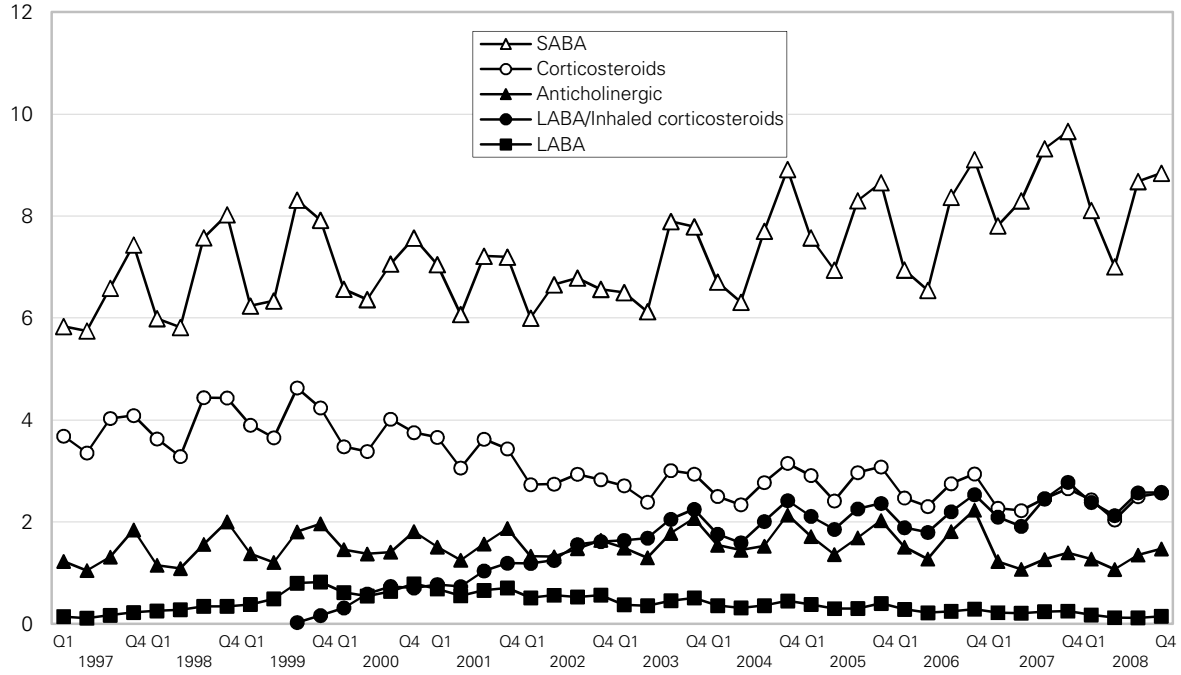
Figure 4.1: Medications for Asthma and Chronic Lung Disease Quarterly Prevalence, Adults
Crude user rates per 1,000 adults, Q1 1997-Q4 2008



'Q1' indicates rates for the 1st quarter (April to June)
'Q4' indicates rates for the 4th quarter (January to March)
'Q2' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2010

Figure 4.2: Medications for Asthma and Chronic Lung Disease Quarterly Incidence, Adults
Crude rates of new users with no use of asthma or chronic disease medications in prior year per 1,000 adults, Q1 1997-Q4 2008



'Q1' indicates rates for the 1st quarter (April to June)
'Q4' indicates rates for the 4th quarter (January to March)
'Q2' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2010

Table 4.1: Prevalent Use (Users per 1,000 Residents) of Inhaled Medications for Asthma and Chronic Lung Disease Among Adults, 1997/98 to 2008/09

Medication or Group of Medications	1997Q1 users/1,000	2008Q4 users/1,000	Change in rate per quarter	Age effect 65-84 vs 19-44	Socioeconomic status Low vs High	Region effect Rural vs Urban	Sex effect Male vs Female
SABA	24.99	32.36	1 Slight increase*	2.02 202% higher*	1.27 27% higher*	0.9 NS	0.96 NS
Corticosteroids only	15.21	10.65	0.99 Slight decrease*	3.44 344% higher*	1.18 18% higher*	0.94 NS	0.85 15% lower*
LABA	0.41	1.23	1.01 1% increase*	8.86 886% higher*	1.15 NS	0.85 NS	1.04 NS
LABA/Corticosteroid Combination	0.03 1999Q3	16.78	1.09 9% increase*	4.37 437% higher*	1.04 NS	1.05 NS	0.89 NS
Anticholinergics	5.36	9.84	1.01 1% increase*	33.97 3397% higher*	1.51 51% higher*	1.04 NS	1.25 25% higher*

*Indicates a statistically significant effect ($p<0.05$)

Note: Results for change in rate per quarter, age, socioeconomic status (SES), region, and sex effect are presented as relative rates (adjusted for age, SES, region, sex and time).

Source: Manitoba Centre for Health Policy, 2010

Table 4.2: Incident Use (Users per 1,000 Residents) of Inhaled Medications for Asthma and Chronic Lung Disease Among Adults, 1997/98 to 2008/09

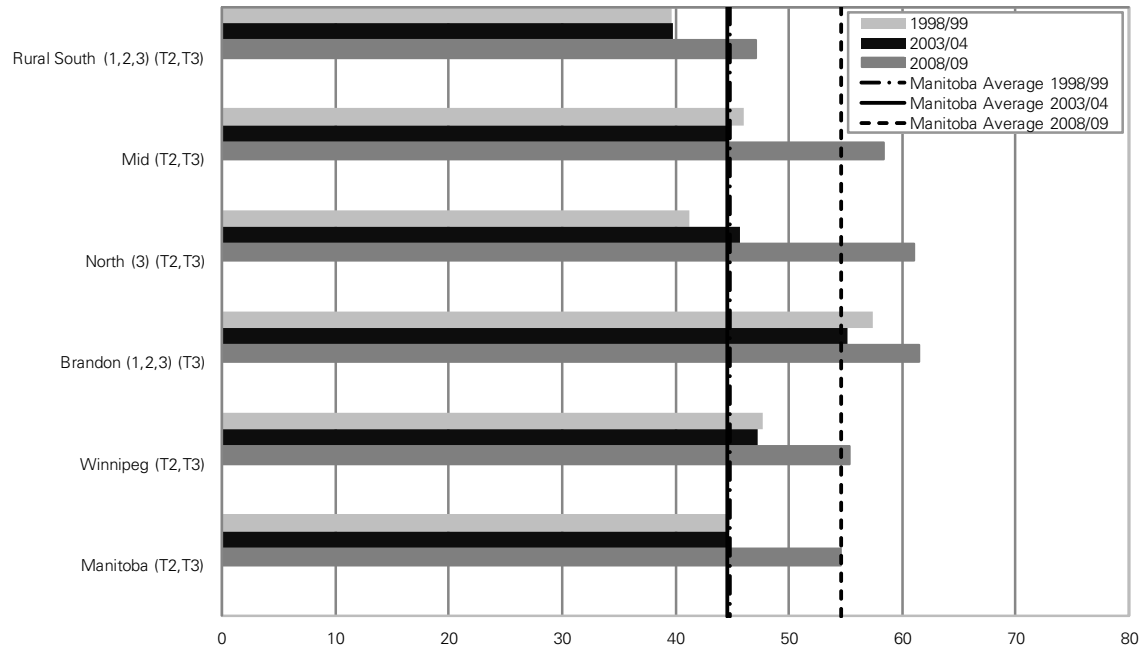
Medication or Group of Medications	1997Q1 users/1,000	2008Q4 users/1,000	Change in rate per quarter	Age effect 65-84 vs 19-44	Socioeconomic status Low vs High	Region effect Rural vs Urban	Sex effect Male vs Female
SABA	5.83	8.84	1.01 1% increase*	1.24 24% higher*	1.18 18% higher*	0.97 NS	0.76 24% lower*
Corticosteroids only	3.68	2.57	0.99 1% decrease*	1.4 40% higher*	1.16 16% higher*	0.96 NS	0.69 31% lower*
LABA	0.14	0.15	0.98 2% decrease*	5.18 518% higher*	1.23 23% higher*	0.89 NS	0.9 NS
LABA/Corticosteroid Combination	0.03 1999Q3	2.58	1.05 5% increase*	2.62 262% higher*	1.07 NS	0.98 NS	0.86 14% lower*
Anticholinergics	1.23	1.47	1 No change	12.25 1225% higher*	1.44 44% higher*	1.18 18% higher*	1.07 NS

*Indicates a statistically significant effect ($p<0.05$)

Note: Results for change in rate per quarter, age, socioeconomic status (SES), region, and sex effect are presented as relative rates (adjusted for age, SES, region, sex and time).

Source: Manitoba Centre for Health Policy, 2010

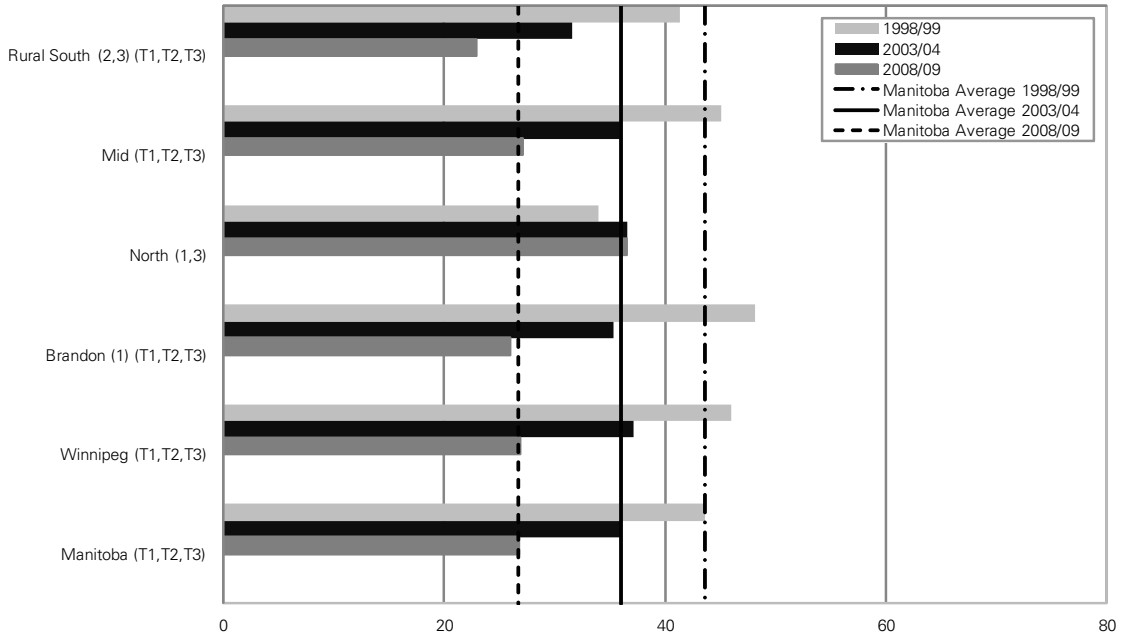
Figure 4.3: SABA Users per 1,000 Adults by Region
Adjusted by (2003/04) age, sex, and SES per 1,000 residents aged 18+



'1'- indicates area's rate was statistically different from Manitoba average in 1998/99.
'2'- indicates area's rate was statistically different from Manitoba average in 2003/04.
'3'- indicates area's rate was statistically different from Manitoba average in 2008/09.
'T1'- indicates change over time (1998/99 versus 2003/04) was statistically different for that area.
'T2'- indicates change over time (1998/99 versus 2008/09) was statistically different for that area.
'T3'- indicates change over time (2003/04 versus 2008/09) was statistically different for that area.

Source: Manitoba Centre for Health Policy, 2010

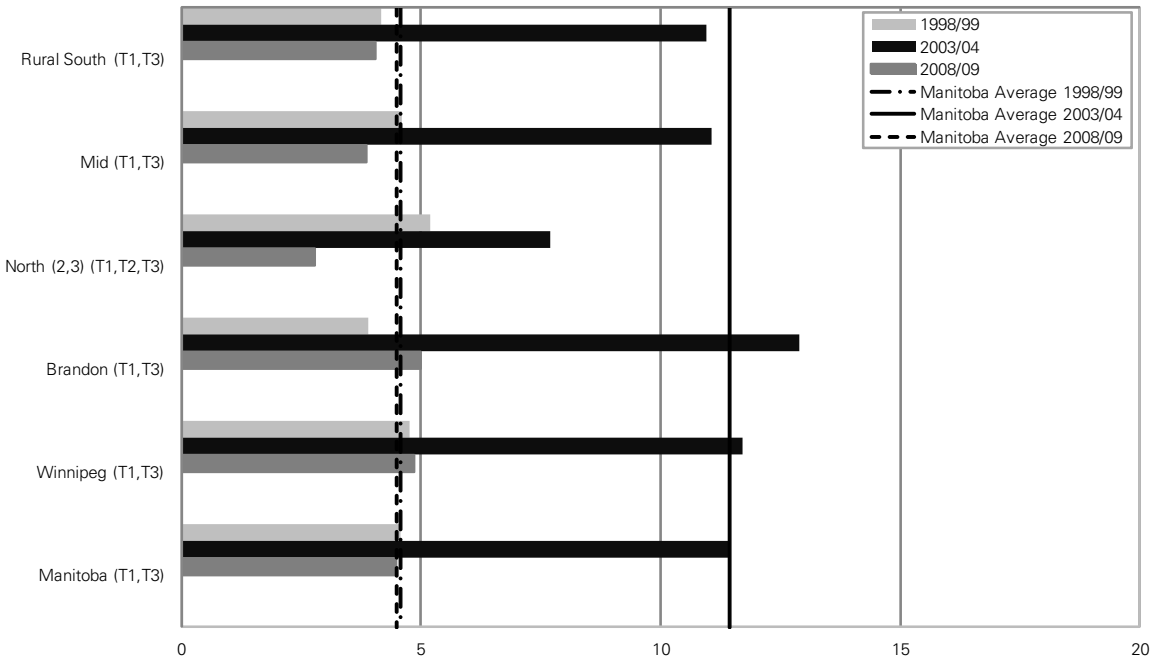
Figure 4.4: Inhaled Corticosteroid Users per 1,000 Adults by Region
Adjusted by (2003/04) age, sex, and SES per 1,000 residents aged 18+



'1'- indicates area's rate was statistically different from Manitoba average in 1998/99.
'2'- indicates area's rate was statistically different from Manitoba average in 2003/04.
'3'- indicates area's rate was statistically different from Manitoba average in 2008/09.
'T1'- indicates change over time (1998/99 versus 2003/04) was statistically different for that area.
'T2'- indicates change over time (1998/99 versus 2008/09) was statistically different for that area.
'T3'- indicates change over time (2003/04 versus 2008/09) was statistically different for that area.

Source: Manitoba Centre for Health Policy, 2010

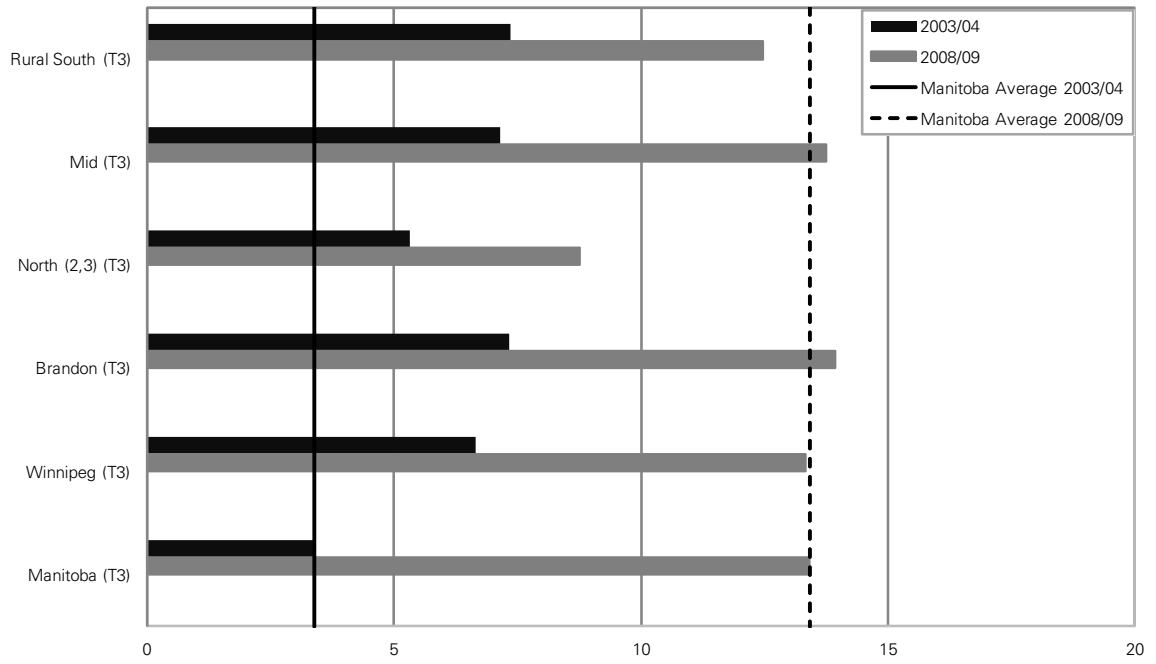
Figure 4.5: LABA Users per 1,000 Adults by Region
Adjusted by (2003/04) age, sex, and SES per 1,000 residents aged 18+



'1'- indicates area's rate was statistically different from Manitoba average in 1998/99.
'2'- indicates area's rate was statistically different from Manitoba average in 2003/04.
'3'- indicates area's rate was statistically different from Manitoba average in 2008/09.
'T1'- indicates change over time (1998/99 versus 2003/04) was statistically different for that area.
'T2'- indicates change over time (1998/99 versus 2008/09) was statistically different for that area.
'T3'- indicates change over time (2003/04 versus 2008/09) was statistically different for that area.

Source: Manitoba Centre for Health Policy, 2010

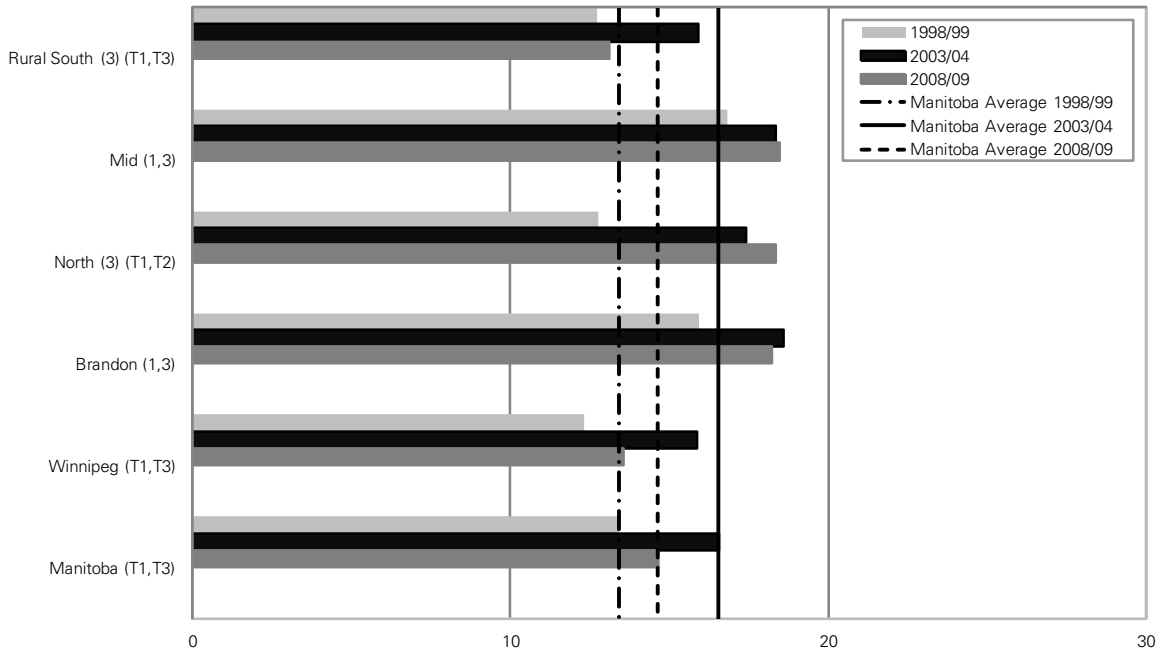
Figure 4.6: LABA/Inhaled Corticosteriod Combination Users per 1,000 Adults by Region
Adjusted by (2003/04) age, sex, and SES per 1,000 residents aged 18+



'1'- indicates area's rate was statistically different from Manitoba average in 1998/99.
'2'- indicates area's rate was statistically different from Manitoba average in 2003/04.
'3'- indicates area's rate was statistically different from Manitoba average in 2008/09.
'T1'- indicates change over time (1998/99 versus 2003/04) was statistically different for that area.
'T2'- indicates change over time (1998/99 versus 2008/09) was statistically different for that area.
'T3'- indicates change over time (2003/04 versus 2008/09) was statistically different for that area.

Source: Manitoba Centre for Health Policy, 2010

Figure 4.7: Anticholinergic Users per 1,000 Adults by Region
Adjusted by (2003/04) age, sex, and SES per 1,000 residents aged 18+



'1'- indicates area's rate was statistically different from Manitoba average in 1998/99.
'2'- indicates area's rate was statistically different from Manitoba average in 2003/04.
'3'- indicates area's rate was statistically different from Manitoba average in 2008/09.
'T1'- indicates change over time (1998/99 versus 2003/04) was statistically different for that area.
'T2'- indicates change over time (1998/99 versus 2008/09) was statistically different for that area.
'T3'- indicates change over time (2003/04 versus 2008/09) was statistically different for that area.

Source: Manitoba Centre for Health Policy, 2010

Table 4.3: Use of Asthma Medication Prior to LABA or LABA/Steroid Combination Use for Adults with Asthma by Year
Count and proportion of new LABA or LABA/inhaled corticosteroid combination users* who used asthma medications in the prior year

		Medication in year prior to LABA or LABA/inhaled corticosteroid combination					
Fiscal Year	**Total LABA or LABA/steroid combination users**	**Inhaled corticosteroids (ICS)**	**Oral steroids**	**ICS or oral steroids**	**SABA**	**Montelukast/ Zafirlukast**	**Any asthma medication**
2002/03	3114	1264 (40.6%)	632 (20.3%)	1564 (50.2%)	1950 (62.6%)	209 (6.7%)	2355 (75.6%)
2003/04	3901	1225 (31.4%)	733 (18.8%)	1667 (42.7%)	2421 (62.1%)	277 (7.1%)	2857 (73.2%)
2004/05	4120	1068 (25.9%)	763 (18.5%)	1542 (37.4%)	2460 (59.7%)	239 (5.8%)	2896 (70.3%)
2005/06	4622	1054 (22.8%)	836 (18.1%)	1621 (35.1%)	2705 (58.5%)	267 (5.8%)	3184 (68.9%)
2006/07	4504	923 (20.5%)	758 (16.8%)	1418 (31.5%)	2607 (57.9%)	321 (7.1%)	3053 (67.8%)
2007/08	4861	884 (18.2%)	824 (17.0%)	1482 (30.5%)	2858 (58.8%)	348 (7.2%)	3309 (68.1%)
2008/09	5299	862 (16.3%)	945 (17.8%)	1560 (29.4%)	3159 (59.6%)	369 (7.0%)	3643 (68.7%)
Total	30421	7280 (23.9%)	5491 (18.1%)	10854 (35.7%)	18160 (59.7%)	2030 (6.7%)	21297 (70.0%)

* with a dignosis for asthma (one physician claim, one hospital claim, or one prescription for an asthma medication) and no anticholinergics or cystic fibrosis diagnosis from 2002/03 - 2008/09

Source: Manitoba Center for Health Policy, 2010

Table 4.4: Use of Asthma Medication Prior to LABA Use for Adults with Asthma by Year
Count and proportion of new LABA users* who used asthma medications +/- 90 days

		Medication 90 days prior to or after LABA		
Fiscal Year	**Total LABA users**	**Inhaled corticosteroids (ICS)**	**Oral steroids**	**ICS or oral steroids**
2002/03	733	452 (61.7%)	123 (16.8%)	476 (64.9%)
2003/04	609	288 (47.3%)	93 (15.3%)	329 (54.0%)
2004/05	507	233 (46.0%)	81 (16.0%)	266 (52.5%)
2005/06	456	205 (45.0%)	80 (17.5%)	241 (52.9%)
2006/07	394	163 (41.4%)	63 (16.0%)	192 (48.7%)
2007/08	310	130 (41.9%)	38 (12.3%)	146 (47.1%)
2008/09	205	74 (36.1%)	27 (13.2%)	86 (42.0%)
Total	3214	1545 (48.1%)	505 (15.7%)	1736 (54.0%)

* with a diagnosis for asthma (one physician claim, one hospital claim, or one prescription for an asthma medication) and no anticholinergics or cystic fibrosis diagnosis from 2002/03-2008/09

Source: Manitoba Center for Health Policy, 2010

Table 4.5: Factors Predictive of Incident LABA or LABA Corticosteroid Combination Use without Oral or Inhaled Corticosteroids in Year Prior
Odds ratio estimates for incident adult users of LABA or LABA corticosteroid combination with asthma*, 2002/03-2008/09

Variable	Odds Ratio (95% Confidence Interval)
Age (years, continuous)	0.995 (0.993, 0.996)
Sex (males vs females)	1.176 (1.103, 1.253)
Year 2008/09 (vs 2002/03)	1.382 (1.231, 1.551)
Year 2007/08 (vs 2002/03)	1.384 (1.232, 1.554)
Year 2006/07 (vs 2002/03)	1.406 (1.251, 1.580)
Year 2005/06 (vs 2002/03)	1.309 (1.169, 1.466)
Year 2004/05 (vs 2002/03)	1.282 (1.144, 1.436)
Year 2003/04 (vs 2002/03)	1.150 (1.028, 1.286)
Number of other medications in prior year (continuous)	0.977 (0.968, 0.987)
Number of hospitalizations in prior year (continuous)	1.097 (1.018, 1.182)
Number of major ADGs in prior year (continuous)	0.946 (0.907, 0.988)
Number of prescriptions for asthma in prior year (continuous)	0.846 (0.838, 0.854)
Number of prescriptions for antibiotics in prior year (continuous)	0.920 (0.907, 0.934)
Use of leukotriene receptor antagonists in prior year (yes vs no)	0.535 (0.472, 0.606)
Physician (general practitioner vs specialist)	1.986 (1.790, 2.203)
Physician training (North America vs other)	0.772 (0.725, 0.822)
Physician payment (fee for service vs other)	1.168 (1.032, 1.320)
Number of years since physician licensure in MB (continuous)	1.021 (1.015, 1.027)

Bold = statistically significant (p<0.05)

Note: Model adjusted for all the variables listed above as well as patient characteristics (region of residence, socioeconomic status, number of physician visits in the year prior to the first prescription, being hospitalized within 3 days of the first prescription) prescriber characteristics (hospital affiliation). Individuals were included in the model only once, if they had one incident prescription for a LABA or LABA/inhaled corticosteroid combination from 2002/2003 through 2008/2009 and if they had a value for all of the other variables included in the model.

* with a dignosis for asthma (one physician claim, one hospital claim, or one prescription for an asthma medication)

Source: Manitoba Centre for Health Policy, 2010

Table 4.6: Factors Predictive of Incident LABA Use without Oral or Inhaled Corticosteroids within 90 Days
Odds ratio estimates for incident adult users of LABA with asthma*, 2002/03-2008/09

Variable	Odds Ratio (95% Confidence Interval)
Sex (males vs females)	1.268 (1.052, 1.529)
Year 2008/09 (vs 2002/03)	2.491 (1.592, 3.898)
Year 2007/08 (vs 2002/03)	2.116 (1.491, 3.004)
Year 2006/07 (vs 2002/03)	1.798 (1.306, 2.475)
Year 2005/06 (vs 2002/03)	1.618 (1.199, 2.184)
Year 2004/05 (vs 2002/03)	1.780 (1.351, 2.347)
Year 2003/04 (vs 2002/03)	1.525 (1.189, 1.955)
Number of other medications in prior year (continuous)	0.965 (0.940, 0.991)
Number of prescriptions for asthma in prior year (continuous)	0.869 (0.841, 0.898)
Number of prescriptions for antibiotics in prior year (continuous)	0.927 (0.887, 0.970)
Physician (general practitioner vs specialist)	1.971 (1.478, 2.627)

Bold = statistically significant (p<0.05)

Note: Model adjusted for all the variables listed above as well as patient characteristics (age, region of residence, socioeconomic status, number of physician visits, and hospitalizations, being hospitalized within three days of the first prescription, number of major ADGs, use of monteleukast or zafirlukast in the year prior to the first prescription) and prescriber characteristics hospital affiliation, location of training, years since licensure in Manitoba, type of reimbursement).

* with a dignosis for asthma (one physician claim, one hospital claim, or one prescription for an asthma medication)

Source: Manitoba Centre for Health Policy, 2010

Children

A total of 291,528 children in 1997/98, down to 290,532 children in 2008/09 formed the denominator in this analysis.

Children: Prevalence

Prevalent utilization of the inhaled medications for asthma among children was greatest for SABA, as prevalent use of these agents increased from 25.8 to 27.3 per 1,000 pediatric residents per quarter over the full study period (see Figure 4.8). This was followed by single agent inhaled corticosteroids; however, the use of this category only increased from 14.2 to 15.3 users per 1,000 children by the end of the study period. The use of LABA/inhaled corticosteroid combinations increased from 0.07 to 3.4 users per 1,000 pediatric residents, while use of single agent LABA remained low.

Children: Sociodemographic characterstics

For all agents studied, there was greater prevalent utilization among children for males, following adjustment for other factors (see Table 4.7). There was lower utilization of SABA, inhaled corticosteroids, and LABA/inhaled corticosteroid combinations among rural as compared to urban children, after adjustment for other factors. There was lower prevalent utilization of LABA/inhaled corticosteroid combinations among children with low as compared to high socioeconomic status, following adjustment for other factors. There was greater use of inhaled corticosteroids, but lower use of most other agents (except SABA) among children aged five to eight as compared to 13–18, after adjustment for other factors.

Children: Incidence

Incident utilization of the inhaled medications for asthma among children was greatest for SABA, as new use of these agents increased over the study period, from 10.7 to 13.7 per 1,000 pediatric residents (see Figure 4.9). This was followed by single agent inhaled corticosteroids, however the new use of this category increased only slightly from 5.3 to 6.6 per 1,000 pediatric residents per quarter by the end of the study period. The new use of LABA/inhaled corticosteroid combinations in children increased from 0.07 to 0.9 new users per 1,000 pediatric residents per quarter. New use of single agent LABA increased but remained low.

Children: Sociodemographic characterstics

For all agents studied, there was greater incident utilization among children for males, following adjustment for other factors (see Table 4.8). For most agents studied (except anticholinergics), there was lower incident utilization among rural children as compared to urban children, following adjustment for other factors. There was lower incident utilization of LABA and LABA/inhaled corticosteroid combinations among children with low as compared to high socioeconomic status, following adjustment for other factors. There was greater use of SABA and inhaled corticosteroids, but lower use of LABA and LABA/inhaled corticosteroid combinations among children aged five to eight as compared to 13–18, after adjustment for other factors.

Children: Regional Variation

When adjusted for age, sex, and socioeconomic status, the prevalent utilization of SABAs in children did not change over the time period evaluated in all regions (see Figure 4.10). Prevalent SABA use in children in the Rural South and the North regions was significantly lower than the Manitoba average at all three time periods. Prevalent children's SABA use in Winnipeg was significantly higher than the Manitoba average at all three time periods. Prevalent SABA use in children in Brandon was greater than the Manitoba average in 2008/09 only.

When adjusted for age, sex, and socioeconomic status, the prevalent utilization of inhaled corticosteroids in children did not consistently change over the time period evaluated (see Figure 4.11). Use of this class of medications in children declined from 1998/99 to 2003/04 in Brandon, Winnipeg, and Manitoba overall. Prevalent use of inhaled corticosteroids in children in the Rural South and the North regions was significantly lower than the Manitoba average at all three time periods. Prevalent use of inhaled corticosteroids in children in Winnipeg was significantly higher than the Manitoba average at all three time periods. Prevalent use of inhaled corticosteroids in children in Brandon was higher than the Manitoba average in 1998/99 and 2008/09.

When adjusted for age, sex, and socioeconomic status, the prevalent utilization of LABAs or LABA/inhaled corticosteroids in children increased over the time period evaluated in all regions (see Figure 4.12). There was no significant regional variation of the use of these agents.

Children: Optimal use evaluation

For 7,414 pediatric Manitobans with an incident prescription for a LABA or LABA/inhaled corticosteroid combination from 2002/03 through 2008/09, and a diagnosis of asthma in the year prior to the incident LABA or LABA/inhaled corticosteroid combination prescription, only 43.4% had been prescribed an oral or inhaled corticosteroid (see Table 4.9). This proportion decreased from 54.0% in 2002/03 to 37.0% in 2008/09.

For 643 pediatric Manitobans with an incident prescription for a LABA from 2002/03 through 2008/09 and a diagnosis of asthma, only 54.4% were prescribed an oral or inhaled corticosteroid within 90 days of this first prescription (see Table 4.10). This proportion decreased from 71.3% in 2002/03 to 33.3% in 2008/09.

Optimal prescribing of LABA/inhaled corticosteroids or LABA for asthma includes use of oral or inhaled corticosteroids prior to the LABA or LABA/corticosteroid combination (Fanta, 2009; Lougheed et al., 2010). From 2002/03 through 2008/09, there were 5,843 incident users of LABA or LABA/inhaled corticosteroid combination among Manitoba children (without prescriptions for anticholinergic inhalers or a diagnosis of cystic fibrosis and with a diagnosis of asthma in the three years prior to the incident LABA or LABA/corticosteroid prescription) included in the model. Of these, only 2,185 (37.4%) received a prescription for oral or inhaled corticosteroids in the year prior to the first prescription (the outcome variable was not receiving a prescription for oral or inhaled corticosteroids in the year prior to the first prescription). A total of 1.58% were excluded from the model because of missing values for some variables.

Age, number of different medications, number of prescriptions for antibiotics, number of prescriptions for other asthma medications, and use of leukotriene receptor antagonists influenced the likelihood of receiving a LABA or LABA/inhaled corticosteroid combination without previous use of oral or inhaled corticosteroids (see Table 4.11). Manitoba children were more likely to receive an incident LABA or LABA/inhaled corticosteroid combination without previous use of oral or inhaled corticosteroids as their age increased. Manitoba children were less likely to receive an incident LABA or LABA/inhaled corticosteroid combination without previous use of oral or inhaled corticosteroids as they had more different medications, more prescriptions for antibiotics or other asthma medications, or if they used a leukotriene receptor antagonists.

Prescriber specialist status, location of training, and years since licensure in Manitoba significantly influenced the likelihood of receiving a LABA or LABA/inhaled corticosteroid combination without previous use of oral or inhaled corticosteroids. Prescribers trained in North America were less likely than

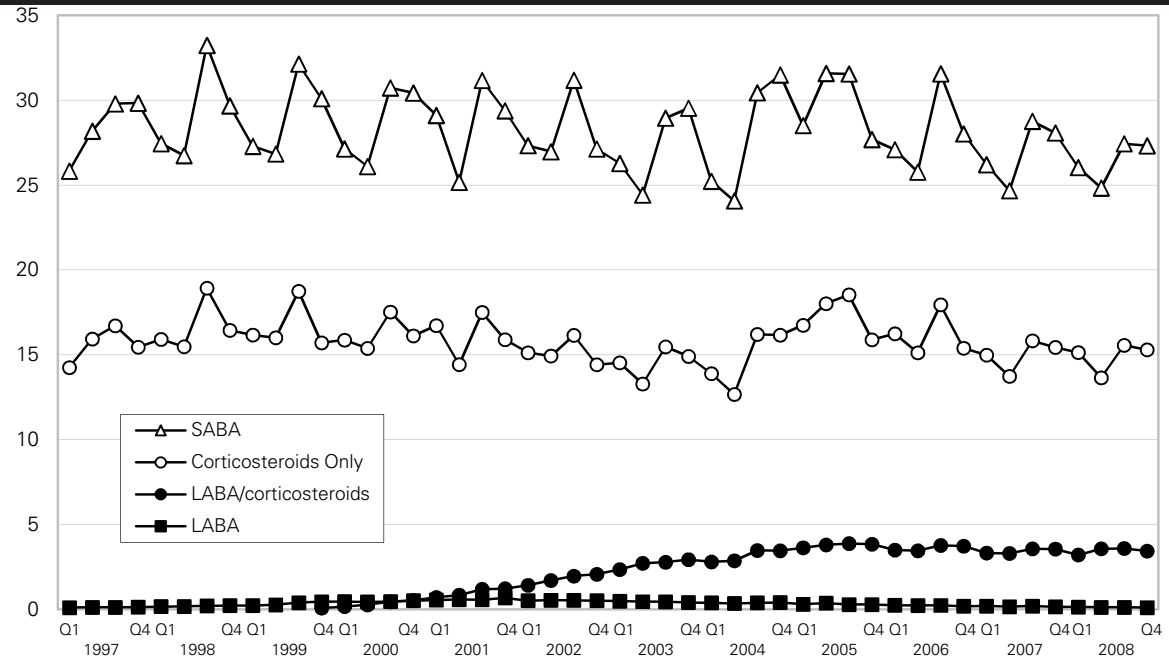
other prescribers to initiate LABA or LABA/inhaled corticosteroid combination without previous use of oral or inhaled corticosteroids. General practitioners and prescribers with more years since licensure in Manitoba were more likely than other prescribers to initiate LABA or LABA/inhaled corticosteroid combination without previous use of oral or inhaled corticosteroids.

Optimal prescribing of single entity LABA for asthma includes co–prescription of inhaled corticosteroids (Chowdhury & Dal Pan, 2010; Kuehn, 2010; Lougheed et al., 2010; Martinez, 2005). From 2002/03 through 2008/09, there were 501 incident users of LABA therapy among Manitoba children (without prescriptions for anticholinergic inhalers or a diagnosis of cystic fibrosis and with a diagnosis of asthma in the three years prior to the incident LABA prescription) included in the model. Of these, only 268 (53.5%) received a prescription for oral or inhaled corticosteroids 90 days before or after the first prescription (the outcome variable was not receiving a prescription for oral or inhaled corticosteroids 90 days before or after the first prescription). A total of 0.99% were excluded from the model because of missing values for some variables.

Age, year, number of different medications, number of ambulatory visits, number of other asthma medications, number of other medications and year of first prescription influenced the likelihood of receiving a LABA without co–prescribed corticosteroids (see Table 4.12). Manitoba children were more likely to receive an incident LABA without co–prescribed corticosteroids as age and number of physician visits increased. With each year after 2002/03, Manitoba children were more likely to receive an incident LABA without co–prescribed corticosteroids as compared to 2002/03. Manitoba children were less likely to receive a new LABA prescription without co–prescribed corticosteroids, as they had a greater number of different medications and more prescriptions for other asthma medications.

General practitioners were more likely than other prescribers to initiate LABA or LABA/inhaled corticosteroid combination without previous use of oral or inhaled corticosteroids.

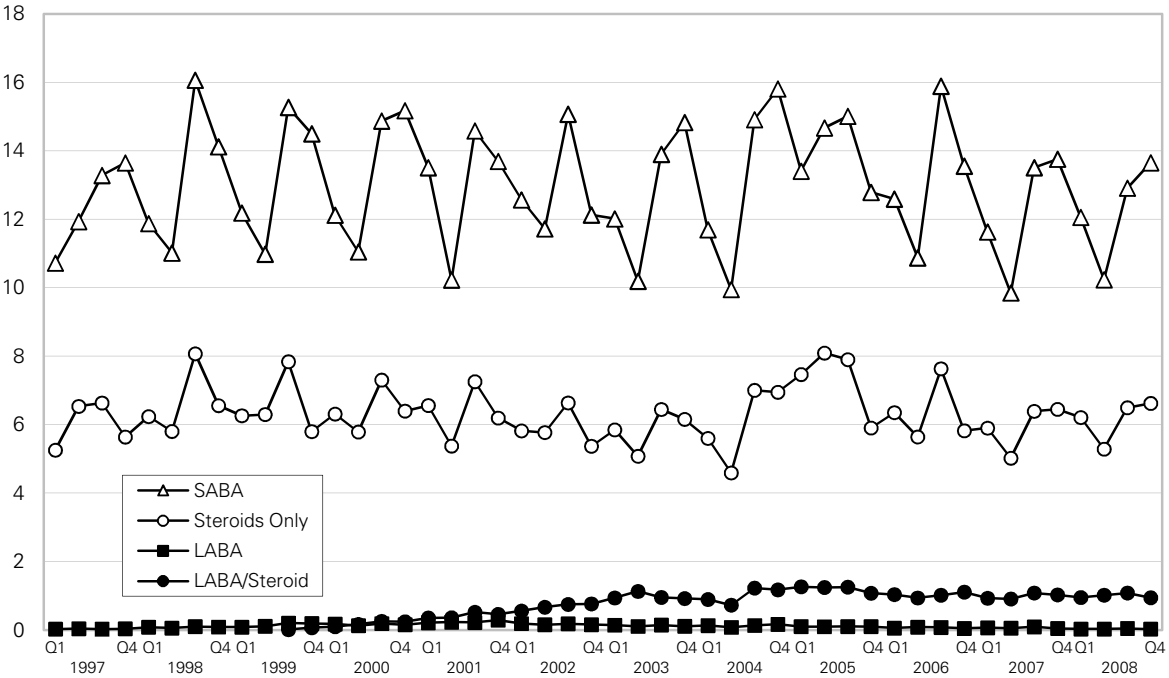
Figure 4.8: Inhaled Medications for Asthma Quarterly Prevalence, Children
Crude user rates per 1,000 children aged 0-18 years, Q1 1997-Q4 2008



'Q1' indicates rates for the 1st quarter (April to June)
'Q4' indicates rates for the 4th quarter (January to March)
'Q2' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2010

Figure 4.9: Medications for Asthma and Chronic Lung Disease Quarterly Incidence, Children
Crude rates of new users with no use of asthma or chronic disease medications in prior year per 1,000 children aged 0-18 years, Q1 1997-Q4 2008



'Q1' indicates rates for the 1st quarter (April to June)
'Q4' indicates rates for the 4th quarter (January to March)
'Q2' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2010

Table 4.7: Prevalent Use (Users/1,000 residents) of Inhaled Medications for Asthma Among Children, 1997/98 to 2008/09

Medication or Group of Medications	1997Q1 users/1,000	2008Q4 users/1,000	Change in rate per quarter	Age effect 5-8 vs 13-18	Socioeconomic status Low vs High	Region effect Rural vs Urban	Sex effect Male vs Female
SABA	25.83	27.32	1 NS	1.14 NS	1.09 NS	0.65 35% lower*	1.32 32% higher*
Corticosteroids only	14.24	15.29	1 NS	1.88 88% higher*	1 NS	0.67 33% lower*	1.49 49% higher*
LABA	0.1	0.1	0.99 1% decrease*	0.42 58% lower*	0.88 NS	0.98 NS	1.27 27% higher*
LABA/Corticosteroid Combination	0.07 1999Q3	3.43	1.06 6% increase*	0.42 58% lower*	0.75 25% lower*	0.7 30% lower*	1.54 54% higher*
Anticholinergics	0.29	0.13	0.98 2% decrease*	0.69 31% lower*	1.28 NS	3.46 346% higher*	1.43 43% higher*

*Indicates a statistically significant effect ($p<0.05$)

Note: Results for change in rate per quarter, age, socioeconomic status (SES), region, and sex effect are presented as relative rates (adjusted for age, SES, region, sex and time).

Source: Manitoba Centre for Health Policy, 2010

Table 4.8: Incident Use (Users/1,000 residents) of Inhaled Medications for Asthma Among Children, 1997/98 to 2008/09

Medication or Group of Medications	1997Q1 users/1,000	2008Q4 users/1,000	Change in rate per quarter	Age effect 5-8 vs 13-18	Socioeconomic status Low vs High	Region effect Rural vs Urban	Sex effect Male vs Female
SABA	10.72	13.65	1 slight increase*	1.31 31% higher*	0.99 NS	0.69 31% lower*	1.19 19% higher*
Corticosteroids only	5.26	6.62	1 No change	1.74 74% higher*	0.98 NS	0.68 32% lower*	1.35 35% higher*
LABA	0.02	0.03	0.99 1% decrease*	0.47 53% lower*	0.85 15% lower*	0.85 15% lower*	1.2 20% higher*
LABA/Corticosteroid Combination	0.07 1999Q4	0.94	1.04 4% increase*	0.5 50% lower*	0.75 25% lower*	0.71 29% lower*	1.37 37% higher*
Anticholinergics	0.13	0.07	0.99 1% decrease*	0.79 NS	1.34 34% higher*	4.04 404% higher*	1.32 32% higher*

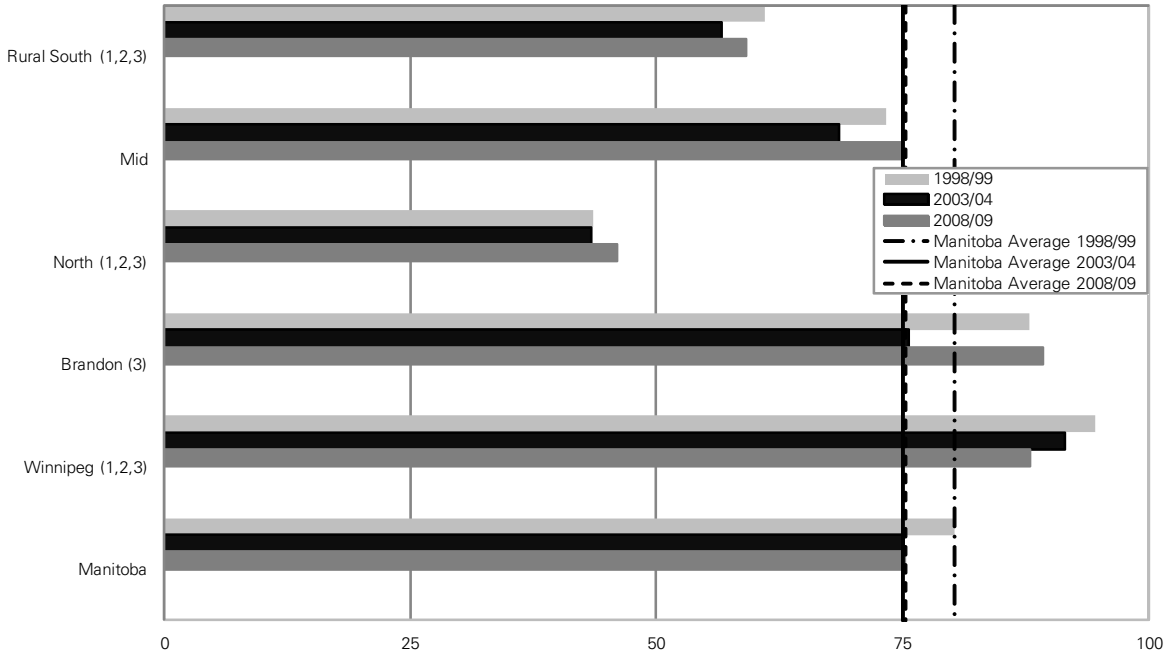
*Indicates a statistically significant effect ($p<0.05$)

Note: Results for change in rate per quarter, age, socioeconomic status (SES), region, and sex effect are presented as relative rates (adjusted for age, SES, region, sex and time).

Source: Manitoba Centre for Health Policy, 2010

Figure 4.10: SABA Users per 1,000 Children by Region

Adjusted by (2003/04) age, sex, and SES per 1,000 residents aged 0-18

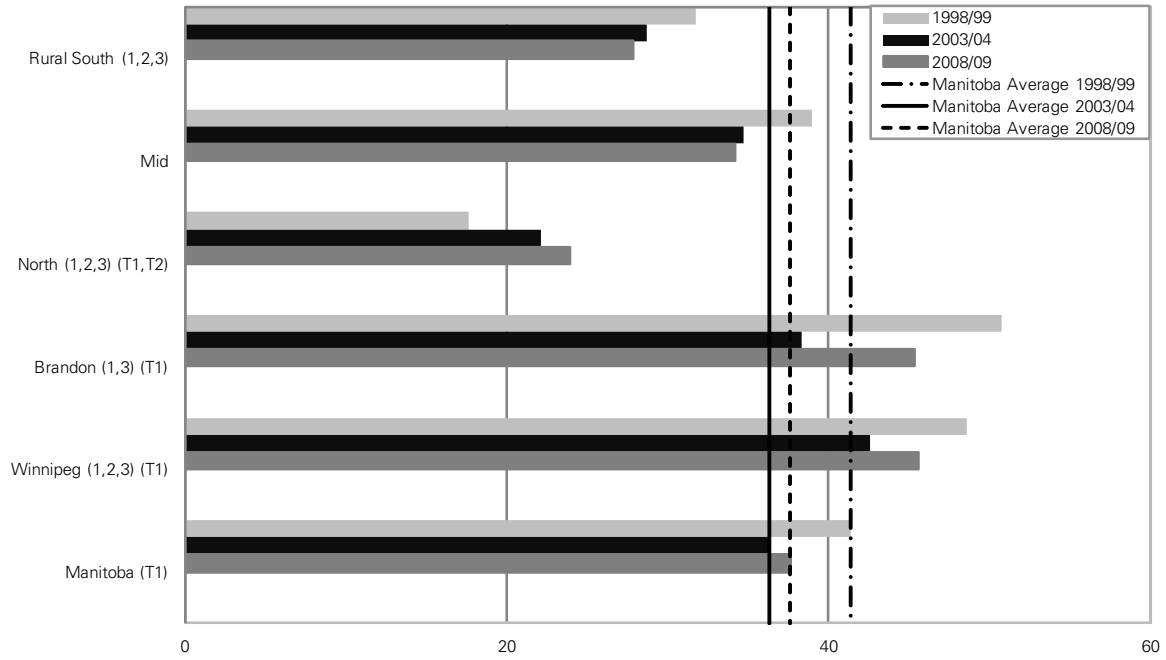


'1'- indicates area's rate was statistically different from Manitoba average in 1998/99.
'2'- indicates area's rate was statistically different from Manitoba average in 2003/04.
'3'- indicates area's rate was statistically different from Manitoba average in 2008/09.
'T1'- indicates change over time (1998/99 versus 2003/04) was statistically different for that area.
'T2'- indicates change over time (1998/99 versus 2008/09) was statistically different for that area.
'T3'- indicates change over time (2003/04 versus 2008/09) was statistically different for that area.

Source: Manitoba Centre for Health Policy, 2010

Figure 4.11: Inhaled Corticosteroid Users per 1,000 Children by Region

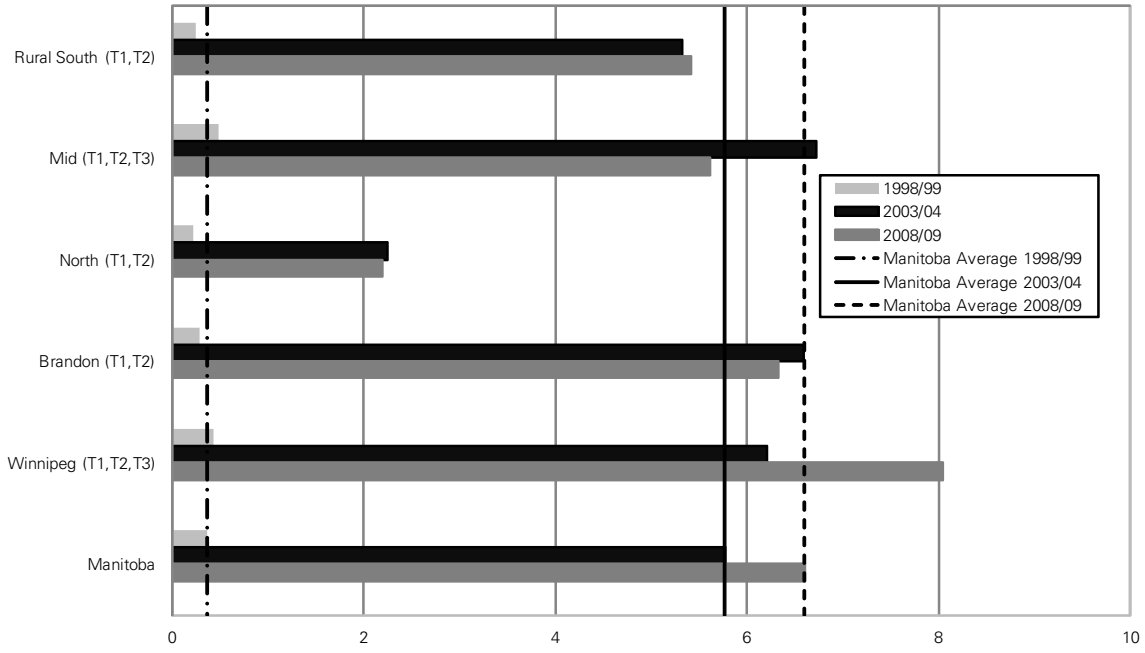
Adjusted by (2003/04) age, sex, and SES per 1,000 residents aged 0-18



'1'- indicates area's rate was statistically different from Manitoba average in 1998/99.
'2'- indicates area's rate was statistically different from Manitoba average in 2003/04.
'3'- indicates area's rate was statistically different from Manitoba average in 2008/09.
'T1'- indicates change over time (1998/99 versus 2003/04) was statistically different for that area.
'T2'- indicates change over time (1998/99 versus 2008/09) was statistically different for that area.
'T3'- indicates change over time (2003/04 versus 2008/09) was statistically different for that area.

Source: Manitoba Centre for Health Policy, 2010

Figure 4.12: LABA or LABA/Inhaled Corticosteriod Combination Users per 1,000 Children by Region
Adjusted by (2003/04) age, sex, and SES per 1,000 residents aged 0-18



'1'- indicates area's rate was statistically different from Manitoba average in 1998/99.
'2'- indicates area's rate was statistically different from Manitoba average in 2003/04.
'3'- indicates area's rate was statistically different from Manitoba average in 2008/09.
'T1'- indicates change over time (1998/99 versus 2003/04) was statistically different for that area.
'T2'- indicates change over time (1998/99 versus 2008/09) was statistically different for that area.
'T3'- indicates change over time (2003/04 versus 2008/09) was statistically different for that area.

Source: Manitoba Centre for Health Policy, 2010

Table 4.9: Use of Asthma Medication Prior to LABA or LABA/Corticosteroid Combination Use for Children with Asthma by Year
Count and proportion of new LABA or LABA/inhaled corticosteroid combination users*
who used asthma medications in the prior year

		Medication in year prior to LABA or LABA/inhaled corticosteroid combination					
Fiscal Year	**Total LABA or LABA/steroid combination users**	**Inhaled corticosteroids (ICS)**	**Oral steroids**	**ICS or oral steroids**	**SABA**	**Montelukast/ Zafirlukast**	**Any asthma medication**
2002/03	828	379 (45.8%)	191 (23.1%)	447 (54.0%)	546 (65.9%)	116 (14.0%)	649 (78.4%)
2003/04	1084	414 (38.2%)	248 (22.9%)	522 (48.2%)	709 (65.4%)	134 (12.4%)	807 (74.4%)
2004/05	1090	350 (32.1%)	232 (21.3%)	447 (41.0%)	726 (66.6%)	159 (14.6%)	832 (76.3%)
2005/06	1272	416 (32.7%)	282 (22.2%)	543 (42.7%)	854 (67.1%)	197 (15.5%)	963 (75.7%)
2006/07	1076	336 (31.2%)	234 (21.7%)	442 (41.1%)	705 (65.5%)	161 (15.0%)	799 (74.3%)
2007/08	1049	325 (31.0%)	223 (21.3%)	443 (42.2%)	693 (66.1%)	183 (17.4%)	800 (76.3%)
2008/09	1015	262 (25.8%)	207 (20.4%)	376 (37.0%)	670 (66.0%)	208 (20.5%)	766 (75.5%)
Total	7414	2482 (33.5%)	1617 (21.8%)	3220 (43.4%)	4903 (66.1%)	1158 (15.6%)	5616 (75.7%)

* with a dignosis for asthma (one physician claim, one hospital claim, or one prescription for an asthma medication) and no anticholinergics or cystic fibrosis diagnosis from 2002/03 - 2008/09

Source: Manitoba Center for Health Policy, 2010

Table 4.10: Use of Asthma Medication Prior to LABA Use for Children with Asthma by Year
Count and proportion of new LABA users* who used asthma medications +/- 90 days

		Medication 90 days prior to or after LABA		
Fiscal Year	**Total LABA users**	**Inhaled corticosteroids (ICS)**	**Oral steroids**	**ICS or oral steroids**
2002/03	164	110 (67.1%)	37 (22.6%)	117 (71.3%)
2003/04	114	57 (50.0%)	23 (20.2%)	61 (53.5%)
2004/05	126	64 (50.8%)	15 (11.9%)	65 (51.6%)
2005/06	90	41 (45.6%)	11 (12.2%)	45 (50.0%)
2006/07	62	23 (37.1%)	8 (12.9%)	25 (40.3%)
2007/08	57	25 (43.9%)	10 (17.5%)	27 (47.4%)
2008/09	30	7 (23.3%)	5 (16.7%)	10 (33.3%)
Total	643	327 (50.9%)	109 (17.0%)	350 (54.4%)

* with a dignosis for asthma (one physician claim, one hospital claim, or one prescription for an asthma medication) and no anticholinergics or cystic fibrosis diagnosis from 2002/03 - 2008/09

Source: Manitoba Center for Health Policy, 2010

Table 4.11: Factors Predictive of Incident LABA or LABA/Corticosteroid Combination Use without Oral or Inhaled Corticosteroids in Year Prior
Odds ratio estimates for incident child users or LABA or LABA corticosteroid combination with asthma*, 2002/03 - 2008/09

Variable	Odds Ratio (95% Confidence Interval)
Age (years, continuous)	1.104 (1.087, 1.121)
Number of other medications in prior year (continuous)	0.904 (0.865, 0.944)
Number of prescriptions for asthma in prior year (continuous)	0.618 (0.593, 0.643)
Number of prescriptions for antibiotics in prior year (continuous)	0.940 (0.903, 0.978)
Use of leukotriene receptor antagonists in prior year (yes vs no)	0.561 (0.469, 0.671)
Physician (general practitioner vs specialist)	1.680 (1.445, 1.954)
Physician training (North America vs other)	0.846 (0.728, 0.982)
Number of years since physician licensure in MB (continuous)	1.026 (1.011, 1.041)

Bold = statistically significant (p<0.05)

Note: Model adjusted for all the variables listed above as well as patient characteristics (sex, region of residence, socioeconomic status, number of physician visits and hospitalizations, number of major ADGs, in the year prior to the first prescription) prescriber characteristics (hospital affiliation, type of reiumbursement) and year of first prescription.
* with a dignosis for asthma (one physician claim, one hospital claim, or one prescription for an asthma medication)

Source: Manitoba Centre for Health Policy, 2010

Table 4.12: Factors Predictive of Incident LABA Use without Oral or Inhaled Corticosteroids within 90 Days
Odds ratio estimates for incident child users or LABA with asthma*, 2002/03-2008/09

Variable	Odds Ratio (95% Confidence Interval)
Age (years, continuous)	1.179 (1.112, 1.251)
Year 2008/09 (vs 2002/03)	11.806 (2.804, 49.705)
Year 2007/08 (vs 2002/03)	3.389 (1.368, 8.396)
Year 2006/07 (vs 2002/03)	2.948 (1.232, 7.056)
Year 2005/06 (vs 2002/03)	3.380 (1.631, 7.002)
Year 2004/05 (vs 2002/03)	3.065 (1.587, 5.918)
Year 2003/04 (vs 2002/03)	2.325 (1.260, 4.292)
Number of other medications in prior year (continuous)	0.760 (0.659, 0.877)
Number of ambulatory visits in year prior (continuous)	1.113 (1.042, 1.190)
Number of other asthma medications (continuous)	0.829 (0.740, 0.930)
Physician (GP vs specialist)	1.726 (1.052, 2.832)

Bold = statistically significant ($p<0.05$)

Note: Model adjusted for all the variables listed above as well as patient characteristics (sex, region of residence, socioeconomic status, number of hospitalizations, number of major ADGs, number of prescriptions for antibiotics, use of monteleukast or zafirlukast in the year prior to the first prescription) and prescriber characteristics (hospital affiliation, location of training, years since licensure in Manitoba, type of reimbursement)

* with a dignosis for asthma (one physician claim, one hospital claim, or one prescription for an asthma medication)

Source: Manitoba Centre for Health Policy, 2010

Discussion

There was a rapid increase in the utilization of LABA/inhaled corticosteroid combinations in both adults and children. By the end of the study period, 1.7% of the adult population and 0.03% of the pediatric population had used a LABA/inhaled corticosteroid combination. These results are consistent with what other authors have observed (Allen–Ramey, Samet, Rand, & Joseph, 2004; Bollinger, Smith, LoCasale, & Blaisdell, 2007; Boyter & Steinke, 2005; Cohen, Taitz, & Jaffe, 2007; DiSantostefano, Davis, Yancey, & Crim, 2008; Dormuth et al., 2006; Kozyrskyj et al., 2009; Phillips & McDonald, 2008; Turner, Thomas, von Ziegenweidt, & Price, 2009). We also observed an overall decline in utilization of single–entity inhaled corticosteroids; use of these agents was largely replaced by LABA/inhaled corticosteroid combinations (DiSantostefano et al., 2008).

Sociodemographic factors influencing the use of medications for asthma and chronic obstructive pulmonary disease were as expected and consistent with other studies. These include a greater use of all medications amongst boys (Fanta, 2009) and a seasonal pattern of medication use for children (Butz et al., 2008). We also observed, as have others, the increasing use of medications with increasing age for adults (Haupt, Wettermark, & Nilsson, 2008). We observed a lower use of the costly LABA/inhaled corticosteroids among children with low socioeconomic status, suggesting that cost sharing may impact access to these medications (Kozyrskyj, Mustard, & Simons, 2003).

Optimal prescribing of LABA/inhaled corticosteroids or LABA for asthma includes use of oral or inhaled corticosteroids prior to the LABA or LABA/corticosteroid combination (Fanta, 2009; Lougheed et al., 2010). For both adults and children with asthma, the minority of individuals (30.7% of adults and 37.4% of children) with a new prescription for LABA or LABA/inhaled corticosteroid combination had been prescribed an oral or inhaled corticosteroid in the year prior to the incident LABA/inhaled corticosteroid combination prescription. This proportion declined for both adults and children over the study period 2002/03 through 2008/09. This was despite the requirement for only a single prescription for an oral or inhaled corticosteroid in the year prior. This finding is similar to a Quebec study that found that only 39.6% of individuals prescribed a LABA/inhaled corticosteroid combination (without anticholinergics or a diagnosis of cystic fibrosis) between 2000–2003 had received a prescription for inhaled corticosteroids in the year prior (36.3% in 2002 and 33.2% in 2003, respectively (Breton et al., 2007). With similar methodology (except with a more specific diagnosis of asthma in our analysis), we observed that 38.0% of new adult users of LABA/inhaled corticosteroid combination in 2002/03, and 31.9% in 2003/04, had received a prescription for inhaled corticosteroids in the year prior. Breton et al. performed a sensitivity analyses of individuals receiving a new prescription for a LABA/inhaled corticosteroid combination with a diagnosis for asthma within the year prior to the first prescription, and they still found that only 56.4% of these users had a prescription for inhaled corticosteroids in the year prior to the first LABA/inhaled corticosteroid combination in 2000–2003; this result was similar to the current study (Breton et al., 2007). Breton et al. also found that only 2.5% of new users of LABA/inhaled corticosteroid combinations had used inhaled corticosteroids for more than 75% of the time before the LABA/inhaled corticosteroid prescription (2007). Like these authors, we observed that patients with greater markers of asthma severity and uncontrolled asthma (use of other medications, number of prescriptions for asthma medications, number of prescriptions for antibiotics, use of leukotriene receptor antagonists, or referral to a specialist) were more likely to receive steroids prior to the LABA. Also like these authors, we found that general practitioners were less likely to prescribe steroids prior to the LABA (Breton et al., 2007). In a US study of new users of LABA, use of a controller (inhaled corticosteroid, leukotriene receptor antagonists, theophylline, mast cell stabilizer, or oral or injectable corticosteroid) within six months was observed in only 40% of asthmatics (Stockl, Le, Harada, & Zhang, 2008).

Optimal prescribing of single entity LABA for asthma includes co–prescription of inhaled corticosteroids (Chowdhury & Dal Pan, 2010; Kuehn, 2010; Lougheed et al., 2010; Martinez, 2005). Only just over half of LABA users (53.8 for adults and 53.5 for children) received prescriptions for inhaled or oral steroids within 90 days of the first LABA prescription, and this proportion decreased over time. Patient characteristics suggestive of greater asthma severity or uncontrolled asthma conferred greater likelihood of receipt of steroids with the LABA. We found that general practitioners were less likely to prescribe steroids with the LABA.

One explanation for the use of new LABA or LABA/inhaled corticosteroid combination without an oral or inhaled corticosteroid in the year prior is that prescribers are using these agents for conditions other than asthma such as chronic obstructive lung disease (COPD) or bronchitis (Breton et al., 2007). Individuals may also have asthma and chronic obstructive lung disease. Individuals, particularly young children, who we categorized as having asthma, may not actually have asthma (Turner et al., 2009). These are possible explanations for the use of LABA alone with no prescription for inhaled or oral corticosteroids within 90 days. Smoking related chronic obstructive pulmonary disease is a possibility, but for these individuals, it is likely that they would receive a prescription for an anticholinergic (and we excluded individuals with any prescriptions for anticholinergics in all years of data) as anticholinergics are more effective than SABA in COPD (O'Donnell et al., 2007). However, our data did not demonstrate significantly greater utilization of steroids prior to LABA or LABA/inhaled corticosteroid combinations in children (who presumably would not be experiencing chronic obstructive pulmonary disease) than in adults. We also observed that only 60% of adults and 66% of children filled at least one prescription for a SABA in the one year prior to LABA or LABA/inhaled corticosteroid combination, and only 70% and 76% of adults and children, respectively, filled at least one prescription for any asthma medication in the one year prior to the first LABA or LABA/inhaled corticosteroid combination. This suggests that numerous individuals are receiving LABA or LABA/inhaled corticosteroid combinations as their first prescription for any asthma therapy. Other off–label use of these agents for other respiratory conditions, such as respiratory tract infections, bronchiolitis, bronchitis, and other allergic diseases in pediatrics, has been described and remains a possibility for adults (Baiardi et al., 2010). The findings that general practitioners prescribed more LABAs without corticosteroids may be partially explained by confounding by indication; individuals with asthma are more likely to see a specialist.

Another possible explanation could be that individuals are receiving physician samples for inhaled corticosteroids, which would not be captured in the DPIN system. However, it seems unlikely that such a large percentage of LABA/inhaled corticosteroid or LABA users would receive samples. Additionally, as generic inhaled corticosteroids became available, the likelihood of physician samples of inhaled corticosteroids has declined. It is possible that individuals receiving a LABA may have filled an inhaled corticosteroid 91 days or greater before or after and, therefore, be using the two agents together. However, since most inhalers for inhaled corticosteroids contain between 60 and 240 doses (Fanta, 2009) and most inhaled corticosteroids should be administered twice daily, it would only be expected that an inhaled corticosteroid metered dose inhaler would last between 30 and 120 days. It is also possible that individuals may use multiple inhalers at once, not use the whole inhaler, or lose inhalers, which are limitations of considering a filled prescription as use of a medication (Turner et al., 2009).

Additional studies are required to evaluate whether the clinical practice of using a LABA alone or in combination with an inhaled corticosteroid without prior use of inhaled or oral corticosteroids will result in an increase in asthma related morbidity or mortality (Fanta, 2009; Stockl et al., 2008); however, some data suggest that LABA increase the risk for asthma related intubations and deaths, even when used with concomitant inhaled corticosteroids (Salpeter et al., 2010). In the meantime, health professionals,

such as pharmacists, can continue to encourage prescribing and adherence to therapy in accordance with asthma guidelines and using LABA and LABA/inhaled corticosteroid combinations as step–up therapy (Blais, Laurier, & Pare, 2008). Further education for patients and health professionals about the role of LABA in the treatment of asthma, especially in light of the warnings about the use of LABAs (Chowdhury & Dal Pan, 2010), is required.

Not all Canadian provinces have open listings for LABAs. In October 2003, the Regie de l'assurance maladie du Quebec (provincial public prescription medication insurance plan) introduced a prior authorization process for LABA/inhaled corticosteroid combination therapy to limit the use of these medications to treatment of asthma and other reversible obstructive diseases of the respiratory tract in persons whose control of the disease is insufficient despite the use of inhaled corticosteroid (Guenette & Gaudet, 2010). A recent analyses of this pharmaceutical policy demonstrated no impact on first asthma related hospitalization or emergency department visit (Guenette & Gaudet, 2010).

In summary, current asthma guidelines recommend the use of corticosteroids prior to the use of LABA and do not recommend LABA without the use of corticosteroids due to concern for increased asthma morbidity with LABA. The use of LABA without prior corticosteroids in Manitobans with asthma is increasing, despite asthma guidelines. Similarly, the use of LABA without the use of corticosteroids in Manitobans with asthma is increasing. Asthma patients are more likely to be prescribed asthma medications not according to guidelines if they have less severe asthma, or see general practitioners. Challenges to the interpretation of this data include the difficulty of using administrative data to diagnose asthma. Further education for patients and physicians about the role of LABA in the treatment of asthma, especially in light of the warnings about the use of LABAs, is required.

Chapter 5: Biologic Agents

Biologic medications refer to a broad group of protein–based medications produced using living organisms, such as plants, animals, and microorganisms such as yeast and bacteria. These medications are complex to manufacture and cannot be synthesized in a laboratory using chemical processes alone, but require the application of recombinant DNA technology to produce large molecule proteins with molecular diversity (Revers & Furczon, 2010a). Numerous groups of medications are included in the broad definition of biologics; however, in order to distinguish older technologies for biologic medications (e.g., vaccines), an accepted definition for biologics includes only recombinant proteins (e.g., erythropoietin) and monoclonal antibodies (e.g., rituximab) (Revers & Furczon, 2010b). Common features of these groups of medications include an effect on the immune system, subcutaneous or intravenous route of administration, and high cost. For example, for the treatment of psoriasis at maintenance dose, therapy with the various biologic agents approved for use (adalimumab, etanercept, efalizumab, infliximab, and alefacept) ranges from $19,191–$29,976 annually (CADTH) (Canadian Agency for Drugs and Technologies in Health, 2008). Several of these medications are dispensed and administered only through hospitals (for in– or outpatients), such as the use of erythropoietic therapies for the treatment of anemia of chronic kidney disease for hemodialysis patients or the use of rituximab for non–Hodgkin lymphoma. These medications are therefore not part of the DPIN system.

The focus of this report is on biologic agents used to treat **rheumatoid arthritis**, ankylosing spondylitis, **inflammatory bowel disease,** and **psoriasis**. The biologic agents evaluated in this deliverable include the tumor necrosis factor (TNF) alpha inhibitors infliximab, etanercept, and adalimumab and the interleukin–1 antagonist anakinra. These agents are injectable and therefore given subcutaneously or intravenously. They are used for the treatment of severe rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis, inflammatory bowel disease, and psoriasis. We also included the biological response modifiers abatacept (used for rheumatoid arthritis), alefacept, and the monoclonal antibody efalizumab (used for psoriasis). Prescriptions for the medications included in this report are generally filled at retail pharmacies (part of the DPIN system) and self administered by the patient (for subcutaneous injections), through outpatient infusion clinics (for intravenous infusions), or outpatient hospital visits. For the purposes of this report the term "all biologic agents" refers to the biologic agents included in this report, namely etanercept, infliximab, adalimumab, anakinra, alefacept, abatacept, and efalizumab.

Rheumatoid arthritis is a chronic, systemic, inflammatory disorder that causes joint stiffness, swelling, erosions or decalcification, and deformity (Venables & Maini, 2010). Ankylosing spondylitis is a chronic, systemic inflammatory disorder characterized by back pain and other complications (Braun, 2009). Psoriatic arthritis is an inflammatory joint disease associated with psoriasis (Wollina, Unger, Heinig, & Kittner, 2010). For treatment of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, the agents act by inhibiting the action of TNF (includes etanercept, infliximab, and adalimumab). They have been shown to reduce disease activity and improve physical functioning and quality of life when used alone or in combination with other medications. Anakinra is not as potent as other anti TNF medications, so it is not included in recent guidelines. As of 2008, there is no evidence for combinations of biologics as a treatment of rheumatoid arthritis (Saag et al., 2008). These agents are considered to be interchangeable by recent American College of Rheumatology guidelines (Saag et al., 2008).

Inflammatory bowel disease (IBD) is comprised of two major disorders: ulcerative colitis and Crohn's disease. Ulcerative colitis is characterized by recurring inflammation of the inner lining of rectum and other portions of the colon. Crohn's disease is characterized by deeper tissue inflammation and

may involve the entire gastrointestinal tract (Peppercorn, 2010). For the treatment of inflammatory bowel disease, infliximab and adalimumab are used for individuals who have demonstrated failure or intolerance of corticosteroids and immunosuppressive agents, who are steroid dependent despite immunosuppressive agents, or who have failed corticosteroids and are too unwell to wait for the effects of methotrexate or azathioprine (Van Assche, Vermeire, & Rutgeerts, 2008).

Psoriasis is a chronic skin disorder that causes areas of thickened, inflamed, red skin, often covered with silvery scales. Approximately one–third of people with psoriasis also have psoriatic arthritis, a condition that causes joint pain and swelling (Feldman & Pearce, 2010). Etanercept, infliximab, adalimumab, alefacept, and efalizumab are indicated to treat severe psoriasis (Ferrandiz, Carrascosa, & Boada, 2010).

All of the biologic agents used to treat rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, and psoriasis included in this report are generally second line therapy for the various conditions they are used to treat. The biologic agents are used for the treatment of severe rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, and psoriasis in people who have not responded to or are unable to tolerate the usual first line therapies.

Biologic agents have been associated with injection site reactions and infusion reactions (including anaphylaxis). Other risks associated with this group of medications include opportunistic infections (infections caused by organisms that do not cause infections in immunocompetent individuals, but can cause very serious infections in immunocompromised individuals, e.g. fungal infection), solid cancers, lymphoma, and leukemia (Ferrandiz et al., 2010; Saag et al., 2008; Stallmach, Hagel, & Bruns, 2010).

In Manitoba, etanercept, infliximab, adalimumab, and anakinra (and other biologics) are Part 3 of the Manitoba Drug Benefits and Interchangeability Formulary with prior approval for certain criteria and prescribing limited to specialists. Part 3 status is reserved for products that require physicians to contact Pharmacare to obtain special approval for use (by telephone or in writing). EDS is granted on a case by case basis for specific criteria for use of the medication, and it is generally for one or three years coverage, which can be renewed. Approval for use is granted on a case by case basis for these agents and usually involves severe disease and failure of or intolerance to the usual first line agents. Infliximab, etanercept, and adalimumab are covered for the treatment of severe rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis for individuals with an inadequate response on optimal doses of disease–modifying antirheumatic drugs (Canadian Agency for Drugs and Technologies in Health, 2006a; Canadian Agency for Drugs and Technologies in Health, 2007; Canadian Agency for Drugs and Technologies in Health, 2010). Infliximab was not recommended for listing by the Common Drug Review of the Canadian Agency for Drugs and Technologies in Health (CADTH) for the treatment of ulcerative colitis (Canadian Agency for Drugs and Technologies in Health, 2009a). Adalimumab was recommended for listing by CADTH for the treatment of severe debilitating psoriasis (Canadian Agency for Drugs and Technologies in Health, 2008). The biological response modifiers abatacept (used for rheumatoid arthritis), alefacept, and the monoclonal antibody efalizumab (used for psoriasis) were never approved for coverage by the Manitoba Drug Benefits and Interchangeability Formulary. Efalizumab was withdrawn from the Canadian market in June 2009 (Healthcare Professional Communication, 2009). It is important to note that there are numerous other formularies in Manitoba (First Nations and Inuit Health Branch, private insurance, Department of Veterans Affairs) that might impact Manitoba residents covered by these formularies. All formularies generally restrict the use of biologic agents to individuals and prescribers that meet certain criteria.

Methods

We evaluated the utilization of biologic agents used to treat rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, and psoriasis in the Manitoba population over time. Prevalent and incident utilization for the population of Manitoba was determined for the following medications: etanercept, infliximab, adalimumab, anakinra, alefacept, abatacept, and efalizumab. Details about the medications included in these categories are presented in Appendix Table 1.1.

Incident users were those users of etanercept, infliximab, adalimumab, anakinra, alefacept, abatacept, and efalizumab who had not received a prescription for the medication of interest in one year prior to the year of interest (however, they could have received an alternate biologic agent prior to this first prescription).

Prevalent and incident utilization is presented as prevalent and incident users per 1,000 for the overall adult population of Manitoba. The influence of sociodemographic characteristics on prescribing over the entire study period (1997/98–2008/09) was conducted with generalized estimating equations. Regional analysis of medication utilization for the fiscal years 1998/99, 2003/04, and 2008/09 compares prevalent users (annual rates, adjusted for age, sex, and socioeconomic status) across five regions of Manitoba (Rural South, Mid, North, Winnipeg, and Brandon) and Manitoba overall.

Optimal Use Evaluation

For incident utilization of TNF alpha inhibitors (etanercept, infliximab, and adalimumab) in adult Manitobans, we evaluated the following criteria:

- Proportion of incident users of TNF alpha inhibitors (etanercept, infliximab, and adalimumab) or anakinra (from 2000/01 through 2008/09) who had evidence in physician or hospital claims in the three years prior to the incident prescription that the medications were being used for rheumatoid arthritis (ICD–9–CM: 714, ICD–10–CA: M05–M06); ankylosing spondylitis (ICD–9–CM: 720, ICD–10–CA: M45, M46); inflammatory bowel disease (ICD–9–CM: 555, 556, ICD–10–CA: K50, K51); or psoriasis (includes psoriatic arthritis) (ICD–9–CM: 696, ICD–10–CA: L40–L45) (Crown, Bresnahan, Orsini, Kennedy, & Leonardi, 2004).

- Proportion of incident users of TNF alpha inhibitors (etanercept, infliximab, and adalimumab) or anakinra (from 2000/01 through 2008/09) who switched to another TNF alpha inhibitor (etanercept, infliximab, and adalimumab) or anakinra at any point within the first year of therapy after being initiated on the first agent.

Results

A total of 802,794 adults in 1997/98, up to 859,108 adults in 2008/09 formed the denominator for this analysis.

Prevalence

Prevalent utilization of biologic agents used to treat rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, and psoriasis increased from the beginning of 2001 when the first agents became available to the end of the study period (see Figure 5.1). There were insufficient prescriptions to evaluate alefacept, abatacept, and efalizumab; however, their utilization was included in the total (all biologic agents). Use of all biologic agents in this evaluatation increased from 0.01 to 1.3 users per 1,000 residents over the study period. Etanercept was the most commonly utilized medication (prevalent users increased from 0.01 to 0.6 users per 1,000 residents) followed by infliximab (prevalent users

increased from 0.01 to 0.32 per 1,000 residents). Use of adalimumab increased from 0.05 in the third quarter of 2004, when it became available, to 0.4 by the end of the study period. Utilization of anakinra was minimal.

Sociodemographic characteristics

Aside from infliximab, there was greater prevalent utilization of biologic agents among those aged 45–64 as compared to those aged 19–44, following adjustment for other factors (see Table 5.1). There was lower use of all biologic agents in males as compared to females. We also observed lower use of infliximab, adalimumab, and the all biologics group in rural areas as compared to urban areas, after adjusting for other factors in the model.

Incidence

New use of biologic agents used to treat rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, and psoriasis increased from 0.01 to 0.14 users per 1,000 residents per quarter over the study period (see Figure 5.2). There were insufficient prescriptions to evaluate alefacept, abatacept, and efalizumab; however, their utilization was included in the total (all biologic agents). Etanercept was the most commonly utilized medication; incident users increased from 0.01 to 0.07 users per 1,000 residents per quarter at the beginning of 2006, then declined to 0.06 by the end of the study period. New use of infliximab increased from 0.01 to 0.02 per 1,000 residents per quarter. Use of adalimumab spiked to 0.05 new users per 1,000 residents in the third quarter of 2004 when it became available, then increased gradually to 0.09 new users per 1,000 residents per quarter by the end of the study period. Utilization of anakinra was minimal.

Sociodemographic characteristics

There was greater incident utilization of biologic agents, except for infliximab, among those aged 45–64 as compared to those aged 19–44, following adjustment for other factors (see Table 5.2). We also observed lower utilization of all biologic agents in males as compared to females; however, we did not observe a consistent effect of socioeconomic status or region of residence on the use of biologic agents.

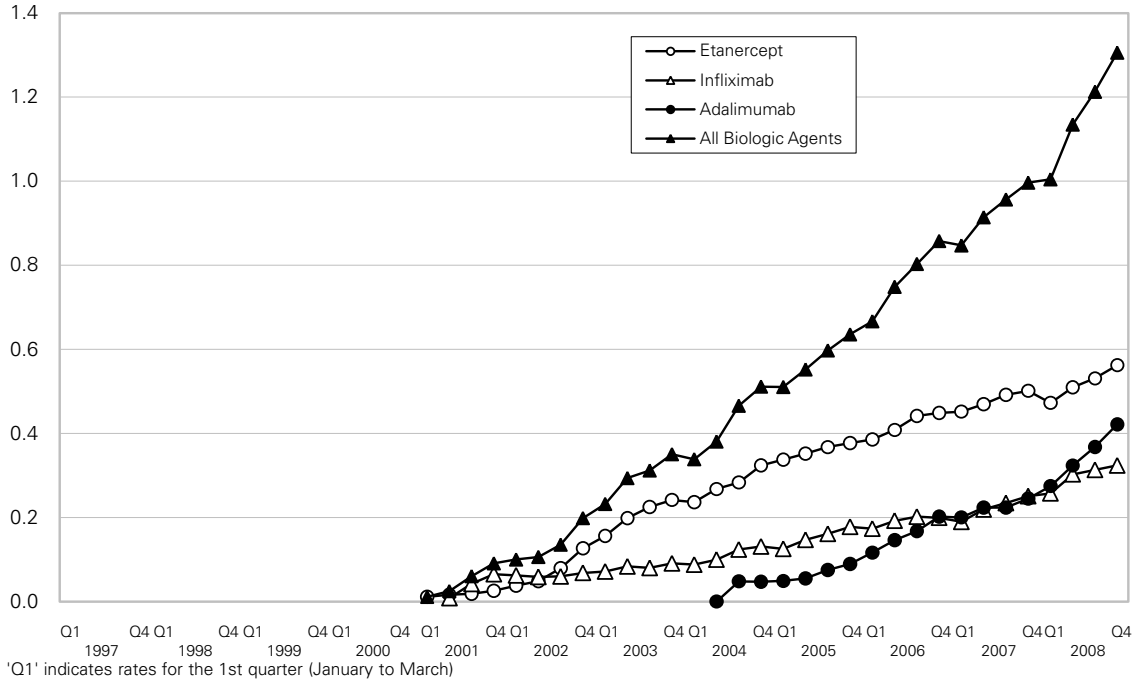
Regional variation

When adjusted for age, sex, and socioeconomic status, the prevalent utilization of biologic agents in adults increased over the time period evaluated in all regions (see Figure 5.3). Prevalent use of all biologics in the Rural South region was significantly lower than the Manitoba average in 2008/09.

When adjusted for age, sex, and socioeconomic status, the prevalent utilization of etanercept increased for adults over the time period evaluated across all regions of Manitoba (see Figure 5.4). Prevalent use for etanercept in the Rural South was significantly lower than the Manitoba average in 2008/09.

When adjusted for age, sex, and socioeconomic status, the prevalent utilization of infliximab increased for adults over the time period evaluated across all regions (see Figure 5.5). There was no significant regional variation.

Figure 5.1: Medications for Biologic Agents Quarterly Prevalence, Adults
Crude user rates per 1,000 adults, Q1 1997-Q4 2008

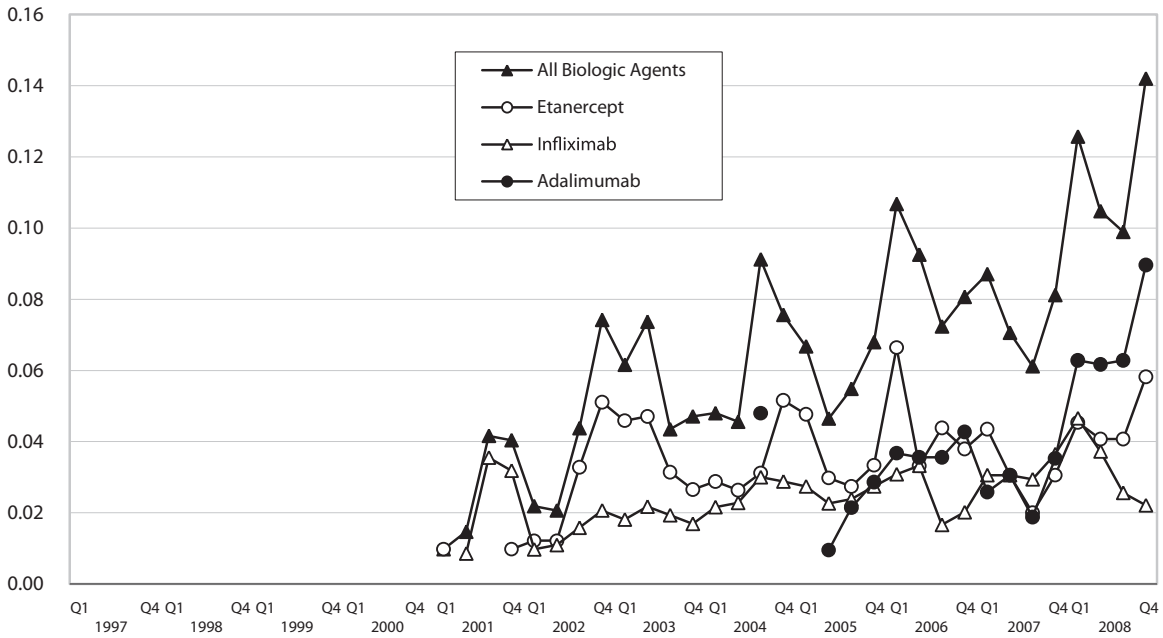


'Q1' indicates rates for the 1st quarter (January to March)
'Q4' indicates rates for the 4th quarter (October to December)
'Q2' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2010

Note: all biologic agents = etanercept, infliximab adalimumab, anakinra, alefacept, abatacept and efalizumab

Figure 5.2: Medications for Biologic Agents Quarterly Incidence, Adults
Crude rates of new users with no use of biologic agent medications in prior year per 1,000 adults, Q1 1997-Q4 2008



'Q1' indicates rates for the 1st quarter (April to June)
'Q4' indicates rates for the 4th quarter (January to March)
'Q2' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2010

Note: all biologic agents = etanercept, infliximab adalimumab, anakinra, alefacept, abatacept and efalizumab

Table 5.1: Prevalent Use (Users per 1,000 Residents) of Biologics Among Adults, 2001/02 to 2008/09

Medication or Group of Medications	2001/02 users/1,000	2008/09 users/1,000	Change in rate per quarter	Age effect 45-64 vs 19-44	Socioeconomic status Low vs High	Region effect Rural vs Urban	Sex effect Male vs Female
All biologics	0.01	1.31	1.1 10% increase*	2.23 223% higher*	0.88 NS	0.81 19% lower*	0.57 43% lower*
Etanercept	0.01	0.56	1.08 8% increase*	3.41 341% higher*	1.03 NS	0.88 NS	0.62 38% lower*
Infliximab	0.01	0.32	1.07 7% increase*	0.95 NS	0.83 NS	0.76 24% lower*	0.82 18% lower*
Adalimumab	0.05 2004/05	0.42	1.14 14% increase*	2.68 268% higher*	0.76 24% lower*	0.79 21% lower*	0.5 50% lower*

*Indicates a statistically significant effect ($p<0.05$)

Note: all biologic agents = etanercept, infliximab, adalimumab, anakinra, alefacept, abatacept, and efalizumab

Source: Manitoba Centre for Health Policy, 2010

Table 5.2. Incident Use (Users per 1,000 Residents) of Biologics among Adults, 2001/02 to 2008/09

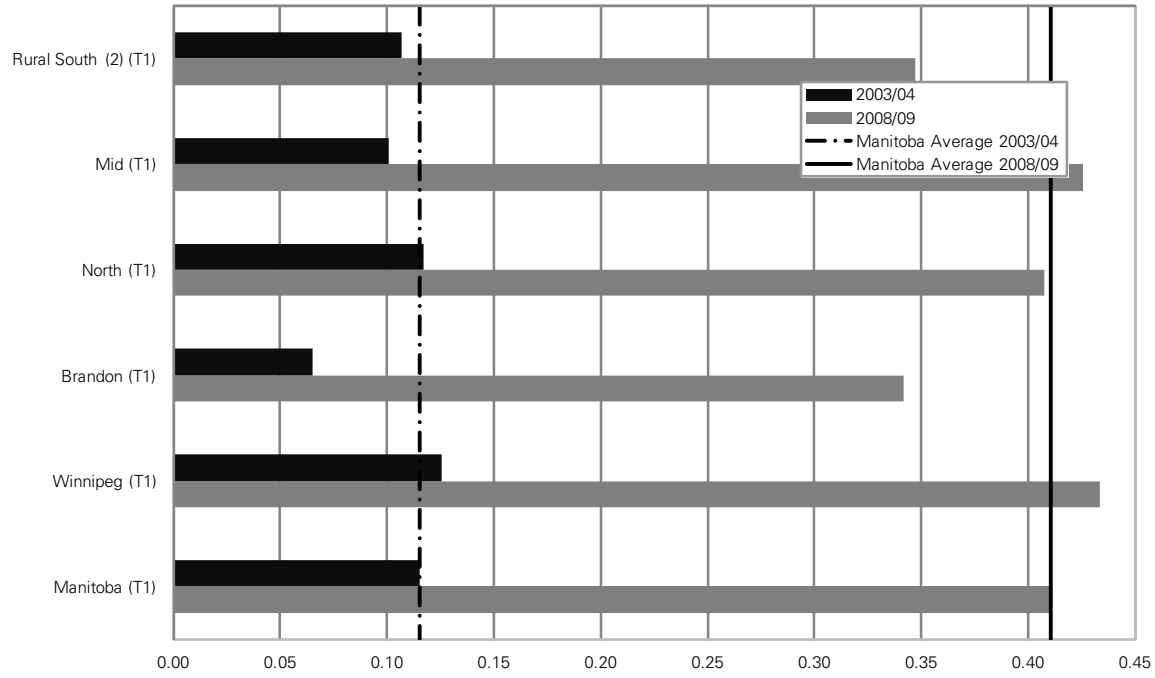
Medication or Group of Medications	2001/02 users/1,000	2008/09 users/1,000	Change in rate per quarter	Age effect 45-64 vs 20-44	Socioeconomic status Low vs High	Region effect Rural vs Urban	Sex effect Male vs Female
All biologics	0.11	0.47	1.04 4% increase*	1.52 152% higher*	0.94 NS	0.88 NS	0.66 34% lower*
Etanercept	0.03	0.19	1.03 3% increase*	2.6 260% higher*	1 NS	0.89 NS	0.57 43% lower*
Infliximab	0.08	0.13	1.02 2% increase*	0.7 30% lower*	0.84 16% lower*	0.84 16% lower*	0.82 18% lower*
Adalimumab	0.05 2004/05	0.28	1.09 9% increase*	2.12 212% higher*	0.97 NS	0.93 NS	0.56 34% lower*

*Indicates a statistically significant effect ($p<0.05$)

Note: all biologic agents = etanercept, infliximab adalimumab, anakinra, alefacept, abatacept and efalizumab

Source: Manitoba Centre for Health Policy, 2010

Figure 5.3: All Biologic Users per 1,000 Adults by Region
Adjusted by (2003/04) age, sex, and SES per 1,000 residents aged 18+

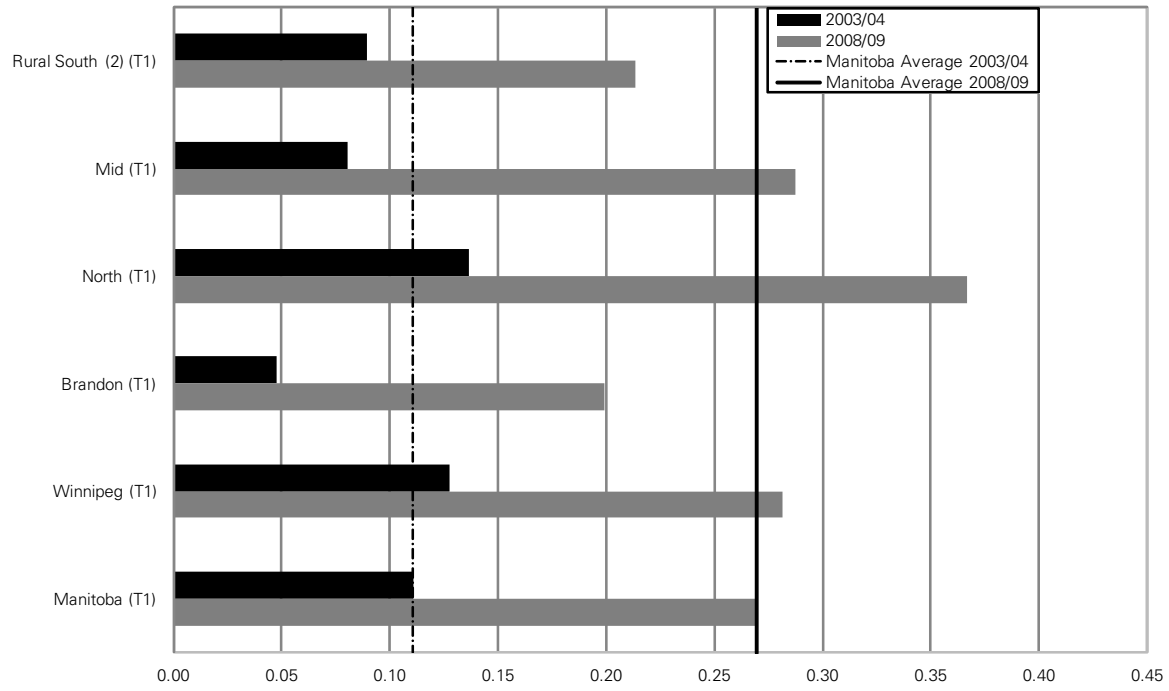


'1'- indicates area's rate was statistically different from Manitoba average in 2003/04.
'2'- indicates area's rate was statistically different from Manitoba average in 2008/09.
'T1'- indicates change over time (2003/04 versus 2008/09) was statistically different for that area.

Note: all biologic agents = etanercept, infliximab adalimumab, anakinra, alefacept, abatacept and efalizumab

Source: Manitoba Centre for Health Policy, 2010

Figure 5.4: Etanercept Users per 1,000 Adults by Region
Adjusted by (2003/04) age, sex, and SES per 1,000 residents aged 18+

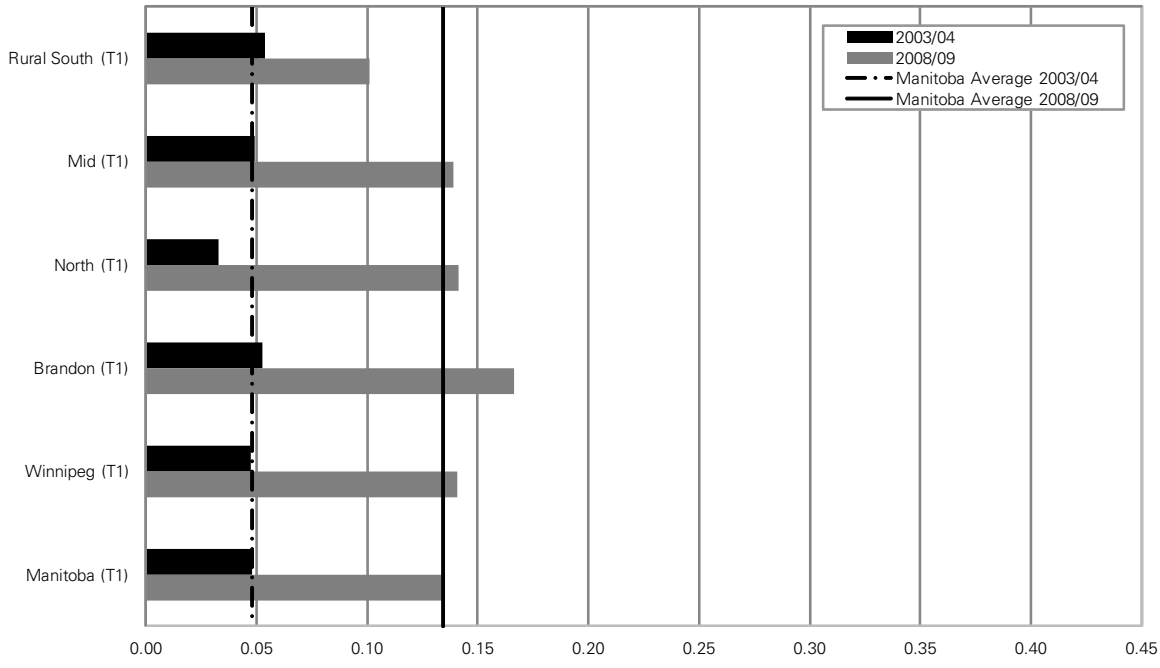


'1'- indicates area's rate was statistically different from Manitoba average in 2003/04.
'2'- indicates area's rate was statistically different from Manitoba average in 2008/09.
'T1'- indicates change over time (2003/04 versus 2008/09) was statistically different for that area.

Note: all biologic agents = etanercept, infliximab adalimumab, anakinra, alefacept, abatacept and efalizumab

Source: Manitoba Centre for Health Policy, 2010

Figure 5.5: Infliximab Users per 1,000 Adults by Region
Adjusted by (2003/04) age, sex, and SES per 1,000 residents aged 18+



'1'- indicates area's rate was statistically different from Manitoba average in 2003/04.
'2'- indicates area's rate was statistically different from Manitoba average in 2008/09.
'T1'- indicates change over time (2003/04 versus 2008/09) was statistically different for that area.

Note: all biologic agents = etanercept, infliximab adalimumab, anakinra, alefacept, abatacept and efalizumab

Source: Manitoba Centre for Health Policy, 2010

Optimal use evaluation

The majority of incident users of etanercept were for rheumatoid arthritis; however, over time, the proportion of etanercept users with psoriasis increased. The majority of infliximab users had evidence of inflammatory bowel disease (see Table 5.3). The majority of adalimumab users had rheumatoid arthritis.

More than 95% of the incident users of the biologic agents used to treat rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, and psoriasis were using the medication for one of the approved indications (see Table 5.4).

Once initiated on therapy with a TNF alpha inhibitor or anakinra, the majority of incident users did not switch to another TNF alpha inhibitor within the first year of therapy (see Table 5.5). Of the incident users of a TNF alpha inhibitor who switched from one agent to another, the majority of etanercept and infliximab users switched to adalimumab and the majority of adalimumab users who switched changed to etanercept.

Table 5.3: Proportion of Incident Biologics Users with a Diagnosis for RA, IBD, AS or Psoriasis in Three Years Prior to Prescription

Year	Etanercept (n=732)				Infliximab (n=535)				Adalimumab (n=316)			
	RA	IBD	AS	Psoriasis	RA	IBD	AS	Psoriasis	RA	IBD	AS	Psoriasis
2000/01	100.00	0	0	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
2001/02	96.15	0	7.69	7.69	56.45	38.71	4.84	4.84	N/A	N/A	N/A	N/A
2002/03	87.64	1.12	8.99	10.11	14.89	87.23	4.26	4.26	N/A	N/A	N/A	N/A
2003/04	93.60	0.80	11.20	11.20	39.68	60.32	6.35	12.70	N/A	N/A	N/A	N/A
2004/05	83.48	2.61	14.78	13.04	29.07	70.93	5.81	3.49	97.62	2.38	0.00	4.76
2005/06	84.48	1.72	10.34	19.83	28.24	67.06	9.41	9.41	90.74	0.00	7.41	14.81
2006/07	78.43	0.65	12.42	24.18	18.82	80.00	7.06	5.88	78.74	6.30	3.15	27.56
2007/08	71.70	0.00	16.04	26.42	15.74	74.07	7.41	10.19	74.47	18.09	7.45	19.15
2008/09	71.70	3.14	11.95	35.22	23.01	67.26	14.16	11.50	50.00	19.75	13.03	33.61

RA - Rheumatoid Arthritis: ICD-9-CM (714), ICD-10-CA (M05-M06)
IBD - Inflammatory Bowel Disease: ICD-9-CM (555, 556), ICD-10-CA (K50, K51)
AS - Ankyosing Spondylitis: ICD-9-CM (720), ICD-10-CA (M45-M46)
Psoriasis: ICD-9-CM (696), ICD-10-CA (L40-L45)

Source: Manitoba Centre for Health Policy, 2010

Table 5.4: Proportion of Incident Users that had a Physician Claim for RA, IBD, Ankylosing Spondylitis or Psoriasis in Three Years Prior to Prescription

	Year								
Drug	2000/01	2001/02	2002/03	2003/04	2004/05	2005/06	2006/07	2007/08	2008/09
Etanercept	100.00	96.15	97.75	97.60	96.52	98.28	99.35	99.06	96.23
Infliximab	95.16	100.00	100.00	100.00	97.67	96.47	97.65	98.15	97.35
Adalimumab	N/A	N/A	N/A	N/A	97.62	98.15	98.43	93.62	99.58
Anakinra	N/A	N/A	100.00	100.00	100.00	N/A	100.00	N/A	N/A
All biologics	100.00	95.40	98.48	98.93	96.77	96.97	98.65	97.25	97.53

Note -all biologic agents = etanercept, infliximab adalimumab, anakinra, alefacept, abatacept and efalizumab

Source: Manitoba Centre for Health Policy, 2010

Table 5.5: Biologic Incident Users that have Switched to Another Biologic Drug

Original Drug	Replacement Drug				
	No Switch	Anakinra	Adalimumab	Infliximab	Etanercept
Etanercept	72.36%	1.24%	19.55%	6.52%	
Infliximab	81.51%	0.62%	11.09%		6.63%
Adalimumab	88.65%	0.36%		1.62%	9.01%
Anakinra	41.18%		26.47%	5.88%	26.47%

Source: Manitoba Centre for Health Policy, 2010

Discussion

Manitoba has observed an increase in utilization of biologic agents to treat rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, and psoriasis over time, within the context of a prior approval process based on individual patient and prescriber characteristics. By 2008/09, 0.15% of the adult population had received prescriptions for these medications. This increase in utilization reflects the launch of new agents and an increase in the randomized controlled trial evidence for efficacy of these agents in the management of severe rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, and psoriasis. Given the lack of information regarding disease severity and comorbid conditions, assessment regarding optimal provision of care is limited. We were able to account for one of these conditions as the indication for use in more than 95% of new users of etanercept, infliximab, adalimumab, anakinra, alefacept, abatacept, and efalizumab by evaluating the physician visits and hospitalizations for medical claims three years prior to the incident prescription. This suggests that minimal prescribing for other indications occurs in Manitoba. Numerous factors have been shown to impact prescribing practices and utilization of biologic therapies, including physician preference, formulary coverage, adverse effects, patient preference, and prescription cost sharing (Curtis et al., 2010; DeWitt, Glick, Albert, Joffe, & Wolfe, 2006; Gleason, Starner, Gunderson, Schafer, & Sarran, 2009; Kamal et al., 2006; Yazici, McMorris, Darkow, & Rosenblatt, 2009). A recent survey of rheumatologists in the United States demonstrated that TNF inhibitors were not limited to individuals with moderate and severe rheumatoid arthritis (Kamal et al., 2006). An analysis of a large claims database of employer– and government–funded healthcare insurance plans in the United States found that the use of biologics for rheumatoid arthritis increased from 3% in 1999 to 26% in 2006, with 15% of biologic users initiated directly onto biologics without previous use of other medications for rheumatoid arthritis (Yazici, Shi, & John, 2008). An analysis of Medicaid claims in Tennessee found that by the end of 2004, 22% of patients treated for rheumatoid arthritis were treated with biologics (Grijalva, Chung, Stein, Mitchel, Jr., & Griffin, 2008). These data suggest that without specific criteria for use, more patients would be prescribed these medications. A patient specific prior approval process for coverage of these medications, by the Manitoba Drug Benefits and Interchangeability Formulary and the income based Manitoba Pharmacare system, likely serves to limit less than optimal prescribing and prohibitive costs to patients who utilize biologic agents to treat rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, and psoriasis.

Other studies have documented, as we did, the rapid increase in the use of TNF inhibitors to treat rheumatoid arthritis with very low use of anakinra (Grijalva et al., 2008; Lee et al., 2009; Yazici et al., 2008; Yazici et al., 2009). The pattern of increased use in females has been described, as rheumatoid arthritis and psoriasis occur more frequently in women than men (Grijalva et al., 2008; Harris & Schur, 2010; Lee et al., 2009). In our data the majority of etanercept and adalimumab was for rheumatoid arthritis. Yazici et al. (2008) observed a decline in the proportion of etanercept use for the treatment of rheumatoid arthritis, with a subsequent increase in other biologics; however, this was not a population based study. We did not observe this trend, perhaps reflecting Manitoba's prior approval process or the inclusion of all biologics for the treatment of rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, and psoriasis in this study.

When all biologic agents to treat rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, and psoriasis were considered together, we did not observe significant differences in prevalent or incident utilization by socioeconomic status. Some data suggest that lower socioeconomic status may be associated with the development of rheumatoid arthritis (Pedersen, Jacobsen, Klarlund, & Frisch,

2006), and that high socioeconomic status may be associated with inflammatory bowel disease (Green, Elliott, Beaudoin, & Bernstein, 2006). However, a clear link between socioeconomic status and the development of these conditions has not been established (Feldman & Pearce, 2010; Harris & Schur, 2010; Peppercorn, 2010). A survey of Canadians with inflammatory bowel disease did not reveal any variation in the use of infliximab by income or Canadian province in 2001; however, infliximab was only used by 4% of the study population (Hilsden, Verhoef, Best, & Pocobelli, 2003).

Only 11–28% of new users of TNF inhibitors switched within the first year of therapy. An analysis of a large claims database of employer– and government–funded healthcare insurance plans in the United States found that 58% of 8,218 individuals initiated on a biologic therapy for rheumatoid arthritis switched to another agent over a mean of 3.3 years of follow–up (Yazici et al., 2008). Reasons for switching could include lack of efficacy with anakinra (Canadian Agency for Drugs and Technologies in Health, 2010), inadequate response (Canadian Agency for Drugs and Technologies in Health, 2010; Kamal et al., 2006; Saag et al., 2008; Van Assche et al., 2008), adverse effects (Greenberg et al., 2010; Kamal et al., 2006; Stallmach et al., 2010), or the development of neutralizing antibodies which reduce efficacy of the biologic medication, particularly with infliximab for inflammatory bowel disease (Van Assche et al., 2008).

Numerous questions about the use of biologic agents used to treat rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, and psoriasis remain. Specifically, the effectiveness and toxicity over the long term in patients outside the setting of a randomized controlled trial, dosage patterns in the population, and medication discontinuation rates are areas for further study. It is unknown if the coverage requirement for patients to be referred to a specialist to receive coverage for these agents impacts the appropriate and or timely access to this group of medications.

In summary, Manitoba has observed the utilization of biologic agents—to treat rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, and psoriasis in the setting of a prior approval process based on individual patient and prescriber characteristics—increase with time. By 2008/09, 0.15% of the adult population had received prescriptions for these medications. This increase in utilization reflects an increase in the randomized controlled trial evidence for efficacy for these agents. More than 95% of users of the biologic agents had a diagnosis of one of the approved indications for use. A patient–specific prior approval process for coverage of these medications by the Manitoba Drug Benefits and Interchangeability Formulary, likely serves to limit inappropriate prescribing of these biologic agents.

Chapter 6: Summary and Conclusions

Analysis Strengths and Challenges

This report provides a complete picture of prescribing across several categories of medications for all Manitobans over an 11–year period (1997/98–2008/09). It describes a population–based profile of utilization of antipsychotics, benzodiazepines and related medications in older adults; medications and test strips for diabetes mellitus; inhalers for asthma and chronic obstructive lung disease; and biologic agents to treat rheumatoid arthritis, inflammatory bowel disease, ankylosing spondylitis, and psoriasis. This report assesses a range of societal influences on medication utilization, such as patient sociodemographic factors, and prescriber characteristics. This report evaluates the impact of these same characteristics on measures of optimal medication use based on recent literature and guidelines—namely the use of inhaled or oral corticosteroids prior to the use of inhaled LABA for asthma, the use of LABA with concomitant inhaled or oral corticosteroids, avoiding the use of high dose SGAs in older adults, and reserving higher cost new medications for diabetes mellitus as second line therapy.

Limitations of the analyses are the same as those limitations of other studies using prescription and health care administrative databases. There is a potential to both overestimate and underestimate the use of medications within the population. Prescription use was derived from records of dispensed prescriptions. Not everyone who seeks medical attention and receives a prescription for a medication fills the prescription. This may incompletely capture the intent of physician prescribing in Manitoba. Physician sampling of medications are not captured in the prescription medication records in the Population Health Research Data Repository in Manitoba which contributes to underestimating the number of users of medications, particularly, newer medications. Alternately, individuals may fill prescriptions but not actually take the medication, thus overestimating the number of active users of medications in Manitoba. Some individuals are not included in the DPIN system, namely those who are incarcerated or have prescriptions covered through the Royal Canadian Mounted Police. Some individuals receiving prescriptions at remote nursing stations may not be included in the DPIN system. These individuals make up a very small proportion of the Manitoba population, as most prescriptions for remote Manitoba communities are filled in Winnipeg and flown in. Finally, it should be noted that only approximately 73% of PCHs fill prescriptions at community pharmacies (and are, therefore, included in the DPIN system). Medication use in PCHs where prescriptions are filled through hospitals is not known (Doupe et al., 2006).

Medical histories were derived from diagnosis data on physician claims and hospitalization data. These medical histories may underestimate the prevalence of a given condition in the population because they require contact with the health care system and were dependent on physician reimbursement records, which do not completely record all underlying comorbidities and disease severity. In primary care, the use of administrative data may underestimate the prevalence of a disease in the population as most ambulatory physician visits can only result in a single billing code and, therefore, a single diagnosis. This may be particularly common with individuals with multiple or complex medical conditions. There is also potential for the use of administrative data to overestimate the prevalence of a given condition in the population due to misclassification. Additionally, administrative data files do not include individuals without Manitoba Health cards.

It is also very likely that several unmeasured factors also had an influential role on use of medications. These include, but are not limited to: physician access, distance of prescriber from academic centres, group or solo prescriber practice, continuing professional development activities, other unmeasured

prescriber characteristics, prescriber–patient interactions, pharmaceutical marketing, change and dissemination of clinical practice guidelines, physician sampling of newly marketed medications, and patient perception of the benefits and safety of medications. The impact of these factors on prescribing at a population level in Manitoba deserves further investigation.

It is difficult to determine if all pharmaceutical use deemed optimal or less than optimal in this research was truly optimal or less than optimal for a given patient. The lack of information regarding disease severity and other individual level details may misclassify individuals as receiving less than optimal therapy.

Conclusions and Recommendations

This study describes incident and prevalent utilization of antipsychotics, benzodiazepines, and related medications in older adults; medications and test strips for diabetes mellitus; inhalers for asthma and chronic obstructive lung disease; and biologic agents to treat rheumatoid arthritis, inflammatory bowel disease, ankylosing spondylitis, and psoriasis by sociodemographic characteristics and region of residence within the province of Manitoba. Eleven years of prescription drug data (1997/98–2008/09) have been employed using previously developed population based indicators of medication utilization.

The rates of utilization and increases in utilization of these categories of commonly prescribed medications are consistent with those in other Canadian provinces and with other studies employing Manitoba's prescription drug data.

In a national comparison of spending on pharmaceuticals in Canada, it was found that age adjusted overall spending on prescription medications in Manitoba was 7.6% below the national average in 2007; the cost driver most associated with this was a lower volume of prescriptions (Morgan et al., 2008). This value was between the highest age adjusted spending in Quebec (13.4% above national average) and the lowest in British Columbia (27.7% below national average). However, the age standardized average annual rate of change in inflation–adjusted per capita spending by province from 1998–2007 increased in Manitoba by 8.0%, which was higher than the national average of 5.1% (Morgan et al., 2008). In fact, although overall prescription drug spending was lower in Manitoba in 2007 than in other provinces, the increase in spending over time was greater in Manitoba than other provinces.

Key Findings

Antipsychotics, benzodiazepines and related medications in older adults

The use of second generation antipsychotics, benzodiazepines, and related medications in older adults in Manitoba is increasing and is especially high in residents of personal care homes (PCH), despite recommendations to avoid these agents in older adults with dementia if possible. By 2008/09, 27% of older adults who reside in personal care home received a prescription for a second generation antipsychotic. The most commonly used agent was risperidone. High dose second generation antipsychotics are less then optimal due to an increased risk for dose related adverse effects, such as falls and movement disorders. From 2002/03–2007/08, only 10.2% of new users of second generation antipsychotics received high doses of these agents. Users of high dose antipsychotics were younger, more likely to be male, have psychosis or dementia, and be taking fewer other medications. No prescriber or environment characteristics (including PCH environment and type of PCH) predicted this less than optimal prescribing.

Medications and glucose test strips for diabetes mellitus

The use of metformin, the most appropriate first line agent for the treatment of type 2 diabetes mellitus, has increased dramatically over time, which is consistent with guidelines and recommendations. By 2008/09, metformin accounted for more than 82% of first prescriptions for medications to treat diabetes. The use of test strips for self monitoring of blood glucose has also increased dramatically over time. Recent (2009) recommendations suggest that individuals receiving no oral anti–diabetic agents, or anti–diabetic agents that do not cause hypoglycemia should not monitor blood glucose regularly. Rather, they should be used only under special circumstances such as when they are ill or changing their medication regimen. This suggests that up to 40% of all Manitobans using test strips and 24–27% of test strips used in Manitoba may have been in excess of what recent evidence and recommendations support. The use of more costly newer agents as the first prescription for the treatment of diabetes was minimal (3.5%), as these agents are generally not covered by Manitoba Pharmacare and are used for specific patient circumstances. Individuals were more likely to receive a new medication for diabetes as a first prescription for a diabetes medication if they lived in a rural location; were younger; had more ambulatory physician visits and hospitalizations; or saw a specialist, a fee–for–service physician, or longer practicing physician. These findings suggest that the Manitoba Pharmacare criteria for the new agents for diabetes were adhered to.

Inhaled medications for the treatment of asthma and chronic lung disease

Current asthma guidelines recommend the use of corticosteroids prior to the use of LABA and do not recommend LABA without the use of corticosteroids due to concern for increased asthma morbidity with LABA. The use of LABA without prior corticosteroids in Manitobans with asthma is increasing, despite asthma guidelines. Similarly, the use of LABA without corticosteroids in Manitobans with asthma is increasing. Asthma patients are more likely to be prescribed asthma medications not according to guidelines if they have less severe asthma or see general practitioners. Challenges to the interpretation of this data include the difficulty of using administrative data to diagnose asthma. Further education for patients and physicians about the role of LABA in the treatment of asthma, especially in light of the warnings about the use of LABAs, is required.

Biologic agents

Manitoba has observed the utilization of biologic agents increase with time. By 2008/09, 0.15% of the adult population had received prescriptions for these medications. This increase in utilization reflects the increase in the randomized controlled trial evidence for efficacy of these agents. More than 95% of users of the biologic agents had a diagnosis of one of the approved indications for use. A patient–specific prior approval process for coverage of these medications by the Manitoba Drug Benefits and Interchangeability Formulary likely serves to limit inappropriate prescribing of these biologic agents.

Data Recommendations

Data for the use of pharmaceuticals is limited to prescriptions dispensed in community pharmacies. Data on medications supplied to personal care homes (PCHs) from hospital–based pharmacies, as well as medications supplied to patients admitted to hospitals are not available to MCHP for analysis. As hospitals, are likely important places for initiating new therapies after important medical events or procedures, these data would be useful to further understand how pharmaceuticals are initiated and used in Manitoba.

Studies of appropriateness, effectiveness, and persistence with therapies will be facilitated by enhanced merging of clinical and/or survey–based data with administrative data.

Recommendations for Future Research

This report is one of several in the continued series on pharmaceutical use in Manitoba and lays the foundation for others that will incorporate assessments of the appropriateness and health outcomes of medication use in the analysis.

Other classes of medications

Several other commonly prescribed classes of medications were not included in this deliverable and could be considered for further population–based analysis of sociodemographic, prescriber, or environment characteristics impacting optimal use. Examples of such classes of medications include proton pump inhibitors, newer anticonvulsants (e.g., gabapentin), and antithrombotics (e.g., clopidogrel).

Persistence

This deliverable did not evaluate persistence or adherence with therapies, which is known to be suboptimal for many classes of important medications. Persistence with medications contributes to utilization. Examples of categories of medications where persistence with therapy could impact clinical outcomes include the statins and antihypertensives.

Cost effectiveness

This deliverable did not address cost effectiveness, which is an area of important further study for all of the medications analyzed in this report.

References

Risperdal Product Monograph. Toronto, ON: Janssen Ortho; 2008.

Alessi–Severini S, Biscontri RG, Collins DM, Kozyrskyj A, Sareen J, Enns MW. Utilization and costs of antipsychotic agents: a Canadian population–based study, 1996–2006. *Psychiatr Serv.* 2008;59(5):547–553.

Alexander GC, Sehgal NL, Moloney RM, Stafford RS. National trends in treatment of type 2 diabetes mellitus, 1994–2007. *Arch Intern Med.* 2008;168(19):2088–2094.

Alexopoulos GS, Schultz SK, Lebowitz BD. Late–life depression: a model for medical classification. *Biol Psychiatry.* 2005;58(4):283–289.

Allen–Ramey FC, Samet JM, Rand CS, Joseph CL. Trends in use of inhaled corticosteroids for asthma management: 1994–1998. *Ann Epidemiol.* 2004;14(3):161–167.

APA Practice Guidelines. Practice Guideline for the Treatment of Patients with Alzheimer's Disease and Other Dementias. American Psychiatric Association. 2009. http://www.psychiatryonline.com/popup.aspx?aID=152666&print=yes. Accessed July 30, 2010.

Baiardi P, Ceci A, Felisi M, et al. In–label and off–label use of respiratory drugs in the Italian paediatric population. *Acta Paediatr.* 2010;99(4):544–549.

Baker DW, Hayes RP, Massie BM, Craig CA. Variations in family physicians' and cardiologists' care for patients with heart failure. *Am Heart J.* 1999;138(5 Pt 1):826–834.

Ballard C, Hanney ML, Theodoulou M, et al. The dementia antipsychotic withdrawal trial (DART–AD): long–term follow–up of a randomised placebo–controlled trial. *Lancet Neurol.* 2009;8(2):151–157.

Barnett AH, Krentz AJ, Strojek K, et al. The efficacy of self–monitoring of blood glucose in the management of patients with type 2 diabetes treated with a gliclazide modified release–based regimen. A multicentre, randomized, parallel–group, 6–month evaluation (DINAMIC 1 study). *Diabetes Obes Metab.* 2008;10(12):1239–1247.

Bartlett G, Abrahamowicz M, Grad R, Sylvestre MP, Tamblyn R. Association between risk factors for injurious falls and new benzodiazepine prescribing in older adults. *BMC Fam Pract.* 2009;10:1.

Blais R, Laurier C, Pare M. Effect of feedback letters to physicians and pharmacists on the appropriate use of medication in the treatment of asthma. *J Asthma.* 2008;45(3):227–231.

Bollinger ME, Smith SW, LoCasale R, Blaisdell C. Transition to managed care impacts health care service utilization by children insured by Medicaid. *J Asthma.* 2007;44(9):717–722.

Boyc KS, Yurgin N, Lage MJ. Trends in the prescription of antidiabetic medications in France: evidence from primary care physicians. *Adv Ther.* 2007;24(4):803–813.

Boyter AC, Steinke DT. Changes in prescribing of inhaled corticosteroids (1999–2002) in Scotland. *Pharmacoepidemiol Drug Saf.* 2005;14(3):203–209.

Braun J. Therapy of spondyloarthritides. *Adv Exp Med Biol.* 2009;649:133–147.

Breton MC, Lelorier J, Forget A, Blais L. Use of combination therapy in asthma: are they prescribed according to guidelines. *Respir Med.* 2007;101(9):1916–1923.

Brodaty H, Ames D, Snowdon J, et al. A randomized placebo–controlled trial of risperidone for the treatment of aggression, agitation, and psychosis of dementia. *J Clin Psychiatry.* 2003;64(2):134–143.

Butz AM, Thompson RE, Tsoukleris MG, et al. Seasonal patterns of controller and rescue medication dispensed in underserved children with asthma. *J Asthma.* 2008;45(9):800–806.

Cadieux G, Tamblyn R, Dauphinee D, Libman M. Predictors of inappropriate antibiotic prescribing among primary care physicians. *CMAJ.* 2007;177(8):877–883.

Cameron C, Coyle D, Ur E, Klarenbach S. Cost–effectiveness of self–monitoring of blood glucose in patients with type 2 diabetes mellitus managed without insulin. *CMAJ.* 2010a;182(1):28–34.

Cameron C, Virani A, Dean H, Evans M, Dolovich L, Dahl M. Utilization and expenditure on blood glucose test strips in Canada. *Can J Diabetes.* 2010b;34(1):34–40.

Cameron CG, Bennett HA. Cost–effectiveness of insulin analogues for diabetes mellitus. *CMAJ.* 2009;180(4):400–407.

Canadian Agency for Drugs and Technologies in Health. *CEDAC Final Recommendation and Reasons for Recommendation: Adalimumab Resubmission*. Ottawa, ON: Canadian Agency for Drugs and Technologies in Health; 2006a.

Canadian Agency for Drugs and Technologies in Health. *CEDAC Final Recommendation and Reconsideration and Reasons for Recommendation: Insulin Glargine Resubmission*. Ottawa, ON: Canadian Agency for Drugs and Technologies in Health; 2006b.

Canadian Agency for Drugs and Technologies in Health. *CEDAC Final Recommendation and Reasons for Recommendation: Adalimumab Resubmission # 2*. Ottawa, ON: Canadian Agency for Drugs and Technologies in Health; 2007.

Canadian Agency for Drugs and Technologies in Health. *CEDAC Final Recommendation and Reason for Recommendation: Adalimumab*. Ottawa, ON: Canadian Agency for Drugs and Technologies in Health; 2008.

Canadian Agency for Drugs and Technologies in Health. *CEDAC Final Recommendation and Reasons for Recommendation: Infliximab*. Ottawa, ON: Canadian Agency for Drugs and Technologies in Health; 2009a.

Canadian Agency for Drugs and Technologies in Health. *CEDAC Final Recommendation: Insulin Detemir*. Ottawa, ON: Canadian Agency for Drugs and Technologies in Health; 2009b.

Canadian Agency for Drugs and Technologies in Health. *Optimal therapy recommendations for the prescribing and use of blood glucose test strips*. Ottawa, ON: Canadian Agency for Drugs and Technologies in Health; 2009c.

Canadian Agency for Drugs and Technologies in Health. *Optimal therapy recommendations for the prescribing and use of insulin analogues*. Ottawa, ON: Canadian Agency for Drugs and Technologies in Health; 2009d.

Canadian Agency for Drugs and Technologies in Health. *CADTH Therapeutic Review Panel Final Recommendations*. Ottawa, ON: Canadian Agency for Drugs and Technologies in Health; 2010.

Canadian Diabetes Association. Canadian Diabetes Association 2008 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. *Can J Diabetes.* 2008;32(Suppl 1):S1–S201.

Canadian Institute for Health Information. *Antipsychotic Use in Seniors: An Analysis Focusing on Drug Claims, 2001 to 2007*. Ottawa, ON: Canadian Institute for Health Information; 2009.

Castelino RL, Bajorek BV, Chen TF. Targeting suboptimal prescribing in the elderly: a review of the impact of pharmacy services. *Ann Pharmacother.* 2009;43(6):1096–1106.

Chen DT, Wynia MK, Moloney RM, Alexander GC. U.S. physician knowledge of the FDA–approved indications and evidence base for commonly prescribed drugs: results of a national survey. *Pharmacoepidemiol Drug Saf.* 2009;18(11):1094–1100.

Chen Y, Johansen H, Thillaiampalam S, Sambell C. Asthma. Statistics Canada. 2005. http://www.statcan.gc.ca/studies–etudes/82–003/archive/2005/7790–eng.pdf. Accessed October 14, 2010.

Chiang CW, Chiu HF, Chen CY, Wu HL, Yang CY. Trends in the use of oral antidiabetic drugs by outpatients in Taiwan: 1997–2003. *J Clin Pharm Ther.* 2006;31(1):73–82.

Chin MH, Friedmann PD, Cassel CK, Lang RM. Differences in generalist and specialist physicians' knowledge and use of angiotensin–converting enzyme inhibitors for congestive heart failure. *J Gen Intern Med.* 1997;12(9):523–530.

Chowdhury BA, Dal Pan G. The FDA and safe use of long–acting beta–agonists in the treatment of asthma. *N Engl J Med.* 2010;362(13):1169–1171.

Cohen A, Rabbani A, Shah N, Alexander GC. Changes in glitazone use among office–based physicians in the U.S., 2003–2009. *Diabetes Care.* 2010;33(4):823–825.

Cohen FJ, Neslusan CA, Conklin JE, Song X. Recent antihyperglycemic prescribing trends for US privately insured patients with type 2 diabetes. *Diabetes Care.* 2003;26(6):1847–1851.

Cohen S, Taitz J, Jaffe A. Paediatric prescribing of asthma drugs in the UK: are we sticking to the guideline? *Arch Dis Child.* 2007;92(10):847–849.

Crown WH, Bresnahan BW, Orsini LS, Kennedy S, Leonardi C. The burden of illness associated with psoriasis: cost of treatment with systemic therapy and phototherapy in the US. *Curr Med Res Opin.* 2004;20(12):1929–1936.

Curtis JR, Chen L, Harrold LR, Narongroeknawin P, Reed G, Solomon DH. Physician preference motivates the use of anti–tumor necrosis factor therapy independent of clinical disease activity. *Arthritis Care Res (Hoboken).* 2010;62(1):101–107.

Daumit GL, Crum RM, Guallar E, et al. Outpatient prescriptions for atypical antipsychotics for African Americans, Hispanics, and whites in the United States. *Arch Gen Psychiatry.* 2003;60(2):121–128.

Davidson MB. Counterpoint: Self–monitoring of blood glucose in type 2 diabetic patients not receiving insulin: a waste of money. *Diabetes Care.* 2005;28(6):1531–1533.

De Deyn PP, Katz IR, Brodaty H, Lyons B, Greenspan A, Burns A. Management of agitation, aggression, and psychosis associated with dementia: a pooled analysis including three randomized, placebo–controlled double–blind trials in nursing home residents treated with risperidone. *Clin Neurol Neurosurg.* 2005;107(6):497–508.

Defilippi JL, Crismon ML. Antipsychotic agents in patients with dementia. *Pharmacotherapy.* 2000;20(1):23–33.

Dewa CS, Remington G, Herrmann N, Fearnley J, Goering P. How much are atypical antipsychotic agents being used, and do they reach the populations who need them? A Canadian experience. *Clin Ther.* 2002;24(9):1466–1476.

DeWitt EM, Glick HA, Albert DA, Joffe MM, Wolfe F. Medicare coverage of tumor necrosis factor alpha inhibitors as an influence on physicians' prescribing behavior. *Arch Intern Med.* 2006;166(1):57–63.

Dey AN, Bloom B. Summary health statistics for U.S. children: national health interview survey, 2003. National Center for Health Statistics. http://www.cdc.gov/nchs/data/series/sr_10/sr10_223.pdf. Accessed October 14, 2010. Last edited 2005.

DiSantostefano RL, Davis KJ, Yancey S, Crim C. Ecologic analysis of asthma–related events and dispensing of inhaled corticosteroid– and salmeterol–containing products. *Ann Allergy Asthma Immunol.* 2008;100(6):558–565.

Domino ME, Swartz MS. Who are the new users of antipsychotic medications? *Psychiatr Serv.* 2008;59(5):507–514.

Dormuth CR, Glynn RJ, Neumann P, Maclure M, Brookhart AM, Schneeweiss S. Impact of two sequential drug cost–sharing policies on the use of inhaled medications in older patients with chronic obstructive pulmonary disease or asthma. *Clin Ther.* 2006;28(6):964–978.

Doro P, Benko R, Kosik E, Matuz M, Toth K, Soos G. Utilization of oral antihyperglycemic drugs over a 7–year period (1998–2004) in a Hungarian population and adherence to drug therapy. *Eur J Clin Pharmacol.* 2005;61(12):893–897.

Dorsey ER, Rabbani A, Gallagher SA, Conti RM, Alexander GC. Impact of FDA black box advisory on antipsychotic medication use. *Arch Intern Med.* 2010;170(1):96–103.

Doupe M, Brownell M, Kozyrskyj A, et al. Using Administrative Data to Develop Indicators of Quality Care in Personal Care Homes. Manitoba Centre for Health Policy. 2006. http://mchp–appserv.cpe.umanitoba.ca/reference/pch.qi.pdf. Accessed May 8, 2010.

Dyck R, Osgood N, Lin TH, Gao A, Stang MR. Epidemiology of diabetes mellitus among First Nations and non–First–Nations adults. *CMAJ.* 2010;182(3):249–256.

Ernst P, McIvor A, Ducharme FM, et al. Safety and effectiveness of long–acting inhaled beta–agonist bronchodilators when taken with inhaled corticosteroids. *Ann Intern Med.* 2006;145(9):692–694.

Fanta CH. Asthma. *N Engl J Med.* 2009;360(10):1002–1014.

Farmer A, Wade A, Goyder E, et al. Impact of self monitoring of blood glucose in the management of patients with non–insulin treated diabetes: open parallel group randomised trial. *BMJ.* 2007;335(7611):132.

Feldman SR, Pearce DJ. Epidemiology, pathophysiology, clinical manifestations, and diagnosis of psoriasis. *UpToDate*. 2010. http://www.uptodate.com/patients/content/topic.do?topicKey=~wZXXeRujzDoDp. Accessed July 30, 2010.

Ferrandiz C, Carrascosa JM, Boada A. A new era in the management of psoriasis? The biologics: facts and controversies. *Clin Dermatol.* 2010;28(1):81–87.

Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. *Arch Intern Med.* 2003;163(22):2716–2724.

Franciosi M, Pellegrini F, De Berardis G, et al. The impact of blood glucose self–monitoring on metabolic control and quality of life in type 2 diabetic patients: an urgent need for better educational strategies. *Diabetes Care.* 2001;24(11):1870–1877.

Fransoo R, Martens P, Burland E, The Need to Know Team, Prior H, Burchill C. Manitoba RHA Indicators Atlas 2009. Manitoba Centre for Health Policy. 2009. http://mchp–appserv.cpe.umanitoba.ca/reference/RHA_Atlas_Report.pdf. Accessed July 30, 2010.

French DD, Chirikos TN, Spehar A, Campbell R, Means H, Bulat T. Effect of concomitant use of benzodiazepines and other drugs on the risk of injury in a veterans population. *Drug Saf.* 2005;28(12):1141–1150.

Gill SS, Bronskill SE, Normand SL, et al. Antipsychotic drug use and mortality in older adults with dementia. *Ann Intern Med.* 2007;146(11):775–786.

Gleason PP, Starner CI, Gunderson BW, Schafer JA, Sarran HS. Association of prescription abandonment with cost share for high–cost specialty pharmacy medications. *J Manag Care Pharm.* 2009;15(8):648–658.

Gomes T, Juurlink DN, Shah BR, Paterson JM, Mamdani MM. Blood glucose test strips: options to reduce usage. *CMAJ.* 2010;182(1):35–38.

Green C, Blanchard JF, Young TK, Griffith J. The epidemiology of diabetes in the Manitoba–registered First Nation population: current patterns and comparative trends. *Diabetes Care.* 2003;26(7):1993–1998.

Green C, Elliott L, Beaudoin C, Bernstein CN. A population–based ecologic study of inflammatory bowel disease: searching for etiologic clues. *Am J Epidemiol.* 2006;164(7):615–623.

Greenberg JD, Reed G, Kremer JM, et al. Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORRONA registry. *Ann Rheum Dis.* 2010;69(2):380–386.

Grijalva CG, Chung CP, Stein CM, Mitchel EF, Jr., Griffin MR. Changing patterns of medication use in patients with rheumatoid arthritis in a Medicaid population. *Rheumatology (Oxford).* 2008;47(7):1061–1064.

Guenette L, Gaudet M. Impact of prior authorization for asthma medications on the use of emergency health services: a retrospective cohort study among newly diagnosed patients with asthma. *Clin Ther.* 2010;32(5):965–972.

Guerci B, Drouin P, Grange V, et al. Self–monitoring of blood glucose significantly improves metabolic control in patients with type 2 diabetes mellitus: the Auto–Surveillance Intervention Active (ASIA) study. *Diabetes Metab.* 2003;29(6):587–594.

Hagen BF, Armstrong–Esther C, Quail P, et al. Neuroleptic and benzodiazepine use in long–term care in urban and rural Alberta: characteristics and results of an education intervention to ensure appropriate use. *Int Psychogeriatr.* 2005;17(4):631–652.

Hanania NA, Darken P, Horstman D, et al. The efficacy and safety of fluticasone propionate (250 microg)/salmeterol (50 microg) combined in the Diskus inhaler for the treatment of COPD. *Chest.* 2003;124(3):834–843.

Hanlon JT, Boudreau RM, Roumani YF, et al. Number and dosage of central nervous system medications on recurrent falls in community elders: the Health, Aging and Body Composition study. *J Gerontol A Biol Sci Med Sci.* 2009;64(4):492–498.

Harris ED, Schur PH. Epidemiology, risk factors for, and possible causes of rheumatoid arthritis. *UpToDate*. 2009 (September 30).

Haupt D, Wettermark B, Nilsson JL. Dispensed volumes of anti–asthmatic drugs related to the prevalence of asthma and COPD in Sweden. *Pharmacoepidemiol Drug Saf.* 2008;17(5):461–467.

Health Canada. Important drug safety information: Risperdal (risperidone) and cerebrovascular adverse events in placebo–controlled dementia trials– Janssen–Ortho Inc. Health Canada. 2002. http://www.hc–sc.gc.ca/dhp–mps/medeff/advisories–avis/prof/_2002/risperdal_hpc–cps–eng.php. Accessed August 29, 2008.

Health Canada. Increased mortality associated with the use of atypical antipsychotic drugs in elderly patients with dementia. Health Canada. 2005a. http://www.hc–sc.gc.ca/dhp–mps/medeff/advisories–avis/prof/_2005/atyp–antipsycho_hpc–cps–eng.php. Accessed August 29, 2008.

Health Canada. Zyprexa (olanzapine) and cerebrovascular adverse events in placebo–controlled elderly dementia trials–Eli Lilly Canada Inc. Health Canada. 2004. http://www.hc–sc.gc.ca/dhp–mps/medeff/advisories–avis/prof/_2004/zyprexa_hpc–cps–eng.php. Accessed August 29, 2008.

Health Canada. Important drug safety information on SEREVENT®. Health Canada. 2005b. http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2005/serevent_2_hpc-cps-eng.php. Accessed October 14, 2010.

Health Canada. Cardiac Safety of Avandia® (rosiglitazone maleate)–For Health Professionals. Health Canada. 2007. http://www.hc–sc.gc.ca/dhp–mps/medeff/advisories–avis/prof/_2007/avandia_hpc–cps_4–eng.php. Accessed January 26, 2009.

Healthcare Professional Communication. Health Canada Recommendation to Suspend RAPTIVA (efalizumab) in Canada. 2009. http://www.hc-sc.gc.ca/index-eng.php. Accessed July 30, 2010.

Hilsden RJ, Verhoef MJ, Best A, Pocobelli G. A national survey on the patterns of treatment of inflammatory bowel disease in Canada. *BMC Gastroenterol.* 2003;3:10.

Ipp E, Aquino RL, Christenson P. Point: Self–monitoring of blood glucose in type 2 diabetic patients not receiving insulin: the sanguine approach. *Diabetes Care.* 2005;28(6):1528–1530.

Jameson JP, Baty PJ. Pharmacist collaborative management of poorly controlled diabetes mellitus: a randomized controlled trial. *Am J Manag Care.* 2010;16(4):250–255.

Jeste DV, Blazer D, Casey D, et al. ACNP White Paper: update on use of antipsychotic drugs in older adults with dementia. *Neuropsychopharmacology.* 2008;33(5):957–970.

Jeste DV, Lacro JP, Bailey A, Rockwell E, Harris MJ, Caligiuri MP. Lower incidence of tardive dyskinesia with risperidone compared with haloperidol in older patients. *J Am Geriatr Soc.* 1999a;47(6):716–719.

Jeste DV, Rockwell E, Harris MJ, Lohr JB, Lacro J. Conventional vs. newer antipsychotics in elderly patients. *Am J Geriatr Psychiatry.* 1999b;7(1):70–76.

Johns Hopkins University Bloomberg School of Public Health. *Johns Hopkins ACG Case–Mix System Documentation & Application Manual Version 5.0*. Baltimore, MD: Johns Hopkins University; 2001.

Johns Hopkins University Bloomberg School of Public Health. *Johns Hopkins ACG Case–Mix System Version 6.0 Release Notes (Systems Documentation)*. Baltimore, MD: Johns Hopkins University; 2003.

Kamal KM, Madhavan SS, Hornsby JA, Miller LA, Kavookjian J, Scott V. Use of tumor necrosis factor inhibitors in rheumatoid arthritis: a national survey of practicing United States rheumatologists. *Joint Bone Spine.* 2006;73(6):718–724.

Kardos P, Wencker M, Glaab T, Vogelmeier C. Impact of salmeterol/fluticasone propionate versus salmeterol on exacerbations in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2007;175(2):144–149.

Katz IR, Jeste DV, Mintzer JE, Clyde C, Napolitano J, Brecher M. Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomized, double–blind trial. Risperidone Study Group. *J Clin Psychiatry.* 1999;60(2):107–115.

Kibriya MG, Ali L, Banik NG, Khan AK. Home monitoring of blood glucose (HMBG) in type–2 diabetes mellitus in a developing country. *Diabetes Res Clin Pract.* 1999;46(3):253–257.

Kliber A, Lynd LD, Sin DD. The effects of long–acting bronchodilators on total mortality in patients with stable chronic obstructive pulmonary disease. *Respir Res.* 2010;11:56.

Kozyrskyj A, Lix L, Dahl M, Soodeen R. High-Cost Users of Pharmaceuticals: Who are They? Manitoba Centre for Health Policy. 2005. http://mchp-appserv.cpe.umanitoba.ca/reference/high-cost.pdf. Accessed July 30, 2010.

Kozyrskyj AL, Mustard CA, Simons FE. Inhaled corticosteroids in childhood asthma: income differences in use. *Pediatr Pulmonol.* 2003;36(3):241–247.

Kozyrskyj A, Raymond C, Dahl M, et al. Effects of Manitoba Pharmacare Formulary Policy on Utilization of Prescription Medications. Manitoba Centre for Health Policy. 2009. http://mchp–appserv.cpe.umanitoba.ca/reference/Rx%20Policy.pdf. Accessed July 30, 2010.

Kozyrskyj A, Raymond C, Racher A. Characterizing early prescribers of newly marketed drugs in Canada: a population–based study. *Eur J Clin Pharmacol.* 2007;63(6):597–604.

Kuehn BM. FDA offers advice to reduce risks of long–acting beta–agonists in asthma care. *JAMA.* 2010;303(14):1353–1354.

Lee SJ, Chang H, Yazici Y, Greenberg JD, Kremer JM, Kavanaugh A. Utilization trends of tumor necrosis factor inhibitors among patients with rheumatoid arthritis in a United States observational cohort study. *J Rheumatol.* 2009;36(8):1611–1617.

Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta–analysis: I. Psychotropic drugs. *J Am Geriatr Soc.* 1999;47(1):30–39.

Lemiere C, Becker A, Boulet LP, et al. Should combination therapy with inhaled corticosteroids and long–acting beta2–agonists be prescribed as initial maintenance treatment for asthma? *CMAJ.* 2002;167(9):1008–1009.

Lix L, Yogendran M, Burchill C, Metge C, et al. Defining and Validating Chronic Diseases: An Administrative Data Approach. Manitoba Centre for Health Policy. 2006. http://mchp–appserv.cpe.umanitoba.ca/reference/chronic.disease.pdf.

Lougheed MD, Lemiere C, Dell SD, et al. Canadian Thoracic Society Asthma Management Continuum–2010 Consensus Summary for children six years of age and over, and adults. *Can Respir J.* 2010;17(1):15–24.

Lusignan S, Sismanidis C, Carey IM, DeWilde S, Richards N, Cook DG. Trends in the prevalence and management of diagnosed type 2 diabetes 1994–2001 in England and Wales. *BMC Fam Pract.* 2005;6(1):13.

Manitoba Health. Manitoba Drug Benefits Interchangability Formulary. *Bulletin.* 2008;59.

Marcum ZA, Handler SM, Wright R, Hanlon JT. Interventions to improve suboptimal prescribing in nursing homes: A narrative review. *Am J Geriatr Pharmacother.* 2010;8(3):183–200.

Martens P, Fransoo R, The Need to Know Team, et al. What Works? A First Look at Evaluating Manitoba's Regional Health Programs and Policies at the Population Level. Manitoba Centre for Health Policy. 2008. http://mchp–appserv.cpe.umanitoba.ca/reference/What%20Works.pdf. Accessed July 30, 2010.

Martens PJ, Bartlett J, Burland E, et al. Profile of Metis Health Status and Healthcare Utilization in Manitoba: A Population–Based Study. Manitoba Centre for Health Policy. 2010. http://mchp–appserv.cpe.umanitoba.ca/reference/Metis_Health_Status_Full_Report.pdf. Accessed October 14, 2010.

Martinez FD. Safety of long–acting beta–agonists––an urgent need to clear the air. *N Engl J Med.* 2005;353(25):2637–2639.

Menec VH, MacWilliam L, Soodeen R, Mitchell L. The Health and Health Care Use of Manitoba's Seniors: Have They Changed Over Time? Manitoba Centre for Health Policy. 2002. http://mchp–appserv.cpe.umanitoba.ca/reference/seniors.pdf. Accessed July 30, 2010.

Merlo J, Wessling A, Melander A. Comparison of dose standard units for drug utilisation studies. *Eur J Clin Pharmacol.* 1996;50(1–2):27–30.

Morgan S, Raymond C, Mooney D, Martin D. The Canadian RX Atlas. Centre for Health Services and Policy Research. http://www.chspr.ubc.ca/node/960. Accessed October 27, 2008. Last edited 2008.

Mosca L, Linfante AH, Benjamin EJ, et al. National study of physician awareness and adherence to cardiovascular disease prevention guidelines. *Circulation.* 2005;111(4):499–510.

National Asthma Control Task Force. *The Prevention and Management of Asthma in Canada: A Major Challenge Now and in the Future*. Ottawa, ON: Public Health Agency of Canada; 2000.

Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest.* 2006;129(1):15–26.

Ni CM, Greenstone I, Lasserson TJ, Ducharme FM. Addition of inhaled long–acting beta2–agonists to inhaled steroids as first line therapy for persistent asthma in steroid–naive adults and children. *Cochrane Database Syst Rev.* 2009;(4):CD005307.

O'Donnell DE, Aaron S, Bourbeau J, et al. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease–2007 update. *Can Respir J.* 2007;14 Suppl B:5B–32B.

O'Donnell DE, Hernandez P, Kaplan A, et al. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease–2008 update–highlights for primary care. *Can*

Respir J. 2008;15 Suppl A:1A–8A.

O'Kane MJ, Bunting B, Copeland M, Coates VE. Efficacy of self monitoring of blood glucose in patients with newly diagnosed type 2 diabetes (ESMON study): randomised controlled trial. *BMJ.* 2008;336(7654):1174–1177.

Page RL, Linnebur SA, Bryant LL, Ruscin JM. Inappropriate prescribing in the hospitalized elderly patient: defining the problem, evaluation tools, and possible solutions. *Clin Interv Aging.* 2010;5:75–87.

Patel H, Srishanmuganathan J, Car J, Majeed A. Trends in the prescription and cost of diabetic medications and monitoring equipment in England 1991–2004. *J Public Health (Oxf).* 2007;29(1):48–52.

Pedersen M, Jacobsen S, Klarlund M, Frisch M. Socioeconomic status and risk of rheumatoid arthritis: a Danish case–control study. *J Rheumatol.* 2006;33(6):1069–1074.

Peel E, Douglas M, Lawton J. Self monitoring of blood glucose in type 2 diabetes: longitudinal qualitative study of patients' perspectives. *BMJ.* 2007;335(7618):493.

Peppercorn MA. Definition of and risk factors for inflammatory bowel disease. *UpToDate*. 2010. http://www.uptodate.com/patients/content/topic.do?topicKey=~qqqcT5WOlNiGUn.

Percudani M, Barbui C, Fortino I, Petrovich L. Epidemiology of first– and second–generation antipsychotic agents in Lombardy, Italy. *Pharmacopsychiatry.* 2005;38(3):128–131.

Phillips C, McDonald T. Trends in medication use for asthma among children. *Curr Opin Allergy Clin Immunol.* 2008;8(3):232–237.

Rabi DM, Johnson JA, Edwards AL. Self–monitoring of blood glucose for individuals with type 2 diabetes not using insulin: leaving no cornerstone unturned. *Can J Diabetes.* 2010;34(1):24–26.

Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical antipsychotic drugs and the risk of sudden cardiac death. *N Engl J Med.* 2009;360(3):225–235.

Reid RJ, Roos NP, MacWilliam L, Frohlich N, Black C. Assessing population health care need using a claims–based ACG morbidity measure: a validation analysis in the Province of Manitoba. *Health Serv Res.* 2002;37(5):1345–1364.

Revers L, Furczon E. An introduction to biologics and biosimilars. Part 1: Biologics: what are they and where do they come from? *CPJ.* 2010a;143(3):134–139.

Revers L, Furczon E. An introduction to biologics and biosimilars. Part II: Subsequent entry biologics: Biosame or biodifferent? *CPJ.* 2010b;143(4):184–191.

Rhodes L, Moorman JE, Reed SC, Mannino DM. Self–reported asthma prevalence and control among adults–United States, 2001. *JAMA.* 2003;289:2639–2640.

Robinson CA. FDA's recommendations on the use of long–acting {beta}2 agonists in the management of asthma. *Ann Pharmacother.* 2010;44(10):1651–1654.

Rochester CD, Leon N, Dombrowski R, Haines ST. Collaborative drug therapy management for initiating and adjusting insulin therapy in patients with type 2 diabetes mellitus. *Am J Health Syst Pharm.* 2010;67(1):42–48.

Rochon PA. Drug prescribing for older adults. *UptoDate.* 2010;18(1). http://www.uptodate.com/patients/content/topic.do?topicKey=~hFWFDt6C2406eq.

Rochon PA, Normand SL, Gomes T, et al. Antipsychotic therapy and short–term serious events in older adults with dementia. *Arch Intern Med.* 2008;168(10):1090–1096.

Rochon PA, Stukel TA, Bronskill SE, et al. Variation in nursing home antipsychotic prescribing rates. *Arch Intern Med.* 2007;167(7):676–683.

Saag KG, Teng GG, Patkar NM, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease–modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum.* 2008;59(6):762–784.

Salpeter SR, Buckley NS, Ormiston TM, Salpeter EE. Meta–analysis: effect of long–acting beta–agonists on severe asthma exacerbations and asthma–related deaths. *Ann Intern Med.* 2006;144(12):904–912.

Salpeter SR, Wall AJ, Buckley NS. Long–acting beta–agonists with and without inhaled corticosteroids and catastrophic asthma events. *Am J Med.* 2010;123(4):322–328.

Salzman C, Jeste DV, Meyer RE, et al. Elderly patients with dementia–related symptoms of severe agitation and aggression: consensus statement on treatment options, clinical trials methodology, and policy. *J Clin Psychiatry.* 2008;69(6):889–898.

Scherbaum WA, Ohmann C, Abholz HH, Dragano N, Lankisch M. Effect of the frequency of self–monitoring blood glucose in patients with type 2 diabetes treated with oral antidiabetic drugs–a multi–centre, randomized controlled trial. *PLoS One.* 2008;3(8):e3087.

Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta–analysis of randomized placebo–controlled trials. *JAMA.* 2005;294(15):1934–1943.

Shea B. CADTH: Promoting evidence–based optimal therapy for diabetes. *CPJ.* 2009;142(5):220–223.

Singh SR, Ahmad F, Lal A, Yu C, Bai Z, Bennett H. Efficacy and safety of insulin analogues for the management of diabetes mellitus: a meta–analysis. *CMAJ.* 2009;180(4):385–397.

Skaer TL, Sclar DA, Robison LM. Trends in the prescribing of oral agents for the management of type 2 diabetes mellitus in the United States, 1990–2001: does type of insurance influence access to innovation? *Diabetes Educ.* 2006;32(6):940–953.

Stalhammar J, Berne C, Svardsudd K. Do guidelines matter? A population–based study of diabetes drug use during 20 years. *Scand J Prim Health Care.* 2001;19(3):163–169.

Stallmach A, Hagel S, Bruns T. Adverse effects of biologics used for treating IBD. *Best Pract Res Clin Gastroenterol.* 2010;24(2):167–182.

Steinman MA, Landefeld CS, Gonzales R. Predictors of broad–spectrum antibiotic prescribing for acute respiratory tract infections in adult primary care. *JAMA.* 2003;289(6):719–725.

Stockl KM, Le L, Harada AS, Zhang S. Use of controller medications in patients initiated on a long–acting beta2–adrenergic agonist before and after safety alerts. *Am J Health Syst Pharm.* 2008;65(16):1533–1538.

Street JS, Clark WS, Gannon KS, et al. Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer disease in nursing care facilities: a double–blind, randomized, placebo–controlled trial. The HGEU Study Group. *Arch Gen Psychiatry.* 2000;57(10):968–976.

Tamblyn R, Abrahamowicz M, du BR, McLeod P, Bartlett G. A 5–year prospective assessment of the risk associated with individual benzodiazepines and doses in new elderly users. *J Am Geriatr Soc.* 2005;53(2):233–241.

Tamblyn R, McLeod P, Hanley JA, Girard N, Hurley J. Physician and practice characteristics associated with the early utilization of new prescription drugs. *Med Care.* 2003;41(8):895–908.

Tariot PN, Schneider L, Katz IR, et al. Quetiapine treatment of psychosis associated with dementia: a double–blind, randomized, placebo–controlled clinical trial. *Am J Geriatr Psychiatry.* 2006;14(9):767–776.

Trifiro G, Spina E, Brignoli O, Sessa E, Caputi AP, Mazzaglia G. Antipsychotic prescribing pattern among Italian general practitioners: a population–based study during the years 1999–2002. *Eur J Clin Pharmacol.* 2005;61(1):47–53.

Turner S, Thomas M, von Ziegenweidt J, Price D. Prescribing trends in asthma: a longitudinal observational study. *Arch Dis Child.* 2009;94(1):16–22.

UK Prospective Diabetes Study Group. Effect of intensive blood–glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet.* 1998;352(9131):854–865.

Valiyeva E, Herrmann N, Rochon PA, Gill SS, Anderson GM. Effect of regulatory warnings on antipsychotic prescription rates among elderly patients with dementia: a population–based time–series analysis. *CMAJ.* 2008;179(5):438–446.

Van Assche G, Vermeire S, Rutgeerts P. Optimizing treatment of inflammatory bowel diseases with biologic agents. *Curr Gastroenterol Rep.* 2008;10(6):591–596.

Venables PJW, Maini RN. Clinical features of rheumatoid arthritis. *UpToDate*. 2010. http://www.uptodate.com/patients/content/topic.do?topicKey=~ffFME46crxyP6M.

Verrue CL, Petrovic M, Mehuys E, Remon JP, Vander SR. Pharmacists' interventions for optimization of medication use in nursing homes : a systematic review. *Drugs Aging.* 2009;26(1):37–49.

Walley T, Hughes D, Kendall H. Trends and influences on use of antidiabetic drugs in England, 1992–2003. *Pharmacoepidemiol Drug Saf.* 2005;14(11):769–773.

Wang PS, Schneeweiss S, Avorn J, et al. Risk of death in elderly users of conventional vs. atypical antipsychotic medications. *N Engl J Med.* 2005;353(22):2335–2341.

Wollina U, Unger L, Heinig B, Kittner T. Psoriatic arthritis. *Dermatol Ther.* 2010;23(2):123–136.

Woo V, Cheng AYY, Hanna A, Berard L. Self–monitoring of blood glucose in individuals with type 2 diabetes not using insulin: commentary. *Can J Diabetes.* 2010;34(1):19–23.

World Health Organization. World Health Organization Collaborating Centre for Drug Statistics Methodology. 2009. http://www.whocc.no/atcddd. Accessed July 30, 2010.

Wysowski DK, Armstrong G, Governale L. Rapid increase in the use of oral antidiabetic drugs in the United States, 1990–2001. *Diabetes Care.* 2003;26(6):1852–1855.

Yazici Y, Krasnokutsky S, Barnes JP, Hines PL, Wang J, Rosenblatt L. Changing patterns of tumor necrosis factor inhibitor use in 9074 patients with rheumatoid arthritis. *J Rheumatol.* 2009;36(5):907–913.

Yazici Y, McMorris BJ, Darkow T, Rosenblatt LC. Patient and physician perception of the infusion process of the biologic agents abatacept, infliximab, and rituximab for the treatment of rheumatoid arthritis. *Clin Exp Rheumatol.* 2009;27(6):907–913.

Yazici Y, Shi N, John A. Utilization of biologic agents in rheumatoid arthritis in the United States: analysis of prescribing patterns in 16,752 newly diagnosed patients and patients new to biologic therapy. *Bull NYU Hosp Jt Dis.* 2008;66(2):77–85.

Zhong KX, Tariot PN, Mintzer J, Minkwitz MC, Devine NA. Quetiapine to treat agitation in dementia: a randomized, double–blind, placebo–controlled study. *Curr Alzheimer Res.* 2007;4(1):81–93.

Glossary

Aggregated Diagnosis Groups (ADGs)
Formerly known as Ambulatory Diagnostic Groups, ADG's continue to be part of the Adjusted Clinical Group (ACG) case–mix system. The ACG method groups every ICD–9/ICD–9–CM medical diagnosis codes assigned to a patient into one of 32 different ADGs based on five clinical and expected utilization criteria: 1) duration of the condition (acute, recurrent, or chronic); 2) severity of the condition (e.g., minor and stable versus major and unstable); 3) diagnostic certainty (symptoms focusing on diagnostic evaluation versus documented disease focusing on treatment services); 4) etiology of the condition (infectious, injury, or other); and 5) specialty care involvement (medical, surgical, obstetric, haematology, etc.).

Antipsychotics
Antipsychotics are a broad class of medications used to treat a variety of psychiatric conditions. The class consists of newer or second generation antipsychotics (SGAs) also named 'atypical' antipsychotics, which include clozapine, risperidone, olanzapine, and quetiapine, and the older or first generation antipsychotics (FGAs) also indentified as "typical " antipsychotics. Examples of FGAs include haloperidol and phenothiazines.

Anatomical Therapeutic Chemical (ATC) Classification
A drug classification system widely used in Europe and for research purposes. The drugs are divided into different groups at five levels according to the organ or system on which they act and/or therapeutic and chemical characteristics: 1) anatomical group, 2) therapeutic main group, 3) therapeutic/ pharmacological subgroup, 4) chemical/therapeutic/pharmacological subgroup, and 5) subgroup for chemical substance. ATC classifications are available online and are updated and published once a year by the World Health Organization Collaborating Centre for Drug Statistics Methodology. The ATC system is becoming used more commonly in Canada.

Age
The age of an individual that is calculated based as of December 31 of the fiscal year.

Asthma
A disease in which inflammation of the airways causes airflow into and out of the lungs to be restricted. In this report, asthma was defined as one physician claim, one hospital claim for ICD–9–CM: 464, 466, 490, 491, 493 or ICD–10–CA: J04, J05, J20, J21, J40, J41, J42, J45, J441, J448 **or** one prescription for an asthma medication (listed in Appendix Table 1.1) in a three–year period (Lix et al., 2006).

Chronic Obstructive Pulmonary Disease (COPD)
COPD is an obstructive pulmonary disorder usually caused by smoking. It typically involves partially reversible airway obstruction and lung hyperinflation, exertional dyspnea, cough and/or sputum production, and frequent respiratory tract infections and increasing frequency of exacerbations (O'Donnell et al., 2007).

Defined Daily Dose (DDD)

The assumed average maintenance dose per day for a drug product when used for its major indication in everyday practice. It standardizes the measurement of drug utilization within and between drug entities, can be used to describe drug utilization across a population, and measure various aspects of intensity. This is a technical unit of measurement and does not necessarily reflect the actual amount or dose used; it is also limited to solid drug forms only. DDDs are assigned per Anatomical Therapeutic Chemical (ATC) Classification 4th level by the WHO Collaborating Centre for Drug Statistics Methodology in Norway. In this report, DDD was used as a measure of intensity of use.

Diabetes Mellitus

A chronic condition in which the pancreas no longer produces enough insulin (type 1 diabetes) or when cells stop responding to the insulin that is produced (type 2 diabetes), so that glucose in the blood cannot be absorbed into the cells of the body. The most common endocrine disorder, diabetes mellitus affects many organs and body functions, especially those involved in metabolism; and it can cause serious health complications including renal failure, heart disease, stroke, and blindness. Symptoms include frequent urination, fatigue, excessive thirst, and hunger. Also called insulin–dependent diabetes, type 1 diabetes begins most commonly in childhood or adolescence and is controlled by regular insulin injections. The more common form of diabetes, type 2, can usually be controlled with diet and oral medication. Another form of diabetes called gestational diabetes can develop during pregnancy and generally resolves after the baby is delivered.

In this report, diabetes mellitus was defined as either a) two or more physician visits or one hospitalization with a diagnosis of diabetes (ICD–9–CM: 250, ICD–10–CA: E10–E14); or b) one or more prescriptions to treat diabetes (Fransoo et al., 2009).

Drug Program Information Network (DPIN)

A database containing prescription drug claims from the Drug Programs Information Network (DPIN), an electronic, on–line, point–of–sale prescription drug database. Initiated in 1994, it connects Manitoba Health and all pharmacies in Manitoba to a central database maintained by Manitoba Health. Information about pharmaceutical dispensations, prescriptions identified as a potential drug utilization problem, non–adjudicated claims, and ancillary programs and non–drug products is captured in real time for all Manitoba residents (including Registered First Nations), regardless of insurance coverage or final payer. DPIN facilitates payment administration for eligible drug costs, incorporating functions such as real–time adjudication, and collects high–quality data on all prescriptions issued to Manitobans, such as drug, dosage, and prescription date. Information is not available for some facilities and areas, such as prison and some northern communities.

Fiscal Year

For most Canadian government agencies and health care institutions, the fiscal year is defined as starting April 1 and ending the following year at March 31. For example, the 2005/06 fiscal year would be April 1, 2005 to March 31, 2006, inclusive.

Generalized Estimating Equation (GEE)

A method of estimation used in the analysis of longitudinal data, which consists of repeated measures of an individual or cluster of individuals over time. These repeated measures from any one individual or cluster are correlated with each other and are, therefore, no longer independent. GEEs use the data to estimate the correlation between a single individual or cluster's response and provide a correct estimate of each effect's variance.

Inflammatory Bowel Disease

A group of disorders characterized by inflammation of intestines (i.e., the intestines become red and swollen). The most common inflammatory bowel diseases are Crohn's disease and ulcerative colitis. Crohn's disease is a chronic autoimmune disease that can affect any part of the gastrointestinal tract but most commonly occurs in the ileum (the area where the small and large intestine meet). Colitis is an inflammation of the large intestine that is caused by many different disease processes, including acute and chronic infections, primary inflammatory disorders (ulcerative colitis, Crohn's colitis, lymphocytic and collagenous colitis), lack of blood flow (ischemic colitis), and history of radiation to the large bowel.

International Classification of Diseases (ICD) Codes

A classification system of diseases, health conditions, and procedures developed by the World Health Organization (WHO), which represents the international standard for the labelling and numeric coding of diseases and health related problems. Within this system, all diseases/conditions are assigned numbers in hierarchical order. There are several versions of the ICD coding system, including ICD–8, ICD–9, ICD–9–CM (Clinical Modifications), ICD–O (Oncology), ICD–10, and ICD–10–CA (Canadian Enhancements). For Manitoba, the ICD–9 coding system ended on March 31, 2004 and the ICD–10 coding system began on April 1, 2004.

Logistic Regression

The regression technique used when the outcome is a binary, or dichotomous, variable. Logistic regression models the probability of an event as a function of other factors.

Personal Care Home (PCH)

Residential facilities for predominantly older persons with chronic illness or disability, also known as nursing homes. They may be proprietary (for profit) or non–proprietary. Non–proprietary PCHs may further be classified as secular or ethno–cultural (associated with a particular religious faith or language other than English) as well as either freestanding or juxtaposed with an acute care facility. In order to be admitted to a PCH an application form must be completed and reviewed by a panel which determines whether the person requires admission. Many persons who apply to enter a PCH have been home care clients for a considerable period of time, but their care needs have become too great to manage in the community. They generally continue to receive home care until admitted to a PCH. Finally, it should be noted that only approximately only approximately 75% of PCH fill prescriptions at community pharmacies (and are therefore included in the DPIN system). Medication use for PCH where prescriptions are filled through hospitals is not known (Doupe et al., 2006).

Population Health Research Data Repository

A comprehensive collection of administrative, registry, survey, and other databases primarily comprised of residents of Manitoba. This repository is housed at the Manitoba Centre for Health Policy. It was developed to describe and explain patterns of health care and profiles of health and illness, facilitating inter–sectoral research in areas such as health care, education, and social services. The administrative health database, for example, holds records for virtually all contacts with the provincial health care system, the Manitoba Health Services Insurance Plan (including physicians, hospitals, personal care homes, home care, and pharmaceutical prescriptions), of all registered individuals. MCHP acts as a steward of the information in the Repository for agencies such as Manitoba Health.

Prescription

Any prescription dispensed in a retail pharmacy and recorded in the provincial prescription database (Drug Programs Information Network (DPIN)). This includes prescriptions paid out–of–pocket and prescriptions reimbursed by Manitoba's Pharmacare and Family Services drug insurance programs, federal drug insurance programs such as Health Canada and Veteran Affairs, and private drug insurance programs.

Psoriasis

Psoriasis is a chronic skin disorder that causes areas of thickened, inflamed, red skin, often covered with silvery scales. Approximately one–third of people with psoriasis also have psoriatic arthritis, a condition that causes joint pain and swelling (Feldman & Pearce, 2010).

Psychosis

Medical condition involving a loss of contact with reality, often with symptoms such as hallucinations (sensing things that are not present or do not exist) or delusions (fixed false beliefs in events or facts). For this report, psychosis was defined as any claim for a psychotic (ICD–9–CM: 295–299, ICD–10–CA: F2, F3, F84, R410 in any diagnosis field for physician or hospital claims in one year prior to the prescription of interest) (Daumit et al., 2003).

Quarter

In this report, drug utilization was described in a particular quarter of a fiscal year. The first quarter (Q1) of each year was April–June, the second quarter (Q2) was July–September, the third quarter (Q3) was October–December and the fourth quarter (Q4) was January–March.

Region of Residence

In this report, region of residence was categorized as being rural or urban as determined by the postal code registered with Manitoba Health. Those who were registered to Winnipeg or Brandon were categorized as urban, while the rest of Manitoba was considered to be rural. Some analyses categorized Manitoba residents as being part of five regions by Regional Health Authority (RHA) as follows: Rural South (South Eastman, Central, and Assiniboine RHAs); Mid (North Eastman, Interlake, and Parkland RHAs); North (NOR–MAN, Burntwood, and Churchill RHAs); Brandon; and Winnipeg.

Rheumatoid Arthritis

A chronic, inflammatory autoimmune disorder that causes the immune system to attack the joints. It is a disabling and painful inflammatory condition, which can lead to substantial loss of mobility due to pain and joint destruction. The disease is also systemic in that it often also affects many extra–articular tissues throughout the body including the skin, blood vessels, heart, lungs, and muscles.

Socioeconomic Status

As Manitoba has an income based deductible for the provincial Pharmacare program, prescription drug users were divided into three groups, based on out of pocket expenses for prescription medications and median neighbourhood income quintile (from Statistics Canada census files) as follows:

- Lower income: individuals in the lowest and second lowest median neighbourhood income quintile
- Higher income: individuals residing in the neighbourhoods with the three highest median neighbourhood income quintiles.
- Income unknown: individuals who cannot be assigned a neighbourhood income from the census data. This category includes individuals residing in facilities such as personal care homes, psychiatric facilities, prisons, or wards of the Public Trustee and Child and Family services.

Specialist

Physician specialty of specialist, as recorded in the Manitoba Physician Practice database. This included physicians in the area of psychiatrist, pediatrician, medical specialist, surgeon, and anaesthetist.

Appendix 1.1: Medication List for Drug Categories

Table A1.1: Medication List for Drug Categories

Chapter	Drug Category	Group ATC	Generic Name	ATC	DDD* (mg)
Antipsychotics	First generation antipsychotics	N05A	Chlorpromazine	N05AA01	300
			Fluperthixol	N05AF01	6
			Fluphenazine	N05AB02	10
			Haloperidol	N05AD01	8
			Loxapine	N05AH01	100
			Mesoridazine	N05AC03	200
			Methotrimeprazine	N05AA02	300
			Pericyazine	N05AC01	50
			Perphenazine	N05AB03	30
			Pimozide	N05AG02	4
			Pipotiazine	N05AC04	
			Prochlorperazine	N05AB04	100
			Thioridazine	N05AC02	300
			Thiothixene	N05AF04	30
			Trifluoperazine	N05AB06	20
			Zuclopenthixol	N05AF05	30
	Second generation antipsychotics	N05A	Olanzapine	N05AH03	10
			Risperidone	N05AX08	5
			Quetiapine	N05AH04	400
Benzodiazepines and related medications	Benzodiazepines	N05B	Alprazolam	N05BA12	1
			Bromazepam	N05BA08	10
			Chlordiazepoxide	N05BA02	30
			Clobazam	N05BA09	20
			Clonazepam	N03AE01	8
			Diazepam	N05BA01	10
			Flurazepam	N05BA17	0.75
			Lorazepam	N05BA06	2.5
			Oxazepam	N05BA04	50
			Temazepam	N05CD07	20
			Triazolam	N05CD05	0.25
	Z drugs	N05C	Zopiclone	N05CF01	7.5
			Zaleplon	N05CF03	10
Medications for Diabetes Mellitus	Insulins - New	A10A	Insulin Lispro	A10AB04	
			Insulin Aspart	A10AD05	
			Insulin Glargine	A10AE04	
			Insulin Detemir	A10AE05	
	Insulins - Old	A10A	Insulin Zinc (Beef/Pork)	A10AA01	
			Insulin Isophane(NPH) (Beef)	A10AA02	
			Insulin Dna Origin Human	A10AB01	
			Insulin (Regular) Pork	A10AB03	
			Insulin NPH Human DNA Origin	A10AC01	
			Insulin (Lente) Pork	A10AC03	
			Insulin & Insulin Isophane (NPH)	A10AD01	
			Insulin Zinc Human Biosynthet	A10AE01	
	Sulfonylureas - New	A10BB	Glimepiride	A10BB12	2
	Sulfonylureas - Old	A10BB	Acetohexamide	A10BB31	500
			Chlorpropamide	A10BB02	375
			Gliclazide	A10BB09	160
			Glimepiride	A10BB12	2
			Glyburide	A10BB01	7
			Tolbutamide	A10BB03	1500
	Glitazones (Thiazolidenediones) - New	A10B	Rosiglitazone	A10BG02	
			Pioglitazone	A10BG03	30
	Metformin - Old	A10B	Rosiglitazone/Metformin	A10BD03	
			Metformin	A10BA02	2000mg
	Meglitinides - New	A10BX	Nateglinide	A10BX03	360
			Repaglinide	A10BX02	4
	Acarbose - New	A10BBF	Acarbose	A10BF01	300

Table A1.1: Continued

Chapter	Drug Category	Group ATC	Generic Name	ATC	DDD* (mg)
Medications for Asthma and Chronic Obstructive Pulmonary Disease	Steroids, inhaled	R03BA	Beclomethasone	R03BA01	
			Ciclesonide	R03BA08	
			Flunisolide	R03BA03	
			Fluticasone	R03BA03	
			Inhaled Budesonide	R03BA02	
			Triamcinolone	R03BA06	
	Short acting beta agonists	R03A	Fenoterol	R03AC04	
			Inhaled Salbutamol	R03AC02	
			Isoproterenol	R03AB02	
			Terbutaline	R03AC03	
	Long acting beta agonists	R03A	Inhaled Salmeterol	R03AC12	
			Formoterol	R03AC13	
	Steroid, inhaled in combination with long acting beta agonists	R03A	Salmeterol/Fluticasone	R03AK06	
			Formoterol/Budesonide	R03AK07	
	Anticholinergic, inhaled	R03	Ipratropium	R03BB01	
			Ipratropium/Salbutamol	R03AK04	
			Ipratropium/Fenoterol	R03AK03	
			Tiotropium	R03BB04	
	Leukotriene receptor antagonists	R03DC	Monteleukast	R03DC03	
			Zafirlukast	R03DC01	
	Other medications for asthma and chronic obstructive lung disease		Aminophylline	R03DA05	
			Theophylline	R03DA04	
			Oxitriphylline	R03DA02	
			Orciprenaline	R03AB03	
			Ketotifen	R06AX17	
			Cromoglicic Acid	R03BC01	
			Epinephrine	R03AA01	
			Nedocromil	R03BC03	
			Omalizumab	R03DX05	
			Oxtriphylline & Guaifenesin	R03DA52	
			Sodium Cromoglycate	R01AC01	
			Dexamethasone	H02AB02	
			Hydrocortisone	H02AB09	
			Methylprednisolone	H02AB04	
			Prednisolone	H02AB06	
			Prednisone	H02AB07	
Antibiotics	Fluoroquinolones	J01MA	Ciprofloxacin	J01MA02	
			Gatifloxacin	J01MA16	
			Gemifloxacin	J01MA15	
			Levofloxacin	J01MA12	
			Moxifloxacin	J01MA14	
			Nalidixic Acid	J01MB02	
			Norfloxacin	J01MA01	
			Ofloxacin	J01MA01	
	Other Beta Lactans (cephalosporins & carbopenems)	J01D	Cefalexin	J01DA01	
			Cefuroxime	J01DA06	
			Cefprozil	J01DA10	
			Cefaclor	J01DA08	
				J01DC04	
			Cefadroxil	J01DA09	
				J01DB05	
			Meropenem	J01DH02	
			Ertapenem Sodium	J01DH03	
			Cefazolin Sodium	J01DA04	
				J01DB04	
			Cefotaxime	J01DD01	
				J01DA10	
			Cefotetan Disodium	J01DC05	
			Cefoxitin Sodium	J01DA05	
			Cefprozil	J01DC10	
			Ceftazidime	J01DA11	
				J01DD02	
			Ceftriaxone	J01DD04	
			Cefuroxime Axetil	J01DA06	
				J01DC02	
			Cephalexin	J01DA01	
				J01DB01	
			Cilastatin Sodium	J01DH51	
			Meropenem	J01DH02	
			Ertapenem Sodium	J01DH03	
			Cefixime	J01DD08	
				J01DA23	

Table A1.1: Continued

Chapter	Drug Category	Group ATC	Generic Name	ATC	DDD* (mg)
	Macrolides, oral dosage forms	J01FA	Azithromycin	J01FA10	
			Clarithromycin	J01FA09	
			Clarithromycin	J01FA09	
			Erythromycin	J01FA01	
			Erythromycin	J01FA01	
			Spiramycin	J01FA02	
			Telithromycin	J01FA15	
	Penicillins	J01C	Penicillin	J01CE10	
				J01CE01	
				J01CE02	
				J01CE08	
			Ampicillin	J01CA01	
			Pivampicillin	J01CA02	
			Amoxicillin	J01CA04	
				J01CR02	
			Pivmecillinam	J01CA08	
			Piperacillin	J01CA12	
			Cloxacillin	J01CF02	
			Flucloxacillin	J01CF05	
			Piperacillin/Tazobactam	J01CR05	
	Trimethoprin and sulphonamides	J01E	Sulfadiazine Trimethoprim	J01EE02	
			Sulfamethoxizole /Trimethoprim	J01EE01	
			Sulfisoxazole	J01EB05	
			Trimethoprim	J01EA01	
	Tetracyclines	J01AA	Doxycycline	J01AA02	
			Minocycline	J01AA08	
			Tetracycline	J01AA07	
	Other	J01F	Clindamycin	J01FF01	
			Lincomycin	J01FF02	
		J01G	Amikacin	J01GB06	
			Gentamicin Sulfate	J01GB03	
			Metronidazole	J01XD01	
			Streptomycim	J01GA01	
			Tobramycin	J01GB01	
		J01R	Erythromycin/Sulfisoxazole	J01RA02	
		J01X	Colistimethate Sodium	J01XB01	
			Fosfomycin Tromethamine	J01XX05	
			Fusidate Sodium	J01XC01	
			Linezolid	J01XX08	
			Methenamine	J01XX55	
			Metronidazole	J01XD01	
			Nitrofurantoin	J01XE01	
			Notrofurantoin	J01XX01	
			Vancomycin	J01XA01	
Biologics		L04A	Abatacept	L04AA24	
			Adalimumab	L04AA17	
			Alefacept	L04AA15	
			Anakinra	L04AA14	
			Efalizumab	L04AA21	
			Etanercept	L04AA11	
			Infliximab	L04AB02	

*Note: For oral dosage forms where available

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