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Trends In The Utilization of Antiglaucoma Medication: An Analysis of Canadian Drug Insurance Claims

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A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science

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by

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Abstract

Objectives: To assess: i) utilization of generic anti-glaucoma drugs in Canada; ii) the impact of the 2010 Ontario Drug System Reform on generic anti-glaucoma drug usage in Ontario.

Methods: Monthly drug insurance cost and claims from January 2001 to January 2013 were used as proxies for drug utilization. Evaluation of the impact of the 2010 reform was conducted using interrupted time series analysis with ARIMA models.

Results: Generic antiglaucoma medication utilization increased in Ontario during Quarter 3, 2006. Increases in utilization across study provinces were observed in Quarter 4, 2011. The 2010 reform was not associated with changes in generic drug utilization.

Conclusion: The results of the study demonstrated that introduction of new generic equivalents increases in the utilization of generics drugs. Lowering the price of generic medications did not lead to a change in the utilization. Alternative strategies should be implemented to increase generic drug use in glaucoma treatment.

Keywords

Ophthalmic medication, Glaucoma, Generic Drug, Drug utilization patterns, Time series, Interrupted time series analysis, Autoregressive Moving Average Model, Transparent Drug System for Patients Act, Bill 102, Ontario Drug System Reform.

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List of Abbreviations

ACG	Angle Closure Glaucoma
AGIS	Advanced Glaucoma Intervention Study
Bill 102	Transparent Drug System for Patients Act
D	Diopters
DIDFA	Drug Interchangeability and Dispensing Fee Act
DIN	Drug Identification Number
FDA	Food and Drug Administration
IOP	Intraocular Pressure
NTG	Normal Tension Glaucoma
OAG	Open Angle Glaucoma
ODBA	Ontario Drug Benefit Act
ODBP	Ontario Drug Benefit Program
PDCRA	Prescription Drug Cost Regulation Act
POAG	Primary Open Angle Glaucoma
PPI	Proton Pump Inhibitor
UK	United Kingdom
US	United States of America

Chapter 1

1 Introduction

Glaucoma is a chronic ocular disorder in which the optic nerve is systematically damaged, resulting in progressive vision loss. Treatments for glaucoma are focused towards the prevention of disease progression, and often begin with the use of topical ophthalmic medication. These medications aim to reduce intraocular pressure, and thereby reduce disease progression, through affecting aqueous humour dynamics. Currently, there are 5 major classes of antiglaucoma medication: cholinergic agonists, α-adrenergic agonists, β-adrenergic receptor antagonists, carbonic anhydrase inhibitors, and prostaglandins. Generic equivalents for many of these medications are currently available.

To address rising healthcare costs, various provincial government have enacted laws which limit the cost of generic medications. In Ontario, reforms to the provincial drug insurance program, Ontario Drug Benefit Program, were made in 2006 and 2010 with aims to cap the price of generic equivalents to 50% and 25% of the price of the reference product, respectively. Moreover, the 2010 reform enacted laws which extended price ceilings for the generic medication within the private market. While several studies have examined the impact of the reforms on overall drug expenditures within the public drug insurance program, none have looked at the impact specifically within the private and public antiglaucoma medication market.

Hence, this study aimed to describe the utilization of generic antiglaucoma medication between January 2001 and January 2013 across several provinces in Canada. Furthermore, we made use of time series techniques to determine the impact of the 2010 Ontario Drug System Reform on the dispensing of antiglaucoma medication across several Canadian provinces.

The results of the study revealed that the utilization of antiglaucoma medication is heavily influenced by the introduction and availability of novel antiglaucoma medication, whether the drug is a generic or brand name compound. The impact of the drug plan

reforms remains relatively muted. Hence, in order to control rising healthcare costs, policy makers should consider alternative methods such as encouraging increases in utilization of generic medications for glaucoma treatment.

Chapter 2

2 Literature Review

2.1 Glaucoma: An Introduction

Glaucoma is a group of ocular neuropathic disorders estimated to be the second leading cause of blindness worldwide.[1,2] Commonly associated with increased intraocular pressure (IOP), vision loss due to glaucoma is caused by the gradual degeneration of retinal ganglion cells and their axons.[3] As a result, the profile of the optic nerve head changes ("cupping") and vision progressively deteriorates in a characteristic pattern, typically beginning with the peripheral vision. Glaucomatous vision loss is permanent as the disease damages the optic nerve, and is thus responsible as the leading cause of irreversible blindness worldwide.

Fortunately, glaucoma progression can be controlled by efforts to reduce intraocular pressure, making this the leading cause of preventable blindness worldwide.[4] Treatment often begins with the use of antiglaucoma medications aimed at the control or reduction of intraocular pressure. Once medication options have been exhausted, patients are referred for laser trabeculoplasty or more invasive intraocular surgeries in order to minimize progression of the disease.

The prevalence of glaucoma increases significantly with age, and the problem of glaucoma will continue to increase as the world's population ages.[5–7]

2.2 Classification and Types of Glaucoma

Glaucoma is classified based on 1) etiology or 2) mechanism. Etiology refers to classifying the type of glaucoma based on the underlying disease which leads to the modifications in aqueous humour dynamics or retinal ganglion cell loss.[4] Etiological classification divides glaucoma into primary and secondary forms, where primary forms are thought to be a result of anterior chamber and conventional outflow pathway obstruction and is independent of other ocular or systemic disorders.[4] On the other hand, classification of secondary glaucoma is dependent on a partial understanding of an

underlying, predisposing ocular or systemic event.[4] While etiologic classifications are currently used extensively in clinical practice, its reliance on an incomplete understanding of the pathophysiology may limit its clinical relevance. Moreover, as the knowledge of the mechanisms behind the disease increases, mechanistic approaches to defining glaucoma offers an alternative classification system.[4]

Mechanistic approaches to defining glaucoma aims to classify patients based on the mechanisms of aqueous outflow obstruction. These mechanisms are varied depending on the characteristics of the iridocorneal angle, the angle formed between the iris and cornea. This classification system separates glaucoma into three categories: a) open-angle glaucoma (OAG), b) angle-closure glaucoma (ACG) and c) developmental anomalies of the iridocorneal angle.[4]

2.2.1 Open Angle Glaucoma

In open-angle glaucoma, the iridocorneal angle remains unobstructed, but the outflow of aqueous humor is diminished, often resulting in heightened intraocular pressure.[3] The obstruction may be located prior to the iridocorneal angle, within the trabecular meshwork, or distal to the meshwork.[4] Another clinical feature of primary open angle glaucoma (POAG) is the cupping of the optic nerve, which can lead to a corresponding loss of vision.[3] Critiques of this classification system state that this approach fails to account for causes and mechanisms that do not affect intraocular pressure, such as genetic factors. Furthermore, there is ambiguity when classifying glaucoma with multiple mechanisms of outflow obstruction.[4]

Strategies for dealing with POAG are all targeted at controlling IOP by medication or surgical interventions.[3] Cases of open-angle glaucoma where IOP is not elevated are often called normal tension glaucoma (NTG). Estimates of normal tension glaucoma is thought to range from 30%-50% of POAG patients.[8] NTG is typically characterized by an appearance of POAG but diurnal IOP remains < 22 mmHg.

2.2.2 Angle Closure Glaucoma

Angle-closure glaucoma is characterized by the narrowing of, and restriction to, the iridocorneal angle, causing diminished aqueous outflow and heightened intraocular pressure. One of the most common posterior mechanisms for angle-closure glaucoma is pupillary block, where the peripupillary iris is in apposition to the lens and limits the flow of aqueous humour from the ciliary bodies into the anterior chamber.[9] This causes an increase in the pressure within the posterior chamber and a subsequent forward bowing of the iris, leading to blockage in the iridocorneal angle. Anterior mechanisms of angle-closure glaucoma involves a narrowing of the iridocorneal angle as a result of the iris being "pulled" into close proximity to the cornea and trabecular meshwork. Angle-closure glaucoma can also be further classified based on the extent of closure in the iridocorneal angle and the pattern of intraocular pressure elevation. Acute angle closure, often resulting from total angle closure, may result in a sudden onset of intraocular pressure elevation and is accompanied by sudden, severe pain, blurred vision, headaches, nausea and other ocular anomalies. Subacute angle closure is defined by sudden increases in intraocular pressure which are spontaneously alleviated, which may be symptomatic with intermittent headaches. Chronic angle closure occurs when there is permanent closure of the anterior chamber angle, however, this type of angle closure is often asymptomatic. Most angle-closure glaucoma cases are resolved using laser or surgical treatment options.

2.2.3 Glaucoma Due to Developmental Anomalies

Incomplete development of structures within the outflow pathway of aqueous humour may also lead to glaucoma. Developmental defects such as a high insertion of the anterior uvea, incomplete development of the trabecular meshwork and incorrect iridocorneal adhesions are clinically recognized defects that are seen in congenital and many other forms of glaucoma.[4]

2.3 Epidemiology of Glaucoma

2.3.1 Prevalence of Glaucoma

Glaucoma was predicted to affect 60.5 million people worldwide by 2010, increasing to 79.6 million by 2020 and corresponding to a mean prevalence of 1.96%.[10] Angle-closure glaucoma is estimated to the leading cause of glaucoma in Asia, however its prevalence in North America and Europe is much lower compared to the rest of world, accounting for approximately 10% of all glaucoma cases in the United States.[9] Several population-based studies have been conducted in the United States to determine the prevalence of glaucoma across various locations, with estimates ranging from 1.97% to 3.69%.[11–15] These studies have revealed that there are significant variations among ethnic and racial groups. The Baltimore Eye Survey concluded that the prevalence of glaucoma was 3.69%, with age-adjusted prevalence rates four to five times higher among the blacks compared to whites.[11] The differences in the prevalence may be reflective of the varying case definitions of glaucoma and differing age distributions within these studies. However, these variations may also be indicative of the impact of the large genetic heterogeneity within these ethnic groups.[4]

In the Canadian context, there is a substantial gap in the literature regarding the prevalence of glaucoma.[16] Population-based studies have been limited in size and geographical location, and are thus limited in the applicability of their results to the general Canada populace. A study of 18,000 individuals in the Scarborough, Ontario area conducted in 1965 found a glaucoma prevalence of 2.26%.[17] Self reported glaucoma prevalence derived from national surveys such as the National Population Health Survey and the Canadian Community Health Survey was estimated to range from 1.1% to 1.8% between 1994-2003, representing a 64% increase in prevalence during this time period.[18] Furthermore, the study showed that the age-specific prevalence of self-reported glaucoma increased with age, increasing from a prevalence of 2.7% among adults over the age of 40 to 10.99% for those over the age of 80.[18] The Toronto epidemiology glaucoma survey, published in 2011, reported that 7.5% of eligible participants stated they had glaucoma.[19] Furthermore, among participants who reported not having glaucoma who voluntarily completed a clinical assessment, 3.9% were diagnosed with glaucoma. However, this

study was limited in sample size (n = 975) and the author remarked that the proportion of eligible participants who volunteered for clinical assessment had higher than average family history of glaucoma, which may have contributed to the higher prevalence observed.[19] In 2007, it was estimated that 24,937 Canadians suffer from severe vision loss due to glaucoma, accounting for 3.1% of all vision loss cases in Canada.[20]

2.3.2 Risk Factors

2.3.2.1 Age

Population studies of glaucoma have demonstrated that the risk is positively correlated with age. A meta-analysis of multiple population surveys of prevalence of open angle glaucoma conducted by The Eye Diseases Prevalence Research Group concluded that the prevalence increases 10-fold when comparing a group of white adults aged 40-49 and a group of adults 80 years old and older.[21] Furthermore, results from the Early Manifest Glaucoma Trial suggested that being 68 years or older is associated with a 1.47 times increase in the risk of developing glaucoma compared to younger persons.[22] The positive association between age and risk of open-angle glaucoma is evident in other population studies conducted in various countries, which concluded that the association is observed regardless of race.[11,23–25] Current literature speculates that age may be a proxy risk factor for currently unassociated causative factors, such as increasing deterioration of ocular tissue or social problems such as poor adherence to treatment medication.[26]

2.3.2.2 Race

Primary open angle glaucoma is most prevalent among the Black population, followed by the White, Asian and Hispanic populations. The incidence of OAG among Blacks is estimated to be two to five times greater than White individuals.[27] Furthermore, the Eye Disease Prevalence Research Group demonstrated that the prevalence of OAG within each age group was higher among the Black population compared to White individuals.[21] Interestingly, conclusions from the Advanced Glaucoma Intervention Study (AGIS) did not determine Black race to be a significant risk factor for disease progression.[28] While this result contradicted findings from other population based studies, it is important to note that the AGIS recruited advanced glaucoma patients, which may yield results not

directly comparable to other findings. Prevalence of OAG among the Asian population is more varied, with southern Asians (from countries in Southeast Asia and India) reflecting OAG prevalence similar to the white population, while northern Asians (from China and Mongolia) have lower than average OAG prevalence.[29] However, the prevalence of angle closure glaucoma remains substantively higher among the Asian population.[30]

2.3.2.3 Family History

Family history of OAG is an important predictor for incidence of OAG, particularly if the individual is a first-degree relative.[31–34] The Baltimore Eye Survey provided evidence demonstrating that the association between incidence of glaucoma is stronger between siblings (OR 3.7) than when the relative is a parent (OR 2.2) or child (OR 1.1).[32] An Australian study following 3271 patients in a prospective cohort study determined that a family history of glaucoma was associated with a 2.1 times increase in the risk of developing glaucoma.[5] However, studies that examined the impact of family history among patients with established glaucoma did not find a signification association with disease progression.[22,35] The positive association between family history and risk of OAG was also shown in the Barbados Family Study, which was an observational study of the families of OAG patients.[36]

2.3.2.4 Myopia

Several studies have supported the association between myopia and the risk of open-angle glaucoma.[37–41] A population study of White Australians showed increasing risk of glaucoma with increasing myopia. Individuals with moderate to high myopia (greater than -3 D) were reported to have significantly higher risk than lower myopia patients (OR 3.3).[41] Similar results were seen in a study of White Americans, which concluded that patients with myopia (greater than – 1 D) were 60% more likely to have glaucoma. Furthermore, studies in Asia have demonstrated the association between a high myope (greater than -6 D) and the risk of visual field loss due to glaucoma progression.[38,39] Several longitudinal studies have also shown that presence of myopia is associated with increasing risk of glaucoma.[42–44]

2.3.2.5 Intraocular Pressure

There is strong evidence supporting elevated intraocular pressure as a risk factor for the development of OAG. Population and longitudinal studies on the prevalence of glaucoma have determined that there is a significant dose-response relationship between intraocular pressure and disease progression.[5,22,45,46] In particular, conclusions from the Ocular Hypertension Treatment Study suggests that a reduction of 20% in intraocular pressure is associated with a halving of the five year risk of disease development.[45] Similarly, the European Glaucoma Prevention Study determined that each mmHg increase in IOP, sustained for a year, is associated with a 9% increase in the risk of developing open-angle glaucoma.[47] Results from a randomized clinical trial on the efficacy of glaucoma treatments has further demonstrated that control of intraocular pressure resulted in lower rates of disease progression compared to participants who had no treatment.[45,48,49]

The long term effects of fluctuations in intraocular pressure remain controversial. Studies such as the European Glaucoma Prevention Study and the Ocular Hypertension Treatment Study have demonstrated long-term intraocular pressure fluctuations not to be associated with increased risk of disease progression.[47,50,51] On the contrary, results from the Advance Glaucoma Intervention Study suggested increased risk of progression with fluctuations in intraocular pressure, particularly among those with lower baseline intraocular pressure.[52,53] Although elevated intraocular pressure is a strong risk factor for glaucoma, it is important to note that a significant amount of glaucoma cases are of the normal tension variety. Studies on the prevalence of glaucoma estimated that normal tension glaucoma accounts for approximately one third of untreated open-angle glaucoma patients in the Barbados Eye Study, and up to 85% among untreated Chinese open-angle glaucoma patients.[54,55]

The only clinically treatable risk factor for glaucoma remains control of and decreasing intraocular pressure. To this end, several medication and surgical procedures have been utilized in clinical practice.

2.4 Cost of Glaucoma

While many economic analyses have been conducted to determine the cost effectiveness of specific medications or surgical techniques used in glaucoma treatment, there is little literature on the societal burden of glaucoma. Canadian estimates of the direct healthcare cost for treating primary open angle glaucoma ranged from $461 to $697 (in 2001 Canadian dollars) per patient per year, varying by disease severity.[56] However, the study estimated cost by assuming total adherence to medication therapy and therefore may underestimate the true cost of treatment, as additional treatment costs may be incurred due to non-optimal adherence which may lead to accelerated glaucoma progression.[56] Direct healthcare costs estimated from a retrospective chart review of 265 patient yielded similar results. Stratified by mean deviation scores, with mild (> -5 decibels), moderate (-5 to -12 decibels), and advanced (< -12 decibels) glaucoma severity, the estimated direct costs ranged from $385 to $460 to $563 (in 2001 Canadian dollars), respectively.[57] A follow-up study of a smaller subset of 132 patients which included the effects of corneal thickness on glaucoma severity determined the cost of disease to range from $406 to $432 to $465 when stratified by the same severity levels.[58] However, these studies only considered medically related costs in the analyses. Hence, societal costs such as hours of lost work, lower rates of employment, higher caregiver and supportive device requirements were unaccounted for.[56–58]

In terms of a health care system level estimate of the burden of illness, a 2002 report by Health Canada estimated that $54.7 million (in 1998 Canadian dollars) was spent on treating glaucoma.[59] Moreover, a recent report conducted for the CNIB and the Canadian Ophthalmological Society estimated that the cost of glaucoma to the Canadian healthcare system was $549 million (in 2007 Canadian dollars). However, this estimate was based on the assumption that the ratio of glaucoma drug expenditure to total drug expenditure is the same as glaucoma-related health system expenditure (including medication and other direct medical cost) to the total health system expenditure.[20] For example, if glaucoma-related drug expenditure was 3% of total drug expenditure, then the authors assume that the glaucoma-related health system expenditure will also be 3% of total health system expenditure. This assumption may not hold in practice. For instance, the proportion of

hospitalization costs for glaucoma patients compared to patients with other illnesses may not be identical to the proportion of drug costs. This is evident in the fact that most glaucoma surgical interventions are ambulatory, while other diseases, such as cardiovascular disease, require multi-day stays within the hospital. Thus, $549 million may be an overestimation of the true burden of illness for glaucoma.

Similar costs are seen in other countries.[60] An American study utilizing insurance claims data estimated the direct healthcare burden due to glaucoma to be approximately $2.9 billion for the US populace (in 2004 US dollars), with the majority of the costs attributed to outpatient and pharmaceutical services.[61] Furthermore, a review of commercial insurance claims in the United States suggested that the average primary open angle glaucoma specific costs among its enrollees was $1570, with median cost of $840 (in 2004 US dollars).[62] A retrospective study of primary open angle glaucoma patient records concurred with the above results, which demonstrated that the average annual direct healthcare costs ranged from $623 to $2511 for patients who are suspected, but not diagnosed, of having primary open angle glaucoma and end-stage primary open angle glaucoma, respectively.[63] The major cost component across all disease severities remained medication costs.[63] However, like in the Canadian context, these studies only examined medication and other direct healthcare costs, and fail to account for indirect costs, such as lost productivity by the patient or the caregivers.

Results from European studies concur with North American findings.[64–67] A chart review of French and Swedish glaucoma patients revealed that the average annual treatment cost per glaucoma patient to be €390 in France and €531 in Sweden, with approximately half of this estimate attributed to the cost of medication (49.6% in France and 48.7% in Sweden).[64] These estimates were further replicated by a review of patient charts across Europe, which demonstrated that healthcare costs range from €455 to €969, depending on disease severity. Furthermore, the study concluded that up to 42% to 56% of the direct healthcare cost is attributed to cost of medication, depending on the nation of interest.[65] Estimates of the annual healthcare costs, excluding surgery, of late stage glaucoma were found to average €830 among France, Denmark, Germany and the United Kingdom. The costs increased to €3534 when the estimated cost of paid assistance in the home was

included to better approximate the total maintenance cost of disease.[66] Based on a review of the literature of costs in several European nations, Poulsen et al. concluded that the annual direct healthcare cost per patient to range from €429 to €523, while annual total societal cost per patient to range from €11758 to €19111.[67]

From these studies, it is evident that the major direct medical cost driver of glaucoma is the cost of medication. In order to contain the rapidly increasing healthcare costs, there is a strong political and institutional push to support the use of generic medication in therapy.[68] However, the utilization impact of these cheaper generic antiglaucoma medications remains largely unstudied.

2.5 Medication Therapy in Glaucoma Treatment

Medication therapy for glaucoma involves the prescriptions of various chemical agents aimed at decreasing the pressure within the eye. The mode of action of these medications can generally be classified into two categories: medications that 1) improve aqueous outflow, usually by increasing drainage of the aqueous humour; or 2) minimize aqueous inflow, usually by decreasing production of the aqueous humour. Furthermore, medications used in long-term treatment of glaucoma are commonly grouped into 5 different classes: cholinergic agonists or miotics, α-adrenergic agonists, β-Adrenergic receptor antagonists, carbonic anhydrase inhibitors, and prostaglandin analogues.[69]

2.5.1 Cholinergic agonists (Miotics)

The first commercial medication utilized for treatment of glaucoma was pilocarpine (Brand name: Isopto Carpine), introduced in the 1870s.[69] This drug simulated the effects of acetylcholine, stimulating the muscarinic receptors on human ciliary muscle cells. This caused the muscles to contract, leading a cascade that results in a change in the structure of the trabecular meshwork and an increase in aqueous outflow.[70] In ACG patients, it is also believed the miotics lower intraocular pressure by relieving the pupillary block.[4] Pilocarpine was the medication of choice for over 75 years before a new type of drug appeared. However, as it requires multiple applications per day, utilization of cholinergic agonists has dramatically decreased in favour of newer medications that require fewer daily applications.

2.5.2 α-Adrenergic Agonists

Epinephrine first became commercially available for glaucoma treatment in the 1950s.[71] Epinephrine acts to decrease intraocular pressure in several ways. Early after administration, it elicits a reduction in the production of aqueous humour, however, such actions are often transient in nature. After long term administration, it is believed that the drug improves aqueous humour outflow.[72] Dipivefrin, a modified version of epinephrine, was significantly more lipophilic and marketed for its higher corneal penetrability.[73] However, side effects such as systemic hypotension, especially in a paediatric population, caused many of the early α-adrenergic agonists to be less favoured as treatment agents.[74] As a result, both dipivefrin and ophthalmic epinephrine are no longer available in the Canadian market.

Since epinephrine and dipivefrin, other more selective α-adrenergic agonists have been introduced. Apraclonidine (Brand name: Iopidine) was approved in 1987 by the FDA and in 1992 by Health Canada, followed by brimonidine (Brand name: Alphagan) in 1997 by Health Canada.[75–77] These drugs primarily act to reduce aqueous production, although there are studies that suggested that they act to increase outflow and possibly even cause increases in prostaglandin levels.[4,78,79] Furthermore, as these medications do not exhibit the blood-brain barrier penetrability of pilocarpine, it does not elicit the same side effects, making it a much more suitable agent for glaucoma management.

2.5.3 β-Adrenergic Receptor Antagonists (β-blockers)

The first commercially available β-adrenergic receptor antagonist was propranolol, introduced in 1967. Unfortunately, due to severe adverse side effects such as corneal anesthesia, it was quickly withdrawn from use.[80] A turning point in glaucoma management medication came in 1978, when the first timolol maleate (Brand name: Timoptic), a non-selective β-adrenergic receptor inhibitor, was approved by the FDA.[69] It was approved for use by Health Canada the following year.[81] Within years of its introduction, timolol maleate quickly became the most utilized medication, as it required less applications per day and has minimal ocular side effects.[69,82] Adrenergic antagonists

lower intraocular pressure through the sympathetic system, thereby affecting aqueous humour dynamics and decreasing the amount of aqueous humour produced.[4,83]

Since the availability of timolol maleate, other β-adrengeric antagonists have been developed for glaucoma treatment. Levobunolol (Brand name: Betagan), another non-selective β-adrengeric antagonist, is an analog of propranolol that was approved by Health Canada in 1985.[84] Betaxolol hydrochloride (Brand name: Betoptic S), a cardioselective, β_1-adrengeric antagonist, was approved as an ophthalmic agent in 1994.[85] Levobunolol acts with the same modality as timolol, causing a reduction in aqueous production.[86] Although other β-adrenergic receptor inhibitors have been approved in other nations, these medications have not been introduced to the Canadian market.

2.5.4 Carbonic Anhydrase Inhibitors

Acetazolamide (Brand name: Diamox) was approved in 1954 as the first carbonic anhydrase inhibitor. First commercialized as an oral preparation, the systemic nature of these oral preparations commonly led to widespread, and often unsafe, ocular and systemic side effects.[87–94] Ocular side effects include transient myopia, blurred vision and irritation, and periorbital dermatitis in severe cases.[91,93,94] Systemically, carbonic anhydrase inhibitors are shown to be associated with side effects such as paresthesia near the mouth and in the fingers and toes, metabolic acidosis, gastrointestinal discomfort, and in some rare cases, blood dyscrasia.[87–90,92] Due to the numerous, and often severe, side effects, oral preparations of carbonic anhydrase inhibitors were unfavoured for long-term glaucoma treatment.

The first topical carbonic anhydrase inhibitor, dorzolamide (Brand name: Trusopt) was approved by the FDA in 1995 and by Health Canada in the subsequent year.[95] While less potent than its oral counterparts, dorzolamide had lower occurrences of systemic side effects and so is more useful in long-term glaucoma management.[96,97] Another carbonic anhydrase inhibitor, brinzolamide (Brand name: Azopt), was approved by Health Canada in 1998.[98]

Carbonic Anhydrase inhibitors lower intraocular pressure by decreasing aqueous production through affecting carbonic anhydrase enzymes in the ciliary epithelium. Both dorzolamide and brinzolamide inhibit carbonic anhydrase isoenzyme II. Through inhibiting the production and transport of bicarbonate into the aqueous chamber, it prevents the flow of sodium and water into the chamber, decreasing aqueous production.[99] Furthermore, some studies have demonstrated that oral carbonic anhydrase inhibitors cause metabolic acidosis, a condition known to reduce IOP.[87]

2.5.5 Prostaglandins

Latanoprost (Brand name: Xalatan) was the first prostaglandin analogue approved by the FDA in 1996 and Health Canada in 1997.[100,101] Several other prostaglandin agents have since been approved for clinical use. Unoprostone (Brand name: Rescula) became available for use in the USA in 2000 and in Canada since 2006.[102,103] Travoprost (Brand name: Travatan) was introduced to the US in 2001 and in Canada in 2008. In 2001, bimatoprost (Brand name: Lumigan) was approved by the FDA, with approval from Health Canada arriving in 2002.[104,105] The newest prostaglandin agent, Tafluprost, was approved by the FDA in 2012 but has yet to be approved for clinical use in Canada.[106]

The prostaglandin hormone is a naturally occurring metabolic product of 20-carbon arachidonic acid which has been demonstrated to cause ocular hypertension, inflammation and a breakdown of the blood-aqueous barrier when large topical doses are given to animal models.[107–109] At lower concentrations, the hormone induces ocular hypotony and does not cause ocular inflammation, which promoted research and development of this drug class into an antiglaucoma agent.[110,111] The prostaglandin class of medication act on prostanoid receptors distributed throughout the eye.[112] Unfortunately, the precise mechanism by which prostaglandins reduce IOP remains unclear. Studies have suggested that the drug works to increase uveoscleral outflow through remodelling of the ciliary muscle extracellular matrix.[113] Prostaglandins have been demonstrated to decrease the amount of collagen molecules in the uveoscleral outflow pathways, thereby improving aqueous outflow.[114] Due to their need of fewer applications and lack of severe side effects, prostaglandins have enjoyed much success and have since become the most commonly prescribed medication in glaucoma

management and are the recommended first-line therapeutic agent by the Canadian Ophthalmologic Society and the American Academy of Ophthalmology.[115,116]

The generic medication availability of the medications included in the analyses for this study is presented in Figure 2.1. Most of the glaucoma medications in this study have at least one generic equivalent available within the Canadian market prior to the 2010 Ontario Drug System Reform. Cosopt was the only medication in this analysis which had its first generic equivalent introduced in 2010. Furthermore, Xalatan, Probeta and Xalacom all had their first generic equivalents in the post-reform period (Post-July 2007). Epifrin was discontinued by Allergan for distribution in the Canadian market on January 26, 2010. However, it is important to note that the generic market for antiglaucoma medication is volatile and continuously changing. Hence, this study will focus on the medications that were available during the study time frame.

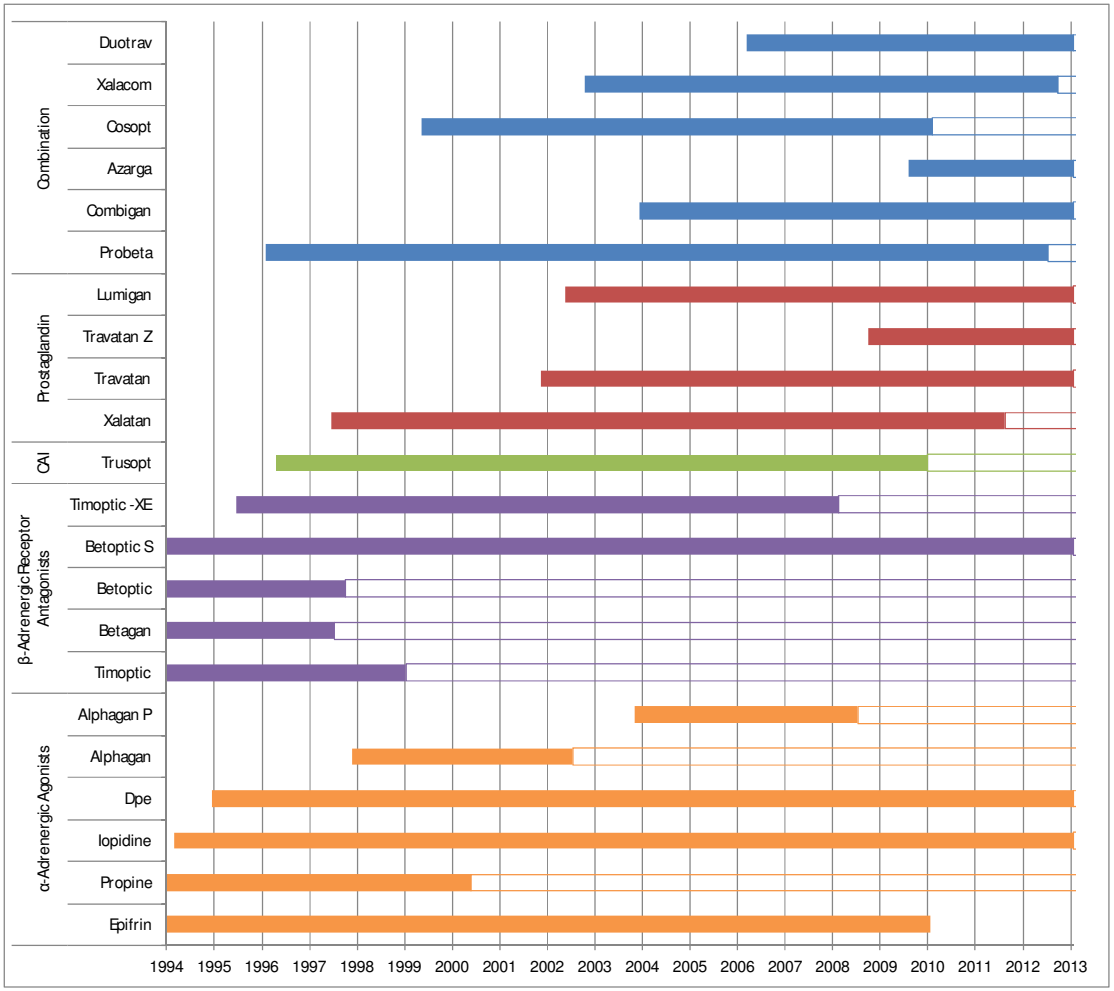

Figure 2.1 Availability of generic equivalents for study medications. Shaded bars indicate the time period during which only the brand name compound was available. Unshaded bars indicate the presence of a generic equivalent.

2.6 Glaucoma Treatment Paradigm

Maintenance of visual function and health related quality of life are the overall goals in glaucoma management. This is typically achieved through the careful monitoring of visual function and providing support for the patient. Should a patient's glaucoma continue to progress, medical interventions may be considered to help the patient achieve his or her intraocular pressure targets. The treatment paradigm would differ based on numerous considerations and should include a benefit vs. risk analysis alongside the patient.

According to the practice guidelines established by the Canadian Ophthalmological Society and the American Academy of Ophthalmology, treatment for glaucoma is typically initiated with the use of medication therapy.[115,116] Prostaglandins are the most effective at controlling intraocular pressure and are associated with fewer systemic side effects, and are thus one of the most popular initial eye drops for novel patients. Other medications, as highlighted in the above section, could be utilized when cost, side effects, intolerance, and patient preferences are considered. Furthermore, multi-medication, or combination, therapies may be considered before a patient is referred for alternative treatments.

Laser trabeculoplasty procedures are often considered as an adjunctive therapy to those who have failed to control their intraocular pressure using medications. Moreover, there is an increasing push to use laser trabeculoplasty as an initial treatment option for glaucoma.

More invasive procedures, such as trabeculectomy or non-penetrating filtration surgeries, are often employed only when other methods have been unsuccessful or are likely to be unsuccessful at achieving the intraocular pressure targets. In cases where these procedures cannot be safely conducted or are unable to produce the desired results, tube (aqueous) shunts and cyclodestructive procedures may be considered to control the patient's intraocular pressure.

Other procedures done in combination with glaucoma treatments may also be utilized if the patient suffered from other visual co-morbidities such as cataracts.

2.7 Utilization Patterns of Glaucoma Medication

2.7.1 Database Analyses

Retrospective studies on the utilization of glaucoma medication have demonstrated close associations between the introduction of new antiglaucoma medications and changes in the medication utilization patterns. Researchers in a Canadian setting reported similar results, with utilization of antiglaucoma medications highly correlated with new entrants to the medication market.[117–119] A chart review from 3 ophthalmology offices in Alberta from 1998-1999 showed that the majority of patients began treatment with β-blockers (52%), while only approximately a quarter of patients used prostaglandin as a first-line therapeutic agent (27%).[118] The authors further studied the use of medication in second-line therapy, with 34% of patients using a prostaglandin, 32% using a combination of prostaglandin and β-blockers, and 20% using other combinations of β-blockers.[118] A Quebec study examining the utilization of topical antiglaucoma medication among glaucoma patients revealed that the majority was prescribed a β-blockers, with over half of the patients prescribed timolol (55.3%) and a further 22.4% prescribed betaxolol.[117] Surprisingly, prostaglandin utilization only accounted for 6.6% of total antiglaucoma medication prescriptions, however, this could be attributed to fact that prostaglandins were restricted as secondary line therapeutic agents prior to the study time frame. Hence these medication were not available as a first-line therapeutic agent, which may have hindered its utilization in practice.[117] A study on the use of combination therapy in British Columbia from 2004 to 2007 highlighted that the popular initial class of therapeutic agent was prostaglandins (51.78% in 2004 to 56.60% in 2007).[119] Interestingly, the study found that the second most common utilized class to be combination medications (12.29% in 2004 to 18.63% in 2007), with β-blockers being the third most commonly used (20.19% to 11.56%).[119]

In an American context, Stein et al. used data from the Medicare Current Beneficiary Survey to determine factors that affect antiglaucoma medication usage. In their analysis

of utilization between 1992 and 2002, they demonstrated that the majority of patients undergo therapy with β-blockers but utilization of these medications rapidly decreased once newer types of medications, such as CAIs and prostaglandins are introduced to the market. Carbonic anhydrase inhibitors had the highest level of increased utilization (OR 1.90 per year), followed by prostaglandin use (OR 1.58 per year).[120] A population study of Marshland, Wisconsin patients demonstrated that the utilization of all antiglaucoma medications beside the prostaglandin class was decreasing from 1985-2005.[121] β-blockers were the primary prescribed agent from the beginning of the study till 2000, when the utilization of prostaglandins overtook use of β-blockers.[121] Likewise, a cross-sectional review of 100 patient records from 1999 – 2003 in the United States revealed that patients who have documented glaucoma were most likely prescribed β-blockers (47%) and prostaglandins (44%).[122]

Internationally, one of the earliest studies conducted on utilization was within the Nordic countries, which concluded that the approval of β-blockers in 1978 quickly led to a decrease in the use of cholinergic agonists, and that the use of β-blockers surpassed that of cholinergic agonists in 1987.[82] Similar trends were seen in other nations. A study of antiglaucoma medication utilization between 1995 and 2006 in several European countries demonstrated that once introduced, prostaglandins quickly overtook β-blockers in utilization. The use of prostaglandins surpassed β-blockers as the primary antiglaucoma agent of choice in the UK during 2003, France during 2004 and in Germany and Italy during 2005 (estimated).[123] A study by De Natale et al. on utilization in Italy, which provides free glaucoma drugs to its citizens, demonstrated that from 1997 to 2002, use of β-blockers dropped significantly from 79% in 1997 to 55% in 2002. Meanwhile, use of prostaglandin and carbonic anhydrase inhibitors rose from 0% to 18% and 5% to 14%, respectively.[124] A study of the prescribing patterns at an Israeli health maintenance organization between 2000 and 2003 concluded that while β-blockers had the highest prescription rate, their use, along with pilocarpines, were in steady decline.[125] Meanwhile, use of prostaglandin and α-adrenergic agonists increased consistently, and the introduction of Cosopt led to a dramatic reversal of the use of dorzolamide.[125] In this study, the utilization pattern, as determined from drug insurance claims, of antiglaucoma medication belonging to the aforementioned drug classes were analyzed.

2.7.2 Survey of Clinicians

The physician's perspective on medication utilization was also accessed in several studies. A survey of Australian and New Zealand ophthalmologists conducted in 2003-2004 found highly dichotomized results.[126] The majority of ophthalmologists from Australia preferred prostaglandins as the first line agent of choice (83%), whereas New Zealand ophthalmologists preferred β-blockers (90%).[126] However this study had a relatively low response rate of 51%, and the results may be indicative of the differences in government restrictions on the prostaglandin-class medication.[126] A 1998 survey of US ophthalmologists revealed that the preferred first line agent was a β-blockers (73%) with prostaglandins being selected in only 11% of the respondees. This low rate of utilization of prostaglandin could be due to the short amount of time between the introduction of the first prostaglandin in 1996 and when the study was conducted, thereby limiting the amount of time available for physician uptake.[127]

2.8 The Pharmaceuticals Market and the Utilization of Generic Pharmaceuticals in Canada

Drug development begins with research and development into novel compounds to determine their clinical efficacy and safety profile. Upon discovery of a novel medicinal compound, the data are presented to the Therapeutic Products Directorate at Health Canada for approval. Once the regulatory requirements are deemed met by Health Canada, the company receives a Notice of Compliance for the drug, which allows them to market the compound to the Canadian populace. Adoption of the novel drugs into publicly funded drug plan formularies remains at the discretion of the province and plan managers. Prior to 2003, each public drug plan reviewed the clinical and cost evidence of these approved medicines independently to decide on the acceptance of the drug into their respective drug plan. In 2003, the Common Drug Review of the Canadian Agency for Drugs and Technologies in Health was formed with the goal of creating a system to reduce multiple drug reviews and provide a standardized process for evaluating the comparative benefits and costs of new drugs. With the goal of providing formulary listing recommendations, most provincially funded drug plans, with the exception of Quebec, and several federal drug programmes, are currently part of this process.[128] Private drug

plans hosts their own formularies which may or may not mirror those of the publicly funded plans.

The division between generic and brand name pharmaceutical products in Canada is governed by several key pieces of legislation regarding the patent protection of innovator ("brand name") pharmaceutical products. Typically, the patent protects the innovator product for a period of 20 years, of which half is usually spent within the research and development phase. After the patent expires, drug manufactures are allowed to introduce generic equivalents pending evidence of bioequivalence to the Canadian Reference Product (the brand name drug) and obtaining approval from Health Canada and provincial regulators.[129] Like the reference products, inclusions of these generic medications into the drug plan formularies are at the discretion of the individual plan managers.

From a healthcare plan perspective, the introduction of generic equivalents is intended to provide competition to the innovator medication once the patent protection expires. A recent report suggests that within a short period of patent expiration, a multitude of interchangeable generic equivalents are available from competitiors.[130] To compete in this highly competitive field, many generic manufacturers provide rebates to pharmacies in exchange for stocking their product. These rebates are essentially kickbacks from generics manufacturers paid to pharmacies in exchange for stocking their products, and are a substantive portion of the pharmacies' income (an average rebate was approximately equal to 40% of the invoice price).[130] However, independent research has shown that these savings are not reflected in lower costs to public and private drug plans, nor to the patients who pay out of pocket.[130,131]

Dispensing of generic medication presents another layer to the unique and complex framework for prescribing medication. Provinces can legislate whether to adopt a permission product selection rule, where a pharmacy can choose to substitute a prescription with an approved generic equivalent. Those against permissive product selection have argued that by leaving the choice to the dispensing pharmacist, the decision to substitute might not be in the best interest of the patient, but rather substitutes

will only be dispensed if there is a positive pay-off for the pharmacy.[132] Alternatively, provinces can choose to make product selection mandatory, in which prescriptions must be substituted with the generic where available unless "No Substitution" is explicitly stated by the prescribing physician.[132] Furthermore, provincial governments can enact price selection rules to contain medication costs. These price selection rules can limit the cost reimbursement to pharmacies to that of the generic equivalent, leaving the patient to cover the remainder of the cost difference. In Ontario, both mandatory product selection and price selections were enacted in July 2010, with mandatory substitution to a generic equivalent and fixing prices of generics to a certain percentage of the reference product. Recently, provinces across Canada have passed legislation to regulate and reduce the price of generic medication. The next section will highlight some of the changes each provincial drug plan has implemented. Details regarding the changes to the legislation in Ontario with the Transparent Drug System for Patients Act in 2006 and the Ontario Drug System Reform in 2010 are presented thereafter.

2.9 Impact of Pricing Policies on Drug Expenditure and Utilization Patterns

In Ontario, the use of legislation to regulate the price of generic medications began in May 1993 with amendments to the Prescription Drug Cost Regulation Act (PDCRA) and the Ontario Drug Benefit Act (ODBA).[133] These amendments ensured that the maximum reimbursement by the Ontario Drug Benefit Program (ODBP) for the first generic drug of a brand name product is 75% of the reference price. Subsequent generic products are reimbursed only 90% of the first generic price (or 67.5% of the reference price).[133] Further regulation changes in November 1998 to the Drug Interchangeability and Dispensing Fee Act (DIDFA, which replaced the PDCRA) lowered the price of the first generic equivalent to 70% of the reference price (and therefore subsequent generics to 63% of the reference price).[133] Anis et al., in their evaluation of the impact of these reforms on the price of generic medications, concluded that these regulations did not decrease the cost of generics as the provincial government had intended.[133] Instead, the authors found that the introduction of these regulations effectively eliminated the natural competition that existed prior to these regulations and eliminated the incentives for newer

(subsequent) generic entrants to compete with incumbent generic products with lower prices.[133] This led to a clustering of generic manufacturers to price their medications around the maximum allowable price and reduced potential savings, which were opposite of the regulation's intentions.[133] Unfortunately, the impact of these regulations on ODBP drug expenditures were not assessed.

Reference pricing policies in British Columbia have also been studied. Starting in 1995, British Columbia implemented its Reference Pricing program for five therapeutic class: Nitrates, Angiotensin-converting enzyme inhibitors (ACE inhibitors), Dihydropyridine calcium channel blockers (CCBs), Histamine-2 receptor antagonists, and Nonsteroidal anti-inflammatory drugs.[134] This program aimed to control drug expenditure by fully subsidizing the price of the lowest costing drug within each class. Patients who wish to receive more expensive drugs will be required to pay for the cost difference, or obtain special permission for full subsidy from the government.[134] The impact of this policy on the drug costs associated with nitrates, ACE inhibitors and CCBs was evaluated by Grootendorst et al.[135] They concluded that the policy was associated with an annual reduction of $7.7 million in the British Columbia Pharmacare program, totalling approximately $24 million between October 1995 to May 1999.[135] In terms of generic utilization changes, the authors noted that there was a significant increase in the use of the reference standard product (the generic) with a corresponding decrease in the use of restricted (brand name) products.[135]

International studies on the impact of pricing regulations on generic drug prices have demonstrated similar results, where these pricing regulations on generic drugs have stifled competition between generic manufacturers and reduced the potential for drug expenditure savings from being realized.[136] A review of European pricing policies on generic competition found that, like what was observed in Ontario, these policies tend to cause generic prices to cluster at the maximum allowed price, which is often higher than what would occur in the absence of these policies.[137] Interestingly, this review also observed that prices of generics already at the reference price will not reduce their prices, even if a lower-priced generic is introduced.[137] This finding again indicates that the presence of reference pricing (and/or price ceiling) policies eliminated price competition

between generic manufacturers, as these manufacturers no longer voluntary reduce their price in the face of lower-price competition.[137] Again, this study resonated with findings from other studies in which price ceiling or reference pricing strategies on generic drugs are not the optimal method to reduce drug expenditures.[137] These policies reduce competition among manufacturers, leading to inefficient realization of the benefits of competition.[137]

Furthermore, most studies conclude that the implementation of reference pricing policies is not particularly effective in reducing drug expenditures. Findings by Giuliani in the German market showed that the introduction of reference pricing policies did indeed cause a short term reduction in expenditures, but that reduction was quickly followed by a steady increase.[138] Furthermore, the study concluded that the steady increase was a result of a growth in the utilization of medications that were not subject to the reference pricing policies, such as medications with new active ingredients that the manufacturers produce.[138] Hence, the introduction of reference pricing in Germany had the opposite intended effect due to uncontrolled factors in the pharmaceutical industries.[138] Other international studies have also determined that the reductions in expenditures due to reference pricing policies are short lived in nature.[139,140]

Most of these studies evaluated the impact of the introduction of reference pricing or price ceiling policies on drug expenditures and generic drug utilization. However, this study will focus on evaluating the impact of long term changes in utilization due to these policies, in addition to the introduction of said policies. Moreover, many of these studies are based on policies that impact only the reimbursement paid by the public drug plan, whereas this study is evaluating the impact of a policy that aims to limit both the cost of generic drugs in public and private drug plans.

2.10 Action to Reduce Cost of Generic Medication in Other Provinces

Cost of medication is one of the largest cost components in healthcare expenditure, accounting for 15.9% of Canadian health care spending in 2012.[141] Expenditures on prescription medications increased by an average annual rate of 10.1% between 1998 and

2007.[142] In 2010, several provinces implemented policies to curb healthcare and drug expenditures by restricting the amount reimbursed for generic drugs to ensure that the public and private drug plans remain sustainable.[143] Quebec made reforms to the amount payable for its generic medication effective 2008 with the Loi sur l'assurance medicaments (Bill 130), which limits the cost of the first generic of a brand name medication to 60% of the brand name price, and subsequent generics to 54% of the brand name price. Further announcements were made in November 2010 to reduce prices of generics to 25% of the brand name over three years, beginning with a decrease to 37.5% in November 2010, reducing to 30% by April 2011 and finally 25% by April 2012. Moreover, Quebec also has a "Most-Favoured-Nation" legislation, which requires that the sales prices of generic medication within Quebec match the lowest paid in Canada, hence essentially matching Ontario's pricing scheme.

British Columbia enacted policies in July 2010 to reduce reimbursement for all generic medication introduced after January 1, 2009 to 42% of the brand name equivalent, while reimbursement for existing generics introduced prior to January 1, 2009 remained at 50% of the brand equivalent. Further reductions saw the maximum reimbursement lowered to 40% in July 4, 2011, and to 35% in April 2, 2012.[144]

Similar plans were adopted by Nova Scotia with its "Fair Drug Pricing Act", which reduced the prices of generic medication paid by its public drug plan to 45% of the brand name equivalent by July 2011, decreasing to 35% by July 2012.[145] Saskatchewan followed suit by lowering existing generic medication prices to 45% of the brand name price by June 1, 2011, lowering to 35% by April 1, 2012. Generic drugs introduced after May 4, 2011 will be priced at 40% of the brand name equivalent, dropping to 35% by April 1, 2012.[146]

Alberta reduced the price of existing generics as of April 1, 2010 from 75% to 65% of the brand name equivalent. New generics introduced into the market will be priced at 45% of the brand name drug. Prices of all generics were further reduced to 35% of their brand name equivalents effective July 1, 2012. Further reductions were enacted in its 2013

budget, where the Alberta government is again lowering reimbursement for generic medication to 18% of the brand equivalent.[147]

New Brunswick has also introduced legislation to address the rising cost of medication within its public drug program. The New Brunswick government announced on March 22, 2012 that it will reduce the price of the generic medication to 40% of the brand name drug, effective June 1, 2012. Further reductions were made to lower this price to 35% of the brand price by December 1, 2012.[148]

In order to address the impact on pharmacy revenues due to the decrease in generic drug prices, many of the provinces have made changes to the alternative sources of revenue for pharmacies. Most of these price reductions are accompanied with legislation which increases the dispensing fees that pharmacies are eligible to charge. Other provinces allow allowances to be billed in addition to medication and dispensing fees, but these are subject to phasing out over time.

2.11 Ontario Drug System Reforms

The drug system reform was initiated by the Ontario government in an effort to reduce public expenditure on the provincial drug plan. In 2006, the Ontario government enacted the Transparent Drug System for Patients Act (Bill 102) to reduce the cost paid by the Ontario Drug Benefit program for generic medication to 50% of the brand reference price. Maximum markup for drugs dispensed to patients covered by the public drug plan was also decreased from 10% to 8%. Furthermore, the act prohibits the payment of rebates to pharmacies by the generic manufacturers. To compensate the pharmacies, professional allowances were introduced. These allowances enable generic manufacturers to pay pharmacies up to 20% of invoice price for drugs dispensed under the public drug plan to stock their product and offset the cost of providing non-dispensing activities such as advising patients or hosting flu clinics. Dispensing fees were also increased from $6.54 to $7.00 for publicly funded prescriptions. However, price ceiling, markup and dispensing fees for privately funded patients or patients who pay out of pocket remain unregulated.[149] Bill 102 also included amendments to the Drug Interchangeability and Dispensing Fees Act, an act that permits pharmacists to interchange a patient's

prescriptions for brand name medication with interchangeables approved by the Ontario government. Bill 102 introduced changes to widen the definition of interchangeables to include products that have "similar active ingredients in a similar dosage form" as the reference product.[150]

The government made further amendments to the ODBA and the DIDFA, effective on July 1, 2010, to further reduce the cost of medication on the public drug program.[151] In essence, the amendments had three goals. (i) Reduction of the cost of generic drugs dispensed to Ontario Drug Benefit beneficiaries to 25% of the brand reference price. Prices paid by private insurance and non-insured patients, which were previously unrestricted, will be initially capped at 50% of the brand reference price, to 35% effective April 1, 2011, and finally to 25% to match the public sector by April 1, 2012. One exception to this price ceiling is for the non-solid dosage interchangeable drugs, which will be capped at the 35% of the brand reference price. (ii) Professional allowances, which are funds paid by generic medication manufacturers to pharmacies to stock their medications and for patient-focused activities, will be eliminated in the public sector. Caps on the professional allowances for the private sector will fall from 50%, to 35% and 25% of the allowances paid prior to the reform, mirroring the price drop in drug costs. Professional allowances for the private market will be completely eliminated by April 2013, following amendments to the DIDFA. (iii) Dispensing fees charged by pharmacies for the public sector were adjusted based on their location and proximity to other pharmacies in the area. Fees were stratified into four categories to replace the current single fee model, with more rural and underserved pharmacies eligible for higher dispensing fees. Prices, allowances and dispensing fees for generic drugs that are not listed on the Ontario Drug Benefit Formulary remains to be unregulated.[152–156]

2.12 Studies on the Impact of the Transparent Drug System for Patients Act and the 2010 Ontario Drug System Reform

There has been minimal research on the impact of *Transparent Drug System* for Patients Act on the cost and utilization of drugs in Ontario. One thesis examined the effects of the introduction of the Bill 102 on the out-of-pocket drug expenditure for patients who are not covered by public drug plans (private patients).[157] The thesis concluded that the

introduction of the Bill was associated with an 18% increase in the out-of-pocket drug expenditure when comparing Ontario private patients to those in provinces that did not implement a similar act.[157] Furthermore, the study determined that the Bill increased the propensity for Ontario private patients to suffer from drugs expenditures greater than 5% of its household income.[157]

Little research evaluating the impact of the 2010 Ontario Drug System Reform on the cost of healthcare in Ontario has been published. In one study, Law et al. determined that the legislation and implementation of the policy reform has led to a 6 month cost savings of $181 to $194 million to the Ontario public drug program in post-legislation 2010, accounting for dispensing fees. Furthermore, the study predicted that that the annual total cost savings to the Canadian healthcare system to be approximately $1.28 billion if other provinces adopt similar reimbursement schemes as Ontario.[158] Industry reports of the impact of the system reform estimated a reduction of 13.8% in average generic drug cost, which represents a savings of 2.55% in the total drug plan costs. Accounting for the increases in dispensing fee and in pharmacy mark-up, the net savings of the system reform is estimated to be 2% of the total drug plan costs.[159]

2.13 Summary of the Gaps in the Literature

Policies that encourage generic substitution and decrease the reimbursement scheme for generic medication have been demonstrated to decrease total drug expenditure and increase the utilization of generic drugs.[134,135,139,160–163] However, whether the adoption of similar policies, namely the 2006 Transparent Drug System for Patients Act and the 2010 Ontario Drug System Reform, has a similar effect on the utilization of generic medication among Ontario patients remains unknown. As demonstrated in this chapter, the literature evaluating the impact of the two drug system reforms in Ontario during 2006 and 2010 is sparse. The few studies that have examined the impact of these reforms have focused primarily on the changes in drug expenditure at a provincial level, or the changes within Ontario patients who are not covered by public insurance. In terms of provincial drug expenditure, studies have demonstrated that these reforms have been associated with a decrease in the drug costs.[158] Furthermore, changes to the price ceilings implemented by the provincial government have been found to increase the drug expenditures of patients

who pay out-of-pocket for their medications.[157] In addition, there is a lack of literature on the utilization of generic medication within the glaucoma market, particularly in a Canadian setting.

Chapter 3

3 Study Rationale and Objectives

In the previous chapter, a comprehensive literature review was presented. It demonstrated that studies on the utilization patterns of generic medication glaucoma therapy in Canada and worldwide are scant. Furthermore, although there is one study and several industry reports evaluating the impact of the 2010 Drug System Reform on the cost of prescription medication in Ontario, none have empirically analyzed the change in generic equivalent utilization since the reform. Hence, in this study, we propose objectives to address both these gaps in the literature to meaningfully contribute to the body of knowledge of the use of generic antiglaucoma medication in Canada and to empirically demonstrate the impact of generic drug price ceiling reforms on utilization and drug expenditure.

3.1 Study Objectives

The objectives of this thesis are:

1. Describe the trend of existing generic utilization in antiglaucoma medication across Canadian provinces between January 2001 and January 2013.

Rationale: Such a study will reveal the level of utilization of generic medication within glaucoma treatment. As medication costs remain the highest cost component in glaucoma treatment, results of this study can determine whether programs and policies are needed to increase the level of generic utilization to decrease the drug expenditures of Canadian glaucoma patients.

2. Assess the impact of the 2010 Ontario Drug System Reform on generic antiglaucoma drug utilization and expenditure in Ontario.

Rationale: Results of this study will provide empirical evidence of the impact of the adjustment to generic drug price ceiling on the utilization of these drugs. Demonstrating the effectiveness (or lack thereof) of the price-ceiling reform on increasing utilization and decreasing expenditures may guide policy-makers in introducing appropriate methods to

promote the use of the generic drug use in lowering rising drug costs. Furthermore, understanding the response in drug utilization and drug expenditure can inform policy-makers when preparing future modifications to the drug system. Lastly, the findings may be of interest to foreign policy-makers who are planning to introduce price ceilings on prescription medication to contain rising healthcare costs across the globe.

Chapter 4

4 Methods

4.1 Study Design

The study design was a descriptive study of the use of generic medication in glaucoma treatment across various Canadian provinces between January 2001 and January 2013. The trends in the volume of medications dispensed, percentage of medication dispensed as a generic equivalent, and the generic medication utilization rate will be described through the study timeframe. This study stratified the analyses by claims made to public and private health insurance.

A time series analysis was also conducted to determine the impact of the 2010 Ontario Drug System Reform on generic antiglaucoma medication utilization among Ontario glaucoma patients. The analysis was conducted using an autoregressive integrated moving average (ARIMA) model to ascertain whether the observed utilization rate post-reform is congruent with predictions made from pre-policy trends.

4.2 Medications Used in Glaucoma Treatment

Medications in the drug classes presented in the literature review were considered as agents used in glaucoma treatment. For this study, only ophthalmic solutions or topical gellan preparations were examined, with solid tablet formulations excluded. Only non-solid formulations were included in the analyses as the drug reform has enacted a different pricing structure towards non-solid formulation medications. Thus an analysis of both solid and non-solid formulation antiglaucoma medication may mask the effect of the policy on utilization of these medications. Estimates derived from the dataset show that solid formulation medications accounts for 1.6% to 8.1% and 1.2% to 2.9% for private and public insured claims, respectively, across the study provinces. Hence, due to the small market share of solid formulations in the antiglaucoma drug market, the impact of these medications on the generalizability of the study results to all antiglaucoma medication is limited.

All antiglaucoma medications that were available from January 2001 to January 2013 were included in the analysis. A comprehensive list of the medication with the drug class, trade name, drug identification number, manufacturer, and dosage strength are presented in Table 4.1. Please note that the availability of medication may differ among provinces.

Table 4.1 List of Study Medication

Therapeutic Agent / Drug Class	Trade Name	Drug Identification Number	Manufacturer	Dosage Strength
Adrenergic Agonists	Epifrin	1090	Allergan	0.5%
Adrenergic Agonists	Propine *	529117	Allergan	0.1%
Adrenergic Agonists	Iopidine	888354	Alcon Canada	1%
Adrenergic Agonists	Ratio-Dipivefrin *	2032376	Teva Canada Ltd	0.1%
Adrenergic Agonists	Iopidine *	2076306	Alcon Canada	0.5%
Adrenergic Agonists	Dpe *	2152525	Alcon Canada	0.1%
Adrenergic Agonists	Probeta *	2209071	Allergan	0.5%
Adrenergic Agonists	Alphagan *	2236876	Allergan	0.2%
Adrenergic Agonists	Pms-Dipivefrin *	2237868	Pharmascience	0.1%
Adrenergic Agonists	Apo-Dipivefrin *	2242232	Apotex Inc	0.1%
Adrenergic Agonists	Ratio-Brimonidine *	2243026	Teva Canada Ltd	0.2%
Adrenergic Agonists	Pms-Brimonidine *	2246284	Pharmascience	0.2%
Adrenergic Agonists	Alphagan P *	2248151	Allergan	0.15%
Adrenergic Agonists	Apo-Brimonidine *	2260077	Apotex Inc	0.2%
Adrenergic Agonists	Apo-Brimonidine P *	2301334	Apotex Inc	0.15%
Adrenergic Agonists	Sandoz-Brimonidine *	2305429	Sandoz Canada Inc	0.2%
Beta Blocking Agents	Timoptic *	451193	Merck Canada Inc	0.25%
Beta Blocking Agents	Timoptic *	451207	Merck Canada Inc	0.5%
Beta Blocking Agents	Betagan *	637661	Allergan	0.5%
Beta Blocking Agents	Betoptic	695688	Alcon Canada	0.5%
Beta Blocking Agents	Betagan *	751286	Allergan	0.25%
Beta Blocking Agents	Apo-Timop *	755826	Apotex Inc	0.25%
Beta Blocking Agents	Apo-Timop *	755834	Apotex Inc	0.5%
Beta Blocking Agents	Mylan-Timolol *	893773	Mylan Pharma	0.25%
Beta Blocking Agents	Mylan-Timolol *	893781	Mylan Pharma	0.5%
Beta Blocking Agents	Betoptic S *	1908448	Alcon Canada	0.25%

Beta Blocking Agents	Ratio-Levobunolol *	2031159	Teva Canada Ltd	0.25%
Beta Blocking Agents	Ratio-Levobunolol *	2031167	Teva Canada Ltd	0.5%
Beta Blocking Agents	Teva-Timolol *	2048515	Teva Canada Ltd	0.5%
Beta Blocking Agents	Teva-Timolol *	2048523	Teva Canada Ltd	0.25%
Beta Blocking Agents	Pms-Timolol *	2083345	Pharmascience	0.5%
Beta Blocking Agents	Pms-Timolol *	2083353	Pharmascience	0.25%
Beta Blocking Agents	Sandoz-Timolol *	2166712	Sandoz Canada Inc	0.25%
Beta Blocking Agents	Sandoz-Timolol *	2166720	Sandoz Canada Inc	0.5%
Beta Blocking Agents	Timoptic-Xe *	2171880	Merck Canada Inc	0.25%
Beta Blocking Agents	Timoptic-Xe *	2171899	Merck Canada Inc	0.5%
Beta Blocking Agents	Novo-Levobunolol	2197456	Teva Canada Ltd	0.25%
Beta Blocking Agents	Novo-Levobunolol	2197464	Teva Canada Ltd	0.5%
Beta Blocking Agents	Levobunolol *	2231714	Rivex Pharma	0.25%
Beta Blocking Agents	Levobunolol *	2231715	Rivex Pharma	0.5%
Beta Blocking Agents	Sandoz-Betaxolol	2235971	Sandoz Canada Inc	0.5%
Beta Blocking Agents	Pms-Levobunolol *	2237991	Pharmascience	0.5%
Beta Blocking Agents	Dom-Timolol	2238771	Dominion Pharmacal	0.5%
Beta Blocking Agents	Ratio-Timolol	2240248	Teva Canada Ltd	0.25%
Beta Blocking Agents	Ratio-Timolol *	2240249	Teva Canada Ltd	0.5%
Beta Blocking Agents	Apo-Levobunolol *	2241574	Apotex Inc	0.5%
Beta Blocking Agents	Apo-Levobunolol *	2241575	Apotex Inc	0.25%
Beta Blocking Agents	Sandoz-Levobunolol *	2241715	Sandoz Canada Inc	0.25%
Beta Blocking Agents	Sandoz-Levobunolol *	2241716	Sandoz Canada Inc	0.5%
Beta Blocking Agents	Sandoz-Timolol	2241731	Sandoz Canada Inc	0.25%

Beta Blocking Agents	Sandoz-Timolol	2241732	Sandoz Canada Inc	0.5%
Beta Blocking Agents	Timolol Maleate-Ex *	2242275	Alcon Canada	0.25%
Beta Blocking Agents	Timolol Maleate-Ex *	2242276	Alcon Canada	0.5%
Beta Blocking Agents	Combigan *	2248347	Allergan	0.2/0.5%
Beta Blocking Agents	Duotrav *	2278251	Alcon Canada	0.004/0.5%
Beta Blocking Agents	Apo-Timop Gel *	2290812	Apotex Inc	0.5%
Beta Blocking Agents	Azarga *	2331624	Alcon Canada	1%/0.5%
Beta Blocking Agents	Combigan *	9857298	Allergan	0.2/0.5%
Beta Blocking Agents	Duotrav *	9857333	Alcon Canada	0.004/0.5%
Carbonic Anhydrase Inhibitors	Trusopt *	2216205	Merck Canada Inc	2%
Carbonic Anhydrase Inhibitors	Azopt *	2238873	Alcon Canada	1%
Carbonic Anhydrase Inhibitors	Cosopt *	2240113	Merck Canada Inc	2/0.5%
Carbonic Anhydrase Inhibitors	Cosopt *	2258692	Merck Canada Inc	2/0.5%
Carbonic Anhydrase Inhibitors	Trusopt	2269090	Merck Canada Inc	2%
Carbonic Anhydrase Inhibitors	Apo-Dorzo/Timop *	2299615	Apotex Inc	20mg
Carbonic Anhydrase Inhibitors	Sandoz-Dorzolamide	2316307	Sandoz Canada Inc	2%
Carbonic Anhydrase Inhibitors	Sandoz-Dorzol/Timol	2344351	Sandoz Canada Inc	2%/.5%
Prostaglandin Analogs	Xalatan *	2231493	Pfizer	0.005%
Prostaglandin Analogs	Travatan *	2244896	Alcon Canada	0.004%
Prostaglandin Analogs	Xalacom *	2246619	Pfizer	0.005%
Prostaglandin Analogs	Co Latanoprost *	2254786	Cobalt Pharma	0.05mg/ml
Prostaglandin Analogs	Apo-Latanoprost *	2296527	Apotex Inc	50mcg/ml
Prostaglandin Analogs	Travatan Z *	2318008	Alcon Canada	0.004%
Prostaglandin Analogs	Sandoz-Latanoprost *	2367335	Sandoz Canada Inc	50mcg/ml

Prostaglandin Analogs	Gd-Latanoprost *	2373041	Genmed	50mcg
Prostaglandin Analogs	Travatan Z *	9857332	Alcon Canada	0.004%
Prostaglandin Analogs	Lumigan*	2324997 9857368 9857398	Allergan	0.01%

* Denotes drugs which are available on the Ontario Drug Benefit Formulary

4.3 Dataset Description

Medication dispensing claims were used as a proxy to estimate the utilization of antiglaucoma medication among Canadian patients. This study utilized data from the PharmaStat database supplied by IMS Brogan, a division of IMS Health Canada.[164] IMS Brogan maintains a variety of healthcare related databases, including the PharmaStat and CompuScript databases which are used extensively in pharmacoepidemiological research.[165–172] Studies utilizing these databases are focused on examining the change in utilization of medication over time, cost changes in dispensing over time, or on the impact of policies on drug use. The CompuScript database was used by Fischer et al. in their evaluation of the trends in opioid use and to determine the impact of prescription monitoring programs on the utilization of opioids in 10 Canadian provinces.[167] The dataset enabled the authors to determine there were significant differences in the level of opioid dispensed between the provinces.[167] Furthermore, they concluded that there was an increase in the level of opioids dispensed, and that this increase is driven predominately by an increases in "strong opioid" use.[167] The CompuScript database was also utilized by Law et al. in their analysis of the impact of the 2010 Ontario Drug System Reform on public drug expenditure.[166] They concluded that the reform was associated with a decrease in drug expenditure of approximately $181 to $194 million in the 6 months after the reform was introduced.[166] Data derived from CompuScript have also be used to determine the impact of the introduction of OxyContin-OP in the US on prescribing patterns of OxyContin in Canada and in evaluating the cost of self-monitoring of blood glucose in diabetes management among Canadian diabetics.[165,168] The PharmaStat database has been used in studies examining the cost of osteoporosis in Canada and used in drawing comparisons of the utilization of prescription medication between different areas in Canada.[169,170,173] Moreover, it has been used to quantify the

effect of the Common Drug Review on the adoption of new drugs by various provincial jurisdictions.[128] More recently, it has been used to evaluate the impact of generic drug entry on private drug plan expenditures.[174] Its extensive use in drug utilization and expenditure research is indicative of the quality and reliability of the PharmaStat database.

The PharmaStat database aggregates Canadian drug plan reimbursement data from a sampling frame of approximately 5600 pharmacies across Canada. Retail sales from this sampling frame are then projected to provide Canada-wide and province-specific sales estimates. The database reports total formulary sales for most public drug plans, including claims from provincial drug benefit programs and federal Non-Insured Health Benefit (NIHB) programs. Furthermore, it reports the direct payments from private insurance plans to pharmacies, providing coverage of 67% of all private prescriptions in Canada.[175] In Ontario, the coverage of private drug plan exceeds 80%. The database yields key information such as the name of the drug, name of the active chemical agent, type of drug, formulation, the drug identification number (DIN), manufacturer, generic status. Outcomes obtained from the database include the volume of claims, the number of units sold, and the total cost of the claims. In this study, the volume of claims was used to determine the utilization of antiglaucoma medication.

Examples of how claims are recorded in the database are presented in Table 4.2.

Table 4.2 Examples of Claims Records

Patient	Prescription	Number of visits to the pharmacy in one year	Number of yearly claims within the database
A	Timolol for 365 days	1	1
B	Initial Timolol for 90 days, with 3 refills	4	4
C	Initial Timolol for 120 days, with 2 refills	3	3

4.4 Independent Variables

4.4.1 Generic Status

Study medications were further stratified into two groups for all analyses. The first group consisted of brand name medications. The second group consisted of medications deemed as generics. Generic status of these medications was derived from the IMS PharmaStat database.

To ascertain that the generic status of the study medications was correctly identified in the PharmaStat databases, the recorded status was validated by comparing the drug name, drug identification number (or its equivalent in other provinces) against the records within their respective provincial drug benefit formulary. Drugs which were classified as an interchangeable within the formulary for a brand name product were considered as a generic. The drug name was also compared with the Notice of Compliance database maintained by Health Canada to identify subsequent entry (generic) status.[176]

4.4.2 Time

In the descriptive analysis, time provided the scale by which the outcome measures are plotted. For the time series analysis, the outcome measures were stratified into two groups. The first category included outcome measures that are from the time period prior to the 2010 Ontario Drug System Reform. The second category included outcome measures that are from the post reform time period. The impact of the 2010 Ontario Drug System Reform was evaluated through comparisons of these two groups.

4.4.3 Drug Insurance Status

The outcome measures were divided into two categories, with analyses conducted separately for each category. The first category included publicly insured cost and claims. The second category included privately insured cost and claims.

4.5 Outcome Measures

Four outcome measures were constructed to represent the use of generic antiglaucoma medication. First, analyses were conducted using the monthly volume of claims of

generic antiglaucoma medication to provide a crude representation of the utilization of generic drugs.

Second, a monthly generic percentage dispensed was constructed to model the utilization. This construct was defined by summing the monthly prescriptions filled for generic antiglaucoma equivalents; the sum was then divided by the total volume of both generic and branded prescriptions of antiglaucoma medication filled within the month and expressed as a percentage.

Third, a monthly dispensing rate of generic medication was constructed by dividing the monthly number of claims for generics by the estimated monthly population for each province studied. The monthly population was estimated for the study time frame of 2001-2013 from the CANSIM database maintained by Statistics Canada.[177] The CANSIM database reports on a wide variety of socioeconomic variables, ranging from population demographics, labour, finance, to travel and tourism. In particular, this study made use of the population estimates and projections tables which provided annual estimates of the population size, stratified by age group and sex, for July 1st across provinces and territories.[178] Monthly estimates of the provincial population size was determined by fitting a trend line to the annual estimates from 2000-2012 and the equation was used to interpolate the monthly values. The monthly dispensing rate of generic antiglaucoma medication for each province was determined by dividing the monthly dispensing volume of generic antiglaucoma medication by the corresponding estimated monthly population size. This measure was expressed as the dispensing rate per 100,000 residents per month.

Lastly, the monthly total cost of all insured claims for antiglaucoma medication was estimated by summing the cost associated with each medication under examination.

The monthly dispensing volume of generic antiglaucoma, estimated population size in Ontario per month, the monthly generic percentage dispensed, the monthly dispensing rate, and the monthly total cost of medication were captured in an Excel database for conversion to a SAS dataset (SAS, version 9.3, Cary NC).

4.6 Data Analyses

4.6.1 Descriptive Analysis

The monthly volume of generic claims, the monthly generic percentage dispensed, the monthly dispensing rate of generic equivalents, and the monthly total cost of antiglaucoma medications were plotted by provinces and over the study time frame to provide a visual description of the use of generic antiglaucoma medication. This analysis was further stratified by publicly insured claims and privately insured claims and included the medications listed in Table 4.1.

4.6.2 Time Series Analysis

A time series is a set of ordered observations which have been sampled over discrete, equally spaced and neighbouring time intervals.[179] As a result, time series data have increased likelihood to be correlated which presents a unique problem during analysis.[179] An assumption in many classical statistical analyses, such as regression analysis, requires that the data be independent and identically distributed. This assumption is often violated when used with time series data due to the high level of autocorrelation among nearby observations. Time series analysis are modified methods to modelling the data by taking into account the autocorrelation into the analyses, often by including prior observations of the dependent variable as explanatory variables in a type of regression model.[180] Autoregressive integrated moving average (ARIMA) models is a class of time series modelling technique which accounts for the "noise" generated by the autocorrelation within the data.[181] Once the "noise", such as trends and seasonality, are adjusted for, the impact of an exogenous intervention can be determined with the inclusion of an intervention component into the ARIMA model.[181]

In particular, a seasonal, interventional ARIMA model developed using data from January 2001 to January 2013 was used to estimate the effect of the policy introduction. This model allowed for the quantification of the reform's impact on the monthly volume of generic claims, monthly generic percentage dispensed, the monthly dispensing rate of generic equivalents, and the monthly total cost of antiglaucoma medications. The ARIMA modelling technique was first developed within the field of econometrics and

was used for the forecasting of financial data, but has since been adopted for use in healthcare research.[182–186] It has since been utilized in studies which evaluate the impact of publications and policy change on practice and prescribing patterns and other health-related outcomes.[187–190]

The use of time series methods requires the data to be stationary, meaning the data has a constant mean and variance across all time points. This requirement was assessed using the augmented Dickey-Fuller test and the correlogram, which provides information on the autocorrelation, partial autocorrelation, and inverse autocorrelation. Differencing between lags was introduced into the model as necessary to maintain the stationary property. Various permutations of the ARIMA model parameters were tested beginning with the least parsimonious, lowest order model. The Ljung-Box χ^2 statistic was calculated to assess the autocorrelation between lags and to measure whether the calculated residuals were uncorrelated white noise.[191] The optimal combination of the orders of autoregressive (AR) and moving average (MA) was selected by assessment of the correlogram and the autocorrelations. Maximum likelihood methods were used for estimation of the model parameters.[192] The use of maximum likelihood for estimation generally results in better estimates than using exact least squares or conditional least squares methods.[193] All p-values were two-sided.

In this study, the 2010 Ontario Drug System Reform was modelled as the intervention event. The effect of this reform on utilization of generic antiglaucoma medication was assessed by inclusion of an intervention parameter. In a sensitivity analysis, the 2006 Transparent Drug System for Patients Act was also introduced as an intervention to evaluate the effect of both drug reforms on generic utilization trends. Ramp, point, and step functions were utilized to incorporate the intervention parameter into the model. Ramp functions are utilized to describe situations when an intervention causes the linear trend to change slope. Step interventions cause a permanent change in the level of the output variable. A point or pulse function is similar to a step function, but elicits a temporary change in the level of the output variable. The level of the output variable may return to its original state once the point intervention has concluded.[182] Studies have utilized a ramp function to model the effect of the introduction of new legislation or

health advisories on various health-related outcomes.[184,188–190,194] Step functions are also utilized in research to model the impact of interventions such as prevention programmes and policy changes.[195–197]

The use of a ramp function may be the most appropriate given that there may be a lag time between the introduction of the reform and a change in physician prescribing patterns. Furthermore, a pharmacy may not change its dispensing practices until current stock of medications is sold. However, as a sensitivity analysis, all three types of interventions functions will be assessed in the analysis.

Subsequent analyses were conducted to evaluate the impact of both the 2006 Transparent Drug System for Patients Act and the 2010 Ontario Drug System Reform on the aforementioned outcome measures. Both reforms were included in the analyses through the use of an intervention parameter introduced by a ramp function.

The β estimate of the intervention parameters were examined to determine the statistical significance of the impact of the intervention. Two-sided p-values were calculated with statistical significance defined as $p < 0.05$. Two models for each outcome measure were constructed to evaluate the impact of the drug system reform on utilization among publicly insured patients and privately insured patients. Identification of the model parameters for the order of correlation, order of integration and order of moving average, and model estimates were conducted using SAS 9.3 and SAS/ETS 9.3 (SAS Institute, Cary, NC).

Chapter 5

5 Results

5.1 Data Availability

Monthly dispensing claims were obtained from the PharmaStat database for Alberta, Manitoba, Ontario, Quebec, New Brunswick, Nova Scotia, and Newfoundland. Dispensing claims for privately insured prescriptions over all 145 months from January 2001 to January 2013 were available for the provinces in this study. Data for prescriptions covered by public drug plans were staggered in availability, with only Alberta and Ontario having claims available from January 2001 to January 2013. A full list of the availability for dispensing claims is presented in Figure 5.1.

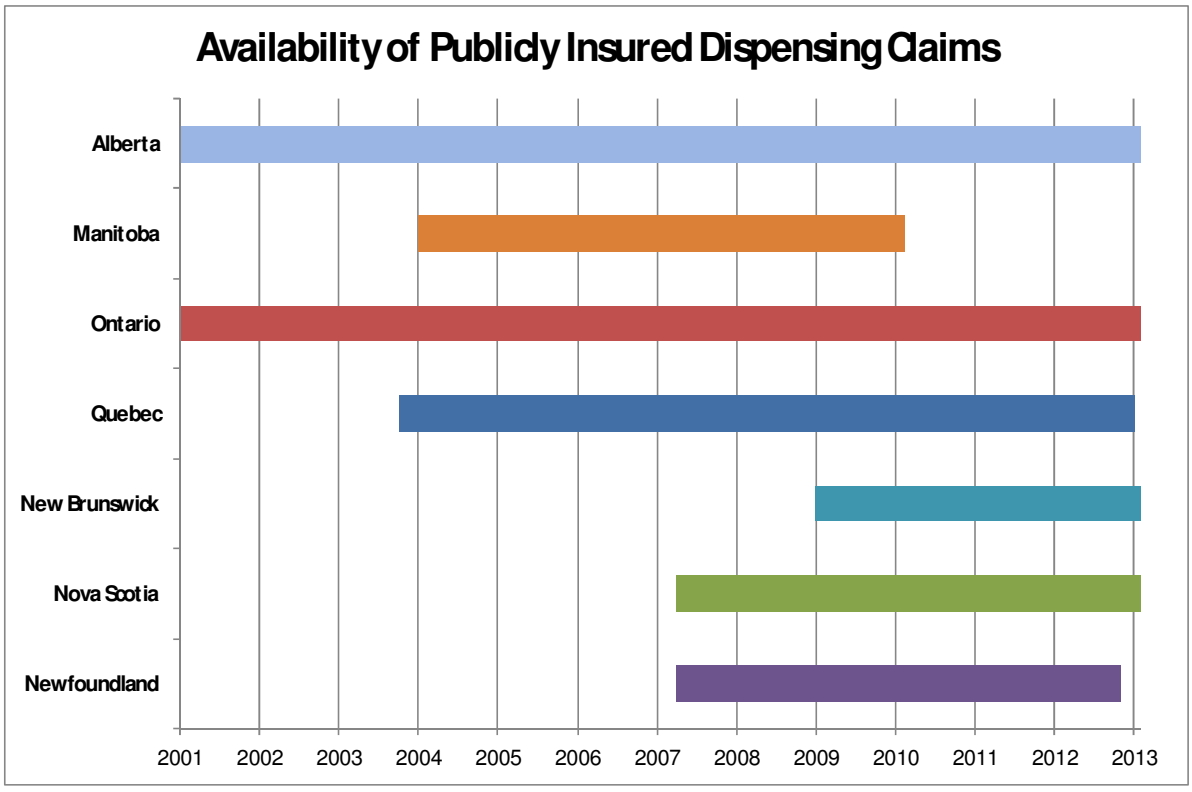

Figure 5.1 Availability of Dispensing Claims.

5.2 Results of the Generic Status Validation

Generic status indicators from IMS Brogan were mostly correct for the medications included in this study. One error was found for Timolol Maleate-EX (Manufacturer: Alcon Canada; DIN: 02242275, 02242276). Entries for Timolol Maleate-EX were reclassified as a generic product for all analyses.

5.3 Descriptive Results

5.3.1 Volume of Generic Claims

The monthly dispensing volume of generic medications across the study provinces are presented in Figures 5.2 and 5.3 for publicly and privately insured claims, respectively. From January 2001 to January 2013, the volume of generic antiglaucoma medications dispensed among insured claims increased across all provinces. As expected, the largest increases in the volume of claims were found within the provinces with the largest populations, Ontario and Quebec, across both public and privately insured claims.

Annual fluctuations in the volume of publicly insured claims were observed over the study time frame across all study provinces. In Ontario, considerable fluctuations were seen over the study time frame. A large decrease in volume of generic claims was observed during 2002; however this decrease was mitigated by a substantive increase during 2003. In the same year, the volume of generic claims began to fall, and this decrease continued till 2006, at which point it quickly rebounded to over 20,000 claims per month. The volume of claims continued to fluctuate, with an overall decreasing trend, till late 2011. A significant increase was observed during 2012, with the volume of claims more than doubling the volume prior to 2011. This increased volume was sustained for the rest of the study frame (Figure 5.2).

Substantive increases in the volume of claims occurred in Quebec during 2004, which stabilized in from 2005 to 2011. During 2012, an increase similar to what was observed in Ontario was also seen in Quebec, although the magnitude of increase was smaller.

Among the remaining study provinces, notable increases were observed in Manitoba during 2008. Increases were also observed in Alberta and Nova Scotia during 2011 and in New Brunswick and Newfoundland during 2012 (Figure 5.2).

Considerable changes were also observed among privately insured claims (Figure 5.3), and trends mostly followed what was observed in the publicly insured volume of claims. In Ontario, the first substantive deviation was the increase observed in 2001. However, the increase was again mitigated by a decrease during 2002. The volume of claims increased again in 2003 before decreasing till 2006, much like in public claims. Substantive increases were again observed in 2006, stabilizing from 2007 to 2009. A minor decrease was seen from 2009 to 2011, with significant increases in volume during 2012 which was maintained for the remainder of the study frame (Figure 5.3).

Similar trends in the volume of generic claims were also observed in Quebec. Substantial increases were observed in 2001 – 2002, with volumes dropping over the remainder of 2002. Increases in the volume of claims were again observed during 2004, which the increased volume of claims sustained till 2011. During 2012, a large increase was seen, much like what was detected in Ontario (Figure 5.3).

Among the rest of the provinces, increases were observed in New Brunswick during 2001, and again during 2005. The volume of claims then stabilized till 2011 before increasing during 2012. Alberta, Nova Scotia, and Newfoundland all saw increases in the volume of claims during 2011, which stabilized till the end of the study timeframe. Similarly, Manitoba saw increases during 2012, which were sustained till 2013 (Figure 5.3).

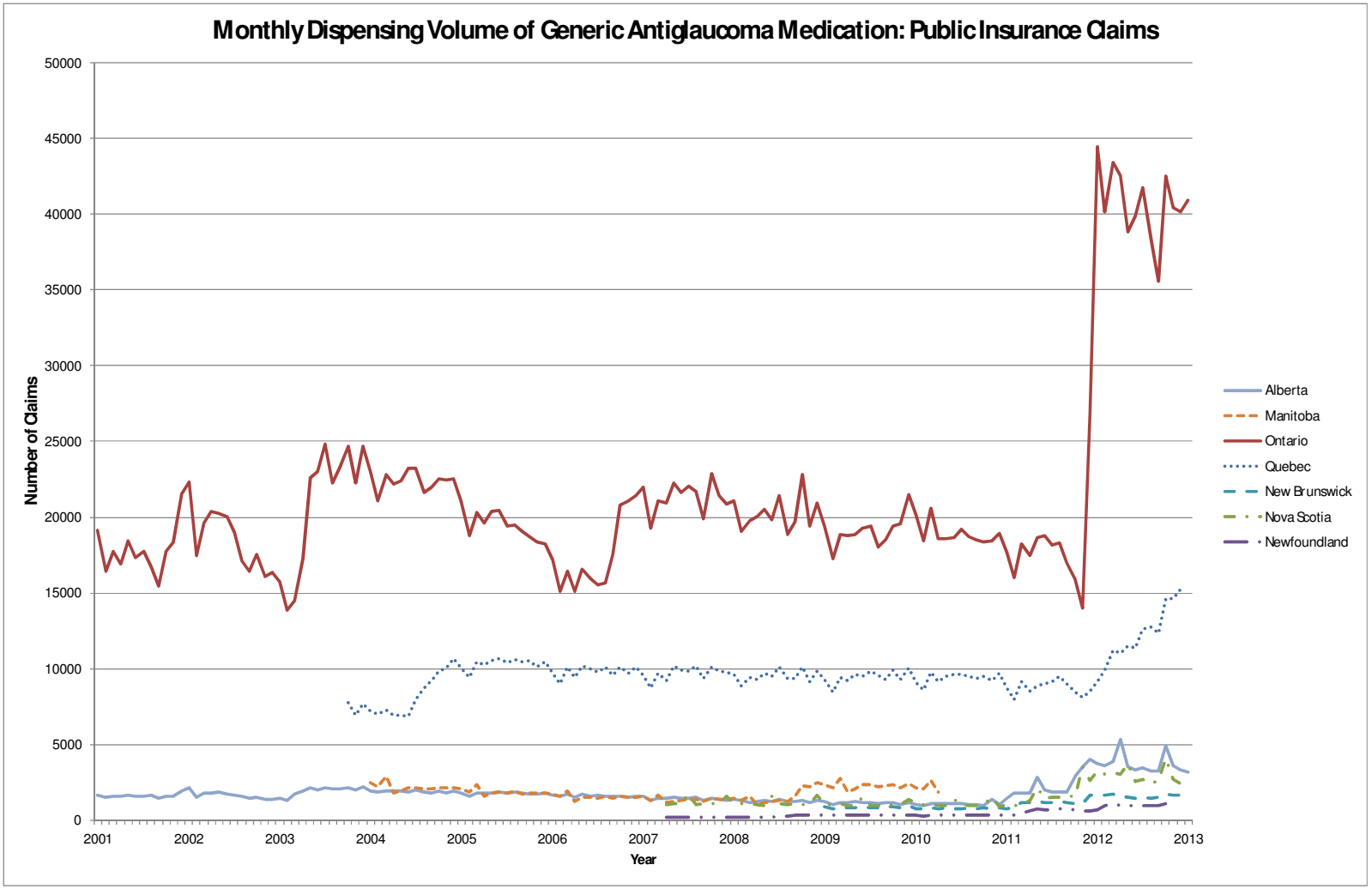

Figure 5.2 Monthly volume of generic antiglaucoma medication claims for publicly insured prescriptions throughout January 2001 – January 2013.

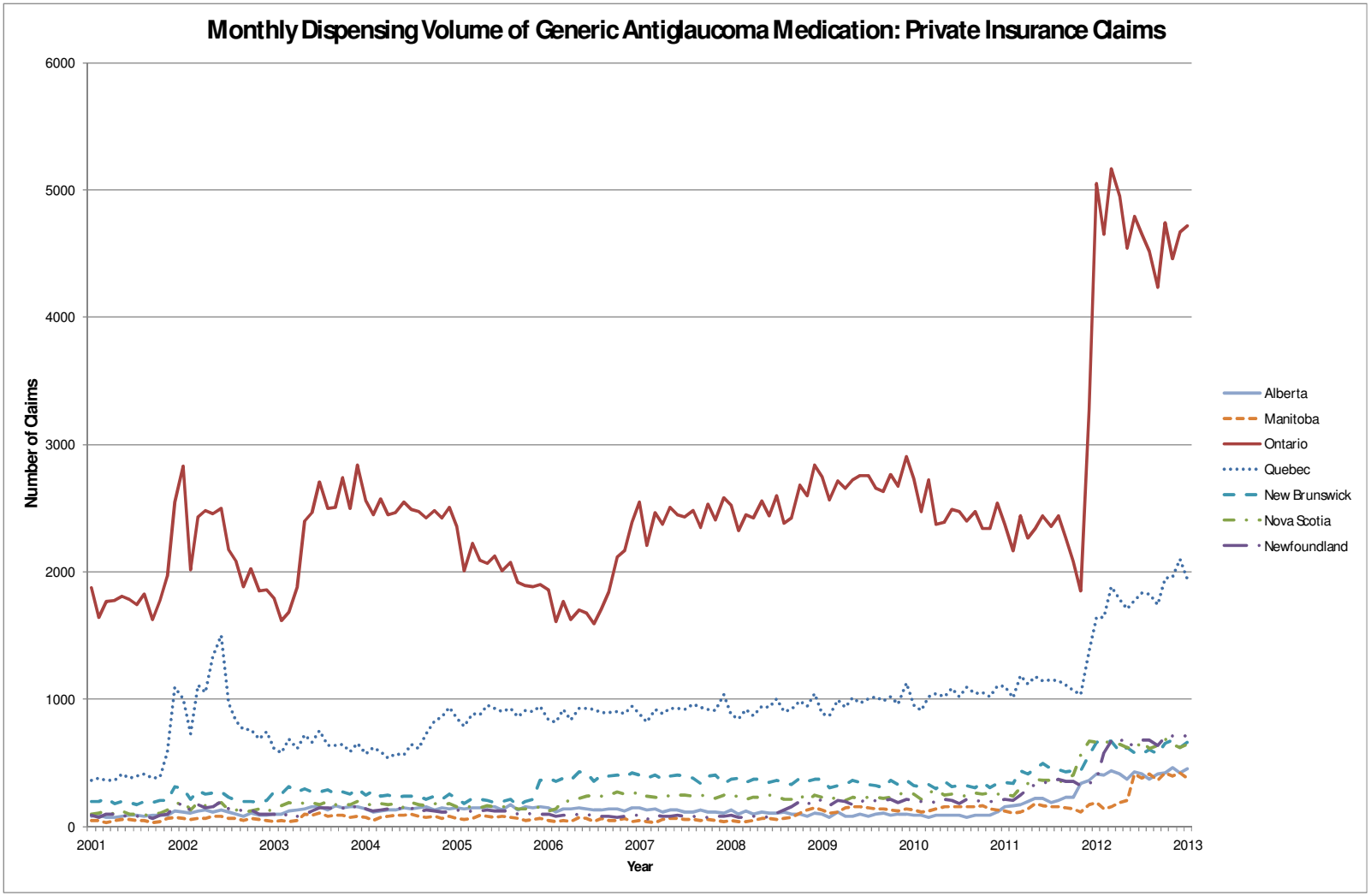

Figure 5.3 Monthly volume of privately insured antiglaucoma medication dispensed as generic equivalents throughout January 2001 – January 2013.

5.3.2 Generic Percentage Dispensed

Among publicly insured claims (Figure 5.4), the generic percentage dispensed between Ontario and Alberta closely approximates one another, with the percentage dispensed higher in Ontario. In both provinces, there was an increase in the generic percentage dispensed during 2001, with a substantive decrease during 2002. An increase was observed on both provinces again in 2003, following by a decrease in the same year till 2006 for Ontario and 2010 for Alberta. The generic percentage dispensed increased in Ontario in 2006 and experienced a slight decrease till 2011, where it significantly increased, more than doubling 2011 percentages. The percentage dispensed then decreased approximately 8% in 2012, and stabilized for the remainder of the study time frame. In Alberta, the decrease from 2003 continued till 2010, where it increased before reaching a plateau in the first half of 2011. Increases were again seen in the latter half of 2011, peaking during early 2012. Like in Ontario, the generic percentage dispensed then fell approximately 8% during 2012, prior to stabilizing till 2013 (Figure 5.4).

The publicly insured generic percentage dispensed in Quebec increased during 2004 before slowly decreasing during 2005 till 2011. The percentage then increase by approximately 6% between 2012 and 2013, surpassing the 2004 peak (Figure 5.4).

Among the remaining provinces, Manitoba's generic percentage dispensed decrease from 2003 to 2008, before increasing during the second half of 2008. The percentage then stabilized from 2009 to 2010 (end of data availability). Within the Atlantic provinces, increases were observed in Newfoundland during 2008, which stabilized from 2009 to 2010, before increasing significantly in 2011 and again in 2012. New Brunswick displayed similar patterns, with increases in the generic percentage dispensed during 2010, which stabilized throughout 2011, before increasing again in late 2011. Lastly, trends in Nova Scotia mirrored those of New Brunswick, with increases in 2010 and in late 2011 (Figure 5.4).

Results from the private insured claims present a similar picture to that of the publicly insured claims. All of the study provinces saw an increase in the generic percentage dispensed during 2001, which stabilized during the first half of 2002. During the latter months of 2002, the generic percentage decreased before rebounding in most provinces during 2003 (with the exception of Quebec which did not rebound). The generic percentages then steadily decreased in all study provinces from 2003 onwards (Figure 5.5).

The similar trends between provinces diverged after the increase in 2003. In Ontario, the decreasing trend continued until 2006, where a significant increase of approximately 5% in the generic percentage dispensed was observed. This increase then stabilized till 2010, at which point a slight decrease was observed. The decrease ended during 2011, with a doubling of the percentage observed in the first half of 2012. The percentage fell a couple percentage points in 2012 before stabilizing till 2013 (Figure 5.5). After the increase in 2003, the percentage dispensed in Alberta slightly decreased over the 8 years, culminating in a decrease of approximately 10%. The percentage then experienced a significant increase of roughly 20% between 2011 and 2012, before stabilizing at 25% till 2013 (Figure 5.5). Within Manitoba claims, the percentage dispensed decreased from 2003 until 2008, at which point an approximately 13% increase was observed during the latter half of 2008. This increase was followed by a slight decrease (approximately 5%) over the next three years, and a substantial increase in 2012 (Figure 5.5).

Interestingly, the generic percentage dispensed among both privately and publicly insured claims remained the lowest in Quebec over the majority of the study time frame. The decrease in 2003 continued till 2004 in Quebec, whereupon the percentage increased 3% during the latter half of 2004. The rate then decreased slightly over 7 years, before increasing once again during 2012 (Figure 5.5).

Among the Atlantic provinces, the generic percentage dispensed in New Brunswick increased during 2005, nearly doubling the percentage dispensed prior to 2005. The percentage then fell slightly over the next 5 years, but increased approximately 10% during the latter half of 2010. A slight decrease of approximately 5% followed during

2011, at the end of which a substantive increase of nearly 20% was observed. The percentage then decrease before stabilizing around 40% till 2013. In Nova Scotia, the decrease from 2003 continued till 2006, at which point the percentage increased approximately 10%. This rate then stabilized until 2009, whereupon the percentage had a slight increasing trend till 2011. Further increases occurred in Nova Scotia during 2012 (approximately 20%), however, the rate fell slightly (approximately 5%) during 2012 before stabilizing in 2013 (Figure 5.5). The decrease in generic percentage dispensed from 2003 continued in Newfoundland until 2008, upon which an increase of approximately 8% occurred. The rate then stabilized between 2009 and 2010, before experiencing an increase for the first half of 2011. The percentage then decreased approximately 3% in the latter half of 2011. The percentage dispensed nearly 25% in 2012 and stabilized as the province with the highest generic percentage dispensed (Figure 5.5).

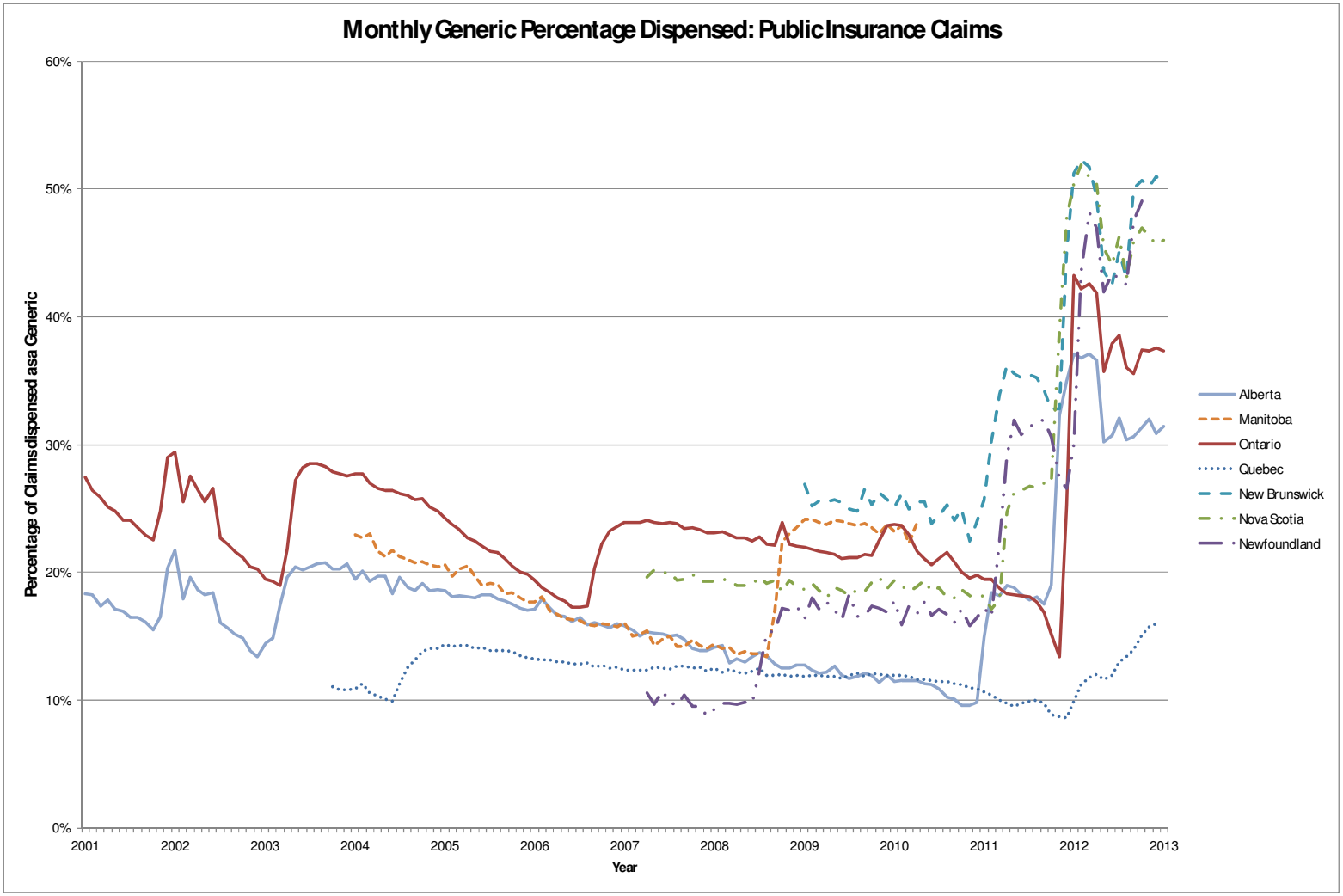

Figure 5.4 Monthly percentage of publicly insured antiglaucoma medication dispensed as generic equivalents throughout January 2001 – January 2013.

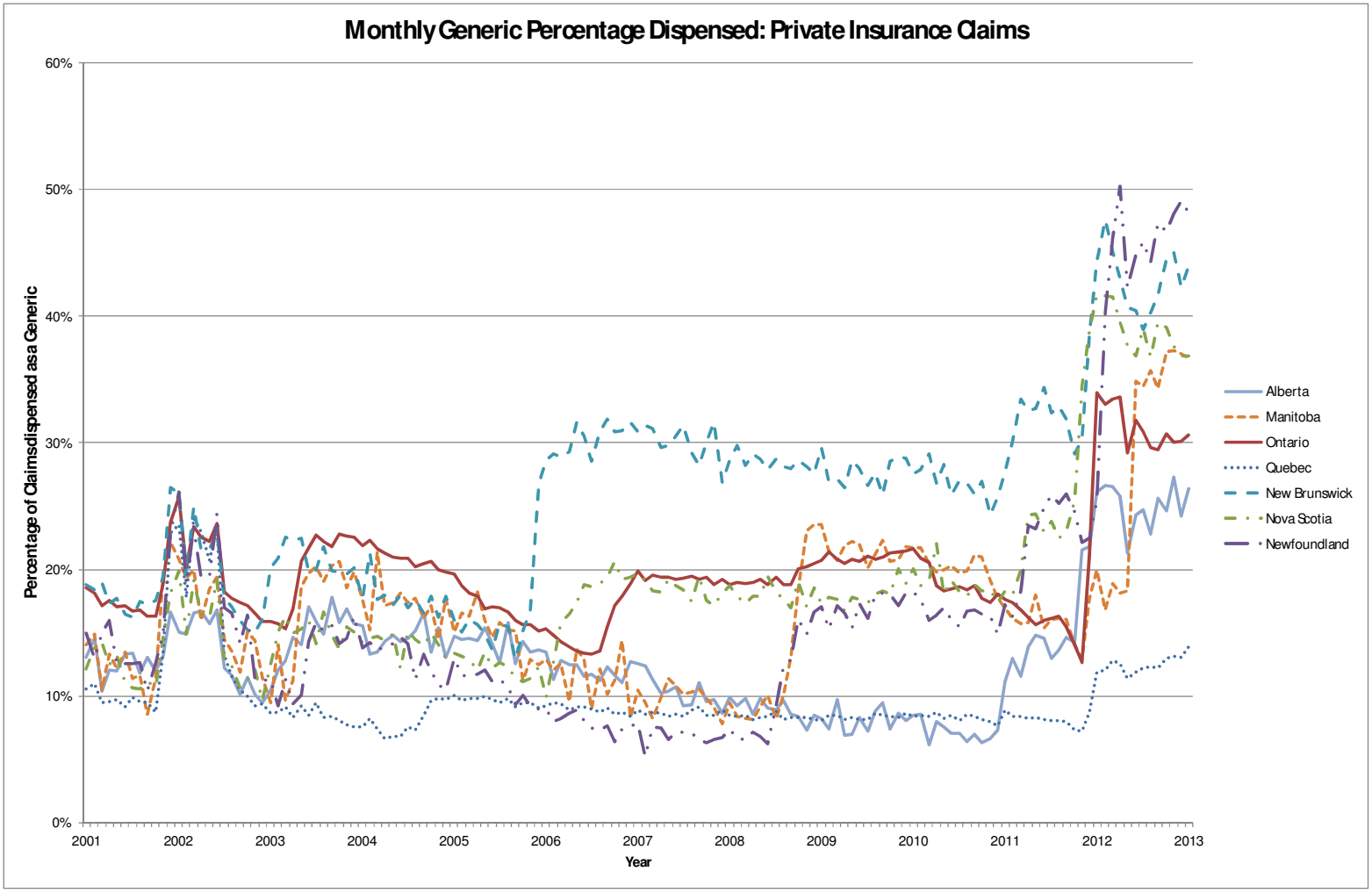

Figure 5.5 Monthly percentage of privately insured antiglaucoma medication dispensed as generic equivalents throughout January 2001 – January 2013.

5.3.3 Generic Dispensing Rate

The monthly generic dispensing rate of antiglaucoma medication across the study provinces are presented in figures 5.6 and 5.7 for publicly and privately insured claims, respectively. Among the publicly insured claims (Figure 5.6), a similar trend was observed between Ontario and Alberta. Both provinces saw a small spike in the dispensing rate during 2001 to 2002, followed by a decrease during the remainder of 2002. An increase in both provinces occurred during 2003, which was immediately followed by a steady decrease starting in the latter half of 2003. This decrease continued in Ontario until 2006, where the rate increased slightly over the latter half of 2006. From this point, the generic dispensing rate began a small decline between 2007 and 2011, before significantly increasing during 2012 (Figure 5.6). In Alberta, the decrease in the generic dispensing rate which began in 2003 continued till 2010. The rate began a fluctuating increase between 2011 and 2013, culminating at rates nearly triple that of 2003 values. Interestingly, the dispensing rate for generic antiglaucoma medication was the lowest in Alberta across the study time frame among both privately and publicly insured claims (Figure 5.6).

Significant annual trends were observed in Manitoban dispensing rates, with a large surge in the rate during the first February of each year. In terms of trends, there was an overall decreasing trend in the generic dispensing rate between 2004 and 2008, with rates increasing during 2009 and 2010 (Figure 5.6).

In Quebec, the rate increased during 2004, before stabilized between 2005 through 2011, upon which a significant and sustained increase occurred during 2012-2013 (Figure 5.6).

Among the Atlantic provinces, New Brunswick was relatively stable from 2009 to 2010. However, significant increases were observed during 2011 to 2013, which resulted in more than a doubling of the generic dispensing rate. Similarly in Nova Scotia, the generic dispensing rate was stable from 2007 to 2010, before rapidly increasing during 2011 to 2013. This increase culminated in a near tripling in the generic dispensing rate, compared to 2010 values. Significant bi-annual trends were also observed. The dispensing rate in

New Brunswick was stable between 2007 and 2008, before increasing slightly during the latter half of 2008. This was followed by another period of stability between 2009 and 2010. Like in the other Atlantic provinces, the generic dispensing rate in Newfoundland increase substantively between 2011 and 2013, which led to a quadrupling of 2008 rates (Figure 5.6).

The privately insured generic dispensing rate (Figure 5.7) mirrored many of the trends seen in the publicly insured rates, albeit with a much lower intensity. Much like in the other outcome measures, there was a spike in the generic dispensing rates in 2001 and parts of 2002 following by a decrease in the remainder 2002 across all study provinces. The spikes observed in Ontario during 2003, 2006, and 2012, closely resembles what is observed in the publicly funded claims (Figure 5.7). Alberta's relatively low rates made it difficult to distinguish trends in the dispensing rate. However, a decreasing trend between 2004 and 2010 was noted before a significant increase in the rate was observed during 2011 to 2013 (Figure 5.7).

A small spike in generic dispensing rate was seen in Manitoba during 2002, and again in 2003. Past 2003, the dispensing rate had a slight decreasing trend till 2008. In the second half of 2008, the generic dispensing rate substantively increased, nearly doubling the rate observed earlier in the year. The increased rate was sustained till 2012, upon which the rate significantly increased again to double 2011 rates (Figure 5.7).

The rate in Quebec also displayed a spike during 2001 and 2002 before falling down to pre-spike rates over the remainder of 2002. The rate then continued on a slightly increasing trend between 2003 and 2011. During 2012, the generic dispensing rate increased substantively, doubling 2011 rates (Figure 5.7).

Interestingly, the highest generic dispensing rates were observed among the Atlantic provinces. The rate in all three Atlantic provinces spiked during 2001 and 2002. In New Brunswick, the rate spiked again over the latter half of 2002 before slowly decreasing over 2003 to 2005. Another spike over the second half of 2005 saw the New Brunswick rate double early 2005 values. This increase was sustained over 2006 to 2010, at which point the rate increased again from 2010 to 2013. In Newfoundland, the rate increased in

2003, before slowly decreasing from 2003 to 2007. The rate spiked again in 2008, doubling 2007 values, and again in 2011, to over 7 times that of 2007 values. These increases were sustained till 2013. Rates in Nova Scotia were the lowest among the three Atlantic provinces, but the trends observed in New Brunswick were also observed in Nova Scotia. The generic dispensing rate increased slightly in the latter half of 2003, prior to a slow decrease from 2003 to 2005. The rate increased again in 2006 to approximately 1.5 times of 2005 values and was sustained from 2006 to 2010. A significant increase was then observed in 2011-2013, with the rate ending at approximately 2.5 times that of 2010 values (Figure 5.7).

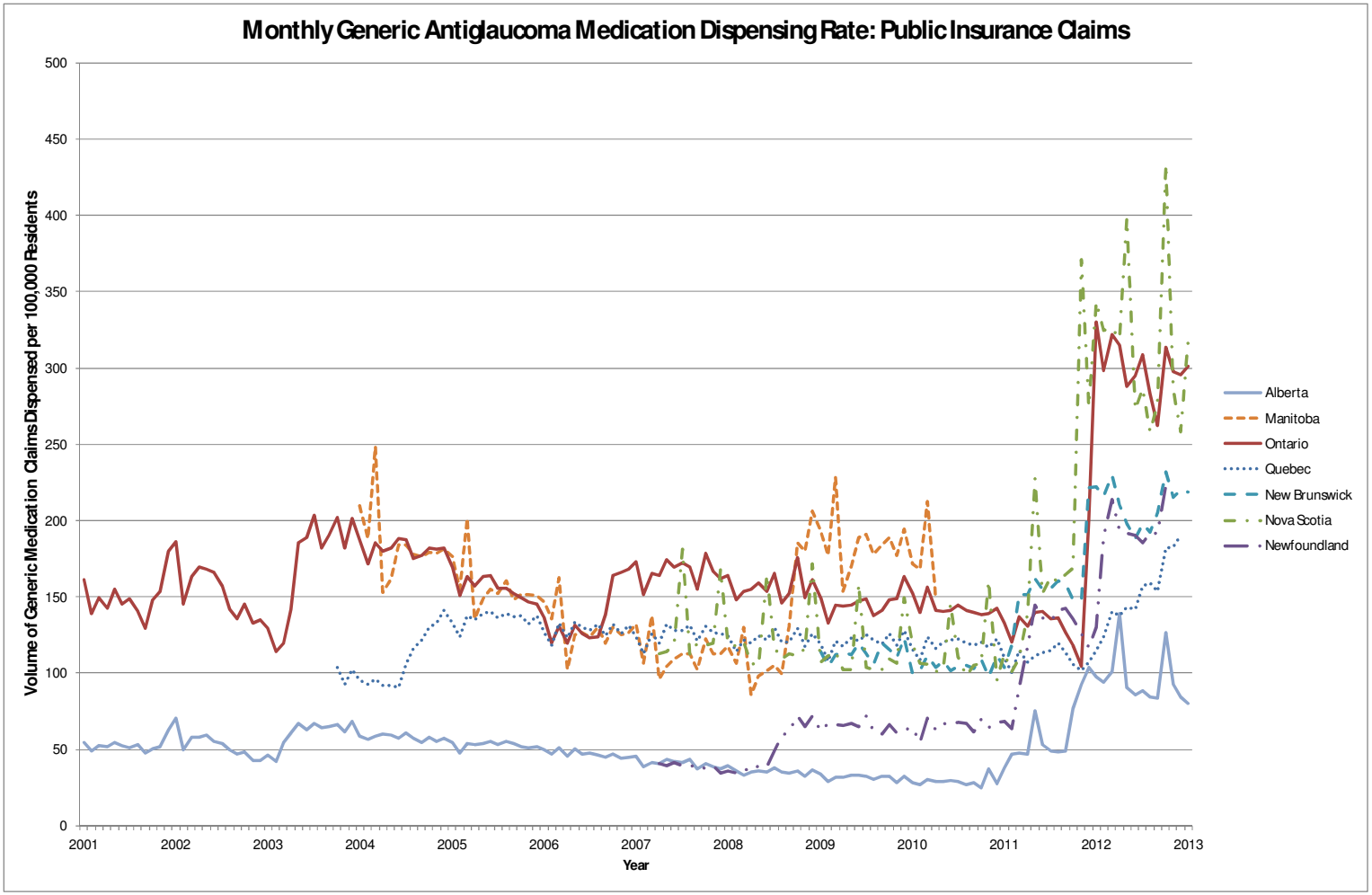

Figure 5.6 Monthly rate of privately insured antiglaucoma medication dispensed as generic equivalents per 100,000 residents throughout January 2001 – January 2013.

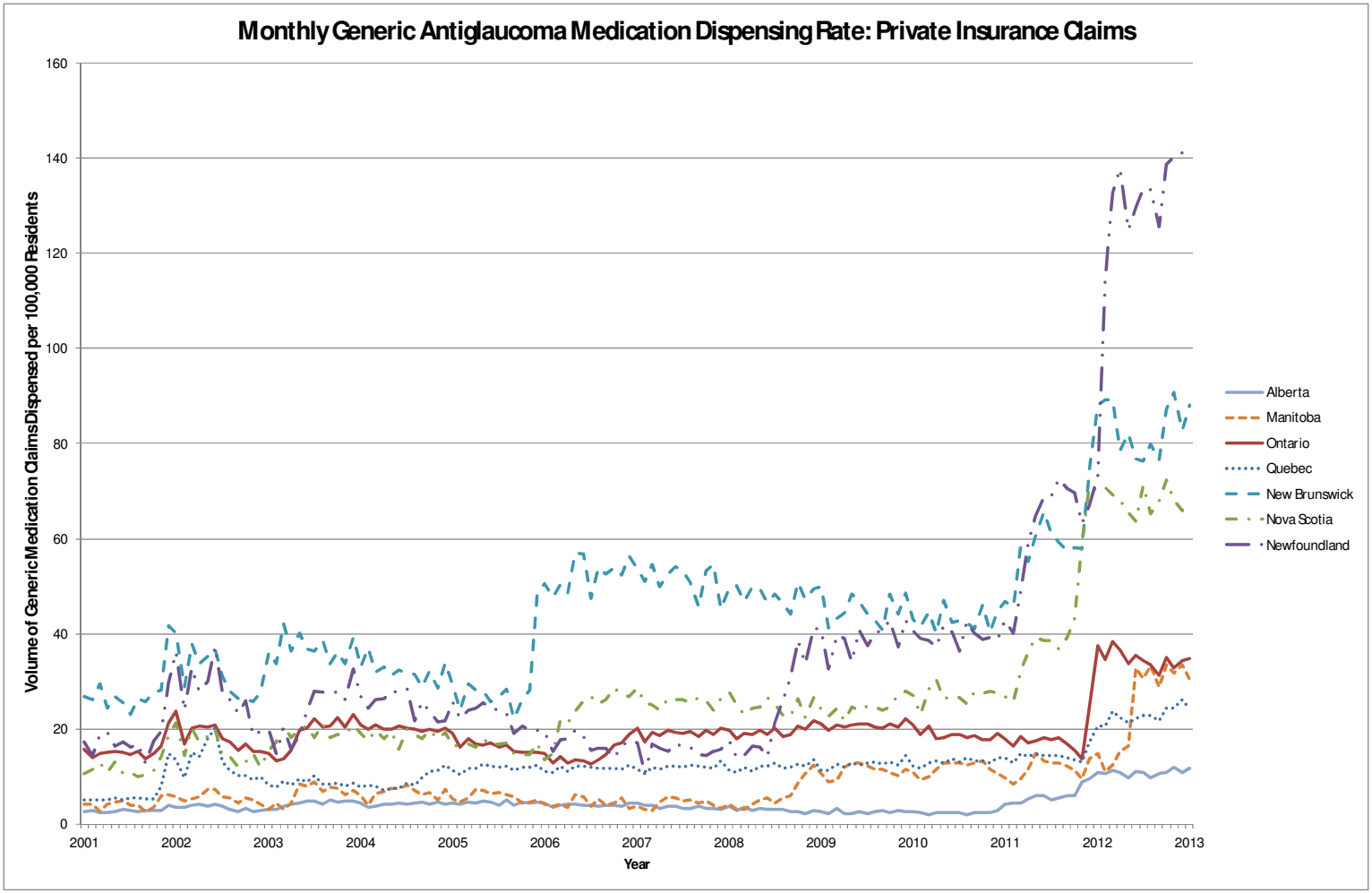

Figure 5.7 Monthly rate of privately insured antiglaucoma medication dispensed as generic equivalents per 100,000 residents throughout January 2001 – January 2013.

5.3.4 Total Cost of Antiglaucoma Medication Claims

The monthly cost of all antiglaucoma medication claims across the study provinces are presented in figures 5.8 and 5.9 for publicly and privately insured claims, respectively. The monthly cost of both public and privately insured claims increased steadily across all study provinces between January 2001 and January 2012. Pronounced annual fluctuations were observed across all provinces throughout the study time frame.

One point of interest is the considerable decrease in total cost of antiglaucoma medication claims in Ontario during late 2011 and during 2012. This decrease was observed in both publicly and privately insured claims, and is in contrast to the other study provinces, where the total cost of antiglaucoma medications remained steady or slightly increased.

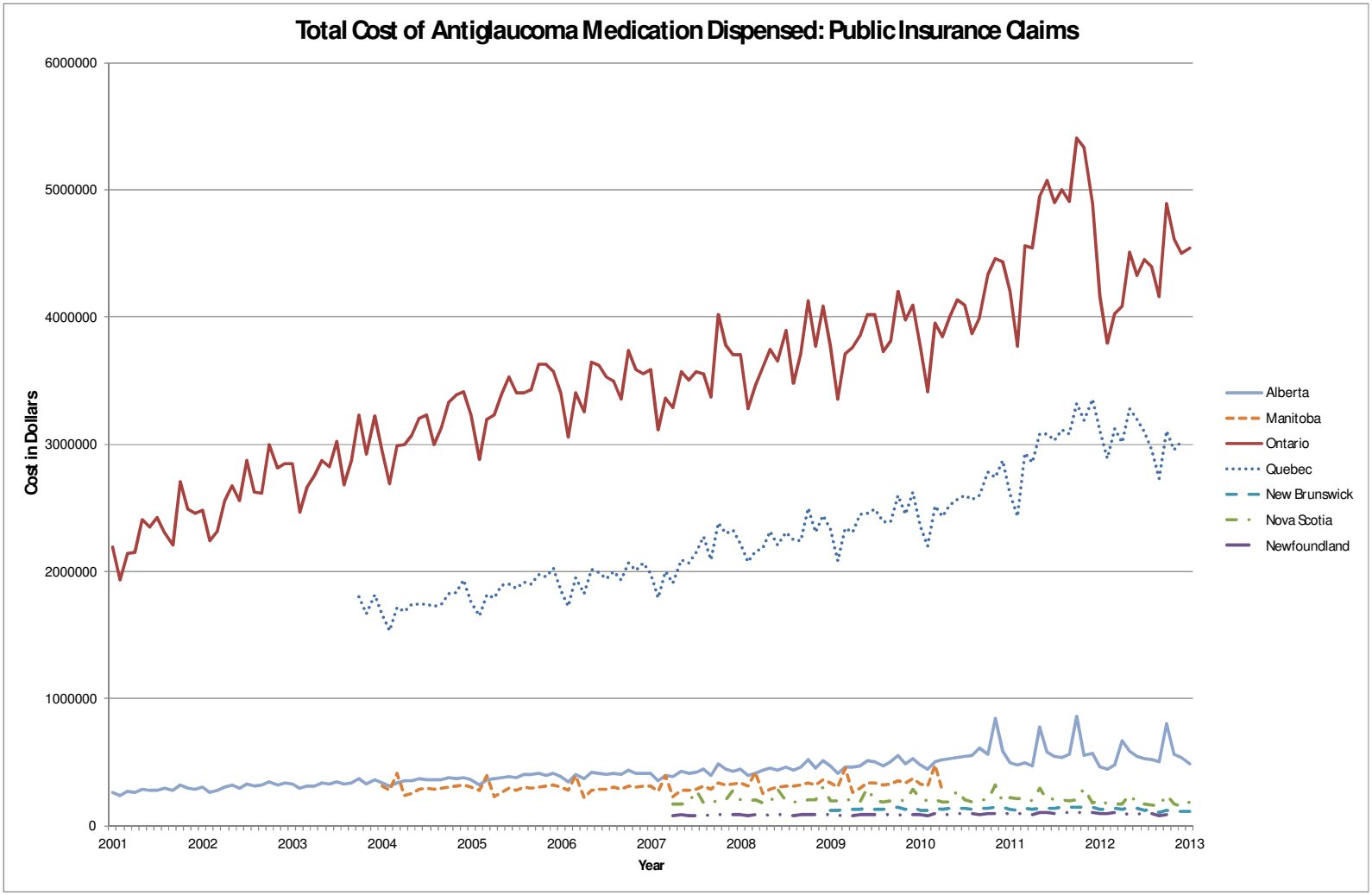

Figure 5.8 Monthly cost of all publicly insured claims for antiglaucoma medication dispensed throughout January 2001 – January 2013.

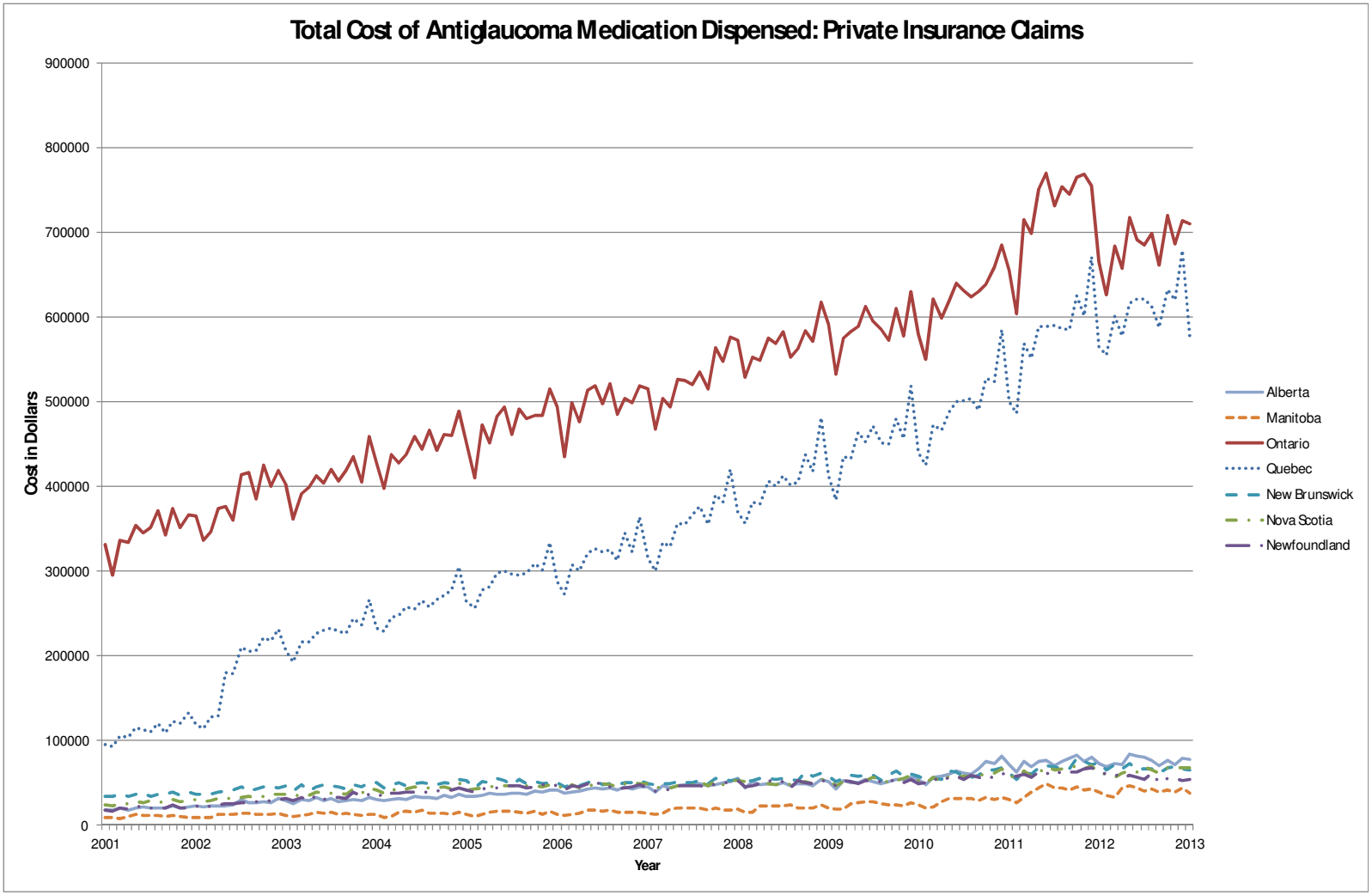

Figure 5.9 Monthly cost of all privately insured claims for antiglaucoma medication dispensed throughout January 2001 – January 2013.

5.3.5 Summary of Descriptive Results

Across all three outcome measures, utilization of generic antiglaucoma medications fluctuated annually during the study time frame but an overall increase from 2001 to 2013 was observed. Utilization within the public drug plans was significantly higher than utilization within the private drug plans, with the former being twice to ten times higher, depending on the province. Significant increases across all outcome measures were observed across all provinces during the latter months of 2011 and during 2012. This increase was observed in both private and public drug plans, where data was available.

5.4 Time Series Analysis Results

Interrupted time series analysis using an ARIMA model was used to determine the level of association between the 2010 Ontario Drug System Reform and the various outcome measures. Results from these analyses suggested a lack of association between the 2010 Ontario Drug System Reform and the outcome measures. Furthermore, these analyses indicated that the use of price-ceiling policies may not be effective in increasing the utilization of cheaper generic antiglaucoma medication. Moreover, the lack of statistically significant associations between the drug reform and total drug cost in glaucoma treatment suggested that this reform is ineffective in decreasing drug expenditures.

The Time Series Forecasting System tool within SAS/ETS 9.3 was used to assess the congruency of the data to the requirements of the ARIMA modelling technique and to determine the best fitting orders of autoregression, integration, and moving average for the model. The Augmented Dickey-Fuller test was used to determine the order of differencing needed to ensure the stationary requirements of ARIMA modelling are met. The Ljung-Box χ^2 statistic was calculated for the stationary data to ensure that autocorrelation exists between the lags. The ideal model was determined by comparisons of goodness-of-fit measures which include the mean square error, adjusted R-square, and Schwarz Bayesian Information Criterion. These selection criteria were selected as they include the appropriate penalty for models with large numbers of parameters.[199]

To maintain comparable groups between the pre-reform and post-reform periods, medications that changed generic status were excluded from the time series analysis. Hence, the latanoprost was removed as the first generic equivalent was introduced to the Canadian market after the drug reform came into effect (Notice of Compliance for Apo-latanoprost was issued on August 19, 2011, it was added to the Ontario Drug Benefit Formulary on December 15, 2011).

5.4.1 Volume of Generic Claims

The model ARIMA (1,1,2)(1,0,0)12 was fitted to the volume of the publicly insured generic claims from January 2001 to January 2013. Tests with the three intervention functions did not result in differing results, and thus the July 2010 Drug System Reform was modelled as the intervention using a ramp function. The statistics of fit using the three functions are presented in Table 5.1. Results from the ARIMA procedure indicated that the 2010 reform was not statistically associated with a change in the volume of publicly funded claims, after taking into account previous trends in generic medication use ($p = 0.7234$). Coefficient estimates from the ARIMA procedure with a ramp intervention function are highlighted in Table 5.2.

Table 5.1 Statistics of Fit of the most appropriate model for each intervention function of the volume of generic medication for publicly insured patients.

Statistic of Fit	Value		
	Ramp ARIMA (1,1,2)(1,0,0)12	Step (1,1,2)(1,0,0)12	Point (1,1,2)(1,0,0)12
Number of Nonmissing Observations	144	144	144
Number of Observations	145	145	145
Number of Missing Actuals	0	0	0
Number of Missing Predicted Values	1	1	1
Number of Model Parameters	5	5	5
Root Mean Square Error	1546.9	1544.4	1544.0
Adjusted R-Square	0.596	0.597	0.597
Schwarz Baynesian	2139.9	2139.5	2139.4

Information Criterion

Table 5.2 Coefficient estimates from the ARIMA with a ramp intervention function for the volume of generic medication for publicly insured patients.

Model Parameter	Estimate	Standard Error	T	P-value
Moving Average, Lag 1	-0.53163	0.1884	-2.8222	0.0055
Moving Average, Lag 2	0.26479	0.0900	2.9423	0.0038
Autoregressive, Lag 1	-0.61158	0.1850	-3.3055	0.0012
Seasonal Autoregressive, Lag 12	0.36762	0.0873	4.2102	<0.0001
Ramp: July 2010	100.21207	282.5263	0.3547	0.7234

The monthly volume of privately insured generic claims in Ontario from January 2001 to January 2013 was fitted with the model ARIMA (1,1,0)(1,1,0)12. A ramp function was utilized to model the 2010 drug reform as there was no difference in the result of ARIMA modelling detected using any of the three intervention functions. The statistics of fit using the three functions are presented in Table 5.3. Results from the ARIMA procedure indicate that the 2010 reform was not statistically associated with a change in the volume of privately insured claims, after taking into account previous trends in generic medication use ($p = 0.7870$). Coefficient estimates from the ARIMA procedure with a ramp intervention function are highlighted in Table 5.4.

Table 5.3 Statistics of Fit of the most appropriate model for each intervention function of the volume of generic medication for privately insured patients.

Statistic of Fit	Value		
	Ramp ARIMA (1,1,0)(1,1,0)12	Step (1,1,0)(1,0,0)12	Point (1,1,0)(1,0,0)12
Number of Nonmissing Observations	132	144	144
Number of Observations	145	145	145
Number of Missing Actuals	0	0	0
Number of Missing Predicted Values	13	1	1
Number of Model Parameters	3	3	3
Root Mean Square Error	194.00813	180.03592	180.00199
Adjusted R-Square	0.627	0.724	0.724
Schwarz Baynesian	1405.4	1510.5	1510.5

Information Criterion

Table 5.4 Coefficient estimates from the ARIMA with a ramp intervention function for the volume of generic medication for privately insured patients.

Model Parameter	Estimate	Standard Error	T	P-value
Autoregressive, Lag 1	-0.13181	0.0885	-1.4897	0.1388
Seasonal Autoregressive, Lag 12	-0.52146	0.0811	-6.4261	<0.0001
Ramp: July 2010	11.51598	42.5260	0.2708	0.7870

5.4.2 Generic Percentage Dispensed

The impact of the 2010 Ontario Drug System Reform on the publicly insured generic percentage dispensed was assessed using an ARIMA (1,0,3) model with the use of a ramp function. Modelling with a ramp function suggested a statistically significant association between the 2010 Drug Reform and a decrease in the generic percentage dispensed ($p = 0.0437$). However, this statistical significance was not observed when a step or point function was utilized to model the intervention. Table 5.5 presents statistics of fit from the best fitting models within each of the three functions. Table 5.6 lists the coefficient estimates from the ARIMA procedure with a ramp function.

Table 5.5 Statistics of Fit of the most appropriate model for each intervention function of the generic percentage dispensed as a generic for publicly insured patients.

Statistic of Fit	Value		
	Ramp ARIMA (1,0,3)	Step ARIMA (1,0,3)	Point ARIMA (1,0,3)
Number of Nonmissing Observations	144	144	144
Number of Observations	145	145	145
Number of Missing Actuals	0	0	0
Number of Missing Predicted Values	1	1	1
Number of Model Parameters	6	6	6
Root Mean Square Error	0.01661	0.01676	0.01678
Adjusted R-Square	0.875	0.873	0.873
Schwarz Baynesian Information Criterion	-1150.3	-1147.7	-1147.5

Table 5.6 Coefficient estimates from the ARIMA with a ramp intervention function for the generic percentage dispensed among publicly insured patients.

Model Parameter	Estimate	Standard Error	T	P-value
Intercept	0.32745	0.0121	27.1190	<0.0001
Moving Average, Lag 1	-0.40367	0.1027	-3.9318	0.0001
Moving Average, Lag 2	0.01543	0.1187	0.1300	0.8967
Moving Average, Lag 3	-0.26685	0.0928	-2.8766	0.0047
Autoregressive, Lag 1	0.79715	0.0740	10.7783	<0.0001
Ramp: July 2010	-0.00260	0.0013	-2.0357	0.0437

An ARIMA (2,1,1) model with the intervention modelled using a ramp function was fitted to the generic percentage dispensed for the privately insured claims. Intervention modelling using a point, step, or ramp function did not affect the non-significant of the impact of the 2010 Drug System Reform on the percentage dispensed in either the publicly or privately insured patient population. Statistics of fit for the most appropriate model for each of the intervention functions are presented in Table 5.7. The 2010 drug reform was not associated with a statistically significant change in the generic percentage dispensed (p=0.7377). Table 5.8 presents results from the ARIMA modelling with a ramp intervention function.

Table 5.7 Statistics of Fit of the most appropriate model for each intervention function of the generic percentage dispensed among privately insured claims.

Statistic of Fit	Value		
	Ramp ARIMA (2,1,1)	Step ARIMA(2,1,1)	Point ARIMA(2,1,1)
Number of Nonmissing Observations	144	144	144
Number of Observations	145	145	145
Number of Missing Actuals	0	0	0
Number of Missing Predicted Values	1	1	1
Number of Model Parameters	4	4	4
Root Mean Square Error	0.01632	0.01631	0.01630
Adjusted R-Square	0.835	0.835	0.835
Schwarz Baynesian Information Criterion	-1165.3	-1165.6	-1165.8

Table 5.8 Coefficient estimates from the ARIMA with a ramp intervention function for the generic percentage dispensed among privately insured claims.

Model Parameter	Estimate	Standard Error	T	P-value
Moving Average, Lag 1	-0.94822	0.0401	-23.6464	<0.0001
Autoregressive, Lag 1	-0.86358	0.0890	-9.6977	<0.0001
Autoregressive, Lag 2	-0.13675	0.0871	-1.5691	0.1189
Ramp: July 2010	-0.0009817	0.0029	-0.33556	0.7377

5.4.3 Generic Dispensing Rate

The generic dispensing rate of publicly insured antiglaucoma medication per 100,000 Ontario residents from January 2001 to January 2013 was fitted using various ARIMA models, depending on the type of intervention function used. The 2010 Ontario Drug System Reform introduced as an intervention using a ramp function as no differences was observed in the significance of the intervention using either a ramp, step or point function. The most appropriate model, along with statistics of fit, for each of the intervention functions are presented in Table 5.9. No significant change in the publicly insured generic dispensing rate attributable to the drug reform was observed (p=0.5911). Coefficient estimates from the ARIMA modelling with a ramp intervention function are listed in Table 5.10.

Table 5.9 Statistics of Fit of the most appropriate model for each intervention function of the generic dispensing rate per 100,000 residents for publicly insured patients.

Statistic of Fit	Value		
	Ramp ARIMA (1,1,2)(0,1,1)12	Step ARIMA(1,1,2)(0,1,1)12	Point ARIMA(1,1,2)(1,0,1)12
Number of Nonmissing Observations	132	132	144
Number of Observations	145	145	145
Number of Missing Actuals	0	0	0
Number of Missing Predicted Values	13	13	1
Number of Model	5	5	6

Parameters			
Root Mean Square Error	11.59694	11.60319	11.36156
Adjusted R-Square	0.661	0.660	0.662
Schwarz Baynesian Information Criterion	671.4094	671.55195	729.72680

Table 5.10 Coefficient estimates from the ARIMA with a ramp intervention function for the generic dispensing rate per 100,000 residents for publicly insured claims.

Model Parameter	Estimate	Standard Error	T	P-value
Moving Average, Lag 1	-0.72779	0.1418	-5.1326	<0.0001
Moving Average, Lag 2	0.19377	0.1005	1.9288	0.0560
Seasonal Moving Average, Lag 12	0.86454	0.1405	6.1547	<0.0001
Autoregressive, Lag 1	-0.68407	0.1215	-5.6286	<0.0001
Ramp: July 2010	1.04822	1.9459	0.5387	0.5911

An ARIMA (1,1,0)(1,1,0)12 model was fitted to the generic dispensing rate of privately insured generic medication per 100,000 Ontario residents from January 2001 to January 2013. Again, a ramp function was utilized to introduce the intervention as no differences were observed between the three functions in the significance of the impact of the drug reform. The statistics of fit for the most appropriate model for each intervention function is presented in Table 5.11. ARIMA estimates suggested no significant change in the generic dispensing rate as a result of the drug reform (p=0.7956). Estimates from the ARIMA model with a ramp intervention function are presented in Table 5.12.

Table 5.11 Statistics of Fit of the most appropriate model for each intervention function of the generic dispensing rate per 100,000 residents for privately insured patients.

Statistic of Fit	Value		
	Ramp ARIMA (1,1,0)(1,1,0)12	Step ARIMA(1,1,0)(1,1,0)12	Point ARIMA(2,1,0)(1,1,0)12
Number of Nonmissing	132	132	132

Observations			
Number of Observations	145	145	145
Number of Missing Actuals	0	0	0
Number of Missing Predicted Values	13	13	13
Number of Model Parameters	3	3	4
Root Mean Square Error	1.54674	1.54697	1.54535
Adjusted R-Square	0.556	0.556	0.553
Schwarz Baynesian Information Criterion	129.79220	129.83149	134.43806

Table 5.12 Coefficient estimates from the ARIMA with a ramp intervention function for the dispensing rate of generic medication per 100,000 residents for privately insured claims.

Model Parameter	Estimate	Standard Error	T	P-value
Moving Average, Lag 1	-0.12900	0.0887	-1.4550	0.1481
Seasonal Moving Average, Lag 12	-0.52283	0.0797	-6.5570	<0.0001
Ramp: July 2010	0.08783	0.3384	0.2595	0.7956

5.4.4 Total Cost of Antiglaucoma Medication Claims

The monthly total cost of publicly insured antiglaucoma medication over the study time frame was fitted using various ARIMA models, depending on the type of intervention function used. Introducing the 2010 Ontario Drug System Reform using a ramp function led to a statistically significant association between the reform and an increase in monthly total cost of publicly insured antiglaucoma claims (p=0.0027), but this significance was not observed when using a step or point function. The models, along with statistics of fit, for each of the intervention functions are presented in Table 5.13. Coefficient estimates from the ARIMA modelling with a ramp intervention function are listed in Table 5.14.

Table 5.13 Statistics of Fit of the ARIMA model for each intervention function of the total cost of antiglaucoma medication claims for publicly insured patients.

Statistic of Fit	Value		
	Ramp ARIMA	Step	Point ARIMA

	(12,1,2)	ARIMA(12,1,3)	(12,1,1)
Number of Nonmissing Observations	144	144	144
Number of Observations	145	145	145
Number of Missing Actuals	0	0	0
Number of Missing Predicted Values	1	1	1
Number of Model Parameters	15	16	14
Root Mean Square Error	90824.0	92687.3	95013.8
Adjusted R-Square	0.982	0.981	0.981
Schwarz Baynesian Information Criterion	3362.6	3373.4	3370.6

Table 5.14 Coefficient estimates from the ARIMA with a ramp intervention function for the total cost of antiglaucoma medication claims for publicly insured claims.

Model Parameter	Estimate	Standard Error	T	P-value
Moving Average, Lag 1	0.71807	0.1226	5.8559	<0.0001
Moving Average, Lag 2	-0.49559	0.1190	-4.1645	<0.0001
Autoregressive, Lag 1	0.13429	0.1022	1.3136	0.1913
Autoregressive, Lag 2	-0.11117	0.0991	-1.1222	0.2639
Autoregressive, Lag 3	0.01549	0.0775	0.1999	0.8419
Autoregressive, Lag 4	-0.32948	0.0752	-4.3813	<0.0001
Autoregressive, Lag 5	0.22826	0.0855	2.6706	0.0085
Autoregressive, Lag 6	-0.11841	0.0844	-1.4030	0.1630
Autoregressive, Lag 7	-0.01287	0.0773	-0.1665	0.8680
Autoregressive, Lag 8	-0.22790	0.0767	-2.9707	0.0035
Autoregressive, Lag 9	0.09908	0.0856	1.1576	0.2492
Autoregressive, Lag 10	-0.20367	0.0817	-2.4933	0.0139
Autoregressive, Lag 11	0.07954	0.0802	0.9921	0.3230
Autoregressive, Lag 12	0.56752	0.0851	6.6717	<0.0001
Ramp: July 2010	33867	12690	3.0629	0.0027

One statistically significant positive association between the 2010 Ontario Drug System Reform and the total cost of privately insured medication was observed when the intervention was introduced using a point function (p=0.0447). However, this significance did not carry over when a ramp or step function was used. The statistics of fit for the models for each intervention function is presented in Table 5.15. Estimates from the ARIMA models with a ramp intervention function are presented in Table 5.16.

Table 5.15 Statistics of Fit of the ARIMA model for each intervention function of the total cost of antiglaucoma medication claims for privately insured patients.

Statistic of Fit	Value		
	Ramp ARIMA (2,1,2)(1,1,0)	Step ARIMA (2,1,2)(1,1,0)	Point ARIMA (3,1,0)(1,1,0)
Number of Nonmissing Observations	132	132	132
Number of Observations	145	145	145
Number of Missing Actuals	0	0	0
Number of Missing Predicted Values	13	13	13
Number of Model Parameters	6	6	5
Root Mean Square Error	11855.6	11769.7	11989.3
Adjusted R-Square	0.989	0.990	0.989
Schwarz Baynesian Information Criterion	2505.8	2503.8	2503.8

Table 5.16 Coefficient estimates from the ARIMA models for the total cost of antiglaucoma medication claims for privately insured patients.

Model Parameter	Estimate	Standard Error	T	P-value
Moving Average, Lag 1	-0.64223	0.1093	-5.8769	<0.0001
Moving Average, Lag 2	-0.55769	0.1026	-5.4335	<0.0001
Autoregressive, Lag 1	-1.12497	0.0722	-15.5914	<0.0001
Autoregressive, Lag 2	-0.87359	0.0599	-14.5782	<0.0001
Seasonal Autoregressive, Lag 12	-0.42391	0.0947	-4.4786	<0.0001
Ramp: July 2010	2757	2330	1.1836	0.2388

Chapter 6

6 Discussion

6.1 Descriptive Analysis

This population-based study of the utilization of generic antiglaucoma medications found that the use of these drugs increased in the time span between January 2001 and January 2013. This increase in the level of utilization may be consequences of the introduction of the first generic equivalent of brand name antiglaucoma compounds or due to the influences of policies that limited the price of generics, thereby making these medications cheaper to use. Results from this study indicated that the utilization rate of privately insured generic antiglaucoma medications ranged from 10.54% to 18.76% between provinces in January 2001, increasing to 13.91% to 48.14% in January 2013. While such increases in the use of cheaper, generic equivalents are beneficial in terms of cost-savings for both private and public drug insurance plans, this finding indicated that level of generic drug utilization in privately insured glaucoma patients during 2012 is lower in comparison to the overall generic prescription drug utilization rate of 63.2%, as estimated by the Canadian Generic Pharmaceutical Association.[200] Hence, there may be additional cost savings which can be realized if the utilization of generic medication in glaucoma treatment continues to increase.

6.1.1 Volume of Generic Claims

The decreasing trend in the volume of both privately and publicly insured generic antiglaucoma medication claims across study provinces post 2002 may be reflective of the increased usage of prostaglandins in glaucoma therapy. Patients who were previously prescribed a generic antiglaucoma medication, such as timolol maleate, may have switched over to brand name prostaglandins and other combination medications, due to its greater effectiveness in controlling intraocular pressure and lower rates of systemic side effects. As a result, these patients now utilized a brand name compound and would not contribute to the volume of generic claims, leading to the decrease in utilization observed. Such a conclusion agrees with previous research which demonstrated that upon

introduction, prostaglandins, namely latanoprost, quickly became the most popular therapeutic agent for glaucoma and displaced the market shares of older therapeutic agents.[119,123,124]

The approval of Ratio-Brimonidine, which is a generic equivalent of Alphagan (Notice of Compliance issued on June 17th, 2002), may have contributed to the observed increase in the volume of generic claims in Ontario during 2003.[201] The introduction of the first generic equivalent may have caused a rapid migration of patients who use to receive Alphagan towards the cheaper, generic equivalent. As a result, a large increase in the volume of generic claims was observed once the generic was made available for patients.

In contrast to the decreasing trend observed in the other provinces, there was an increase in the volume of generic medications dispensed in Ontario during Quarter 3, 2006. This increase may be associated with the introduction of the 2006 Transparent Drug System for Patients Act, which lowered the cost of generic medications and widened the definition of interchangeability under the DIDFA.[150] The decreased cost of generic medications may have made it more affordable for patients and may have encouraged substitution from brand name medications to its generic equivalents, thereby explaining the increased volume of claims observed. Similar increases in the utilization of generic equivalents were observed in Austria among the usage of generic PPIs and statin medication after various reforms and initiatives (including reference pricing reform similar to the 2006 reform) were introduced.[160] Furthermore, this reform may have caused more prescriptions being substituted with a generic equivalent as a result of the increased availability of generic choices, thereby leading to the increase in utilization observed. The fact that the increase was observed only in the province of Ontario, where the policy change was enacted, adds credibility to this explanation.

Interestingly, the substantive increase in the volume of generic claims observed across all provinces beginning in Quarter 3, 2011 coincides with the introduction of generic latanoprost to the Canadian market (Notice of Compliance for Apo-latanoprost was issued on August 19, 2011). This observation may indicate that the introduction of the first generic equivalent for a therapeutic class has a significant impact on the utilization

of generic drugs. This association between the approval of the first generic equivalent and the increase in generic utilization could possibly be mediated by mandatory generic substitutions rules enacted by many drug plans.[130,202–204] These laws mandate that a prescription must be dispensed using a generic equivalent, where available. Thus, an increase in generic utilization is understandable as patients will be dispensed the newly approved generic equivalents in favour of Xalatan (the brand name latanoprost product).

6.1.2 Generic Percentage Dispensed

Much like in the volume of claims, the decrease in generic percentage dispensed observed during 2003 across all provinces may be a consequence of the introduction of Travatan to the Canadian market. This brand name prostaglandin was rapidly prescribed in glaucoma treatment. As a result, patients who were using older generic antiglaucoma medication may have been switched to this new prostaglandin, resulting in the observed decrease in generic percentage dispensed.

The increase in the generic percentage dispensed across the provinces (except Quebec) in Quarter 1, 2003 may be due to the introduction of generic brimonidine to the Canadian market. This introduction may have lead many patients who received Alphagan to be instead dispensed generic brimonidine. As a result, the utilization of generic medication increase and the corresponding generic percentage dispensed also increased. A rationale for the lack of change in Quebec may be due to its unique reimbursement scheme, which provided full cost reimbursement for Alphagan, even after a generic equivalent is available. Hence, patients lost the financial incentive to substitute prescriptions for Alphagan with its generic equivalent. Additional details regarding this unique reimbursement scheme is provided below.

The increase in the generic percentage dispensed observed in Ontario beginning in Quarter 2, 2006 may be a result of the introduction of the 2006 Transparent Drug System for Patients Act. The possible ramifications of this reform are presented above, and may have led to an increase in the volume of generic claims. This in turn would have led to a corresponding decrease in the volume of brand name claims. Hence, this may have resulted in the observed increase in the generic percentage dispensed.

Increases in generic percentage dispensed observed during Quarter 2, 2008 in Manitoba and Newfoundland may be due to changes in their respective drug program policies. Effective April 1st, 2008, the Manitoban Pharmacare program raised the deductible rates for its beneficiaries. This increase may have provided financial incentives for patients to substitute their brand name prescriptions with a generic equivalent in order to lessen the impact of the increase in deductible fees. However, this change in the deductible may only have a small impact on the change in generic percentage dispensed as it was only a 5% change in the rate (from between 2.56% and 5.51%, to between 2.69% and 5.79%). An alternative rationale for the observed increase is the introduction of Apo-Timop Gel, a generic version of Timoptic-XE, to the province of Manitoba during August 2008. Hence, patients who previously received Timoptic-XE may have had their prescription substituted with Apo-Timop Gel, thereby contributing to the increase in generic percentage dispensed. Similarly, Timolol Maleate-EX was introduced to Newfoundland during July 2008 which may have contributed to the corresponding increase in generic percentage dispensed. The latter explanation is more relevant as the increase was observed in both private and public insurance claims, whereas the former explanation should only affect publicly insured claims.

The increases in generic percentage dispensed during Quarter 3, 2010 observed in New Brunswick, Nova Scotia, Alberta and Newfoundland may be due to the introduction of Apo-Dorzo-Timol, Sandoz-Dorzol-Timop, Sandoz-Dorzolamide, which are generic equivalents of Cosopt and Trusopt, respectively. Having these generic equivalents available may have led patients to substitute their brand name prescriptions with the corresponding generic drug, and thus causing the increase in generic percentage dispensed observed.

Again, like in the volume of claims, the increased generic percentage dispensed observed in Quarter 4, 2011 across all provinces are most likely associated with the introduction of generic latanoprost during that period. This introduction of the generic equivalent of this popular antiglaucoma agent may have patients who were previously using Xalatan, Travatan or Lumigan to substitute their prescriptions with the generic latanoprost. This in turn may explain the substantive increases in generic percentage dispensed.

The low dispensing percentage observed in the province of Quebec may be due to its unique reimbursement policy. Quebec offers full reimbursement for the price of brand name medications listed on its formulary for 15 years, even if generic equivalents are introduced within that time frame.[205] This is in contrast to the policies in other provinces, which often limit the amount reimbursed for brand name medication to the price(s) of the generic equivalent(s).[130] As a result, patients in Quebec lose the economic incentives to switch to a cheaper generic medication, which may explain the low dispensing percentages in the province.[205] In fact, estimates by Canadian Generic Pharmaceutical Association identified Quebec as the provinces with the lowest generic market share in 2012, and that the differences in generic market share across the provinces was due to the heterogeneity between the various drug programs implemented.[206]

6.1.3 Generic Dispensing Rate

Results from the generic dispensing rate outcome measure revealed similar trends to the other outcome measures. Introduction of the first generic equivalent for brand name compound remain one of the strongest driving forces for changes in the generic dispensing rate. However, the generic dispensing rate revealed that the dispensing rate is the lowest in Alberta, and highest in the Atlantic provinces. These results will be discussed below.

Compared to the other provinces included in this study, generic dispensing rates were lowest in Alberta. There are two possible explanations for this observation. First, the low rates of generic antiglaucoma medication dispensed in Alberta compared to the other provinces may be due to a lower demand for antiglaucoma medication in general (including both brand name and generic medication). This explanation is supported by the younger age distribution in Alberta. For example, the percentage of Alberta between the ages of 15-64 and 65 and older are 70.1% and 11.1%, respectively, while the corresponding national percentages are 68.5% and 14.8% (in 2011).[207] Hence, the prevalence of glaucoma may be lower in Alberta as glaucoma is typically a disease of the elderly. This may lead to a decreased demand for antiglaucoma medication in general, and explain the lower rates of generic antiglaucoma medication dispensed. An alternative explanation for the low generic dispensing rate in Alberta may be an under-utilization of

generic medication compared to the other provinces in the study. However, taking into consideration the relatively high generic percentage dispensed in comparison to the other provinces, it does not appear that Alberta is under-utilizing generic antiglaucoma medication.

With respect to the increased generic dispensing rate seen in the Atlantic provinces, a possible explanation may be the fact that the percentage of people 65 and older are higher in these provinces than national average. According to Statistics Canada, the proportion of people over the age of 65 in 2011 is 16.5%, 16.6%, and 16.0% in New Brunswick, Nova Scotia, and Newfoundland and Labrador, respectively, compared to the national estimate of 14.8%.[207] Hence, the prevalence of glaucoma may be higher in these provinces relative to the other provinces in the study. Thus, there may be greater demand for antiglaucoma medication, explaining the observed greater generic dispensing rates observed.

6.1.4 Total Cost of Antiglaucoma Medication Claims

In terms of the total cost of antiglaucoma medication, the considerable decrease in total cost observed in Ontario during Quarter 4, 2011 may be due to the introduction of generic latanoprost to the Canadian market. Much like in the other outcome measures, this introduction may have caused a shift from the expensive, brand name Xalatan, Travatan or Lumigan to the cheaper generic latanoprost, causing the total cost of antiglaucoma medication to decrease. Another point which adds credibility to this explanation is that the decrease was observed in the other provinces as well, which would indicate that the catalyst for change must originate at the national level. Such a change can be spurred by the approval of a generic medication for the Canadian market.

Due to this study being the first to examine the utilization patterns of generic antiglaucoma medication in Canada, comparisons to other scholarly works cannot be made regarding the results of the study.

6.2 Time Series Analysis

The 2010 Ontario Drug System Reform sought to reduce the public and private drug expenditure by lowing maximum reimbursement and enacting price ceiling on the price of generic medications, respectively. Within the non-solid dosage forms, the reform mandated the cost of generic equivalent to no more than 35% of the reference product. Hence, we aimed to determine the impact of this reform on the utilization and total drug expenditures on antiglaucoma medication within Ontario. It is proposed that the reform should lead to a decrease in both the public and private drug expenditures as the prices of generic equivalents are often lower than that of the brand name counterparts; furthermore, due to the lower drug costs, the use of generic equivalents may become a more attractive opinion and therefore utilization may increase as result.

The results from the time series analysis of the impact of the 2010 Ontario Drug System Reform yielded mixed results. Several statistically significant associations were observed between the outcome measures and the drug system reform. Namely, a decrease in the publicly insured generic percentage dispensed was associated with the reform while an increase in the total cost of both privately and publicly insured claims were associated with the reform. The significant results could be understood when examined together. The decrease in percentage of generic antiglaucoma medication associated with the 2010 reform may suggest that brand name medications saw increased utilization in the post-reform time frame. This decrease in the use of generic medications (and the subsequent increase use of brand name medication) may be due to the removal of the professional allowanced mandated as part of the reform. The discontinuation of professional allowances removes the financial incentives of pharmacies to substitute brand name prescriptions with its generic equivalents.[205] Consequently, this increase in the use of relatively more expensive brand name drug may lead to an increase in total cost of both privately and publicly insured medications and thus explain the increase in total drug costs associated with the drug system reform.

However, it is important to note that none of the other outcome measures demonstrated statistical significance with the 2010 Ontario Drug System Reform. Moreover, each of these significance results was observed in only one of the three methods used to introduce

the intervention parameter. This inconsistency in the statistical significance between the intervention parameters suggests that the observed significance may be spurious. Furthermore, the lack of consensus among the outcome measures provide further evidence that the significant associations observed may be invalid.

The non-significant results from the time series analysis may be reflective of the parameter of the study, where only antiglaucoma medications in the non-solid formulations were included. Due to the unique reimbursement scheme when price caps for non-solid dosages are higher than in solid formulations, the impact of the reform may be muted. The higher price caps for generic medication may reduce the financial incentives for patients to request their medication be substituted with a generic equivalent. As a result, changes in use of generic medication in glaucoma treatment may be lower and non-significant compared to studies evaluating the impact of the reforms on solid formulation medications.

Based on the literature review, this is the first study looking at the impact of drug pricing reforms on the utilization of generic antiglaucoma medications worldwide. Outside of the field of glaucoma, prior research has been conducted on the impact of the 2010 Ontario Drug System Reform on drugs costs. However, methodological differences limit the comparability of results. For instance, Law et al., in their study into the short-term impact of the 2010 reform, determined that the drug reform was responsible for a $181 to $194 million decrease in generic drug expenditure in the 6 months after the introduction of the reform. However, it is important to note that while our study only looked at the impact on antiglaucoma medications, their study was examining the impact on all generic medication expenditures. Hence, the cost saving they observed may not hold for the glaucoma medication market, resulting in the discrepancies between the results.

Internationally, a study from Austria examined the impact of a plethora of other reforms and initiatives to contain drug expenditures, including reference pricing reforms, on the utilization of proton pump inhibitors and statins.[160] The study determined that these reforms and initiatives were correlated with an increased usage of PPIs and statins. However, it did not determine specifically the impact of the introduction of reference

pricing reforms on the utilization of these drugs.[160] The impact of reference pricing in Germany were also examined, which identified that the introduction of reference pricing in 1993 lead to a 36% increase in the sales of the four largest generic manufacturers and a decrease in 16.5% in sales among the top seven research intensive drug manufacturers.[161] This finding suggests that the introduction of price limiting policies, much like the Ontario reforms, may consequently increase the utilization of generic equivalents at the expense of brand name compounds. Similar observations were seen in the Swedish markets, where reference pricing was introduced in 1993.[163] When comparing first 6 months of 1993 with the remainder of 1993, the market share for brand name compounds decrease from 65% to 51%, while the market share for generic equivalents increased.[162] This shift in the market shares translated to a savings of about 5% of the total drug expenditure.[162]

The results of this study do not agree with many of the studies that examine the impact of the introduction of reference pricing, which suggest that such policies should increase the utilization of generic compounds. However, it is important to note that there are significant differences between these studies and the present study. Firstly, the current study examined only the impact on antiglaucoma medications, whereas the other studies examined the impact of these policies on all medications. Second, differences in the methods used to determine the reference price may impact the financial incentives a patient faces when making the decision to substitute with a generic equivalent. For example, the reference in Germany is determined by taking the average of all the drugs within the interchangeable group, whereas in Canada, the reference price is set at an arbitrary percentage of the brand name compound.[139] These differences may limit the appropriateness of comparing the results of these international studies with those of this study.

The effect of both the 2006 and 2010 Ontario Drug System Reform was also evaluated. However, much like in the above analysis, no persistent statistically significant result was observed in that neither the 2006 or 2010 reforms were statistically significantly associated with a change in the outcome measures of this study. Hence, the result of this sub-analysis was included in Appendix A.

6.3 Study Strengths

This study has several strengths. Based on the literature review, this study is the first to describe the utilization patterns of generic medication in glaucoma treatment in Canada. Moreover, it is one of a few studies that have empirically measured the impact of the Ontario Drug System Reforms on the utilization of generic medications in Ontario. Furthermore, since the population-based analyses included all insured claims for antiglaucoma medication within the provinces examined, the study avoided the potential for bias such as selection bias which may influence the results observed.

6.4 Study Limitations

This study also has several limitations. First, only insured claims for prescription antiglaucoma medication dispensed was available. Hence, this study does not consider the utilization of generic antiglaucoma medication among patients who are uninsured and pay out-of-pocket. However, it is expected that the majority of the prevalent cases of glaucoma are among the elderly and are thus insured by a public drug insurance plan. Moreover, a 2002 estimate by the Fraser Group indicated that only 2% of Canadians do not have access to any form of drug plan coverage, and thus would not be captured within the database.[208] Estimates from the Canadian Institute for Health Information suggested that approximately 16% of total drug expenditures in Canada are financed by out-of-pocket payments by Canadians.[209] However, this estimate included any co-payments that households paid as part of their insurance agreements and therefore the number of non-insured Canadians may be substantively lower. As only a small fraction of Canadians do not have any form of drug insurance, the sample utilized and results obtained in this study should provide a generalizable view of the utilization of generic antiglaucoma medication in Canada.

Second, the database did not identify patients who were covered by both public and private insurance plans during the study time frame. As a result, duplicity of claims may result which are not accounted for within the database, as patients who have public coverage for a portion of the drug cost may also utilize a private drug plan to pay for the remaining cost. This scenario may result in a claim to appear in both the private and

public drug claims databases. Hence, the analyses of private drug claims may not reflect the true drug utilization patterns of patients who are covered solely by a private drug plan. Unfortunately, given the nature of the dataset, it was impossible to determine how many of claims were made by patients who are covered by both public and private insurance plans.

Third, this study utilized data that was aggregated at a provincial level, and thus was unable to capture the differences in generic medication utilization at the local health region level. For this reason, effects of geographical factors, such as urbanicity, on generic medication utilization could not be assessed. Such subgroup analyses may reveal interesting results as the lack of access to healthcare in rural areas, coupled with concerns regarding differences in effectiveness and rates of side effects between brand name products and generic equivalents may lead rural clinicians to avoid the use of generic medications. The aggregate nature of the data also limited the ability to explore differences in utilization among different subgroup of patients, such as severe glaucoma patients versus mild glaucoma patients, or younger versus older patients. Furthermore, utilization patterns among patients in differing socio-economic classes could not be assessed.

Fourth, this study only evaluated the utilization of non-solid formulation medication for glaucoma treatment. As a result, solid formulation medications (ie. tablet form) were excluded from the analysis. This segregation was necessary as there is a difference in the reimbursement scheme for non-solid formulation versus solid formulation medications. Based on the literature review, there are no studies conducted which examined the market share of solid formulations within the antiglaucoma medication market. However, from the dataset utilized in this study, the average monthly market share of solid formulations across the study provinces ranged from 1.6% to 8.1% and 1.2% to 2.9% for private and public insured claims, respectively. Hence, the impact of the non-solid formulations on the results generated within this study may be negligible.

Lastly, another limitation of this study was that unmeasured confounders were unaccounted for, which may introduce shocks to our data that could not be adjusted for by the modelling technique. An example of such confounding elements would be a population change beyond

expectation, which could arise due to atypical levels of immigration. Such an element may be an above average increase in the proportion of elderly immigrants, which may potentially lead to an increase in the number of glaucoma patients and an increase in the utilization of glaucoma medication that is unrelated to the policy changes examined. However, given that the data was stationary upon differing, the impact of these unmeasured confounders is minimal.

6.5 Study Implications

The study results demonstrated by the end of 2012, when generic equivalents were available for all five antiglaucoma medication classes, only approximately half of all medications prescribed were dispensed as a generic equivalent. Hence, potential cost savings to drug insurance plans may be realized by encouraging increased utilization of generic equivalents. However, such a push may be difficult as there is contention in the ophthalmological field regarding the equivalence of generic ophthalmic solutions to the brand reference products. Although a generic drug must prove bioequivalence in order to obtain approval from Health Canada, such claims for ophthalmic drugs are often derived from studies in animal models, and may not be reflective of the drug's activity in humans.[210] Moreover, generic manufacturers of aqueous solutions (which include all ophthalmic solutions) can request waivers to avoid demonstrating *in vivo* bioequivalence.[211] Instead the manufacturers need only provide comparisons of the formulation, physicochemical properties, and device attributes between the reference product and their generic compound.[211] Furthermore, studies have cited differences in the excipients (non-active ingredients) and bottle design between the brand name and generic products which may impact the equivalency, and ultimately its therapeutic value.[212,213] These concerns may lead a clinician to hesitate in prescribing generic equivalents for his or her patients. Patient perceptions towards generic medications may also limit its used in practice.[214,215]

The findings of this study also suggested that the introduction of a price ceiling on generic medication may not translate to an increase in utilization. Hence, efforts to increase utilization of generic medication should instead focus on other modifiable factors that may influence the choice to use a generic equivalent. For example, public

awareness programs regarding the equivalency between generic medication and brand name drugs may change patient perceptions towards generics and increase their confidence in the use of these drugs. Furthermore, more stringent testing for ophthalmic generic equivalents may convince clinicians to prescribe generic medications for their patients.

6.6 Future Research

More research is needed to fully understand the impacts of a price limiting policy such as the 2010 Ontario Drug System Reform on the utilization of generic medications. Adopting the methodologies used in this study, further research can be conducted on the other provinces within Canada as most have enacted policies to introduce a price-ceiling for generic medications. Collectively, the results of these studies can provide a more comprehensive assessment of price-limiting reforms on the utilization patterns of generic drugs

Furthermore, research on the association between different covariates, such as geographical location, socioeconomic status and disease severity on generic antiglaucoma drug utilization may provide interesting results regarding the utilization pattern. Understanding how these covariate influence the use of generic equivalents can guide the development of novel programs to increase the use of these drugs and potentially reduce the cost of treatment for glaucoma patients.

6.7 Conclusion

In this study, the utilization patterns of generic antiglaucoma medications were examined through the use of Canadian insured drug claim records. It was demonstrated that there was an overall increase in the utilization of generic antiglaucoma medications between January 2001 and January 2013 in all of the provinces examined. Furthermore, there was insufficient evidence to suggest that the 2010 Ontario Drug System Reform was associated with a change in the utilization of generic antiglaucoma medication in Ontario. Based on these results, policy makers should target efforts aiming to increase the

utilization of generic medication on other factors which influences one's decisions to using generic medication.

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Appendix A

Analysis of the Impact of both the 2006 Transparent Drug System for Patients Act and the 2010 Ontario Drug System Reform

Further analyses were conducted to determine the impact of the 2006 Transparent Drug System for Patients Act and the 2010 Ontario Drug System Reform on the various outcome measures. One significant result was observed for the analysis regarding the monthly total cost of publicly insured antiglaucoma medication claims. Modelling both interventions through the use of a ramp function, both the 2006 and 2010 reform was associated with an increase in the monthly total cost, however, only the 2010 intervention parameter was statistically significant ($p=0.0476$). No other significant results were obtained from the analysis of the remaining outcome measures. Results from the best fitting ARIMA models are presented below.

Volume of Generic Claims

Public

Appendix A 1 Coefficient estimates from an ARIMA (1,1,2)(1,0,0)12 with a ramp intervention function for the volume of generic medication for publicly insured patients.

Model Parameter	Estimate	Standard Error	T	P-value
Moving Average, Lag 1	-0.53140	0.1889	-2.8127	0.0056
Moving Average, Lag 2	0.26519	0.0905	2.9294	0.0040
Autoregressive, Lag 1	-0.61114	0.1855	-3.2948	0.0013
Seasonal Autoregressive, Lag 12	0.36837	0.0876	4.2062	<0.0001
Ramp: October 2006	36.45401	244.4055	0.1492	0.8817
Ramp: July 2010	71.52658	341.6514	0.2094	0.8345

Private

Appendix A 2 Coefficient estimates from an ARIMA (1,1,0)(1,1,0)12 with a ramp intervention function for the volume of generic medication for privately insured patients.

Model Parameter	Estimate	Standard Error	T	P-value
Autoregressive, Lag 1	-0.13752	0.0888	-1.5490	0.1239
Seasonal Autoregressive, Lag 12	-0.52740	0.0814	-6.4786	<0.0001
Ramp: October 2006	35.40628	42.3358	0.8363	0.4045
Ramp: July 2010	11.47448	42.2359	0.2717	0.7863

Generic Percentage Dispensed

Public

Appendix A 3 Coefficient estimates from an ARIMA (1,0,3) with a ramp intervention function for the generic percentage dispensed for publicly insured patients.

Model Parameter	Estimate	Standard Error	T	P-value
Intercept	0.23945	0.0072	33.0394	<0.0001
Moving Average, Lag 1	-0.61511	0.1188	-5.1782	<0.0001
Moving Average, Lag 2	-0.13376	0.1457	-0.9181	0.3602
Moving Average, Lag 3	-0.41399	0.0901	-4.5949	<0.0001
Autoregressive, Lag 1	0.59099	0.1133	5.2148	<0.0001
Ramp: October 2006	-0.0007306	0.000371	-1.9693	0.0509
Ramp: July 2010	0.00159	0.0012	1.3771	0.1707

Private

Appendix A 4 Coefficient estimates from an ARIMA (2,1,2) with a ramp intervention function for the generic percentage dispensed for privately insured patients.

Model Parameter	Estimate	Standard Error	T	P-value
Moving Average, Lag 1	-1.50635	0.3160	-4.7670	<0.0001
Moving Average, Lag 2	-0.52467	0.3093	-1.6965	0.0921
Autoregressive, Lag 1	-1.43003	0.2825	-5.0613	<0.0001
Autoregressive, Lag 2	-0.58807	0.2181	-2.6963	0.0079
Ramp: October 2006	0.00084047	0.0018	0.4754	0.6353
Ramp: July 2010	-0.0005194	0.0028	-0.1853	0.8532

Generic Dispensing Rate

Public

Appendix A 5 Coefficient estimates from an ARIMA (1,1,2)(0,1,1)12 with a ramp intervention function for the generic dispensing rate for publicly insured patients.

Model Parameter	Estimate	Standard Error	T	P-value
Moving Average, Lag 1	-0.72789	0.1424	-5.1114	<0.0001
Moving Average, Lag 2	0.19369	0.1009	1.9198	0.0571
Seasonal Autoregressive, Lag 12	0.86526	0.1416	6.1110	<0.0001
Autoregressive, Lag 1	-0.68437	0.1220	-5.6091	<0.0001
Ramp: October 2006	-0.15685	1.8090	-0.0867	0.9310
Ramp: July 2010	1.12843	2.1573	0.5231	0.6018

Private

Appendix A 6 Coefficient estimates from an ARIMA (1,1,0)(1,1,0)12 with a ramp intervention function for the generic dispensing rate for privately insured patients.

Model Parameter	Estimate	Standard Error	T	P-value
Autoregressive, Lag 1	-0.13456	0.0890	-1.5124	0.1329
Seasonal Autoregressive, Lag 12	-0.52859	0.0800	-6.6086	<0.0001
Ramp: October 2006	0.27821	0.3371	0.8254	0.4107
Ramp: July 2010	0.08750	0.3362	0.2603	0.7951

Total Cost of Antiglaucoma Medication

Public

Appendix A 7 Coefficient estimates from an ARIMA (13,1,2) with a ramp intervention function for the total cost of claims for publicly insured patients.

Model Parameter	Estimate	Standard Error	T	P-value
Moving Average, Lag 1	0.72716	0.2365	3.0753	0.0026
Moving Average, Lag 2	-0.53079	0.1517	-3.4997	0.0006
Autoregressive, Lag 1	0.13542	0.2489	0.5441	0.5873
Autoregressive, Lag 2	-0.14724	0.1052	-1.3995	0.1641
Autoregressive, Lag 3	-0.01232	0.0902	-0.1367	0.8915
Autoregressive, Lag 4	-0.35385	0.0807	-4.3861	<0.0001
Autoregressive, Lag 5	0.20842	0.0939	2.2194	0.0282
Autoregressive, Lag 6	-0.14893	0.0913	-1.6305	0.1055
Autoregressive, Lag 7	-0.03254	0.0808	-0.4027	0.6878
Autoregressive, Lag 8	-0.25196	0.0801	-3.1475	0.0021
Autoregressive, Lag 9	0.07799	0.0910	0.8568	0.3932
Autoregressive, Lag 10	-0.23442	0.0864	-2.7140	0.0076
Autoregressive, Lag 11	0.05485	0.0859	0.6384	0.5244
Autoregressive, Lag 12	0.53650	0.0906	5.9184	<0.0001
Autoregressive, Lag 13	-0.02399	0.1935	-0.1239	0.9016
Ramp: October 2006	13896	8400	1.6542	0.1006
Ramp: July 2010	26426	13213	2.0000	0.0476

Private

Appendix A 8 Coefficient estimates from an ARIMA (2,1,2)(1,1,0)12 with a ramp intervention function for the total cost of claims for privately insured patients.

Model Parameter	Estimate	Standard Error	T	P-value
Moving Average, Lag 1	-0.63805	0.1104	-5.7782	<0.0001
Moving Average, Lag 2	-0.55208	0.1037	-5.3260	<0.0001
Autoregressive, Lag 1	-1.12467	0.0731	-15.3756	<0.0001
Autoregressive, Lag 2	-0.87176	0.0606	-14.3757	<0.0001
Seasonal Autoregressive, Lag 12	-0.42154	0.0953	-4.4253	<0.0001

Ramp: October 2006	1487	2313	0.6427	0.5216
Ramp: July 2010	2764	2329	1.1868	0.2376

Curriculum Vitae

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