Utilization of Benzodiazepines and Antipsychotics Amongst Senior Citizens in Newfoundland and Labrador

by © Zachary E.M. Giovannini-Green

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Abstract

The utilization of benzodiazepines and antipsychotics amongst senior citizens in the community and in long-term care has long been a concern for families and health care providers. The two studies presented in this thesis examined prescription patterns in seniors over sixty-five; first over time, then over geographical area. The use of benzodiazepines and antipsychotics remained stable over the three years of the study. Within the community, benzodiazepines and antipsychotics were also more prescribed in urban than rural areas. The difference in prevalence of benzodiazepine prescriptions in long-term care facilities was significant depending on the regional authority, whereas it was not significant for antipsychotic prescriptions. This research into the utilization of benzodiazepines and antipsychotics in the province is valuable because it provides a more thorough examination into utilization than has been previously undertaken in Newfoundland and Labrador.

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List of Abbreviations and Symbols

Adjusted Odds Ratio (aOR)
Anatomical Therapeutic Chemical (ATC) Classification System
Canadian Institute for Health Information (CIHI)
Canadian Medical Association (CMA)
Choosing Wisely Canada (CWC)
Chronic Disease Score (CDS)
Crude Odds Ratio (cOR)
Defined Daily Dose (DDD)
Department of Health and Community Services (DHCS)
Extrapyramidal Symptoms (EPS)
Food and Drug Administration (FDA)
Gamma-aminobutyric acid (GABA)
Guaranteed Income Supplement (GIS)
Human Research Ethics Board (HREB)
Intermediate-Acting (IA)
Long-Acting (LA)
Long-Term Care (LTC)
Medical Care Plan (MCP)
Neuroleptic Malignant Syndrome (NMS)
Newfoundland and Labrador Centre for Applied Health Research (NLCAHR)
Newfoundland and Labrador Centre for Health Information (NLCHI)
Newfoundland and Labrador Prescription Drug Program (NLPDP)
Newfoundland and Labrador Medical Association (NLMA)
Old Age Security (OAS)
Obsessive Compulsive Disorder (OCD)
Post-Traumatic Stress Disorder (PTSD)
Regional Health Authority (RHA)
Short-Acting (SA)
World Health Organization (WHO)

Chapter 1

Introduction

1.1 BACKGROUND

Concern has been expressed by both clinicians and researchers regarding the prescription patterns of benzodiazepines and antipsychotics to senior citizens living both in the community and in long-term care (Smith et al., 2008). Seniors are living longer today than before and this is being facilitated (at least in part) by the advances in medicine. However, these advances have also led to the proliferation of prescription drugs in the country. This phenomenon has been documented for psychoactive drugs in all age groups including seniors (Verdoux et al., 2010). An increase in prescription drugs is particularly worrying for seniors due to their advanced age and inherent frailty. This has resulted in multiple organizations such as Health Canada and the Canadian Institute for Health Information (CIHI) publishing several warnings about the serious negative effects that result from the prescription of these drugs to the elderly (Health Canada, 2012; Government of Canada, 2014; CIHI, 2014).

A number of studies have been conducted in North America to study the epidemiology of the prescription of benzodiazepines and antipsychotics, which comprise two classes of psychoactive drugs. An American study of over 12,000 nursing home residents found that of the 13% taking benzodiazepines, 42% had no appropriate indication for the prescription (Stevenson et al., 2010). A Quebec study of

pharmaceutical records by Préville et al. (2012) found that of the 2,320 seniors studied, 48% received a potentially inappropriate prescription of benzodiazepines.

Chen et al. (2010) found that 30% of American facility-dwelling residents received prescriptions for antipsychotics. Of these, 32% had no appropriate indication for receiving their prescription. In government run long-term care facilities in Canada, 23.9% of seniors receiving antipsychotics had no appropriate diagnosis to warrant the prescription according to the 2017 information released by CIHI. By comparison, the rate for public long-term care facilities in Newfoundland and Labrador has been estimated to be 37.5% (CIHI, 2017).

Seniors constitute a demographic separate from middle-aged adults due to their often complex healthcare needs and altered response to medications, the latter due to a changing physiology. On average, seniors require more medical treatment than any other segment of the population. In 2008, Canadians 65 years and over made up 44% of healthcare spending but only 14% of the population (CIHI, 2010). According to the Canadian Medical Association (CMA), Canadians over 65 are more likely visit family physicians, visit hospitals, and stay on average 1.5 times longer in hospitals per visit than non-senior adults. Additionally, seniors are prescribed significantly more medications than younger adults with polypharmacy being an issue. A Canadian study of 3,132 community dwelling seniors found that 27% regularly took five or more medications concurrently. Of these, 12% required medical attention for adverse reaction caused by their medications in the past twelve months (Reason et al., 2012). However, few clinical drug studies include seniors due to their relatively frail physical condition and the increased risk of mortality (Luo et al., 2016).

Importantly, seniors are at higher risk of adverse effects than younger adults because of changes in their physiology, leading to altered pharmacokinetics of their medications. These differences cover three major areas: distribution, hepatic metabolism, and renal elimination (Ruscin & Linnebur, 2017). First, because body fat percentage increases significantly with age, the elimination half-life of lipophilic drugs tends to increase, increasing the amount of drug stored in the fat cells of the body. Second, hepatic metabolism (primarily phase I metabolism) in the elderly can decrease up to 40% with age, leading to a build-up of the drug in the system and increasing the risk of adverse effects. For this reason drugs that are metabolized via phase II metabolism or conjugation (such as lorazepam and oxazepam) are preferred for the treatment of elderly patients. Third, renal elimination of drugs decreases with age in the elderly, also causing the buildup of the drug in the system. The total amount of drug excreted renally varies widely depending on the specific agent and should be taken into account when prescribing.

Seniors are more susceptible to adverse drug effects in clinical drug trial studies (Luo et al., 2016). Typically however, patients in the older age groups are excluded from clinical trials, therefore we know less about how medications may affect them. Given the high potential for adverse effects and the fact that seniors comprise such a high proportion of healthcare spending every year, extreme diligence is required in monitoring and inquiring about adverse drug reactions. One way to improve the monitoring of commonly prescribed and high risk medications for seniors is to study their utilization patterns both in the community and long-term care settings.

1.2 SENIORS IN NEWFOUNDLAND AND LABRADOR

Unlike other provinces in Canada with a high proportion of urban residents, Newfoundland and Labrador has a large proportion of its citizens living in rural communities (Statistics Canada, 2011). A rural community is defined as having a population of less than 1,000 people and a population density of less than 400 people per square kilometre (Statistics Canada, 2011). Using this definition, 41% of Newfoundlanders and Labradorians live in rural communities according to the 2011 census. Compared to the three other Atlantic provinces, Newfoundland and Labrador has the lowest proportion of rural dwelling residents (with New Brunswick, Prince Edward Island, and Nova Scotia ranging from 43% to 53%). The prevalence of rural dwelling is still much higher than Ontario where only 14% of the population lives in rural areas (Statistics Canada, 2011).

Newfoundland and Labrador also has one of the oldest populations in the country. According to 2016 data from Stats Canada, 19% of the province's population is over the age of 65 as compared to the national average of 16.8%. Senior citizens in Newfoundland and Labrador who receive old age security (OAS) and the guaranteed income supplement (GIS) are eligible to have most of their prescription costs covered by the Newfoundland and Labrador Prescription Drug Program (NLPDP). Since approximately 80% of seniors use this program, the NLPDP is an important way of monitoring the prescription of drugs to seniors (Department of Health and Community Services, 2017).

Seniors living in long-term care facilities comprise a specific portion of the total demographic of seniors, being on average older and in need of more advanced care (DHCS, 2017). Long-term care facilities are provincially operated care homes in

Newfoundland and Labrador which can operate at one or more of four levels. Each level increasing from one through four indicates an increase in the needs and requirements of residents in that level of care. For example, residents in facilities with level three and level four care require ongoing supervision from medical staff due to their advanced and complex needs(Western Health, 2016). There are currently 37 long-term care facilities in the province that are run by the provincial Department of Health and Community Services of which 19 are in Eastern Health, 11 are in Central Health, four are in Western Health, and three are in Labrador-Grenfell Health (DHCS, 2017).

1.3 BENZODIAZEPINE USE IN SENIORS

1.3.1 Overview of Benzodiazepines

Benzodiazepines are a group of drugs designed to suppress the nervous system and are officially indicated by Health Canada for use to treat a number of conditions such as anxiety and panic disorders, insomnia, seizures, muscle spasms, alcohol withdrawal, and to sedate hospital patients prior to surgery (CPhA, 2017; Bandelow et al., 2014; Schutte-Rodin et al., 2008). Benzodiazepines also continue to be used without Health Canada approval to treat other conditions such as agitation, restless leg syndrome, obsessive compulsive disorder (OCD) and post-traumatic stress disorder (PTSD) (van Ameringen et al., 2014; Mellman et al., 2002).

Benzodiazepines are classified as depressants, which affect the central nervous system of the body via the neurotransmitter gamma-aminobutyric acid (GABA) (Government of Canada, 2014). Benzodiazepines were originally developed in 1955 and

first introduced in 1960 as an anti-anxiety medication, or anxiolytic. They were introduced to the market in order to replace another anxiolytic group of drugs, the barbiturates, due to the latter's high risk of death when taken in overdose. Beginning in the 1970s, the prescription of benzodiazepines became widespread. For a list of benzodiazepines prescribed in Canada, please see Table 1.1.

1.3.2 Epidemiology of Benzodiazepine Use in Canada

One of the first studies of the utilization of benzodiazepines in Canada was performed by Busto et al. (1989). The study involved patients admitted to the Clinical Institute of the Addiction Research Foundation in Toronto for the years between 1978 and 1987. According to the authors, the utilization of benzodiazepines remained steady for the first five years at 33 standard units per 1,000 people per day but after 1983 steadily increased reaching 48 units per 1,000 people per day by 1987.

In more recent years, use of benzodiazepines in community dwelling seniors has decreased from the rates seen in previous decades. A Quebec study by Egan et al. (2000) studying 1,423 seniors for a 180 day period found a 19.8% prevalence of benzodiazepine use. A similar study in Ontario followed over one million seniors for five years from 1993 to 1998. It was found that prevalence of seniors receiving benzodiazepines decreased over time from 25.1% to 22.5% (Tu et al., 2001). Finally, a study from Manitoba analyzed the cross sectional data of between 154,890 and176,498 seniors for a sixteen year period from 1996 to 2012 (Alessi-Severini et al., 2014).

A lesser degree of research has been done on the prevalence of benzodiazepine research in long-term care facilities, however difference across the country become

apparent. An Ontario retrospective cohort study of 57,504 residents living in long-term care found that 38% percent of new entrants to long-term care received at least one benzodiazepine prescription (Bronskill et al., 2013). Of these, 49% were given at least a further two prescriptions in a twelve month period, totalling at least 100 pills. A study from Alberta (Hagen et al., 2015) examined the records of 2,443 long-term care residents for a twelve month period. These residents lived in 24 different facilities (ten urban and fourteen rural) and it was found that the prevalence of benzodiazepine prescription in the urban facilities was higher than in the rural facilities (15.7% versus 7.6%).

Research has also been conducted to measure the strength of the dose administered to seniors in Canada. Bartlett et al. (2004) followed 78,367 community dwelling seniors in Quebec for five years from 1989 to 1994. The authors found that the average uninterrupted usage of benzodiazepines was 75.5 days and that the seniors in the study received on average approximately half of the dosage usually recommended for adults.

Not all provinces, however, are experiencing a decrease in benzodiazepine use. As mentioned earlier in this paper, Newfoundland and Labrador has the highest proportion of seniors in Canada. A report commissioned in 2003 by the Newfoundland and Labrador Centre for Applied Health Research (NLCAHR) describes prescription drug use in Newfoundland and Labrador for 1999 including benzodiazepines (NLCAHR, 2003). It was found that benzodiazepines were in the top five drug classes prescribed to people in the province, making up 7.6% of total prescriptions. Lorazepam was also in the top ten individual agents prescribed, making up 1.8% of total prescriptions. Finally, benzodiazepine prescription was highest in the Western Health Regional Health Authority

(RHA), followed by the Eastern and Central Health authorities. While the report specifies the use of benzodiazepines by health region, it does not distinguish between urban and rural areas, nor does it capture changes over time. In addition, there is no information provided about dosage of the drugs in question.

The other Atlantic provinces display a similar demographic distribution to Newfoundland and Labrador (Statistics Canada, 2016); that is they have a higher percentage of both senior citizens and total residents living in rural areas. This may contribute to a difference observed in the trend of benzodiazepine use in this area. Smith et al. (2008) found that the prevalence of seniors in Nova Scotia receiving benzodiazepines increased from 123 DDDs per 1,000 people per day in 2000 to 138 DDDs per 1,000 people per day in 2003.

1.3.3 Adverse Effects of Benzodiazepines

More common adverse effects of benzodiazepines include dizziness, drowsiness and fatigue, muscle weakness, and slowed reaction times. Less common but more severe side effects include heart palpitations, racing heart beat (tachycardia), memory impairment, depression, muscle spasms, and seizures. Alcohol should be avoided while taking benzodiazepines as both depress the central nervous system and can cause loss of consciousness, respiratory failure, and death if used together (Canadian Pharmacists Association, 2017). While the sedative effects of benzodiazepines can cause a person to fall asleep, prolonged use has been demonstrated to worsen overall sleep quality (Poyares et al., 2004).

As previously mentioned, seniors have proven to be more susceptible to all adverse effects of medications including benzodiazepines. Symptoms of benzodiazepine use consistently recorded in seniors include cognitive impairment (Bogunovic & Greenfield, 2004), falls and fractures (van Strien et al., 2013), motor vehicle accidents (Thomas, 1998), and delirium (Alagiakrishnan & Wiens, 2004).

A concern for the long-term use of benzodiazepines is dependency. Dependency usually occurs only when benzodiazepine use significantly exceeds the recommended two to four weeks prescription (Greenblatt & Shader, 1978). Dependency can either be physical or psychological, the distinction being that physical dependence provokes "objective changes" in physiology while psychological dependence creates strong cravings but no physical symptoms. Dependency is usually associated with an increased tolerance of the drug requiring an increasing dose, thereby proportionally increasing the risk of adverse effects (Greenblatt & Shader, 1978).

Use of short-acting benzodiazepines such as lorazepam (Ativan), as opposed to long-acting benzodiazepines, have been shown to significantly decrease the time it takes to develop either physical or psychological dependence (Nelson & Chouinard, 1999). Discontinuation of benzodiazepines after long-term use may result in withdrawal symptoms. These may include recurrence of symptoms that caused the prescription of benzodiazepines in the first place such as insomnia, anxiety and panic attacks, as well as headaches and muscle stiffness. Abrupt discontinuation of benzodiazepine treatment can lead to severe reactions such as seizures, delirium tremens, and coma (Péturrson, 1994).

Despite the seeming lack of consistency there are in fact guidelines for the prescription of benzodiazepines that have been in place for some time. The World Health

Organization (WHO, 1996) published an extensive document that explained in detail the precautions that should be taken when prescribing benzodiazepines (WHO, 1996). Within Canada, provincial medical associations have also issued their own guidelines (CPSA, 2015). Based on evidence gathered, Choosing Wisely Canada has also issued recommendations to not use benzodiazepines in seniors as first line therapies for insomnia, agitation, or delirium (CWC, 2017). The Canadian Deprescribing Network has also published guidelines to assess appropriateness of benzodiazepine use and has algorithms to aid in reducing the dose or stopping their use (Canadian Deprescribing Network, 2016).

1.4 ANTIPSYCOTIC USE IN SENIORS

1.4.1 Overview of Antipsychotics

Antipsychotics are a class of medication used to treat psychosis, a severe mental disorder in which thoughts and emotions become impaired to the point that contact is lost with external reality. These medications are officially recommended by Health Canada for the treatment of schizophrenia and related disorders, as well as psychotic symptoms in bipolar disorder. Antipsychotics can also be used to treat severe non-responsive cases of major depressive disorder and Tourette's syndrome (CAMH, 2012). Antipsychotics are used off label to treat a host of other psychiatric conditions including obsessive-compulsive disorder, post-traumatic stress disorder, anorexia, and insomnia (Baylor College of Medicine, 2012).

Health Canada currently has a black box warning in place for antipsychotic prescription to seniors with dementia, indicating that their use is associated with a significantly increased risk of death (Health Canada, 2012). Risperidone (brand name Risperdal) is the only antipsychotic officially indicated by Health Canada to treat severe and acute dementia-related agitation and aggression in seniors and is approved for short-term use only (Health Canada, 2012). Despite this, antipsychotic prescription has become increasingly common in the treatment of seniors with other behavioural issues stemming from dementia such as wandering or calling out, neither of which are appropriate symptoms warranting treatment with antipsychotics. This trend should be of concern to policy makers as seniors are at a higher risk than the general population of serious adverse effects from antipsychotic use (Jašović-Gašić et al., 2012).

Antipsychotics were discovered and subsequently came into use starting in the 1950s. This group of drugs were later referred to as first generation or typical antipsychotics. It was discovered early on that typical antipsychotics caused a variety of adverse effects including severe movement disorders including muscle spasms, rigidity, and tremors. Collectively, these disorders are referred to as extrapyramidal symptoms (EPS) (Meyer & Simpson, 1997). Researchers soon began to search for an alternative to the medications that were causing such severe and debilitating adverse effects. Clinical testing began for what was supposed to be an alternative to the typical antipsychotic, the second generation or atypical antipsychotic. In 1990, the first atypical antipsychotic (clozapine) was approved by the FDA for general use in the United States. Since that time, the prescription and number of atypical antipsychotic agents has increased

dramatically due at least in part to the purportedly decreased risk of EPS that they offer (Shen, 1999). For a list of antipsychotics prescribed in Canada, please see Table 1.2.

1.4.2 Epidemiology of Antipsychotic Use in Canada

The rate of antipsychotic prescription in long-term care facilities across Canada has been repeatedly been identified as a serious problem. Though national utilization rates have dropped from 32% to 24% in the past four years, there is still work to be done. Nearly a quarter (23.9%) of Canadian seniors in long-term care for the 2015-2016 year were receiving antipsychotics with no appropriate diagnosis to warrant their use (CIHI, 2017). Antipsychotic prescriptions have been linked in the literature to a number of demographic factors including female sex, older age, and lower income (Sivanthan et al., 2015). In the long-term care setting, behavioural problems, conflicts with staff members and family, as well as social isolation were also all significantly correlated with the prescription of antipsychotics (Foebel et al., 2015).

A study by Hagen et al. (2006) examined two Canadian long-term care facilities (N=289) where residents in one facility (N=178) moved facilities and residents in the other (N=111) remained. Prevalence of antipsychotic prescriptions was measured in both facilities before, during, and after the move for one set of residents. Prevalence of antipsychotic use remained relatively stable in the "remain" facility (between 30.3% and 33.1%, p=0.88). On the other hand, prevalence in the "move" facility rose at every measure from 21.5% to 32.6% to 36.9% (p=0.002).

An Ontario study by Rochon et al. (2007) collected data on 47,322 residents from 485 different provincially regulated facilities during the month of December 2003. The

authors organized these facilities into quintiles according the prevalence of antipsychotic prescription. Out of the total number of residents, 15,317 (32.4%) received antipsychotics. The average within the quintiles ranged from 20.9% to 44.3% indicating a significant difference ($p>0.005$). These studies are troubling given the serious adverse effects that can occur when seniors are prescribed antipsychotics without careful consideration.

1.4.3 Adverse Effects of Antipsychotics

Both typical and atypical antipsychotics have been associated with serious adverse effects. However, since the two generations differ significantly from each other the adverse effects are also different. More common adverse effects of typical antipsychotics include a lengthening of the QT interval which increases the risk of an irregular heartbeat. Other common adverse effects include dry mouth, constipation and urinary retention, weight gain, hyperglycemia and sexual dysfunction (Muench & Hamer, 2010). Less common adverse effects of typical antipsychotics include blurred vision, rashes, alopecia, nausea and vomiting, jaundice, and hypertension. More serious effects include tachycardia, cardiac arrest and sudden cardiac death. The most noticeable of adverse effects from typical antipsychotics are EPS that affect the central nervous systems. Common types of EPS are muscle spasms (dystonia), motor restlessness (akathesia), muscle rigidity (parkinsonism), and jerky, irregular motions (tardive dyskinesia) (Beaumont, 2000). A major concern with typical antipsychotics is neuroleptic malignant syndrome (NMS), a potentially fatal condition which causes muscle rigidity, fever,

fluctuating blood pressure and pulse as well as changing levels of consciousness (CPhA, 2017).

Atypical antipsychotics were developed specifically to decrease the risk of EPS but other adverse effects are still a risk in those taking them, particularly seniors. Common adverse effects when taking atypical antipsychotics include dry mouth, constipation and urinary retention, hypotension, seizures, sedation and weight gain. Less common adverse effects include a prolonged QT interval and an increased risk of type 2 diabetes (Muench & Hamer, 2010). Atypical antipsychotic use amongst both community and facility dwelling seniors has also been shown to significantly increase the risk of potentially fatal pneumonia (Stephenson, 2010). Interestingly enough, studies comparing typical and atypical antipsychotics have shown that although atypicals show a significantly reduced risk of extrapyramidal symptoms in seniors, the risk of falls in seniors does not significantly decrease (Hien et al, 2005).

Choosing Wisely Canada has recently released a toolkit to aid long-term care facilities in the proper and effective use of antipsychotics (CWC, 2017). The toolkit includes several suggestions to reduce antipsychotic prescriptions: 1) Create an interdisciplinary team of professionals to review residents who are receiving antipsychotics, 2) Agree on which symptoms require antipsychotic prescription (e.g. psychotic symptoms, physical aggression), and which do not (wandering, insomnia), 3) Whenever possible prescribe only one antipsychotic and in the lowest effective dose, tapering the dose off as quickly as possible, and 4) Train facility staff to recognize factors that may be causing certain behaviours in seniors (e.g. tiredness, depression, stress) and find ways to solve these problems without pharmacological intervention.

1.5 STUDY OBJECTIVES

This thesis will address a gap in the knowledge concerning the way benzodiazepines and antipsychotics are prescribed in Newfoundland and Labrador. This thesis can be described by a primary research question: What are the patterns of use over time and across geographic regions for antipsychotics and benzodiazepines in senior citizens living in long-term care and the community in Newfoundland and Labrador? In order to implement an effective intervention, it is critical to first have an accurate and detailed understanding of the current utilization of benzodiazepines and antipsychotics in the province. The thesis objectives will be accomplished by conducting two different studies, each of which address specific aspects of drug utilization.

The first study will examine patterns of utilization for benzodiazepines and antipsychotics over a period of three years from 2011 to 2014. The objective of this study is to answer the following question: What differences appear, if any, when utilization of benzodiazepine and antipsychotic prescriptions are studied over time in community and facility dwelling seniors in the province? It will describe patterns for both community and long-term care dwelling seniors who are eligible for public drug insurance in the province.

The second study will compare variations of utilization of antipsychotic and benzodiazepine medications as they occur depending on geographic location. The objective of this study is to answer the following question: What patterns appear when comparing utilization of benzodiazepine and antipsychotic prescriptions across geographic areas? Community dwelling seniors will be compared on the basis of whether they live in an urban or rural area. Residents living in long-term care facilities will be

categorized by the regional health authority (RHA) in which they reside, as well as at the facility level.

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Table 1.1: List of Benzodiazepine Agents with Common Doses and Half Lives

Sub Class	Agent	Common Dose*	Half Life**
Anticonvulsant	Clonazepam	8 mg	20-50 hrs (LA)
Anxiolytics	Diazepam	10 mg	20-100 hrs (LA)
	Chlordiazepoxide	30 mg	30-100 hrs (LA)
	Oxazepam	50 mg	5-15 hrs (SA)
	Potassium Clorazepate	20 mg	20-100 hrs (LA)
	Lorazepam	2.5 mg	10-20 hrs (IA)
	Bromazepam	10 mg	12-20 hrs (IA)
	Clobazam	20 mg	71-82 hrs (LA)
	Alprazolam	1 mg	6-26 hrs (SA)
Sedative/Hypnotics	Flurazepam	30 mg	40-100 hrs (LA)
	Nitrazepam	5 mg	16-38 hrs (IA)
	Triazolam	0.25 mg	2-5 hrs (SA)
	Temazepam	20 mg	10-20 hrs (IA)

*Common doses taken from WHO website (WHO, 2016)
**Half-life information taken from RxTx website (RxTx, 2018)

LA=long acting
IA=intermediate acting
SA=short acting

N.B.: Half-life may vary significantly depending on age of the patient as well as the route of administration (oral versus injection)

Table 1.2: List of Antipsychotic Agents with Common Doses and Half Lives

Sub Class	Agent	Common Dose*	Half Life**
Typical	Chlorpromazine	300 mg	~30 hrs
	Levomepromazine	300 mg	~20 hrs
	Perphenazine	30 mg	8-12 hrs
	Prochlorperazine	100 mg	4-8 hrs
	Trifluoperazine	20 mg	10-20 hrs
	Periciazine	50 mg	~12 hrs
	Haloperidol	8 mg	14-36 hrs
	Flupentixol	6 mg	~35 hrs
	Zuclopenthixol	30 mg	~20 hrs
Atypical	Ziprasidone	80 mg	7-10 hrs
	Clozapine	300 mg	6-26 hrs
	Olanzapine	10 mg	30-60 hrs
	Quetiapine	400 mg	7-12 hrs
	Risperidone	5 mg	~20 hrs
	Aripiprazole	15 mg	~75 hrs

*Common doses taken from WHO website (WHO, 2016)
**Half-life information taken from RxTx website (RxTx, 2018)

N.B.: Half-life may vary significantly depending on age of the patient as well as the route of administration (oral versus injection)

Chapter 2

Time-trends in the Utilization of Antipsychotic and Benzodiazepine Prescribing in Newfoundland and Labrador

2.1 INTRODUCTION

2.1.1 Background

Seniors constitute one of the most vulnerable demographics in our society due to factors such as higher rates of serious chronic disease, loss of independence, and lower incomes. The utilization of both benzodiazepines and antipsychotics has come under scrutiny in Canada and in other parts of the world, particularly for their use in the senior population and potential for adverse effects. Both benzodiazepines and antipsychotics are listed as potentially inappropriate medication classes in the updated Beer's list and STOPP/START criteria, as they increase the risk of serious side effects in seniors (American Geriatrics Society, 2015; Pharmacist's Letter/Prescriber's Letter, 2011). Specifically, benzodiazepines increase the risk of cognitive impairments (Edelstein et al., 2014), falls and fractures (Smith et al., 2008), delirium (Alagiakrishnan & Wiens, 2004), and motor vehicle accidents (Thomas, 1998). Moreover, benzodiazepine users often develop dependence (Cunningham et al., 2010) and the risk of side effects may be exacerbated when the drugs are taken long-term (Huybrechts et al., 2011; Bartlett et al., 2009). Similarly, seniors are sensitive to the adverse effects of antipsychotics, which increase the risks of cerebrovascular events (Vasilyeva et al., 2013), hip fractures (Pratt et

al., 2012), bacterial infections (Huybrechts et al., 2012), and all-cause mortality (Verdoux et al., 2010).

Despite the documented side effects, the proportion of seniors in the general population taking psychoactive medications over the last few decades has increased in the developed world (Verdoux et al., 2010; Smith et al., 2008). Benzodiazepines and antipsychotics continue to be used in both the community and long-term care settings in Canada's senior population. Benzodiazepines and antipsychotics are most prevalent in long-term care facilities where they are often used as the cheapest and most efficient way to manage behavioural issues in residents (Jašović-Gašić et al., 2012).

According to Canadian Institute for Health Information (CIHI) research in five different provinces, benzodiazepines and antipsychotics are used by approximately 22% and 5% respectively of seniors in the community (CIHI, 2012). In long-term care, a major concern is the use of antipsychotics which was reported to be on average 39% nationwide in 2014 (CIHI, 2016). CIHI estimates that 37.5% of seniors living in Newfoundland and Labrador who are receiving antipsychotic medication have not been diagnosed with psychosis, the main indication for its use. This is in comparison with the Canadian average of 23.9% (CIHI, 2017).

2.1.2 Purpose of Study and Objectives

To further understand the trends of use over time at a population level, this study investigated the utilization of benzodiazepines and antipsychotics among senior citizens using public drug coverage in Newfoundland and Labrador.

2.2 METHODS

2.2.1 Population and Inclusion/Exclusion Criteria

The population for this study comprised all senior citizens age 65 years and older living in Newfoundland and Labrador (NL) who received publically funded drug coverage between April 1st, 2011 and March 31st, 2014 under the provincial prescription drug program (NLPDP). Individuals were categorized as either living in the community or in long-term care facilities. For the long-term care setting, only facilities funded by the province were included in the analysis. Individuals were excluded from the study if they spent longer than 7 days outside long term care facilities while being transferred, if their demographic information was missing, or if their registered postal code was from outside the province. This project has been approved by the Health Research Ethics Board (HREB #2016.324).

2.2.2 Data Sources

All data linkages were performed at the Newfoundland and Labrador Centre for Health Information (NLCHI) and data was de-identified before being released. Data linkage was required to amalgamate information from the following three databases:

1) The Provincial Client Registry, which contains personal demographic information such as Medical Care Plan (MCP) number, sex, month and year of birth, and postal code.
2) The Newfoundland and Labrador Prescription Drug Plan (NLPDP) database, containing prescription records for individuals who receive Old Age Security (OAS) benefits and the Guaranteed Income Supplement (GIS) (Department of

Health and Community Services, 2017). Approximately 80% of the total populations of seniors 65 years and older in the province are eligible for NLPDP coverage. The NLPDP claims database contains typical administrative prescription data such as the drug dispensed, date of dispensation, drug dosage, quantity dispensed, and days' supply. Benzodiazepines and antipsychotics studied were identified by their Anatomical Therapeutic Chemical (ATC) code (for example, all ATC codes for psychoactive medications begin the letter N) (See Appendices 4.1 and 4.2).

3) The Long-Term Care (LTC) Module of the Provincial Meditech database which contains a list of seniors living in long-term care facilities along with admission and discharge dates.

2.2.3 Measuring Drug Utilization

Three different methods were used to measure drug utilization over time for seniors living in Newfoundland and Labrador. In addition, the prescription of each individual agent was analyzed to determine any patterns in terms of use. The three methods applied for this analysis were as follows:

1) The prevalence of benzodiazepines, antipsychotics, and concurrent use of both drug classes was calculated as the ratio of the total number of users per quarter for each drug class of interest to the total number of NLPDP beneficiaries per quarter. The primary definition of a benzodiazepine or antipsychotic user was an individual dispensed two or more prescriptions per quarter for the drug of interest.

2) The rate of prescription records per 1,000 was calculated by the ratio of the total number of benzodiazepine or antipsychotic prescriptions to the total number of prescriptions per quarter. Only paid prescription claims were included in the calculations.
3) To account for differences in drug quantities and doses the total number of defined daily doses (DDDs) per quarter per drug was calculated. A DDD is defined by the World Health Organization (WHO) as the "assumed average dose per day of a drug in adults, as prescribed for its main indication" (WHO Collaborating Centre for Drug Statistics Methodology, 2009). The total DDD measures the relative volume of each prescription and is calculated by multiplying the strength of the dose by the number of days' supply and dividing by one DDD. DDD is commonly reported as DDD per 1,000 persons per day, this measurement taking into account the length of the prescription in days.

2.2.4 Statistical Analysis

All analyses were conducted separately for seniors living in the community and those in long-term care facilities. Mean and standard deviation as well as number and frequency were used to summarize the study population for continuous and categorical variables respectively. Due to the longitudinal nature of the study, each of the patients was measured repeatedly during the study period with the units of comparison being quarters. These measurements are therefore not independent from each other, which violates the assumption of independence. This correlation is addressed by the

Generalized Estimating Equation (GEE) technique. Appropriate link functions were used for prevalence by person (logit link function), rate of prescription (log link function), and volume of prescription (identify link function). Age, sex, and chronic disease score were included as covariates in each model. The chronic disease score (CDS) is a prescription based comorbidity score whereby individuals are given one point per drug class up to a total of 24 points. A higher chronic disease score is associated with an increased risk of one year all-cause hospitalization and mortality (Lix et al., 2016). An autoregressive autocorrelation structure was used for all GEE models. All models were tested for usual assumptions such as linearity and homoscedasticity with no violations being found. As with other methods, results are considered statistically significant if the p-value is less than 0.05.

A series of additional analyses were conducted to test the robustness of the results on the definition of drug users. Specifically, a distinction was made between two types of drug user: 1) Those receiving at least two prescriptions per quarter, and 2) "Chronic drug users" defined as those receiving two or more prescriptions per quarter for two or more quarters. All statistical analyses were conducted using SPSS, version 23.

2.3 RESULTS

2.3.1 Overview

Out of the original 53,746 seniors in the database, a total of 1,028 seniors were excluded from the analysis. There were a total of 4,966,944 prescriptions dispensed to 52,718 individuals within the study period. Of these, 49,875 (94.6%) lived in the

community and were dispensed 4,579,704 prescriptions. The median age for seniors in the community was 73 years, 43% of them were male, median CDS was four (Table 2.1). Each senior received on average nine prescriptions per quarter for an average of ten quarters. There were 2,843 (5.4%) seniors within long-term care facilities who were dispensed a total of 388,240 (7.8%) prescriptions. The median age for seniors in long-term care was 84 years, 31% were male, median CDS was five (Table 2.2). Each senior received on average 24 prescriptions per quarter for an average of six quarters. The majority of prescriptions for both drug classes in were issued for one month in the community and in long-term care (See Appendices 2.1-2.4).

2.3.2 Benzodiazepine Prescriptions in the Community

In the community 15,455 of the 49,875 seniors (31.0%) in the database received at least one prescription for benzodiazepines within the three year period. Despite being statistically significant ($p<0.001$), there was minimal change over time (OR=0.990; 95%CI=0.987,0.992). There were a total of 221,405 benzodiazepine prescriptions written, and 10,665 seniors (21.4%) received two or more benzodiazepine prescriptions per quarter (Table 2.3). The median age for seniors taking benzodiazepines was 74 years and males made up 3,467 (or 32.5%) of seniors. Over the series of twelve quarters, between 20.8% and 22.4% of seniors were prescribed two or more benzodiazepines per quarter (Figure 2.1). Of these, each senior received on average three prescriptions for benzodiazepines per quarter for an average of seven quarters out of twelve. Of the total number of seniors in the community, 7,863 (15.8%) were chronic benzodiazepine users. The prescribing rate for benzodiazepines in the community ranged from 47 to 49 with an

average of 48 prescriptions per 1,000 total prescriptions (Figure 2.2) and there was minimal change over time (p=0.09). The total number of DDDs for benzodiazepine prescriptions was 5,521,747. The number of DDDs/1,000 people/day over the twelve quarters was between 130 and 135 with an average of 132 (Figure 2.3). Despite being statistically significant (p<0.001), there was minimal change in the DDD scores of benzodiazepine prescriptions over time (B=-0.166, 95CI=-0.210,-0.121).

Table 2.3 reports the use of individual benzodiazepine agents in the community. The intermediate-acting benzodiazepine lorazepam was the most commonly prescribed of the individual agents (5,932 seniors or an average of 55.6%), followed by temazepam (2,153 seniors or an average of 20.2%) (Appendix 1.1). The most commonly prescribed short-acting benzodiazepine was oxazepam, being prescribed to 1,047 seniors (or an average of 9.8%). For lorazepam, the total DDD over the three year period was 1,870,196. The DDDs/1,000 people/day over the twelve quarters was between 51 and 55 with an average score of 52 (Appendix 1.2). For temazepam, the total DDD over the three year period was 1,425,386. The DDDs/1,000 people/day over the twelve quarters was between 27 and 30 with an average score of 29. For oxazepam, the total DDD over the three year period was 253,373. The DDDs/1,000 people/day over the twelve quarters was between seven and nine with an average score of eight.

2.3.3 Benzodiazepine Prescriptions in Long-Term Care

In long-term care 1,486 of the 2,843 seniors (52.2%) in the database received a prescription for benzodiazepines within the three year period. There was no significant change in prevalence over time (p=0.198). There were a total of 17,301 benzodiazepine

prescriptions written, and 1,046 seniors (36.8%) received two or more benzodiazepines per quarter (Table 2.4). Of the 1,046 seniors, males made up 304 (29.1%) and the median age was 83 years. Over the series of twelve quarters between 30.3% and 39.4% received two or more benzodiazepine prescriptions per quarter (See Figure 2.4). On average each senior received four prescriptions for benzodiazepines per quarter for four consecutive quarters. Finally, of the total number of seniors in long-term care, 743 (26.1%) were chronic benzodiazepine users. The prescribing rate for benzodiazepines in long-term care was between 42 and 47 with an average of 45 per thousand total prescriptions (Figure 2.5) and was stable over time (p=0.296). The total number of DDDs for benzodiazepine prescriptions was 398,971. The number of DDDs/1,000 people/day over the twelve quarters was between 160 and 207 and was stable over time (p=0.923) with an average DDD score of 192 (Figure 2.6).

Similar to the community, lorazepam was the most commonly prescribed of the individual agents (760 seniors or 72.7%), followed by temazepam (207 seniors or 19.8%) taking benzodiazepines twice or more per quarter (Appendix 1.5). The most commonly prescribed short-acting benzodiazepine was oxazepam, being prescribed to 121 seniors or 11.6% of those taking benzodiazepines (Table 2.4). For lorazepam, the total DDD over the three year period was 161,775. The DDDs/1,000 people/day over the twelve quarters was between 92 and 119 with an average score of 111 (Appendix 1.6). For temazepam, the total DDD over the three year period was 125,987. The DDDs/1,000 people/day over the twelve quarters was between 39 and 53 with an average score of 48. For oxazepam, the total DDD over the three year period was 25,217. The DDDs/1,000 people/day over the twelve quarters was between ten and twenty-two with an average score of fifteen.

2.3.4 Antipsychotic Prescriptions in the Community

In the community 3,066 of the 49,875 seniors (6.1%) in the database received a prescription for antipsychotics within the three year period. Despite being statistically significant ($p<0.001$), there was minimal change over time (OR=0.984; 95%CI=0.978,0.989). There were a total of 57,136 antipsychotic prescriptions written, of which 2,321 of seniors (4.7%) received two or more antipsychotics per quarter (Table 2.3). The median age for seniors taking antipsychotics was 76 years and 912 (of 39.3%) were male. Over the series of twelve quarters, between 4.4% and 5.0% of seniors were prescribed two or more antipsychotics per quarter (See Figure 2.1). On average each senior received four antipsychotic prescriptions per quarter for five consecutive quarters. Finally, of the total number of seniors in the community, 1,851 (3.7%) were chronic antipsychotic users. The prescribing rate for antipsychotics ranged between twelve and thirteen with an average of twelve prescriptions per 1,000 total prescriptions (Figure 2.2), which remained stable over time ($p=0.320$). The total number of DDDs for antipsychotic prescriptions was 442,248. The DDDs/1,000 people/day over the twelve quarters was between twelve and thirteen with an average of thirteen (Figure 2.3). Despite being statistically significant ($p=0.001$), there was minimal change in the DDDs of antipsychotic prescriptions over time (B=-0.147, 95CI=-0.236,-0.058).

Table 2.3 reports the use of individual antipsychotic agents in the community. The atypical antipsychotic quetiapine was the most commonly prescribed of the individual agents (1,455 seniors or 62.7% of antipsychotic users), followed by risperidone (611 seniors or 26.3% of antipsychotic users) (Appendix 1.3). For quetiapine, the total DDD over the three year period was 206,006. The DDDs/1,000 people/day over twelve

quarters was between two and three with an average score of two (Appendix 1.4). For risperidone, the total DDD over the three year period was 86,002. The DDDs/1,000 people/day over twelve quarters remained at a score of one.

2.3.5 Antipsychotic Prescriptions in Long-Term Care

In long-term care, 1,273 of the 2,843 seniors (44.8%) in the database received a prescription for antipsychotics within the three year period, which remained stable over time (p=0.342). There were a total of 21,495 antipsychotic prescriptions written, of which 1,134 seniors (39.9%) received two or more antipsychotic prescriptions per quarter (Table 2.4). The median age for seniors taking antipsychotics was 83 years and 394 (or 34.7%) were male. Over the series of twelve quarters, between 34.3% and 42.2 % of seniors were prescribed two or more antipsychotics per quarter with an average of 39.9% (See Figure 2.4). Finally, of the total number of seniors in long-term care, 903 (31.8%) were chronic antipsychotic users. The prescribing rate for antipsychotics was between 53 and 62 with an average of 55 per 1000 total prescriptions (Figure 2.5), which remained stable over time (p=0.898). The total number of DDDs for antipsychotic prescriptions was 127,778. The DDDs/1,000 people/day was stable over the twelve quarters (p=0.688) at between 40 and 52 with an average score of 46.

As in the community, quetiapine was most commonly prescribed of the individual agents in long-term care and was received by 797 seniors (70.3% of antipsychotic users) taking antipsychotics twice or more per quarter (Appendix 1.7). The other commonly prescribed agent was the atypical antipsychotic risperidone, being prescribed to 342 seniors (30.2% of users). For quetiapine, the total DDD over the three year period was

90,563. The DDDs/1,000 people/day over the twelve quarters was between 18 and 26 with an average score of 23 (Appendix 1.8). For risperidone, the total DDD over the three year period was 37,503. The DDDs/1,000 people/day over the twelve quarters was between eight and thirteen with an average score of ten.

2.3.6 Combined Utilization of Benzodiazepines and Antipsychotics

There were 1,173 out of 49,875 seniors (2.4%) living in the community who received two or more benzodiazepine and antipsychotic prescriptions per quarter in the same quarter. Of the 1,173 seniors, males made up 412 (35.1%) of the population and the median age was 74 years. Over the series of twelve quarters between 2.2% and 2.6% of seniors were chronic users of both benzodiazepines and antipsychotics (Figure 2.1). These seniors received an average of three benzodiazepine and three antipsychotic prescriptions per quarter for a total of six psychoactive prescriptions per quarter for an average of five quarters. Of the total number of seniors in the community, 1,037 (2.1%) were chronic users of both benzodiazepines and antipsychotics.

In long-term care 495 out of 2,843 seniors (17.4%) received two or more benzodiazepine and antipsychotic prescriptions per quarter. Of the 495 seniors, males made up 169 (34.1%) of the population and the median age was 82 years. Over the series of twelve quarters between 13.8% and 20.2% of seniors received prescriptions for two or more of each psychoactive drug class per quarter (Figure 2.4). These seniors received an average of four benzodiazepine prescriptions and four antipsychotic prescriptions per quarter for a total of eight psychoactive prescriptions per quarter for an average of four

quarters. Of the total number of seniors in long-term care, 329 seniors (11.6%) were chronic users of both benzodiazepines and antipsychotics.

2.4 DISCUSSION

2.4.1 Summary

The use of benzodiazepines and antipsychotics remained stable between 2011 and 2014 in the community and long term care settings in Newfoundland and Labrador seniors who were beneficiaries under the provincial drug plan. The use of benzodiazepines in the community setting was lower than in long-term care; however, over one in five seniors in the community and one in three seniors in long-term care facilities used a benzodiazepine in NL. A pattern of prescribing a single preferred agent for both benzodiazepines (lorazepam) and antipsychotics (quetiapine) appears prevalent in both the community and long-term care.

2.4.2 Time Trends in Benzodiazepine Utilization

The proportion of benzodiazepine use in the community was similar to data gathered from other provinces studying seniors on public drug plans (CIHI, 2012). The volume of benzodiazepines as described by DDDs in the Newfoundland community was similar (132 versus 130) to that found in a similar study done in Nova Scotia (Smith et al., 2008). Despite the high rates of use in long-term care facilities as seen in this study, there are fewer studies examining benzodiazepine use in the long-term care setting than in the community. In addition, given the differences in populations studied, direct comparisons

cannot be made between this study and others. From the data available, however, Newfoundland and Labrador facilities seem to have a higher prevalence than other provinces, a difference that may not be entirely due to a skewed population (Bronskill et al., 2013; Hagen et al., 2005).

Of some note is the trend of prescribing one particular benzodiazepine agent (lorazepam) to a majority of seniors. This may be explained by one or more factors: 1) lorazepam has fewer drug interactions vs other benzodiazepines, 2) lorazepam has no active metabolites, and 3) lorazepam is metabolized via conjugation, which unlike oxidation is not impaired by deficiencies in liver function (Powlovich, 2015). This can be considered somewhat reassuring since lorazepam is relatively safe in comparison to other benzodiazepines, however the overall prevalence of its prescription should cause concern for both clinicians and policy makers.

2.4.3 Time Trends in Antipsychotic Utilization

Overall use of antipsychotics in Newfoundland and Labrador long-term care facilities was higher than the rates reported from the national data (45% versus 39%) (CIHI, 2016). In the long-term care setting, the slight dip in proportion of seniors receiving psychoactive drugs (Figure 2.3) can be attributed to the fact that between January and April of 2012, the number of seniors in long-term care in Newfoundland and Labrador increased by twenty percent from 1,086 to 1,307 residents. There is a gap in the literature discussing the utilization and prevalence of antipsychotics in the community. This may be due to the less frequent prescription of antipsychotic medications to seniors in the community, especially relative to the long-term care setting. The average number

of DDDs per person per day for antipsychotics in the community may seem low relative to the number of prescriptions and relative for the same score for benzodiazepines. Since DDD score is based on the assumption that the drug is being prescribed for its main indication, the very low score indicates considerable off label use.

2.4.4 Limitations of the Study

A brief survey of the limitations of this study should be made in order to properly understand the results that it produced. This study was conducted using only data from seniors serviced by the NLPDP, who by definition are of lower income, which has been repeatedly associated with poorer health outcomes (Raphael, 2002). These seniors form a specific demographic and the exclusion of higher income seniors from the study means that the results may be skewed in relation to the total senior population in this province. Additionally, as one finds with nearly all large datasets, there were seniors who had to be removed from the study because either their relevant data was missing or could not be used. A total of 1,028 seniors were excluded from the study in comparison to the 52,718 seniors included in the study. It is therefore unlikely that those excluded from the study had any real effect as the demographic characteristics of those affected by the exclusions were similar to those included. The number of those excluded was relatively small compared to the overall number of subjects.

As this was a secondary study of data collected for another purpose, some information was missing that could have been useful to the current research question. For example, reason for the prescription (i.e. diagnosis) would be helpful in order to better analyze any differences in specific prescriptions as well as track the most commonly

diagnosed condition. The lack of this information means that there is no way to accurately assess the appropriateness of prescriptions written for seniors. Since only the number of medications prescribed is available in this dataset and not the number of medications actually taken, drug compliance cannot be accurately measured. The lack of information on physicians means results in the inability to verify whether or not a senior had multiple physicians, nor can any patterns be identified within groups of seniors being treated by the same physician.

2.4.5 Conclusion

This study was designed to measure utilization of benzodiazepines and antipsychotics in Newfoundland and Labrador. It was found that the prevalence and rate of prescriptions for both benzodiazepines and antipsychotics remained stable over the duration of the study. Studies from other parts of Canada showed that the prevalence of benzodiazepine and antipsychotics prescriptions for seniors on public drug coverage was found to be higher in Newfoundland and Labrador than other regions (Alessi-Severini et al., 2014; Smith et al., 2008, Sivanthan et al., 2015; CIHI, 2017). This is not an ideal comparison however, as the Newfoundland and Labrador data is skewed towards a particular demographic. Further study is required to fully understand the context of potentially inappropriate use of benzodiazepines and antipsychotics among all seniors in the province and to implement policies to incentivize optimal prescribing of these agents.

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Table 2.1: Demographic and Clinical Characteristics for the Community Setting

Quarters	Age (mean, SD)	% male (mean)	CDS (median, IQR)
1-4	74.36, +/-7.45	43.1	4.00, 3.00-6.00
5-8	73.40, +/-7.45	43.1	4.00, 3.00-6.00
9-12	72.54, +/-7.42	43.1	4.00, 2.00-5.00
P-value	<0.001	<0.001	<0.001

Table 2.2: Demographic and Clinical Characteristics for the Long-Term Care Setting

Quarters	Age (mean, SD)	% male (mean)	CDS (median, IQR)
1-4	84.25, +/-8.09	30.1	6.00, (4.00-7.00)
5-8	84.49, +/-8.05	31.5	5.00, (4.00-7.00)
9-12	84.03, +/-8.69	32.4	5.00, (4.00-7.00)
P-value	0.035	0.007	<0.001

Table 2.3: Prevalence, Rate, and Volume of Psychoactive Prescriptions in the Community

Drug Class/ Sub Class	Agent	Number People With 1+ Rxs per Quarter (%)	Number People With 2+ Rxs per Quarter (%)	Number of Rxs Filled	Total DDD
Total		49,875	49,875	4,579,704	
Benzodiazepines		15,455 (31.0)	10,665 (21.4)	221, 405	5,521,747
Intermediate/Long Acting					
	Lorazepam	9,290 (60.1)	5,932 (55.6)	86,441	1,870,196
	Temazepam	2,604 (16.8)	2,153 (20.2)	35,667	1,425,386
	Clonazepam	2,549 (16.5)	2,079 (19.5)	32,660	1,529,930
	Diazepam	1,051 (6.8)	728 (6.8)	11,615	416,350
	Bromazepam	881 (5.7)	737 (6.9)	14,247	328,799
	Chlordiazepoxide	242 (1.6)	202 (1.9)	3,715	108,484
	Nitrazepam	209 (1.4)	165 (1.5)	2,753	159,554
	Potassium Clorazepate	159 (1.0)	141 (1.3)	1,626	42,179
	Flurazepam	74 (0.5)	58 (0.5)	808	22,704
	Clobazam	61 (0.4)	57 (0.5)	1,067	31,326
Short Acting					
	Oxazepam	1,332 (8.6)	1,047 (9.8)	15,622	253,373
	Alprazolam	828 (5.4)	689 (6.5)	13,425	403,986
	Triazolam	167 (1.1)	129 (1.2)	1,759	63,679
Antipsychotics		3,066 (6.1)	2,321 (4.7)	546,131	519,824
Atypical					
	Quetiapine	1,769 (57.7)	1,455 (62.7)	30,733	206,006
	Risperidone	692 (22.6)	611 (26.3)	11,769	86,002
	Olanzapine	160 (5.2)	160 (6.9)	5,315	158,738
	Clozapine	*	*	142	2,894
	Aripiprazole	*	*	75	1,117
	Ziprasidone	*	*	71	2,456
Typical					
	Haloperidol	188 (6.1)	135 (5.8)	1,768	26,915
	Prochlorperazine	363 (11.8)	100 (4.3)	864	3,230
	Levomepromazine	110 (3.6)	100 (4.3)	1,804	4,230
	Perphenazine	53 (1.7)	49 (2.1)	1,385	9,303
	Chlorpromazine	74 (2.4)	42 (1.8)	961	9,993
	Trifluoperazine	35 (1.1)	35 (1.5)	1,069	11,364
	Flupentixol	27 (0.9)	25 (1.1)	562	3,408
	Zuclopenthixol	9 (0.3)	8 (0.3)	302	3886
	Periciazine	*	*	9	101

(* indicates five or fewer subjects which cannot be reported for privacy reasons)

Table 2.4: Prevalence, Rate, and Volume of Psychoactive Prescriptions in Long-Term Care

Drug Class/ Sub Class	Agent	Number People With 1+ Rxs per Quarter (%)	Number People With 2+ Rxs per Quarter (%)	Number of Rxs	Total DDD
Total		2,843	2,843	388,240	
Benzodiazepines		1,486 (52.2)	1,046 (36.8)	17,301	715,453
Intermediate/Long Acting					
	Lorazepam	1,136 (76.4)	760 (72.7)	8,523	161,775
	Temazepam	226 (15.2)	207 (19.8)	2,959	125,987
	Clonazepam	192 (12.9)	178 (17.0)	2,384	12,468
	Diazepam	75 (5.0)	58 (5.5)	597	26,622
	Bromazepam	35 (2.4)	34 (3.3)	511	16,471
	Nitrazepam	10 (0.7)	10 (1.0)	144	9,069
	Chlordiazepoxide	9 (0.6)	7 (0.7)	87	5,247
	Potassium Clorazepate	*	*	67	3,292
	Clobazam	6 (0.4)	*	48	3,169
	Flurazepam	*	*	*	*
Short Acting					
	Oxazepam	135 (9.1)	121 (11.6)	1,718	25,217
	Alprazolam	19 (1.3)	17 (1.6)	251	9,654
	Triazolam	7 (0.5)	*	10	906
Antipsychotics		1,273 (44.8)	1,134 (39.9)	21,495	151,541
Atypical					
	Quetiapine	866 (68.0)	797 (70.3)	14,098	90,563
	Risperidone	372 (29.2)	342 (30.2)	5,514	37,503
	Olanzapine	27 (2.1)	27 (2.4)	578	23,291
	Clozapine	*	*	14	549
	Aripiprazole	*	*	6	245
Typical					
	Haloperidol	113 (8.9)	86 (7.6)	615	6,038
	Levomepromazine	16 (1.3)	16 (1.4)	161	632
	Chlorpromazine	15 (1.2)	13 (1.1)	147	3,681
	Prochlorperazine	22 (1.7)	12 (1.1)	82	439
	Flupentixol	*	*	61	719
	Perphenazine	*	*	49	274
	Trifluoperazine	*	*	25	1,260
	Zuclopenthixol	*	*	9	332

(* indicates five or fewer subjects which cannot be reported for privacy reasons)

Figure 2.1: Prevalence of Seniors in the Community Receiving Two or More Psychoactive Prescriptions

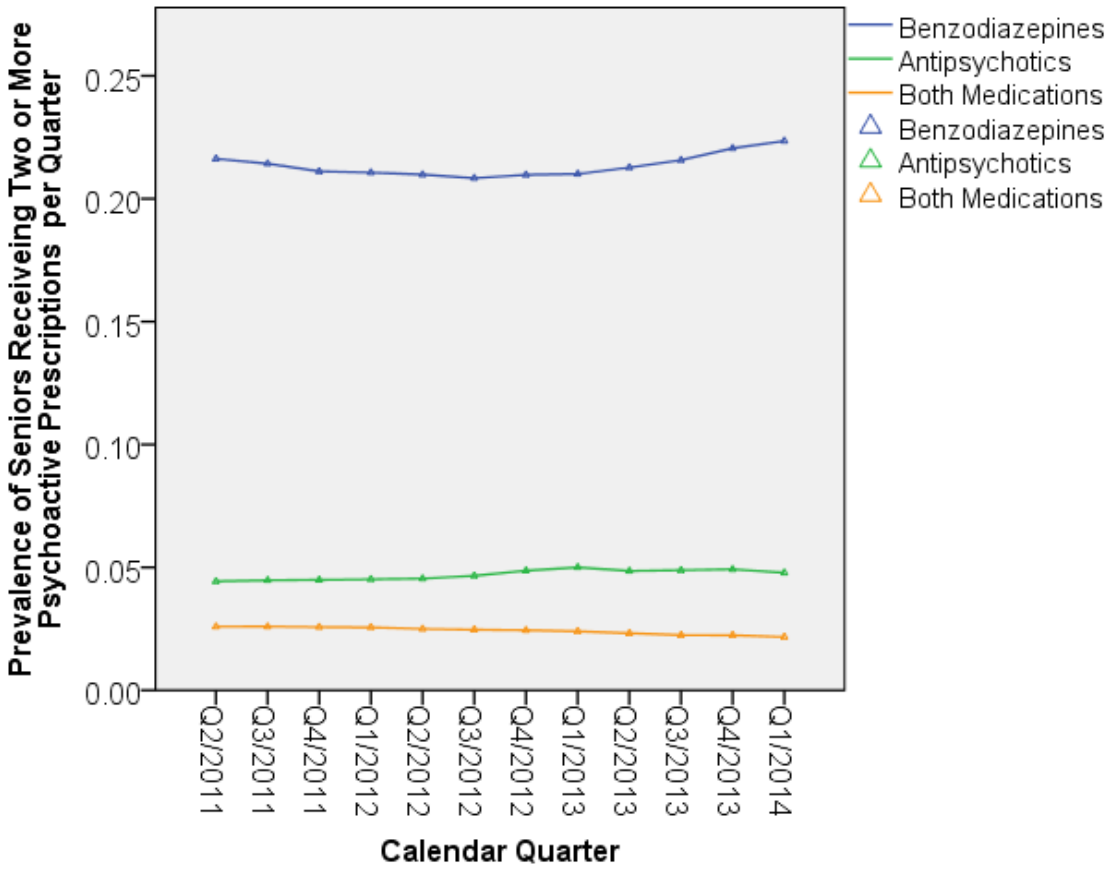


Figure 2.2: Rate of Psychoactive Prescriptions Filled in the Community per 1,000 Total Prescriptions

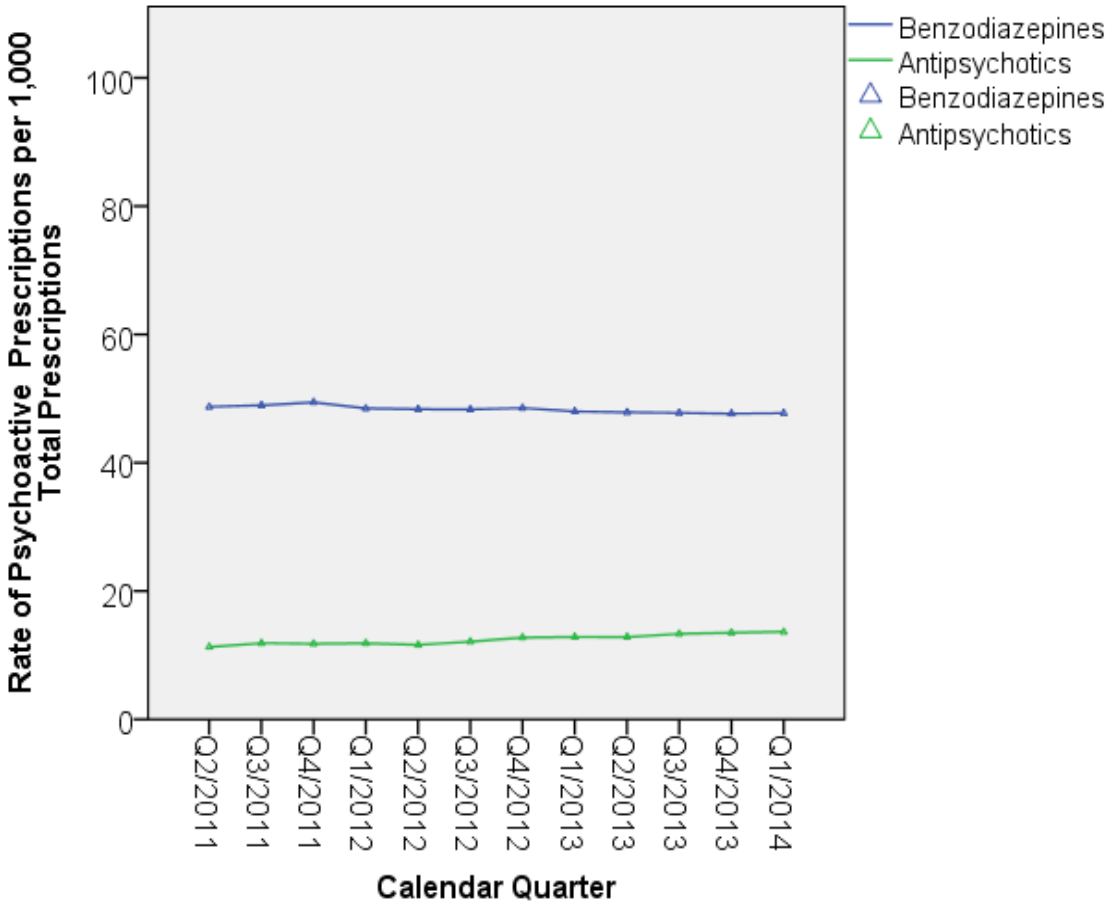


Figure 2.3: Volume of Psychoactive Prescriptions Filled in the Community in DDDs/1,000 People/Day

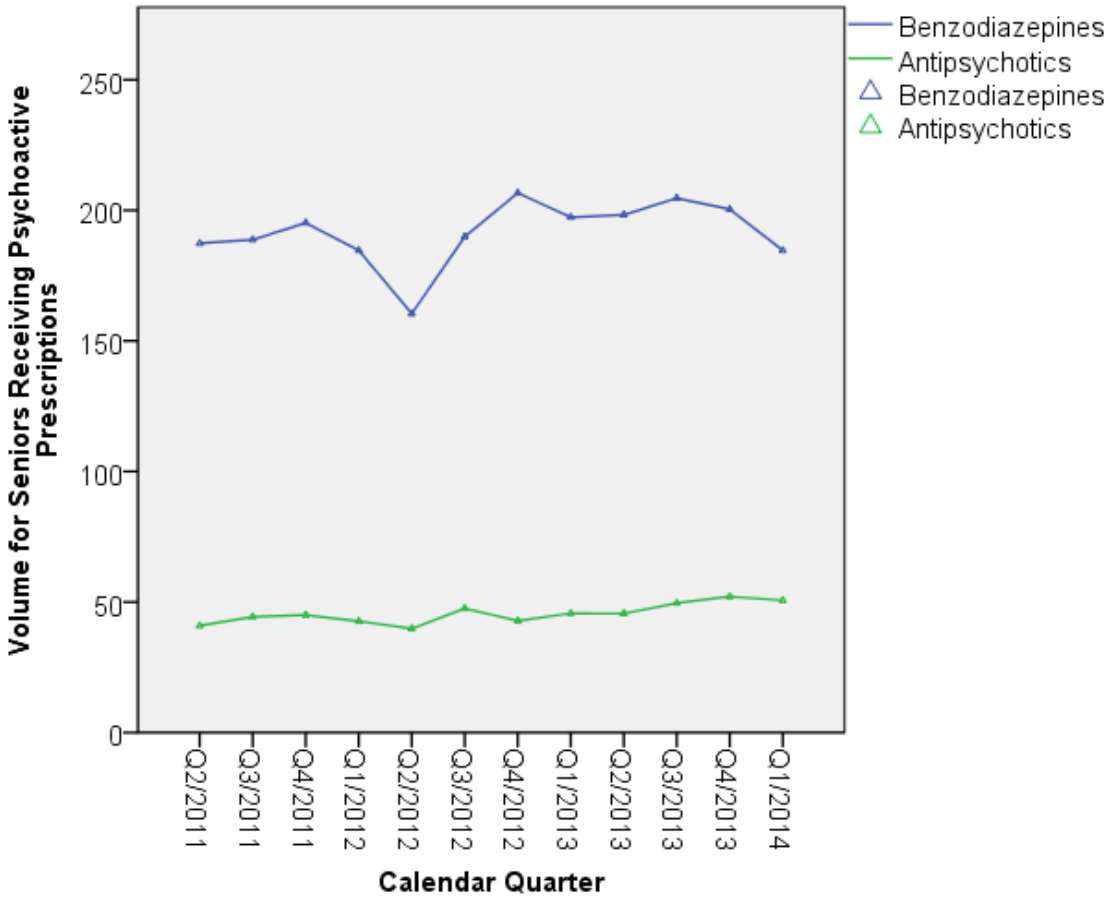


Figure 2.4: Prevalence of Seniors in Long-Term Care Receiving Two or More Psychoactive Prescriptions

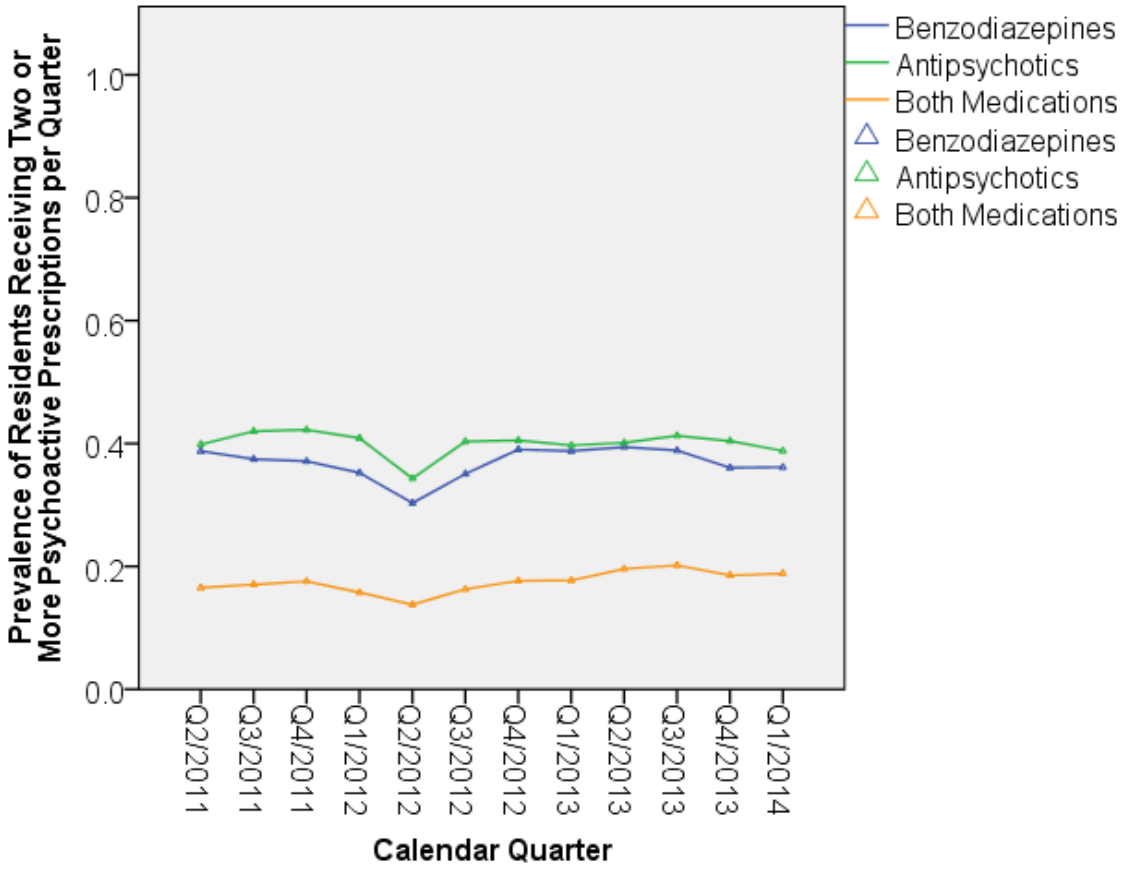


Figure 2.5: Rate of Psychoactive Prescriptions Filled in Long-Term Care per 1,000 Total Prescriptions

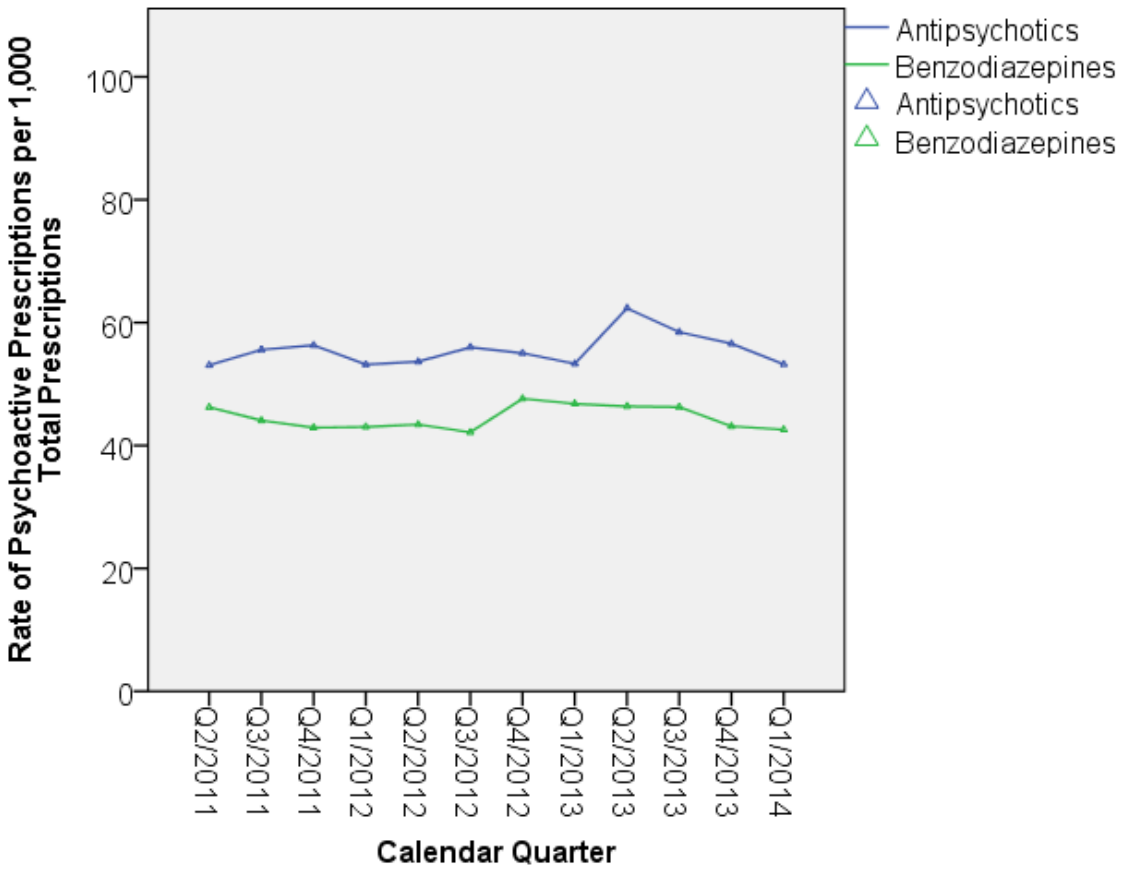
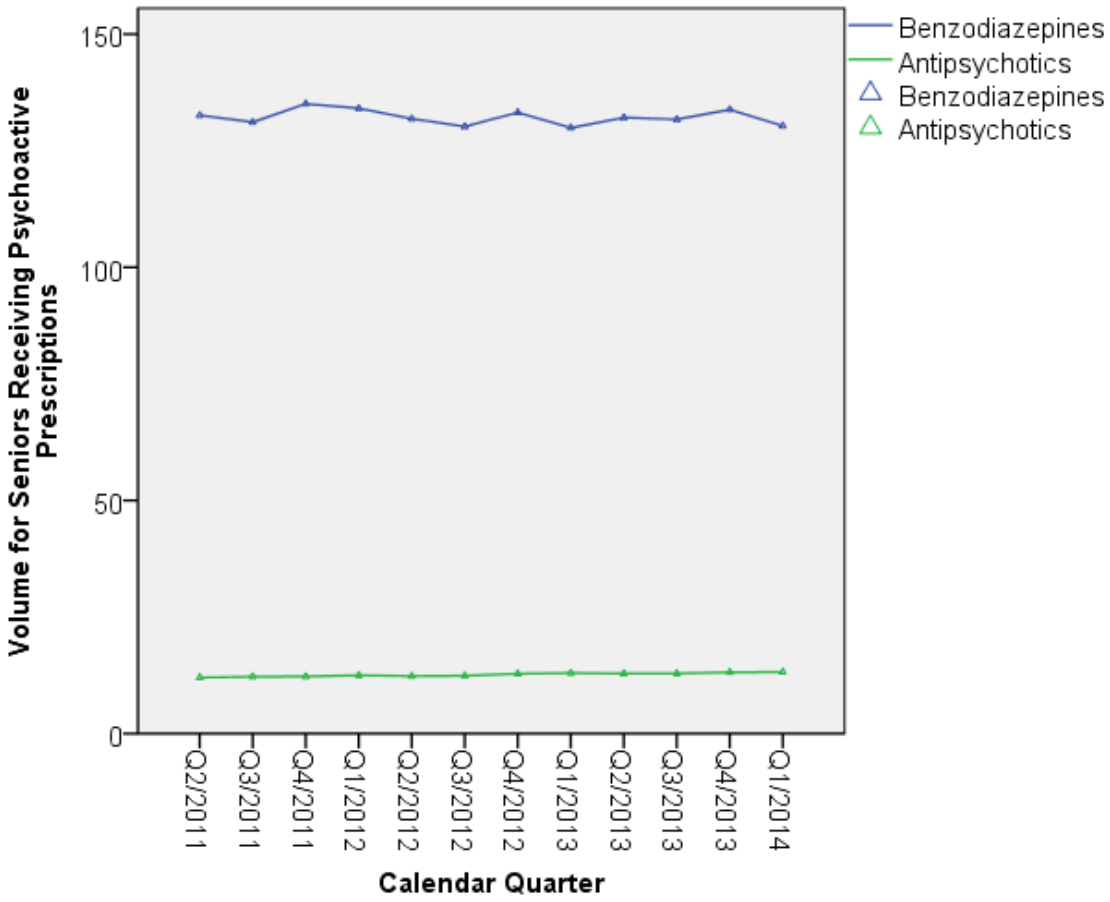


Figure 2.6: Volume of Psychoactive Prescriptions Filled in Long-Term Care in DDDs/1,000 people/Day



Chapter 3

Geographic Variation in the Utilization of Benzodiazepines and Antipsychotics Across Long-Term Care Facilities and the Community Dwelling Seniors in Newfoundland and Labrador

3.1 INTRODUCTION

3.1.1 Background

The high rates of potentially inappropriate benzodiazepine and antipsychotic prescriptions among seniors have been well documented in Canada and in other parts of the world (Smith et al., 2008; Martinsson et al., 2012). However, this problem is not uniform across geographical regions. Studies conducted in Canada and the United States have shown substantive variation in prescribing practices for benzodiazepines and antipsychotics across geographic areas including differences between urban and rural settings and among long-term care facilities (Stevenson et al., 2010).

Studies describing benzodiazepine utilization among community dwelling seniors in the US have shown that benzodiazepines (particularly anxiolytics) are prescribed approximately 1.5 to 2.5 times more often in rural areas than in urban areas (Edelstein et al, 2014), although not all evidence is consistent. A Canadian study found no difference in the use of benzodiazepines in among rural and urban areas (both equal 10.9%) (Alessi-Severini et al., 2013).

Similar studies have been done concerning antipsychotics in Canada. Alessi-Severini and colleagues have shown that among community dwellers, antipsychotics were

more commonly prescribed to urban seniors than rural seniors ($p<0.05$, OR = 0.88) (Alessi-Severini et al., 2013). In Ontario, a study of residents in long-term care found that there was some variation between the different regions of the province in terms of antipsychotic prescriptions, ranging from 25.4% to 32.4% (Health Quality Ontario, 2015). Similarly, a study conducted across multiple states in the US found that antipsychotic prescription in long-term care facilities were significantly influenced by region and increased significantly as size of the facility increased (Chen et al., 2010).

3.1.2 Purpose of Study and Objectives

To further understand variations in benzodiazepine and antipsychotic utilization across geographic regions in Newfoundland and Labrador, data was collected from two different cohorts of seniors: 1) community dwelling seniors and 2) seniors living in long-term care facilities.

3.2 METHODS

3.2.1 Population and Inclusion/Exclusion Criteria

The population for this study was composed of senior citizens 65 years and older who, between April 1st, 2011 and March 31st, 2014, received publically funded drug coverage under the provincial prescription drug program (NLPDP) while living in Newfoundland and Labrador. Seniors were recorded as residing in either communities or in long-term care facilities. Seniors were excluded if their demographic information (e.g. age, sex) or postal code was missing. In the long-term care setting, only provincially

funded facilities were included in the database, excluding private nursing homes. Residents in long-term care facilities were excluded from the study if they spent longer than 7 days outside facilities while being transferred from facility to facility. For long-term care residents, those who spent more than 7 days outside a facility while being transferred were removed from analysis. To avoid double counting, individuals moving from the community into long-term care during the course of the study were analyzed only as long-term care residents. As an exploratory analysis, the variability among individual long-term care facilities was also analyzed. For this analysis, long-term care facilities where fewer than thirty residents received the drug of interest (either benzodiazepines or antipsychotics) were excluded as the number of subjects would be too small to be statistically valid. This project has been approved by the Health Research Ethics Board (HREB #2016.324).

3.2.2 Data Sources

The study population was derived from three provincially maintained databases:

1) The NL Prescription Drug Plan (NLPDP) database, which contains prescription records for individuals who receive the Guaranteed Income Supplement (GIS) and Old Age Security (OAS) benefits (Department of Health and Community Services, 2017). Information collected by the NLPDP database includes drug dispensed, date of dispensation, drug dosage, quantity dispensed, and days' supply.

2) The Provincial Client Registry, which contains personal demographic information such as Medical Care Plan (MCP) number, sex, month and year of birth, and postal code.
3) The Long-Term Care (LTC) Module of the Provincial Meditech database, containing information on seniors living in long-term care facilities as well as their dates of admission and discharge.

All data linkages were performed at the Newfoundland and Labrador Centre for Health Information (NLCHI) and information was de-identified before being released.

3.2.3 Definitions of Geographic Regions

3.2.3.1 Geographic Regions in the Community

Seniors living in the community were categorized as living in either urban or rural areas based on Canada Post area codes. The second character of the postal code identifies whether the address is rural or urban. Canada Post postal codes reflect Statistics Canada definitions which delineate urban versus rural communities. An urban area is defined as consisting of greater than 1,000 people with a population density of greater than 400 per square kilometer (Statistics Canada, 2011).

3.2.3.2 Geographic Regions in Long-Term Care

Seniors living in long-term care facilities were categorized by their location in one of the four regional health authorities (RHA) in the province: Eastern Health, Central Health, Western Health, or Labrador-Grenfell Health. Each long-term care facility in the

four RHAs of the province was randomly assigned a number from 1 to 37 to maintain anonymity.

3.2.4 Measuring Drug Utilization

For the purposes of this study, any senior who received at least one prescription for benzodiazepines or antipsychotics was defined as a user. The database used detailed the specific drug each senior received as well as the strength of each dose. Each drug is identified by its Anatomical Therapeutic Chemical (ATC) code (See Appendices 4.1 and 4.2). Drug utilization for both benzodiazepine and antipsychotic prescriptions was measured using three different metrics:

1) Prevalence was calculated as the ratio of the total number of users per quarter for benzodiazepines and antipsychotics over the total number of NLPDP beneficiaries per quarter.
2) Rate of prescription was calculated as the ratio of the number of benzodiazepine or antipsychotic prescriptions records per 1,000 over the total number of prescriptions per quarter. Calculation included only prescriptions claims confirmed as paid.
3) Volume, as the total number of defined daily doses (DDDs) per quarter per drug, was calculated. The World Health Organization (WHO) defines DDD as the "assumed average dose per day of a drug in adults, as prescribed for its main indication" (WHO Collaborating Centre for Drug Statistics Methodology, 2009). Total DDD is calculated by obtaining the product of the

strength of the dose and the number of days' supply then dividing by one DDD. Total DDD is generally reported in the literature as DDDs per 1,000 people per day with takes into account the number of days in the prescription.

3.2.5 Statistical Analysis

All analyses for seniors living in the community and seniors in long-term care facilities were conducted separately from each other. The data analyzed covered a three year period from April 2011 to March 2014. Descriptive statistics were used to summarize the study population. The significant differences between groups for continuous variables were examined by t-test and discrete variables were tested using chi-squared tests. To adjust other confounders, multivariate regression models were used.

Specifically, logistic regression models were used to test regional differences in the prevalence of people taking either benzodiazepines or antipsychotics (dichotomous variable). Poisson regression models were used to analyze differences in the rate of prescriptions use between regions (count variable). Linear regression modelling was used to measure differences in volume across geographic locales (proportion variable). Volume was measured as the defined daily dose per 1,000 people per day. The primary variable for the modelling was area in the community setting and facility in the long-term care setting. Individual facilities where at least thirty residents received either benzodiazepine or antipsychotic prescriptions were analyzed for prevalence, rate, and volume.

For the multivariate analyses age, sex, and chronic disease score were used as covariates in the models. Age was measured as a continuous variable and sex as a binary

variable (male=0, female=1), as it was recorded in the dataset. The chronic disease score (CDS) is a prescription based comorbidity score where one point is given to an individual corresponding to each drug class they are prescribed with a maximum score of 24 points. An increased chronic disease score is associated with an increased risk of one year all-cause hospitalization and mortality (Lix et al., 2016). Potential interactions between facility size and prevalence were also analysed.

The models were constructed using backwards elimination with nonsignificant variables being removed one at a time. Testing was completed on all models as well as all two-way interactions for the models. No violations of the usual assumptions such as linearity and homoscedasticity were found. All statistical analyses were conducted using SPSS, version 23.

3.3 RESULTS

3.3.1 Overview of the Community

Out of the original 53,746 seniors in the database overall, 1,028 seniors were excluded from the analysis, most of which were community dwelling. After the exclusion, there were 49,875 seniors in the community, of whom 18,480 (37.1%) lived in urban areas and 31,395 (62.9%) lived in rural areas. Of the 4,579,704 prescriptions filled in the community, 1,748,256 (38.2%) of them were filled in urban areas and 2,830,448 (61.8%) of them were filled in rural areas. In urban areas the median age was 74 years, 38.7% of seniors were male, the median CDS was four, and the average senior received ten prescriptions per quarter for an average of nine quarters. In rural areas the median age

was 73 years, 43.9% of them were male, median CDS was four, and the average senior received ten prescriptions per quarter for an average of nine quarters (Table 3.1).

3.3.2 Overview of Long-Term Care Facilities

Of the 2,843 seniors in long-term care facilities 1,983 (69.8%) were in Eastern Health, 659 (23.2%) were in Central Health 153 (5.4%) were in Western Health, and 48 (1.7%) were in Labrador-Grenfell Health. There was a total of 388,240 prescriptions filled, of which 310,914 (80.1%) were filled in the Eastern Health, 59,502 (15.3%) were filled in the Central Health, 11,237 (2.9%) were filled in Western Health, and 6,587 (1.7%) were filled in Labrador-Grenfell Health.

In Eastern Health the median age for seniors in long-term care was 84 years, 30.8% were male, the median CDS was five, and the average senior received 26 prescriptions per quarter for an average of six quarters. In Central Health the median age for seniors in long-term care was 84 years, 31.0% were male, the median CDS was five, and the average senior received twenty prescriptions per quarter for an average of four quarters. In Western Health the median age for seniors in long-term care was 82 years, 34.6% were male, the average CDS was five, and the average senior received 23 prescriptions per quarter for an average of three quarters. In Labrador-Grenfell Health the median age for seniors in long-term care was 85 years, 22.9% were male, the average CDS was 4.5 and the average senior received nineteen prescriptions per quarter for an average of seven quarters (Table 3.2).

3.3.3 Benzodiazepine Prescription in the Community

Of the 18,480 seniors living in urban areas, 5,632 (30.5%) received at least one prescription for benzodiazepines during the three year period. Of the 31,395 seniors living in rural areas 8,227 (26.2%) received at least one prescription for benzodiazepines within the three year period (Table 3.3). When age, sex, and CDS were controlled for, prevalence was significantly higher for seniors in urban areas versus rural areas ($p<0.001$; OR=1.273; 95%CI=1.217,1.332). The average rate of benzodiazepine prescriptions per 1,000 total prescriptions was 55 in urban areas and 44 in rural areas. After controlling for age, sex and CDS the difference in rate of prescription between areas was significantly higher in urban areas ($p<0.001$; OR=1.139; 95%CI=1.101,1.178). The average volume measured by DDDs per 1,000 people per day was 166 in urban areas and 116 in rural areas. After controlling for age, sex and CDS the difference in volume between areas was significant with volume in urban areas being higher ($p<0.001$; DDD difference=63.1; 95%CI=48.2,78.1).

3.3.4 Antipsychotic Prescription in the Community

Of the 18,480 seniors living in urban areas, 1,308 (7.1%) received at least one prescription for antipsychotics within the three year period. Of the 31,395 seniors living in rural areas, 1,758 (5.6%) received at least one prescription for antipsychotics within the three year period (Table 3.3). However when age, sex, and CDS were controlled for, prevalence was significantly higher for seniors in urban areas versus rural areas ($p<0.001$; OR=1.266 ; 95%CI=1.172,1.368). The average rate of antipsychotic prescription per 1,000 total prescriptions per was fifteen in urban areas and ten in rural areas. After

controlling for age, sex and CDS the difference in rate of prescription between areas was significant with urban areas having a higher rate ($p<0.001$; OR=1.105; 95%CI=1.022, 1.194). The average volume, measured as DDDs per 1,000 people per day, was nineteen in urban areas and ten in rural areas. After controlling for age, sex and CDS the difference in volume between areas was significant with urban areas having a higher volume ($p=0.005$; DDD Difference=7.3; 95%CI=-2.8,17.3).

3.3.5 Benzodiazepine Prescription in Long-Term Care

The prevalence of benzodiazepine prescriptions in long-term care was 56.2% (N=1,114 people) in Eastern Health, 54.8% (N=361 people) in Central Health, 56.2% (N=86 people) in Western Health, and 29.2% (N=14) in Labrador-Grenfell Health (Table 3.4). After controlling for age, sex, and CDS the overall difference in the prevalence of benzodiazepine prescriptions is significant (Wald Chi-Square $p=0.005$). When comparing pairwise differences however, Labrador-Grenfell Health facilities were the only facilities that had significantly lower prevalences than Eastern Health facilities ($p<0.001$; OR=0.857; 95%CI=0.398,1.405).

The average rate of benzodiazepine prescriptions in long-term care was 47 per 1,000 total prescriptions in Eastern Health, 50 per 1,000 in Central Health, 50 per 1,000 in Western Health, and twenty per 1,000 in Labrador-Grenfell Health. After controlling for age, sex, and CDS there was no significant difference overall in the rate of benzodiazepine prescription between the four RHAs (Wald Chi-Square $p=0.590$). The volume of benzodiazepine prescriptions in long-term care (as measured in DDDs per 1,000 people per day) was 191 in Eastern Health, 122 in Central Health, 158 in Western

Health, and 105 in Labrador-Grenfell Health. After controlling for age, sex, and CDS there was no significant difference in volume of benzodiazepines prescribed between the four RHAs (Wald Chi-Square p=0.110).

After controlling for age, sex, and CDS, the difference in prevalence between facilities for benzodiazepine prescription was significant (Wald Chi-Square p<0.001), with results ranging from 36% to 73% (Figure 3.1). There was no interaction between age, sex, or CDS and facility size. Rate of benzodiazepine prescriptions was also significant (Wald Chi-Square p=0.038), with results from 30 to 80 benzodiazepine prescriptions per 1,000 total prescriptions (Figure 3.2). The volume of benzodiazepine prescriptions was not statistically significant (Wald Chi-Square p=0.130) after controlling for age, sex, and (Figure 3.3).

3.3.6 Antipsychotic Prescription in Long-Term Care

The prevalence of antipsychotic prescriptions in long-term care was 48.0% (N=952 people) in Eastern Health, 43.2% (N=285 people) in Central Health, 45.1% (n=69 people) in Western Health, and 35.4% (N=17 people) in Labrador-Grenfell Health (Table 3.2). After controlling for age, sex, and CDS there was no significant difference in the prevalence of antipsychotic prescription between the four RHAs (p=0.120). The rate of antipsychotic prescriptions in long-term care was 58 per 1,000 total prescriptions in Eastern Health, 47 per 1,000 in Central Health, 50 per 1,000 in Western Health, and 50 per 1,000 in Labrador-Grenfell Health. After controlling for age, sex, and CDS there was no significant difference in the rate of antipsychotic prescriptions between the RHAs (p=0.125). The volume of antipsychotic prescriptions in long-term care (as measured in

DDDs/1,000 people/day) was 95 in Eastern Health, 65 in Central Health, 62 in Western Health, and 52 in Labrador-Grenfell Health. After controlling for age, sex, and CDS there was no significant difference in volume of antipsychotics prescribed between the RHAs ($p=0.088$).

After controlling for age, sex, and CDS, the difference in prevalence between facilities for antipsychotic prescription was significant ($p<0.001$) with results ranging from 35% to 78% (Figure 3.4). There was no interaction between age, sex, or CDS and facility size. After controlling for age, sex, and CDS, neither rate or volume of antipsychotic prescriptions was statistically significant across the facilities ($p=0.248$ and $p=0.087$ respectively) (Figures 3.5 & 3.6).

3.4 DISCUSSION

3.4.1 Summary

In the community setting the prevalence, rate, and volume of prescriptions was significantly higher in urban areas for both benzodiazepines and antipsychotics. In the long-term care setting the prevalence of benzodiazepine prescriptions was significantly different across the four RHAs ($p>0.005$). However, when analysed in a pairwise fashion, only Labrador-Grenfell Health had a prevalence significantly different (and lower) from Eastern Health.

3.4.2 Geographic Distribution in the Community

Benzodiazepines in the community setting were more likely to be prescribed to urban residents in terms of prevalence, rate, and volume. The results from this study differ from others comparing urban versus rural benzodiazepine prescription (Alessi-Severini et al., 2013; Edelstein et al., 2014). Most studies conducted in North America found no significant difference between prescription patterns of benzodiazepines in urban versus rural settings, or found higher levels in rural settings.

Female sex and advanced age in seniors have both been linked to have been linked to prescription of benzodiazepines and antipsychotics (Bartlett et al., 2009; Sivanthan et al., 2015). These variables, however, were controlled for by the regression used for this analysis. With that being said, other variables may play a role in the dissimilarity in prevalence, rate, and volume of benzodiazepine prescriptions between in urban and rural dwelling seniors in the province. For benzodiazepines, prescriptions have been associated with diagnoses of chronic pain, depression, and low alcohol consumption (Bartlett et al. 2009; Dias dos Anjos Cunha et al., 2015). For antipsychotics, prescriptions have been associated with a diagnosis of depression and relatively lower income (Stevenson et. al, 2010; Sivanthan et al., 2015).

3.4.3 Geographic Distribution in Long-term Care

In long-term care, RHA significantly influenced the prevalence of benzodiazepines with Labrador-Grenfell residents significantly less likely to receive a prescription. Rate and volume of benzodiazepine prescription remained relatively stable. The prevalence, rate, and volume of antipsychotic prescriptions remained stable for all

regional health authorities. One of the factors that may contribute to the difference in prevalence of psychoactive prescriptions is size of the facility. As shown in the study by Chen et al. (2010) the size of a facility is significantly and positively correlated to prescription prevalence of psychoactive drugs. Eastern Health facilities house 70% of facility dwelling seniors and also have nine of the ten largest facilities in the province.

The other more intangible factor is the idea of the culture of the regional authority and the facilities within them. For this reason it may also be useful to examine facilities individually. While each regional health authority has a different administration, each long-term care facility with the authority is run by individuals who each have their own unique approach to patient care. Hughes et al. (2007) wrote that the individual culture of a facility greatly influences how things are done including which residents do or do not receive prescriptions for potentially harmful medications. Various agencies in Canada have created list of ways to change the culture of a facility to better implement healthy prescribing practices. These include getting consent from resident/family, agreeing on appropriateness criteria, establish regular reviews, and pursuing non-pharmacologic interventions (Alberta Health Services, 2016; Bueckert et al., 2016).

3.4.4 Limitations of the Study

A brief overview of the limitations of this study should be examined to properly understand the results that it produced. This study was conducted using only data from seniors serviced by the NLPDP. Seniors not receiving NLPDP were excluded from the study. This means that the results are not be generalizable to all seniors in Newfoundland and Labrador, particularly those whose income is high enough not to be eligible for

provincial drug coverage. The relatively smaller sizes of the samples for the Western and Labrador-Grenfell regions also made it that some of the results of the regression analysis were less firmly robust than in the Eastern and Central regions. This would have affected the power of the overall statistical power. Finally, as one finds with almost the entirety of large datasets, there were seniors who had to be removed from the study because either their relevant data was missing or could not be used. Those excluded totalled 1,028 seniors, in comparison to the 52,718 seniors included in the study. It is unlikely that those excluded from the study had any real effect as the number of those excluded in relatively small and their demographic characteristics were similar to those included in the study.

As his is first research of its kind to be done in province, further research is necessary to fully understand the utilization of psychoactive medication in Newfoundland and Labrador. As this was a secondary study of administrative data, some information was missing that could have been useful to the current research question. It was impossible to tell an initial prescription from a refill or ordered prescriptions versus a prescription being filled as required. Since this dataset only shows the number of medications prescribed and not the number of medications actually taken, drug compliance cannot be accurately measured though it could be different depending on geographic area. The lack of information about prescribing physicians results in the inability to verify whether or not a senior had multiple physicians. It is also impossible to determine whether or not the physician was a specialist, or whether any patterns be identified within groups of seniors being treated by the same physician. In terms of

regional health authority for the long-term care setting, further research should examine the interaction between level of care and the prevalence of psychoactive prescription.

3.4.5 Conclusion

This study was designed to measure the geographic variation of benzodiazepines and antipsychotics in Newfoundland and Labrador. It was found that the prevalence and rate of prescriptions for both benzodiazepines and antipsychotics was significantly influenced by geography in both the community and long-term care settings. Other studies from different parts of North America reached similar conclusions but the distribution patterns in this province appears higher to those regions previously studied, possibly being explained by the demography of the study subjects. Further study is required that includes all seniors in the province and specifically includes diagnosis and severity in order to gain a better understanding of what is and what is not inappropriate prescribing amongst our seniors. After this has been established health care providers and policy makers must collaborate to draw up viable ways to optimize prescription practices.

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Table 3.1: Demographic and Clinical Characteristics for the Community Setting

Area	Sample Size	Age (mean, SD)	% male (mean)	CDS (median, IQR)
Urban	18,488	76.94, +/- 8.02	38.7	4.00, 2.00-5.00
Rural	31,395	75.66, +/- 7.55	45.4	4.00, 2.00-5.00
P-Value		p<0.001	p<0.001	p=0.961

Table 3.2: Demographic and Clinical Characteristics for the Long-Term Care Setting

LTC Facility	Sample Size	Age (mean, SD)	% male (mean)	CDS (median, IQR)
Eastern	1,983	85.21, +/-8.50	30.8	5.00, 4.00-7.00
Central	659	85.26, +/-7.95	31.0	5.00, 3.00-7.00
Western	153	83.71, +/-7.43	34.6	5.00, 4.00-7.00
Labrador-Grenfell	48	86.23, +/-7.77	22.9	4.50, 3.00-7.00
P-Value		p=0.129	p=0.486	p=0.373

Abbreviation(s):

CDS: chronic disease score

Table 3.3: Utilization of Benzodiazepines and Antipsychotics in the Community

Drug Class/Utilization	Urban	Rural
Benzodiazepine		
Sample Size	5,632	8,227
Prevalence (%)	30.5	26.2
cOR (95%CI)	1.234 (1.186,1.285)	ref
aOR (95%CI)	1.273 (1.217,1.332)	ref
Rate (Rxs/1,000 Total)	55	44
cRR (95%CI)	1.156 (1.115,1.198)	ref
aRR (95%CI)	1.139 (1.101,1.178)	ref
Volume (DDD/1,000 People/Day)	166	116
cDiff (95%CI)	58.8 (44.2,73.3)	ref
aDiff (95%CI)	63.1 (48.2,78.1)	ref
Antipsychotic		
Sample Size	1,308	1,758
Prevalence (%)	7.1	5.6
cOR (95%CI)	1.284 (1.193,1.383)	ref
aOR (95%CI)	1.266 (1.172,1.368)	ref
Rate (Rxs/1,000 Total)	15	10
cRR (95%CI)	1.112 (1.021,1.210)	ref
aRR (95%CI)	1.105 (1.022, 1.194)	ref
Volume (DDD/1,000 People/Day)	19	10
cDiff (95%CI)	8.2 (-2.2,18.7)	ref
aDiff (95%CI)	7.3 (-2.8,17.3)	ref

Abbreviations:

cOR: crude odds ratio

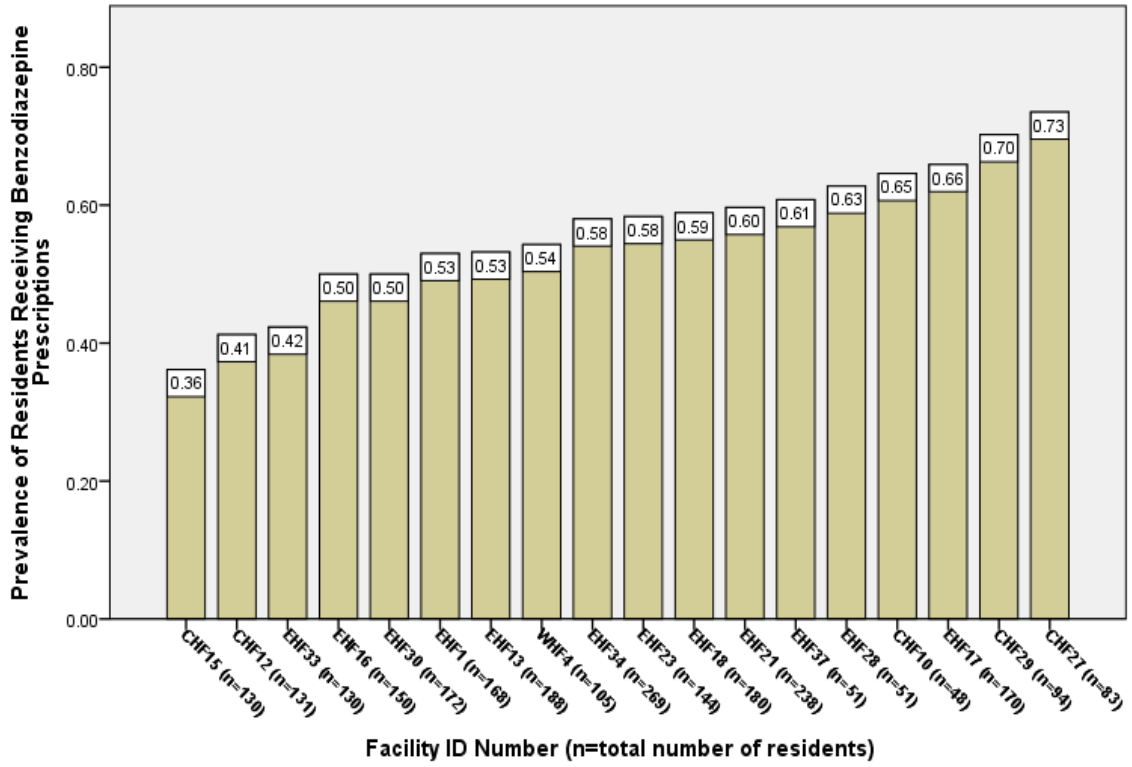
aOR: adjusted odds ratio

DDD: defined daily dose

Table 3.4: Utilization of Benzodiazepines and Antipsychotics in Long-Term Care

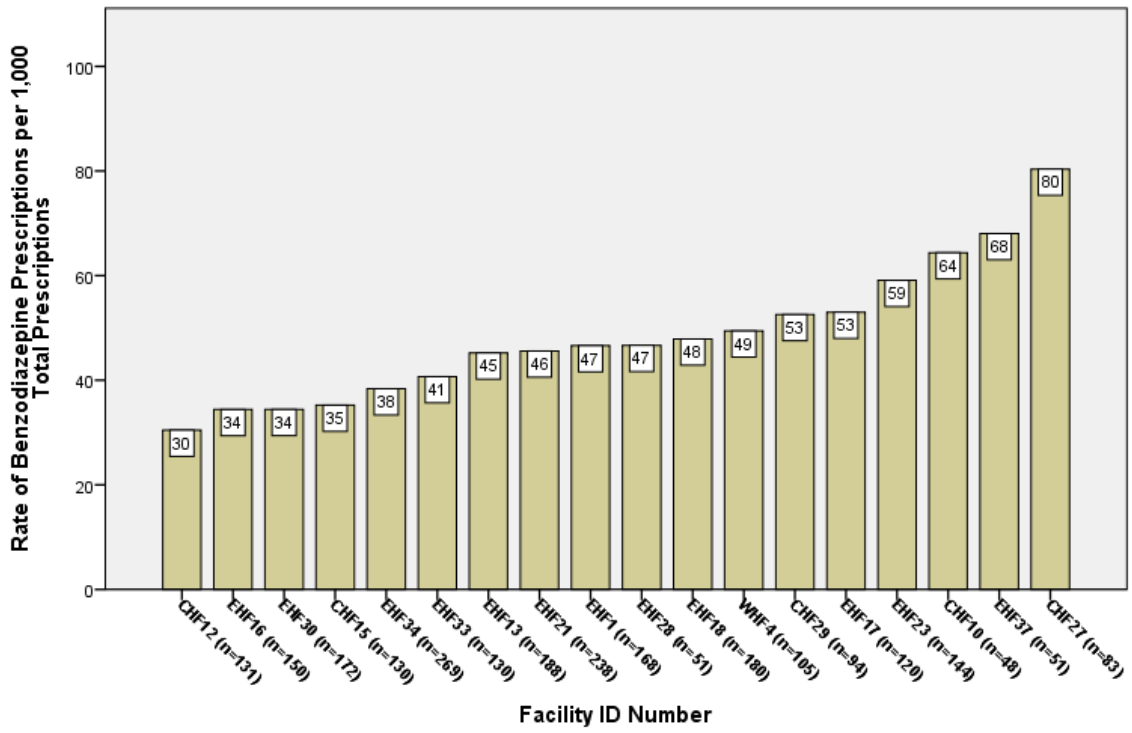
Drug Class/Utilization	Eastern	Central	Western	L-Grenfell
Benzodiazepine				
Sample Size	1,114	361	86	14
Prevalence (%)	56.2	54.8	56.2	29.2
cOR (95%CI)	ref	0.945 (0.792,1.128)	1.001 (0.719,1.395)	0.321 (0.171,0.602)
aOR (95%CI)	ref	0.984 (0.812,1.192)	0.954 (0.665,1.367)	0.295 (0.150,0.578)
Rate (Rxs/1,000 Total)	47	50	50	20
cRR (95%CI)	ref	1.089 (0.959,1.237)	1.050 (0.827,1.334)	0.857 (0.398,1.405)
aRR (95%CI)	ref	1.083 (0.964,1.218)	1.060 (0.849,1.324)	1.046 (0.656,1.668)
Volume (DDD/1,000 People/Day)	191	122	158	105
cDiff (95%CI)	ref	-69.4 (-129.0,-9.8)	-34.0 (-144.7,76.8)	-86.9 (-351.5,177.8)
aDiff (95%CI)	ref	-71.9 (-131.2,-12.5)	-46.5 (-156.9,64.0)	-68.0 (-331.8,195.8)
Antipsychotic				
Sample Size	952	285	69	17
Prevalence (%)	47.8	43.2	45.1	35.4
cOR (95%CI)	ref	0.825 (0.691,0.986)	0.890 (0.639,1.238)	0.594 (0.327,1.080)
aOR (95%CI)	ref	0.837 (0.697,1.005)	0.830 (0.589,1.168)	0.630 (0.340,1.167)
Rate (Rxs/1,000 Total)	58	47	50	50
cRR (95%CI)	ref	0.866 (0.775,0.968)	0.779 (0.598,1.014)	1.082 (0.720,1.626)
aRR (95%CI)	ref	0.897 (0.814,0.987)	0.882 (0.699,1.113)	0.997 (0.666,1.495)
Volume (DDD/1,000 People/Day)	95	65	62	52
cDiff (95%CI)	ref	-30.2 (-55.4,-4.9)	-33.0 (-80.1,14.1)	-43.3 (-134.5,47.8)
aDiff (95%CI)	ref	-27.5 (-52.1,-2.9)	-33.2 (-79.2,12.8)	-36.5 (-125.3,52.3)

Figure 3.1: Prevalence of Seniors in Long-term Care Receiving One or More Benzodiazepine Prescriptions by Facility



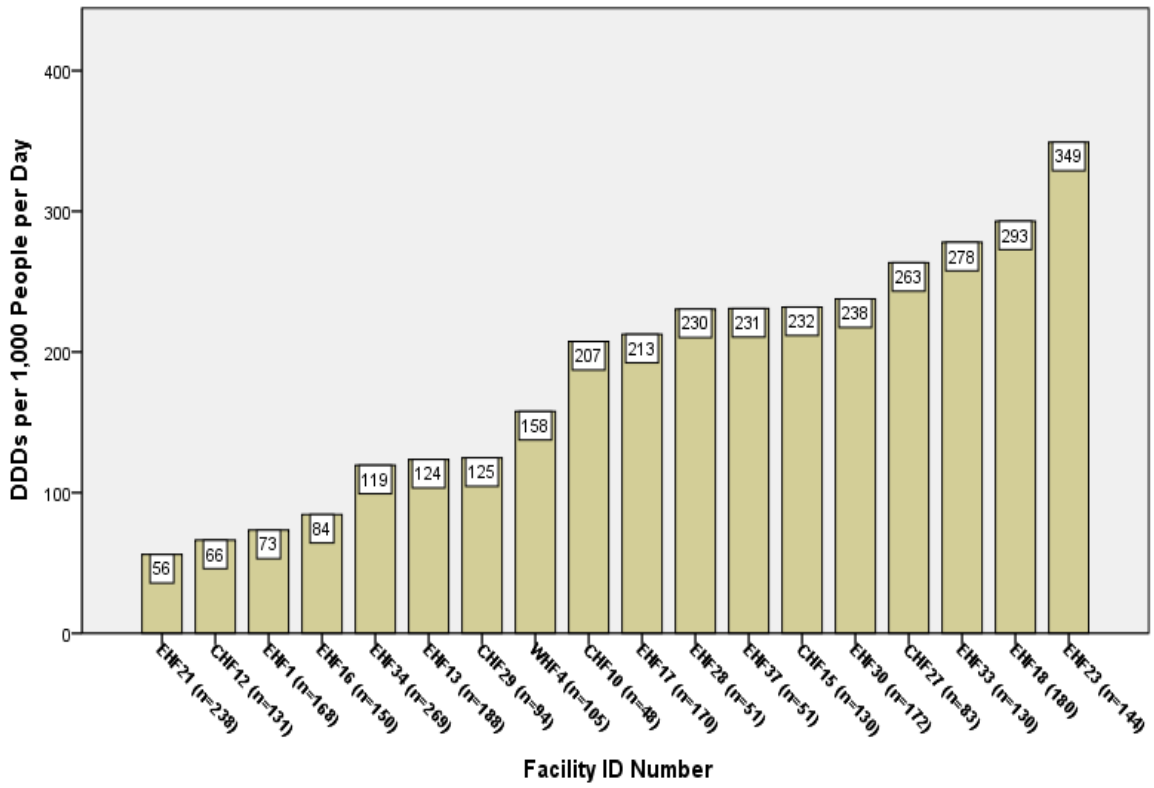
EHF = Eastern Health Facility
CHF = Central Health facility
WHF = Western Health Facility

Figure 3.2: Rate of Benzodiazepine Prescriptions Filled in Long-Term care per 1,000 Total Prescriptions by Facility



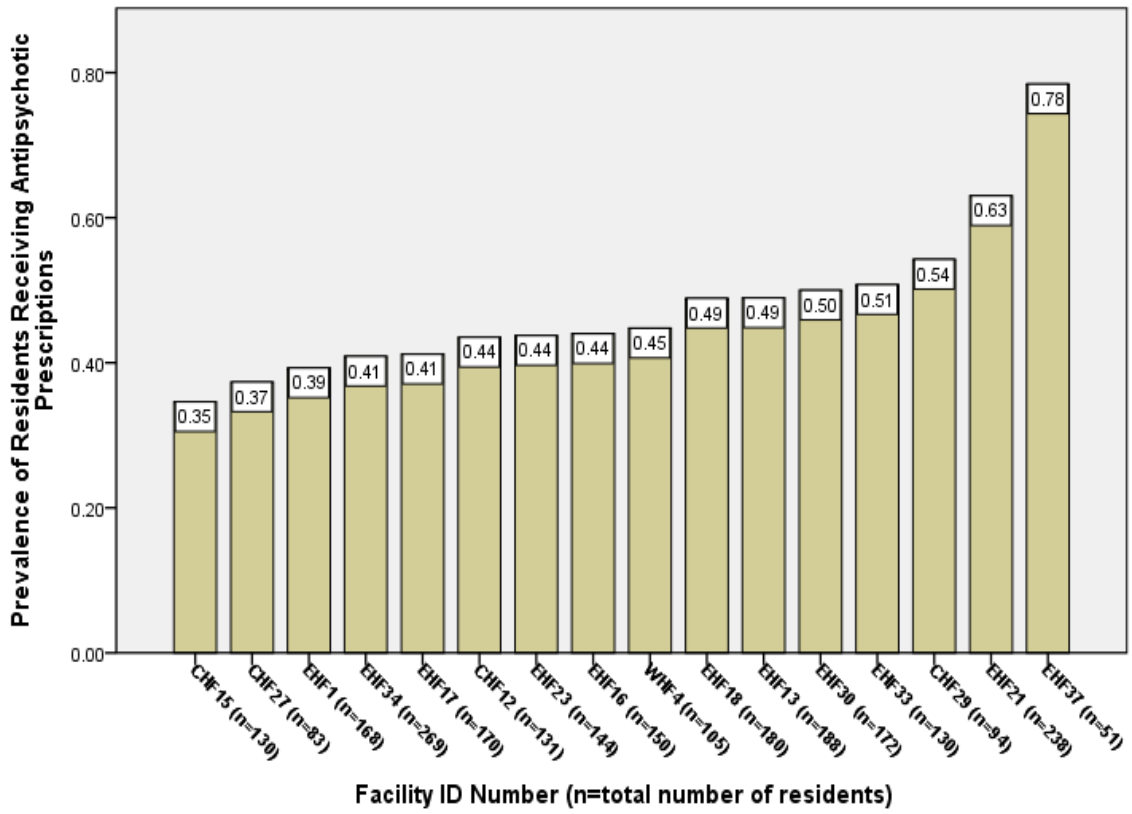
EHF = Eastern Health Facility
CHF = Central Health facility
WHF = Western Health Facility

Figure 3.3: Volume of Benzodiazepine Prescriptions Filled in Long-Term Care by Facility Measured as DDDs per 1,000 People per Day



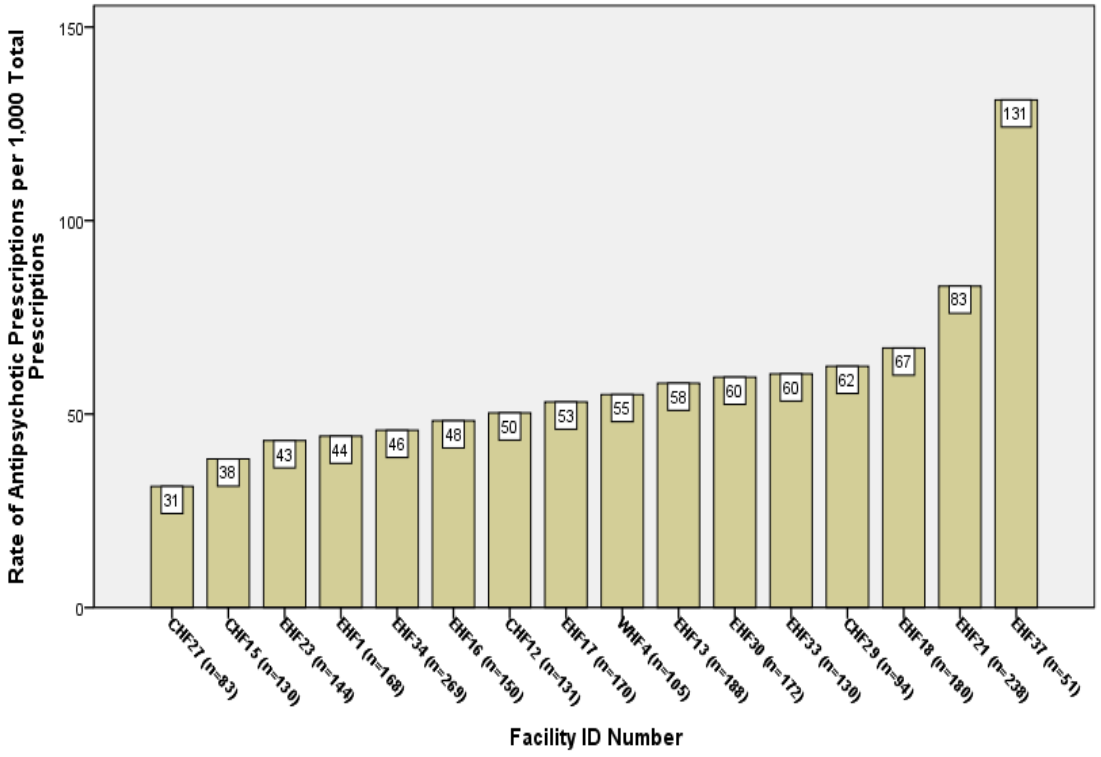
EHF = Eastern Health Facility
CHF = Central Health facility
WHF = Western Health Facility

Figure 3.4: Prevalence of Seniors in Long-term Care Receiving One or More Antipsychotic Prescriptions by Facility



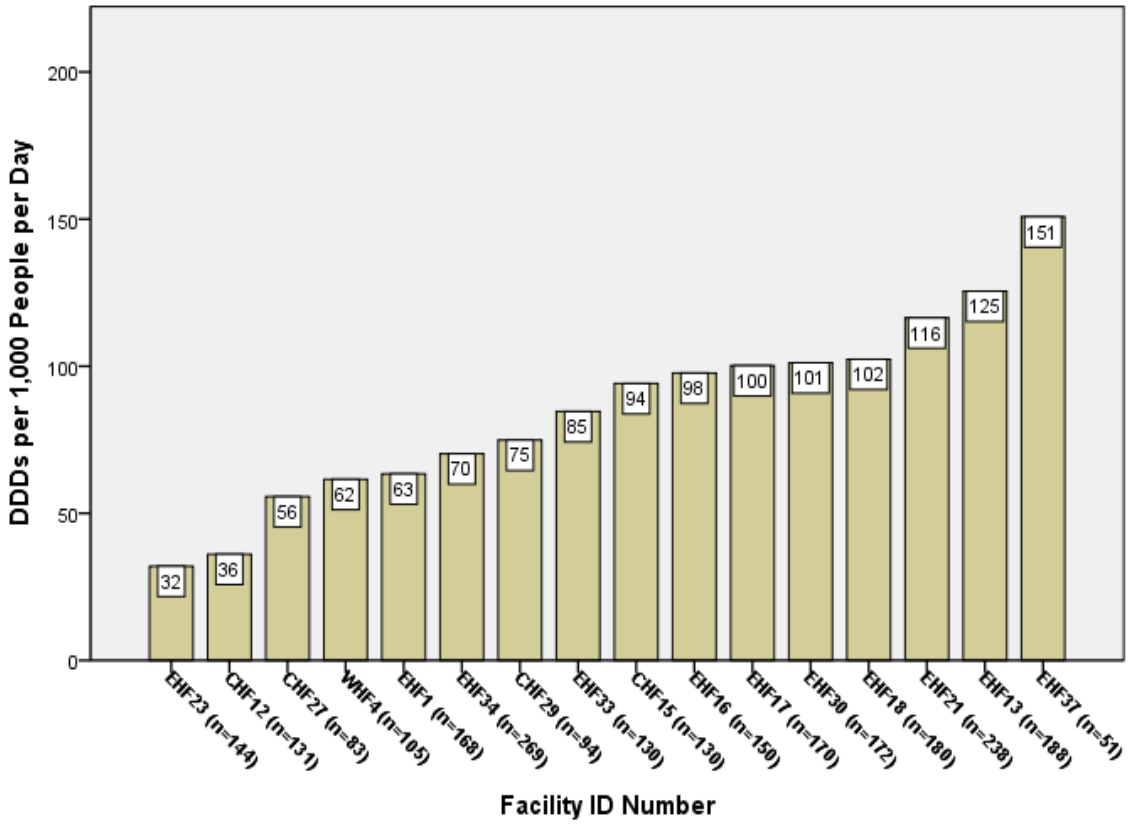
EHF = Eastern Health Facility
CHF = Central Health facility
WHF = Western Health Facility

Figure 3.5: Rate of Antipsychotic Prescriptions Filled in Long-Term care per 1,000 Total Prescriptions by Facility



EHF = Eastern Health Facility
CHF = Central Health facility
WHF = Western Health Facility

Figure 3.6: Volume of Antipsychotic Prescriptions Filled in Long-Term Care by Facility Measured as DDDs per 1,000 People per Day



EHF = Eastern Health Facility
CHF = Central Health facility
WHF = Western Health Facility

Chapter 4

Discussion and Conclusion

4.1 SUMMARY OF MAJOR ISSUES

The studies conducted in this thesis have been undertaken to develop a better understanding of the patterns of utilization of benzodiazepines and antipsychotics amongst seniors in Newfoundland and Labrador. Interest is this area has, at least in part, been prompted by the publishing of several warnings by multiple government agencies in Canada about the proliferation of prescription drugs in the country which have been associated with serious adverse effects in seniors (Health Canada, 2012; Government of Canada, 2014; CIHI, 2014).

Seniors in Canada comprise 14% of the total population but account for 44% of healthcare expenditures due to higher medication use, more frequent visits to family doctors, and longer and more frequent stays in hospitals (CIHI, 2010; CMA, 2013). An additional factor that exacerbates the situation in Newfoundland and Labrador is that the province, along with the rest of Atlantic Canada, has one of the highest median ages in the country (Stats Canada, 2016). For these reasons, an in-depth examination of benzodiazepine and antipsychotic utilization for seniors should provide valuable insight to clinicians and policy makers in the province.

4.2 SUMMARY OF THE STUDIES

The rate of benzodiazepine and antipsychotic prescriptions stayed constant during the three year study period in both the long term care and community settings for seniors who were provincial drug plan beneficiaries in Newfoundland and Labrador. The prevalence of prescriptions for both drug classes in the community was significantly higher in urban versus rural areas. Prevalence of prescriptions in long-term care facilities was significantly different across the four RHAs with Labrador-Grenfell Health having the lowest for both benzodiazepine and antipsychotic prescriptions. Single agents for both benzodiazepines (lorazepam) and antipsychotics (quetiapine) were shown to comprise the majority of prescriptions in both the community and long-term care settings.

4.3 DISCUSSION OF STUDY ONE RESULTS

4.3.1 Time Trends for Benzodiazepine Prescription

In the community, utilization remained stable over time in terms of prevalence, rate, and volume. An average of 21.4% of seniors received two or more prescriptions for benzodiazepines per quarter at a rate of 48 prescriptions per 1,000 total prescriptions. The average volume of benzodiazepine prescriptions as indicated by DDDs per 1,000 people per day in Newfoundland and Labrador was similar if slightly higher (132 versus 130) than found in a study conducted in Nova Scotia (Smith et al., 2008) and remained stable over time. The similarity can be expected since Nova Scotia has a comparable demographic distribution to Newfoundland and Labrador by age and sex (Stats Canada, 2015).

Prevalence and rate for benzodiazepine prescriptions in long-term care facilities remained stable over time. An average of 36.8% of seniors received at least two benzodiazepine prescriptions per month at a rate of 45 prescriptions per 1,000 total prescriptions. The volume of benzodiazepine prescriptions as indicated by DDDs per 1,000 people per day remained stable at an average of 192.

The higher prevalence and volume of benzodiazepine prescriptions is to be expected in long-term care residents given their age and the increasing complexity of their medical needs, prompting their entrance into facilities in the first place. However, since seniors have a much higher risk of adverse effects, this practice can be risky for their long-term care. Reference has already been made of the fact that lorazepam is the most commonly prescribed benzodiazepine for seniors. This may be attributed to the fact that it produces fewer drug interactions than other benzodiazepines, has no active metabolites, and uses a system of metabolization that is appropriate for the elderly (Powlovich, 2015). Another reason that lorazepam may be preferred over other benzodiazepines is the relatively shorter half-life of the drug, decreasing buildup in the system which in turn decreases the risk of adverse effects (Salzman, 1990).

The prescription of benzodiazepines for insomnia in seniors is considered inappropriate as the drug agents chosen tend to be of the longer-acting variety, meaning they stay in the patients' system for longer, increasing the risk of adverse effects. As has been mentioned in previous chapters, benzodiazepine use (especially long-term use) increases the risk of cognitive impairments, falls and fractures, and motor vehicle accidents (Smith et al., 2008; Edelstein et al., 2014; Thomas, 1998). Despite warnings from the literature, this study shows that more than one quarter of seniors in the

community who were chronic users of benzodiazepines were prescribed intermediate- or long-acting benzodiazepines. In addition, more than one fifth of residents in long-term care facilities were prescribed these benzodiazepines on a long-term basis, which is a significant predictor of adverse drug events.

4.3.2 Time Trends for Antipsychotic Prescription

Antipsychotic prescription levels in the community remained stable over time in term of prevalence, rate, and volume. An average of 4.7% of seniors received two or more prescriptions for antipsychotics per quarter at a rate of 12 prescriptions per 1,000 total prescriptions. The volume of antipsychotic prescriptions as indicated by DDDs per 1,000 people per day was 13. As mentioned in previous chapters, there is a gap in the literature on the use of antipsychotics in the community. A likely reason is that they are prescribed so infrequently in the community setting due to the rarity of the symptoms requiring their use. The black box warning that exists on their prescription to seniors may further discourage their use. Another reason may be that seniors with symptoms of dementia which would be treated by antipsychotics would have difficulty living in a community setting as they would require significant care.

The Canadian Institute for Health Information (CIHI, 2016) reported the national prevalence of antipsychotic prescriptions in nursing homes to be 39% in 2014. In comparison, the rate for the three years covered by this study remained stable at an average of 44.8% with 39.9% of residents receiving two or more prescriptions per quarter. Rate remained stable over time at 55 prescriptions per 1,000 total prescriptions. Volume also remained stable over time at 46 DDDs per 1,000 people per day. There is

some question as to why prevalence of prescription in Newfoundland and Labrador exceeds the national average. The work-place "culture" of the facilities would appear to be a good starting point for study. Hughes et al. (2007) discussed how differences in individual facilities due to staff differences affected prescription rates. As shown in the second study, there are differences in the utilization of benzodiazepines and antipsychotics across the facilities. Given the low volume of antipsychotic prescription as well as the high prevalence (45%), it can be reasonably assumed that most antipsychotic prescriptions being issued in long-term care facilities are not for the treatment of psychosis, their main indication (CAMH, 2012). The introduction of provincial policy on psychoactive prescription in long-term care would be a vial step in addressing these differences.

Another approved indication for the prescription of antipsychotics in seniors (for risperidone only) is the short-term treatment of severe symptoms of Alzheimer's disease (Health Canada, 2012). The results of this study indicate, however, that only 29% of facility residents receiving antipsychotics received them for one quarter only and only 11% received on prescription. The other 71% or residents received at least two prescriptions per quarter for a minimum of two quarters. Since no data is available to indicate the diagnosis warranting the prescription of antipsychotics it is uncertain why residents received these prescriptions. Statistics Canada (2016) states that the average rate of dementia in long-term care facilities is 45% across the country. If these numbers are accurate for the data in this study, then all residents with dementia in long-term care facilities must have been treated for significant psychosis or severe and violent symptoms of Alzheimer's disease at least once during a three year period. A more plausible

explanation for these results is that there appears to be an over utilization of antipsychotic medications in long-term care facilities in the province, especially since 31% of residents were chronic users of antipsychotics, which significantly increase the risk of adverse effects**.**

According to studies released by the Canadian Institute for Health Information (CIHI, 2012; CIHI, 2016), the total prevalence of antipsychotic prescriptions for seniors has decreased in some provinces but increased in others. British Columbia, Ontario, and Manitoba saw decreases in their overall antipsychotics prescribing patterns but provinces in the Maritimes reported an increase. Factors contributing to this phenomenon may include the increasing median age of the Atlantic provinces (Statistics Canada, 2011) as well as the more developed policies by other provinces in other parts of Canada which influence Canada wide policy as a result of more research being conducted in these provinces (Bueckert et al., 2017).

The class of antipsychotic (typical versus atypical) has also changed over time throughout the country as the newer atypicals became more widely available. Use of atypical antipsychotics has been increasing over the past few decades since their release while the use of typical antipsychotics has been correspondingly decreasing. It is worth noting that while atypical antipsychotics were designed specifically to decrease the frequency of EPS, there are studies suggesting that they do not significantly decrease the risk of falls and fractures in seniors, a major concern in this vulnerable population (Hien Le et al., 2005; Steinberg & Lykos, 2012).

4.4 DISCUSSION OF STUDY TWO RESULTS

4.4.1 Geographic Distribution of Benzodiazepine Use

Results from this study show that urban dwelling seniors in the community setting were more likely to be prescribed benzodiazepines than rural dwelling seniors. They received significantly more benzodiazepine prescriptions and in higher doses (indicated by DDDs per 1,000 people per day) than their rural dwelling counterparts.

Differences in the prevalence, rate, and volume of benzodiazepine prescriptions may be due to the difference in lifestyle that exists between urban and rural dwelling seniors. One possible explanation of these results is that urban dwelling seniors may be more likely to live alone relative to rural dwelling seniors, resulting in an increased feeling of isolation and anxiety requiring treatment with benzodiazepines. Rhee et al. (2011) found that seniors living with caregivers were significantly less likely than those living alone to be prescribed antipsychotics, the same could be true for benzodiazepines.

In the long-term care setting, the prevalence of benzodiazepine prescription remained similar among the Eastern, Central, and Western Health regions but was significantly ($p<0.05$) lower for the Labrador-Grenfell Health region. This may be due to the fact that the Labrador-Grenfell Health authority has fewer residents in facilities compared to the other authorities. The small number of people in these facilities would also enable more personal care of residents, lowering the need for the prescription of psychoactive medications to regulate disruptive behaviour.

The prevalence of benzodiazepine prescriptions was significantly different for the facilities where at least 30 residents received benzodiazepine prescriptions. Currently, prescribers in each facility have their own criteria that determine whether a resident

requires a prescription. Policy changes could institute province-wide regulations that would standardize the criteria required to prescribe a medication to a resident, especially when the medication in question causes well documented and serious adverse effects. Regular mandated review of a patient's medication use and a systematic application of deprescribing guidelines would also help optimize benzodiazepine use in long term care facilities.

4.4.2 Geographic Distribution of Antipsychotic Use

The prevalence, rate and volume of antipsychotic prescriptions in the community were all significantly higher in urban areas relative to rural areas. An explanation for this finding has already been presented in the previous section, where Rhee et al. (2011) found that seniors who lived with care givers were significantly less likely to be prescribed antipsychotic medication.

Prevalence, rate, and volume were all highest in the facilities in the Eastern Health RHA, with prevalence being significantly lower in the Labrador-Grenfell region facilities when compared in a pairwise fashion ($p>0.05$). All other outcomes showed no significant difference across the four RHAs. One reason that could contribute to Eastern Health consistently having higher results for all three outcomes is facility size. The Eastern Health region has nine of the most populated long-term care facilities in the province, the largest of which has 156 residents. As shown in the study by Chen et al. (2010) the size of a facility is significantly and positively correlated to prescription prevalence of psychoactive drugs. Operating style and work culture at facilities can also affect the prescription of psychoactive medications. The American study by Hughes et al. (2007)

reports that such "cultures" dictate important aspects of facilities including the prescription of medications to its residents.

4.5 LIMITATIONS OF THE STUDIES

Taken together, study one and study two give a fairly comprehensive overview of the patterns of utilization for benzodiazepines and antipsychotics amongst seniors in Newfoundland and Labrador. There are limitations, however, that need to be considered when interpreting the findings. The analysis of seniors living in the community setting relied upon data from those receiving coverage under the NLPDP. Therefore, the results cover that portion of seniors in Newfoundland and Labrador (approximately 80%) and not the total senior population. Similarly, data from long-term care facilities that are publicly funded were included in the analysis, thus excluding those living in private care homes.

Data used for analysis in these studies were initially collected for administrative purposes. It would have been useful to have access to data that would have expanded and enhanced the research questions undertaken in these studies. For example, reason for the prescription (that is the diagnosis) would be helpful to correlate a diagnosis with a prescription and monitor the most commonly diagnosed conditions in seniors. The available data tracks the number of medications prescribed but not the number of medications taken. Drug compliance, therefore, cannot accurately be measured. The lack of information on physicians prescribing medications results in the inability to verify whether or not a senior received prescriptions from multiple physicians. Any patterns of

prescriptions within groups of seniors being treated by the same physician could not be determined with the existing data.

Additionally, long-term care facilities fill out resident assessment instruments (RAIs) annually for each of their residents. RAIs are a series of assessment tools that document what treatments or interventions a resident is receiving and the resident's progress in response to them. The information from RAIs could prove vital for understanding which residents are receiving psychoactive prescriptions and how they are responding to treatment when linked with other databases.

Finally, seniors with missing or unusable data important to the study had to be excluded from the analysis. An example of this would be a home address given as being outside of Newfoundland and Labrador for a senior. The address on file may have been a previous home address for the resident or the address of their primary contact. Residents in long-term care who remained out of facilities for greater than one week between stays were also removed from the analysis.

4.6 CHALLENGES AND BARRIERS TO CHANGE

When compared to the Canadian average, the province of Newfoundland and Labrador has the highest prevalence of seniors aged 65 and over. In 2013, the treatment of seniors over 65 in Canada constituted 44% of healthcare spending (CMA, 2013). Given that Newfoundland and Labrador has the highest prevalence of seniors in the country, one would expect the burden put on our provincial healthcare system to be significant.

The Canadian Agency for Drugs and Technologies in Healthcare (CADTH) released a document in 2014 comparing policies each province had in place to monitor drug use at the provincial level. Newfoundland and Labrador at the time, was one of three provinces that did not have a prescription monitoring program. The situation was only remedied in May of 2016 with the introduction of a province wide system that allows pharmacist to monitor all prescriptions (including benzodiazepines and antipsychotics). If a patient is filling multiple prescriptions at different pharmacies and/or from different doctors, this information will appear on the system.

Another challenge is the long wait times for patients to see a specialist who can appropriately prescribe psychoactive medications. As an example, the Newfoundland and Labrador Medical Association (NLMA, 2011) states that the average wait time in the province for a psychiatrist after referral from a family physician is 30 weeks, the second highest out of all provinces. Over 30% of patients will wait more than a year to be seen. In 2015, Newfoundland and Labrador was one of only two provinces in Canada (the other being Prince Edward Island) that had no board certified geriatricians practicing (CMA, 2015). This situation has only recently been remedied. The prescription of psychoactive medications such as benzodiazepines and antipsychotics require a thorough interview process and significant time spent with the patient to find the correct drug and dose. While it in unnecessary for all seniors to be managed by a geriatrician, complicated cases would preferably be referred to them. This would help mitigate the problem that the fast-paced and stressful nature of a (usually privately owned) family practice is not set up to handle the complex needs of some seniors despite the physician's best efforts.

4.7 IMPACT OF STUDY AND FURTHER RESEARCH

This research into the utilization of benzodiazepines and antipsychotics in Newfoundland and Labrador provided an in-depth examination into aspects of prevalence, rate, and volume as well as geography. The level of analysis is valuable because it allows comparison of rural versus urban areas as well as a more in-depth view of regional health authorities than has been previously available. Further research should be conducted that connects diagnosis and outcomes data with prescribing data. This would highlight any possible connections between diagnosis of a condition, severity of outcome, and the type of drug which was prescribed for the condition in terms of rate and volume of the dose. In addition, having physician prescribing information would enable the researcher to explore any potential patterns in prescribing for individual physicians. An extension of this work to incorporate data for all seniors in the province would be a logical next step using the already existing pharmacy network. This would provide a more comprehensive view of the utilization patterns of benzodiazepines and antipsychotics in Newfoundland and Labrador.

Future research into the utilization of benzodiazepines and antipsychotics should consider the use of quasi-experimental studies such as interrupted time-series analysis or cohort studies. This would be done in order to examine the programs already initiated within Newfoundland and Labrador to evaluate their effectiveness. Some interesting examples of initiatives currently in place include the de-prescribing program set up by the medication therapy services (MTS) clinic at Memorial University. This campaign aims to help patients discontinue medications (including benzodiazepines and antipsychotics) which they no longer need or may even be doing them harm (School of Pharmacy, 2017).

Additionally, the Central and Western Health RHAs through the Canadian Foundation for Healthcare Improvement (CFHI) initiated a de-prescribing program aimed exclusively at the discontinuation of antipsychotic prescriptions for residents in long-term care settings in 2015. This initiative has now spread province wide with the other two health authorities taking part.

4.8 RECOMMENDATIONS FOR POLICY MAKERS AND PRACTIONERS

During the course of this research, several issues became apparent. Some of these relate to the data available for analysis, while others became obvious as results of the analysis were revealed. The following are some of the recommendations that emerged from this work.

These studies on the use of benzodiazepines and antipsychotics relied on secondary data compiled for primarily administrative purposes. While these data served the research reasonably well, consideration should be given to compiling and managing a database that more directly addresses research needs and serves policy formulation. Consideration should also be given to the value of using quasi-experimental studies as part of future research initiatives.

With the recent electronic connection of pharmacies in the province (May 2016), more data became available for future research analysis. If these data are to be utilized to their full potential, consideration should be given to devoting more resources, both human and electronic, for this purpose.

Guidelines such as those advised by the WHO (1996) and followed to various degrees by some provincial governments should be studied for potential adoption in this province. These guidelines include, for example, the need of continuing education for clinicians, particularly as it relates to important diagnostic information and appropriate medication prescription.

As part of the Choosing Wisely initiative the document, When Psychosis Isn't the Diagnosis, was published in July 2017 (Bueckert et al., 2017). Already health authorities and individual facilities in Newfoundland and Labrador have begun to implement some of the recommendations contained in the document. Serious consideration should be given to the full discussion and recommendations contained in the publication. Provincial policies should include the full adoption of these recommendations province wide.

4.9 CONCLUSION

The main objective of this research was to measure variation in the utilization of benzodiazepines and antipsychotics in Newfoundland and Labrador over time and across geographic and administrative areas.

Results indicated that the prevalence and rate of prescriptions for both benzodiazepines and antipsychotics remained stable over the duration of the study. It was also found that the prevalence and rate of prescriptions for both benzodiazepines and antipsychotics were significantly influenced by geography in both the community and long-term care settings. Comparable studies from other parts of North America reached

similar conclusions about antipsychotics but the distribution patterns of benzodiazepine prescriptions in this province were different from other regions studied.

The results of the research also show the prevalence for benzodiazepine prescriptions to seniors in Newfoundland and Labrador communities being similar to the rest of Canada (CIHI, 2012). However, the prevalence of antipsychotic prescriptions to residents in Newfoundland and Labrador long-term care facilities was higher than the Canadian average (CIHI, 2016). With the data currently available to us it is not possible to tell whether or not the prevalence of these prescriptions is appropriate. Further study is required that specifically includes diagnosis and severity of condition in order to gain a better understanding of appropriate prescribing practices for seniors.

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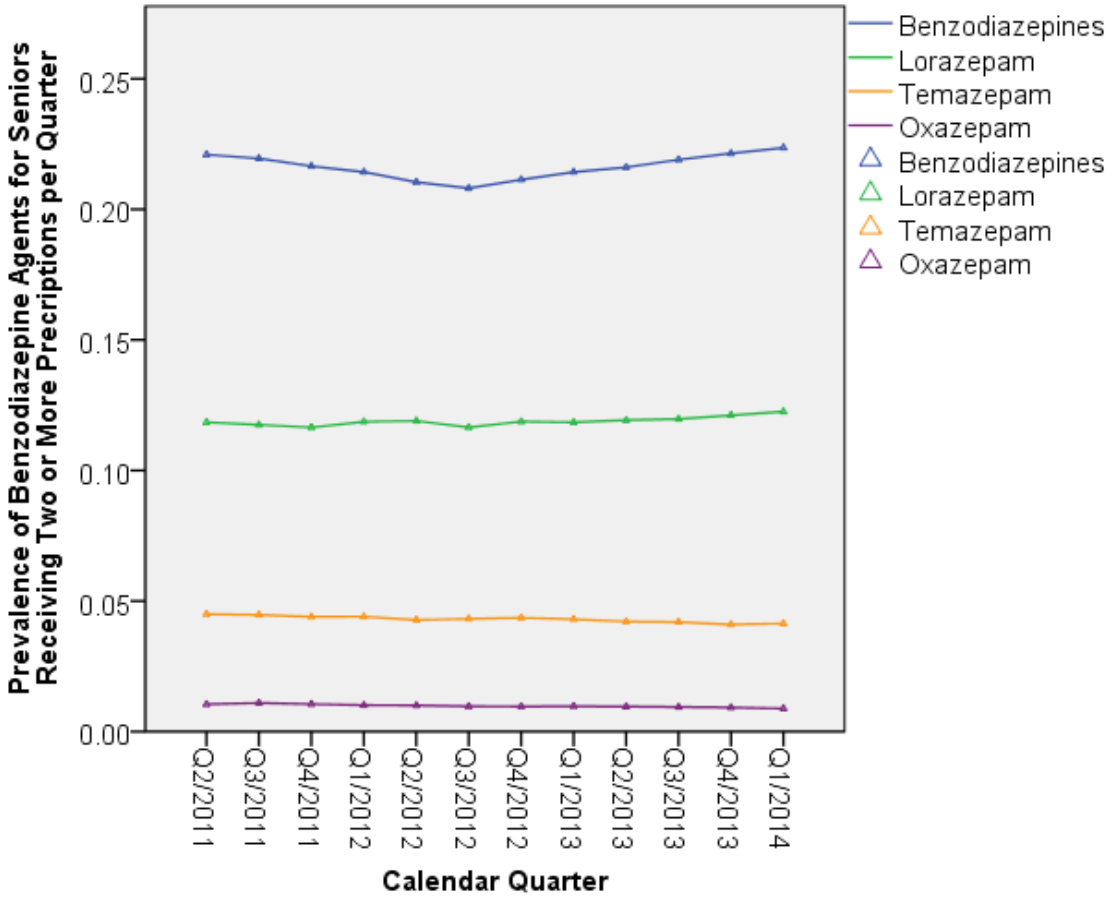
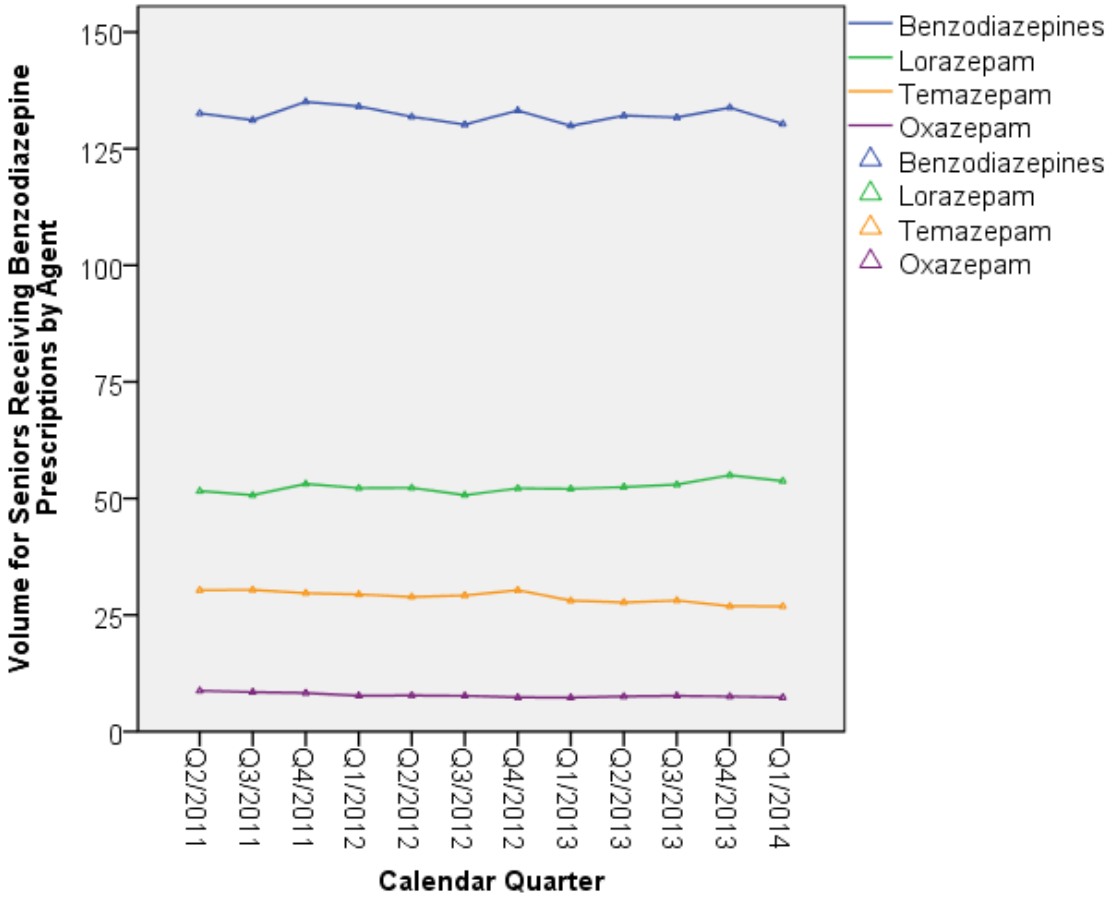
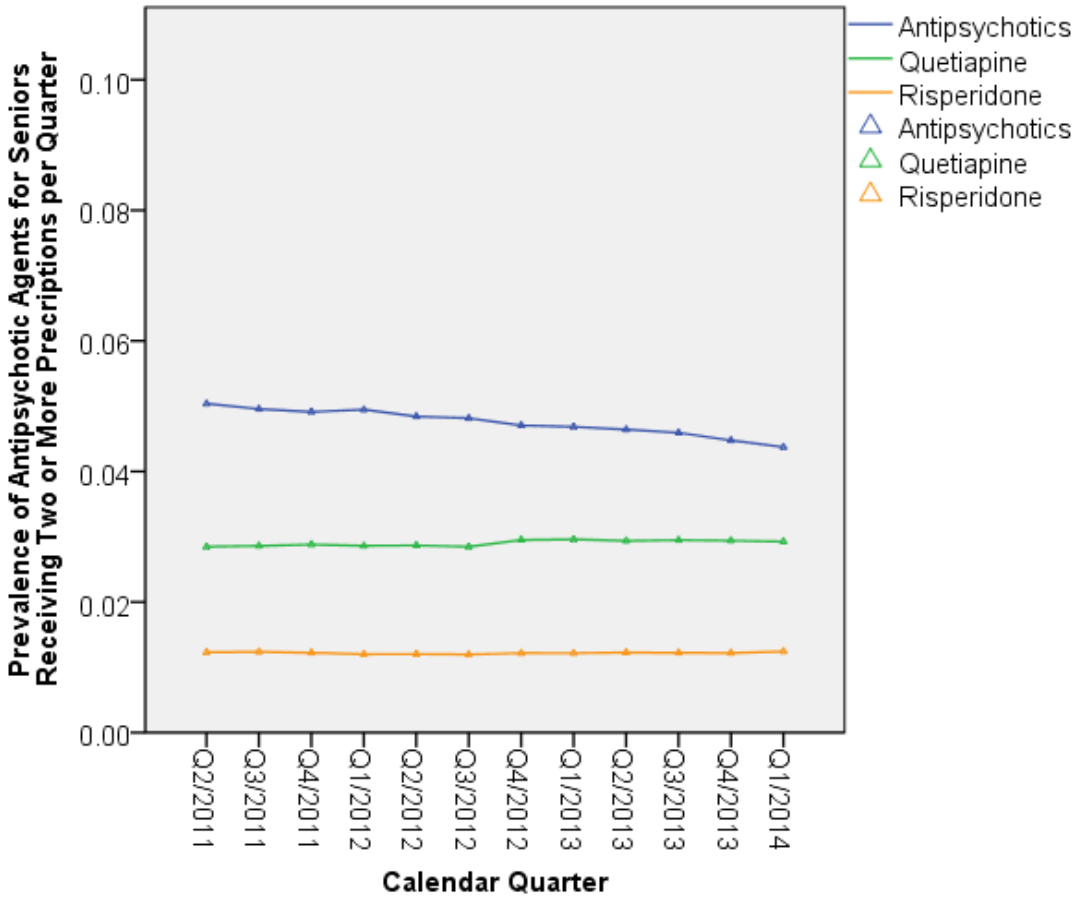
Appendix 1.1: Prevalence of Individual Benzodiazepine Agents for Seniors in the Community



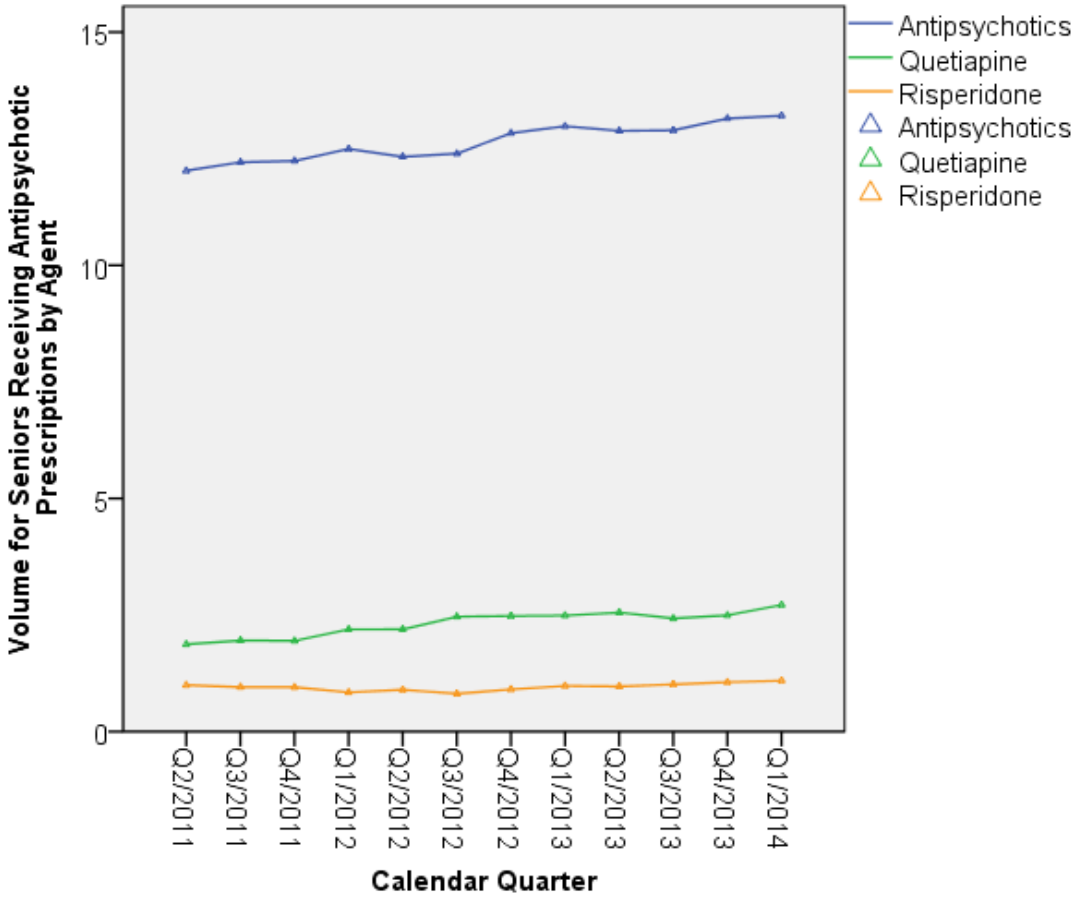
Appendix 1.2: Volume of Individual Benzodiazepine Agents for Seniors in the Community in DDDs/1,000 People/Day



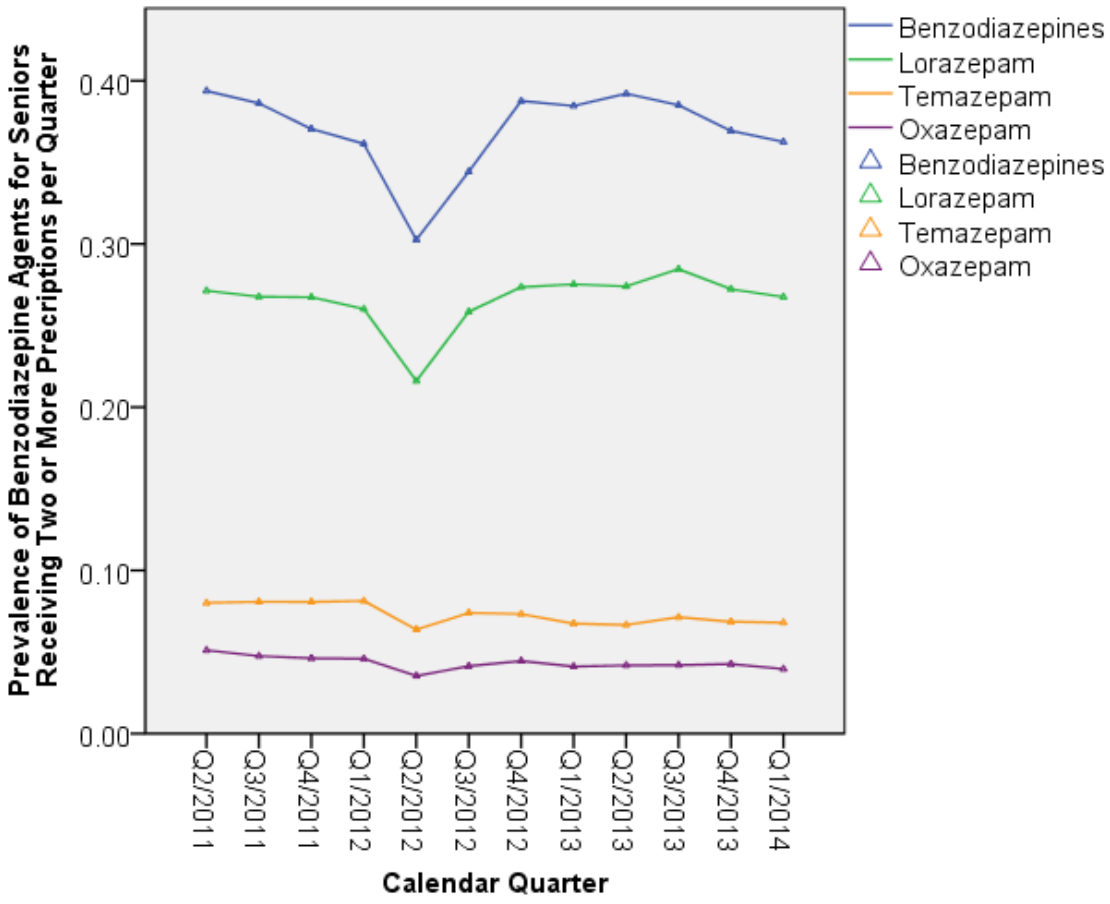
Appendix 1.3: Prevalence of Individual Antipsychotic Agents for Seniors in the Community



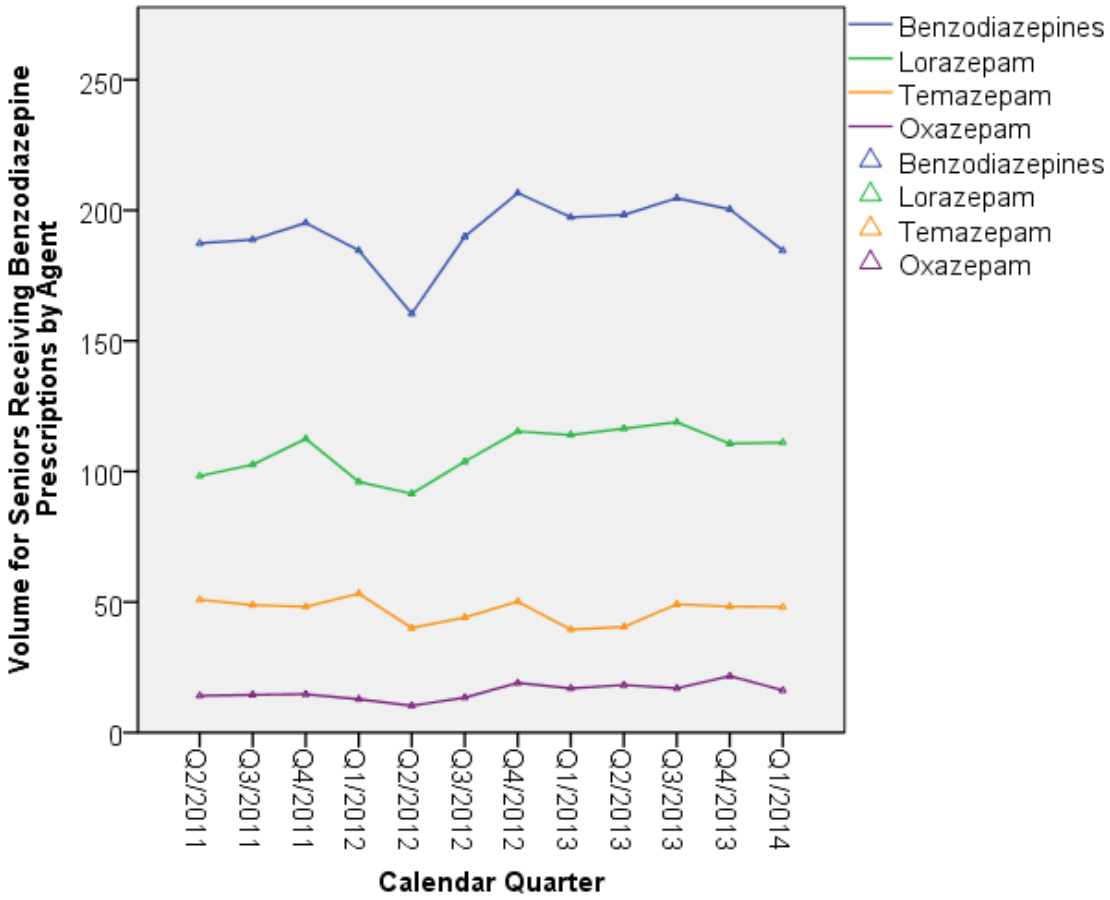
Appendix 1.4: Volume of Individual Antipsychotic Agents for Seniors in the Community in DDDs/1,000 People/Day



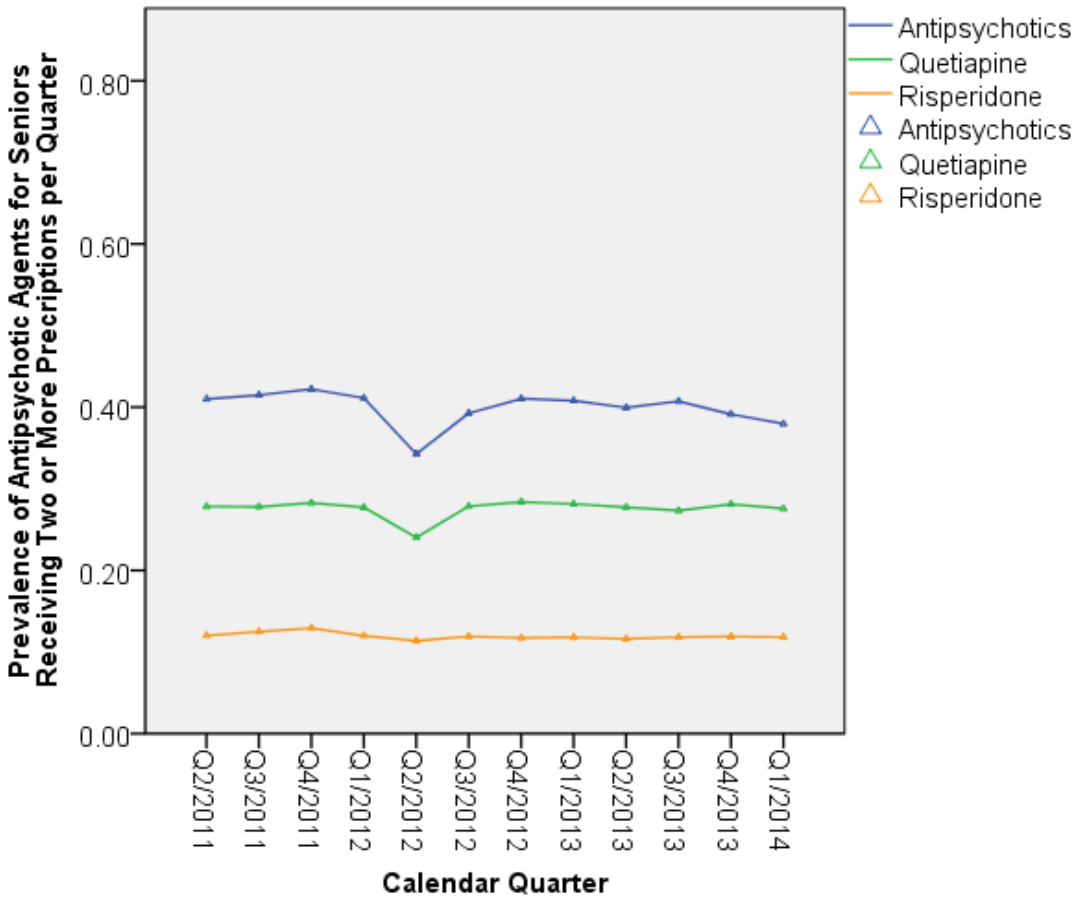
Appendix 1.5: Prevalence of Individual Benzodiazepine Agents for Seniors in Long-Term Care



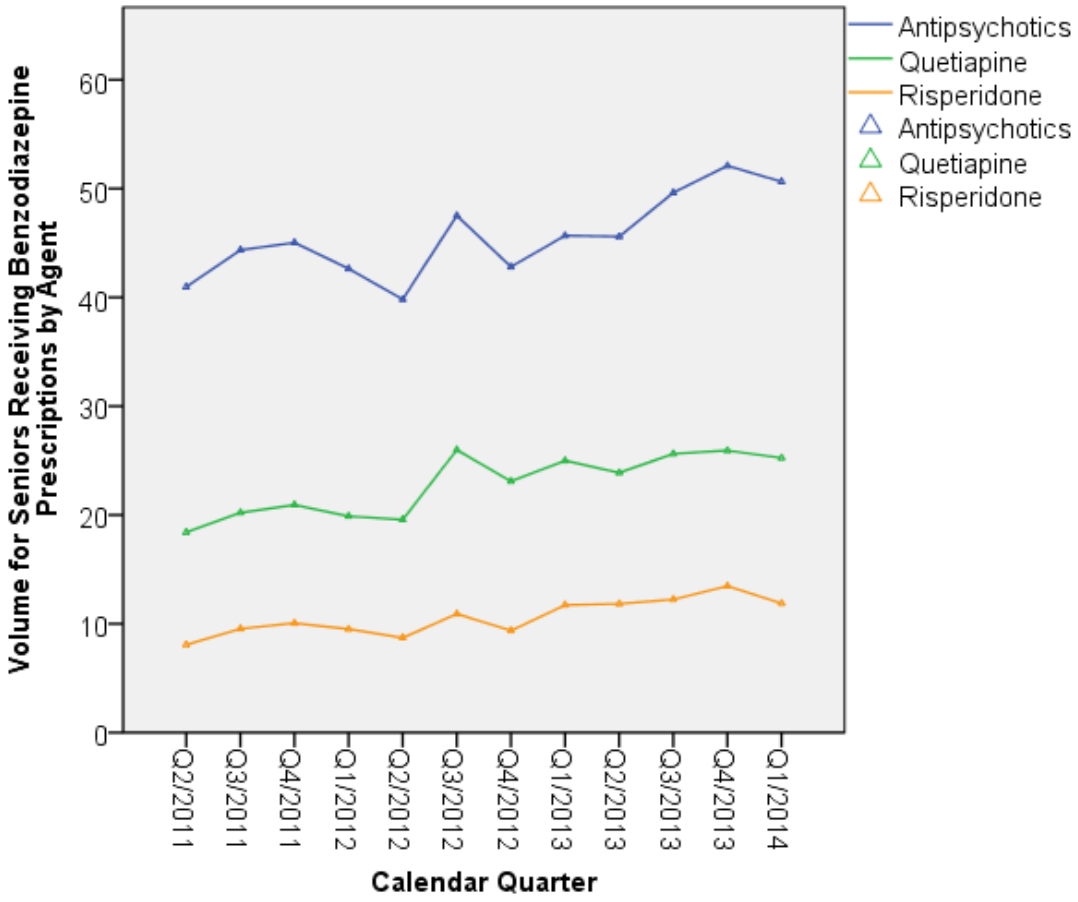
Appendix 1.6: Volume of Individual Benzodiazepine Agents for Seniors in Long-Term Care in DDDs/1,000 People/Day



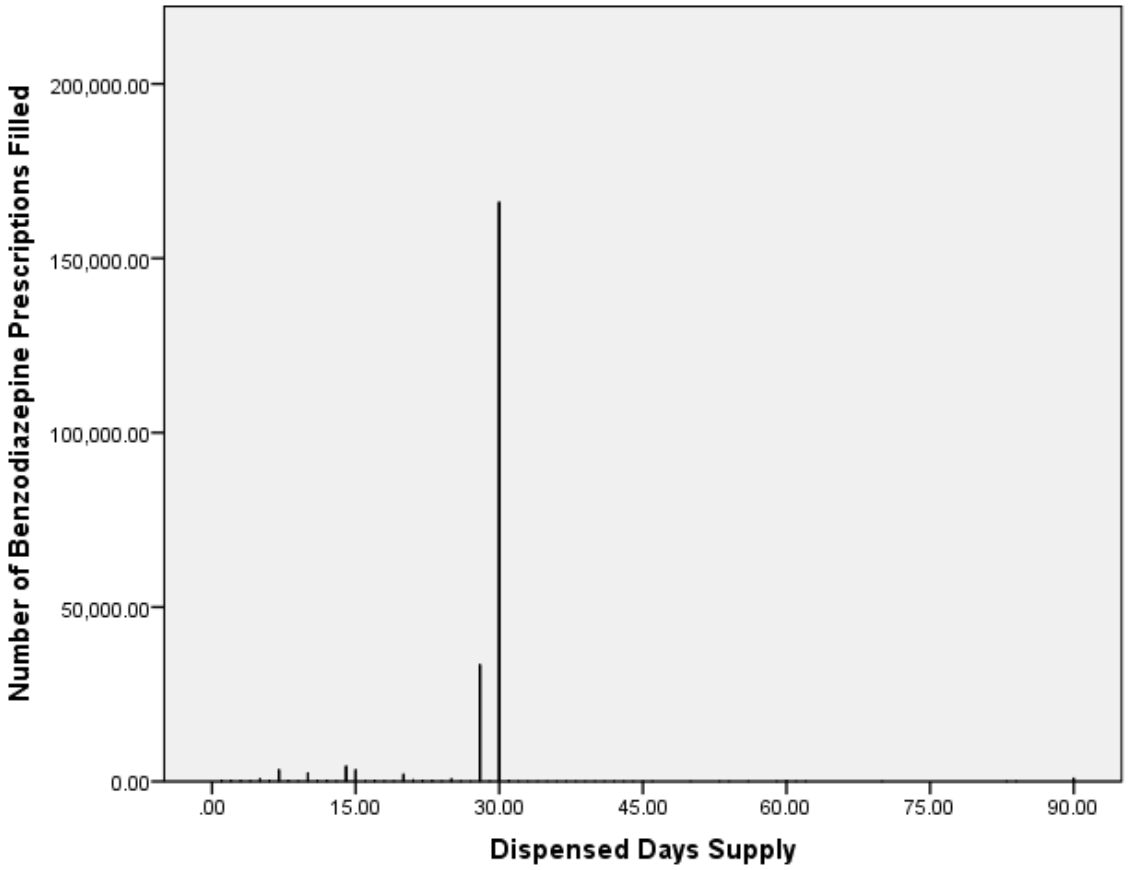
Appendix 1.7: Prevalence of Individual Antipsychotic Agents for Seniors in Long-Term Care



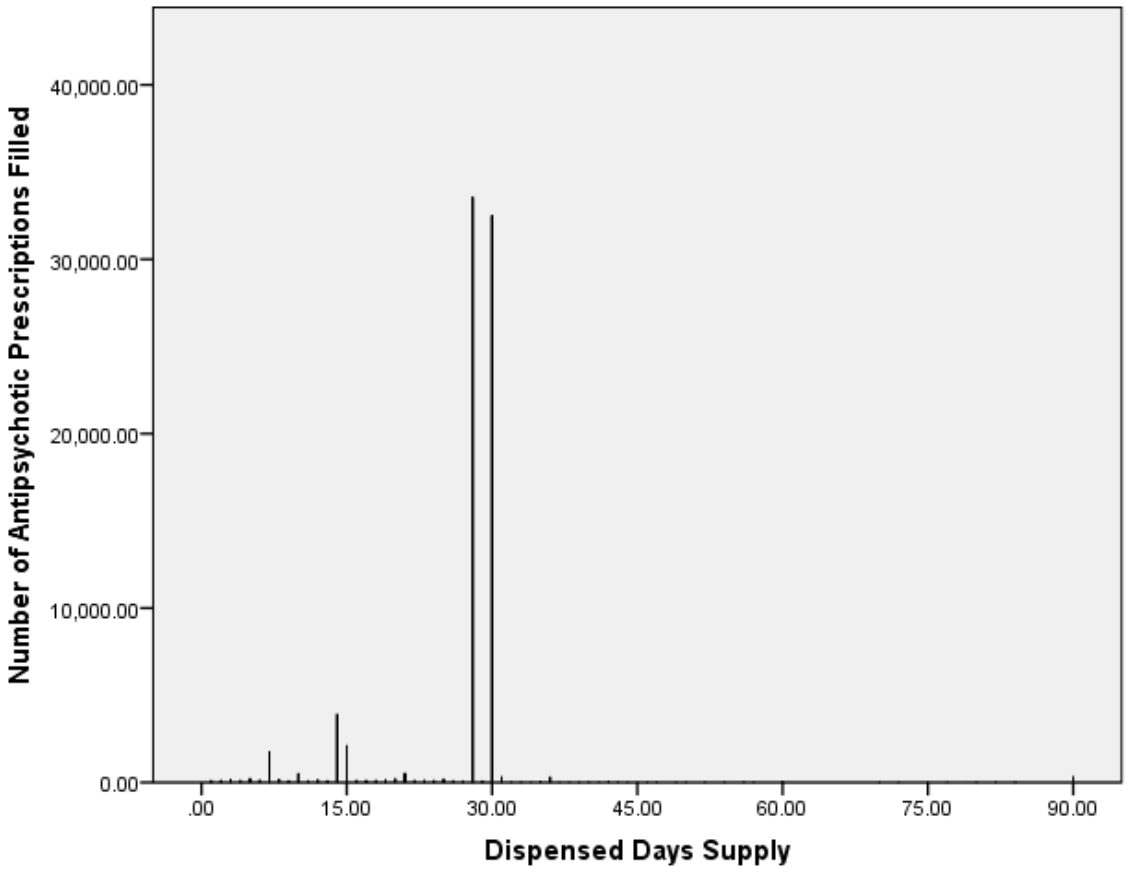
Appendix 1.8: Volume of Individual Antipsychotic Agents for Seniors in Long-Term Care in DDDs/1,000 People/Day



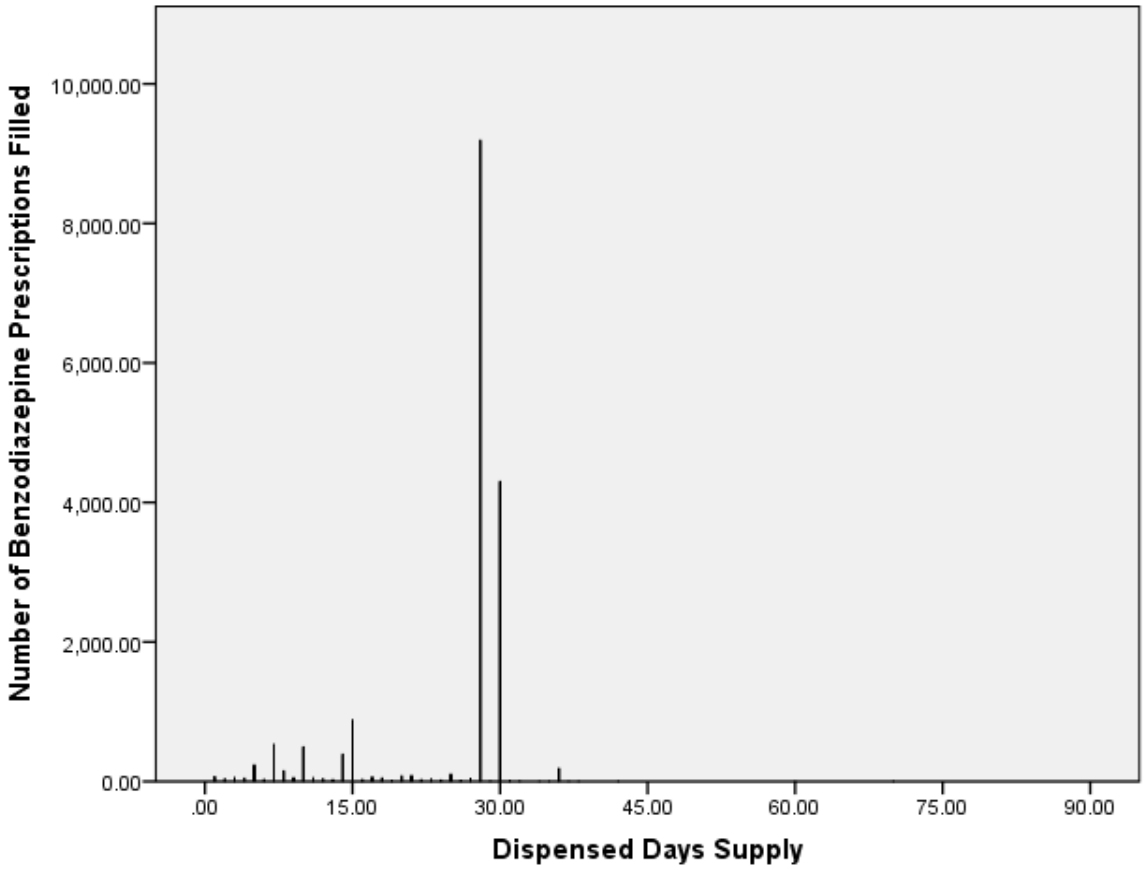
Appendix 2.1: Average Days' Supply for Benzodiazepine Prescriptions in the Community



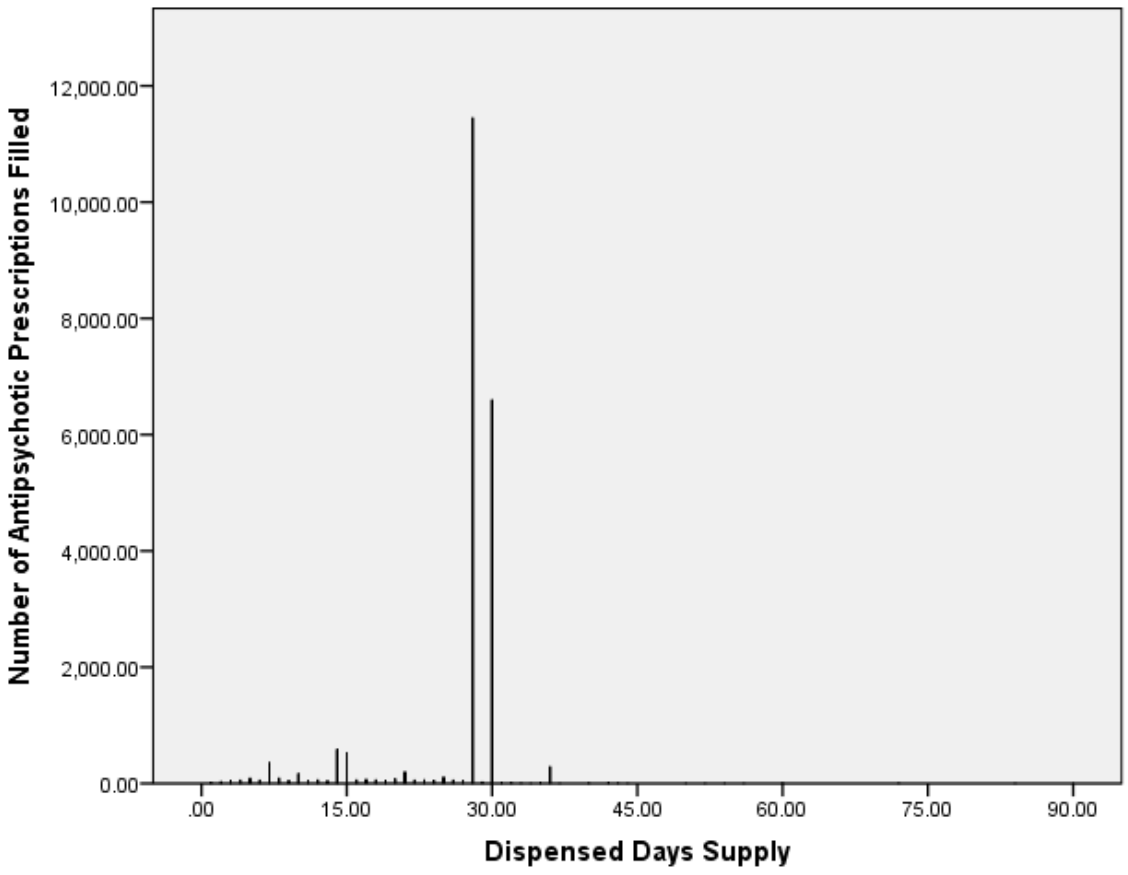
Appendix 2.2: Average Days' Supply for Antipsychotic Prescriptions in the Community



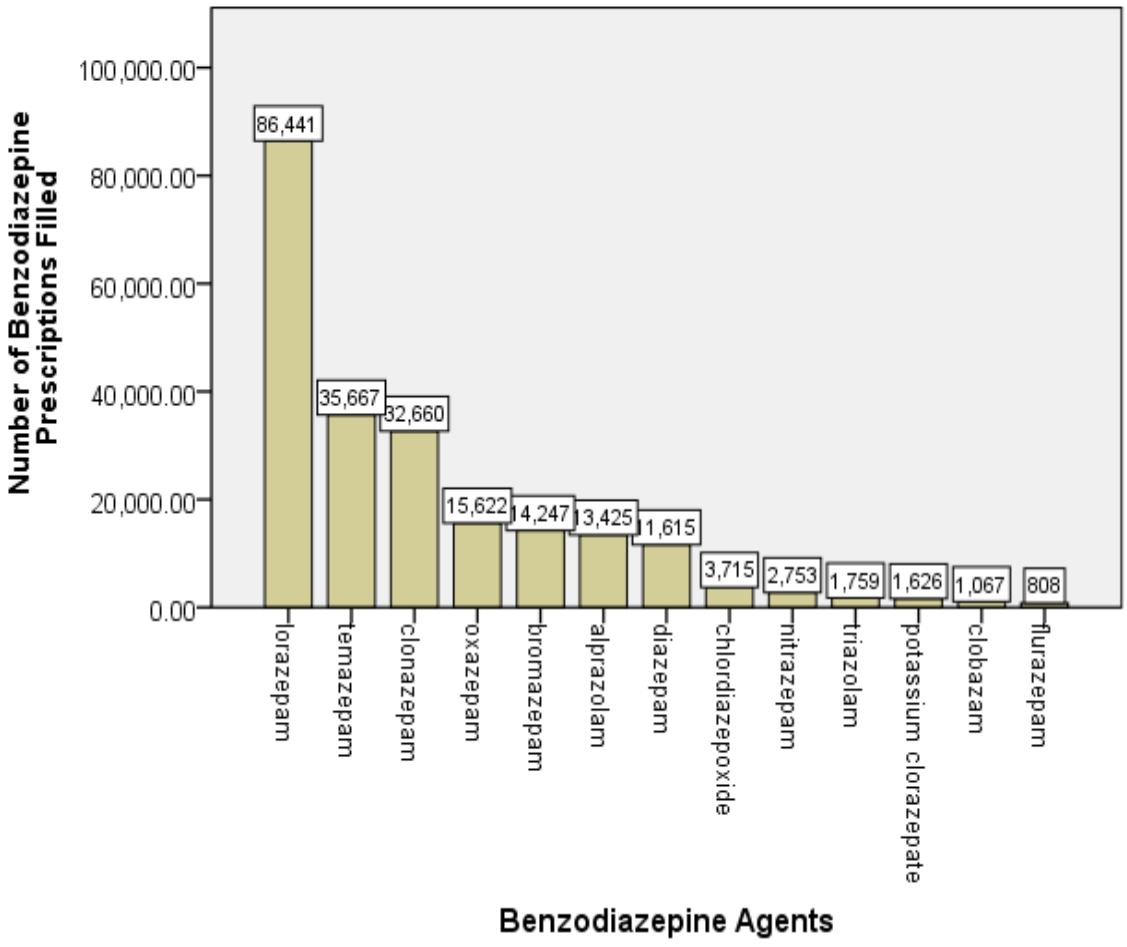
Appendix 2.3: Average Days' Supply for Benzodiazepine Prescriptions in Long-Term Care



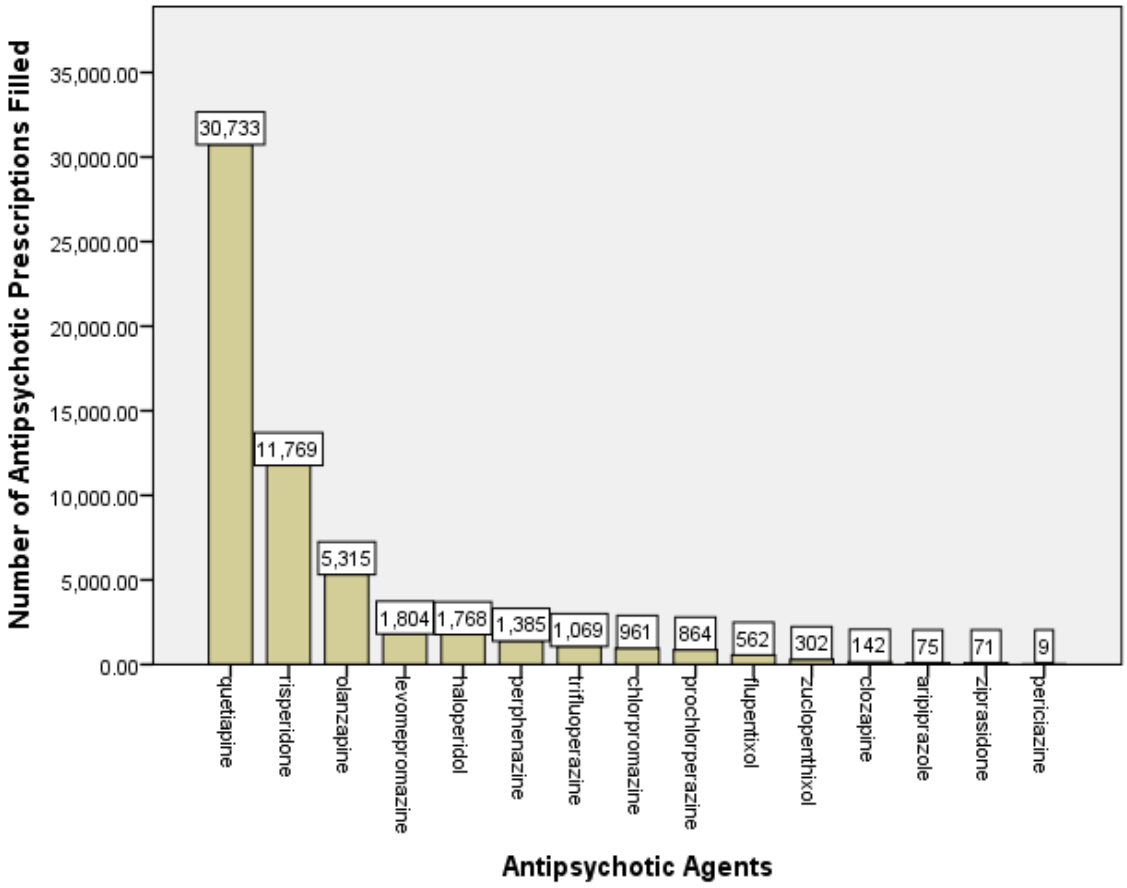
Appendix 2.4: Days' Supply for Antipsychotic Prescriptions in Long-Term Care



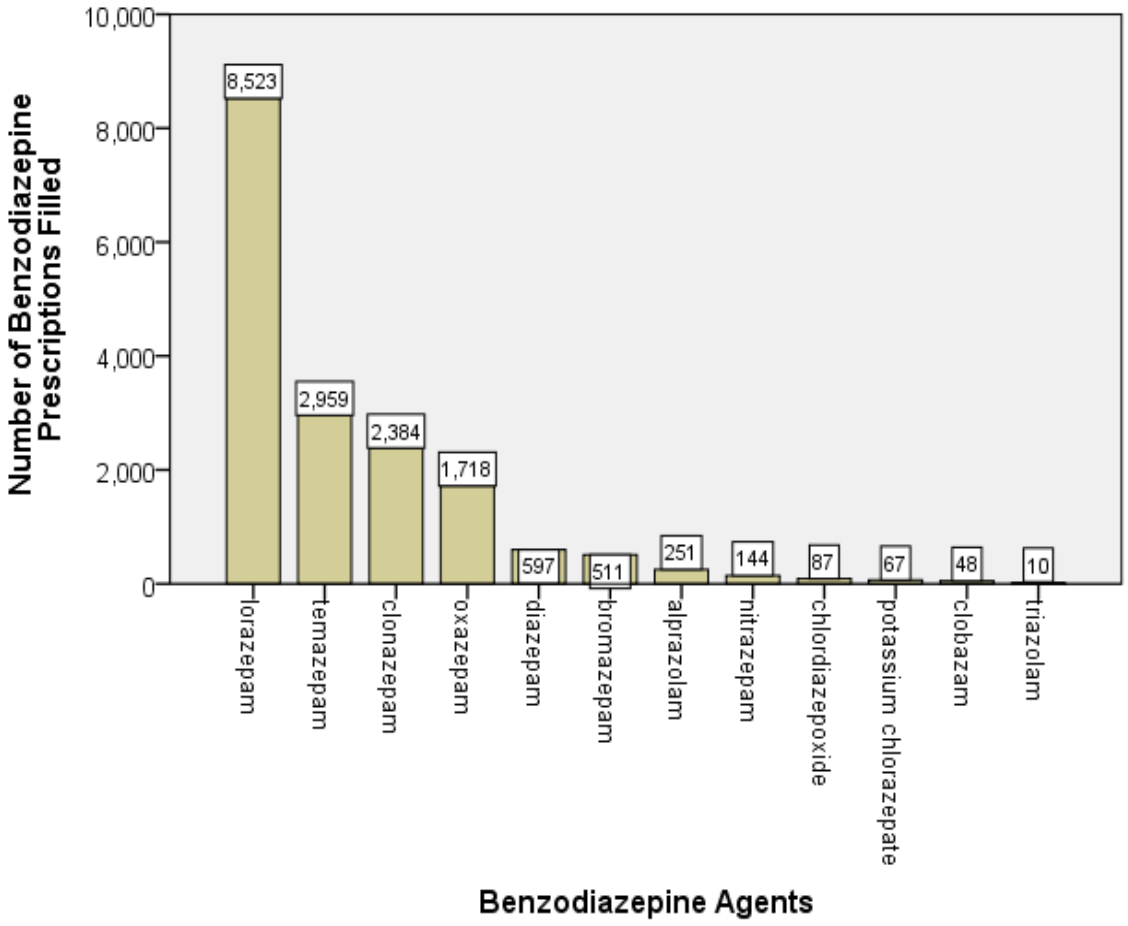
Appendix 3.1: Benzodiazepine prescriptions filled in the community by individual agent



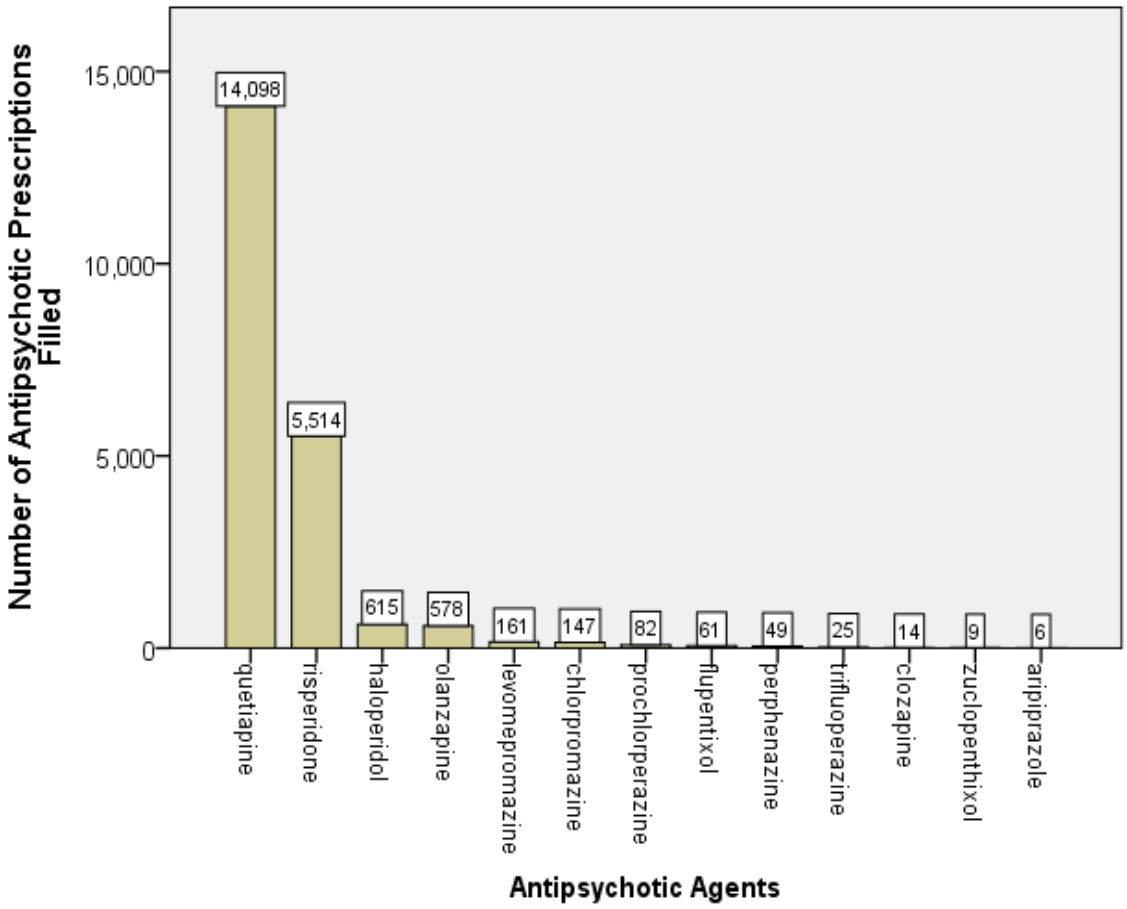
Appendix 3.2: Antipsychotic prescriptions filled in the community by individual agent



Appendix 3.3: Benzodiazepine prescriptions filled in long-term care by individual agent



Appendix 3.4: Antipsychotic prescriptions filled in long-term care by individual agent



Appendix 4.1: Anatomical Therapeutic Chemical (ATC) codes for all benzodiazepine agents

Drug Class	Sub Class	Agent	ATC Code
Benzodiazepines			
	Anticonvulsants	Clonazepam	N03AE01
	Anxiolytics	Diazepam	N05BA01
		Chlordiazepoxide	N05BA02
		Oxazepam	N05BA04
		Potassium Clorazepate	N05BA05
		Lorazepam	N05BA06
		Bromazepam	N05BA08
		Clobazam	N05BA09
		Alprazolam	N05BA12
	Sedative/Hypnotics	Flurazepam	N05CD01
		Nitrazepam	N05CD02
		Triazolam	N05CD05
		Temazepam	N05CD07

Appendix 4.2: Anatomical Therapeutic Chemical (ATC) Codes for all antipsychotic agents

Drug Class	Sub Class	Agent	ATC Code
Antipsychotics			
	Typical	Chlorpromazine	N05AA01
		Levomepromazine	N05AA02
		Perphenazine	N05AB03
		Prochlorperazine	N05AB04
		Trifluoperazine	N05AB06
		Periciazine	N05AC01
		Haloperidol	N05AD01
		Flupentixol	N05AF01
		Zuclopenthixol	N05AF05
	Atypical	Ziprasidone	N05AE04
		Clozapine	N05AH02
		Olanzapine	N05AH03
		Quetiapine	N05AH04
		Risperidone	N05AX08
		Aripiprazole	N05AX12