A Ten-Year Retrospective Comparison of Benzodiazepine Usage Between Rural and Urban Residents of Newfoundland and Labrador

by Ryan Batten ©

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Abstract

Background: Benzodiazepines are believed to be one of the most overprescribed medications worldwide. Inappropriate prescribing of benzodiazepines can lead to serious adverse effects including cognitive impairment, falls in the elderly, and decreased motor function. Guidelines have been developed to address overprescribing, however analysis of prescribing patterns before and after implementing these guidelines shows inappropriate use is still present.

Objectives: This thesis examined benzodiazepine prescribing patterns in a sample of Newfoundland patients. Various definitions for inappropriate prescriptions were used: within 30, 45 and 60 days of previous prescription. Comparisons were assessed between rural and urban areas of Newfoundland, Canada.

Methods: Patients with a benzodiazepine prescription between 2007 and 2017, through the Newfoundland and Labrador Prescription Drug Program, were included in this study. Descriptive statistics were used to describe prescribing patterns. Regression analyses were used to examine the association between prescribing / usage and age, sex, prescriber specialty and location of residence (urban / rural).

Results: Using the various definitions for inappropriate prescribing, the rate of inappropriate prescribing was between 71.7% and 74.9%. Individuals in urban areas had a higher quantity of inappropriate prescriptions, less than 30 days apart, compared to those in rural areas. Additionally, the percentage of inappropriate prescriptions did not decrease during the ten-year timeframe examined.

Conclusions: Inappropriate prescribing remained prevalent in a Newfoundland and Labrador sample. Results from this study highlight that we need to remain vigilant pursuing strategies that encourage appropriate prescribing of this drug class.

General Summary

Benzodiazepines are commonly overprescribed and can have serious adverse effects. In an attempt to reduce overprescribing, national guidelines were introduced. The potential impact of these guidelines on prescribing can be explored through examining prescribing rates before and after their introduction. This thesis used data from the Newfoundland and Labrador Centre for Health Information to determine what prescribing rates were from 2007 to 2017. Findings suggest that benzodiazepine prescribing was inappropriate in 71.7% of the prescriptions examined. Furthermore, prescriptions were predominantly prescribed by a general practitioner to females. Individuals living in urban areas were prescribed a significantly higher quantity of pills and for a longer duration than those in rural areas. These findings demonstrate the need for interventions to reduce inappropriate prescribing in those individuals most at risk.

Authorship Statement

I hereby declare that I am the sole author of this master’s thesis and that I have not used any sources other than those listed in the bibliography and identified as references. All members of the supervisory committee contributed to discussion about the study design and analysis. All reviewed this thesis and gave approval for the final version. All supervisory committee members will be co-authors on any manuscript arising from the work.

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I would like to acknowledge the Newfoundland and Labrador Centre for Health Information for granting me access to the data that made this research possible.

Dedication

This thesis is dedicated to my parents whose unwavering love for me and support of my education made it possible for me to pursue this path. I also dedicate this thesis to my fiancée and my sister who have supported me throughout this process. I couldn’t have done this without you.

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List of Abbreviations

BZD: Benzodiazepine

BZRA: Benzodiazepine and Z-drugs

COPD: Chronic Obstructive Pulmonary Disease

CVD: Cardiovascular Disease

CME: Continuing Medical Education

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition

ER: Emergency Room

FDA: Food and Drug Administration, United States

GAD: Generalized Anxiety Disorder

GBP: Great British Pound

GP: General Practitioner

MCP: Medical Care Plan

NL: Newfoundland and Labrador

NLCHI: Newfoundland and Labrador Centre for Health Information

NLPDP: Newfoundland and Labrador Prescription Drug Program

Z-drugs: Zopiclone, eszopiclone, zaleplon and zolpidem

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Chapter 1: Introduction

1.1 Benzodiazepines, 1960s to Present

Benzodiazepines were introduced in 1960 as an anxiolytic with the purpose of replacing barbiturates. Barbiturates were associated with serious adverse effects, including acute poisoning, addiction (Mehdi, 2012; Roberts and Buckley, 2011), and fatal outcomes due to a narrow therapeutic index. As a result of these negative effects, prescribers switched to benzodiazepines due to the belief that the adverse effect profile was not as severe as barbiturates. Chlordiazepoxide was the first benzodiazepine marketed, under the name Librium, followed by diazepam, under the name Valium (Mehdi, 2012).

Benzodiazepines were believed to be effective in treating anxiety conditions without many of the negative side effects associated with barbiturates (chronic fatigue, vision problems, mood swings, addiction and dependence). Indications for benzodiazepine use expanded over time to include management of illnesses such as epilepsy and as a myorelaxant (Neutel, 2005).

By the 1970s, benzodiazepine prescribing had increased significantly, with diazepam becoming the most widely prescribed drug in Europe and the USA (Speaker, 1997). This prescribing trend continued throughout the 1970s. In 1977, benzodiazepines were the most prescribed drug globally, and in 1978, over 2.3 billion doses of diazepam were sold in the United States (Washton & Zweben, 2011; Dell'osso & Lader, 2013). This trend continued throughout the 1980s; in 1980, approximately 40 billion doses of benzodiazepines were consumed globally each day (Tyrer, 1980). Between 1969 and 1982, diazepam was the most prescribed drug in America (Dell'osso & Lader, 2013).

As the prevalence of this drug class increased, so did reports of adverse effects. As adverse effects, such as abuse liability, physical dependence and perceived addictiveness, were identified efforts were made to address them by changing prescribing guidelines (Rosenbaum, 2005). In New York State, interventions were implemented to decrease the consumption of benzodiazepines in the late 1980s. When there was an attempt to decrease the prescribing of benzodiazepines, prescribers returned to the previous, more harmful alternative, barbiturates (Neutel, 2005; Rosenbaum, 2005). Concerns associated with benzodiazepine use from the 1980s continued into the 1990s. A study examining adults with anxiety disorders between 1989-1991 concluded that approximately one third of adults did not receive any medication for treatment of their disorder, with approximately one third still not receiving medication in a 1996 follow-up (Salzman et al., 2001).

During this time period, prescribers were hesitant to prescribe benzodiazepines for patients as it was perceived that these individuals were seeking a "high" or a "buzz" (Rosenbaum, 2005). Due to this hesitancy, other treatments were used for conditions inappropriately. For example, for patients with Generalized Anxiety Disorder (GAD), there was an increase in antidepressant usage for those who did not have comorbid depression or another anxiety disorder (Rosenbaum, 2005).

Throughout the 2000s, hesitancy to prescribe benzodiazepines lessened. Between 1996 and 2013, the number of adults who filled a benzodiazepine prescription increased from 8.1 million to 13.5 million (Bachhuber et al., 2016). During this period, some American adults were being prescribed more than one benzodiazepine resulting in an increase from 1.1 kg to 3.6 kg of lorazepam-equivalents per 100,000 adults (National Institute on Drug Abuse, 2018). Benzodiazepine prescribing continued to increase throughout the 2000s. For example, between

2009 and 2016, the total number of benzodiazepines dispensed increased by 226% in the United States (U.S Drug Enforcement Administration [DEA], 2016).

In recent years, benzodiazepines have been used by adolescents and young adults as a recreational substance, primarily alprazolam (Xanax) and lorazepam (Ativan). As of 2013, misuse of benzodiazepines within the past month for young adults aged 12 and older, was estimated at 1.7 million people in the United States (SAMHSA, 2014).

Due to increasing research highlighting the adverse effects of benzodiazepine usage, there was an attempt to create drugs with a wider therapeutic index (increased or same therapeutic effect with reduction of toxicity), resulting in the creation of 'Z-drugs'. Zolpidem (Ambien) was introduced in the United States in 1992; however, as research increased on this class of drugs it was recognized, they were also associated with dependence and abuse (Victorri-Vigneau et al., 2014; Nielsen., 2017).

1.2 Benzodiazepine Prescribing

In 1960, benzodiazepines were introduced to replace barbiturates and treat anxiety, stress and insomnia (Hollister, 1983). Benzodiazepines are separated into two categories: short acting and long acting, based upon the half-life of the drug. Decisions to use a short-acting or long-acting benzodiazepine for an indication vary based upon the desired effects.

Over time, the range of indications increased to include acute stress attacks and sleep disorders (National Institute on Drug Abuse, 2005), as well as post-traumatic stress disorder (Guina et al., 2015), schizophrenia and bipolar disorder (Brunette et al., 2003).

Findings from several research groups concluded that inappropriate prescribing was prevalent, and benzodiazepines should typically be restricted to short-term usage (e.g., Swinson et al., 2006). Cunningham et al. (2010) conducted a study in British Columbia between 1996 and 2006, concluding that benzodiazepine usage increased in middle aged individuals over the 10-year time frame studied (Cunningham et al., 2010). Similarly, a study comparing the prescribing patterns of benzodiazepines between Nova Scotia and Australia reported that the rate of prescribing was twice as high in Nova Scotia (Smith et al., 2008).

Variations based upon geography have also been observed. Edelstein et al. (2014) determined that in less urban areas, 19.7% reported a psychotropic medication compared to 14.2% in more urban areas. As well, those residing in rural Pennsylvania were 1.5 times as likely to use anxiolytics than those living in urban areas (Edelstein et al., 2014). This led to potential hypotheses such as individuals living in an urban area have increased access to health care resources.

Benzodiazepines may be prescribed for anxiety disorders (including panic attacks), insomnia, seizure disorders and other indications approved by Health Canada (Health Canada, 2019). However, prescribing of benzodiazepines for inappropriate indications and periods of time has been reported. Bartlett et al (2004) examined benzodiazepine use in Québec for a 5-year period, concluding that the average length of use of benzodiazepines among the elderly was 75 days, substantially longer than the two to four-week recommended duration.

When benzodiazepines are prescribed for durations longer than recommended, efficacy reduces over time and the risk of an adverse effect increases. Seniors are at an increased risk due to age-related changes in drug pharmacokinetics and pharmacodynamics resulting in an increased risk for drug toxicity (Handler et al., 2006).

Despite recommendations that benzodiazepine (BZD) prescribing should be limited to two to four weeks, research has shown that in some cases, BZDs are used for weeks, months or even years (Barnas et al., 1991; Ishigooka et al., 1998; Egan et al., 2000; Neutel et al., 2003).

It is important that prescribers re-evaluate patients' drug usage to ensure that prescriptions are within the established guidelines to mitigate the potential for abuse and adverse events. There have been reports that women are more likely to receive a benzodiazepine for non-medical reasons such as coping with stress and grief or adjusting to childbirth and menopause (British Columbia Ministry of Health, 2008).

As the body of literature increased on adverse effects and prevalence of inappropriate prescribing, medical associations and governing bodies began to issue guidelines for appropriate prescribing and necessary precautions that should be taken when prescribing them. Globally, one such public health agency is the World Health Organization which published a document detailing precautions for benzodiazepine prescribing (WHO, 1996). Various countries have also issued guideline (at various points in time) for benzodiazepine prescribing, in an attempt to reduce inappropriate prescriptions. In Canada, provincial medical associations have issued guidelines to address the overprescribing of benzodiazepines (Newfoundland & Labrador Pharmacy Board, 2019).

Other initiatives have been created that focus on reducing the prescribing of harmful medications, benzodiazepines among them. One such initiative is the Canadian Deprescribing Network, which focuses on knowledge translation through the creation of algorithms that can be used to stop the use of certain medication, including benzodiazepines, or to reduce the dosage safely (Canadian Deprescribing Network, 2017). Other approaches to reduce the overprescribing of medication, including benzodiazepines, are national campaigns such as Choosing Wisely

Canada and drug recovery initiatives (Government of Canada, 2014; Choosing Wisely Canada, 2017).

1.3 Polydrug Use

Polypharmacy, the prescription of multiple medications concurrently, can be an issue across all medications, including benzodiazepines. When certain substances are ingested concurrently, the results can be harmful. Specifically, when benzodiazepines are combined with substances that act upon the central nervous system, such as opioids and alcohol, harmful effects (including death) can occur. Benzodiazepines are involved in more than 30 percent of overdoses involving opioids (National Institute on Drug Abuse, 2018). Both drug classes sedate users and suppress breathing, which is often the cause of overdose fatalities (National Institute on Drug Abuse, 2018).

Sun et al. (2017) examined the concurrent use of benzodiazepines and opioids between 2001 and 2013, with concurrent usage rising from 9 percent to 17 percent, respectively. One study comparing the overdose death rates between individuals receiving opioids and benzodiazepines concurrently and those receiving opioids only; the authors concluded that the death rate was 10 times higher in the population receiving both medications (Dasgupta et al., 2016). Due to the risk of fatality when opioids and benzodiazepines are ingested concurrently, the United States Food and Drug Administration issued black box warnings on both classes of medication to highlight the extreme risk.

It is projected that there will be 700,400 opioid overdose deaths between 2016 and 2025 in the United States alone (Chen et al., 2019). Benzodiazepines were estimated to be involved in 31% of opioid overdoses in 2011 (Jones et al., 2015). It is important to reduce inappropriate prescribing of benzodiazepines, not only because of their adverse effects generally, but specifically to aid in reducing opioid overdoses and the chance of interactions with other medications.

In recent years, benzodiazepines have been used by adolescents and young adults for recreational use, referred to as “Xans” in popular culture. As a result, drug diversion has become an increasing area of concern for adolescents and young adults (RCMP, 2010).

When benzodiazepines are consumed recreationally, alcohol is typically consumed concurrently. As noted, misuse of benzodiazepines combined with alcohol can be especially dangerous as both suppress the central nervous system (Jones et al., 2014). Combination of these two substances is of major concern for young adults; those between 18 and 25 have the highest prevalence of benzodiazepine misuse in the United States (SAMHSA, 2014). Kurtz et al. (2016) examined young adults in Miami involved in the ‘club scene’, concluding that 87.4% of the study sample had misused benzodiazepines.

While polysubstance use is of concern, such as opioids and alcohol, polypharmacy is also of concern and typically affects the senior population due in part to the likelihood of being prescribed medications for comorbidities. A study examining polypharmacy in adults over 65 years of age determined that 72.9 percent of the population was exposed to five drugs or more, while 28.4 percent of participants took 10 drugs or more (Blanco-Reina et al., 2016).

When consuming multiple medications, there can be harmful drug-drug interactions amongst the drugs; however, for benzodiazepines, there is an added concern of patients being prescribed more than one benzodiazepine concurrently. Patients that are prescribed multiple benzodiazepines are at an increased risk for adverse effects due to the medications competing for the same receptor.

Drug diversion, the transfer of a legally prescribed substance from the individual to another for illicit use, is of particular concern. Prescription drugs are commonly passed on by, taken from or shared amongst friends and family members (Public Safety Canada, 2011b; Florida Office of the Attorney General, 2012; Wisconsin State Council on Alcohol and Other Drug Abuse, 2012). A 2009 report by the Royal Canadian Mounted police determined that benzodiazepines were one of the top diverted controlled prescription drugs across Canada that year (RCMP, 2010). Furthermore, the report concluded that most prescription drugs were obtained through legitimate domestic sources (RCMP, 2010). A 2011 Ontario Student Drug Use and Health Survey reported 67% of youth who used an opioid pain reliever non-medically in the past year, had obtained the drugs from an individual in the same household (Boak et al., 2017). Those using prescription medication for non-medical purposes may not be aware of the potential adverse effects or potential drug-drug interactions.

Adolescents consuming benzodiazepines recreationally have the potential for an adverse effect due to three potential avenues: benzodiazepine use solely, the combination of benzodiazepines, and recreational substances such as alcohol or polypharmacy. The first two avenues have been previously discussed; however, the third is equally important. One of the issues with the consumption of benzodiazepines recreationally is the potential drug-drug interaction if the consumer is currently using another medication.

When benzodiazepines are combined with alcohol, the result can be harmful. It is important to educate the public on proper use of prescription medication and to inform patients, not least to encourage informed decisions, about medication use. In 2017, approximately 375,000 kids had taken a prescription medication not prescribed to them (Drug Free Kids Canada, 2017).

Among the most commonly abused prescription drug medications in this group are benzodiazepines (DFK, 2017).

1.4 Adverse Effects of Benzodiazepines

Long-term usage of benzodiazepines has been linked to adverse effects: some are reversible while others are not. Dependence and tolerance are the most commonly reported adverse effects, however there is potential for more harmful adverse effects such as an increased risk of Alzheimer's disease (Billioti de Gage et al., 2014) and hip fractures (Bartlett et al., 2009).

Research focused on the adverse effects related to benzodiazepine usage have typically focused on populations of seniors. Some reasons why seniors are often studied for benzodiazepine usage include the physiological changes that occur as humans age and the accessibility to prescribed medication for those in a long-term care facility.

As people age, physiological changes occur, affecting the pharmacokinetics of drug metabolism resulting in increased sensitivity to BZDs and a decreased ability to metabolize certain medications in seniors (American Geriatrics Society, 2015). This decreased ability to metabolize certain medications can result in an increased susceptibility to adverse effects in seniors. While adverse effects are evident across all ages, seniors are particularly at increased risk for hip fractures, Alzheimer's disease and others.

While seniors are an important population in which to study the adverse effects of benzodiazepine use, they are not the only at-risk population. These effects occur in all adults, especially in those using benzodiazepines for long periods.

Common adverse effects include dependence, tolerance, withdrawal, confusion, drowsiness, memory loss and slurred speech (Neutel, 2005; Health Canada, 2019). Severe adverse effects are related to benzodiazepine long-term usage including an increased risk of hip fractures in the elderly, cognitive decline, unwanted sedation, a reduction in coordination, a potential increased risk of Alzheimer's disease and risk of automobile accidents (Ray et al., 1987; Salzman, 1993; Gales and Menard, 1995; Neutel, 1995; Neutel et al., 1996; Rickels et al., 1999; Neutel et al. 2002; Lenze et al., 2003; Kallin et al., 2004).

Adverse effects due to the consumption of benzodiazepines are of concern on their own, however polysubstance use with benzodiazepines can substantially increase the risk. A commonly reported effect is dependency as a result of benzodiazepine usage, which occurs when prescribed for greater than the recommended two to four-week period (Greenblatt and Shader, 1978). Dependence can refer to either the physical or psychological, such as cravings, dependency that occurs from extended use. Development of dependence is related to the length of the prescription but can also differ based upon the classification of the benzodiazepine that is prescribed. Short acting benzodiazepines such as lorazepam (Ativan) take less time to develop dependence compared to long-acting benzodiazepines (Nelson and Chouinard, 1999).

Another common adverse effect that is often associated with dependence is tolerance which results in an increased dose being required. By increasing the dose, the risk of an adverse effects is also increased (Greenblatt and Shader, 1978). Long-term usage of benzodiazepines can result in dependency and tolerance; however, withdrawal can also occur after long-term usage.

While tolerance can be developed by consuming benzodiazepines for longer than the recommended time, Rickels & Schweizer (1998) reported that one third of patients were unable to discontinue therapy.

1.5 Study Objectives

Risks of inappropriate benzodiazepine prescribing are well documented; however, research has predominantly focused on prescribing patterns in those aged 65 years and older. Far less research has focused on younger and middle-aged adults. Due to the island of Newfoundland's unique geography, it is important to examine the prescribing patterns in rural versus urban areas since there is little research focusing on geographic variation in prescribing patterns. Newfoundland's unique geography includes many rural and remote communities, so these differences might be particularly important locally. This thesis will address that gap in the literature, as well as explore current benzodiazepine prescribing practices in comparison to recommended guidelines.

This thesis will explore the similarities and differences between rural and urban benzodiazepine usage, as well as the prescribing patterns of benzodiazepines for *all* adults, not just seniors, compared to the recommended guidelines. It also utilizes a longer time period than many studies.

The primary research question for this study is: What are the similarities and differences between rural and urban benzodiazepine prescribing in Newfoundland and Labrador over a ten-year period from 2007 to 2016? When addressing the current benzodiazepine prescribing patterns, it is important to assess current prescribing patterns and previous patterns, allowing for comparisons over time.

These thesis objectives will be accomplished by examining benzodiazepine prescribing patterns for all adults aged at least 18 years of age in Newfoundland and Labrador, using data from the Newfoundland and Labrador Centre for Health Information from 2007 to 2016. Patterns will be assessed based on geographic location (rural vs. urban) and stratified by prescriber specialty (general practitioners and specialists), sex (females vs males) and age range (18-24, 25-44, 45-64, 65-84, 85+).

Chapter 2: Literature Review

2.1 Introduction

Benzodiazepines (BZDs), were introduced in 1960 to replace barbiturates as an anxiolytic. They were initially believed to be effective in treating conditions with minimal side effects compared to barbiturates. Initially introduced to treat anxiety and insomnia, the range of indications increased to include acute stress attacks and sleep disorders (National Institute on Drug Abuse, 2005), as well as post-traumatic stress disorder (Guina et al., 2015), epilepsy, muscle tension (Neutel, 2005), schizophrenia and bipolar disorder (Brunette et al., 2003).

Research on the association between adverse effects and benzodiazepine usage continued, with reporting of adverse effects documented across numerous research studies, showing increased severity and frequency. Dependence and tolerance are commonly reported by long-term users, however there is potential for more harmful adverse effects such as an increased risk of Alzheimer's disease (Billioti de Gage et al., 2014) and hip fractures (Bartlett et al., 2009). Other severe adverse effects include cognitive decline, unwanted sedation, a reduction in coordination, and risk of automobile accidents (Ray et al., 1987; Salzman, 1993; Gales and Menard, 1995; Neutel, 1995; Neutel et al., 1996; Rickels et al., 1999; Neutel et al. 2002; Lenze et al., 2003; Kallin et al., 2004).

In response to these reported adverse effects, several research groups concluded that inappropriate prescribing was prevalent, and BZDs should typically be restricted to short-term usage (Swinson et al., 2006). Despite recommendations that benzodiazepine (BZD) prescribing should be limited to two to four weeks, research has shown that in some cases, BZDs are used for many weeks, months or even years (Barnas et al., 1991; Ishigooka et al., 1998; Egan et al., 2000; Neutel et al., 2003).

Benzodiazepines will be discussed in the following sections, focusing on the epidemiology, prescribing patterns, inappropriate use and adverse effects associated with their use.

2.2 Epidemiology of Benzodiazepines

2.2.1 Global Epidemiology of Benzodiazepines

Benzodiazepines (BZDs) are used globally to treat various indications, resulting in prescribing pattern variations by region. In 2008, usage varied amongst several European countries, varying from 5.8% to 16.3% (Huerta et al., 2016). Some countries have attempted to address this issue through the implementation of guidelines and providing a recommended duration of use. In many countries, benzodiazepines continue to be overprescribed.

Kapil et al. (2014) estimated that 26.1% of the UK adult population had ever taken a BZD or Z-drug. Another study conducted in the UK, examining 1391 patients' BZD prescriptions between 1991 and 2009, concluded that prescriptions were considered appropriate in only one-third of cases (Dell'osso & Lader., 2011). Within Europe, prescribing differs by country. Hughes et al. (2016) examined the proportion of patients prescribed a benzodiazepine at least once between 2007 and 2015 in Scotland. During this time, the proportions decreased: 83.8% (n = 109) in 2007, 70.5% (n = 122) in 2011, and 51.7% (n = 138) in 2015; however, there was an increase in the proportion of those prescribed a nonbenzodiazepine ("Z-drug") from 30% (n = 39) in 2007, 46.2% (n = 80) in 2011, and 52.4% (n = 140) in 2015.

In France, based on a 2001 cross-sectional telephone survey, the prevalence of benzodiazepine usage was estimated to be 7.5% (Lagnaoui et al., 2004). Magrini et al. (1996) examined the prevalence of benzodiazepine use in an Italian adult population, determining that use in the past-week was 8.6%, with 5% in males and 11.8% in females. For those that were exposed to a benzodiazepine, 56% were chronic users, defined as daily for more than 6 months and 70.1% for those over the age of 65 (Magrini et al., 1996).

Ohayon et al. (2002) examined a population aged 15 years or older consisting of participants from France, Germany, Italy, and the United Kingdom. Of the sample, 1.5% used hypnotics while 4.3% used an anxiolytic, concluding that anxiolytics are extensively prescribed in France and Italy. Another study examining 12,536 individuals 25 years of age or older in Sweden determined that 27.3% had been prescribed a benzodiazepine for 1-90 days, as well as a prescription of 90 - 270 days after first clinical diagnosis of depression, anxiety and/or insomnia (Sjöstedt et al., 2017). In Norway, anxiolytic and hypnotic sales decreased throughout the 1990s, but then increased annually by 3-6% (Grytten., 1998; Rønning., 2003). Based upon official sale statistics in 2000, approximately 5% of the Norwegian population used anxiolytics or hypnotics daily (Rønning., 2003; NOMESCO., 2003).

Benzodiazepine usage continues to be of concern in Europe, similar to Middle Eastern Countries. Patel et al. (2013) examined the prevalence of benzodiazepine use in Pakistan: amongst 355 individuals, 129 (36%) reported benzodiazepine use currently. Among those taking benzodiazepines, 67% were taking them daily, with a mean duration of use of 93.07±203 weeks (Patel et al., 2013). Patel et al. (2008) determined that benzodiazepines are also the most common form of deliberate self-harm in Pakistan, observed in women more than men.

Raoof et al. (2008) reported that 30.4% of the study sample had used a benzodiazepine at one point in life, with 42.4% using them for more than 12 months; 36.5% were warned about the long-term addiction possibility associated with benzodiazepine usage. The most common indication for which a benzodiazepine was prescribed was sleep disturbance, differing from the most common indication for BZDs in North America. A study conducted by Khawaja et al. (2005) determined the point prevalence of benzodiazepine usage at a tertiary care university hospital in Pakistan to be 21.2%.

In Thailand, in 2007, 1.6% of the general population indicated they had misused anxiolytics or hypnotics at some point during their life (Assanangkornchair et al., 2010). Examining usage in Taiwan between 1997 and 2004, Chien et al. (2007) reported the prevalence of anxiolytic-hypnotic use increased from 3.0% to 7.3% respectively. Fang et al. (2009) determined that the annual prevalence in 2000 was higher at 18.6% based on a sample of 187,000 individuals. Examining benzodiazepine usage in Lebanon, Ramadan et al. (2016) determined that 33% had experienced side effects and 40% had been taking a benzodiazepine for more than one year.

Benzodiazepine prescribing in Japan was examined by Nakao et al. (2009), reporting 19.9% of inpatients being prescribed a benzodiazepine. Prescribing by department was determined to be highest in neurology (35.8%) and cardiac surgery (35.8) (Nakao et al., 2009). These prescribing patterns in Japan vary from the predominant use of benzodiazepines in North America, where BZDs are primarily prescribed for anxiety and insomnia.

In 2001, 90 million benzodiazepine prescriptions were written for mood and anxiety disorders with 31 million prescriptions written for alprazolam alone in the United States (Stahl., 2002). While it was anticipated that this rate of prescribing would decrease, 85 million benzodiazepine prescriptions were written for the same indications in the United States in 2007 (Rickels, 2013). In 2008, the annual prevalence of benzodiazepines was estimated at 5.2% of the US population with long-term usage increasing from 14.7% (18-35 years) to 31.4% (65-80 years) as age increased (Olfson et al., 2015). Estimates from SAMHSA (2011) determined that approximately 272,000 emergency department visits involved nonmedical use of a benzodiazepine in the United States in 2008, with 40% of those visits also involving alcohol. In 2011, this increased to approximately 426,000 visits, with 24.2% involving alcohol (SAMHSA., 2013).

The frequency of benzodiazepines and similar sedative-hypnotics has been reported to be approximately 3.4% in Canada, based on a 2006 study (Kassam et al., 2006). In summary, research clearly demonstrates that inappropriate benzodiazepine prescribing is evident globally. Our study focused on prescribing and usage in the province of Newfoundland and Labrador over a ten-year period and examined trends, sex and urban vs. rural differences.

2.2.2 Epidemiology of Benzodiazepines in the Canadian Provinces

Table 2.1. *Benzodiazepine Usage in Canadian Provinces (2017)*[1]

Province[2]	Defined Daily Doses per 1,000 population for BZRA[3]
Newfoundland and Labrador	25,722
Nova Scotia	17,692
Prince Edward Island	21,906
New Brunswick	31,555
Quebec	14,723
Ontario	9,173
Manitoba	15,463
Saskatchewan	10,659
Alberta	13,291
British Columbia	9,656
Canada	12,248

[1]Pan-Canadian Trends in the Prescribing of Opioids and Benzodiazepines, 2012 to 2017. Canadian Institute for Health Information. Available at: https://www.cihi.ca/sites/default/files/document/opioid-prescribing-june2018-en-web.pdf
[2]Not including Canadian Territories
[3]BZRA: Benzodiazepine and benzodiazepine-related drugs

In 2004, the annual prevalence of BZD use was estimated at 4% of the Canadian population (Olfson et al., 2015). Potentially inappropriate prescriptions in Canada in 2013, filled by adults 65 years of age and older, cost approximately 419 million dollars (Morgan et al., 2016). Hogan et al. (2003) reported benzodiazepine use across Canada, with use being highest in Quebec (35.9%) and lowest in the Prairies (18.2%) and Atlantic Canada (6.6%).

In British Columbia, 4.9% of the population filled a benzodiazepine prescription less than 100 days in total supply, while another 3.5% filled a BZD prescription for more than 100 days in total supply in 2006 (Cunningham et al., 2010). BZD users in this population were typically women, which accounted for two-thirds of the prescriptions, and older with nearly half over 65 and more than a quarter 75 or older (Cunningham et al., 2010). The prevalence of benzodiazepine usage in British Columbia increased from 7.8% in 1996 to 8.4% in 2006 (Cunningham et al., 2010).

In Alberta, 10% of the population (over 10 years of age) was dispensed a BZD or Z-drug in 2015 (Weir et al., 2018). Per 100 patients, one consumed a benzodiazepine from 10-19 years of age, increasing to 14 per 100 for 50-59 and 30 for 90 years and older (Weir et al., 2018). Differences in sex were also observed: 13% of females were dispensed a BZRA (benzodiazepines and z-drugs) in 2015, compared to 8% of males (Weir et al., 2018). 71% of patients had a maximum period of usage longer than 30 days (mean = 90, SD = 95) on average with the number of distinct prescribers (mean = 1.5, SD = 1.0) (Weir et al., 2018).

Quinn et al. (1992) reported benzodiazepine use in a Saskatchewan population to be 5.5%, with an average of 4.7 prescriptions per person and 255 per 1000 people prescribed a BZD.

Alessi-Severinin et al. (2013) examined the change in BZRA use in adults 65 years of age or older in Manitoba. Incident of use of a BZRA in 1998 was 13.14 users per 1000 persons and 13.66 users per 1000 persons in 2009 (Alessi-Severinin et al., 2013). The prevalence of use of a BZRA was 108.6 per 1000 persons in 1997/98 and 109.1 / 1000 persons in 2008/2009 (Alessi-Severinin et al., 2013).

Tu et al. (2001) reported the prevalence of people dispensed a benzodiazepine in Ontario decreased from 25.1% in 1993 to 22.5% in 1998 for the study population (age 65 and older). Prevalence of BZD usage increased for all six years studied when stratified by age, approximately 20% for the 65-69 age group and 30% for greater than 85 years of age (Tu et al., 2001).

Préville et al. (2012) examined benzodiazepine usage in Quebec, concluding that 32% of survey respondents had a mean daily dose of 6.1 milligrams of equivalent diazepam for an average of 205 days per year. Additionally, 48% of BZD users had received a potentially inappropriate benzodiazepine prescription within the previous year. Furthermore, 23% of BZD users had received at least one prescription of a medication concurrent with a BZD that had the potential for a serious drug-drug interaction. A 1977 study examining benzodiazepine usage in Quebec reported that in a 1977 family medicine center, diazepam was the second most commonly prescribed drug (Rosser, 1980). Mariner et al. (1982) reported that diazepam was the second most commonly used medication, after Aspirin, among urban women in Quebec.

A recent study of benzodiazepine use among older adults in Quebec, reported 24.3% of benzodiazepine users received long-acting drugs (Olfson et al., 2014). In British Columbia, an estimated 8.4% of the population used a benzodiazepine in 2006, with 3.5% filling benzodiazepine prescriptions in excess of 100 days of supply (Cunningham et al., 2010).

Black et al. (2018) reported benzodiazepine usage across provinces in Canada for those 65 years of age or older, reporting New Brunswick having the highest prescribing (43,989 units).

In 2012, there were 25.5 million prescriptions of BZDs and Z-drugs in Canada (Canadian Institute for Health Information, 2018); Newfoundland and Labrador had the highest defined daily doses dispensed of BZDs.

2.2.3 Benzodiazepine Usage in Newfoundland and Labrador

In 2017, in Newfoundland and Labrador, the defined daily doses dispensed of BZDs per 1,000 persons was 15,932, ranking highest amongst the Canadian provinces (Canadian Institute for Health Information, 2018). When analyzing benzodiazepine and Z-drugs (BZRA) combined, the defined daily doses dispensed per 1,000 persons was 25,722, a 0.5% increase from the previous year (Canadian Institute for Health Information, 2018). Newfoundland was the only province with an increase between 2016 and 2017 for BZRAs.

A significant proportion of the Newfoundland and Labrador population comprises seniors: 19.4% are over the age of 65, compared to 16.9% nationally (Statistics Canada, 2016). However, with increasing drug diversion and young adults using benzodiazepines illicitly, it is also important to examine usage across all age groups.

Further, Newfoundland's unique geography and dispersion of communities warrants a focused exploration of benzodiazepine usage in urban and rural communities. There are differences in these regions in access to health care services and providers, as well as other variables that may impact prescribing patterns. Finally, it is worthwhile to examine prescribing trends over time.

2.2.4 Benzodiazepine Usage by Age

Seniors are a large benzodiazepine user group in the general population and are likely to receive an inappropriate prescription. For example, Bergman et al. (2007) examined nursing home residents aged 65 years and older, concluding that over 70% had one or more potentially inappropriate prescriptions. Combined with the potential for severe adverse effects, seniors are often researched regarding benzodiazepine usage. It is important to focus on seniors since physiological changes occur with aging, affecting the metabolism of pharmacological interventions, including benzodiazepines. Seniors are also more susceptible to adverse effects as some have the potential for a more negative outcome. Hip fractures are one adverse effect that can occur with long-term benzodiazepine usage which requires surgery. Seniors have an increased risk of mortality due to surgical complications than young adults. Due to seniors being more susceptible to adverse effects, such as hip fractures due to falls, benzodiazepine prescribing is often examined in this population (Wagner et al., 2004). However, seniors are not the only population that use benzodiazepines and research has also examined BZD usage in younger populations.

Between 2006 and 2013, the prevalence rate of benzodiazepine usage amongst those aged 0 - 24 years in Sweden increased from 0.81 per 100 inhabitants to 0.99 per 100 inhabitants, based on 117,739 individuals who had filled at least one benzodiazepine prescription (Sidorchuk et al., 2018). In a Canadian population, 32.3% of short-term users were aged 18-44 with 42% in the 45-64 category (Weymann et al., 2017). Benzodiazepine prescribing has been researched in minors, with an increase of 10.2% between 2009 and 2012 in an Irish population; with 15% prescribed a benzodiazepine for longer than four weeks (Murphy et al., 2015).

Young adults are also more likely to misuse prescription medication recreationally than seniors (those 65 years of age and older). Among a nightclub-going sample, most frequently young adults, prevalence of use approaches 65%–90% lifetime (Grov et al., 2009; Kelly and Parsons 2007; Kurtz et al. 2013). A study examining prevalence of benzodiazepine usage conducted using a sample of drug-using young adults 18–29 years of age recruited at clubs found a prevalence of 47.1% recent (past four months) usage (Kelly and Parsons 2007).

In the United States, Olfson et al. (2015) reported approximately 5.2% of US adults between 18 and 80 years of age were prescribed a benzodiazepine. Additionally, benzodiazepine use increased between age groups from 2.6% (18-35 years) to 5.4% (36-50 years) to 7.4% (51-64 years) to 8.7% (65-80 years).

Lifetime anxiety disorder prevalence is also increasing, with an average onset age for diagnosis of panic disorder, major depression and generalized anxiety disorder of 23 - 30 years old (Kessler et al., 2012). Smartphones are ubiquitous in society, contributing to the increase in rates of anxiety diagnoses. Furthermore, excessive smartphone usage can result in disturbed sleep patterns which may lead to a prescriber using a benzodiazepine for the treatment of insomnia in young adults (Khan et al., 2015).

Panic disorder, major depression, and generalized anxiety disorder diagnoses often result in a benzodiazepine prescription for the indication. In young adults, excessive prescriptions can lead to drug diversion. Drug diversion has become a major issue in adolescents and young adults, through the popularization of consuming prescription medication recreationally via pop culture.

Long-term benzodiazepine usage also increased with age from 14.7% (18-35 years) to 31.4% (65-80 years) (Olfson et al., 2015). Neutel (2005) examined the differences between age groups, concluding that those aged 40-59 were 2.9 times more likely than the 20-39 group to use a BZD, and the 60+ demographic, 5.8 times more likely.

With the emergence of smartphone technology, rates of depression and anxiety have increased. A study involving 210 Korean female students concluded that 30.5% had a high risk of smartphone addiction (Lee et al., 2015). Matar Boumosleh and Jaalouk (2017) examined a population of Lebanese university students of 688 undergraduate students concluding that 26.5% felt anxious. Benzodiazepines are prescribed for anxiety; however, inappropriate lengths of usage need to be examined in younger populations (less than 30 years of age).

2.3 Clinical Use of Benzodiazepines

Benzodiazepines act upon the gamma-aminobutyric acid (GABA) receptors suppressing the central nervous system effects, resulting in anxiolytic, sedative, hypnotic, skeletal muscle relaxant and antiepileptic effects (McEvoy et al., 2002; Barker et al., 2004). When benzodiazepines were initially introduced, they were intended to treat anxiety and insomnia (CPS, 2003; Alessi-Severini, S. et al., 2014; Katzman, M. et al, 2014). Indications for which benzodiazepines are used has increased to include nervousness and sleep problems (Curran, 1991; Barbee, 1993; King, 1994; Kirby et al., 1999; Jorm et al., 2000; Sonnenberg et al., 2012). BZDs are also used for the treatment of psychotic states, depression, social phobia (including social anxiety disorder), obsessive-compulsive disorder, drug withdrawal and the adverse effects caused by antidepressants and antipsychotics (Pollack, 1993; Barker et al., 2004).

Benzodiazepines may also be prescribed as a myorelaxant and post-surgery for brief periods (Neutel, C., 2005) or for the management of post-traumatic stress disorder, schizophrenia, bipolar disorder, tremors in multiple sclerosis patients and epilepsy (Brunette et al., 2003; Mehdi, 2012; Guina et al., 2015; Meador et al., 2015).

Health Canada allows for the prescribing of benzodiazepines for the following indications: anxiety, insomnia, alcohol withdrawal, muscle spasms, and an anesthetic before surgery. Commonly marketed benzodiazepines include alprazolam (Xanax), clonazepam (Klonopin), diazepam (Valium), lorazepam (Ativan), flunitrazepam (Rohypnol), chlordiazepoxide (Librium), and midazolam (Versed). Z-drugs, commonly referred to as BZD clones, are a drug class similar to BZDs and often used to treat insomnia and anxiety. Commonly marketed Z-drugs include zopiclone (Imovane), eszopiclone (Lunesta) and zolpidem (Ambien).

2.4 Inappropriate Use

Globally, benzodiazepines are one of the most commonly prescribed medications and one of the most inappropriately prescribed medications. Inappropriate prescribing can be defined by inappropriate indication, dosage, strength, duration and / or multiple benzodiazepines prescribed concurrently. Inappropriate usage can also include patients misusing benzodiazepines or by using the medication concurrently with known medications that interact with BZDs. Inappropriate use will be further discussed in this section.

2.4.1 Inappropriate Prescribing (Duration, Strength, Multiple BZDs, Indications)

Inappropriate use has multiple definitions. This section will focus on inappropriate duration, strength and the prescription of multiple benzodiazepines concurrently; however, it is likely benzodiazepines are also used for other inappropriate indications.

Guidelines recommend that benzodiazepine usage be restricted to two to four weeks; however, prescribers do not always adhere to these guidelines. Long-term benzodiazepine prescriptions, defined as greater than 30 days, for any indication contradicts various guidelines (Copperstock & Hill, 1982; APA, 1990; WHO, 1996; Katzman et al., 2014). Usage varies by countries, with indications that between 0.5% and 5.8% of the adult population use benzodiazepines for 1 year or longer (Barker et al., 2004).

Sonnenberg et al. (2012) reported on benzodiazepine usage in a Dutch population aged 55 – 64 years of age; long-term usage was 70% of total BZD usage in 1992 and 80% in 2002. A Quebec study noted that benzodiazepines were used for longer than 12 weeks in 88.4% of the study sample (Bernard et al., 2018). A systematic review including 13 studies reported usage ranging from 1 to 34 years with a mean of 9.9 years (Barker et al., 2004).

Olfson et al. (2015) reported the proportion of benzodiazepine use that was long-term increased with age: for 18-35 years old, 14.7% was long-term while it was 31.4% for those 65-80 years old. Variables associated with long-term benzodiazepine usage include age, sex and low socioeconomic status. Sundquist et al. (2017) reported that individuals aged 85 years and older were three times as likely to be prescribed a benzodiazepine than those aged 25 - 44 with clinically diagnosed depression, anxiety and / or insomnia.

In the elderly, inappropriate prescribing rates (based upon different definitions of an inappropriate prescription) have been reported to be between 14% and 23% of all prescriptions (Brekke et al., 2008). 20-25% of inappropriate prescriptions in the elderly are related to benzodiazepine prescriptions (Tannenbaum et al., 2014). Fride Tvete et al. (2015) reported women having a lower risk than men for excessive use, and those with low household income being associated with a high risk for excessive benzodiazepine use.

Inappropriate prescribing may refer to the strength of the benzodiazepine prescribed. As usage is continued, tolerance develops, resulting in the prescribing of an increased strength being provided to the patient. Continual increase of strength is not an effective or safe method to treat the patient (Katzman et al., 2014).

Specifically, in seniors, this can be problematic due to pharmacological changes that occur as humans age resulting in an increased duration of the effects of benzodiazepines on the elderly. A study conducted in Sweden analyzed long-term benzodiazepine usage rates based upon participants from multiple research centers located throughout Sweden, concluding that older age was associated with higher long-term benzodiazepine use (Sjöstedt et al., 2017).

2.4.2 Polydrug / Polysubstance Use

Benzodiazepine usage greater than recommended guidelines, or greater than 30 days, can result in harmful effects. While inappropriate prescribing results in hazardous effects on patients, so can polysubstance use. Benzodiazepines are overprescribed in middle-aged individuals and more frequently in those 65 years of age and older. In 2016, 1 in 4 Canadian seniors were prescribed 10+ drug classes (CIHI, 2018). Use of other medications is a strong predictor for initiating BZD usage (OR: 1.85) (Bartlett et al., 2009).

While BZD overprescribing is most prevalent in those aged 65 years and older, this population is also at risk for being prescribed a medication that has a drug interaction with a benzodiazepine. A study conducted by Ramadan et al. (2016) reported that 18.3% of those using benzodiazepines were taking drugs that should not be prescribed with BZDs. An example of this is in the treatment of generalized anxiety disorder, where benzodiazepines have been used in conjunction with an antidepressant (Louvet et al., 2015); in some of these cases, patients have difficulty discontinuing the BZD.

A large study including 547, 709 residents of an Alberta population who received an opioid prescription found that 24% also received prescriptions for a BZRA (Sharma et al., 2019). Currently, there is an opioid epidemic in North America resulting in hospitalizations and death in some. Benzodiazepines, when consumed with opioids can result in fatality leading the Food and Drug Administration (FDA) to issue a black box warning that is required to be present on both medications. A concern about benzodiazepine usage is the impact that can occur as a result of consuming a benzodiazepine in combination with additional drugs. This consumption of various drugs can result in drug interactions which can have harmful effects. Benzodiazepines can also be used recreationally by young adults, resulting in drug-drug interactions that are previously unknown.

2.4.3 Misuse of Benzodiazepines

Benzodiazepines are misused for multiple reasons such as to help sleep, to get high or for social reasons (Kapil et al., 2014). Data from the National Survey on Drug Use and Health (NSDUH) indicated that 9.8% of sedative/tranquilizer misusers met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for abuse and/or dependence (Becker, Fiellin, and Desai 2007).

Similar to pharmaceutical opioids, a large proportion of the literature focused on problematic use addresses concerns with prescribing practices (Grossbard et al. 2014). There is a paucity of research on the epidemiology and health consequences of recreational BZD misuse among high-risk groups. Benzodiazepines can be misused, with some cases resulting in hospitalization, which can be classified into different categories. The resulting emergency room (ER) visits are typically classified into benzodiazepine ER visits due to medical use and those due to non-medical use.

Based upon 1500 respondents, Kapil et al. (2014) reported the most common reasons to misuse benzodiazepines and Z-drugs were to help sleep (66.4%), cope with stress (37.1%) or to get high (31%). Of these respondents, 55.2% received the medications from healthcare professionals. This highlights the importance of reviewing prescribing guidelines and practice.

One category is the misuse of benzodiazepines is due to incorrect dosage. This can occur from patients consuming more than the prescribed dosage, potentially due to a feeling of tolerance when no tolerance is present. Another source of benzodiazepine misuse is consuming another individual's prescription which was not originally intended for them.

Among suicide attempts by poisonings due to a substance, benzodiazepines are used for 30% to 40% of attempts in western countries, with this increasing to 80% in Pakistan (Khawaja et al., 2006).

Benzodiazepines are misused in a variety of ways. Through inappropriate prescribing, polydrug use and misuse, these can all lead to an individual experiencing adverse effects associated with benzodiazepines usage. Often the misuse of other substances, such as opioids, coincides with the misuse of benzodiazepines. Illicit drug use, such as opioids, has been reported to be used concurrently with benzodiazepine usage (Tucker et al., 2016).

After reviewing some drug manufacturer information, it is important to discuss the indications for which benzodiazepines are intended compared to why they were prescribed. Healthcare providers need to be aware of this difference and that benzodiazepines were used to treat insomnia and as an anxiolytic initially.

Benzodiazepines are prescribed primarily as an anxiolytic and for insomnia. It is important to differentiate between GAD and anxiety associated with the stresses of everyday life. This difference is specified in the drug monographs from pharmaceutical companies manufacturing benzodiazepines (Health Canada, 2019). Regardless, benzodiazepines are still prescribed – often inappropriately -for the stresses associated with everyday life. In the drug monograph, the length of use is also specified to be between two and four weeks. For example, the drug monograph for Ativan (lorazepam) states that long-term usage is not recommended (Wyeth, 2019). Even with these recommendations by the pharmaceutical companies, this is not necessarily a deterrent for prescribers or patients.

For clinical long-term use of benzodiazepines, it is important to examine continued benefit. Continued benefit refers to the benefit of the drug to the user as the drug is continued, such that if a drug is continued to be used, the positive effect remains (although this is often not the case with benzodiazepines).

2.5 Adverse Effects

Benzodiazepines were initially introduced as a safer alternative to barbiturates in the 1960s. As described, prescriptions of benzodiazepines increased, with it becoming one of the most prescribed medications globally. As research began to examine the adverse effects associated with usage, the list of reported adverse effects grew to include hip fractures due to falls, dependence and cognitive impairment. These effects range from withdrawal symptoms to a potential increased risk of Alzheimer's disease. This section will discuss the adverse effects associated with benzodiazepine usage.

Examining benzodiazepine usage in Lebanon, Ramadan et al. (2016) reported that 33% had experienced side effects and 40% had been taking a benzodiazepine for more than one year. Glass et al. (2005) determined that adverse events were more common with sedatives than placebo.

Due in part to the adverse effects associated with long-term benzodiazepine use, there were attempts to create an alternative drug that had similar therapeutic effects, but a lower possibility of adverse effects. As a result, Z-drugs were introduced to have the intended effect. As research increased on Z-drugs, however, it became apparent that adverse effects were similar to those of benzodiazepines.

2.5.1 Cognitive Decline, Unwanted Sedation, Reduced Motor Coordination

Benzodiazepine usage, especially long-term usage, has been associated with a decline in cognitive function. A meta-analysis examining risks and benefits of sedative-hypnotics determined that cognitive adverse events are 4.78 times more common and adverse psychomotor events are 2.61 times more common in those using a sedative compared to a placebo (Glass et al., 2005).

Associations between dementia and benzodiazepine usage have been reported (Billioti de Gage et al., 2014; Gray et al., 2016; Islam et al., 2016). Billioti de Gage et al. (2014) analyzed the correlation between benzodiazepine use and the risk of Alzheimer’s disease. They reported an odds ratio of 1.51 associated with an increased risk of Alzheimer’s disease in those that used benzodiazepines. Notably, impairment can remain for months after the benzodiazepine is discontinued (Cunningham et al., 2010).

While cognitive decline has been associated with benzodiazepine usage, decreased motor skills have also been reported. Psychomotor impairment can significantly impact driving performance. Daurat et al. (2013) examined the effects of lorazepam on driving, specifically lane departure, determining that under the influence of lorazepam, driving performance was worse than having a blood alcohol concentration above 0.05. A meta-analysis examining sedative-hypnotics with the risks and benefits determined that cognitive adverse events are 4.78 times more common and adverse psychomotor events 2.61 times more common in those using a sedative compared to a placebo (Glass et al., 2005).

While benzodiazepines have the potential to increase the risk of Alzheimer's disease, BZDs may also have negative health impacts on those who are already affected with Alzheimer's.

After discontinuation of the benzodiazepine, it is possible for the cognitive impairments to regress and in some cases, the individual may return to the same level of cognitive function that was previously experienced. Thus, while there has been research highlighting the increased risk of Alzheimer's disease from benzodiazepine consumption, it is important to also consider individuals who have dementia and are prescribed a benzodiazepine.

2.5.2 Falls, Hip Fractures in the Elderly, Balance

Falls are of significant concern in those aged 65 years and older: approximately 28-35% of those 65 years and older fall each year (Yu et al., 2017), and it is the second leading cause of accidental or unintentional death globally (WHO, 2018). Risk of falls is already high in this population and is further compounded by benzodiazepine usage, especially long-term usage.

Ming and Zecevic (2018) conducted a systematic review including studies from differing countries and reported an increased risk of falling of 1.2 to 3.7 times for older adults when taking a benzodiazepine. Donnelly et al. (2017) conducted a systematic review examining the risk of hip fracture for those using benzodiazepines and Z-drugs, finding that both were significantly associated with an increased risk of hip fracture with a relative risk of 1.52 and 1.90, respectively.

Research has demonstrated that benzodiazepine usage is associated with an increased risk of hip fractures, with this association also being present for short-term usage. Short term use of BZDs, defined as up to fourteen days since initial prescription, resulted in a 140% increased risk (compared to non-exposure); Z-drugs had an increased risk of 139% (Donnelly et al., 2017). Falls and hip fractures in the elderly have been widely reported; however, it was initially believed that the association was due to long-term use. However, Wagner et al. (2004) reported that hip fractures in the elderly are associated with benzodiazepines even after two weeks of use.

Psychomotor skills are impaired with long-term benzodiazepine usage which can contribute to the risk of a fall, but also impairs other motor skills such as driving. A 2010 study highlighted the importance of reduced balance from a single dose of a hypnotic medication, such as a benzodiazepine (Mets et al., 2010).

Z-drugs were initially believed to have a reduced adverse effect profile while achieving similar hypnotic results clinically to BZDs. As research increased on Z-drugs, however, it became apparent that many of the adverse effects associated with benzodiazepine usage were similarly observed in Z-drug use. One of these adverse effects is the increased risk of falls and a hip fracture, and again, increased risks with long-term usage (Ackroyd-Stolarz et al., 2009; Bartlett et al., 2009; Bronskill et al., 2018).

2.5.3 Tolerance, Withdrawal and Dependence

People with benzodiazepine usage longer than 3-4 weeks are likely to develop withdrawal symptoms upon cessation (Petursson & Lader, 1981; Brett & Murnion., 2015). Dependence had previously been thought to be observed only in individuals using benzodiazepines for extended periods of above-normal therapeutic doses. However, research has demonstrated that even for benzodiazepines used at a normal therapeutic dose, physiological and pharmacological dependence can be observed when the medication is ceased (Barker et al., 2004).

Benzodiazepines with a short half-life and high potency (such as alprazolam, lorazepam, and triazolam) increase the risk of dependence (Nelson & Chouinard, 1999). Dependence is most commonly discussed in the context of prescription drug use among individuals for which the medication is intended; however, it can also develop in those using the medication recreationally. (Kurtz et al., 2016).

2.5.4 Additional Adverse Effects

Benzodiazepines have been associated with many adverse effects. Besides those previously discussed, other adverse effects have also been reported; including rebound seizures, rebound insomnia, mortality amongst those with chronic obstructive pulmonary disease (COPD), suicide risk, stroke, cardiovascular disease (CVD), mortality and pneumonia (Obiora et al., 2013; Airagnes et al., 2016; Kroll et al., 2016; Brandt & Leong, 2017; Donovan et al., 2019). In all, BZD usage has been associated with numerous and serious adverse effects.

2.6 Burden on the Healthcare System

Inappropriate benzodiazepine prescribing is not only harmful but can also significantly impact the healthcare system through both direct and indirect costs. In Canada, potentially inappropriate prescriptions filled by older adults cost an estimated 419 million dollars; in Newfoundland and Labrador, this cost was $128 per person aged 65 years or older (Morgan et al., 2016).

Indirect costs associated with benzodiazepine overprescribing include the time and burden on the healthcare system measured in increasing wait times due to adverse effects and costs associated with utilization of hospital equipment and personnel. For example, annual costs of hip fractures in the United States had an estimated cost of $10.3–15.2 billion dollars (Donnelly et al., 2017). In the United Kingdom, this is estimated at 2 billion Great British Pounds (GBP) (NICE, 2011). These costs are not solely due to benzodiazepine overprescribing: inappropriate prescriptions may lead to adverse effects, such as hip fractures, that place further burden on the healthcare system.

2.7 Study Objectives

Benzodiazepines are overprescribed; however, research has predominantly focused on prescribing patterns in those aged 65 years and older. It is important to examine the prescribing of benzodiazepines in all adults, not just seniors.

While research has been conducted comparing rural and urban areas (Fourrier et al., 2001; Laganoui et al., 2004; Alessi-Severinin et al., 2014; Mattos et al., 2016; Weymann et al., 2017; Agarwal et al., 2019; Sharma et al., 2019), there are limitations and no previous research could be found that has examined rural / urban benzodiazepine usage in Newfoundland and Labrador (NL). In 2016, NL had 519,716 residents with 311,356 dispersed across 269 towns (Statistics Canada, 2017). Due to this unique geography, it is important to examine prescribing patterns between rural and urban regions. In 2017, NL had the highest rate of benzodiazepine daily doses dispensed per 1,000 persons in Canada and was the only province with an increase between 2016 and 2017 (CIHI, 2018). In light of the economic and social burden of BZDs and the documented increase of BDZ usage in NL, it is valuable to further explore prescribing and usage patterns in the province.

The primary research question for this study is: What are the similarities and differences between rural and urban benzodiazepine prescribing patterns in Newfoundland and Labrador, among those 18 years of age or older, over ten years from 2007 to 2016? We hypothesized that there was a significant difference between rural and urban usage, with rural areas being prescribed more inappropriate prescriptions than individuals in urban areas.

Chapter 3: Methodology

3.1 Overview

3.1.1 Study Design

A retrospective cohort study utilizing secondary data was used to examine benzodiazepine prescribing patterns from 2007 to 2016. Data was collected for participants that received a benzodiazepine prescription living in Newfoundland (a subregion of Newfoundland and Labrador).

Specifically, the cohort was from the Newfoundland and Labrador Prescription Drug Program (NLPDP). The NLPDP is a program that offers financial assistance for eligible prescriptions. It is responsible for covering individuals when other services will not; as such, it is a payor of last resort.

Within the NLPDP there are five different programs: The Foundation Plan, 65Plus Plan, Access Plan, Assurance Plan and Select Needs Plan. Both the Foundation and Access Plan provide coverage for eligible prescriptions for those who receive income support benefits or are of low income. The 65Plus Plan is for individuals 65 years of age or older who received old age security benefits. The Assurance Plan covers medications in families where eligible drug costs exceed: 5% of net income for those who earn less than $40,000, 7.5% of net income for those who earn $40,000 to $75,000 or 10% of net income for those who earn $75,000 to $150,00. The Select Needs Plan provides 100% coverage for those with Cystic Fibrosis and Growth Hormone Deficiency.

Data from the NLPDP is extracted from an administrative dataset for applying reimbursement through this program by the Newfoundland and Labrador Centre for Health Information (NLCHI). Using data from this database, for those who were prescribed a benzodiazepine, rates of inappropriate prescription were determined and compared across a ten-year period, from 2007 to 2017.

3.1.2 Purpose of Study and Objectives

Examining benzodiazepine usage among those, aged 18 years of age or older, living on the island of Newfoundland from 2007 to 2016, while comparing differences in usage between rural and urban areas, was the objective of this study. Using the NLPDP database, benzodiazepine prescribing, and usage were examined stratifying by age, sex and prescriber specialty.

3.2 Definitions

Benzodiazepine usage can be measured in a variety of ways. The sections below provide clarification of study definitions, measures and outcomes.

3.2.1 Definition of Benzodiazepine Usage

Benzodiazepine prescribing and benzodiazepine usage are different terms. For this study, it was assumed that the benzodiazepines which were prescribed were used by the patients for the indications that they were intended and for the intended duration. It is acknowledged that in reality this may not be the case. It is possible that a patient did not use the medication for the complete duration of the prescription. As this was secondary data, there was no way of determining whether or not benzodiazepines were used as intended and for the prescribed length of time. For the purpose of this study, it was assumed that all benzodiazepine prescriptions were used fully; therefore, the terms benzodiazepine prescribing, and benzodiazepine usage are used interchangeably throughout.

3.2.2 Definition of Rural versus Urban

Benzodiazepine usage was examined over a ten-year period, and differences between urban and rural usage were described. Statistics Canada's definition of rural versus urban was used: those populations with less than 1,000 individuals being classified as rural (Statistics Canada, 2001). The 2011 Statistics Canada Census was used to determine community populations by NLCHI. During the fiscal years 2009, 2012 and 2013, the next available Medical Care Plan (MCP) code was used to obtain the postal code. This was completed by NLCHI prior to the team receiving the dataset.

3.3 Methods

3.3.1 Study Sample and Inclusion / Exclusion Criteria

Research on benzodiazepines predominantly focuses on a senior population; however, usage of these drugs is not limited to this age group. Prescribing has been observed across all adult age groups. For this study, individual-level patient data from the NLPDP was used. All adults aged 18 and older that were prescribed a benzodiazepine in the NLPDP were included in the analysis.

3.3.2 Data Sources

A ten-year period from April 2007 to March 2017 was used for analysis of benzodiazepine prescribing patterns year-over-year. Dates for this timeframe were based upon the fiscal year, for example: April 2007 to March 2008 for each of the ten years.

As noted, data for this study came from the NLPDP database. This database is comprised of participants in the five plans under the program: The Foundation Plan, the 65 Plus Plan, The Access Plan, The Assurance Plan and The Select Needs Plan. To access the data, ethics approval was first obtained by the Health Research Ethics Board, followed by a data application to NLCHI in March 2018. The full dataset was acquired in September 2018.

3.3.3 Measuring Equivalent Benzodiazepine Usage

Benzodiazepines can be classified into short-acting or long-acting drugs. As a result, it can be difficult to compare benzodiazepines in different classes. One example of this is diazepam, a long-acting benzodiazepine, compared to lorazepam, a short-acting benzodiazepine.

Standardizing the various benzodiazepines to an equivalent dose of diazepam, allows for easier comparison. Table 3.1 was used to convert benzodiazepine usage to an equivalent benzodiazepine dosage of 5 mg of diazepam. These equivalences are recommended by the National Pain Centre at McMaster based upon the Canadian Pharmacy Association (1995) and Kalvik (1995).

Table 3.1. *Equivalent Benzodiazepine Usage (McMaster University)*

Benzodiazepine	**Equivalent to 5 mg diazepam (mg)**
Alprazolam	0.5
Bromazepam	3 – 6
Chlordiazepoxide	10 – 25
Clobazam[1]	10
Clonazepam	0.5-1
Clorazepate	7.5
Flurazepam	15
Lorazepam	0.5-1
Midazolam[2]	3.75
Nitrazepam	5 – 10
Oxazepam	15
Temazepam	10 – 15
Triazolam	0.25

[1]Brandt, J., Alessi-Severini, S., Singer, A., & Leong, C. (2019). Novel Measures of Benzodiazepine and Z-Drug Utilisation Trends in a Canadian Provincial Adult Population (2001-2016). J Popul Ther Clin Pharmacol, 26(1), e22-e38. doi:10.22374/1710-6222.26.1.3
[2]Manthey, L., Van Veen, T., Giltay, E. J., Stoop, J. E., Neven, A. K., Penninx, B. W. J. H., & Zitman, F. G. (2011). Correlates of (inappropriate) benzodiazepine use: the Netherlands Study of Depression and Anxiety (NESDA). 71(2), 263-272. doi:10.1111/j.1365-2125.2010.03818.x

3.3.4 Inappropriate Prescription

For this study, a prescription was defined what was issued to an individual, regardless of duration or quantity of pills. Since the data is based upon prescription claims, a prescription was for each claim. Guidelines have recommended that benzodiazepine prescriptions be limited to a duration of two to four weeks. As such, an inappropriate prescription was analyzed using three different definitions to allow for comparison among them: 30 days, 45 days and 60 days.

If a prescription was dispensed within 30 days of the previous prescription being issued, it was classified as an inappropriate prescription. This method was repeated for 45 days and 60 days respectively, with individual analyses for each of the different inappropriate prescription durations.

3.4 Outcome Measures

3.4.1 Benzodiazepine Usage

Benzodiazepine usage was measured using a variety of indicators: duration of prescription, quantity prescribed and percentage of inappropriate benzodiazepine prescriptions. For this study, it was assumed that all individuals who were prescribed a benzodiazepine used the medication for the duration of the prescription.

3.4.2 Prescription Duration

Duration of prescription was measured as the duration of the medication in days.

3.4.3 Quantity Prescribed

Quantity prescribed was measured using two metrics. Quantity dispensed was the total number of pills that a patient was prescribed. Quantity per day was measured as the quantity dispensed divided by the prescription duration. For example, if the quantity prescribed was 60 days, and prescription duration was 30 days, then the quantity per day was calculated as 2 per day.

3.4.4 Aggregate Quantity Prescribed

Using the quantity prescribed and the diazepam equivalent, an aggregate quantity prescribed was calculated by multiplying the 5 mg equivalent of diazepam by the quantity prescribed. Using this measure allows for comparisons between different durations and type of benzodiazepines, for example: comparing a 14-day prescription of lorazepam and a 60-day prescription of diazepam.

3.4.5 Inappropriate Prescription

Various guidelines have reported that benzodiazepines should be restricted to 30 days or less (Copperstock & Hill, 1982; APA, 1990; WHO, 1996; Katzman et al., 2014). For this study, an inappropriate prescription was defined as inappropriate if a new prescription was issued within 30 days of the previous prescription ending. Three different durations (30, 45 and 60 days) were used to analyze the inappropriate prescription rate based upon the three definitions of an inappropriate prescription. Percentage of inappropriate prescriptions was calculated as the number of inappropriate prescriptions divided by the total number of prescriptions (ranging from 0 to 1.0). A linear regression was used to examine the association between variables and the percentage of inappropriate prescriptions for 30, 45 and 60 days between prescriptions.

3.4.6 Dispensed Days' Supply

Dispensed days' supply was defined as the duration for which a prescription was issued.

3.4.7 Drug Generic Name

Drug generic names were reported as medication corresponding to the appropriate benzodiazepine.

3.5 Data Analysis

3.5.1 Sample Size

All participants who were part of the NLPDP that were prescribed a benzodiazepine were included in this study. There were 63,517 unique individuals who were prescribed a benzodiazepine from 2007 to 2016 in Newfoundland.

3.5.2 Statistical Analysis

3.5.2.1 Descriptive Statistics

Descriptive statistics were used to summarize the population and demographic characteristics. Frequencies and percentages were used to assess the categorical variables for quantity dispensed, dispensed days' supply, drug generic name, and prescriber specialty. Age was calculated based on the first prescription that an individual received. A chi-squared test was used to examine the difference between urban and rural areas. For the variables with expected cell counts less than 5, Fisher exact tests were used.

Means and standard deviation were used to described continuous variables including quantity dispensed, dispensed days average pills per day, drug strength, diazepam equivalent and aggregate quantity prescribed. Differences between rural and urban areas were examined by a t-test. Statistical significance was determined at $p < 0.05$. All analyses were conducted using SAS software version 9.4 (SAS Institute, Cary NC).

3.5.2.2 Linear Regression

Linear regression was used in the multivariate analyses to identify significant risk factors for number of inappropriate prescriptions, as well as the percentage of inappropriate prescriptions. Effects of residence location (urban / rural), age, sex and prescriber specialty were examined, and the interaction term of age and urban / rural status.

The independent variable used for the regression analyses was the number of total inappropriate prescriptions, and the percentage of inappropriate prescriptions. Rural /

urban status was the dependent variable with age group, prescriber specialty and sex were the covariates used in the analyses. Lower order terms were included when assessing the interaction term of age and urban/rural status. In Newfoundland, there are age differences in urban areas compared to rural areas. For example, in St. John's, the median age is 39.4 years while in St. Anthony the median age is 49 years (Statistics Canada, 2017).

After conducting the linear regression, model diagnostics were examined visually for any outliers using a plot of Cook's distance (Appendix 3). If there were outliers, they were examined individually and the effect of removing them on the estimates. Similarly, a plot of studentized residuals was examined to assess the appropriateness of using a linear regression for the analyses (Appendix 3). All analyses were conducted using SAS software, the genmod procedure, version 9.4 (SAS Institute, Cary NC).

3.6 Ethics and Confidentiality

This study was approved by the Health Research Ethics Board in Newfoundland and Labrador. Prior to accessing the secondary data, a separate approval was obtained from NLCHI regarding confidentiality. Each study participant was given an identification number by NLCHI. Any information that included identifiable information was held by NLCHI and not released to any member of the research team.

Chapter 4: Results

This chapter presents the study findings in four sections. Demographics and baseline characteristics of benzodiazepine prescribing are described in the first section. The second section provides an overview of various metrics for benzodiazepine prescribing / usage, including quantity dispensed and prescription duration. Comparisons between mean values for benzodiazepine usage variables including quantity dispensed, equivalent milligrams of diazepam equivalence and drug strength are compared in the third section. Lastly, factors associated with inappropriate benzodiazepine prescribing are explored using multivariate linear regression.

4.1 Sample Characteristics

All individuals, over the age of 18, who were prescribed a benzodiazepine between 2007 and 2016 were included in this study; a total of 63,517 individuals. Table 4.1 shows the various prescription claim status'. Over 90% of individuals prescribed a benzodiazepine were categorized as "SETTLED-PAID", which refers to a prescription for which reimbursement was processed. For this category, it was assumed that all the medications which were prescribed were used by the patient.

Table 4.1 – *Prescription Claim Status*

Prescription Claim Status	**Frequency (%)**
IN ERROR – RETURN TO PROVIDER	118,793 (5.61)
SETTLED – CANCELLED	5 (0.00)
SETTLED – PAID	1,915,086 (90.51)
SETTLED – REVERSED	80,429 (3.80)
TO PAY – TO PAY	1 (0.00)
TO PROCESS – ORIGINAL CLAIM	1,542 (0.07)
Total	2,115,856

Table 4.2 – *Benzodiazepine Prescriptions among Study Sample*

Year[1]	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	**Total**
Individuals	19,042	19,778	20,937	21,936	23,977	24,284	24,032	24,002	23,973	24,379	63,517[2]
Total Prescriptions[3]	180,182	188,028	189,979	211,271	222,993	224,384	225,731	225,768	223,406	224,114	2,115,856
Rural (%)	33,435 (18.56)	35,968 (19.13)	36,441 (19.18)	38,161 (18.06)	41,426 (18.58)	43,118 (19.22)	43,661 (19.34)	43,579 (19.30)	43,645 (19.54)	43,113 (19.24)	402,547 (19.03)
Urban (%)	146,747 (81.44)	152,060 (80.87)	153,538 (80.82)	173,110 (81.94)	181,567 (81.42)	181,266 (80.78)	182,070 (80.66)	182,180 (80.70)	179,761 (80.46)	181,001 (80.76)	1,713,309 (80.97)

[1]Year refers to the fiscal year.
[2]Total number of individuals if summed is 214,112. Number of unique ids / individuals is 63,517.
[3]This is the total number of prescriptions, including all prescription claim status

When analyzing benzodiazepine prescriptions all 2,115,856 prescriptions were used however when analyzing benzodiazepine usage, only the “Settled-Paid” prescriptions were used.

Table 4.2 shows the total number of prescriptions and individuals in each year. Between 2007 and 2016 the percentage of benzodiazepines that were prescribed to an individual in a rural area varied between 18.06% and 19.54%. In 2007 18,778 individuals received 180,182 prescriptions while in 2014, 22,492 individuals received 225,768 prescriptions.

Table 4.3 – *Patient Demographics*

		Rural (N, %)	Urban (N, %)	Total	p-value[1]
April 2007 to Mar 2008	Age[2] (Mean/Std)	62.8 (16.2)	60.4 (18.0)	61.0 (17.6)	p < 0.01
	18-24	76 (1.75)	414 (2.82)	490 (2.57)	p < 0.01
	25-44	569 (13.12)	2,679 (18.22)	3,248 (17.06)	
	45-64	1,367 (31.52)	4,746 (32.27)	6,113 (32.10)	
	65-84	2,044 (47.13)	5,686 (38.67)	7,730 (40.59)	
	85+	281 (6.48)	1,180 (8.02)	1,461 (7.67)	
	Female (N) (%)	2,811 (64.81)	9,626 (65.46)	12,437 (65.31)	p = 0.43
	n	4,337	14,705	19,042	
April 2008 to Mar 2009	Age (Mean/Std)	62.2 (16.0)	59.8 (18.1)	60.4 (17.7)	p < 0.01
	18-24	92 (2.08)	494 (3.22)	586 (2.96)	p < 0.01
	25-44	566 (12.82)	2,868 (18.67)	3,434 (17.36)	
	45-64	1,443 (32.68)	5,017 (32.66)	6,460 (32.66)	
	65-84	2,089 (47.32)	5,871 (38.22)	7,960 (40.25)	
	85+	225 (5.10)	1,113 (7.24)	1,338 (6.77)	
	Female (N) (%)	2,900 (65.7)	10,211 (66.5)	13,111 (66.3)	p = 0.33
	N	4,415	15,363	19,778	
April 2009 to Mar 2010	Age (Mean/Std)	62.9 (16.3)	60.4 (18.2)	60.9 (17.8)	p < 0.01
	18-24	91 (1.94)	536 (3.30)	627 (2.99)	p < 0.01
	25-44	601 (12.84)	2,913 (17.92)	3,514 (16.78)	
	45-64	1,437 (30.71)	5,162 (31.75)	6,599 (31.52)	
	65-84	2,258 (48.25)	6,375 (39.21)	8,633 (41.23)	
	85+	293 (6.26)	1,271 (7.82)	1,564 (7.47)	
	Female (N) (%)	3,056 (65.3)	10,733 (66.0)	13,789 (65.9)	p = 0.36
	N	4,680	16,257	20,937	
April 2010 to Mar 2011	Age (Mean/Std)	62.4 (16.2)	59.9 (18.3)	60.4 (17.9)	p < 0.01
	18-24	97 (1.99)	637 (3.73)	734 (3.35)	p < 0.01
	25-44	639 (13.14)	3,120 (18.27)	3,759 (17.14)	
	45-64	1,544 (31.75)	5,422 (31.76)	6,966 (31.76)	
	65-84	2,305 (47.40)	6,630 (38.83)	8,935 (40.73)	
	85+	278 (5.72)	1,264 (7.40)	1,542 (7.03)	
	Female (N) (%)	3,168 (65.1)	11,250 (65.9)	14,418 (65.7)	p = 0.33
	N	4,863	17,073	21,936	
April 2011 to Mar 2012	Age (Mean/Std)	62.3 (16.3)	59.8 (18.5)	60.3 (18.1)	p < 0.01
	18-24	108 (2.06)	695 (3.71)	803 (3.35)	p < 0.01
	25-44	700 (13.38)	3,505 (18.70)	4,205 (17.54)	
	45-64	1,693 (32.36)	5,935 (31.66)	7,628 (31.81)	
	65-84	2,415 (46.17)	7,138 (38.08)	9,553 (39.84)	

	85+	315 (6.02)	1,473 (7.86)	1,788 (7.46)	
	Female (N) (%)	3,390 (64.8)	12,296 (65.6)	15,686 (65.4)	p = 0.29
	N	5,231	18,746	23,977	
April 2012 to Mar 2013	Age (Mean/Std)	62.6 (16.4)	59.9 (18.6)	60.5 (18.2)	p < 0.01
	18-24 25-44 45-64 65-84 85+	131 (2.37) 696 (12.62) 1,736 (31.47) 2,599 (47.11) 355 (6.43)	706 (3.76) 3,527 (18.79) 5,816 (30.99) 7,178 (38.25) 1,540 (8.21)	837 (3.45) 4,223 (17.39) 7,552 (31.10) 9,777 (40.26) 1,895 (7.80)	p < 0.01
	Female (N) (%)	3,361 (60.9)	12,260 (65.3)	15,891 (65.4)	p = 0.50
	N	5,517	18,767	24,284	
April 2013 to Mar 2014	Age (Mean/Std)	63.1 (16.6)	59.9 (18.8)	60.7 (18.3)	p < 0.01
	18-24 25-44 45-64 65-84 85+	130 (2.37) 722 (13.14) 1,572 (28.60) 2,683 (48.82) 389 (7.08)	730 (3.94) 3,505 (18.91) 5,591 (30.16) 7,198 (38.83) 1,512 (8.16)	860 (3.58) 4,227 (17.59) 7,163 (29.81) 9,881 (41.12) 1,901 (7.91)	p < 0.01
	Female (N) (%)	3,598 (65.5)	12,130 (65.4)	15,728 (65.4)	p = 0.97
	N	5,496	18,536	24,032	
April 2014 to Mar 2015	Age (Mean/Std)	63.2 (16.4)	60.0 (18.9)	60.7 (18.4)	p < 0.01
	18-24 25-44 45-64 65-84 85+	123 (2.30) 670 (12.55) 1,557 (29.17) 2,620 (49.08) 368 (6.89)	749 (4.01) 3,557 (19.06) 5,507 (29.51) 7,315 (39.19) 1,536 (8.23)	872 (3.63) 4,227 (17.61) 7,064 (29.43) 9,935 (41.39) 1,904 (7.93)	p < 0.01
	Female (N) (%)	3,471 (65.0)	12,218 (65.5)	15,689 (65.4)	p = 0.55
	N	5,338	18,664	24,002	
April 2015 to Mar 2016	Age (Mean/Std)	63.0 (16.8)	59.9 (18.9)	60.6 (18.5)	p < 0.01
	18-24 25-44 45-64 65-84 85+	163 (3.04) 669 (12.47) 1,473 (27.47) 2,698 (50.31) 360 (6.71)	734 (3.94) 3,604 (19.37) 5,430 (29.18) 7,340 (39.44) 1,502 (8.07)	897 (3.74) 4,273 (17.82) 6,903 (28.79) 10,038 (41.87) 1,862 (7.77)	p < 0.01
	Female (N) (%)	3,469 (64.7)	12,166 (65.4)	15,635 (65.2)	p = 0.35
	N	5,363	18,610	23,973	
April 2016 to Mar 2017	Age (Mean/Std)	63.0 (16.9)	59.7 (19.0)	60.4 (18.6)	p < 0.01
	18-24 25-44 45-64 65-84 85+	172 (3.12) 700 (12.72) 1,509 (27.42) 2,762 (50.18) 361 (6.56)	818 (4.33) 3,653 (19.35) 5,477 (29.02) 7,459 (39.52) 1,468 (7.78)	990 (4.06) 4,353 (17.86) 6,986 (28.66) 10,221 (41.93) 1,829 (7.50)	p < 0.01
	Female (N) (%)	3,565 (64.8)	12,270 (65.0)	15,835 (65.0)	p = 0.74

	N	5,504	18,875	24,379	

[1] t-tests used for comparing continuous variables (mean age). Chi-squared tests used for categorical variables (age groups and sex)
[2]Age was calculated based on the first prescription that an individual received

Mean age varied across the ten-year period. Individuals in rural areas had a higher mean age than those in urban areas by approximately 3 years. The distribution of age groups varied between rural and urban areas, specifically a higher percentage of individuals were in the 65-84 age group in rural areas. Percentage of females did not vary significantly between urban and rural areas, only numerical differences were observed.

4.2 Benzodiazepine Prescribing / Usage

Benzodiazepine prescribing was analyzed using quantity dispensed, dispensed days' supply and diazepam equivalents. This section will focus on frequencies and percentages of these variables.

Table 4.4 – *Number of Prescriptions Stratified by Quantity Dispensed*

Year		**Quantity Dispensed[1] n (%)**									
		Less than 7	**7**	**7-14[2]**	**14-30[2]**	**30**	**30-45[2]**	**45-60[2]**	**60**	**More than 60**	**p-value[3]**
April 2007 to March 2008	Rural	1,008 (3.01)	368 (1.10)	336 (1.00)	3,507 (10.49)	11,202 (33.50)	675 (2.02)	1,195 (3.57)	7,640 (22.85)	7,504 (22.44)	p < 0.01
	Urban	5,203 (3.55)	5,565 (3.79)	2,691 (1.83)	20,151 (13.73)	39,499 (26.92)	5,324 (3.63)	5,635 (3.84)	28,409 (19.36)	34,270 (23.35)	
April 2008 to March 2009	Rural	1,196 (3.33)	600 (1.67)	407 (1.13)	3,535 (9.83)	12,132 (33.73)	640 (1.78)	1,216 (3.38)	8,558 (23.79)	7,684 (21.36)	p < 0.01
	Urban	4,284 (2.82)	4,278 (2.81)	2,595 (1.71)	21,489 (14.13)	42,758 (28.12)	5,008 (3.29)	6,199 (4.08)	30,537 (20.08)	34,912 (22.96)	
April 2009 to March 2010	Rural	1,095 (3.00)	516 (1.42)	322 (0.88)	3,882 (10.65)	12,698 (34.85)	594 (1.63)	1,379 (3.78)	8,582 (23.55)	7,373 (20.23)	p < 0.01
	Urban	5,360 (3.49)	3,622 (2.36)	2,390 (1.56)	22,919 (14.93)	42,624 (27.76)	4,845 (3.16)	6,583 (4.29)	30,687 (19.99)	34,508 (22.48)	
April 2010 to March 2011	Rural	346 (0.91)	368 (0.96)	338 (0.89)	4,270 (11.19)	13,416 (35.16)	685 (1.80)	1,337 (3.50)	9,219 (24.16)	8,182 (21.44)	p < 0.01
	Urban	8,496 (4.91)	4,062 (2.35)	2,933 (1.69)	27,319 (15.78)	45,045 (26.02)	5,223 (3.02)	8,260 (4.77)	33,625 (19.42)	38,147 (22.04)	

April 2011 to March 2012	Rural	472 (1.14)	259 (0.63)	403 (0.97)	4,543 (10.97)	14,269 (34.44)	846 (2.04)	1,678 (4.05)	10,124 (24.44)	8,832 (21.32)	p < 0.01
	Urban	7,580 (4.17)	3,680 (2.03)	3,268 (1.80)	29,091 (16.02)	46,855 (25.81)	5,837 (3.21)	9,426 (5.19)	35,539 (19.57)	40,291 (22.19)	
April 2012 to March 2013	Rural	615 (1.43)	247 (0.57)	518 (1.20)	4,808 (11.15)	14,779 (34.28)	728 (1.69)	1,800 (4.17)	10,410 (24.14)	9,213 (21.37)	p < 0.01
	Urban	6,730 (3.71)	4,423 (2.44)	3,182 (1.76)	29,765 (16.42)	45,789 (25.26)	5,670 (3.13)	9,653 (5.33)	35,464 (19.56)	40,590 (22.39)	
April 2013 to March 2014	Rural	726 (1.66)	377 (0.86)	508 (1.16)	5,173 (11.85)	14,417 (33.02)	629 (1.44)	1,888 (4.32)	10,589 (24.25)	9,354 (21.42)	p < 0.01
	Urban	6,612 (3.63)	4,308 (2.37)	2,841 (1.56)	29,940 (16.44)	45,599 (25.04)	5,618 (3.09)	9,979 (5.48)	35,242 (19.36)	41,931 (23.03)	
April 2014 to March 2015	Rural	884 (2.03)	531 (1.22)	412 (0.95)	5,101 (11.71)	14,350 (32.93)	598 (1.37)	1,958 (4.49)	10,768 (24.71)	8,977 (20.60)	p < 0.01
	Urban	7,203 (3.95)	4,419 (2.43)	2,696 (1.48)	30,977 (17.00)	43,782 (24.03)	5,904 (3.24)	10,835 (5.95)	34,825 (19.11)	41,548 (22.80)	
April 2015 to March 2016	Rural	949 (2.17)	463 (1.06)	570 (1.31)	6,084 (13.94)	13,770 (31.55)	649 (1.49)	1,900 (4.35)	10,622 (24.34)	8,638 (19.79)	p < 0.01
	Urban	5,462 (3.04)	4,203 (2.34)	2,948 (1.64)	32,011 (17.81)	43,708 (24.31)	5,266 (2.93)	10,805 (6.01)	35,029 (19.49)	40,329 (22.43)	
April 2016 to March 2017	Rural	719 (1.67)	301 (0.70)	491 (1.14)	6,044 (14.02)	13,690 (31.75)	656 (1.52)	2,005 (4.65)	10,262 (23.80)	8,945 (20.75)	p < 0.01
	Urban	6,905 (3.81)	3,985 (2.20)	3,849 (2.13)	33,189 (18.34)	42,821 (23.66)	4,984 (2.75)	11,180 (6.18)	34,386 (19.00)	39,702 (21.93)	

[1] Quantity of pills dispensed in number of pills: n (%)

[2] 7-14: greater than 7 and less than 14; 14-30: greater than or equal to 14 and less than 30; 30-45: greater than 30 and less than 45; 45-60: greater than or equal to 45 and less than 60

[3] p-value is the comparison between rural and urban

Table 4.4 shows the distribution of quantities dispensed. The most commonly prescribed benzodiazepine quantities (measured in pills) were 30, 60 and more than 60 pills. Approximately 30% of prescriptions per year were for a quantity of 30 pills and 20% were for a quantity of 60 pills. Throughout the ten-year time period, the distribution of quantities dispensed varied minimally.

Table 4.5 – *Number of Prescriptions Stratified by Dispensed Days' Supply*

Year		**Dispensed Days' Supply[1] n (%)**									
		Less than 7	**7**	**7-14[2]**	**14-30[2]**	**30**	**30-45[2]**	**45-60[2]**	**60**	**More than 60**	**p-value[3]**
April 2007 to March 2008	Rural	1,181 (3.53)	1,167 (3.49)	732 (2.19)	4,566 (13.66)	23,981 (71.72)	399 (1.19)	68 (0.20	405 (1.21)	936 (2.80)	$p < 0.01$
	Urban	7,371 (5.02)	14,482 (9.87)	3,513 (2.39)	23,649 (16.12)	90,340 (61.56)	2,645 (1.80)	372 (0.25)	1,374 (0.94)	3,001 (2.05)	
April 2008 to March 2009	Rural	1,445 (4.02)	1,434 (3.99)	770 (2.14)	4,785 (13.30)	26,471 (73.60)	261 (0.73)	35 (0.10)	200 (0.56)	567 (1.58)	$p < 0.01$
	Urban	6,332 (4.16)	13,569 (8.92)	3,601 (2.37)	25,365 (16.68)	98,585 (64.83)	1,916 (1.26)	259 (0.17)	796 (0.52)	1,637 (1.08)	
April 2009 to March 2010	Rural	1,310 (3.59)	1,330 (3.65)	718 (1.97)	5,310 (14.57)	27,031 (74.18)	136 (0.37)	27 (0.07)	167 (0.46)	412 (1.13)	$p < 0.01$
	Urban	7,229 (4.71)	12,961 (8.44)	3,506 (2.28)	27,032 (17.61)	99,219 (64.62)	1,650 (1.07)	159 (0.10)	592 (0.39)	1,190 (0.78)	
April 2010 to March 2011	Rural	555 (1.45)	1,300 (3.41)	804 (2.11)	5,679 (14.88)	29,148 (76.38)	70 (0.18)	32 (0.08)	164 (0.43)	409 (1.07)	$p < 0.01$
	Urban	10,985 (6.35)	14,567 (8.41)	4,012 (2.32)	33,289 (19.23)	107,708 (62.22)	696 (0.40)	171 (0.10)	488 (0.28)	1,194 (0.69)	
April 2011 to March 2012	Rural	735 (1.77)	1,145 (2.76)	851 (2.05)	6,771 (16.34)	31,153 (75.20)	71 (0.17)	41 (0.10)	225 (0.54)	434 (1.05)	$p < 0.01$
	Urban	10,591 (5.83)	13,793 (7.60)	4,409 (2.43)	39,050 (21.51)	110,875 (61.07)	574 (0.32)	202 (0.11)	596 (0.33)	1,477 (0.81)	
April 2012 to March 2013	Rural	990 (2.30)	1,008 (2.34)	851 (1.97)	7,228 (16.76)	32,236 (74.76)	161 (0.37)	44 (0.10)	135 (0.31)	465 (1.08)	$p < 0.01$
	Urban	9,754 (5.38)	14,175 (7.82)	4,145 (0.82)	40,618 (22.41)	109,891 (60.62)	561 (0.31)	137 (0.08)	500 (0.28)	1,485 (0.82)	

April 2013 to March 2014	Rural	1,146 (2.62)	1,117 (2.56)	847 (1.94)	7,847 (17.97)	32,030 (73.36)	62 (0.14)	26 (0.06)	113 (0.26)	473 (1.08)	p < 0.01
	Urban	9,272 (5.09)	13,670 (7.51)	3,977 (2.18)	42,505 (23.35)	110,302 (60.58)	363 (0.20)	156 (0.09)	370 (0.20)	1,455 (0.80)	
April 2014 to March 2015	Rural	1,163 (2.67)	1,427 (3.27)	889 (2.04)	7,794 (17.88)	31,711 (72.77)	49 (0.11)	37 (0.08)	92 (0.21)	417 (0.96)	p < 0.01
	Urban	9,753 (5.35)	14,549 (7.99)	4,106 (2.25)	43,888 (24.09)	107,567 (59.04)	306 (0.17)	158 (0.09)	438 (0.24)	1,424 (0.78)	
April 2015 to March 2016	Rural	1,340 (3.07)	1,672 (3.83)	968 (2.22)	8,422 (19.30)	30,680 (70.29)	43 (0.10)	31 (0.07)	124 (0.28)	365 (0.84)	p < 0.01
	Urban	8,063 (4.49)	15,295 (8.51)	4,098 (2.28)	44,227 (24.60)	106,034 (58.99)	290 (0.16)	130 (0.07)	366 (0.20)	1,258 (0.70)	
April 2016 to March 2017	Rural	1,019 (2.36)	1,442 (3.34)	920 (2.13)	8,596 (19.94)	30,376 (70.46)	49 (0.11)	36 (0.08)	140 (0.32)	535 (1.24)	p < 0.01
	Urban	9,967 (5.51)	16,099 (8.89)	4,244 (2.34)	44,589 (24.63)	103,936 (57.42)	224 (0.12)	114 (0.06)	388 (0.21)	1,440 (0.80)	

[1] Dispensed days supply measured in days: n (%)
[2]7-14: greater than 7 and less than 14; 14-30: greater than or equal to 14 and less than 30; 30-45: greater than 30 and less than 45; 45-60: greater than or equal to 45 and less than 60
[3] p-value is the comparison between rural and urban

Table 4.5 shows the number of prescriptions in each category, stratified by rural / urban area across ten years. The two most frequently prescribed durations were 14-30 days and 30 days, approximately 60 to 65% of prescriptions were for 30 days.

Table 4.6 – *Number of Prescriptions Stratified by Drug Generic Name (All Years)*

Drug Generic Name		**Number[1] n (%)**	**p-value[2]**
Alprazolam	Rural	20,633 (21.62)	$p < 0.01$
	Urban	74,802 (78.38)	Urban
	Total (%)	95,435 (4.51)	
Bromazepam	Rural	24,796 (23.00)	$p < 0.01$
	Urban	83,021 (77.00)	
	Total (%)	107,817 (5.10)	
Chlordiazepoxide	Rural	5,975 (27.05)	$p < 0.01$
	Urban	16,110 (72.95)	
	Total (%)	22,085 (1.04)	
Clobazam	Rural	5,832 (20.82)	$p < 0.01$
	Urban	22,177 (79.18)	
	Total (%)	28,009 (1.32)	
Clonazepam	Rural	74,209 (15.33)	$p < 0.01$
	Urban	409,835 (80.24)	
	Total (%)	484,044 (22.9)	
Clorazepate	Rural	2,805 (19.76)	$p < 0.01$
	Urban	11,392 (80.24)	
	Total (%)	14,197 (0.67)	
Diazepam	Rural	22,757 (15.36)	$p < 0.01$
	Urban	125,431 (84.64)	
	Total (%)	148,188 (7.00)	
Flurazepam	Rural	2,557 (18.50)	$p < 0.01$
	Urban	11,263	

		(81.50)	
	Total (%)	13,820 (0.65)	
Lorazepam	Rural	162,649 (21.71)	$p < 0.01$
	Urban	586,710 (78.29)	
	Total (%)	749,359 (35.4)	
Midazolam	Rural	41 (17.01)	$p < 0.01$
	Urban	200 (82.99)	
	Total (%)	241 (0.01)	
Nitrazepam	Rural	4,117 (18.08)	$p < 0.01$
	Urban	18,659 (81.92)	
	Total (%)	22,776 (1.08)	
Oxazepam	Rural	21,181 (21.51)	$p < 0.01$
	Urban	18,659 (78.49)	
	Total (%)	39,840 (1.08)	
Temazepam	Rural	48,255 (15.92)	$p < 0.01$
	Urban	254,842 (84.08)	
	Total (%)	303,097 (14.3)	
Triazolam	Rural	6,740 (23.80)	$p < 0.01$
	Urban	21,575 (76.20)	
	Total (%)	28,315 (1.34)	
Null		1	
	Total	**2,115,856**	

[1]Measured as number of prescriptions (%)
[2]Comparison between rural and urban areas.

Lorazepam was the most commonly prescribed benzodiazepine, comprising 35% of total prescriptions. Clonazepam and temazepam were the second and third-most prescribed benzodiazepine with 22% and 14%, respectively. Table 4.6 shows the breakdown of prescriptions by drug generic name, with a significant higher number of prescriptions (greater than 50%) being issued to individuals in urban areas compared to rural areas.

Across the ten-year timeframe, clonazepam increased from year 1 to the last year examined. Similarly, increases were observed in lorazepam across the timeframe. Table 4.7 shows the generic drug name across each of the years.

Table 4.7 – *Number of Prescriptions Stratified by Drug Generic Name*

	Drug Generic Name – Year by Year[1] n (%)									
Drug Generic Name	April 2007 to March 2008	April 2008 to March 2009	April 2009 to March 2010	April 2010 to March 2011	April 2011 to March 2012	April 2012 to March 2013	April 2013 to March 2014	April 2014 to March 2015	April 2015 to March 2016	April 2016 to March 2017
Alprazolam	9,388 (5.21)	10,021 (5.33)	9,314 (4.90)	10,354 (4.90)	10,327 (4.63)	9,775 (4.36)	9,396 (4.16)	9,237 (4.10)	8,897 (3.98)	8,726 (3.89)
Bromazepam	10,421 (5.78)	10,600 (5.64)	10,400 (5.47)	11,460 (5.42)	11,894 (5.33)	11,576 (5.16)	11,093 (4.91)	10,845 (4.80)	10,049 (4.50)	9,479 (4.23)
Chlordiazepoxide	2,553 (1.42)	2,687 (1.43)	2,403 (1.26)	2,374 (1.12)	2,330 (1.04)	2,254 (1.00)	2,115 (0.94)	1,941 (0.86)	1,816 (0.01)	1,612 (0.72)
Clobazepam	2,151 (1.20)	2,275 (1.21)	2,326 (1.22)	2,701 (1.28)	3,063 (1.37)	3,218 (1.43)	3,099 (1.37)	3,048 (1.35)	3,072 (1.38)	3,057 (1.36)
Clonazepam	32,207 (17.87)	35,612 (18.93)	37,806 (19.90)	45,012 (21.31)	50,716 (22.74)	52,890 (23.57)	55,504 (24.59)	56,210 (24.90)	57,766 (25.86)	60,321 (26.92)
Clorazepate	2,033 (1.11)	2,009 (1.07)	1,897 (1.00)	1,903 (0.90)	1,318 (0.59)	1,130 (0.50)	1,044 (0.46)	1,068 (0.47)	935 (0.42)	860 (0.38)
Diazepam	14,411 (8.00)	15,100 (8.03)	14,489 (7.63)	15,494 (7.33)	15,398 (6.91)	15,516 (6.91)	15,201 (6.73)	15,084 (6.68)	14,156 (6.34)	13,339 (5.95)
Flurazepam	2,698 (1.50)	2,454 (1.31)	2,020 (1.06)	1,982 (0.94)	587 (0.26)	721 (0.3)	779 (0.35)	871 (0.39)	781 (0.35)	958 (0.42)
Lorazepam	58,791 (32.63)	61,840 (32.89)	64,252 (33.82)	72,756 (34.44)	78,237 (35.1)	79,218 (35.3)	80,535 (35.68)	83,424 (36.70)	84,101 (37.65)	86,141 (38.4)
Midazolam	4 (0.00)	1 (0.00)	3	6 (0.00)	23 (0.0)	20 (0.00)	20 (0.00)	31 (0.00)	59 (0.00)	74 (0.00)
Nitrazepam	2,139 (1.19)	2,234 (1.19)	2,360 (1.24)	2,675 (1.27)	2,681 (1.2)	2,296 (1.02)	2,278 (1.01)	2,241 (0.1)	1,934 (0.87)	1,938 (0.86)
Oxazepam	10,321 (5.73)	9,735 (5.18)	9,780 (5.15)	10,624 (5.03)	11,106 (4.98)	10,465 (4.67)	10,328 (4.58)	9,262 (4.10)	8,380 (3.75)	8,471 (3.78)
Temazepam	26,961 (14.96)	27,210 (14.47)	27,003 (14.21)	31,298 (14.81)	34,573 (15.50)	33,896 (15.11)	32,762 (14.51)	31,624 (14.01)	30,165 (13.50)	27,575 (12.30)
Triazolam	6,100 (3.39)	6,190 (3.29)	5,926 (3.12)	2,632 (1.25)	740 (0.33)	1,408 (0.63)	1,577 (0.70)	883 (0.4)	1,295 (0.58)	1,564 (0.70)
Total	180,182	188,028	189,979	211,271	222,993	224,384	225,731	225,768	223,406	224,114

[1]Measured as number of persons (%). Percentages are shown based on each year (i.e., 5.2% of benzodiazepine prescriptions between April 2007 and March 2008 was alprazolam)

Table 4.8 – *Number of Prescriptions by Prescriber Specialty (Year to Year)*

Year	Prescriber Specialty[1]	Urban / Rural Classification	Total[2] n (%)	p-value[3]
April 2007 to March 2008	GP	Rural	33,067 (18.47)	p < 0.01
		Urban	145,958 (81.53)	
	Other	Rural	368 (31.81)	
		Urban	789 (68.19)	
April 2008 to March 2009	GP	Rural	35,695 (19.10)	p < 0.01
		Urban	151,221 (80.90)	
	Other	Rural	273 (24.55)	
		Urban	839 (75.45)	
April 2009 to March 2010	GP	Rural	36,082 (19.12)	p < 0.01
		Urban	152,649 (80.88)	
	Other	Rural	359 (28.77)	
		Urban	889 (71.23)	
April 2010 to March 2011	GP	Rural	37,723 (17.97)	p < 0.01
		Urban	172,142 (82.03)	
	Other	Rural	438 (31.15)	
		Urban	968 (68.85)	
April 2011 to March 2012	GP	Rural	41,111 (18.53)	p < 0.01
		Urban	180,803 (81.47)	
	Other	Rural	315 (29.19)	
		Urban	764 (70.81)	
April 2012 to March 2013	GP	Rural	42,702 (19.12)	p < 0.01
		Urban	180,647 (80.88)	
	Other	Rural	416	

			(40.19)	
		Urban	619 (59.81)	
April 2013 to March 2014	GP	Rural	42,868 (19.23)	p < 0.01
		Urban	180,085 (80.77)	
	Other	Rural	793 (28.55)	
		Urban	1,985 (71.45)	
April 2014 to March 2015	GP	Rural	41,984 (19.11)	p < 0.01
		Urban	177,729 (80.890)	
	Other	Rural	1,595 (26.34)	
		Urban	4,460 (73.66)	
April 2015 to March 2016	GP	Rural	41,609 (19.26)	p < 0.01
		Urban	174,381 (80.74)	
	Other	Rural	2,036 (27.45)	
		Urban	5,380 (72.55)	
April 2016 to March 2017	GP	Rural	40,353 (18.87)	p < 0.01
		Urban	173,492 (81.13)	
	Other	Rural	2,760 (26.88)	
		Urban	7,509 (73.12)	

[1]Other: any prescriber specialty except for general practitioner (GP)
[2]Measured as number of prescriptions: n (%)
[3]Comparison between rural and urban by prescriber specialty using chi-squared test

Across all years, more than 95% of prescriptions were written by general practitioners (GPs). In year 1, 99.36% of prescriptions were from GPs compared to 0.64% from other specialities. Interestingly, when stratifying by prescriber specialty differences were observed between rural and urban areas. Furthermore, between April 2012 and March 2013 19.23% of prescriptions by a GP where to an individual living in a rural area compared to 40.19% of those by any other prescriber specialty. Table 4.8 shows the distribution of prescriptions between rural and urban areas.

4.3 Average Benzodiazepine Usage

Table 4.9 – *Sex, Prescriber and Location Frequencies*

Variable	**Sample Size n (%)**
Male	772,764 (36.5)
Female	1,343,092 (63.5)
GP	2,082,301 (98.4)
Other[1]	33,555 (1.6)
Urban	1,713,309 (81.0)
Rural	402,547 (19.0)
Total	2,115,856 (100.0)

[1]Other: any prescriber specialty except for general practitioner (GP)

The total frequencies and percentages of prescriptions by sex, prescriber specialty and urban / rural classification are shown in Table 4.9. Benzodiazepines were more frequently prescribed to females, by GPs and to those residing in urban areas (defined as greater than 1,000 individuals). 2,082,301 prescriptions were prescribed by a GP compared to 33,555 by other prescribers.

Table 4.10- *Average Quantity Dispensed*[1]

Variable		Mean (Std Dev)[2]	Sample Size (n)	Min / Max[2]	p-value[3]
Male	Rural	51.90 (34.6)	144,719	0.20 / 280	p < 0.01
	Urban	51.0 (37.8)	626,703	0.5 / 280	
Female	Rural	51.8 (33.1)	257,444	0.5 /280	p < 0.01
	Urban	50.9 (35.8)	1,084,582	0.2 / 284	
GP	Rural	51.9 (33.7)	392,813	0.2 / 280	p < 0.01
	Urban	51.1 (36.6)	1,687,093	0.2 / 284	
Other[3]	Rural	47.2 (29.6)	9,350	0.5 / 280	p < 0.01
	Urban	43.6 (34.4)	24,192	0.2 / 270	
Urban		51.0 (36.6)	1,711,285	0.2 / 284	p < 0.01
Rural		51.8 (33.6)	402,163	0.2 / 280	
Age: 18 - 24	Rural	41.4 (32.8)	5,741	0.5 / 270	p = 0.89
	Urban	41.3 (34.3)	35,389	1 / 270	
Age: 25 - 44	Rural	51.7 (39.3)	46,757	0.2 / 280	p < 0.01
	Urban	46.2 (37.2)	324,685	0.2 / 280	
Age: 45 - 64	Rural	53.9 (35.9)	136,499	0.5 / 280	p < 0.01
	Urban	52.8 (39.1)	659,783	0.5 / 280	
Age: 65 - 84	Rural	51.9 (31.1)	187,561	1 / 270	p < 0.01
	Urban	53.9 (34.5)	573,266	0.5 / 280	
Age: 85 +	Rural	42.4 (24.9)	25,605	1 / 270	P = 0.32
	Urban	42.2 (25.6)	118,162	0.5 / 284	
Total		**51.12 (36.02)**	**2,113,448**	**0.2 / 284**	

[1] Quantity dispensed measured as number of pills
[2]Outliers removed using 3*SD: (3*77.64). Using 2,115,856 prescriptions: mean = 51.57, std dev = 77.64
[3] p-value is the comparison between rural and urban
[4]Other: any prescriber specialty except for general practitioner (GP)

Overall, 51 pills were dispensed per prescription (Table 4.10). This was approximately equal when comparing sex and place of residence. When comparing individuals in the 25-44 age group, those living in a rural area were prescribed an average of 5 more pills than those living in an urban area. Quantities dispensed were higher in rural areas, with minimal differences between males and females. When the prescription was issued by a GP, it was higher than other specialities.

Table 4.11- *Average Dispensed Days' Supply*[1]

Variable		Mean (Std Dev)	Sample Size (n)	Min / Max[2]	p-value[3]
Male	Rural	26.4 (7.91)	142,473	0 / 57	$p < 0.01$
	Urban	23.6 (9.94)	620,994	0 / 58	
Female	Rural	27.1 (6.86)	253,296	0 / 59	$p < 0.01$
	Urban	25.0 (8.94)	1,070,846	0 / 58	
GP	Rural	26.9 (7.26)	386,499	0 / 59	$p < 0.01$
	Urban	24.5 (9.31)	1,667,762	0 / 58	
Other[4]	Rural	26.8 (7.40)	9,270	0 / 56	$p < 0.01$
	Urban	21.6 (10.6)	24,078	0 / 56	
Urban		24.5 (9.34)	1,691,840	0 / 58	$p < 0.01$
Rural		26.9 (7.26)	395,769	0 / 59	
Age: 18 - 24	Rural	20.5 (10.3)	5,720	1 / 54	$p < 0.01$
	Urban	19.8 (10.7)	35,279	1 / 56	
Age: 25 - 44	Rural	23.5 (9.68)	46,484	0 / 57	$p < 0.01$
	Urban	20.5 (11.1)	322,939	0 / 56	
Age: 45 - 64	Rural	26.0 (8.32)	135,142	0 / 56	$p < 0.01$
	Urban	23.3 (10.0)	655,332	0 / 57	
Age: 65 - 84	Rural	28.4 (5.03)	183,272	0 / 59	$p < 0.01$
	Urban	27.8 (5.91)	561,651	0 / 58	
Age: 85 +	Rural	28.0 (4.92)	25,151	1 / 56	$p < 0.01$
	Urban	27.2 (6.19)	116,639	0 / 56	
Total		**24.91 (9.03)**	**2,087,609**	**0 / 59**	

[1]Average dispensed days supply measured as number of days
[2]Outliers removed using 3*SD: (3*11.29). Using 2,115,856 prescriptions: mean = 25.68, std dev = 11.29
[3]p-value is the comparison between rural and urban
[4]Other: any prescriber specialty except for general practitioner (GP)

Overall, the average duration of a benzodiazepine prescription was 25 days. Those in rural areas had a higher mean duration by approximately two days (Table 4.11). Among individuals 25-44, those living in a rural area had a significantly higher mean dispensed days supply of 3 days compared to those living in an urban area. Comparing within each of the 5 age groups, those in rural areas had significantly higher dispensed days supply compared to those living in urban areas.

Table 4.12 – *Average Number of Pills per Person per Day*[1]

Variable		**Mean (Std Dev)**	**Sample Size (n)**	**Min / Max**[2]	**p-value**[3]
Male	Rural	1.95 (1.11)	144,297	0.066 / 10	p < 0.01
	Urban	2.21 (1.31)	626,027	0.033 / 10	
Female	Rural	1.90 (1.09)	257,485	0.066 / 10	p < 0.01
	Urban	2.07 (1.25)	1,084,341	0.033 / 10	
GP	Rural	1.92 (1.10)	392,434	0.066 / 10	p < 0.01
	Urban	2.12 (1.27)	1,686,289	0.033 / 10	
Other[4]	Rural	1.78 (0.98)	9,348	0.048 / 10	p < 0.01
	Urban	2.09 (1.23)	24,079	0.067 / 10	
Urban		2.12 (1.27)	1,710,368	0.033 / 10	p < 0.01
Rural		1.92 (1.10)	401,782	0.048 / 10	
Age: 18 - 24	Rural	1.99 (1.10)	5,742	0.067 / 10	p < 0.01
	Urban	2.11 (1.24)	35,397	0.067 / 10	
Age: 25 - 44	Rural	2.21 (1.28)	46,745	0.067 / 10	p < 0.01
	Urban	2.33 (1.35)	323,778	0.036 / 10	
Age: 45 - 64	Rural	2.07 (1.17)	136,145	0.048 / 10	p < 0.01
	Urban	2.30 (1.35)	659,803	0.033 / 10	
Age: 65 - 84	Rural	1.79 (0.98)	187,550	0.066 / 10	p < 0.01
	Urban	1.92 (1.13)	573,354	0.033 / 10	
Age: 85 +	Rural	1.50 (0.84)	25,600	0.06 / 10	p < 0.01
	Urban	1.57 (0.93)	118,036	0.067 / 10	
Total		**2.08 (1.24)**	**2,112,150**	**0.033 / 10**	

[1]Average number of pills per person per day: n
[2]Outliers removed using 3*SD: (3*2.66). Using 2,115,840 prescriptions: mean = 2.11, std dev = 2.66
[3]p-value is the comparison between rural and urban
[4]Other: any prescriber specialty except for general practitioner (GP)

Table 4.12 indicates the average number of pills per day was 2.08. Individuals living in an urban area were prescribed more pills per day on average, than those living in a rural area. Among individuals in the 45-64 age group, individuals living in an urban area were prescribed more pills per day than those living in a rural area. Comparing values within age groups, those living in an urban area were prescribed more pills per day than those in rural areas.

Table 4.13 - *Drug Strength*[1]

Variable		Mean (Std Dev)	Sample Size (n)	Min / Max[2]	p-value[3]
Male	Rural	6.72 (9.92)	144,889	0.125 / 30	p < 0.01
	Urban	7.24 (10.30)	627,865	0.125 / 30	
Female	Rural	5.39 (8.84)	257,651	0.125 / 30	p < 0.01
	Urban	6.28 (9.73)	1,085,431	0.125 / 30	
GP	Rural	5.87 (9.27)	393,190	0.125 / 30	p < 0.01
	Urban	6.66 (9.96)	1,689,098	0.125 / 30	
Other[4]	Rural	5.96 (9.03)	9,350	0.125 / 30	p < 0.01
	Urban	4.69 (8.10)	24,198	0.125 / 30	
Urban		6.63 (9.94)	1,713,296	0.125 / 30	p < 0.01
Rural		5.87 (9.27)	402,540	0.125 / 30	
Age: 18 - 24	Rural	4.34 (7.83)	5,744	0.125 / 30	p < 0.01
	Urban	3.75 (7.26)	35,488	0.125 / 30	
Age: 25 - 44	Rural	4.22 (7.62)	46,798	0.125 / 30	p < 0.01
	Urban	5.40 (9.18)	324,967	0.125 / 30	
Age: 45 - 64	Rural	6.06 (9.52)	136,756	0.125 / 30	p < 0.01
	Urban	7.14 (10.30)	660,774	0.125 / 30	
Age: 65 - 84	Rural	6.05 (9.39)	187,634	0.125 / 30	p < 0.01
	Urban	6.83 (9.98)	573,894	0.125 / 30	
Age: 85 +	Rural	6.90 (9.58)	25,608	0.125 / 30	p < 0.01
	Urban	7.14 (9.78)	118,173	0.125 / 30	
Total		**6.50 (9.82)**	**2,115,836**	**0.125 / 30**	

[1]Drug strength measured in milligrams (mg)
[2]Outliers removed using 3*SD: (3*9.82). Using 2,115,836 prescriptions: mean = 6.49, std dev = 9.82
[3]p-value is the comparison between rural and urban
[4]Other: any prescriber specialty except for general practitioner (GP)

Mean drug strength for all prescriptions was 6.50 milligrams (Table 4.13). Among males, those living in an urban area were prescribed a higher drug strength than those in a rural area.

Overall, those living in an urban area had a higher average prescription drug strength than those in rural areas. It is important to note that this does not account for the difference in potency of the medication; the following table (Table 4.14) of diazepam equivalent, however, does account for this.

Table 4.14 – *Prescription Strength Standardized to Equivalents of 5mg Diazepam*[1]

Variable		Mean (Std Dev)	Sample Size (n)	Min / Max[2]	p-value[3]
Male	Rural	2.82 (3.54)	144,889	0.27 / 12	p < 0.01
	Urban	3.31 (3.93)	627,865	0.27 / 12	
Female	Rural	2.31 (3.05)	257,651	0.29 / 12	p < 0.01
	Urban	2.81 (3.56)	1,085,430	0.27 / 12	
GP	Rural	2.50 (3.25)	393,190	0.27 / 12	p < 0.01
	Urban	3.00 (3.71)	1,689,097	0.27 / 12	
Other[4]	Rural	2.25 (2.99)	9,350	0.29 / 12	p < 0.01
	Urban	2.41 (3.16)	24,198	0.27 / 12	
Urban		2.99 (3.71)	1,713,295	0.27 / 12	p < 0.01
Rural		2.49 (3.24)	402,540	0.27 / 12	
Age: 18 - 24	Rural	1.95 (2.65)	5,744	0.29 / 12	p = 0.98
	Urban	1.95 (2.68)	35,488	0.27 / 12	
Age: 25 - 44	Rural	2.12 (2.80)	46,798	0.29 / 12	p < 0.01
	Urban	2.81 (3.59)	324,967	0.29 / 12	
Age: 45 - 64	Rural	2.71 (3.45)	136,756	0.29 / 12	p < 0.01
	Urban	3.37 (3.98)	660,774	0.27 / 12	
Age: 65 - 84	Rural	2.44 (3.19)	187,634	0.27 / 12	p < 0.01
	Urban	2.80 (3.52)	573,893	0.27 / 12	
Age: 85 +	Rural	2.53 (3.28)	25,608	0.29 / 12	p < 0.01
	Urban	2.64 (3.35)	118,173	0.27 / 12	
Total		**2.90 (3.63)**	**2,115,835**	**0.27 / 12**	

[1]Number of 5 mg diazepam equivalents. For example: 0.5 mg of alprazolam is equivalent to 5 mg of diazepam. Therefore, a drug strength of 2 mg of alprazolam would be equivalent to 4-5mg diazepam equivalents.
[2]Outliers removed using 3*SD: (3*3.63). Using 2,115,856 prescriptions: mean = 2.90, std dev = 3.63
[3]p-value is the comparison between rural and urban
[4]Other: any prescriber specialty except for general practitioner (GP)

The average number of diazepam equivalents was 2.90 (Table 4.14). Comparing within sex, males that lived in an urban area had a higher average number of diazepam equivalents than males living in a rural area. Similarly, results were observed in females, with those living in urban areas having a higher average number of diazepam equivalents than females living in a rural area. Among individuals in the 45-64 age group, the average number of diazepam equivalents was significantly higher in those living in an urban area than a rural area.

Table 4.15- *Aggregate Quantity Prescribed*[1]

Variable		Mean (Std Dev)	Sample Size (n)	Min / Max[2]	p-value[3]
Male	Rural	110.0 (129.0)	142,538	0.27 / 720	p < 0.01
	Urban	125.0 (150.0)	612,212	0.33 / 735	
Female	Rural	96.4 (113.0)	256,158	0.25 / 730	p < 0.01
	Urban	110.0 (133.0)	1,073,321	0.13 / 725	
GP	Rural	102.0 (199.0)	389,405	0.27 / 720	p < 0.01
	Urban	116.0 (140.0)	1,661,581	0.13 / 735	
Other[4]	Rural	84.3 (99.0)	9,291	0.25 / 720	p < 0.01
	Urban	79.0 (97.1)	23,952	0.20 / 720	
Urban		115.0 (140.0)	1,685,533	0.13 / 735	p < 0.01
Rural		101.0 (119.0)	398,696	0.25 / 720	
Age: 18 - 24	Rural	69.6 (94.0)	5,719	0.25 / 720	p = 0.96
	Urban	69.6 (101.0)	35,242	0.5 / 720	
Age: 25 - 44	Rural	88.3 (109.0)	46,372	0.27 / 720	p < 0.01
	Urban	101.0 (136.0)	320,224	0.13 / 720	
Age: 45 - 64	Rural	108.0 (128.0)	134,663	0.33 / 720	p < 0.01
	Urban	125.0 (150.0)	643,823	0.17 / 735	
Age: 65 - 84	Rural	102.0 (116.0)	186,396	0.67 / 720	p < 0.01
	Urban	119.0 (135.0)	568,323	0.5 / 720	
Age: 85 +	Rural	90.6 (107.0)	25,546	0.67 / 720	p < 0.01
	Urban	93.5 (115.0)	117,921	0.5 / 720	
Total		**112.49 (136.20)**	**2,084,229**	**0.133 / 735**	

[1]Aggregate quantity measured as quantity of pills dispensed * number of 5 mg diazepam equivalents. For example: 10 pills of 2.0 mg alprazolam (equivalent to 4-5mg diazepam equivalents) would be equal to an aggregate quantity of 40 pills of 5 mg diazepam equivalents.
[2]Outliers removed using 3*SD: (3*203.22). Using 2,115,856 prescriptions: mean = 126.42, std dev = 203.22
[3]p-value is the comparison between rural and urban
[4]Other: any prescriber specialty except for general practitioner (GP)

The average aggregate quantity prescribed was 112.49 (136.2) pills of 5mg diazepam equivalent. Those in urban areas had a significantly higher quantity of pills 5mg diazepam equivalent compared to those in rural areas (115 vs 101) (Table 4.15). Similarly, among males there was a higher average aggregate quantity in those living in an urban area compared to those living in a rural area. Among the 25-44 age group, those living in an urban area had an average of 101 pills of 5mg diazepam equivalent compared to 88.3 in those living in a rural area.

4.4 Inappropriate Prescription Regression Analyses

4.4.1 Prescriptions within 30 days

The total number of prescriptions was 2,115,856 and the total number of inappropriate prescriptions was 1,515,931. Therefore, the ratio of inappropriate prescriptions was 71.65% when using prescriptions less than 30 days apart. Tables 4.16 and 4.17 display the results of the regression analysis predicting both the total number and percentage of inappropriate prescriptions within 30 days. When analyzing the data, a p-value of less than 0.05 was considered statistically significant.

Table 4.16 – *Linear Regression Results for Total Number of Inappropriate Prescriptions within 30 days*

Variable[1]	**Estimate**	**Standard Error**	**95% CI**	**P value**
Intercept	3.92	0.122	3.69 to 4.16	
Sex				$p < 0.05$[2]
Female (ref)	-			
Male	-0.168	0.0705	-3.06 to -0.0294	
Prescriber Specialty				$p = 0.92$[2]
GP (ref)	-			
Other	-0.0188	0.181	-0.374 to 0.336	
Age Group * Urban / Rural				$p < 0.01$[2]
Urban				
Age Group				
18 – 24	-2.26	0.203	-2.65 to -1.86	$p < 0.01$[3]
25 – 44	-0.26	0.147	-0.545 to 0.033	$p = 0.08$[3]
45 - 64	1.06	0.143	0.781 to 1.340	$p < 0.01$[3]
65 - 84	-0.205	0.136	-0.472 to 0.0628	$p = 0.13$[3]
85+ (ref)	-			
Rural				
Age Group				
18 - 24	-2.22	-2.22	-3.08 to -1.36	$p < 0.01$[3]
25 - 44	-1.13	-1.13	-1.75 to -0.504	$p < 0.01$[3]
45 - 64	-0.375	-0.375	-0.949 to 0.199	$p = 0.20$[3]
65 - 84	-0.347	-0.347	-0.896 to 0.202	$p = 0.22$[3]
85+ (ref)	-			

[1]Dependent variable: number of inappropriate prescriptions; independent variable: urban/rural status; covariates: sex, prescriber specialty, age group; interaction term: age group*urban rural status
[2]Analysis of Variance (ANOVA)/ Type 3 Sum of Squares test
[3]Result of comparison of marginal effects

Table 4.17 – *Linear Regression Results for Percentage of Inappropriate Prescriptions within 30 days*

Variable[1]	Estimate	Standard Error	95% CI	P value
Intercept	0.415	0.0048	0.406 to 0.424	
Sex				$p < 0.01$[2]
Female (ref)	-			
Male	-0.0091	0.00279	-0.0146 to -0.0036	
Prescriber Specialty				$p = 0.12$[2]
GP (ref)	-			
Other	-0.0110	0.00718	-0.0251 to 0.00304	
Age Group * Urban / Rural				$p < 0.01$[2]
Urban				
Age Group				
18 - 24	-0.198	0.0080	-0.214 to -0.183	$p < 0.01$[3]
25 - 44	-0.112	0.0058	-0.124 to -0.101	$p < 0.01$[3]
45 - 64	-0.0401	0.0057	-0.0512 to -0.0291	$p < 0.01$[3]
65 - 84	-0.0324	0.0054	-0.0430 to -0.0218	$p < 0.01$[3]
85+ (ref)	-			
Rural				
Age Group				
18 - 24	-0.228	0.0174	-0.2617 to -0.1934	$p < 0.01$[3]
25 - 44	-0.147	0.0126	-0.172 to -0.123	$p < 0.01$[3]
45 - 64	-0.0842	0.0116	-0.107 to -0.0615	$p < 0.01$[3]
65 - 84	-0.045	0.0111	-0.0668 to -0.0233	$p < 0.01$[3]
85+ (ref)	-			

[1]Dependent variable: percentage of inappropriate prescriptions; independent variable: urban/rural status; covariates: sex, prescriber specialty, age group; interaction term: age group*urban rural status
[2]Analysis of Variance (ANOVA)/ Type 3 Sum of Squares test
[3]Result of comparison of marginal effects

Table 4.16 shows results from the regression analysis for total inappropriate prescriptions within 30 days. After assessing the outliers and the impact on the estimates, two individuals were removed from the regression analysis for number of inappropriate prescriptions (no individuals were removed for the percentage of inappropriate prescriptions regression). Estimates prior to removing the outliers and after removing the outliers are shown in Appendix 3. Similarly, diagnostic graphs for the regression analyses (plots of studentized residuals and Cook's distance) are shown in Appendix 3.

Males had a significantly lower average number of inappropriate prescriptions than females. A significant interaction term between urban/rural and age group was also observed in the multivariate regression model. Among people living in rural areas, compared to people aged 85+, those in the 18-24 and 25-44 age group had a significantly lower average number of inappropriate prescriptions. Among people living in urban areas, in comparison with people aged 85+, those in the 18-24 age group had a significantly higher average number of inappropriate prescriptions while those in the 45-64 age group had a significantly higher average number of inappropriate prescriptions

Results from the multivariate analysis using percentage of inappropriate prescriptions, within 30 days, is shown in table 4.17. Compared to females, males had a significantly lower average percentage of inappropriate prescriptions. A significant interaction term between urban/rural and age group was observed in the regression model. Among those living in an urban area, people in the 18-24, 25-44, 45-64 and 65-84 age groups had a significantly lower percentage of inappropriate prescriptions compared to people in the 85+ age group. Similarly, among people living in rural areas, those in the 18-24, 25-44, 45-64, 65-84 age groups had a significantly lower percentage of inappropriate prescriptions compared to those in the 85+ age group.

4.4.2 Prescriptions within 45 days

The ratio of inappropriate prescriptions was 73.41% when using prescriptions less than 45 days apart. Tables 4.18 and 4.19 display the results of the regression analysis for: the total number and percentage of inappropriate prescriptions within 45 days. After assessing the outliers and the impact on the estimates, two individuals were removed from the regression analysis for number of inappropriate prescriptions (no individuals were removed for the percentage of inappropriate prescriptions regression). Estimates prior to removing the outliers and after removing the outliers are shown in Appendix 3. Similarly, diagnostic graphs for the regression analyses (plots of studentized residuals and Cook's distance) are shown in Appendix 3. When analyzing the data, a p-value of less than 0.05 was considered statistically significant.

Table 4.18 – *Linear Regression Results for Total Number of Inappropriate Prescriptions within 45 days*

Variable[1]	Estimate	Standard Error	95% CI	P value
Intercept	4.03	0.124	3.79 to 4.26	
Sex				$p < 0.05$[2]
Female (ref)	-			
Male	-0.169	0.0716	-0.309 to -0.354	
Prescriber Specialty				$p = 0.97$[2]
GP (ref)	-			
Other	-0.0071	0.0716	-0.3678 to 0.354	
Age Group * Urban / Rural				$p < 0.01$[2]
Urban				
Age Group				
18 - 24	-2.32	0.206	-2.72 to -1.91	$p < 0.01$[3]
25 - 44	-0.270	0.150	-0.564 to 0.0235	$p = 0.07$[3]
45 - 64	1.10	0.145	0.814 to 1.382	$p < 0.01$[3]
65 - 84	-0.216	0.139	-0.487 to 0.056	$p = 0.12$[3]
85+ (ref)	-			
Rural				
Age Group				
18 - 24	-2.27	0.447	-3.14 to -1.39	$p < 0.01$[3]
25 - 44	-1.16	0.324	-1.79 to -0.525	$p < 0.01$[3]
45 - 64	-0.362	0.298	-0.945 to 0.221	$p < 0.01$[3]
65 - 84	-0.351	0.285	-0.909 to -0.351	$p = 0.22$[3]
85+ (ref)	-			

[1]Dependent variable: number of inappropriate prescriptions; independent variable: urban/rural status; covariates: sex, prescriber specialty, age group; interaction term: age group*urban rural status
[2]Analysis of Variance (ANOVA)/ Type 3 Sum of Squares test
[3]Result of comparison of marginal effects

Table 4.19 – *Linear Regression of Percentage of Inappropriate Prescriptions within 45 days*

Variable[1]	Estimate	Standard Error	95% CI	P value
Intercept	0.430	0.00490	0.420 to 0.440	
Sex				p < 0.01[2]
Female (ref)	-			
Male	-0.0091	0.0028	-0.0147 to -0.0036	
Prescriber Specialty				p = 0.13[2]
GP (ref)	-			
Other	-0.0109	0.0073	-0.0252 to 0.0034	
Age Group * Urban / Rural				p < 0.01[2]
Urban				
Age Group				
18 - 24	-0.206	0.0082	-0.222 to -0.190	p < 0.01[3]
25 - 44	-0.116	0.0059	-0.128 to -0.104	p < 0.01[3]
45 - 64	-0.0403	0.0057	-0.0516 to -0.0291	p < 0.01[3]
65 - 84	-0.0341	0.0055	-0.0448 to -0.0233	p < 0.01[3]
85+ (ref)	-			
Rural				
Age Group				
18 - 24	-0.235	0.0177	-0.270 to -0.201	p < 0.01[3]
25 - 44	-0.153	0.0128	-0.178 to -0.128	p < 0.01[3]
45 - 64	-0.0867	0.0118	-0.110 to -0.0636	p < 0.01[3]
65 - 84	-0.0488	0.0113	-0.071 to -0.0267	p < 0.01[3]
85+ (ref)	-			

[1]Dependent variable: percentage of inappropriate prescriptions; independent variable: urban/rural status; covariates: sex, prescriber specialty, age group; interaction term: age group*urban rural status
[2]Analysis of Variance (ANOVA)/ Type 3 Sum of Squares test
[3]Result of comparison of marginal effects

Table 4.18 shows results from the regression analysis for total inappropriate prescriptions within 45 days. Males had a significantly lower average total inappropriate prescriptions than females. A significant interaction term between urban/rural and age group was also observed in the multivariate regression model. Among people living in rural areas, in comparison with people aged 85+, people aged 18-24 and 25-44 had a significantly lower average number of inappropriate prescriptions. Similarly, among people living in urban areas, people aged 18-24 had a significantly lower average number of inappropriate prescriptions compared to people in the 85+ age group while those in the 45-64 age group had a significantly higher number of inappropriate prescriptions.

Results from the multivariate analysis using percentage of inappropriate prescriptions, within 45 days, is shown in table 4.19. Compared to females, males had a significantly lower average percentage of inappropriate prescriptions. A significant interaction term between urban/rural and age group was observed in the regression model. Among those living in an urban area, people in the 18-24, 25-44, 45-64 and 65-84 age groups had a significantly lower average percentage of inappropriate prescriptions compared to people in 85+ age group. Similarly, among people living in rural areas, those in the 18-24, 25-44, 45-64 and 65-84 age groups had a significantly lower average percentage of inappropriate prescriptions compared to people in the 85+ age group.

4.4.3 Prescriptions within 60 days

The ratio of inappropriate prescriptions was 74.88% when using prescriptions less than 60 days apart. Tables 4.20 and 4.21 display the results of the regression analysis predicting both the total number and percentage of inappropriate prescriptions within 60 days.

After assessing the outliers and the impact on the estimates, two individuals were removed from the regression analysis for number of inappropriate prescriptions (no individuals were removed for the percentage of inappropriate prescriptions regression). Estimates prior to removing the outliers and after removing the outliers are shown in Appendix 3. Similarly, diagnostic graphs for the regression analyses (plots of studentized residuals and Cook's distance) are shown in Appendix 3. When analyzing the data, a p-value of less than 0.05 was considered statistically significant.

Table 4.20 – *Linear Regression Results for Total Number of Inappropriate Prescriptions within 60 days*

Variable[1]	Estimate	Standard Error	95% CI	P value
Intercept	4.14	0.126	3.89 to 4.38	
Sex				$p < 0.05$[2]
Female (ref)	-			
Male	-0.175	0.0727	-0.317 to -0.0323	
Prescriber Specialty				$p = 0.99$[2]
GP (ref)	-			
Other	-0.0035	0.187	-0.369 to 0.362	
Age Group * Urban / Rural				$p < 0.01$[2]
Urban				
Age Group				
18 - 24	-2.38	0.209	-2.79 to -1.97	$p < 0.01$[3]
25 - 44	-0.304	0.152	-0.602 to -0.0066	$p < 0.05$[3]
45 - 64	1.10	0.147	0.816 to 1.39	$p < 0.01$[3]
65 - 84	-0.237	0.141	-0.513 to 0.0384	$p = 0.09$[3]
85+ (ref)	-			
Rural				
Age Group				
18 - 24	-2.33	0.453	-3.22 to -1.45	$p < 0.01$[3]
25 - 44	-1.20	0.328	-1.84 to -0.56	$p < 0.01$[3]
45 - 64	-0.392	0.302	-0.98 to 0.20	$p = 0.19$[3]
65 - 84	-0.382	0.289	-0.948 to 0.184	$p = 0.19$[3]
85+ (ref)	-			

[1]Dependent variable: number of inappropriate prescriptions; independent variable: urban/rural status; covariates: sex, prescriber specialty, age group; interaction term: age group*urban rural status
[2]Analysis of Variance (ANOVA)/ Type 3 Sum of Squares test
[3]Result of comparison of marginal effects

Table 4.21 – *Linear Regression of Percentage of Inappropriate Prescriptions within 60 days*

Variable	Estimate	Standard Error	95% CI	P value
Intercept	0.443	0.0050	0.434 to 0.453	
Sex				p < 0.01[2]
Female (ref)	-			
Male	-0.0093	0.0029	-0.0149 to -0.0037	
Prescriber Specialty				p = 0.11[2]
GP (ref)	-			
Other (ref)	-0.0118	0.0074	-0.20263 to 0.0027	
Age Group * Urban / Rural				p < 0.01[2]
Urban				
Age Group				
18 - 24	-0.211	0.0083	-0.227 to -0.195	p < 0.01[3]
25 - 44	-0.120	0.0060	-0.132 to -0.109	p < 0.01[3]
45 - 64	-0.0421	0.0058	-0.0535 to -0.0307	p < 0.01[3]
65 - 84	-0.0358	0.0056	-0.0467 to -0.0249	p < 0.01[3]
85+ (ref)	-			
Rural				
Age Group				
18 - 24	-0.242	0.0179	-0.277 to -0.207	p < 0.01[3]
25 - 44	-0.157	0.0130	-0.183 to -0.132	p < 0.01[3]
45 - 64	-0.0901	0.0119	-0.114 to -0.067	p < 0.01[3]
65 - 84	-0.0519	0.0114	-0.074 to -0.0295	p < 0.01[3]
85+ (ref)	-			

[1]Dependent variable: percentage of inappropriate prescriptions; independent variable: urban/rural status; covariates: sex, prescriber specialty, age group; interaction term: age group*urban rural status
[2]Analysis of Variance (ANOVA)/ Type 3 Sum of Squares test
[3]Result of comparison of marginal effects

Table 4.20 shows results from the regression analysis for total inappropriate prescriptions within 60 days. Males had a significantly lower average number of inappropriate prescriptions than females. A significant interaction term between urban/rural and age group was also observed in the multivariate regression model. Among people living in rural areas, in comparison with people aged 85+, people aged 18-24 and 25-44 had a significantly lower average number of inappropriate prescriptions. Among people living in urban areas, in comparison with people aged 85+, people aged 18-24 and 25-44 had a significantly higher average number of inappropriate prescriptions. Similarly, among people living in an urban area those in the 45-64 has a significantly higher average number of inappropriate prescriptions than those in the 85+ age group.

Results from the multivariate analysis using percentage of inappropriate prescriptions, within 60 days, is shown in table 4.21. Compared to females, males had a significantly lower average percentage of inappropriate prescriptions. A significant interaction term between urban/rural and age group was observed in the regression model. Among those living in an urban area, people in the 18-24, 25-44, 45-64 and 65-84 age groups had a significantly lower average percentage of inappropriate prescriptions compared to people in the 85+ age group. Similarly, among people living in rural areas, those in the 18-24, 25-44, 45-64, 65-84 age groups had a significantly lower average percentage of inappropriate prescriptions compared to people in the 85+ age group.

4.5 Benzodiazepine Prescribing from 2007 to 2017

Benzodiazepine prescribing fluctuated slightly from year to year. Figure 4.1 shows the difference in dispensed days' supply from the fiscal year 2007 (April 2007 to March 2008) to the fiscal year 2016 (April 2016 to March 2017). Days' supply remained between 27 and 29 over the 10-year time frame for rural areas, and between 24 and 26 for urban areas.

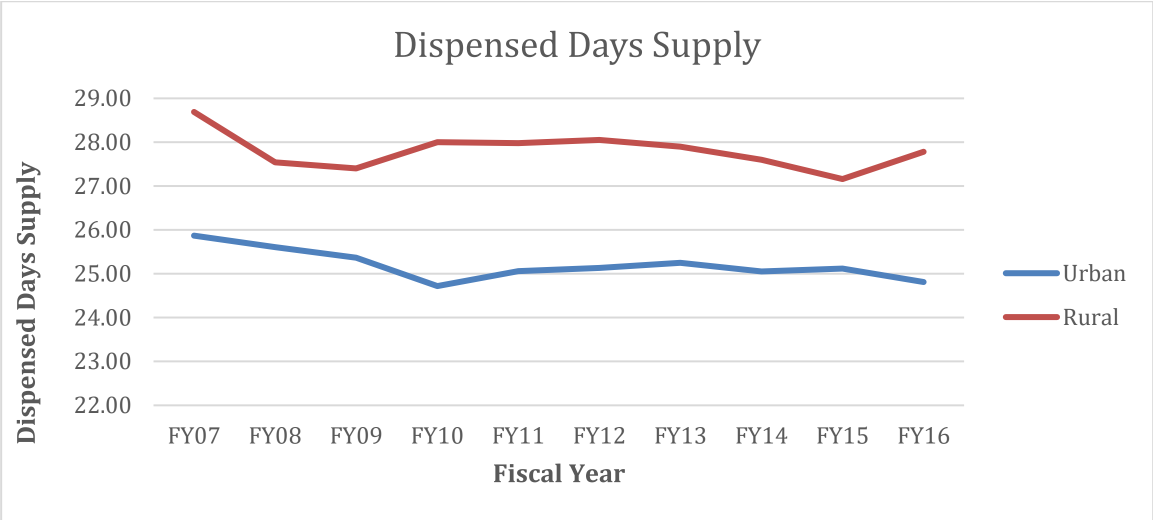

Figure 4.1 – *Mean Dispensed Days' Supply from 2007 to 2017*

Quantity of pills dispensed remained consistent between 50.5 and 53 for urban areas. For rural areas, the quantity was highest between April 2007 – March 2008 and lowest in the 2009 fiscal year.

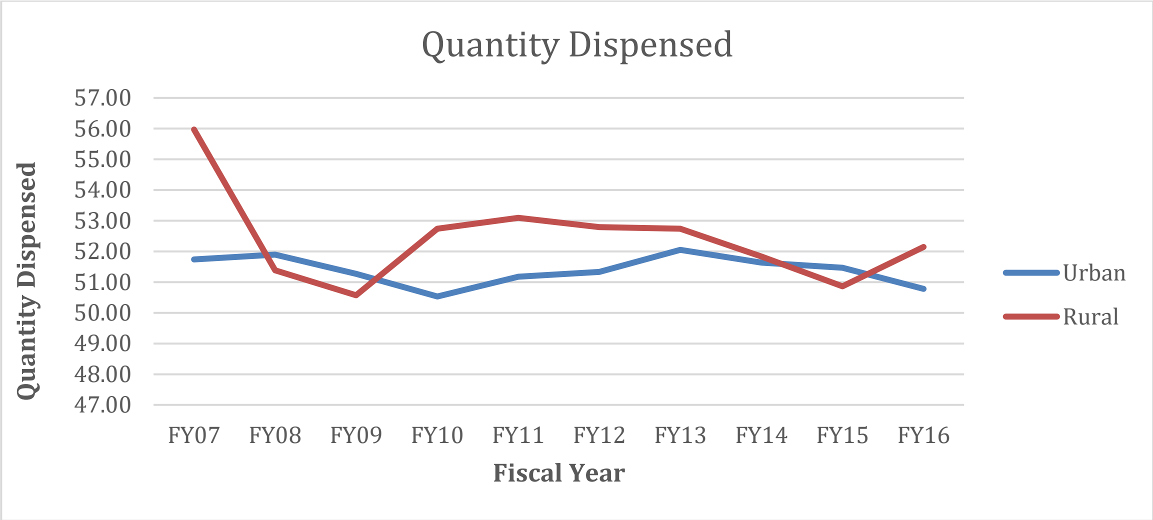

Figure 4.2 – *Mean Quantity Dispensed from 2007 to 2017*

Quantity of pills dispensed remained consistent between 50.5 and 53 for urban areas. For rural areas, the quantity was highest between April 2007 – March 2008 and lowest in the 2009 fiscal year.

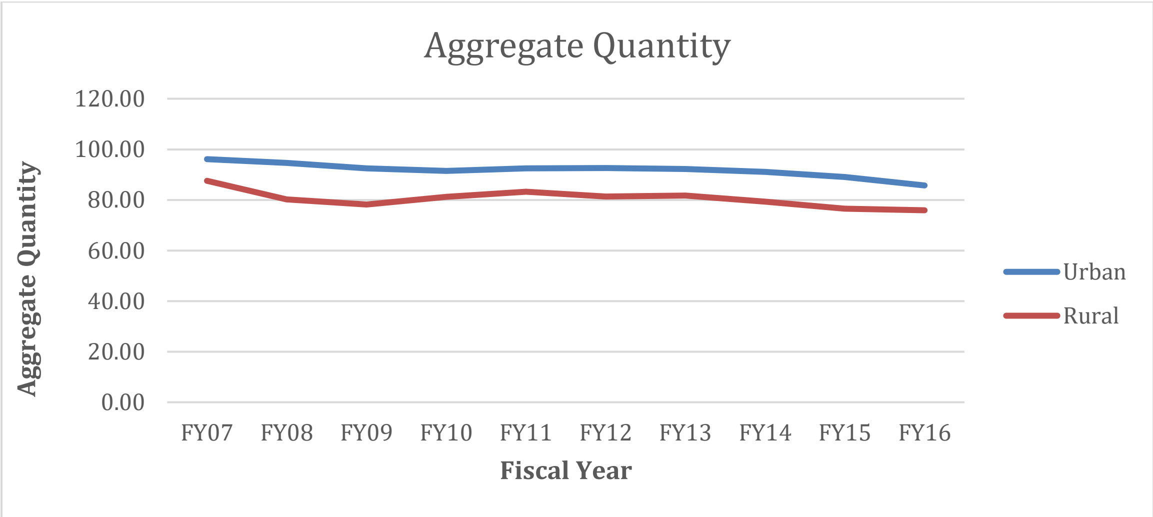

Figure 4.3 – *Mean Aggregate Quantity from 2007 to 2017*

Figure 4.4 shows the average number of inappropriate prescriptions by year, with it being the lowest in the 2007 fiscal year; however, it remained between 6 and 7 between April 2008 and

March 2017. Figure 4.5 shows similar results when analyzing the percentage of inappropriate prescriptions.

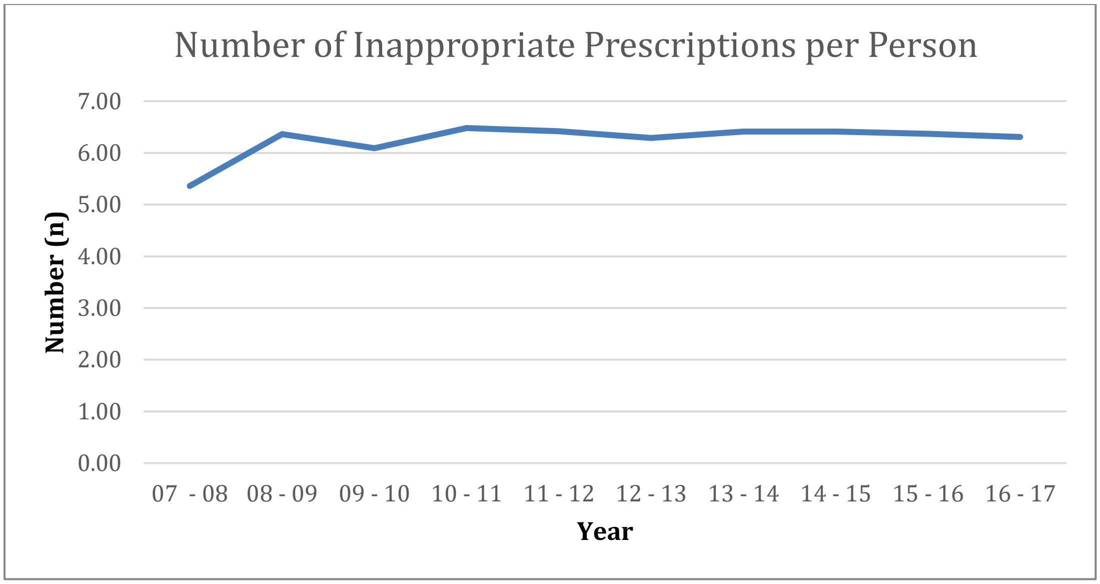

Figure 4.4 – *Number of Inappropriate Prescriptions from 2007 to 2017*

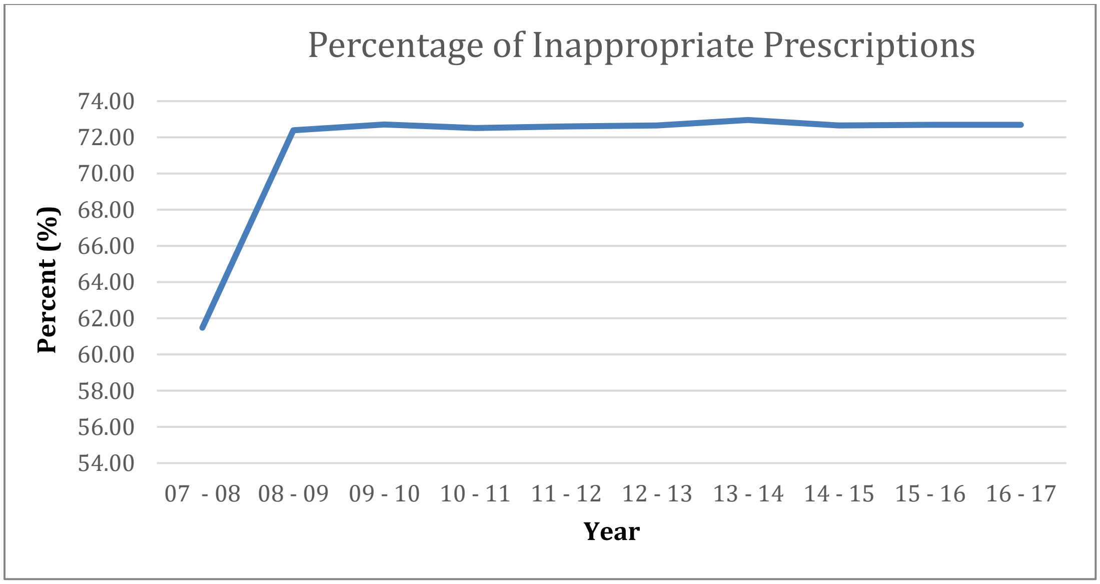

Figure 4.5 – *Percentage of Inappropriate Prescriptions from 2007 to 2017*

Chapter 5: Discussion and Conclusion

5.1 Main Findings

Benzodiazepines are a class of drugs, which were initially intended to aid in treatment of a variety of indications, specifically anxiety and depression. As research increased on benzodiazepine usage, the prevalence of long-term usage was highlight. Furthermore, the association between adverse effects and long-term benzodiazepine use has been well-documented. It is important to examine the prevalence of inappropriate benzodiazepine usage at various time points, to identify the rate of inappropriate prescribing.

This thesis analyzed benzodiazepine usage in Newfoundland (a subregion of the province of Newfoundland and Labrador (NL)) over a ten-year period; specifically comparing prescriptions between urban and rural areas in Newfoundland. Prescribing / usage patterns were assessed and compared to recommended guidelines. Linear regression analysis showed that benzodiazepine prescribing was frequently inappropriate, with over 70% of prescriptions being prescribed within 30 days of each other for the same individual. Furthermore, inappropriate prescribing was prevalent throughout the 10 years, with sex and the interaction term between age group and urban / rural areas, being significantly associated with inappropriate prescribing.

These are key findings and highlight the need for promotion of appropriate prescribing guidelines to both practitioners and patients through ongoing continuing education efforts such as seminars, continuing medical education (CME) sessions or other efforts to increase awareness of inappropriate benzodiazepine usage to prescribers. We analyzed different benzodiazepine usage metrics including quantity and strength of benzodiazepine prescribed. We also analyzed derived variables such as aggregate quantities of diazepam equivalent. Across all study metrics, overprescribing was evident. While drug therapy decisions are ultimately made by clinicians, knowledge translation strategies to share these results may improve prescribers' decision making to alter the current overprescribing patterns.

Different interventions have been used to address benzodiazepine overprescribing. For example, Tannenbaum et al. (2014) analyzed the effects of an educational intervention in reducing benzodiazepine prescribing. In that study, both the intervention and control groups had an average of 9.9 medications per day; however, the intervention's group average use was 9.6 years compared to 11.2 years in the control group. This demonstrates that an educational intervention may be effective in reducing overprescribing.

Other methods have included seminars and guidelines; however, reassessing usage after these interventions have been implemented would be necessary to determine the long-term effectiveness in decreasing benzodiazepine overprescribing. Research is needed to determine the most effective intervention.

5.2 Interpretation of findings compared to previous published work

Five studies in particular will be used for comparison to the findings presented in this thesis: Manthey et al., 2011; Mattos et al., 2016; Jacob et al., 2017; Mokhar et al., 2018; and Weir et al., 2018. These studies provide insights regarding benzodiazepine usage and allow comparison to the current study's sample and measures. Other relevant literature is included to allow comparison with study results; however, there remains limited research utilizing samples of all age groups and further studies could also elaborate on inappropriate durations of benzodiazepine usage.

5.2.1 Patient / Study Characteristics

Overall, the current literature appears to focus on a population of seniors, with a paucity of studies focusing on urban and rural areas and younger age groups. ***To our knowledge, this is the first study that assessed benzodiazepine usage in a sample of Newfoundland adults aged 18 and older, using a longitudinal study design***. In this study, we also assessed urban and rural prescribing and usage.

In the previous studies mentioned, some excluded patients under the age of 50 (Mattos et al., 2016; Jacob et al., 2017; Mokhar et al., 2018), while other study populations encompassed all adult ages (Manthey et al., 2011; Weir et al., 2018). The main objective of our study was to examine benzodiazepine usage in urban and rural areas of Newfoundland, among adults of all ages. Our sample described earlier in the thesis, included adults aged 18 years or older. Weir et al. (2018) included individuals 10 years of age, while Manthey et al. (2011) included ages 18 – 65. For our study, the mean age was 57.19 (standard deviation was 19.66) ranging from 18 to 105. Age groups that Weir et al. (2018) and Manthey et al. (2011) used were more similar to our study than those in the other three studies (Mattos et al., 2016; Jacob et al., 2017; Mokhar et al., 2018).

For our study, 80.97% of individuals were in living in urban areas compared to 19.03% in a rural area when they were first prescribed a benzodiazepine. Mattos et al. (2016) reported 71.6% of participants to be urban-dwelling adults. Weymann et al. (2017) reported 94% of benzodiazepine users being in an urban area. Other researchers discussed in section 5.2 did not analyze urban versus rural areas.

Among the studies examined, the percent of females was 88.7 in Mattos et al. (2016), 65.2% in Jacob et al. (2017), 62.79% in Weir et al. (2018), 66.1% in Manthey et al. (2011) and 68.5% in Mokhar et al (2018). Our study had 63.12% females, which was similar to prior research.

Over 63,500 individuals were included in our study, which allowed us to identify prescriptions in rural areas and stratify by drug generic names which may not be observable in studies with a smaller sample size. It is also possible that due to our large sample size, and consequently the power of our study, small differences were observed that may not be clinically relevant. Sample size varied amongst the studies explored in this section: 426 in Mattos et al. (2016), 32,182 in Jacob et al. (2017), 372,870 in Weir et al. (2018), 2,852 in Manthey et al. (2011) and 340 in Mokhar et al. (2018). Furthermore, among the 63,517 individuals in our study, 2,115,856 prescriptions were prescribed throughout the ten-year period. Weir et al. (2018) examined 2,463,585 BZRA dispensations in 372,870 individuals; while similar in number to our sample, the study duration was only one year.

One of the primary strengths of our study is that it is a ten-year longitudinal study, allowing for us to examine temporal trends prior to and after guidelines had been updated. Jacob et al. (2017) examined a four-year period, whereas Manthey et al. (2011) conducted an 8-year longitudinal analysis. Other researchers conducted studies for a period of one year (Mattos et al., 2016; Weir et al., 2018; Mokhar et al., 2018).

5.2.2 Benzodiazepine Prescribing Metrics

Various benzodiazepine metrics were analyzed: drug generic name, quantity dispensed, dispensed days' supply, drug strength, diazepam equivalent and aggregate quantity.

For our study, the three most prescribed drugs were clonazepam (22.88%), lorazepam (35.42%) and temazepam (14.33%). Two of the previous studies reported the distribution of drug generic names. The top three benzodiazepines in one study were: tetrazepam, lorazepam and diazepam: 25.8%, 21.3% and 12.7%, respectively (Jacob et al., 2017). Mokar et al (2018) reported the top three as zopiclone (38.1%), oxazepam (18.1%) and lorazepam (13.8%). Lorazepam was the most prescribed benzodiazepine in our study, with it being the second most prescribed and third most prescribed in other studies (Jacob et al., 2017; Mokar et al., 2018).

We also examined the mean quantity dispensed and dispensed days' supply with results being 51.12 pills and 24.91 days. One of the previous studies had a mean dispensed days' supply of 27 days (Weir et al., 2018) which was similar to the results from our study. Four of the other studies discussed did not examine dispensed days' supply or the mean quantity dispensed and so could not be compared.

Using the drug strength, a mean of 2.90 5mg diazepam equivalents was calculated in our study. Diazepam equivalent average was found to be 1.74 in our study, which was comparable to a defined daily dose of 1.0 in Weir et al. (2018) and 0.73 in Mokar et al. (2018).

5.2.3 Benzodiazepine Use Stratified

A component of this study was to compare different benzodiazepine metrics described in sections 4.2 and 4.3 and to stratify them by sex, prescriber specialty, urban / rural status and age.

Differences were observed for quantity dispensed when comparing rural and urban areas stratifying by sex, prescriber specialty and urban/rural areas. Among individuals in the 25-44 age group, individuals living in a rural area were prescribed an average of 5 more pills than those living in an urban area. Similarly, among individuals aged 45-64, those living in a rural area were prescribed an average of approximately 3 more pills than those living in an urban area.

Previous studies have focused on the odds of being prescribed a benzodiazepine; however, for this study, we wanted to examine further differences. Among males, those living in an urban area were prescribed approximately 1 milligram higher than those living in a rural area. Overall, those in urban area were prescribed a significantly higher drug strength on average than those in rural areas. It is important to note that this measurement, drug strength, does not account for different classes of benzodiazepines (long-acting compared to short-acting).

Using the diazepam equivalent, these measurements were standardized to a 5-milligram diazepam equivalent to allow for more accurate comparisons. After applying this standardization, the trends remained similar. Comparing rural and urban areas among males, those living in urban areas had a higher diazepam equivalent compared to those in rural areas (3.31 compared to 2.82 5-mg diazepam equivalents). For individuals in the 45-64 age group, those in urban areas were prescribed a significantly higher number of diazepam equivalents compared to those in rural areas. Similar results were observed for those in the 25-44, 65-84 and 85+ age groups. Prior research has revealed that 14-23% of all prescriptions for elderly patients were inappropriate (Brekke et al., 2008). This demonstrates that individuals in an urban area are prescribing more benzodiazepines than those in a rural area (after transforming to a comparable metric), highlighting that prescribers/patients in an urban setting should be cognizant of potential for overprescribing.

An aggregate quantity was calculated, by multiplying the quantity of pills by the 5 mg diazepam equivalent. Individuals that were males, living in an urban area were prescribed 125-5mg diazepam equivalents compared to 110 among males living in a rural area. Similarly, among females, those living in an urban area were prescribed a higher number of 5mg diazepam equivalents compared to those living in a rural area. Overall, those living in urban areas were prescribed a significantly higher number of 5mg diazepam equivalents compared to those living in rural areas. Among those in the 65-84 age group, there was a significantly higher aggregate quantity prescribed to those living in urban areas compared to those in rural areas. Similar results were shown among the 25-44, 45-64 and 85+ age groups. Study findings highlight the importance of examining benzodiazepine prescribing across all ages since overprescribing can occur in groups other than seniors.

5.2.4 Regression Analysis

Various guidelines have reported that benzodiazepines should be restricted to 30 days or less (Copperstock & Hill, 1982; APA, 1990; WHO, 1996; Katzman et al., 2014). For this study, an inappropriate prescription was defined as inappropriate if a new prescription was issued within 30 days of the previous prescription ending.

Results from the regression analyses demonstrated that the interaction of age and urban rural status is a significant predictor of inappropriate benzodiazepine prescribing regardless of the outcome being 30, 45 or 60 days. Manthey et al. (2011) conducted a multivariate analysis resulting in age being significantly associated with benzodiazepine usage, while Mattos et al. (2016) reported that age was not when using a multivariate binary logistic regression.

For total number of inappropriate prescriptions, regardless of the length of prescription in days, sex was statistically significant. When using the percentage of inappropriate prescriptions, sex was also statistically significant ($p < 0.01$), however it may not be clinically relevant due to high power of our study (as a function of the sample size of our study). Mattos et al. (2016)

reported that the odds ratio was 1.71 for females to receive a benzodiazepine prescription, although this result was not statistically significant.

Overall, results from the linear regression show that males are more likely to have a lower number of inappropriate prescriptions compared to females. The current literature suggests that females and seniors, have an increased probability of receiving a benzodiazepine prescription, which aligns with some of the results from our study. While differences were observed for number of inappropriate prescriptions between male and females, while statistically significant, this may not be clinically relevant due to the large sample size. Differences were also observed among age groups when comparing individuals in urban and rural areas.

5.2.5 Benzodiazepine Prescribing over a Ten-Year Period

Guidelines were updated in 2014 in Canada by Katzman et al. (2014), recommending that benzodiazepines be used only for short term durations (less than 30 days). In our study, dispensed days' supply did not reduce over the ten-year period, although only three years were included subsequent to the updated guidelines.

Furthermore, aggregate quantity did not decrease over the timeframe examined. It was hypothesized that the rates of inappropriate prescribing would decrease after these guidelines were introduced. However, both the total number of inappropriate prescriptions and percentage of inappropriate prescriptions remained high (> 50%). Thus, inappropriate prescribing in this province is still high, despite updated guidelines. It is unknown why this is the case, nor what individual, practice or health system factors might be implicated in the overprescribing trends observed here. This highlights the need for interventions to change prescribing behavior.

Rigorously designed studies that measure prescribing pre and post intervention would be useful to examine the effectiveness of these methods.

5.2.6 Benzodiazepine Use Compared to Canadian Provinces

Rates of inappropriate prescribing and benzodiazepine usage were assessed in Newfoundland and Labrador for this study. Based upon duration, the results ranged from 72.7% to 74.9%.

Cunningham et al. (2010) reported 3.5% of British Columbians used benzodiazepines long-term. A study conducted in Alberta, found 26.2% of individuals to have used benzodiazepines for a period of more than 121 days consecutively (Weir et al., 2018). In Ontario, Davies et al. (2018) reported that 73.5% of participants were prescribed more than one benzodiazepine in 2013. This study also reported a slight decrease in those prescribed more than one benzodiazepine between 1999 and 2013 from 74.2% to 73.5%.

Canadian provinces were examined and compared in 2013 by Black et al. (2018), concluding that benzodiazepines were second-most prescribed in Newfoundland and Labrador (second only to New Brunswick). Comparing the results of these studies to our study, signifies that inappropriate prescribing remains high in Newfoundland compared to other provinces.

5.3 Strengths and Limitations

A ten-year time period was used for analyzing both prescriptions and usage allowing a longer observation of prescribing patterns than most studies, including three years after guidelines were introduced. Including all adult age groups allowed for inclusion of prescriptions that were typically underrepresented in previous studies, specifically the 18-24 age group.

Secondary data was used, which was initially collected for billing. Using this secondary data allowed for a large sample, 63,517 individuals, to be included in the analysis.

A limitation of this study is the generalizability of the NLPDP to the general population. Due to the prescription drug coverage of the five programs comprising the NLPDP, the ability to apply these findings to the broader Newfoundland population may be limited. Seniors and those in low-income families may constitute a large proportion of the sample used in this study.

Another limitation of this study is the inability to distinguish between prescription and usage. We included only those that were “Settled-Paid;” when analyzing usage; however, an individual may have stopped using the medication due to adverse effects or not requiring it anymore. Furthermore, the definition used for overprescribing may overestimate the percentage of inappropriate prescriptions. Similarly, a limitation of this study is the prescriber data being classified in only two categories, GP or Other. Since individual prescriber information was not provided, it was not possible to assess broader prescriber effects.

Rural areas were defined based upon a population less than 1,000 (Statistics Canada, 2017). Participants’ area codes were used to determine the place of residence, and a classification of urban or rural area. Community populations were determined using the 2011 census. A population with more than 1,000 people in 2007 could have more than 1,000 in 2017. The 2011 Census was used for each year to account for these changes, but it remains a limitation. Furthermore, there are other definitions that could have been used such as those defined by the Newfoundland and Labrador Statistics Agency which may change the results of our analyses. If a larger population threshold was chosen, it would result in more rural areas than in our study.

When classifying prescriptions as being filled in an urban or rural area, an individual may have moved within a given fiscal year, particularly those in the more mobile younger age groups.

The data would not be updated until the beginning of the next fiscal year. Furthermore, there were no MCP files associated with the 2009, 2012 and 2013 fiscal years. As a result, the following year was used by the data custodian to determine the MCP number and the consequent urban / rural location.

Dispensed days' supply may have been estimated rather than an objective measurement. When a prescription was issued, physicians may have prescribed the medication as "take 1 tablet twice a day when needed". Some individuals may have taken two pills a day, while others may have taken one pill every two days. Pharmacists inputting the days' supply is an estimation of how long a quantity will last.

5.4 Implications for Future Research and Practice

A large proportion of benzodiazepines are prescribed for inappropriate durations. Benzodiazepines are inappropriately prescribed at a high rate: in this study, > 70%. This finding strongly suggests the need for intervention, both in current medical training curricula and in continuing education programs. Prescribers should be encouraged to complete continuing education on the multitude of adverse effects associated with prolonged benzodiazepine usage. Furthermore, prescribers should be educated on risk factors for long-term benzodiazepine usage and updated on the recommended duration of two to four weeks. Even this, however, is not a guarantee that prescribing behavior will change, and carefully designed interventions will be needed to determine the predictors and mechanisms of behavior change.

General practitioners (GPs) were responsible for more than 96% of benzodiazepine prescriptions in this study. This is not surprising as GPs provide the bulk of primary care in this jurisdiction. However, it suggests they should be the first group receiving additional educational interventions such as seminars, Continuing Medical Education and providing professional development credit for completing these. Ultimately, intervention research is urgently needed to test the most appropriate method of delivery and content of educational (or other) interventions aiming to reduce inappropriate usage of benzodiazepines.

There are a number of intervention methods available, including direct marketing and local opinion leader's having an impact on professional behaviour change (Johnson & May, 2015). Education interventions are another alternative, such as Choosing Wisely nationally, Deprescribing or SaferMedsNL locally (Choosing Wisely Canada, 2017; Canadian Deprescribing Network, 2017; SaferMedsNL, 2020). Ivers et al (2012) concluded that using audits and feedback lead to improvements in professional practice. Furthermore, there are financial incentive interventions, such as the French pay-for-performance; however, Rat et al. (2014) reported an increase in benzodiazepine prescribing between 2011 and 2012. These findings suggest there is not yet consensus on what intervention method is most effective for altering inappropriate benzodiazepine prescribing trends, and intervention research is urgently needed in this area.

Future research should also be conducted on national trends in benzodiazepine usage and the associated risk factors. Frequent adverse effects have been reported; however, the association between the gene affecting drug metabolism of benzodiazepines and associated adverse effects should be further explored. With the increasing availability of genome sequencing, this will be of increasing importance for the prescribers' decision making.

5.5 Conclusion

Benzodiazepines are believed to be one of the most overprescribed medications worldwide. The objective of this study was to examine the prescribing patterns of benzodiazepines among individuals, 18 years of age or older, living on the island of Newfoundland between 2007 and 2016. Using descriptive statistics, and regression analyses various metrics were calculated to assess the rate of overprescribing (based upon duration). Overprescribing was found to be prevalent throughout this time frame, with the implementation of guidelines ineffective at reducing benzodiazepine prescribing in this sample of Newfoundland adults. Inappropriate prescribing, specifically long-term use, has been associated with adverse effects including cognitive decline, falls, hip fracture in the elderly, tolerance and dementia. Close cooperation between policy makers, researchers, as well as prescribers and patients will be critical to address these inappropriate prescribing patterns.

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Appendix 1: Year First Prescription was Written

Year	Frequency	Percent
2007	19,042	29.98
2008	6,085	9.58
2009	5,158	8.12
2010	5,151	8.11
2011	5,771	9.09
2012	5,021	7.90
2013	4,519	7.11
2014	4,194	6.60
2015	4,191	6.60
2016	4,385	6.90

Appendix 2: Ethics Approval

Ethics Office
Suite 200, Eastern Trust Building
95 Bonaventure Avenue
St. John's, NL
A1B 2X5

January 29, 2018

Faculty of Medicine
Disciple of Clinical Epidemiology

Dear Mr. Batten:

Researcher Portal File # 20181183
Reference # 2017.254

RE: "A ten year retrospective comparison of benzodiazepine usage between rural and urban residents of Newfoundland and Labrador"

Your application received a delegated review by a sub-committee of the Health Research Ethics Board (HREB). ***Full approval*** of this research study is granted for one year effective **January 24, 2018**.

This is your ethics approval only. Organizational approval may also be required. It is your responsibility to seek the necessary organizational approval from the Regional Health Authority (RHA) or other organization as appropriate. You can refer to the HREA website for further guidance on organizational approvals.

This is to confirm that the HREB reviewed and approved or acknowledged the following documents (as indicated):

- Application, approved
- Research proposal, approved
- List of variables, approved
- Letter to data custodian, approved

MARK THE DATE

This approval will lapse on January 24, 2019 . It is your responsibility to ensure that the Ethics Renewal form is submitted prior to the renewal date; you may not receive a reminder. The Ethics Renewal form can be found on the Researcher Portal as an Event form.

If you do not return the completed Ethics Renewal form prior to date of renewal:

Appendix 3: Regression Diagnostic Graphs

Inappropriate Prescriptions – 30 days definition

<u>Percentage of Inappropriate Prescriptions – 30 days</u>

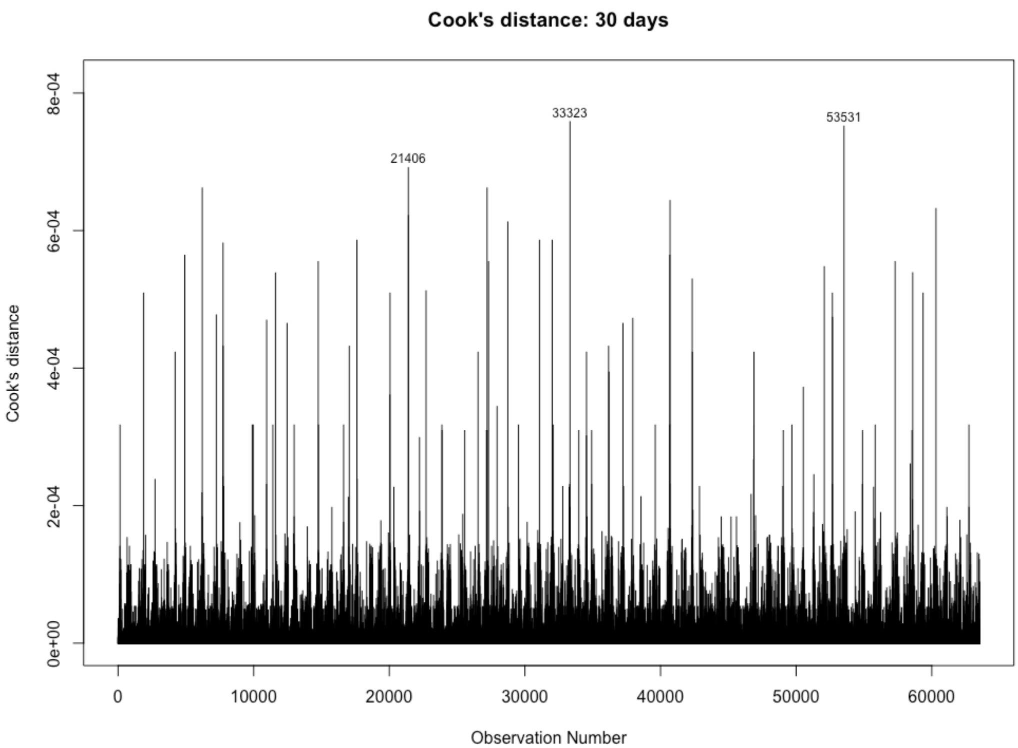

Figure 1 - *Plot of Cook's distance*

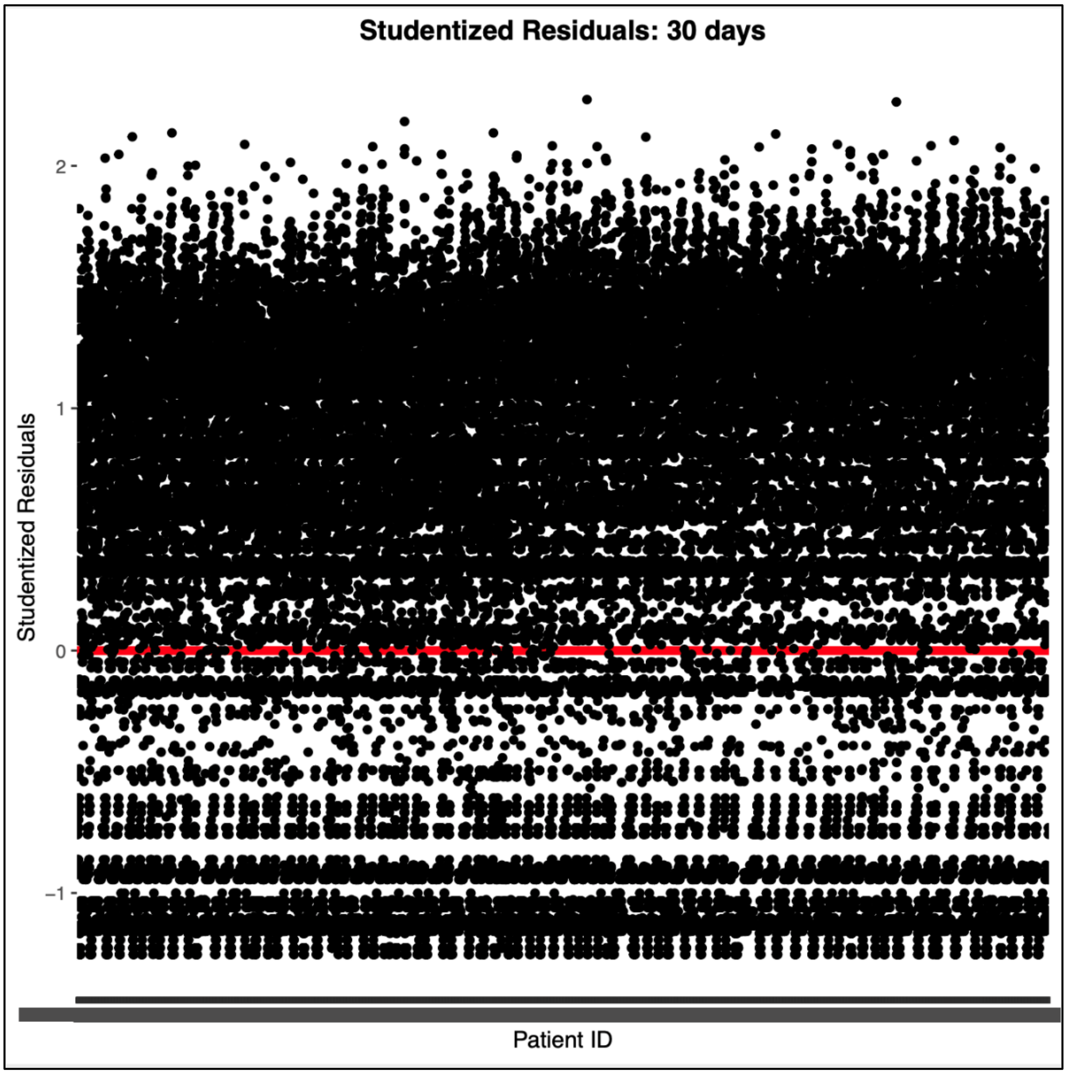

Figure 2 – *Plot of Studentized Residuals*

Number of Inappropriate Prescriptions – 30 days

Before Removing Outliers

Table 1 - *Estimates Prior to Removing Outliers*

Variable	Estimate	Standard Error	95% CI	P value[1]
Intercept	3.92	0.122	3.69 to 4.16	
Sex				p < 0.05
Female (ref)	0			
Male	0.168	0.0705	0.0294 to 0.306	
Prescriber Specialty				p = 0.92
GP (ref)	0			
Other	-0.0188	0.181	-0.374 to 0.336	
Age Group * Urban / Rural				p < 0.01
Urban				
Age Group				
18 – 24	-0.0352	0.484	-0.983 to 0.913	p = 0.94
25 – 44	0.873	0.351	0.185 to 1.56	p < 0.05
45 - 64	1.44	0.325	0.798 to 2.07	p < 0.01
65 - 84	0.143	0.311	-0.468 to 0.753	p = 0.65
85+ (ref)	0			
Rural				
Age Group				
18 - 24	0.0352	0.484	-0.913 to 0.983	p = 0.94
25 - 44	-0.873	0.351	-1.56 to -0.185	p < 0.05
45 - 64	-1.44	0.325	-2.07 to -0.798	p < 0.01
65 - 84	-0.143	0.311	-0.753 to 0.468	p = 0.65
85+ (ref)	0			

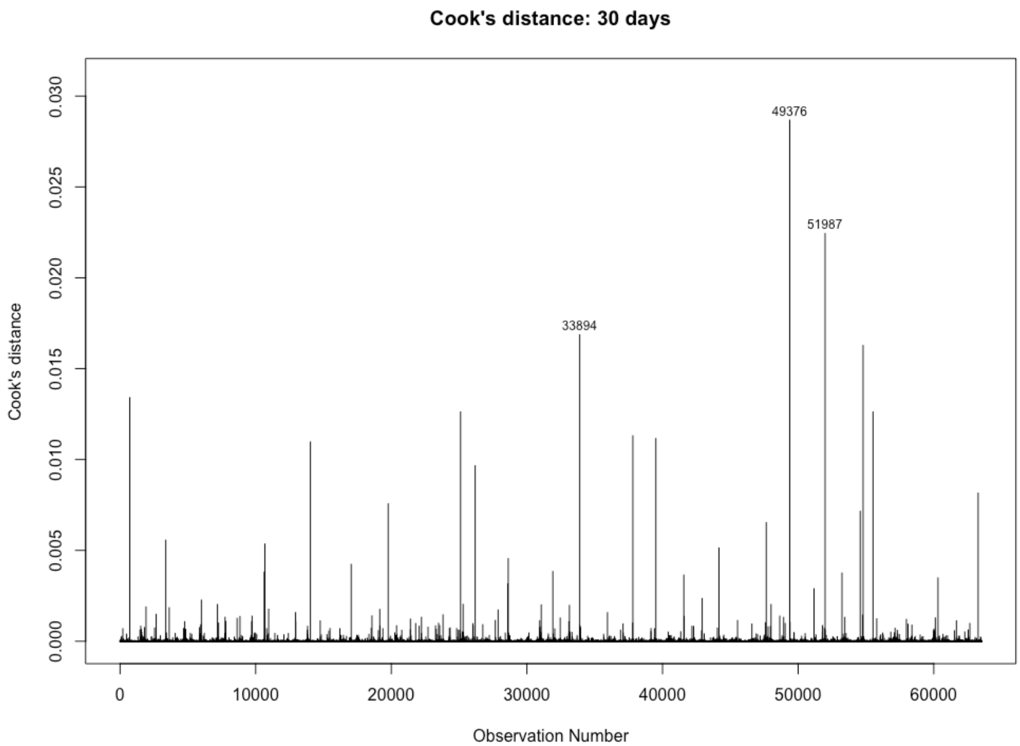

Figure 3 - *Plot of Cook's distance*

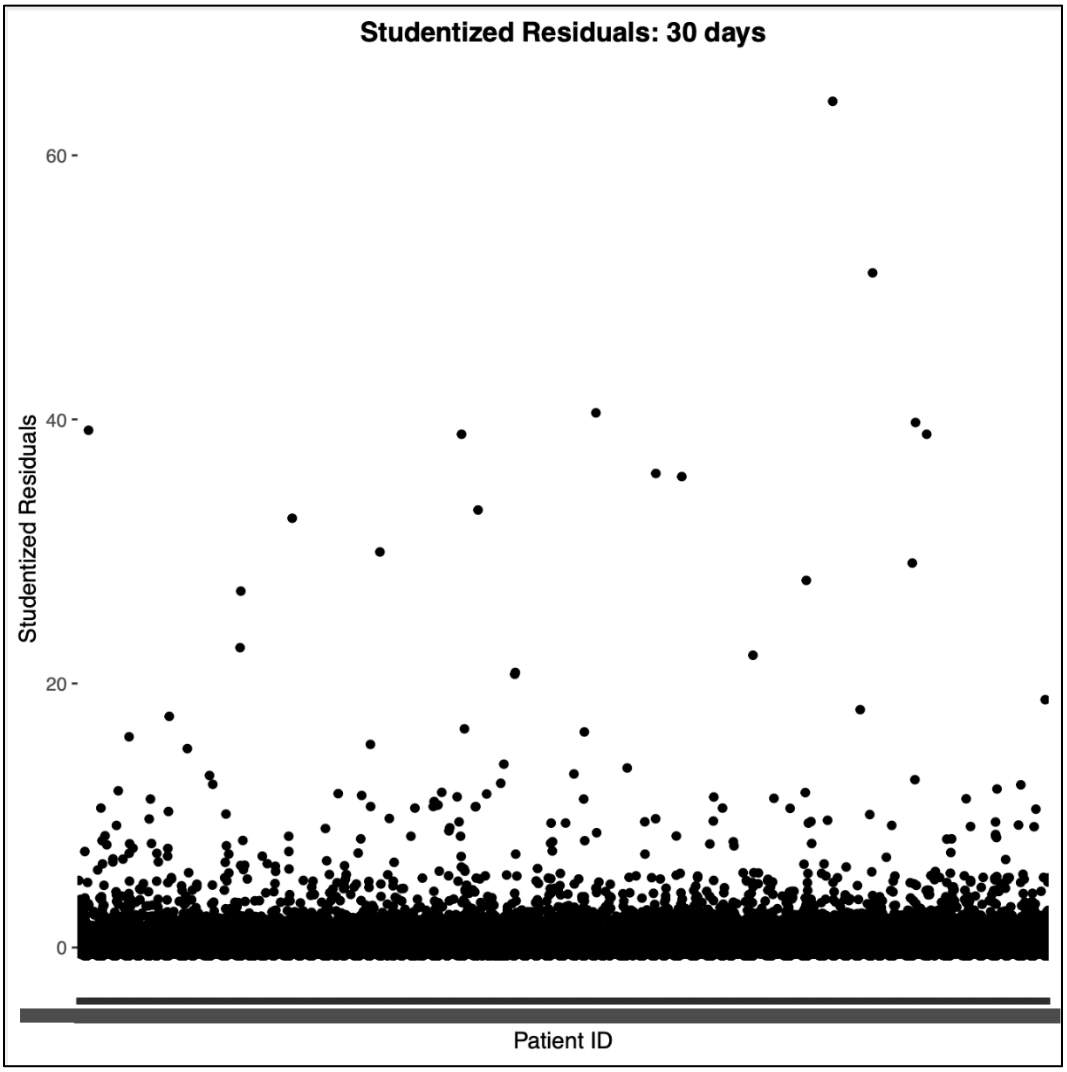

Figure 4 – *Plot of Studentized Residuals*

After Removing Outliers

Estimates After Removing Outliers

Variable	Estimate	Standard Error	95% CI	P value[1]
Intercept	3.92	0.116	3.69 to 4.16	
Sex				p < 0.01
Female (ref)	0			
Male	0.193	0.0669	0.0615 to 0.324	
Prescriber Specialty				p = 0.98
GP (ref)	0			
Other	-0.00354	0.172	-0.340 to 0.333	
Age Group * Urban / Rural				p < 0.01
Urban				
Age Group				
18 – 24	-0.0377	0.459	-0.937 to 0.862	p = 0.93
25 – 44	0.828	0.333	0.176 to 1.48	p < 0.05
45 - 64	1.39	0.309	0.787 to 2.00	p < 0.01
65 - 84	0.141	0.295	-0.437 to 0.720	p = 0.63
85+ (ref)	0			
Rural				
Age Group				
18 - 24	0.0377	0.459	-0.862 to 0.937	p = 0.93
25 - 44	-0.828	0.333	-1.48 to -0.176	p < 0.05
45 - 64	-1.39	0.309	-2.00 to -0.787	p < 0.01
65 - 84	-0.141	0.295	-0.720 to 0.437	p = 0.63
85+ (ref)	0			

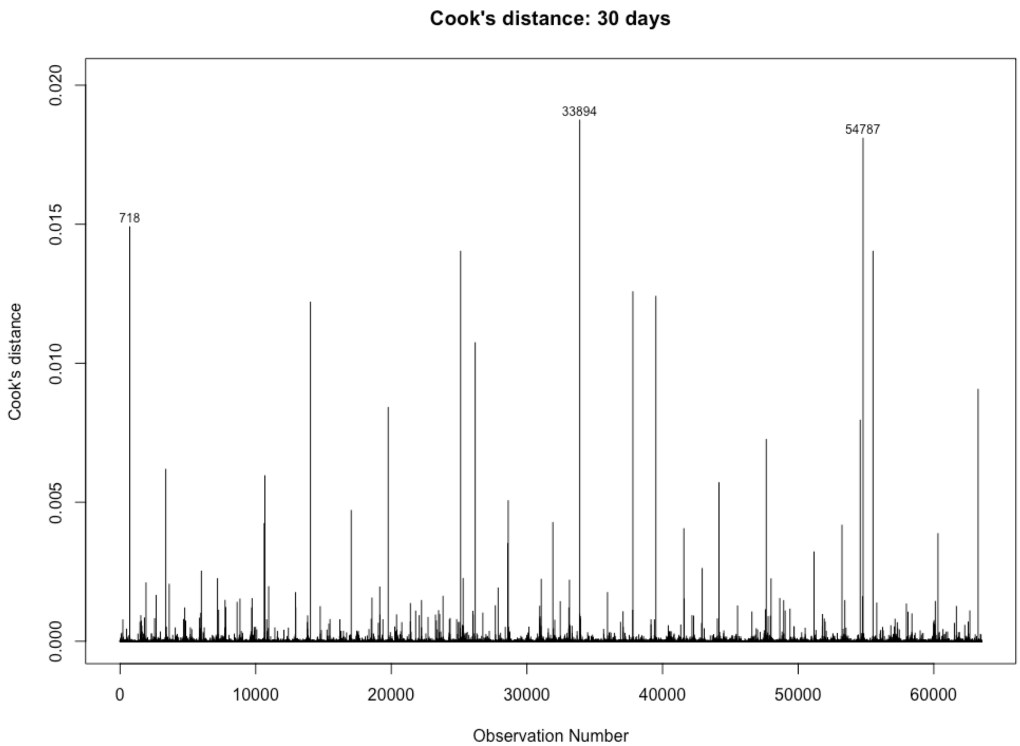

Figure 5 - *Plot of Cook's distance*

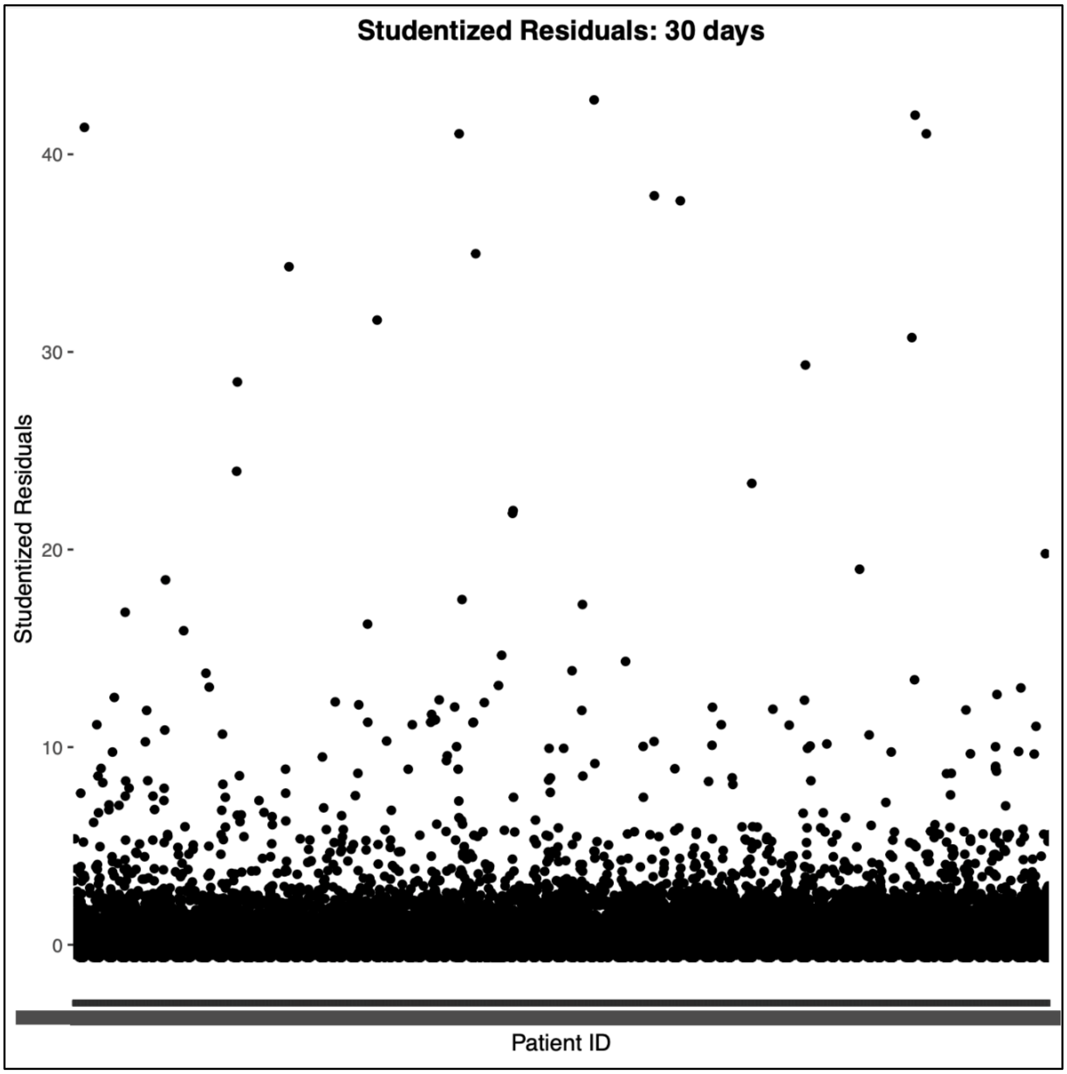

Figure 6 – *Plot of Studentized Residuals*

Percentage of Inappropriate Prescriptions – 45 days

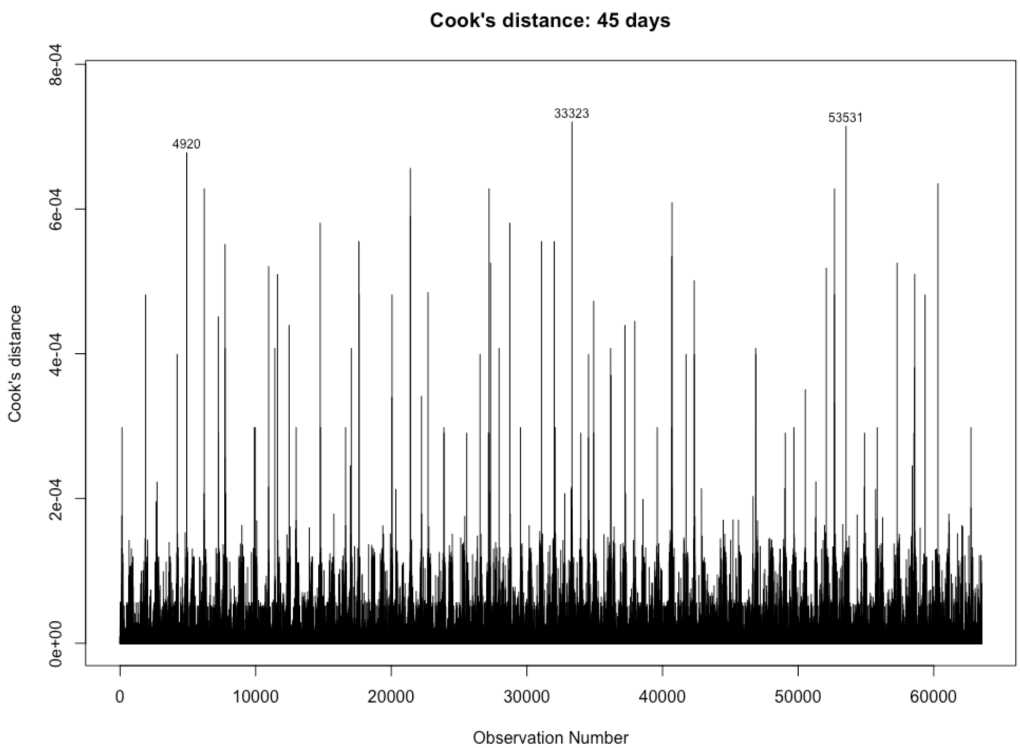

Figure 7 - *Plot of Cook's distance*

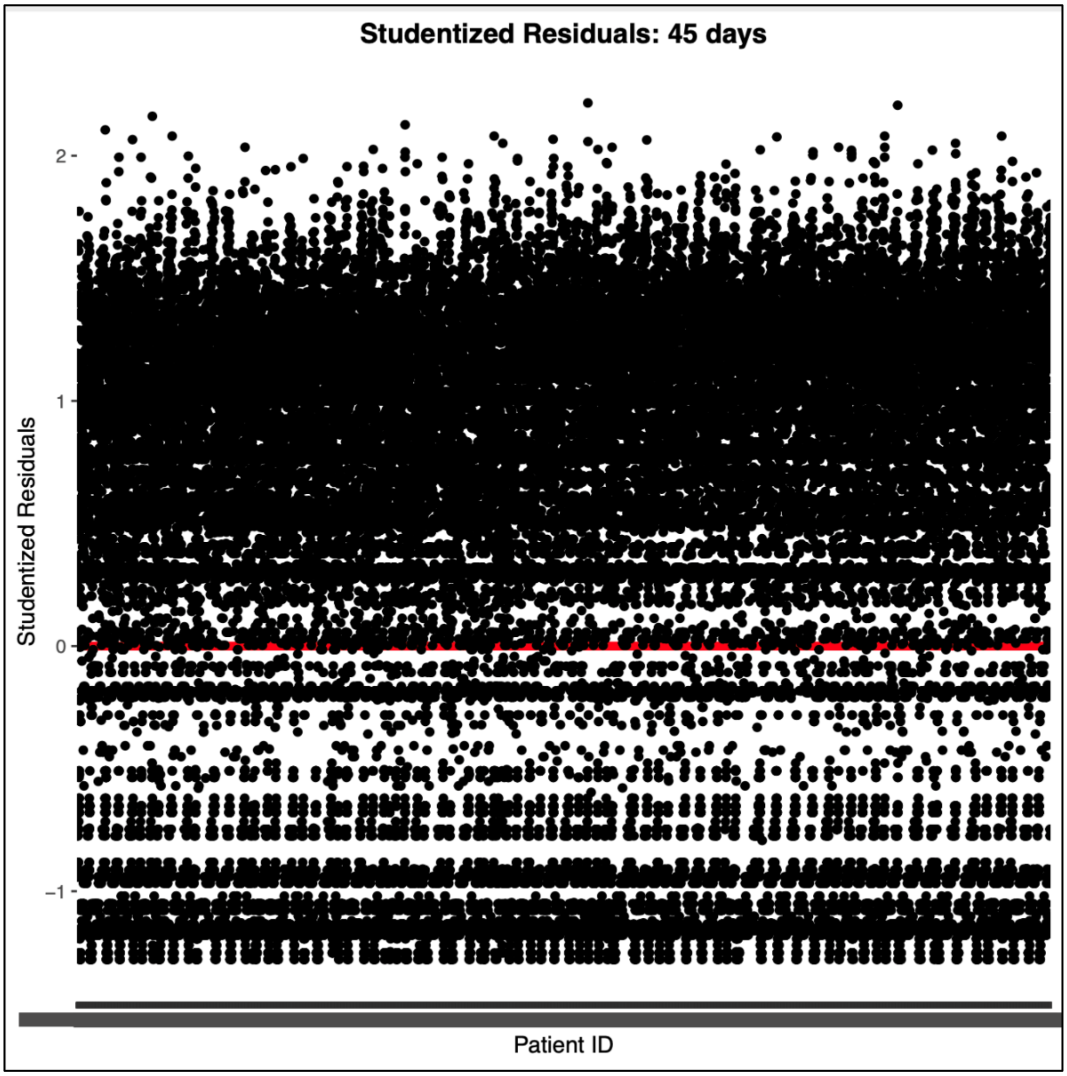

Figure 8 – *Plot of Studentized Residuals*

Number of Inappropriate Prescriptions – 45 days

Before Removing Outliers

Estimates Before Removing Outliers

Variable	Estimate	Standard Error	95% CI	P value[1]
Intercept	4.03	0.124	3.79 to 4.27	
Sex				$p < 0.05$
Female (ref)	0			
Male	0.169	0.0716	0.0286 to 0.309	
Prescriber Specialty				$p = 0.97$
GP (ref)	0			
Other	-0.00713	0.184	-0.368 to 0.354	
Age Group * Urban / Rural				$p < 0.01$
Urban				
Age Group				
18 – 24	-0.0498	0.492	-1.01 to 0.914	$p = 0.92$
25 – 44	0.889	0.357	0.190 to 1.59	$p < 0.05$
45 - 64	1.46	0.331	0.812 to 2.11	$p < 0.01$
65 - 84	0.135	0.316	-0.485 to 0.755	$p = 0.67$
85+ (ref)	0			
Rural				
Age Group				
18 - 24	0.0498	0.492	-0.914 to 1.01	$p = 0.92$
25 - 44	-0.889	0.357	-1.59 to -0.190	$p < 0.05$
45 - 64	-1.46	0.331	-2.11 to -0.812	$p < 0.01$
65 - 84	-0.135	0.316	-0.755 to 0.485	$p = 0.67$
85+ (ref)	0			

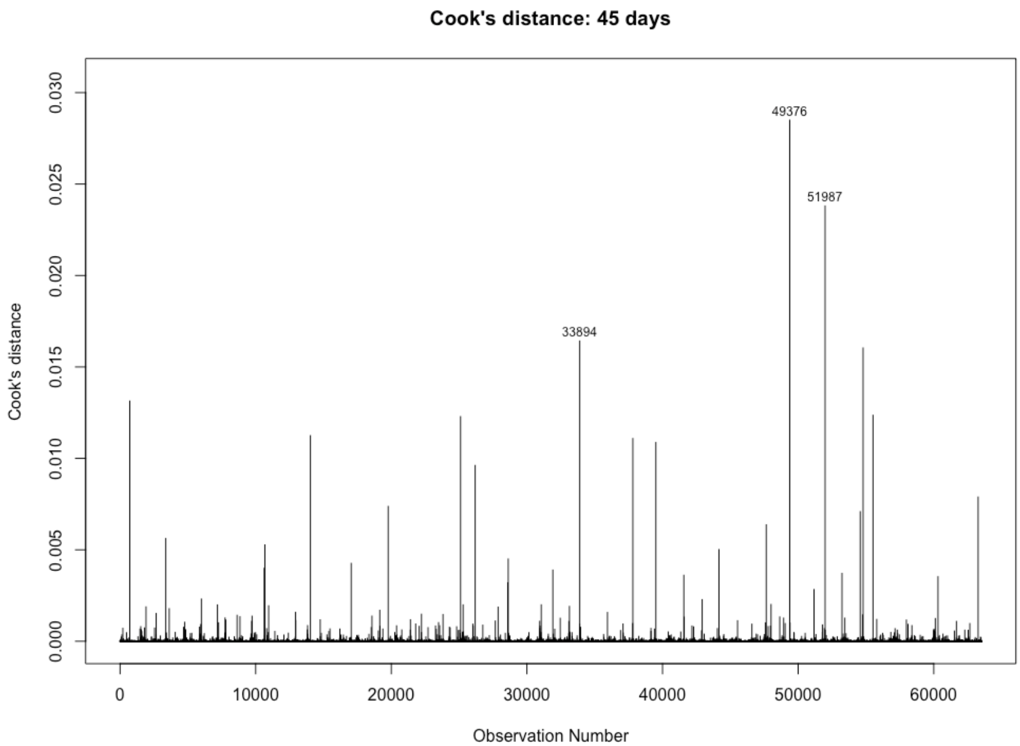

Figure 9 - *Plot of Cook's distance*

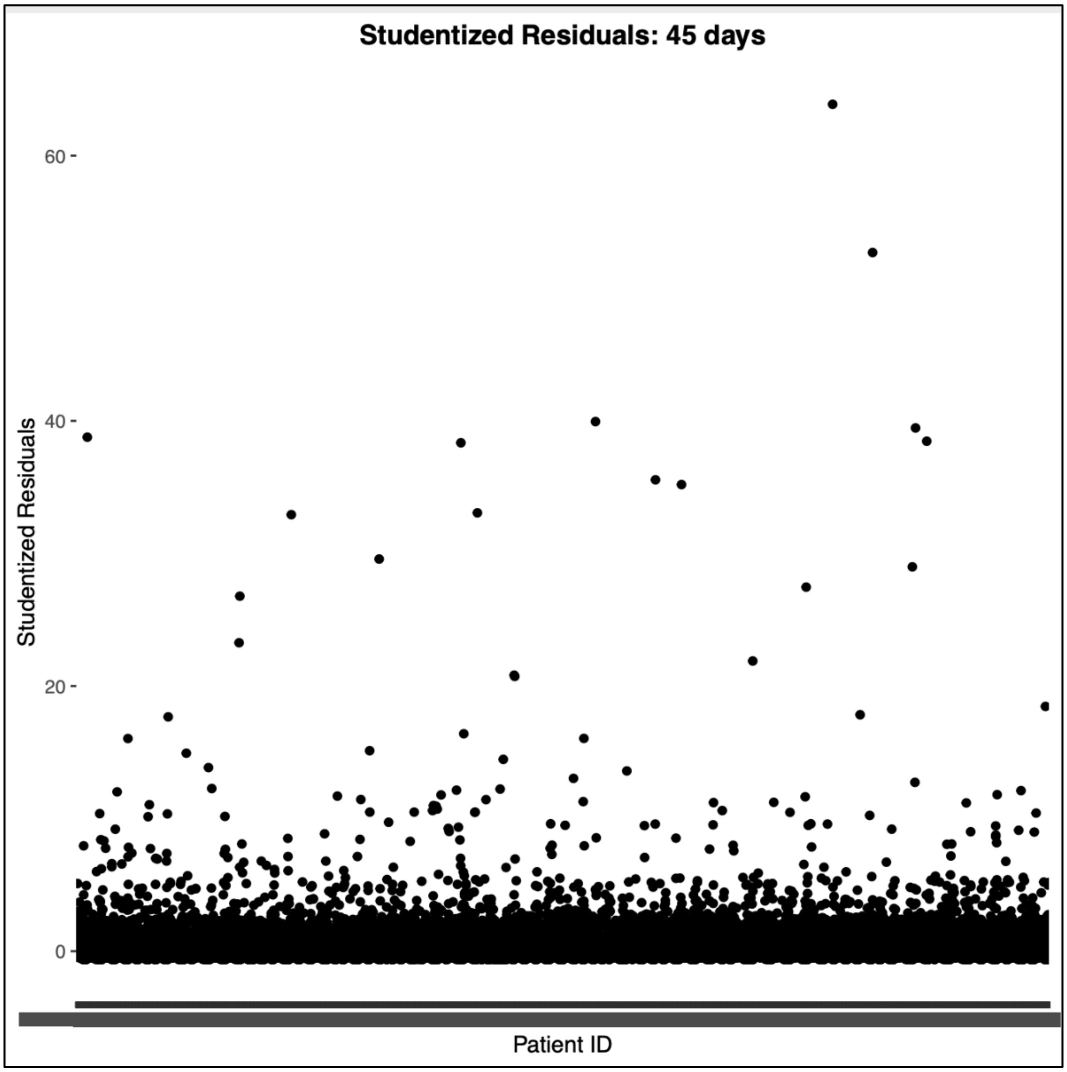

Figure 10 – *Plot of Studentized Residuals*

After Removing Outliers

Estimates After Removing Outliers

Variable	Estimate	Standard Error	95% CI	P value[1]
Intercept	4.03	0.117	3.80 to 4.26	
Sex				p < 0.01
Female (ref)	0			
Male	0.195	0.0679	0.0617 to 0.328	
Prescriber Specialty				p = 0.96
GP (ref)	0			
Other	0.00864	0.174	-0.333 to 0.350	
Age Group * Urban / Rural				p < 0.01
Urban				
Age Group				
18 – 24	-0.0525	0.466	-0.965 to 0.861	p = 0.91
25 – 44	0.842	0.338	0.180 to 1.50	p < 0.05
45 - 64	1.42	0.313	0.801 to 2.03	p < 0.01
65 - 84	0.134	0.300	-0.454 to 0.722	p = 0.66
85+ (ref)	0			
Rural				
Age Group				
18 - 24	0.0525	0.466	-0.861 to 0.965	p = 0.91
25 - 44	-0.842	0.338	-1.50 to -0.180	p < 0.05
45 - 64	-1.42	0.313	-2.03 to -0.801	p < 0.01
65 - 84	-0.134	0.300	-0.722 to 0.454	p = 0.66
85+ (ref)	0			

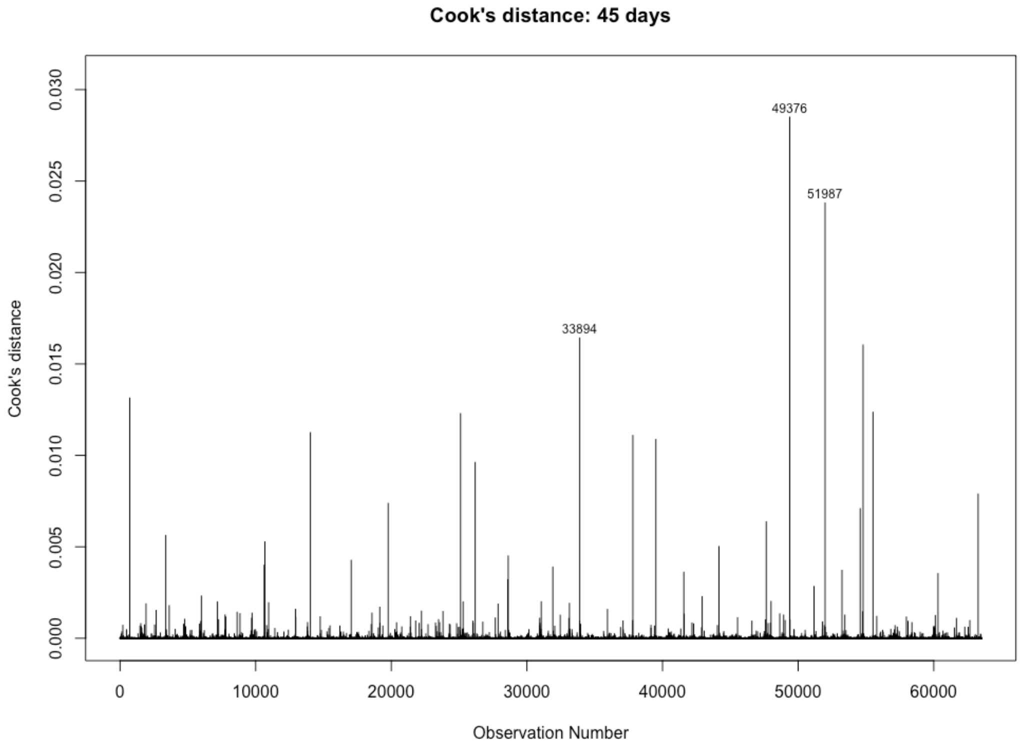

Figure 11 - *Plot of Cook's distance*

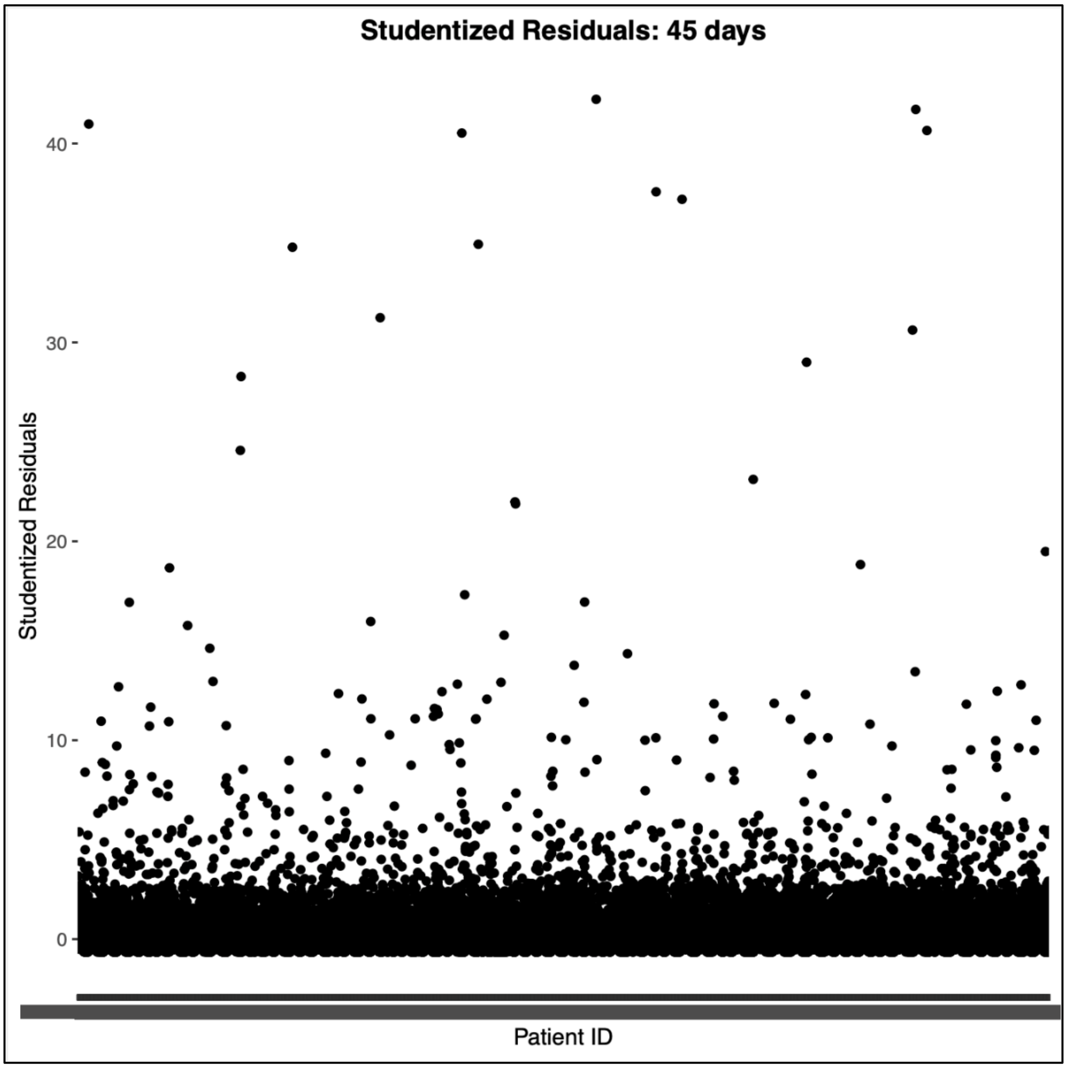

Figure 12 – *Plot of Studentized Residuals*

Percentage of Inappropriate Prescriptions – 60 days

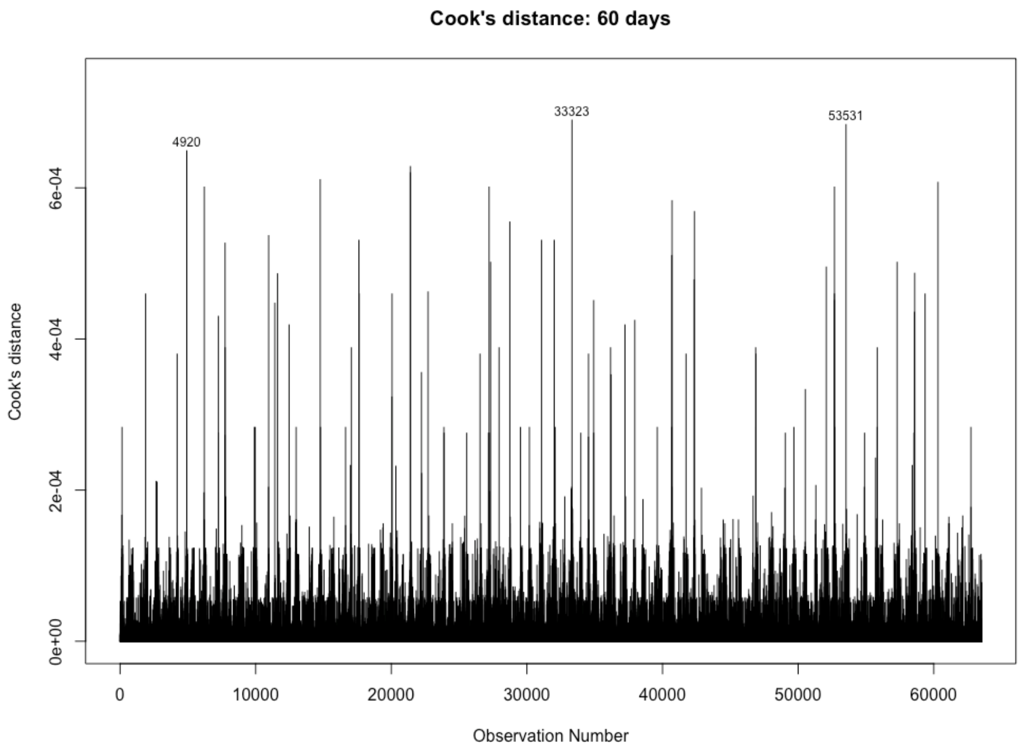

Figure 13 - *Plot of Cook's distance*

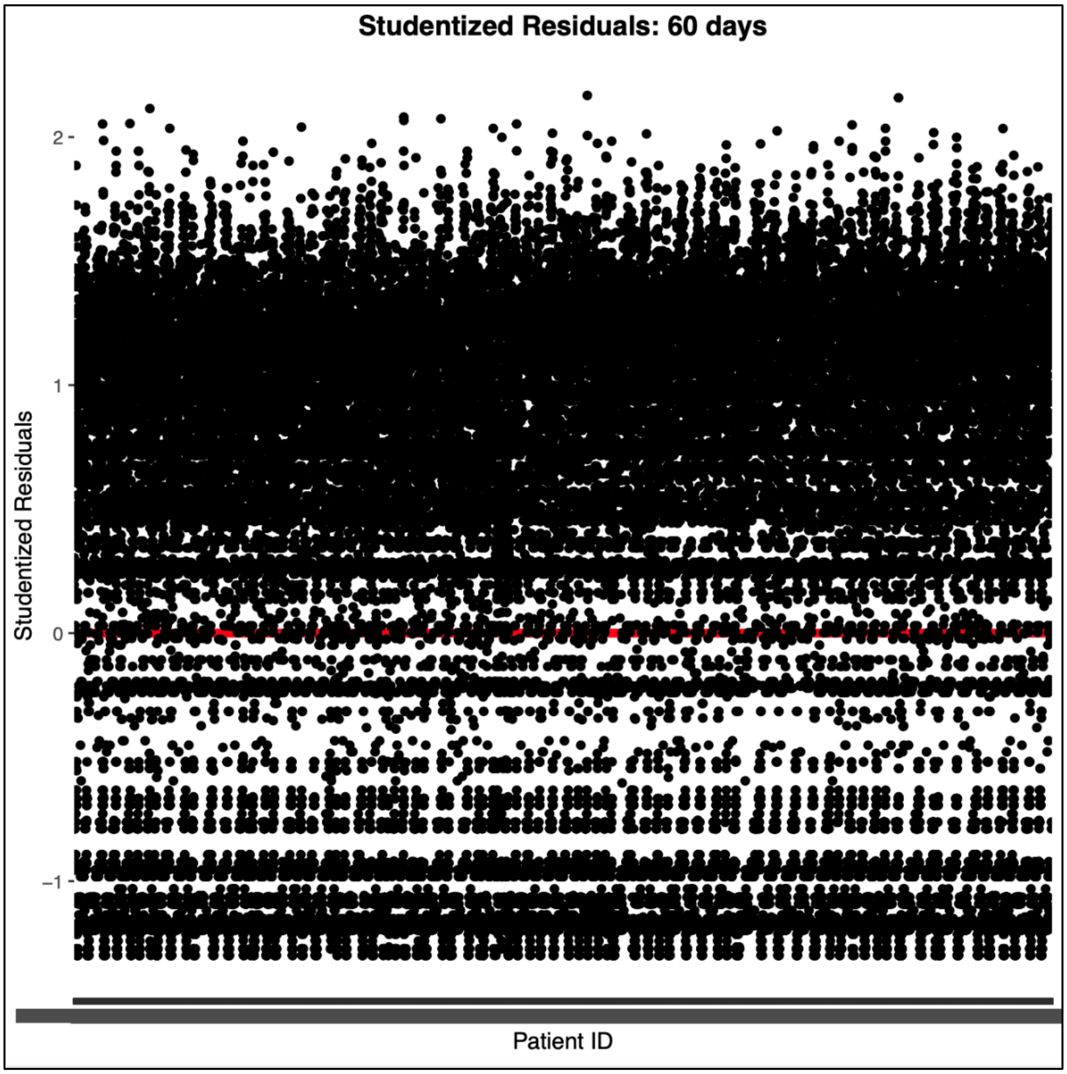

Figure 14 – *Plot of Studentized Residuals*

Number of Inappropriate Prescriptions – 60 days

Before Removing Outliers

Estimates Before Removing Outliers

Variable	Estimate	Standard Error	95% CI	P value[1]
Intercept	4.14	0.126	3.89 to 4.38	
Sex				p < 0.05
Female (ref)	0			
Male	0.175	0.0727	0.0323 to 0.317	
Prescriber Specialty				p = 0.99
GP (ref)	0			
Other	-0.00350	0.187	-0.369 to 0.362	
Age Group * Urban / Rural				p < 0.01
Urban				
Age Group				
18 – 24	-0.0477	0.499	-1.03 to 0.930	p = 0.92
25 – 44	0.897	0.362	0.188 to 1.61	p < 0.05
45 - 64	1.50	0.336	0.839 to 2.15	p < 0.01
65 - 84	0.145	0.321	-0.485 to 0.930	p = 0.65
85+ (ref)	0			
Rural				
Age Group				
18 - 24	0.0477	0.499	-0.930 to 1.03	p = 0.92
25 - 44	-0.897	0.362	-1.61 to -0.188	p < 0.05
45 - 64	-1.50	0.336	-2.15 to -0.839	p < 0.01
65 - 84	-0.145	0.321	-0.774 to 0.485	p = 0.65
85+ (ref)	0			

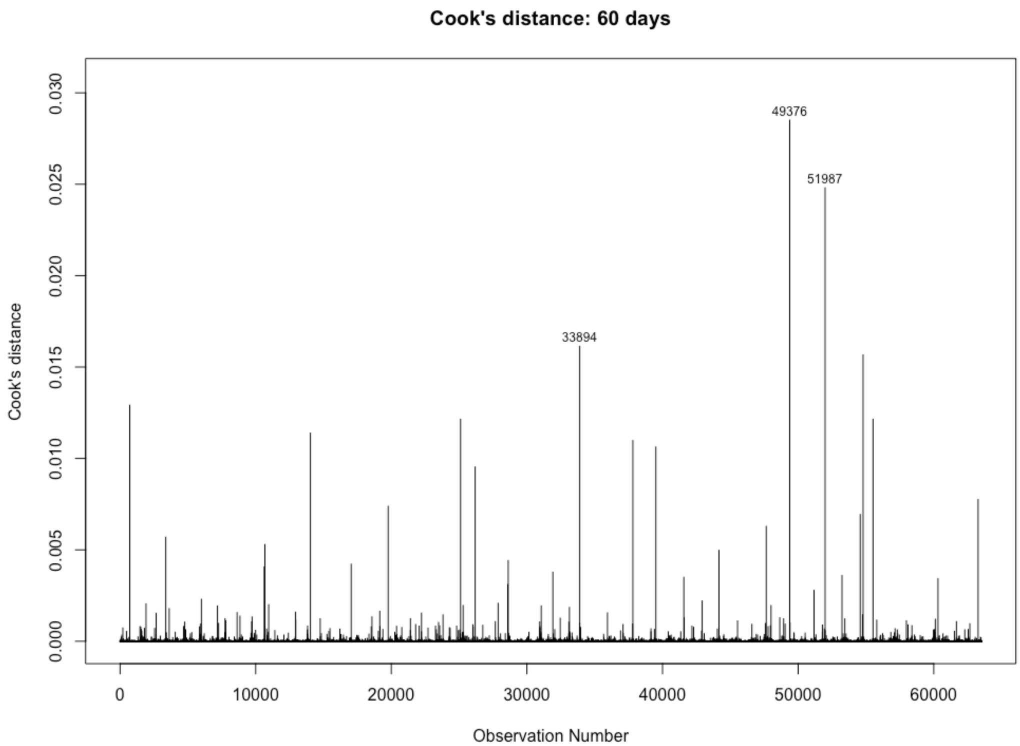

Figure 15 - *Plot of Cook's distance*

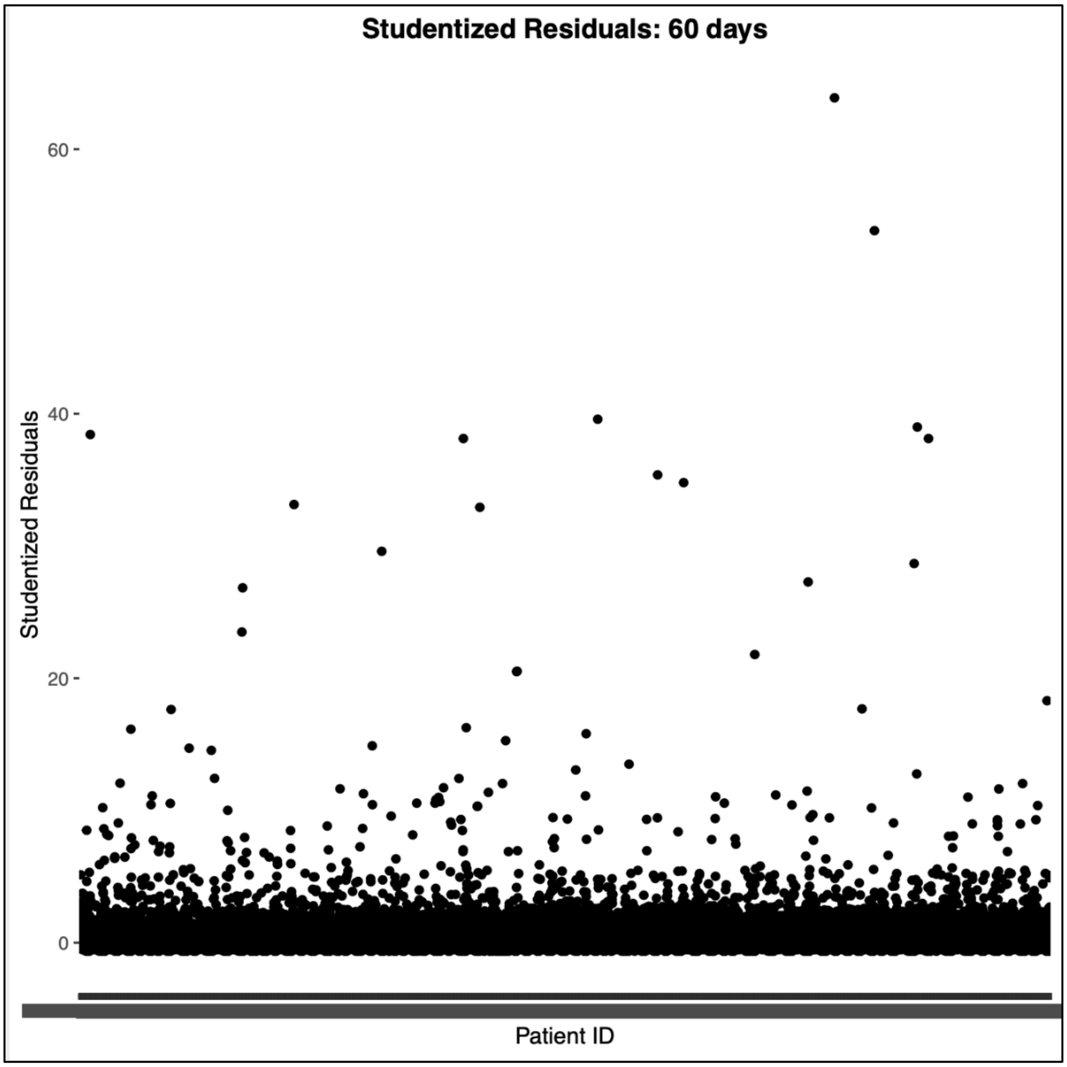

Figure 16 – *Plot of Studentized Residuals*

After Removing Outliers

Estimates After Removing Outliers

Variable	Estimate	Standard Error	95% CI	P value[1]
Intercept	4.13	0.119	3.90 to 4.36	
Sex				p < 0.01
Female (ref)	0			
Male	0.201	0.0688	0.0662 to 0.336	
Prescriber Specialty				p = 0.94
GP (ref)	0			
Other	0.0127	0.177	-0.334 to 0.359	
Age Group * Urban / Rural				p < 0.01
Urban				
Age Group				
18 – 24	-0.0504	0.472	-0.976 to 0.875	p = 0.92
25 – 44	0.849	0.342	0.178 to 1.52	p < 0.05
45 - 64	1.45	0.318	0.829 to 2.07	p < 0.01
65 - 84	0.143	0.304	-0.452 to 0.739	p = 0.64
85+ (ref)	0			
Rural				
Age Group				
18 - 24	0.0504	0.472	-0.875 to 0.976	p = 0.92
25 - 44	-0.849	0.342	-1.52 to -0.178	p < 0.05
45 - 64	-1.45	0.318	-2.07 to -0.829	p < 0.01
65 - 84	-0.143	0.304	-0.739 to 0.452	p = 0.64
85+ (ref)	0			

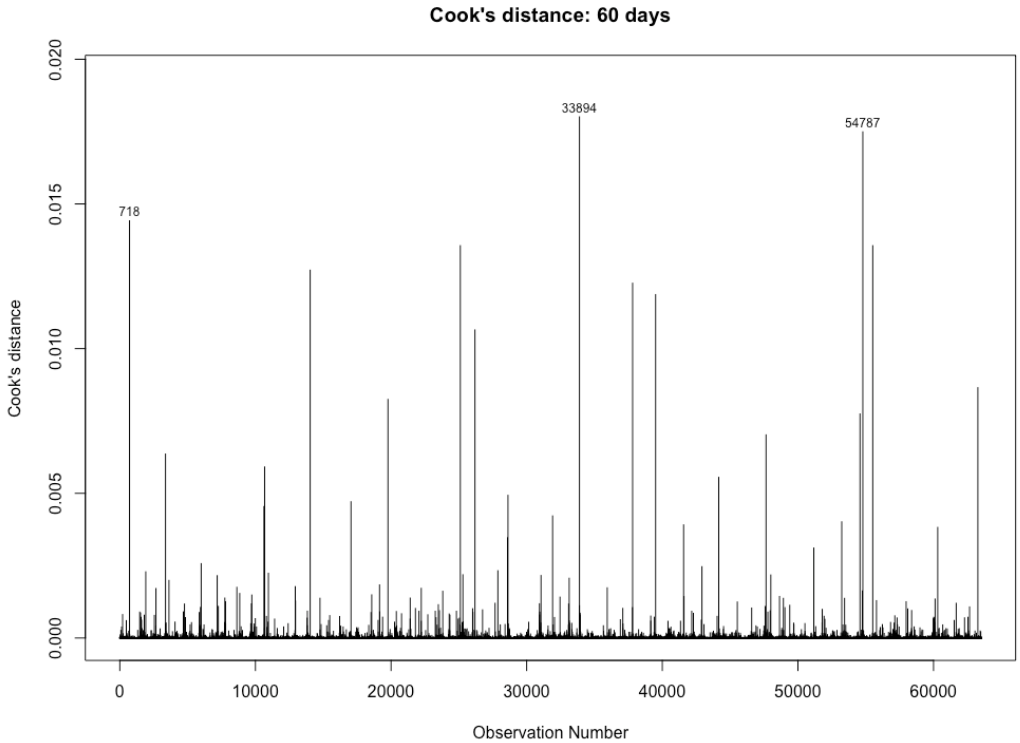

Figure 17 - *Plot of Cook's distance*

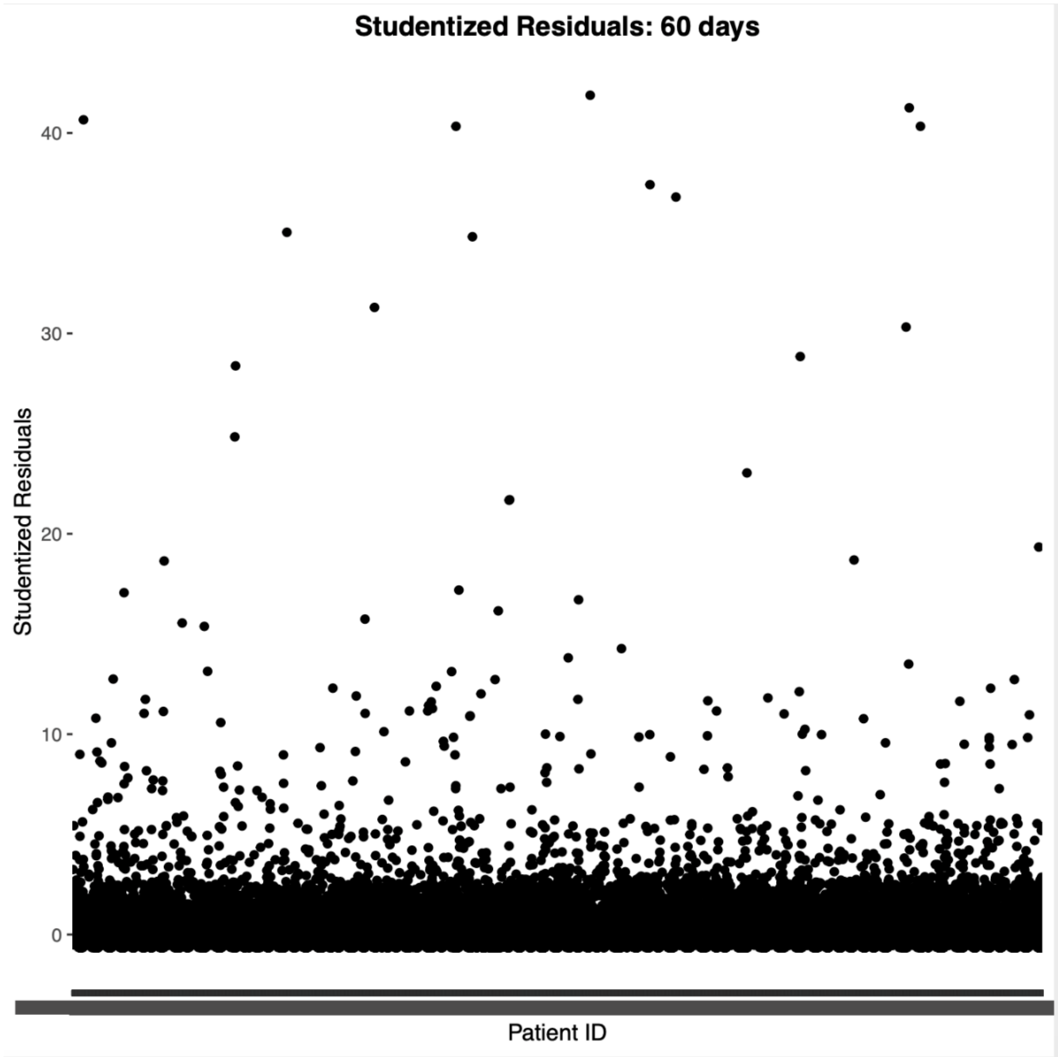

Figure 18 – *Plot of Studentized Residuals*

Appendix 4: SAS Program and Output

Percentage of Inappropriate Prescriptions (30 days definition)

```
proc genmod data=percent-inapp-30days;
class Sex(ref="F") UrbanRuralStatus Age-Group
PrescriberSpeciality(ref='GP')/param=ref;
model percent-inapp = Age-Group Sex UrbanRuralStatus PrescriberSpeciality
 UrbanRuralStatus*Age-Group / dist=normal link=identity type3;
Estimate “M vs F” Sex 1 -1;
Estimate “Other vs GP” PrescriberSpeciality 1 -1;
Estimate “Urban: Age-Group=1 vs Age-Group=5” Age-Group 1 0 0 0 -1 UrbanRuralStatus*Age-
Group 0 0 0 0 0 1 0 0 0 -1;
Estimate “Urban: Age-Group =2 vs Age-Group =5” Age-Group 0 1 0 0 -1 UrbanRuralStatus*
Age-Group 0 0 0 0 0 0 1 0 0 -1;
Estimate “Urban: Age-Group =3 vs Age-Group =5” Age-Group 0 0 1 0 -1 UrbanRuralStatus*
Age-Group 0 0 0 0 0 0 0 1 0 -1;
Estimate “Urban: Age-Group =4 vs Age-Group =5” Age-Group 0 0 0 1 -1 UrbanRuralStatus*
Age-Group 0 0 0 0 0 0 0 0 1 -1;
Estimate “Rural: Age-Group =1 vs Age-Group =5” Age-Group 1 0 0 0 -1 UrbanRuralStatus*
Age-Group 1 0 0 0 -1 0 0 0 0 0;
Estimate “Rural: Age-Group =2 vs Age-Group =5” Age-Group 0 1 0 0 -1 UrbanRuralStatus*
Age-Group 0 1 0 0 -1 0 0 0 0 0;
Estimate “Rural: Age-Group =3 vs Age-Group =5” Age-Group 0 0 1 0 -1 UrbanRuralStatus*
Age-Group 0 0 1 0 -1 0 0 0 0 0;
Estimate “Rural: Age-Group =4 vs Age-Group =5” Age-Group 0 0 0 1 -1 UrbanRuralStatus*
Age-Group 0 0 0 1 -1 0 0 0 0 0;
run;
```

The GENMOD Procedure

Model Information	
Data Set	FOLDERS.FINALTHESISANALYSIS_30DAYS
Distribution	Normal
Link Function	Identity
Dependent Variable	prop

Number of Observations Read	63517
Number of Observations Used	63517

Class Level Information					
Class	**Value**	**Design Variables**			
Sex	**F**	0			
	M	1			
UrbanRuralStatus	**Rural**	1			
	Urban	0			
Age_Group	**1**	1	0	0	0
	2	0	1	0	0
	3	0	0	1	0
	4	0	0	0	1
	5	0	0	0	0
PrescriberSpeciality	**GP**	0			
	Other	1			

Parameter Information					
Parameter	**Effect**	**Sex**	**UrbanRuralStatus**	**Age_Group**	**PrescriberSpeciality**
Prm1	Intercept				
Prm2	Age_Group			1	
Prm3	Age_Group			2	
Prm4	Age_Group			3	
Prm5	Age_Group			4	
Prm6	Sex	M			
Prm7	UrbanRuralStatus		Rural		
Prm8	PrescriberSpeciality				Other
Prm9	UrbanRural*Age_Group		Rural	1	
Prm10	UrbanRural*Age_Group		Rural	2	
Prm11	UrbanRural*Age_Group		Rural	3	
Prm12	UrbanRural*Age_Group		Rural	4	

The GENMOD Procedure

Criteria For Assessing Goodness Of Fit			
Criterion	**DF**	**Value**	**Value/DF**
Deviance	64E3	7267.1161	0.1144
Scaled Deviance	64E3	63517.0000	1.0002
Pearson Chi-Square	64E3	7267.1161	0.1144
Scaled Pearson X2	64E3	63517.0000	1.0002
Log Likelihood		-21275.9403	
Full Log Likelihood		-21275.9403	
AIC (smaller is better)		42577.8806	
AICC (smaller is better)		42577.8863	
BIC (smaller is better)		42695.6484	

Algorithm converged.

Analysis Of Maximum Likelihood Parameter Estimates									
Parameter			**DF**	**Estimate**	**Standard Error**	**Wald 95% Confidence Limits**		**Wald Chi-Square**	**Pr > ChiSq**
Intercept			1	0.4150	0.0048	0.4055	0.4244	7391.44	<.0001
Age_Group	1		1	-0.1983	0.0080	-0.2140	-0.1825	608.94	<.0001
Age_Group	2		1	-0.1122	0.0058	-0.1237	-0.1008	368.87	<.0001
Age_Group	3		1	-0.0401	0.0057	-0.0512	-0.0291	50.40	<.0001
Age_Group	4		1	-0.0324	0.0054	-0.0430	-0.0218	35.84	<.0001
Sex	M		1	0.0091	0.0028	0.0036	0.0146	10.65	0.0011
UrbanRuralStatus	Rural		1	-0.0205	0.0113	-0.0427	0.0017	3.26	0.0709
PrescriberSpeciality	Other		1	-0.0110	0.0072	-0.0251	0.0030	2.36	0.1244
UrbanRural*Age_Group	Rural	1	1	-0.0293	0.0192	-0.0668	0.0083	2.33	0.1270
UrbanRural*Age_Group	Rural	2	1	-0.0351	0.0139	-0.0623	-0.0078	6.36	0.0117
UrbanRural*Age_Group	Rural	3	1	-0.0441	0.0129	-0.0694	-0.0188	11.69	0.0006
UrbanRural*Age_Group	Rural	4	1	-0.0127	0.0123	-0.0369	0.0115	1.05	0.3049
Scale			1	0.3382	0.0009	0.3364	0.3401		

Note: The scale parameter was estimated by maximum likelihood.

LR Statistics For Joint Tests			
Source	**DF**	**Chi-Square**	**Pr > ChiSq**
Age_Group	4	1014.90	<.0001
Sex	1	10.65	0.0011
UrbanRuralStatus	1	3.26	0.0709

The GENMOD Procedure

LR Statistics For Joint Tests			
Source	DF	Chi-Square	Pr > ChiSq
PrescriberSpeciality	1	2.36	0.1244
UrbanRural*Age_Group	4	22.54	0.0002

Note: Under full-rank parameterizations, Type 3 effect tests are replaced by joint tests. The joint test for an effect is a test that all the parameters associated with that effect are zero. Such joint tests might not be equivalent to Type 3 effect tests under GLM parameterization.

Contrast Estimate Results										
		Mean Confidence Limits					L'Beta Confidence Limits			
Label	Mean Estimate			L'Beta Estimate	Standard Error	Alpha			Chi-Square	Pr > ChiSq
M vs F	-0.0091	-0.0146	-0.0036	-0.0091	0.0028	0.05	-0.0146	-0.0036	10.65	0.0011
Other vs GP	-0.0110	-0.0251	0.0030	-0.0110	0.0072	0.05	-0.0251	0.0030	2.36	0.1244
Urban: Age-Group=1 vs Age-Group=5	-0.1983	-0.2140	-0.1825	-0.1983	0.0080	0.05	-0.2140	-0.1825	608.94	<.0001
Urban: Age-Group =2 vs Age-Group =5	-0.1122	-0.1237	-0.1008	-0.1122	0.0058	0.05	-0.1237	-0.1008	368.87	<.0001
Urban: Age-Group =3 vs Age-Group =5	-0.0401	-0.0512	-0.0291	-0.0401	0.0057	0.05	-0.0512	-0.0291	50.40	<.0001
Urban: Age-Group =4 vs Age-Group =5	-0.0324	-0.0430	-0.0218	-0.0324	0.0054	0.05	-0.0430	-0.0218	35.84	<.0001
Rural: Age-Group =1 vs Age-Group =5	-0.2275	-0.2617	-0.1934	-0.2275	0.0174	0.05	-0.2617	-0.1934	170.66	<.0001
Rural: Age-Group =2 vs Age-Group =5	-0.1473	-0.1720	-0.1226	-0.1473	0.0126	0.05	-0.1720	-0.1226	136.17	<.0001
Rural: Age-Group =3 vs Age-Group =5	-0.0842	-0.1070	-0.0615	-0.0842	0.0116	0.05	-0.1070	-0.0615	52.69	<.0001
Rural: Age-Group =4 vs Age-Group =5	-0.0450	-0.0668	-0.0233	-0.0450	0.0111	0.05	-0.0668	-0.0233	16.44	<.0001

Number of Inappropriate Prescriptions (30 days definition)

```
proc genmod data = number-inapp-30days;
class Sex(ref="F") UrbanRuralStatus Age-Group
PrescriberSpeciality(ref='GP')/param=ref;
model num-inapp = Age-Group Sex UrbanRuralStatus PrescriberSpeciality
 UrbanRuralStatus*Age-Group / dist=normal link=identity type3;
Estimate “M vs F” Sex 1 -1;
Estimate “Other vs GP” PrescriberSpeciality 1 -1;
Estimate “Urban: Age-Group=1 vs Age-Group=5” Age-Group 1 0 0 0 -1 UrbanRuralStatus*Age-
Group 0 0 0 0 0 1 0 0 0 -1;
Estimate “Urban: Age-Group =2 vs Age-Group =5” Age-Group 0 1 0 0 -1 UrbanRuralStatus*
Age-Group 0 0 0 0 0 0 1 0 0 -1;
Estimate “Urban: Age-Group =3 vs Age-Group =5” Age-Group 0 0 1 0 -1 UrbanRuralStatus*
Age-Group 0 0 0 0 0 0 0 1 0 -1;
Estimate “Urban: Age-Group =4 vs Age-Group =5” Age-Group 0 0 0 1 -1 UrbanRuralStatus*
Age-Group 0 0 0 0 0 0 0 0 1 -1;
Estimate “Rural: Age-Group =1 vs Age-Group =5” Age-Group 1 0 0 0 -1 UrbanRuralStatus*
Age-Group 1 0 0 0 -1 0 0 0 0 0;
Estimate “Rural: Age-Group =2 vs Age-Group =5” Age-Group 0 1 0 0 -1 UrbanRuralStatus*
Age-Group 0 1 0 0 -1 0 0 0 0 0;
Estimate “Rural: Age-Group =3 vs Age-Group =5” Age-Group 0 0 1 0 -1 UrbanRuralStatus*
Age-Group 0 0 1 0 -1 0 0 0 0 0;
Estimate “Rural: Age-Group =4 vs Age-Group =5” Age-Group 0 0 0 1 -1 UrbanRuralStatus*
Age-Group 0 0 0 1 -1 0 0 0 0 0;
run;
```

The GENMOD Procedure

Model Information	
Data Set	FOLDERS.FINALTHESISANALYSIS_30DAYS
Distribution	Normal
Link Function	Identity
Dependent Variable	num_inapp

Number of Observations Read	63517
Number of Observations Used	63517

Class Level Information					
Class	**Value**	**Design Variables**			
Sex	**F**	0			
	M	1			
UrbanRuralStatus	**Rural**	1			
	Urban	0			
Age_Group	**1**	1	0	0	0
	2	0	1	0	0
	3	0	0	1	0
	4	0	0	0	1
	5	0	0	0	0
PrescriberSpeciality	**GP**	0			
	Other	1			

Parameter Information					
Parameter	**Effect**	**Sex**	**UrbanRuralStatus**	**Age_Group**	**PrescriberSpeciality**
Prm1	Intercept				
Prm2	Age_Group			1	
Prm3	Age_Group			2	
Prm4	Age_Group			3	
Prm5	Age_Group			4	
Prm6	Sex	M			
Prm7	UrbanRuralStatus		Rural		
Prm8	PrescriberSpeciality				Other
Prm9	UrbanRural*Age_Group		Rural	1	
Prm10	UrbanRural*Age_Group		Rural	2	
Prm11	UrbanRural*Age_Group		Rural	3	
Prm12	UrbanRural*Age_Group		Rural	4	

The GENMOD Procedure

Criteria For Assessing Goodness Of Fit			
Criterion	**DF**	**Value**	**Value/DF**
Deviance	64E3	4624608.5155	72.8227
Scaled Deviance	64E3	63517.0000	1.0002
Pearson Chi-Square	64E3	4624608.5155	72.8227
Scaled Pearson X2	64E3	63517.0000	1.0002
Log Likelihood		-226302.0669	
Full Log Likelihood		-226302.0669	
AIC (smaller is better)		452630.1337	
AICC (smaller is better)		452630.1394	
BIC (smaller is better)		452747.9015	

Algorithm converged.

Analysis Of Maximum Likelihood Parameter Estimates									
Parameter			**DF**	**Estimate**	**Standard Error**	**Wald 95% Confidence Limits**		**Wald Chi-Square**	**Pr > ChiSq**
Intercept			1	3.9245	0.1218	3.6859	4.1632	1038.82	<.0001
Age_Group	1		1	-2.2553	0.2027	-2.6526	-1.8580	123.80	<.0001
Age_Group	2		1	-0.2556	0.1474	-0.5446	0.0333	3.01	0.0829
Age_Group	3		1	1.0607	0.1426	0.7812	1.3402	55.32	<.0001
Age_Group	4		1	-0.2045	0.1364	-0.4718	0.0628	2.25	0.1338
Sex	M		1	0.1675	0.0705	0.0294	0.3057	5.65	0.0175
UrbanRuralStatus	Rural		1	-0.4279	0.2861	-0.9886	0.1329	2.24	0.1348
PrescriberSpeciality	Other		1	-0.0188	0.1811	-0.3737	0.3361	0.01	0.9172
UrbanRural*Age_Group	Rural	1	1	0.0352	0.4838	-0.9130	0.9834	0.01	0.9420
UrbanRural*Age_Group	Rural	2	1	-0.8727	0.3508	-1.5603	-0.1851	6.19	0.0129
UrbanRural*Age_Group	Rural	3	1	-1.4354	0.3254	-2.0733	-0.7976	19.45	<.0001
UrbanRural*Age_Group	Rural	4	1	-0.1427	0.3113	-0.7529	0.4676	0.21	0.6468
Scale			1	8.5328	0.0239	8.4860	8.5799		

Note: The scale parameter was estimated by maximum likelihood.

LR Statistics For Joint Tests			
Source	**DF**	**Chi-Square**	**Pr > ChiSq**
Age_Group	4	408.78	<.0001
Sex	1	5.65	0.0175
UrbanRuralStatus	1	2.24	0.1348

The GENMOD Procedure

LR Statistics For Joint Tests			
Source	**DF**	**Chi-Square**	**Pr > ChiSq**
PrescriberSpeciality	1	0.01	0.9172
UrbanRural*Age_Group	4	51.68	<.0001

Note: Under full-rank parameterizations, Type 3 effect tests are replaced by joint tests. The joint test for an effect is a test that all the parameters associated with that effect are zero. Such joint tests might not be equivalent to Type 3 effect tests under GLM parameterization.

Contrast Estimate Results										
		Mean Confidence Limits					**L'Beta Confidence Limits**			
Label	**Mean Estimate**			**L'Beta Estimate**	**Standard Error**	**Alpha**			**Chi-Square**	**Pr > ChiSq**
M vs F	-0.1675	-0.3057	-0.0294	-0.1675	0.0705	0.05	-0.3057	-0.0294	5.65	0.0175
Other vs GP	-0.0188	-0.3737	0.3361	-0.0188	0.1811	0.05	-0.3737	0.3361	0.01	0.9172
Urban: Age-Group=1 vs Age-Group=5	-2.2553	-2.6526	-1.8580	-2.2553	0.2027	0.05	-2.6526	-1.8580	123.80	<.0001
Urban: Age-Group =2 vs Age-Group =5	-0.2556	-0.5446	0.0333	-0.2556	0.1474	0.05	-0.5446	0.0333	3.01	0.0829
Urban: Age-Group =3 vs Age-Group =5	1.0607	0.7812	1.3402	1.0607	0.1426	0.05	0.7812	1.3402	55.32	<.0001
Urban: Age-Group =4 vs Age-Group =5	-0.2045	-0.4718	0.0628	-0.2045	0.1364	0.05	-0.4718	0.0628	2.25	0.1338
Rural: Age-Group =1 vs Age-Group =5	-2.2201	-3.0813	-1.3589	-2.2201	0.4394	0.05	-3.0813	-1.3589	25.53	<.0001
Rural: Age-Group =2 vs Age-Group =5	-1.1284	-1.7524	-0.5043	-1.1284	0.3184	0.05	-1.7524	-0.5043	12.56	0.0004
Rural: Age-Group =3 vs Age-Group =5	-0.3747	-0.9485	0.1991	-0.3747	0.2928	0.05	-0.9485	0.1991	1.64	0.2005
Rural: Age-Group =4 vs Age-Group =5	-0.3471	-0.8962	0.2019	-0.3471	0.2802	0.05	-0.8962	0.2019	1.54	0.2153

Percentage of Inappropriate Prescriptions (45 days definition)

```
proc genmod data=percent-inapp-30days;
class Sex(ref="F") UrbanRuralStatus Age-Group
PrescriberSpeciality(ref='GP')/param=ref;
model percent-inapp = Age-Group Sex UrbanRuralStatus PrescriberSpeciality
 UrbanRuralStatus*Age-Group / dist=normal link=identity type3;
Estimate “M vs F” Sex 1 -1;
Estimate “Other vs GP” PrescriberSpeciality 1 -1;
Estimate “Urban: Age-Group=1 vs Age-Group=5” Age-Group 1 0 0 0 -1 UrbanRuralStatus*Age-
Group 0 0 0 0 0 1 0 0 0 -1;
Estimate “Urban: Age-Group =2 vs Age-Group =5” Age-Group 0 1 0 0 -1 UrbanRuralStatus*
Age-Group 0 0 0 0 0 0 1 0 0 -1;
Estimate “Urban: Age-Group =3 vs Age-Group =5” Age-Group 0 0 1 0 -1 UrbanRuralStatus*
Age-Group 0 0 0 0 0 0 0 1 0 -1;
Estimate “Urban: Age-Group =4 vs Age-Group =5” Age-Group 0 0 0 1 -1 UrbanRuralStatus*
Age-Group 0 0 0 0 0 0 0 0 1 -1;
Estimate “Rural: Age-Group =1 vs Age-Group =5” Age-Group 1 0 0 0 -1 UrbanRuralStatus*
Age-Group 1 0 0 0 -1 0 0 0 0 0;
Estimate “Rural: Age-Group =2 vs Age-Group =5” Age-Group 0 1 0 0 -1 UrbanRuralStatus*
Age-Group 0 1 0 0 -1 0 0 0 0 0;
Estimate “Rural: Age-Group =3 vs Age-Group =5” Age-Group 0 0 1 0 -1 UrbanRuralStatus*
Age-Group 0 0 1 0 -1 0 0 0 0 0;
Estimate “Rural: Age-Group =4 vs Age-Group =5” Age-Group 0 0 0 1 -1 UrbanRuralStatus*
Age-Group 0 0 0 1 -1 0 0 0 0 0;
run;
```

The GENMOD Procedure

Model Information	
Data Set	FOLDERS.FINALTHESISANALYSIS_45DAYS
Distribution	Normal
Link Function	Identity
Dependent Variable	prop

Number of Observations Read	63517
Number of Observations Used	63517

Class Level Information					
Class	**Value**	**Design Variables**			
Sex	**F**	0			
	M	1			
UrbanRuralStatus	**Rural**	1			
	Urban	0			
Age_Group	**1**	1	0	0	0
	2	0	1	0	0
	3	0	0	1	0
	4	0	0	0	1
	5	0	0	0	0
PrescriberSpeciality	**GP**	0			
	Other	1			

Parameter Information					
Parameter	**Effect**	**Sex**	**UrbanRuralStatus**	**Age_Group**	**PrescriberSpeciality**
Prm1	Intercept				
Prm2	Age_Group			1	
Prm3	Age_Group			2	
Prm4	Age_Group			3	
Prm5	Age_Group			4	
Prm6	Sex	M			
Prm7	UrbanRuralStatus		Rural		
Prm8	PrescriberSpeciality				Other
Prm9	UrbanRural*Age_Group		Rural	1	
Prm10	UrbanRural*Age_Group		Rural	2	
Prm11	UrbanRural*Age_Group		Rural	3	
Prm12	UrbanRural*Age_Group		Rural	4	

The GENMOD Procedure

Criteria For Assessing Goodness Of Fit			
Criterion	**DF**	**Value**	**Value/DF**
Deviance	64E3	7498.3076	0.1181
Scaled Deviance	64E3	63517.0000	1.0002
Pearson Chi-Square	64E3	7498.3076	0.1181
Scaled Pearson X2	64E3	63517.0000	1.0002
Log Likelihood		-22270.5470	
Full Log Likelihood		-22270.5470	
AIC (smaller is better)		44567.0940	
AICC (smaller is better)		44567.0997	
BIC (smaller is better)		44684.8618	

Algorithm converged.

Analysis Of Maximum Likelihood Parameter Estimates									
Parameter			**DF**	**Estimate**	**Standard Error**	**Wald 95% Confidence Limits**		**Wald Chi-Square**	**Pr > ChiSq**
Intercept			1	0.4300	0.0049	0.4204	0.4396	7690.69	<.0001
Age_Group	1		1	-0.2059	0.0082	-0.2219	-0.1899	636.41	<.0001
Age_Group	2		1	-0.1160	0.0059	-0.1277	-0.1044	382.08	<.0001
Age_Group	3		1	-0.0403	0.0057	-0.0516	-0.0291	49.34	<.0001
Age_Group	4		1	-0.0341	0.0055	-0.0448	-0.0233	38.49	<.0001
Sex	M		1	0.0091	0.0028	0.0036	0.0147	10.32	0.0013
UrbanRuralStatus	Rural		1	-0.0200	0.0115	-0.0426	0.0026	3.01	0.0827
PrescriberSpeciality	Other		1	-0.0109	0.0073	-0.0252	0.0034	2.24	0.1342
UrbanRural*Age_Group	Rural	1	1	-0.0293	0.0195	-0.0675	0.0089	2.27	0.1322
UrbanRural*Age_Group	Rural	2	1	-0.0372	0.0141	-0.0649	-0.0095	6.94	0.0084
UrbanRural*Age_Group	Rural	3	1	-0.0464	0.0131	-0.0721	-0.0207	12.52	0.0004
UrbanRural*Age_Group	Rural	4	1	-0.0147	0.0125	-0.0393	0.0098	1.38	0.2400
Scale			1	0.3436	0.0010	0.3417	0.3455		

Note: The scale parameter was estimated by maximum likelihood.

LR Statistics For Joint Tests			
Source	**DF**	**Chi-Square**	**Pr > ChiSq**
Age_Group	4	1056.90	<.0001
Sex	1	10.32	0.0013
UrbanRuralStatus	1	3.01	0.0827

The GENMOD Procedure

LR Statistics For Joint Tests			
Source	**DF**	**Chi-Square**	**Pr > ChiSq**
PrescriberSpeciality	1	2.24	0.1342
UrbanRural*Age_Group	4	22.82	0.0001

Note: Under full-rank parameterizations, Type 3 effect tests are replaced by joint tests. The joint test for an effect is a test that all the parameters associated with that effect are zero. Such joint tests might not be equivalent to Type 3 effect tests under GLM parameterization.

Contrast Estimate Results										
		Mean					L'Beta			
		Confidence Limits					Confidence Limits			
Label	**Mean Estimate**			**L'Beta Estimate**	**Standard Error**	**Alpha**			**Chi-Square**	**Pr > ChiSq**
M vs F	-0.0091	-0.0147	-0.0036	-0.0091	0.0028	0.05	-0.0147	-0.0036	10.32	0.0013
Other vs GP	-0.0109	-0.0252	0.0034	-0.0109	0.0073	0.05	-0.0252	0.0034	2.24	0.1342
Urban: Age-Group=1 vs Age-Group=5	-0.2059	-0.2219	-0.1899	-0.2059	0.0082	0.05	-0.2219	-0.1899	636.41	<.0001
Urban: Age-Group =2 vs Age-Group =5	-0.1160	-0.1277	-0.1044	-0.1160	0.0059	0.05	-0.1277	-0.1044	382.08	<.0001
Urban: Age-Group =3 vs Age-Group =5	-0.0403	-0.0516	-0.0291	-0.0403	0.0057	0.05	-0.0516	-0.0291	49.34	<.0001
Urban: Age-Group =4 vs Age-Group =5	-0.0341	-0.0448	-0.0233	-0.0341	0.0055	0.05	-0.0448	-0.0233	38.49	<.0001
Rural: Age-Group =1 vs Age-Group =5	-0.2352	-0.2699	-0.2006	-0.2352	0.0177	0.05	-0.2699	-0.2006	176.76	<.0001
Rural: Age-Group =2 vs Age-Group =5	-0.1532	-0.1784	-0.1281	-0.1532	0.0128	0.05	-0.1784	-0.1281	142.84	<.0001
Rural: Age-Group =3 vs Age-Group =5	-0.0867	-0.1098	-0.0636	-0.0867	0.0118	0.05	-0.1098	-0.0636	54.11	<.0001
Rural: Age-Group =4 vs Age-Group =5	-0.0488	-0.0709	-0.0267	-0.0488	0.0113	0.05	-0.0709	-0.0267	18.71	<.0001

Number of Inappropriate Prescriptions (45 days definition)

```
proc genmod data = number-inapp-30days;
class Sex(ref="F") UrbanRuralStatus Age-Group
PrescriberSpeciality(ref='GP')/param=ref;
model num-inapp = Age-Group Sex UrbanRuralStatus PrescriberSpeciality
 UrbanRuralStatus*Age-Group / dist=normal link=identity type3;
Estimate “M vs F” Sex 1 -1;
Estimate “Other vs GP” PrescriberSpeciality 1 -1;
Estimate “Urban: Age-Group=1 vs Age-Group=5” Age-Group 1 0 0 0 -1 UrbanRuralStatus*Age-
Group 0 0 0 0 0 1 0 0 0 -1;
Estimate “Urban: Age-Group =2 vs Age-Group =5” Age-Group 0 1 0 0 -1 UrbanRuralStatus*
Age-Group 0 0 0 0 0 0 1 0 0 -1;
Estimate “Urban: Age-Group =3 vs Age-Group =5” Age-Group 0 0 1 0 -1 UrbanRuralStatus*
Age-Group 0 0 0 0 0 0 0 1 0 -1;
Estimate “Urban: Age-Group =4 vs Age-Group =5” Age-Group 0 0 0 1 -1 UrbanRuralStatus*
Age-Group 0 0 0 0 0 0 0 0 1 -1;
Estimate “Rural: Age-Group =1 vs Age-Group =5” Age-Group 1 0 0 0 -1 UrbanRuralStatus*
Age-Group 1 0 0 0 -1 0 0 0 0 0;
Estimate “Rural: Age-Group =2 vs Age-Group =5” Age-Group 0 1 0 0 -1 UrbanRuralStatus*
Age-Group 0 1 0 0 -1 0 0 0 0 0;
Estimate “Rural: Age-Group =3 vs Age-Group =5” Age-Group 0 0 1 0 -1 UrbanRuralStatus*
Age-Group 0 0 1 0 -1 0 0 0 0 0;
Estimate “Rural: Age-Group =4 vs Age-Group =5” Age-Group 0 0 0 1 -1 UrbanRuralStatus*
Age-Group 0 0 0 1 -1 0 0 0 0 0;
run;
```

The GENMOD Procedure

Model Information	
Data Set	FOLDERS.FINALTHESISANALYSIS_45DAYS
Distribution	Normal
Link Function	Identity
Dependent Variable	num_inapp

Number of Observations Read	63517
Number of Observations Used	63517

Class Level Information					
Class	**Value**	**Design Variables**			
Sex	**F**	0			
	M	1			
UrbanRuralStatus	**Rural**	1			
	Urban	0			
Age_Group	**1**	1	0	0	0
	2	0	1	0	0
	3	0	0	1	0
	4	0	0	0	1
	5	0	0	0	0
PrescriberSpeciality	**GP**	0			
	Other	1			

Parameter Information					
Parameter	**Effect**	**Sex**	**UrbanRuralStatus**	**Age_Group**	**PrescriberSpeciality**
Prm1	Intercept				
Prm2	Age_Group			1	
Prm3	Age_Group			2	
Prm4	Age_Group			3	
Prm5	Age_Group			4	
Prm6	Sex	M			
Prm7	UrbanRuralStatus		Rural		
Prm8	PrescriberSpeciality				Other
Prm9	UrbanRural*Age_Group		Rural	1	
Prm10	UrbanRural*Age_Group		Rural	2	
Prm11	UrbanRural*Age_Group		Rural	3	
Prm12	UrbanRural*Age_Group		Rural	4	

The GENMOD Procedure

Criteria For Assessing Goodness Of Fit			
Criterion	**DF**	**Value**	**Value/DF**
Deviance	64E3	4774975.9454	75.1906
Scaled Deviance	64E3	63517.0000	1.0002
Pearson Chi-Square	64E3	4774975.9454	75.1906
Scaled Pearson X2	64E3	63517.0000	1.0002
Log Likelihood		-227318.2504	
Full Log Likelihood		-227318.2504	
AIC (smaller is better)		454662.5008	
AICC (smaller is better)		454662.5065	
BIC (smaller is better)		454780.2686	

Algorithm converged.

Analysis Of Maximum Likelihood Parameter Estimates									
Parameter			**DF**	**Estimate**	**Standard Error**	**Wald 95% Confidence Limits**		**Wald Chi-Square**	**Pr > ChiSq**
Intercept			1	4.0320	0.1237	3.7895	4.2745	1061.94	<.0001
Age_Group	1		1	-2.3150	0.2060	-2.7187	-1.9113	126.33	<.0001
Age_Group	2		1	-0.2701	0.1498	-0.5636	0.0235	3.25	0.0714
Age_Group	3		1	1.0977	0.1449	0.8137	1.3818	57.39	<.0001
Age_Group	4		1	-0.2156	0.1386	-0.4873	0.0560	2.42	0.1197
Sex	M		1	0.1690	0.0716	0.0286	0.3094	5.57	0.0183
UrbanRuralStatus	Rural		1	-0.4467	0.2907	-1.0165	0.1231	2.36	0.1244
PrescriberSpeciality	Other		1	-0.0071	0.1840	-0.3678	0.3535	0.00	0.9691
UrbanRural*Age_Group	Rural	1	1	0.0498	0.4916	-0.9136	1.0133	0.01	0.9193
UrbanRural*Age_Group	Rural	2	1	-0.8886	0.3565	-1.5873	-0.1899	6.21	0.0127
UrbanRural*Age_Group	Rural	3	1	-1.4599	0.3307	-2.1080	-0.8117	19.49	<.0001
UrbanRural*Age_Group	Rural	4	1	-0.1352	0.3164	-0.7553	0.4849	0.18	0.6691
Scale			1	8.6704	0.0243	8.6229	8.7182		

Note: The scale parameter was estimated by maximum likelihood.

LR Statistics For Joint Tests			
Source	**DF**	**Chi-Square**	**Pr > ChiSq**
Age_Group	4	421.63	<.0001
Sex	1	5.57	0.0183
UrbanRuralStatus	1	2.36	0.1244

The GENMOD Procedure

LR Statistics For Joint Tests			
Source	**DF**	**Chi-Square**	**Pr > ChiSq**
PrescriberSpeciality	1	0.00	0.9691
UrbanRural*Age_Group	4	52.49	<.0001

Note: Under full-rank parameterizations, Type 3 effect tests are replaced by joint tests. The joint test for an effect is a test that all the parameters associated with that effect are zero. Such joint tests might not be equivalent to Type 3 effect tests under GLM parameterization.

Contrast Estimate Results

Label	Mean Estimate	Mean Confidence Limits		L'Beta Estimate	Standard Error	Alpha	L'Beta Confidence Limits		Chi-Square	Pr > ChiSq
M vs F	-0.1690	-0.3094	-0.0286	-0.1690	0.0716	0.05	-0.3094	-0.0286	5.57	0.0183
Other vs GP	-0.0071	-0.3678	0.3535	-0.0071	0.1840	0.05	-0.3678	0.3535	0.00	0.9691
Urban: Age-Group=1 vs Age-Group=5	-2.3150	-2.7187	-1.9113	-2.3150	0.2060	0.05	-2.7187	-1.9113	126.33	<.0001
Urban: Age-Group =2 vs Age-Group =5	-0.2701	-0.5636	0.0235	-0.2701	0.1498	0.05	-0.5636	0.0235	3.25	0.0714
Urban: Age-Group =3 vs Age-Group =5	1.0977	0.8137	1.3818	1.0977	0.1449	0.05	0.8137	1.3818	57.39	<.0001
Urban: Age-Group =4 vs Age-Group =5	-0.2156	-0.4873	0.0560	-0.2156	0.1386	0.05	-0.4873	0.0560	2.42	0.1197
Rural: Age-Group =1 vs Age-Group =5	-2.2652	-3.1403	-1.3901	-2.2652	0.4465	0.05	-3.1403	-1.3901	25.74	<.0001
Rural: Age-Group =2 vs Age-Group =5	-1.1587	-1.7928	-0.5246	-1.1587	0.3235	0.05	-1.7928	-0.5246	12.83	0.0003
Rural: Age-Group =3 vs Age-Group =5	-0.3621	-0.9452	0.2209	-0.3621	0.2975	0.05	-0.9452	0.2209	1.48	0.2235
Rural: Age-Group =4 vs Age-Group =5	-0.3508	-0.9088	0.2071	-0.3508	0.2847	0.05	-0.9088	0.2071	1.52	0.2178

Percentage of Inappropriate Prescriptions (60 days definition)

```
proc genmod data=percent-inapp-30days;
class Sex(ref="F") UrbanRuralStatus Age-Group
PrescriberSpeciality(ref='GP')/param=ref;
model percent-inapp = Age-Group Sex UrbanRuralStatus PrescriberSpeciality
 UrbanRuralStatus*Age-Group / dist=normal link=identity type3;
Estimate “M vs F” Sex 1 -1;
Estimate “Other vs GP” PrescriberSpeciality 1 -1;
Estimate “Urban: Age-Group=1 vs Age-Group=5” Age-Group 1 0 0 0 -1 UrbanRuralStatus*Age-
Group 0 0 0 0 0 1 0 0 0 -1;
Estimate “Urban: Age-Group =2 vs Age-Group =5” Age-Group 0 1 0 0 -1 UrbanRuralStatus*
Age-Group 0 0 0 0 0 0 1 0 0 -1;
Estimate “Urban: Age-Group =3 vs Age-Group =5” Age-Group 0 0 1 0 -1 UrbanRuralStatus*
Age-Group 0 0 0 0 0 0 0 1 0 -1;
Estimate “Urban: Age-Group =4 vs Age-Group =5” Age-Group 0 0 0 1 -1 UrbanRuralStatus*
Age-Group 0 0 0 0 0 0 0 0 1 -1;
Estimate “Rural: Age-Group =1 vs Age-Group =5” Age-Group 1 0 0 0 -1 UrbanRuralStatus*
Age-Group 1 0 0 0 -1 0 0 0 0 0;
Estimate “Rural: Age-Group =2 vs Age-Group =5” Age-Group 0 1 0 0 -1 UrbanRuralStatus*
Age-Group 0 1 0 0 -1 0 0 0 0 0;
Estimate “Rural: Age-Group =3 vs Age-Group =5” Age-Group 0 0 1 0 -1 UrbanRuralStatus*
Age-Group 0 0 1 0 -1 0 0 0 0 0;
Estimate “Rural: Age-Group =4 vs Age-Group =5” Age-Group 0 0 0 1 -1 UrbanRuralStatus*
Age-Group 0 0 0 1 -1 0 0 0 0 0;
run;
```

The GENMOD Procedure

Model Information	
Data Set	FOLDERS.FINALTHESISANALYSIS_60DAYS
Distribution	Normal
Link Function	Identity
Dependent Variable	prop

Number of Observations Read	63517
Number of Observations Used	63517

Class Level Information					
Class	Value	Design Variables			
Sex	F	0			
	M	1			
UrbanRuralStatus	Rural	1			
	Urban	0			
Age_Group	1	1	0	0	0
	2	0	1	0	0
	3	0	0	1	0
	4	0	0	0	1
	5	0	0	0	0
PrescriberSpeciality	GP	0			
	Other	1			

Parameter Information					
Parameter	Effect	Sex	UrbanRuralStatus	Age_Group	PrescriberSpeciality
Prm1	Intercept				
Prm2	Age_Group			1	
Prm3	Age_Group			2	
Prm4	Age_Group			3	
Prm5	Age_Group			4	
Prm6	Sex	M			
Prm7	UrbanRuralStatus		Rural		
Prm8	PrescriberSpeciality				Other
Prm9	UrbanRural*Age_Group		Rural	1	
Prm10	UrbanRural*Age_Group		Rural	2	
Prm11	UrbanRural*Age_Group		Rural	3	
Prm12	UrbanRural*Age_Group		Rural	4	

The GENMOD Procedure

Criteria For Assessing Goodness Of Fit			
Criterion	**DF**	**Value**	**Value/DF**
Deviance	64E3	7705.2809	0.1213
Scaled Deviance	64E3	63517.0000	1.0002
Pearson Chi-Square	64E3	7705.2809	0.1213
Scaled Pearson X2	64E3	63517.0000	1.0002
Log Likelihood		-23135.2862	
Full Log Likelihood		-23135.2862	
AIC (smaller is better)		46296.5725	
AICC (smaller is better)		46296.5782	
BIC (smaller is better)		46414.3403	

Algorithm converged.

Analysis Of Maximum Likelihood Parameter Estimates									
Parameter			**DF**	**Estimate**	**Standard Error**	**Wald 95% Confidence Limits**		**Wald Chi-Square**	**Pr > ChiSq**
Intercept			1	0.4432	0.0050	0.4335	0.4530	7952.52	<.0001
Age_Group	1		1	-0.2109	0.0083	-0.2271	-0.1947	649.76	<.0001
Age_Group	2		1	-0.1203	0.0060	-0.1321	-0.1085	399.96	<.0001
Age_Group	3		1	-0.0421	0.0058	-0.0535	-0.0307	52.24	<.0001
Age_Group	4		1	-0.0358	0.0056	-0.0467	-0.0249	41.34	<.0001
Sex	M		1	0.0093	0.0029	0.0037	0.0149	10.46	0.0012
UrbanRuralStatus	Rural		1	-0.0205	0.0117	-0.0433	0.0024	3.07	0.0798
PrescriberSpeciality	Other		1	-0.0118	0.0074	-0.0263	0.0027	2.56	0.1095
UrbanRural*Age_Group	Rural	1	1	-0.0312	0.0197	-0.0699	0.0075	2.50	0.1138
UrbanRural*Age_Group	Rural	2	1	-0.0370	0.0143	-0.0651	-0.0090	6.68	0.0097
UrbanRural*Age_Group	Rural	3	1	-0.0480	0.0133	-0.0741	-0.0220	13.08	0.0003
UrbanRural*Age_Group	Rural	4	1	-0.0161	0.0127	-0.0410	0.0088	1.61	0.2052
Scale			1	0.3483	0.0010	0.3464	0.3502		

Note: The scale parameter was estimated by maximum likelihood.

LR Statistics For Joint Tests			
Source	**DF**	**Chi-Square**	**Pr > ChiSq**
Age_Group	4	1083.68	<.0001
Sex	1	10.46	0.0012
UrbanRuralStatus	1	3.07	0.0798

The GENMOD Procedure

LR Statistics For Joint Tests			
Source	**DF**	**Chi-Square**	**Pr > ChiSq**
PrescriberSpeciality	1	2.56	0.1095
UrbanRural*Age_Group	4	22.59	0.0002

Note: Under full-rank parameterizations, Type 3 effect tests are replaced by joint tests. The joint test for an effect is a test that all the parameters associated with that effect are zero. Such joint tests might not be equivalent to Type 3 effect tests under GLM parameterization.

Contrast Estimate Results

Label	Mean Estimate	Mean Confidence Limits		L'Beta Estimate	Standard Error	Alpha	L'Beta Confidence Limits		Chi-Square	Pr > ChiSq
M vs F	-0.0093	-0.0149	-0.0037	-0.0093	0.0029	0.05	-0.0149	-0.0037	10.46	0.0012
Other vs GP	-0.0118	-0.0263	0.0027	-0.0118	0.0074	0.05	-0.0263	0.0027	2.56	0.1095
Urban: Age-Group=1 vs Age-Group=5	-0.2109	-0.2271	-0.1947	-0.2109	0.0083	0.05	-0.2271	-0.1947	649.76	<.0001
Urban: Age-Group =2 vs Age-Group =5	-0.1203	-0.1321	-0.1085	-0.1203	0.0060	0.05	-0.1321	-0.1085	399.96	<.0001
Urban: Age-Group =3 vs Age-Group =5	-0.0421	-0.0535	-0.0307	-0.0421	0.0058	0.05	-0.0535	-0.0307	52.24	<.0001
Urban: Age-Group =4 vs Age-Group =5	-0.0358	-0.0467	-0.0249	-0.0358	0.0056	0.05	-0.0467	-0.0249	41.34	<.0001
Rural: Age-Group =1 vs Age-Group =5	-0.2421	-0.2773	-0.2070	-0.2421	0.0179	0.05	-0.2773	-0.2070	182.25	<.0001
Rural: Age-Group =2 vs Age-Group =5	-0.1574	-0.1828	-0.1319	-0.1574	0.0130	0.05	-0.1828	-0.1319	146.58	<.0001
Rural: Age-Group =3 vs Age-Group =5	-0.0901	-0.1135	-0.0667	-0.0901	0.0119	0.05	-0.1135	-0.0667	56.86	<.0001
Rural: Age-Group =4 vs Age-Group =5	-0.0519	-0.0743	-0.0295	-0.0519	0.0114	0.05	-0.0743	-0.0295	20.59	<.0001

Number of Inappropriate Prescriptions (60 days definition)

```
proc genmod data = number-inapp-30days;
class Sex(ref="F") UrbanRuralStatus Age-Group
PrescriberSpeciality(ref='GP')/param=ref;
model num-inapp = Age-Group Sex UrbanRuralStatus PrescriberSpeciality
 UrbanRuralStatus*Age-Group / dist=normal link=identity type3;
Estimate “M vs F” Sex 1 -1;
Estimate “Other vs GP” PrescriberSpeciality 1 -1;
Estimate “Urban: Age-Group=1 vs Age-Group=5” Age-Group 1 0 0 0 -1 UrbanRuralStatus*Age-
Group 0 0 0 0 0 1 0 0 0 -1;
Estimate “Urban: Age-Group =2 vs Age-Group =5” Age-Group 0 1 0 0 -1 UrbanRuralStatus*
Age-Group 0 0 0 0 0 0 1 0 0 -1;
Estimate “Urban: Age-Group =3 vs Age-Group =5” Age-Group 0 0 1 0 -1 UrbanRuralStatus*
Age-Group 0 0 0 0 0 0 0 1 0 -1;
Estimate “Urban: Age-Group =4 vs Age-Group =5” Age-Group 0 0 0 1 -1 UrbanRuralStatus*
Age-Group 0 0 0 0 0 0 0 0 1 -1;
Estimate “Rural: Age-Group =1 vs Age-Group =5” Age-Group 1 0 0 0 -1 UrbanRuralStatus*
Age-Group 1 0 0 0 -1 0 0 0 0 0;
Estimate “Rural: Age-Group =2 vs Age-Group =5” Age-Group 0 1 0 0 -1 UrbanRuralStatus*
Age-Group 0 1 0 0 -1 0 0 0 0 0;
Estimate “Rural: Age-Group =3 vs Age-Group =5” Age-Group 0 0 1 0 -1 UrbanRuralStatus*
Age-Group 0 0 1 0 -1 0 0 0 0 0;
Estimate “Rural: Age-Group =4 vs Age-Group =5” Age-Group 0 0 0 1 -1 UrbanRuralStatus*
Age-Group 0 0 0 1 -1 0 0 0 0 0;
run;
```

The GENMOD Procedure

Model Information	
Data Set	FOLDERS.FINALTHESISANALYSIS_60DAYS
Distribution	Normal
Link Function	Identity
Dependent Variable	num_inapp

Number of Observations Read	63517
Number of Observations Used	63517

Class Level Information					
Class	**Value**	**Design Variables**			
Sex	**F**	0			
	M	1			
UrbanRuralStatus	**Rural**	1			
	Urban	0			
Age_Group	**1**	1	0	0	0
	2	0	1	0	0
	3	0	0	1	0
	4	0	0	0	1
	5	0	0	0	0
PrescriberSpeciality	**GP**	0			
	Other	1			

Parameter Information					
Parameter	**Effect**	**Sex**	**UrbanRuralStatus**	**Age_Group**	**PrescriberSpeciality**
Prm1	Intercept				
Prm2	Age_Group			1	
Prm3	Age_Group			2	
Prm4	Age_Group			3	
Prm5	Age_Group			4	
Prm6	Sex	M			
Prm7	UrbanRuralStatus		Rural		
Prm8	PrescriberSpeciality				Other
Prm9	UrbanRural*Age_Group		Rural	1	
Prm10	UrbanRural*Age_Group		Rural	2	
Prm11	UrbanRural*Age_Group		Rural	3	
Prm12	UrbanRural*Age_Group		Rural	4	

The GENMOD Procedure

Criteria For Assessing Goodness Of Fit			
Criterion	**DF**	**Value**	**Value/DF**
Deviance	64E3	4914480.3677	77.3873
Scaled Deviance	64E3	63517.0000	1.0002
Pearson Chi-Square	64E3	4914480.3677	77.3873
Scaled Pearson X2	64E3	63517.0000	1.0002
Log Likelihood		-228232.8027	
Full Log Likelihood		-228232.8027	
AIC (smaller is better)		456491.6054	
AICC (smaller is better)		456491.6111	
BIC (smaller is better)		456609.3732	

Algorithm converged.

Analysis Of Maximum Likelihood Parameter Estimates									
Parameter			**DF**	**Estimate**	**Standard Error**	**Wald 95% Confidence Limits**		**Wald Chi-Square**	**Pr > ChiSq**
Intercept			1	4.1383	0.1255	3.8922	4.3843	1086.92	<.0001
Age_Group	1		1	-2.3809	0.2090	-2.7905	-1.9714	129.83	<.0001
Age_Group	2		1	-0.3044	0.1520	-0.6022	-0.0066	4.01	0.0451
Age_Group	3		1	1.1043	0.1470	0.8162	1.3924	56.43	<.0001
Age_Group	4		1	-0.2372	0.1406	-0.5128	0.0384	2.85	0.0916
Sex	M		1	0.1747	0.0727	0.0323	0.3171	5.78	0.0162
UrbanRuralStatus	Rural		1	-0.4579	0.2949	-1.0359	0.1202	2.41	0.1206
PrescriberSpeciality	Other		1	-0.0035	0.1867	-0.3694	0.3624	0.00	0.9851
UrbanRural*Age_Group	Rural	1	1	0.0477	0.4987	-0.9298	1.0251	0.01	0.9239
UrbanRural*Age_Group	Rural	2	1	-0.8967	0.3616	-1.6055	-0.1879	6.15	0.0132
UrbanRural*Age_Group	Rural	3	1	-1.4967	0.3355	-2.1542	-0.8392	19.90	<.0001
UrbanRural*Age_Group	Rural	4	1	-0.1445	0.3210	-0.7736	0.4845	0.20	0.6525
Scale			1	8.7962	0.0247	8.7479	8.8447		

Note: The scale parameter was estimated by maximum likelihood.

LR Statistics For Joint Tests			
Source	**DF**	**Chi-Square**	**Pr > ChiSq**
Age_Group	4	428.17	<.0001
Sex	1	5.78	0.0162
UrbanRuralStatus	1	2.41	0.1206

The GENMOD Procedure

LR Statistics For Joint Tests			
Source	DF	Chi-Square	Pr > ChiSq
PrescriberSpeciality	1	0.00	0.9851
UrbanRural*Age_Group	4	53.04	<.0001

Note: Under full-rank parameterizations, Type 3 effect tests are replaced by joint tests. The joint test for an effect is a test that all the parameters associated with that effect are zero. Such joint tests might not be equivalent to Type 3 effect tests under GLM parameterization.

Contrast Estimate Results										
		Mean Confidence Limits					L'Beta Confidence Limits			
Label	Mean Estimate			L'Beta Estimate	Standard Error	Alpha			Chi-Square	Pr > ChiSq
M vs F	-0.1747	-0.3171	-0.0323	-0.1747	0.0727	0.05	-0.3171	-0.0323	5.78	0.0162
Other vs GP	-0.0035	-0.3694	0.3624	-0.0035	0.1867	0.05	-0.3694	0.3624	0.00	0.9851
Urban: Age-Group=1 vs Age-Group=5	-2.3809	-2.7905	-1.9714	-2.3809	0.2090	0.05	-2.7905	-1.9714	129.83	<.0001
Urban: Age-Group =2 vs Age-Group =5	-0.3044	-0.6022	-0.0066	-0.3044	0.1520	0.05	-0.6022	-0.0066	4.01	0.0451
Urban: Age-Group =3 vs Age-Group =5	1.1043	0.8162	1.3924	1.1043	0.1470	0.05	0.8162	1.3924	56.43	<.0001
Urban: Age-Group =4 vs Age-Group =5	-0.2372	-0.5128	0.0384	-0.2372	0.1406	0.05	-0.5128	0.0384	2.85	0.0916
Rural: Age-Group =1 vs Age-Group =5	-2.3333	-3.2211	-1.4455	-2.3333	0.4530	0.05	-3.2211	-1.4455	26.53	<.0001
Rural: Age-Group =2 vs Age-Group =5	-1.2011	-1.8444	-0.5578	-1.2011	0.3282	0.05	-1.8444	-0.5578	13.39	0.0003
Rural: Age-Group =3 vs Age-Group =5	-0.3924	-0.9839	0.1991	-0.3924	0.3018	0.05	-0.9839	0.1991	1.69	0.1935
Rural: Age-Group =4 vs Age-Group =5	-0.3817	-0.9477	0.1843	-0.3817	0.2888	0.05	-0.9477	0.1843	1.75	0.1863