12-10-2020 9:40 AM

Population-based Studies on Medications and Fall-related Injury in Older Adults

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A thesis submitted in partial fulfillment of the requirements for the Doctor of Philosophy degree in Health and Rehabilitation Sciences

Abstract

Background: Fall-related injuries in older adults result in serious consequences to individuals and health care system, especially with the increasing aging population. The purpose of this study was to (1) describe medication prescription patterns within one year prior to fall-related injuries; (2) identify medication classes prescribed within 30 days prior to the injury that were associated to fall-related injury; and (3) examine the association between fall-related injuries and continuous use or new initiation of most commonly prescribed medications.

Methods: Studies used administrative health care data in Ontario. Study 1 described the frequency of medications prescribed to older adults within one year before they had fall-related injuries. Study 2 and 3 were case-control studies. The cases were older adults aged 66 years and older, who had a fall-related injury between January 2010 and December 2014. Controls were older adults with same age, sex and residence area as the cases. In study 2, medications prescribed to both groups were recorded and logistic regression was conducted to examine the association between medications and injuries. Study 3 defined continuous use as medication use for more than 90 days and new initiation was defined as starting a medication within 30 days prior to injuries. Logistic regression was conducted to examine the association between injuries and continuous use or new initiation of medications.

Results: Within one year before the injury, 27.2% of older adults were prescribed antidepressants, 25.0% opioids, 16.6% anxiolytics, and 36.4% were prescribed 5-9 medications and 41.2% were prescribed 10 or more medications. After adjustment for sex, age group, residence area, income and number of medications prescribed, laxatives, antibiotics and bronchodilators were identified to increase the risk of fall-related injury. Continuous use of antidepressants, anticholinesterases and antithrombin agents and new initiation of antidepressants, opioids and cephalosporins were reported to increase the risk for injuries.

Conclusion: Findings of this thesis uncovered several medication classes such as antibiotics and bronchodilators were associated with increased risk of fall-related injury. Both,

continuous use and new initiation of particular medication classes were associated with injuries. Well-designed prospective cohort studies are needed to provide more convincing evidence.

Keywords

medication prescription, continuous use, new initiation, fall-related injuries, older adults

Summary for Lay Audience

Fall-related injuries in older adults can result in serious harm to individuals and health care system, especially with the world increasing aging population. The purpose of this study was to (1) describe the types of medications older adults used within one year before they experienced a fall that resulted in an injury; (2) identify if medications prescribed within 30 days before the fall that were associated with increased the risk of fall-related injury; and (3) find out whether continuous use of a medication or start of a new medication were associated with increased the risk of fall-related injury. Data was extracted from databases hosted by IC/ES. We recorded the medication prescribed to older adults and calculate the percentage of medication users. Our result was, within one year before the injury, 27.2% of older adults used antidepressants, 25.0% opioids, 16.6% anxiolytics, 36.4% used 5-9 different medications and 41.2% used 10 or more different medications. Then we used case-control study design and logistic regression to find out the possibility of having fall-related injury when an older adult took certain kind of medication. We also identified the possibility of having fall-related injuries when an older adult took certain kind of medication for over 90 days or start a new medication within 30 days prior to the injury. After taking sex, age group, residence area, income level and number of medications used into consideration, we found that users of laxatives, antibiotics and inhaled medications for asthma were more likely to have fall-related injury. Continuous use of antidepressants, medications for dementia and blood thinners and new initiation of antidepressants, opioids and cephalosporins were associated with increased risk for fall-related injuries. Findings of this thesis uncovered several medication classes such as antibiotics and bronchodilators that were associated with increased risk of fall-related injury, which was not reported in previous studies. It was also suggested that continuous use and new initiation of particular medication classes were associated with injuries. Well-designed cohort studies are needed in the future to provide more convincing evidence.

Co-Authorship Statement

I, Yu Ming, acknowledge that the three manuscripts (Chapters 2, 3 and 4) included in this dissertation resulted from collaborations with coauthors. In all three articles the primary intellectual contributions were from the first author, Yu Ming who conducted literature reviews, developed the ethics approval application, developed research data creation plan (DCP), designed the research methodologies, collected data, extraction and analyses, drafted and revised the manuscript.

Members of thesis advisory committee: Dr Aleksandra A. Zecevic (Supervisor), Dr Robert G. Booth, Dr Susan W. Hunter, Dr Rommel G. Tirona and Dr Andrew M Johnson met regularly to provide guidance and support as well as editing for publication.

Study 1 (Chapter 2): Medication prescribed within one year prior to fall-related injuries in Ontario older adults. *Canadian Journal on Aging*, Submitted on Oct 7th, 2020.

Yu Ming and Dr Aleksandra A. Zecevic shared the conception of this study. Yu Ming's sole contribution to this study is 75%. Dr Zecevic revised the manuscript critically for important intellectual content and gave final approval of the version to be published. Dr Richard G. Booth provided his professional guidance in dealing with secondary datasets, analyzing and interpreting the results. He revised the manuscript critically for important intellectual content. Dr Susan W. Hunter provided her guidance in analyzing the data and interpreting the results. She revised the manuscript critically for the method, result and discussion section. Dr Rommel G. Tirona provided his professional guidance in classifying medications and interpreting the results. Dr Andrew M. Johnson provided his professional guidance in analyzing the data and interpreting the results. All the authors gave final approval of the version to be published.

Study 2 (Chapter 3): Association between fall-related injuries and medication classes prescribed to older adults within one month prior to the injury. *Clinical Intervention on Aging*, submitted on Sep 9th, 2020.

Yu Ming and Dr Zecevic conceptualized the design and method of this case-control study, Yu Ming contributed 75% of the work of this study. Dr Zecevic provided guidance in designing the study, extracting data and analyzing the results. She revised the manuscript critically for important intellectual content. Dr Booth provided his guidance in extracting data, analyzing and interpreting the results. He provided his valuable experience in dealing with IC/ES database and publications. Dr Hunter provided her guidance in analyzing the data and interpreting the results. Dr Tirona provided his valuable background information about different medication classes and his guidance in interpreting the results. Dr Johnson provided his guidance in analyzing the data and interpreting the results. Dr Zecevic, Dr Booth, Dr Hunter, Dr Tirona and Dr Johnson revised the manuscript critically for important intellectual content and gave final approval of the version to be published.

Study 3 (Chapter 4): Association between continuous use or new initiation of medications and fall-related injuries in older adults

Yu Ming and Dr Zecevic conceptualized the design and method of this case-control study, Yu Ming contributed 75% of the work of this study. Dr Zecevic provided guidance in designing the study, extracting data and analyzing the results. She revised the manuscript critically for important intellectual content. Dr Booth provided his guidance in extracting data, analyzing and interpreting the results. He provided his valuable experience in dealing with IC/ES database and publications. Dr Hunter provided her guidance in analyzing the data and interpreting the results. Dr Tirona provided his valuable background information about different medication classes and provided his guidance in interpreting the results. Dr Johnson provided his guidance in analyzing the data and interpreting the results. Dr Zecevic, Dr Booth, Dr Hunter, Dr Tirona and Dr Johnson are in the process of revising the manuscript critically for important intellectual content.

Acknowledgments

First and foremost, I would like to express my extremely sincere gratitude to my supervisor, Dr Aleksandra Zecevic, for her consistent guidance and support during my Ph.D. studies. I cannot even adequately express the thankfulness that I have for what you have contributed not only to my professional development, but to my personal growth as well. You are an outstanding researcher and supervisor. Thank you for encouraging me, for challenging me, for comforting me, for caring about me in every aspect, and for providing me with many opportunities. Your professionalism on research, excellent communication skills, open attitude about novelty and the unknown, and your optimism have benefited me and influenced me very deeply. I am so thankful that when I first landed on this new country, and also this new academic world, you provided me with your generous knowledge and selfless support. You made me feel that I made a right decision on my own life and on my children's life to immigrate to Canada. I feel very appreciative that you arranged weekly individual meetings with me to talk about my research progress, you responded so quickly to every question that I proposed and understood me when I needed support. Moreover, I received excellent training on qualitative and quantitative research and gained indispensable experience through working with you. I hope that we could be friends forever and the learning process from each other will never end.

I would like to thank Dr Richard G. Booth, one of my advisory committee members, for your strategic wisdom and professionalism in dealing with big data. This thesis would not have been possible without your tremendous guidance and support. I am so grateful that you guided and helped me during drafting the data creation plan, analyzing the data and submitting the manuscripts for publication. You are so generous in providing your experience in working with IC/ES, sharing your tips on managing data and giving me feedbacks and advice on my writing. It was so amazing and relaxing to know that you would always be there to help me if I got stuck, to push me a little bit further, and to always have my back.

I would also like to thank Dr Susan W. Hunter, one of my advisory committee members, for your extensive expertise in quantitative studies. You are always so straight and concise to the point when giving me comments and suggestions. Dr Rommel G. Tirona, thank you very much for your professional support on medications and for being so patient and tolerant with me. Dr

Andrew M Johnson, thank you so much for providing me with your expertise in using statistical computing software such as R and SAS. I hope I could have the chance in the future to learn more from you.

There are a lot of other faculty and staff members I would like to extend my deepest appreciation for all of their assistance throughout my academic career, especially Roxanne Isard, John Constella and Emericks Rivas. Your passionate support and professionalism benefited me so much in my graduate study.

Special acknowledgement goes to my thesis examination committee members. Thank you very much for reviewing my thesis and challenging me with insightful ideas to improve.

Finally, I would like to express my deepest gratitude to my family. Dad, hope your girl would never let you down. I will miss you forever. Thank you very much, mom, for always being there in my life. I really appreciate it that you have worked so hard to show your love for us in the most selfless way. Thank you, my husband, for being supportive to me all the time. Thank you for letting me to pursue my dreams without being worried about the burden of life itself. Thank you, my kids. You are definitely my greatest achievement in life.

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List of Abbreviations

Acronyms	In Full
ACEIs	Angiotensin-Converting Enzyme Inhibitors
ADRs	Adverse Drug Reactions
aORs	Adjusted Odds Ratios
ARBs	Angiotensin II Receptor Blockers
ATC	Anatomical Therapeutic Chemical
BBs	Beta-Blocking Agents
BPH	Benign Prostatic Hyperplasia
CCBs	Calcium Channel Blockers
CIs	Confidence Intervals
CIHI	Canadian Institute for Health Information
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Diseases
DINs	Drug Identification Numbers
DCP	Data Creation Plan
ED	Emergency Department
FRID	Fall Risk-Increasing Drug
GERD	Gastro-esophageal Reflux Disease
ICD	International Classification of Diseases
IC/ES	Institute for Clinical Evaluative Sciences
IRR	Incidence Rate Ratio
LHINs	Local Health Integration Networks
NACRS	National Ambulatory Care Reporting System
NSAIDs	Non-steroid anti-inflammatory drugs
ODB	Ontario Drug Benefit
OR	Odds Ratio
PAR	Population Attributable Risk
PHAC	Public Health Agency of Canada
PPI	Proton pump inhibitor
RAS	renin-angiotensin system
RPDB	Registered Persons Database
SSRIs	Selective serotonin reuptake inhibitors
Swedish NBHW	Swedish National Board of Health and Welfare
TBI	Traumatic brain injury
TCAs	Tricyclic antidepressants
WHO	World Health Organization
WHOCC	World Health Organization Collaborating Centre

Chapter 1

1 Introduction

1.1 World Aging Population

Ageing is an inevitable process of living and, conventionally, it is measured by chronological age where people who are 65 years or older are referred to as "older adults" (Orimo et al., 2006; World Health Organization [WHO], 2020). Although the ageing process is not homogeneous across the world due to different genetics, lifestyles, overall health and environment, most developed countries in the world have accepted the definition of older adults as people who are 65 years or older. In recent years, steady progress has been made in reducing mortality in the early and middle years of life, which led to the dramatic increase of ageing population globally. Better sanitation, improvements in housing, education and nutrition, advances in preventive and therapeutic medicine all contribute to a longer life expectancy (Kirkwood, 2017).

In 2019, the world population aged 65 years and older was almost 700 million (World Bank, 2020), which constitutes 9.1% of the total population. According to WHO report, there were 900 million people 60 years and older in 2015, but in 2050, the number is expected to increase to 2 billion. For people who are 80 years and older, the world-wide numbers will be increasing from 125 million in 2015 to 434 million in 2050 (WHO, 2018a). Population trends are similar in Canada and the province of Ontario. The number of people aged 65 and over in Ontario is projected to almost double from 2.4 million (16.9% of population) in 2018 to 4.6 million (23.4%) by 2046 (Ontario Ministry of Finance, 2020).

An ageing world brings many opportunities as well as challenges, not only for older adults and their families, but for the society as well. A longer life provides a chance for pursue of new lifestyles and more contribution to families and communities. But if the extended lifespan is dominated by chronic comorbidities, reduced mobility and declined mental capacity, the implications of longer life for older adults and the society are rather negative. Falls in older adults are one of the major public health concerns because falls

can lead to loss of functional ability and independence, increased admissions or re-admissions to health care facilities and hospitals, and inestimable medical and social costs (Alexander & Hunter, 2017; Masud & Morris, 2001).

1.2 Falls and Fall-Related Injuries in Older Adults

A fall is defined by WHO as "an event which results in a person coming to rest inadvertently on the ground or floor or other lower level" (WHO, 2018b). Nearly one third of older adults fall every year globally (Chang et al., 2010; Tinetti et al., 2006), but the rate of falls varied in different regions, with a prevalence of about 20% in China (Wu & Ouyang, 2017), Japan (Tanimoto et al., 2014) and Canada (Pearson et al., 2014), 29% in US (Bergen et al., 2016) and 30-35% in European countries (National Institute of Prevention and Health Education, 2008; Rapp et al., 2014; Sandmark et al., 2012). The rate of falls increases with age, with nearly 50% of older adults who are 80 years and older experiencing a fall each year (de Negreiros Cabral et al., 2013; Rubenstein & Josephson, 2002).

Falls are the leading cause of fatal and non-fatal injury in older adults (Bergen et al., 2016; Public Health Agency of Canada [PHAC], 2014). Falls account for 40% of all injury-related deaths (WHO, 2007) and more than 80% of all injury-related hospital admissions (Kannus et al., 2006; Peel et al., 2002). Between 30-50% falls result in minor injuries, such as bruises or lacerations, while 5-10% of falls lead to serious injuries such as fractures or traumatic brain injury (Cameron et al., 2012; Gillespie et al., 2012; Goldacre et al., 2002; Health Quality Ontario, 2008; Masud & Morris, 2001; Rubenstein & Josephson, 2002). An estimated 7 million older adults in US reported a fall-related injury in 2014 (Bergen et al., 2016). In 2017, 8.4 million older adults in Western European regions (22 countries including France, Germany, Greece, Italy, etc) sought medical attention due to a fall-related injury, and about 54,000 older adults died of fall-related injury (Haagsma et al., 2020). In 2009-2010, a total of 256,011 Canadian older adults reported a fall-related injury, where 35% were fractures, 30% sprains or strains, 19% scrapes, bruises or blisters, 6% cuts or punctures, 3% dislocations, 2% concussions and brain injury, and 5% other injury (PHAC, 2014).

Although there is substantial of research published on "fall-related injury", or "injurious fall" or "fall injury", a lack of standardized definition of a "fall-related injury" has been reported repeatedly as a major methodological limitation, especially when comparing outcomes of different studies (Lamb et al., 2005; Hauer et al., 2006; Schwenk et al., 2012). Some studies used fractures, especially hip fracture, as a proxy for the fall-related injury (Tanaka et al., 2018; Wong et al, 2020). However, this definition ignores a wide range of injuries, such as head and internal injuries, which can also lead to serious consequences requiring higher level of care, such as hospitalizations. The continuous improvements in healthcare system and enhanced reliability of injury reporting systems through administrative databases, identifying fall-related injury based on the healthcare service use became a practical and credible way to study this topic (Campbell et al., 1997; Elley et al., 2008; Schwenk et al., 2012). In this thesis, fall-related injury was operationally defined as any injury caused by a fall that resulted in an admission to the Emergency Department (ED) or hospital. Different fall-related injury types include: superficial injuries, open wounds, fractures, dislocations, sprains or strains of joints and ligaments, nerve injuries, blood vessels injuries and injuries to internal organs (Canadian Institute of Health Information [CIHI], 2018a; WHO, 2019).

On an individual level, besides the immediate suffering from a fall-related injury, common adverse consequences are fear of falling (Pereira et al., 2020), reduced quality of life (Gill et al., 2013; Boyé et al. 2013), higher possibility of admission to long-term care (Gill et al., 2013), prolonged hospital stays (PHAC, 2014), and increased risk of death (Skelton & Todd, 2004; Stevens et al., 2006). On a societal level, fall-related injuries pose a substantial economic burden to the public health care system. In 2004, the estimated cost of fall-related injuries among Canadian older adults was more than $2 billion Canadian dollars (Scott et al., 2010). Florence and his colleagues reported that, in 2015, the estimated medical costs related to both fatal and nonfatal falls was approximately US $50 billion US dollars. For non-fatal falls, Medicare paid $28.9 billion, Medicaid $8.7 billion and private and other payers $12.0 billion. Overall medical spending for fatal falls was estimated to be $754 million US dollars (Florence et al., 2018). In 2006-2007, the direct cost of fall-related injury was estimated at $558.5 million in New South Wales, Australia, and the cost of hospital admissions accounted for 84.6%

of the total cost (Watson et al., 2011). The financial burden of fall-related injuries is substantial and global.

Despite significant advances in fall and fall-related injury prevention research, increasing implementation of fall prevention practices, and enhanced consciousness of individuals' safety and self-protection, the trend of fall-related injuries around the world remains unclear. Watson and Mitchell (2011) observed a hospitalization rate due to falls increased by 1.7% each year from 1998-2008 in New South Wales, Australia, but the rate of fractures resulting from falls declined by −0.4% and the non-fracture rate increased by 6.1% per year. In 2001-2010, a decreasing incidence was observed in the Swedish older adults in younger age groups (65-79 years), with greater decreases in females (14.6% in females vs 10.5% in males), while an increasing trend of hospitalized fall-related injuries was observed in 80 years and older age group (Nilson et al., 2016), with greater increases in males (4.3% in females vs 11.4% in males). Superficial injuries showed greater increases than fractures in those aged 80 years and above (Nilson et al., 2016). Even after controlling for US population growth, ED visit rates for falls continued to grow (Shankar et al., 2017). Between 2003 and 2010, the ED visit rate for falls and fall-related injuries in American older adults increased from 60.4 to 68.8/1,000 population. Older adults aged 75-84 years accounted for the greatest rate increase, with ED visit rates increasing from 56.2 to 82.1/1,000 population (Shankar et al., 2017). In Canada, the number of older adults who reported a fall-related injury increased from 47.2 per 1,000 population in 2003 to 57.5 per 1,000 population in 2009/2010 (PHAC, 2014).

Due to rapid growth of aging population around the world, undesirable consequences of fall-related injuries and complex trends in different injury types across countries, it is of great importance to further research on fall-related injuries so that practical and individualized fall prevention protocols could be developed and implemented efficiently.

1.2.1 Risk factors for falls and fall-related injury

Unclear trends in the older adult population and increased aging population make fall-related injury a major health concern. Even after assuming that the falls rates for age and gender remain constant overtime, a forecasted 55% increase in the number of older

people between 2014 and 2030 in US, would result in 48.8 million falls and 11.9 million injuries in 2030 (Bergen et al., 2016), unless there are effective prevention programs implemented national wide. A thorough investigation of risk factors and mechanism of falls and fall-related injuries is necessary for creating meaningful injury prevention programs.

Fortunately, falling is not a normal part of aging and can be prevented at some occasions. Although the present research is about injury, it is inevitable to reflect little deeper into immediate cause of injury – the fall. Multiple risk factors are proved to be associated with falls and they are categorized as biological, behavioral, environmental and socioeconomic (WHO, 2007). Some of the risk factors are difficult to change while others are modifiable. Biological risk factors such as age, gender, race and socioeconomic risk factors such as low income and education levels, inadequate housing, limited access to health and social care are non-modifiable or very difficult to change. But, there are risk factors that are potentially modifiable, for example, physical or cognitive alteration due to aging (biological), excess alcohol use, sedentary lifestyle, intake of multiple medications (behavioral), slippery floor or stairs, insufficient lighting or uneven sidewalks (environmental).

Fall-related injury, on the other hand, was often entangled with falls in previous studies. Risk factors for fall-related injury have yet to be reported systematically. History of falls (Ravindran & Kutty, 2016), psychotropic medication (Haasum & Johnell, 2017; Johnell et al., 2017; Yu et al., 2017), anti-hypertensive agents (Shimbo et al., 2016), nutritional condition (Sim et al., 2018), multiple chronic diseases (Cartagena et al. 2017), and depression (Kvelde et al., 2015; Ravindran & Kutty, 2016) were among the risk factors previously reported to be associated with fall-related injury after the age of 65. Both a fall or fall-related injury are a result of complex interactions of risk factors requiring multifactorial prevention strategies.

Interventions reported to be effective in lowering the risk of fall-related injuries include physical exercise to improve balance (Hill, 2018), managing chronic diseases (Chang et al., 2004; Cheng et al., 2018), visual impairment (Reed-Jones et al., 2011), and changing

personal behaviors (Larsson et al., 2010). Many countries and health organizations have declared the prevention of falls in older adults as an important health priority (Lamb et al., 2005; Skelton & Todd, 2004; the Canadian Patient Safety Institute, 2015; WHO, 2007). It is forecasted that achieving a 20% reduction in falls between 2010 and 2035 among adults aged 65 years and older in Canada would save 4,400 lives and avoid a total cost of $10.8 billion Canadian dollars (Parachute, 2015).

1.3 Medication Use in Older Adults

Older adults are the largest consumers of prescription medications worldwide. In US, older adults comprised 13% of total population, but accounted for 34% of the prescription medication use and 30% of over-the-counter medication use (National Council on Patient information and Education, 2020). About 87% of older adults took one or more prescription medications, and 36% took at least five medications concurrently (Qato et al., 2016). CIHI reported that older adults made up only 17% of the total population in Canada, but they accounted for almost 40% of all spending on prescription medications and 55% of public drug program spending (CIHI, 2018b).

Medications play crucial role in older adults' health by effectively treating the chronic diseases, alleviating pain and increasing quality of life. However, physiological changes in the aging body and polypharmacy make older adults susceptible to adverse drug reactions (ADRs) that could lead to falls and fall-related injury.

1.3.1 Pharmacodynamics and pharmacokinetics of drugs in an aging body

The premarketing clinical drug trials usually exclude elderly participants, thus the pharmacokinetics (i.e., medication's absorption, distribution, metabolism and excretion) and pharmacodynamics (i.e., the physiologic effects of the medication) are unknown or unclear in older adults. Research shows that drug absorption is reduced in the older adults due to decreased gastrointestinal blood flow, loss of mucosal intestinal surface and reduced gastric acidity (Hughes, 1998; Mangoni & Jackson, 2004). Moreover, the weakening gastrointestinal movement and slower gastric emptying time increases the medication absorption (Mangoni & Jackson, 2004). These are just some complex factors

that make it difficult to evaluate the medication absorption in older adults. But there are more.

With advancing age, the total body fat increases 18-36%, while the muscle mass decreases by 30% (Vestal, 1997; Thürmann, 2020). These changes result in a prolonged half-life (i.e., the time that a medication decreases to half of its starting concentration in the body) of lipophilic drugs such as antidepressants, long-acting benzodiazepines and antiepileptics. This means that the time medications exert their therapeutic effect and adverse effects increases (Hammerlein et al., 1998; Thürmann, 2020). Similarly, the body water content in older adults shrinks by 15-20% (Reeve et al., 2015), resulting in an apparent decrease in the distribution volume of medications such as digoxin, diuretics and lithium (Huang et al., 2012). Dosage reductions must be considered to avoid potential toxicity of these drugs (Hammerlein et al., 1998; Cusack, 2004). The serum albumin usually declines by 15-20% in frail or malnourished older adults (Cusack, 2004), which increases the plasma concentration of free (unbound part to protein) or active fraction of some medications. The effect of highly protein-bound medications, such as phenytoin, diazepam and valproic acid, in a reduced serum albumin environment is enlarged.

Usually, there are no abnormal changes in hepatic function indexes as the body ages, but the activity of hepatic metabolism of esterase is decreased which results in prolonged half-lives of medications such as metoprolol, morphine and verapamil (Kinirons & O'Mahony, 2004; Le Couteur et al., 2012). The age-related reduction in liver parenchymal cells and a decrease of liver blood flow also affect the liver's ability to metabolize drugs (Kinirons & O'Mahony, 2004; Le Couteur et al., 2012). A combination of these factors further compounds the drug clearance ability in older adults, causing drug effect enhancement and more potential for adverse reactions.

Further, drug excretion in older adults declines due to reduced kidney mass, renal blood flow, glomerular filtration rate and tubular secretion rate (Huang et al., 2012). Estimated GFR can adequately represent the elimination of drugs through kidney function and the dosage of medications can be adjusted according (Reeve et al., 2015).

What is more, genetics, lifelong living habits and environmental factors can lead to high heterogeneity in pharmacokinetics and pharmacodynamics of drugs among older adults (Huang et al., 2012). It is unlikely that a frail 90-year-old man with multiple chronic diseases and a robust, healthy 70-year-old man would have the same response to a specific drug or dosage. The heterogeneity in later life and reduced homeostasis further increase the complexity of managing medication therapy and ADRs in older adults.

1.3.2 Polypharmacy

Polypharmacy is defined as concurrent use of multiple medications by a patient. However, there is no agreement or standard to the exact minimum number of medications that define 'polypharmacy', and suggestions vary from 2 to 11 medications (Ferner & Aronson, 2006; Masnoon et al., 2017). Although polypharmacy usually refers to the use of prescribed medications, it is also necessary to consider the number of over-the-counter and herbal supplements used by the patient.

Older adults often use multiple medications due to co-existence of several chronic diseases (Crentsil et al., 2010). Gao and his colleagues (Gao et al., 2018) reported that during the study period of 1991-1994 the number of older adults in England who were taking five or more drugs concurrently was 1 in 8 (12%), but from 2008-2011, this rate increased dramatically to nearly 1 in 2 (49.6%). In 2016, 65.7% of Canadian older adults took five or more prescription drugs and 26.5% older adults took ten or more different prescription drugs (CIHI, 2018b).

Although sometimes polypharmacy is deemed necessary and appropriate, it increases the potential of drug-drug interactions and risk of ADRs (Weng et al., 2013). Polypharmacy also leads to problems with adherence, especially when older adults have visual or cognitive impairment (Wimmer et al., 2017). Older adults who receive care from different physicians and specialists, and those who fill their prescriptions at different pharmacies, can exaggerate the effect of polypharmacy by using medications with similar therapeutic purpose or increased dosage (Kuo et al., 2014).

Pharmacological changes of drugs in an aging body and polypharmacy predispose older adults to an increased risk of falls, injuries, hospital admissions and diminished quality of life (Chen et al., 2014; Chung, 2014; Huang et al., 2012; Rowe, et al., 1976; Tan et al., 2015). Report from CIHI indicate that in 2011, one in 200 Canadian older adults was hospitalized as a result of ADRs, and 2.8% of all hospitalizations of older adults were due to ADRs (CIHI, 2013).

1.4 Medications and Fall-related Injury

Since 1980s, researchers began to pay attention to the association between medications and falls. Several observational studies reported that benzodiazepines, antipsychotics (most of them were tranquillizers), and tricyclic antidepressants were associated with increased risk of falls and hip fracture in older adults (Davie et al., 1981; Macdonald, 1985; Ray et al., 1987; Tinetti et al., 1988). The concept that drugs might increase the risk of falls was first proposed by Cumming and colleagues in 1991. The authors created a list of medications that included diuretics and psychotropics (Cumming et al., 1991). In 2007, van der Velde and colleagues presented a list of drugs associated with increased risk of falls according to previous studies, and it was the first time the acronym FRID for fall risk-increasing drugs was used (van der Velde et al., 2007). The National Board of Health and Welfare (NBHW) in Sweden produced an updated FRID list in 2010, and an additional list of medications that cause or worsen orthostatic blood pressure, known as a relevant fall risk factor (the Swedish NBHW, 2010). This FRIDs list used Anatomical Therapeutic Chemical (ATC) codes proposed by WHO to identify medication classes (Appendix A). Although there is no consensus on which medications should be included in FRID list, most studies recognize psychotropic medications such as opioids (N02A), antiepileptics (N05A), anxiolytics (N05B), hypnotics and sedatives (N05C) and antidepressants (N06A) as FRIDs (Axmon et al., 2018; Winter et al., 2016; Zia et al., 2017).

FRIDs are important independent risk factors for both falls and fall-related injury and had been studied extensively. Psychotropic medications can be defined as a class of drugs that can cross the blood-brain barrier and act directly on the central nervous system (CNS) (Bloch et al., 2010; Hill & Wee, 2012; Kawakami et al., 2019). Common psychotropic

drugs include antiepileptics, anti-Parkinson agents, anxiolytics, hypnotics, antipsychotics, antidepressants and drugs used in dementia. A substantial proportion of older adults use one or more psychotropic drugs, from 20% of community-dwelling older adults (Du et al., 2017; Préville et al., 2001) to nearly 80% of older adults lived in long-term care facilities (Galik & Resnick, 2013; Mann et al., 2009). A series of systematic reviews conducted in 2018 summarized the association between common medication classes and falls, fall-related injuries, and recurrent falls in older adults (de Vries et al., 2018; Seppala, Wermelink, et al., 2018; Seppala, van de Glind, et al., 2018). Older adults using opioids were 78% more likely to have a fall-related injury (five-study pooled adjusted OR [aOR]=1.78, 95%CI [1.54-2.06]; I^2=85%). Antidepressants were associated with increasing the risk of fall-related injury by 72% (five-study pooled aOR=1.72, 95%CI [1.51-1.95], I^2=72%). Benzodiazepines were associated with increasing the risk of fall-related injury by 70% (one study reported aOR=1.70, 95%CI [1.03-2.81]). Older adults who used antiepileptics were 43% more likely to have a fall-related injury (two-study pooled aOR=1.43, 95%CI [1.10-1.86], I^2=0%).

Hypertension is a very common chronic disease in older adults, with prevalence of 27% in people younger than 60 years and 74% in those older than 80 years (Lloyd-Jones et al., 2005). Antihypertensive drugs are among the most frequently prescribed medications in older adults. Canadian Institute for Health Information reported that in 2016, 24.5% of Canadian older adults were prescribed angiotensin-converting enzyme inhibitors (ACEIs), 23.5% were prescribed beta-blocking agents (BBs), 21.9% dihydropyridine calcium channel blockers (CCBs) and 15.7% angiotensin II antagonists (CIHI, 2018b). Another study of 4,961 older adults with hypertension showed that 56.6% were prescribed renin-angiotensin system (RAS) blockers, 54.2% diuretics, 45.9% BBs, and 34.2% CCBs.

Although antihypertensive drugs were not classified as FRIDs, their association with falls and fall-related injuries in older adults was studied extensively. Diuretics (C03), BBs (C07), CCBs (C08), and RAS inhibitors (C09) are all listed as drugs that may cause or worsen orthostatic hypotension in the list produced by Swedish NBHW.
Antihypertensive drugs can potentially result in fall-related injury, due to syncope or

dizziness caused by orthostatic hypotension. However, results of previous studies on antihypertensive drugs and fall-related injuries are conflicting. Leipzig and his colleagues completed a meta-analysis on the effect of diuretics (Leipzig et al., 1999). They reported that furosemide and thiazides were weak risk factors for fall injuries in older adults (pooled OR=1.08; 95%CI [1.02-1.16]), while CCBs and ACEIs were not risk factors. Another systematic review and meta-analysis conducted by Wiens et al. (2006) suggested a lower risk of fractures in older adults using BBs and diuretics (pooled RR=0.86 95%CI [0.81-0.92] for diuretics and pooled RR=0.81, 95%CI [0.73-0.89] for BBs), but an enhanced risk of fractures in older adults using CCBs (pooled RR=1.96; 95%CI [1.16-3.30]). For the past forty years, psychotropic medications have been consistently and clearly recognized as FRIDs, while the evidence that antihypertensives are also FRIDs was less clear. Overall, research had been mainly focused on psychotropic medications and antihypertensives' association with falls and fall-related injuries.

1.5 Background Summary and Knowledge Gap

As described, risks for falls are multifactorial. However, research has not produced strong evidence on risk factors for fall-related injuries for older adults. Some studies focused on specific groups of older adults such as those with vestibular dysfunction (Marchetti, 2003), or with chronic kidney disease (Kistler et al., 2018), or with lower limb amputations (Wong et al., 2016). Other studies focused on specific settings, such as hospitals (Fischer et al., 2005), or particular racial group, such as Chinese (Pi et al., 2016; Li et al., 2016), Korean (Kim et al., 2018) and Indonesian (Pengpid &Peltzer, 2018). Majority of studies reporting the risk factors for fall-related injuries in older adults are combined with risk factors for falls. Fall-related injuries lead to high morbidity and mortality (McClure et al., 2008), thus it is necessary to study injuries caused by falls independently to gather evidence and inform strategies for injury prevention.

Research on medication use in older adults either focused on older adults in general (CIHI, 2018b; Neoh et al., 2017), or on one or two specific classes of medication frequently used by older adults such as antihypertensive drugs (Mohd et al., 2012), blood sugar lowering drugs (Clemens et al., 2015), sedatives and hypnotics (Kassam et al., 2006; Tseng et al., 2018), and opioids (Weesie et al., 2020; Wilder-Smith, 2005). A

literature review by Peng and colleagues (2019) revealed the need for a comprehensive, population-based report on medication use in older adults before they had a fall-related injury. It is clear that more knowledge on medication use prior to injury is necessary. Logical first step is a descriptive study to determine the patterns and prevalence of medication prescribing to older adults before fall-related injury. This study will serve to generate future research questions on the association between fall-related injury and types, numbers and duration of medication use.

A clear and complete recognition of risk factors is essential in injury prevention. In 1980, William Haddon developed of a systematic analysis for the preventative approaches with Haddon "phase-factor" matrix (Haddon, 1980). Although it was originally designed for traffic injuries, the matrix was soon adapted for prevention of various types of injuries, including fall-related injuries in older adults (Sattin, 1992). Medication use was recognized as one of the pre-event host factors for fall-related injuries in older adults and thus the prevention focused on limiting excess prescribing of high-risk psychotropic medications (Sattin, 1992). However, current research on association between medications and fall-related injuries in older adults is limited and confined to psychotropic drugs and anti-hypertensive drugs (de Vries et al., 2018; Seppala, Wermelink, et al., 2018; Seppala, van de Glind, et al., 2018; Wiens et al., 2006; Zang, 2013), leaving out a wide range of medication classes commonly prescribed to older adults. For example, in developed countries, statins were prescribed to 40-50% older adults (CIHI, 2018b; Chee et al., 2018; Ofori-Asenso et al., 2018), proton pump inhibitors to 20-30% older adults (CIHI, 2018b; Kanno, & Moayyedi, 2019), non-steroid anti-inflammatory drugs (NSAIDs) to 7% older adults (Wongrakpanich et al., 2018) and insulin to 7% older adults (Clemens et al., 2015). Similarly, in 2016, 51.7% older adults in Ontario were prescribed with statins, 32.5% proton pump inhibitors. Other medication classes were also commonly prescribed to Ontario older adults, for example, 16.6% older adults in Ontario were prescribed thyroid hormones, 14.4% biguanides, 14.2% penicillins with extended spectrum, and 11.4% fluoroquinolones (CIHI, 2018b). Studies on the risk of fall-related injury while using these medication classes are scarce and the results often conflicting (Seppala, van de Glind, et al., 2018). Therefore, it is necessary to expand

inquiry beyond FRIDs to include more medication classes and explore their association with fall-related injury.

1.6 Purpose of Dissertation

The overall purpose of this dissertation was to provide a comprehensive evidence on medication classes prescribed to older adults prior to their fall-related injuries and evaluate their association.

The purpose of Study 1 was: (a) to provide a comprehensive list of medication classes prescribed to older adults within one year prior to their fall-related injuries. The purpose of Study 2 was to evaluate the association between fall-related injuries and most frequently prescribed medication classes prescribed within 30 days prior to the injuries. The purpose of Study 3 was to explore association between continuously used and newly initiated medications and fall-related injury in older adults.

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Chapter 2

2 Medication Prescribed within One Year prior to Fall-Related Injuries in Ontario Older Adults

2.1 Introduction

Falls are the leading cause of both fatal and non-fatal injury in older adults (Bergen & Stevens, 2016). Nearly one third of older adults fall every year (Chang et al., 2010; Tinetti et al., 2006). Minor injuries, such as bruises or lacerations, occur in 30-50% of falls, while 5-10% of falls lead to serious injuries such as hip fractures or traumatic brain injury (Cameron et al., 2012; Gillespie et al., 2012; Goldacre et al., 2002; Health Quality Ontario, 2008; Masud & Morris, 2001; Rubenstein & Josephson, 2002). Fall-related injuries can also result in adverse consequences such as reduced quality of life (Gill et al., 2013), higher possibility of admission to long-term care facilities (Gill et al., 2013), and increased risk of death (Skelton & Todd, 2004).

Numerous fall-related risk factors in older adults have been identified through past research, specific use of certain medications or combinations of medications in particular was reported to be associated with both increased falls and fall-related injury in this population (Ambrose et al., 2013; Huang et al., 2012). For instance, psychotropic medications and concurrent use of more than four medications have consistently been found to increase falls risk in older adults (Hartikainen et al., 2007; Leipzig et al., 1999; Park et al., 2015; Woolcott et al., 2009). With increasing knowledge on the association between medications and falls or fall-related injuries, certain classes of medications were reported repeatedly to be associated with falls and it was van der Velde who first proposed the acronym FRID for fall risk-increasing drugs. FRIDs include antihypertensive agents, diuretics, antidepressants, analgesics, anti-epileptics, and sedative/ hypnotics (van der Velde et al., 2007; The Swedish National board of Health and Welfare, 2010) which increase falls and fall-related injuries within older adult populations (Bauer et al., 2012; Winter et al., 2016; Zia et al., 2017).

While previous research has commonly investigated the association between specific and known FRIDs, and fall-related injuries (e.g., benzodiazepines (Davies et al., 2018;

Donnelly et al., 2017); anti-hypertensive medications (Verma et al., 2018, de Vries et al., 2018); antidepressants (Kurdyak et al., 2007, Axmon et al., 2018), limited evidence currently exists regarding medication classes of other than FRIDs that were prescribed to older adults prior to a fall-related injury. Providing a more comprehensive picture of medication classes prescribed to older adults before the occurrence of a fall-related injury is necessary to expand our knowledge on medications that may induce any fall-related injury. Therefore, the purpose of this study was: (1) to describe medication classes and numbers of medication classes prescribed to older adults within one year prior to the fall-related injury; and (2) to describe medication classes prescribed to older adults within one year prior to fall-related fractures and fall-related brain injury, as these two types of injury are of high prevalence and can cause serious consequences (Court-Brown et al., 2017; Peterson & Kegler, 2020; Teo et al., 2018)

2.2 Methods

2.2.1 Study Design and Setting

We conducted a population-based, descriptive study of medication classes prescribed to older adults (>65 years of age) who experienced at least one fall-related injury between January 1, 2010 and December 31, 2014, using Ontario healthcare administrative data held by the provincial data steward IC/ES. The extraction of eligible participants in this study was conducted by IC/ES analysts, based on a carefully prepared data creation plan (DCP, Appendix B). Ontario is the largest province in Canada, with a population of 14.7 million and 2.6 million older adults over the age of 65 (Statistics Canada, 2020), all of whom have access to universal healthcare services. IC/ES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data. IC/ES is a prescribed entity under the section 45 of Ontario's Personal Health Information Protection Act. Section 45 authorizes IC/ES to collect personal health information, without consent, for the purpose of analysis or compiling statistical information with respect to the management of, evaluation or monitoring of, the allocation of resources to or planning for all or part of the health system. Projects conducted under section 45, by definition, do not require review by a Research Ethics Board. This project was conducted under section

45, and was approved by IC/ES' Privacy and Legal Office. However, ethics approval for this series of studies was required in Western University, and it was obtained from the Research Ethics Board at Western University, London, Ontario, Canada (HSREB #109335, detailed information was provided in Appendix C).

2.2.2 Population

Older adults aged 66 years and older, who experienced a fall-related injury over the study period (January 1, 2010 to December 31, 2014), and resided in Ontario, were included in this study. A fall-related injury was defined by combining the ICD-10-CA codes (Canadian Institute of Health Information [CIHI], 2018a; WHO, 2019a) for falls (W00-W19) with codes for injury (S00-S99, T00-T14) (Appendix D). To be included, each person's diagnosis necessitated containing at least one W code for falls and at least one S or T code for injuries. The Emergency Department visit date for a fall-related injury was defined as the index date. Fall-related injuries of interest in this study were: (1) any fall-related injury, (2) fall-related fracture; and (3) fall-related traumatic brain injury. Fall-related fracture was identified through presence of at least one specific fracture S code (S02, S12, S22, S32, S42, S52, S62, S72, S82, S92, T08, T10, T12, T142) and one W code (W00-W19). Fall-related traumatic brain injury was identified by presence of at least one specific concussion and brain injury code (S06, S099) and one W code (W00-W19).

2.2.3 Data Sources

We used records arising from several databases held by IC/ES, including: (1) the Ontario Drug Benefit (ODB) database, which provides prescription drug coverage data for residents over the age of 65, including individuals in long-term care homes (Government of Ontario, 2019); (2) the Discharge Abstract Database (DAD), which records information on all hospital admissions and discharge diagnosis; (3) the National Ambulatory Care Reporting System (NACRS), which captures information on visits to emergency departments and community-based ambulatory care facilities; and (4) the Ontario Registered Persons Database (RPDB), which contains demographic information for Ontario residents. These datasets were linked using a unique encoded identifier,

which ensured the confidentiality of personal and health information. We assessed older adult comorbidities using the various IC/ES-derived data sets, applying validated case definitions, including diabetes, chronic obstructive pulmonary diseases, asthma, hypertension, and dementia. Sociodemographic data (i.e., age, sex, and income quintile) was extracted from the RPDB, primary diagnosis data arose from both NACRS and DAD, and medication prescriptions were drawn from ODB.

2.2.4 Medication Information

Medication information extracted from the ODB database used the Drug Identification Number (DIN) assigned by Health Canada (Health Canada, 2018). Each DIN uniquely identifies the manufacturer, trade name, active ingredients, strength of active ingredients, pharmaceutical form and route of administration (Health Canada, 2018). For better understanding and comparability with the results of other studies, DIN codes were converted and categorized into Anatomical Therapeutic Chemical (ATC) level 5 codes (see Appendix E). The ATC classification system was devised by the World Health Organization (WHO) to categorize medications based on the system or organ upon which they act, as well as their therapeutic and chemical features (WHO, 2019b). In the ATC classification system, each medication is classified in a hierarchy with 5 levels. Medication use information was reported on the 4th level of ATC codes in this study. ATC 4th level is the level used to count number of different medications as it is the level which aggregates medications just above their descriptive chemical substance (Krause, 2008).

2.2.5 Outcomes

The primary outcome of this study were medication classes prescribed to older adults within one year prior to any fall-related injury, fall-related fractures and fall-related traumatic brain injuries. We quantified any fall-related injury and presented pattens in medication classes prescribed within the year prior to injury. We also explored medication prescription patterns within one year prior to both fall-related fractures and fall-related brain injuries. Finally, the number of ATC 4th level medication classes prescribed to each older adult within a year was calculated and summarized into four

categories: 0-4 medication classes, 5-9 medication classes, 10-14 medication classes and 15 or more medication classes (CIHI, 2018a).

2.2.6 Statistical Analysis

Descriptive analysis summarized the cohort baseline characteristics, such as age, sex, age group, and income quintile. Income quintile is a measure of socioeconomic status that divides the population living in the same dissemination area into 5 income groups (1 represents the lowest income; 5 represents the highest income) with approximately 20% of the population in each group (CIHI, 2016). The dissemination area was determined from the older adults' residential postal code and statistics Canada Census data (Wilkins, 2010). Comorbidities (i.e., diabetes, chronic obstructive pulmonary diseases, asthma, hypertension and dementia) were also analyzed using descriptive statistics. The fall-related injury (any injury type) was reported for each year and as a five-year total (2010-2014).

The percentage of people prescribed each ATC 4th level medication class was calculated by dividing the number of people who were prescribed a certain class within a year prior to a fall-related injury (numerator) by the total number of older adults who experienced a fall-related injury (denominator). The formulas are listed below. FRI-OA stands for older adults who had a fall-related injury.

$$\text{Percentage of older adults who were prescribed certain medication class prior to a fall-related injury} = \frac{\text{Number of FRI-OAs prescribed certain medication class}}{\text{Total numbers of FRI-OAs}}$$

$$\text{Percentage of female/male FRI-OAs prescribed Certain Medication Class} = \frac{\text{Number of Female/Male prescribed certain medication class}}{\text{Number of Female/Male FRI-OAs}}$$

$$\text{Percentage of different Age Group (66-74, 75-84, 85+) FRI-OA prescribed certain medication class} = \frac{\text{Number of Age Group FRI-OA prescribed certain medication class}}{\text{Number of different Age Group FRI-OAs}}$$

The top 20 medication classes with the highest number of users were summarized as the percentage of female and male users, and percentage of different age-group users (i.e., 66-74, 75-84, 85+). The same analysis was repeated for subgroups of older adults who experienced fall-related fractures and fall-related TBIs. The difference between percentages of female and male older adults prescribed certain medication classes was determined by Wilcoxon rank-sum test and the comparison among different age groups was determined by Kruskal-Wallis test. The numbers of different ATC 4th level medication classes prescribed to older adults within one year prior to the fall-related injuries were counted for each older adult and were categorized into 4 different groups: 0-4, 5-9, 10-14 and 15 or more medication classes (CIHI, 2018b). All analyses were conducted with SAS 9.4 (SAS Institute, 2013). All the SAS codes for extracting and analyzing data were provided in Supplementary Content of this thesis.

2.3 Results

A total of 288,251 older adults experienced any fall-related injury from 2010 to 2014. Fall-related fractures made up 40.0% of all fall-related injuries, superficial injuries were 23.2%, open wound were 16.3%, traumatic brain injury were 12.1%, sprains and strains were 5.0%, other injuries were 3.5%. The mean age was 78.3±7.8 years old and 63.2% of the older adults were female. Over three quarters (76.9%) were diagnosed with hypertension, 30.5% with diabetes, 26.9% with COPD, 15.8% with dementia and 15.0% with asthma (Table 2.1) For number of medications prescribed, 3.5% of the study population were not prescribed any medication classes within one year before the injury, while 18.9% were prescribed 1-4 different medication classes, 36.4% were prescribed 5-9 different medication classes, 26.0% were prescribed 10-14 different medication classes and 15.2% were prescribed more than 15 different medication classes. Frequency distribution of different numbers of medication classes prescribed to older adults prior to fall-related injuries was presented in Figure 2.1.

Table 2.1 *Characteristics of Older Adults who Experienced Fall-Related Injuries in 2010-2014*

	2010	**2011**	**2012**	**2013**	**2014**	**2010-2014**
Age (Mean±SD)	78.7±7.6	78.5±7.7	78.5±7.8	78.1±7.9	77.8±8.0	78.3±7.8
Age Median	79	79	79	78	78	78
Total Number	56,203	56,230	55,945	58,950	60,923	288,251
Age 66-74 (n, %)	18,673 (33.2)	19,296 (34.3)	19,842 (34.8)	22,160 (37.6)	23,813 (39.1)	103,424 (35.9)
Age 75-84 (n, %)	22,429 (39.9)	22,014 (39.2)	21,551 (38.5)	21,644 (36.7)	21,752 (35.7)	109,400 (38.0)
Age 85+ (n, %)	15,091 (26.9)	14,920 (26.5)	14,912 (26.7)	15,146 (25.7)	15,358 (25.2)	75,427 (26.2)
Sex Female (n, %)	36,562 (65.1)	35,976 (64.0)	35,315 (63.4)	36,492 (61.9)	37,656 (61.8)	182,136 (63.2)
Income Quintile						
1(lowest)	11,687 (20.88)	11,325 (20.22)	11,169 (20.04)	11,668 (19.87)	13,868 (22.80)	59,717 (20.79)
2	11,525 (20.59)	11,455 (20.46)	11,521 (20.68)	11,953 (20.35)	13,486 (22.17)	59,940 (20.87)
3	11,134 (19.89)	10,922 (19.50)	10,921 (19.60)	11,480 (19.55)	11,816 (19.43)	56,273 (19.59)
4	10,887 (19.45)	11,146 (19.90)	11,208 (20.11)	11,920 (20.30)	10,581 (17.40)	55,742 (19.41)
5	10,737 (19.18)	11,151 (19.91)	10,902 (19.57)	11,712 (19.94)	11,069 (18.20)	55,571 (19.35)
Comorbidities						
Diabetes (n, %)	16,639 (29.6)	16,926 (30.1)	17,036 (30.5)	18,200 (30.9)	19,161 (31.5)	87,962 (30.5)
COPD (n, %)	15,388 (27.4)	15,207 (27.0)	15,223 (27.2)	15,781 (26.8)	15,963 (26.2)	77,572 (26.9)
Asthma (n, %)	8379 (14.9)	8,374 (14.9)	8,283 (14.8)	8,951 (15.2)	9,192 (15.1)	43,179 (15.0)
Hypertension (n, %)	43,325 (77.1)	43,332 (77.1)	43,197 (77.2)	45,113 (76.5)	46,556 (76.4)	221,523 (76.9)
Dementia (n, %)	9,329 (16.6)	9,175 (16.3)	8.934 (16.0)	9,130 (15.5)	9,007 (14.8)	45,575 (15.8)

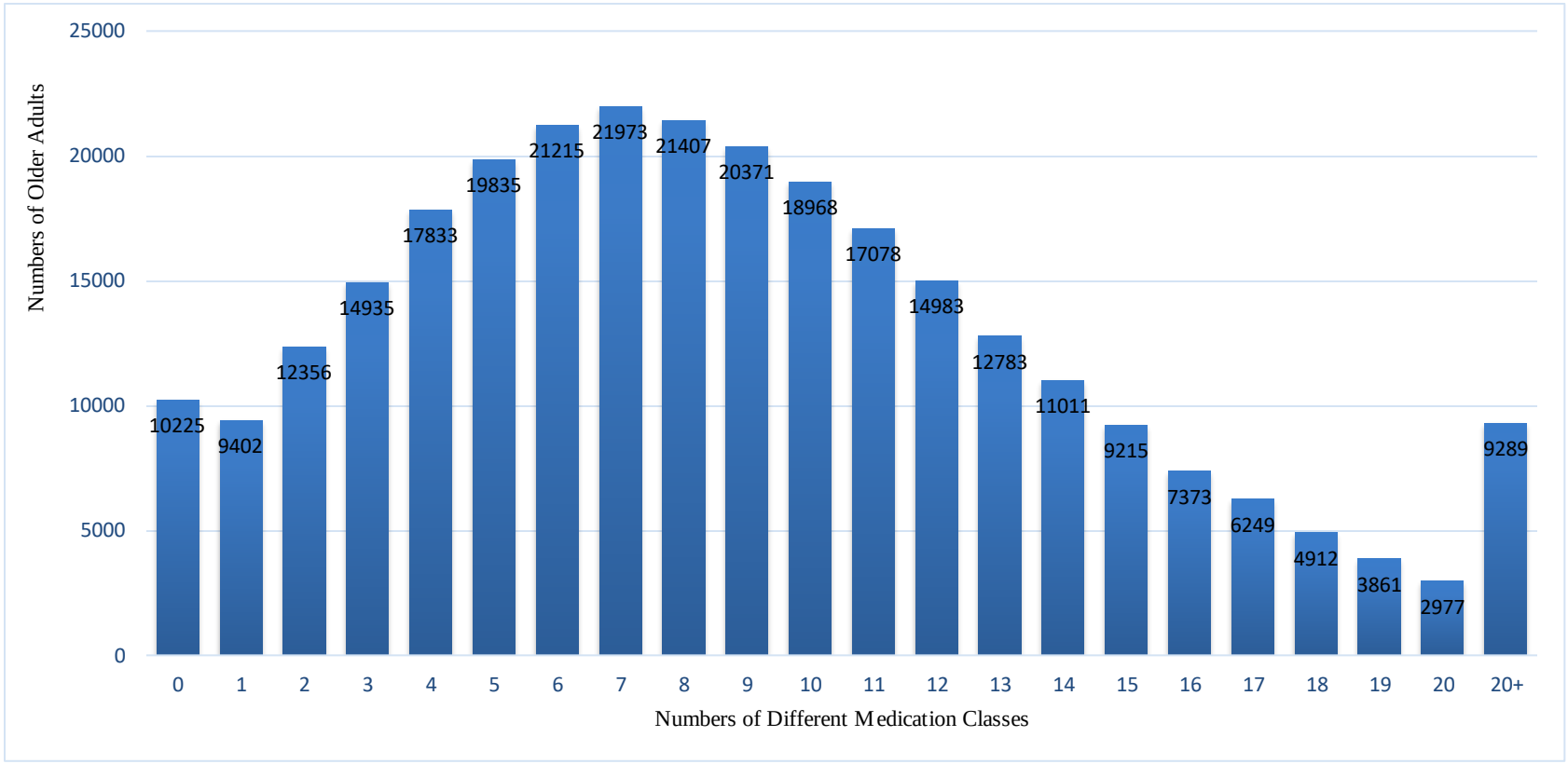


Figure 2.1 Frequency Distribution of Different Numbers of Medication Classes Prescribed to Older Adults Prior to Fall-related Injuries

Complete medication classes prescribed are provided in Appendix F, Table A1. The top 10 drug classes prescribed within a year before any fall-related injury included HMG-CoA reductase inhibitors (C10AA), proton pump inhibitors (PPIs, A02BC), angiotensin converting enzyme inhibitors (ACEIs, C09AA), beta-blocking agents (C07AB), natural opium alkaloids (N02AA), dihydropyridine derivatives (C08CA), biphosphonates (M05BA), thyroid hormones (H03AA), glucocorticoids for systematic use (H02AB) and benzodiazepine derivatives (N05BA).

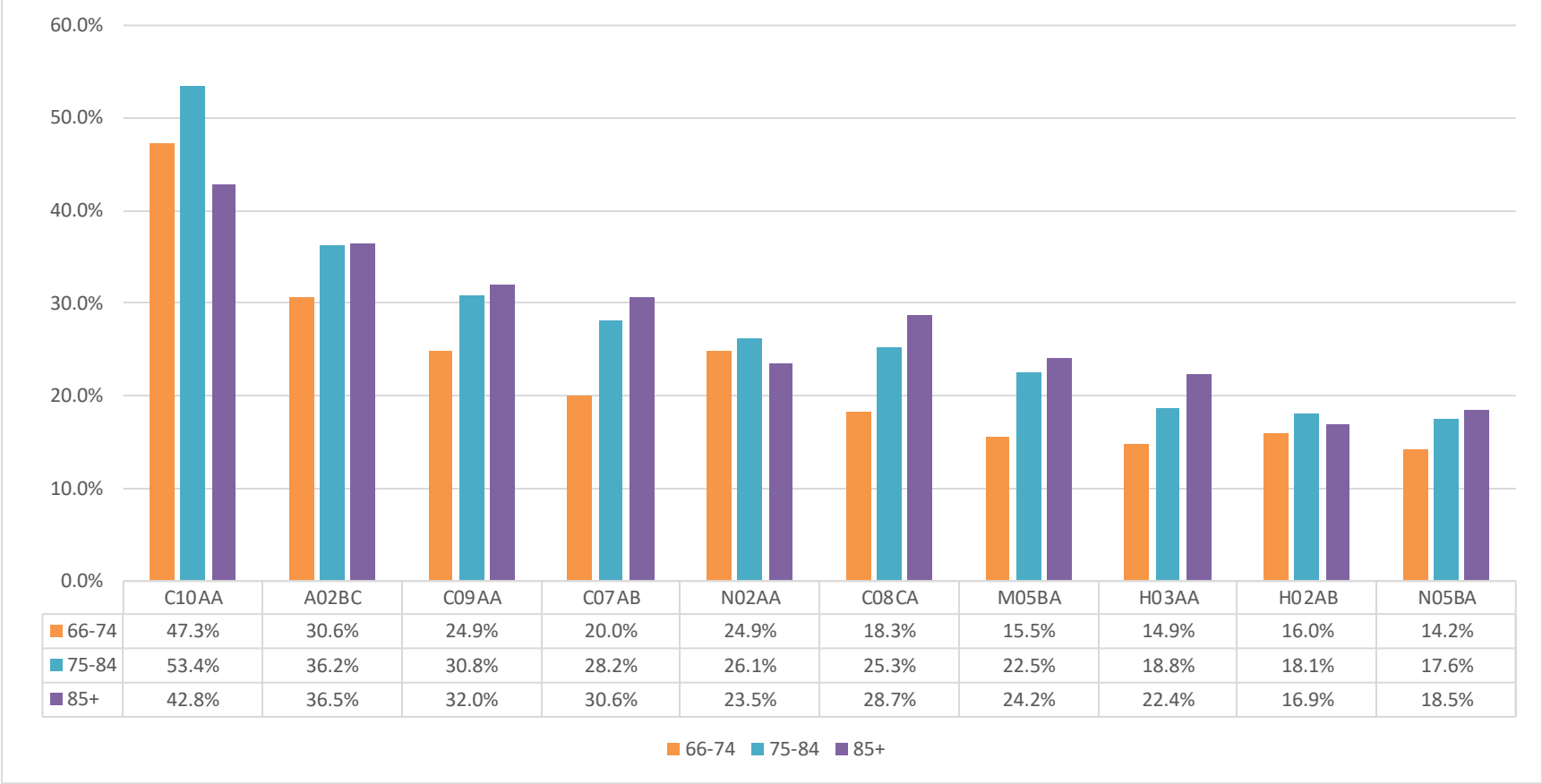
HMG-CoA reductase inhibitors, commonly known as statins and used to treat high cholesterol, were the most commonly prescribed medication class, used by nearly half (48.5%) of the study population. They were also the most frequently prescribed medication class in analyses stratified by sex and age sub-groups (Table 2.2 and Figure 2.2). More than half (54.8%) of males were using statins before they experienced an all cause fall-related injury. In the 75-84 age group, 53.4% used statins and the percentage dropped to 42.8% in the group of 85 years and older adults.

Proton pump inhibitors (PPIs) were the second most commonly prescribed drug class, with 34.3% of all older adults. PPIs are usually used to treat gastroesophageal reflux and peptic ulcer diseases. For age groups 75-84 and 85 years and older, a slightly greater percentage of PPI use was found (36.2% and 36.5% respectively), while the age group 66-74 years old had somewhat lower prevalence (30.6%).

Four drug classes for the management of hypertension were noted among the top 10 drug classes. ACEIs were prescribed to 33.9% of male and 26.1% females. A higher percentage of males were also prescribed beta-blocking agents (Males: 27.8% vs. Females: 24.8%). However, agents acting on the renin-angiotensin system (RAS) and thiazides were prescribed in higher percentage to females than males (Table 2.2). The prescription of agents for treatment of high blood pressure increased with age. The percentage of 85 years and older age group prescribed ACEIs (C09AA), beta-blocking agents (C07AB), and dihydropyridine derivatives (C08CA) were the highest among the three age groups, while the 66-74 age group had of lowest prescription frequency (Figure 2.2).

Table 2.2 *Top 20 Medication Classes Prescribed to Older Adults Prior to a Fall-related Injury, Percentage of Users, 2010-2014*

ATC code	Drug Class	Common Use	Percentage of Use			
			Total (%)	Female (%)	Male (%)	p value
C10AA	HMG CoA reductase inhibitors	High cholesterol	48.5	44.7	54.8	<.01
A02BC	Proton pump inhibitors	Gastroesophageal reflux, peptic ulcer disease	34.3	35.8	31.7	<.01
C09AA	ACE inhibitors, plain	High blood pressure	29.0	26.1	33.9	<.01
C07AB	Beta blocking agents, selective	High blood pressure, heart failure	25.9	24.8	27.8	<.01
N02AA	Natural opium alkaloids	Management of moderate to severe pain	25.0	25.0	25.0	0.72
C08CA	Dihydropyridine derivatives	High blood pressure, heart failure, angina	23.7	24.8	21.8	<.01
M05BA	Biphosphonates	Prevent bone density loss, treat osteoporosis	20.4	28.2	7.1	<.01
H03AA	Thyroid hormones	Hypothyroidism	18.3	23.1	10.0	<.01
H02AB	Glucocorticoids	Autoimmune and inflammatory disorders, cancer, asthma, COPD	17.0	16.6	17.7	<.01
N05BA	Benzodiazepine derivatives	Agitation, anxiety, insomnia, seizures	16.6	19.0	12.4	<.01
C03CA	Sulfonamides, plain	High blood pressure, heart failure	16.5	16.0	17.5	<.01
C09CA	Agents acting on the renin-angiotensin system	High blood pressure, heart or kidney disease	16.3	17.7	13.8	<.01
C03AA	Thiazides, plain	High blood pressure, heart or kidney disease	15.2	17.0	12.1	<.01
J01MA	Fluoroquinolones	Respiratory and urinary tract infections	15.2	15.2	15.1	0.56
N06AB	Selective serotonin reuptake inhibitors	Depression	14.7	16.4	11.9	<.01
A10BA	Biguanides	Type 2 diabetes	14.3	12.9	16.8	<.01
J01CA	Penicillins with extended spectrum	Bacterial infection	13.6	13.6	13.7	0.58
R03CC	Selective beta-2-adrenoreceptor agonists	COPD, asthma	13.1	13.3	12.8	<.01
A06AA	Softeners, emollients	constipation	12.9	12.8	13.1	0.04
N06AX	Other antidepressant (TCAs)	Depression	12.5	13.5	10.7	<.01



	C10AA	A02BC	C09AA	C07AB	N02AA	C08CA	M05BA	H03AA	H02AB	N05BA
66-74	47.3%	30.6%	24.9%	20.0%	24.9%	18.3%	15.5%	14.9%	16.0%	14.2%
75-84	53.4%	36.2%	30.8%	28.2%	26.1%	25.3%	22.5%	18.8%	18.1%	17.6%
85+	42.8%	36.5%	32.0%	30.6%	23.5%	28.7%	24.2%	22.4%	16.9%	18.5%

Figure 2.2 Top 10 Medications Prescribed to Older Adults of Different Age Group Before They Experienced Fall-Related Injuries.

Note C10AA, HMG CoA reductase inhibitors; A02BC, proton pump inhibitors; C09AA, ACEIs; C07AB, beta blocking agents; N02AA, Natural opium alkaloids; C08CA, dihydropyridine derivatives; M05BA, biphosphonates; H03AA, thyroid hormones; H02AB, glucocorticoids for systematic use; N05BA, benzodiazepine derivatives

Biphosphonates and thyroid hormones were prescribed to 28.3% and 23.1% of females, but only to 7.1% and 10.0% males. These two medication classes emerged as the most gender specific among the older adults who experienced any fall-related injury. The percentage of older adults prescribed these two drug classes also increased with age with the age group 85 years and older having the highest percentage (Figure 2.2).

The central nervous system agents, notably natural opium alkaloids, were prescribed to a quarter of female and male older adults. The highest percentage of opioids prescription was noted for the age group 75-84 years. Older adults 85 years and older were prescribed less opioids than the other two age groups. Benzodiazepine derivatives were prescribed to 19.0% females and 12.4% males, with an increase with age to 18.5% in the group of older adults who were 85 years and older. For antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and other antidepressants (mostly tricyclic antidepressants [TCAs]), there was a higher percentage of female users than male users, namely 16.4% female, 11.9% male for SSRIs and 13.5% female, 10.7% male for TCAs (Table 2.2).

Fall-related fractures were diagnosed in 115,230 older adults (40.0% of all older adults with any fall-related injury). More women (70.7%) than men (29.3%) experienced fall-related factures. For 85 years and older age group, the number of females (22,231) was almost three times as many as males (7,742). Statins and PPIs were still the top two most commonly prescribed medication classes. A higher percentage of males were prescribed statins, ACEIs, and BBs than females, while a higher percentage of females were prescribed biphosphonates, dihydropyridine derivatives and thyroid hormones. As for age differences, adults 85 years and older had the highest percentage of prescribed ACEIs, BBs, biphosphonates, dihydropyridine derivatives, thyroid hormones, benzodiazepine derivatives, sulfonamides, SSRIs, fluoroquinolones, emollients and other antidepressants (Table 2.3).

Table 2.3 *Top 20 Medication Classes Prescribed to Older Adults with Fall-Related Fracture, Usage Rate by Sex and Age Group*

ATC Codes	Drug Class	Total (%)	Sex			Age group			
			Female (%)	Male (%)	p-value[a]	66-74 (%)	75-84 (%)	85+ (%)	p-value[b]
C10AA	HMG CoA reductase inhibitors	45.4	42.5	52.4	<.01	44.6	50.4	39.6	<.01
A02BC	Proton pump inhibitors	33.1	33.9	31.0	<.01	29.2	35.1	35.4	<.01
C09AA	ACE inhibitors, plain	27.6	25.5	32.8	<.01	23.1	29.5	31.0	<.01
N02AA	Natural opium alkaloids	24.5	24.2	25.2	<.01	23.7	26.0	23.5	<.01
C07AB	Beta blocking agents, selective	24.5	23.7	26.2	<.01	18.4	26.8	29.3	<.01
M05BA	Biphosphonates	23.6	30.0	8.1	<.01	18.9	26.1	26.5	<.01
C08CA	Dihydropyridine derivatives	23.6	24.3	21.8	<.01	17.7	25.2	29.2	<.01
H03AA	Thyroid hormones	18.6	22.3	9.7	<.01	15.1	18.9	22.7	<.01
N05BA	Benzodiazepine derivatives	16.6	18.5	12.1	<.01	13.9	17.8	18.7	<.01
H02AB	Glucocorticoids	16.1	15.5	17.4	<.01	15.3	17.0	15.8	<.01
C09CA	Agents acting on the renin-angiotensin system	15.7	16.7	13.3	<.01	14.1	17.0	16.0	<.01
C03CA	Sulfonamides, plain	15.5	14.9	16.9	<.01	8.3	15.3	25.2	<.01
C03AA	Thiazides, plain	14.7	16.1	11.3	<.01	12.8	15.7	15.7	<.01
N06AB	Selective serotonin reuptake inhibitors	14.6	15.7	11.9	<.01	13.0	14.9	16.4	<.01
J01MA	Fluoroquinolones	14.3	14.2	14.6	0.14	11.6	14.8	17.3	<.01
J01CA	Penicillins with extended spectrum	13.0	13.0	13.1	0.51	13.7	13.3	11.7	<.01
A10BA	Biguanides	12.7	11.7	15.3	<.01	14.1	14.0	9.2	<.01
R03CC	Selective beta-2-adrenoreceptor agonists	12.4	12.3	12.4	0.62	12.6	12.9	11.4	<.01
A06AA	Softeners, emollients	12.2	11.9	13.0	<.01	7.8	13.3	16.5	<.01
N06AX	Other antidepressants	12.1	12.8	10.3	<.01	10.9	12.1	13.5	<.01

Note a: Wilcoxon rank-sum test; b: Kruskal-Wallis test.

Table 2.4 *Top 20 Medication Classes Prescribed to Older Adults with Fall-Related Traumatic Brain Injury, by Sex and Age Group*

ATC Codes	Drug Class	Total (%)	Sex			Age group			
			Female (%)	Male (%)	p-value[a]	66-74 (%)	75-84 (%)	85+ (%)	p-value[b]
C10AA	HMG CoA reductase inhibitors	52.0	48.2	57.4	<.01	49.5	57.3	47.3	<.01
A02BC	Proton pump inhibitors	35.5	37.5	32.5	<.01	31.8	37.3	36.9	<.01
C09AA	ACE inhibitors, plain	30.3	27.3	34.6	<.01	26.1	31.9	32.7	<.01
C07AB	Beta blocking agents, selective	28.7	27.7	30.2	<.01	22.1	30.8	33.2	<.01
C08CA	Dihydropyridine derivatives	25.1	26.5	23.1	<.01	19.3	26.9	29.2	<.01
N02AA	Natural opium alkaloids	24.9	25.4	24.1	<.01	25.0	25.7	23.5	<.01
M05BA	Biphosphonates	19.4	28.1	7.0	<.01	13.9	20.9	23.3	<.01
H03AA	Thyroid hormones	19.1	24.8	11.0	<.01	15.7	19.0	23.1	<.01
C03CA	Sulfonamides, plain	18.1	17.5	19.0	<.01	10.3	17.5	27.6	<.01
C09CA	Agents acting on the renin-angiotensin system	17.4	19.3	14.8	<.01	15.8	19.0	17.0	<.01
H02AB	Glucocorticoids	17.3	17.2	17.5	0.34	16.1	18.3	17.4	<.01
N05BA	Benzodiazepine derivatives	17.2	20.0	13.2	<.01	15.7	17.8	18.0	<.01
A10BA	Biguanides	16.6	15.2	18.6	<.01	18.2	18.1	12.6	<.01
N06AB	Selective serotonin reuptake inhibitors	16.5	18.6	13.6	<.01	15.2	16.9	17.4	<.01
J01MA	Fluoroquinolones	16.1	16.2	16.0	0.64	13.0	16.5	18.9	<.01
C03AA	Thiazides, plain	15.3	17.6	12.1	<.01	13.4	16.7	15.5	<.01
J01CA	Penicillins with extended spectrum	14.4	14.7	14.0	0.06	15.5	14.2	13.7	<.01
A06AA	Softeners, emollients	14.4	14.2	14.6	0.30	10.1	15.2	18.1	<.01
N06AX	Other antidepressants	13.4	14.8	11.5	<.01	13.1	13.0	14.4	<.01
R03CC	Selective beta-2-adrenoreceptor agonists	12.8	13.3	12.0	<.01	13.0	12.9	12.2	0.14

Note a: Wilcoxon rank-sum test; b: Kruskal-Wallis test

Fall-related traumatic brain injury was observed in 34,810 older adults (12.1% of all older adults with any fall-related injury), 20,246 occurred in females (58.7%) and 14,364 in males (41.3%). A third (31.7%) of older adults who experienced fall-related traumatic brain injury were in the 66-74 age group; with 39.9% and 28.4% in the 75-84 and 85+ years old age groups, respectively. Statins and PPIs were the top two most common classes of medications. A higher percentage of males diagnosed with fall-related traumatic brain injury were prescribed statins and ACEIs than females, while higher percentage of females were prescribed biphosphonates and thyroid hormones. As for age groups, adults 85 years and older had the highest prescriptions of ACEIs, BBs, dihydropyridine derivatives, biphosphonates, thyroid hormones, sulfonamides, benzodiazepine derivatives, SSRIs, fluoroquinolones, emollients and other antidepressants (Table 2.4).

2.4 Discussion

Using health care administrative data, this population study has described the medication classes prescribed to older adults in one year prior to a fall-related injury and two specific fall-injury types, namely fracture and traumatic brain injury. The results showed that among older adults sustaining any fall-related injury, 48.5% were prescribed statins, 34.3% PPIs, 25.0% opioids, and16.6% anxiolytics. Similar patterns of medication prescription were also found for fall-related fractures and traumatic brain injury. Notably, 36.4% of older adults were prescribed 5-9 different medication classes and 41.2% were prescribed 10 or more medication classes within one year prior to fall-related injuries.

The findings of this study indicated that medications prescribed to older adults who had any fall-related injury were similar, but not the same to medications prescribed to the general population of older adults in Ontario (CIHI, 2018b). CIHI reported that, in the whole year of 2016, there were 51.7% and 17.3% of Ontario general population of older adults (OGP-OAs) who were prescribed statins and agents acting on RAS (CIHI, 2018b), while in our study, 48.5% and 16.3% of older adults who had fall related injury (FRI-OAs) were prescribed statins and agents acting on RAS within the year before the injury. However, compared to prescription in OGP-OAs, higher percentage of FRI-OAs were

prescribed with ACEIs, BBs, opioids, biphosphonates, benzodiazepine derivatives, thiazides, and SSRI. For example, CIHI reported there were 15.4% of OGP-OAs prescribed opioids, while in our study, 25.0% of FRI-OAs were prescribed opioids the year before their fall-related injury. The percentage of being prescribed SSRI in FRI-OAs and OGP-OAs were 14.6% and 10.5% respectively, biphosphonates were 20.4% and 9.4% respectively, benzodiazepine derivatives were 15.2% and 10.8% respectively.

The above comparison confirmed that all medication classes (except biphosphonates) with a higher percentage of prescription in older adults who had any fall-related injury were recognized as FRIDs. These classes of medications have been repeatedly identified to be related to falls and fall-related injury (Lee & Holbrook, 2017; Machado-Duque et al., 2018; Richardson et al., 2015; Seppala, Wermelink, et al., 2018). Most studies currently identify anti-hypertensive agents, antidepressants, antiepileptics, analgesics, sedatives and hypnotics, anti-Parkinsonian drugs, antipsychotics, and anxiolytics as FRIDs. In this aspect, our findings support previous studies on FRIDs and their association with falls and fall-related injury.

In this study, however, a number of other medication classes such as statins (48.5%), PPIs (34.3%), biphosphonates (20.4%), thyroid hormones (18.3%), glucocorticoids (17.0%), and fluoroquinolones (15.2%) were prescribed to a high percentage of older adults. Unfortunately, research regarding the association between these medication classes and fall-related injuries has not been well established (de Vries et al., 2018; Seppala, van de Glind, et al., 2018). The link between these commonly prescribed medication classes and fall-related injury in older adults needs to be further explored.

Of all fall-related injury types, fractures are the most common (PHAC, 2014). Findings in this study showed that medications prescribed prior to fall-related fractures were similar to medication prescribed prior to any fall-related injury. Hip fractures were extensively used in research as fall-related outcome because they were almost always caused by falls and were hospitalized, minimizing the number of missing cases (Hayes et al., 1996; Manchado-Duque et al., 2018, Payne et al., 2013, Thaler et al., 2016). A number of studies reported different percentages of older adults using certain medications prior to

hip fractures because their lookback windows were dissimilar. For example, Wang et al. (2000) reported 2.2% of older adults were prescribed statins within 180 days prior to hip fractures, while Rejnmark et al. (2004) reported that 66% of Danish older adults used statins within five years prior to hip fracture. A Swedish population-based study reported 53% of older adults who were 75 years and older used diuretics, 43% BBs, 18% CCBs, 30% agents acting on RAS, 33% opioids, 25% anxiolytics, 37% hypnotics and sedatives and 29% antidepressants within one year prior to a hip fracture (Thorell et al., 2014). Percentage of older adults prescribed antihypertensive medications and psychotropic medications in Thorell's study (2014) were much higher than ours. Possible explanation could be that their participants were older and their only outcome was hip fractures.

Fall-related TBIs in older adults are gaining increasing recognition in recent studies (Kannus et al., 2007; Hartholt et al., 2011). Currently only anticoagulants and antiplatelet agents were reported to be associated with TBIs due to an increased risk of intracranial bleeding (Boltz et al., 2015; Qiu et al., 2019). However, our finding indicated that higher percentage of statins, PPIs, ACEIs, BBs, sulfonamides, SSRIs and biguanides were prescribed prior to fall-related TBIs than fall-related fractures, which offers a good starting point for further exploration of the association between these medications and fall-related TBIs.

Medications can be seen as a surrogate for a person's health status and the number of medications a valid proxy for multi-comorbidities (Schneeweiss et al., 2001). Using multiple medications concurrently is common in older adults with multi-comorbidities and is associated with adverse outcomes such as mortality, falls, injuries, adverse drug reactions, and prolonged length of stay in hospital (Caughey et al., 2010; Correa-Pérez et al., 2017; Milton et al., 2008). The risk of having adverse consequences and experiencing harm increased with each additional medication because of complicated drug-drug and drug-disease interactions (Maher et al., 2014). Our study showed that 77.6% of older adults who had any fall-related injury were prescribed five or more different classes of medication within one year before the injury and 41.2% were prescribed ten or more different classes of medication. CIHI reported that 65.7% general population of older adults in Canada were prescribed five or more medication classes and 26.5% were

prescribed ten or more medication classes in the year of 2016 (CIHI, 2018b). Compared with the general population of older adults, a higher percentage of older adults who experienced fall-related injuries were prescribed multiple medication classes before the injury. Untangling multiple medications prescribed to older adults by enhancing communication between patients and healthcare providers, improving cooperation of pharmacists, family doctors, and specialists in prescribing practices will be important in future research.

2.4.1 Strengths and Limitations

The strengths of this study are the large number of observations and provincial representativeness. This study included data for over a quarter million older adults and provided detailed information on demographics, comorbidities and strictly defined fall-related injury using ICD-10-CA codes. All the data were obtained from IC/ES databases which were reported to have excellent data completeness (Levy et al., 2003) and high quality as in previous studies (Aiken et al., 2016; Liu et al., 2018; Macri et al., 2017).

Several limitations are associated with this study. First is the inherent limitation of administrative data that may lead to underreporting of some diagnoses (Sarrazin & Rosenthal, 2012), which might have been omitted during the coding process. Second, only dispensed drugs were recorded in the ODB database and the information collected through the ODB database could be an underestimation of prescriptions. Additionally, prescription (and even dispensing) cannot be equated with actual use, therefore the registry data could be an overestimation of drug use in our population of older adults.

This study laid the foundation for the consecutive studies in this program of research. With the knowledge of medication classes being prescribed to older adults prior to a fall-related injury, a comparison of medication classes prescription patterns between older adults who had a fall-related injury and older adults without a fall-related injury is now possible, which is essential in the upcoming case-control studies examining the association between medication and fall-related injuries. Future research could also include examine the association between medication prescribed to older adults and different types of fall-related injuries and evaluate the effectiveness of interventions

aimed at improving the appropriateness of prescribing in older adults to reduce the occurrence of fall-related injury.

2.5 Conclusion

This study described the medications classes and numbers of medication classes prescribed to older adults prior to a fall-related injury. Gender difference in medication prescribed was noted, specifically more females were prescribed antidepressants and anxiolytics. A higher percentage of people 85 years and older were prescribed antihypertensive agents, anxiolytics and antidepressants. There were 77.6% of older adults who were prescribed five or more different medication classes prior to any fall-related injury. Well-designed cohort studies are needed to determine the association between medication classes and different types of fall-related injuries.

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Chapter 3

3 Association between Fall-related Injury and Medication Prescribed to Older Adults within One Month Prior to the Injury

3.1 Introduction

Roughly 30% of older adults aged 65 years or older fall every year (Chang et al., 2010; Tinetti et al., 2006). Falls are the leading cause of non-fatal injuries and death among older adults in many countries and regions (Bergen et al., 2016; Ellingsen et al., 2018; National Council of Aging, 2018; Public Health Agency of Canada, 2014). Not all falls result in injuries, some minor injuries that may or may not require medical treatment or consultation, occur in 30-50% of falls, while 5-10% of falls lead to serious injuries such as fractures, dislocation of joints, or brain injury (Cameron et al., 2012; Gillespie et al., 2012; Goldacre et al., 2002; Health Quality Ontario, 2008). Although there is no consensus on the definition of fall-related injury, most studies refer to it as "an injury requiring emergency or inpatient treatment" (Schwenk et al., 2012). Fall-related injuries can result in adverse consequences both to individuals and to the public health care system (Burns et al., 2016; Gill et al., 2013, Scott et al., 2010). Disability resulting from falls increased by 54% in United States between 1990 and 2010 (Murray et al., 2013). In 2010, injurious falls in older adults in Canada resulted in over $3.3 billion in direct costs to the public health care system (Parachute, 2015). The total cost of fall-related injury in U.S was $50 billion in 2015 (National Council of Aging, 2018). Subsequently, it has become increasingly recognized that fall-related injury is a growing public health concern, especially with an increasing aging demographic (He et al., 2016).

The risk factors for fall-related injuries in older adults are multifactorial. History of previous falls, age, mobility and balance problems, and certain medication classes were reported to be associated with fall-related injuries (Gillespie et al., 2012; Mccoy, et al., 2017; Nilsson et al., 2016). Many studies demonstrated that use of certain medications and concurrent use of more than four medications enhanced the risk of falls and fall-related injury in older adults (Ambrose et al., 2013; Huang, et al., 2012; Pan et al., 2014; Hart et al., 2019). A recent systematic review reported that loop diuretics enhanced the

risk of falls by 36%, and antipsychotics, analgesics such as opioids, antidepressants and benzodiazepines were associated with increasing the risk for injurious falls by 60-80% in older adults (Seppala, Wermelink, et al., 2018). Polypharmacy was also identified as being associated with an increased risk of fall-related injuries and fractures (Iihara et al., 2016; Pan et al., 2014).

However, previous studies have focused mainly on fall-risk increasing drugs (FRIDs) such as anti-hypertensives and drugs acting on the nervous system. Currently lacking in the research literature are studies examining the association between medications currently not listed on the established FRID list (the Swedish National Board on Health and Welfare, 2010) and fall-related injury in older adults. Furthermore, there is a lack of robust evidence related to whether exposure to statins, proton pump inhibitors (PPIs), antiplatelets, glucose-lowering medications, laxatives, and anticholinergic drugs are associated with fall-related injury (Seppala, van de Glind, et al., 2018). This is important as these are considered commonly prescribed medications. For example, Canadian Institute for Health Information ([CIHI], 2018a) reported that these types of medication have been prescribed to 30-50% of older adults in the province of Ontario, Canada. Therefore, it is necessary to expand inquiry beyond FRIDs to include more medication classes and explore their association with fall-related injury. The purpose of this study was to evaluate the association between fall-related injuries and medication classes prescribed to older adults within 30 days prior to the injury.

3.2 Methods

3.2.1 Study Design

We conducted a population-based, case-control study using administrative secondary health care data for Canada's most populous province of Ontario. Ontario is the largest province in Canada, with a population of 14.7 million and 2.6 million older adults over the age of 65 (Statistics Canada, 2020), all of whom have access to universal healthcare services. The extraction of eligible participants in this study was conducted by IC/ES analysts, based on a carefully prepared data creation plan (DCP, Appendix B). IC/ES is an independent, non-profit research institute whose legal status under Ontario's health

information privacy law allows it to collect and analyze health care and demographic data. IC/ES is a prescribed entity under the section 45 of Ontario's Personal Health Information Protection Act. Section 45 authorizes IC/ES to collect personal health information, without consent, for the purpose of analysis or compiling statistical information with respect to the management of, evaluation or monitoring of, the allocation of resources to or planning for all or part of the health system. Projects conducted under section 45, by definition, do not require review by a Research Ethics Board. This project was conducted under section 45, and was approved by IC/ES' Privacy and Legal Office. However, ethics approval for this series of studies was required in Western University, and it was obtained from the Research Ethics Board at Western University, London, Ontario, Canada (HSREB #109335, detailed information was provided in Appendix C).

3.2.2 Data Sources

We used records from three databases held by IC/ES: (1) the Ontario Drug Benefit (ODB) database, which provides prescription drug coverage data for residents over the age of 65, including individuals in long-term care homes (Government of Ontario, 2019); (2) the National Ambulatory Care Reporting System (NACRS), which captures information on visits to emergency departments (EDs) and community-based ambulatory care facilities; and (3) the Ontario Registered Persons Database (RPDB), which contains demographic information for Ontario residents. These datasets were linked using unique encoded identifiers and analyzed at IC/ES, which ensured the confidentiality of personal and health information.

Diagnoses were extracted from NACRS database and medication prescribed within 30 days was drawn from the ODB database. Age, sex, residence area (i.e., Local Health Integration Networks [LHINs]), and neighborhood income quintile were extracted from RPDB dataset. LHINs are the 14 health authorities that are responsible for the regional public healthcare service in Ontario (LHINs, 2020). Neighborhood income quintile is a measure of socioeconomic status that divides the population living in same dissemination area into 5 income groups (1 represents the lowest income; 5 represents the highest income) with approximately 20% of the population in each group (CIHI, 2016).

3.2.3 Selection of Cases and Controls

The cases in this case-control study had to fulfill the following criteria: (a) residing in Ontario; (b) 66 years and older, (c) visited ED for fall-related injury between January 1, 2010 and December 31, 2014. The ODB program covers the cost of prescription medications for all Ontarians 65 years and older, therefore those under the age of 66 were excluded to avoid incomplete medication information in their first year of eligibility. Patients who visited an ED for fall-related injury were captured by the NACRS database. The ICD-10-CA codes (CIHI, 2018b; World Health Organization [WHO], 2020) were used to confirm patients' diagnosis. Fall-related injury in this study was defined by combining the ICD-10-CA codes for falls W00-W19, and codes for injury S00-S99 or T00-T14 (Appendix D). The date when the patient was admitted to the ED due to a fall-related injury was defined as the index date. For individuals who have had multiple entries to EDs, only the information of first entry was used. Cases were excluded if they had experienced an in-hospital fall-related injury, were transferred from another ED, left the ED without being registered, had a scheduled ED visit or died in ED. Controls were older adults without a fall-related injury diagnosis extracted from Ontario RPDB, and matched to cases by the same age, sex, and LHIN, with no fixed ratio. An index date was assigned randomly to each control within the five-year study period. As the authors had no access to the database hosted by IC/ES, all of the above operations were completed by an IC/ES analyst according to a pre-agreed DCP (Appendix B) to generate the matched dataset, which was then provided to the research team.

3.2.4 Medication Use

Use of a certain medication class within 30 days prior to a fall-related injury was regarded as one of the risk factors for fall-related injury. Medications prescribed to case and control groups were extracted from ODB datasets. ODB datasets uses Drug Identification Numbers (DIN) assigned by Health Canada (Health Canada, 2018) to identify different medications. Each DIN included information on medication's manufacturer, trade name, active ingredients, strength of the active ingredients, pharmaceutical form, and route of administration (Health Canada, 2018). In order to better understand and compare findings of this study with the results of other studies,

DIN codes were converted to Anatomical Therapeutic Chemical (ATC) level 5 codes and grouped into 4th level codes. In ATC classification system, each medication is classified in a hierarchy with five levels (WHO, 2019). The 1st level includes fourteen anatomical main groups. These main groups are divided into 2nd level which is the pharmacological or therapeutic group. The 3rd and 4th levels are chemical, pharmacological or therapeutic subgroups and the 5th level is the chemical substance. ATC 4th level is the level used to count number of different medications because it is the level which aggregates medications just above their descriptive chemical substance (Krause, 2008). The numbers of older adults who were prescribed with each ATC 4th level medication class in both the case and control groups were calculated and the analysis of the association between each medication class and fall-related injury was conducted.

3.2.5 Statistical Analysis

The difference between case and control groups characteristics such as age, sex, income quintile, residence area (LHINs), and the number of medication classes prescribed were evaluated by Wilcoxon rank sum test, with a significance level of .01. Due to multiple testing, a conservative Bonferroni adjustment for p-value of each individual test was applied. If the adjusted p-value >1, we define it as 1.00. Older adults were categorized into three age groups, aged 66-74, 75-84, and 85+. The number of medication classes prescribed to each older adult within 30 days of the fall-related injury was calculated and classified into one of four categories: 0-4, 5-9, 10-14, and 15 or more different medication classes (CIHI, 2018a). An examination of the extracted data revealed that there were significant differences between the case and control groups on matched factors such as age, sex and LHINs, so the matching seemed to be incomplete. To address the potential for residual confounding, these factors were included in the adjusted multivariable model. Univariate logistic regression was used to calculate the unadjusted Odds Ratios (ORs) and 99% confidence intervals (CIs) for medication classes. Medication classes for topical use (ATC 'D' codes) and treatment of cancer (ATC 'L' codes) were excluded. Multivariate logistic regression model was conducted for each medication class, adjusted for sex, age group, residence area (LHINs), neighborhood income quintile, and number of medication classes prescribed. The corresponding ORs

were recorded as adjusted ORs (aORs). Attributable risk among the exposed group (older adults who were prescribed with each medication class) and population attributable risk were calculated for each medication class. All the analysis was conducted with SAS 9.4 (SAS Institute, 2013).

3.3 Results

This study included 1,005,066 community-dwelling older adults. The case group included 255,270 older adults who experienced a fall-related injury over the five-year period. The mean age of the cases was 77.7±7.7 years and 61.1% were female. The control group included 749,796 older adults, with a mean age of 75.1±7.5 years old and 54.0% female. The case and control groups were similar in income quintile distribution but were significantly different in LHINs, age group constitution, female percentage, and number of prescribed medication classes (Table 3.1).

Table 3.1 *Characteristics of Case and Control Group*

Characteristics	Case (n = 255,270)	Control (n = 749,796)	*p* value[a]	aORs[b] (99%CI)
Age Mean±SD	77.7±7.7	75.1±7.5		
Age group 66-74 (N, %)	100,027 (39.2)	405,172 (54.0)	<.01	Reference
Age group75-84 (N, %)	96,874 (37.9)	235,486 (31.4)	<.01	1.57 [1.55, 1.59]
Age group 85+ (N, %)	58,396 (22.9)	109,138 (14.6)	<.01	1.85 [1.82, 1.88]
Female (N, %)	157,957 (61.1)	415,513 (54.6)	<.01	1.30 [1.29, 1.32]
Local Health Integration Networks, LHINs (N, %)				
LHIN 01 Erie St. Claire	13,652 (5.3)	39,302 (5.2)	.23	1.21 [1.16, 1.25]
LHIN 02 South West	21,286 (8.3)	54,948 (7.3)	<.01	1.42 [1.37, 1.47]
LHIN 03 Waterloo Wellington	12,654 (5.0)	37,835 (5.0)	.30	1.21 [1.16, 1.26]
LHIN 04 Hamilton Niagara[c]	32,006 (12.5)	87,984 (11.7)	<.01	1.28 [1.23, 1.32]
LHIN 05 Central West	10,915 (4.3)	38,676 (5.2)	<.01	Reference
LHIN 06 Mississauga Halton	17,264 (6.8)	56,762 (7.6)	<.01	1.08 [1.05, 1.12]
LHIN 07 Toronto Central	20,608 (8.1)	63,701 (8.5)	<.01	1.12 [1.08, 1.16]
LHIN 08 Central	29,636 (11.6)	95,770 (12.8)	<.01	1.09 [1.05, 1.12]
LHIN 09 Central East	30,768 (12.1)	92,220 (12.3)	<.01	1.19 [1.15, 1.23]
LHIN 10 South East	13,040 (5.1)	34,213 (4.6)	<.01	1.41 [1.36, 1.47]
LHIN 11 Champlain	24,762 (9.7)	72,939 (9.7)	1.00	1.21 [1.17, 1.25]
LHIN 12 North Simcoe Muskoka	9,797 (3.8)	26,681 (3.6)	<.01	1.35 [1.29, 1.41]
LHIN 13 North East	13,621 (5.3)	35,414 (4.7)	<.01	1.38 [1.33, 1.49]
LHIN 14 North West	5,261 (2.1)	13,351 (1.8)	<.01	1.42 [1.33, 1.49]
Neighborhood Income Quintile (N, %)[d]				
1	52,413 (20.5)	150,600 (20.1)	<.01	0.94 [0.92, 0.96]
2	53,161 (20.8)	156,131 (20.8)	1.00	0.97 [0.95, 0.99]
3	50,081 (19.6)	146,952 (19.6)	1.00	0.98 [0.96, 1.00]
4	49,793 (19.5)	144,927 (19.3)	.26	1.01 [0.99, 1.03]
5 (highest income)	49,822 (19.5)	151,186 (20.2)	<.01	Reference
Number of Medication Classes (N, %)				
0-4	179,175 (70.2)	635,056 (84.7)	<.01	Reference
5-9	55,233 (21.6)	90,111 (12.0)	<.01	1.95 [1.92, 1.98]
10-14	17,194 (6.7)	21,036 (2.8)	<.01	2.50 [2.43, 2.57]
15+	3,667 (1.4)	3,593 (0.5)	<.01	3.23 [3.04, 3.44]

Note. [a] Bonferroni-adjusted p value;

[b] adjusted ORs were obtained by putting age group, sex, LHINs, income quintile and number of medications into a multivariate regression model.

[c] LHIN4: Hamilton Niagara Haldimand Brant;

[d] Neighborhood income quintile is a measure of socioeconomic status that divides the population living in same dissemination area into 5 income groups (1 represents the lowest income; 5 represents the highest income) with approximately 20% of the population in each group

One hundred and fifty medication classes entered the univariate and multivariate regression model. Given the numerous study covariates, only association between fall-related injury and ATC 4th medication classes with an aOR>1.20 and more than 10,000 older adult users were presented in Table 3.2. Proton pump inhibitors (PPIs, A02BC), statins (C10AA), pennicillins with extended spectrum (J01CA) and biphosphonates (M05BA) were associated with increasing the odds of fall-related injury by 20-30%. Drugs for constipation (A06AA, A06AB), testosterones (G04CB), anticholinesterases (N06DA), and drugs for asthma (R03CC) were associated with increasing the odds of fall-related injury by over 50%. Older adults prescribed with non-steroid anti-inflammatory drugs (NSAIDs) such as propionic acid derivatives (M01AE), anti-epileptics (N03AX) were over two times more likely to experience fall-related injury than non-users (M01AE: aOR=2.36, 99%CI [2.24-2.49]; N03AX: aOR=2.02, 99%CI [1.92-2.13]). Using opioids (N02AA) increased the likelihood of having a fall-related injury by 3.5 times (aOR=3.55, 99%CI [3.48-3.62]).

The attributable risk (AR) percentages among exposed group and population attributable risk (PAR) percentages were shown in Table 3.3. Low PARs indicate that either the risk of experiencing fall-related injury is low, or that prescription of particular medication is not prevalent (or both). Avoiding prescribing these medications will have little effect in preventing fall-related injuries. A high PAR indicates that avoiding prescribing these medications could be effective in preventing fall-related injuries. For example, 76.87% of older adults who were prescribed natural opium alkaloids experienced fall-related injuries and 13.04% of all cases of fall-related injuries could be prevented if no natural opium alkaloids were prescribed. The findings of Study 1 indicate that avoiding prescriptions of proton pump inhibitors, emollients, contact laxatives, platelet aggregation inhibitors, statins, biphosphonates, SSRIs, TCAs, anticholinesterases and selective beta-2-adrenoreceptor agonists could have considerable impacts on reducing the fall-related injuries in older adults.

Table 3.2 *Association between Different Medication Classes and Fall-related Injury in Older Adults*

ATC codes	Drug Classes and Indications	Common Indications	Crude OR (99%CI)	aOR* (99%CI)
A02BC	Proton pump inhibitors	for gastric ulcer and GERD	1.97 [1.93, 2.00]	1.21 [1.19, 1.24]
A06AA	Softeners, emollients	for constipation	2.90 [2.81, 2.99]	1.70 [1.64, 1.75]
A06AB	Contact laxatives	for constipation	2.69 [2.59, 2.79]	1.58 [1.52, 1.64]
B01AC	Platelet aggregation inhibitors excl. heparin	prevent thrombosis	2.19 [2.12, 2.27]	1.31 [1.27, 1.36]
C10AA	HMG CoA reductase inhibitors	lower lipids	1.72 [1.70, 1.75]	1.25 [1.23, 1.27]
C10AZ	Other lipid modifying agents	lower lipids	1.75 [1.67, 1.83]	1.32 [1.25, 1.38]
G04BD	Drugs for urinary frequency and incontinence	for incontinence	2.28 [2.17, 2.40]	1.34 [1.27, 1.41]
G04CA	Alpha-adrenoreceptor antagonists	for benign prostatic hyperplasia	1.78 [1.72, 1.84]	1.36 [1.32, 1.41]
G04CB	Testosterone-5-alpha reductase inhibitors	for benign prostatic hyperplasia	1.97 [1.88, 2.07]	1.58 [1.50, 1.66]
J01CA	Penicillins with extended spectrum	for bacterial infection	1.50 [1.43, 1.57]	1.27 [1.21, 1.34]
M01AB	Acetic acid and related substances	anti-inflammation	1.64 [1.56, 1.73]	1.36 [1.29, 1.44]
M01AE	Propionic acid derivatives	anti-inflammation	2.68 [2.55, 2.83]	2.36 [2.24, 2.49]
M01AH	Coxibs	anti-inflammation	1.91 [1.82, 2.02]	1.40 [1.32, 1.48]
M05BA	Biphosphonates	preventing osteoporosis	1.93 [1.89, 1.98]	1.30 [1.27, 1.33]
N02AA	Natural opium alkaloids	for moderate to severe pain	4.32 [4.24, 4.41]	3.55 [3.48, 3.62]
N03AX	Other antiepileptics	for epilepsy	3.07 [2.92, 3.23]	2.02 [1.92, 2.13]
N05AH	Diazepines, oxazepines, thiazepines and oxepines	for schizophrenia	2.34 [2.25, 2.44]	1.28 [1.23, 1.34]
N06AA	Non-selective monoamine reuptake inhibitors	for anxiety, tension and depression	1.91 [1.82, 2.00]	1.25 [1.19, 1.31]
N06AB	Selective serotonin reuptake inhibitors	for anxiety, tension and depression	2.98 [2.91, 3.06]	1.84 [1.79, 1.90]
N06AX	Other antidepressants	for anxiety, tension and depression	2.59 [2.52, 2.66]	1.54 [1.49, 1.58]
N06DA	Anticholinesterases	for Alzheimer's and myasthenia gravis	2.82 [2.74, 2.91]	1.53 [1.48, 1.58]
R03CC	Selective beta-2-adrenoreceptor agonists	for asthma/COPD	2.30 [2.22, 2.39]	1.57 [1.51, 1.63]

Note. *OR adjusted for sex, age group, LHINs, income quintiles, and number of medication classes prescribed;
GERD: gastro-esophageal reflux disease. BPH: benign prostatic hyperplasia. COPD: chronic obstructive pulmonary disease

Table 3.3 *Attributable Risk Percentage of Exposed Group and Population Attributable Risk (PAR) for Each Medication Class*

ATC codes	Drug name	AR_e (99%CI)*	PAR (%)
A02BC	Proton pump inhibitors	49.12 [48.22-50.01]	7.66
A06AA	Softeners, emollients	65.48 [64.43-66.50]	3.86
A06AB	Contact laxatives	62.84 [61.45-64.18]	2.38
B01AC	Platelet aggregation inhibitors excl. heparin	54.34 [52.78-55.84]	2.25
C10AA	HMG CoA reductase inhibitors	41.92 [41.04-42.79]	9.09
C10AX	other lipid modifying agents	42.70 [39.91-45.37]	0.79
G04BD	Drugs for urinary frequency and incontinence	56.05 [53.77-58.22]	1.03
G04CA	Alpha-adrenoreceptor antagonists	43.75 [41.91-45.54]	1.81
G04CB	Testosterone-5-alpha reductase inhibitors	49.30 [46.80-51.69]	0.94
J01CA	Penicillins with extended spectrum	33.23 [29.91-36.40]	0.56
M01AB	Acetic acid and related substances	39.09 [35.76-42.24]	0.57
M01AE	Propionic acid derivatives	62.73 [60.73-64.62]	1.17
M01AH	Coxibs	47.73 [44.90-50.41]	0.75
M05BA	Biphosphates	48.26 [47.02-49.47]	3.94
N02AA	Natural opium alkaloids	76.87 [76.40-77.32]	13.04
N03AX	Other antiepileptics	67.40 [65.68-69.03]	1.38
N05AH	Diazepines, oxazepines, thiazepines and oxepines	57.30 [55.59-58.94]	1.78
N06AA	Non-selective monoamine reuptake inhibitors	47.56 [45.02-49.98]	0.93
N06AB	Selective serotonin reuptake inhibitors	66.45 [65.57-67.31]	5.33
N06AX	Other antidepressants	61.31 [60.23-62.35]	4.14
N06DA	Anticholinesterases	64.59 [63.45-65.70]	3.36
R03CC	Selective beta-2-adrenoreceptor agonists	56.51 [54.87-58.09]	1.97

Note *AR_e=Attributable Risk Percentage among exposed group (Exposed refers to older adults who were prescribed certain medication class)

3.4 Discussion

This population-based, case control study examined the association between fall-related injury and medication classes prescribed to older adults within 30 days prior to the injury. The result of our study provided novel findings on several mediation classes that were associated with increased odds of fall-related injury in older adults, such as medication classes used for benign prostatic hyperplasia, bacterial infections and bronchodilators.

Previous studies have reported a positive association between fall-related injury in older adults and drugs acting on the central nervous system (CNS) such as opioids (N02A) (Söderberg et al., 2013), antiepileptics (N03) (Resnick et al., 2012; Sylvestre et al., 2012), anti-Parkinson agents (N04) (Resnick et al., 2012), antipsychotics (N05A) (Byers, et al., 2008; Resnick et al., 2012), antidepressants (N06A) (Kerse et al., 2008; Sterke et al., 2012), and anticholinesterases (N06DA) (Richardson et al., 2015; Salahudeen et al., 2015). Findings from our study were consistent with these studies, but unique to our study is that all of our assessments on different medication classes came from the same population, while other studies had various target populations (Kerse et al., 2008; Resnick et al., 2012; Sylvestre et al., 2012); or were focused on one or two specific medication classes (Kerse et al., 2008; Söderberg et al., 2013). The explanations why these medication classes were associated with falls and fall-related injuries focused on side effects such as confusion, blurred vision, dizziness, sedation, postural hypotension, and extra-pyramidal effects (Daoust et al., 2018; Hill & Wee, 2012; Joe & Forester, 2010; Masud et al., 2013; Quach et al., 2013).

Kelly et al. (2003) and Kuschel et al (2015) used population-based, administrative data to identify a wide range of medication classes that were associated with fall-related injury in older adults (Kelly et al., 2003; Kuschel et al., 2015). Both studies captured medication prescription within 30 days prior to the fall-related injury in older adults. Kelly et al. (2003) used health registry data from Alberta, Canada in 1997/1998 fiscal year. They found that narcotic pain killers, anti-convulsants (anti-epileptics), and anti-depressants were independently associated with an increased risk of sustaining injurious falls. The authors tried to eliminate the influence of comorbidities by using various comorbidities as confounding factors. However, this is complicated because multiple medication classes

could be used in the treatment of one comorbidity while one medication class could be used to treat multiple comorbidities. The real effect of each single medication class on injurious falls is difficult to fully define. Kuschel and colleagues (2015) reported twenty most commonly prescribed ATC 3rd medication classes and their association with fall-related injuries using Swedish public health data. Additional to CNS drugs (N02A, N02B, N05C and N06A), drugs for peptic ulcer (A02B), constipation drugs (A06A), antithrombotic agents (B01A), Vitamin B12 (B03B), Calcium (A12A), and NSAIDs (M01A) were reported to be independently associated with fall injuries. Consistent with Kuschel et al., our study found a positive association between PPIs (A02BC), constipation drugs (A06AA, A06AB), anti-thrombotic agents (B01AC, B01AE), and NSAIDs (M01AB, M01AE, and M01AH) and fall-related injury. What is new in our findings, is positive association of lipid-lowering agents (statins, C10AA), drugs for benign prostatic hyperplasia (G04CA and G04CB), pennicillins with extended spectrum (J01DB), biphosphonates (M05BA), and selective β-2-adrenoreceptor agonists for asthma (R03CC) with fall-related injuries in older adults.

A recent systematic review by de Vries et al. (2018) reported that statins had a protective effect on fall-related injury in older adults. Contrary to this, our study identified that statins were associated with increased odds of fall-related injuries (aOR= 1.25, 99%CI [1.23-1.27]). Other studies have described that the side effects of statins, such as myopathy and muscle weakness, were more prevalent and serious in elderly patients than younger patients (Horodinschi et al., 2019; Mansi et al., 2013). Muscle disorders associated with statins contribution to older adults' physical deconditioning and frailty (Curfman, 2017) could in part explain increased risk for fall-related injury. According to the CIHI 2018 report, statins were prescribed to nearly half of Canadian older adults, but percentage of statins users decreased with age (CIHI, 2018a). Future studies are needed to explore the impact of statins on fall-related injury in different age groups of older adults. They will provide clinicians with more confidence in balancing the risk and benefit in prescribing statins to older adults.

The finding that α -adrenoreceptor antagonists (G04CA) and testerones-5 α reductase inhibitors (G04CB) might increase the odds of fall-related injury in older adults by 36-

58% was rather new. The α-adrenoreceptor antagonists are used for the treatment of hypertension, so it is plausible that known side effects of α-adrenoreceptor antagonists, such as orthostatic hypotension, dizziness, drowsiness and fatigue could lead to fall-related injuries (Sica, 2005). Testerones-5 α reductase inhibitors have some cardiovascular side effects, such as syncope and hypotension that could also lead to falls and serious fall-related consequences (Lee & Cho, 2018). Welk et al. (2015) did not find that using 5 α reductase inhibitors was related to fractures (OR = 0.88, 95% CI [0.70-1.10]), but they explained that physicians prescribed 5 α reductase inhibitors only to older adults that were judged to have low risk of falls or fractures.

Our study also found several anti-bacterial infection agents were associated with increased odds of fall-related injury. For example, first-generation cephalosporins (J01DB) were associated with increasing the odds of fall-related injury by 2.8 times (aOR=2.79, 99%CI [2.64-2.96]). Users of penicillins with extended spectrum (J01CA) were 27% more likely to have a fall-related injury than non-users (aOR=1.27, 99%CI [1.21-1.34]). The findings that some NSAIDs were also positively associated with fall-related injury indicated that infection itself could have an impact in the occurrence of fall-related injury. Future research that will take infection into consideration as a confounding factor might better demonstrate the association between anti-inflammatory and anti-infective agents and fall-related injury in older adults.

It was not expected to see biphosphonates (M05BA), commonly used to treat osteoporosis, on the list of medications that were associated with increased odds for fall-related injury (aOR=1.30, 99%CI [1.27-1.33]). This was contrary to Caffarelli et al. (2017) who found that biphosphonates offer a null or protective effect on falls in older adults. A possible explanation for this contradictory finding may be that individuals taking biphosphonates for osteoporosis are more suspectable to fall-related injuries due to the nature of the medical condition (Kärkkäinen et al., 2010; Uusi-Rasi et al., 2013). We were unable to tease apart the role of osteoporosis diagnosis in our analysis.

Selective β-2-adrenoreceptor agonists, also known as bronchodilators, are used as mainstay treatment for respiratory diseases, such as bronchial asthma and COPD. Mayo

and colleagues (1989) reported bronchodilators were not associated with increased odds of falls in hospitals among older adults, but studies examining the association between bronchodilators and fall-related injury were scarce. In our study, selective β-2-adrenoreceptor agonists were independently associated with fall-related injury (aOR=1.43, 95% CI [1.39 - 1.47]). The CIHI reported that selective β-2-adrenoreceptor agonists were prescribed to 13.1% Ontario older adults in 2016 (CIHI, 2018a), which makes them a common medication class prescribed to older adults, and continued investigation into their relation to fall-related injury is necessary.

We noticed that income level (neighborhood income quintile) was not associated with fall-related injuries in older adults, after adjustments for sex, age group, residence area (LHINs) and number of medication classes prescribed. Previously, socioeconomic status was reported to be associated with higher risk of falls and worse outcomes after injuries (Cruz et al., 2012; Gill et al., 2005; Vieira et al., 2018). It was well-accepted that individuals with low socioeconomic status had greater difficulty in accessing health services and consequently prevent factors that could lead to falls (Cruz et al., 2012; Gill et al., 2005; Vieira et al., 2018). However, similar to our findings, two population-based studies conducted in different countries (Denmark, Indonesian) did not report the association between income level and falls or fractures (Bonnerup Vind et al., 2011; Pengpid et al., 2018). Further, a systematic review investigating the association between socioeconomic status and osteoporotic fractures did not find that lower income level was related to higher risk of fractures (Brennan et al., 2009). None of these studies provided an explanation for the failure to find association between income level and falls or fractures. In our opinion, the lack of association between the income level and fall-related injuries could be an indicator of the improving equality of access to health care services in the general older adult population in Ontario.

3.4.1 Strengths and Limitations

This was a population-based study investigating the association between medication prescribed within 30 days of fall-related injury in older adults using province-wide (Ontario) administrative health data. The major strengths are provincial representativeness and large size with over a million older adults in the case and control

groups. The dataset included detailed information on demographics, comorbidities, prescribed medication classes, and strictly defined fall-related injuries using ICD-10-CA codes. Second, data obtained from IC/ES databases has been recognized to have high data completeness (Levy et al., 2003) and high quality (Aiken et al., 2016; Liu et al., 2018; Macri et al., 2017). Third, due to study's population-based design, the results can be generalized to the entire population of older adults in Ontario, Canada. Fourth, all the index events were recorded on the day cases went to the ED because of a fall-related injury, so recall bias is minimal.

Several limitations are associated with this study. First, the algorithm used to match cases and controls did not have a fixed ratio and the matching was not successful when groups were compared on the matching factors. In response, the multivariable logistic regression modeling was adjusted for the matching variables to account for any residual confounding. Second, we evaluated only fall-related injuries leading to ED visit, therefore these results cannot be generalized to less severe fall-related injuries. Third, only prescribed and dispensed drugs were recorded in ODB database, but neither prescription nor dispensation can be equated with actual use, which is an unfortunate limitation of this type of research. Further, we recorded medications prescribed one month prior to a fall-related injury, but we were not able to ascertain whether a medication was used for a long-term or it was a new initiation. We believe that the timing of medication use is of importance and will address this in our future research. Fourth, some comorbidities might be associated with fall-related injuries, but the detailed information on indications for prescription was not available in the original databases from which we extracted our dataset. Hence, our results could include a degree of overestimation of the association between medications and fall-related injuries. What is more, confounding by indication was not fully addressed in this study. Confounding by indication occurs when selecting a particular intervention also affects the outcome (Kyriacou & Lewis, R, 2016; Salas & Stricker, 1999). For example, patients with more severe diseases are likely to receive more intensive care and treatment, therefore when comparing the interventions, the more intensive intervention will appear to result in poorer outcomes. The degree of severity of a disease affects both treatment selection and patient outcome and these factors could be related to fall-related injuries. Hence, findings

from this study should be viewed with caution. Last but not least, there was a lack of indicators for the frailty in both case and control groups. For example, surgeries and other medical procedures could substantially but temporarily increase the number of prescribed medications in the peri-operative period, which in an administrative dataset might be mimicking the frailty. Unfortunately, in this study, we did not have enough information to address the impact of frailty on fall-related injuries.

3.5 Conclusion

This study examined the association between fall-related injury in older adults and medication classes prescribed to them within 30 days prior to the injury. Our findings acknowledged persistent association of CNS drugs with the fall-related injuries, and provided additional associations between fall-related injury and statins, PPIs, antithrombotic agents, laxatives, drugs for benign prostatic hyperplasia, antibiotics, biphosphonates, and bronchodilators. Well-designed prospective cohort studies probing into the effects of comorbidities, Injury Severity Scores and detailed prescription indications are needed to provide more convincing evidence for clinicians and physicians.

3.6 Reference

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Chapter 4

4 Association between Continuous use or New Initiation of Medications and Fall-Related Injuries in Older Adults

4.1 Introduction

The rapid growth of world aging population and its related challenges have become major concern to individuals, families and the societies. It was reported that 20-30% of community dwelling older adults aged 65 years or older fall every year (Chang et al., 2010; Tanimoto et al., 2014; Tinetti et al., 2006; Wu & Ouyang, 2017). Falls are the leading cause of non-fatal and fatal injuries for older adults in many countries and regions (Bergen et al., 2016; Ellingsen et al., 2018; National Council of Aging, 2018; Public Health Agency of Canada, 2014). About 30-50% falls result in minor injuries such as bruises, sprains and strains that may or may not require medical treatment, while 5-10% of falls lead to serious consequences such as fractures and brain injury (Cameron et al., 2012; Gillespie et al., 2012; Goldacre et al., 2002; Health Quality Ontario, 2008). Fall-related injuries can result in decreased independence and quality of life, disability, prolonged length of stay in hospitals and increased risk of early admissions to long-term care facilities (Burns et al., 2016; Gill et al., 2013, Scott et al., 2010), as well as cause substantial economic burden to the public health care system (National Council of Aging, 2018; Parachute, 2015; Zecevic et al., 2012). It was estimated that about 0.9%-1.5% of total health care cost were the fall-related expenses in the US, Europe and Australia (Heinrich et al., 2009). Fall-related injuries have become a serious health risk in later life, that will continue to grow with an increasing older adult population (He et al., 2016).

The mechanism of fall-related injuries in older adults is complicated and multifactorial. History of falls, old age, mobility and balance problems, and use of psychotropic medications and cardiovascular medications were reported to be associated with fall-related injuries (Gillespie et al., 2012; Mccoy et al., 2017; Nilsson et al., 2016). Most importantly, the prescription of medications to older adults increased significantly over the last twenty years (Clemens et al., 2015; Craftman et al, 2016; Jackevicius et al., 2009;

Minard et al., 2016), further increasing this prominent modifiable risk factor for fall-related injuries.

Previous studies have focused mainly on the association of cross-sectional use of certain medication classes and fall-related injuries (de Vries et al., 2018; Leipzig et al., 1999a; Leipzig et al., 1999b; Seppala, Wermelink, et al., 2018; Seppala, van de Glind, et al., 2018; Zang, 2013). However, medication initiation, change in dosage and long-term use are significant concerns, as are medications' therapeutic effects and side effects (Barker et al., 2004; Engelke et al., 2019; Huybrechts et al., 2011; Hyttinen et al.,2017; Schmieder et al., 2009). Daoust and colleagues (2018) reported that opioids use were associated with increasing the risk of falls 2.5 times in first two weeks of drug initiation. Butt et al. (2013) reported that within 14 days of new initiation of any antihypertensive drug were associated with doubled risk of falls (Incidence rate ratio [IRR]= 1.94 and 95% Confidence Intervals [CIs] [1.75-2.16]). A recent systematic review reported that chronic antihypertensive drug use was not associated with falls, but there was a highly elevated risk of falls in the first day after the drug initiation (Kahlaee et al., 2018). A clear gap in the current literature is limited understanding of the association between fall-related injuries and new initiation or continuous use of medications. The purpose of this study was to explore the association between chronically used or newly initiated medication classes and fall-related injury in older adults.

4.2 Methods

4.2.1 Study Design

We conducted a population-based, case-control study using administrative secondary health care data for Canada's most populous province of Ontario. Ontario is the largest province in Canada, with a population of 14.7 million and 2.6 million older adults over the age of 65 (Statistics Canada, 2020), all of whom have access to universal healthcare services. The extraction of eligible participants in this study was conducted by IC/ES analysts, based on a carefully prepared data creation plan (DCP, Appendix B). IC/ES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic

data. IC/ES is a prescribed entity under the section 45 of Ontario's Personal Health Information Protection Act. Section 45 authorizes IC/ES to collect personal health information, without consent, for the purpose of analysis or compiling statistical information with respect to the management of, evaluation or monitoring of, the allocation of resources to or planning for all or part of the health system. Projects conducted under section 45, by definition, do not require review by a Research Ethics Board. This project was conducted under section 45, and was approved by IC/ES' Privacy and Legal Office. However, ethics approval for this series of studies was required in Western University, and it was obtained from the Research Ethics Board at Western University, London, Ontario, Canada (HSREB #109335, detailed information was provided in Appendix C).

4.2.2 Data Sources

We used records from three databases held by IC/ES: (1) the Ontario Drug Benefit (ODB) database, which provides prescription drug coverage data for residents over the age of 65, including individuals in long-term care homes (Government of Ontario, 2019); (2) the National Ambulatory Care Reporting System (NACRS), which captures information on visits to emergency departments (EDs) and community-based ambulatory care facilities; and (3) the Ontario Registered Persons Database (RPDB), which contains demographic information for Ontario residents. These databases were linked using unique encoded identifiers, which ensured the confidentiality of personal and health information.

Age, sex, residence area (i.e., Local Health Integration Networks [LHINs]), and neighborhood income quintile were extracted from RPDB dataset. LHINs are the health authorities that are responsible for the regional public healthcare service in Ontario, Canada. There are 14 LHINs in operation in Ontario (Local Health Integration Networks, 2020). Neighborhood income quintile is a measure of socioeconomic status that divides the population living in same dissemination area into five income groups (1 represents the lowest income; 5 represents the highest income) with approximately 20% of the population in each group (Canadian Institute for Health Information [CIHI], 2016).

4.2.3 Selection of Cases and Controls

The cases in this case-control study had to fulfill the following criteria: (a) residing in Ontario; (b) 66 years and older, (c) visited ED for fall-related injury between January 1, 2010 and December 31, 2014. The ODB program covers the cost of prescription medications for all Ontarians 65 years and older, therefore those under the age of 66 were excluded to avoid incomplete medication information in their first year of eligibility. Patients who visited an ED for fall-related injury were captured by the NACRS database. The ICD-10-CA codes (CIHI, 2018b; World Health Organization [WHO], 2020) were used to confirm patients' diagnosis. Fall-related injury in this study was defined by combining the ICD-10-CA codes for falls W00-W19, and codes for injury S00-S99 or T00-T14 (Appendix D). The date when the patient was admitted to the ED due to a fall-related injury was defined as the index date. For individuals who have had multiple entries to EDs, only the information of first entry was used. Cases were excluded if they had experienced an in-hospital fall-related injury, were transferred from another ED, left the ED without being registered, had a scheduled ED visit or died in ED. Controls were older adults without a fall-related injury diagnosis extracted from Ontario RPDB, and matched to cases by the same age, sex, and LHIN, with no fixed ratio. An index date was assigned randomly to each control within the five-year study period. As the authors had no access to the database hosted by IC/ES, all of the above operations were completed by an IC/ES analyst according to a pre-agreed DCP (Appendix B) to generate the matched dataset, which was then provided to the research team.

4.2.4 Medication Use

Continuous use or new initiation of a medication class prior to fall-related injury was regarded as one of the risk factors for fall-related injuries. Continuous use of a medication is operationally defined as more than 90 days of refill of a medication within three months prior to a fall-related injury. New initiation of a medication is operationally defined as any new prescription of a medication within 30 days prior to a fall-related injury. The newly initiated medication must not have appeared in the person's prescription list within 365 days to 31 days prior to the injury. ODB datasets uses Drug Identification Numbers (DIN), an eight-digit number, assigned by Health Canada (Health

Canada, 2018) to identify different medications. Each DIN included information on medication's manufacturer, trade name, active ingredients, strength of the active ingredients, pharmaceutical form, and route of administration (Health Canada, 2018). In order to better understand and compare findings of this study with the results of other studies, DIN codes were converted to Anatomical Therapeutic Chemical (ATC) level 5 codes and grouped into 4th level codes. In ATC classification system, each medication is classified in a hierarchy with 5 levels (WHO, 2019). The 1st level includes fourteen anatomical main groups, these main groups are divided into 2nd level, which is the pharmacological or therapeutic group. The 3rd and 4th levels are chemical, pharmacological or therapeutic subgroups and the 5th level the chemical substance. ATC 4th level was used to report continuous use and new initiation of different medications because it is the level which aggregates medications just above their descriptive chemical substance (Krause, 2008).

4.2.5 Statistical Analysis

The difference between case and control groups in characteristics such as age, sex, income quintile, LHINs, the number of medication classes prescribed with, presence of COPD, asthma, dementia, diabetes and hypertension were evaluated by Wilcoxon rank sum test, with an alpha of .01. Older adults were categorized into three groups, aged 66-74, 75-84, and 85+. The number of medication classes prescribed to each older adult within 30 days of the fall-related injuries was calculated and classified into one of four categories: 0-4, 5-9, 10-14, and 15 or more different medication classes. Number of continuous users and new users of each medication class in both case and control group were calculated. To ensure the power, only top 30 most frequent medication classes for continuous use and for new initiation were included in the regression analysis. Univariate logistic regression was used to calculate the crude Odds Ratios (ORs) and 99% confidence intervals (CIs) for continuous use or new initiation of each medication class. Multivariate logistic regression models were conducted for each included medication class, adjusted for sex, age group, LHIN, neighborhood income quintile, and number of medication classes prescribed. The corresponding ORs were recorded as adjusted ORs (aORs). All the analysis was conducted with SAS 9.4 (SAS Institute, 2013).

4.3 Results

This study included 1,005,066 community-dwelling older adults. The case group included 255,270 older adults who experienced fall-related injuries over the five-year period. The mean age of the cases was 77.7±7.7 years and 61.1% were female. The control group included 749,796 older adults, with a mean age of 75.1±7.5 years old and 54.0% female. The case and control groups were similar in income quintile distribution but were significantly different in LHINs, age group constitution, female percentage, and number of prescribed medication classes (Table 3.1).

For medication classes with continuous use, HMG-CoA reductase inhibitor (statin, C10AA) was the most commonly prescribed among older adults who experienced fall-related injuries (Table 4.1). Eight different anti-hypertensive medications were among the top 30 medication classes with most common continuous use. Continuous use of psychotropic agents such as antidepressants (N06AB and N06AX), benzodiazepine derivatives (N05BA), opioids (N02AA) and anticholinesterases (N06DA) were also very common. Other medications with continuous use were proton pump inhibitors (A02BC), laxatives (A06AA), glucose sugar lowering drugs (A10BA, A10BB), thyroid hormones (H03AA) and biphosphonates (M05BA). After adjustment for sex, age group, number of medications prescribed, income quintile and residence area (LHINs), continuous use of selective serotonin reuptake inhibitors (SSRIs, medication for depression) were associated with increasing the odds of fall-related injuries almost by two times (aOR=1.96, 99%CI [1.91-2.01]). Other medications that could increase the odds of fall-related injuries by over 50% were drugs for benign prostate hyperplasia (G04CA and G04CB), antithrombin agents (B01AC) and anticholinesterases (N06DA) for treating Alzheimer's disease. Organic nitrates (C01DA) and H2-receptor antagonist (lowering the production of stomach acid) were negatively related to fall-related injuries.

Table 4.1 *Association Between Top 30 most Common Medications with Continuous Use and Fall-related Injury in Older Adults*

ATC code	Medication Class	Number of Users			Unadjusted ORs (99% CIs)	Adjusted ORs* (99% CIs)
		Case	Control	Total		
A02BA	H2-receptor antagonists	5,343	13,837	19,180	1.14 [1.10, 1.17]	0.87 [0.83, 0.91]
A02BC	Proton pump inhibitors	48,280	86,250	134,530	1.97 [1.65, 2.34]	1.40 [1.38, 1.42]
A06AA	Softeners, emollients	9,810	13,810	23,620	2.13 [2.08, 2.19]	1.37 [1.32, 1.42]
A10BA	Biguanides	23,371	53,109	76,480	1.32 [1.30, 1.34]	1.17 [1.15, 1.20]
A10BB	Sulfonylureas	12,073	27,299	39,372	1.31 [1.29, 1.34]	1.12 [1.09, 1.16]
B01AA	Vitamin K antagonists	9,422	16,677	26,099	1.69 [1.64, 1.73]	1.22 [1.18, 1.26]
B01AC	Platelet aggregation inhibitors	12,938	19,568	32,506	1.99 [1.95, 2.04]	1.56 [1.51, 1.61]
B03AD	Iron in combination with folic acid	7,720	12,699	20,419	1.81 [1.76, 1.86]	1.19 [1.14, 1.23]
C01DA	Organic nitrates	6,744	14,738	21,482	1.35 [1.32, 1.39]	0.78 [0.75, 0.81]
C03AA	Thiazides, plain	23,513	58,028	81,541	1.21 [1.19, 1.23]	1.10 [1.08, 1.13]
C03CA	Sulfonamides, plain	21,463	39,165	60,628	1.67 [1.64, 1.70]	N/A
C07AB	Beta blocking agents, selective	42,537	92,690	135,227	1.42 [1.40, 1.44]	1.18 [1.16, 1.20]
C08CA	Dihydropyridine derivatives	38,097	88,173	126,270	1.35 [1.33, 1.37]	1.15 [1.13, 1.17]
C08DB	Benzothiazepine derivatives	10,318	18,718	29,036	1.65 [1.61, 1.69]	1.34 [1.29, 1.38]
C09AA	ACE inhibitors, plain	48,459	117,654	166,113	1.26 [1.24, 1.27]	1.10 [1.09, 1.12]
C09CA	Agents on RAS	26,181	60,570	86,751	1.30 [1.28, 1.32]	1.17 [1.15, 1.20]
C09DB	ARBs and CCBs	7,274	19,629	26,903	1.09 [1.06, 1.12]	1.13 [1.09, 1.17]
C10AA	HMG CoA reductase inhibitors	85,971	195,116	281,087	1.44 [1.43, 1.46]	1.37 [1.35, 1.39]
C10AX	Other lipid modifying agents	7,930	15,842	23,772	1.49 [1.45, 1.53]	1.45 [1.40, 1.50]
G04CA	Alpha-adrenoreceptor antagonists	13,440	27,968	41,408	1.44 [1.41, 1.47]	1.40 [1.36, 1.44]
G04CB	Testosterone-5-alpha reductase inhibitors	6,811	12,494	19,305	1.62 [1.57, 1.67]	1.66 [1.59, 1.73]
H03AA	Thyroid hormones	34,551	69,421	103,972	1.53 [1.51, 1.56]	1.25 [1.23, 1.28]
M04AA	Preparations inhibiting uric acid production	8,050	17,818	25,868	1.34 [1.30, 1.37]	1.19 [1.14, 1.23]
M05BA	Biphosphonates	16,170	32,050	48,220	1.52 [1.49, 1.55]	1.19 [1.16, 1.22]
N02AA	Natural opium alkaloids	7,693	11,281	18,974	2.04 [1.98, 2.10]	1.34 [1.29, 1.40]
N05BA	Benzodiazepine derivatives	13,724	24,991	38,715	1.65 [1.61, 1.68]	1.18 [1.14, 1.21]
N06AB	SSRIs	20,475	24,259	44,734	2.61 [2.56, 2.66]	1.96 [1.91, 2.01]
N06AX	Other antidepressants	16,001	21,066	37,067	2.31 [2.27, 2.36]	1.62 [1.57, 1.67]
N06DA	Anticholinesterases	11,194	12,913	24,107	2.62 [2.55, 2.69]	1.58 [1.52, 1.64]
R03BB	Anticholinergics	9,885	17,933	27,818	1.65 [1.60, 1.69]	1.27 [1.22, 1.31]

Note ACE inhibitors: angiotensin converting enzyme inhibitors; RAS: renin-angiotensin system; ARBs: Angiotensin II receptor blockers; CCBs: calcium channel blockers; N/A: not available

* adjusted for sex, age group, income quintile, residence area (Local Health Integration Networks) and number of medication classes prescribed in 30 days

Table 4.2 *Association between Top 30 New Initiated Medication Classes and Fall-related Injury*

ATC code	Medication Class	Number of Users			Unadjusted ORs (99% CIs)	Adjusted ORs* (99% CIs)
		Case	Control	Total		
A02BC	Proton pump inhibitors	2,010	4,255	6,265	1.39 [1.32, 1.47]	1.08 [1.01, 1.16]
A06AA	Softeners, emollients	1,650	2,559	4,209	1.90 [1.79, 2.02]	1.26 [1.16, 1.37]
A06AB	Contact laxatives	1,555	2,348	3,903	1.95 [1.83, 2.08]	1.30 [1.19, 1.42]
A06AD	Osmotically acting laxatives	1,840	2,789	4,629	1.95 [1.84, 2.07]	1.32 [1.22, 1.43]
B03AD	Iron in combination with folic acid	804	1,501	2,305	1.58 [1.45, 1.72]	N/A
C01DA	Organic nitrates	913	1,947	2,860	1.38 [1.27, 1.49]	0.91 [0.82, 1.01]
C03CA	Sulfonamides, plain	1,236	2,103	3,339	1.73 [1.61, 1.86]	N/A
C07AB	Beta blocking agents, selective	953	1,719	2,672	1.63 [1.51, 1.77]	1.15 [1.04, 1.28]
C08CA	Dihydropyridine derivatives	758	1,674	2,432	1.33 [1.22, 1.45]	N/A
C09AA	ACE inhibitors, plain	938	2,046	2,984	1.35 [1.25, 1.46]	N/A
C09CA	agents on the renin-angiotensin system	660	1,431	2,091	1.36 [1.24, 1.49]	1.45 [1.15, 1.84]
C10AA	HMG CoA reductase inhibitors	1,106	2,562	3,668	1.27 [1.18, 1.36]	1.11 [1.01, 1.22]
H02AB	Glucocorticoids	2,542	4,921	7,463	1.52 [1.45, 1.60]	1.17 [1.10, 1.25]
J01CA	Penicillins with extended spectrum	2,385	4,869	7,254	1.44 [1.37, 1.52]	1.24 [1.16, 1.33]
J01DB	First-generation cephalosporins	1,951	2,750	4,701	2.09 [1.98, 2.22]	1.56 [1.44, 1.69]
J01DC	Second-generation cephalosporins	631	1,389	2,020	1.34 [1.22, 1.47]	N/A
J01FA	Macrolides	1,945	4,358	6,303	1.31 [1.25, 1.39]	1.08 [1.01, 1.16]
J01MA	Fluoroquinolones	2,931	5,296	8,227	1.63 [1.56, 1.71]	1.13 [1.06, 1.20]
J01XE	Nitrofuran derivatives	1,410	2,093	3,503	1.99 [1.86, 2.13]	1.40 [1.28, 1.54]
M01AB	Acetic acid derivatives, related substances	747	1,367	2,114	1.61 [1.47, 1.76]	1.50 [1.33, 1.70]
M01AE	Propionic acid derivatives	1,083	1,863	2,946	1.71 [1.59, 1.85]	1.53 [1.38, 1.70]
N02AA	Natural opium alkaloids	4,409	6,515	10,924	2.01 [1.93, 2.09]	1.58 [1.50, 1.67]
N05BA	Benzodiazepine derivatives	1,523	2,653	4,176	1.69 [1.59, 1.80]	1.17 [1.08, 1.28]
N06AB	Selective serotonin reuptake inhibitors	1,332	1,247	2,579	3.15 [2.91, 3.40]	2.14 [1.93, 2.38]
N06AX	Other antidepressants	1,417	1,417	2,834	2.94 [2.73, 3.17]	1.94 [1.76, 2.15]
R03BA	Glucocorticoids (drugs for COPD)	750	1,815	2,565	1.21 [1.12, 1.32]	0.89 [0.80, 1.00]
R03BB	Anticholinergics	701	1,316	2,017	1.57 [1.43, 1.72]	N/A
R03CC	Selective beta-2-adrenoreceptor agonists	1,757	2,466	4,223	2.10 [1.98, 2.24]	1.49 [1.37, 1.62]
S01AA	Antibiotics-ophthalmologicals	672	1,438	2,110	1.37 [1.25, 1.51]	N/A
S01BA	Corticosteroids, plain	985	2,133	3,118	1.36 [1.26, 1.47]	1.17 [1.06, 1.30]

Note. ACE inhibitors: angiotensin converting enzyme inhibitors; COPD: chronic obstructive pulmonary disease; N/A: not available

* adjusted for sex, age group, income quintile, residence area (Local Health Integration Networks) and number of medication classes prescribed in 30 days

Natural opium alkaloids (opioids) were the most commonly new-initiated medications in older adults before they had fall-related injuries. Anti-hypertensive agents and psychotropic agents were also very common. Interestingly, there were six different medications for treatment of infections in the top 30 most commonly new-initiated medications (Table 4.2). New initiation of SSRIs and other antidepressants were associated with increasing the odds of fall-related injuries by more than two times (SSRIs: aOR=2.14, with 99%CI [1.93-2.38]; other antidepressants: aOR=1.94 with 99%CI [1.76-2.15]). New initiation of opioids (N02AA), first-generation cephalosporins (J01DB), propionic acid derivatives (M01AE), and acetic acid derivatives (M01AB) were also associated with increasing the odds of fall-related injuries by over 50%. Except for agents acting on renin-angiotensin system (C09CA), new initiation of other antihypertensive showed no association or minor association with fall-related injuries.

4.4 Discussion

This population-based, case-control study evaluated the association between fall-related injuries and 30 most common medication classes for continuous use and medications that were newly initiated. Continuous use of antidepressants, drugs for benign prostate hyperplasia, anticholinesterases for Alzheimer's disease, emollients for constipation, and antithrombin agents were found to increase the odds of fall-related injuries by over 50%. New initiation of antidepressants, opioids, first-generation cephalosporins, non-steroids anti-inflammatory drugs (NSAIDs), and laxatives also showed to be associated with increased odds for fall-related injuries.

There is no consensus among researchers on how to define continuous use of a medication as it depends on the medication itself. For example, for antibiotics and NSAIDs, more than 14 days of use is considered as long-term. For benzodiazepines and antidepressants, six months is considered as long-term use (Cartwright et al., 2016; Kurko et al., 2015). However, for blood glucose lowering agents and antihypertensive drugs, a year is considered as long-term use (Kahlaee et al., 2018). Older adults diagnosed with chronic diseases often take medications for years and even remaining lifetime (Lornstad et al., 2019; Rossello et al., 2015, Sharma et al., 2015). This study applied three months (90 days) period to define "continuous use" of medications, guided

by acceptance of this definition in previous studies (Ammerman et al., 2019; Aubron et al., 2010; Bargagli et al., 2019; Hart et al., 2019)

Statins are widely prescribed to older adults with high cholesterol in order to reduce the risk of cardiovascular event. In our study, 28.1% older adults used statins for a long-term of over three months. This rate was comparable to findings of Wang et al. (2016) who reported a chronic statin use rate in 31.4% older adults. The association between continuous use of statins and continuous use odds of fall-related injuries in older adults was unexpected (aOR=1.37, 99%CI [1.35, 1.39]). Some clinical trials demonstrated that statins had a decreased survival benefit in sicker patients, especially among older adults with heart failure (Kjekshus et al., 2007) and those undergoing dialysis (Wanner et al., 2005). However, a systematic review summarized three studies on statin use as an exposure to the risk of falls (Seppala, van de Glind, et al., 2018), and reported a pooled OR of 0.80 (95%CI [0.65,0.98]). The authors explained that statins' protective association with falls might be explained by statins' reducing white matter lesion progression, thus delaying the balance impairments. However, this meta-analysis did not take into consideration the duration of statin use, so further research was recommended on the statin use duration in older adults and better differentiation of participants (e.g., different age groups or health status). Important distinction here is that our study reports association with injuries due to falls, not falls themselves.

Proton pump inhibitors (PPIs) were prescribed to 32.1% of Canadian older adults in 2016 (CIHI, 2018b). Although we did not find that new initiation of PPIs were associated with increased odds of fall-related injuries, continuous use of PPIs was identified to be associated with increasing the odds of injury by 40% (aOR=1.40, 99%CI [1.38-1.42]). Lewis et al. (2014) reported that PPI therapy for longer than one year was associated with continuous use odds of hip fracture in older adults (aOR=2.04, 95%CI [1.23-3.37]). Yang et al. (2006) showed that the strength of the association continuous use with increasing duration of PPI therapy (1 year of PPI therapy aOR=1.22, 95% CI, [1.15-1.30]; 2 years, aOR=1.41, 95% CI, 1.28-1.56]; and 4 years, 1.59 [95% CI, 1.39- 1.80]; P.001 for all comparisons). A possible explanation for why PPIs increase the risk of fracture might be that PPIs reduce intestinal calcium and vitamin D absorption and thus might contribute to

a decrease in bone mineral density (Dharmarajan et al., 2008). Another mechanism might lie in the fact that PPI users were found to have a 18% lower level of Vitamin B12. Ample evidence shows that long-term Vitamin B12 deficiency could result in gait disorders, muscle weakness, cognitive decline and impaired vision (Lewis et al., 2014; Marcuard et al., 1994; Stabler, 2013), all of which are risk factors for fall-related injuries.

Although researchers have noticed that initiation or continuous use of antihypertensive agents were related to falls, studies on the association with fall-related injuries remain rare. A systematic review using more than 28 days of medication therapy as continuous use reported that continuous use of antihypertensive agents did not increase the risk of falls in older adults (Kahlaee et al., 2018). But our study showed that continuous use of angiotensin-converting enzyme inhibitors (ACEIs), BBs, dihydropyridine derivatives, agents acting on the renin-angiotensin system, thiazides, angiotensin II receptor blocker (ARBs) and calcium channel blockers (CCBs) combination were associated with slightly increasing the risk of fall-related injuries. Continuous use of benzothiazepine derivatives were associated with increasing the odds of fall-related injuries by 34% (aOR=1.34, 99%CI [1.29-1.38]).

The Kahlaee et al. (2018) systematic review also reported that new initiation of diuretics, BBs, CCBs, and ACEI/ARBs were associated with increased the risk of falls. Another population-based study using ODB database to explore the new initiation of antihypertensive agents reported that the risk of falls in older adults increased within the period of 45 days after new initiation of diuretics, ACEIs, ARBs, CCBs and BBs (Butt et al., 2013). The same group of researchers demonstrated that initiation of BBs and ACEIs were associated with increased risk of hip fractures in older adults (BBs: aOR=1.58, 95%CI [1.01-2.48]; ACEIs: aOR=1.53, 95%CI [1.12-2.10]), which was in line with our results (Butt et al., 2012). Our findings identified that new initiation of beta-blocking agents (BBs) were only associated with a slightly increased risk of fall-related injuries (aOR=1.15, 99%CI [1.04-1.28]), while new initiation of agents on the renin-angiotensin system were associated with increasing the odds by 45% (aOR=1.45, 99%CI [1.15-1.84]). The findings of our study provided new evidence on the association between continuous use or new initiation of antihypertensive drugs and fall-related injuries in

older adults, identifying the need for additional studies to improve the knowledge in the future.

In addition, our findings showed that continuous use of psychotropic agents such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs) and anticholinesterases for treating Alzheimer's disease in older adults were associated with increasing fall-related injuries odds by 60-96%. Continuous use of opioids also was associated with increasing the odds by 34% (aOR=1.34, 99%CI [1.29-1.40]). New initiation of SSRIs and TCAs were associated with increasing the odds of fall-related injuries almost by two times, while continuous use and new initiation of benzodiazepines was only slightly associated with increased risk of fall-related injuries. The association between psychotropic agents and falls, and fall-related injuries in older adults has been studied extensively. A wide range of psychotropic medications such as analgesics, antiepileptics, antidepressants, sedatives and hypnotics have been confirmed to relate to fall-related injuries (Gray et al., 2020; Seppala, Wermelink, et al., 2018; Seppala, van de Glind, et al., 2018), but few studies focused on the association between the time window of using a medication and fall-related injuries. Our study findings were consistent with Vitry and colleagues (2010), who reported that persistent use of psychotropic medications in female older adults was associated with increasing the risk of experiencing hip fracture by 2.5 times (RR=2.54, 95%CI [1.57-4.11]). Using medication information from ODB database, Liu et al. (1998) reported that new initiation of SSRIs in older adults was associated with increasing the odds of hip fracture by 2.4 times (aOR=2.4, 95%CI [2.0-2.7]), and new initiation of tertiary-amine TCAs were associated with increasing the odds of hip fracture by 50% (aOR=1.5, 95%CI [1.3-1.7]). Findings from our study not only indicated that new initiation of SSRIs and TCAs were related to fall-related injuries, but also that continuous use of SSRIs and TCAs could be associated with increased odds of fall-related injuries.

Very few studies focused on continuous use or new initiation of medication classes other than psychotropic agents or antihypertensive agents. Findings from our study, that continuous use of two medication classes for treatment of benign prostate hyperplasia (G04CA and G04CB), anti-thrombotic agents (B01AA and B01AC) and emollients for

constipation (A06AA) was associated with increased risk of fall-related injuries made an original contribution to the current knowledge. Our study also showed that new initiation of some laxatives (A06AA, A06AB and A06AD), antibiotics (J01CA, J01DB and J01XE), NSAIDs (M01AB and M01AE) and selective beta-2-adrenoreceptor agonists could increase the risk of fall-related injuries by 30-50%. Further studies need to adjust for indications for these medications to provide further evidence on their association with fall-related injuries in older adults.

Most previous studies ascertained medication use in older adults at the baseline or at the time of fall or fall-related injuries, without information on whether the medication was newly initiated or has been used for a long-term (Leipzig et al., 1999a; Leipzig et al., 1999b; Seppala, Wermelink, et al., 2018; Seppala, van de Glind, et al., 2018). Findings from our study provided evidence about a "window" of opportunity to incorporate preventive strategies such as education or closer monitoring over a specific time in the pharmacotherapy process.

4.4.1 Strengths and Limitations

The major strengths of this population-based study are provincial representativeness and large size of over a million observations in case and control groups of older adults. Second, the data obtained from IC/ES databases had satisfying data completeness (Levy et al., 2003) and high quality as reported consistently in previous studies (Aiken et al., 2016; Liu et al., 2018; Macri et al., 2017). Third, due to study's population-based design, the results can be generalized to the entire population of older adults in Ontario, Canada. Fourth, the recall bias is minimal as all the fall-related injuries were recorded on the day cases presented to the ED.

Several limitations are associated with this study. First, the controls were matched with cases by sex, age and residence area (LHIN), but as the matching ratio was not fixed, resulting in great imbalance between the case and control group (Table 3.1). We adjusted for sex, age group, residence area (LHIN), income quintiles and number of medication classes prescribed, in regression analysis so that these imbalances were considered. Second, only prescribed and dispensed drugs were recorded in ODB database, but

chronic comorbidities and aging-related reduction in cognitive function could lead to low adherence to prescribed medications in older adults (Hennein et al., 2018). Hence, neither prescription nor dispensation can be equated with actual use. Third, some comorbidities might be associated with fall-related injuries, but the detailed information on indications for prescription was not available in the original dataset. Hence our results could include a degree of overestimation of the association between medication and fall-related injuries. What is more, confounding by indication (Kyriacou & Lewis, R, 2016; Salas & Stricker, 1999) was not fully addressed in this study. For example, patients with more severe diseases are likely to receive more intensive care and treatment and when comparing the interventions, the more intensive intervention will appear to result in poorer outcomes. Hence, findings from this study should be viewed with caution. Fourth, there was a lack of indicators on the frailty for both case and control group. For example, surgeries and other medical procedures could increase the frailty, accompanied by an obvious increasing in the number of medications prescribed during the peri-operation period. But in this study, we did not have enough information to address the impact of frailty on fall-related injuries.

4.5 Conclusion

This study examined the association between fall-related injuries in older adults and continuous use or new initiation of medication classes prior to the injury. Findings revealed that both continuous use and new initiation of particular medication classes were associated with fall-related injuries. Namely, continuous use of antidepressants, drugs for benign prostate hyperplasia, anticholinesterases for Alzheimer's disease, emollients for constipation and antithrombin agents were found to increase the risk of fall-related injuries. New initiation of antidepressants, opioids, first-generation cephalosporins, non-steroids anti-inflammatory drugs, and laxatives showed to be associated with increased risk for fall-related injuries. This evidence suggests existence of a "window" of opportunity for application of injury prevention strategies while closely monitoring timing in the process of pharmacotherapy. Future research should consider exploration of comorbidities and particular indications for prescription to provide more convincing evidence on the association of medication and fall-related injuries in older adults.

4.6 Reference

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Chapter 5

5 Discussion

5.1 Main findings

The main purpose of this dissertation was: 1) to provide a comprehensive list of medication classes prescribed to older adults within one year prior to their fall-related injuries, 2) to evaluate the association between fall-related injuries and most frequently prescribed medication classes prescribed within 30 days prior to the injuries, and 3) to explore association between chronically used and newly initiated medications and fall-related injury in older adults.

Study 1, was descriptive to set the stage and help determine research questions for consecutives studies. Findings alerted us to the difference between the medication classes prescribed to older adults who experienced the fall-related injury and the medication classes prescribed to the general population of older adults. To explore further, in Study 2, we established case control group, recorded the medication classes prescribed to both groups, and conducted logistic regression to find out which medications were positively related to fall-related injury. Through this project, we recognized the importance of initiation and duration of medication use in relation to the fall-related injury. Hence, in Study 3, we explored whether the medication classes were prescribed for a long-term or were initiated within one month prior to the injury. The associations between continuous use or new initiations and fall-related injury were identified by multivariate logistics regression.

The main findings are briefly summarized as follows:

- Among older adults sustaining any fall-related injury, 48.5% were prescribed statins, 34.3% proton pump inhibitors (PPIs), 29.0% angiotensin converting enzyme inhibitors (ACEIs), 25.0% opioids, 16.6% benzodiazepine derivatives, and 14.7% selective serotonin receptor inhibitors (SSRIs) within one year prior to the injury. (Study 1)

- Similar patterns of medication prescription were found for fall-related fractures and traumatic brain injury. Among older adults who had fall-related fracture, 45.4% were prescribed statins, 33.1% PPIs, 27.6% ACEIs, 24.5% opioids and 14.6% SSRIs. Among older adults who had fall-related traumatic brain injury, 52% were prescribed statins, 35.5% PPIs, 30.3% ACEIs, 24.9% opioids and 16.5% SSRIs. (Study 1)
- More than third, 36.4%, of older adults were prescribed 5-9 different medication classes and 41.2% were prescribed 10 or more medication classes within one year prior to fall-related injury. (Study 1)
- Consistent with previous studies, we reported that use of laxatives, psychotropic agents and anti-inflammation drugs within one month prior to an injury can increase the odds of fall-related injury in older adults. (Study 2)
- Relatively new to the current knowledge is that we identified that statins, drugs for benign prostatic hyperplasia, biphosphonates, penicillins with extended spectrum, and bronchodilators also were associated with increased risk of fall-related injury. (Study 2)
- After adjusting for sex, age group, income level, residence area and number of medications prescribed, continuous use (more than 90 consecutive days) of statins, PPIs, SSRIs, α-adrenoreceptor antagonists, platelet aggregation inhibitors and anticholinesterases was associated with increasing the odds of fall-related injury in older adults by nearly 50%. (Study 3)
- After adjusting for sex, age group, income levels, residence area and number of medications prescribed, new initiation (starting a medication within one month prior to a fall-related injury) of opioids, first-generation cephalosporins, selective β2-adrenoreceptor agonists, SSRIs and other antidepressants (mostly tricyclic antidepressants [TCAs]) was associated with increasing the odds of fall-related injury in older adults by 50%. (Study 3)

It is well established that medications are modifiable risk factors for falls and fall-related injuries (de Vries et al., 2018; Leipzig et al., 1999a; Leipzig et al., 1999b; Seppala, Wermelink et al., 2018; Seppala, van de Glind et al., 2018; Woolcott et al., 2009).

Previous studies reporting medication use in Canadian older adults mainly focused on a specific medication class, such as benzodiazepines (Kassam et al., 2006), antihypertensive medications (Verma et al., 2018), antihyperglycemic medications (Clemens et al., 2015), statins (Minard et al., 2016) and opioids (Sharma et al., 2019), already suspected to contribute to fall-related injuries. Very few studies were broader in scope and provided an overview of medication use in older adults before they had fall-related injuries. That is why the Study 1 investigated patterns of medications prescribed to older adults within one year prior to a fall-related injury. With this new knowledge we are now able to explore the difference in medication use between older adults who experienced fall-related injuries and the community dwelling older adults. We chose one-year lookback window to make Study 1 comparable to CIHI report in 2018 because CIHI published a report on medications prescribed to the general population of Canadian older adults within the year of 2016 (CIHI, 2018). Compared to the findings for general older adults in Ontario in CIHI 2018 report, a higher percentage of older adults who have experienced fall-related injury were prescribed with ACEIs (26.2% vs. 29.0%), BBs (23.3% vs. 25.9%), opioids (15.4% vs. 25.0%), biphosphonates (9.4% vs. 20.4%), benzodiazepine derivatives (10.4% vs. 16.1%), thiazides (15.2% vs. 10.8%) and SSRIs (10.5% vs. 14.7%). All these medication classes (except for biphosphonates) were previously included in the FRIDs lists (Bauer et al., 2012; the Swedish National board of Health and Welfare, 2010; Winter et al., 2016; Zia et al., 2017), which partly supported the that these medications were associated with fall-related injuries. Another major difference was polypharmacy, of the number of medication classes prescribed within the past year.

The effects of polypharmacy have been repeatedly cited in literature as detrimental due to potential for adverse drug reactions and drug-drug interactions, especially with decline in hepatic and renal function in aging bodies (Chen et al., 2014; Chung, 2014; Huang et al., 2012; Rowe, et al., 1976; Tan et al., 2015). According to CIHI report, 39.4% older adults were prescribed 5 to 9 different medication classes and 26.5% were prescribed with 10 or more different medication classes within the year of 2016. Our Study 1 showed that 36.4% of older adults who experienced fall-related injury were prescribed 5-9 different medication classes and 41.2% were prescribed 10 or more different medication classes

within the year prior to the injury. It is impossible to confirm in both studies if these medications were prescribed concurrently, nonetheless, the higher number of medication classes used by injured older adults is concerning and requires further exploration.

Associations between medication classes commonly prescribed such as statins, PPIs, biphosphonates, antibiotics and fall-related injuries in older adults has not been well established (de Vries et al., 2018; Seppala, van de Glind, et al., 2018). Most previous studies strictly selected study participants which confined the generalizability of their findings. Our Study 2 was a population-based, case-control study which is methodologically comparable to the Canadian study by Kelly et al. (2003) and Swedish study by Kuschel et al (2015). Both studies were population-based and used administrative data to identify a wide range of medication classes associated with fall-related injury in older adults. Both studies captured medication prescription within 30 days prior to the fall-related injury. Kelly et al. (2003) used 1997/1998 fiscal year health registry data from Alberta, Canada. However, the two studies differ in the adjustments for cofounders. Kelly et al. (2003) used sex, age, income, seventeen different medications and seventeen different comorbidities (e.g., eye disorder, nutritional deficiencies, hypertension, depression, dementia, incontinence, etc.) as confounding factors. They found that only narcotic pain killers, anti-convulsants (anti-epileptics), and anti-depressants were independently associated with an increased risk of sustaining injurious falls. The authors acknowledged that taking so many comorbidities into consideration was complicated because multiple medication classes could be used in the treatment of one comorbidity, while a single medication class could be used to treat multiple comorbidities. The real effect of every single medication class on fall-related injuries is difficult, if not impossible, to fully address. That is partly the reason why we chose to not to take five comorbidities we had data for into consideration as confounders. Instead, we used the number of medication classes as an indicator for the possible number of comorbidities. The second study, by Kuschel and colleagues (2015), reported twenty most commonly prescribed ATC 3rd medication classes and their association with fall-related injuries using Swedish public health data. They reported that CNS drugs (N02A, N02B, N05C and N06A), drugs for peptic ulcer (A02B), constipation drugs (A06A), antithrombotic agents (B01A), Vitamin B12 (B03B), Calcium (A12A), and NSAIDs

(M01A) were independently associated with fall-related injuries. Consistent with their results, our Study 2 found (at ATC 4th level) a positive association between PPIs (A02BC), constipation drugs (A06AA, A06AB), anti-thrombotic agents (B01AC, B01AE), and NSAIDs (M01AB, M01AE, and M01AH) and fall-related injury. Relatively new contribution to the current knowledge from our study are additional medication classes such as lipid-lowering agents (statins, C10AA), drugs for benign prostatic hyperplasia (G04CA and G04CB), pennicillins with extended spectrum (J01DB), biphosphonates (M05BA), and selective β-2-adrenoreceptor agonists for asthma (R03CC) that were positively associated with fall-related injuries in older adults. Pharmacologically, it is plausible that statins and drugs for benign prostatic hyperplasia could increase the risk of fall-related injuries because these medications were reported to induce muscle disorders and cardiovascular side effects such as orthostatic hypotension (Curfman, 2017; Lee & Cho, 2018; Sica, 2005). Mechanisms of how antibiotics, bisphosphonate and bronchodilators can lead to fall-related injuries need to be explored further. Collectively, these studies provide evidence that clinicians should not underestimate the risk of fall-related injuries when prescribing some of the most frequent medications to older adults.

Starting a new medication, changing a dosage, or prescribing a medication for a very long-term use are significant concerns in pharmacotherapy, as medications' therapeutic effects and side effects are closely related to the initiation and duration of medication use (Barker et al., 2004; Engelke et al., 2019; Huybrechts et al., 2011; Hyttinen et al.,2017; Schmieder et al., 2009). To explore the association between medication classes and fall-related injuries, Study 3 identified top 30 most commonly prescribed medications as new initiations and for continuous use. Consistent with previous studies (Kahlaee et al., 2018; Vitry et al., 2010; Yang et al., 2006), continuous use of antihypertensives, antidepressants and proton pump inhibitors (PPIs) were reported to increase the risk of fall-related injuries. New initiation of antihypertensives and antidepressants was also associated with higher risk of fall-related injuries. What emerged as novel in our findings, was that continuous use of two medication classes (G04CA and G04CB) for treatment of benign prostate hyperplasia, anti-thrombotic agents (B01AA and B01AC) and emollients for constipation (A06AA) were also associated with inceasing the risk of fall-related injuries.

For new initiations, our study showed that some laxatives (A06AA, A06AB and A06AD), antibiotics (J01CA, J01DB and J01XE), NSAIDs (M01AB and M01AE) and selective beta-2-adrenoreceptor agonists could increase the risk of fall-related injuries by 30-50%. The findings from Study 3 provided evidence about a "window" of opportunity for implementation of injury prevention strategies for older adults such as education or closer monitoring over a specific time in the pharmacotherapy process.

The findings of these studies provide clear evidence to support better clinical decisions to the family doctors, physicians, geriatricians, pharmacists and other health care professionals on association between medication classes and fall-related injury in older adults. Previous studies focused predominantly on psychotropic medications and antihypertensive agents and their mechanisms on inducing falls in older adults, while our studies reported additional medication classes that might be associated with the occurrence of fall-related injuries in older adults, such as statins, PPIs, biphosphonates, bronchodilators and antibiotics. These medication classes are also among the most extensively prescribed ones, so their impact on fall-related injuries should not be underestimated or ignored.

5.2 Clinical Implications and Knowledge Translation

The main part of this thesis focused on identifying medication classes as risk factors for fall-related injuries in older adults. This purpose was in line with World Health Organization (WHO) falls prevention strategy on improving the identification and assessment of determinants of falls (WHO, 2007) and the Canadian Patient Safety Institute's (CPSI) injury reduction strategy on multifactorial risk assessment and individualized interventions for those at high risk of fall-related injuries. In our extensive study of medication classes that were associated with fall-related injuries, we identified several commonly prescribed medication classes that might contribute to fall-related injuries in older adults. In addition to psychotropic agents and medications for cardiovascular system disease, other medications such as laxatives, antithrombotic agents, antibiotics and bronchodilators were also reported to increase the risk of fall-related injuries (Study 2). The impact of these medication classes on fall-related injuries was rarely studied, yet they are frequently prescribed to older adults. Findings from this

thesis provide evidence to family doctors, physicians, geriatricians and pharmacists to support their informed decisions about deprescribing or balancing benefits and harms of prescribing, should their goal be to lower the risk of fall-related injuries.

We also reported that the duration of medication use was an important concern to balance medications' therapeutic effects and side effects. In our study, the continuous use of antidepressants, drugs for benign prostate hyperplasia, anticholinesterases for Alzheimer's disease, emollients for constipation and antithrombin agents was associated with increased risk of fall-related injury. New initiation of antidepressants, opioids, first-generation cephalosporins, non-steroids anti-inflammatory drugs, and laxatives was also associated with increased risk of fall-related injury. This association between timing of medication use and fall-related injury provided evidence to clinicians on a time window for incorporating intensive monitoring and injury prevention strategies. Medication review has been reported to be effective in preventing fall-related injuries both as a single intervention (Blalock et al., 2010; Boyé et al., 2016; Sjöberg et al., 2013) or combined as a component of multifactorial prevention protocols (Matchar et al., 2017; Mikolaizak et al., 2017; Salimen et al., 2009). But the details on the best way to perform medication review are still under investigation (American Geriatrics Society, 2019; Huckerby & Johal, 2015; Jokanovic et al., 2016). Knowledge from Study 3 provided evidence about the opportune time to perform medication review and which medication classes to focus on. This knowledge is also of value for older adults and their caregivers, to be more vigilant during specific times of pharmacotherapy.

Calling back to William Haddon's injury prevention theory (Haddon, 1980; Sattin, 1992), this thesis provided evidence for several aspects of injury prevention strategies that require more focus. For example, reevaluating the necessity for extensive statin use in older adults, especially in the oldest-old age group; enhancing the importance of systematic medication review at meaningful time points such as initiation of a new medication or after a pre-set period of continuous use; expanding the research to explore the association between medication use and fall-related injuries in different age group, for different injury types and different duration of medication use; or improving individualized prescription for older adults.

According to the definition by the Canadian Institutes for Health Research (CIHR), knowledge translation is "a dynamic and iterative process that includes synthesis, dissemination, exchange and ethically-sound application of knowledge to improve the health of Canadians, provide more effective health services and products and strengthen the health care system" (CIHR, 2019, "knowledge translation", para 1). While conducting studies for this thesis, the author identified that all Canadian drugs databases use DIN codes and there was no convenient way for quick conversion of DIN codes to their chemical names and matching ATC codes. For the purpose of this thesis, over 6,600 DINs were converted to 305 ATC 4th level codes in accordance with Drug Product Database online query Drug Product Database online query (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp) managed by Health Canada. This website contains detailed information about medication's generic names, ATC codes, DINs, dosage, and similar. However, it is burdened with irrelevant information (e.g., approved but not on market drugs, off-market drugs), which makes conversion between DIN and ATC very difficult. What is more, the main webpage is not user-friendly because it contains many search query categories. For a quick reference, direct ATC-DIN or DIN-ATC conversion would be beneficial. With assistance from a professor and students at the Computer Science department at Western University, we designed an innovative, user-friendly website for the quick conversion between DINs, ATCs and their chemical names. We envision users to be researchers analyzing data from Canadian drug databases, pharmacists across Canada, analysts completing big data extractions and analysis (e.g., IC/ES, Statistics Canada), students in medical and pharmaceutical schools, and graduate students comparing published findings in research papers.

5.3 Methodological Considerations and Limitations

It is well-acknowledged that all studies have methodological limitations. The section below discusses several most important considerations in epidemiological studies in general and specifically how they were addressed in the studies included in this thesis.

Study 2 and Study 3 were case-control studies. In general, case-control studies begin with participants who have the outcome of interest ("cases") and compare them to participants

who do not have the outcome of interest ("controls"). The case-control studies look retrospectively to compare how frequently the case and control groups were exposed to a risk factor and determine the relationship between the risk factor and outcome of interest (Carlson & Morrison, 2009; Schulz & Grimes, 2002).

5.3.1 Selection of Control Group

Choosing a control group can greatly affect the case-control study's vulnerability to bias. Control group should arise from the same general population as the cases, and it should be similar in every aspect except the outcome of interest (Borgan et al., 2018; Carlson & Morrison, 2009; Melamed & Robinson, 2019). The case group in our studies included all older adults who were 66 years and older who had experienced a fall-related injury between 2010 and 2014. Controls were matched by same age, sex and LHINs (residence area). Both cases and controls were community-dwelling older adults in Ontario. This ensured that the control group members represent the population at risk of becoming cases, independent of the exposure being studied (Schulz & Grimes, 2002). The imbalance of sex, age group and residence area (LHINs) in our studies can be explained by the cases and controls not being matched with a fixed ratio. Take age group as an example (Table 3.1). There were 100,027 cases and 405,127 controls in 66-74 age group, the ratio of case and control was 1 to 4.05. However, in the 85 years and older group, the ratio of cases and controls was only 1 to 1.86. That is why there was a higher percentage of older adults in control group who were 66 to 74 years old than in the case group.

5.3.2 Measurement of exposure information

Exposure history in case-control studies was usually ascertained by interviewing the participants or analyzing historical medical charts or records. The general concern for case-control study is that cases will always be more likely to recall past exposures than controls, which increases recall bias. Interviewers of cases tend to investigate more thoroughly on exposure history than controls, which is interviewer bias. Exposure history in our studies (medications prescribed to older adults) was obtained from ODB database. Every older adult 65 years of age or older in Ontario is automatically entered in ODB program and this database contains records for every prescription medication filled

(Government of Ontario, 2019). A study by Levy et al. (2003) reported an overall error rate of 0.7% (95% CI 0.5% to 0.9%) in ODB database suggesting high coding reliability and low potential that results of studies using ODB data will be compromised by coding accuracy. We believe that the information bias in this study was very low.

5.3.3 Precision

The precision is achieved with fewer random errors or random variations present in a study. Random errors cannot be avoided completely as they are unknown and unpredictable. Sample selection and measurements of key variables can introduce random errors (Carlson & Morrison, 2009; Flannelly et al., 2018; Melamed & Robinson, 2019). An effective approach to minimize random errors is to use large sample size so that the general population can be represented to a larger extent by samples. In this study, a sample size of over a million individuals was large enough to dilute possible effects of random errors. Generally speaking, a large sample-sized study with more balanced group (e.g., similar exposed and unexposed individuals) will produce more precise estimates (Rothman et al., 2008). Considering that exposure to medications was impossible to be very high, our study included the most commonly prescribed medication classes as exposures and thus the precision of the estimates was enhanced. For example, the exposure rates for statins in case and control group were 21.7% and 13.8%, exposure rates for biphosphonates in case and control group were 8.2% and 4.4% respectively. We also used narrow 99%CIs for each estimate of association to enhance precision.

5.3.4 Internal validity

Validity refers to a lack of systematic errors while precision refers to a lack of random errors. Internal validity describes the extent to which a cause-and-effect established in a study cannot be explained by other factors. Whether the outcome of interest can be attributed to the exposure, and not to other causes is the key issue in assessing the internal validity of a study. A confounding variable is a third variable in a study examining the cause-and-effect relationship, also known as a confounder or a confounding factor. A confounding variable may be related to both the dependent (risks) and independent factors (outcomes). It is very important to address confounding bias in case-control

studies (Rothman et al., 2008). Usually, this type of bias can be managed in the research design stage by matching or it can be handled in the analysis stage using analytical techniques such as stratification or adjustments in logistic regression models (Borgan et al., 2018; Carlson & Morrison, 2009; Rothman et al., 2008). In this study, we planned carefully in our DCP to match controls with cases by age, sex and residence area (LHINs), with a ratio of 1 (cases) to 5 (controls). However, this strict matching protocol resulted in unavailability of controls in the Ontario RPD database, so we adjusted for these factors in our multivariate logistic regression model. Neighborhood income quintile and number of medication classes prescribed were also taken into consideration as confounding factors. These were carefully chosen based on previous literature (Ek et al., 2019; Jin et al., 2017; Johnson et al., 2015; Towne et al., 2017). Still, controlling for all confounding factors is impossible in observational studies (Pearce, 2016; VanderWeele, 2019), thus resulting in residual confounding. The secondary data that comprised the dataset used in studies of this thesis have been originally collected for other purposes, such as surveillance of diseases or monitoring the use of public health care resource. Here, this administrative data was used here to examine novel research questions. Therefore, a lack of information on confounding factors such as participants' lifestyles, environmental factors and comorbidities was inevitable.

Furthermore, research on medications presents its own challenges. On one hand, it is necessary to understand the specific indications for which the medications were prescribed, so that the impact of the disease can be separated from the impact of medication used for the disease. On the other hand, medications were used to treat a specific disease, so the impact of medications and disease were interwoven with each other. It is very common that one medication is used for multiple diseases and also that one disease could be treated with multiple medications. Another important factor involved in medication treatment that was not adjusted for in this thesis is the drug-drug interaction. In our population, considerable percentage of older adults were prescribed multiple medications. The risk of an adverse drug event has been estimated at 13% for two drugs, 58% for five drugs, and 82% for seven or more drugs (Fulton & Allen, 2005). It is likely that the increased risk for fall-related injuries might also be related to drug-drug interactions (Bennett et al., 2014). Practically speaking, it is tremendously difficult

to sort out the singular or combined impact of any specific medication or comorbidity pairing, especially when we study a wide range of medications. Since we could not fully address the confounding factors, the results of our studies need to be viewed with caution.

5.3.5 External Validity

External validity, also known as generalizability, is the degree to which the result or conclusion could be generalized to other places and at other times (Rothman et al., 2008). In our studies, we included over a million community-dwelling older adults in Ontario. We believe the study results are generalizable to other places with similar socioeconomic levels, lifestyles and health care policies, such as other provinces in Canada, Australia and countries of Western Europe.

5.4 Future Research Directions

The methodological limitations and limitations of results from our studies suggest several future research directions. First, well-designed prospective cohort studies are required to provide more convincing results on the association between medications and fall-related injuries. More research attention is needed to explore medication classes not reported to be associated to fall-related injuries in previous studies. Second, the definition of continuous use cannot be generalized. For example, for antihypertensives, use longer than three-month is considered chronic, while for antibiotics, use longer than two weeks is considered as chronic. Future research needs to determine a medication-specific definition of continuous use and identify the optimal time for implementing preventative strategies for different medication classes. This could also apply to new initiation of different medications as they have different half-lives. Third, except for duration of medication use, the dosage of each medication is also important in producing therapeutic and side effects. Future studies focused on the dosage of different medications and their association with fall-related injuries are necessary. Fourth, as medications' impacts and diseases' impacts are inextricably bounded up with each other, it is of great importance to clarify the strength and limitations of whether to separate the impacts of the two or not and how to make the separation practically and clinically meaningful.

5.5 Conclusion

Nearly one third of community dwelling older adults fall every year and almost one third of the falls result in injuries which require medical consultation or treatment. Total healthcare system costs of fall-related injuries are high, partly because of the high incidence, but also due to the high costs per incident. Fortunately, over the past 30 years of research, many modifiable risk factors have been identified, making the fall-related injuries in older adults preventable to some extent. However, the complexity of multi-comorbidities, latent risk of adverse drug reactions, and poor adherence to pharmacotherapy in older adults makes it extremely challenging for physicians, pharmacist and geriatricians in clinical treatment. From the author's own experience as a physician, the presence of diseases is something real and medications are necessary to mitigate the symptoms, improve quality of life and extend life expectancy. When prescribing medications to older adults, physicians face a dilemma, potentially increase the risk of fall-related injuries by following clinical best practice guidelines to manage the disease, or not. With the accumulation of risks, especially in oldest-old, fall-related injuries have a potential to change lives of older adults and their families, impose unwelcomed clinical, caregiving and economic consequences. Numerous studies, guidelines and fall prevention protocols have included lists of fall-risk increasing drugs and were available both to clinicians and older adults. But, what about medications not included on the list? Are they safe to use without caution? Based on the findings of three studies included in this thesis, the answer is no. Our studies offer a comprehensive description of medications prescribed to older adults prior to fall-related injuries, identify several medication classes that have not been included on FRIDs lists before, and demonstrate that both continuous use and new initiation of medications could increase the risk of fall-related injuries. Results from this thesis provide new evidence for more medication classes that might be associated with fall-related injuries and require further attention from both clinicians and researchers. With continued advances in pharmacotherapy, ever deepening ethical dilemma is: Where are the limits of acceptable risk when adding new medications to clinical treatments? Growing number of older adults, exposed to this modifiable risk factor for fall-related injury, are looking for this answer.

5.6 References

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Appendices

Appendix A List of Fall Risk-Increasing Drugs

Drugs that cause high risk of falling	
N02A	Opioids
N05A (excluding Lithium)	Antipsychotics
N05B	Anxiolytics
N05C	Hypnotics and sedatives
N06A	Antidepressants
Drugs that cause orthostatism/hypotension	
C01D	Vasodilators used in cardiac diseases (nitrates)
C02	Antihypertensives
C03	Diuretics
C07	Beta-blockers
C08	Calcium channel blockers
C09	Agents acting on the renin-angiotensin system
G04CA	Alpha-adrenoreceptor antagonists
N04B	Dopaminergic agents (anti-Parkinson drugs)

Note adapted from the FRID list by the Swedish National Board of Health and Welfare

Appendix B: Data Creation Plan for IC/ES

Project Initiation
This Section must be Completed Prior to Project Dataset(s) Creation

Project Title:	The association between selected health indicators, prescription medications and serious fall-related injuries in older adults (REVISED July 2019)	
Project TRIM number:		
Research Program:	DASDAS	
Site:	ICES WesternICES Western	
Project Objectives:	*Insert Project Objectives as listed in the approved ICES Project PIA*	
	The objective of this study is to investigate the association between selected health indicators, prescription medications and serious fall-related injuries in older adults	
ICES Project PIA Initial Approval Date:	*The ICES Employee or agent who is responsible for creating the Project Dataset(s) is responsible for ensuring there is an approved ICES Project PIA and verifying the date of approval prior to creating the Project Dataset(s)*	
	2017-Jul-12	
Principal Investigator (PI):	Aleksandra Zecevic	
Check the applicable box if the PI is an ICES Student/Trainee	☐ ICES Student ☐ ICES Fellow ☐ ICES Post-Doctoral Trainee ☐ Visiting Scholar	
Responsible ICES Scientist:	*Name the Responsible ICES Scientist if the PI is not a Full Status ICES Scientist*	
Project Team Member(s) Responsible for Project Dataset Creation and/or Statistical Analysis and date joined (list all):	*All person(s) (ICES Analyst, Appointed Analyst, Analytic Epidemiologist, PI, and/or Student) responsible for creating the Project Dataset(s) and/or statistical analysis on the Research Analytics Environment (RAE) and the date they joined the project must be recorded*	
	Aleksandra Zecevic, Yu Ming Nicolette Lappan	2017-Jul-12 2018-Nov-6
Other ICES Project Team Members and date joined (list all):	*All other Research Project Team Members (e.g., Research Administrative Assistants, Research Assistants, Project Managers, Epidemiologists) and the date they joined the project must be recorded*	
		yyyy-mon-dd
Confirmation that DCP is consistent with Project Objectives:	*The following individuals must confirm that the ICES Data provided for in this DCP is relevant (e.g., with respect to cohort, timeframe, and variables) and required to achieve the Project Objectives stated in the ICES Project PIA prior to initial Project Dataset creation: 1) PI; 2) Responsible ICES Scientist if the PI is not a Full Status ICES Scientist, or a second ICES Scientist or the Scientific Program Lead if the PI is creating both the DCP and the Project Dataset[s]; 3) ICES Research*	

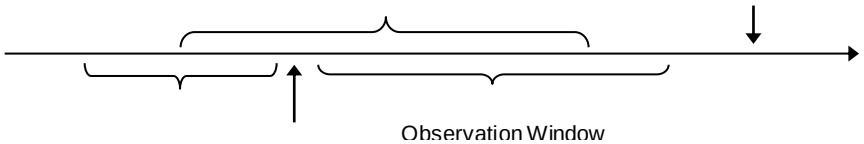
Project Initiation This Section must be Completed Prior to Project Dataset(s) Creation			
	and Analysis Staff creating the DCP; and 4) ICES Analytic Staff (ICES Employee or agent responsible for creating the Project Dataset[s]). This may be delegated either verbally or via e-mail.		
	Principal Investigator Aleksandra Zecevic	☐	2017-Aug-21
	Responsible ICES Scientist or Second ICES Scientist/Lead	☐	yyyy-mon-dd
	ICES Research and Analysis Staff Creating the DCP	☐	yyyy-mon-dd
	ICES Analytic Staff	☐	yyyy-mon-dd
Designated ICES Research and Analysis Staff accountable for Project Documentation:	*The person named (ICES staff) is accountable for ensuring that the approved ICES Project PIA, ICES Project PIA Amendments, and DCP are saved on the T Drive, ensuring ICES Project PIA Amendments are submitted as required, ensuring DCP Amendments are documented, and sharing the final DCP with the PI/Responsible ICES Scientist at project completion*		
DCP Creation Date and Author:	*Date DCP was finalized prior to Project Dataset(s) creation*	*Name of person who created the DCP*	
	Date	***Name***	
	2017-Aug-20 2019-Jul-8	***Yu Ming, Aleksandra Zecevic*** ***Nicolette Lappan***	

ICES Data This Section must be Completed Prior to Project Dataset(s) Creation	
The ICES Employee or agent who is responsible for creating the Project Dataset(s) must ensure that this list includes only data listed in the ICES Project PIA *Changes to this list after initial ICES Project PIA approval require an ICES Project PIA Amendment*	*Mandatory for all datasets that are available by individual year*
General Use Datasets – Health Services	***Years (where applicable)***
See listSee list	
See listSee list	
General Use Datasets – Care Providers	
See listSee list	
See listSee list	
General Use Datasets – Population	
See listSee list	
See listSee list	
General Use Datasets – Coding/Geography	
See listSee list	
See listSee list	
General Use Datasets - Facilities	
See listSee list	
General Use Datasets - Other	
See listSee list	
See listSee list	
Controlled Use Datasets	
See listSee list	
See listSee list	
Other Datasets	

Project Amendments and Reconciliation			
ICES Project PIA Amendment History (add additional rows as needed):	*Privacy approval date*	*Person who submitted amendment*	*Note that any changes to the list of ICES Data or Project Objectives require an ICES Project PIA Amendment*
	Date	***Name***	***Amendment***
	yyyy-mon-dd		
DCP Amendment History (add additional rows as needed):	*Date DCP amended*	*Person who made the DCP amendment*	*Note that any DCP amendments involving changes to the list of ICES Data or Project Objectives require an ICES Project PIA Amendment*
	Date	***Name***	***Amendment***
	yyyy-mon-dd		
Date Programs/DCP reconciled	*The person(s) creating the dataset and/or analyzing the data are responsible for ensuring that the final DCP reflects the final program(s) when the project is completed*		
	yyyy-mon-dd		

Project Cohort	
Study Design	☒ Cohort study ☐ Matched cohort study ☒ Case-control study ☐ Cross-sectional study ☐ Other (specify):
Index Event / Inclusion Criteria	• Serious Fall-Related Injuries and Death (Appendix E – ICD-10 W, S and T codes). When cutting a cohort of cases, please keep information on all 10 diagnostic codes from NACRS (e.g., dx10code1 – dx10code10), so we can confirm W code is combined with S or T code (e.g., S and W, T and W, S&T and W) to make it "fall-related". **Case group** inclusion criteria: a) Older adults 65 years and older b) Residents of Ontario c) Presented to Emergency Department d) Diagnosed with a serious fall-related injury or death due to fall-related injury. Fall-related injury is defined by combining ICD-10 codes for falls W00-W19 with ICD-10 codes for injuries S00-S99 or T00-T14. The time between codes W00-W19 and codes S00-S99 or T00-T14 should be the same day. Descriptive information (e.g., breakdown of S00-S99 or T00-T14 and W00-W19 codes) should be included into the dataset to allow analysis of injury types.) e) Diagnosed between Jan 1 2006 and Dec 31 2015. **Control group** a) Matched to the case group by sex, age Charlson Comorbidity Index score, and LHIN, with a ratio of 1.5 to 1.

Project Cohort		
	b) Exclude the patients having serious fall-related injuries (codes W00-W19, codes S00-S99 or T00-14) between Jan 1, 2006 and Dec 31, 2015. • The date of visiting Emergency Department due to serious fall-related injury will be defined as the index event date. • For individuals with repetitive serious fall-related injuries during the observation period, the first time and consecutive visits to ED due to serious fall-related injury will be taken into account.	
Estimated Size of Cohort (if known)		
Exclusions (in order)	*Step*	Description
	1	Invalid IKN
	2	Incomplete information (e.g, missing age or missing sex information, non-Ontario residents, died before ED visits)
	3	<65 years old at the index event date
	4	Patients who have experienced in-hospital serious fall-related injuries
	5	Excluding diagnoses that are suspected, questionable, rule out.
	6	Excluding transferred ED visits.
	7	Excluding ED visits from which a patient left without being seen.
	8	Excluding scheduled ED visits.

Project Time Frame Definitions	
	
Accrual Start/End Dates	2006 Jan 1st to 2015 December 31st
Max Follow-up Date	2017 Jan 1st
When does observation window terminate?	12 months after the index date
Lookback Window(s)	12 months (till 2005 Jan 1st)

Variable Definitions (add additional rows as needed)	
Main Exposure or Risk Factor	For the full list of variables, please refer to Appendix B – Variables from NACRS, CIHI-DAD, RAI-HC and ODB.
Primary Outcome Definition	Serious fall-related injuries (ICD-10 codes W00-W19 combined with S00-S99 or T00-T14 ICD-10 codes)

Variable Definitions (add additional rows as needed)	
Secondary Outcome Definition(s)	Death
Baseline Characteristics	Case and Control: age, sex, Charlson Comorbidity Index score, LHIN
Other Variables	Variables needed from NACRS, CIHI-DAD, RAI-HC and ODB databases are provided in attached file (Appendix B). IMPORTANT: to reduce number of observations we decided NOT to proceed with analysis of OHIP data, hence we excluded it in this revision.

Analysis Plan and Dummy Tables (expand/modify as needed)

Descriptive Tables (insert or append dummy tables), e.g.: See Appendix C and Appendix D

Quality Assurance Activities

RAE Directory of SAS Programs	
RAE Directory of Final Dataset(s)	*The final analytic dataset for each cohort includes all the data required to create the baseline tables and run all the models. It should include all covariates for all models such as patient risk factors, hospital characteristics, physician characteristics, exposure measures (continuous, categorical) and outcomes. It should include covariates that were considered but didn't make the final cut. This would permit an analyst to easily re-run the models in the future.*

RAE README file available: ☐Yes ☐No

Date results of quality assurance tools for final dataset shared with project team (where applicable):

%assign	yyyy-mon-dd
%evolution	yyyy-mon-dd
%dinexplore	yyyy-mon-dd
%track / %exclude	yyyy-mon-dd
%codebook	yyyy-mon-dd

Additional comments:

Table 1. Baseline characteristics according to primary/secondary exposure
Descriptive statistics, measures of central tendency and dispersion for continuous variables, and frequency tables for categorical variables. Trends in the data across time will also be analyzed.

Table 2. Outcomes according to primary/secondary exposure: See dummy tables in Appendix D

Analysis Plan and Dummy Tables (expand/modify as needed)

Table 3. Covariates (baseline characteristics) according to outcomes: See dummy tables in Appendix D

Statistical Model(s)

Type of model	Cox Proportional Hazard Regression
Primary independent variable	Risk factors mentioned above
Dependent variable	Serious fall-related injuries and death
Covariates	
Sensitivity Analyses	N/A

Appendix C Ethics Approval

Western Research

Research Ethics

Western University Health Science Research Ethics Board
HSREB Delegated Initial Approval Notice

Principal Investigator: Dr. Aleksandra Zecevic
Department & Institution: Health Sciences\Faculty of Health Sciences, Western University

Review Type: Delegated
HSREB File Number: 109335
Study Title: The Association Between Health Indicators and Serious Fall-related Injuries in Older Adults

HSREB Initial Approval Date: July 10, 2017
HSREB Expiry Date: July 10, 2018

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Revised Western University Protocol	Revised REB application with accepted changes (clean copy).	2017/06/23
Data Collection Form/Case Report Form	Data collection form revision 1.	2017/06/23
Other	references	
Other	Confirmation of Feasibility from ICES (Institution for Clinical Evaluative Sciences) Data Analytic Service	

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Ethics Officer, on behalf of Dr. Marcelo Kremenchutzky, HSREB Vice Chair

EO: Erika Basile ___ Grace Kelly ___ Katelyn Harris___ Nicola Morphet ___ Karen Gopaul ___ Patricia Sargeant ___

Western University, Research, Support Services Bldg., Rm. 5150
London, ON, Canada N6G 1G9 t. 519.661.3036 f. 519.850.2466 www.uwo.ca/research/ethics

Western Research

Date: 12 July 2018

To: Aleksandra Zecevic

Project ID: 109335

Study Title: The Association Between Health Indicators and Serious Fall-related Injuries in Older Adults

Application Type: Continuing Ethics Review (CER) Form

Review Type: Delegated

REB Meeting Date: 07/Aug/2018

Date Approval Issued: 12/Jul/2018

REB Approval Expiry Date: 10/Jul/2019

*****Lapse in Approval: July 11, 2018 to July 12, 2018*****

Dear Aleksandra Zecevic,

The Western University Research Ethics Board has reviewed the application. This study, including all currently approved documents, has been re-approved until the expiry date noted above.

REB members involved in the research project do not participate in the review, discussion or decision.

Western University REB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The REB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Daniel Wyzynski, Research Ethics Coordinator, on behalf of Dr. Joseph Gilbert, HSREB Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

Western Research

Date: 7 July 2019

To: Aleksandra Zecevic

Project ID: 109335

Study Title: The Association Between Health Indicators and Serious Fall-related Injuries in Older Adults

Application Type: Continuing Ethics Review (CER) Form

Review Type: Delegated

REB Meeting Date: 16/Jul/2019

Date Approval Issued: 07/Jul/2019

REB Approval Expiry Date: 10/Jul/2020

Dear Aleksandra Zecevic,

The Western University Research Ethics Board has reviewed the application. This study, including all currently approved documents, has been re-approved until the expiry date noted above.

REB members involved in the research project do not participate in the review, discussion or decision.

Western University REB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The REB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Daniel Wyzynski, Research Ethics Coordinator, on behalf of Dr. Joseph Gilbert, HSREB Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

Western Research

Date: 15 June 2020

To: Aleksandra Zecevic

Project ID: 109335

Study Title: The Association Between Health Indicators and Serious Fall-related Injuries in Older Adults

Application Type: Continuing Ethics Review (CER) Form

Review Type: Delegated

REB Meeting Date: 16/Jun/2020

Date Approval Issued: 15/Jun/2020

REB Approval Expiry Date: 10/Jul/2021

Dear Aleksandra Zecevic,

The Western University Research Ethics Board has reviewed the application. This study, including all currently approved documents, has been re-approved until the expiry date noted above.

REB members involved in the research project do not participate in the review, discussion or decision.

Western University REB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The REB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Daniel Wyzynski, Research Ethics Coordinator, on behalf of Dr. Joseph Gilbert, HSREB Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

Appendix D: ICD-10 codes used in this thesis

ICD-10 codes for Injuries and Falls

Falls

W00 Fall on same level involving ice and snow

W01 Fall on same level from slipping, tripping and stumbling

W02 Fall involving skates, skis, sport boards and in-line skates

W03 Other fall on same level due to collision with, or pushing by, another person

W04 Fall while being carried or supported by other persons

W05 Fall involving wheelchair

W06 Fall involving bed

W07 Fall involving chair

W08 Fall involving other furniture

W09 Fall involving swing

W10 Fall on and from stairs and steps

W11 Fall on and from ladder

W12 Fall on and from scaffolding

W13 Fall from, out of or through building or structure

W14 Fall from tree

W15 Fall from cliff

W16 Diving or jumping into water causing injury other than drowning or submersion

W17 Other fall from one level to another

W18 Fall on same level in or from bathtub

W19 Unspecified fall

Injury

S00-S09 Injuries to the head

S10-S19 Injuries to the neck

S20-S29 Injuries to the thorax

S30-S39 Injuries to the abdomen, lower back, lumbar spine and pelvis

S40-S49 Injuries to the shoulder and upper arm

S50-S59 Injuries to the elbow and forearm

S60-S69 Injuries to the wrist and hand

S70-S79 Injuries to the hip and thigh

S80-S89 Injuries to the knee and lower leg

S90-S99 Injuries to the ankle and foot

T00-T07 Injuries involving multiple body regions

T08-T14 Injuries to unspecified parts of trunk, limb or body region

Fractures

S02 Fracture of skill and facial bones

S12 Fracture of neck

S22 Fracture of rib(s), sternum and thoracic spines

S32 Fracture of lumbar spine and pelvis

S42 Fracture of shoulder and upper arm

S52 Fracture of forearm

S62 Fracture at wrist and hand level

S72 Fracture of femur

S82 Fracture of lower leg, including ankle

S92 Fracture of foot, except ankle

T02 Fractures involving multiple body regions

T08 Fracture of spine, level unspecified

T10 Fracture of upper limb, level unspecified

T12 Fracture of lower limb, level unspecified

T142 Fracture of unspecified body region

Traumatic Brain Injury

S06 intracranial injury

S099 unspecified injury of head

Appendix E: Anatomical Therapeutic Classifying system codes and Drug Identification Number

A Drug Identification Number (DIN) is a computer-randomly-generated eight-digit number assigned by Health Canada to a drug product prior to being marketed in Canada. It uniquely identifies all drug products sold in a dosage form in Canada and is located on the label of prescription and over-the-counter drug products that have been evaluated and authorized for sale in Canada. A DIN uniquely identifies the following product characteristics: manufacturer; product name; active ingredient(s); strength(s) of active ingredient(s); pharmaceutical form; route of administration. A DIN lets the user know that the product has undergone and passed a review of its formulation, labeling and instructions for use. A drug product sold in Canada without a DIN is not in compliance with Canadian law (Health Canada, 2018).

The Anatomical Therapeutic Chemical (ATC) Classification is an internationally accepted classification system for medicines that is maintained by the World Health Organisation (WHO). It is controlled by the WHO Collaborating Centre for Drug Statistics Methodology (WHOCC) and was first published in 1976. The WHO assigns ATC codes to all active substances contained in medicines based on the therapeutic indication for the medicine. Using the ATC code, active substances are classified in groups at five different levels according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties.

The first level of the code indicates the anatomical main group and consists of one letter. There are 14 main groups.

Code	Contents
A	Alimentary tract and metabolism
B	Blood and blood forming organs
C	Cardiovascular system
D	Dermatologicals
G	Genito-urinary system and sex hormones
H	Systemic hormonal preparations, excluding sex hormones and insulins
J	Anti-infectives for systemic use

L	Antineoplastic and immunomodulating agents
M	Musculo-skeletal system
N	Nervous system
P	Antiparasitic products, insecticides and repellents
R	Respiratory system
S	Sensory organs
V	Various

The second level of the code indicates the therapeutic subgroup and consists of two digits. The third level of the code indicates the therapeutic/pharmacological subgroup and consists of one letter. The fourth level of the code indicates the chemical/ therapeutic/ pharmacological subgroup and consists of one letter. The fifth level of the code indicates the chemical substance and consists of two digits. Take metformin as an example:

Level	Code	Content	
1	A	Alimentary tract and metabolism	Anatomical main group
2	A10	Drugs used in diabetes	Therapeutic subgroup
3	A10B	Oral blood glucose lowering drugs	Pharmacological subgroup
4	A10BA	Biguanides	Chemical subgroup
5	A10BA02	Metformin	Chemical substance

Medication information extracted from ODB database are all in DIN codes, so the conversion of DINs to ATC codes is necessary for better understanding of the result and easy comparison with other publications.

Appendix F: Table A1

Table A1

Numbers of Older Adults being Prescribed with Different Medication Classes within One Year Prior to Fall-related Injuries

ATC Codes	Drug Class	Female					Male					Total	
		66-74	75-84	85+	Total	%	66-74	75-84	85+	Total	%	No	%
A02BA	H2-receptor antagonists	3180	4049	3088	10317	5.7	1762	2309	1380	5451	5.1	15768	5.5
A02BB	Prostaglandins	149	129	73	351	0.2	30	41	24	95	0.1	446	0.2
A02BC	Proton pump inhibitors	20449	25546	19100	65095	35.7	11144	14059	8441	33644	31.7	98739	34.3
A02BX	Other drugs for peptic ulcer and (GORD)	313	344	180	837	0.5	143	166	92	401	0.4	1238	0.4
A03AB	Synthetic anticholinergics, quaternary ammonium compounds	43	34	73	150	0.1	33	38	24	95	0.1	245	0.1
A03FA	Propulsives	2578	3302	2390	8270	4.5	1151	1443	823	3417	3.2	11687	4.1
A04AA	Serotonin (5HT3) antagonists	556	378	124	1058	0.6	375	333	77	785	0.7	1843	0.6
A05AA	Bile acids and derivatives	101	96	48	245	0.1	38	39	9	86	0.1	331	0.1
A06AA	Softeners, emollients	5198	9364	8785	23347	12.8	3480	5960	4444	13884	13.1	37231	12.9
A06AB	Contact laxatives	4250	7242	6522	18014	9.9	2811	4592	3556	10959	10.3	28973	10.1
A06AC	Bulk-forming laxatives	795	1512	1414	3721	2.0	447	953	816	2216	2.1	5937	2.1
A06AD	Osmotically acting laxatives	4405	6337	6058	16800	9.2	3201	4336	3049	10586	10.0	27386	9.5
A07AA	Antibiotics	1212	1346	850	3408	1.9	559	659	352	1570	1.5	4978	1.7
A07DA	Antipropulsives	654	1082	1198	2934	1.6	391	541	401	1333	1.3	4267	1.5
A07EA	Corticosteroids acting locally	3577	3842	2360	9779	5.4	2007	2473	1338	5818	5.5	15597	5.4
A07EC	Aminosalicylic acid and similar agents	210	185	80	475	0.3	115	85	37	237	0.2	712	0.2
A09AA	Enzyme preparations	119	147	103	369	0.2	87	112	41	240	0.2	609	0.2
A10AB	Insulins and analogues for injection, fast-acting	1503	1126	482	3111	1.7	1494	1112	295	2901	2.7	6012	2.1

A10AC	Insulins and analogues for injection, intermediate-acting	615	583	298	1496	0.8	503	505	155	1163	1.1	2659	0.9
A10AE	Insulins and analogues for injection, long-acting	1979	1558	627	4164	2.3	1999	1430	426	3855	3.6	8019	2.8
A10BA	Biguanides	8771	9660	5014	23445	12.9	7615	7466	2771	17852	16.8	41297	14.3
A10BB	Sulfonylureas	4130	4924	2829	11883	6.5	3924	4141	1762	9827	9.3	21710	7.5
A10BD	Combinations of oral blood glucose lowering drugs	418	304	97	819	0.4	398	232	72	702	0.7	1521	0.5
A10BF	Alpha glucosidase inhibitors	172	191	90	453	0.2	142	145	47	334	0.3	787	0.3
A10BG	Thiazolidinediones	651	624	200	1475	0.8	564	495	134	1193	1.1	2668	0.9
A10BH	Dipeptidyl peptidase 4 (DPP-4) inhibitors	1779	1697	695	4171	2.3	1650	1339	511	3500	3.3	7671	2.7
A10BX	Other blood glucose lowering drugs, excl. insulins	43	79	37	159	0.1	28	51	16	95	0.1	254	0.1
A11CC	Vitamin D and analogues	499	837	629	1965	1.1	458	668	395	1521	1.4	3486	1.2
B01AA	Vitamin K antagonists	2280	5597	5833	13710	7.5	2643	5344	3576	11563	10.9	25273	8.8
B01AB	Heparin group	505	537	323	1365	0.7	371	476	206	1053	1.0	2418	0.8
B01AC	Platelet aggregation inhibitors excl. heparin	2830	5263	5008	13101	7.2	3413	4923	3042	11378	10.7	24479	8.5
B01AE	Direct thrombin inhibitors	317	884	809	2010	1.1	381	793	560	1734	1.6	3744	1.3
B01AF	Direct factor Xa inhibitors	758	1037	714	2509	1.4	526	785	486	1797	1.7	4306	1.5
B01AX	Other antithrombotic agents	20	26	16	62	0.0	18	23	13	54	0.1	116	0.0
B03AD	Iron in combination with folic acid	3393	5997	5509	14899	8.2	2075	3733	2846	8654	8.2	23553	8.2
B03BA	Vitamin B12 (cyanocobalamin and analogues)	2196	3648	3523	9367	5.1	1119	1986	1559	4664	4.4	14031	4.9
B03BB	Folic acid and derivatives	1303	1610	1091	4004	2.2	737	890	559	2186	2.1	6190	2.1
B03XA	Other antianemic preparations	75	141	83	299	0.2	43	106	63	212	0.2	511	0.2
B05AA	Blood substitutes and plasma protein fractions	177	348	296	821	0.5	69	128	107	304	0.3	1125	0.4

B05BB	Solutions affecting the electrolyte balance	426	484	245	1155	0.6	318	379	174	871	0.8	2026	0.7
B05XA	Electrolyte solutions	15	25	16	56	0.0	7	9	9	25	0.0	81	0.0
C01AA	Digitalis glycosides	779	2358	3301	6438	3.5	892	1812	1525	4229	4.0	10667	3.7
C01BC	Antiarrhythmics, class Ic	185	245	131	561	0.3	90	128	64	282	0.3	843	0.3
C01CA	Adrenergic and dopaminergic agents	36	83	32	151	0.1	50	108	51	209	0.2	360	0.1
C01DA	Organic nitrates	3102	5853	6997	15952	8.8	2937	4645	3545	11127	10.5	27079	9.4
C02AB	Methyldopa	60	105	118	283	0.2	25	41	25	91	0.1	374	0.1
C02AC	Imidazoline receptor agonists	309	217	118	644	0.4	82	71	33	186	0.2	830	0.3
C02CA	Alpha-adrenoreceptor antagonists	221	333	282	836	0.5	451	761	429	1641	1.5	2477	0.9
C02DB	Hydrazinophthalazine derivatives	171	324	277	772	0.4	155	270	129	554	0.5	1326	0.5
C03AA	Thiazides, plain	9338	12533	9169	31040	17.0	4603	5321	2940	12864	12.1	43904	15.2
C03BA	Sulfonamides, plain	1769	2527	1806	6102	3.4	1148	1518	781	3447	3.2	9549	3.3
C03CA	Sulfonamides, plain	5460	10254	13402	29116	16.0	4101	7758	6709	18568	17.5	47684	16.5
C03DA	Aldosterone antagonists	1204	1821	1921	4946	2.7	1055	1478	957	3490	3.3	8436	2.9
C03DB	Other potassium-sparing agents	629	832	632	2093	1.1	219	251	191	661	0.6	2754	1.0
C03EA	Low-ceiling diuretics and potassium-sparing agents	1189	1600	1349	4138	2.3	342	468	331	1141	1.1	5279	1.8
C04AD	Purine derivatives	114	221	240	575	0.3	142	237	136	515	0.5	1090	0.4
C07AA	Beta blocking agents, non-selective	857	1126	884	2867	1.6	545	681	418	1644	1.5	4511	1.6
C07AB	Beta blocking agents, selective	11055	18228	15896	45179	24.8	9634	12649	7206	29489	27.8	74668	25.9
C07AG	Alpha and beta blocking agents	400	641	521	1562	0.9	541	821	444	1806	1.7	3368	1.2
C07BB	Beta blocking agents, selective, and thiazides	180	234	128	542	0.3	80	67	35	182	0.2	724	0.3
C07CA	Beta blocking agents, non-selective, and other diuretics	21	38	29	88	0.0	10	14	9	33	0.0	121	0.0
C08CA	Dihydropyridine derivatives	11153	17993	15951	45097	24.8	7725	9698	5722	23145	21.8	68242	23.7

C08DA	Phenylalkylamine derivatives	240	357	298	895	0.5	144	162	96	402	0.4	1297	0.4
C08DB	Benzothiazepine derivatives	2993	4920	4251	12164	6.7	1870	2522	1499	5891	5.6	18055	6.3
C09AA	ACE inhibitors, plain	13192	18661	15763	47616	26.1	12529	15070	8356	35955	33.9	83571	29.0
C09BA	ACE inhibitors and diuretics	1985	2166	1370	5521	3.0	1604	1344	581	3529	3.3	9050	3.1
C09CA	agents acting on the renin-angiotensin system	9578	13183	9416	32177	17.7	5568	6204	2923	14695	13.8	46872	16.3
C09DA	Angiotensin II receptor blockers (ARBs) and diuretics	3124	3452	2029	8605	4.7	1747	1451	508	3706	3.5	12311	4.3
C09DB	ARBs and calcium channel blockers	832	832	451	2115	1.2	471	391	144	1006	0.9	3121	1.1
C10AA	HMG CoA reductase inhibitors	27117	33976	20398	81491	44.7	21800	24490	11904	58194	54.8	139685	48.5
C10AB	Fibrates	972	1162	467	2601	1.4	852	703	236	1791	1.7	4392	1.5
C10AC	Bile acid sequestrants	437	532	460	1429	0.8	189	246	157	592	0.6	2021	0.7
C10AD	Nicotinic acid and derivatives	74	65	14	153	0.1	132	90	28	250	0.2	403	0.1
C10AX	Other lipid modifying agents	2878	3148	1170	7196	4.0	2601	2442	707	5750	5.4	12946	4.5
C10BX	HMG CoA reductase inhibitors, other combinations	481	681	442	1604	0.9	442	508	206	1156	1.1	2760	1.0
D01AA	Antibiotics	305	404	393	1102	0.6	150	180	117	447	0.4	1549	0.5
D01AC	Imidazole and triazole derivatives	3499	4741	4472	12712	7.0	1862	2453	1767	6082	5.7	18794	6.5
D01AE	Other antifungals for topical use	1257	1299	969	3525	1.9	1091	1116	676	2883	2.7	6408	2.2
D05AX	Other antipsoriatics for topical use	509	391	198	1098	0.6	444	353	140	937	0.9	2035	0.7
D06AX	Other antibiotics for topical use	3713	5171	5205	14089	7.7	2433	3659	2758	8850	8.3	22939	8.0
D06BX	Other chemotherapeutics	645	620	341	1606	0.9	245	275	119	639	0.6	2245	0.8
D07AA	Corticosteroids, weak (group I)	3848	5128	4542	13518	7.4	2120	3029	2199	7348	6.9	20866	7.2
D07AB	Corticosteroids, moderately potent (group II)	971	1099	773	2843	1.6	474	616	378	1468	1.4	4311	1.5
D07AC	Corticosteroids, potent (group III)	2290	2734	2014	7038	3.9	1525	2063	1242	4830	4.6	11868	4.1

D07AD	Corticosteroids, very potent (group IV)	1366	1317	789	3472	1.9	612	754	393	1759	1.7	5231	1.8
D07XC	Corticosteroids, potent, other combinations	200	198	177	575	0.3	121	146	97	364	0.3	939	0.3
D10AF	Antiinfectives for treatment of acne	58	31	8	97	0.1	43	48	14	105	0.1	202	0.1
D10AH	Antiinfectives for treatment of acne	79	78	66	223	0.1	49	47	20	116	0.1	339	0.1
G01AG	Triazole derivatives	195	157	83	435	0.2	N/A	N/A	N/A	N/A	0.0	440	0.2
G03BA	3-oxoandrosten (4) derivatives	6	4	3	13	0.0	541	370	118	1029	1.0	1042	0.4
G03CA	Natural and semisynthetic estrogens, plain	2917	2596	1530	7043	3.9	N/A	N/A	N/A	7	0.0	7050	2.4
G03HA	Antiandrogens, plain	2	1	0	3	0.0	31	96	82	209	0.2	212	0.1
G03XA	Antigonadotropins and similar agents	482	585	390	1457	0.8	12	10	6	28	0.0	1485	0.5
G03CA	Natural and semisynthetic estrogens, plain	2917	2596	1530	7043	3.9	N/A	N/A	N/A	7	0.0	7050	2.4
G03HA	Antiandrogens, plain	2	1	0	3	0.0	31	96	82	209	0.2	212	0.1
G03XA	Antigonadotropins and similar agents	482	585	390	1457	0.8	12	10	6	28	0.0	1485	0.5
G04BD	Drugs for urinary frequency and incontinence	2922	4248	3447	10617	5.8	1134	1898	1187	4219	4.0	14836	5.1
G04CA	Alpha-adrenoreceptor antagonists	841	1051	767	2659	1.5	6362	9975	6452	22789	21.5	25448	8.8
G04CB	Testosterone-5-alpha reductase inhibitors	N/A	N/A	N/A	N/A	0.0	3031	4997	3357	11385	10.7	11389	4.0
H02AB	Glucocorticoids	10186	11888	8114	30188	16.6	6354	7872	4605	18831	17.7	49019	17.0
H03AA	Thyroid hormones	12594	16233	13300	42127	23.1	2769	4286	3574	10629	10.0	52756	18.3
H03BA	Thiouracils	60	72	58	190	0.1	14	26	8	48	0.0	238	0.1
H04AA	Glycogenolytic hormones	80	98	85	263	0.1	72	84	36	192	0.2	455	0.2
J01AA	Tetracyclines	309	288	190	787	0.4	226	240	104	570	0.5	1357	0.5

J01CA	Penicillins with extended spectrum	9185	9310	6284	24779	13.6	5536	5849	3128	14513	13.7	39292	13.6
J01CF	Beta-lactamase resistant penicillins	571	669	691	1931	1.1	439	583	379	1401	1.3	3332	1.2
J01CR	Combinations of penicillins, incl. beta-lactamase inhibitors	1500	1419	1137	4056	2.2	1024	1038	570	2632	2.5	6688	2.3
J01DB	First-generation cephalosporins	18	31	21	70	0.0	15	15	13	43	0.0	113	0.0
J01DC	2nd-generation cephalosporins	1764	2008	1704	5476	3.0	1037	1343	815	3195	3.0	8671	3.0
J01DD	3rd-generation cephalosporins	297	445	379	1121	0.6	207	253	197	657	0.6	1778	0.6
J01EA	Trimethoprim and derivatives	116	213	193	522	0.3	57	101	65	223	0.2	745	0.3
J01EE	Intermediate-acting sulfonamides	2985	4057	3695	10737	5.9	1350	1864	1217	4431	4.2	15168	5.3
J01FA	Macrolides	8142	7044	4229	19415	10.7	4178	4042	2096	10316	9.7	29731	10.3
J01FF	Lincosamides	1726	1740	976	4442	2.4	973	970	497	2440	2.3	6882	2.4
J01GB	Other aminoglycosides	14	21	11	46	0.0	9	18	N/A	31	0.0	77	0.0
J01MA	Fluoroquinolones	7489	9948	8864	26301	14.4	4765	6388	4268	15421	14.5	41722	14.5
J01XA	Glycopeptide antibacterials	20	34	21	75	0.0	9	22	12	43	0.0	118	0.0
J01XD	Imidazole derivatives	1515	1550	866	3931	2.2	872	860	423	2155	2.0	6086	2.1
J01XE	Nitrofuran derivatives	5186	7225	5696	18107	9.9	751	1310	1047	3108	2.9	21215	7.4
J01XX	Other antibacterials	N/A	N/A	N/A	14	0.0	8	N/A	N/A	13	0.0	27	0.0
J02AB	Imidazole derivatives	25	23	16	64	0.0	42	39	26	107	0.1	171	0.1
J02AC	Triazole derivatives	159	144	78	381	0.2	81	99	41	221	0.2	602	0.2
J04AK	Other drugs for tuberculosis	16	17	12	45	0.0	6	12	N/A	22	0.0	67	0.0
J04AM	Combinations of drugs for treatment of tuberculosis	33	43	39	115	0.1	22	36	16	74	0.1	189	0.1
J05AB	Nucleosides and nucleotides	887	1001	714	2602	1.4	466	556	272	1294	1.2	3896	1.4
J05AF	Nucleoside and nucleotide reverse transcriptase inhibitors	36	12	N/A	52	0.0	64	18	N/A	87	0.1	139	0.0
J05AH	Neuraminidase inhibitors	262	1017	2450	3729	2.0	219	535	778	1532	1.4	5261	1.8
L01AA	Nitrogen mustard analogues	46	111	56	213	0.1	49	89	41	179	0.2	392	0.1
L01AB	Alkyl sulfonates	108	90	28	226	0.1	33	23	N/A	56	0.1	282	0.1
L01BA	Folic acid analogues	1047	1046	431	2524	1.4	366	339	149	854	0.8	3378	1.2

L01BC	Pyrimidine analogues	63	83	14	160	0.1	31	46	20	97	0.1	257	0.1
L01XE	Protein kinase inhibitors	43	48	12	103	0.1	37	39	14	90	0.1	193	0.1
L01XX	Other antineoplastic agents	75	156	147	378	0.2	52	91	64	207	0.2	585	0.2
L02AB	Progestogens	52	100	107	259	0.1	60	110	68	238	0.2	497	0.2
L02AE	Gonadotropin releasing hormone analogues	N/A	N/A	N/A	N/A	0.0	487	1269	1087	2843	2.7	2844	1.0
L02BA	Anti-estrogens	243	291	230	764	0.4	10	30	30	70	0.1	834	0.3
L02BB	Anti-androgens	N/A	N/A	N/A	N/A	0.0	225	684	675	1584	1.5	1586	0.6
L02BG	Aromatase inhibitors	978	971	514	2463	1.4	N/A	N/A	N/A	10	0.0	2473	0.9
L03AA	Colony stimulating factors	98	45	15	158	0.1	31	26	6	63	0.1	221	0.1
L04AA	Selective immunosuppressants	240	175	46	461	0.3	202	105	15	322	0.3	783	0.3
L04AB	Tumor necrosis factor alpha (TNF-α) inhibitors	108	90	28	226	0.1	33	23	N/A	56	0.1	282	0.1
L04AD	Calcineurin inhibitors	270	169	97	536	0.3	203	160	62	425	0.4	961	0.3
L04AX	Other immunosuppressants	189	139	62	390	0.2	101	91	24	216	0.2	606	0.2
M01AE	Propionic acid derivatives	4491	3622	1766	9879	5.4	2570	1973	748	5291	5.0	15170	5.3
M01AH	Coxibs	3717	3891	2288	9896	5.4	1698	1729	778	4205	4.0	14101	4.9
M03BX	Other centrally acting agents	1119	850	306	2275	1.2	566	412	135	1113	1.0	3388	1.2
M04AA	Preparations inhibiting uric acid production	1240	2250	1920	5410	3.0	2683	3815	2010	8508	8.0	13918	4.8
M05BA	Biphosphonates	14187	21354	15912	51453	28.2	1867	3299	2316	7482	7.1	58935	20.4
M05BX	Other drugs affecting bone structure and mineralization	446	896	679	2021	1.1	14	35	28	77	0.1	2098	0.7
N02AA	Natural opium alkaloids	15408	17873	12311	45592	25.0	10350	10711	5437	26498	25.0	72090	25.0
N02AB	Phenylpiperidine derivatives	608	922	877	2407	1.3	334	407	237	978	0.9	3385	1.2
N02AJ	Opioids in combination with non-opioid analgesics	13685	15531	10035	39251	21.6	9283	9555	4712	23550	22.2	62801	21.8
N02BA	Salicylic acid and derivatives	1351	2294	1931	5576	3.1	1239	1785	1078	4102	3.9	9678	3.4
N03AA	Barbiturates and derivatives	164	172	89	425	0.2	134	133	58	325	0.3	750	0.3
N03AB	Hydantoin derivatives	716	710	437	1863	1.0	713	666	311	1690	1.6	3553	1.2
N03AE	Benzodiazepine derivatives	2372	1967	1049	5388	3.0	1060	916	369	2345	2.2	7733	2.7

N03AF	Carboxamide derivatives	538	491	284	1313	0.7	377	308	130	815	0.8	2128	0.7
N03AG	Fatty acid derivatives	603	340	153	1096	0.6	432	278	90	800	0.8	1896	0.7
N03AX	Other antiepileptics	3036	3026	1889	7951	4.4	1638	1656	757	4051	3.8	12002	4.2
N04AA	Tertiary amines	64	47	21	132	0.1	65	49	6	120	0.1	252	0.1
N04BA	Dopa and dopa derivatives	924	1653	1001	3578	2.0	1023	1971	860	3854	3.6	7432	2.6
N04BB	Adamantane derivatives	102	74	16	192	0.1	97	103	13	213	0.2	405	0.1
N04BC	Dopamine agonists	742	719	400	1861	1.0	455	514	189	1158	1.1	3019	1.0
N04BD	Monoamine oxidaseB inhibitors	24	29	14	67	0.0	38	37	11	86	0.1	153	0.1
N04BX	Other dopaminergic agents	91	119	39	249	0.1	117	176	48	341	0.3	590	0.2
N05AA	Phenothiazines-aliphatic sidechain	168	111	75	354	0.2	124	102	56	282	0.3	636	0.2
N05AB	Phenothiazines piperazine structure	899	855	373	2127	1.2	537	487	160	1184	1.1	3311	1.1
N05AC	Phenothiazines piperidine structure	79	98	52	229	0.1	24	15	7	46	0.0	275	0.1
N05AD	Butyrophenone derivatives	182	349	416	947	0.5	179	319	222	720	0.7	1667	0.6
N05AH	Diazepines, oxazepines, thiazepines and oxepines	2178	3160	3404	8742	4.8	1431	1993	1413	4837	4.6	13579	4.7
N05AN	Lithium	295	194	78	567	0.3	187	97	18	302	0.3	869	0.3
N05AX	Other antipsychotics	778	1585	2049	4412	2.4	562	958	789	2309	2.2	6721	2.3
N05BA	Benzodiazepine derivatives	10302	13766	10602	34670	19.0	4420	5446	3334	13200	12.4	47870	16.6
N05CD	Benzodiazepine derivatives	1207	1537	1184	3928	2.2	656	808	515	1979	1.9	5907	2.0
N06AA	Non-selective monoamine reuptake inhibitors	4182	4347	2208	10737	5.9	1452	1437	695	3584	3.4	14321	5.0
N06AB	Selective serotonin reuptake inhibitors	9510	11206	9084	29800	16.4	4198	5191	3221	12610	11.9	42410	14.7
N06AG	Monoamine oxidase A inhibitors	50	41	12	103	0.1	28	24	7	59	0.1	162	0.1
N06AX	Other antidepressants	7940	8789	7339	24068	13.2	3806	4399	2873	11078	10.4	35146	12.2
N06BA	Centrally acting sympathomimetics	145	99	72	316	0.2	104	88	32	224	0.2	540	0.2
N06DA	Anticholinesterases	1295	6300	7831	15426	8.5	997	3746	3319	8062	7.6	23488	8.1
N07AA	Anticholinesterases	47	47	29	123	0.1	30	50	25	105	0.1	228	0.1
N07AB	Choline esters	48	57	46	151	0.1	28	53	44	125	0.1	276	0.1

N07BA	Drugs used in nicotine dependence	237	48	N/A	288	0.2	196	43	N/A	240	0.2	528	0.2
P03AC	Pyrethrines	90	141	217	448	0.2	63	82	77	222	0.2	670	0.2
R01AD	Corticosteroids (nasal preparations)	3002	2786	1547	7335	4.0	1577	1726	876	4179	3.9	11514	4.0
R02AX	Other nasal preparations	32	33	21	86	0.0	21	19	7	47	0.0	133	0.0
R03BA	Glucocorticoids (drugs for COPD)	4821	4940	3189	12950	7.1	2184	2743	1522	6449	6.1	19399	6.7
R03BB	Anticholinergics	4553	6158	4246	14957	8.2	3341	5164	3197	11702	11.0	26659	9.2
R03CB	Non-selective beta-adrenoreceptor agonists	77	84	79	240	0.1	44	40	34	118	0.1	358	0.1
R03CC	Selective beta-2-adrenoreceptor agonists	9090	9039	6065	24194	13.3	4754	5607	3227	13588	12.8	37782	13.1
S01AA	Antibiotics-ophthalmologicals	2063	2660	2028	6751	3.7	1127	1658	1080	3865	3.6	10616	3.7
S01AD	Antivirals-ophthalmologicals	68	61	45	174	0.1	45	53	36	134	0.1	308	0.1
S01AE	Fluoroquinolones	76	100	96	272	0.1	43	63	63	169	0.2	441	0.2
S01BA	Corticosteroids, plain	3520	4958	2405	10883	6.0	1919	2855	1334	6108	5.8	16991	5.9
S01BC	Antiinflammatory agents,	1240	1800	811	3851	2.1	694	1121	460	2275	2.1	6126	2.1
S01EA	Sympathomimetics in glaucoma	707	1336	1315	3358	1.8	496	945	669	2110	2.0	5468	1.9
S01EB	Parasympathomimetics	71	152	251	474	0.3	46	83	98	227	0.2	701	0.2
S01EC	Carbonic anhydrase inhibitors	1022	1975	2204	5201	2.9	677	1377	1031	3085	2.9	8286	2.9
S01ED	Beta blocking agents	909	1681	1946	4536	2.5	503	1002	820	2325	2.2	6861	2.4
S01EE	Prostaglandin analogues	2491	4673	5003	12167	6.7	1475	2805	2221	6501	6.1	18668	6.5
S01FA	Anticholinergics	162	198	177	537	0.3	172	214	126	512	0.5	1049	0.4
S01GX	Other antiallergics	792	988	591	2371	1.3	321	404	235	960	0.9	3331	1.2
S01HA	Local anesthetics	139	98	58	295	0.2	110	89	27	226	0.2	521	0.2
S01LA	Antineovascularisation agents	318	1107	1530	2955	1.6	241	620	638	1499	1.4	4454	1.5
S02CA	Corticosteroids and anti-infectives (otologicals)	421	487	266	1174	0.6	253	308	171	732	0.7	1906	0.7
V06DC	Carbohydrates	9727	11013	5692	26432	14.5	7991	8510	3329	19830	18.7	46262	16.0

Note. Medication classes that were prescribed to less than six persons were reported as N/A to protect the patients' privacy

Curriculum Vitae

Name: Yu Ming

Education Background

Sep 1996 - Jul 2003
Nankai University, Tianjin, China
7-year Undergraduate and Graduate Joint Program
Major: Clinical Medicine
GPA: 84%
Degree: Master's Degree of Internal Medicine

Sep 2014 - present
Western University, Ontario, Canada
Major: Health and Aging, Health and Rehabilitation Sciences
Course Average: 83
Admitted to master program, transferred to PhD program in Sep 2015, take a maternity leave from Apr 2016-Mar 2017

Working Experience

Aug 2003 - Jun 2014
Transplantation Department of Tianjin First Center Hospital, Tianjin, China
Position title: Attending Physician
Responsibilities: clinical diagnosis and treatment in the ICU of Transplantation Department; patients' administration pre and post-transplantation; treatment of anti-infection, anti-rejection, acute renal failure, cardiac cerebral function protection, nutrition, and surgery complications prevention for patients with liver, kidney, heart, liver-kidney combined, and pancreas-kidney combined transplantations; participate in number of clinical research programs related to the perioperative period of organ transplantation; participate in compiling and translating of medicine-related documentation.

Sep 2014-Apr 2020
Western University, London, Ontario
Position title: Graduate Teaching Assistant
Responsibilities: Assist faculty or other instructional staff in postsecondary institutions by performing teaching or teaching-related duties, such as teaching lower level courses, developing teaching materials, preparing and giving examinations, and grading examinations or papers.

Publications

Li, D., Yuan, W., Ma, X.T., Cai, H., Ming, Y., Li, J., Zhao, C. H. (2003). The extraction, purification and function research of human recombinant fusion protein IL6/IL2. *High Technology Letters*,(11), 27-30.

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Ming, Y., (2011). Application/Comparison on PCT and CRP in Testing Bacterial Infection, *Jilin Medical Journal,32*(30), 248-249.

Wang, Y., Liu, Y.H., Ming, Y., Liu, L. (2013). Perioperative liquid management for 36 adult Liver-Kidney Combined Transplantation patients, *Chinese Critical Care Medicine. (25)*7,432-434.

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Ming, Y., Zecevic, A., Hunter, W. S., Miao, W., & Tirona, R. (2020). The Effectiveness of Medication Review on Prevention of Fall-Related Injuries in Older Adults: A Systematic Review and Meta-Analysis. *Canadian Geriatrics Journal,* submitted on Jun 29th, 2020.

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Ming, Y., Zecevic, A., Booth, R., Hunter, Tirona, R. & Johnson, A. (2020). Association between Fall-related Injury and Medication Prescribed to Older Adults within One Month prior to the Injury. *Clinical Intervention on Aging*, submitted on Sep 9th, 2020.

Presentations

Ming Y, Zecevic A. (2016). The influence of different classes of medications and polypharmacy on elderly recurrent fallers in community: A Systematic literature review. Watch Your Step! National Fall Prevention Conference, Calgary, Canada.

Ming Y, Zecevic A. (2016). The influence of different classes of medications and polypharmacy on elderly recurrent fallers in community: A Systematic literature review. The Gerontological Society of America's 2016 Annual Scientific Meeting, New Orleans, United States.

Ming Y, Zecevic A, Hunter S, Miao W, Tirona R. (2018). The Effectiveness of Medication Review on Prevention of Fall-Related Injuries in Older Adults: A Systematic Review and Meta-Analysis. The Gerontological Society of America's 2018 Annual Scientific Meeting, New Boston, United States.

Ming Y, Zecevic A, Hunter S, Miao W, Tirona R. (2019). The Effectiveness of Medication Review on Prevention of Fall-Related Injuries in Older Adults: A Systematic Review and Meta-Analysis. The 48th Annual Scientific and Education Meeting of Canadian Association on Gerontology, Moncton, New Brunswick, Canada.

Ming Y, Zecevic A, Booth R, Hunter S, Tirona R, Johnson A. (2020). Medication Prescribed to Older Adults within One Year prior to a Fall-related Injury. Accepted as Poster section in the Gerontological Society of America's 2020 Annual Scientific Meeting.

Ming Y, Zecevic A, Booth R, Hunter S, Tirona R, Johnson A. (2020). Medication Prescribed to Older Adults within One Year prior to a Fall-related Injury. Digital Presentation at Connecting Communities: Fall Prevention Across the Lifespan. Canadian Fall Prevention Virtual Conference 2020.

Awards and Funding

- New Techniques Award from Tianjin Health Bureau
  Title: "Pre-operation Application of Protein A Immunoadsorption in the Treatment of Sensitized Recipients of Kidney Transplantation."
  Project conducted in 2013, and the award received in May 2014
  Responsibilities: in charge of study design, data collection and sorting, case selection and visiting, and project application.
- Western University of Health Sciences Mid-Career Stimulus Grant
  May 2017-April 2018 (Completed)
  Funding Sources: Western University of Health Sciences
  Principal Applicant: Aleksandra Zecevic Co-investigator: Yu Ming
- Ontario Graduate Scholarship

  Sep 2018-Aug 2019 (Awarded)

Certificates

- SAS Certified Base Programmer for SAS9 (Nov, 2018)
- SAS Certified Advanced Programmer for SAS9 (Jan, 2019)