Investigating the Association between Atypical Antipsychotic Medication Use and Falls among Personal Care Home Residents in the Winnipeg Health Region

by

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Abstract

Falls among older adults (age 65 years and older) residing in personal care homes (PCHs) are an important health concern. Atypical antipsychotic drugs (AADs) have been shown to be associated with fall risk among older adults. However, previous studies face some methodological limitations that affect the quality, consistency, and comparability of these studies. Therefore, a population-based study was undertaken to examine the effect of AAD use on the risk of falling among older PCH residents.

A nested case-control study was conducted using the administrative healthcare records and Minimum Data Set for PCHs (MDS) housed at the Manitoba Centre for Health Policy (MCHP) in the Faculty of Medicine, University of Manitoba. The study period was from April 1, 2005 to March 31, 2007. Cases (n=626) were fallers as recorded in MDS. Using incidence density sampling, each case was matched to four controls on length of PCH stay, age, and sex (n=2,388). Exposure to AADs was obtained from the Drug Program Information Network database (DPIN). Conditional logistic regression (CLR) was used to model the effects of AAD use on the risk of falling while accounting for matching and for confounding of other covariates.

While the adjusted odds of falling was statistically greater for AAD users versus nonusers (adjusted OR = 1.60, 95% CI 1.10-2.32), this association was type and dose dependent. Compared to nonusers, the odds of falling was greater for quetiapine users, regardless of this drug's dose, and high dose risperidone users. On the other hand, low dose risperidone and olanzapine, irrespective of drug dose, use was not associated with the risk of falling. Furthermore, the effect of AAD use, in general, on the risk of falling

was significantly greater for people with wandering problems (adjusted OR = 1.84, 95% CI 1.09-3.09).

Despite some methodological limitations, this research has provided some unique findings that enhance our understanding of AAD use as a fall risk factor. Study findings allow policymakers to further develop evidence-based interventions specific to AADs in order to better manage falls in the PCH setting. However, a great deal of research is still needed to address other important unanswered questions such as duration of AAD use and fall risk, and also differences in the association of AAD use and fall risk across geography and profit status of PCHs.

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The results and conclusions presented are those of the authors. No official endorsement by Manitoba Health is intended or should be inferred.

Dedication

This dissertation is dedicated to the memory of my brother,

Huseyin Gro Bozat (1984-2002)...

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List of Abbreviations

AAD	Atypical antipsychotic drug
ADGs	Aggregated diagnostic groups
ADL	Activities of daily living
ATC	Anatomic therapeutic chemical classification
BPSD	Behavioural and psychological symptoms of dementia
CI	Confidence intervals
CIE	Change in estimate
CLR	Conditional logistic regression
CPS	Cognitive performance scale
ICD-10-CA	The Tenth Revision of the International Statistical Classification of Diseases and Related Health Problems in Canada
BZD	Benzodiazepine
DPIN	Drug Programs Information Network
GEE	Generalized estimating equation
HD	Haloperidol
ID	Identification
MCHP	Manitoba Centre for Health Policy
MDS	Minimum Data Set for personal care homes
MDS-HC	Minimum Data Set for home care
MR	Medical records

N/A	Not applicable
NR	Not reported
NS	Not significant
OBRA 87	Omnibus Reconciliation Act of 1987
OR	Odds ratio
OLZ	Olanzapine
PCH	Personal care home
PDD	Prescribed daily dose
PHIN	Personal health identification number
PRN	pro-re-nata (as needed)
PS	Power and sample size program
RAI-MDS©	Resident Assessment Instrument Minimum Data Set 2.0
RCT	Randomized controlled trial
QTP	Quetiapine
RIS	Risperidone
SAS®	Statistical analysis system
SD	Standard deviation
t1/2	Half-live
TADs	Typical antipsychotic drugs
WHO	World Health Organization
WHR	Winnipeg health region

List of Copyrighted Materials

Written permission from the World Health Organization was obtained to adopt the Figure 3 ("Risk factor model for falls in older age"), published in the *World Health Organization global report on falls prevention in older age (2007), Geneva*. The adopted material can be found on page 24 (Figure 2.4) of this dissertation.

Chapter 1

Introduction

Falls are an important health concern amongst personal care home (PCH)-dwelling older adults,[1] as 30% to 50% of these individuals fall at least once each year (American Geriatrics Society, British Geriatrics Society, & American Academy of Orthopaedic Surgeons Panel on Falls Prevention, 2001; Chen et al., 2005). Falls often result in fractures (Canadian Institute for Health Information, 2003) and/or hospitalization (Smartrisk, 2009); they are also associated with increased long-term pain, loss of mobility, as well as reduced confidence and general quality of life (World Health Organization, 2007). Understanding fall risk factors is therefore an important component of quality care and patient safety in the PCH environment. While much is known about fall risk factors and effective fall intervention strategies for community-dwelling older adults, the equivalent information for PCH residents is relatively sparse. Further, research demonstrates that lessons learned in the community environment cannot necessarily be transferred to PCHs, as individuals in these latter environments are typically much frailer with several comorbidities (Vu, Weintraub, & Rubenstein, 2004).

Falls have been established as a complex phenomenon and are thought to result from an interaction of multiple risk factors (Ganz, Bao, Shekelle, & Rubenstein, 2007; World Health Organization, 2007). Antipsychotic drugs are an important fall risk factor,

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[1] Throughout this dissertation, "older adults" or "older personal care home residents" refer to adults age 65 years and older. Also, PCHs in Manitoba are commonly referred to as nursing homes in the United States and most other Canadian provinces.

in part because of the established association between use of these drugs and falls (Bloch et al., 2011; Cumming, 1998; French et al., 2007; Horikawa et al., 2005; Iinattiniemi, Jokelainen, & Luukinen, 2009; Kelly et al., 2003; Leipzig, Cumming, & Tinetti, 1999a; Mustard & Mayer, 1997; Neutel, Perry, & Maxwell, 2002; van Doorn et al., 2003; Woolcott et al., 2009; Yip & Cumming, 1994), and also due to their high use in Canadian PCHs (Raymond et al., 2010). Evidence from Manitoba shows that 30% of PCH residents receive antipsychotic drugs shortly after they are admitted to a PCH (i.e., from 91 to 190 days after being admitted to a PCH) (Doupe et al., 2006). Of these residents, the vast majority (83%) receive newly marketed atypical antipsychotic drugs (AADs), also called second generation antipsychotics. These AADs have generally replaced the use of typical antipsychotic drugs (TADs) (older or first generation antipsychotics) in the PCH environment (Kozyrskyj et al., 2009; Raymond et al., 2010), as they are thought to have an equivalent drug efficacy combined with an improved patient safety profile (Beasley, Jr., Tollefson, & Tran, 1997; Frenchman & Prince, 1997; Motsinger, Perron, & Lacy, 2003).

Despite this evidence of improved safety, the literature generally concludes that AAD use is also associated with an increased fall risk in both community- (Landi et al., 2005; Rochon et al., 2008) and PCH-dwelling older adults (Brodaty et al., 2003; de Deyn et al., 2005; Frenchman, 2005; Hien et al., 2005; Kallin, Gustafson, Sandman, & Karlsson, 2004; Katz et al., 1999; Katz, Rupnow, Kozma, & Schneider, 2004; Martin, Slyk, Deymann, & Cornacchione, 2003; Mintzer et al., 2006; Rochon et al., 2008; Street et al., 2000; Suh, Greenspan, & Choi, 2006). However, this research has generally focused on earlier developed AADs (i.e., risperidone and/or olanzapine), and little is

known about the fall risk profile of quetiapine (the most recently developed AAD). This is particularly important in Manitoba, as quetiapine use rates in PCHs has increased dramatically in this province, from 0.9 users per 1,000 PCH residents in 1997, to 67.6 users per 1,000 PCH residents in 2008 (Raymond et al., 2010). Lastly, there is limited evidence testing the dose-response association between AAD use and fall risk (overall as group or for individual drugs).

The Present Research

This research links clinical data from the PCH environment (the Resident Assessment Instrument Minimum Data Set 2.0, hereafter referred to as RAI-MDS©),[1] to administrative healthcare records housed at the Manitoba Centre for Health Policy (MCHP) in the Faculty of Medicine, University of Manitoba, to investigate the association between AAD use and falls among older PCH residents in the Winnipeg health region (WHR). Linkage of these data provides a unique opportunity to further understand the fall risk profile of PCH residents, specifically as it relates to AAD use.

The following hypotheses were tested in this research:

1. Compared to nonusers, AAD use will increase the risk of falling among older PCH residents;
2. The association between AAD use and the risk of falling will vary depending on the type and dose of AAD used;
3. The association between AAD use, as a group, and the risk of falling will

[1] The Canadian version of RAI-MDS is copyright© Canadian Institute for Health Information, 2005; subsequent references to RAI-MDS© in this dissertation acknowledge this copyright status.

depend on certain person characteristics (e.g., fall history, wandering, and use of drugs other than AADs).

Summary and Organization of this Dissertation

The information provided in this dissertation is organized into six chapters.

Chapter 2 reviews the fall epidemiology in older adults, and provides evidence related to the significance of falls. Biological and medical, behavioural, socioeconomic, and environmental fall risk factors are discussed in this chapter. Chapter 3 reviews literature that describes how AADs are used by older adults. This is followed by a systematic review and methodological critique of the literature focusing on the association between AAD use and falls both in community- and PCH-dwelling older adults.

Chapter 4 describes the methodology used in this research, focusing on the study design, the data sources used, strategies for defining cases and controls, measurement of AAD use and other study covariates, and the statistical analyses used. Chapter 5 presents the descriptive, unadjusted, and adjusted results of this research. A discussion of these results is provided in Chapter 6. Policy implications and future research directions are also presented in this chapter.

Chapter 2

Background on Falls in Older Adults

This chapter reviews the epidemiology of falls in older adults and discusses the evidence related to the significance of falls. The biological and medical, behavioural, socioeconomic, and environmental risk factors of falls is also discussed, for both community- and personal care home (PCH)- dwelling older adults. Identification of these risk factors is important for implementing better fall management strategies.

Conceptual Definition of a Fall

A fall is usually defined as "inadvertently coming to rest on the ground, floor or other lower level, excluding intentional change in position to rest on furniture, wall or other objects" (World Health Organization, 2007). A fall resulting from a violent action, epileptic seizure, or loss of consciousness is commonly excluded from this fall definition (Kellog International Work Group on the Prevention of Falls by the Elderly, 1987). Additionally, in the International Classification of Diseases, falls are considered as one category of external causes of unintentional injury, and are coded as W00-W19 in the ICD-10-CA (The Tenth Revision of the International Statistical Classification of Diseases and Related Health Problems in Canada) (Canadian Institute for Health Information, 2009b).

Fall Epidemiology

Frequency of falls.

Falls in older adults are an important health concern as worldwide, an estimated 28% to 35% of older adults fall each year (World Health Organization, 2007). About 40% of these older adults experience recurrent falls (i.e., two or more falls) (Chen et al., 2005; World Health Organization, 2007). The absolute numbers of falls and related consequences are expected to increase in the future as the population of older adults increases.

Falls in older adults vary according to the environment in which the person lives. Fall rates are generally higher in PCH- versus community-dwelling older adults, with 30% to 50% of PCH residents falling at least once each year (American Geriatrics Society et al., 2001; Chen et al., 2005). A similar pattern is reported for fall-related injuries. For example, 10% to 25% of falls in a PCH, compared to 5% of falls in a community, result in fracture or hospital admission (Vu et al., 2004). These higher fall and injurious fall rates for PCH residents are likely attributed to their greater level of frailty, cognitive impairment, and comorbidity, as compared to their community-dwelling counterparts (Public Health Agency of Canada, 2005).

Fall-related mortality.

Worldwide, adults over the age of 80 years, particularly females, have higher fall-related mortality rates than younger persons (see Figure 2.1) (Peden, McGee, & Sharma, 2002). These mortality rates, however, are marked by geographical differences. In 2000, fall-related mortality rates for people age 80 years and older were highest in Europe and

lowest in South-East Asia (Peden et al., 2002). High-income countries in the region of America (i.e., Canada, United States of America, and Bahamas) had the second highest fall-related mortality rates. These international differences could be driven by incompleteness of data in some regions of the world, or by genetic, cultural, dietary, and environmental factors. For example, in some cultures, falling in older adults may be seen as a natural part of aging or as "unavoidable accidents", therefore, it may not be seen as a priority (World Health Organization, 2007).

In Canada, fall-related mortality is also an important concern. Falls are the number one reason for mortality from unintentional injury in older adults (Health Canada, 1999). The Public Health Agency of Canada (2005) reports that, using age-standardized data, the mortality rates from falls have increased significantly over time amongst older adults, from 8.1 deaths per 10,000 population in 1997-1999, to 9.4 deaths per 10,000 population in 2000-2002. Furthermore, fall-related age- and sex-standardized mortality rates appear to vary among Canadian provinces (see Figure 2.2) (Smartrisk, 2009). Using age- and sex-standardized data, 0.7 deaths were reported for every 10,000 Canadian people in 2004. Newfoundland and Labrador had the lowest mortality rates due to falls, at 0.3 deaths per 10,000 population, while Nova Scotia had the highest rate, at 1.3 deaths per 10,000 population. In 2004, Manitoba had the second highest fall-related mortality rate, with 1.0 deaths per 10,000 population.

Fall-related injuries.

In Canada, fall-related hospitalization rates are higher for those age 65 years and older both in the community and the PCH settings (Smartrisk, 2009). Amongst these

older adults, fall-related hospitalization rates are highest for people age 85 years and older (see Figure 2.3) (Public Health Agency of Canada, 2005). These rates are especially high for females aged 85 years and older, with 460 fall-related hospitalizations per 10,000 population. According to the Canadian Institute for Health Information (2003), amongst older adults, 85% of hospitalizations from injuries are due to falls. Most of the injuries resulting in these hospitalizations are due to fractures and dislocations (74%), followed by lacerations and contusions (12%), and head injuries (8%) (Canadian Institute for Health Information, 2003).

In addition to fall-related hospitalizations, many older adults are thought to experience "post-fall syndrome" after falling. Symptoms of this syndrome include the onset of confusion, immobilization, or depression, often followed by a loss of independence and autonomy, especially when conducting daily activities (World Health Organization, 2007). Falls can therefore impact many dimensions of a person's life, including the need for PCH placement. Recent evidence from British Columbia estimates that falling precipitates 40% of PCH admissions (Ministry of Health Planning, 2004). This same study suggests that those not admitted to a PCH may become more dependent on others, often creating additional caregiver burden for friends and families.

Like mortality, fall-related injuries also vary according to the environment in which an older adult lives. These injuries are much more common among older adults living in residential care facilities (i.e., chronic care hospitals, PCHs, and homes for the aged) versus older adults living in the community (Public Health Agency of Canada, 2005). Additionally, the average length of stay for fall-related hospitalizations is thought

to be about 19% longer for older adults in residential care as compared to those living in the community (Public Health Agency of Canada, 2005).

Economic impact of falls.

Falls have a significant financial impact on Canadians, as it relates to the healthcare system, older adults themselves, and to their caregivers. In Canada, older adults accounted for 46% of direct healthcare costs arising from fall-related injuries in 2004 (Smartrisk, 2009). Unless the incidence of falls and fall-related injuries can be reduced, these economic costs will likely escalate with aging populations.

Potential Fall Risk Factors among Older Adults

Falls impose a significant burden to the general quality of life of older adults, and to the Canadian healthcare system. Understanding fall risk factors amongst older adults is therefore important for developing and implementing effective fall management strategies. The following section summarizes the current literature on fall risk factors among both community- and PCH-dwelling older adults.

Falls have been established as a complex phenomenon and fall risk factors are thought to work independently and/or interactively to influence falls (Ganz et al., 2007; World Health Organization, 2007). Researchers have described these risk factors and grouped them in various ways. Traditionally, they have been divided into intrinsic (related to the health of an individual) and extrinsic (related to the environment in which a person lives) factors (American Geriatrics Society et al., 2001; Landi et al., 2005; Vu et al., 2004). However, a more recent World Health Organization's (WHO) “risk factor model” has emerged, which better captures the interrelationship among fall risk factors,

and also more closely reflects the broad determinants of health (see Figure 2.4) (British Columbia Ministry of Health Planning, 2004; Manitoba Health, 2005; World Health Organization, 2007). This model groups fall risk factors into biological and medical, behavioural, environmental, and socioeconomic categories. It is expected that as the number of these risk factors increases, the risk of falling and related injuries also increases (American Geriatrics Society et al., 2001; Public Health Agency of Canada, 2005).

Biological and medical risk factors.

Biological and medical fall risk factors may result from the natural aging process, a person's gender, or the presence of acute and chronic health conditions (British Columbia Ministry of Health Planning, 2004). More details about these risk factors are provided in the following text.

Advanced age.

The literature consistently shows that older adults, especially those age 80 years and older, are more likely to fall and sustain fall-related injuries (Aizenberg, Sigler, Weizman, & Barak, 2002; British Columbia Ministry of Health Planning, 2004; Manitoba Health, 2005; Public Health Agency of Canada, 2005). Other risk factors described in the WHO's risk factor model, including cognitive decline and physical disability such as poor balance and gait disorder, often occur amongst the oldest adults.

Gender.

Evidence suggests that older women are more likely than men to fall and/or to sustain fall-related injuries (British Columbia Ministry of Health Planning, 2004; Doupe et al., 2006; Landi et al., 2005; Mustard & Mayer, 1997; Neutel et al., 2002). This difference may be explained by gender-related differences in health seeking behaviours. For example, a study conducted in England suggests that men and women have different perspectives on the meaning of the risk of falling; this may influence their actions to prevent falls (Horton, 2007). In addition, biological difference between men and women may also contribute to their different fall risk. For example, the age-related decline in muscle and bone mass is usually much greater in women than men, especially post-menopause, which can lead to a greater fall risk and fall-related injuries among women (World Health Organization, 2007).

Chronic and acute disease.

The existing literature demonstrates that fall risk is proportional to the number of diseases that an individual has (Doupe et al., 2006; Kallin, Jensen, Olsson, Nyberg, & Gustafson, 2004; Landi et al., 2005; Lawlor, Patel, & Ebrahim, 2003; Yip & Cumming, 1994). For example, in Manitoba, hospitalized fall events were 1.4 times greater for PCH residents diagnosed with two or more versus zero or one categories of chronic disease (Doupe et al., 2006). This effect may be explained by increased frailty, reduced physical activity, and the side effects of drugs used to treat these diseases.

Among chronic illnesses, dementia is a major contributor of falls among older adults, increasing fall risk nearly two fold (van Doorn et al., 2003). Patients with

dementia may be at greater risk for falls due to the behavioural challenges often associated with dementia, such as wandering and agitation, or because of the drug treatment therapies that are often provided to these residents. Additionally, patients with dementia are more likely to have a higher level of functional impairment which, in turn, is related to the falls (Harrison, Booth, & Algase, 2001).

Other chronic diseases such as Parkinson's disease (Landi et al., 2005; Northridge, Nevitt, & Kelsey, 1996), arthritis (American Geriatrics Society et al., 2001), cardiovascular disease (Doupe et al., 2006; Lee, Kwok, Leung, & Woo, 2006), bowel and bladder incontinence (Chiarelli, Mackenzie, & Osmotherly, 2009; Tinetti, Inouye, Gill, & Doucette, 1995; Yip & Cumming, 1994), and stroke (Lee et al., 2006; Tinetti, Williams, & Mayewski, 1986) have been associated with higher fall risk in older adults. Acute diseases such as flu and other infections also increase resident frailty and physical impairment, which may contribute to fall risk. In a study conducted in Sweden, researchers noted that acute diseases precipitated 38.6% of falls (Kallin et al., 2004).

Muscle weakness, poor physical fitness, and physical disability.

It is widely recognized that muscle weakness, particularly in the lower body, and poor levels of physical fitness are significant fall risk factors (British Columbia Ministry of Health Planning, 2004; Friedman et al., 1995; Public Health Agency of Canada, 2005; Rubenstein & Josephson, 2002). Older adults with muscle weakness are more likely to tire easily and have difficulties completing activities of daily living (ADL) such as dressing, walking, and getting out of bed, and thus may be more prone to falls.

Fall risk has been shown to increase with certain physical disabilities. Examples of these disabilities include gait and balance problems (Ganz et al., 2007; Harlein, Dassen, Halfens, & Heinze, 2009; Horikawa et al., 2005; Yip & Cumming, 1994), diminished independence in ADLs, having hearing and vision impairments (British Columbia Ministry of Health Planning, 2004), and having foot problems (American Geriatrics Society et al., 2001; Ganz et al., 2007).

Transition.

Some evidence suggests that the risk of falling increases amongst older adults in transitional stages of their life such as being recently admitted to a PCH or being close to death. Researchers in Manitoba reported that the risk of hospitalized falls was greatest for PCH residents 30 days following their first admission and 60 days preceding death (Doupe et al., 2011a). Similarly, some evidence shows that the incidence of falling doubled after PCH residents were relocated to a new facility (Friedman et al., 1995). These results may reflect the time required for residents to adapt to their new living environment, or in the case of death, extreme resident frailty.

Behavioural risk factors.

Behavioural risk factors refer to a person's choices and actions that may increase their risk of falling (World Health Organization, 2007). This includes prescription drug use, fall history, and various life-style factors. Collectively, these risk factors are thought to be particularly important in fall management, as they are potentially modifiable.

Prescription drug use.

Considerable research has focused on the extent that prescription drugs contribute to fall risk, in part because drug exposure may represent an important modifiable risk factor (Leipzig et al., 1999a; Winterstein, Sauer, Hepler, & Poole, 2002). Drug use may affect falls primarily through sedation, drowsiness, orthostatic hypotension, neuromuscular incoordination, or movement disorders (Howland, 2009).

High volume of drugs (Polymedicine).

Older adults tend to have a number of medical problems and are hence often prescribed higher volume of drugs. Polymedicine is usually defined as 'the inappropriate use of multiple drug regimens' (Leipzig, Cumming, & Tinetti, 1999b). There is no consensus on the definition of polymedicine, which currently includes taking two or more drugs (Veehof, Stewart, Haaijer-Ruskamp, & Jong, 2000), four or more drugs (Wyles & Rehman, 2005), five or more drugs (Flaherty, Perry, Lynchard, & Morley, 2000; Koh, Fatimah, & Li, 2003; Mamun, Lien, Goh-Tan, & Ang, 2004), and nine or more drugs (Doupe et al., 2006). Doupe et al. (2006) reported that in Manitoba, the percent of people taking nine or more categories of prescription drugs almost doubled upon PCH admission, from 4.8% of people before admission to 9.0% shortly afterwards.

Many drugs have multiple pharmacological effects, and by combining drugs the risk of side effects, including falling, increases. Studies have shown that fall risk and related injuries is directly proportional to the number of drugs a person uses both in the community (Cumming, 1998; Landi et al., 2005; Lee et al., 2006; Leipzig et al., 1999a) and PCH settings (Cumming, 1998; Leipzig et al., 1999a). Conversely, in a study

conducted on community-dwelling older women in Brazil, researchers reported that polymedicine was not a significant fall risk factor after adjustment for factors such as circulatory disease, cataract or glaucoma, arthritis, alcohol use, age, and body mass index (Rozenfeld, Camacho, & Veras, 2003). Different yet, in a population-based study in the Netherlands, researchers reported that polymedicine only increased fall risk when at least one of the drugs was considered as high risk (notably drugs effecting central nervous system and cardiovascular system) (Ziere et al., 2006).

Benzodiazepines.

Benzodiazepines are a broad class of medications that are used to treat anxiety disorders, insomnia, seizures, and panic disorders (Canadian Pharmacists Association, 2009). They are classified as having long, intermediate, and short half-lives (t1/2). Several researchers have documented a strong association between benzodiazepines and falls in older adults (Bloch et al., 2011; Cumming, 1998; Leipzig et al., 1999a; Mustard & Mayer, 1997; Ryynanen, Kivela, Honkanen, Laippala, & Saano, 1993; Souchet, Lapeyre-Mestre, & Montastruc, 2005; Woolcott et al., 2009). While some researchers report that fall risk increases only for people taking benzodiazepines with a long t1/2 (Cumming et al., 1991; Cummings et al., 1995; Ray, Griffin, & Downey, 1989), others report increased fall risks for benzodiazepines with short and intermediate t1/2 (Cumming & Klineberg, 1993; Landi et al., 2005; Ray, Thapa, & Gideon, 2000) . Ray et al. (2000) further described that in older PCH residents, the effect of benzodiazepine use is dose-dependent. After adjustment for several other risk factors, as compared to non-diazepam users, these authors reported that the odds of falling was 1.30 fold higher for residents taking

diazepam at a dose of 2mg per day, and 2.21 fold higher for residents taking diazepam at a dose of at 8 mg per day. Similar findings have been reported in other studies, for other classes of benzodiazepines (Maxwell, Neutel, & Hirdes, 1997; Neutel, Hirdes, Maxwell, & Patten, 1996).

Antidepressants.

Antidepressants are used to treat depression and other mood and anxiety disorders (Katz, De Coster, Bogdanovic, Soodeen, & Chateau, 2004). A growing body of evidence demonstrates an association between antidepressants, especially tricyclic antidepressants and selective serotonin reuptake inhibitors, and falls in older adults (Bloch et al., 2011; Kallin et al., 2004; Leipzig et al., 1999a; Liu et al., 1998; Mustard & Mayer, 1997; Ruthazer & Lipsitz, 1993; Souchet et al., 2005; Sterke, Verhagen, van Beeck, & van der Cammen, 2008; Thapa, Gideon, Cost, Milam, & Ray, 1998; Tinetti, Speechley, & Ginter, 1988; Woolcott et al., 2009). Initially, selective serotonin reuptake inhibitors were thought to be safe. However, a study conducted among older PCH residents in the United States showed that these drugs had the same potential to affect falls as the tricyclic antidepressants (Thapa et al., 1998).

Other Drugs.

Several additional categories of prescribed medications have been shown to increase fall risk in older adults. These include those affecting the cardiovascular system, i.e., antiarrhythmics (Leipzig et al., 1999b), digoxin (Leipzig et al., 1999b), antihypertensives (Myers, Baker, Van Natta, Abbey, & Robinson, 1991; Woolcott et al., 2009), beta-blockers (Rozenfeld et al., 2003), and diuretics (Leipzig et al., 1999b; Myers

et al., 1991; Rozenfeld et al., 2003; Woolcott et al., 2009), and those affecting the endocrine system including antidiabetics (Lee et al., 2006).

Fall history.

It is widely recognized that fall history is one of the strongest determinants of subsequent fall risk (American Geriatrics Society et al., 2001; Ganz et al., 2007; Kallin et al., 2004; Martin et al., 2003; Myers et al., 1991). Previous falls may result in the decline in a person's ability to carry out daily activities, which in turn, may impact muscle strength and the loss of coordination and/or balance (Manitoba Health, 2005). In addition, fear of falling may develop as a reaction to a previous fall (Cwikel & Fried, 1992; Delbaere, Close, Brodaty, Sachdev, & Lord, 2010; Delbaere, Crombez, Vanderstraeten, Willems, & Cambier, 2004; Landi et al., 2005; May, Nayak, & Isaacs, 1985; Rao, 2005; Tinetti et al., 1988; Whitehead, Wundke, & Crotty, 2006).

Life-style factors.

Life-style factors are related to a person's behaviours that may put the individual at a greater fall risk. These behaviours include drinking excessive amounts of alcohol, not eating enough healthy food, not doing enough physical activity, and not wearing appropriate footwear (British Columbia Ministry of Health Planning, 2004; World Health Organization, 2007). However, the direct relation between life-style and fall risk is not well-documented. As one exception, some researchers have shown community-dwelling older adults who were not doing enough physical activity to be at increased fall risk (Iinattiniemi et al., 2009).

Environmental risk factors.

In both the PCH and community settings, some features in a person's environment may increase their risk of falling. This includes insufficient lighting, loose rugs, slippery floors, steps without handrails, obstacles in the room and hallways, and beds that are too high (British Columbia Ministry of Health Planning, 2004; Cwikel & Fried, 1992; World Health Organization, 2007). A systematic review of literature suggests that environmental risk factors are the leading cause of falls, accounting for about 25% to 45% of falls in most studies (Rubenstein & Josephson, 2002). The following section describes physical restraint use and PCH characteristics as environmental fall risk factors.

Personal care home characteristics.

Specific PCH environmental risk factors are not well documented. One Manitoba study looked at the influence of PCH risk factors, i.e., ownership (for-profit versus not-for-profit), bed number, and nursing or health care aide working hours, on hospitalized falls (Doupe et al., 2006); none of these factors were significant predictors. Other studies have examined the effect of PCH staff characteristics on falls (Rubenstein, Josephson, & Robbins, 1994; Theodos, 2003). Rubenstein et al. (1994) found an increase in falls during the time that residents were not as closely observed by PCH staff, such as during breaks and at shift changes. Similarly, Theodos demonstrated that fall rate was higher when agency or relief staffs were working, presumably because these staffs were not as familiar with the residents.

Physical restraint use.

Physical restraints were originally used in PCHs to help prevent falls and related injuries. However, a number of studies have reported that physical restraint use actually precipitates falls (Capezuti, Evans, Strumpf, & Maislin, 1996; Capezuti, Maislin, Strumpf, & Evans, 2002; Capezuti, Strumpf, Evans, Grisso, & Maislin, 1998; Rubenstein et al., 1994; Tinetti, Liu, & Ginter, 1992; Yip & Cumming, 1994). For example, in one study, the risk of obtaining a fall-related injury was ten times greater for PCH residents who were restrained versus those who were not (Tinetti et al., 1992). In addition, Capezuti et al. (2002) examined the association between bilateral side rail use and falls and related injuries among PCH residents. These authors suggest that bilateral side rail use increases fall and related injury risk. They explained that for cognitively impaired people, there is virtually no awareness of intended function of restraint and it will invariably be perceived as a barrier. Therefore, it results trip over the side rail. As most PCH residents with this type of physical restraint had severe functional, cognitive, and/or behavioral challenges, authors acknowledged the challenges with attributing their study results entirely to the use of restraints (Capezuti et al., 1996).

Socioeconomic risk factors.

It is widely accepted that social risk factors strongly influence health (World Health Organization, 2010). Numerous authors have reported that people with lower income, lower education, inadequate housing, a lack of support networks or a lack of access to appropriate health or social services, are all at a greater risk for chronic health conditions (British Columbia Ministry of Health Planning, 2004). However, the direct

relation between socioeconomic factors and fall risk is not well-documented. As one exception, data from the Canadian Community Health Survey data (cycle 2.1; 2002/03) demonstrate that injurious fallers are more likely to be widowed, separated or divorced, and have a household income of less than $15,000 (Public Health Agency of Canada, 2005). Researchers have also suggested that community-dwelling older adults with a low level of social support and who live alone have higher fall risk (Cwikel & Fried, 1992). Conversely, a study focusing on older adult PCH residents reported that marital status and income level were not significantly related to hospitalized falls (Doupe et al., 2006).

Chapter Summary

Falls in older adults are a significant health problem in Canada and elsewhere, impacting the quality of life for older adults, and contributing to high healthcare costs. A substantial amount of literature identifies the many different types of fall risk factors which, in turn can inform recommendations pertinent to effective fall management strategies. Researchers have explained that falls often result from complex interactions across all risk factor groups. The WHO's risk factor model presents a useful framework for understanding fall risk factors partitioned into biological and medical, behavioural, environmental and socioeconomic categories.

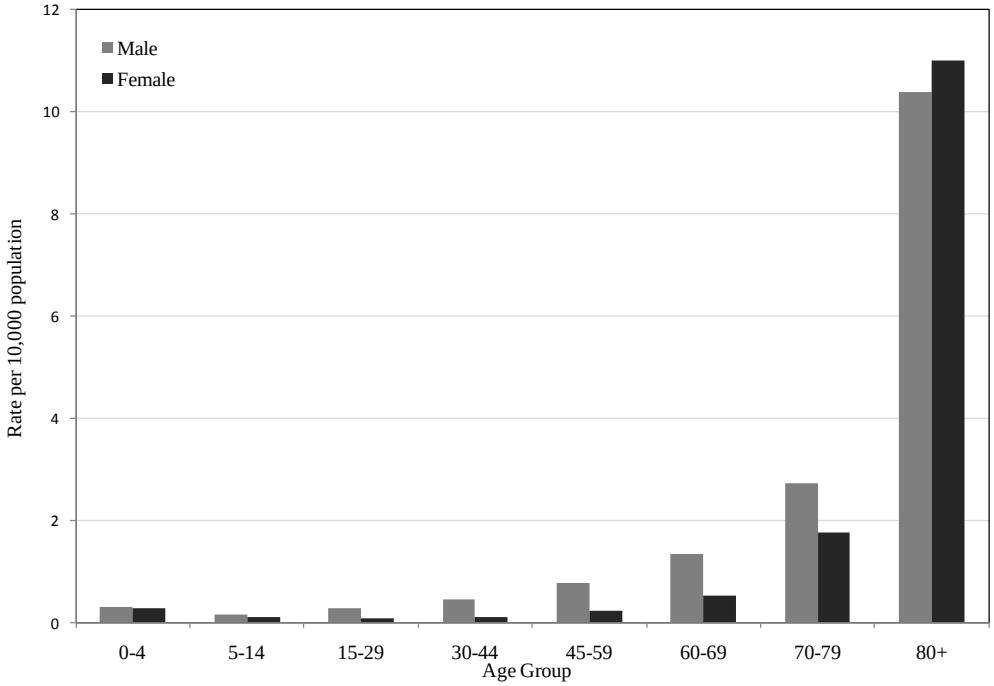

Figure 2.1 Fall-related mortality rates in World Health Organization regions by age group and sex, 2000. Adapted from "The Injury Chart Book: a Graphical Overview of the Global Burden of Injuries" by Peden, M., McGee, K., & Sharma, G., 2002, Geneva: World Health Organization, p.45.

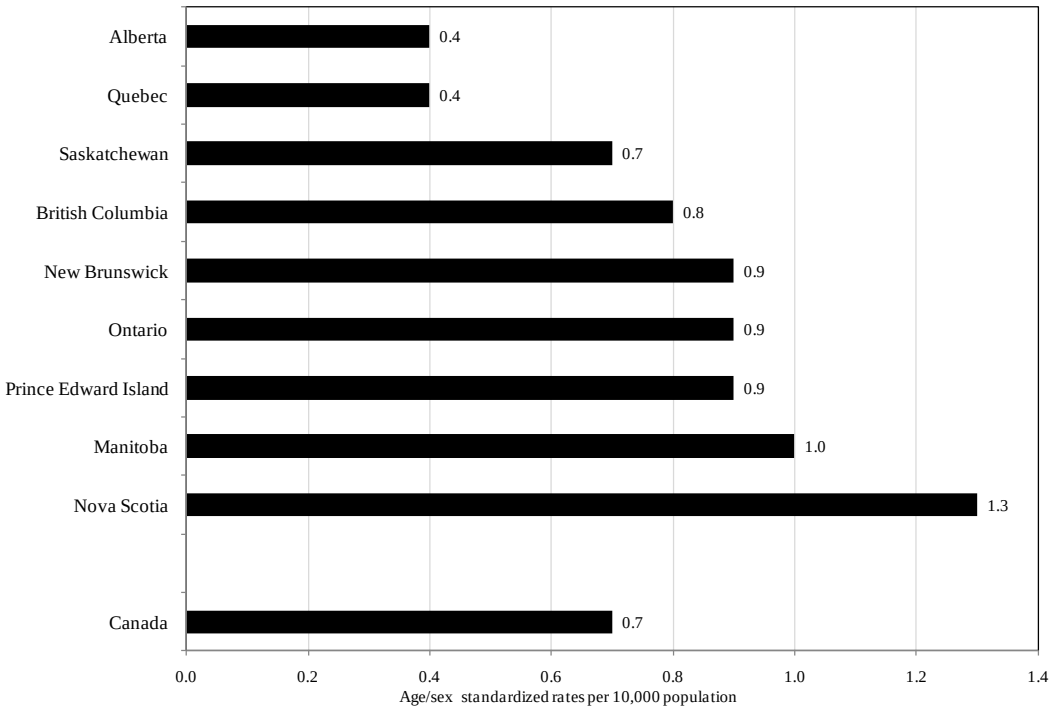

Figure 2.2 Fall-related mortality rates in Canada by province, 2004. Adapted from "The Economic Burden of Injury in Canada" by SMARTRISK, 2009, Toronto, Ontario, p.31.

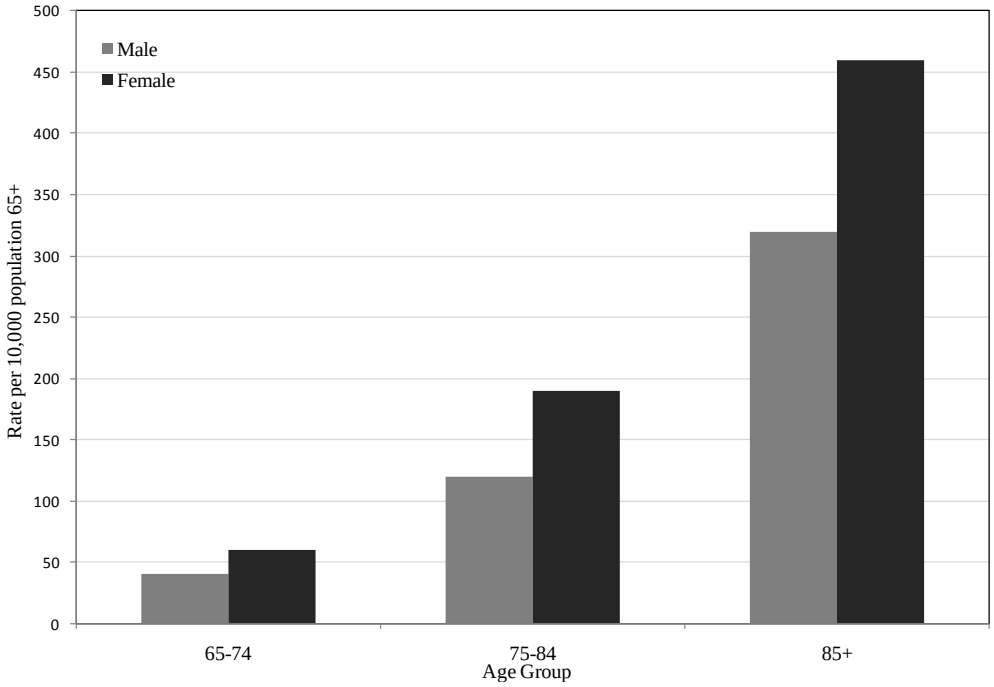

Figure 2.3 Fall-related hospitalization rates by age group and sex, Canada, 2002/03. Adapted from "Report on Seniors' Falls in Canada" by the Public Health Agency of Canada, 2005, Ottawa, Ontario, p.18.

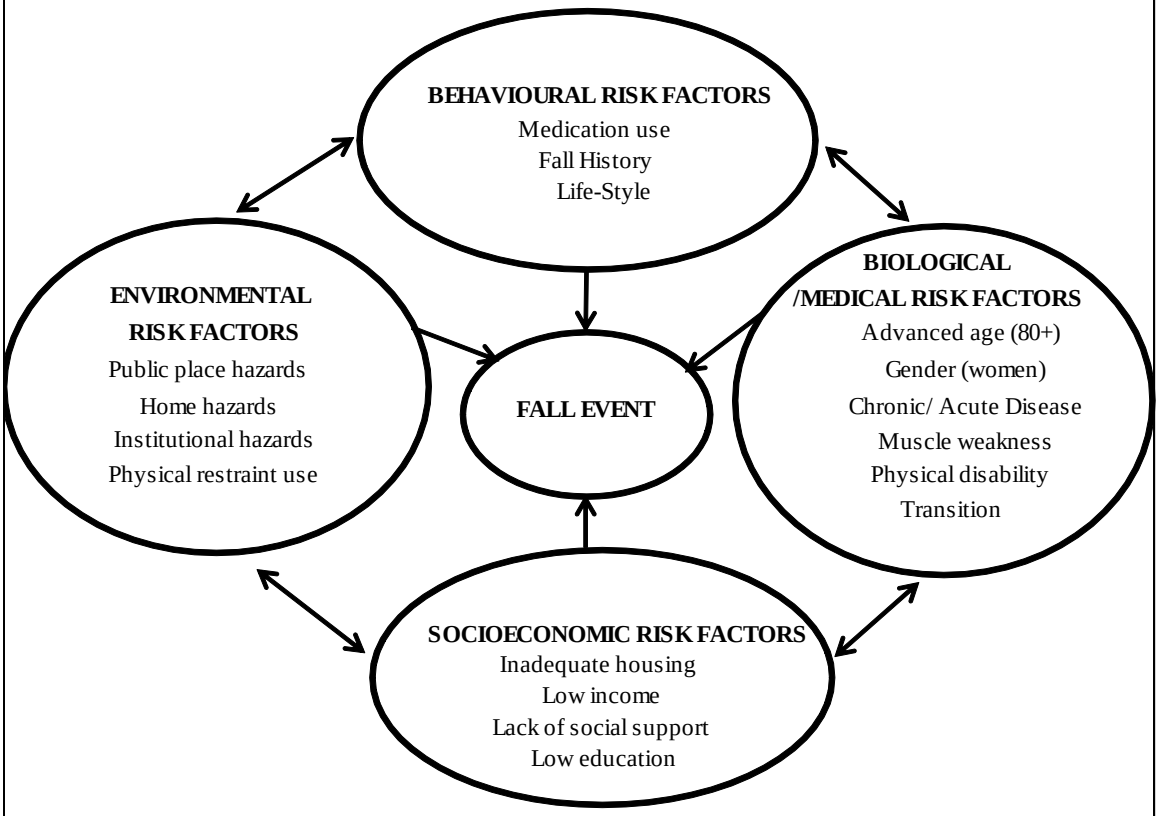

Figure 2.4 Risk factor model for falls in older adults. Adapted from "WHO Global Report on Falls in Older Age" by the World Health Organization, 2007, Geneva, p.5.

Chapter 3

Atypical Antipsychotic Drug Use and Falls

This chapter describes the utilization of atypical antipsychotic drugs (AADs) in older adults, and provides a systematic review of the literature describing the association between AAD use and falls in both community- and personal care home (PCH)-dwelling older adults.

Utilization of Atypical Antipsychotic Drugs in Older Adults

Antipsychotic drugs, also known as neuroleptics, are indicated for treating a number of psychiatric disorders such schizophrenia and bipolar disorders (Canadian Pharmacists Association, 2009). However, these drugs are commonly used for the treatment of behavioral problems associated with dementia (Liperoti et al., 2003; Motsinger et al., 2003). These drugs are subclassified as AADs, also known as newer or second generation antipsychotics, and typical antipsychotic drugs (TADs), also known as older or first generation antipsychotics. Specific AADs include risperidone, olanzapine, and quetiapine, while common TADs include haloperidol, trifluoperazine, thioridazine, and loxapine.

Utilization trends of atypical antipsychotic drugs.

Use of TADs has declined over time since AADs came onto the market in 1993. AADs are thought to have an equivalent drug efficacy combined with an improved patient safety profile compared to TADs (Beasley, Jr. et al., 1997; Frenchman & Prince, 1997; Motsinger et al., 2003). A recent study conducted on PCH residents in Manitoba

showed that from 1997/98 to 2008/09, AAD use increased from 15.0 to 268.5 users per 1,000 PCH residents, while TAD use declined from 169.3 to 47.7 users per 1,000 PCH residents (Raymond et al., 2010). This decline in TAD use is likely related to their potential side effects, such as hypotension and sedation (Katz et al., 1999), anticholinergic effects (Nassisi, Korc, Hahn, Bruns, Jr., & Jagoda, 2006), and extrapyramidal symptoms (Avorn, Monane, Everitt, Beers, & Fields, 1994; Bouman & Pinner, 2002; Chan, Pariser, & Neufeld, 1999).

Types of atypical antipsychotic drugs.

Among AADs, clozapine was the first marketed drug in Canada. This drug however, has had limited use due to its severe side effects. In particular, this drug is thought to increase the risk of agranulocytosis - a condition where bone marrow fails to make sufficient white blood cells (Health Canada, 2004a). Since clozapine, four others AADs have been marketed, including risperidone, olanzapine, quetiapine, and aripiprazole. During the 2007/08 fiscal year in Manitoba, risperidone was the most commonly dispensed AAD to older PCH residents (167.0 users per 1,000 PCH residents), followed by quetiapine and olanzapine (67.6 and 49.1 users per 1,000 PCH residents, respectively) (Raymond et al., 2010). Risperidone is the only AAD approved for short-term symptomatic management of inappropriate behaviour due to aggression or psychosis in older adults with severe dementia (Canadian Pharmacists Association, 2009; Health Canada, 2005). Aripiprazole became available in the Canadian market in 2009, and is widely used in pediatric age groups (Greenaway & Elbe, 2009).

Risks associated with AAD use began to emerge in the 2000s. In response to this safety concern, Health Canada issued three warnings about the possible side effects of AADs. The first warning was issued in 2002, and stated that risperidone may be associated with cerebrovascular accidents in patients with dementia (Health Canada, 2002). In 2004, Health Canada issued a similar warning about olanzapine (Health Canada, 2004b). In 2005, Health Canada circulated a third warning to health professionals about increased all-cause mortality associated with the use of risperidone, olanzapine, and quetiapine in older adults diagnosed with dementia (Health Canada, 2005). Similar warnings were issued by the United States Food and Drug Administration and the United Kingdom Committee on Safety Information (Lee et al., 2004).

Recommended dose and duration of atypical antipsychotic drugs.

Evidence-based guidelines developed in Canada (Herrmann & Gauthier, 2008) and the United States (American Psychiatric Association: work group on Alzheimer's Disease and other dementias, 2007) for the management of Alzheimer's Disease and other dementias recommend that AADs should be prescribed at their lowest effective dose, and that clinicians should consider a reduction in dose or withdrawing antipsychotic use after three months of behavioural stability. Within the United States, the Omnibus Reconciliation Act of 1987 (OBRA 87) recommends that older PCH residents should receive no more than 2 mg/day of risperidone, 150 mg/day of quetiapine, or 7.5 mg/day of olanzapine (Centers for Medicare and Medicaid Services, 1999). According to OBRA 87, physicians must consider dose reduction in two separate quarters (with at least one month between the attempts) within the first year in which a resident is admitted on an

antipsychotic medication or after the facility has initiated an antipsychotic medication, unless clinically contraindicated. After the first year, dose reduction must be attempted annually. Additionally, this act suggests that effects of AADs should be evaluated during the monthly medication regimen review by a pharmacist, quarterly Minimum Date Set (MDS) review by nursing staff, and evaluation of a resident's progress by the physician. In Manitoba, there is no existing comprehensive regulation to monitor the appropriate use of AADs among PCH residents. Developing such a regulation would help to incorporate evidence-based findings into AAD and monitoring practices in the PCH setting.

Comparing the use of atypical antipsychotic drugs in community- versus personal care home-dwelling older adults.

Utilization of AADs by older adults varies by location of residence. Commonly, more PCH- versus community-dwelling older adults use AADs. For example, in Manitoba, in 2008/09, 26.9% of older PCH residents were reported to use AADs compared to 1.4% of community-dwelling older adults (Raymond et al., 2010). The higher percentage of AAD use in PCHs is likely due to the higher prevalence of dementia in this population (Canadian Institute for Health Information, 2009a). Indeed, a population-based study in Manitoba showed that the odds of being dispensed antipsychotics were 2.9 fold greater for residents who had been diagnosed with dementia (Doupe et al., 2006). This study reported that, on average, 65.3% of PCH residents had a previous diagnosis of dementia. This is much higher than the estimated prevalence of dementia among the entire older adult population age 55 or older in Manitoba (10.6%) (Martens et al., 2010).

Atypical Antipsychotic Drug Use and Falls Literature

The association between AAD use and falls in older adults has been studied by several researchers. A comprehensive review of these studies was conducted in preparation for this research to examine both the strength and the consistency of the association between AAD use and the risk of falling among older adults, and to explore sources of methodological heterogeneity in the published studies.

Search strategy.

Articles published in English were collected using computerized databases the MEDLINE, EMBASE, Scopus, The Cochrane Collaboration, and Google Scholar. A manual search for the articles cited within the previously identified publications completed the compilation. The keywords used were terms "neuroleptic", "second generation antipsychotic"," atypical antipsychotic", "risperidone", "olanzapine", "quetiapine", "accidental fall", and "fall". Articles were selected if they were (a) studies involving older adults, (b) pertaining to falls, and (c) targeting any types of AADs. Any other exclusion criteria were not imposed. Based on these selection criteria, thirteen relevant studies were identified. Information collected from the included studies consisted of year of publication, objective, characteristics of study population (size, age, setting, and health status), country of origin, study design, method of fall and exposure to AAD use ascertainment, and statistical methods. If provided, adjusted ORs and 95% CIs and the covariates that were adjusted for were also extracted.

Basic details of the reviewed studies.

Study objective.

The objective of the majority of these studies was to assess the overall efficacy and safety of AADs, with falling often described as being one component of patient safety (see Table 3.1) (Brodaty et al., 2003; de Deyn et al., 2005; Frenchman, 2005; Katz et al., 1999; Martin et al., 2003; Mintzer et al., 2006; Rochon et al., 2008; Street et al., 2000; Suh et al., 2006). Other authors conducted their research to investigate the association between several types of drugs (including AADs) and falls (Kallin et al., 2004; Landi et al., 2005). The main objective of remaining studies was specifically to test the association between AAD use and falls (Hien et al., 2005; Katz et al., 2004).

Study population.

In these selected studies, the characteristics of the study population, including study sample size, age of participants, study setting, and participants' health status, varied substantially (see Table 3.1). For example, the sample size of study populations ranged from 114 (Suh et al., 2006) to 41,241 (Rochon et al., 2008). Age of the study population also varied, from 55 and older (Brodaty et al., 2003; de Deyn et al., 2005; Katz et al., 1999; Katz et al., 2004; Martin et al., 2003; Mintzer et al., 2006), 61 and older (Street et al., 2000), 65 and older (Hien et al., 2005; Kallin et al., 2004; Suh et al., 2006), to 66 and older (Rochon et al., 2008).

Most of the reviewed studies were conducted on older adults residing in PCHs (Brodaty et al., 2003; De Deyn et al., 2005; Frenchman, 2005; Hien et al., 2005; Kallin et al., 2004; Katz et al., 1999; Katz et al., 2004; Martin et al., 2003; Mintzer et al., 2006;

Rochon et al., 2008; Street et al., 2000; Suh et al., 2006). Some of these studies included other older adult populations, such as those living in chronic disease hospitals (Katz et al., 1999; Katz et al., 2004), residential care facilities, geriatric and psychogeriatric clinics, and rehabilitation units (Kallin et al., 2004), and the community (Rochon et al., 2008). Landi and colleagues (2005) conducted their research on only community-dwelling older adults.

In the majority of the reviewed studies, researchers focused their analyses on people diagnosed with dementia (Brodaty et al., 2003; De Deyn et al., 2005; Frenchman, 2005; Katz et al., 1999; Katz et al., 2004; Martin et al., 2003; Mintzer et al., 2006; Street et al., 2000; Suh et al., 2006). One research team also excluded persons with a fall history, osteoporosis, Parkinson's disease, or restraint use (Martin et al., 2003).

Location of research.

The majority of the reviewed literature has been conducted in the United States (see Table 3.1) (Frenchman, 2005; Katz et al., 1999; Katz et al., 2004; Martin et al., 2003; Mintzer et al., 2006; Street et al., 2000). The rest of the studies were carried out in other countries including Italy (Landi et al., 2005), Australia (Brodaty et al., 2003; Hien et al., 2005), Sweden (Kallin et al., 2004), and Korea (Suh et al., 2006). Findings from these countries may not be generalizable to the Canadian older adult population, due, in part, to differences in environmental factors such as the PCH setting and healthcare system. Notably, only one Canadian study was found in the literature (Rochon et al., 2008). This study, however, did not focus on AAD use and falls per say, but rather included falls as one component of “serious events”.

Methodological review of the studies.

Study design.

The reviewed studies were conducted using a variety of study designs (see Table 3.2). Most authors conducted their research using randomized controlled trials (RCTs) (Brodaty et al., 2003; De Deyn et al., 2005; Katz et al., 1999; Katz et al., 2004; Mintzer et al., 2006; Street et al., 2000; Suh et al., 2006). This experimental design, where subjects are randomly assigned to groups, is considered as the gold standard for the evaluation of drug safety and effectiveness (Persaud & Mamdani, 2006). However, these RCTs face some limitations. For example, many of these trials have highly selective exclusion criteria, limiting both the generalizability and the comparability of findings across studies. For example, Katz et al. (2004) excluded users of other AADs, TADs, antidepressants, lithium, carbamazepine, antiparkinson drugs, or valproic acid from the study population. In addition, the time period of these studies was relatively short, ranging from 6 weeks (Street et al., 2000) to 18 weeks (Suh et al., 2006), and, therefore, cannot be used to evaluate the long term effects of AADs. Small sample size in these trials, ranging from 114 (Suh et al., 2006) to 625 (Katz et al., 1999), may also effect the power of these studies. Lastly, RCTs require substantial investment in time and money.

Some of the limitations of RCTs can be overcome by using well-designed observational studies. This type of analyses provides ‘real’ clinical scenarios and thus readily applicable findings. The majority of observational studies in the literature have been cross-sectional (Frenchman, 2005; Kallin et al., 2004; Landi et al., 2005; Martin et al., 2003), while a cohort design has been used less often (Hien et al., 2005; Rochon et

al., 2008). Cross-sectional studies assess the main exposure and outcome at the same time, and therefore, it is often not possible to record the ordering of events between drug use and falls. This limitation does not exist in cohort and case-control studies because the main exposure is measured preceding the outcome.

Measurement of the fall outcome.

Most studies have identified fall as the outcome of interest, defined as having one or more falls (see Table 3.2) (Brodaty et al., 2003; de Deyn et al., 2005; Frenchman, 2005; Kallin et al., 2004; Katz et al., 1999; Katz et al., 2004; Landi et al., 2005; Martin et al., 2003; Mintzer et al., 2006; Street et al., 2000). Martin et al. (2003) also studied the risk factors for recurrent (i.e., having two or more falls) falls. Still yet, other researchers have measured fall rates (Frenchman, 2005; Katz et al., 2004), or have used survival analyses to measure time to first fall (Hien et al., 2005; Katz et al., 2004). Suh et al. (2006) were the only ones to describe the effect of AADs on falls during the first eight weeks of AAD use. Additionally, most of the reviewed studies measure both injurious and non-injurious falls. As one exception, Rochon et al. (2008) measured only injurious falls as a component of serious events requiring hospitalization.

In most studies, fall data were ascertained using medical records including occurrence reports (Frenchman, 2005; Hien et al., 2005; Katz et al., 2004; Martin et al., 2003; Mintzer et al., 2006), the minimum data set for home care (MDS-HC) (Landi et al., 2005), and administrative healthcare data (Rochon et al., 2008). Researchers have also used patient recall methods to ascertain falls (Brodaty et al., 2003; Kallin et al., 2004; Street et al., 2000). Each of these strategies has strengths and limitations. For example,

patient recall methods, while easy to obtain, are often limited by recall bias. Also, MDS-HC data do not report exact fall dates and capture falls intermittently. Administrative healthcare data are typically available for entire populations, but only include falls that result in hospitalization.

Measurement of main exposure.

In the pharmacoepidemiological literature, drug exposure should be well defined to ensure quality, consistency, and comparability across studies. However, in the reviewed studies, AAD use measurement is often inadequately defined and faces some methodological challenges such as violation of temporality in cross-sectional studies (i.e., where fall outcomes could have preceded drug utilization) (Frenchman, 2005; Kallin et al., 2004; Landi et al., 2005; Martin et al., 2003) (see Table 3.2). In both cohort studies, AAD use was measured prior to the fall outcome (Hien et al., 2005; Rochon et al., 2008). However, these studies are limited in that drug use was assessed only once, at baseline, with no subsequent drug use measurement during the follow-up period. Within this literature, the majority of researchers have studied how exposure to risperidone and/or olanzapine impact fall risk, while no authors have investigated the effect of quetiapine. This is particularly important given the previously discussed trends of increasing quetiapine use among older adults residing in both PCHs and the community (see Chapter 1 - "Introduction").

Four RCTs report the risk of falling by dose of either risperidone (de Deyn et al., 2005; Katz et al., 1999; Katz et al., 2004) or olanzapine (Street et al., 2000). However, the dose of interest for risperidone in these studies was low (i.e., 2 mg/day or less for

risperidone). None of the studies have investigated the association between higher doses of risperidone and falls. Obtaining evidence in this area will help to define the appropriate dose of AADs prescribed to older adults relating to falls.

Exposure to a drug is often difficult to measure, and the source of information used may affect results. Four of the reviewed observational studies gathered drug use data from medical records (Frenchman, 2005; Hien et al., 2005; Landi et al., 2005; Martin et al., 2003) and only one study did so using administrative drug claims and prescription databases (Rochon et al., 2008). Subject recall was used to collect drug information by some researchers (Kallin et al., 2004). Medication records have the advantage of not being subject to recall bias, but may be influenced by health care providers' attention in recording information (West, Strom, & Poole, 2005). Researchers have demonstrated that prescriptions are at times poorly documented in medical records as compared to a administrative prescription database (Kirking, Ammann, & Harrington C.A., 1996). Several other researchers have showed that administrative prescription databases are a valid and reliable data source for studying prescription drug use (Kozyrskyj & Mustard, 1998; Roos et al., 1993). These databases are typically population-based, and are not subject to recall bias when defining dates of dispensation and the volumes of drugs dispensed. However, administrative drug claims and prescription databases measures drug use based on dispensation records, and not on actual consumption.

Adjustment for confounders.

Since falls result from a complex interaction of risk factors, confounding becomes a problem in studies that focus on medication-associated falls. Therefore, researchers

should assess and possibly control for a wide range of factors to avoid confounding, including confounding by indication. In pharmacoepidemiological studies, confounding by indication occurs when a person at risk for an outcome takes a drug for a disease that itself can increase the risk of the outcome (Psaty et al., 1999).

AADs are commonly prescribed to older adults diagnosed with dementia due to behavioural and psychological symptoms or cognitive impairment. Each of these diseases is an independent fall risk factor. In the reviewed observational studies, some researchers adjusted for dementia, cognitive function, or wandering in their statistical modeling (see Table 3.2) (Hien et al., 2005; Kallin et al., 2004; Landi et al., 2005), while other restricted their analyses to study participants with dementia (Frenchman, 2005; Martin et al., 2003; Rochon et al., 2008). Similarly, only two studies adjusted for fall history in their statistical models (Hien et al., 2005; Kallin et al., 2004), while others excluded these individuals from their analyses (Martin et al., 2003).

Some researchers have adjusted their analyses for medication use as a potential fall risk factors, including use of antidepressants, TADs, benzodiazepines, cholinesterase inhibitors, and the number of different drugs (Hien et al., 2005; Kallin et al., 2004; Landi et al., 2005; Rochon et al., 2008). Others have adjusted their analyses for illnesses such as Parkinson's disease (Hien et al., 2005), depression (Landi et al., 2005), and the presence of comorbidity (Landi et al., 2005), and also additional factors such as resident sex and age (Hien et al., 2005; Kallin et al., 2004; Landi et al., 2005), balance (Hien et al., 2005; Kallin et al., 2004), activities of daily living (ADL) (Landi et al., 2005), the presence of foot and gait problems (Landi et al., 2005), fear of falling (Landi et al., 2005), length of PCH stay and type of PCH facility (Hien et al., 2005). Lastly, of all studies reviewed,

only Katz et al. (2004) investigated if the effect of AADs on fall risk varied by person characteristics. These researchers reported a significant interaction between wandering and risperidone use, and specifically found that in individuals who exhibit wandering, 1 mg/day but not 2 mg/day of risperidone reduced fall risk during a 3 month follow-up. Further research is required to determine if certain individuals using AADs have a particularly high fall risk.

Summary of literature findings.

Despite the methodological differences of the reviewed studies, researchers have consistently shown that AADs as a group are significantly associated with falls among both community- and PCH-dwelling older adults (see Table 3.3). For instance, among community-dwelling older adults in Italy, and after adjustment for several other risk factors, the odds of falling was 45% higher in AAD users (i.e., clozapine, risperidone, olanzapine, or quetiapine, collectively) compared to nonusers (95% CI 1.00-2.11) (Landi et al., 2005). Similarly, in a Canadian study, serious events, which includes falls, were significantly higher among overall AAD users compared to nonusers in both the community (adjusted odds ratio=3.19, 95% CI 2.77-3.68) and PCH setting (adjusted odds ratio=1.92, 95% CI 1.68-2.21) (Rochon et al., 2008).

Some researchers have shown that the association between AADs and falls depends on the specific type of AADs. Compared to nonusers of AADs, risperidone users are consistently shown as not having a greater risk of falling (Brodaty et al., 2003; de Deyn et al., 2005; Hien et al., 2005; Kallin et al., 2004; Katz et al., 2004; Mintzer et al., 2006). However, researchers have reported that olanzapine users have a greater fall risk

as compared to non-AAD users (Hien et al., 2005). In this study, the adjusted odds of falling were 74% greater for olanzapine users versus nonusers (95% CI 1.04-2.90). For studies including both olanzapine and risperidone users, authors have consistently reported that the odd of falling is significantly greater for olanzapine users only (Frenchman, 2005; Martin et al., 2003).

Some but not all researchers have reported a dose- response association between AADs and falls, with higher dose users generally having a greater fall risk. As compared to nonusers, some evidence suggests that higher (1.5-2 mg/day) but not lower (1 mg/day) dose risperidone users have an increased fall risk (de Deyn et al., 2005; Katz et al., 1999). Katz et al (2004) reported similar findings for both falls and injurious falls. These same authors reported a significant interaction between wandering and risperidone use, and specifically found that in individuals who exhibit wandering, 1 mg/day but not high doses 2 mg/day of risperidone reduced fall risk during a 3-month follow-up.

Chapter Summary

AADs are increasingly being used among older adults living in both community and PCH settings. Risperidone is the most commonly used type of AAD, followed by quetiapine and olanzapine. Despite having an improved safety profile, the related literature generally concludes that AAD use is associated with an increased fall risk. However, these previous studies face some methodological limitations which affect the quality, consistency, and comparability of these studies. These limitations can be summarized as: a) highly selective exclusion criteria, short follow-up and small sample size in RCTs b) the violation of the temporality between AAD use and fall events, c)

minimal adjustment for potential confounders, d) unknown fall risk associated with the widely used quetiapine, e) limited studies to test if the association between AADs and falls depends on AAD type and dose, or depends on patient characteristics, and f) limited Canadian-based evidence.

Adequately powered RCTs are considered as the gold standard for the evaluation of drug safety and effectiveness. However, in addition to the above limitations related to RCTs, these trials require substantial investment in time and money, and larger sample sizes. These limitations of RCTs could be overcome by using well-designed observational studies. A nested case-control design (NCC) is a time-efficient and cost-effective way of analyzing large cohorts without affecting the advantages of cohort studies.

Future observational studies should address the above summarized limitations. For example, to address limitations related to minimal adjustment for confounders, a conceptual framework should be used to inform the inclusion of select confounding variables. Further, administrative healthcare databases should be considered as a possible data source, given the population-based drug dispensation data available in these data, and given the ability to link these data to MDS. Also, including newly-marketed drug, quetiapine, testing if the association between AADs and falls depend on type, dose, and patient characteristics will fill the gap in the literature, and provide evidence to help guide AAD use policies in PCH and community settings.

Table 3.1
Atypical Antipsychotic Drug (AAD) Use and Falls Literature: Basic Study Details

Author(s)	Study Objective	Study Population				Location
		Size	Age	Setting	Health Status	
Katz et al. (1999)	To assess efficacy and safety of RIS	625	55+	PCH + chronic disease hospital	People with dementia	United States
Street et al. (2000)	To assess efficacy and safety of OLZ	206	61+	PCH	People with Alzheimer's Disease	United States
Martin et al. (2003)	To assess the adverse events associated with RIS and OLZ	360	55+	PCH	People with dementia *Exclusion:* People with history of falls, osteoporosis, Parkinson, or restraint use	United States
Brodaty et al. (2003)	To assess efficacy and safety of RIS	345	55+	PCH	People with dementia	Australia
Kallin et al. (2004)	To test the association between drug use and falls	3,604	65+	Residential care facilities+ PCH+ geriatric and psycho-geriatric clinics+ rehabilitation units	All participants	Sweden
Katz et al. (2004)	To test the association between use/dosage of RIS and falls	537	55+	PCH+ chronic disease hospital	People with dementia *Exclusion:* Users of other AADs, TADs, antidepressants, lithium, carbamazepine, antiparkinson drugs, or valproic acid	United States
Landi et al. (2005)	To test the association between use of BZD/ antipsychotics/ non-BZD sedative - hypnotics/ antidepressants and falls	2,854	NR	Community	People with no comatose, paraplegia, or terminal illness	Italy
Hien et al. (2005)	To compare the association of AADs and TADs with falls	2,005	65+	PCH	People with no bed-bound or bilateral lower limb amputation	Australia
Frenchman (2005)	To compare efficacy and safety of OLZ and RIS	289	NR	PCH	Ambulatory people with dementia or other psychotic disorders *Exclusion:* BZD users	United States
Mintzer et al. (2005)	To assess efficacy and safety of low dose RIS	473	55+	PCH	People with Alzheimer's Disease	United States
De Deyn et al. (2005)	To assess risk-benefit of RIS	1,191	55+	PCH	People with dementia	United States
Suh et al. (2006)	To compare the efficacy of RIS and haloperidol	114	65+	PCH	People with dementia	Korea
Rochon et al. (2008)	To estimate the risk of serious event within 30 days of initiating an antipsychotic drug	41,241	66+	PCH + community	People with dementia and prescription for an antipsychotic drug	Canada

Note. RIS=Risperidone; PCH=Personal care home; OLZ=Olanzapine; TADs=Typical antipsychotic drugs; BZD=Benzodiazepine; NR=Not reported.

Table 3.2

Atypical Antipsychotic Drug (AAD) Use and Falls Literature: Details of Methodology

Author(s)	Study Design	Time Period	Outcome			Exposure					Adjusted Confounders	Analysis Type
			Measure	Definition	Data	Definition	Data	Reference	Dose	Type		
Katz et al. (1999)	RCT	12-week	Fall	NR	NR	Randomized with placebo, RIS 0.5, 1.0, or 2.0 mg/day	N/A	Placebo	RIS 0.5, 1.0, or 2.0mg/day	RIS	N/A	Frequency
Street et al. (2000)	RCT	6-week	Accidental injury[a]	NR	Recall	Randomized with placebo, OLZ 5, 10, 15 mg/day	N/A	Placebo	OLZ 5, 10, 15 mg/day	OLZ	None	Fisher's exact test
Martin et al. (2003)	Observational (Cross-sectional)	1999-2000	Fall (1+), recurrent fall (2+)	NR	MR	Treatment of RIS <=2mg/ day or OLZ<=10mg /day for at least 90-day	MR	Compares RIS and OLZ	No	RIS& OLZ	None	Fisher's exact test
Brodaty et al. (2003)	RCT	12-week	Fall	NR	Recall	Randomized with placebo / RIS <=2 mg/day	N/A	Placebo	No	RIS	N/A	Frequency
Kallin et al. (2004)	Observational (Cross-sectional)	2000	Fall	"Unintentionally coming to rest on the floor or other level from a walking, standing, sitting or lying position."	Recall	RIS/OLZ use at the time of survey	Recall	Nonusers	No	RIS& OLZ	Fall history, "can get up with a chair", "walks with helper", pain, cognitive impairment, antidepressant, sex, age	Logistic Regression
Katz et al. (2004)	RCT	12-week	Fall, time to first fall and rate of falls	NR	Incident reports +MR	Randomized with placebo, RIS 0.5, 1.0, or 2.0 mg/day	N/A	Placebo	RIS 0.5, 1.0, or 2.0 mg/day	RIS	Wandering	Faller: Chi-square test; Time to first fall: Survival analysis; Rate of falls: Poisson analysis
Landi et al. (2005)	Observational (Cross-sectional)	2000-02	Fall	NR	MDS-HC	AAD use over 90-day MDS-HC assessment time	MR	Nonusers	No	Clozapine, RIS, OLZ, & QTP	Age, sex, comorbidity, polymedicine, depression, ADL, CPS, foot problems, wandering, gait problems, fear of falling, TADs, antidepressant, BZD	Logistic regression

Table 3.2

Atypical Antipsychotic Drug (AAD) Use and Falls Literature: Details of Methodology (continued)

Author(s)	Study Design	Time Period	Outcome			Exposure					Adjusted Confounders	Analysis Type
			Measure	Definition	Data	Definition	Data	Reference	Dose	Type		
Hien et al. (2005)	Observational (Cohort)	1999-2003	Time to first fall	"Unintentionally coming to rest on the ground, floor or other lower level, whether or not an injury occurred."	Incident reports +MR	AAD use at baseline	MR	Nonusers	No	RIS & OLZ	Age, sex, type of facility, length of stay, fall history, Parkinson's disease, illness severity, standing balance test, cognitive function, TADs, antidepressant, sedatives/ anxiolytics	Survival analysis
Frenchman (2005)	Observational (Cross-sectional)	Sept-Oct 2001	Fall and rate of falls	NR	MR	Use of RIS/OLZ for 2-month to treat BPSD	MR	Compares RIS and OLZ	No	OLZ & RIS	None	t-test
Mintzer et al. (2005)	RCT	8-week	Fall	NR	MR	Randomized with placebo, RIS 1.0mg/day, or 1.5mg/day	N/A	Placebo	No	RIS	None	t-test
De Deyn al. (2005)	Meta analysis of 3 RCTs	12-week	Fall	NR	Literature	Randomized with placebo, RIS <0.75mg/day, 0.75-1.5mg/day, or 1.5-2mg/day	Literature	Placebo	RIS <0.75, 0.75-1.5, or 1.5-2mg/day	RIS	NR	Descriptive pooled Analysis
Suh et al. (2006)	RCT	18-week	Mean of falls	NR	NR	Randomized with haloperidol and RIS (0.5-1.5mg/day)	N/A	Compares RIS and haloperidol	No	RIS	NR	GEE
Rochon et al. (2008)	Observational (Cohort)	1997-2004	Hospitalized events which include falls/hip fractures	NR	Admin. data	New use of an antipsychotic, but definition of "new use" is NR.	Admin. data	Nonusers	No	OLZ, QTP, &RIS	Volume of drugs, antidepressant, cholinesterase inhibitor, psychiatrist visit, head tomography	Conditional logistic regression

Note. RCT=randomized controlled trial; NR=not reported; RIS=risperidone; N/A=not applicable; OLZ=olanzapine; MR=medical records; MDS-HC=Minimum Data Set for home care; QTP=quetiapine; ADL=activities of daily living; CPS=cognitive performance scale; TADs=typical antipsychotic drugs; BZD=benzodiazepine; BPSD=behavioural and psychological symptoms of dementia; GEE=generalized estimating equations. [a]Accidental injury" includes fall, abrasion, cut or laceration, fracture, or skin tear.

Table 3.3
Atypical Antipsychotic Drug (AAD) Use and Falls Literature: Results

Author (s)	% of Fall	% of AAD use	Unadjusted Estimates (95% CI)	Adjusted Estimates (95% CI)
Katz et al. (1999)	Placebo:20.2%; RIS 0.5mg/day:16.1%; RIS 1mg/day:12.8%; RIS 2mg/day: 24.8% (P-value: NR)	RCT	NR	NR
Street et al. (2000)[a]	Placebo:27.7%; OLZ 5mg/day:25%; OLZ 10mg/day:24.0% ; OLZ 15mg/day:37.7% (NS, P-value: NR)	RCT	NR	NR
Martin et.al. (2003)	Overall faller (1+) OLZ :17.9%; RIS: 6.9% (p<0.001) Recurrent faller (2+) OLZ :7.8%; RIS: 3% (P<0.033)	All cohort	NR	NR
Brodaty et al. (2003)	Placebo:27.1%; RIS: 25.1% (P-value: NR).	RCT	NR	NR
Kallin et al. 2004	8.4% fallers over 7-day Rates of fall/year: 4.3	RIS: 8.0% in fallers, 6.4% in non-fallers OLZ: 3.7% in fallers, 2.0% in non-fallers	RIS: 1.26 (0.81-1.95) OLZ: 1.89 (0.99-3.62) HD: 1.19 (0.68-2.09)	Antipsychotics, i.e., RIS, OLZ, &HD 1.38 (1.04-1.82)
Katz et al. (2004)	Overall faller: 20.3% Placebo: 22.3%; RIS 0.5mg/day:18.0%; RIS 1mg/day:12.7% (p<0.04); RIS 2mg/day: 27.3% Rates of falls/month Placebo: 0.15; RIS 0.5mg/day: 0.11 RIS 1mg/day: 0.09 (p<0.04); RIS 2mg/day: 0.20.	RCT	Overall RIS use: NR (p=0.464). RIS 0.5 mg/day: 0.74 (0.44-1.27); RIS 1 mg/day: 0.53 (0.29-0.98); RIS 2 mg/day: 1.31 (0.81-2.10).	RIS &wandering interaction= p<0.001 Among highest level of wandering at baseline, RIS 0.5 mg/day: 0.78 (0.39-1.55), RIS 1.0 mg/day: 0.28 (0.12-0.67), RIS 2.0 mg/day: 0.99 (0.50-1.96). Among low level of wandering at baseline, RIS 0.5 mg/day: 0.67 (0.29-1.57), RIS 1.0 mg/day: 0.92 (0.39-2.14), RIS 2.0 mg/day: 1.81 (0.91-3.56).
Landi et al. (2005)	37% fallers over 90-day	NR	NR	AADs: 1.45 (1.00-2.11) TADs: 1.49 (1.10-2.51)

Table 3.3

Atypical Antipsychotic Drug (AAD) Use and Falls Literature: Results (continued)

Author (s)	% of Fall	% of AAD use	Unadjusted Estimates (95% CI)	Adjusted Estimates (95% CI)
Hien et al. (2005)	Over 30-day, Overall Fallers (1+): 11%; Recurrent Fallers (2+): 23% of fallers	RIS&OLZ use: 6%; RIS: 31.7% OLZ: 68.3%	OLZ: 2.35 (1.43-3.87) RIS: 1.70 (0.75-3.82) TADs: 1.48 (0.96-2.26)	OLZ: 1.74 (1.04-2.90) RIS: 1.32 (0.57-3.06) TADs: 1.35 (0.87-2.09)
Frenchman (2005)	Over 45-days, % of fallers: 28.4% OLZ:38% ; RIS: 19% (p<0.001). Rates of Fall/month OLZ:0.2; RIS: 0.1 (p<0.001).	Entire cohort	NR	NR
Mintzer et al. (2006)	Placebo:12.6%; RIS:11.1% (p-value NR).	RCT	NR	NR
De Deyn et al. (2005)	Placebo:20.6% Overall RIS:19.2% RIS <0.75 mg/day: 19.4% RIS 0.75-1.5mg/day: 14.9% RIS 1.5-2mg/day:24% (p-value NR)	NR	NR	NR
Suh et al. (2006)	Mean of falls in RIS & HD, respectively, Baseline: 1.72&1.37, Week 2:1.59 & 1.37, Week 4:1.57 & 1.34, Week 6:1.42 & 1.68, Week 8:1.32 & 1.76 (p<0.04).	RCT	NR	NR
Rochon et al. (2008)[b]	Community- Nonuser:0.4%; AADs:1.2%; TADs:1.2% PCH- Nonuser:0.5%; AADs:1.0%; TADs:1.2%	Community- RIS :72.0%; OLZ:20.0%; QTP:8% PCH- RIS: 73.1%; OLZ:20.2%; QTP:6.7%	Community- AADs:3.54(3.09-4.05); TADs:4.19 (3.66-4.79) PCH- AADs:1.76 (1.54-2.01); TADs:2.23 (1.96-2.53)	Community- AADs:3.19 (2.77-3.68); TADs:3.81 (3.31-4.39) PCH- AADs:1.92 (1.68-2.21); TADs:2.38 (2.08-2.72)

Note. CI=confidence intervals; RIS=risperidone; NR=not reported; RCT=randomized controlled trial; OLZ=olanzapine; NS =not significant; HD=haloperidol; TADs=typical antipsychotic drugs; [a]Outcome is "accidental injury" which includes fall, abrasion, cut or laceration, fracture, or skin tear. [b]Outcome is hospitalized events which include fall/hip fractures.

Chapter 4

Methods

This study links clinical data from the Resident Assessment Instrument Minimum Data Set 2.0 (RAI-MDS 2.0©) to the Manitoba Health administrative healthcare data housed at the Manitoba Centre for Health Policy (MCHP) of the Faculty of Medicine, University of Manitoba, to examine the association between atypical antipsychotic drug (AAD) use and falls among older personal care home (PCH) residents in the Winnipeg health region (WHR). This chapter describes the methods used to conduct this research, focusing on data sources; study design; the measurement of AAD use, study covariates, and fall outcomes; and statistical analyses techniques used.

Data Sources

Manitoba Health administrative healthcare data, housed at the MCHP, were used to conduct this research. Manitoba Health provides universal healthcare coverage to all Manitoba residents regardless of their age or income. These data form a comprehensive, population-based administrative claims database that includes data on physician, hospital, PCH, home care, and pharmaceutical use for all residents of Manitoba. These administrative files are an essential part of this research, for identifying PCH admission and separation dates, drug dispensation information, medical health conditions, and hospitalized falls. The following specific databases were linked to conduct this research: 1) Drug Programs Information Network (DPIN) database, 2) PCH database, 3) Hospital separation abstracts, 4) Physician claims database, 5) Vital Statistics mortality, and 6) Manitoba Health Registry.

While these administrative databases contain a rich supply of information, important clinical measures for PCH residents are not included in these files, such as their extent of challenges conducting activities of daily living (ADL) tasks, their degree of cognitive impairment, and their incontinence. To include these and other related measures including balance problems, unsteady gait, restraint use, foot problem, and range of motion, the RAI-MDS© database was linked to the aforementioned databases housed at the MCHP.

A scrambled unique health services number called the personal health identification number (PHIN) enables linkage across all databases housed at the MCHP. This scrambled PHIN is assigned by Manitoba Health to every person registered for health insurance in Manitoba. Permission to link these databases was approved by the University of Manitoba Health Research Ethics Board, Manitoba Health Information Privacy Committee, and the Winnipeg Regional Health Authority Research Ethics Committee. These approval letters are provided in Appendix A.

Drug programs information network database.

Researchers have shown that DPIN is a valid and reliable data source for studying prescribed drug use (Kozyrskyj & Mustard, 1998; Roos et al., 1993). This database contains a record of all prescription drugs dispensed by retail pharmacies in Manitoba. Records in this file are generated from the transaction of claims for reimbursement from dispensing retail pharmacies. For residents of PCHs, pharmaceuticals approved under the Health Services Insurance Act are supplied free-of-charge. Services not captured in DPIN include drugs dispensed from hospital pharmacies and at PCHs that obtain drugs through

a hospital pharmacy. Furthermore, DPIN is a dispensation database, and does not capture information on actual use and dispensation of over-the-counter drugs for individuals living in the community.

For the purpose of this study, the following information in DPIN was used: drug information number, drug name, strength, dosage form, the date of the prescription dispensation, total quantity dispensed, and total day supply. The World Health Organization Anatomic Therapeutic Chemical (ATC) classification system code is also included in DPIN (WHO Collaborating Centre for Drug Statistics Methodology, 2002), and was used to measure exposure to AADs by specific drug type. The ATC system for drug classification is widely used in pharmacoepidemiologic research, and its use would allow comparisons with other studies. Total quantity dispensed, strength, and total day supply information in DPIN was used to measure dosage of AADs dispensed.

Personal care home database.

The PCH database contains all persons assessed, admitted to, and/or separated from a PCH licensed by the Province of Manitoba. These data contain all residents of for-profit and not-for-profit PCHs in both urban and rural Manitoba. Information included in this database includes PCH assessment, admission and separation dates, as well as PCH identifiers, reason of separation, and levels of care. In this study, PCH data were used to identify the eligible individuals and PCHs within the study period (from April 1, 2005 to March 31, 2007) required building a study cohort. Furthermore, PCH admission date was used to measure the length of PCH stay for each study participant.

Hospital separation abstracts.

A hospital separation abstract is completed upon a patient's separation from an acute or chronic care hospital. Information obtained from this database includes hospital admission and separation dates, and diagnostic codes. These data were used to identify PCH residents who were hospitalized due to a fall, and their date of hospitalization. Hospital separation abstracts were also used to identify PCH residents who were previously diagnosed with select diseases known to increase fall risk such as arthritis, Parkinson's disease, and dementia (see Table 4.4).

Physician claims database.

The physician claims database contains the billing claims generated by physicians for medically essential services to Manitoba Health registered patients. Patients' diagnosis codes and dates of services were obtained from this database. Similar to hospital separation abstracts, information in this database was used to identify residents previously diagnosed with arthritis, Parkinson's disease, and dementia (see Table 4.4).

Vital statistics mortality database.

The Vital Statistics mortality database has information on each resident's date and cause of death. This database was used to identify each resident's proximity to death during a given fall period.

Manitoba health registry database.

All Manitoba residents registered with the Manitoba Health insurance plan are included in this registry. For this research, participants' age and sex were obtained from the registry.

Resident assessment instrument minimum data set.

RAI-MDS© consists of an assessment tool (Minimum Data Set, MDS) and resulting applications (Canadian Institute of Health Information, 2005). It is an ongoing and extensive assessment tool for PCH residents, and was developed at the University of Michigan in the early 1990s. The general goal of MDS[1] is to identify a resident's strengths, needs, and preferences to guide the staff in developing a comprehensive, appropriate, and individualized care plan (Canadian Institute of Health Information, 2005). MDS contains over 450 screening, clinical, and functional status assessment items. The validity and reliability of various MDS metrics have been well established in the United States-based literature (Del Rio, Goldman, Kapella, Sulit, & Murray, 2006; Gambassi et al., 1998; Hawes et al., 1995; Landi et al., 2000; Mor et al., 2003; Mor, 2004; Morris et al., 1994; Snowden et al., 1999). For example, Hawes et al. (1995) showed that individual ADL items, measures of cognitive skills for decision making, and continence items in MDS exhibit excellent inter-rater reliability (i.e., kappa correlation coefficient of 0.7 or higher). Further, Morris et al. (1994) compared results of the cognitive performance scale to those of the mini-mental state examination test, and

[1] From this point forward, MDS refers to both the actual assessment tool and the resulting applications.

reported these two scales to share 74% of variance (Morris et al., 1994). Similarly, others have shown that results from the MDS ADL long form scale correlate well with the Barthel ADL Index (Pearson's correlation coefficient score of 0.74) (Landi et al., 2000).

For PCH residents, MDS assessments occur on a quarterly and an annual (full) basis. As a general rule, full assessments should be completed by the 14th day following each resident's PCH admission date, and annually thereafter. Quarterly assessments should be completed every 92 days following the last full or quarterly assessment, to track each resident's status between comprehensive full assessments. MDS assessments must be conducted and coordinated by a registered nurse. Once the assessment is complete, a registered nurse signs and certifies the completeness and accuracy of the assessment; this is called a locked assessment (Canadian Institute of Health Information, 2005). Thus, all analyses in this study included only locked full and quarterly MDS assessments.

MDS has been used in over 30 countries around the world. In Manitoba, MDS was initiated in not-for-profit PCHs in WHR in 2004. Commencing 2007, MDS was gradually implemented in for-profit PCHs in WHR. At the time of this research, only MDS data from not-for-profit Winnipeg PCHs were available for use at MCHP. In addition, a recent study conducted in Manitoba has shown that MDS data collected during the first fiscal year (April 1, 2004 to March 31, 2005) have some limitations, and that less than half of newly admitted residents during this time were assessed as per MDS standards (Doupe et al., 2011b). Therefore, researchers suggested that MDS data for this year should not be used. This same research shows much improved MDS standards

commencing April 1, 2005. Based on these findings, MDS data in the 2005/06 and 2006/07 fiscal years were used in this study.

Data on Falls

As the primary outcome, fall data were captured using MDS. In the United States, independent, dual assessment of falls showed excellent inter-rater reliability (kappa correlation coefficient of 0.9) (Hawes et al., 1995). The MDS manual describes a fall as "any unintentional change in position where the resident ends up on the floor, ground or other level" (Canadian Institute of Health Information, 2005). The manual suggests that falls should be recorded based on consultations with the residents, the resident's family, and a review of the resident's medical records including incident reports, current nursing care plan, and monthly summaries (Canadian Institute of Health Information, 2005).

Fall data captured in MDS (item j4a) do not include an actual fall date, but rather identify people who fell one or more times in the 30 days preceding each MDS assessment. A basic schematic of this MDS item is provided in Figure 4.1. For the purposes of this research, MDS assessment date minus 30 days is labeled as the fall assessment period (during which residents were assessed for falling). This period begins with an index date and ends with the MDS assessment date. The index date is essential for measuring AAD use, and more information about this index date is provided in a later section.

Given the absence of an actual fall date in MDS, the outcome of interest in this research is the falling. Also, falls are identified only intermittently in MDS (i.e., for a 30 day window between consecutive MDS assessments), with implications for study results

and future research directions. As one advantage however, at least in comparison to falls reported in the hospital abstract file, both non-injurious and injurious falls are reported in MDS during each fall assessment period.

Validity of fall measurement.

Validity assesses whether a scale measures what it is intended to measure (Bannigan & Watson, 2009). In this study, fall outcome measurement was evaluated on the basis of face validity and concurrent criterion validity.

Face validity.

Face validity is the degree to which a measurement scale looks reasonable (Bannigan & Watson, 2009). In this study, face validity of the study outcome was evaluated by comparing the faller prevalence in MDS with published literature. Over the 30-day assessment time, 28% (n=652) of the overall study cohort was identified as fallers based on MDS data. While this prevalence appears to be higher than the fall prevalence (11% over 30 days) reported by Hien et al. (2005), it is comparable to two other studies with fall prevalence of 28.4% over 45 days (Frenchman, 2005) and accidental injury of 28.6% over 42 days (Street et al., 2000). Several factors help to explain the unique findings of Hien et al. (2005). For example, Hien et al. (2005) used occurrence reports to measure falls as compared to MDS data used in the present study, medical records used by Frenchman et al. (2005), and resident recall used by Street et al. (2000). In addition, Hien et al. (2005) conducted their research in Australia, while the other studies were conducted in North America – either in Canada (the present study) or in the United States

(Street et al., 2000; Frenchman, 2005). Hien et al. (2005) did not provide a definition of falls in their research.

Concurrent criterion validity.

Concurrent criterion validity compares the results of a given test to those of a "gold standard" criterion measured at the same time (Bannigan & Watson, 2009). In this study, concurrent criterion validity analyses were conducted by comparing MDS recorded fallers to fallers recorded on hospital separation abstract files. The analyses were conducted on the original (entire) cohort of 2,325 PCH residents, with 10,496 MDS assessments completed between April, 2005 and March 31, 2007. MDS data were linked to the hospital separation abstract files housed at the MCHP using each resident's unique encrypted PHIN. Date-specific fall data from the hospital separation abstract files (ICD-10-CA codes W00 to W19) were captured as per MDS fall items j4a ("fell in past 30 days"). A 7-day allowance was provided at the beginning and at the end of each fall assessment period to avoid possible data error. Two measures were used to evaluate the validity of the fall data, i.e., sensitivity and specificity. Figure 4.2 shows the calculation of both measures for the purpose of this study.

Results showed that for the 1-30 day period preceding each assessment (MDS item j4a), 35 falls were reported in the hospital separation abstract files (see Table 4.1). Of these falls, 29 were also recorded in MDS. As a result, MDS had a sensitivity of 82.9%, indicating the ability to correctly identify hospitalized falls for the 30-day period preceding an assessment date. From the hospital separation abstract files, there were 10,461 non-fall events. Of these, 9,241 were also recorded as non-falls in MDS, resulting

in a specificity of 88.3%. These results indicate that fall outcome has concurrent criterion validity.

Study Design

This research was conducted using a nested case-control (NCC) design. Researchers have shown that this type of design provides similar estimates that are obtained on full cohorts, with significant gains in computational time efficiency (Essebag, Platt, Abrahamowicz, & Pilote, 2005; Lubin, 1986; Lubin & Gail, 1984; Rothman, Greenland, & Lash, 2008). In addition, the NCC design requires controls to be matched on time, which is an important confounder in many epidemiological studies (Etminan, 2004; Jick, Garcia Rodriguez, & Perez-Gutthann, 1998; Lubin, 1986). Lastly, matching on confounding variables in a NCC design prevents having a large imbalance of cases and controls at the study design stage rather than at the analysis stage (Mandrekar & Mandrekar, 2004; Matthews & Brill, 2005). The steps used to implement the NCC design are described in the following text.

Assembling the study cohort.

The source population for this study includes all existing and newly admitted residents of not-for-profit PCHs in the WHR from April 1, 2005 to March 31, 2007. Appendix B contains the list of PCHs included in this study. A study cohort of 2,316 PCH residents with a total of 8,753 (locked) MDS assessments were assembled based on select PCH, person, and assessment level inclusion criteria (see Figure 4.3).

Personal care home-level inclusion criteria.

A PCH must have dispensed its medication from a retail-based pharmacy because, as noted earlier, DPIN does not capture drug dispensation information for hospital-based pharmacies. In addition, a PCH must have collected MDS between the dates of April 1, 2005 and March 31, 2007, to be included in this study.

Person-level inclusion criteria.

To be included in this research, a cohort member must have had two or more MDS assessments. This criterion was included so that MDS-based covariates from a previous assessment (assessment 1) could be used to predict the odds of falling during the next assessment (assessment 2).

Assessment-level inclusion criteria.

For use in this research, MDS assessments must have been completed at least 30 days after each resident's PCH admission date. This was done to ensure that a fall recorded in this research occurred during the PCH stay (not prior to PCH admission). In addition, as the focus of this study was on older adult PCH residents, MDS assessments were excluded prior to each participant's 65^{th} birth date. Similarly, MDS assessments were excluded if residents had been living in Manitoba for fewer than five years at the date of assessment. This criterion was chosen to permit measuring diagnostic covariates (dementia, arthritis, and Parkinson's disease) using administrative data.

To be included in this study, participants must have had no clozapine dispensation record within one-year preceding an MDS assessment date, in which case the assessment was removed from the analyses. This criterion was chosen to remove clozapine users from this research, due to the rarity of this drug use. Another assessment-level criterion

was that for individuals with more than one MDS assessment recording a fall, only the first MDS assessment with a fall event was included. Lastly, some participants were not identified as being AAD users on their index date, but were dispensed AADs during the following fall assessment period. These individuals were excluded from the analyses, as it was not possible to determine if AAD use commenced before or after a fall.

Formation of a risk set and selection of matched controls.

Risk set (incidence density) sampling was used to select the matched controls for each case (Beaumont, Steenland, Minton, & Meyer, 1989). Risk set sampling is closely related to the Cox's proportional hazards model, except that instead of including all participants, a sample of participants with no outcome event is selected (Pearce, 1989). A risk set for each case was created by including corresponding controls (non-fallers) who had "survived" (i.e., not yet fallen) up to the time of a case (Etminan, 2004). Using this approach, at each given assessment period, potential controls for cases included individuals who had not yet fallen, meaning that previously used controls could be used during multiple assessment periods.

In this study, based on the current evidence in the literature, length of PCH stay (+/- 30 days), age (-/+1 year), and sex were considered as important potential confounders, and were therefore selected as matching variables. Length of PCH stay was a continuous variable and was defined as the number of days of care from the PCH admission date to the index date. Age was included as a continuous variable, as age in years at the time of index date. Using these criteria, for a given assessment period, potential controls must have been the same sex, been within one year of age, and had a

PCH length of stay within 30 days, in order to be matched to a given case. At each assessment period, four controls were randomly selected from the risk set of each case.

Figure 4.4 illustrates a hypothetical example of the selection of potential controls for a case matched on length of PCH stay. In this example, there were three cases (Identification [ID] 1, 3, and 5) among eight participants. The first faller among these participants was participant ID 5. (S)he became a faller at the time of his/her third assessment, after 180 days of PCH stay. At this time, participants IDs 1, 2, 3, 6, 7, and 8 were eligible to be potential controls for participant ID 5, because these individuals had not yet fallen during any pervious MDS assessment period, and had an MDS assessment within 30 days of the corresponding case occurrence. Second example showing that ID 3 is second faller, who can be matched to IDs 1, 6, and 8, and that ID 5 is not eligible because she or her has already fallen. Lastly, ID 1 is the last faller, after 360 days of length of PCH stay, and can be matched to ID 8 who had not yet fallen.

In total, after all inclusion and exclusion criteria, 636 fallers and 1,680 non-fallers were identified using MDS data during the study period. After the matching process, almost all of the cases (90.0%) had four controls based on length of PCH stay, sex, and age matching criteria. However, some cases had an insufficient number of controls: 22 cases (3.5%) had three controls, 29 cases (4.6%) had two controls, and 12 cases (1.9%) had one control only. These cases and their controls were still included in the analyses. Furthermore, 10 cases (1.6%) did not have any potential controls in their risk set, and these cases were excluded from the analyses. After these exclusions, the final number of cases and controls were 626 and 2,388, respectively.

Measurement of Exposure to Atypical Antipsychotic Drugs

Information on AAD dispensation was obtained from the DPIN data for each PCH resident. Refill frequency of AAD dispensation is provided in Appendix C. AADs in this study included the following medications at the fifth level ATC code: N05AX08 (risperidone), N05AH03 (olanzapine), or N05AH04 (quetiapine). A schematic of the strategy used to measure AAD exposure is depicted in Figure 4.5. These strategies were developed to help ensure that AAD exposure preceded any fall event, and also used clearance periods to cover the period of potential excess risk after discontinuation of AAD use.[1] To assess the overall effect of AAD use on fall risk, exposure to AADs was measured as the dispensation of oral solid AADs, independent of drug type or dose, for one year preceding each Index Date. Clearance periods were included just prior to each Index Date and during each fall assessment period.

Based on these strategies, six possible AAD use patterns were developed. Nonusers were coded as participants with no recorded use of AADs during the clearance period preceding the Index Date and the 30-day fall assessment period, whether or not AAD use was recorded during the year preceding the Index Date (AAD use patterns 1 and 2, respectively, in Figure 4.5). Four subgroups of AAD users were also developed. These subgroups are consistent in that AAD use was recorded on the Index Date and

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[1] Clearance period is defined as the number of days between the calculated end date of a dispensation and the start date of the following dispensation. Since the time for total elimination is different for each type of AAD, a clearance period was identified according to the type of AAD dispensed. The elimination half-life of these drugs for older adults are estimated to be 23 hours for risperidone, 51.8 hours for olanzapine, and 10.5 hours for quetiapine (Canadian Pharmacists Association, 2009). When a treatment is stopped, it takes about five half-life durations for the serum level of a drug to be mostly eliminated from the body (Sharif, 2003; Thomson, 2004). Thus, the clearance period was identified as 4 days for risperidone, 10 days for olanzapine and 2 days for quetiapine. For residents taking multiple types of AADs, the drug clearance period was defined using the longest elimination half-life.

during the preceding clearance period. While for each subgroup AAD use was also recorded during the fall assessment period, subgroups 3 and 4 used AADs consistently throughout this time (i.e., days between subsequent dispensation records were shorter than clearance periods), while subgroups 5 and 6 did so intermittently. Based on these results, we can only say, with certainty, that AAD exposure preceded a fall event in subgroups 3 and 4. However, because subgroups 5 and 6 were relatively small in number (3% of users; see Figure 4.5), the decision was made to combine subgroups 3 through 6 as AAD users.

Measurement of type of atypical antipsychotic drugs.

AAD users were further classified by drug type. For each user, AAD type was determined based on the most recent dispensation record preceding the Index Date. Type of AAD was classified as risperidone, olanzapine, quetiapine, and multiple type users. Multiple type users included AAD users: 1) who were on multiple types of AADs concurrently, and 2) who switched AAD type during the 30-day assessment period. The majority of AAD users (99.3%) did not change their type of AAD over the 30-day assessment period.

Measurement of dose of atypical antipsychotic drugs.

AAD users were also classified by drug dose. For each user, AAD dose was identified based on the most recent AAD dispensation record preceding the Index Date. This is expressed as the prescribed daily dose (PDD), which is a commonly used metric in pharmacoepidemiologic studies (Lieberman & Nelson, 1993). PDD for each dispensation of AADs was calculated using the following formula:

PDD = total quantity dispensed *strength / total days supply

After calculating PDD, AAD dose was categorized as “low” or “high” according to the United States Centers for Medicare and Medicaid Services for fulfilling the Omnibus Reconciliation Act of 1987 (OBRA 87) (Centers for Medicare and Medicaid Services, 1999). According to this guideline, for older adult PCH residents, low dose AADs have a PDD of no more than 2 mg/day of risperidone, 7.5 mg/day of olanzapine, or 150 mg/day of quetiapine. Similar AAD dose strategies have been used by others (McKenzie, Mullooly, McFarland, Semradek, & McCamant, 1999). Based on these criteria, the majority of AAD users (97.1%) had no change in their dose category during the 30-day fall assessment period. Users who changed dose during this period typically transitioned from low to high AAD dose (in which case they were labeled as high dose users).

Validity of exposure to atypical antipsychotic drugs measurement.

Exposure to AADs measurement was evaluated on the basis of face validity and construct validity.

Face validity.

Face validity of the main exposure variable, AADs use, can be evaluated by comparing the AAD use prevalence with published literature. This study showed that 25.1% of cases and controls were an AAD user. This distribution is comparable to other studies in the literature showing from 24% to 31% of PCH residents received an AAD (Champoux et al., 2005; Doupe et al., 2006; Hagen et al., 2005; Oborne, Hooper, Li,

Swift, & Jackson, 2002; Snowdon, Day, & Baker, 2006).

Construct validity.

Construct validity compares the results of a test to related constructs under investigation (Bannigan & Watson, 2009). In this study, construct validity of exposure to AAD was assessed by testing the association between schizophrenia and AAD use. AADs are indicated for treating patients diagnosed with schizophrenia (Canadian Pharmacists Association, 2009). Therefore, it is expected that exposure to AAD use, as measured in this study, should be associated with a diagnosis of schizophrenia. Algorithm and diagnostic codes used to identify schizophrenia are outlined in Tables 4.4 and 4.5. Similar algorithm have been used by other researchers (Doupe et al., 2008). Tests of association were conducted using unconditional logistic regression with AAD use as the outcome variable and schizophrenia as the explanatory variable in the model.

Descriptive results showed that a higher proportion of patients diagnosed with schizophrenia were AAD users (57.6%) compared to those with not diagnosed with schizophrenia (24.5%) (see Table 4.2). Furthermore, unconditional logistic regression analysis showed that compared to patients not diagnosed with schizophrenia, the odds of being an AAD user was 4.19 fold greater for those diagnosed with schizophrenia (95% confidence intervals [CI] 2.72-6.44).

Given that in older adults AADs are commonly used to treat behavioural problems associated with dementia (Liperoti et al., 2003; Motsinger et al., 2003), similar interim analyses were conducted to test the association between AAD use and dementia (data not shown). Algorithm and diagnostic codes used to identify dementia are outlined

in Tables 4.4 and 4.5. Descriptive results revealed that higher proportion of patients diagnosed with dementia was AAD users (29.2%) compared to those not diagnosed with dementia (9.0%). Furthermore, unconditional logistic regression analysis showed that the odds of being an AAD user was 4.19 times greater for those diagnosed with dementia as compared patients with no diagnosis of dementia (95% CI 2.61-6.73). These results indicate that AAD measurement has construct validity.

Measurement of Study Covariates

Based on evidence from the literature and the availability of risk factors in either the MDS data or administrative files, the potential covariates used in this research are presented Figure 4.6. These measures are classified based on the WHO's risk factor model, adapted for the purpose of this study. In total, 22 measures were identified as potential study covariates. These covariates were grouped into the categories of function (five variables), drugs other than AADs (six variables), medical health conditions (four variables), cognition (three variables), and others (four variables).

Univariate and interim analyses were first conducted, testing the association between each covariate and the likelihood of falling. All covariates were expressed as categorical measures, and participants with the lowest odds of falling were identified as the reference group. Each covariate was first developed using several categories, and based on interim analyses adjoining categories were collapsed when: 1) the sample size for any category was less than 20 individuals, and 2) the odds of falling did not differ statistically across categories. Lists of covariates are provided in Table 4.3 and 4.4 (for MDS data and administrative health records, respectively). These tables provide the

original categories and coding of all covariates, and as well as the derived (collapsed) categories based on this analysis. Further details about these covariates are provided in the following text.

Function-related covariates.

Function-related covariates included activities of daily living (ADL), unsteady gait, balance problem, foot problem, and limitations in range of motion. Data for all these covariates were obtained from MDS. Table 4.3 summarizes which MDS items were used to create these covariates, their original categories in MDS, and their derived categories developed for use in this study.

Use of drugs other than atypical antipsychotics-related covariates.

Use of drugs other than AADs included antidepressants, benzodiazepines, typical antipsychotics, antihypertensives and diuretics, opioid analgesics, and number of different drugs (see Appendix D for a medication list in each drug category). Data for exposures to these drugs were obtained from the PCH prescription drug file in the DPIN database. Based on the exposure to each drug, participants were classified as nonuser, partial, or current users. In keeping with other studies, the clearance period for these drugs are defined as seven days (Avidan et al., 2005; Hudson, Rahme, Richard, & Pilote, 2007; Ray, Chung, Murray, Hall, & Stein, 2009; Ray et al., 2000).

Nonusers were coded as participants with no recorded use of these drugs during the clearance period preceding the Index Date and the 30-day fall assessment period, whether or not AAD use was recorded during the year preceding the Index Date. Current users were coded as participants with recorded use of these drugs during the clearance

period preceding the Index Date and consistently during the 30-day fall assessment period (i.e., days between subsequent dispensation records were shorter than clearance period). Lastly, partial users were participants with recorded use of these drugs during the clearance period preceding the Index Date but intermittently during the 30-day fall assessment period (i.e., days between subsequent dispensation records were longer than clearance period). Also, the total number of different drugs dispensed to residents within each 30-day period was counted using the fourth level ATC class, excluding over-the-counter drugs, and participants were coded as nonuser, users (one to eight drugs), and heavy users (nine and more drugs).

Medical health conditions-related covariates.

Medical health conditions-related covariates included arthritis, Parkinson's disease, comorbidity level, and frequency of bowel and/or bladder incontinence. Participants with arthritis were identified using a validated algorithm developed for use with administrative data (see Table 4.4) (Lix, Yogendran, & Mann, 2008). The diagnostic codes and drugs used in the analyses to define arthritis are outlined in Table 4.5. Similar strategies were used to define participants with Parkinson's disease (Noyes, Liu, Holloway, & Dick, 2007; Swarztrauber, Anau, & Peters, 2005; Szumski & Cheng, 2009).

Comorbidity level was assessed using the Johns Hopkins Adjusted Clinical Group Case-Mix Adjustment System. Researchers have validated this system for use in Manitoba (Reid, MacWilliam, Roos, Bogdanovic, & Black, 1999). In this study, comorbidity was defined as the number of major aggregated diagnostic groups (ADGs) a person had in the year prior to their Index Date. Comorbidity level was categorized as

"low" if a person had zero or one major ADG, "medium" if a person had two or three major ADGs, or "high" if a person had four or more ADGs.

Cognition-related covariates.

Dementia, wandering, and cognitive performance were identified as cognition-related covariates. Wandering and cognitive performance were measured using MDS (see Table 4.3 for description of these covariates). Participants previously diagnosed with dementia were identified using the algorithm outlined in Table 4.4. The diagnosis codes used to define dementia are shown in Table 4.5.

Other covariates.

Other covariates included in the analyses were marital status, fall history, proximity to death, and physical restraint use. Proximity to death was measured by linking MDS to the Vital Statistics mortality database. This covariate was defined as the number of days from the Index Date to each person's date of death. This measure was categorized into 0 to180 days until death, versus 181 days or more until death. All other covariates were measured using MDS, as summarized in Table 4.3.

Statistical Analysis

Conditional logistic regression (CLR) analysis was used to test the effect of AAD use on the odds of falling. CLR analysis was conducted by using "proc logistic" procedure in Statistical Analysis System (SAS®) software with a "strata" statement to identify the each risk set matched on length of PCH stay, age, and sex. CLR was used versus unconditional logistic regression, as the latter approach may result in biased

inferences when the number of parameters in a model is large, especially with fewer cases (Peduzzi, Concato, Kemper, Holford, & Feinstein, 1996; SAS Institute Inc., 2008). This study used 626 matched case-control sets and 22 study covariates. If data were analyzed with unconditional logistic regression, 625 intercept parameters and 22 slope parameters (total of 647 parameters) would have been estimated, which is larger than the number of cases in this study. CLR, however, does not provide an intercept for each set, but rather estimates the joint product of likelihood for each case-control set (SAS Institute Inc., 2008). This approach is similar to Cox proportional hazards analyses (Langholz & Goldstein, 1996).

Adjustment for confounding.

All study covariates listed in Figure 4.6 were initially assessed for inclusion in the final model as confounders. A variable was selected for inclusion in the final model if: a) it's inclusion in the baseline CLR model changed the odds ratio (OR) estimates of AAD use by >2% (i.e., the change in estimate [CIE] approach), b) it was shown consistently in the literature to significantly influence fall risk, and c) it was not an effect measure modification based on the analyses testing the possible interactions between main effect of AAD use and covariates as it would be inappropriate to adjust for potential confounding by a variable in the presence of effect measure modification.

For each covariate, CIE was calculated using the following formula (Sonis, 1998):

CIE= [(adjusted OR - crude OR) /adjusted OR] x 100

An initial base model was first chosen for this analysis, including the main exposure variable (AAD use) and all variables selected as being most important based on

the literature (i.e., challenges with ADLs, having a balance problem, antidepressant use, benzodiazepine use, number of different drugs use, wandering, cognitive impairment, and fall history). Subsequent models sequentially added each remaining covariate to this base model, and CIE was calculated for each remaining covariate. Among these remaining covariates, only those with the highest CIE (greater than 2%) were kept in the model (includes proximity to death, having Parkinson's disease, and use of antihypertensives and diuretics). The results from CIE analyses are presented in Table 4.6. Lastly, interaction effect analysis showed that there was a significant interaction between main effect of AAD use and wandering (see Table 5.14). Therefore, wandering was not considered as confounder in the final model. The final list of all covariates considered for inclusion in the final model is presented in Table 4.7.

Interaction analysis.

Interaction tests were included in the final model, to test if the effect of AAD varied by drug type and dose, or certain person characteristics. To conduct the AAD type and dose interaction analysis, a separate AAD exposure variable were created to identify both the dose and type of AAD use (i.e., risperidone-low dose, risperidone-high dose, olanzapine-low dose, olanzapine-high dose, quetiapine-high dose, quetiapine-low dose, multiple-high dose, and multiple-low dose), with nonusers identified as the reference group.

To conduct the interaction analysis between AAD use and certain person characteristics, additional interaction terms were created between each covariate and the generic AAD exposure variable (i.e., users versus nonusers). These analyses tested if the

overall effect of AAD use on fall risk varied by person characteristics (i.e., hypothesis #3 of this research). Likelihood ratio test was used to assess if the model with interaction term fits better than the model without interaction term. This test is calculated by taking the twice positive difference in the both models' log-likelihoods (Allison, 1999). A cutoff point of P-value <0.1 was used for statistical significance of an interaction term.

Sample Size Calculation

Sample size calculation for this study was conducted using the power and sample size program (PS) version 3.0, which uses the method of Dupont for matched cases and controls (Dupont, 1988). Sample size calculation demonstrated that 435 cases with four matched controls per case were required to develop the models in this research. This sample size would detect OR of 1.4 with type I and type II errors set at 0.05 and .20, respectively (see Figure 4.7). An OR of 1.4 was selected based on the average adjusted ORs found in the literature (Hien et al., 2005; Kallin et al., 2004; Landi et al., 2005).

Additional Analyses

Additional follow-up analyses were conducted for two purposes. First, while it is essential in this research to ensure that AAD exposure preceded the fall event, this was complicated given the various patterns of AAD use observed (see Figure 4.5), and also given the lack of a specific fall date in MDS data. Two additional analyses were conducted to investigate the extent these limitations influenced study results. The following text explains the methodology of both additional analyses.

Sensitivity analysis.

Sensitivity analysis was conducted on a subgroup of AAD users where drug exposure definitely preceded the fall event (AAD use patterns 3 and 4 in Figure 4.5) to explore the consistency of results by excluding subgroups 5 and 6 (both of which used AAD intermittently) from AAD user category. Similar to main analysis, sensitivity analysis tested the three study hypothesis stated in Chapter 1 (Introduction).

Analysis using hospital fall data.

Additional analyses were conducted on the entire sample of main analysis using hospital fall data, where an exact hospitalized fall date was measured, to investigate the extent the lack of a specific fall date in MDS influenced the study results. Similar methodology as the main analysis using the fall data in MDS was used for comparability of results.

For this specific analysis, cases were defined as study participants with a first record of a hospital admission for falls (ICD-10-CA code W0, W11-W19) from April 1st, 2005 to March 31st, 2007. For each case, four controls were randomly selected from the risk set of each case based on length of PCH stay (-/+ 30 days), sex, and age (-/+1 year) matching criteria. Almost all of the cases (95.7%) had four controls. The final number of cases and controls were 96 and 379, respectively (total=475).

For this analysis, the "Index Date" was defined as the date that a person was hospitalized due to a fall event. AAD use was assessed one year prior to the Index Date and people were categorized as nonusers and users (see Figure 4.8). Nonusers were defined as persons with no recorded use of AADs within the 365 days preceding the

Index Date, or persons whose supply of most recent prescription preceding the Index Date ended prior to the clearance period. Users were persons whose supply of most recent prescription preceding the Index Date lasted at least until the Index Date or ended no more than the clearance period prior to the Index Date. For each AAD use, type and dose was measured based on the most recent AAD dispensed preceding the Index Date. Similar to the main analysis, hospital fall data-based analysis tested the three study hypothesis stated in Chapter 1 (Introduction).

Chapter Summary

This chapter describes the methodology used in this research to test the three study hypotheses stated in Chapter 1 (Introduction). An NCC study was conducted using the linked administrative healthcare records and MDS data, housed at the MCHP in the Faculty of Medicine, University of Manitoba. CLR analysis was used to test the effects of AAD use on fall risk, before and after adjustment for a range of covariates. Confounders were selected for inclusion in the final model using multiple approaches.

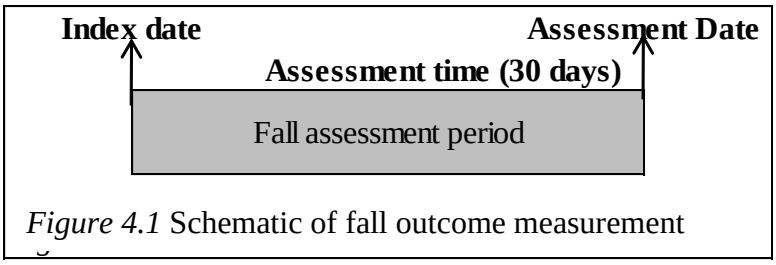

Figure 4.1 Schematic of fall outcome measurement

		Hospital separation abstracts	
		Faller	Not Faller
MDS	Faller	a	b
	Not Faller	c	d

Sensitivity = a / (a+c)*100
Specificity = d / (b+d)*100

Figure 4.2 Calculation of fall validation measures. MDS = Minimum Data Set for personal care homes. Adopted from Defining and validating chronic diseases: An administrative data approach. An update with ICD-10-CA by Lix, L., Yogendran, M., & Mann, J. (2008), Winnipeg, Manitoba: Manitoba Centre for Health Policy.

Table 4.1

Comparison of Fall Data in the Minimum Data Set for Personal Care Homes (MDS) and the Hospital Separation Abstracts: MDS item j4a ("Fell in past 30 days"), n

	Hospital separation abstracts		
MDS	Faller	Not faller	Total
Faller	29	1,220	1,249
Not faller	6	9,241	9,247
Total	35	10,461	10,496

Sensitivity =82.9%

Specificity =88.3%

Inclusion criteria	Inclusion Level	N (%) Eligible People	N (%) Eligible Assessments
Residents of not-for-profit PCHs dispensing their medication from a retail-based pharmacy.	PCH-level	3,206	
Residents of PCHs collecting MDS between the dates of April 1, 2005 and March 31, 2007.	PCH-level	2887 (90.1)	14,519
Residents with two or more MDS assessments.	Person-level	2,512 (87.1)	11,632 (80.1)
Assessments completed after 30-day of PCH admission.	Assessment-level	2,511 (99.96)	11,628 (99.96)
Assessments with residents age 65 and older on the index date.	Assessment-level	2,389 (95.1)	10,794 (92.9)
Assessments with residents having at least 5 years of Manitoba Health coverage preceding the index date.	Assessment-level	2,329 (97.5)	10,514 (97.4)
Assessments with no clozapine dispensation record within one-year preceding the index date or over the 30-day assessment time.	Assessment-level	2,325 (99.8)	10,496 (99.8)
Assessments with no previous MDS assessments recording a fall in the 30 days prior to the assessment date.	Assessment-level	2,325 (100.0)	8,883 (84.6)
Assessments with atypical antipsyhcotic drug use pattern continued over the assessment time	Assessment-level	2,316 (99.6)	8,753 (98.5)

Figure 4.3 Schematic of assembling the study cohort and their assessments. PCH = personal care home; MDS = Minimum Data Set for personal care homes.

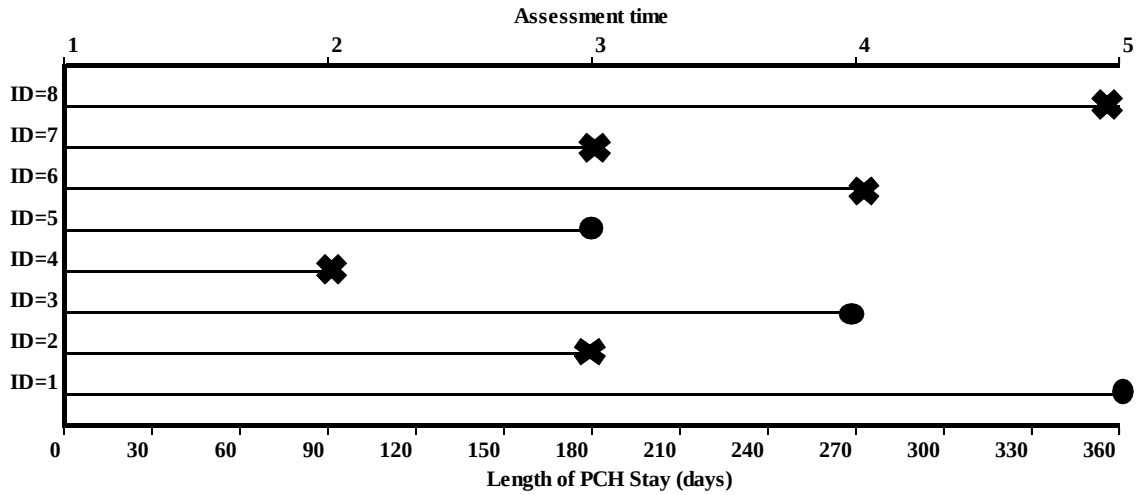

Figure 4.4 Schematic of selection of controls matched on length of personal care home stay (PCH) for hypothetical data of eight participants. Solid circles indicate the assessment with case occurrence, and all subsequent assessments were excluded from the analyses. X's indicate a non-faller's last assessment during the study period. Horizontal lines indicate a person's length of PCH stay.

There were three cases among eight participants, i.e., IDs 1, 3, and 5. Selected controls and their assessment times for each case's risk set were:

1st risk set (Case ID 5 at assessment time 3) = ID 1, ID 2, ID 3, ID 6, ID 7, and ID 8.

2nd risk set (Case ID 3 at assessment time 4) = ID 1, ID 6, and ID 8.

3rd risk set (Case ID 1 at assessment time 5) = ID 8.

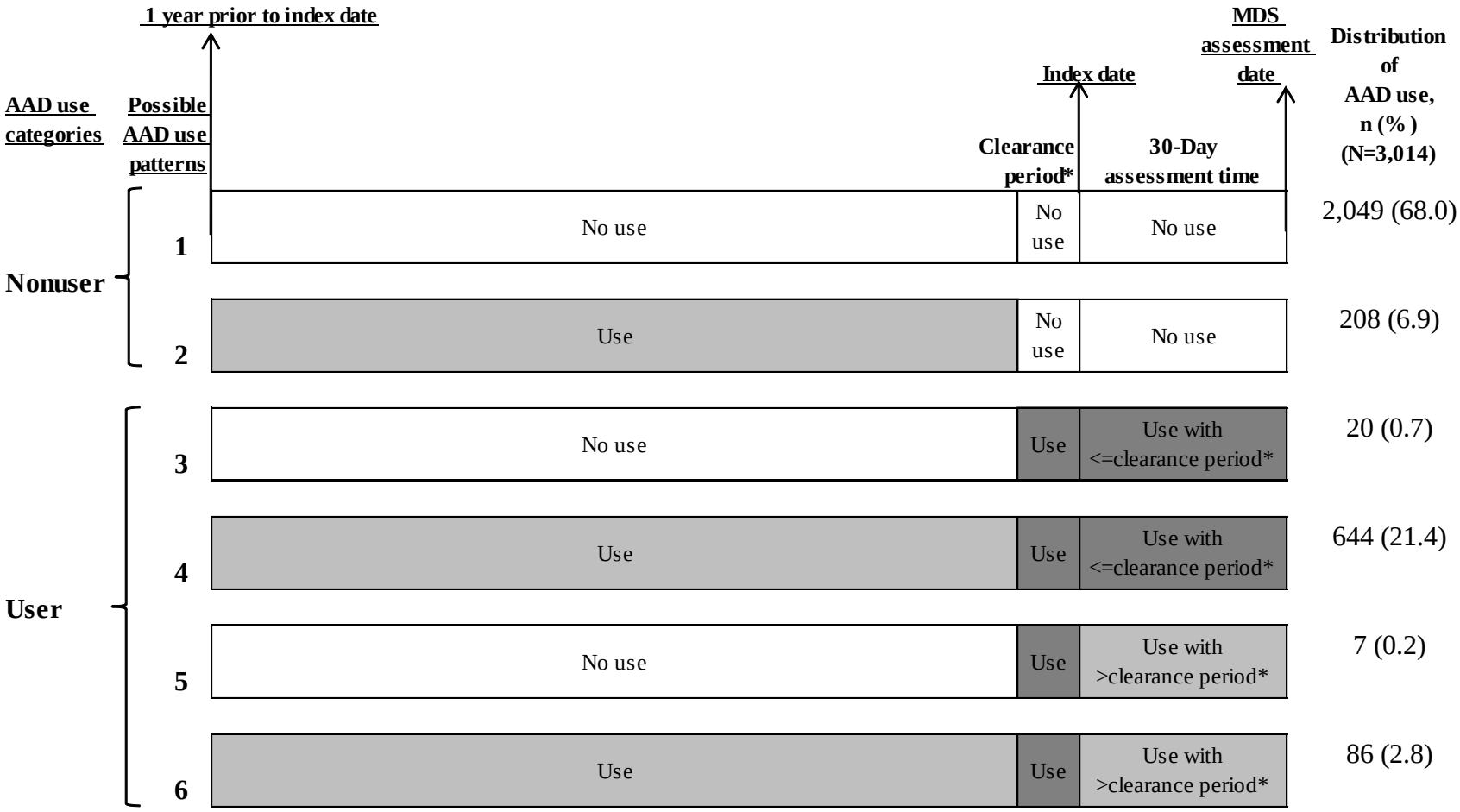

Figure 4.5 Measurement of atypical antipsychotic drug (AAD) use. MDS = Minimum Data Set for personal care homes. <= indicates less than and > indicates greater than clearance period.
*Clearance period was 4 days for risperidone, 10 days for olanzapine, and 2 days for quetiapine. For persons on two or more different types of AADs, the clearance period was based on the drug with the longest elimination half-life.

Table 4.2
Validation of Atypical Antipsychotic Drug (AAD) Use Measurement

	Exposure to AAD measurement			Test of Association		
Diagnosis of Schizophrenia	Nonuser (n=1,182)	User (n=424)	Total (n=1,606)	Unadjusted OR[a]	(95% CI)	P-value
No	1,143 (75.5)	371 (24.5)	1,514	Reference Group		
Yes	39 (42.4)	53 (57.6)	92	4.19	(2.72-6.44)	<.0001

Note. OR = odds ratio; CI = confidence intervals.

[a]OR from unconditional logistic regression model with AAD use as the outcome variable.

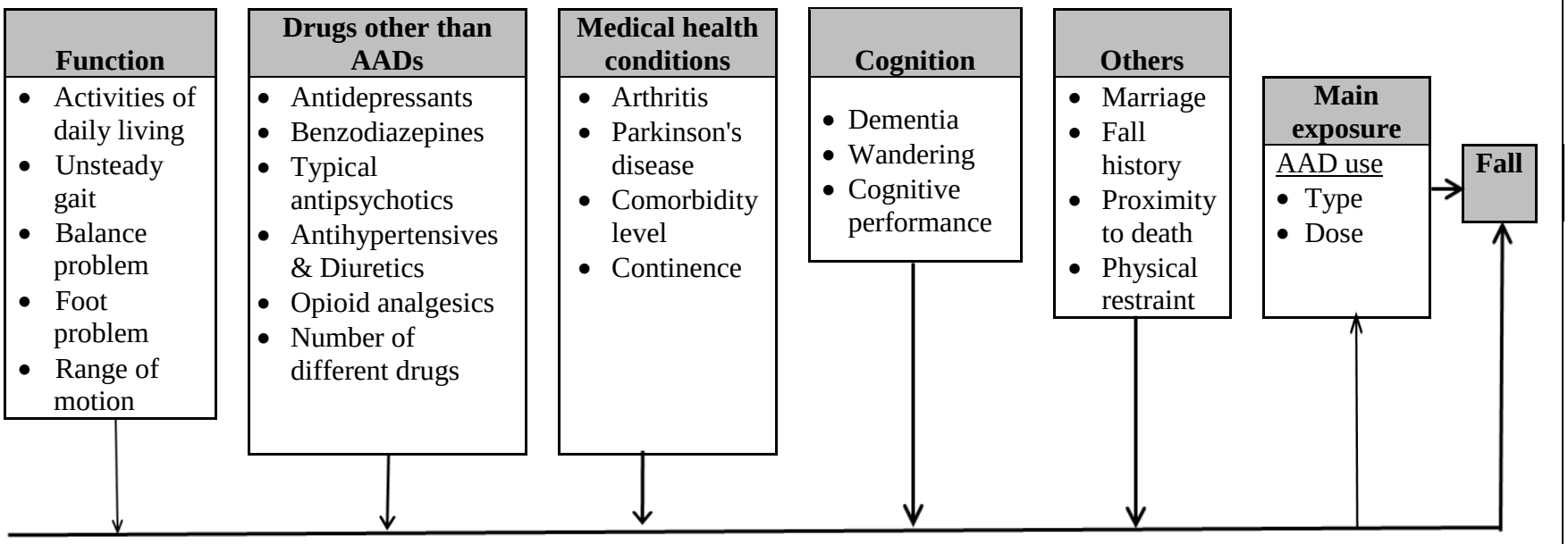

Figure.4.6 Study covariates. AAD = atypical antipsychotic drug

Table 4.3
Study Covariates Used from the Minimum Data Set for Personal Care Homes (MDS) to Conduct this Research

Study Covariate(s)	Included MDS items	Original categories and coding	Derived categories and coding (original coding)
Function-related covariates			
ADL	ADL Long Form Summary Scale[a] G1Aa: Bed mobility; G1Ab:Transfer; G1Ae: Locomotion; G1Ag:Dressing; G1Ah:Eating; G1Ai:Toilet use; G1Aj:Personal hygiene	The scale ranges from 0 (independent) to 28 (completely dependent).	0:Independent (0-2) 1:Partially dependent (3-21) 2:Totally dependent (22-28)
Unsteady gait	J1n: Unsteady gait	0: No; 1: Yes	0: No (0); 1: Yes (1)
Balance problem	G3a: Test for balance while standing	0: Maintained position 1: Unsteady, but able to rebalance with help 2:Partial help/doesn't follow directions 3: Not able to attempt test without help	0:Steady (0) 1:Partially unsteady (1&2) 2:Totally unsteady (3)
Foot problem	M6a: One or more foot problems M6c: Open lesions on the foot M6f: Application of dressings	0: No; 1: Yes	0: No (0); 1: Yes (1)
Range of motion	G4aAb: Arm; G4aAc: Hand G4aAd: Leg; G4aAe: Foot	0: No limitation 1: Limitation on 1 side 2: Limitation on both sides	0: No (0); 1: Yes (1&2)
Medical health conditions-related covariate			
Continence	H1a: Bowel Continence H1b: Bladder Continence	0:Continent 1:Usually continent 2:Occasionally incontinent 3:Frequently incontinent 4:Incontinent	0:Continent (0-1) 1:Partially incontinent (2&3) 2:Totally incontinent (4)
Cognition-related covariates			
Wandering	E4Aa: Wandering	0: Not occurred 1: Occurred 1-3 days 2: Occurred 4-6 days 3: Occurred daily	0: No (0); 1: Yes (1-3)
Cognitive performance	Cognitive Performance Scale[a] B1: Comatose B2a: Short-term memory B4: Cognitive skills for daily decision-making C4: Making self understood G1Ah: Eating	This scale ranges from 0 (intact) to 6 (severe impairment).	0: Intact (0&1) 1:Partially impaired (2-5) 2:Severely impaired (6)
Other Covariates			
Marital status	A5: Marital Status	1: Never married; 2: Married 3: Widowed; 4: Separated 5: Divorced; 9: Unknown	0:Not married (1,3,4,5,9) 1:Married (2)
Fall history	J4b: Fell in past 31 to 180 days	0: No; 1: Yes	0: No (0); 1: Yes (1)
Physical restraint	P4a: Full bed rails; P4b: Half rail P4c: Trunk restraint; P4d: Limb restraint P4e: Chair prevents rising	0: Not used 1: Used less than daily 2: Used daily	0=No (0) 1:Half rail only (1& 2 in P4b) 2: Other restraints (1&2 in P4a, P4c, P4d, or P4e)

Note. ADL = Activities of daily living.
[a] An outcome scale provided as a part of the MDS system.

Table 4.4
Disease Identification Algorithms Used in the Analyses, Developed from Administrative Healthcare Records

Disease	Criteria for being defined as having the disease	Time period
Arthritis[a]	1 or more hospitalizations OR 2 or more physician visits OR 2 or more prescription drug records in combination with 1 or more physician visits	5 years prior to the index date
Dementia[b]	1 or more hospitalizations OR 1 or more physician visits	5 years prior to the index date
Parkinson's Disease	1 or more hospitalizations OR 2 or more physician visits OR 2 or more prescription drug records in combination with 1 or more physician visits	5 years prior to the index date
Schizophrenia[c]	1 or more hospitalizations OR 1 or more physician visits	5 years prior to the index date

[a]Source: Lix, L., Yogendran, M., & Mann, J. (2008). *Defining and validating chronic diseases: an administrative data approach. An update with ICD-10-CA*, Winnipeg, Manitoba: Manitoba Centre for Health Policy. [b]Source: Martens, P. J., Bartlett, J., Burland, E., Prior, H., Burchill, C., Huq, S. et al. (2010). *Profile of Metis health status and healthcare utilization in Manitoba: A population-based study*, Winnipeg, Manitoba: Manitoba Centre for Health Policy. [c]Source: Doupe, M., Kozyrskyj, A., Soodeen, R., Derksen, S., Burchill, C., Huq, S. (2008). *An initial analysis of emergency departments and urgent care in Winnipeg*, Winnipeg, Manitoba: Manitoba Centre for Health Policy.

Table 4.5
Diagnosis Codes and Drugs Used in the Analyses to Define Diseases

Disease	ICD-9-CM Diagnosis Codes	ICD-10-CA Diagnosis Codes	Generic Drug names
Arthritis[a]	714,715, 446, 710, 720, 274, 711-713, 716-719, 721, 739 725-729	M05-M06, M15-M19, M07, M10, M11-M14, M30-M36, M00-M03, M20-M25, M65-M79	Sulfasalazine, Minocycline, Cyclophosphamide, Methotrexate, Cyclosporine, Leflunomide, Azathioprine, Methotrexate, Sodium Aurothiomalate, Auranofin, Aurothioglucose, Penicillamine, Hydroxychloroquine, Etanercept, Infliximab, Anakinra, Adalimumab, Oxycodone, Pentazocine, Morphine combinations, Codeine, combinations excluding psycholeptics, Codeine in combination, Acetaminophen, Acetaminophen in combination with codeine, Hydrocodone, Codeine, Opium alkaloids with morphine, Methylprednisolone, Prednisolone, Prednisone, Triamcinolone, Cortisone, Valdecoxib, Phenylbutazone, Indometacin, Sulindac, Tolmetin, Diclofenac, Etodolac, Ketorolac, Diclofenac in combination, Piroxicam, Tenoxicam, Meloxicam, Ibuprofen, Naproxen, Ketoprofen, Fenoprofen, Flurbiprofen, Tiaprofenic acid, Oxaprozin, Mefenamic acid, Celecoxib, Rofecoxib, Nabumetone, Anti–inflammatory agents for topical use, Capsicum, Preparation with salicylic acid derivations, Dimethyl sulfoxide, Preparation inhibiting uric acid production, Acetylsalicylic acid, Choline salicylate, Diflunisal

Table 4.5
Diagnosis Codes and Drugs Used in the Analyses to Define Diseases (continued)

Disease	ICD-9-CM Diagnosis Codes	ICD-10-CA Diagnosis Codes	Generic Drug names
Dementia[b]	290, 291, 292, 294, 331, 797	F00, F01, F02, F03, F04, F05.1, F06.5, F06.6, F06.8, F06.9, F09, F10 – F19, G30, G31.0, G31.1, G31.9, G32.8, G91, G93.7, G94, R54 (but not including: F10.0, F10.1, F10.2, F10.3, F10.4, F10.8, F10.9, F11.1, F11.2, F12.1, F12.2, F13.1, F13.2, F14.1, F14.2, F15.1, F15.2, F16.1, F16.2, F17.1, F17.2, F18.1, F18.2, F19.1, F19.2)	N/A
Parkinson's Disease	332.0	G20	Levodopa, levodopa and decarboxylase inhibitor, bromocriptine, pergolide, ropinirole, pramipexole, selegiline, rasagiline, amantadine
Schizophrenia[c]	295	F20, F21, F23.2, F25	N/A

Note. N/A, not applicable.
[a]Source: Lix, L., Yogendran, M., & Mann, J. (2008). *Defining and validating chronic diseases: an administrative data approach. An update with ICD-10-CA,* Winnipeg, Manitoba: Manitoba Centre for Health Policy. [b]Source: Martens, P. J., Bartlett, J., Burland, E., Prior, H., Burchill, C., Huq, S. et al. (2010). *Profile of Metis health status and healthcare utilization in Manitoba: A population-based study,* Winnipeg, Manitoba: Manitoba Centre for Health Policy. [c]Source: Doupe, M., Kozyrskyj, A., Soodeen, R., Derksen, S., Burchill, C., Huq, S. (2008). *An initial analysis of emergency departments and urgent care in Winnipeg,* Winnipeg, Manitoba: Manitoba Centre for Health Policy.

Table 4.6

Summary of Change in Estimate[a] (CIE) Analyses: Main Exposure is Atypical Antipsychotic Drug (AAD) Use

Variables	OR	(95% CI)	% CIE[b]
Base model[c]	1.09	(0.88-1.36)	
Proximity to death	1.14	(0.91-1.43)	4.2
Parkinson's disease	1.17	(0.94-1.47)	2.8
Hypertensives & diuretics	1.20	(0.96-1.51)	2.4
Incontinence	1.22	(0.97-1.53)	1.1
Typical antipsychotics	1.19	(0.95-1.50)	-0.8
Dementia	1.20	(0.95-1.51)	-0.6
Unsteady gait	1.20	(0.95-1.50)	-0.5
Foot problem	1.20	(0.95-1.50)	-0.5
Comorbidity	1.20	(0.95-1.50)	-0.5
Arthritis	1.20	(0.95-1.51)	-0.3
Marital status	1.20	(0.96-1.51)	-0.2
Range of motion	1.20	(0.96-1.51)	-0.1
Physical restraint use	1.20	(0.96-1.51)	-0.1
Opioid analgesics	1.20	(0.96-1.51)	0.0

Note. OR = odds ratio; CI = confidence intervals.
[a]CIE was calculated as ((adjusted OR - crude OR)/adjusted OR)*100. [b]The percent change in the estimate of the AAD use due to the inclusion of this variable. [c]Base model is adjusted for activities of daily living, balance problem, antidepressant use, benzodiazepine use, number of different drugs, wandering, cognitive impairment, and fall history.

Table 4.7

List of Selected Confounders

Selecting Approach	Selected Confounders
Literature	Activities of daily living
	Balance problem
	Antidepressant use
	Benzodiazepine use
	Number of different drugs
	Cognitive impairment
	Fall history
Change in estimate	Proximity to death
	Parkinson's disease
	Antihypertensives and diuretics use

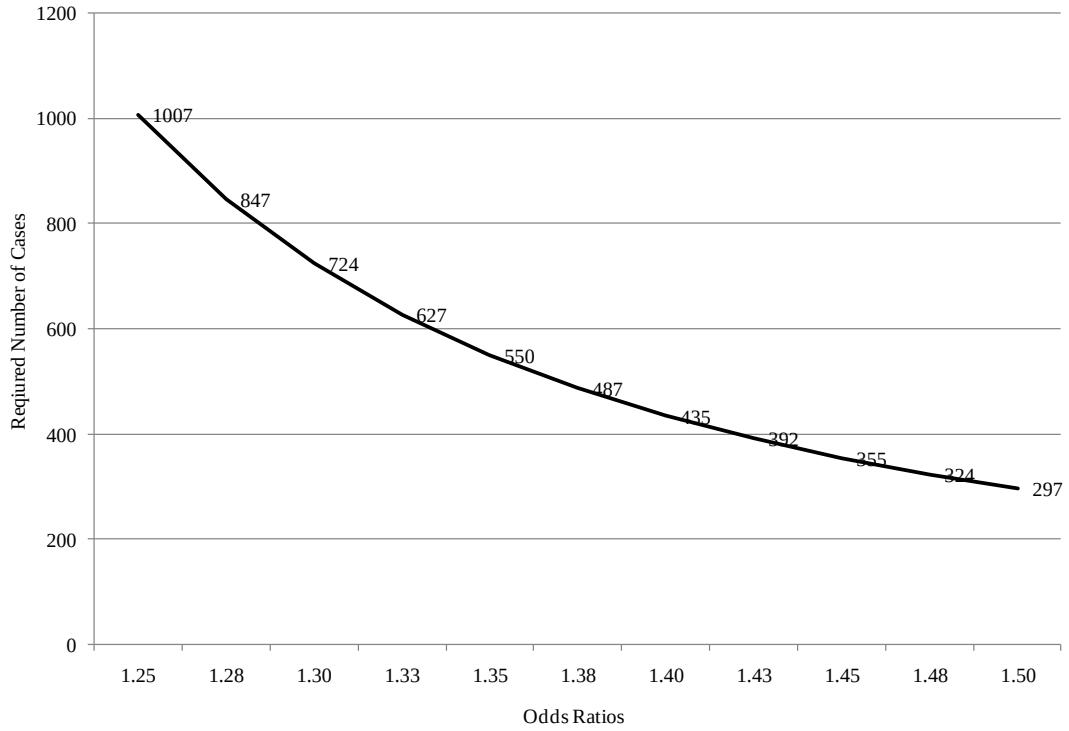

Figure 4.7 Sample size calculation for a range of odds ratios in a matched case-control study, assuming a type I error rate (α)=0.05, power=0.8, exposure prevalence=30%, and correlation of exposure prevalence in matching sets=0.2.

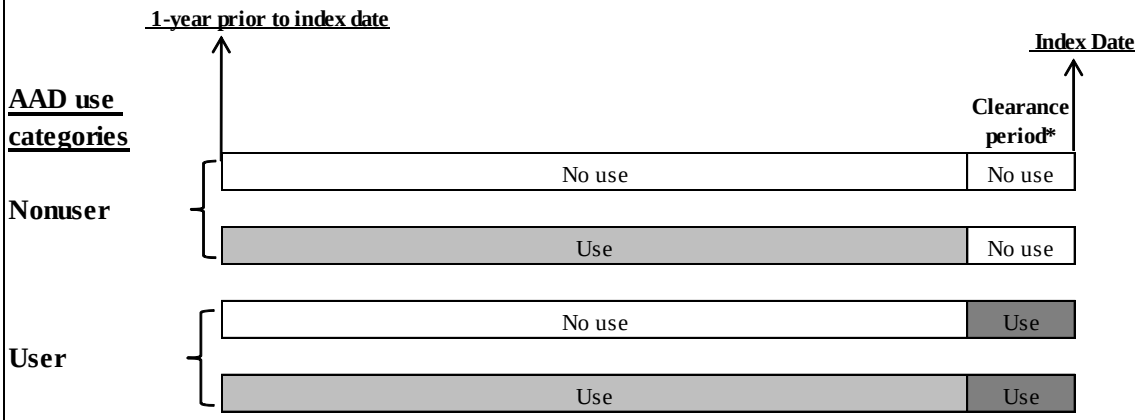

Figure 4.8 Measurement of atypical antipsychotic drug (AAD) use for hospital fall data-based analysis. MDS = Minimum Data Set for personal care homes. *Clearance period was 4 days for risperidone, 10 days for olanzapine, and 2 days for quetiapine. For persons on two or more different types of AADs, the clearance period was based on the drug with the longest elimination half-life.

Chapter 5

Study Results

This chapter provides a detailed review of the descriptive, unadjusted conditional logistic regression (CLR), and adjusted CLR results. As per the section entitled "Additional Analyses" in the Methods chapter, a sensitivity analysis was also conducted on subgroups of AAD users, where drug exposure definitely preceded the fall event. A summary of these results are provided in this chapter. Similarly, analyses were also conducted using the hospital fall data, where actual hospitalized fall dates are recorded. These analyses provide some insight as to the extent that the current study design (i.e., not having an actual fall date in the MDS data) affects study results.

Descriptive Analyses

Characteristics of cases, controls, and source cohort.

Matching variables.

Within the assembled study cohort, cases were matched to four controls on length of PCH stay, age, and sex as per incidence density sampling (see Chapter 5-"Methods" for detailed information on how cases and controls were selected). Table 5.1 compares cases and controls based on these matching variables. Overall, controls were well-matched to cases in terms of their length of personal care home (PCH) stay, age, and sex. The average length of PCH stay was 21.4 months (standard deviation (SD) 15.5) for cases and 21.7 months (SD 15.5) for controls. The majority of the cases and controls were older than age 85 years. The average age of cases was 87.3 years (SD 6.9) as

compared to 87.4 years (SD 6.4) for controls. Furthermore, 74.6% of cases versus 76.8% of controls were female.

Selected cases and controls were also similar to the overall (source) cohort (Table 5.1). For example, the average age of the source cohort was 87.2 years (SD 7.1) as compared to 87.4 years (SD 6.5) for selected cases and controls. However, the source cohort had a slightly higher average length of PCH stay (27.3 months, SD 16.0), as compared to cases and controls (21.6 months, SD 15.5). This variability in PCH length of stay supports the literature showing that new PCH residents fall more frequently. This would mean that cases selected in the research, and therefore matched controls, would have shorter lengths of stay versus the overall (source) cohort.

Study covariates.

This section compares the characteristics of cases and controls based on the different categories of study covariates (see Figure 4.5 in Chapter 4-Methods).

Function-related measures.

Overall, the distribution of function-related measures varied between cases and controls (see Table 5.2). In general, more cases versus controls had some type of functional challenge, with the exception of range of motion. For example, unsteady gait and foot problems were more common in cases than in controls. Further, for non-dichotomous measures (activities of daily living [ADL] and balance), a greater proportion of cases tended to have partial challenges, while more controls had significant functional challenges. For example, a higher portion of cases (78.6%) versus controls (56.7%) were

partially dependent when completing ADL tasks. Conversely, more controls (22.3%) versus cases (9.1%) were totally dependent when completing these tasks.

Other drug use-related measures.

Overall, the distribution of other drug use measures was similar between cases and controls, with the exception that slightly more cases were current antidepressant and heavy drug users (nine and more drugs) (see Table 5.3). For example, 35.3% of cases were current users of antidepressants compared to 29.2% of controls. Similarly, 8.6% of cases were heavy drug users as compared to 6.7% of controls. Furthermore, a larger proportion of cases versus controls were partial users of antihypertensives and diuretics (6.9% of cases versus 3.7% of controls).

Medical health conditions, cognition, and other measures.

In general, a greater proportion of cases versus controls had some type of medical health conditions, especially as it relates to fall history, wandering, being proximal to death, and having some type of physical restraint use (see Table 5.4). For example, 18.4% of cases were shown to wander frequently as compared to only 7.5% of controls. Also, a higher proportion of cases (14.7%) were proximal to death versus controls (5.4%). Similar to function measures, in some but not all instances a greater proportion of cases tended to have less severe medical challenges, while controls were more severely impaired. For example, while a high proportion of cases (70.1%) versus controls (58.4%) had partial cognitive impairment, more controls (8.5%) versus cases (2.6%) were severely impaired. This similar trend is reported for levels of incontinence and physical restraint use, but not for comorbidity levels.

Patterns of atypical antipsychotic drug use.

Table 5.5 compares cases and controls by patterns of AAD use, type, and dose. Overall, these distributions differed quite substantially between cases and controls. For instance, a larger proportion of cases (30.2%) versus controls (23.8%) were defined as AAD users. Amongst AAD users, risperidone was the most commonly dispensed AAD type for both cases (61.9%) and controls (67.4%). While a larger proportion of cases (17.4%) versus controls (11.8%) were dispensed quetiapine, the opposite trend as found for olanzapine. Overall, 13.8% of cases were dispensed this drug as compared to 15.7% of controls. Lastly, a larger proportion of cases (15.9%) versus controls (9.1%) were prescribed higher doses of AADs. This trend was consistent within individual AAD types, as a greater proportion of cases versus controls were dispensed higher dose drugs (see Table 5.6). This was especially true, however, for risperidone and quetiapine, and was much less the case for olanzapine. As another way to summarize these results, quetiapine is the only drug in which a higher proportion of cases versus control were dispensed this medication, at both the high and low dose.

Characteristics of atypical antipsychotic drug users.

This section compares the characteristics of AAD users and nonusers based on the different categories of select study covariates. To avoid correlated data, analysis was limited to only the first instance (earliest index date) of a subject who was sampled repeatedly.

Function- and other drug use- related measures.

Overall, the distribution of function-related measures varied slightly between users and nonusers of AADs (see Table 5.7). In general, a greater proportion of users tended to have partial functional challenges, while nonusers had greater proportion of significant functional challenges. For example, a higher proportion of users (67.5%) versus nonusers (59.6%) were partially dependent when completing ADL tasks. Conversely, more nonusers (21.2%) versus users (18.2%) were totally dependent when completing these tasks.

Overall, the distribution of other drug use measures varied between users and nonusers of AADs, with the exception that distribution of antihypertensive and diuretic use was similar across these groups (see Table 5.7). For example, 38.9% of AAD users were current users of antidepressants compared to 28.4% of nonusers. Similarly, 22.8% of AAD users were also benzodiazepine users as compared to 17.2% of nonusers. Furthermore, a slightly larger proportion of AAD users (8.0%) versus nonusers (7.1%) were heavy drug users (nine or more different drugs).

Medical health conditions, cognition, and other measures.

In general, a greater proportion of AAD users versus nonusers had some type of cognitive challenge (see Table 5.8). For example, 21.0% of AAD users were shown to wander frequently as compared to only 7.6% of nonusers. Also, a high proportion of AAD users (75.2%) versus nonusers (55.1%) had partially impaired cognitive performance. However, the distribution of fall history and proximity to death was similar between users and nonusers. For example, 17.2% of users had a fall history compared to 15.7% of nonusers. Similarly, 7.6% of users were proximal to death as compared to 8.5%

of users. Furthermore, a slightly higher proportion of nonusers versus users had Parkinson's disease (20.5% of cases versus 24.5% of controls).

Unadjusted Results

Effect of atypical antipsychotic drug use on the risk of falling.

Compared to nonusers, the odds of falling was 1.87 fold greater for AAD users (95% confidence intervals [CI] 1.35-2.59) (see Table 5.9). As per specific AAD types, as compared to non-users, the odds of falling was 2.60 fold greater for quetiapine users (95% CI 1.51-4.48), and 1.84 fold greater for risperidone users (95% CI 1.18-2.86). However, the odds of falling was only 36% higher in olanzapine users compared to nonusers (OR = 1.36, 95% CI 0.84-2.18). Furthermore, both low and high dose AAD users in general were at greater risk of falling versus nonusers. As compared to nonusers, high dose AAD users were 2.39 times more likely to fall during the study period (95% CI 1.35-4.22). Similarly, the odds of falling was 1.46 times greater in low dose AAD users compared to nonusers (OR = 1.46, 95% CI 1.11-1.94).

Without adjustment for other covariates, although AAD dose and type interactions were found to be non-significant (P-value for interaction = 0.163), significantly different dose trends were reported within select AAD types (Table 5.9). For example, compared to nonusers, the odds of falling was only significantly greater for high dose risperidone users (OR = 2.79; 95% CL 1.21-6.46), but was significantly higher for both low (OR = 1.84, 95% CI 1.13-3.01) and higher dose (OR = 3.67, 95% CI 1.41-9.57) quetiapine users. These results coincide with descriptive findings (see Table 5.6),

where, descriptively, more cases versus controls were dispensed quetiapine, regardless of dose, and also higher doses of risperidone.

Adjusted Results

Effect of atypical antipsychotic drug use on the risk of falling.

After adjustment for select confounders (see section "Adjustment for confounding" in Chapter 4- Methods for detailed information on the selection of confounders), the adjusted odds of falls by AAD drug use category are presented in Table 5.10. These results show trends similar to both the descriptive and univariate findings. For example, the adjusted odds of falling were 60% greater for AAD users as compared to nonusers (95% CI 1.10-2.32). Further, among AAD types, the adjusted odds of falling was significantly greater in quetiapine (adjusted OR = 2.41, 95% CI 1.33-4.36) and risperidone users (adjusted OR = 1.94, 95% 1.18-3.17) compared to nonusers. There was no statistically significant association between olanzapine use and the risk of falling (adjusted OR = 1.11, 95%CI 0.66-1.85). Furthermore, the likelihood of falling did not differ by AAD dose generally, as both low and high dose AAD users were at increased risk of falling compared to nonusers. As compared to nonusers, the odds of falling was 1.34 fold greater for low dose AAD users (95% CI 0.99-1.82), and 1.90 fold greater for high dose AAD users (95% CI 1.00-3.63).

Similar to univariate findings, after adjustment for select confounders, while AAD dose and type interactions were found to be non-significant (P-value for interaction = 0.140), different dose trends were reported within certain AAD types (Table 5.10). For example, while low dose risperidone use was not associated with an increased risk of

falling (adjusted OR = 1.20, 95% CI 0.92-1.56), high dose risperidone users were 3.13 times at greater risk of falling compared to nonusers (95% CI 1.23-7.94). Similarly, compared to nonusers, the odds of falling was significantly greater for high dose quetiapine users (adjusted OR = 3.60; 95% CL 1.27-10.17), and a similar trend, while not statistically significant, was reported for lower quetiapine users, likely due to small sample size (adjusted OR = 1.62, 95% CI 0.94-2.77). Conversely, the odds of falling were similar for olanzapine users irrespective of dose of this drug.

Association between select confounders and the risk of falling.

Function- and other drug use- related measures.

Table 5.11 show the adjusted ORs (95% CI) for select function- and other drug use-related variables in the final adjusted CLR model. Similar to descriptive findings, these results show that, after adjustment for all other covariates, the odds of falling was greater for residents with some but not severe functional limitations (i.e., ADL and balance problems). Also similar to descriptive findings, the adjusted odds of falling was significantly greater for heavy drug users (nine and more drugs) (adjusted OR = 1.84, 95% CI 1.07-3.19), and was also significantly greater for current antidepressant users (adjusted OR = 1.26, 95% CI 1.02-1.56). Lastly, there was a significant reverse association between current users of antihypertensive and diuretic drugs and the risk of falling (adjusted OR = 0.74, 95% CI 0.56-0.92).

Medical health conditions, cognition, and other measures.

Table 5.12 shows the adjusted CLR model results to test the effect of other medical conditions, cognition, and other measures on the risk of falling. After adjustment

for all remaining covariates, each of these measures was significantly associated with the odds of falling, with exception of cognitive performance. For instance, the adjusted odds of falling was greater for participants diagnosed with versus without Parkinson's disease (adjusted OR = 1.36. 95% CI=1.20-1.80), and was also significantly greater for patients who had a history of falls (adjusted OR=1.52; 95% CI=1.18-1.96), and who were closer to death at the time of the fall (adjusted OR=3.48; 95% CI=2.53-4.78).

Interaction analyses.

Analyses were also conducted to test if the effect of AAD use depended on select person characteristics. Tables 5.13 and 5.14 show the results from a series of models that examined the interaction effect between main effect of AAD use and each study covariate. There was evidence for an interaction with wandering (P-value for interaction=0.075) (see Table 5.14). This result demonstrates that, while AAD use was not associated with risk of falling for people who didn't have wandering problems (adjusted OR = 1.09, 95% CI 0.85-1.41), significant association was observed for individuals who had wandering problems (adjusted OR = 1.84, 95% CI 1.09-3.09). Further, while there were no evidence of a significant interaction between AAD use and any other selected confounders, the odds of falling was significantly greater for AAD users who were partially ADL dependent (adjusted OR = 1.29, 95% CI 1.00-1.66) (see Table 5.13); conversely, the odds of falling was reduced significantly for AAD users who had partial cognitive impairments (adjusted OR = 0.78, 95% CI 0.60-1.00) (see Table 5.14).

Additional Analyses

Summary of sensitivity analyses results.

As described in the section entitled "Sensitivity analysis" (see Chapter 4-"Methods"), additional analysis was conducted by on subgroups of AAD users where drug exposure definitely preceded the fall event (subgroups 4 and 5 in Figure 4.5). The results from this analysis are shown in Tables 5.15 to 5.18.

Overall, the unadjusted (see Table 5.15) and adjusted results (see Table 5.16) from this sensitivity analysis are similar to the main study findings. For example, this analysis demonstrates that the adjusted odds of falling was 1.71 fold greater (95% CI 1.12-2.62) for AAD users versus nonusers. This was true for both high and low dose quetiapine users, with an adjusted OR of 3.42 (95% 1.08-10.79) and 1.72 (95% CI 0.98-3.03) respectively, and for high dose risperidone users, with adjusted OR of 2.85 (95% CI 1.07-7.58). In addition, similar to the main findings, olanzapine users were not associated with an increased risk of falling regardless of this drug's dose.

Sensitivity analyses were also conducted to test if the effect of AAD depended on select person characteristics (see Tables 5.17 and 5.18). Similar to the main findings, evidence suggests an interaction with wandering (P-value for interaction=0.122). While AAD use was not associated with risk of falling among people who didn't have wandering problems (adjusted OR = 1.07, 95% CI 0.82-1.40), the adjusted odds of falling was 1.72 times greater in AAD users versus nonusers among individuals who had wandering problems (95% CI 1.00-2.98) (see Table 5.18). There were no evidence of significant interaction between AAD use and any other selected confounders.

Summary of hospital fall data-based analyses results.

As described in the section entitled "Sensitivity analysis" (see Chapter 4-Methods), additional analyses were conducted on the entire sample of main analysis using hospital fall data, where an exact hospitalized fall date was measured, to investigate the extent that the lack of a specific fall date in MDS influenced the study results. The results from this analysis are shown in Tables 5.19 to 5.22.

Overall, the association between AADs and being a hospitalized faller followed similar trends to the main analysis using the MDS fall data. However, in general, these latter estimates did not reach statistically significance level, likely due to small sample size. As one exception, the adjusted odds of falling for high dose quetiapine users was significantly greater compared to nonusers (adjusted OR = 12.34, 95% CI 1.20-127.99) (see Table 5.20).

Tests of interaction effects were also similar to the main study findings (see Tables 5.21 and 5.22). There was signification interaction between AAD use and wandering (P-value for interaction=0.091), where the adjusted odds of falling was 2.50 times greater for AAD users who had wandering problems (95% CI 0.79-7.91). This trend was much less evident for AAD users who didn't have wandering problems (adjusted OR = 0.82, 95% CI 0.41-1.55), (see Table 5.22). In addition, these hospital - based analysis showed that there was a significant interaction between AAD use and cognitive performance (P-value for interaction = 0.013). The odds of falling was reduced significantly for AAD users who had partial cognitive impairments (adjusted OR = 0.27, 95% CI 0.08-0.97). This trend was not shown for people who were cognitively intact (adjusted OR = 1.67, 95% CI 0.86-3.23).

Chapter Summary

Analyses of the linked MDS and administrative data demonstrate that AAD users were at greater risk of falling compared to nonusers. However, this association was especially true for quetiapine, regardless of its dose, and high dose risperidone users. Further, olanzapine was not associated with risk of falling regardless of its dose. The effect of AAD use in general on the risk of falling was significantly greater for people with wandering problems. Overall, sensitivity and hospital fall data-based analyses results showed a similar trend in these results. This consistency in findings helps to minimize concerns regarding the development of AAD use groups in this study, and lack of a fall date in MDS data.

Table 5.1
Characteristics of Cases, Controls, and the Source Cohort on Matching Variables[a]

Values are numbers (percentages) unless stated otherwise.

Matching variables	Cases (n=626)	Controls (n=2,388)	Total of Cases & Controls (n=3,014)	Source Cohort (n=8,753)
Length of PCH stay (months)				
Mean (SD)	21.4 (15.5)	21.7 (15.5)	21.6 (15.5)	27.3 (16.0)
1-6	146 (23.3)	573 (24.0)	719 (23.9)	1,249 (14.3)
7-12	96 (15.3)	330 (13.8)	426 (14.1)	1,059 (12.1)
13-24	127 (20.3)	489 (20.5)	616 (20.4)	1,615 (18.5)
25-36	95 (15.2)	381 (16.0)	476 (15.8)	1,577 (18.0)
>=37	162 (25.9)	615 (25.8)	777 (25.8)	3,253 (37.2)
Age group				
Mean (SD)	87.3 (6.9)	87.4 (6.4)	87.4 (6.5)	87.2 (7.1)
65-74	27 (4.3)	66 (2.8)	93 (3.1)	481 (5.5)
75-84	179 (28.6)	688 (28.8)	867 (28.8)	2,462 (28.1)
85-94	329 (52.6)	1304 (54.6)	1,633 (54.2)	4,473 (51.1)
95+	91 (14.5)	330 (13.8)	421 (14.0)	1,337 (15.3)
Sex				
Female	467 (74.6)	1835 (76.8)	2,302 (76.4)	6,990 (79.9)
Male	159 (25.4)	553 (23.2)	712 (23.6)	1,763 (20.1)

Note. PCH = personal care home; SD = standard deviation.
[a]Results for cases and controls ignore the distribution within each case-control set.

Table 5.2
Distribution of Function-Related Measures by Cases and Controls, n(%)

Measures	Cases (n=626)	Controls (n=2,388)	Total of Cases & Controls (n=3,014)
Activities of daily living[b]			
Independent	77 (12.3)	503 (21.0)	580 (19.2)
Partially dependent	492 (78.6)	1,353 (56.7)	1,845 (61.2)
Totally dependent	57 (9.1)	532 (22.3)	589 (19.5)
Unsteady gait			
No	425 (67.9)	1,896 (79.4)	2,321 (77.0)
Yes	201 (32.1)	492 (20.6)	693 (23.0)
Balance problem while standing			
Steady	122 (19.5)	590 (24.7)	712 (23.6)
Partially unsteady	277 (44.3)	698 (29.2)	975 (32.4)
Totally unsteady	227 (36.2)	1,100 (46.1)	1,327 (44.0)
Foot problem			
No	467 (74.6)	1,882 (78.8)	2,349 (77.9)
Yes	159 (25.4)	506 (21.2)	665 (22.1)
Limitation in range of motion			
No	300 (47.9)	1,071 (44.9)	1,371 (45.5)
Yes	326 (52.1)	1,317 (55.1)	1,643 (54.5)

[a]Results for cases and controls ignore the distribution within each case-control set. [b]This variable was derived from the activities of daily living long form summary scale which is provided as a part of the MDS system. It includes bed mobility, transfer, locomotion, dressing, eating, toilet use, and personal hygiene tasks.

Table 5.3

Distribution of Other Drug-Use Related Measures by Cases and Controls, n(%)[a]

Measures	Cases (n=626)	Controls (n=2,388)	Total of Cases & Controls (n=3,014)
Antidepressant use			
Nonuser	377 (60.2)	1,609 (67.4)	1,986 (65.9)
Partial user	28 (4.5)	81 (3.4)	109 (3.6)
Current user	221 (35.3)	698 (29.2)	919 (30.5)
Benzodiazepine use			
Nonuser	467 (74.6)	1,821 (76.3)	2,288 (75.9)
Partial user	34 (5.4)	96 (4.0)	130 (4.3)
Current user	125 (20.0)	471 (19.7)	596 (19.8)
Typical antipsychotic use			
Nonuser	601 (96.0)	2,301 (96.3)	2,902 (96.3)
Partial user	7 (1.1)	14 (0.6)	21 (0.7)
Current user	18 (2.9)	73 (3.1)	91 (3.0)
Antihypertensive & diuretic use			
Nonuser	233 (37.2)	863 (36.1)	1,096 (36.4)
Partial user	43 (6.9)	89 (3.7)	132 (4.4)
Current user	350 (55.9)	1,436 (60.2)	1,786 (59.3)
Opioid analgesic use			
Nonuser	541 (86.4)	2,065 (86.4)	2,606 (86.5)
Partial user	43 (6.9)	133 (5.6)	176 (5.8)
Current user	42 (6.7)	190 (8.0)	232 (7.7)
Number of different drugs			
Nonuser	37 (5.9)	201 (8.4)	238 (7.9)
User (1-8 drugs)	535 (85.5)	2,028 (84.9)	2,563 (85.0)
Heavy user (9+ drugs)	54 (8.6)	159 (6.7)	213 (7.1)

[a]Results for cases and controls ignore the distribution within each case-control set.

Table 5.4
Distribution of Other Medical Health Conditions, Cognition, and Other Measures by Cases and Controls, n (%)[a]

Measures	Category	Cases (n=626)	Controls (n=2,388)	Total of Cases & Controls (n=3,014)
Other medical health conditions related measures				
Arthritis	No	172 (27.5)	618 (25.9)	790 (26.2)
	Yes	454 (72.5)	1,770 (74.1)	2,224 (73.8)
Parkinson's disease	No	448 (71.6)	1,889 (79.1)	2,337 (77.5)
	Yes	178 (28.4)	499 (20.9)	677 (22.5)
Comorbidity level	Low	217 (34.6)	876 (36.7)	1,093 (36.3)
	Medium	329 (52.5)	1,249 (52.3)	1,578 (52.4)
	High	80 (12.9)	263 (11.0)	343 (11.3)
Continence	Continent	259 (41.4)	1,079 (45.2)	1,338 (44.4)
	Partially incontinent	239 (38.1)	635 (26.6)	874 (29.0)
	Frequently incontinent	128 (20.5)	674 (28.2)	802 (26.6)
Cognition related measures				
Dementia	No	79 (12.6)	339 (14.2)	418 (13.9)
	Yes	547 (87.4)	2,049 (85.8)	2,596 (86.1)
Wandering	No	511 (81.6)	2,208 (92.5)	2,719 (90.2)
	Yes	115 (18.4)	180 (7.5)	295 (9.8)
Cognitive performance[b]	Intact	171 (27.3)	791 (33.1)	962 (31.9)
	Partially impaired	439 (70.1)	1,393 (58.4)	1,832 (60.8)
	Severely impaired	16 (2.6)	204 (8.5)	220 (7.3)
Other measures				
Marital status	Married	137 (21.9)	429 (18.0)	566 (18.8)
	Not married	489 (78.1)	1,959 (82.0)	2,448 (81.2)
Fall history	No	493 (78.8)	2,087 (87.4)	2,580 (85.6)
	Yes	133 (21.3)	301 (12.6)	434 (14.4)
Proximity to death	<=180 days	92 (14.7)	130 (5.4)	222 (7.4)
	181+ days	534 (85.3)	2,258 (94.6)	2,792 (92.6)
Physical restraint use	No	198 (31.6)	635 (26.6)	833 (27.6)
	Half rail only	353 (56.4)	1,259 (52.7)	1,612 (53.5)
	Other restraints	75 (12.0)	494 (20.7)	569 (18.9)

[a]Results for cases and controls ignore the distribution within each case-control set. [b]This variable was derived from cognitive performance scale which is provided as a part of the MDS system. It includes comatose, short-term memory, cognitive skills for daily decision-making, making self understood, and eating.

Table 5.5

Patterns of Atypical Antipsychotic Drug (AAD) Use by Cases and Controls, n(%)[a]

Category of AAD use	Cases (n=626)	Controls (n=2,388)	Total of Cases & Controls (n=3,014)
AAD user			
Nonuser	437 (69.8)	1,820 (76.2)	2257 (74.9)
User	189 (30.2)	568 (23.8)	757 (25.1)
Type			
Risperidone	117 (61.9)	383 (67.4)	500 (66.1)
Olanzapine	26 (13.8)	89 (15.7)	115 (15.2)
Quetiapine	33 (17.4)	67 (11.8)	100 (13.2)
Multiple[b]	13 (6.9)	29 (5.1)	42 (5.5)
Dose			
Low Dose	159 (84.1)	516 (90.9)	675 (89.2)
High Dose	30 (15.9)	52 (9.1)	82 (10.8)

[a]Results for cases and controls ignore the distribution within each case-control set. [b]Multiple users include users on two or more types of AADs.

Table 5.6
Cross Tabulation of Dose and Type of Atypical Antipsychotic Drugs (AADs) by Cases and Controls, n(%)[a]

Type of AADs	Dose of AADs	Cases (n=189)	Controls (n=568)	Total of Cases & Controls (n=757)
Risperidone				
	Low dose	107 (56.6)	369 (65.0)	476 (62.9)
	High dose	10 (5.3)	14 (2.5)	24 (3.2)
Olanzapine				
	Low dose	16 (8.5)	64 (11.3)	80 (10.6)
	High dose	10 (5.3)	25 (4.4)	35 (4.6)
Quetiapine				
	Low dose	25 (13.2)	58 (10.2)	83 (11.0)
	High dose	8 (4.2)	9 (1.6)	17 (2.2)
Multiple[b]				
	Low dose	11 (5.8)	25 (4.4)	36 (4.8)
	High dose	s	s	6 (0.8)

Note. s = data suppressed due to small sample size (n=1-5).
[a]Results for cases and controls ignore the distribution within each case-control set. [b]Multiple users include users on two or more types of AADs.

Table 5.7
Distribution of Function- and Other Drug Use-Related Measures by Atypical Antipsychotic Drug (AAD) Use, n(%)

Measures	Categories of AAD use		
	Nonuser (n=1,182)	**User** (n=424)	**Total** (n=1,606)
Function-related measures			
Activity of daily living[a]			
Independent	228 (19.3)	61 (14.3)	289 (18.0)
Partially dependent	704 (59.6)	286 (67.5)	990 (61.6)
Totally dependent	250 (21.1)	77 (18.2)	327 (20.4)
Balance problem			
Steady	255 (21.6)	112 (26.4)	367 (22.9)
Partially unsteady	382 (32.3)	150 (35.4)	532 (33.1)
Totally unsteady	545 (46.1)	162 (38.2)	707 (44.0)
Other drug use-related Measures			
Antidepressant use			
Nonuser	805 (68.1)	239 (56.4)	1044 (65.0)
Partial user	41 (3.5)	20 (4.7)	61 (3.8)
Current user	336 (28.4)	165 (38.9)	501 (31.2)
Benzodiazepine use			
Nonuser	926 (78.3)	297 (70.1)	1223 (76.1)
Partial user	53 (4.5)	30 (7.1)	83 (5.2)
Current user	203 (17.2)	97 (22.8)	300 (18.7)
Antihypertensive & diuretic use			
Nonuser	449 (38.0)	164 (38.7)	613 (38.2)
Partial user	61 (5.1)	18 (4.2)	79 (4.9)
Current user	672 (56.9)	242 (57.1)	914 (56.9)
Number of different drugs			
Nonuser	123 (10.4)	7 (1.7)	130 (8.1)
User (1-8 drugs)	975 (82.5)	383 (90.3)	1358 (84.5)
Heavy user (9+ drugs)	84 (7.1)	34 (8.0)	118 (7.4)

[a]This variable was derived from activity of daily living long form summary scale which is provided as a part of the MDS system. It includes bed mobility, transfer, locomotion, dressing, eating, toilet use, and personal hygiene tasks.

Table 5.8

Distribution of Other Medical Health Conditions, Cognition, and Other Measures by Atypical Antipsychotic Drug (AAD) Use, n(%)

Measures	Categories of AAD use		
	Nonuser (n=1,182)	**User** (n=424)	**Total** (n=1,606)
Medical health conditions-related measure			
Parkinson's disease			
No	893 (75.5)	337 (79.5)	1,230 (76.6)
Yes	289 (24.5)	87 (20.5)	376 (23.4)
Cognition-related measures			
Wandering			
No	1,092 (92.4)	335 (79.0)	1,427 (88.9)
Yes	90 (7.6)	89 (21.0)	179 (11.1)
Cognitive performance[a]			
Intact	435 (36.8)	72 (17.0)	507 (31.6)
Partially impaired	651 (55.1)	319 (75.2)	970 (60.4)
Severely impaired	96 (8.1)	33 (7.8)	129 (8.0)
Other measures			
Fall history			
No	997 (84.4)	351 (82.8)	1,348 (83.9)
Yes	185 (15.6)	73 (17.2)	258 (16.1)
Proximity to death			
1-180 days	101 (8.5)	32 (7.5)	133 (8.3)
181+ days	1,081 (91.5)	392 (92.5)	1,473 (91.7)

[a]This variable was derived from cognitive performance scale which is provided as a part of the MDS system. It includes comatose, short-term memory, cognitive skills for daily decision-making, making self understood, and eating.

Table 5.9
Unadjusted Analyses: Effect of Atypical Antipsychotic Drug (AAD) Use on the Risk of Falling[a]

Categories of AAD use	OR	(95% CI)	P-value
AAD user			
Nonuser		Reference group	
User	1.87	(1.35-2.59)	0.001
Type			
Nonuser		Reference group	
Risperidone	1.84	(1.18-2.86)	0.007
Olanzapine	1.36	(0.84-2.18)	0.208
Quetiapine	2.60	(1.51-4.48)	0.001
Multiple[b]	1.89	(0.75-4.78)	0.181
Dose			
Nonuser		Reference group	
Low Dose	1.46	(1.11-1.94)	0.008
High Dose	2.39	(1.35-4.22)	0.003
Type and Dose Interaction			
Nonuser		Reference group	
Risperidone			
Low dose	1.21	(0.95-1.54)	0.115
High dose	2.79	(1.21-6.46)	0.017
Olanzapine			
Low dose	1.05	(0.60-1.83)	0.872
High dose	1.76	(0.83-3.70)	0.139
Quetiapine			
Low dose	1.84	(1.13-3.01)	0.015
High dose	3.67	(1.41-9.57)	0.008
Multiple[b]			
Low dose	1.96	(0.95-4.06)	0.071
High dose	1.82	(0.33-10.04)	0.493
$P_{interact}$			0.163

Note. OR = odds ratio; CI = confidence intervals.
[a]These estimates were from cases and controls matched on length of PCH stay, age, and sex. [b]Multiple users include users on two or more types of AADs.

Table 5.10
Adjusted Analyses: Effect of Atypical Antipsychotic Drug (AAD) Use on the Risk of Falling[a]

Categories of AAD use	OR	(95% CI)	P-value
AAD user			
Nonuser		Reference group	
User	1.60	(1.10-2.32)	0.013
Type			
Nonuser		Reference group	
Risperidone	1.94	(1.18-3.17)	0.009
Olanzapine	1.11	(0.66-1.85)	0.691
Quetiapine	2.41	(1.33-4.36)	0.004
Multiple[b]	1.26	(0.44-3.62)	0.664
Dose			
Nonuser		Reference group	
Low Dose	1.34	(0.99-1.82)	0.059
High Dose	1.90	(1.00-3.63)	0.051
Type and Dose Interaction			
Nonuser		Reference group	
Risperidone			
Low dose	1.20	(0.92-1.56)	0.188
High dose	3.13	(1.23-7.94)	0.016
Olanzapine			
Low dose	0.95	(0.52-1.71)	0.851
High dose	1.30	(0.58-2.92)	0.519
Quetiapine			
Low dose	1.62	(0.94-2.77)	0.081
High dose	3.60	(1.27-10.17)	0.016
Multiple[b]			
Low dose	1.78	(0.82-3.86)	0.145
High dose	1.90	(0.13-6.28)	0.912
$P_{interact}$			0.140

Note. OR = odds ratio; CI = confidence intervals.
[a]Model adjusted for activities of daily living, balance problem, antidepressant use, benzodiazepine use, antihypertensive or diuretic use, number of different drugs, Parkinson's disease, cognitive impairment, fall history, and proximity to death.
[b]Multiple users include users on two or more types of AADs.

Table 5.11
Adjusted Analyses: Association between Each Potential Confounder and the Risk of Falling: Function- and Other Drug Use-Related Measures[a]

Variable	OR	(95% CI)	P-value
Function-Related Measures			
Activities of daily living			
Independent		Reference group	
Partially dependent	1.76	(1.31-2.35)	<.0001
Totally dependent	0.62	(0.39-1.01)	0.053
Balance problem			
Steady		Reference group	
Partially unsteady	1.64	(1.27-2.12)	<.0001
Totally unsteady	1.07	(0.81-1.43)	0.620
Other Drug Use-Related Measures			
Antidepressant use			
Nonuser		Reference group	
Partial user	1.32	(0.81-2.15)	0.261
Current user	1.26	(1.02-1.56)	0.032
Benzodiazepine use			
Nonuser		Reference group	
Partial user	1.14	(0.72-1.80)	0.576
Current user	0.92	(0.72-1.18)	0.500
Antihypertensive & diuretic use			
Nonuser		Reference group	
Partial user	1.52	(0.98-2.35)	0.062
Current user	0.74	(0.59-0.92)	0.006
Number of different drugs			
Nonuser		Reference group	
User (1-8 drugs)	1.28	(0.85-1.92)	0.235
Heavy user (9+ drugs)	1.84	(1.07-3.19)	0.029

Note. OR = odds ratio; CI = confidence intervals.
[a]Model adjusted for atypical antipsyhcotic drug (AAD) use, type of AAD, dose of AAD, balance problem, antidepressant use, benzodiazepine use, antihypertensive or diuretic use, number of different drugs, Parkinson's disease, cognitive impairment, fall history, and proximity to death.

Table 5.12

Adjusted Analyses: Association between Each Potential Confounder and the Risk of Falling: Medical Health Conditions, Cognition, and Other Measures[a]

Variable	OR	(95% CI)	P-value
Medical health conditions-related measure			
Parkinson's disease			
No	Reference group		
Yes	1.36	(1.20-1.80)	<.0001
Cognition-related measure			
Cognitive performance			
Intact	Reference group		
Partially impaired	1.22	(0.97-1.55)	0.095
Severely impaired	0.64	(0.33-1.26)	0.194
Other measures			
Fall history			
No	Reference group		
Yes	1.52	(1.18-1.96)	0.001
Proximity to death			
181+ days	Reference group		
1-180 days	3.48	(2.53-4.78)	<.0001

Note. OR = odds ratio; CI = confidence intervals.

[a]Model adjusted for atypical antipsychotic drug (AAD) use, type of AAD, dose of AAD, activities of daily living, balance problem, antidepressant use, benzodiazepine use, antihypertensive or diuretic use, number of different drugs, Parkinson's disease, cognitive impairment, fall history, and proximity to death.

Table 5.13

Interaction Effect Analyses: Effect of Atypical Antipsychotic Drug (AAD) Use on the Risk of Falling by Person Characteristics: Function- and Other Drug Use-Related Measures[a]

Variable	OR	(95% CI)	P-value
Function-related measures			
Activities of daily living			
Independent	1.02	(0.54-1.93)	0.942
Partially dependent	1.29	(1.00-1.66)	0.053
Totally dependent	0.88	(0.44-1.76)	0.716
$P_{interact}$			0.499
Balance problem			
Steady	1.32	(0.85-2.05)	0.217
Partially unsteady	1.32	(0.93-1.87)	0.124
Totally unsteady	1.03	(0.72-1.48)	0.873
$P_{interact}$			0.558
Other drug use-related measures			
Antidepressant use			
Nonuser	1.20	(0.89-1.61)	0.230
Partial user	0.94	(0.32-2.74)	0.909
Current user	1.24	(0.87-1.77)	0.231
$P_{interact}$			0.888
Benzodiazepine use			
Nonuser	1.18	(0.91-1.54)	0.220
Partial user	2.21	(0.92-5.32)	0.076
Current user	1.09	(0.69-1.74)	0.713
$P_{interact}$			0.349
Antihypertensive & diuretic use			
Nonuser	1.41	(0.98-2.03)	0.065
Partial user	1.19	(0.46-3.12)	0.719
Current user	1.09	(0.82-1.46)	0.550
$P_{interact}$			0.545
Number of different drugs			
Nonuser	0.63	(0.07-5.41)	0.673
User (1-8 drugs)	1.21	(0.95-1.53)	0.126
Heavy user (9+ drugs)	1.29	(0.64-2.62)	0.477
$P_{interact}$			0.802

Note. OR = odds ratio; CI = confidence intervals.

[a]Results show the odds of falling for AAD users compared to nonusers, within categories of each study covariate selected as a confounder.

Table 5.14
Interaction Effect Analyses: Effect of Atypical Antipsychotic Drug (AAD) Use on the Risk of Falling by Person Characteristics: Medical Health Conditions, Cognition, and Other Measures[a]

Variable	OR	(95% CI)	P-value
Medical health conditions-related measure			
Parkinson's disease			
No	1.22	(0.94-1.57)	0.131
Yes	1.15	(0.74-1.80)	0.538
$P_{interact}$			0.825
Cognition-related measures			
Wandering			
No	1.09	(0.85-1.41)	0.491
Yes	1.84	(1.09-3.09)	0.022
$P_{interact}$			0.075
Cognitive performance			
Intact	1.15	(0.67-1.98)	0.602
Partially Impaired	0.78	(0.60-1.00)	0.050
Severely impaired	0.76	(0.23-2.56)	0.663
$P_{interact}$			0.395
Other measures			
Fall history			
No	1.18	(0.92-1.52)	0.190
Yes	1.29	(0.78-2.14)	0.318
$P_{interact}$			0.751
Proximity to death			
1-180 days	1.56	(0.75-3.27)	0.237
181+ days	1.17	(0.92-1.49)	0.189
$P_{interact}$			0.464

Note. OR = odds ratio; CI = confidence intervals.
[a]Results show the odds of falling for AAD users compared to nonusers, within categories of each study covariate selected as a confounder.

Table 5.15
Unadjusted Sensitivity Analyses: Effect of Atypical Antipsychotic Drug (AAD) Use on the Risk of Falling[a]

Categories of AAD use	OR	(95% CI)	P-value
AAD user			
Nonuser		Reference group	
User	1.90	(1.32-2.72)	0.001
Type			
Nonuser		Reference group	
Risperidone	1.79	(1.13-2.85)	0.014
Olanzapine	1.22	(0.74-2.01)	0.441
Quetiapine	2.41	(1.32-4.38)	0.004
Multiple[b]	2.46	(0.85-7.07)	0.096
Dose			
Nonuser		Reference group	
Low Dose	1.36	(1.01-1.84)	0.042
High Dose	2.63	(1.40-4.96)	0.003
Type and Dose Interaction			
Nonuser		Reference group	
Risperidone			
Low dose	1.20	(0.93-1.56)	0.162
High dose	2.67	(1.11-6.44)	0.028
Olanzapine			
Low dose	0.96	(0.53-1.73)	0.885
High dose	1.55	(0.70-3.41)	0.277
Quetiapine			
Low dose	1.86	(1.11-3.12)	0.020
High dose	3.12	(1.08-9.03)	0.036
Multiple[b]			
Low dose	1.62	(0.74-3.56)	0.228
High dose	3.71	(0.52-26.47)	0.191
$P_{interact}$			0.224

Note. OR = odds ratio; CI = confidence intervals.
[a]These estimates were from cases and controls matched on length of PCH stay, age, and sex. [b]Multiple users include users on two or more types of AADs.

Table 5.16
Adjusted Sensitivity Analyses: Effect of Atypical Antipsychotic Drug (AAD) Use on the Risk of Falling[a]

Categories of AAD use	OR	(95% CI)	P-value
AAD user			
Nonuser		Reference group	
User	1.71	(1.12-2.62)	0.013
Type			
Nonuser		Reference group	
Risperidone	1.83	(1.09-3.08)	0.022
Olanzapine	1.03	(0.60-1.77)	0.917
Quetiapine	2.43	(1.27-4.64)	0.007
Multiple[b]	1.88	(0.51-6.88)	0.341
Dose			
Nonuser		Reference group	
Low Dose	1.27	(0.92-1.76)	0.151
High Dose	2.31	(1.08-4.93)	0.030
Type and Dose Interaction			
Nonuser		Reference group	
Risperidone			
Low dose	1.18	(0.89-1.57)	0.260
High dose	2.85	(1.07-7.58)	0.036
Olanzapine			
Low dose	0.89	(0.47-1.66)	0.706
High dose	1.20	(0.51-2.82)	0.683
Quetiapine			
Low dose	1.72	(0.98-3.03)	0.059
High dose	3.42	(1.08-10.79)	0.036
Multiple[b]			
Low dose	1.45	(0.62-3.35)	0.390
High dose	2.44	(0.21-28.41)	0.476
$P_{interact}$			0.259

Note. OR = odds ratio; CI = confidence intervals.
[a]Model adjusted for activities of daily living, balance problem, antidepressant use, benzodiazepine use, antihypertensive or diuretic use, number of different drugs, Parkinson's disease, cognitive impairment, fall history, and proximity to death.
[b]Multiple users include users on two or more types of AADs over assessment time.

Table 5.17

Sensitivity Interaction Effect Analyses: Effect of Atypical Antipsychotic Drug (AAD) Use on the Risk of Being a Faller by Person Characteristics: Function- and Other Drug Use-Related Measures[a]

Variable	OR	(95% CI)	P-value
Function-related measures			
Activities of daily living			
Independent	0.96	(0.49-1.88)	0.906
Partially dependent	1.25	(0.95-1.64)	0.112
Totally dependent	0.93	(0.45-1.93)	0.853
$P_{interact}$			0.615
Balance problem			
Steady	1.39	(0.88-2.19)	0.160
Partially unsteady	1.30	(0.90-1.90)	0.166
Totally unsteady	0.93	(0.62-1.38)	0.718
$P_{interact}$			0.894
Other drug use-related measures			
Antidepressant use			
Nonuser	1.18	(0.86-1.61)	0.315
Partial user	1.26	(0.34-4.62)	0.730
Current user	1.16	(0.80-1.68)	0.436
$P_{interact}$			0.992
Benzodiazepine use			
Nonuser	1.19	(0.90-1.58)	0.230
Partial user	2.04	(0.75-5.53)	0.162
Current user	1.00	(0.61-1.61)	0.985
$P_{interact}$			0.436
Antihypertensive & diuretic use			
Nonuser	1.30	(0.88-1.91)	0.192
Partial user	1.12	(0.32-4.01)	0.857
Current user	1.11	(0.82-1.50)	0.514
$P_{interact}$			0.812
Number of different drugs			
Nonuser	0.82	(0.09-7.54)	0.861
1-8	1.18	(0.92-1.53)	0.200
9+	1.14	(0.55-2.34)	0.729
$P_{interact}$			0.942

Note. OR = odds ratio; CI = confidence intervals.

[a]Results show the odds of falling for AAD users compared to nonusers, within categories of each study covariate selected as a confounder.

Table 5.18

Sensitivity Interaction Effect Analyses: Effect of Atypical Antipsychotic Drug (AAD) Use on the Risk of Being a Faller by Person Characteristics: Other Medical Health Conditions, Cognition, and Other Measures[a]

Variable	OR	(95% CI)	P-value
Medical health conditions-related measure			
Parkinson's disease			
No	1.20	(0.91-1.57)	0.201
Yes	1.10	(0.69-1.76)	0.697
$P_{interact}$			0.753
Cognition-related measures			
Wandering			
No	1.07	(0.82-1.40)	0.609
Yes	1.72	(1.00-2.98)	0.052
$P_{interact}$			0.122
Cognitive performance			
Intact	1.37	(0.76-2.47)	0.296
Impaired	0.77	(0.59-1.01)	0.058
Severely impaired	0.85	(0.23-3.12)	0.803
$P_{interact}$			0.190
Other measures			
Fall history			
No	1.13	(0.87-1.48)	0.360
Yes	1.35	(0.79-2.31)	0.268
$P_{interact}$			0.555
Proximity to death			
1-180 days	1.50	(0.69-3.25)	0.304
181+ days	1.14	(0.89-1.47)	0.299
$P_{interact}$			0.508

Note. OR = odds ratio; CI = confidence intervals.

[a]Results show the odds of falling for AAD users compared to nonusers, within categories of each study covariate selected as a confounder.

Table 5.19
Unadjusted Hospital Fall Data-Based Analyses: Effect of Atypical Antipsychotic Drug (AAD) Use on the Risk of Being a Hospitalized Faller[a]

Categories of AAD use	OR	(95% CI)	P-value
AAD user			
Nonuser		Reference group	
User	1.27	(0.78-2.05)	0.336
Type			
Nonuser		Reference group	
Risperidone	1.07	(0.58-2.01)	0.823
Olanzapine	1.28	(0.51-3.23)	0.599
Quetiapine	1.86	(0.78-4.51)	0.161
Dose			
Nonuser		Reference group	
Low Dose	1.16	(0.31-4.40)	0.827
High Dose	1.28	(0.77-2.10)	0.334
Type and Dose Interaction			
Nonuser		Reference group	
Risperidone			
Low dose	1.14	(0.61-2.11)	0.689
High dose		NR	
Olanzapine			
Low dose	0.78	(0.52-4.09)	0.468
High dose	1.46	(0.09-6.87)	0.831
Quetiapine			
Low dose	1.62	(0.62-4.26)	0.327
High dose	4.38	(0.60-31.7)	0.144
$P_{interact}$			0.756

Note. OR = odds ratio; CI = confidence intervals, NR = not reported due to no sample within this category.
[a]These estimates were from cases and controls matched on length of PCH stay, age, and sex.

Table 5.20
Adjusted Hospital Fall Data-Based Analyses: Effect of Atypical Antipsychotic Drug (AAD) Use on the Risk of Being a Hospitalized Faller[a]

Categories of AADs use	OR	(95% CI)	P-value
AADs user			
Nonuser		Reference group	
User	0.97	(0.55-1.71)	0.926
Type			
Nonuser		Reference group	
Risperidone	0.79	(0.38-1.64)	0.528
Olanzapine	1.01	(0.38-2.73)	0.978
Quetiapine	1.57	(0.56-4.43)	0.394
Dose			
Nonuser		Reference group	
Low Dose	0.93	(0.52-1.67)	0.635
High Dose	1.51	(0.35-6.57)	0.802
Type and Dose Interaction			
Nonuser		Reference group	
Risperidone			
Low dose	0.83	(0.40-1.73)	0.628
High dose		NR	
Olanzapine			
Low dose	0.53	(0.06-5.13)	0.585
High dose	1.23	(0.41-3.75)	0.710
Quetiapine			
Low dose	1.16	(0.37-3.62)	0.795
High dose	12.34	(1.20-127.99)	0.035
$P_{interact}$			0.484

Note. OR = odds ratio; CI = confidence intervals, NR = not reported due to no sample within this category.

Table 5.21
Hospital Fall Data-Based Interaction Effect Analyses: Effect of Atypical Antipsychotic Drug (AAD) Use on the Risk of Falling by Person Characteristics: Function- and Other Drug Use-Related Measures[a]

Variable	OR	(95% CI)	P-value
Function-Related Measures			
Activities of daily living			
Independent	0.49	(0.13-1.83)	0.290
Partially dependent	1.20	(0.61-2.35)	0.604
Totally dependent	1.74	(0.31-9.84)	0.532
$P_{interact}$			0.417
Balance problem			
Steady	0.77	(0.26-2.25)	0.631
Partially unsteady	1.07	(0.47-2.43)	0.875
Totally unsteady	1.51	(0.50-4.54)	0.462
$P_{interact}$			0.681
Other Drug Use-Related Measures			
Antidepressant use			
Nonuser	0.68	(0.32-1.43)	0.306
User	1.86	(0.80-4.36)	0.151
$P_{interact}$			0.186
Benzodiazepine use			
Nonuser	1.49	(0.73-3.06)	0.272
User	0.55	(0.20-1.50)	0.243
$P_{interact}$			0.133
Antihypertensive & diuretic use			
Nonuser	1.08	(0.43-2.73)	0.875
User	1.08	(0.51-2.30)	0.841
$P_{interact}$			0.996
Number of different drugs			
Nonuser	0.78	(0.22-2.76)	0.706
User (1-8 drugs)	1.18	(0.61-2.26)	0.622
Heavy user (9+ drugs)	0.78	(0.22-2.76)	0.706
$P_{interact}$			0.579

Note. OR = odds ratio; CI = confidence intervals.
[a]Results show the odds of falling for AAD users compared to nonusers, within categories of each study covariate selected as a confounder.

Table 5.22
Hospital Fall Data-Based Interaction Effect Analyses: Effect of Atypical Antipsychotic Drug (AAD) Use on the Risk of Falling by Person Characteristics: Medical Health Conditions, Cognition, and Other Measures[a]

Variable	OR	(95% CI)	P-value
Medical health conditions-related measure			
Parkinson's disease			
No	1.03	(0.45-2.19)	0.623
Yes	1.13	(0.46-6.60)	0.761
$P_{interact}$			0.610
Cognition-related measures			
Wandering			
No	0.80	(0.41-1.55)	0.499
Yes	2.50	(0.79-7.91)	0.119
$P_{interact}$			0.091
Cognitive performance			
Intact	1.67	(0.86-3.23)	0.127
Partially impaired	0.27	(0.08-0.97)	0.044
Severely impaired	0.12	(0.01-2.05)	0.144
$P_{interact}$			0.013
Other measures			
Fall history			
No	1.08	(0.53-2.21)	0.828
Yes	1.07	(0.45-2.57)	0.871
$P_{interact}$			0.975
Proximity to death			
1-180 days	1.26	(0.42-3.79)	0.677
181+ days	1.02	(0.53-1.97)	0.951
$P_{interact}$			0.743

Note. OR = odds ratio; CI = confidence intervals.
[a]Results show the odds of falling for AAD users compared to nonusers, within categories of each study covariate selected as a confounder.

Chapter 6

Discussion

This chapter highlights the findings of this research, and compares the present research to the existing epidemiologic literature, especially as it relates to methodological issues and study results. Limitations, policy implications, and future research directions are also discussed.

Summary of Research Findings

Analyses were conducted to test the three study hypotheses presented in Chapter 1 (Introduction) of this research. These are as follows:

1. Compared to nonusers, atypical antipsychotic drug (AAD) use will increase the risk of falling among older PCH residents;
2. The association between AAD use and the risk of falling will vary depending on the type and dose of AAD used;
3. The association between AAD use and the risk of falling will depend on certain person characteristics (e.g., fall history, wandering, and use of drugs other than AADs).

The analyses for hypothesis 1 shows that compared to nonusers, AAD users as a group were at a greater risk of falling (see Table 5.10). The analyses for hypothesis 2 however, shows that this association varied by AAD type and dose. Compared to nonusers, the odds of falling was greater for quetiapine users, regardless of this drug's dose, and also for high dose risperidone users. On the other hand, low dose risperidone, and both low and high dose olanzapine, was not associated with an increased risk of

falling. Further, the adjusted odds ratios (ORs) for high dose risperidone and high dose quetiapine, while not different from each other, were substantially greater than the values reported in all other AAD use categories.

Lastly, analysis of hypothesis 3 showed evidence of a significant interaction between overall AAD use and wandering (see Table 5.14). While AAD use did not affect fall risk for people without wandering problems, use of AADs increased fall risk for individuals who wandered. No additional significant interactions were found between AAD use and any other selected confounders. Further details of these finding are provided in the following text.

"Compared to nonusers, AAD use will increase the risk of falling among older PCH residents". (Hypothesis 1) "The association between AAD use and the risk of falling will vary depending on the type and dose of AAD used". (Hypothesis 2)

This study shows that without adjustment for other covariates, AAD use significantly increased the risk of falling among older PCH residents (unadjusted ORs = 1.87, 95% confidence intervals [CI] 1.35-2.59) (see Table 5.9). A similar trend is also shown using both descriptive and multivariate analyses techniques. Descriptively, a larger proportion of cases (30.2%) versus controls (23.8%) were defined as AAD users (see Table 5.5). Similarly, the adjusted odds of falling was 60% greater for AAD users as compared to nonusers (95% CI 1.10-2.32 (see Table 5.10).

Findings for hypothesis 2 build on these study results, and show that the association between AAD use and falling depended on the dose and type of AAD used. Descriptively, a greater proportion of cases (fallers) versus controls (non-fallers) received

high doses of risperidone, and also a greater proportion of cases received both low and higher doses of quetiapine (see Table 5.6). Conversely, a smaller proportion of cases versus controls received low dose risperidone or olanzapine.

Similar trends are shown using conditional logistic regression, with and without adjustment for other covariates. For example, the unadjusted odds of falling was significantly greater for both high dose risperidone users (unadjusted OR = 2.79, 95% CI 1.21-6.46), and for both high (unadjusted OR = 3.67, 95% CI 1.41-9.57) and lower dose quetiapine users (unadjusted OR = 1.84, 95% CI 1.13-3.01) (see Table 5.9). Similarly, after adjustment for other covariates, the odds of falling was 62% higher in low dose quetiapine users (adjusted OR=1.62, 95% CI 0.94-2.77), and 260% higher for high dose quetiapine users (adjusted OR=3.60; 95% CI 1.27-10.17) (Table 5.10). Lastly, descriptive, unadjusted, and adjusted results consistently show that fall risk did not increased significantly with olanzapine use. Without adjustment for other covariates, olanzapine users were 1.76 more likely to fall versus non users (95% CI 0.83-3.70) (see Table 5.9). This odds ratio changed to 1.30 after adjustment for study covariates (95% CI 0.58-2.92) (see Table 5.10).

High dose risperidone and high dose quetiapine users were at a greater fall risk than all other AAD use categories. While somnolence and extrapyramidal symptoms are reported as being side effects of risperidone, studies show that the extent of these side effects are dose-dependent (Canadian Pharmacists Association, 2009). This helps to explain why high but not low dose risperidone users are at greater risk of falling. Similarly, somnolence, drowsiness, and sedation are the most reported side effects and reasons for stopping use of quetiapine (Canadian Pharmacists Association, 2009;

Twaites, Wilton, & Shakir, 2007). Physicians may consider quetiapine as a safer option for persons with higher risk of falling due to less reported side effects of extrapyramidal symptoms. However, quetiapine users may be at greater risk due to somnolence, drowsiness, and sedation.

Additional sensitivity and hospitalized fall analyses were conducted to investigate the extent that select methodological limitations influenced study results. Sensitivity analyses were conducted on a subgroup of AAD users where drug exposure definitely preceded the fall event (AAD use patterns 3 and 4 in Figure 4.5). Second, analyses were conducted on the entire sample using hospital fall data, where an exact hospitalized fall date was measured. Overall, the results from both of these analyses were similar to the main study findings, which help to minimize concern regarding these study limitations.

In summary, this study consistently shows that, within the PCH environment, certain AAD users have an increased risk of falling. While high dose risperidone and quetiapine users, regardless of its dose, were at greater risk of falling, low dose risperidone users and all olanzapine users were not with a greater fall risk.

"The association between AAD use and the risk of falling will depend on certain person characteristics". (Hypothesis 3)

In hypothesis 3, analyses were conducted to test if the effect of AAD use depended on select person characteristics (see Tables 5.13 and 5.14). For the purpose of this research, interactions to test this hypothesis were confined to the main effect of AAD use, and were not extended to include multi-way interactions including both AAD type and dose due to the smaller size of some three-way interaction cells. Results show that

compared to nonusers, AAD use was significantly associated with greater risk of falling for people who had wandering problems (adjusted OR = 1.84, 95% CI 1.09-3.09) (see Table 5.4). Conversely, AAD use was not strongly associated with falling for people without wandering problems (adjusted OR = 1.09, 95% CI 0.85-1.41). Similar results were observed during the sensitivity analysis and hospital fall data-based analyses (see Tables 5.18 and 5.22).

Comparing the Present Study to the Current Literature

Methodological issues.

Confounding.

Since fall risk factors are multifactorial, confounding becomes an important problem in studies focusing on medication-associated falls. Therefore, researchers should identify potential confounders and develop ways to measure variation across study groups (Mamdani et al., 2005; Rochon et al., 2005). Although several authors have recognized the importance of adjustment for covariates (Hien et al., 2005; Kallin et al., 2004; Landi et al., 2005; Rochon et al., 2008), to date, most studies have been limited in their ability to adjust for key factors such as limitations when conducting activities of daily living (ADLs) and proximity to death. The present study uses these plus various additional confounding variables to adjust for differences across study groups, using both the MDS data and administrative files housed at Manitoba Centre for Health Policy (MCHP) (see Figure 4.6 to view the list of potential confounders used in this study). This is one mechanism by which the present study adds value to the current literature, by

incorporating a larger number of potentially important risk factors into data analyses, and hence minimizing confounding.

Based on the literature, length of PCH stay, age, and sex were considered as important confounders in the present study, and were therefore controlled at the study design stage, by matching the cases and controls on these variables. Researchers have suggested that AAD use is greater among newly admitted PCH residents (Doupe et al., 2006; Hagen et al., 2005), among older PCH residents (Doupe et al., 2006; Raymond et al., 2010), and among females (Voyer et al., 2005). These factors have also been significantly associated with the risk of falls in older adults (Aizenberg et al., 2002; British Columbia Ministry of Health Planning, 2004; Manitoba Health, 2005; Public Health Agency of Canada, 2005).

Of the other potential confounders measured in the study, ADLs, balance, antidepressant use, benzodiazepine use, the number of different drugs used, cognitive impairment, and fall history were selected based on the breadth of literature demonstrating the impact these variables have on fall risk. Conversely, the presence of Parkinson's disease, antihypertensive or diuretic use, and proximity to death were included as covariates based their significant scores during CIE testing (see section "Adjustment for confounding" in Chapter 4 - Methods for further details).

Confounding by indication, sometimes called a channeling bias, occurs if a drug of interest is a marker for a medical condition that triggers the use of this drug, and at the same time increases the risk of the outcome of interest (Psaty et al., 1999). For example, AADs are commonly prescribed to older adults diagnosed with dementia (Doupe et al., 2006). Persons with dementia are at greater risk for falling as a result of cognitive

impairment and behavioural problems, such as agitation (van Doorn et al., 2003). As a result, AAD users may appear to have a higher risk of falling, not because of their AAD use per say, but rather due to disabilities related to their medical condition. This type of rationale further emphasizes the importance of including covariates such as cognitive performance in the final statistical models. Many existing epidemiologic studies have also included these and related confounders, either by adjustment for these variables in their statistical modeling (Hien et al., 2005; Kallin et al., 2004; Landi et al., 2005) or by restricting analyses to subgroups of study participants (e.g., those with dementia) (Frenchman, 2005; Martin et al., 2003; Rochon et al., 2008).

In addition to cognitive measures, researchers have consistently shown that fall history is an independent risk factor for future falls (American Geriatrics Society et al., 2001; Ganz et al., 2007; Kallin et al., 2004; Martin et al., 2003; Myers et al., 1991). Physicians may prescribe AADs to older adults who have a high risk of falling based on their assumption that AADs have a protective effect. When investigating the effect of AAD use on fall risk, only two previous studies have adjusted for fall history in their statistical models (Hien et al., 2005; Kallin et al., 2004), while another study excluded these individuals from their analyses (Martin et al., 2003). In the present study, analyses were controlled for fall history to avoid its confounding by indication.

Confounding by indication may also explain the current interaction test results between AAD use and wandering. In fact, an interim descriptive analysis conducted between CPS, wandering, and AAD use showed that 100% of AAD users, who had wandering problems, also had some type of cognitive impairment (data not shown). As described previously, CPS is considered as a confounder in the present study and also

was found to be significantly associated with the risk of falling. Therefore, the significant association between AAD use and falls among wanderers could be confounded by CPS.

Use of population-based database.

Researchers suggest that selection bias can be eliminated by including in the analyses all cases from the source population. This is possible by using population-based databases (Csizmadi, Collet, & Boivin, 2005). Further, population-based studies have the advantage of including the entire population of interest, which therefore optimizes external validity. Within the existing literature, only Rochon et al. (2008) conducted their analysis using population-based databases. The use of these databases is therefore an additional strength of this study, particularly with respect to minimizing selection bias and providing generalized findings. As one asterisk to this statement, at the time of this research MDS data were only available on not-for-profit PCH residents in the Winnipeg health region (WHR). This represents an important future research direction, to replicate the current study findings on for-profit PCHs in the WHR, and also in more rural PCH facilities.

Measurement of exposure to atypical antipsychotic drugs.

In the existing literature, AAD exposure is sometime defined inadequately, and faces some additional methodological challenges such as violation of temporality in cross-sectional study designs (i.e., where fall outcomes could have preceded drug utilization) (Frenchman, 2005; Kallin et al., 2004; Landi et al., 2005; Martin et al., 2003). In addition, while AAD use should be measured prior to the fall outcome (Hien et al., 2005; Rochon et al., 2008), existing cohort studies are limited in that drug use is assessed

only once, at baseline, with no subsequent drug use measured at subsequent times of the study period. In this type of design, it is not possible to measure changing patterns of drug use (i.e., discontinuation or new prescription) throughout the study.

To build on the literature, AAD use in the present study was measured just prior to Index Date and during the 30 day assessment period (Figure 4.5 in Chapter 4 - Methods). This approach permits an analyses on the effect of AAD use prior to fall risk, and also more stringently controls for factors such as confounding, by also measuring residents characteristics just prior to the Index Date (i.e., in this study, covariates in the previous MDS assessment were used to adjust fall risk in the subsequent assessment). Lastly, to further ensure that AAD exposure preceded fall risk, follow-up analyses were replicated on a sub-set of AAD users, and using hospital-based records that contain a sub-set of more serious falls, where a more specific fall date was documented.

It is also important to note that while some studies have measured drug use via patient recall and are therefore subject to potential challenges associated with recall bias (Kallin et al., 2004), AAD use in this study was objectively recorded in the Drug Prescribing Information Network (DPIN) system. DPIN objectively records retail-based dispensation of all drugs to all cases and controls in the present study. However, DPIN measures drug use based on dispensation records, and not on actual consumption.

In summary, the present study extends the literature by improving on select methodological challenges. These include incorporating a larger number of potentially important risk factors into data analyses, using of population-based databases, and objectively measuring AAD exposure prior to fall event.

Study results.

In addition to making some methodological advances in the current literature, the present study advances knowledge with respect to AAD use and falls in a PCH environment. While the existing literature investigates the effect of risperidone or olanzapine on fall risk, to date no researchers have investigated the effect of quetiapine in their analysis. Also, to date there is very little evidence demonstrating how AAD type and dose impact fall risk, and that identify AAD users who may be especially vulnerable to falls.

Existing literature has looked at the individual effect of risperidone and olanzapine separately, and there are no published studies investigating the overall impact that AAD use has on fall risk in older PCH residents. This research therefore fills a gap in the literature as it relates to AAD use and fall risk in the PCH environment. In the community setting, Landi et al. (2005) found that AADs were significantly associated with the risk of falling (OR=1.45, 95% 1.00-2.11).This estimate is close to the overall impact of AADs reported in this study (OR=1.60, 95% CI 1.10-2.32).

Previous studies have not looked at fall risk associated with quetiapine use in PCH residents. The significance of this knowledge gap is demonstrated in the present study results, as 13.2% of AAD users were dispensed quetiapine (see Table 5.5), and given existing research demonstrating a trend for increased quetiapine use among older adults residing in both PCHs and the community (Raymond et al., 2010). The present study is the first study to report a unique effect of quetiapine on the risk of falling.

Similar to the non-significant effect of low dose risperidone in the present study, four randomized controlled trials (RCTs) have consistently shown that low dose

risperidone users have no greater risk of falling as compared to nonusers of AADs (Brodaty et al., 2003; de Deyn et al., 2005; Katz et al., 2004; Mintzer et al., 2006). However, the lack of an association between olanzapine use and fall risk in the present study differs from other observational studies, who generally report an increased in fall risk associated with olanzapine use (Frenchman et al., 2005; Hien et al., 2005; Kallin et al., 2004; Martin et al., 2003;). These differences in study results may be explained by the methodological differences including AAD use measurement and adjustment for different confounders. For example, Hien et al. (2005) assessed AAD use only once, at baseline, with no subsequent drug use measurement during the follow-up period. Therefore, it is not possible to measure changing patterns of drug use (i.e., discontinuation or new prescription) throughout the study period. Conversely, AAD use in the present research was measured at baseline (Index Date) and also during 30-day follow-up periods preceding each MDS assessment date. Further, although researchers have recognized the importance of adjustment for covariates, to date, few studies have been able to adjust their analyses for key factors such as ADLs, antihypertensive and diuretic use, the number of different drugs, and proximity to death. A randomized controlled trial (RCT) (Street et al., 2000) reports the risk of falling by dose of olanzapine. Consistent with the present study, researchers have shown that low dose olanzapine use, i.e., 5-10 mg/day, was not associated with falling. However, higher dose olanzapine users, i.e., 15 mg/day, were at greater risk of falling compared to those using placebo.

Four RCTs report the risk of falling by dose of either risperidone (de Deyn et al., 2005; Katz et al., 1999; Katz et al., 2004). However, the dose of interest in each of these

studies was low (i.e., 2 mg/day or less for risperidone). None of these studies have looked at the association between higher doses of risperidone and falls. The findings of the present research (with or without adjustment for other covariates) demonstrate that high dose quetiapine and high dose risperidone users were at greater risk of falling (see Tables 5.9 and 5.10). These findings have direct policy implication and illustrate the importance of measuring higher dose of AAD use in future such studies.

Lastly, of all studies reviewed, only Katz et al. (2004) investigated if the effect of AADs on fall risk varied by person characteristics. These researchers reported a significant interaction between wandering and risperidone use and specifically found that in individuals who exhibit wandering, 1 mg/day but not 2 mg/day of risperidone reduced fall risk. In the present study, a significant interaction was found between AAD users as a group and wandering. Due to smaller sample size of individual AAD user groups, the present study did not investigate multiple way interactions between resident characteristics, AAD type, and dose. Nevertheless, the interaction results of the present study contribute uniquely to the literature, and have some policy implications. For example, physicians should ensure that PCH residents take high dose risperidone and high dose quetiapine as a last resort, and when necessary, prescribe these medications at their lowest effective dose. Patients with wandering challenges who also require AAD prescriptions should be monitored closely.

Limitations of the Present Study

Despite the present study's strengths and unique contribution to the literature, it also faces some methodological limitations. These limitations are generally related to the

different sources of data available, which are discussed in the following text.

Most limitations of this study are related to MDS-based fall data. These limitations can be summarized as not providing a fall date and the severity of a fall, and not being able to define multiple fallers due to the intermittent nature of MDS data. Also, although AAD use was measured objectively using DPIN in this study, the absence of a fall date may have had some impact on defining the temporality between AAD use and falls (i.e., ensuring that AAD use preceded a fall). To minimize this violation of temporality, AAD use was measured prior to each person's Index Date. Two additional analyses were also conducted to investigate the extent that this limitation influenced study results. First, sensitivity analyses were conducted on a subgroup of AAD users where drug exposure definitely preceded the fall event (AAD use patterns 3 and 4 in Figure 4.5). Second, analyses were conducted on the entire sample using hospital fall data, where an exact fall date was measured. These methodological procedures and additional analyses help to minimize these aforementioned limitations of the present research.

Researchers in the United States have shown that falls may be underreported in MDS data (Hill-Westmoreland & Gruber-Baldini, 2005). Further, there is a lack of Canadian evidence assessing the validity of fall data in MDS. It is therefore possible that some of the non-fallers in the present study were actually fallers who were not identified as such in MDS. However, since falls in MDS were measured separately from AAD use in DPIN, any bias related to the faller outcome is not likely to be differential. However, nondifferential misclassification of the faller outcome is still possible. To test the likelihood of nondifferential measurement bias, concurrent criterion validity analyses

were conducted by comparing MDS recorded fallers to fallers recorded in the hospital separation abstracts (see Chapter 4 - "Methods"). Results from this analysis demonstrate that, during all fall assessment periods, the vast majority (82.9%) of hospitalized fallers were also reported as fallers in MDS, while MDS reported many more fallers during this time period. These results indicate that fall outcome in this study has concurrent criterion validity.

It is also important to note that MDS data on falls are commonly completed every 90 days. Furthermore, fallers in this study were identified intermittently for a 30 day window preceding each consecutive MDS assessment, with no fall measurement occurring during the rest of the 90 day window. Collectively, this means that falls were captured intermittently throughout the present study period. This limitation is subject to misclassification of faller outcome, where some people identified as controls may actually have fallen during non-measurement times. To the extent that this has occurred, the present study results may conservatively underestimate the actual effect of AAD use on fall risk. Also, it is possible that AAD drug use could have occurred in some instances as a result of the falls that were not captured during the 30-day assessment times. This limitation, however, is unlikely to be a major issue as most AAD users were taking drugs for a long time.

Since no fall date is available in this research, it was not possible to measure the duration of AAD use at the time of fall occurrence. This issue is a limitation in this study as short-term users of AADs may have a higher fall risk than long-term users or vice versa. Indeed, descriptive interim analyses were conducted by measuring the number of days of AAD use for one year preceding each index date (assuming that this was the

actual fall date). These analyses showed that AAD users were more likely to be long-term users. Furthermore, the number of days of AAD use may be positively correlated with the length of PCH stay. This means that, by matching cases and controls on length of PCH stay, study groups may also be matched on duration of AAD use.

Some limitations in this research are also inherent to admin files, specifically when using DPIN to measure AAD use. DPIN data measures AAD use based on dispensation records, and not on actual consumption. With this limitation it is possible that some AAD users in this study were actually non users. However, given the long term nature of AAD use as reported in this research, and since the drugs are administered by nurses in PCHs, this limitation is likely to have minimal influence on the present study results. Another potential limitation for studies using administrative data is their limited ability to identify pro-re-nata (PRN, or as-needed) prescribed drugs and their actual use. However, the effect of this limitation is more likely to be low, in light of evidence from studies that showed low use of AADs prescribed as PRN (Champoux et al., 2005; Hagen et al., 2005; Snowdon et al., 2006).

By linking MDS to administrative healthcare data, this study was able to control for a variety of potentially confounding factors. However, residual confounding factors are still possible because of lack of information on known confounders, such as lifestyle factors and dietary issues, or on confounders that are yet to be identified in the literature. Further, it is possible that some of the observed results were related to TAD use as it was not included as a confounder in the final model. To assess the extent of this possible limitation, additional interim analysis was conducted by excluding individuals exposed to TADs (data not shown). Overall, the adjusted results from this additional analysis are

similar to the main study findings. This analysis demonstrates that the adjusted odds of falling was significantly greater for both high and low dose quetiapine users, with an adjusted OR of 3.65 (95% 1.22-12.17) and 1.62 (95% CI 0.91-3.15) respectively, and for high dose risperidone users, with adjusted OR of 3.09 (95% CI 1.25-8.01). In addition, similar to the main findings, olanzapine users were not associated with an increased risk of falling regardless of this drug's dose. Lastly, at the time of this study, MDS database was only available for not-for-profit PCHs in the WHR, which may limit the generalizability of the present study findings.

Policy Implications

This research is the first Canadian study to test the association between AAD use and falls. It has provided some unique findings that enhance our understanding of AADs as a fall risk factor, and also helps to understand how these drugs should be best used in PCHs. Within this context, other risk factors are also highlighted to understand if the effect of AADs on falls varies by resident characteristics. The findings of this study may have significant implications for AAD use policies in Canadian PCHs. Study findings allow policymakers to develop evidence-based policies specific to AAD use, to better manage falls in the PCH setting.

First of all, health professionals should be informed in terms of fall risk profile of AADs. Study results showed that quetiapine, especially when taken at high doses, and high dose risperidone have the greatest fall risk among AAD types. Based on this evidence, physicians should consider prescribing high dose quetiapine and high dose risperidone only as a last resort. Study results show that olanzapine may be a much better

AAD of choice for PCH residents, due to its better fall risk profile. In addition, evidence in this research demonstrates the importance of first prescribing the lowest possible effective AAD dose to PCH residents, and increasing this dose only when necessary. These suggested policy enhancements may be particularly important for some PCH residents, particularly those with wandering problem. Risperidone is the only AAD approved for short-term symptomatic management of inappropriate behaviour due to aggression or psychosis in older adults with severe dementia (Canadian Pharmacists Association, 2009; Health Canada, 2005). The present study results demonstrate that physicians should be especially diligent when prescribing AADs to PCH residents with wandering problems, and conduct frequent medical checks on these patients to ensure that these drugs are still needed. This policy implication is particularly relevant in the PCH environment, as the present study demonstrates that 11.1% of residents had wandering problems, and that 49.7% of these residents were taking AADs at the time of this study.

This study highlights the need for better monitoring of AAD use in PCHs. In Manitoba, there is no existing comprehensive regulation or guideline to monitor the appropriate use of AADs among PCH residents. Developing such a regulation would help to incorporate evidence-based findings into AAD and monitoring practices in the PCH setting. Developing and implementing such regulations have shown to successfully improve outcomes in other countries. For example, in the United States, the Omnibus Reconciliation Act of 1987 (OBRA 87) was issued because of concern about inappropriate use of AADs among older PCH residents (Kane & Garrard, 1994). The provisions of this legislation include strict guidelines for physicians with regard to the

prescribing of antipsychotic drugs in PCHs (Conn, Ferguson, Mandelman, & Ward, 1999). Since OBRA 87 was issued, there has been an overall improvement in appropriate use of antipsychotic drugs (Hughes et al., 2000; Keys & DeWald, 2005; Lantz, Giambanco, & Buchalter, 1996; Shorr, Fought, & Ray, 1994). Policymakers should provide leadership role to initiate similar regulations or guidelines in Canadian PCHs.

Existing regulation in the WHR requires PCHs to conduct a multidisciplinary medication assessment every three months (The Manitoba Pharmaceutical Association, 2007). However, based on the findings of this study, residents taking quetiapine and high dose risperidone should be considered at high risk for falling. At minimum, individuals taking these types and dose of AADs should be monitored during these times to help ensure safe prescribing practices.

This study also points to the need to collect better fall data in PCH environments. The MDS data used in this study provides a rich source of information on potential risk factors of falls. However, this database faces some limitations including the need for information on the number of falls a person has experienced, the fall date, and a resident's condition at the time of fall occurrence. Some of these specific data could be obtained by using occurrence report data. However, this database does not include a personal health information number (PHIN), and is therefore not linkable to other administrative databases in Manitoba. Policymakers should consider including PHIN in the occurrence report data and having these data electronically available for all PCHs in the WHR. Monitoring falls will provide opportunities to show the extent and, as PCH residents today are generally considered to be frailer as compared to the past, the changing trends

in fall for PCH residents. This information is required to plan fall management strategies, and initiate new policies as required. The availability of these data will also allow more important fall-related research.

In the present study, the length of PCH stay was considered an important confounder based on evidence showing higher fall risk and AAD use among newly admitted PCH residents (Hagen et al., 2005; Theodos, 2004). Therefore, PCH staff should monitor these individuals for fall risk and recognize the importance of thoroughly orienting them to the PCH environment until they become sufficiently familiar with the facility.

While this research highlights the importance of fall management strategies specific to AADs, researchers suggest that fall management would be most successful by applying multifactorial strategies (Chang et al., 2004; Jensen, Lundin-Olsson, Nyberg, & Gustafson, 2002; Ray et al., 1997). Therefore, policymakers should consider AAD use-related strategies as one component of multifactorial fall management strategies, and provide leadership to plan and apply such strategies in PCH settings. Also, policymakers should fund and support research in this area to promote evidence-based decision-making.

Future Research Directions

This study is one of the first to investigate the different types of AAD use, including type and dose interactions, on fall risk. Results demonstrate an association between AAD use and the risk of falling for all quetiapine and high dose risperidone users, but not for olanzapine users. In addition, the effect of AAD use on the risk of

falling was significantly greater for residents with wandering problems. However, a great deal of research is still needed to further address these and other findings. These are highlighted in the future research recommendations, based on the experiences gained in the present study:

1. While this study is a population-based, it does not include for profit PCHs and those in rural communities in Manitoba, due to lack of MDS data. Therefore, future research should extent to these PCHs to conduct more broad based studies in this area, and look for differences in the association of AAD use and fall risk across geography and profit status.

2. Future studies are needed to address unexplained question about the duration of AAD use and fall risk. This information will help to clarify the extent that AAD use for longer durations impacts fall risk. Health professionals can use this information to more closely monitor when fall risk becomes especially high for AAD users.

3. Intervention studies should assess the unique effect of AADs-related fall management strategies. These studies may include the effects of AAD withdrawal, the effects of modifying AAD dosage, and the effect of education programs on reducing falls.

4. The need to obtain better data on falls is possible in Manitoba, as an occurrence report is required for every fall event. While most occurrence reports are completed electronically, these are presently not linkable to other administrative files, because of lack of PHIN, which enables the linkage across databases. Use of these data would also help to eliminate falls outcome misclassification error, get a more accurate picture of the prevalence of falls in PCHs, who is most at risk and when (pre-admission, close to death,

etc), how fall risk associated with AAD use, if this risk is particularly higher for multiple fallers, etc. .

5. Evidence comparing the fall risk between AADs and typical antipsychotic drugs (TADs) is more limited. This lack of evidence is especially critical given the increase in AAD use in more recent years. Therefore, future research is needed to assess if AADs in general have any advantage over TADs in terms of fall risk.

6. The present study is the first to look at the association between quetiapine and the risk of falling. However, given some of the aforementioned challenges related to confounding by indication, and given the lack of RCT investigating quetiapine use, RCTs are needed to assess the effectiveness and safety profiles of quetiapine in relation to the risk of falling.

Chapter Summary

The results of this research contribute uniquely to the existing literature. Study findings demonstrate that an association between AAD use and fall risk for all quetiapine and high dose risperidone users. In addition, the overall effect of AAD use on fall risk was significantly greater for people with wandering problem. Despite some limitations of this research, these results allow policymakers to develop evidence-based interventions specific to AADs, to better manage falls in the PCH setting. Implementing these interventions may reduce fall occurrence, and thereby, reduce healthcare costs, and improve health outcomes. Further research is still needed to help validate study findings, and to address other important unanswered questions.

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Appendices

Appendix A

Letters of Approvals

UNIVERSITY OF MANITOBA

BANNATYNE CAMPUS
Research Ethics Boards

P126-770 Bannatyne Avenue
Winnipeg, Manitoba
Canada R3E 0W3
Tel: (204) 789-3255
Fax: (204) 789-3414

APPROVAL FORM

Principal Investigator: Songul Bozat-Emre

Ethics Reference Number: H2008:091
Date of Approval: April 14, 2011
Date of Expiry: April 14, 2012

Protocol Title: Temporal Association Between Atypical Antipsychotic Medication Use and Falls Among Personal Care Home Residents in the Winnipeg Regional Health Authority formerly "Association between Atypical Antipsychotic Medication Use and Falls among Personal Care Home Residents in Winnipeg Regional Health Authority"

The following is/are approved for use:

- **Annual Approval**

The above was approved by Dr. John Arnett, Ph.D., C. Psych., Chair, Health Research Ethics Board, Bannatyne Campus, University of Manitoba on behalf of the committee per your submission dated March 28, 2011. The Research Ethics Board is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement, and the applicable laws and regulations of Manitoba. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the *Food and Drug Regulations of Canada*.

This approval is valid until the expiry date only. A study status report must be submitted annually and must accompany your request for re-approval. Any significant changes of the protocol and informed consent form should be reported to the Chair for consideration in advance of implementation of such changes. The REB must be notified regarding discontinuation or study closure.

This approval is for the ethics of human use only. For the logistics of performing the study, approval must be sought from the relevant institution, if required.

Sincerely yours,

John Arnett, PhD., C. Psych.
Chair, Health Research Ethics Board
Bannatyne Campus

Please quote the above Ethics Reference Number on all correspondence.
Inquiries should be directed to the REB Secretary **Telephone**: (204) 789-3255 / Fax: (204) 789-3414

Manitoba

Health and Healthy Living

Health Information Privacy Committee
4045 – 300 Carlton Street
Winnipeg MB R3B 3M9
Phone: (204) 786-7204
FAX: (204) 944-1911

May 1, 2008

Songul Bozat-Emre

File No. 2008/2009 – 02

Dear Ms. Bozat-Emre:

Re: Atypical Antipsychotic Medications Use and Falls among Personal Care Home Residents in Winnipeg Regional Health Authority

Thank you for submitting the requested documentation for the above project. The Health Information Privacy Committee has now ***approved*** your request for data for this project.

Any significant changes to the proposed study design should be reported to the Chair for consideration in advance of their implementation. Also, please be reminded that *all manuscripts and presentation materials resulting from this study must be submitted for review at least 30 days prior to being submitted for publication or presentation.*

Please be aware that you may be required to sign a Researcher Agreement. If you have any questions or concerns, please do not hesitate to contact Marc Silva, at 786-7229.

Yours truly,

for
Dr. R. Walker
Chair, Health Information Privacy Committee

Please quote the file number on all correspondence

cc. L. Barre

Winnipeg Regional Health Authority
Caring for Health

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September 19, 2008

Songul Bozat-Emre
[redacted]

Dear Songul:

Re: Proposal "An Association Between Atypical Antipsychotic Medication Use and Falls Among Personal Care Home Residents in the Winnipeg Regional Health Authority"

We are pleased to inform you that your research access request for the above-named study has been approved by the Winnipeg Regional Health Authority (WRHA) Research Review Committee pending confirmation that the following conditions are met or agreed to:

- You, your co-investigators, and your research assistants comply with the relevant privacy legislation as indicated below.
  - [X] *The Personal Health Information Act*
  - [ ] *The Freedom of Information and Protection of Privacy Act*
  - [ ] *The Personal Health Information Act* and *The Freedom of Information and Protection of Privacy Act*
- You complete and return the attached Confidentiality Agreement(s) to Joelle Zink, WRHA, 1800 – 155 Carlton Street, Winnipeg, MB R3C 4Y1;
- You submit to our attention any significant changes in your proposal prior to implementation or any significant changes during the course of the study;
- You submit a summary of the final results of the study to the WRHA and provide us with a copy of any publications arising from the study;
- It is an expected courtesy that WRHA will be given a minimum of five working days advance notice of publication or presentation of results with policy implications, in order to be prepared for public response;
- You agree to be accountable for appropriate storage and elimination of material.

Thank you for selecting the Winnipeg Regional Health Authority as the site to conduct your research. Please let us know should you encounter any site-related difficulties during the course of your study.

We extend best wishes for successful completion of your study.

Sincerely,

[redacted]

Dr. Michael Moffatt, M.D., MSc., FRCPC
Executive Director, Division of Research and Applied Learning
Chair, Research Review Committee
Winnipeg Regional Health Authority

cc. Dr. B. Postl
Ms. L. Esposito
Dr. Malcolm Doupe
Chair, HREB

Encl: ***PHIA Agreement***

Appendix B

Distribution of Selected Cases and Controls, and the Source Cohort by Personal Care Homes (PCHs) Included in this Study

Table B.1
Distribution of Selected Cases and Controls, and the Source Cohort by Personal Care Homes (PCHs) Included in this Study

PCH Identifier	PCH Name	Cases & Controls (n=3,014)	Source Cohort (n=2,316)
506	Calvary Place Personal Care Home	101	71
509	Misericordia Place	163	109
573	Concordia Place	167	137
596	West Park Manor Personal Care Home	145	116
607	Bethania Mennonite Personal Care Home Inc.	113	119
615	The Saul and Claribel Simkin Centre	118	69
617	Convalescent Home of Winnipeg	110	94
619	Donwood Manor Personal Care Home Inc.	170	100
626	Foyer Valade Inc.	166	119
628	Fred Douglas Lodge	137	103
635	Holy Family Personal Care Home	363	230
636	Pembina Mennonite Personal Care Home	9	37
639	Lions Personal Care Centre	137	104
642	Meadowood Manor	92	61
643	Luther Home	79	52
649	Middlechurch Home of Winnipeg Inc.	133	168
657	Park Manor Personal Care Home	124	82
667	St. Joseph's Residence Inc.	136	71
680	The Sharon Home Inc.	127	150
685	Golden Links Lodge	96	67
688	Taché Centre	328	257

Appendix C
Refill Frequency of Atypical Antipsychotic Drugs

Table C.1

Refill Frequency of Atypical Antipsychotic Drugs

Refill frequency	Number of drug dispensation	%
1-7 days	7,018	81.4
8-14 days	138	1.6
15-30 days	103	1.2
31 days and more	1,366	15.8
Total	8,625	100.0

Appendix D

Medication List for Drug Categories as Used in the Analyses

Table D.1

Medication List for Drug Categories as Used in the Analyses

Drug Category	Generic Drug Name	ATC Code
Antidepressants	Desipramine	N06AA01
	Imipramine	N06AA02
	Clomipramine	N06AA04
	Trimipramine	N06AA06
	Amitriptyline	N06AA09
	Nortriptyline	N06AA10
	Doxepin	N06AA12
	Maprotiline	N06AA21
	Fluoxetine	N06AB03
	Citalopram	N06AB04
	Paroxetine	N06AB05
	Sertraline	N06AB06
	Fluvoxamine	N06AB08
	Escitalopram	N06AB10
	Phenelzine	N06AF03
	Tranylcypromine	N06AF04
	Moclobemide	N06AG02
	Tryptophan	N06AX02
	Trazodone	N06AX05
	Mirtazapine	N06AX11
	Bupropion	N06AX12
	Venlafaxine	N06AX16
	Amitriptyline and psycholeptics	N06CA01
Antihypertensives and diuretics	Methyldopa (levorotatory)	C02AB01
	Methyldopa (racemic)	C02AB02
	Clonidine	C02AC01
	Doxazosin	C02CA04
	Terazosin	C02CA05
	Hydralazine	C02DB02
	Minoxidil (2.5 mg and 10mg)	C02DC01
	Bosentan	C02KX01
	Reserpine and diuretics	C02LA01
	Methyldopa (levorotatory) and diuretics	C02LB01
	Etacrynic acid	C03CC01
	Spironolactone	C03DA01
	Hydrochlorothiazide	C03AA03
	Chlortalidone	C03BA04
	Indapamide	C03BA11
	Furosemide	C03CA01
	Amiloride	C03DB01
	Triamterene	C03DB02
	Bumetanide	C03CA02
	Hydrochlorothiazide and Potassium–sparing agents	C03EA01
	Oxprenolol	C07AA02
	Pindolol	C07AA03

Table D.1
Medication List for Drug Categories as Used in the Analyses (Continued)

Drug Category	Generic Drug Name	ATC Code
Antihypertensives and diuretics (continued)	Propranolol	C07AA05
	Nadolol	C07AA12
	Metoprolol	C07AB02
	Atenolol	C07AB03
	Acebutolol	C07AB04
	Bisoprolol	C07AB07
	Labetalol	C07AG01
	Propranolol and thiazides	C07BA05
	Timolol and thiazides	C07BA06
	Pindolol and other diuretics	C07CA03
	Atenolol and other diuretics	C07CB03
	Amlodipine	C08CA01
	Felodipine	C08CA02
	Nicardipine	C08CA04
	Nifedipine	C08CA05
	Nimodipine	C08CA06
	Verapamil	C08DA01
	Diltiazem	C08DB01
	Captopril	C09AA01
	Enalapril	C09AA02
	Lisinopril	C09AA03
	Perindopril	C09AA04
	Ramipril	C09AA05
	Quinapril	C09AA06
	Benazepril	C09AA07
	Cilazapril	C09AA08
	Fosinopril	C09AA09
	Trandolapril	C09AA10
	Enalapril and diuretics	C09BA02
	Lisinopril and diuretics	C09BA03
	Perindopril and diuretics	C09BA04
	Quinapril and diuretics	C09BA06
	Cilazapril and diuretics	C09BA08
	Losartan	C09CA01
	Eprosartan	C09CA02
	Valsartan	C09CA03
	Irbesartan	C09CA04
	Candesartan	C09CA06
	Telmisartan	C09CA07
	Losartan and diuretics	C09DA01
	Eprosartan and diuretics	C09DA02
	Valsartan and diuretics	C09DA03
	Irbesartan and diuretics	C09DA04
	Candesartan and diuretics	C09DA06
	Telmisartan and diuretics	C09DA07
Atypical Antipsychotics	Olanzapine	N05AH03
	Risperidone	N05AX08
	Quetiapine	N05AH04
	Clozapine	N05AH02
Benzodiazepines	Chlordiazepoxide with clidinium	A03CA02

Table D.1
Medication List for Drug Categories as Used in the Analyses (Continued)

Drug Category	Generic Drug Name	ATC Code
Benzodiazepines (continued)	Clonazepam	N03AE01
	Diazepam	N05BA01
	Chlordiazepoxide	N05BA02
	Oxazepam	N05BA04
	Clorazepate potassium	N05BA05
	Lorazepam	N05BA06
	Bromazepam	N05BA08
	Clobazam	N05BA09
	Alprazolam	N05BA12
	Flurazepam	N05CD01
	Nitrazepam	N05CD02
	Triazolam	N05CD05
	Temazepam	N05CD07
	Zopiclone	N05CF01
Opioid analgesics	Acetaminophen + caffeine + codeine 30 mg (brand and generics)	N02AA59
	Morphine	N02AA01
	Hydromorphone	N02AA03
	Meperidine	N02AB02
	Oxycodone	N02AA05
	Nalbufine	N02AF02
	Butorphanol	N02AF01
	Fentanyl	N02AB03
	Methadone	N07BC02
	Pentazocine	N02AD01
	Alfentanil	N01AH02
Typical Antipsychotics	Chlorpromazine	N05AA01
	Flupenthixol	N05AF01
	Fluphenazine	N05AB02
	Haloperidol	N05AD01
	Loxapine	N05AH01
	Mesoridazine	N05AC03
	Methotrimeprazine	N05AA02
	Periciazine	N05AC01
	Perphenazine	N05AB03
	Pimozide	N05AG02
	Pipotiazine	N05AC04
	Prochlorperazine	N05AB04
	Thioridazine	N05AC02
	Thiotixene	N05AF04
	Trifluoperazine	N05AB06
	Zuclopenthixol	N05AF05