DISCONTINUATION OF ANTIPSYCHOTICS AMONG RESIDENTS OF SASKATCHEWAN LONG-TERM CARE FACILITIES

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ABSTRACT

Background and Objectives: Antipsychotic medications (APMs) are used for the treatment of behavioural symptoms of dementia. The use of APMs among residents of long-term care facilities (LTCFs), who have a high probability of dementia, is correspondingly high, and has been linked to adverse patient outcomes. The study objectives were to: (a) describe facility variation in APM discontinuation rates, (b) test the association between time to APM discontinuation and patient and facility explanatory variables, and (c) conduct a sensitivity analysis about the effect of changes in the measurement of APM discontinuation on variable associations. **Methods:** The study used a population-based retrospective cohort design. Saskatchewan's (SK) administrative health databases for the period from April 1, 2004 to March 31, 2011 were the data sources. The study cohort included all seniors (≥65 years of age) with a first admission to a SK LTCF and an APM dispensation on or after the admission date. Discontinuation was defined as a 70-day gap after the last APM dispensation. Patient-level explanatory variables included socio-demographics, comorbidity, prior medication exposure, behavioural and cognitive status, and health services utilization. Facility-level explanatory variables included size, location, licensing status, and type. Percentage discontinuation across facilities was descriptively analyzed. Cox proportional hazards regression models with adjustment for clustering of patients within LCTFs were used to test associations with time to discontinuation. A sensitivity analysis of APM discontinuation was conducted by shortening (35 days) and lengthening (105 days) the time from last dispensation. **Results:** Among all residents eligible to be cohort members 35.7% were dispensed an APM. A total of 19.5% of the 8358 cohort members discontinued APMs in the observation period. The Kaplan-Meier estimate of the median time to discontinuation was 6.5 years. Demographic, comorbidity, behavioural, and drug exposure variables were most strongly associated with APM discontinuation. Discontinuation was not associated with facility characteristics. Variable associations were insensitive to the definition of APM discontinuation, but changed over time. **Conclusion:** Discontinuation of APMs is low, despite high rates of utilization over long periods of time. Patient characteristics are associated with APM discontinuation, but not facility characteristics, suggesting that LCTFs are applying consistent approaches to patient management. However, low levels of discontinuation suggest that there may be a need for health care providers to regularly

review the prescribing, dispensing, and administration of APMs to LTCF residents in order to ensure appropriate use of these pharmaceuticals.

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DEDICATION

To Thera Glew

For passing on her love of books and learning,

For teaching me working hard means doing your best,

And for her encouraging words that were always supportive.

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LIST OF ABBREVIATIONS

AHFS	American hospital formulary service
APM	Antipsychotic medication
BPSD	Behavioural and psychological symptoms of dementia
CI	Confidence interval
DAD	Discharge abstract database
DIN	Drug identification number
EOR	Episode of residence
HR	Hazard ratio
ISCH	Institutional supportive care home
KM	Kaplan-Meier
LTCF	Long-term care facility
RAI-MDS	Resident assessment instrument - minimum data set
MDS-CBP	Minimum data set – challenging behaviour profile
MDS-CPS	Minimum data set – cognitive performance scale
MSB	Medical services billing
NPI	Neuropsychiatric Inventory
PDD	Prescription drug database
PRS	Person registry system
RR	Relative risk
SK	Saskatchewan

CHAPTER 1 – INTRODUCTION

1.1 Background

The vast majority of residents who live in long-term care facilities (LTCFs) are seniors (65 years of age or older), and this group of adults makes up a significant proportion of the Saskatchewan (SK) population. In 2011 it was estimated that seniors comprised 15% of the provincial population.[1] As this group ages it will place an increased burden on LTCFs in the province.[2] The utilization rate for long-term care increases with age; provincial data show that the utilization rate increased from 20 to 140 beds per 1,000 population among senior aged 65-74 years and ≥ 85 years, respectively.[3] The proportion of the population that is ≥ 65 years is predicted to increase, with estimates ranging from 22% to 25% in the year 2036.[4]

A serious health concern among seniors is dementia. The most common forms of dementia are Alzheimer's disease (64%) and vascular dementia (19%).[5,6] While the overall prevalence of dementia in Canada is 8%,[5] more than half (57%) of seniors who are institutionalized have dementia.[5] In clinical practice, antipsychotic medications (APMs) are used to manage the behavioural symptoms of dementia.[7,8] APMs belong to one of two classes: conventional and atypical.[9] Atypical antipsychotics constitute the majority of current APM drug prescribing in Canada because patients are less likely to experience adverse side effects like extrapyramidal symptoms or tardive dyskinesia.[9] It has been estimated that between a quarter and a third of Canadian LTCF residents are dispensed APMs. One study found that in the provinces of Manitoba, New Brunswick, and Prince Edward Island, more than one third (38%) of seniors residing in nursing homes were dispensed an APM.[10] Two separate studies in Alberta reported APM dispensing rates of 23% and 31%, respectively.[11,12] Antipsychotic dispensing rates were 24% and 32% in two studies conducted among Ontario nursing home residents.[13,14] However, Rochon et al. highlighted that APM prescribing rates varied considerably between Ontario nursing homes, from 3% to 67%. After grouping the facilities by prescribing rate quintile the mean prescribing rates in the lowest and highest quintiles were 21% and 44%, respectively.[14] In a SK study, it was estimated that 31% of LTCF residents were prescribed an APM in 2001.[15]

Observational, population-based studies of LTCF residents has identified a number of adverse outcomes associated with APM use including increased risk of hyperglycemia,[16-18] Parkinsonism,[19] femur fracture,[20] sudden cardiac death,[21,22] and mortality.[20,23-28] Randomized clinical trials have found that elderly patients exposed to APMs experience cognitive decline,[29] adverse metabolic effects (weight gain, decreased HDL, increased girth),[16] and increased mortality.[30,31] However, the causal link between APM exposure and adverse events is unclear because these events are also more common amongst older adults due to their unique health care needs.[32] Additionally, research indicates that APM therapy has limited effectiveness for the behavioural and psychological symptoms of dementia (BPSD).[33-36]

1.2 Statement of the Problem

Research on APM use in elderly patients has focused on the initiation of APMs and adverse events associated with their use. The adverse events literature has shown an association between APM use and outcomes such as metabolic effects, cognitive decline, fractures, sudden cardiac death, and mortality. Also, randomized clinical trials have demonstrated that APM discontinuation is associated with a decreased mortality rate. These two lines of evidence suggest that APM use may not be in the best interests of elderly patients that are not deriving clinical benefits from this treatment.

Clinical practice guidelines for the use of APMs among dementia patients recommend the use of these agents in a safe and informed way. The atypical APMs risperidone, olanzapine, and aripiprazole can be used among patients with severe Alzheimer's disease for treating "severe agitation, aggression and psychosis where there is risk of harm to the patient and/or others."[37] APMs for patients with mild to moderate dementia are cautiously recommended for the treatment of BPSD.[38]

Additionally, when treating BPSD in all patients with dementia or Alzheimer's disease it is recommended that "there should be periodic attempts to taper and withdraw medications after a period of three months of behavioural stability."[38,39] While there may be LTCF residents who are discontinuing APMs, there is currently no detailed description of APM discontinuation among elderly users of APMs in real-world settings.

1.3 Purpose and Objectives

The purpose of this study is to conduct a population-based investigation of APM discontinuation among SK seniors admitted for the first time to a LTCF, who have received an APM drug dispensation while residing in a LTCF. The specific objectives are:

1. Describe the variation in rates of APM discontinuation across SK's LTCFs;
2. Test the association between resident-level and facility-level factors and time to APM discontinuation; and
3. Conduct a sensitivity analysis about the effect that changes in the measurement of APM discontinuation has on the magnitude and direction of variable associations.

CHAPTER 2 – LITERATURE REVIEW

2.1 Medication Compliance, Persistence and Discontinuation

When a medication is prescribed, the patient is expected to take it as recommended by the physician. However, a patient's drug-taking behaviour may deviate from the recommended treatment plan. Compliance, persistence, and discontinuation are terms used to describe the degree of agreement between recommended and actual therapy. Compliance, defined as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing",[40] is typically reported as a percentage, and is sometimes referred to as adherence.[40,41] Persistence is defined as "the duration of time from initiation to discontinuation of therapy",[40] and is typically reported as the number of days for which therapy was available. Discontinuation occurs when persistence is no longer maintained. These definitions highlight the differences between compliance and persistence, particularly that compliance reflects a component of patient autonomy.

2.1.1 APM Discontinuation

Schizophrenia is an indicated use of APMs, and despite the importance of consistent therapy for patients with schizophrenia, it is known that many APM prescriptions are discontinued. A study based on pharmacy refill records found that at the end of a nine-month study period, 52% and 56% of patients discontinued conventional and atypical APMs, respectively.[42] Another observational study that used data from the U.S. Schizophrenia Care and Assessment Program,[43] found that mean time to discontinuation among schizophrenia patients was 197 days for conventional APMs, and 256 days for atypical APMs. After one year, 65% of conventional APM users had discontinued, compared to 45% of atypical APM users. A population-based study in Maryland evaluated time to discontinuation of atypical APMs.[44] The median time ranged from 54 to 61 days. Additionally, discontinuation rates after one year ranged from 89.3% to 92.6%. Finally, in Quebec a population-based study of atypical APM discontinuation found that 95% of patients discontinued within one year, and the median time to discontinuation was less than three months.[45] Interestingly, this paper also examined patients

who re-initiated APM therapy (one-quarter of the sample), and found similarly high discontinuation rates. While it is not expected that residents of LTCF will have discontinuation rates similar to schizophrenia, it is important to note that this drug utilization behaviour has been studied previously.

Differences in discontinuation estimates between studies may be due to variations in the population under study and the operational definition of discontinuation. For example, higher rates of APM discontinuation in population-based studies may be due, in part, to the definition of discontinuation, which considers a medication switch to be a prescription discontinuation. Therefore, a patient may have continued APM therapy on a different agent, but still be considered to have discontinued.

Elderly patients may also be prescribed APMs for the management of behavioural symptoms, but recent evidence suggests discontinuing these drugs may be beneficial. An early study in a single LTCF assessed how agitated behaviours changed among residents after tapering and withdrawal of haloperidol, thioridazine, or lorazepam. This randomized, double blind, crossover study found that agitated behaviours did not worsen or improve after treatment withdrawal. In Canada, a randomized clinical trial with 33 dementia patients found no differences in behavioural, cognition, function, mood, and extrapyramidal symptoms between patients randomized to APM discontinuation or continued therapy.[46] These two studies were limited by their small sample sizes, which may have not had adequate power to detect behavioural changes. A larger (n = 100) randomized, placebo-controlled, clinical trial of APM discontinuation among dementia patients found no differences between treatment groups on the Neuropsychiatric Inventory (NPI) total or subscale scores. Follow-up analysis grouped patients above or below the median NPI value of 14. Patients in the APM discontinuation group (placebo), with an NPI $\leq$ 14, had lower agitation scores than patients continuing APM therapy. Conversely, patients in the APM discontinuation group (placebo), with an NPI score >14, had more behavioural disturbances than patients continuing APM therapy.[47] Similarly, a pilot study in a Norwegian nursing home among patients with dementia showed no significant changes in the NPI, or other psychometric measures, after APM discontinuation.[48] A larger Norwegian study amongst residents with dementia also found that no differences in NPI total or subscale scores between residents randomized to discontinue or maintain APM therapy.[49] The dementia APM withdrawal trial was designed to measure mortality differences between patients

continuing vs. discontinuing APM therapy among patients with Alzheimer's disease. Within one year there was a modest elevation in mortality (5 to 8%) among patients continuing APMs. However, over four years of follow-up, the hazard ratio (HR) for the placebo group (compared to the APM group) was 0.6 (95% confidence interval [CI]: 0.4 to 0.9).[30] Since behavioural control is often the goal of APM therapy among the elderly in long-term care, the APM discontinuation in Alzheimer's disease trial assessed symptom relapse after risperidone discontinuation. After four months of follow-up the HR for symptom relapse between patients discontinuing vs. maintaining risperidone was 1.94 (95% CI: 1.09 to 3.45). Over the subsequent four months the HR increased to 4.88 (95% CI: 1.08 to 21.98).[50] This research suggests that APM discontinuation increases the risk of symptom relapse among patients that have responded to risperidone treatment. Collectively, the research studying the effects of APM withdrawal shows that both benefits (improved survival) and risks (symptom relapse) exist.

Despite the limitations of clinical trials, like small sample size and highly selected populations, observational studies about APM discontinuation among elderly patients are rare. Kleijer et al. analyzed the pattern of behavioural problems of elderly residents of LTCFs diagnosed with dementia using data from the Minimum Data Set (MDS), a clinical assessment tool.[51] Problem behaviours were measured with the MDS-Challenging Behaviour Profile (CBP).[52] Three months after APM discontinuation 30% of patients had improved problem behaviours while 32% had deteriorated.[51] The paucity of research about APM discontinuation among elderly care home residents in the real world highlights the need for a deeper understanding of this issue.

2.1.2 Medication Discontinuation among the Elderly

Despite the lack of research about APM discontinuation among elderly patients, there are studies examining discontinuation of other types of drugs in this population. Cholinesterase inhibitors are used to treat dementia, and in a SK population-based study the median time to their discontinuation was 191 days.[53] After one year of follow-up 66.4% of the sample had discontinued treatment. In France, an observational cohort study evaluating cholinesterase inhibitor use found that 54.7% of patients had discontinued after one year of follow-up.[54] A population-based study in Quebec examined oral bisphosphonate discontinuation, agents used to

treat osteoporosis.[55] Approximately 65% of patients discontinued their prescribed oral bisphosphonate within one year of follow-up. A limitation of these studies is that they use community-dwelling populations, which does not reflect the prescriber/staff treatment intentions that would likely exist within a LTCF. Benzodiazapines are also used in the LTCF setting, and a small Italian study reported on benzodiazepine discontinuation.[56] Among these patients 17.3% of benzodiazepine users discontinued therapy, mainly within the first year of follow-up. It is not clear if the lower discontinuation rate observed in this study is an effect of the LTCF, the drug under study, or between-country differences. Overall, discontinuation varies between drug classes, and the effect that residing in a LTCF has on discontinuation is unknown.

2.2 Predictors of APM Utilization and Variation in Long-term Care Facilities

Antipsychotic utilization can be influenced by characteristics of the individual patient, as well as facility and physician characteristics that comprise the external environment of a LTCF resident. Assessment of the association of individual- and facility-level factors on the probability of initiating, persisting, and discontinuing an APM prescription can contribute to an understanding of how these drugs are utilized among residents of LTCFs.

2.2.1 Patient Predictors of APM Utilization

Patient socio-demographic, comorbidity, behavioural, and other medication use characteristics have been tested for their association with APM utilization, but these studies have not always produced consistent findings.

Increasing age has been associated with a lower likelihood of APM utilization.[57-59] However, inverse associations between age and utilization have not been consistently identified,[10,13] The relationship between sex and APM utilization is also unclear. Some studies have found lower utilization among women, [13,59] while others have found lower utilization among men,[10,60] or no differences.[57] With respect to ethnicity, lower prescribing rates have been noted among Caucasians.[59]

The presence of comorbid conditions may be both positively and negatively associated with APM utilization. Higher scores on the Charlson Comorbidity Index, a global measure of

comorbidity, have been linked with a lower likelihood of APM dispensation.[13] Conversely, the presence of a dementia diagnosis is strongly associated with APM use. Eighty-nine percent of Swedish LTC residents with dementia were prescribed an APM, while 59% of residents without dementia received these agents.[60] In an Ontario study, the odds of a LTCF resident receiving an APM were 3.52 (95% CI: 3.24-3.82) times higher among patients with a history of dementia.[13] A descriptive study from the United Kingdom found that 32% of participants with dementia received an APM, compared to only 10% without dementia.[61] In the USA, a recent study found that 69% of residents with dementia diagnosis and 31% of residents without a dementia diagnosis were receiving an APM.[59] Psychosis has also been noted as a predictor of APM use.[59]

Behavioural measures have also been linked to APM use. Frailty, which has been measured with the Changes in Health, End-Stage Disease and Signs and Symptoms (CHESS) scale, was found to have an inverse association with APM prescribing rates.[59] Impaired cognition, using the Cognitive Performance Scale (CPS), was associated with lower APM use.[59] Conversely, severe behavioural problems, measured using the Behaviour Index, were positively correlated with APM use.[59] The literature indicates that patients with complex care needs are less likely to receive an APM, but APM use is very likely among patients with a brain disease like dementia or psychosis.

Polypharmacy, the use of multiple concurrent medications, can influence the decision of a physician to prescribe an APM, and also the patient's decision to adhere to treatment. A patient's medication history is often used as a predictor variable in APM utilization research, but the estimate of the effect has not been reported.[14,23,62] A literature review of medication adherence among seniors identified an inverse relationship between the number of drugs prescribed and adherence, which was one of the most consistent determinants of adherence identified. [63]

2.2.2 LTCF Predictors of APM Utilization

Characteristics of LTCFs that have been investigated for their association with APM utilization amongst institutionalized residents include size, staffing, geographic location, prevalence of psychotropic drugs, and disease prevalence. No consistent relationship between facility size and APM use has been described, with studies finding both no association,[57] and

decreased APM use with increased facility size.[64] The number of nursing staff in a facility has not been correlated with APM prescribing tendencies.[57,64] Some studies have identified that an increased availability of physicians is linked with higher APM prescribing rates,[64] but other studies have failed to confirm this association.[57] Additionally, the presence of nursing assistants was found to be negatively correlated with APM use, but the assistant-to-nurse ratio was positively correlated.[64] In the US, variations in APM prevalence has been observed, with the highest rates in the Northern United States.[64] The prevalence of other psychotropic agents like anxiolytic, hypnotic, and antidepressant use has been positively correlated with APM prevalence.[64] Finally, prevalence of dementia, behavioural symptoms, or psychiatric diagnoses was found to be positively associated with APM prevalence, while depression was negatively correlated.[64]

2.2.3 Variation amongst LTCFs in APM Utilization

Quantifying variation in APM utilization rates amongst facilities may contribute to an understanding of potential overuses of APMs. Variation has been described in previous research by dividing facility-level APM prescribing into quintiles; an Ontario study showed that the relative risk (RR) of dispensation between individuals in the highest and lowest quintiles was 3.0 (95% CI: 2.74-3.19). When the analysis stratified patients by the presence of diagnosed psychosis, dementia but no psychosis, and no dementia or psychosis the RR was 2.7 (95% CI: 2.35-3.09), 3.1 (95% CI: 2.81-3.39), and 2.9 (95% CI: 2.19-3.81), respectively.[14] A similar US study found that the RR of APM use in the highest versus lowest use facilities, after adjusting for facility and residents characteristics, was 1.37 (95% CI: 1.24-1.51). However, among residents with psychosis the RR was not statistically significant (RR = 1.14, 95% CI: 0.98-1.33). The elevated risk of APM therapy among high prescribing facilities was influenced by whether residents had dementia without psychosis (RR = 1.40, 95% CI: 1.23-1.59) or neither psychosis or dementia (RR = 1.54, 95% CI: 1.24-1.91).[59]

Variation in APM use has also been evaluated by studying differences in prescribing tendency between atypical and conventional APMs. A cross-sectional study using national MDS data from five US states evaluated the relative use of atypical to conventional APMs. Overall, the authors concluded that clinical and demographic differences between atypical and

conventional APM users tend to be relatively small, suggesting that facility, physician, and economic forces may influence the choice of APM.[65] A recent study quantified between-facility variation for prescribing of atypical vs. conventional APMs using a random-effects regression model. Patient and facility fixed effects accounted for 36% and 23% of the explained variance, respectively. A random intercept representing the conventional APM prescribing rate accounted for 81% of the explained variation.[62]

2.3 Summary and Conclusions

Discontinuation of APMs at the population level has mainly been studied among patients with schizophrenia. However, the duration of APM use, and its associated influences, are likely different when studying APM discontinuation in LTCF residents. In this regard, very little has been published, but some studies have examined the effects of APMs. Among older users of APMs, randomized clinical trials have demonstrated a survival benefit of discontinuing these pharmaceuticals, although some patients may be at risk of relapsing symptoms. Research examining the utilization of APMs among older patients appears to have focused on the initiation or the level of prevalent use of these agents. Dementia is a strong predictor of APM use among older LTCF residents. Other individual factors that may also influencing APM use are socio-demographic, disease comorbidity, polypharmacy, and psychological or behavioural problems. LTCF factors were also identified that may influence APM utilization, including facility size, staffing, and geographic location. Variation in facility-level APM prevalence has been documented. However, how patient- and facility-level factors influence this variation has only been described in the context of the choice of initial APM agent. In conclusion, APM discontinuation among elderly LTC residents and the predictive role of patient and facility level factors, from a population-based perspective is largely unknown at this time.

CHAPTER 3 – METHODS

3.1 Data sources

Saskatchewan's administrative health databases were used to conduct this research. Saskatchewan, like other Canadian provinces, has a program of universal health care, which covers a population of approximately 1.03 million people according to the 2011 Statistics Canada Census.[1] All members of the covered population receive health insurance benefits, which includes physician and hospital services, coverage for a large number of prescription medications listed in the provincial formulary, homecare, and access to long-term care for a user fee based on income.[66] Some individuals (members and veterans of the Canadian Forces, Royal Canadian Mounted Police, and federal inmates)[67] are not eligible for provincial health coverage, but make up a less than 1% of the population. Additionally, registered Indians (approximately 9% of the population) do not have their prescription drug costs covered by the province because coverage is provided by a federal health benefits program.[68,69]

The specific databases used for this research were the: Person Registry System (PRS), Discharge Abstracts Database (DAD), Medical Services Database (MSB), Prescription Drug Database (PDD), Institutional Supportive Care Home (ISCH) database, and the Resident Assessment Instrument – Minimum Data Set (RAI-MDS). All databases can be linked using a unique, anonymous, personal identifier to create a longitudinal healthcare utilization history for each person. These databases are maintained by the provincial Ministry of Health and were accessed at the SK Health Quality Council.

The PRS contains information pertaining to dates of health insurance coverage, birthdate, sex, and location of residence. The DAD contains records of hospitalizations and is produced upon discharge. At the start of the 2002/03 fiscal year (fiscal year is April 1 to March 31) a maximum of 25 five-digit diagnosis codes using the Canadian version of the tenth revision of the International Classification of Diseases (ICD-10-CA) are available for all hospital discharge abstracts.[68] Physician services remunerated on a fee-for-service basis are captured in the MSB; each billing claim contains a single three-digit ICD-9 code.[68] Some physicians receive a salary, and their services are not consistently collected because not all salaried physicians submit these administrative claims.[70] The PDD, which captures all dispensations of medications on the

provincial formulary, contains drug dispensation date, American Hospital Formulary Service (AHFS) Pharmacologic-Therapeutic Classification System (http://www.ahfsdruginformation.com/class/index.aspx), drug identification number (DIN), medication strength, dosage form, and quantity dispensed.[68] Individuals accessing the province's long-term care system have their program type, admission and discharge dates, and level of care requirements recorded in the ISCH database. In addition to resident characteristics, this database contains facility specific information such as location, affiliation, licensing status, and type of facility. Facility size, reported as the number of beds, and was provided directly by the SK Ministry of Health as data tables for each fiscal year.

Beginning April 2001 it was mandatory for all LTCFs to complete clinical assessments of their residents using the RAI-MDS 2.0. This tool collects information about a resident's functional, medical, psychiatric, and social status upon admission to a LTCF.[71] Assessments are also conducted quarterly, annually, and when a major change in health status occurs.[71] The quarterly assessments are a subset of the full RAI-MDS instrument.[71]

Several studies have found the reliability and validity of SK's administrative health databases to be good for population health and health services research.[72-78] Additionally, these databases have been used to study the pharmacoepidemiology of psychoactive drugs such as antidepressants, benzodiazepines, and APMs.[79]

3.2 Cohort design

The target population for this retrospective cohort study was seniors (≥ 65 years of age) that were dispensed an APM during their first episode of residence (EOR) in a SK LTCF, between April 1, 2004 and March 31, 2013. The EOR was defined as the time from LTCF admission until the first study end point: death, end of provincial healthcare coverage, LTCF discharge, or end of the study period. The EOR is the observation period during which APM discontinuation is evaluated among the cohort members. Only the first EOR was examined, to maintain a focus on incident users of long-term care. Residents starting their first EOR after April 1, 2012 were excluded. This criterion was used to provide all cohort members with the opportunity to have up to a minimum one year EOR (i.e., until the study ended on March 31, 2013).

Cohort members were required to be registered in the long-term care program, thereby excluding individuals accessing only the day care or temporary/night care programs. If an individual participated in either of these programs, as well as the long-term care program, only the records pertaining to long-term care were considered further. Also, if a resident was younger than 65 years of age when their first EOR began they were excluded because younger residents are fundamentally different than older residents.[80] For example, younger users of LTCFs have fewer deficits in daily living scores, lower use of mobility aids, fewer sensory impairments, and are more likely to have cognitive deficits than older residents.[80] Residents were also required to have one year of provincial healthcare coverage prior to the start of the first EOR in order to describe their disease comorbidities and pharmaceutical exposures. Some residents (3.9%) had gaps in health care coverage, and a gap between records of ≤ 90 days was considered continuous coverage, and a gap > 90 days was considered a loss of coverage. The majority of the gaps (77.5%) were only a single day.

Information on death and end of provincial healthcare coverage dates were obtained from the vital statistics and PRS databases, respectively. The date of LTCF discharge was obtained from the ISCH database. Each resident was first required to have a continuous record of LTCF residence. This was required because sequential ISCH records were observed to occur simultaneously in time, and these cases were classified as overlapping or nested records. Two records were overlapping when the first record's discharge date occurred after the second record's admission date. In these cases a continuous EOR was created by assigning the discharge date of the first record to the day prior to the admission date of the second record. A record was nested if the admission and discharge dates of one record were contained within the period between the admission and discharge dates of another record. The record that had the larger amount of time was retained to eliminate nested records. These changes to overlapping and nested records did not result in the exclusion of any individuals, and allowed the LTCF discharge date to be determined. When a gap of ≥ 1 day existed between the discharge and next admission dates the resident was deemed to be discharged. Additionally, if a resident transferred LTCFs more than 60 days after the start of the EOR then the resident was considered to be discharged. However, transfers within 60 days of the EOR start date were considered a continuation of the same EOR. Transfers were defined as two continuous ISCH records with a change in the LTCF identifier within a 60 day period. This is because admission to a LTCF in

SK is based upon the first available bed, and may not be the preferred LTCF of the resident.[81] When a bed becomes available in the residents preferred LTCF the resident is permitted to transfer to that facility. Among transferring residents, the first transfer occurred for most (74.5%) within 60 days of LTCF admission. Residents with multiple transfers usually experienced their secondary transfers more than 60 days after admission to a LTCF (63.9%).

To evaluate APM discontinuation it was necessary for each resident to be dispensed a minimum of one APM after the start of the first EOR. For some residents the first APM dispensation occurred after the EOR ended; these residents were excluded because they were not eligible to discontinue an APM in the cohort observation period. Similarly, residents that were dispensed an APM on the same day their EOR ended were excluded.

3.3 Measures

3.3.1 Outcome variable

The outcome variable, time to APM discontinuation, was derived from the data contained within the PDD. All drugs assigned the AHFS code for APMs (28:16.08) covered by the SK drug plan during the study period were identified. The generic names of these drugs were collected, and included: chlorpromazine, clozapine, flupenthixol, fluphenazine, haloperidol, loxapine, mesoridazine, olanzapine, pericyazine, perphenazine, pimozide, pipotiazine, prochlorperazine, quetiapine, risperidone, thioridazine, thiothixene, trifluoperazine, ziprasidone, and zuclopenthixol. Additionally, the APM methotrimeprazine was manually included in the generic drug name list because it was classified as a miscellaneous agent (AHFS 28:24.92). A list of all APMs covered by the SK drug plan during the study period is included in Appendix A. Using the generic drug names a list of all associated DINs were identified. Since DINs uniquely identify all drug products sold in Canada,[82] all dispensations for APM agents were identified from the DIN list by linking them with the complete set of dispensation records for cohort members. All dispensations for the agent prochlorperazine were excluded because this agent is primarily used as an anti-nausea agent.

The date of the first APM dispensation was defined as the index date. Cohort members were considered persistent users of APMs until the exposure period from their last dispensation

had elapsed, which was 35 days after the last APM dispensation date. Therefore, the APM discontinuation date was 35 days after the last APM dispensation date. Thirty-five days was chosen because dispensations to residents of LTCFs are commonly filled for the entire LTCF approximately once a month. This was supported by the dispensation data in this study, where 18.9% and 38.5% of subsequent APM dispensations were separated by 22-28 and 29-35 days, respectively. Additionally, 85.0% of all subsequent dispensations were separated by ≤ 35 days.

The time to event for each cohort member was the time between the first APM dispensation, and the earliest study end point. The endpoint under study was APM discontinuation. To establish APM discontinuation a 35 day non-exposure period was added to the discontinuation date, and required to elapse, without any alternative endpoints occurring. Therefore, residents were only considered a discontinued APM user if their EOR did not end within 70 days of the last APM dispensation date. If this condition was not met the resident was considered to be right censored (Figure 3.1).

3.3.2 Explanatory variables

3.3.2.1 Patient-level explanatory variables

Explanatory variables included demographics, comorbidity, behavioural characteristics, drug exposures, and health care utilization. The demographic variables of age and sex were defined from the PRS on the cohort entry date. Age was grouped as 65-74, 75-84, 85-94 and ≥ 95 years of age.[83] Additionally, the fiscal year of the index APM dispensation was included in this variable group.

The Charlson index,[84] the number of distinct prescription medications,[85] and level of care were selected as measures of disease comorbidity. The Charlson index was defined using all diagnoses captured in the hospital DAD and physician MSB in the one-year period prior to the cohort entry date. The Charlson index scores were categorized as 0, 1-2, 3-4, and 5 or more, as per the original publication.[84] All medications covered by the PDD are grouped by a six-digit AHFS code, and these groups were considered to be the same medication. The total number of unique prescription medications used within the year prior to the cohort entry date was a measure of disease comorbidity, and categorized as 0-3, 4-6, and 7 or more distinct prescription

medications. Level of care was determined from the ISCH database at the time of LTCF admission, and categorized into four levels: (1) level 1 (supervisory care) and level 2 (limited personal care), (2) level 3 (intensive personal / nursing care), (3) level 4a (specialized supervisory care, emphasis on management of advanced mental deterioration), and (4) level 4b (supportive care), level 4c (restorative care), and level 4 unclassified.

Psychiatric comorbidities were also identified, and were defined from diagnosis codes in the DAD or MSB within one year of the cohort entry date. These included dementia (including Alzheimer's disease), mood disorders (i.e., depression and anxiety), alcohol and drug use, schizophrenia, and movement disorders (i.e., Parkinson's disease, Huntington disease, and movement tics).[13,14,86] The ICD codes used to select these comorbid conditions are reported in Appendix B.

Behavioural disturbances and cognitive status of LTC residents was determined using the MDS-Challenging Behaviour Profile (MDS-CBP)[52] and the MDS-Cognitive Performance Scale (MDS-CPS)[87], respectively. The MDS-CBP is a 16-item scale ranging from 0 to 30, derived from sections E, B, and F of the full RAI-MDS assessment. The full MDS assessment is completed upon admission to a LTCF, when major changes in functional status occur, and on an annual basis.[71] We considered the MDS-CBP score upon admission to a LTCF. The MDS-CBP score was categorized as: none (MDS-CBP = 0), mild (MDS-CBP = 1 to 4), moderate (MDS-CBP =5-9), severe (MDS-CBP = 10-14), and extreme (MDS-CBP $\geq$ 15).[51] The MDS-CPS provides a measure of cognitive impairment using five MDS items that classifies patients to one of seven groups, ranging from 0 (intact) to 7 (very severe impairment) that correlates with the Mini-Mental State Examination.[87,88] The MDS-CPS scores were grouped to categorize each resident as minimally impaired (0-1), moderately impaired (2-3), and severely impaired (4-6).[59]

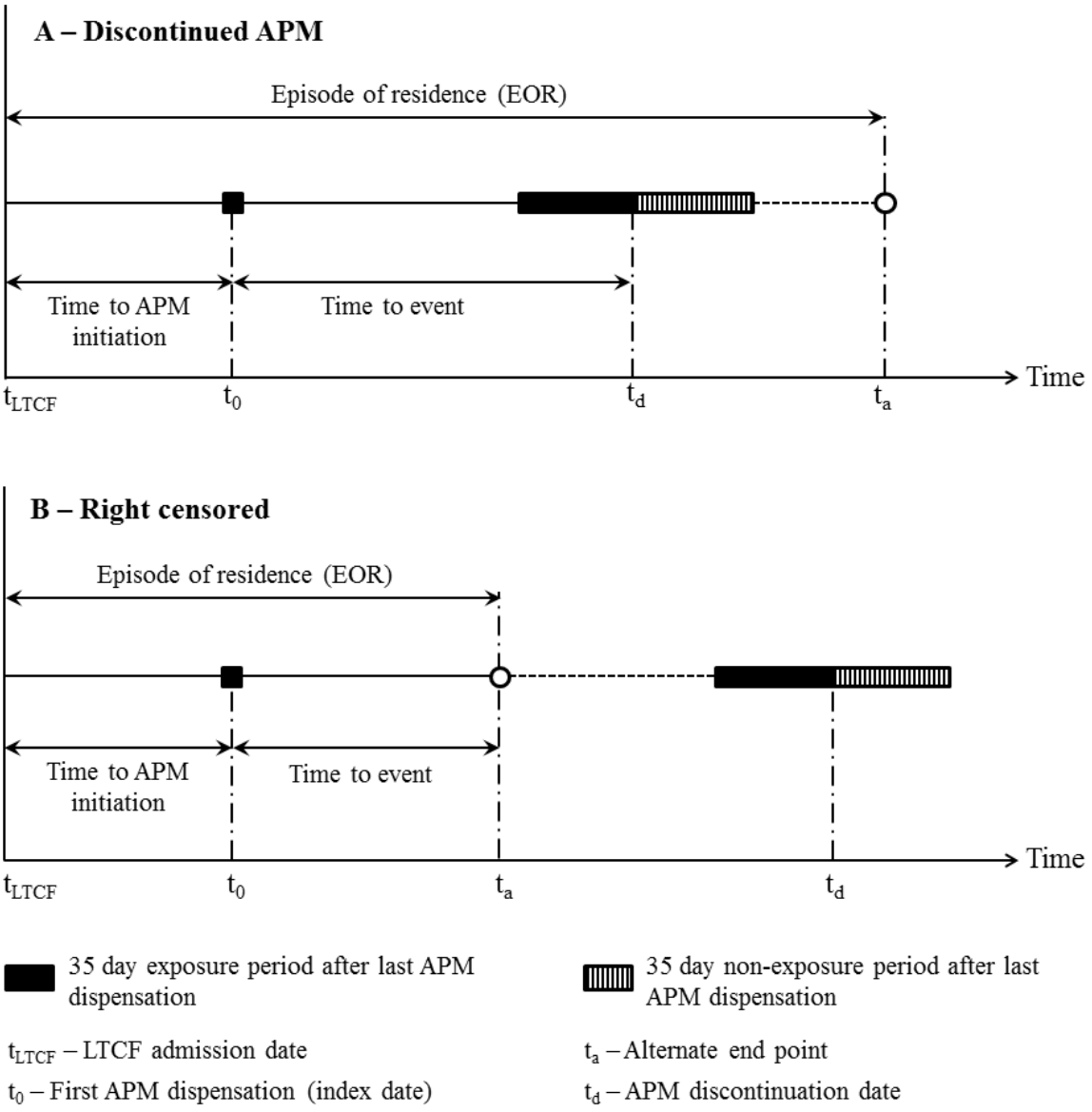

Figure 3.1 Characteristics of time to APM initiation, time to event, and EOR among residents that discontinued APMs (A) or were right censored (B).Time to APM initiation ($t_0 - t_{LTCF}$), time to event (discontinue APM: $t_d - t_0$; right censored: $t_a - t_0$), and EOR ($t_a - t_{LTCF}$).

Psychotropic drug use was determined from the PDD, and included exposure to benzodiazepines, antidepressants, anticholinergic agents, cholinesterase inhibitors, and APMs. These drugs were examined in the year prior to the cohort entry date to evaluate the most recent exposure, and were grouped as not used, prior user, and current user. A drug was considered not used when there was no dispensation record for the specific agent. A prior user had their last dispensation more than 30 days before the cohort entry date, while a current user had a

dispensation within 30 days of the cohort entry date. Finally, the time to APM initiation was defined as the number of days between LTCF admission (i.e., cohort entry date) and the index date. Time to initiation was classified as 0-30 days, 31-90 days, and > 90 days. Psychotropic drugs covered by the SK drug plan during the study period are reported in Appendix A.

Health care utilization was measured by LTCF transfers and hospitalization. The transfer status (yes/no) of a LTCF resident was evaluated during the first 60 days after the cohort entry date (see section 3.2). Hospitalization for more than one day in the year prior to the cohort entry date and after the index date was defined using the DAD.

3.3.2.2 Facility-level explanatory variables

Characteristics describing features of LTCFs was their licensing status, affiliation, type, location, and size; these characteristics were assigned based on the index date for the resident. Facility size was exclusively contained within the data provided by the Ministry of Health, and was defined by the number of long-term care beds classified as small (1-35 beds), medium (36-100 beds), or large (> 100 beds). The location of the LTCF was defined by the health region it was located within, and was grouped as the Regina Qu'Appelle Health Region, Saskatoon Health Region, or other health region. The other health region group included 11 health regions that do not contain a major urban centre. There were four types of facilities: health centres, hospitals, special care homes (nursing home), or integrated facilities. Health centres, hospitals, and integrated facilities are considered a type of LTCF because in smaller, rural centres they have dedicated long-term care beds. Each facility's affiliation was classified as affiliate (operated privately, non-profit), contract (operated privately for profit), or amalgamate (operated publicly, by the health region). Additionally, facilities were identified as either licensed or non-licensed. For some residents the facility affiliation or licensing variables were missing. Since this information was also recorded within the datasets containing facility size information, the missing values were replaced with the values from this data source.

3.4 Descriptive analysis

The cohort was described on resident- and facility-level characteristics using counts, means, and medians, as appropriate. These results were stratified by APM discontinuation status (i.e., discontinued vs. continued). Utilization characteristics of APMs were evaluated between the first dispensation and the end of follow-up for each individual. The number of dispensations, the largest time between two dispensations, the type of index APM, and switching between APMs were reported. Facility-specific discontinuation percentages were calculated by dividing the number of residents discontinuing APMs by the total number of residents of a facility.

Each resident was assigned to a quintile based on the length, in days, of their EOR. The proportion of cohort members that discontinued APMs within each quintile was calculated. Additionally, each individual was divided into quintiles based on the length of time to event, in days. The proportion of total discontinuations within each quintile was used to understand when discontinuations were occurring relative to the first APM dispensation.

APM discontinuations were also described by their frequency, and average and median time to event. Additionally, adjusted estimates of the average and median time to APM discontinuation were calculated using the non-parametric Kaplan-Meier (KM) method. The probability of APM discontinuation was described using non-parametric survival functions.

3.5 Inferential analysis

Semi-parametric Cox proportional hazards regression models were used to analyse the time to event data. Since cohort members were residing within LTCFs, it is possible the independence assumption is violated. This assumption was investigated using a Cox regression model with a random effect for facility. Two such models were run, the first without any predictors and the second with the fully adjusted model with covariate time interactions. Individuals with missing values for any of the explanatory variable were excluded, leaving 7361 individuals from the cohort of 8358 for analysis.

Univariate models were used to describe the unadjusted effect of each covariate. Partially adjusted models included sets of variables: demographics, health status, behavioural characteristics, drug exposure, health care utilization, and LTCF measures. The baseline

partially adjusted model included only the demographic variables, which were age, sex, and index fiscal year (i.e., year first APM was dispensed). All other partially adjusted model included this set of demographic variables, in addition to another variable group. In addition, sequentially adjusted models incorporated each variable group one at a time to produce a fully adjusted model containing all covariates. Reference categories for all explanatory variables were indicated within the tables reporting model results.

The proportional hazards assumption was assessed for the fully adjusted model by testing the correlation between the scaled Schoenfeld residuals and the rank order of the event times for a non-zero slope (Appendix C, Table C1). In addition, three graphical methods were used to confirm the presence of non-proportional hazards. Specifically, the KM probability of APM discontinuation was plotted against time, in days. The KM log cumulative hazard plot and the scaled Schoenfeld residuals were plotted against the natural logarithm of time to event (days). A covariate-time interaction was added to the fully adjusted model for all variables that violated the proportional hazards assumption, to produce the final analytic model. Further interactions were not pursued for two reasons. First, all predictor variables were categorical which would increase the total number of estimated parameters substantially, and possibly result in over-fitting the model. Second, since non-proportional hazards were present the parameter estimates of interaction terms could be biased.

The models were compared using the Akaike Information Criterion (AIC), the Schwartz-Bayesian Criterion (SBC), and the likelihood ratio test (LRT). The LRT is a test of the global null hypothesis that the parameter estimates of the model with more predictors are equal to zero. A significant test statistic indicates that one or more of the covariates are significantly associated with APM discontinuation. The AIC and SBC are related to the LRT, but penalize the log likelihood according to the number of model parameters included (i.e., all covariate levels). An improvement in the fit of the model is detected by a lower value of the AIC or SBC statistics.

The discrimination of the partially and sequentially adjusted models was measured using the c-statistic, which is based on observed and predicted survival.[89] If the c-statistic has a value of 0.5 it indicates that the model prediction is no better than chance, while a value of 1 represents perfect prediction.[90] A c-statistics in the range of 0.7 to 0.8, 0.8 to 0.9, and greater than 0.9 represent acceptable, excellent, and outstanding discriminative performance, respectively.[91]

Other tests of model fit included an evaluation of outliers (Figure D1) and influential data points (Table D1) using deviance and scaled score residuals, respectively (Appendix D).[92] Hazards ratios (HRs) were reported, along with estimated 95% CI. For the fully adjusted model with covariate time interactions the HRs were calculate from the model and reported for the variables with non-proportional hazards at 0, 90, 180, 365, and 730 days. All analyses were conducted using SAS 9.3 using the PHREG procedure, and normally distributed random effects were incorporated with the inclusion of a RANDOM statement to account for clustering of individuals within LTCFs.

3.6 Sub-group and sensitivity analyses

Sub-group analyses were performed for the variables characterizing dementia diagnosis, schizophrenia diagnosis, transfer to a new LTCF, prior APM dispensation, and time to APM initiation. These sub-group analyses were conducted for the analysis of discontinuation within the EOR and time to event quintiles.

Sensitivity analyses were used to assess changes in the results due to informative censoring, violation of proportional hazards, and changes in the measurement of time to discontinuation. The non-informative censoring assumption of the Cox proportional hazards model was evaluated with sensitivity analyses for two extreme violations of this assumption. Complete positive correlation between the censoring and APM discontinuation time was created by assigning all censoring times to be equal to the APM discontinuation date. Second, by assigning the APM discontinuation date to be equal to the longest time to event for censored individuals, complete negative correlation between censoring and APM discontinuation dates was induced in the data. When the proportional hazards assumption was violated, a sensitivity analysis during a period when hazards were proportional was performed by truncating follow-up at 6 months.

Two alternate definitions of APM discontinuation were incorporated to assess the impact on the outcome variable and analytic results. Like the primary definition of APM discontinuation both alternate definitions maintained the 35 day exposure period after the last APM dispensation. But they differed by shortening or lengthening the non-exposure period. When the non-exposure period was shortened to 0 days, residents were classified as discontinuing APMs if their EOR did not end before 35 days had passed since the last APM

dispensation. When the non-exposure period was lengthened to 70 days, only those individuals whose EOR did not end before a total of 105 days had passed since the last APM dispensation were classified as discontinuers.

CHAPTER 4 – RESULTS

4.1 Description of study cohort

A total of 88,016 individuals were eligible to enter the study cohort based on the criteria of having at least one record in the long-term care (i.e., ISCH) database. After applying all study exclusion criteria (Figure 4.1) a total of 8358 were retained in the cohort, which represent 35.7% of LTCF residents eligible to be dispensed an APM. There were 6729 (80.5%) members of the cohort that had continuous use of APMs during the observation period, and 1629 (19.5%) discontinued APM use during the observation period.

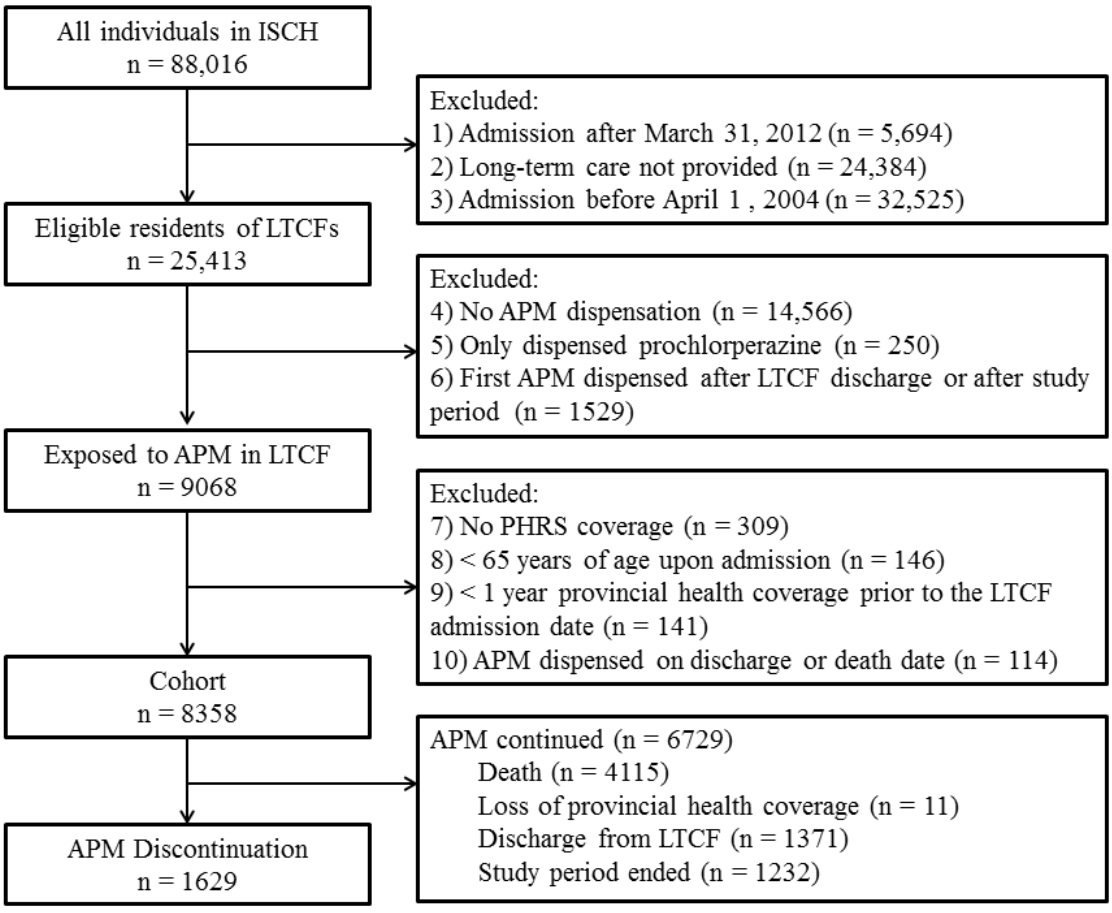

Figure 4.1 Study population flow chart detailing exclusion criteria.

The patient characteristics of the cohort are described in Table 4.1. The average age was 84.5 years (SD = 7.1) and nearly two-thirds of the cohort (63.2%) was female. The Charlson index score had a mean of 1.8 (SD = 2.1), and three-quarters (74.7%) of the cohort had a score between zero and two, indicating low comorbidity. Polypharmacy was common in the year prior to LTCF admission, with 53.3% of residents having dispensations for seven or more different drugs. The level of care was concentrated in the second category, indicating the provision of intensive personal or specialized supervisory care. Among psychiatric comorbidities, dementia (46.7%), schizophrenia (53.0%), and mood disorders (29.3%) were commonly recorded. Approximately half of the cohort (52.6%) had an MDS-CPS score indicating moderate cognitive impairment. The MDS-CBP scores indicate that most cohort members had mild (36.7%) or moderate (26.0%) levels of challenging behaviour on their first RAI-MDS assessment. At least half of the cohort did not have exposure to APMs (50.7%), antidepressants (66.2%), benzodiazepines (74.1%), anticholinergic agents (87.9%), or cholinergic agents (88.5%) in the year prior to LTCF admission. There were 4123 cohort members with APM exposure prior to admission to a LTCF, and 71.2% of them had their most recent dispensation within 30 days of admission. Most members of the study cohort (58.1%) were dispensed their first APM within 30 days of their LTCF admission date. The median time to APM initiation was 22 days. Within 90 days of LTCF admission, three-quarters (76.6%) of the cohort members had been dispensed their first APM. After admission, transfers between LTCFs occurred for approximately one-third (35.5%) of the cohort members. Hospitalization was common (69.7%) before LTCF admission, but less frequent after admission (41.7%).

In terms of the characteristics of facilities in which the cohort members resided, the vast majority of residents were in licensed LTCFs (94.4%) and facilities defined as special care homes (89.8%) (Table 4.2). Nearly half of these LTCFs were located within either the Saskatoon (25.9%) or Regina Qu'Appelle (18.8%) health regions and half (56.6%) were operated as amalgamates (i.e., publicly run). Medium (36-100 beds) and large (> 100 beds) facilities were the most common size of LTCF in which the study cohort resided.

Table 4.1 Patient characteristics of the study cohort.

Variables	Overall (N = 8358)	APM Discontinued (N = 1629)	APM Continued (N = 6729)
Demographic	**n (%)**	**n (%)**	**n (%)**
Age			
65-74 years	903 (10.8%)	163 (10.0%)	740 (11.0%)
75-84 years	3219 (38.5%)	594 (36.5%)	2625 (39.0%)
85-94 years	3770 (45.1%)	783 (48.1%)	2987 (44.4%)
95+ years	466 (5.6%)	89 (5.5%)	377 (5.6%)
Sex			
Female	5285 (63.2%)	1094 (67.2%)	4191 (62.3%)
Male	3073 (36.8%)	535 (32.8%)	2538 (37.7%)
Index fiscal year			
04/05	792 (9.48%)	163 (10.0%)	629 (9.4%)
05/06	940 (11.2%)	221 (13.6%)	719 (10.7%)
06/07	1014 (12.1%)	229 (14.1%)	785 (11.7%)
07/08	1041 (12.5%)	204 (12.5%)	837 (12.4%)
08/09	1043 (12.5%)	243 (14.9%)	800 (11.9%)
09/10	1054 (12.6%)	189 (11.6%)	865 (12.9%)
10/11	1135 (13.6%)	190 (11.7%)	945 (14.0%)
11/12	1089 (13.0%)	159 (9.8%)	930 (13.8%)
12/13	250 (3.0%)	31 (1.9%)	219 (3.3%)
Comorbidity			
Psychiatric comorbidities			
Dementia	3904 (46.7%)	762 (46.8%)	3142 (46.7%)
Schizophrenia	4429 (53.0%)	827 (50.8%)	3602 (53.5%)
Mood disorder	2445 (29.3%)	426 (26.2%)	2019 (30.0%)
Alcohol or drug abuse	206 (2.5%)	31 (1.9%)	175 (2.6%)
Extrapyramidal symptoms	294 (3.5%)	48.0 (3.0%)	246 (3.7%)
Charlson index			
0	2367 (28.3%)	480 (29.5%)	1887 (28.0%)
1-2	3878 (46.4%)	747 (45.9%)	3131 (46.5%)
3-4	1405 (16.8%)	265 (16.3%)	1140 (16.9%)
≥ 5	708 (8.47%)	137 (8.41%)	571 (8.49%)
Level of care			
Level 1	131 (1.6%)	21 (1.3%)	110 (1.6%)
Level 2	3707 (44.4%)	724 (44.4%)	2983 (44.3%)
Level 3	2267 (27.1%)	425 (26.1%)	1842 (27.4%)
Level 4	2251 (26.9%)	459 (28.2%)	1792 (26.6%)
AHFS drug categories, $\bar{x} \pm$ SD (median)	7.3 ± 4.3 (7.0)	6.9 ± 4.1 (7.0)	7.4 ± 4.3 (7.0)
0-3	1584 (19.0%)	350 (21.5%)	1234 (18.3%)
4-6	2322 (27.8%)	448 (27.5%)	1874 (27.8%)
≥ 7	4452 (53.3%)	831 (51.0%)	3621 (53.8%)
Behavioural			
MDS-CPS			
Minimally impaired (0-1)	1300 (15.6%)	289 (17.7%)	1011 (15.0%)
Moderately impaired (2-3)	4395 (52.6%)	878 (53.9%)	3517 (52.3%)
Severely impaired (4-6)	2142 (25.6%)	441 (27.1%)	1701 (25.3%)
Missing	521 (6.2%)	21 (1.3%)	500 (7.4%)

Table 4.1 Continued

Variables	Overall (N = 8358)	APM Discontinued (N = 1629)	APM Continued (N = 6729)
Behavioural			
MDS-CBP			
None (0)	1323 (15.8%)	315 (19.3%)	1008 (15.0%)
Mild (1-4)	3071 (36.7%)	686 (42.1%)	2385 (35.4%)
Moderate (5-9)	2169 (26.0%)	422 (25.9%)	1747 (26.0%)
Severe (10-14)	890 (10.6%)	133 (8.2%)	757 (11.2%)
Extreme (≥ 15)	378 (4.5%)	50 (3.1%)	328 (4.9%)
Missing	527 (6.3%)	23 (1.4%)	504 (7.5%)
Drug exposure			
Days to APM initiation			
0-30 days after admission	4858 (58.1%)	868 (53.3%)	3990 (59.3%)
31-90 days after admission	1543 (18.5%)	295 (18.1%)	1248 (18.5%)
> 90 days after admission	1957 (23.4%)	466 (28.6%)	1491 (22.2%)
Last APM dispensation before LTCF admission			
None in previous year	4235 (50.7%)	901 (55.3%)	3334 (49.5%)
> 30 days	1167 (14.0%)	193 (11.8%)	974 (14.5%)
≤ 30 days	2956 (35.4%)	535 (32.8%)	2421 (36.0%)
Last antidepressant dispensation before LTCF admission			
None in previous year	5537 (66.2%)	1116 (68.5%)	4421 (65.7%)
> 30 days	1150 (13.8%)	200 (12.3%)	950 (14.1%)
≤ 30 days	1671 (20.0%)	313 (19.2%)	1358 (20.2%)
Last benzodiazepine dispensation before LTCF admission			
None in previous year	6191 (74.1%)	1261 (77.4%)	4930 (73.3%)
> 30 days	1096 (13.1%)	188 (11.5%)	908 (13.5%)
≤ 30 days	1071 (12.8%)	180 (11.0%)	891 (13.2%)
Last anticholinergic dispensation before LTCF admission			
None in previous year	7345 (87.9%)	1487 (91.3%)	5858 (87.1%)
> 30 days	603 (7.2%)	84 (5.2%)	519 (7.7%)
≤ 30 days	410 (4.9%)	58 (3.6%)	352 (5.2%)
Last cholinergic dispensation before LTCF admission			
None in previous year	7401 (88.5%)	1407 (86.4%)	5994 (89.1%)
> 30 days	628 (7.51%)	149 (9.2%)	479 (7.1%)
≤ 30 days	329 (3.9%)	73 (4.5%)	256 (3.80%)
Health care utilization			
No transfer to new LTCF	5393 (64.5%)	1065 (65.4%)	4328 (64.3%)
No hospitalization prior to LTCF admission	2529 (30.3%)	522 (32.0%)	2007 (29.8%)
No hospitalization after LTCF admission	4870 (58.3%)	868 (53.3%)	4002 (59.5%)

Abbreviations – AHFS: American hospital formulary system, APM: antipsychotic medication, MDS-CBP: minimum dataset challenging behaviour profile, MDS-CPS: minimum dataset cognitive performance scale, $\bar{x} \pm$ SD: mean ± standard deviation.

Table 4.2 LTCF characteristics of the study cohort.

Variables	Overall (N = 8358)	APM Discontinued (N = 1629)	APM Continued (N = 6729)
	n (%)	**n (%)**	**n (%)**
Facility license status			
Non-licensed	468 (5.6%)	51 (3.2%)	417 (6.20%)
Licensed	7889 (94.4%)	1578 (96.9%)	6311 (93.8%)
Facility affiliation			
Amalgamate (public)	4728 (56.6%)	897 (55.1%)	3831 (56.9%)
Affiliate (private, non-profit)	2686 (32.1%)	560 (34.4%)	2126 (31.6%)
Contract (private, for profit)	943 (11.3%)	172 (10.6%)	771 (11.5%)
Facility type			
Health centre	24 (0.3%)	$< 6^a$	$\geq 6^a$
Hospital	467 (5.6%)	$\geq 6^a$	$\geq 6^a$
Special care home	7508 (89.8%)	1499 (92.0%)	6009 (89.3%)
Integrated facility	358 (4.3%)	76 (4.67%)	282 (4.2%)
Facility location			
Other Health Region	4621 (55.3%)	900 (55.2%)	3721 (55.3%)
Regina Qu'Appelle Health Region	1570 (18.8%)	290 (17.8%)	1280 (19.0%)
Saskatoon Health Region	2166 (25.9%)	439 (26.9%)	1727 (25.7%)
Facility size			
Small (1-35 beds)	1728 (20.7%)	310 (19.0%)	1418 (21.1%)
Medium (36-100 beds)	3308 (39.6%)	689 (42.3%)	2619 (38.9%)
Large (> 100 beds)	2787 (33.3%)	574 (35.2%)	2213 (32.9%)
Missing	535 (6.4%)	56 (3.4%)	479 (7.1%)

Abbreviations – APM: antipsychotic medication, LTCF: long-term care facility, $\bar{x} \pm SD$: mean ± standard deviation.
Notes – a: frequency counts indicated by < 6 and ≥ 6 are are suppressed to protect privacy.

4.2 APM utilization and discontinuation

Utilization of APMs by the study cohort was characterized by dispensation count, time between subsequent dispensations, the type of APM first dispensed, and if a switch in APM occurred (Table 4.3). A quarter (24.5%) of the cohort members received more than 25 APM dispensations, and another 26.5% received 10 to 25 dispensations during the observation period. A few cohort members (11.8%) received only a single APM dispensation (Table 4.3). Generally, dispensation of APMs occurred regularly, with 73.9% of the study cohort members having less than 70 days between any two APM dispensations. Relatively few members of the cohort (2.4%) had a gap of more than a year between two dispensations. The first type of APM dispensed was primarily risperidone (58.9%) or quetiapine (28.9%). Most residents (73.7%) did not switch APMs during the observation period.

Table 4.3 Antipsychotic medication utilization characteristics of among the study cohort.

	Overall (N = 8358) n (%)	**APM Discontinued (N = 1629) n (%)**	**APM Continued (N = 6729) n (%)**
Dispensation count			
1 APM dispensation	989 (11.8%)	341 (20.9%)	648 (9.6%)
2-5 APM dispensations	2102 (25.1%)	451 (27.7%)	1651 (24.5%)
6-9 APM dispensations	1012 (12.1%)	211 (13.0%)	801 (11.9%)
10-25 APM dispensations	2211 (26.5%)	361 (22.2%)	1850 (27.5%)
> 25 APM dispensations	2044 (24.5%)	265 (16.3%)	1779 (26.4%)
Largest gap between APM dispensations			
≤ 35 days	2663 (31.9%)	452 (27.7%)	2211 (32.9%)
36-70 days	3512 (42.0%)	562 (34.5%)	2950 (43.8%)
71-105 days	463 (5.5%)	84 (5.2%)	379 (5.6%)
106-365 days	528 (6.3%)	135 (8.3%)	393 (5.8%)
> 1 year	203 (2.4%)	55 (3.4%)	148 (2.2%)
Missing[a]	989 (11.8%)	341 (20.9%)	648 (9.6%)
Index APM dispensation			
Risperidone	4919 (58.9%)	995 (61.1%)	3924 (58.3%)
Quetiapine	2418 (28.9%)	413 (25.4%)	2005 (29.8%)
Haloperidol	578 (6.9%)	139 (8.5%)	439 (6.5%)
Other	443 (5.3%)	82 (5.0%)	361 (5.4%)
Switched APM			
No	6156 (73.7%)	1136 (69.7%)	5020 (74.6%)
Yes	1213 (14.5%)	152 (9.3%)	1061 (15.8%)
Missing[a]	989 (11.8%)	341 (20.9%)	648 (9.6%)

Abbreviations – APM: antipsychotic medication. *Notes* – a: Only 1 APM dispensation.

Variation in APM discontinuation rates were examined across facilities. The proportion of discontinuers varied from less than 5% to more than 30%, with most facilities ranging between 10% and 30% (Figure 4.2). Only 204 residents were in facilities with discontinuation rates between 0%-5%, and none of these facilities had more than 25 residents. Some facilities had discontinuation rates of 30% or more; a total of 599 individuals were located in these facilities . These residents primarily resided in facilities with discontinuation rates between 30%-40%, but a few facilities had very high discontinuation rates of close to 100%. The average of facility specific discontinuations was calculated for facilities according to affiliation, health region, and size. Discontinuation varied from 17.4% (95% CI: 15.1%-19.7%) among amalgamate facilities to 20.4% (95% CI: 16.9%-24.0%) among affiliates (Figure 4.3). The facilities in the Regina Qu'Appelle health region had the lowest discontinuation (15.2%, 95% CI: 10.9%-19.5%), while discontinuation was highest in Saskatoon facilities (Figure 4.4). Smaller LTCFs had the lowest discontinuation (18.2%, 95% CI: 16.0%-20.3%) and medium facilities had the highest discontinuation (22.5%, 95% CI: 19.2%-25.7%) (Figure 4.5). LTCFs with a missing facility size had low discontinuation (7.5%, 95% CI: 0.9%-14.0%).

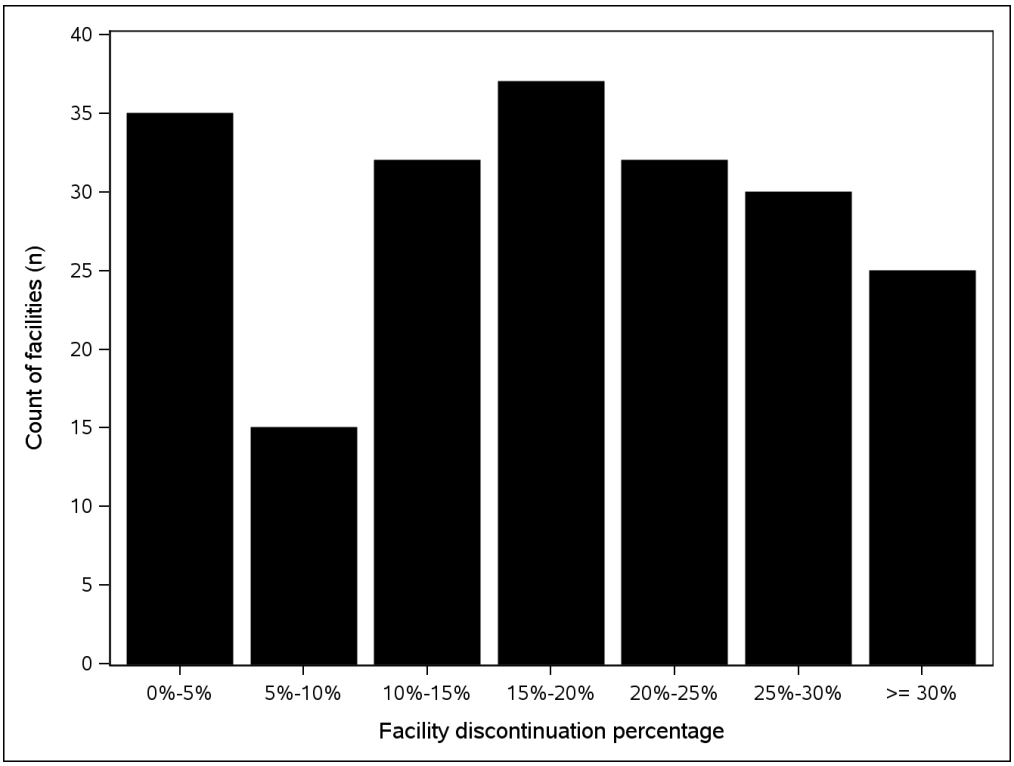

Figure 4.2 Histogram of facility specific discontinuation percentages (n = 206).

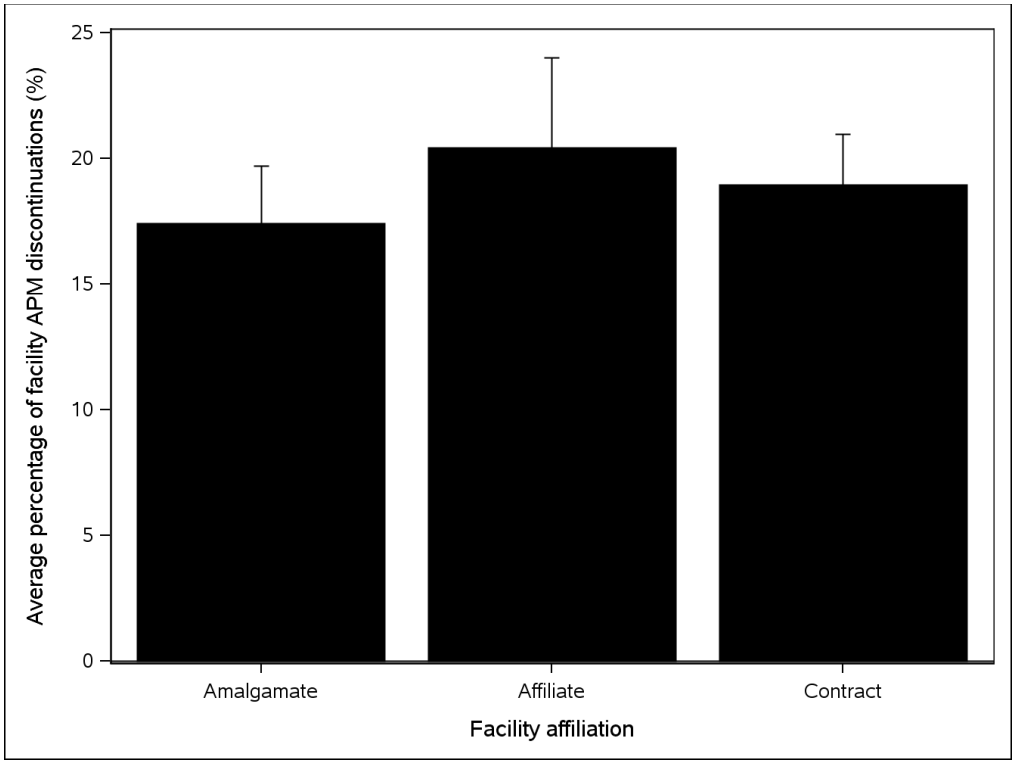

Figure 4.3 Facility specific discontinuation percentages averaged by facility affiliation (n = 206).

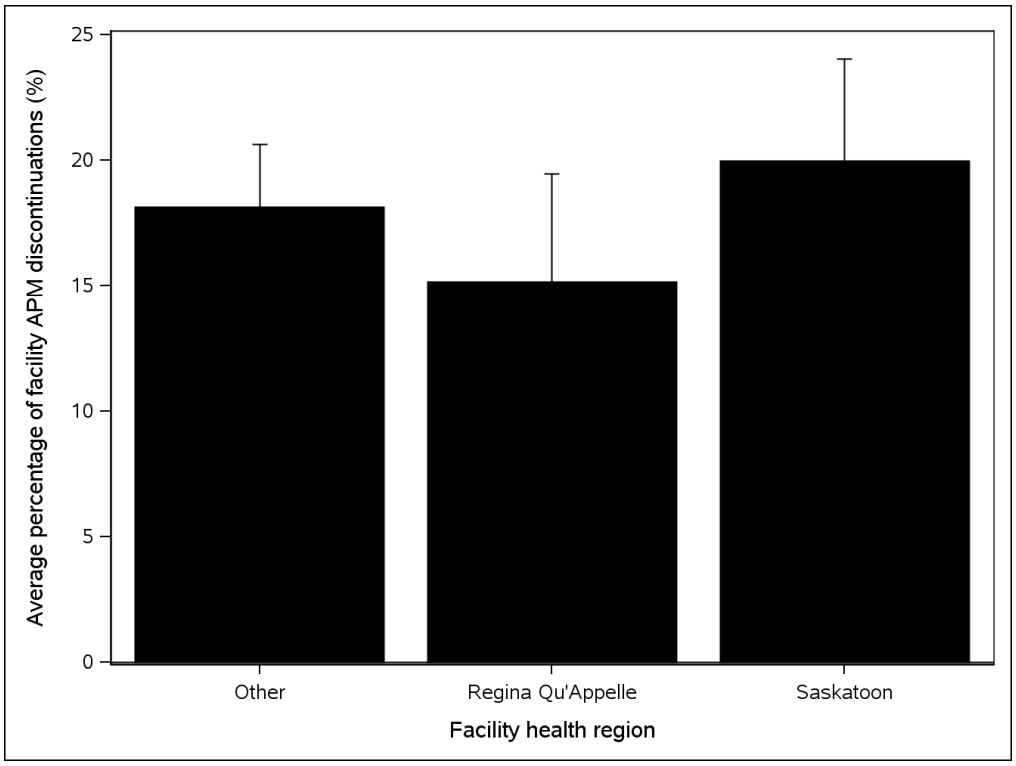

Figure 4.4 Facility specific discontinuation percentages averaged by facility health region (n = 206).

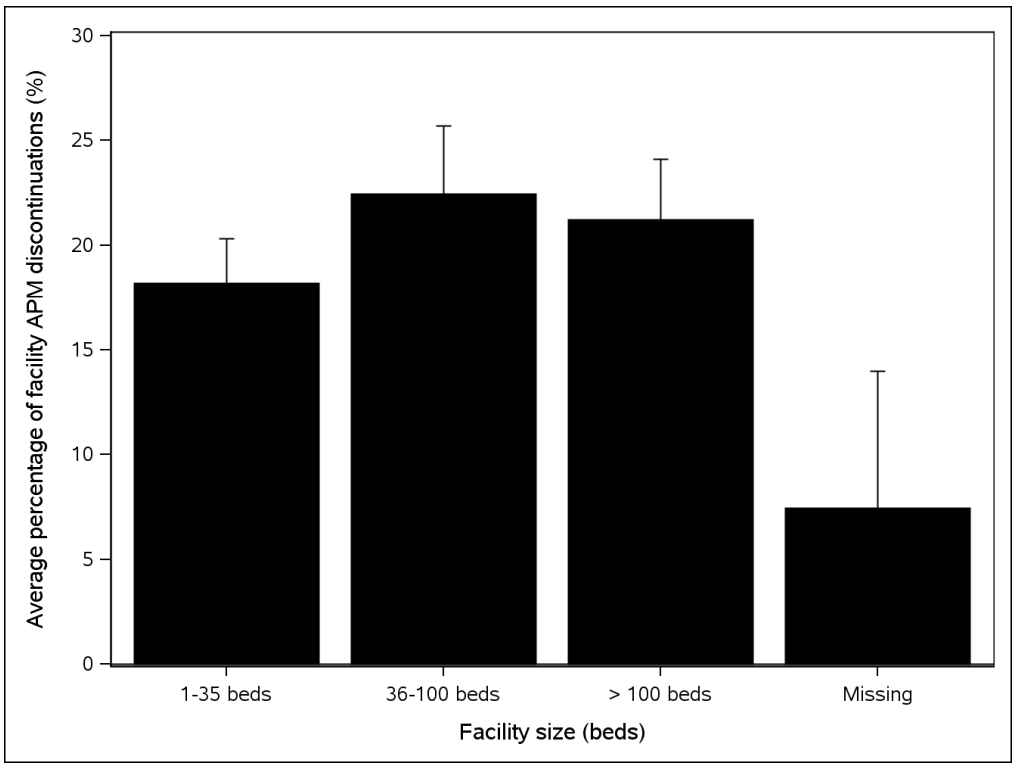

Figure 4.5 Facility specific discontinuation percentages averaged by facility size (n = 206).

The EOR for each resident was calculated and divided into quintiles. More than 60% of the cohort had an EOR greater than 365 days (Table 4.4). Discontinuation was low (2%) for cohort members with an EOR in the first quintile (1-124 days), but higher (32.6%) for cohort members in the fifth EOR quintile (Table 4.4). This trend of discontinuation being concentrated among study cohort members with long EORs was observed when the analysis was stratified by the key study variables of dementia diagnosis, schizophrenia diagnosis, transfer to a new LTCF, APM exposure, and days to APM initiation. Discontinuation increased from 17.9% to 19.1% and 23.8% among residents initiating APMs within 0-30 days, 31-90 days and > 90 days of LTCF admission.

Analysis of the distribution of APM discontinuations by follow-up time quintiles showed that the greatest proportion of discontinuations (27.2%) occurred within 55 days of the first APM dispensation (Table 4.5). The percentage of discontinuations decreased slightly among residents that were within the second (56-169 days) or third (170-447 days) time to event quintiles. Discontinuations occurred the least frequently among the cohort members within the longest times to event quintiles. Only 15.6% and 16.5% of the cohort members that discontinued APMs were in the fourth (448-901 days) and fifth (902-3265 days) time to event quintiles, respectively. The percentage of cohort members that were right censored due to an alternative event occurring before APM discontinuation was relatively constant across time to event quintiles, ranging between 18.1% and 21.0%. Stratification of the results by dementia diagnosis, schizophrenia diagnosis, transfer to a new LTCF, last APM dispensation, and days to APM initiation revealed a similar trend of the discontinuations occurring most frequently within the first time to event quintile. Stratification indicates that a greater percentage of discontinuations occurred in the first time to event quintile (1-55 days) for residents that did not have a diagnosis code for dementia, or schizophrenia. Similarly, cohort members that transferred to a new LTCF, had no prior APM dispensations, or initiated APMs > 90 days after admission to a LTCF had higher percentage of APM discontinuations within the first time to event quintile.

Table 4.4 Characteristics of cohort members who discontinued APMs, stratified by duration of EOR quintile

		EOR day quintiles, n (%)[a]					
		Q1 1-124 days	**Q2 125-395 days**	**Q3 396-754 days**	**Q4 755-1290 days**	**Q5 1291-3265 days**	**Cohort Total**
Overall	Discontinued APM	33 (2.0%)	271 (16.1%)	363 (21.7%)	417 (25.0%)	545 (32.6%)	1629 (19.5%)
	Total	1668	1680	1673	1665	1672	8358
Dementia							
No	Discontinued APM	19 (2.2%)	135 (15.8%)	196 (21.5%)	230 (25.3%)	287 (30.8%)	867 (19.5%)
	Total	850	853	911	908	932	4454
Yes	Discontinued APM	14 (1.7%)	136 (16.4%)	167 (21.9%)	187 (24.7%)	258 (34.9%)	762 (19.5%)
	Total	818	827	762	757	740	3904
Schizophrenia							
No	Discontinued APM	23 (2.8%)	137 (17.5%)	179 (23.7%)	205 (26.6%)	258 (32.4%)	802 (20.4%)
	Total	820	785	756	771	797	3929
Yes	Discontinued APM	10 (1.2%)	134 (15.0%)	184 (20.1%)	212 (23.7%)	287 (32.8%)	827 (18.7%)
	Total	848	895	917	894	875	4429
Transfer to new LTCF							
No	Discontinued APM	21 (2.1%)	170 (16.2%)	218 (20.3%)	274 (25.0%)	382 (33.1%)	1065 (19.7%)
	Total	1019	1051	1075	1094	1154	5393
Yes	Discontinued APM	12 (1.8%)	101 (16.1%)	145 (24.2%)	143 (25.0%)	163 (31.5%)	564 (19.0%)
	Total	649	629	598	571	518	2965
Last APM exposure before LTCF admission							
None in previous year	Discontinued APM	23 (2.9%)	136 (16.6%)	209 (24.5%)	236 (26.5%)	297 (33.6%)	901 (21.3%)
	Total	786	820	854	891	884	4235
> 30 days	Discontinued APM	< 6[b]	≥ 6[b]	39 (18.9%)	49 (22.7%)	67 (29.9%)	193 (16.5%)
	Total	271	250	206	216	224	1167
≤ 30 days	Discontinued APM	≥ 6[b]	≥ 6[b]	115 (18.8%)	132 (23.7%)	181 (32.1%)	535 (18.1%)
	Total	611	610	613	558	564	2956
Days to APM initiation after LTCF admission							
0-30 days	Discontinued APM	27 (2.1%)	189 (18.6%)	197 (21.1%)	197 (24.2%)	258 (32.4%)	868 (17.9%)
	Total	1297	1017	935	813	796	4858
31-90 days	Discontinued APM	6 (1.7%)	63 (15.8%)	69 (22.8%)	86 (32.1%)	71 (31.8%)	295 (19.1%)
	Total	349	400	303	268	223	1543
> 90 days	Discontinued APM	0 (0.0%)	19 (7.2%)	97 (22.3%)	134 (22.9%)	216 (33.1%)	466 (23.8%)
	Total	22	263	435	584	653	1957

Abbreviations – APM: antipsychotic medication, EOR: episode of residence, LTCF: long-term care facility. *Notes* – a: proportions are calculated within each EOR quintile by dividing the discontinued APM count by the total count. b: frequency counts indicated by < 6 and ≥ 6 are are suppressed to protect privacy.

Table 4.5 Frequencies and percentages of cohort members that continued or discontinued APMs, stratified by time to event quintiles.

		Time to event quintile, n (%)[a]					
		Q1 1-55 days	**Q2 56-169 days**	**Q3 170-447 days**	**Q4 448-901 days**	**Q5 902-3265 days**	**Cohort Total**
Overall	Discontinued APM	443 (27.2%)	331 (20.3%)	332 (20.4%)	254 (15.6%)	269 (16.5%)	1629
	Continued APM	1221 (18.1%)	1349 (20.0%)	1341 (19.9%)	1416 (21.0%)	1402 (20.8%)	6729
Dementia							
No	Discontinued APM	274 (31.6%)	163 (18.8%)	159 (18.3%)	151 (17.4%)	120 (13.8%)	867
	Continued APM	678 (18.9%)	682 (19.0%)	742 (20.7%)	739 (20.6%)	746 (20.8%)	3587
Yes	Discontinued APM	169 (22.2%)	168 (22.0%)	173 (22.7%)	103 (13.5%)	149 (19.6%)	762
	Continued APM	543 (17.3%)	667 (21.2%)	599 (19.1%)	677 (21.5%)	656 (20.9%)	3142
Schizophrenia							
No	Discontinued APM	252 (31.4%)	171 (21.3%)	157 (19.6%)	108 (13.5%)	114 (14.2%)	802
	Continued APM	663 (21.2%)	661 (21.1%)	609 (19.5%)	619 (19.8%)	575 (18.4%)	3127
Yes	Discontinued APM	191 (23.1%)	160 (19.3%)	175 (21.2%)	146 (17.7%)	155 (18.7%)	827
	Continued APM	558 (15.5%)	688 (19.1%)	732 (20.3%)	797 (22.1%)	827 (23.0%)	3602
Transfer to new LTCF							
No	Discontinued APM	259 (24.3%)	211 (19.8%)	234 (22.0%)	166 (15.6%)	195 (18.3%)	1065
	Continued APM	746 (17.2%)	844 (19.5%)	872 (20.1%)	937 (21.6%)	929 (21.5%)	4328
Yes	Discontinued APM	184 (32.6%)	120 (21.3%)	98 (17.4%)	88 (15.6%)	74 (13.1%)	564
	Continued APM	475 (19.8%)	505 (21.0%)	469 (19.5%)	479 (20.0%)	473 (19.7%)	2401
Last APM exposure before LTCF admission							
None in previous year	Discontinued APM	320 (35.5%)	184 (20.4%)	168 (18.6%)	125 (13.9%)	104 (11.5%)	901
	Continued APM	732 (22.0%)	686 (20.6%)	700 (21.0%)	662 (19.9%)	554 (16.6%)	3334
> 30 days	Discontinued APM	37 (19.2%)	46 (23.8%)	40 (20.7%)	32 (16.6%)	38 (19.7%)	193
	Continued APM	171 (17.6%)	205 (21.0%)	173 (17.8%)	205 (21.0%)	220 (22.6%)	974
≤ 30 days	Discontinued APM	86 (16.1%)	101 (18.9%)	124 (23.2%)	97 (18.1%)	127 (23.7%)	535
	Continued APM	318 (13.1%)	458 (18.9%)	468 (19.3%)	549 (22.7%)	628 (25.9%)	2421
Days to APM initiation after LTCF admission							
0-30 days	Discontinued APM	190 (21.9%)	189 (21.8%)	182 (21.0%)	136 (15.7%)	171 (19.7%)	868
	Continued APM	654 (16.4%)	880 (22.1%)	723 (18.1%)	831 (20.8%)	902 (22.6%)	3990
31-90 days	Discontinued APM	82 (27.8%)	56 (19.0%)	54 (18.3%)	61 (20.7%)	42 (14.2%)	295
	Continued APM	283 (22.7%)	233 (18.7%)	236 (18.9%)	244 (19.6%)	252 (20.2%)	1248
> 90 days	Discontinued APM	171 (36.7%)	86 (18.5%)	96 (20.6%)	57 (12.2%)	56 (12.0%)	466
	Continued APM	284 (19.0%)	236 (15.8%)	382 (25.6%)	341 (22.9%)	248 (16.6%)	1491

Abbreviations – APM: antipsychotic medication, LTCF: long-term care facility. *Notes* – a: proportions calculated by dividing the quintile discontinued APM count by the cohort total discontinued APM count, with an analogous calculation used for residents that continued APMs.

The primary definition of APM discontinuation specified that a 35 day period of non-exposed follow-up time must be observed with no alternate events occurring within that period. Two alternate definitions that shortened the non-exposure period to 0 days or lengthened the non-exposure period to 70 days were used in a sensitivity analysis. APM discontinuation frequencies were 2298 (27.5%), and 1424 (17.0%) for the shorter non-exposure, and longer non-exposure definitions, respectively (Table 4.6). Using the primary definition of APM discontinuation the time to event, on average, was 1.40 years (SD = 1.59), while the median was 0.80 years (9.6 months) (Table 4.6). These values were nearly identical to the results for both alternate APM discontinuation definitions. The KM non-parametric estimator of the median time to event was 6.5 years under the primary definition of APM discontinuation (Figure 4.2). Shortening the definition of the non-exposure period shortened the median KM estimate of time to event to 4.1 years. The longer non-exposure period definition of discontinuation increased the KM estimate of the median time to event to be greater than 6.5 years.[1]

Table 4.6 Discontinuation counts, crude time to event, and Kaplan-Meier estimates of time to event for three definitions of APM discontinuation.

	APM discontinuation definitions		
	35 days of non-exposure time after APM discontinuation[a]	0 days of non-exposure time after APM discontinuation[b]	70 days of non-exposure time after APM discontinuation[b]
APM discontinued, n (%)	1629 (19.5%)	2298 (27.5%)	1424 (17.0%)
Time to event (years), mean ± SE (median)			
Overall	1.40 ± 1.59 (0.80)	1.40 ± 1.59 (0.80)	1.41 ± 1.59 (0.80)
Discontinued	1.14 ± 1.36 (0.55)	1.20 ± 1.39 (*)	1.13 ± 1.37 (0.56)
Continued	1.47 ± 1.63 (0.88)	1.48 ± 1.65 (0.89)	1.46 ± 1.62 (0.88)
Kaplan-Meier estimates of time to event (years)			
Median (95% CI)	6.5 (5.7 – NE)	4.1 (4.0 – 4.3)	*
Mean ± SE	5.27 ± 0.07	4.40 ± 0.06	5.56 ± 0.07

Abbreviations – APM: antipsychotic medication, SE: standard error, 95% CI: 95% confidence interval. *Notes* – a: primary definition of APM discontinuation. b: definitions of APM discontinuation used for sensitivity analyses. *Symbols* – *, cell size ≤ 5 and suppressed to protect privacy; NE, not estimated.

[1] Cannot report the exact KM median time to event for the 70 day non-exposure period because the number of residents with this time to event is < 6, resulting in the suppression of this value for privacy.

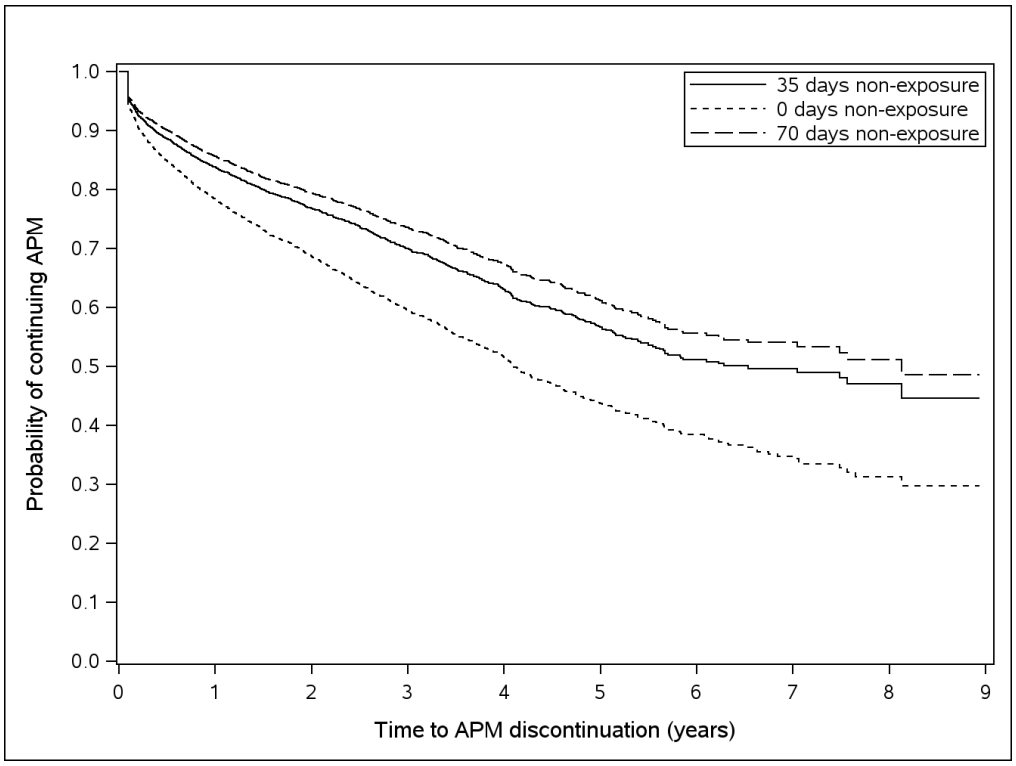

Figure 4.6 Kaplan-Meier survival probability for three definitions of APM discontinuation that varied the length of the non-exposure period after the last APM dispensation.

4.3 Cox regression model results

Clustering of individuals within LTCFs could lead to violation of the independence assumption, but the analysis indicates minimal clustering. The null model (i.e., no predictors) had a covariance (SD) of 0.064 (0.020) and was significant ($p = 0.0003$). The addition of the clustering analysis to the fully adjusted model with covariate time interactions increased the covariance (SD) to 0.111 (0.028), which was also significant ($p < 0.0001$).

Model selection information and fit statistics are reported in Table 4.7. The inclusion of demographic variables (model 2) reduced the AIC when compared to the null model (model 1). The LRT for these nested models was statistically significant ($p < 0.0001$). To examine the contribution of the remaining sets of variables that measured comorbidity, behaviour, drug exposures, health care utilization, and LTCF characteristics, each variable group was individually added to the baseline (i.e., demographic) model. The addition of variables measuring comorbidity (model 3), behavioural (model 4), drug exposure (model 5), and health care utilization (model 6) resulted in a reduced AIC when compared to model 2. The LRT

statistic for each of these nested models was statistically significant (p-value ranged from 0.009 to < 0.0001). The variable group containing LTCF characteristics (model 7) resulted in a non-significant LRT (p = 0.2477).

The groups of explanatory variables were also added sequentially to assess fit as the complexity of the models increased (models 1, 2, 3, 8, 9, 10, 11). The AIC decreased with sequential addition of variables describing demographic characteristics, comorbidity, behavioural traits, drug exposures, health care utilization measures, and LTCF features. All LRTs were statistically significant, except for the LRT associated with the LTCF variables (model 11). Additionally, it should be noted that the AIC of the model including drug exposures (model 9) decreased by only a small amount with the addition of health care utilization (model 10) and LTCF variables (model 11). Finally, the inclusion of covariate-time interactions to adjust for non-proportional hazards resulted in a large decrease in the AIC, and a statistically significant LRT (p < 0.0001; model 12). The violation of the proportional hazards assumption is demonstrated by crossing KM survival curves for sex (Figure 4.7) and dementia (Figure 4.8). The proportional hazards assumption was also violated for prior APM exposure, MDS-CPS, hospitalization before LTCF admission, and facility location (Appendix E).

The SBC increased for most models, which indicates poorer fit after penalizing for the number of included variables. It decreased only after adding covariate-time interactions (model 12). As for the c-statistic, the value for the fully adjusted model (i.e., model 11) indicated good discrimination, but the value was slightly lower than for less complex models.

The HRs for all covariates are reported for univariate, partially adjusted, and fully adjusted main effects models, as well as for the extended Cox model with covariate-time interactions (Table 4.8). For variables that interact with time the HR is reported over time (Table 4.9).

The demographic variables of sex and index year had a statistically significant association with APM discontinuation. The HR for the index fiscal year decreased between 2007/08 and 2011/12 from 0.80 (95% CI: 0.66-0.97) to 0.58 (95% CI: 0.47-0.71). The effect of sex was not proportional over time, and at the start of follow-up the risk of APM discontinuation was 2.66 (95% CI: 2.26-3.13) times greater for females than males (Table 4.9). Over two years of follow-up the HR decreased to 0.92 (95% CI: 0.82-1.04).

Table 4.7 Model fit statistics

Model description	df	AIC	SBC	c-statistic (95% CI)
Model 1: No predictors	0	25288	25288	-
Model 2: Demographic	11	25251	25310	0.92 (0.89-0.95)
Model 3: Demographic + comorbidity	24	25218	25347	0.89 (0.86-0.92)
Model 4: Demographic + behavioural	17	25205	25296	0.89 (0.86-0.92)
Model 5: Demographic + drug exposure	23	25176	25299	0.88 (0.84-0.91)
Model 6: Demographic + health care utilization	14	25246	25321	0.91 (0.88-0.94)
Model 7: Demographic + LTCF	17	25256	25346	0.92 (0.89-0.94)
Model 8: Demographic + comorbidity + behavioural	30	25179	25339	0.87 (0.84-0.90)
Model 9: Demographic + comorbidity + behavioural + drug exposure	42	25121	25345	0.85 (0.81-0.88)
Model 10: Demographic + comorbidity + behavioural + drug exposure + health care utilization	45	25118	25358	0.84 (0.81-0.88)
Model 11: Demographic + comorbidity + behavioural + drug exposure + health care utilization + LTCF	51	25120	25393	0.84 (0.80-0.87)
Model 12: Demographic + comorbidity + behavioural + drug exposure + health care utilization + LTCF + covariate-time interactions	60	22249	22569	-

Abbreviations – AIC: Akaike Information Criterion, df: degrees of freedom, LTCF: long-term care facility, SBC: Schwartz-Bayesian Criterion. *Notes* – An estimate of the survival function cannot be calculated for models with time interactions.

Among comorbidity variables, only dementia had a significant effect on the hazard of APM discontinuation. This effect varied over time, and at the start of follow-up residents with dementia were 0.86 (95% CI: 0.73-1.01) times as likely to discontinue an APM as those without dementia (Table 4.9). After two years no difference in APM discontinuation (HR [95% CI]: 1.01 [0.89-1.15]) was present between cohort members with and without dementia.

The MDS-CPS had a statistically significant association with APM discontinuation that varied over time, while an inconsistent association with the outcome was detected for the MDS-CBP variable. When the first APM was dispensed residents with moderate cognitive impairment were 4.20 (95% CI: 3.29-5.36) times more likely to discontinue APMs than those with mild cognitive impairment. A similar HR (HR [95% CI]: 4.07 [3.09-5.38]) was observed for residents with severe cognitive impairment. After two years of follow-up APM discontinuation was no different between residents with minimal, moderate, or severe cognitive impairment. Considering MDS-CBP scores, residents with mild challenging behaviours were more likely to discontinue (HR [95% CI]: 1.16 [1.00-1.35]), while those with severe challenging behaviours were less likely to discontinue APMs (HR [95% CI]: 0.76 [0.61-0.95]), than residents with no challenging behaviours. However, the hazard of APM discontinuation did not differ between moderate or extreme MDS-CBP scores, relative to no challenging behaviours.

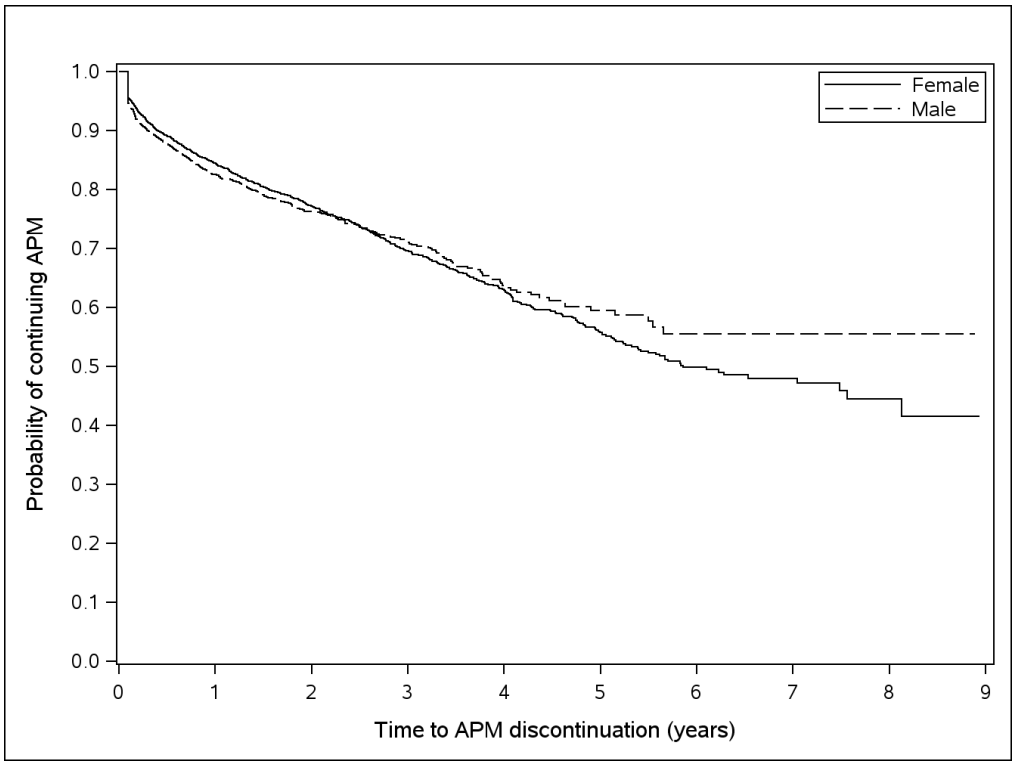

Figure 4.7 Kaplan-Meier survival probability by resident sex.

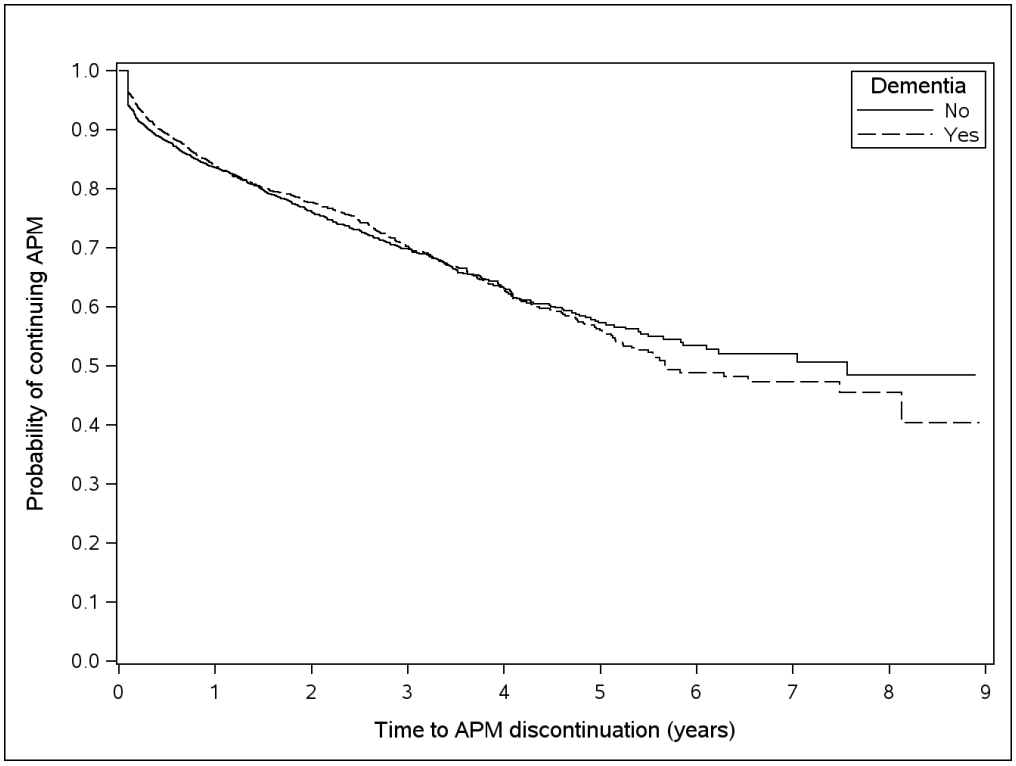

Figure 4.8 Kaplan-Meier survival probability by dementia diagnosis.

Table 4.8 Univariate, partially adjusted, and fully adjusted Cox proportional hazards regression models of APM discontinuation.

Explanatory variables[a]	Univariate model	Partially adjusted model[b]	Fully adjusted model[c]	Covariate-time interaction model [d]
Demographic	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Age				
75-84	1.18 (0.98-1.41)	1.18 (0.99-1.41)	1.10 (0.91-1.31)	1.19 (0.98-1.44)
85-94	1.53 (1.29-1.82)*	1.56 (1.31-1.86)*	1.38 (1.15-1.65)*	1.34 (1.11-1.63)*
≥ 95	1.72 (1.32-2.24)*	1.76 (1.34-2.29)*	1.53 (1.16-2.01)*	1.17 (0.89-1.55)
65-74	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Sex				
Female	1.00 (0.90-1.11)	0.93 (0.83-1.03)	0.93 (0.83-1.04)	*
Male	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Index fiscal year				
04/05	0.73 (0.59-0.89)*	0.72 (0.58-0.88)*	0.77 (0.63-0.95)*	0.98 (0.80-1.21)
05/06	0.97 (0.81-1.17)	0.97 (0.80-1.16)	1.02 (0.85-1.23)	1.00 (0.83-1.21)
06/07	0.94 (0.78-1.13)	0.94 (0.78-1.13)	0.96 (0.80-1.15)	0.87 (0.72-1.05)
07/08	0.82 (0.68-0.99)*	0.81 (0.67-0.98)*	0.84 (0.69-1.01)	0.80 (0.66-0.97)*
09/10	0.89 (0.73-1.08)	0.88 (0.72-1.06)	0.89 (0.73-1.08)	0.76 (0.63-0.93)*
10/11	0.95 (0.78-1.15)	0.93 (0.77-1.13)	0.94 (0.77-1.14)	0.75 (0.61-0.91)*
11/12	0.99 (0.81-1.22)	0.98 (0.79-1.20)	0.97 (0.79-1.19)	0.58 (0.47-0.71)*
12/13	-	-	-	-
08/09	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Comorbidity				
Dementia				
Yes	0.97 (0.88-1.07)	1.05 (0.94-1.16)	1.03 (0.92-1.15)	-
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Schizophrenia				
Yes	0.78 (0.71-0.86)*	0.82 (0.74-0.91)*	0.88 (0.79-0.98)*	1.01 (0.90-1.13)
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Mood disorder				
Yes	0.75 (0.67-0.84)*	0.79 (0.70-0.89)*	0.84 (0.74-0.95)*	0.94 (0.83-1.07)
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Alcohol or drug abuse				
Yes	0.73 (0.51-1.05)	0.87 (0.60-1.26)	0.84 (0.58-1.22)	0.94 (0.65-1.37)
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Extrapyramidal symptoms				
Yes	0.74 (0.56-0.99)*	0.81 (0.60-1.08)	0.87 (0.65-1.17)	1.02 (0.76-1.37)
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Charlson index				
1-2	0.94 (0.83-1.06)	0.94 (0.83-1.06)	0.94 (0.83-1.05)	0.94 (0.83-1.06)
3-4	1.01 (0.86-1.17)	0.99 (0.85-1.16)	0.98 (0.84-1.15)	0.99 (0.84-1.15)
≥ 5	1.00 (0.82-1.21)	1.00 (0.82-1.21)	1.00 (0.82-1.21)	0.95 (0.78-1.16)
0	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Level of care				
Level 2	1.56 (1.00-2.44)*	1.61 (1.03-2.52)*	1.74 (1.10-2.76)*	1.46 (0.91-2.33)
Level 3	1.43 (0.91-2.23)	1.48 (0.94-2.33)	1.70 (1.07-2.71)*	1.32 (0.82-2.11)
Level 4	1.85 (1.18-2.89)*	1.83 (1.17-2.87)*	2.03 (1.27-3.24)*	1.65 (1.02-2.65)*
Level 1	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
AHFS drug category				
4-6	0.89 (0.77-1.03)	0.89 (0.77-1.03)	0.94 (0.81-1.09)	0.88 (0.75-1.02)
≥ 7	0.94 (0.83-1.07)	0.97 (0.85-1.11)	1.11 (0.96-1.29)	0.90 (0.77-1.04)
0-3	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)

Table 4.8 Continued

Explanatory variables[a]	Univariate models	Partially adjusted models[b]	Fully adjusted models[c]	Covariate time interaction models[d]
MDS-CPS				
Moderately impaired (2-3)	0.81 (0.71-0.93)*	0.87 (0.76-1.01)	0.87 (0.75-1.01)	*
Severely impaired (4-6)	0.91 (0.78-1.05)	1.09 (0.93-1.28)	1.11 (0.93-1.32)	*
Minimally impaired (0-1)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
MDS-CBP				
Mild (1-4)	0.95 (0.82-1.08)	0.96 (0.83-1.10)	1.02 (0.88-1.17)	1.16 (1.00-1.35)*
Moderate (5-9)	0.80 (0.69-0.92)*	0.80 (0.68-0.93)*	0.86 (0.73-1.00)	0.95 (0.80-1.12)
Severe (10-14)	0.58 (0.47-0.71)*	0.58 (0.47-0.72)*	0.64 (0.51-0.79)*	0.76 (0.61-0.95)*
Extreme (≥ 15)	0.54 (0.40-0.72)*	0.54 (0.40-0.73)*	0.59 (0.43-0.81)*	0.73 (0.53-1.01)
None (0)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Drug exposure				
Days to APM initiation after LTCF admission				
31-90 days	1.17 (1.03-1.34)*	1.06 (0.92-1.21)	1.01 (0.88-1.17)	0.95 (0.82-1.10)
> 90 days	1.54 (1.37-1.73)*	1.23 (1.08-1.41)*	1.16 (1.01-1.33)*	1.07 (0.93-1.24)
0-30 days	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Last APM dispensation before LTCF admission				
≤ 30 days	0.64 (0.57-0.71)*	0.74 (0.65-0.85)*	0.75 (0.65-0.86)*	*
> 30 days	0.63 (0.54-0.74)*	0.72 (0.61-0.85)*	0.72 (0.60-0.85)*	-
None in previous year	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Last antidepressant dispensation before LTCF admission				
≤ 30 days	0.81 (0.72-0.93)*	0.94 (0.82-1.07)	0.94 (0.82-1.09)	1.12 (0.97-1.29)
> 30 days	0.92 (0.79-1.08)	1.03 (0.88-1.21)	1.03 (0.88-1.22)	1.05 (0.89-1.23)
None in previous year	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Last benzodiazepine dispensation before LTCF admission				
≤ 30 days	0.73 (0.62-0.85)*	0.80 (0.68-0.94)*	0.80 (0.68-0.95)*	0.79 (0.66-0.93)*
> 30 days	0.77 (0.66-0.90)*	0.84 (0.72-0.99)*	0.86 (0.73-1.01)	0.88 (0.75-1.04)
None in previous year	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Last anticholinergic dispensation before LTCF admission				
≤ 30 days	0.75 (0.57-0.98)*	0.89 (0.68-1.16)	0.81 (0.62-1.07)	0.78 (0.60-1.03)
> 30 days	0.74 (0.59-0.93)*	0.86 (0.69-1.08)	0.79 (0.63-1.00)*	0.80 (0.63-1.01)
None in previous year	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Last cholinergic dispensation before LTCF admission				
≤ 30 days	1.07 (0.84-1.35)	1.14 (0.90-1.45)	1.22 (0.96-1.56)	1.31 (1.02-1.67)*
> 30 days	1.19 (1.00-1.41)*	1.28 (1.07-1.52)*	1.40 (1.16-1.67)*	1.38 (1.15-1.66)*
None in previous year	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Health care utilization				
Transfer to new LTCF				
Yes	1.07 (0.96-1.19)	1.02 (0.91-1.14)	0.91 (0.81-1.02)	0.87 (0.77-0.98)*
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Hospitalization prior to LTCF admission				
Yes	1.12 (1.00-1.24)*	1.11 (0.99-1.24)	1.10 (0.97-1.24)	*
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Hospitalization after LTCF admission				
Yes	1.12 (1.01-1.24)*	1.14 (1.03-1.26)*	1.13 (1.02-1.26)*	1.12 (1.01-1.24)*
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
LTCF				
Facility affiliation				
Affiliate (private, non-profit)	1.04 (0.93-1.16)	1.03 (0.91-1.18)	1.09 (0.95-1.25)	1.16 (1.00-1.33)*
Contract (private, for profit)	1.07 (0.91-1.27)	1.12 (0.92-1.36)	1.09 (0.89-1.34)	0.96 (0.78-1.19)
Amalgamate (public)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)

Table 4.8 Continued

Explanatory variables[a]	Univariate models	Partially adjusted models[b]	Fully adjusted models[c]	Covariate time interaction models[d]
Regina Qu'Appelle	0.94 (0.82-1.07)	0.92 (0.78-1.07)	0.98 (0.83-1.16)	*
Saskatoon	1.08 (0.96-1.21)	1.04 (0.90-1.19)	1.10 (0.95-1.27)	*
Other	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Facility size				
Small (1-35 beds)	0.95 (0.82-1.09)	0.92 (0.79-1.07)	0.92 (0.79-1.07)	0.90 (0.77-1.06)
Medium (36-100 beds)	1.10 (0.98-1.23)	1.05 (0.93-1.19)	1.02 (0.90-1.15)	1.01 (0.89-1.14)
Large (> 100 beds)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Time interaction with				
Sex	N/A	N/A	N/A	*
Dementia	N/A	N/A	N/A	*
MDS-CPS	N/A	N/A	N/A	*
Last APM dispensation before LTCF admission	N/A	N/A	N/A	*
Hospitalization prior to LTCF admission	N/A	N/A	N/A	*
Facility location	N/A	N/A	N/A	*

Abbreviations – AHFS: American hospital formulary system, APM: antipsychotic medication, HR (95% CI): Hazard ratio (95% confidence interval), LTCF: long-term care facility, MDS-CBP: minimum dataset challenging behaviour profile, MDS-CPS: minimum dataset cognitive performance scale, N/A: not applicable *Notes* – a: Explanatory variables are grouped by concept, which is indicated by the ***bold-italicized*** terms. b: Partially adjusted models include all group variables and demographic variables. Therefore, the six partially adjusted models include the variable groups demographic, demographic + comorbidity, demographic + behavioural, demographic + drug exposure, demographic + health care utilization, and demographic + LTCF. c: Fully adjusted models include all variables. d: Covariate time interaction model is a fully adjusted model with the addition of time-covariate interactions. *Symbols* - *, $p < 0.05$.

Exposure to APMs, benzodiazepines, and cholinergic agents were all found to have a statistically significant association with APM discontinuation (Tables 4.8 and 4.9). Residents dispensed a benzodiazepine within 30 days of LTCF admission had a significantly lower risk (HR = 0.79, 95% CI: 0.66-0.93) of discontinuing APMs than cohort members without prior benzodiazepine exposure. However, no difference existed between residents not dispensed a benzodiazepine and those that were dispensed one more than 30 days before LTCF admission. Cohort members that were dispensed a cholinergic agent were more likely to discontinue APMs, compared to those without a dispensation. Residents dispensed a cholinergic agent within 30 days (HR [95% CI]: 1.31 [1.02-1.67]), and more than 30 days (HR [95% CI]: 1.38 [1.15-1.66]), prior to LTCF admission were both more likely to discontinue APMs than residents without exposure to these agents. At the start of follow-up residents dispensed an APM within 30 days of being admitted to a LTCF had a higher rate of APM discontinuation (HR [95% CI]: 1.43 [1.20-170]) than residents with no APM exposure. Within a year of follow-up no difference in APM discontinuation (HR [95% CI]: 1.02 [0.88-1.17]) was observed between groups of

residents, and by two years this effect was reversed (HR [95% CI]: 0.72 [0.62-0.84]). Residents dispensed an APM more than 30 days prior to LTCF admission did not differ in APM discontinuations relative to those without APM exposure at the start of follow-up. However, after two years these residents were also less likely to discontinue APMs (HR = 0.75, 95% CI 0.61-0.90).

Table 4.9 Hazard ratios (HR) and 95% confidence intervals (95% CIs) for covariate-time interactions from extended Cox model.

	Follow-up time (days)				
	0 days	90 days	180 days	365 days	730 days
Variables	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Sex					
Female	2.66 (2.26-3.13)	2.34 (2.01-2.72)	2.05 (1.78-2.36)	1.57 (1.38-1.77)	0.92 (0.82-1.04)
Male	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Dementia					
Yes	0.86 (0.73-1.01)	0.88 (0.75-1.02)	0.89 (0.78-1.03)	0.93 (0.83-1.05)	1.01 (0.89-1.15)
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
MDS-CPS					
Moderately impaired (2-3)	4.20 (3.29-5.36)	3.42 (2.72-4.30)	2.79 (2.25-3.45)	1.83 (1.52-2.21)	0.80 (0.68-0.95)
Severely impaired (4-6)	4.07 (3.09-5.38)	3.41 (2.63-4.41)	2.85 (2.24-3.63)	1.98 (1.60-2.44)	0.96 (0.79-1.17)
Minimally impaired (0-1)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Last APM dispensation before LTCF admission					
≤ 30 days	1.43 (1.20-1.70)	1.31 (1.11-1.55)	1.21 (1.03-1.41)	1.02 (0.88-1.17)	0.72 (0.62-0.84)
> 30 days	1.18 (0.93-1.50)	1.11 (0.89-1.39)	1.05 (0.86-1.29)	0.94 (0.78-1.12)	0.75 (0.61-0.90)
None in previous year	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Hospitalization prior to LTCF admission					
Yes	4.80 (3.92-5.88)	3.89 (3.23-4.70)	3.16 (2.65-3.76)	2.05 (1.76-2.39)	0.88 (0.76-1.01)
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Facility Health Region					
Regina Qu'Appelle	1.26 (1.01-1.57)	1.21 (0.99-1.49)	1.17 (0.97-1.41)	1.08 (0.91-1.28)	0.93 (0.78-1.11)
Saskatoon	1.59 (1.30-1.95)	1.48 (1.23-1.78)	1.37 (1.16-1.63)	1.18 (1.01-1.38)	0.87 (0.74-1.04)
Other	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)

Abbreviations – APM: antipsychotic medication, HR (95% CI): Hazard ratio (95% confidence interval), LTCF: long-term care facility, MDS-CPS: minimum dataset cognitive performance scale.

Transfer to a new LTCF, and hospitalization before or after LTCF admission significantly impacted APM discontinuation. Cohort members that transferred to a new LTCF were less likely to discontinue APMs (HR [95% CI]: 0.87 [0.77-0.98]) while hospitalization after LTCF admission increased the risk of APM discontinuation (HR [95% CI]: 1.12 [1.01-1.24]). At the start of follow-up the risk of APM discontinuation was 4.80 (95% CI: 3.92-5.88) times greater among residents with hospitalization prior to LTCF admission. This difference dissipated after two years (HR [95% CI]: 0.88 [0.76-1.01]).

Facility type and location were significantly associated with APM discontinuation. Facilities that were affiliates (i.e., private, non-profit) had a higher APM discontinuation rate (HR [95% CI]: 1.12 [1.01-1.24]) than facilities that were amalgamates (i.e., publicly run). The risk of APM discontinuation within the Regina Qu'Appelle Health Region (HR [95% CI]: 1.26 [1.01-1.57]) and Saskatoon Health Region (HR [95% CI]: 1.59 [1.30-1.95]) was greater than all other health regions at the start of follow-up. Over time this effect diminished and the APM discontinuation rates among the Regina Qu'Appelle (HR [95% CI]: 0.93 [0.78-1.11] and Saskatoon (HR [95% CI]: 0.87 [0.74-1.04]) Health Regions were no different than other health regions.

4.4 Alternate definitions of APM discontinuation

The alternate definitions of APM discontinuation were used in the Cox models; the estimated HRs did not change meaningfully for most of the explanatory variables. (Appendix F). When APM discontinuation was defined with a shorter non-exposure period all of the age categories had an increased risk of discontinuation (Table E1). The HRs for age categories when defined using the longer definition of discontinuation were similar to the primary definition. The overall trend of later index years being associated with a lower risk of discontinuation was consistent regardless of the definition of discontinuation that was adopted. No change in the association between sex and APM discontinuation was observed. Comorbidity variables did not differ between the primary APM discontinuation definition and the alternate definitions. The shorter definition resulted in the HRs for residents with moderate or severe cognitive impairment having larger HRs during the first year of follow-up. After two years the HRs were similar for the primary and alternate definitions of APM discontinuation. No change in HRs was noted for the resident's MDS-CBP score. Additionally, drug exposure, health care utilization, and LTCF variables exhibited no large differences in HRs comparing analyses using the primary and alternate definitions of APM discontinuation.

CHAPTER 5 – DISCUSSION

5.1 Summary

The objectives of this research were to describe how APMs were utilized and discontinued by residents of LTCFs, what factors were predictive of APM discontinuation, and examine the sensitivity of the results to the definition of APM discontinuation. Among the LTCF residents dispensed an APM, relatively few discontinued this medication during the EOR. The facility-specific percentages of LTCF residents discontinuing APMs did not differ substantially between facilities. Additionally, facility-specific discontinuations did not vary substantially by facility characteristics like affiliation, location, or size. Discontinuation was highest early after the index dispensation, but many discontinuations did not occur until several years had passed. The variables that contributed the most to understanding the APM discontinuation were demographic, comorbidity, behavioural, and drug exposure variables. The measured associations of APM discontinuation accounted for non-proportional hazards, which were observed to converge over time. Therefore, the associations of the explanatory variables with APM discontinuation are the most relevant in the period of time shortly after APM initiation.

5.2 Interpretation

Among all residents that were eligible to be dispensed an APM and included in this study, more than one third were dispensed an APM during their EOR in a LTCF. This is a larger percentage of APM users than other estimates of APM utilization derived from Canadian LTCF residents.[11-15] It is also larger than the estimated 28.8% of LTCF residents dispensed an APM reported by Schneider-Linder et. al., which was a study of APM initiation among SK residents of LTCFs.[93] These differences arose because cohort members in the current study were allowed to transfer between facilities within 60 days of their first admission date. If this study right censored individuals on their transfer date the estimated percentage of APM users would decrease. Dispensation of APMs occurred within 22 days for 50% of the cohort, and within 90 days for 76.6% of the cohort, indicating that most residents are dispensed APMs shortly after

admission to a LTCF. The results also suggest that cohort members received regular APM dispensations; the vast majority of the cohort received more than one dispensation (88.2%) and the largest gap between dispensations was ≤ 70 days for three-quarters of residents. Dispensation patterns revealed that for 58.9% and 28.9% of residents the first APM dispensed was the atypical agent risperidone or quetiapine, respectively. This result is very similar to the result found by Schneider-Linder et. al., in which it was estimated that 62.4% of LTCF residents were dispensed risperidone and 23.0% were dispensed quetiapine.[93]

Variation in APM discontinuation rates across facilities was modest and ranged from 5% to 30%. Some facilities had low discontinuation rates close to 0%, while other had high discontinuation rates close to 100%. In both cases these rates were a consequence of a small number of residents within the facilities. There was relatively little variation in the facility specific discontinuation percentages by affiliation, location, and size. Additionally, while the test of the presence of a clustering effect of patients within LTCFs was statistically significant the magnitude of the clustering effect was small. The estimated covariance range from 0.064 to 0.111, indicating that both the heterogeneity between LTCFs and the association between residents in the same LTCF were small. It is possible that clustering is underestimated because of the facilities with high or low discontinuation rates, but given the small number of individuals with such facilities it would not be expected to substantially alter the finding that the size of the clustering effect of residents in facilities is small.

Analyses stratified by dementia diagnosis were investigated because residents with dementia are more likely to receive antipsychotics,[13,59-61] and make up a large proportion of the LTCF population.[5] However, estimates of discontinuation among residents with and without dementia were identical. Analyses stratified by schizophrenia diagnosis were of interest because previous research has indicated that psychosis can be associated with APM utilization.[59] The descriptive analysis showed that discontinuation was slightly higher among those without schizophrenia, but was not appreciably different from those with schizophrenia. In SK people are assigned to a LTCF based on where the first available bed occurs, which may not always coincide with the preference of the patient. However, residents may transfer to their preferred LTCF after their initial admission. Stratification by transfer status did not reveal differences in the percentage of residents discontinuing APMs. Stratification by prior antipsychotic exposure was important to consider because prevalent users are expected to be more adherent to their

therapy than novel users.[94] This means that the analysis conducted with the residents without prior APM exposure represent a new user cohort and the results will be free from survivor bias.[94] No substantial differences in overall APM discontinuation were noted between residents without APM exposure prior to LTCF admission and residents that did receive an APM dispensation. Stratification by time to APM dispensation showed a possible trend towards the percentage of discontinuations increasing with longer times to initiation. Since residents with a greater medical need for an APM could be expected to receive an APM sooner it is possible that that they are also less likely to discontinue APMs. However, residents initiating more than 90 days after admission were unlikely to have prior dispensations, while those initiating APMs with 0-30 or 31-90 days were more likely to have prior APM dispensations. Since novel users of APMs are expected to discontinue APMs more than prevalent users of APMs,[94] it is possible that the differences in discontinuation by time to initiation strata are driven by this effect.

Discontinuation of APMs was also characterized by the EOR, which was found to extend over multiple years for many cohort members. Calculating the percentage of APM discontinuation by EOR quintile highlighted a trend where APM discontinuation increased with EOR quintile length. This trend was observed when the analysis was stratified by patient characteristics such dementia diagnosis, schizophrenia diagnosis, transfer to a new LTCF, exposure to APMs before LTCF admission, and days to APM initiation. The results of this analysis are partially biased, primarily in the first EOR quintile, due to the presence of immortal time. This occurred because the EOR includes the time to APM initiation, during which it is not possible for discontinuation to occur. However, the EOR quintiles are not likely to be strongly influenced by immortal time bias because the majority of the cohort (76.6%) initiated APMs within 90 days of LTCF admission. Additionally, it should be noted that long EORs are not unique to this study, and have been reported among residents of nursing homes in England.[95]

The analysis of APM discontinuation across time to event quintiles revealed that discontinuation was greatest shortly after the first APM dispensation. Additionally, the percentage of discontinuers decreased with increasing lengths of the time. Most of the APM discontinuations (77.0%) in the first time to event quintile (1-55 days) can be attributed to cohort members with only a single dispensation for an APM. Cohort members without dementia had a greater rate of discontinuation within the first time quintile than individuals with dementia. Since a greater proportion of patients with dementia have been documented to utilize APMs,[59-61]

it is not surprising that APMs are discontinued quickly among those without dementia. Residents without a diagnosis of schizophrenia had a greater percentage of discontinuations in the first time quintile than residents with a schizophrenia diagnosis. This would be expected from the recommended clinical management of patients with schizophrenia. However, discontinuation of APMs among schizophrenia patients has been found to be high, although most previous studies focused on a younger population.[43-45] Cohort members with no prior APM exposure or who initiated APMs more than 90 days after admission had the highest rates of discontinuation within the first time to event quintile. As noted previously, these two characteristics are related and the increase in discontinuation may be due to these individuals being novel users of APMs, whom are possibly at higher risk of discontinuation.[94] These results should also be interpreted in combination with the results from the EOR quintile and time to APM initiation analyses. Together they suggest that most residents initiate APMs quickly, some will discontinue APMs soon after initiation, but many do not and continue to receive these agents over a long period of time.

Controlling for censoring using the KM product limit estimator of survival probability estimated median time to discontinuation was 6.5 years. This indicates that after the index APM many residents continue to receiving dispensations for a long period of time, which is consistent with the simpler descriptive analyses of discontinuation counts by time to event and EOR quintiles. Increasing the specificity of the APM discontinuation definition by lengthening the non-exposure period produced an expected decrease in the number of discontinuers, and an increase in the median time to discontinuation. Conversely, APM discontinuations were increased and the median time to discontinuation shortened when a shorter non-exposure period defined discontinuation, because the sensitivity of the definition increased. It is necessary to note that the interpretation of the results from the shortened time to APM discontinuation warrant caution. This is because if discontinuation were being determined prospectively it would not be known which APM dispensation was going to be the last dispensation. Therefore, this definition provides a lower bound for APM discontinuation in this study. Overall, the primary and alternate definitions of discontinuation all produced results showing low discontinuation and a long discontinuation time.

The modeling results indicated that differences in APM discontinuation were partially explained by the resident demographics, comorbid conditions, behavioural traits, and prior drug

exposures. The AIC decreased by > 10 for both partially and sequentially adjusted models when demographic, comorbid, behavioural, and drug exposure variables were added to the model, providing some indication of improvement in model fit.[96] This was supported by statistically significant LRTs. However, the SBC increased, providing conflicting evidence about which model provided the best fit to the data. There was limited evidence that the variables characterizing health care utilization and LTCF features was associated with alternate definitions of APM discontinuation. The AIC decreased slightly when health care utilization variables were added to the partially and sequentially adjusted models, which provides only moderate evidence that these variables contribute meaningfully to model fit. The LRTs for health care utilization variables were significant, but once again the SBC increased. Models including LTCF characteristics exhibited an AIC that decreased minimally, or even increased, non-significant LRTs, and an increasing SBC. Therefore, there is limited evidence to suggest that APM discontinuation is associated with the LTCF characteristics included in this study. Since the SBC strongly favours more parsimonious models and depends on sample size[97] the information gained from this set of variables was minimal. Model discriminative performance was assessed with the c-statistic.[89] The model with only demographic variables had the largest c-statistic, indicating excellent discriminative performance[91], but more complex models resulted in a slight decrease in model discrimination. Others have reported that in order for the c-statistic to increase, an important predictor must enter the model,[98] and that after a baseline model with good discrimination has been built only small increases can be expected with the addition of variables.[99] Therefore, the very good discriminative performance seen with the baseline demographic model in this study suggests that the c-statistic might not be expected to increase substantially. The observed decrease in the c-statistic with increasing model complexity may be due to the fact that the statistic is calculated based on all usable pairs of rank ordered observed and predicted survival.[89] This means that pairs of observations compare all event vs. event and event vs. non-event individuals, and are concordant when observed and predicted survival times are in the same order. The results clearly indicate that the addition of more variables to the regression model changes the predicted survival and results in more discordant pairs, thereby lowering the c-statistic. This may be due to the long time to event observed for some of the members of the cohort. These results are not expected to be influenced by a violation of

independence, because initial analyses showed very little clustering indicating a minimal association between residents within the same LTCF.

The regression analyses identified a number of variables associated with APM discontinuation. Overall, age was not strongly associated with APM discontinuation. This concurs with research indicating no age effect with APM utilization,[10,13] but disagrees with research finding decreased use of APMs with age.[57-59] Index fiscal years closer to the study end date were associated with a lower risk of APM discontinuation. This is likely due to the long time to event within the cohort, which would decrease the likelihood that an individual with late admission into the study would discontinue. In this study women were found to have a greater risk of discontinuation at the start of follow-up. Previous research has been mixed, but others have identified that women utilize APMs less than men, which would agree with an increase in discontinuation[13,59] This relationship could arise if men had more severe dementia upon LTCF admission than women, which could require the treatment of BPSD with APMs. However, some research has not identified differences between men and women in APM utilization,[57] which was observed after 2 years of follow-up in this study.

Dementia was associated with a lower risk of APM discontinuation, which concurs with APM utilization research that has found greater APM use among those with dementia.[13,60,61] Previous research has found that increased comorbidity, measured with the Charlson index, is associated with less APM utilization.[13] Overall, the Charlson index indicated relatively low comorbidity in the cohort and no association with APM discontinuation was found. This could arise because the Charlson index was designed to predict mortality after hospitalization, and has not been validated as a predictor of drug adherence. No other comorbidity variables were associated with discontinuation in this study.

Cognitive impairment and challenging behaviours also characterized the study cohort. Those with greater cognitive impairment were more likely to discontinue APMs at the start of follow-up, which is consistent with the finding that APMs are utilized less among those with cognitive impairment.[59] Severe behavioural problems have previously been reported to be associated with more APM utilization.[59] However, an inconsistent relationship between APM discontinuation and the MDS-CBP was identified from these results. The study identifying the relationship between behaviour and APM use relied on a different measurement scale, which could contribute to the discrepancy observed.

Exposure to APMs before LTCF admission was associated with increased risk of discontinuation at the start of follow-up, particularly among individuals who were dispensed an APM within 30 days of admission. Over time this risk decreased, and resulted in prior APM exposure being associated with less of a risk of discontinuation. Since Schneider-Linder et. al. found that prior APM exposure was associated with APM dispensations[93] it could be expected that previous APM dispensations would have the opposite relationship with discontinuation. A possible explanation is that after admission when resident's medications are reviewed it could be determined that the APM is not necessary, leading to discontinuation. But if APMs were continued after a medication review then discontinuation would be less likely to occur. The other drug exposure that was associated with increased APM discontinuation was cholinergic agents. Since these agents are used in the treatment of dementia, this result could reflect a discontinuation of APMs used to treat BPSD due to the cholinergic agent improving the symptoms of dementia.

Resident transfers were associated with decreased APM discontinuation. This transfer variable was included to account for residents moving to a new LTCF because they have a preferred facility. It is not clear how transferring LTCFs would lead to a decrease in APM discontinuation. A possible explanation is that patient characteristics linked to discontinuation such as comorbidity/health care needs also influence the likelihood transferring. Alternatively, residents that transfer may be more likely to reside in a facility with increased capacity to manage patients without the use of APMs. Hospitalization before LTCF admission was associated with an increased risk of APM discontinuation at the start of follow-up. These patients could have a higher degree of comorbidity, which has been linked to lower APM utilization.[13] It would therefore be consistent that they also discontinue APMs more than cohort members without hospitalization before LTCF admission. Similarly, hospitalization after LTCF admission is associated with increased risk of APM discontinuation. Hospitalized residents could have more comorbidities or their medication regimen could be changed after discharge to discontinue APMs. However, a possible explanation for this relationship is the presence of immeasurable time bias arising from the inability to observe pharmacologic dispensations during hospital stays.[100] This would be expected to increase discontinuation, as measured in this study, in some situations. For example, if a resident was hospitalized and died they could be classified as a discontinuer, even if they continued to receive APMs in hospital. However, it is important

to be cautious in the interpretation of these health care utilization variables because they contributed little information to the overall model fit.

Amongst the LTCF characteristics, only the facility location showed an association with APM discontinuation. This could be related to differential aspects of care provided within LTCFs of these health regions. For example, if facilities within or near the urban centres of Regina and Saskatoon had the infrastructure, staff and procedural policies to facilitate the management of residents without APMs, they would be expected to reduce the use of these agents.

The sensitivity analyses included provide further insight into the results. The sensitivity analysis of APM discontinuation revealed few changes between the model using the primary definition of discontinuation and the models that used alternate definitions. Residents dispensed 4-6 or ≥ 7 medications were found to have a lower risk of discontinuation when discontinuation was defined using a 70 day non-exposure gap. Interestingly, previous research has found that increased polypharmacy decreased adherence to drugs which is opposite of this result. Transferring LTCFs became non-significant for both alternate definitions of discontinuation. Additionally, discontinuation was no longer greater among residents in the Regina Qu'Appelle health region at the start of follow-up. The change in the results for LTCF transfer and facility location also suggest caution in the interpretation of the main results for these variables.

The sensitivity analysis examining positive and negative correlations between discontinuation and censoring indicated that few variables were sensitive to severe violation of this assumption (Appendix G). Most of the changes in the HRs indicated that the results became non-significant for both positive and negative correlation. Specifically this impacted index fiscal year, last cholinergic dispensation, and LTCF transfer. Age and MDS-CBP became significant under the model for positive correlation. The primary results suggested the possibility that increasing challenging behaviour could be related to decreased discontinuation. The increased risk of discontinuation for all levels of the MDS-CBP variable reverses this trend and suggests that this variable is sensitive to the independent censoring assumption. Additionally, the MDS-CPS variable was very sensitive to both positive and negative correlation models over all points in time. Finally, the risk of discontinuation was found to increase for both positive and negative models of prior APM exposure. The results suggest that there is mild sensitivity to positive and negative correlation when the last dispensation was more than 30 days before admission.

Overall, the variables that are most sensitive to violation of the non-informative censoring assumption are the index fiscal year and behavioural characteristics.

Due to violation of the proportional hazards assumption a post-hoc analysis truncating follow-up time to 6 months was conducted to limit the violation of this assumption (Appendix H). The results were very similar to those obtained from the fully adjusted model without covariate-time interactions. Index fiscal year, LTCF transfer, and hospitalization after LTCF admission were no longer significantly associated with APM discontinuation. Residents with schizophrenia or mood disorders were less likely to discontinue APMs, as were residents with increasing scores on the MDS-CBP. However, the estimated effect of sex, cognitive impairment, and prior APM exposure did not have any agreement with the results from the model where these variables interacted with time. Overall, the results from the model evaluating only 6 months of follow-up time were more similar to the results from the analysis not including covariate time-interactions. This could indicate that even over this shorter time frame the results may still be influenced by non-proportional hazards.

5.3 Study strengths and limitations

One strength of this study is the use of population-based data that captures information on all residents of SK, thereby minimizing selection bias and improving the generalizability of the results. Additionally, administrative data in SK have been shown to be accurate and complete for population-based research in several studies.[72-78] However, our study population only included senior citizens, so the results should not be considered representative of a younger LTCF population. Additionally, the inferential analysis included complete cases only, which would be expected to introduce selection bias and reduce generalizability.

A wide range of explanatory variables were included in this study, which enabled analytic control of confounding. However, some variables could not be measured, which would result in a residual confounding effect in the analysis. Variables describing health behaviours and individual-level socioeconomic status were not measureable for LTCF residents within the databases used for this research. Diagnosis codes for the definition of psychiatric disease comorbidities were limited to 3 or 4 digits, and the ability to detect active disease cases has been shown to be limited in administrative data for residents of long-term care.[101] Specifically, the

sensitivity of diagnostic codes for dementia, anxiety disorders, and depression is low, but specificity is high.[101] Schizophrenia was the only psychiatric comorbidity with both high sensitivity and specificity.[101] Therefore, misclassification bias was expected within the diagnosis variables, and using these variables would not result in complete removal of confounding effects. There could also be residual confounding due to unmeasured facility level factors. Examples include staffing levels or the presence of special care units for patients with dementia in a LTCF. Information about the indication for prescribing, if the prescription was intended to be used as needed (i.e., PRN), and in-hospital drug dispensations are also not available. Therefore, dispensation is only a proxy measure of drug exposure. Furthermore, not all medications are covered by the SK drug plan and private purchase of other agents is not captured in the study data sources. This has the potential for incorrectly classifying a resident continuing to receive APMs as discontinuing, which is a source of information bias due to incomplete measurement. Overall, these errors in measurement can lead to misclassification in the exposures and outcomes, which could bias the estimated effect sizes towards the null.[102]

Discontinuation of APMs was operationally defined to occur after the last known APM dispensation. This measure could not be validated, and therefore may result in some misclassification bias. An additional source of misclassification is that some individuals were noted to have large gaps (> 1 year) between APM dispensations, and these individuals could reasonably be considered to have discontinued APMs. Alternate definitions of APM discontinuation only varied the number of non-exposure days to 0 and 70, and additional evaluations of APM discontinuation would strengthen the results by adding a further understanding of the impact of outcome misclassification. Shortening the non-exposure period to 0 days will increase the sensitivity of the outcome definition. Consequently, more discontinuations were observed with this definition and the median time to discontinuation was shorter. Lengthening the non-exposure period to 70 days will increase the specificity of the outcome definition. The analytic results were largely robust to these alternative definitions of APM discontinuation. Given that the number of cohort members that may be misclassified due to large gaps between APM dispensations is small (n = 148), one might hypothesize that the results would not change if these individuals were classified as discontinuers.

One of the issues encountered in this project was non-proportional hazards. Hazards were found to converge over time, which is a phenomenon has been noted in other epidemiologic

research with long follow-up times.[103] The reported HRs would be expected to be biased in this situation, most likely towards the null. This is because the reported HR is an average of the HR at all event times.[104,105] This limitation was addressed by modeling the non-proportional hazards with covariate-time interactions, and conducting an analysis with follow-up time truncated at 6 months.

The assumption of independent censoring was addressed in this project by conducting a sensitivity analysis. While some variables were found to be sensitive to this assumption the degree of violation of this study is not likely as extensive as those used in the sensitivity analysis. It is likely safe to assume that censoring due to the study ending is independent of APM discontinuation. Additionally, given the small number (n = 11) of individuals lost to follow-up due to health coverage it is unlikely to have a meaningful impact on the model results and interpretation. Discharge from long-term care represents the end of the risk period for the resident, which precludes APM discontinuation from being observed. These individuals could represent a healthier population of LTCF residents since they were no longer receiving long-term care. The probability of APM discontinuation among these residents may not be accurately represented by the cohort members remaining in a LTCF. If APM discontinuation is more likely among individuals that are discharged from long-term care then the probability of APM discontinuation is underestimated. This would correspond to a positive correlation between event time and censoring due to LTCF discharge. Death also prevents the observation of APM discontinuation, and can be considered a competing risk, which would bias the results of the analysis.[106,107]

5.4 Significance and future research

This study revealed APMs are utilized regularly over a long period of time among the LTCF incident resident population. This phenomenon may be affecting one-third of residents in LTCFs within the province of SK, Canada. In the examination of APM discontinuation we have identified that about one-fifth of the LTCF residents that are dispensed an APM will stop receiving these pharmaceuticals. It is possible that discontinuation may be higher, because this work adopted a relatively conservative definition of discontinuation. However, more liberal definitions were found to be unlikely to change this finding substantially. The results were

complex to interpret because the proportional hazards assumption was violated. Variables describing resident demographics, comorbidity, drug exposure, and behavioural characteristics of the residents explained APM discontinuation the best. Finally, the analytic results were robust to different definitions of APM discontinuation.

This study contributes to the knowledge about APM utilization among senior citizens in LTCFs by describing the long-term use of these drugs once they are started. This is a novel finding that has not been previously reported. Since discontinuation was low the results imply that APM withdrawal was not occurring for most residents, and presents an opportunity for clinicians to consider changes to the pharmacotherapy of LTCF residents that could be beneficial for their health. However, the evidence for the clinical benefits of APM discontinuation are mixed, and this study only suggests that there could be opportunities to do so in the long-term care population. Additionally, APMs may be utilized to address aggressive behaviours that endanger others, in which case discontinuation would not be recommended.

Future research opportunities are numerous. First, a deeper understanding of how patient characteristics contribute to the discontinuation of APMs could be obtained by including time-varying covariates, particularly for such patient characteristics as dementia diagnosis, cognitive status, problem behaviours, psychotropic drug dispensations, hospitalization, and facility characteristics. Additionally, the finding of increased discontinuation among residents with prior cholinergic exposure could be investigated further because this could indicate that APMs are being discontinued when dementia is treated. Also, the limitations faced due to non-proportional hazards could be addressed using weighted Cox regression techniques, with the benefit that the HRs would be more easily interpretable.[104,105] Additionally, this approach could allow for a more detailed and accurate assessment of interactions between predictor variables. A competing risks analysis could help remove some of the bias that is introduced by assuming that censoring is completely non-informative.[106,107] Additional information about the administration of APMs could contribute a further understanding of the true utilization of these agents in long-term care. This could potentially be assessed using the RAI-MDS which documents antipsychotic administration during a week-long observation period, or with the medication administration record. It is also possible that the dose of APMs administered to LTCF residents may change over time. This is an important issue because clinical recommendations for individuals with dementia receiving APMs suggest tapering the dose if the patient is behaviourally stable.

Additionally, further investigation of APM discontinuation among residents with dementia or schizophrenia is warranted because both diseases were common and would be expected to influence APM utilization. This study also noted that some LTCF residents only received a single APM dispensation, and the factors contributing this pattern of APM utilization could be important for understanding discontinuation. Some facilities were found to have high and low discontinuation rates. Further investigation of these specific facilities could elucidate if the observed rates are truly an artifact of small numbers of residents (i.e., unstable rates), or if these LTCFs are true outliers. Observational studies have also not been performed to replicate the experimental findings of reduced mortality due APM discontinuation, which would further examine the hypothesis that APMs are detrimental for some LTCF residents. Finally, this study focused on residents of LTCFs that are senior citizens; future work focusing on a younger LTCF population would be of interest.

CHAPTER 6 - REFERENCES

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APPENDIX A – PSYCHOTROPIC DRUGS COVERED BY THE SK DRUG FORMULARY DURING THE STUDY PERIOD

Table A1. Antipsychotics, antidepressants, benzodiazepines, anticholinergics, and cholinergic medications covered by the SK provincial drug formulary during the study period.

		SK Drug Formulary Edition[a]										
AHFS Code	**Generic drug name**	**52**	**53**	**54**	**55**	**56**	**57**	**58**	**59**	**60**	**61**	**62**
Antipsychotics[b]												
28:16.08	Aripiprazole										•	•
28:16.08	Chlorpromazine	•	•	•	•	•	•	•	•	•	•	•
28:16.08	Clozapine	•	•	•	•	•	•	•	•	•	•	•
28:16.08	Flupenthixol decanoate	•	•	•	•	•	•	•	•	•	•	•
28:16.08	Flupenthixol dihydrochloride	•	•	•	•	•	•	•	•	•	•	•
28:16.08	Fluphenazine decanoate	•	•	•	•	•	•	•	•	•	•	•
28:16.08	Fluphenazine enanthate	•										
28:16.08	Fluphenazine HCL	•	•	•	•	•	•	•	•	•	•	•
28:16.08	Haloperidol	•	•	•	•	•	•	•	•	•	•	•
28:16.08	Haloperidol decanoate	•	•	•	•	•	•	•	•	•	•	•
28:16.08	Loxapine succinate	•	•	•	•	•	•	•	•	•	•	•
28:16.08	Olanzapine	•	•	•	•	•	•	•	•	•	•	•
28:16.08	Paliperidone palmitate										•	•
28:16.08	Pericyazine	•	•	•	•	•	•	•	•	•	•	•
28:16.08	Perphenazine	•	•	•	•	•	•	•	•	•	•	•
28:16.08	Pimozide	•	•	•	•	•	•	•	•	•	•	•
28:16.08	Pipotiazine palmitate	•	•	•		•	•	•	•	•	•	•
28:16.08	Prochlorperazine	•	•	•	•	•	•	•	•	•	•	•
28:16.08	Quetiapine	•	•	•	•	•	•	•	•	•	•	•
28:16.08	Risperidone	•	•	•	•	•	•	•	•	•	•	•
28:16.08	Thioridazine	•	•	•	•							
28:16.08	Thiothixene	•	•	•	•	•	•	•	•	•	•	•
28:16.08	Trifluoperazine	•	•	•	•	•	•	•	•	•	•	•
28:16.08	Ziprasidone								•	•	•	•
28:16.08	Zuclopenthixol acetate	•	•	•	•	•	•	•	•	•	•	•
28:16.08	Zuclopenthixol decanoate	•	•	•	•	•	•	•	•	•	•	•
28:16.08	Zuclopenthixol dihydrochloride	•	•	•	•	•	•	•	•	•	•	•
28:24.92	Methotrimeprazine	•	•	•	•	•	•	•	•	•	•	•
Antidepressants[c]												
28:16.04	Amitriptyline	•	•	•	•	•	•	•	•	•	•	•
28:16.04	Bupropion HCL	•	•	•	•	•	•	•	•	•	•	•
28:16.04	Citalopram hydrobromide	•	•	•	•	•	•	•	•	•	•	•
28:16.04	Clomipramine HCL	•	•	•	•	•	•	•	•	•	•	•
28:16.04	Desipramine HCL	•	•	•	•	•	•	•	•	•	•	•
28:16.04	Doxepin HCL	•	•	•	•	•	•	•	•	•	•	•
28:16.04	Duloxetine hydrochloride								•	•	•	•
28:16.04	Fluoxetine	•	•	•	•	•	•	•	•	•	•	•
28:16.04	Fluvoxamine maleate	•	•	•	•	•	•	•	•	•	•	•
28:16.04	Imipramine	•	•	•	•	•	•	•	•	•	•	•
28:16.04	Maprotiline	•	•	•	•	•	•	•	•	•	•	•
28:16.04	Mirtazapine	•	•	•	•	•	•	•	•	•	•	•
28:16.04	Moclobemide	•	•	•	•	•	•	•	•	•	•	•
28:16.04	Nefazodone	•	•									

Table A1. Antipsychotics, antidepressants, benzodiazepines, anticholinergics, and cholinergic medications covered by the SK provincial drug formulary during the study period.

		SK Drug Formulary Edition[a]										
AHFS Code	**Generic drug name**	**52**	**53**	**54**	**55**	**56**	**57**	**58**	**59**	**60**	**61**	**62**
Antidepressants[c]												
28:16.04	Nortriptyline	•	•	•	•	•	•	•	•	•	•	•
28:16.04	Paroxetine HCL	•	•	•	•	•	•	•	•	•	•	•
28:16.04	Phenelzine SO_4	•	•	•	•	•	•	•	•	•	•	•
28:16.04	Sertraline hydrochloride	•	•	•	•	•	•	•	•	•	•	•
28:16.04	Tranylcypromine SO_4	•	•	•	•	•	•	•	•	•	•	•
28:16.04	Trazodone	•	•	•	•	•	•	•	•	•	•	•
28:16.04	Trimipramine	•	•	•	•	•	•	•	•	•	•	•
28:16.04	Venlafaxine HCL	•	•	•	•	•	•	•	•	•	•	•
Benzodiazepines[d]												
28:12.08	Clonazepam	•	•	•	•	•	•	•	•	•	•	•
28:12.08	Nitrazepam	•	•	•	•	•	•	•	•	•	•	•
28:12.92	Clobazam	•	•	•	•	•	•	•	•	•	•	•
28:24.08	Alprazolam	•	•	•	•	•	•	•	•	•	•	•
28:24.08	Bromazepam	•	•	•	•	•	•	•	•	•	•	•
28:24.08	Chlordiazepoxide	•	•	•	•	•	•	•	•	•	•	•
28:24.08	Clorazepate dipotassium	•	•	•	•	•	•	•	•	•	•	•
28:24.08	Diazepam	•	•	•	•	•	•	•	•	•	•	•
28:24.08	Flurazepam HCL	•	•	•	•	•	•	•	•	•	•	•
28:24.08	Lorazepam	•	•	•	•	•	•	•	•	•	•	•
28:24.08	Oxazepam	•	•	•	•	•	•	•	•	•	•	•
28:24.08	Temazepam	•	•	•	•	•	•	•	•	•	•	•
28:24.08	Triazolam	•	•	•	•	•	•	•	•	•	•	•
Anticholinergic agents												
12:08.04	Benztropine mesylate	•	•	•	•	•	•	•	•	•	•	•
12:08.04	Ethopropazine	•	•	•	•	•	•	•	•	•	•	•
12:08.04	Procyclidine HCL	•	•	•	•	•	•	•	•	•	•	•
12:08.04	Trihexyphenidyl HCL	•	•	•	•	•	•	•	•	•	•	•
12:08.08	Dicyclomine HCL	•	•	•	•	•	•	•	•	•	•	•
12:08.08	Hyoscine butylbromide	•	•	•	•	•	•	•	•	•	•	•
12:08.08	Ipratropium bromide	•	•	•	•	•	•	•	•	•	•	•
12:08.08	Ipratropium bromide/salbutamol SO_4	•	•	•	•	•	•	•	•	•	•	•
12:08.08	Propantheline bromide	•	•	•								
12:08.08	Tiotropium bromide monohydrate			•	•	•	•	•	•	•	•	•
Cholinergic agents												
12:04.00	Bethanechol chloride	•	•	•	•	•	•	•	•	•	•	•
12:04.00	Donepezil HCL[e]	•	•	•	•	•	•	•	•	•	•	•
12:04.00	Galantamine hydrobromide[e]	•	•	•	•	•	•	•	•	•	•	•
12:04.00	Neostigmine bromide	•	•	•	•	•	•	•	•	•	•	•
12:04.00	Pyridostigmine bromide	•	•	•	•	•	•	•	•	•	•	•
12:04.00	Rivastigmine[e]	•	•	•	•	•	•	•	•	•	•	•

Abbreviations – AHFS: American hospital formulary system, APM: antipsychotic medication, SK: Saskatchewan. *Notes* – a: Drug formulary edition 52 covers begins October 2002 and drug formulary edition ends March 2013. b: The first step of identifying APMs was to use the AHFS code 28:16.08, which included the APM asenapine. However, asenapine was not covered during the study period and is not included in this study. Additionally, other APMs that are not covered by the provincial formulary include promazine and lurasidone. c: Antidepressants that are not covered by the provincial formulary include desvenlafaxine and escitalopram. d: The benzodiazepine midazolam is only covered as part of hospital benefit drug list in formulary editions 52-60, but it is not captured with the prescription drug database. e: The AHFS code this drug is 92:00.00 in the formulary editions 52 to 57. *Symbols* – •, indicates that the prescription drug is covered within the indicated edition of the SK drug formulary.

APPENDIX B – ICD CODES DEFINING PSYCHIATRIC COMORBIDITIES

Table B1. ICD-9 and -10-CA codes for psychiatric comorbidities

Diagnosis	ICD-10-CA	ICD-9
Dementia	F00.0, F00.1, F00.2, F00.9; F01.0, F01.1, F01.2, F01.3, F01.8, F01.9; F02.0, F02.1, F02.2, F02.3, F02.4, F02.8; F03; F05.1; G30.0, G30.1, G30.8, G30.9; G31.0, G31.1, G31.8, G31.9; G32.8; R54	290, 331, 797
Schizophrenia	F20.0, F20.1, F20.2, F20.3, F20.4, F20.5, F20.6, F20.8 F20.9; F21; F23.0, F23.1, F23.2, F23.3, F23.8, F23.9; F25.0, F25.1, F25.2, F25.8, F25.9; F28; F29; F32.3; F33.3	295, 298
Depression	F30; F31.0, F31.1, F31.2, F31.3, F31.4, F31.5, F31.6, F31.7, F31.8, F31.9; F32.1, F32.2, F32.3, F32.8, F32.9; F33.0, F33.1, F33.2, F33.4, F33.8, F33.9; F34.8, F34.9; F38.0, F38.1, F38.8; F39	296, 311
Anxiety	F04; F05.0, F05.8, F05.9; F06.0, F06.1, F06.2, F06.3, F06.4, F06.5, F06.6, F06.7, F06.8, F06.9; F22.0, F22.8, F22.9; F24; F32.0; F34.1; F40.0, F40.1, F40.2, F40.8, F40.9; F41.0, F41.1, F41.2, F41.3, F41.8, F41.9; F42.0, F42.1, F42.2, F42.8, F42.9; F44.0, F44.1, F44.2, F44.3, F44.4, F44.5, F44.6, F44.7, F44.8, F44.9; F45.0, F45.1, F45.2; F48.0, F48.1, F48.8, F48.9; F68.0; F84.0, F84.1, F84.3, F84.4, F84.5, F84.8, F84.9; F99	293,294, 297, 299, 300
Alcohol or drug abuse	F10.0, F10.1, F10.2, F10.3, F10.4, F10.5, F10.6, F10.7, F10.8, F10.9; F11.0, F11.1, F11.2, F11.3, F11.4, F11.5, F11.6, F11.7, F11.8, F11.9; F12.0, F12.1, F12.2, F12.3, F12.4, F12.5, F12.6, F12.7, F12.8, F12.9; F13.0, F13.1, F13.2, F13.3, F13.4, F13.5, F13.6, F13.7, F13.8, F13.9; F14.0, F14.1, F14.2, F14.3, F14.4, F14.5, F14.6, F14.7, F14.8, F14.9; F15.0, F15.1, F15.2, F15.3, F15.4, F15.5, F15.6, F15.7, F15.8, F15.9; F16.0, F16.1, F16.2. F16.3, F16.4, F16.5, F16.6, F16.7, F16.8, F16.9; F17.0, F17.1, F17.2, F17.3, F17.4, F17.5, F17.6, F17.7, F17.8, F17.9; F18.0, F18.1, F18.2, F18.3, F18.4, F18.5, F18.6, F18.7, F18.8, F18.9; F19.0, F19.1, F19.2, F19.3, F19.4, F19.5, F19.6, F19.7, F19.8, F19.9; F55; G31.2; K70.0, K70.1, K70.2, K70.3, K70.4, K70.9	291, 292, 303, 304, 305
Extrapyramidal symptoms	G10; F95.0, F95.1, F95.2, F95.8, F95.9	307, 333

APPENDIX C – ASSESSMENT OF THE PROPORTIONAL HAZARDS ASSUMPTION

Table C1. Pearson correlation coefficients of scaled Schoenfeld residuals and event time rank.

Demographic	**Coefficient**	**p-value**
Age		
75-84	-0.03557	0.1610
85-94	-0.04017	0.1134
≥95	-0.03758	0.1387
Sex		
Female	0.07576	0.0028
Index Fiscal Year		
04/05	-0.06464	0.0108
05/06	-0.02920	0.2499
06/07	-0.05316	0.0361
07/08	-0.05989	0.0182
09/10	-0.01340	0.5977
10/11	-0.05766	0.0230
11/12	-0.03245	0.2010
Comorbidity		
Dementia		
Yes	0.05484	0.0307
Schizophrenia		
Yes	0.00821	0.7465
Mood disorder		
Yes	0.02519	0.3210
Alcohol or drug abuse		
Yes	-0.03371	0.1842
Extrapyramidal symptoms		
Yes	-0.02713	0.2851
Charlson index		
1-2	0.01597	0.5292
3-4	-0.00122	0.9618
≥5	0.00700	0.7829
Level of care		
Level 2	0.00309	0.9031
Level 3	0.01157	0.6486
Level 4	0.00394	0.8768
AHFS drug category		
4-6	0.00743	0.7697
≥7	-0.00810	0.7498
Behavioural		
MDS-CPS		
Moderately impaired (2-3)	0.08193	0.0012
Severely impaired (4-6)	0.10032	<.0001
MDS-CBP		
Mild (1-4)	0.00249	0.9217
Moderate (5-9)	0.04138	0.1030
Severe (10-14)	0.04242	0.0946
Extreme (≥15)	0.03793	0.1350

Table C1. Continued

Drug exposure	**Coefficient**	**p-value**
Days to APM initiation after LTCF admission		
31-90 days	0.01556	0.5400
> 90 days	0.01025	0.6864
Last APM dispensation before LTCF admission		
≤ 30 days	0.08662	0.0006
> 30 days	0.06965	0.0060
Last antidepressant dispensation before LTCF admission		
≤ 30 days	-0.02876	0.2573
> 30 days	-0.04015	0.1136
Last benzodiazepine dispensation before LTCF admission		
≤ 30 days	0.00026	0.9918
> 30 days	-0.00782	0.7580
Last anticholinergic dispensation before LTCF admission		
≤ 30 days	-0.03890	0.1254
> 30 days	-0.00914	0.7188
Last cholinergic dispensation before LTCF admission		
≤ 30 days	0.03120	0.2190
> 30 days	-0.00621	0.8068
Health care utilization		
Transfer to new LTCF		
Yes	-0.02823	0.2661
Hospitalization prior to LTCF admission		
Yes	-0.06699	0.0082
Hospitalization after LTCF admission		
Yes	-0.00742	0.7700
LTCF		
Facility affiliation		
Affiliate (private, non-profit)	-0.03760	0.1384
Contract (private, for profit)	-0.04316	0.0890
Facility Health Region		
Regina Qu'Appelle	0.07051	0.0054
Saskatoon	-0.03176	0.2108
Facility size		
Small (1-35 beds)	-0.03042	0.2308
Medium (36-100 beds)	0.01068	0.6741

APPENDIX D – ASSESSMENT OF POTENTIALLY INFLUENTIAL OBSERVATIONS FOR COX REGRESSION MODEL

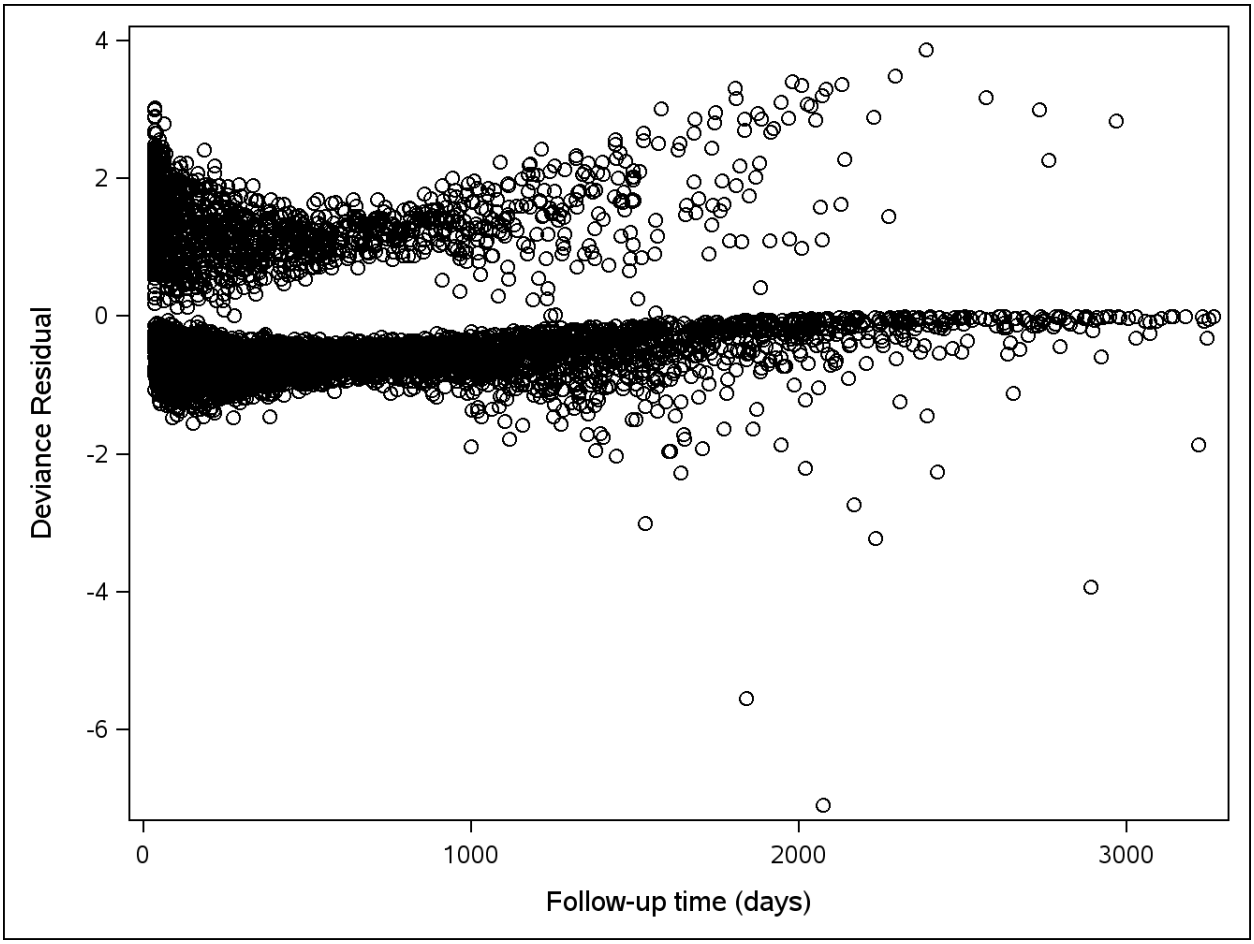

Figure D1. Model deviance residuals from fully adjusted covariate time model plotted against follow-up time to evaluate the presence of potential outliers.

Table D1. Change in the estimated HR after removal of potentially influential data points.

Variables[a]	Estimated	Lower estimate[b]	Upper estimate[b]
Demographic	HR	HR	HR
Age			
75-84	1.19	1.17	1.22
85-94	1.34	1.32	1.37
≥ 95	1.17	1.15	1.20
65-74	1.00 (Ref)	N/A	N/A
Sex			
Female	2.66	2.64	2.69
Male	1.00 (Ref)	N/A	N/A
Index fiscal year			
04/05	0.98	0.97	0.99
05/06	1.00	0.99	1.01
06/07	0.87	0.86	0.88
07/08	0.80	0.79	0.81
09/10	0.76	0.75	0.77
10/11	0.75	0.75	0.75
11/12	0.58	0.58	0.58
12/13	-	-	-
08/09	1.00 (Ref)	N/A	N/A
Comorbidity			
Dementia			
Yes	0.86	0.85	0.87
No	1.00 (Ref)	N/A	N/A
Schizophrenia			
Yes	1.01	1.01	1.01
No	1.00 (Ref)	N/A	N/A
Mood disorder			
Yes	0.94	0.94	0.94
No	1.00 (Ref)	N/A	N/A
Alcohol or drug abuse			
Yes	0.94	0.90	0.97
No	1.00 (Ref)	N/A	N/A
Extrapyramidal symptoms			
Yes	1.02	1.01	1.04
No	1.00 (Ref)	N/A	N/A
Charlson index			
1-2	0.94	0.93	0.95
3-4	0.99	0.98	1.00
≥ 5	0.95	0.94	0.96
0	1.00 (Ref)	N/A	N/A

Table D1. Continued

Comorbidity	Estimated	Lower estimate[b]	Upper estimate[b]
Level of care			
Level 2	1.46	1.39	1.53
Level 3	1.32	1.25	1.39
Level 4	1.65	1.57	1.73
Level 1	1.00 (Ref)	N/A	N/A
AHFS drug category			
4-6	0.88	0.87	0.89
≥ 7	0.90	0.89	0.91
0-3	1.00 (Ref)	N/A	N/A
Behavioural			
MDS-CPS			
Moderately impaired (2-3)	4.20	4.14	4.24
Severely impaired (4-6)	4.07	4.01	4.11
Minimally impaired (0-1)	1.00 (Ref)	N/A	N/A
MDS-CBP			
Mild (1-4)	1.16	1.15	1.18
Moderate (5-9)	0.95	0.94	0.96
Severe (10-14)	0.76	0.75	0.77
Extreme (≥ 15)	0.73	0.72	0.75
None (0)	1.00 (Ref)	N/A	N/A
Drug exposure			
Days to APM initiation after LTCF admission			
31-90 days	0.95	0.94	0.95
> 90 days	1.07	1.06	1.08
0-30 days	1.00 (Ref)	N/A	N/A
Last APM dispensation before LTCF admission			
≤ 30 days	1.43	1.42	1.45
> 30 days	1.18	1.16	1.20
None in previous year	1.00 (Ref)	N/A	N/A
Last antidepressant dispensation before LTCF admission			
≤ 30 days	1.12	1.11	1.13
> 30 days	1.05	1.04	1.06
None in previous year	1.00 (Ref)	N/A	N/A
Last benzodiazepine dispensation before LTCF admission			
≤ 30 days	0.79	0.78	0.80
> 30 days	0.88	0.87	0.89
None in previous year	1.00 (Ref)	N/A	N/A
Last anticholinergic dispensation before LTCF admission			
≤ 30 days	0.78	0.76	0.80
> 30 days	0.80	0.79	0.81
None in previous year	1.00 (Ref)	N/A	N/A

Table D1. Continued

Drug exposure	Estimated	Lower estimate[b]	Upper estimate[b]
Last cholinergic dispensation before LTCF admission			
≤ 30 days	1.31	1.29	1.33
> 30 days	1.38	1.37	1.39
None in previous year	1.00 (Ref)	N/A	N/A
Health care utilization			
Transfer to new LTCF			
Yes	0.87	0.86	0.87
No	1.00 (Ref)	N/A	N/A
Hospitalization prior to LTCF admission			
Yes	4.80	4.75	4.85
No	1.00 (Ref)	N/A	N/A
Hospitalization after LTCF admission			
Yes	1.12	1.11	1.12
No	1.00 (Ref)	N/A	N/A
LTCF			
Facility affiliation			
Affiliate (private, non-profit)	1.16	1.15	1.17
Contract (private, for profit)	0.96	0.95	0.97
Amalgamate (public)	1.00 (Ref)	N/A	N/A
Facility Health Region			
Regina Qu'Appelle	1.26	1.25	1.28
Saskatoon	1.59	1.57	1.60
Other	1.00 (Ref)	N/A	N/A
Facility size			
Small (1-35 beds)	0.90	0.89	0.91
Medium (36-100 beds)	1.01	1.00	1.02
Large (> 100 beds)	1.00 (Ref)	N/A	N/A

Abbreviations – AHFS: American hospital formulary system, APM: antipsychotic medication, HR (95% CI): Hazard ratio (95% confidence interval), LTCF: long-term care facility, MDS-CBP: minimum dataset challenging behaviour profile, MDS-CPS: minimum dataset cognitive performance scale. *Notes* – a: Explanatory variables are grouped by concept, which is indicated by the ***bold-italicized*** terms. b: lower and upper estimated HR are based on the average of the 6 most extreme lower and upper scaled score residuals.

APPENDIX E – KAPLAN-MEIER SURVIVAL CURVES DEMONSTRATING NON-PROPORTIONALITY OF HAZARDS

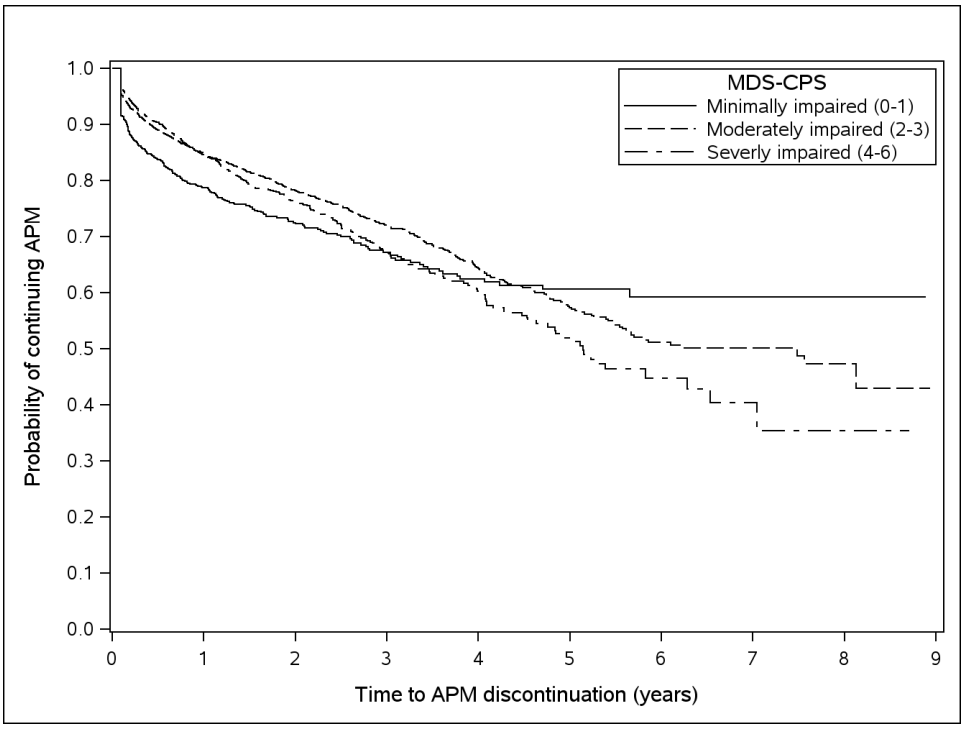

Figure E1. Kaplan-Meier survival probability by resident cognitive impairment.

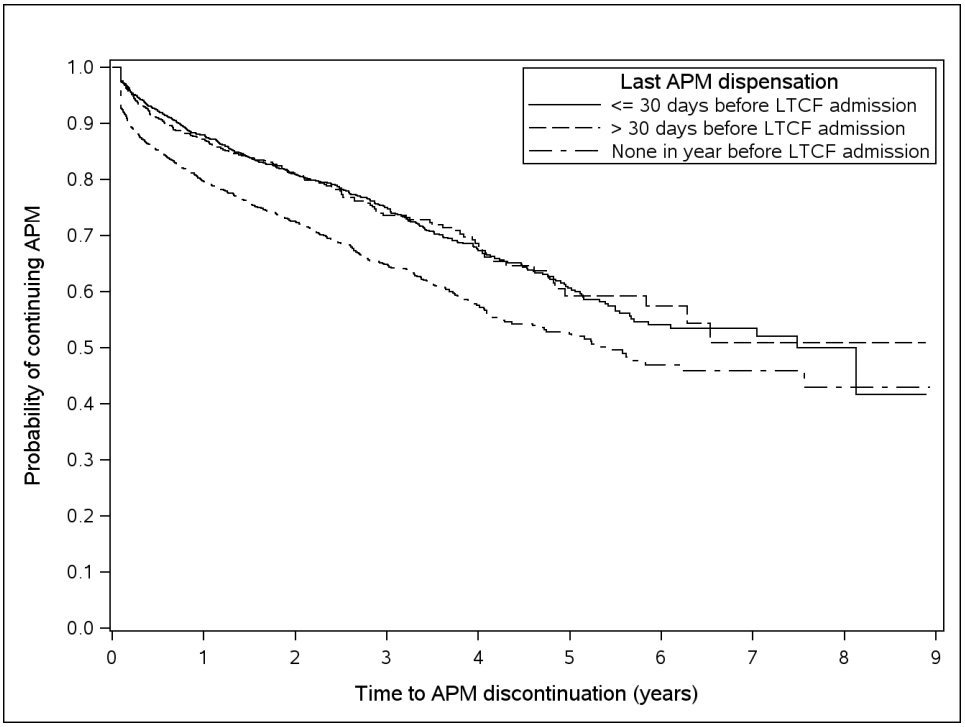

Figure E2. Kaplan-Meier survival probability by last APM dispensation before LTCF admission.

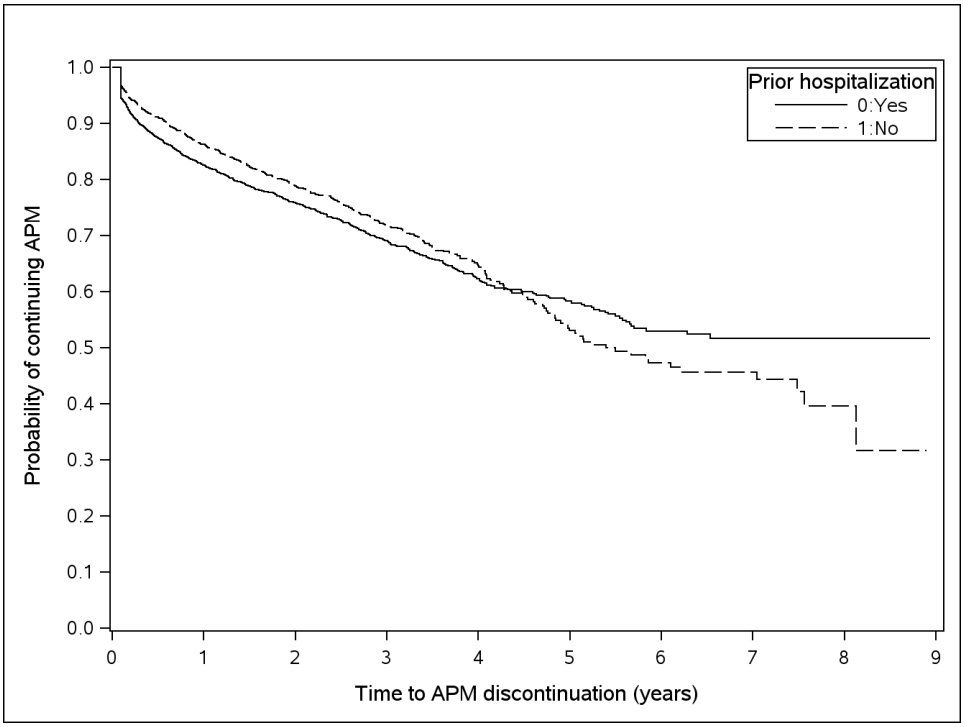

Figure E3. Kaplan-Meier survival probability by hospitalization prior to LTCF admission.

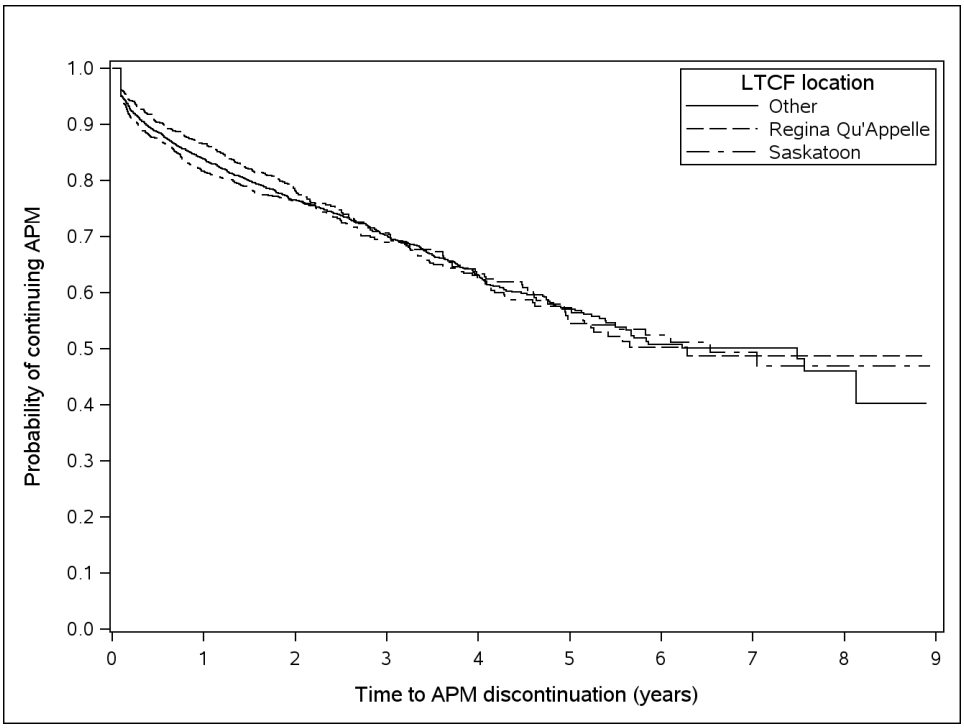

Figure E4. Kaplan-Meier survival probability by LTCF location.

APPENDIX F –COX PROPORTIONAL HAZARDS REGRESSION MODELS FOR ALTERNATE DEFINITIONS OF APM DISCONTINUATION

Table F1. Hazards ratios (HRs) and 95% confidence intervals (95% CIs) for fully adjusted Cox proportional hazards regression models with covariate time interactions for the assessment of model sensitivity to the definition of APM discontinuation.

Explanatory variables[a]	Primary non-exposure gap[b]	Shorter non-exposure gap[b]	Longer non-exposure gap[b]
Demographic	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Age			
75-84	1.19 (0.98-1.44)	1.35 (1.14-1.60)*	1.14 (0.93-1.40)
85-94	1.34 (1.11-1.63)*	1.55 (1.31-1.83)*	1.30 (1.06-1.59)*
≥ 95	1.17 (0.89-1.55)	1.47 (1.16-1.87)*	1.08 (0.80-1.46)
65-74	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Sex			
Female	*	*	*
Male	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Index fiscal year			
04/05	0.98 (0.80-1.21)	1.00 (0.84-1.19)	1.02 (0.82-1.26)
05/06	1.00 (0.83-1.21)	1.02 (0.87-1.19)	1.00 (0.82-1.22)
06/07	0.87 (0.72-1.05)	0.85 (0.72-1.00)	0.81 (0.66-0.99)*
07/08	0.80 (0.66-0.97)*	0.85 (0.73-1.00)	0.75 (0.61-0.92)*
09/10	0.76 (0.63-0.93)*	0.79 (0.67-0.93)*	0.73 (0.59-0.89)*
10/11	0.75 (0.61-0.91)*	0.73 (0.61-0.86)*	0.76 (0.62-0.94)*
11/12	0.58 (0.47-0.71)*	0.56 (0.47-0.67)*	0.55 (0.44-0.69)*
12/13	-	-	-
08/09	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Comorbidity			
Dementia			
Yes	*	*	*
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Schizophrenia			
Yes	1.01 (0.90-1.13)	1.03 (0.93-1.13)	1.05 (0.93-1.18)
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Mood disorder			
Yes	0.94 (0.83-1.07)	0.96 (0.86-1.06)	0.94 (0.82-1.07)
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Alcohol or drug abuse			
Yes	0.94 (0.65-1.37)	0.90 (0.65-1.24)	0.89 (0.59-1.33)
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Extrapyramidal symptoms			
Yes	1.02 (0.76-1.37)	1.05 (0.82-1.34)	1.02 (0.75-1.40)
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Charlson index			
1-2	0.94 (0.83-1.06)	0.98 (0.88-1.08)	0.93 (0.82-1.05)
3-4	0.99 (0.84-1.15)	1.03 (0.90-1.17)	0.95 (0.81-1.13)
≥ 5	0.95 (0.78-1.16)	1.00 (0.85-1.18)	0.97 (0.79-1.19)
0	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)

Table F1. Continued

Explanatory variables[a]	Primary non-exposure gap[b]	Shorter non-exposure gap[b]	Longer non-exposure gap[b]
Level of care			
Level 2	1.46 (0.91-2.33)	1.32 (0.90-1.95)	1.64 (0.97-2.75)
Level 3	1.32 (0.82-2.11)	1.24 (0.84-1.84)	1.46 (0.86-2.47)
Level 4	1.65 (1.02-2.65)*	1.61 (1.08-2.39)*	1.83 (1.08-3.12)*
Level 1	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
AHFS drug category			
4-6	0.88 (0.75-1.02)	0.90 (0.79-1.02)	0.82 (0.70-0.96)*
≥ 7	0.90 (0.77-1.04)	0.93 (0.82-1.06)	0.83 (0.71-0.98)*
0-3	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Behavioural			
MDS-CPS			
Moderately impaired (2-3)	*	*	*
Severely impaired (4-6)	*	*	*
Minimally impaired (0-1)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
MDS-CBP			
Mild (1-4)	1.16 (1.00-1.35)*	1.21 (1.06-1.38)*	1.12 (0.95-1.31)
Moderate (5-9)	0.95 (0.80-1.12)	1.04 (0.90-1.20)	0.89 (0.75-1.06)
Severe (10-14)	0.76 (0.61-0.95)*	0.94 (0.78-1.13)	0.70 (0.55-0.89)*
Extreme (≥ 15)	0.73 (0.53-1.01)	0.96 (0.74-1.24)	0.66 (0.47-0.93)*
None (0)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Drug exposure			
Days to APM initiation after LTCF admission			
31-90 days	0.95 (0.82-1.10)	0.89 (0.78-1.01)	0.93 (0.79-1.08)
> 90 days	1.07 (0.93-1.24)	1.04 (0.93-1.18)	1.10 (0.94-1.28)
0-30 days	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Last APM dispensation before LTCF admission			
≤ 30 days	*	*	*
> 30 days	*	*	*
None in previous year	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Last antidepressant dispensation before LTCF admission			
≤ 30 days	1.12 (0.97-1.29)	1.17 (1.04-1.32)	1.14 (0.98-1.33)
> 30 days	1.05 (0.89-1.23)	1.08 (0.94-1.24)	1.12 (0.94-1.34)
None in previous year	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Last benzodiazepine dispensation before LTCF admission			
≤ 30 days	0.79 (0.66-0.93)*	0.80 (0.70-0.93)*	0.86 (0.72-1.03)
> 30 days	0.88 (0.75-1.04)	0.90 (0.78-1.03)	0.90 (0.75-1.07)
None in previous year	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Last anticholinergic dispensation before LTCF admission			
≤ 30 days	0.78 (0.60-1.03)	0.86 (0.69-1.08)	0.77 (0.57-1.03)
> 30 days	0.80 (0.63-1.01)	0.83 (0.69-1.01)	0.74 (0.57-0.95)*
None in previous year	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Last cholinergic dispensation before LTCF admission			
≤ 30 days	1.31 (1.02-1.67)*	1.24 (1.00-1.54)*	1.47 (1.14-1.89)*
> 30 days	1.38 (1.15-1.66)*	1.28 (1.09-1.50)*	1.33 (1.09-1.63)*
None in previous year	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)

Table F1. Continued

Explanatory variables[a]	Primary non-exposure gap[b]	Shorter non-exposure gap[b]	Longer non-exposure gap[b]
Health care utilization			
Transfer to new LTCF			
Yes	0.87 (0.77-0.98)*	0.92 (0.83-1.02)	0.89 (0.78-1.01)
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Hospitalization prior to LTCF admission			
Yes	*	*	*
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Hospitalization after LTCF admission			
Yes	1.12 (1.01-1.24)*	1.07 (0.98-1.17)	1.13 (1.01-1.26)*
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
LTCF			
Facility affiliation			
Affiliate (private, non-profit)	1.16 (1.00-1.33)*	1.18 (1.04-1.33)*	1.19 (1.02-1.38)*
Contract (private, for profit)	0.96 (0.78-1.19)	1.00 (0.84-1.20)	0.93 (0.74-1.16)
Amalgamate (public)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Facility Health Region			
Regina Qu'Appelle	*	*	*
Saskatoon	*	*	*
Other	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Facility size			
Small (1-35 beds)	0.90 (0.77-1.06)	0.96 (0.84-1.09)	0.82 (0.69-0.98)*
Medium (36-100 beds)	1.01 (0.89-1.14)	1.01 (0.90-1.12)	0.98 (0.86-1.12)
Large (> 100 beds)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Time interaction with			
Sex	*	*	*
Dementia	*	*	*
MDS-CPS	*	*	*
Last APM dispensation before LTCF admission	*	*	*
Hospitalization prior to LTCF admission	*	*	*
Facility location	*	*	*

Abbreviations – AHFS: American hospital formulary system, APM: antipsychotic medication, LTCF: long-term care facility, MDS-CBP: minimum dataset challenging behaviour profile, MDS-CPS: minimum dataset cognitive performance scale. *Notes* – a: Explanatory variables are grouped by concept, which is indicated by the ***bold-italicized*** terms. b: Normal non-exposure gap is a 35 day gap period, while shorter and longer non-exposure gap definitions refer to 0 and 70 day gaps, respectively.*Symbols* - *, $p < 0.05$.

Table F2. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) for covariate-time interactions from extended Cox model for the assessment of model sensitivity to the definition of APM discontinuation.

	Follow-up time (days)				
	0 days	90 days	180 days	365 days	730 days
Variables	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Sex					
Female					
Primary non-exposure gap[a]	2.66 (2.26-3.13)	2.34 (2.01-2.72)	2.05 (1.78-2.36)	1.57 (1.38-1.77)	0.92 (0.82-1.04)
Short non-exposure gap[a]	2.72 (2.37-3.13)	2.38 (2.09-2.71)	2.08 (1.84-2.35)	1.58 (1.42-1.75)	0.91 (0.83-1.01)
Longer non-exposure gap[a]	2.81 (2.36-3.34)	2.46 (2.09-2.89)	2.15 (1.85-2.50)	1.63 (1.43-1.87)	0.95 (0.84-1.08)
Male	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Dementia					
Yes					
Primary non-exposure gap[a]	0.86 (0.73-1.01)	0.88 (0.75-1.02)	0.89 (0.78-1.03)	0.93 (0.83-1.05)	1.01 (0.89-1.15)
Short non-exposure gap[a]	0.77 (0.67-0.88)	0.79 (0.69-0.90)	0.81 (0.72-0.91)	0.86 (0.78-0.95)	0.96 (0.87-1.07)
Longer non-exposure gap[a]	0.81 (0.68-0.97)	0.84 (0.71-0.98)	0.86 (0.74-0.99)	0.91 (0.80-1.03)	1.01 (0.88-1.16)
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
MDS-CPS					
Moderately impaired (2-3)					
Primary non-exposure gap[a]	4.20 (3.29-5.36)	3.42 (2.72-4.30)	2.79 (2.25-3.45)	1.83 (1.52-2.21)	0.80 (0.68-0.95)
Short non-exposure gap[a]	4.84 (3.90-6.01)	3.94 (3.22-4.82)	3.20 (2.65-3.87)	2.09 (1.77-2.47)	0.90 (0.78-1.04)
Longer non-exposure gap[a]	4.20 (3.24-5.44)	3.43 (2.69-4.36)	2.79 (2.23-3.50)	1.84 (1.51-2.25)	0.81 (0.67-0.97)
Severely impaired (4-6)					
Primary non-exposure gap[a]	4.07 (3.09-5.38)	3.41 (2.63-4.41)	2.85 (2.24-3.63)	1.98 (1.60-2.44)	0.96 (0.79-1.17)
Short non-exposure gap[a]	4.72 (3.69-6.03)	3.90 (3.10-4.90)	3.22 (2.60-3.98)	2.17 (1.80-2.62)	1.00 (0.85-1.19)
Longer non-exposure gap[a]	4.12 (3.07-5.53)	3.46 (2.63-4.54)	2.90 (2.25-3.74)	2.02 (1.62-2.53)	0.99 (0.81-1.23)
Minimally impaired (0-1)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Last APM dispensation before LTCF admission					
≤ 30 days					
Primary non-exposure gap[a]	1.43 (1.20-1.70)	1.31 (1.11-1.55)	1.21 (1.03-1.41)	1.02 (0.88-1.17)	0.72 (0.62-0.84)
Short non-exposure gap[a]	1.46 (1.25-1.70)	1.33 (1.15-1.53)	1.21 (1.06-1.39)	1.00 (0.89-1.13)	0.69 (0.61-0.78)
Longer non-exposure gap[a]	1.45 (1.21-1.75)	1.34 (1.12-1.59)	1.23 (1.04-1.45)	1.03 (0.88-1.20)	0.73 (0.62-0.85)
> 30 days					
Primary non-exposure gap[a]	1.18 (0.93-1.50)	1.11 (0.89-1.39)	1.05 (0.86-1.29)	0.94 (0.78-1.12)	0.75 (0.61-0.90)
Short non-exposure gap[a]	1.33 (1.08-1.63)	1.24 (1.03-1.49)	1.16 (0.97-1.38)	1.01 (0.87-1.17)	0.76 (0.65-0.90)
Longer non-exposure gap[a]	1.24 (0.96-1.60)	1.17 (0.92-1.48)	1.10 (0.88-1.36)	0.97 (0.80-1.17)	0.75 (0.61-0.93)
None in previous year	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Hospitalization prior to LTCF admission					
Yes					
Primary non-exposure gap[a]	4.80 (3.92-5.88)	3.89 (3.23-4.70)	3.16 (2.65-3.76)	2.05 (1.76-2.39)	0.88 (0.76-1.01)
Short non-exposure gap[a]	4.87 (4.09-5.80)	3.96 (3.37-4.66)	3.22 (2.77-3.74)	2.11 (1.85-2.40)	0.91 (0.81-1.03)
Longer non-exposure gap[a]	4.72 (3.81-5.86)	3.82 (3.13-4.66)	3.09 (2.57-3.72)	2.00 (1.70-2.35	0.85 (0.73-0.99)
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Facility Health Region					
Regina Qu'Appelle					
Primary non-exposure gap[a]	1.26 (1.01-1.57)	1.21 (0.99-1.49)	1.17 (0.97-1.41)	1.08 (0.91-1.28)	0.93 (0.78-1.11)
Short non-exposure gap[a]	1.13 (0.94-1.37)	1.09 (0.91-1.30)	1.05 (0.89-1.24)	0.98 (0.84-1.13)	0.84 (0.72-0.98)
Longer non-exposure gap[a]	1.16 (0.92-1.46)	1.13 (0.91-1.40)	1.10 (0.90-1.35)	1.05 (0.87-1.26)	0.95 (0.79-1.14)
Saskatoon					
Primary non-exposure gap[a]	1.59 (1.30-1.95)	1.48 (1.23-1.78)	1.37 (1.16-1.63)	1.18 (1.01-1.38)	0.87 (0.74-1.04)
Short non-exposure gap[a]	1.38 (1.16-1.65)	1.29 (1.10-1.52)	1.20 (1.03-1.39)	1.04 (0.91-1.18)	0.77 (0.67-0.90)
Longer non-exposure gap[a]	1.58 (1.28-1.96)	1.47 (1.21-1.79)	1.37 (1.14-1.64)	1.18 (1.00-1.38)	0.87 (0.73-1.05)
Other	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)

Abbreviations – APM: antipsychotic medication, LTCF: long-term care facility, MDS-CPS: minimum dataset cognitive performance scale. *Notes – a:* Primary, shorter and longer non-exposure gaps were 35, 0, and 70 days, respectively.

APPENDIX G – EVALUATION OF STUDY RESULTS UNDER CONDITIONS THAT VIOLATE THE INDEPENDENT CENSORING ASSUMPTION

Table G1. Fully adjusted Cox proportional hazards regression models with covariate time interactions for the assessment of independent censoring.

Explanatory variables[a]	Primary analysis	Positive correlation analysis	Negative correlation analysis
Demographic	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Age			
75-84	1.19 (0.98-1.44)	1.31 (1.21-1.43)*	1.00 (0.93-1.09)
85-94	1.34 (1.11-1.63)*	1.44 (1.32-1.58)*	1.02 (0.94-1.11)
≥ 95	1.17 (0.89-1.55)	1.44 (1.27-1.64)*	1.02 (0.90-1.15)
65-74	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Sex			
Female	*	*	*
Male	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Index fiscal year			
04/05	0.98 (0.80-1.21)	0.99 (0.90-1.10)	1.02 (0.92-1.13)
05/06	1.00 (0.83-1.21)	0.90 (0.82-1.00)*	0.99 (0.90-1.09)
06/07	0.87 (0.72-1.05)	0.90 (0.82-0.99)*	1.02 (0.93-1.12)
07/08	0.80 (0.66-0.97)*	1.01 (0.92-1.11)	1.02 (0.94-1.12)
09/10	0.76 (0.63-0.93)*	1.04 (0.95-1.13)	0.99 (0.90-1.08)
10/11	0.75 (0.61-0.91)*	1.05 (0.96-1.15)	1.03 (0.94-1.13)
11/12	0.58 (0.47-0.71)*	1.06 (0.97-1.16)	1.01 (0.92-1.10)
12/13	-	-	-
08/09	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Comorbidity			
Dementia			
Yes	-	*	-
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Schizophrenia			
Yes	1.01 (0.90-1.13)	1.06 (1.00-1.11)*	0.98 (0.94-1.03)
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Mood disorder			
Yes	0.94 (0.83-1.07)	0.99 (0.94-1.05)	1.01 (0.95-1.06)
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Alcohol or drug abuse			
Yes	0.94 (0.65-1.37)	0.93 (0.79-1.09)	0.96 (0.82-1.12)
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Extrapyramidal symptoms			
Yes	1.02 (0.76-1.37)	1.12 (0.99-1.27)	1.01 (0.90-1.14)
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Charlson index			
1-2	0.94 (0.83-1.06)	0.98 (0.93-1.04)	0.99 (0.94-1.05)
3-4	0.99 (0.84-1.15)	1.00 (0.93-1.07)	0.98 (0.92-1.06)
≥ 5	0.95 (0.78-1.16)	0.97 (0.89-1.06)	0.98 (0.89-1.07)
0	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)

Table G1 Continued

Explanatory variables[a]	Primary analysis	Positive correlation analysis	Negative correlation analysis
Level of care			
Level 2	1.46 (0.91-2.33)	1.01 (0.83-1.22)	1.01 (0.84-1.22)
Level 3	1.32 (0.82-2.11)	0.90 (0.74-1.10)	1.00 (0.82-1.21)
Level 4	1.65 (1.02-2.65)*	1.02 (0.84-1.25)	1.00 (0.82-1.22)
Level 1	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
AHFS drug category			
4-6	0.88 (0.75-1.02)	0.96 (0.90-1.03)	0.97 (0.91-1.04)
≥ 7	0.90 (0.77-1.04)	0.97 (0.91-1.04)	1.00 (0.93-1.07)
0-3	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Behavioural			
MDS-CPS			
Moderately impaired (2-3)	*	*	*
Severely impaired (4-6)	*	*	*
Minimally impaired (0-1)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
MDS-CBP			
Mild (1-4)	1.16 (1.00-1.35)*	1.19 (1.10-1.28)*	1.01 (0.94-1.08)
Moderate (5-9)	0.95 (0.80-1.12)	1.13 (1.04-1.22)*	0.99 (0.91-1.06)
Severe (10-14)	0.76 (0.61-0.95)*	1.21 (1.10-1.33)*	1.00 (0.91-1.10)
Extreme (≥ 15)	0.73 (0.53-1.01)	1.28 (1.13-1.46)*	0.99 (0.88-1.12)
None (0)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Drug exposure			
Days to APM initiation after LTCF admission			
31-90 days	0.95 (0.82-1.10)	0.93 (0.87-0.99)*	0.97 (0.91-1.03)
> 90 days	1.07 (0.93-1.24)	0.88 (0.82-0.94)*	1.01 (0.94-1.08)
0-30 days	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Last APM dispensation before LTCF admission			
≤ 30 days	*	*	*
> 30 days	-	*	*
None in previous year	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Last antidepressant dispensation before LTCF admission			
≤ 30 days	1.12 (0.97-1.29)	1.06 (0.99-1.13)	1.01 (0.95-1.08)
> 30 days	1.05 (0.89-1.23)	1.05 (0.98-1.13)	1.00 (0.93-1.08)
None in previous year	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Last benzodiazepine dispensation before LTCF admission			
≤ 30 days	0.79 (0.66-0.93)*	0.92 (0.85-0.99)*	1.00 (0.93-1.07)
> 30 days	0.88 (0.75-1.04)	0.97 (0.90-1.04)	1.01 (0.94-1.08)
None in previous year	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Last anticholinergic dispensation before LTCF admission			
≤ 30 days	0.78 (0.60-1.03)	1.03 (0.92-1.15)	1.02 (0.91-1.14)
> 30 days	0.80 (0.63-1.01)	1.09 (0.99-1.19)	0.99 (0.90-1.09)
None in previous year	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Last cholinergic dispensation before LTCF admission			
≤ 30 days	1.31 (1.02-1.67)*	1.10 (0.98-1.24)	1.02 (0.91-1.15)
> 30 days	1.38 (1.15-1.66)*	1.07 (0.98-1.17)	1.04 (0.95-1.14)
None in previous year	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Health care utilization			
Transfer to new LTCF			
Yes	0.87 (0.77-0.98)*	0.96 (0.91-1.01)	1.01 (0.96-1.07)
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)

Table G1 Continued

Explanatory variables[a]	Primary analysis	Positive correlation analysis	Negative correlation analysis
Hospitalization prior to LTCF admission			
Yes	*	*	*
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Hospitalization after LTCF admission			
Yes	1.12 (1.01-1.24)*	0.94 (0.89-0.98)*	1.01 (0.96-1.06)
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
LTCF			
Facility affiliation			
Affiliate (private, non-profit)	1.16 (1.00-1.33)*	1.10 (1.03-1.18)*	1.02 (0.96-1.09)
Contract (private, for profit)	0.96 (0.78-1.19)	1.09 (0.99-1.19)*	1.01 (0.92-1.10)
Amalgamate (public)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Facility Health Region			
Regina Qu'Appelle	*	*	*
Saskatoon	*	*	*
Other	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Facility size			
Small (1-35 beds)	0.90 (0.77-1.06)	1.04 (0.97-1.11)	1.00 (0.93-1.07)
Medium (36-100 beds)	1.01 (0.89-1.14)	1.05 (0.99-1.11)	1.00 (0.95-1.06)
Large (> 100 beds)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Time interaction with			
Sex	*	*	*
Dementia	*	-	-
MDS-CPS	*	*	*
Last APM dispensation before LTCF admission	*	*	*
Hospitalization prior to LTCF admission	*	*	*
Facility location	*	*	*

Abbreviations – AHFS: American hospital formulary system, APM: antipsychotic medication, LTCF: long-term care facility, MDS-CBP: minimum dataset challenging behaviour profile, MDS-CPS: minimum dataset cognitive performance scale. *Notes* – a: Explanatory variables are grouped by concept, which is indicated by the ***bold-italicized*** terms. b: Partially adjusted models include all group variables and demographic variables. Therefore, the six partially adjusted models include the variable groups demographic, demographic + comorbidity, demographic + behavioural, demographic + drug exposure, demographic + health care utilization, and demographic + LTCF. c: Fully adjusted models include all variables. d: Covariate time interaction model is a fully adjusted model with the addition of time-covariate interactions. *Symbols* - *, $p < 0.05$.

Table G2. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) for covariate-time interactions from extended Cox model for the assessment of independent censoring.

	Follow-up time (days)				
	0 days	90 days	180 days	365 days	730 days
Variables	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Sex					
Female					
Primary analysis	2.66 (2.26-3.13)	2.34 (2.01-2.72)	2.05 (1.78-2.36)	1.57 (1.38-1.77)	0.92 (0.82-1.04)
Positive correlation analysis	2.36 (2.18-2.55)	2.08 (1.94-2.24)	1.84 (1.72-1.97)	1.42 (1.34-1.51)	0.86 (0.82-0.91)
Negative correlation analysis	2.45 (2.09-2.87)	2.38 (2.04-2.77)	2.31 (1.99-2.69)	2.18 (1.89-2.51)	1.94 (1.72-2.20)
Male	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Dementia					
Yes					
Primary analysis	0.86 (0.73-1.01)	0.88 (0.75-1.02)	0.89 (0.78-1.03)	0.93 (0.83-1.05)	1.01 (0.89-1.15)
Positive correlation analysis	0.87 (0.81-0.95)	0.88 (0.82-0.95)	0.88 (0.83-0.95)	0.89 (0.84-0.95)	0.92 (0.87-0.97)
Negative correlation analysis	0.90 (0.78-1.03)	0.90 (0.79-1.03)	0.90 (0.79-1.03)	0.91 (0.80-1.03)	0.92 (0.83-1.02)
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
MDS-CPS					
Moderately impaired (2-3)					
Primary analysis	4.20 (3.29-5.36)	3.42 (2.72-4.30)	2.79 (2.25-3.45)	1.83 (1.52-2.21)	0.80 (0.68-0.95)
Positive correlation analysis	7.24 (6.32-8.30)	5.89 (5.18-6.70)	4.79 (4.24-5.41)	3.13 (2.82-3.49)	1.36 (1.24-1.48)
Negative correlation analysis	63.7 (46.1-88.1)	56.4 (41.2-77.3)	49.9 (36.7-67.8)	38.8 (29.1-51.8)	23.7 (18.4-30.5)
Severely impaired (4-6)					
Primary analysis	4.07 (3.09-5.38)	3.41 (2.63-4.41)	2.85 (2.24-3.63)	1.98 (1.60-2.44)	0.96 (0.79-1.17)
Positive correlation analysis	7.10 (6.10-8.26)	5.79 (5.03-6.67)	4.73 (4.14-5.40)	3.11 (2.77-3.50)	1.37 (1.24-1.51)
Negative correlation analysis	59.1 (42.1-83.0)	52.5 (37.7-73.0)	46.5 (33.8-64.2)	36.4 (26.9-49.2)	22.4 (17.1-29.2)
Minimally impaired (0-1)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Last APM dispensation before LTCF admission					
≤ 30 days					
Primary analysis	1.43 (1.20-1.70)	1.31 (1.11-1.55)	1.21 (1.03-1.41)	1.02 (0.88-1.17)	0.72 (0.62-0.84)
Positive correlation analysis	1.85 (1.70-2.01)	1.67 (1.54-1.81)	1.50 (1.40-1.62)	1.22 (1.14-1.30)	0.80 (0.75-0.85)
Negative correlation analysis	1.48 (1.28-1.71)	1.46 (1.27-1.68)	1.44 (1.26-1.65)	1.40 (1.23-1.59)	1.33 (1.18-1.49)
> 30 days					
Primary analysis	1.18 (0.93-1.50)	1.11 (0.89-1.39)	1.05 (0.86-1.29)	0.94 (0.78-1.12)	0.75 (0.61-0.90)
Positive correlation analysis	1.56 (1.40-1.74)	1.45 (1.31-1.60)	1.35 (1.23-1.48)	1.16 (1.07-1.26)	0.87 (0.80-0.94)
Negative correlation analysis	1.55 (1.28-1.89)	1.53 (1.27-1.86)	1.51 (1.25-1.82)	1.47 (1.23-1.75)	1.39 (1.19-1.62)
None in previous year	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Hospitalization prior to LTCF admission					
Yes					
Primary analysis	4.80 (3.92-5.88)	3.89 (3.23-4.70)	3.16 (2.65-3.76)	2.05 (1.76-2.39)	0.88 (0.76-1.01)
Positive correlation analysis	4.80 (4.36-5.27)	4.06 (3.71-4.44)	3.43 (3.16-3.73)	2.44 (2.26-2.62)	1.24 (1.16-1.32)
Negative correlation analysis	4.18 (3.50-4.99)	3.99 (3.36-4.75)	3.82 (3.23-4.52)	3.48 (2.97-4.08)	2.90 (2.53-3.34)
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Facility Health Region					
Regina Qu'Appelle					
Primary analysis	1.26 (1.01-1.57)	1.21 (0.99-1.49)	1.17 (0.97-1.41)	1.08 (0.91-1.28)	0.93 (0.78-1.11)
Positive correlation analysis	1.47 (1.33-1.63)	1.39 (1.27-1.53)	1.32 (1.21-1.45)	1.18 (1.09-1.28)	0.95 (0.88-1.03)
Negative correlation analysis	1.35 (1.13-1.61)	1.34 (1.13-1.59)	1.32 (1.12-1.56)	1.29 (1.11-1.51)	1.24 (1.08-1.42)
Saskatoon					
Primary analysis	1.59 (1.30-1.95)	1.48 (1.23-1.78)	1.37 (1.16-1.63)	1.18 (1.01-1.38)	0.87 (0.74-1.04)
Positive correlation analysis	1.41 (1.28-1.55)	1.35 (1.23-1.48)	1.29 (1.19-1.41)	1.18 (1.10-1.27)	0.99 (0.92-1.06)
Negative correlation analysis	1.75 (1.50-2.03)	1.72 (1.48-1.99)	1.69 (1.46-1.95)	1.63 (1.42-1.86)	1.52 (1.35-1.71)
Other	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)

Abbreviations – APM: antipsychotic medication, HR (95% CI): Hazard ratio (95% confidence interval), LTCF: long-term care facility, MDS-CPS: minimum dataset cognitive performance scale.

APPENDIX H – MODEL RESULTS WHEN FOLLOW-UP WAS TRUNCATED AT 6 MONTHS

Table H1. Hazards ratios (HRs) and 95% confidence intervals (95% CIs) when follow-up time was truncated at 6 months.

Explanatory variables[a]	Full	Full-interaction	6-month follow-up time
Demographic	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Age			
75-84	1.10 (0.91-1.31)	1.19 (0.98-1.44)	1.19 (0.89-1.59)
85-94	1.38 (1.15-1.65)*	1.34 (1.11-1.63)*	1.54 (1.15-2.05)*
≥ 95	1.53 (1.16-2.01)*	1.17 (0.89-1.55)	1.69 (1.15-2.49)*
65-74	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Sex			
Female	0.93 (0.83-1.04)	*	0.83 (0.71-0.97)*
Male	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Index fiscal year			
04/05	0.77 (0.63-0.95)*	0.98 (0.80-1.21)	0.88 (0.64-1.23)
05/06	1.02 (0.85-1.23)	1.00 (0.83-1.21)	1.11 (0.83-1.48)
06/07	0.96 (0.80-1.15)	0.87 (0.72-1.05)	1.00 (0.75-1.33)
07/08	0.84 (0.69-1.01)	0.80 (0.66-0.97)*	0.96 (0.72-1.29)
09/10	0.89 (0.73-1.08)	0.76 (0.63-0.93)*	0.92 (0.69-1.23)
10/11	0.94 (0.77-1.14)	0.75 (0.61-0.91)*	1.07 (0.81-1.40)
11/12	0.97 (0.79-1.19)	0.58 (0.47-0.71)*	1.06 (0.80-1.40)
12/13	-	-	-
08/09	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Comorbidity			
Dementia			
Yes	1.03 (0.92-1.15)	*	0.96 (0.81-1.13)
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Schizophrenia			
Yes	0.88 (0.79-0.98)*	1.01 (0.90-1.13)	0.84 (0.72-0.99)*
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Mood disorder			
Yes	0.84 (0.74-0.95)*	0.94 (0.83-1.07)	0.79 (0.66-0.95)*
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Alcohol or drug abuse			
Yes	0.84 (0.58-1.22)	0.94 (0.65-1.37)	1.06 (0.64-1.77)
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Extrapyramidal symptoms			
Yes	0.87 (0.65-1.17)	1.02 (0.76-1.37)	1.03 (0.67-1.57)
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Charlson index			
1-2	0.94 (0.83-1.05)	0.94 (0.83-1.06)	0.90 (0.76-1.07)
3-4	0.98 (0.84-1.15)	0.99 (0.84-1.15)	0.93 (0.75-1.17)
≥ 5	1.00 (0.82-1.21)	0.95 (0.78-1.16)	1.01 (0.76-1.33)
0	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Level of care			
Level 2	1.74 (1.10-2.76)*	1.46 (0.91-2.33)	1.49 (0.72-3.06)
Level 3	1.70 (1.07-2.71)*	1.32 (0.82-2.11)	1.40 (0.67-2.92)
Level 4	2.03 (1.27-3.24)*	1.65 (1.02-2.65)*	1.74 (0.84-3.62)
Level 1	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)

Table H1. Continued

Explanatory variables[a]	Full	Full-interaction	6-month follow-up time
AHFS drug category			
4-6	0.94 (0.81-1.09)	0.88 (0.75-1.02)	0.85 (0.69-1.06)
≥ 7	1.11 (0.96-1.29)	0.90 (0.77-1.04)	1.07 (0.86-1.32)
0-3	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Behavioural			
MDS-CPS			
Moderately impaired (2-3)	0.87 (0.75-1.01)	*	0.76 (0.63-0.93)*
Severely impaired (4-6)	1.11 (0.93-1.32)	*	0.82 (0.64-1.05)
Minimally impaired (0-1)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
MDS-CBP			
Mild (1-4)	1.02 (0.88-1.17)	1.16 (1.00-1.35)*	0.99 (0.81-1.20)
Moderate (5-9)	0.86 (0.73-1.00)	0.95 (0.80-1.12)	0.71 (0.56-0.90)*
Severe (10-14)	0.64 (0.51-0.79)*	0.76 (0.61-0.95)*	0.55 (0.39-0.76)*
Extreme (≥ 15)	0.59 (0.43-0.81)*	0.73 (0.53-1.01)	0.49 (0.30-0.81)*
None (0)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Drug exposure			
Days to APM initiation after LTCF admission			
31-90 days	1.01 (0.88-1.17)	0.95 (0.82-1.10)	0.91 (0.74-1.13)
> 90 days	1.16 (1.01-1.33)*	1.07 (0.93-1.24)	1.09 (0.89-1.32)
0-30 days	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Last APM dispensation before LTCF admission			
≤ 30 days	0.75 (0.65-0.86)*	*	0.59 (0.48-0.73)*
> 30 days	0.72 (0.60-0.85)*	*	0.61 (0.48-0.79)*
None in previous year	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Last antidepressant dispensation before LTCF admission			
≤ 30 days	0.94 (0.82-1.09)	1.12 (0.97-1.29)	1.06 (0.86-1.32)
> 30 days	1.03 (0.88-1.22)	1.05 (0.89-1.23)	1.10 (0.88-1.39)
None in previous year	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Last benzodiazepine dispensation before LTCF admission			
≤ 30 days	0.80 (0.68-0.95)*	0.79 (0.66-0.93)*	0.80 (0.61-1.03)
> 30 days	0.86 (0.73-1.01)	0.88 (0.75-1.04)	0.93 (0.73-1.18)
None in previous year	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Last anticholinergic dispensation before LTCF admission			
≤ 30 days	0.81 (0.62-1.07)	0.78 (0.60-1.03)	1.01 (0.71-1.45)
> 30 days	0.79 (0.63-1.00)*	0.80 (0.63-1.01)	0.80 (0.58-1.11)
None in previous year	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Last cholinergic dispensation before LTCF admission			
≤ 30 days	1.22 (0.96-1.56)	1.31 (1.02-1.67)*	0.94 (0.61-1.44)
> 30 days	1.40 (1.16-1.67)*	1.38 (1.15-1.66)*	1.60 (1.22-2.10)*
None in previous year	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Health care utilization			
Transfer to new LTCF			
Yes	0.91 (0.81-1.02)	0.87 (0.77-0.98)*	0.96 (0.81-1.14)
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Hospitalization prior to LTCF admission			
Yes	1.10 (0.97-1.24)	*	1.29 (1.06-1.56)*
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Hospitalization after LTCF admission			
Yes	1.13 (1.02-1.26)*	1.12 (1.01-1.24)*	1.12 (0.96-1.30)
No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)

Table H1. Continued

Explanatory variables[a]	Full	Full-interaction	6-month follow-up time
LTCF			
Facility affiliation			
Affiliate (private, non-profit)	1.09 (0.95-1.25)	1.16 (1.00-1.33)*	1.24 (1.02-1.52)*
Contract (private, for profit)	1.09 (0.89-1.34)	0.96 (0.78-1.19)	1.33 (0.99-1.77)
Amalgamate (public)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Facility Health Region			
Regina Qu'Appelle	0.98 (0.83-1.16)	*	0.80 (0.63-1.03)
Saskatoon	1.10 (0.95-1.27)	*	1.20 (0.97-1.48)
Other	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Facility size			
Small (1-35 beds)	0.92 (0.79-1.07)	0.90 (0.77-1.06)	1.03 (0.83-1.29)
Medium (36-100 beds)	1.02 (0.90-1.15)	1.01 (0.89-1.14)	1.01 (0.84-1.22)
Large (> 100 beds)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Time interaction with			
Sex	N/A	*	N/A
Dementia	N/A	*	N/A
MDS-CPS	N/A	*	N/A
Last APM dispensation before LTCF admission	N/A	*	N/A
Hospitalization prior to LTCF admission	N/A	*	N/A
Facility location	N/A	*	N/A

Abbreviations – AHFS: American hospital formulary system, APM: antipsychotic medication, LTCF: long-term care facility, MDS-CBP: minimum dataset challenging behaviour profile, MDS-CPS: minimum dataset cognitive performance scale. *Notes* – a: Explanatory variables are grouped by concept, which is indicated by the ***bold-italicized*** terms. c: Fully adjusted models include all variables. d: Covariate time interaction model is a fully adjusted model with the addition of time-covariate interactions. *Symbols* - *, $p < 0.05$.