

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Psychotropic Medication Use and Mortality in Long-Term Care Residents

Michael J. Stones, Sarah Worobetz, Jason Randle, Carlina Marchese, Shauna Fossum, Dane Ostrom and Peter Brink

Abstract

This chapter examines associations between psychotropic medications and mortality in long-term care home (LTCH) settings. We report new findings with census-level data from all new admissions to long-term care homes in the province of Ontario, Canada (i.e., 20,414 new residents). The data include three linked sets that indicate mortality during the financial years 2010–2011 and 2011–2012. One dataset, the Resident Assessment Instrument 2.0 (RAI 2.0), provides information on demographics, functional capability, clinical conditions, clinical diagnoses, mortality risk, and psychotropic medications. The latter include antipsychotics, antidepressants, analgesics, anxiolytics, and hypnotics. Administration of the RAI 2.0 occurs at resident intake, at quarterly intervals and annually. New analyses reported here examine predictors of daily and *pro re nata* (i.e., PRN or “as needed”) prescriptions of psychotropic medications. However, the most important analyses concern predictors of mortality within intervals of up to 90 days from the final RAI 2.0 assessment. After control for confounding variables, the findings indicate (1) attenuated mortality with daily prescription of frequently prescribed psychotropics (i.e., antipsychotics, antidepressants, and analgesics), (2) augmented mortality with PRN prescriptions for each type of psychotropic medication, and (3) evidence that PRN prescribing overturns beneficial effects of daily prescriptions, whereas the latter reduces the deleterious effects of PRN prescribing.

Keywords: mortality, medication, psychotropic, antipsychotic, analgesic, antidepressant, anxiolytic, hypnotic, aging, elderly, gerontology, long-term care, dementia

1. Introduction

This chapter illustrates a truism that pathways pursued in scientific investigation often deviate from linear trajectories. The research we report here evolved from concerns about ongoing practices in the continuing care of older people, a serendipitous convergence of people with compatible research needs and desires, and totally unanticipated findings in need of further investigation. This section of the chapter traces the earlier stages of that progression.

1.1 Concern about associations of antipsychotic medication and mortality in older people

The research that follows evolved from participation by the lead author in unpublished work in the late 1990s commissioned by the Canadian Institute for Health Information (CIHI). The purpose was to analyze early Canadian data on version two of the Minimum Data Set (MDS 2.0), which is the former name of the RAI 2.0. In 1996, this tool became mandated for use in all chronic care hospitals, now known as complex community care (CCC) facilities in the Canadian Province of Ontario. The residents of these facilities are mainly older people in receipt of continuing care and/or rehabilitation associated with disabling chronic illness.

The findings from that work that was most troubling included high frequencies of physical restraint and chemical management in Canadian facilities compared to findings with the same tool in other countries. Although Canadian physical restraint levels lessened in frequency since that time, such is not the case for chemical management. Hence the enduring interest in chemical management by these authors.

The purpose of chemical management is to address symptoms that fall under the umbrella of behavioral and psychological symptoms of dementia (BPSD). The definition of the latter at a 1996 Consensus Conference of the International Psychogeriatric Association (IPA) is as follows: “symptoms of disturbed perception, thought content, mood or behavior that frequently occur in patients with dementia” [1]. The behavioral symptoms include physical aggression, loud vocalization, restlessness, agitation, and wandering. The psychological symptoms include anxiety, depressive mood, hallucinations, and delusions.

Current estimates suggest that over half the patients with dementia are at risk to such symptoms, which typically arise during the middle or later stages of the disease. Chemical management may include analgesics to lessen pain and discomfort, along with antidepressants, anti-anxiety medication and antipsychotics, all of which address behavioral and psychological symptoms [2]. The most frequent concerns about chemical management relate to antipsychotic medication. These are drugs first developed for the treatment of psychosis [3]. Presently, antipsychotic drugs fall within two categories. Typical antipsychotics include those initially developed to treat psychosis, while atypical antipsychotics were developed later to reduce adverse side effects of the former.

Concerns about harmful effects of antipsychotics in dementia patients are legitimate. The adverse effects of these drugs include high rates of cardiovascular events, cardiac arrhythmias, cerebrovascular events, cognitive decline, extrapyramidal symptoms, pneumonia, falls and fractures, and others [4]. However, the most serious concern is an elevated risk of mortality. Notice of such concerns began early this millennium with evidence that these adverse effects were over and above those associated with old age, an underlying dementia, and behavioral and psychological symptoms that might precipitate the use of antipsychotics [5].

In 2002, the manufacturer of a typical antipsychotic medication warned of an increased risk of adverse cardiovascular events [5]. Subsequently, the US Federal Food and Drug Administration (FDA) required “black box” warnings about the use of atypical antipsychotics (in 2005) and typical antipsychotics (in 2008). The warning states: “WARNING: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.” Health authorities in other countries subsequently expressed similar concerns.

Conclusions from the most recent and most extensive meta-analysis of studies that relate the use antipsychotic medication to the mortality of elderly people [6] are as follows. Mortality risk with antipsychotic medication (1) is twice that of people without such prescription, (2) comparable between typical and

atypical antipsychotics, (3) highest during the initial half-year of use, (4) higher at higher dosage, and (5) comparable between people with or without diagnosed dementia. One interpretation of these five points is that people with more severe dementia-related psychosis are at greater risk of mortality, with that risk lessening 6 months after they begin that course of medication. However, findings from placebo-controlled trials indicate antipsychotic use is associated with an increase in mortality above and beyond the baseline dementia symptoms. The authors of this meta-analysis also recommended a restricted use of antipsychotic medication with older people and encouraged the deployment of de-prescribing practices.

Final thoughts by those authors concur with comments made earlier by authors of this chapter [7]. Ralph and Espinet [6] anticipate greater cultural disapproval about the sedation of older people through antipsychotic, anxiolytic, and hypnotic medications. They envision attitudinal changes within the health and legal professions to consider such practices examples of systemic elder abuse that requires legal reform. A current drive toward the de-prescribing of antipsychotic medication to elderly people is consistent with these beliefs [8].

1.2 Preliminary study of antipsychotic medication and mortality in older people

When Sarah Worobetz, a doctoral student at Lakehead University, wanted to research relationships between antipsychotic medication and mortality in older people, after control for a wide range of variables we describe subsequently, faculty members Michael Stones and Peter Brink were happy to oblige. These researchers had a working familiarity with the RAI 2.0. They hoped to obtain census level data, with linkages to other mortality relevant datasets, to provide Sarah with the means to conduct her research. Peter Brink successfully submitted a proposal to CIHI for access to access these data.

The RAI 2.0 is a standardized assessment tool used routinely in LTCH and CCC facilities in Ontario and other settings across the world. The tool contains over 350 items relevant to medical diagnoses; physical, cognitive, social, and emotional functioning; and treatment categories that include medication use. It also indexes mortality within the relevant facilities. The trained health care professionals responsible for RAI 2.0 assessments obtain that information from multiple sources, such as direct observation, medical records, and communication with family members and other health care professionals. Objective scales on the RAI 2.0 consist of sets of items selected for relevance to a given construct. Evaluation of such scales may be against “gold standard” measures of the constructs (e.g., measures of activities of daily living, cognitive status, depression, aggression, and pain) or relevant outcomes (e.g., mortality risk). From a measurement perspective, previous findings on data quality and the reliability and validity of RAI 2.0 measures are positive [8–10].

The antipsychotic medication item on the RAI 2.0 falls within a psychotropic category that also contains items on antidepressant, analgesic, anxiolytic, and hypnotic medications. The wording of each of these items asks for the number of days during the past week that the resident received the medication. This form of measurement differs from that common to previous studies of psychotropic medication and mortality, which invariably report specific medications and dosages but not frequency of medication use.

The other databases provided by CIHI are the Discharge Abstract Database (DAD) and the National Ambulatory Care Reporting System (NACRS). The DAD contains demographic, administrative, and clinical data for hospital discharges (inpatient acute, chronic, and rehabilitation) and day surgeries. The NACRS contains data for hospital-based and community-based emergency and ambulatory care (e.g., day surgery and outpatient clinics). Both datasets contain mortality data pertaining to their respective contexts. CIHI encrypted the personal and facility identifiers across

datasets to ensure anonymity of residents. Brink merged these three datasets for purposes of analysis. Consequently, the merged file contains mortality data both within LTCH and CCC facilities and for those discharged to other health care settings.

The dataset analyzed by Worobetz includes all admission, quarterly and annual RAI 2.0 assessment for residents aged over 65 years in all LTCH and CCC facilities in Ontario during the financial years 2010–2011 and 2011–2012. The data are from 102,658 residents of approximately 760 facilities with a mean of 5.83 assessments per resident. Approximately 70% of residents are female and 30% male, with a mean age over all assessments of approximately 84 years. Approximately 86% of residents live in LTCH and 14% in CCC facilities. The mean length of stay prior to the first assessment was approximately 20 months, with the age at entry approximately 82 years. The distribution of antipsychotic prescriptions shows that approximately 69% of residents are without medication, 29% have daily prescriptions, and 2% have prescriptions of 1–6 days per week, which for purposes of this research we describe as PRN prescriptions. The total mortality rate during the 2-year period of data collection is approximately 32%.

The initial findings by Worobetz on relationships between mortality and type of antipsychotic prescription came as a big surprise. Her analysis by generalized linear mixed modeling (GLMM) appointed LTCH as a random effect variable (i.e., independent entities) with residents clustered (i.e., showing covariation) within their respective facilities. Such modeling is appropriate because of differences among facilities with respect to admission criteria, population size, staffing levels, types of programming, treatment protocols, etc., with localized interpersonal exchanges within facilities that foster covariation among residents. Compared to residents with no prescription for antipsychotic medication, her findings show attenuated mortality for those with daily prescription, but augmented mortality for those with PRN prescription. A possible interpretation is that these findings are consistent with earlier evidence of a protective effect of antipsychotics after 6 months but an increased mortality risk for residents prescribed antipsychotics on a PRN basis because they began to exhibit relevant symptoms.

Subsequent GLMM analyses by Worobetz included all residents, only those from LTCH, only those from CCC, new admissions, residents with dementia, and combinations of the preceding. The fixed effect variables in such analyses included not just prescriptions for antipsychotic medication but multivariate control for confounding variables such as demographics, scores on RAI 2.0 scales (e.g., activity limitation, cognitive status, aggression, depression, and mortality risk), temporal changes on those scales, and medical diagnoses (e.g., cancer, dementia, maniac depression, and schizophrenia [11]). The findings from all these analyses consistently show highest mortality among residents with PRN prescriptions on the final assessment.

1.3 Studies of other psychotropic medications and mortality in older people

The preceding findings provide reasons to broaden the scope of investigation to encompass mortality in relation to prescriptions of other types of psychotropic medication. We begin this section with brief discussion of prescribing practices and mortality associated with analgesics, antidepressants, anxiolytics and hypnotics, which in the RAI 2.0 fall within an item-set of psychotropic medications. Then follows discussion of problems associated with PRN prescribing practices. Finally, we report findings from separate analyses of mortality against these types of psychotropic medications.

Prescribing practices with analgesics show the following trends. Although rates for PRN prescription in elderly care services are generally low, some reports indicate highest levels for analgesics [12]. Worldwide, scheduled rates for analgesic use (that include acetaminophen and opioids) in LTCH show a historical increase, whereas

rates for scheduled plus PRN rates show no such increase [13]. Recent findings from the Czech Republic suggest that a large proportion of LTCH residents with pain receive no analgesic medication and a moderate proportion of those that receive analgesic medication continue to report pain. These findings of analgesic under-prescription are consistent with those from North America and elsewhere in Europe. The lowest frequency of reported pain and lowest prevalence of analgesic administration are for residents with moderate-to-severe dementia [14], which suggests this group's susceptibility to under-detection and under-prescribing of this medication.

Anti-depressant medications find frequent use in older people, with average prevalence rates of approximately 25% [15, 16]. Recent evidence suggests no association between antidepressant prescriptions and augmented risk of all-cause mortality [17, 18]. However, best practice guidelines recommend caution when prescribing because low adherence may increase risks of fatal cardiovascular and cerebrovascular injuries [19]. On the other hand, high adherence appears to lower mortality risk [20]. The findings give rise to hypotheses that intermittent use of antidepressants (e.g., comparable to PRN prescribing) has unfavorable implications for mortality whereas regular use (e.g., associated with daily prescription) has favorable implications. However, we will discuss other interpretations later in the chapter.

A recent review suggests that benzodiazepines are the most frequently prescribed anxiolytic medications for geriatric anxiety [21]. However, consensus is low about whether anxiolytic and hypnotic medications have unfavorable implications for mortality risk amongst older adults [22]. On the other hand, a large-scale retrospective cohort study of patients in UK primary care concluded that anxiolytic and hypnotic drugs were associated with significantly increased risk of mortality over a 7-year period, after adjusting for a range of potential confounders [23].

A number of studies and reviews examined PRN prescription in psychiatric and LTCH settings [24–27]. Summary findings indicate higher PRN use for residents with lower care needs, frequent use alongside regularly scheduled medications, and recent entry into a facility. Contextual factors also have a strong influence on PRN prescribing. These include general levels of activity and disturbance on the ward, staffing level, perceived competence of staff, and familiarity of the staff with residents. The reports also indicate frequent omissions and errors in records of PRN usage. Findings that relate mortality to PRN usage appear to be absent in the literature.

Following the thesis research by Worobetz, subsequent analyses of the same dataset examined relationships of mortality to prescriptions of anesthetics (Jason Randle), antidepressants (Carlina Marchese and Shauna Fossum), anxiolytics (Michael Stones), and hypnotics (Dane Ostrom). We describe the sampling procedure in the following section. The main findings show significantly higher mortality with PRN prescriptions for each type of psychotropic medication compared with daily or null prescription. These findings persist even after statistical control of relevant confounding variables. They provide the impetus for the new analyses that follow.

2. New analyses on relationships between psychotropic medication and mortality

We try here to expand the scope and level of precision beyond those present in previous analyses, each of which examined associations of mortality with a single psychotropic medication. First, we analyze the effects on mortality of all the psychotropic prescriptions within a series of multivariate analyses that includes the psychotropic medications. Second, we introduce a verified measure of mortality risk into the array of control variables. Third, we examine intervals for mortality of 90 days from the final RAI 2.0 assessment (i.e., the scheduled date of the next

assessment) and shorter periods within that interval. Fourth, we examine predictors of daily and PRN prescriptions of psychotropic medications. Fifth, we examine the effects on mortality for residents receiving only daily, only PRN, or both daily and PRN prescriptions of psychotropic medication.

2.1 Methods

Section 1.2 described the three datasets linked and encrypted by CIHI. Here we report analyses that restrict data entry to (1) scheduled intake, quarterly and yearly assessments, (2) in LTCH settings, (3) for residents aged 65+ years, (4) with an intake assessment during the financial year 2010/2011, and (5) subsequent assessments that do not exceed first yearly assessment (i.e., <13 months after the intake assessment). Consequently, the data enable computation of a census level 1-year incidence rate for mortality among LTCH residents aged 65 years and older.

The analyses that follow begin at a descriptive level and proceed to an inferential level. The latter analyses were performed using the SPSS 25 GLMM program. The target variables in different analyses include mortality within 90 days of the final assessment, time to mortality within that interval, and frequencies of daily and PRN prescriptions for psychotropic medication categories. The random variable in all analyses identifies the LTCH at intake assessment. Evidence of statistical significance for the random variable would confirm that levels on the target variable differ across the LTCH spectrum.

The fixed effects in different analyses include the following RAI 2.0 measures: demographics (gender, age at assessment); scales (Activities of Daily Living Hierarchy, Cognitive Performance Scale, Depression Rating Scale, Aggressive Behavior Scale, Pain Scale and the Changes in Health, End-Stage Disease, and Symptoms and Signs Scale); diagnoses (insomnia and dementia), and medications (antipsychotic, antidepressant, analgesic, anxiolytic, and hypnotic). Convincing evidence from earlier and more recent publications [28] attest to good data quality and psychometric properties associated with RAI 2.0 measures.

2.2 Results

Here we describe the sample with respect to demographics, psychotropic medication use, and mortality. The sample of 20,414 residents of 631 LTCH includes approximately 38% admissions from inpatient acute care, 28% from a private home, 13% from residential board and care, and 10% from home care. The remaining 11% of admissions are from residences with 24-hour nursing care, inpatient continuing care, inpatient rehabilitation, or inpatient psychiatry. The sample comprises 33.6% men and 66.4% women. The age distribution for men has a mean of 83.03 years and standard deviation of 7.37 years, with respective estimates for women of 85.29 and 7.19 years.

Table 1 shows percentage frequencies for residents prescribed psychotropic medication during the week before the final assessment. Daily prescription is highest for analgesics followed by antidepressants followed by antipsychotics. More than half the residents use analgesics daily, nearly half use antidepressants daily, and approximately 30% receive daily antipsychotics. The frequency of PRN usage is low. The highest frequencies are 7.5% for analgesics and 3.3% for anxiolytics.

Frequencies of daily prescriptions for different types of psychotropic medication are as follows: 33.4% of residents receive one medication; 31.5% receive two medications; 17.6% use three or four (i.e., 3+) medications; and 17.4% of residents have no daily psychotropic medication. Frequencies for PRN prescriptions of psychotropic medication are as follows: 10.9% of residents use one medication; 1.6% use two or three (i.e., 2+) medications; and 87.5 of residents have no

Prescription of psychotropic medication			
Medication type	None (%)	PRN (%)	Daily (%)
Antipsychotic	69.2	1.4	29.4
Antidepressant	50.9	1.4	47.7
Analgesic	34.6	7.5	57.9
Anxiolytic	84.9	3.3	11.8
Hypnotic	93.7	0.7	5.6

Table 1.
Percentage frequencies for usage of psychotropic medications.

psychotropic medication on a PRN basis. Frequencies for combinations of daily and PRN prescriptions are as follows: 74.6% of residents have only daily prescriptions for psychotropic medications; 4.5% have only PRN prescriptions; 8.0% have both daily and PRN prescriptions; and 12.9% have no prescription. These findings indicate that about half the residents receive two or more psychotropic medications daily, 12.5% receive one or more on a PRN basis, and 8.0% have both daily and PRN prescriptions.

Probabilistic mortalities within 90 days of the final assessment are 18.1% overall, 21.1% for males and 16.3% for females. The percentages of residents dying within different time periods after the final assessment are as follows: 2.2% mortality within 7 days after the final assessment, 6.1% within 8–30 days, and 9.8% within 31–90 days. The proportion of residents with no mortality within 90 days is 82%.

2.2.1 Analysis of mortality’s association with prescriptions of psychotropic medications

The purpose is to evaluate whether findings from separate analyses of relationships between mortality and types of psychotropic medication replicate in multi-variate analysis that includes all such medications and potential confounders. The most significant findings from the earlier research indicate highest mortality with PRN prescription for each type of psychotropic medication. Replication in multi-variate analysis would suggest that such relationships exist independently of any covariation in prescribing practices across types of medication.

The target variable in this analysis is mortality within 90 days of the final assessment, with 90 days being the time before the next scheduled assessment. The reference category for this variable is absence of mortality. The distribution of the target variable is binomial and related to a linear model by a complementary log-log link. SPSS 25 recommends such a linkage in survival analysis, where some observations have no termination event.

The fixed effects include demographic variables (i.e., men/women, age at the final assessment); measures of functional capability (i.e., Cognitive Performance Scale, Activities of Daily Living Hierarchy); and prescribed frequency of usage for each type of psychotropic medication (i.e., none, PRN, daily). The analysis accords with conventional GLMM practices that include centering of continuous measures on their grand mean and comparison of levels on a nominal variable with a reference category. For the present nominal measures, the respective reference categories are male gender and zero frequency of usage for a psychotropic medication.

Findings for the random variable in this and all subsequent analyses indicate significant differences (at $p < 0.001$) in levels of the target variable of mortality across facilities. The findings for fixed effects in **Table 2** indicate lower mortality in women than men and higher mortality at older ages. Mortality also increases with

Model term	Odds ratio	Sig.	95% confidence interval	
			Lower	Upper
Intercept	0.21	0.000	0.19	0.23
Female	0.68	0.000	0.64	0.73
Male				
Age at assessment	1.03	0.000	1.03	1.04
Activities of daily living	1.49	0.000	1.46	1.53
Cognitive performance	0.98	0.144	0.96	1.01
Daily antipsychotic	0.92	0.040	0.85	1.00
PRN antipsychotic	1.59	0.000	1.28	1.96
No antipsychotic				
Daily antidepressant	0.78	0.000	0.72	0.83
PRN antidepressant	1.37	0.004	1.11	1.69
No antidepressant				
Daily analgesic	0.98	0.555	0.91	1.05
PRN analgesic	1.72	0.000	1.53	1.93
No analgesic				
Daily anxiolytic	0.99	0.899	0.89	1.11
PRN anxiolytic	1.40	0.000	1.20	1.64
No anxiolytic				
Daily hypnotic	1.08	0.301	0.93	1.25
PRN hypnotic	1.77	0.000	1.31	2.40
No hypnotic				

Table 2.
Fixed effect odds ratios including daily, PRN and No psychotropic predictors of mortality within 90 days of the final assessment.

activity limitation, as indexed by higher scores on the activities of daily living scale. The findings for psychotropic medications show significantly lower mortality for daily antipsychotic and antidepressant prescription compared with no prescriptions. The findings for PRN prescriptions show significantly higher mortality for all types of psychotropic medication relative to no prescription and (in subsequent paired comparisons) daily prescription.

Figures 1–5 illustrate the magnitude of these findings, which are present in both men and women.

The findings from this analysis replicate in a multivariate context those from separate analyses of each psychotropic medication. We conclude, therefore, that associations between PRN prescription and higher mortality are independent for each type of psychotropic medication. Compared to previous research, the findings of lower mortality with daily antipsychotic and antidepressant prescription are unusual for the former but not the latter. However, we have no reason to doubt their validity, based as they are on census level data from an entire province. It is possible that confounding factors that contribute to earlier reports of augmented mortality with antipsychotic medication include failures to distinguish daily from intermittent usage and to identify adherence to daily prescription regimens. The presence of either confound might overturn protective effects associated with antipsychotic medication.

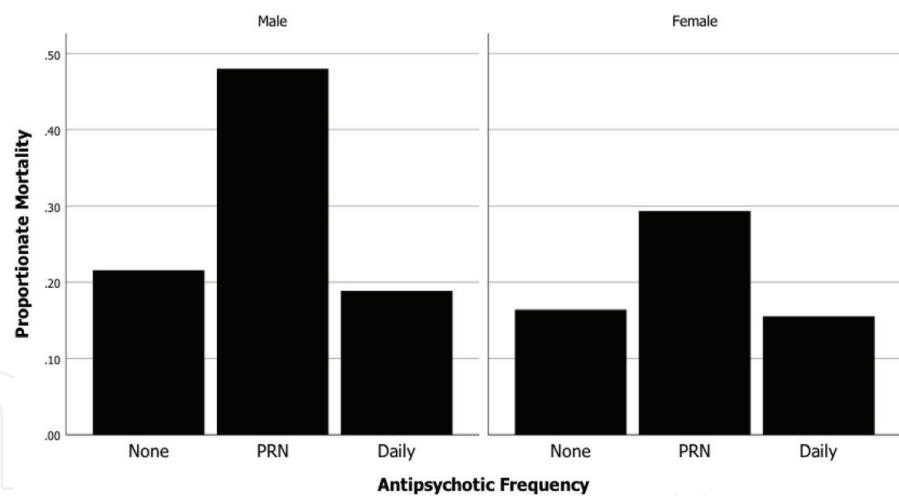


Figure 1.
Proportionate mortality by antipsychotic frequency in men and women.

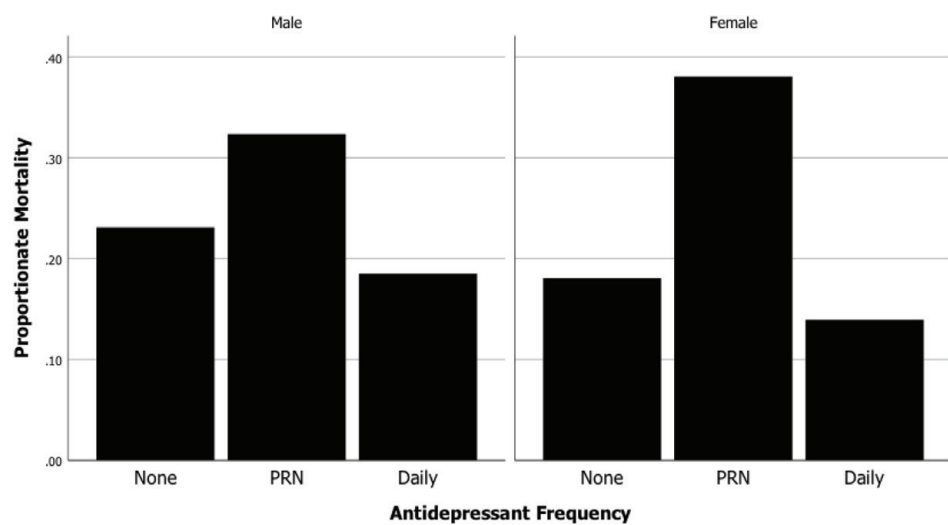


Figure 2.
Proportionate mortality by antidepressant frequency in men and women.

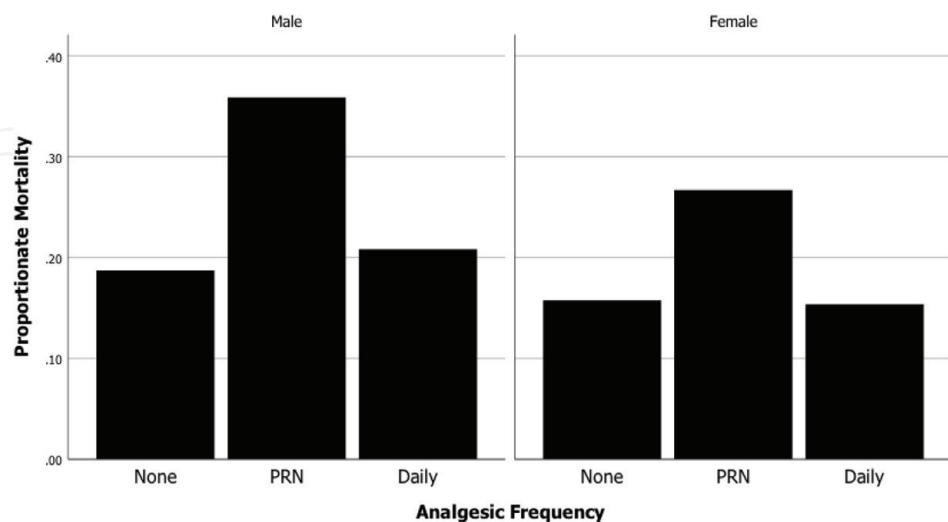


Figure 3.
Proportionate mortality by analgesic frequency in men and women.

2.2.2 Analysis of time to mortality against prescriptions for psychotropic medications

The purpose of this analysis is to advance findings from the preceding analysis in two ways. The first is to replace the binary target variable with a nominal variable

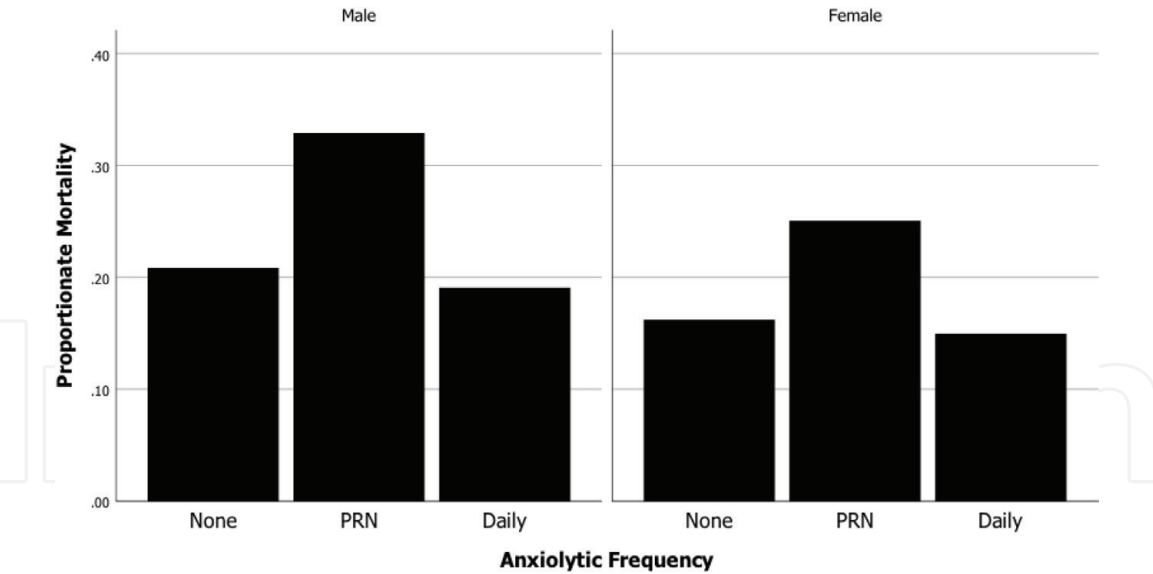


Figure 4.
Proportionate mortality by anxiolytic frequency in men and women.

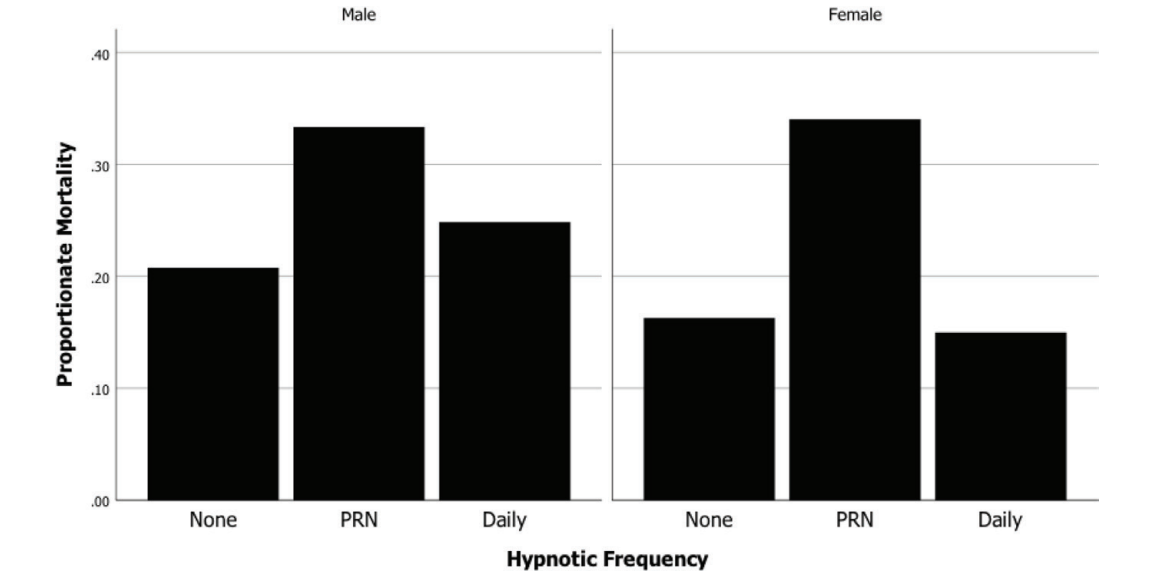


Figure 5.
Proportionate mortality by hypnotic frequency in men and women.

of time to death. The categories are 1–7, 8–30 and 31–90 days after the final assessment. We chose these categories to index mortality shortly, soon, and sometime after the final assessment but before the next scheduled assessment. The reference category is no recorded death. This analysis allows to use examine relationships between mortality and psychotropic prescriptions using a finer temporal scale.

The second advance is to include the CHES scale [10] as a fixed effect. The CHES is arguably the strongest current predictor of mortality for people within continuing care contexts. For example, mortality in the present database is <10% for residents with the lowest score but >85% for residents with the highest score. Consequently, inclusion of the CHES helps us to test between two interpretations of PRN/mortality relationships. On the one hand, if nearness of death is the primary reason for PRN prescription (i.e., prescribed mainly for palliative reasons), its relationship to mortality should nullify after inclusion of the CHES as a fixed effect. On the other hand, if PRN prescription increases the risk of subsequent mortality, a relationship should endure despite inclusion of the CHES as a fixed effect.

The target variable in this analysis has a multinomial distribution with a generalized logit link. The random and fixed effects are the same as in the preceding analysis except for the addition of the CHESS as a fixed effect. The fixed effect coefficients for this analysis comprise a multi-layered table, wherein each layer represents a different time to death category. However, we present each layer as a separate table in order to improve ease of readability.

Tables 3–5 respectively show findings from 1–7, 8–30, 31–90 days from the final assessment. The findings for demographic, functional capability and mortality risk measures show the following trends. Over all three mortality intervals, mortality is lower in women than men, higher at older ages, higher with greater activity limitation and higher with higher CHESS scores. For the interval 8–30 days after the final assessment, mortality is lower with higher cognitive impairment (i.e., higher scores on the scale).

Compared to a reference category of no medication, the findings for prescribed medications show the following. **Table 3** shows mortality 1–7 days from the final assessment to be significantly lower with daily antidepressant prescription but significantly higher with PRN prescription of antipsychotics, analgesics and antidepressants.

Table 4 shows mortality 8–30 days after the final assessment is significantly lower with daily antidepressant and daily analgesic prescriptions but significantly higher with PRN anxiolytics and PRN analgesic prescriptions.

Model term	Odds ratio	Sig.	95% confidence interval	
			Lower	Upper
Intercept	0.017	0.000	0.013	0.022
Female	0.533	0.000	0.432	0.659
Male				
Age at assessment	1.032	0.000	1.017	1.048
Activities of daily living	1.625	0.000	1.484	1.780
Cognitive performance	0.986	1.000	0.922	1.053
CHESS scale	2.489	0.000	2.294	2.700
Daily antipsychotic	0.859	0.222	0.670	1.102
PRN antipsychotic	2.139	0.009	1.273	3.594
No antipsychotic				
Daily antidepressant	0.606	0.000	0.487	0.755
PRN antidepressant	1.696	0.045	1.010	2.847
No antidepressant				
Daily analgesic	1.104	0.395	0.863	1.410
PRN analgesic	2.655	0.000	1.916	3.681
No analgesic				
Daily anxiolytic	0.997	0.903	0.716	1.388
PRN anxiolytic	1.006	0.942	0.617	1.640
No anxiolytic				
Daily hypnotic	1.104	0.586	0.711	1.716
PRN hypnotic	1.592	0.318	0.666	3.806
No hypnotic				

Table 3.
Fixed effect odds ratios for predictors of mortality within 7 days after the final assessment.

Model term	Odds ratio	Sig.	95% confidence interval	
			Lower	Upper
Intercept	0.089	0.000	0.077	0.103
Female	0.596	0.000	0.525	0.677
Male				
Age at assessment	1.022	0.000	1.013	1.031
Activities of daily living	1.495	0.000	1.423	1.572
Cognitive performance	0.947	0.047	0.909	0.986
CHESS scale	1.883	0.000	1.786	1.986
Daily antipsychotic	0.881	0.084	0.761	1.020
PRN antipsychotic	1.335	0.280	0.872	2.043
No antipsychotic				
Daily antidepressant	0.675	0.000	0.594	0.768
PRN antidepressant	1.152	0.497	0.758	1.753
No antidepressant				
Daily analgesic	0.824	0.007	0.719	0.943
PRN analgesic	1.574	0.000	1.274	1.946
No analgesic				
Daily anxiolytic	0.885	0.337	0.721	1.086
PRN anxiolytic	1.482	0.006	1.113	1.974
No anxiolytic				
Daily hypnotic	1.049	0.624	0.802	1.370
PRN hypnotic	1.585	0.148	0.872	2.880
No hypnotic				

Table 4.
Fixed effect odds ratios for predictors of mortality 8–30 days after the final assessment.

During the 31–90 day interval after the final assessment, **Table 5** shows significantly lower mortality with daily antidepressant prescription but significantly higher mortality with PRN analgesic, anxiolytic, and hypnotic prescriptions.

At one or more levels of the target variable, the findings from this analysis replicate those from the preceding analysis that relate male gender, older age and greater activity limitation to significantly augmented mortality. They also replicate findings of augmented mortality with PRN prescription for all types of psychotropic medication. They further extend relationships of attenuated mortality to include daily prescription of both analgesic and antidepressant medication. The only failure of replication is the absence of significantly attenuated mortality with daily prescription of antipsychotic medication, despite a coefficient close to significance for the 8–30 day interval. Other significant findings include attenuated mortality with cognitive impairment (i.e., higher scores on the scale) at the 8–30 day interval and augmented mortality at each level of the target variable with higher estimates of mortality risk on the CHESS.

The inclusion of the CHESS provides a rationale to interpret findings of attenuated or augmented mortality associated with psychotropic prescriptions. The presence of such findings after control for the CHESS supports an interpretation that

Model term	Odds ratio	Sig.	95% confidence interval	
			Lower	Upper
Intercept	0.140	0.000	0.124	0.158
Female	0.650	0.000	0.587	0.720
Male				
Age at assessment	1.039	0.000	1.031	1.046
Activities of daily living	1.326	0.000	1.277	1.377
Cognitive performance	0.986	0.901	0.953	1.020
CHESS scale	1.542	0.000	1.474	1.614
Daily antipsychotic	0.989	0.807	0.882	1.108
PRN antipsychotic	1.436	0.092	1.003	2.056
No antipsychotic				
Daily antidepressant	0.822	0.000	0.743	0.909
PRN antidepressant	1.226	0.269	0.854	1.758
No antidepressant				
Daily analgesic	0.894	0.052	0.803	0.995
PRN analgesic	1.406	0.000	1.172	1.687
No analgesic				
Daily anxiolytic	1.011	0.689	0.866	1.181
PRN anxiolytic	1.392	0.006	1.093	1.772
No anxiolytic				
Daily hypnotic	1.080	0.376	0.875	1.333
PRN hypnotic	1.990	0.006	1.243	3.186
No hypnotic				

Table 5.
Fixed effect odds ratios for predictors of mortality 31–90 days after the final assessment.

the medicinal prescriptions have direct or indirect effects on mortality beyond the levels of risk measured by the tool. An alternative interpretation that the findings on mortality are secondary to altered prescribing practices with perceived closeness to death seems less plausible.

2.2.3 Analysis of predictors of multiple daily and PRN psychotropic prescriptions

LTCH residents may receive more than a single type of psychotropic medication on a daily or PRN basis. The purpose of these analyses is to identify variables that contribute to the number of such prescriptions. The target variable in both analyses is the number of psychotropic categories prescribed on a daily or PRN basis. We modeled the target as an ordinal measure with a cumulative logit link in mixed multinomial logistic regression models. Levels on the daily prescription distribution are 0, 1, 2, 3 and 4+ ordinal categories. Levels on the PRN prescription distribution are 0, 1, 2 and 3+ ordinal categories.

The fixed effects include the same demographic, functional capability and mortality risk measures as in the preceding analyses. Other measures are scales (i.e., Depression, Aggressive Behavior, and Pain scales), diagnoses (i.e., Anxiety Disorder, and Dementia) and conditions (i.e., Insomnia) that might influence psychotropic medication use. We added a final fixed effect of the total number of prescribed medications.

Model term	Odds ratio	Sig.	95% confidence interval	
			Lower	Upper
Threshold for Number = 0	0.225	0.000	0.214	0.237
Threshold for Number = 1	1.504	0.000	1.433	1.579
Threshold for Number = 2	9.442	0.000	8.970	9.939
Threshold for Number = 3	87.211	0.000	81.593	93.216
Female	1.047	0.002	1.017	1.079
Male				
Age at assessment	0.973	0.000	0.971	0.974
Activities of daily living	1.015	0.003	1.005	1.025
Cognitive performance	1.118	0.000	1.105	1.131
Depression scale	1.108	0.000	1.100	1.115
Aggressive behavior scale	1.067	0.000	1.060	1.074
Pain scale	1.208	0.000	1.187	1.230
CHESS scale	0.915	0.000	0.900	0.929
Anxiety disorder	2.744	0.000	2.599	2.896
No anxiety disorder				
Insomnia	1.124	0.000	1.079	1.170
No insomnia				
Dementia	1.393	0.000	1.348	1.439
No dementia				
Total medications	1.191	0.000	1.187	1.195

Table 6.
Fixed effect odds ratios for predictors of number of daily medications for the final assessment.

The findings in **Table 6** show fixed findings for daily prescriptions of psychotropic medication. The table includes thresholds (i.e., intercepts) at different levels of the target variable and coefficients for the predictors. Predictors of significantly higher frequencies of daily prescription include categorical measures of female gender, anxiety disorder, insomnia, and dementia; higher scores on scales measuring activity limitation, cognitive impairment, depression, aggressive behavior, and pain; and the total number of medications. These findings suggest that residents prescribed more types of psychotropic medication have higher levels on multiple conditions that might benefit from psychotropic intervention. Findings that seem at odds with the preceding are relationships of younger age and lower mortality risk (i.e., on the CHESS) to higher frequencies of daily psychotropic prescriptions.

Table 7 shows fixed effect findings for PRN prescriptions of psychotropic medication. Significant predictors of higher levels of PRN prescribing are limited to the Aggressive Behavior, Pain, and CHESS scales, and the presence of insomnia. Age and diagnosed dementia have negative relationships with the number of PRN prescriptions.

The most revealing differences in outcome of the two preceding analyses relate to diagnosed dementia and the CHESS scale. Diagnosed dementia relates positively to the number of daily but negatively to the number of PRN prescriptions. Conversely, higher mortality risk relates negatively to the number of daily but positively to the number of PRN prescriptions.

Model term	Odds ratio	Sig.	95% confidence interval	
			Lower	Upper
Threshold for Number = 0	7.737	0.000	6.970	8.587
Threshold for Number = 1	73.344	0.000	63.257	85.040
Threshold for Number = 2	399.408	0.000	303.212	526.123
Female	1.033	0.496	0.941	1.134
Male				
Age at assessment	0.993	0.029	0.988	0.999
Activities of daily living	1.019	0.252	0.987	1.052
Cognitive performance	0.977	0.194	0.942	1.012
Depression scale	1.008	0.437	0.988	1.028
Aggressive behavior scale	1.085	0.000	1.064	1.107
Pain scale	1.334	0.000	1.268	1.404
CHESS scale	1.214	0.000	1.165	1.266
Anxiety disorder	0.991	0.917	0.838	1.173
No anxiety disorder				
Insomnia	1.618	0.000	1.444	1.812
No insomnia				
Dementia	0.789	0.000	0.710	0.877
No dementia				
Total medications	0.996	0.423	0.986	1.006

Table 7.
Fixed effect odds ratios for predictors of number of PRN medications for the final assessment.

2.2.4 Analysis of mortality against multiple daily and PRN psychotropic prescriptions

The purpose of this analysis is to ascertain relationships between mortality within 90 days of the final assessment and the distribution of prescriptions of psychotropic medications at the final assessment. The target variable has a binomial distribution with a complementary log-log link. The fixed effect variables include the same demographic, functional capability and mortality risk measures as previous analyses. Categories within the distribution of prescriptions include (1) no prescriptions, (2) daily and PRN prescriptions, (3) PRN prescriptions only and (4) daily prescriptions only. The reference category is zero prescriptions.

The findings in **Table 8** show significantly lower mortality for women than men and for residents with greater cognitive impairment (i.e., lower scores on the scale). Mortality is significantly higher at older ages and for residents scoring higher on activity limitation and the CHESS measure of mortality risk. Findings for the distribution of prescriptions show significantly attenuated mortality for residents with daily prescriptions only, significantly augmented mortality residents with PRN prescriptions only, and significantly augmented mortality for residents with both daily and PRN prescriptions. Paired comparisons with Bonferroni correction show significant differences across all four categories.

We interpret these findings as follows. Antipsychotics, antidepressants and analgesics have the highest rates of daily prescription. Daily prescription of each of those psychotropics attenuates mortality in at least one of our analyses. Consequently, the present association between attenuated 90-day mortality in residents with only daily prescriptions is unsurprising. For similar reasons, findings of augmented mortality in

Model term	Odds ratio	Sig.	95% confidence interval	
			Lower	Upper
Intercept	0.21	0.000	0.19	0.23
Female	0.67	0.000	0.63	0.72
Male				
Age at assessment	1.03	0.000	1.02	1.03
Activities of daily living	1.36	0.000	1.32	1.40
Cognitive performance	0.97	0.007	0.95	0.99
CHESS scale	1.58	0.000	1.53	1.62
Only daily prescriptions	0.76	0.000	0.69	0.84
Only PRN prescriptions	1.42	0.000	1.21	1.66
Daily and PRN prescriptions	1.17	0.025	1.02	1.34
No prescriptions				

Table 8.
Fixed effect odds ratios for mortality within 90 days of the final assessment.

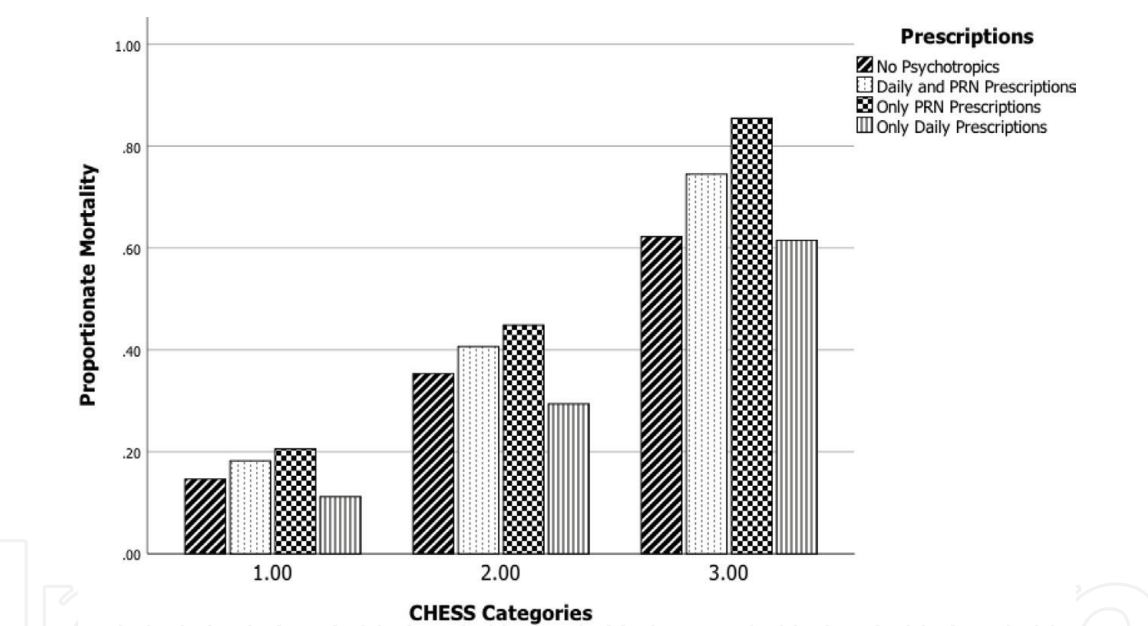


Figure 6.
Proportionate mortality by prescription regimens and CHESS categories.

residents with only PRN prescriptions are also unsurprising. The new ground breaking findings, however, concern residents with both daily *and* PRN prescriptions. This combination significantly augments mortality from levels that typify daily prescription and no prescription, but significantly attenuates levels that typify only PRN prescriptions. **Figure 6** shows that the respective mortality levels are independent of mortality risk, as estimated by categories of CHESS scores. Consequently, we infer that PRN prescription may overturn protective effects associated with daily prescriptions, whereas the latter may reduce the deleterious effects of PRN prescribing.

2.2.5 Additional analyses

Because of the statistical significance of LTCH as a random effect in all the preceding analyses, we report here on additional analyses that explore whether

particular differences among LTCH contribute to fixed effect relationships to mortality. Specifically, the analyses include facility-level covariates that correspond with previously significant, resident-level fixed effect terms. These centered facility-level covariates are LTCH means for age, level of activity limitation, and mortality risk (i.e., CHESS scores); and percentages of residents by gender and psychotropic prescription on a PRN basis. The findings indicate that these facility-level variables have significant zero-order relationships with mortality in the same directions as the corresponding resident-level measure. However, all are nonsignificant when added to the list of fixed effects described in the preceding section (i.e., Section 2.2.4), with the odds-ratios and significance levels for resident-level terms showing minimal change from those in **Table 8**. We conclude, therefore, that the findings with resident-level fixed effects show negligible influence due to distributions in LTCH.

2.3 Discussion

This chapter charts a journey of scientific investigation with the following milestones:

1. Concern about excess mortality with the use of antipsychotic medication.
2. Findings that limit the preceding relationship to PRN prescription.
3. Findings that excess mortality with PRN prescription applies to all types of psychotropic medication.
4. Findings of attenuated mortality with daily prescription for some types of psychotropic medication but augmented mortality with PRN prescription for all types of medication.
5. Evidence to support the preceding after control for confounders that include a proven indicator of mortality risk.
6. Findings that diagnosed dementia relates positively to the number of daily but negatively to the number of PRN prescriptions, whereas higher mortality risk relates negatively to the number of daily but positively to the number of PRN prescriptions.
7. Evidence that a combination of daily and PRN prescriptions of psychotropics overturns protective effects against mortality associated with the former but lowers deleterious effects associated with PRN prescribing.

The journey began with concern about excess mortality with the use of antipsychotic medication but ends with evidence for minor protective effects of daily prescription. How do we account for this discrepancy? Consider, first, the quality of measurement and, second, the appropriateness of the analyses. We have confidence in the data quality and psychometric adequacy (i.e., reliability and validity) of the RAI 2.0 measures. For nearly 30 years, efforts by researchers from across the world tried to ensure good measurement quality. A recent example is research on 15 years of archived data in Canada. Those authors report favorable outcomes, concluding that the RAI 2.0 provides a “robust, high quality data source” ([28], p. 27). If our data possess unrecognized error in measurement, similar error likely contaminates findings from many hundred referred publications that rely on RAI 2.0 data.

Second, we consider the technical details of our methodology to be appropriate. The decision to restrict analysis to data from new admissions ensures that the findings from over 20,000 residents provide 1-year incidence rates (rather than prevalence rates) for mortality. Such restriction also ensures that the data from all residents begin with comparable intake assessments. Earlier in this chapter, we provide conceptual reasons to justify the appropriateness of GLMM analysis. In every analysis, findings of significant random effects for LTCH provide empirical justification. Our wish for the future is that more researchers adopt similar modeling in order to avoid incorrect assumptions that measurement error is uncorrelated in clustered data.

We also ought to mention here that the statistical models show reasonable data fit in every analysis. The final model in **Table 8** provides an example. Compared to a simplified model that includes only demographics as fixed effects, the proportions of correct classification in the full model improve by 16.3% for predicted mortality (i.e., from 50 to 66.3%) and by 2.4% for the prediction of nonmortality (i.e., from 82.1 to 84.5%). These gains are fairly impressive given the lopsided skew in mortality data.

We conclude from the preceding is that our findings are trustworthy. How then can we account for findings from other studies of excessive mortality among elderly people prescribed with antipsychotic medication? We offer three possible interpretations. The first is a failure by many or most such studies to distinguish between daily and PRN prescribing. The second is a failure to provide information about PRN prescription of other psychotropic medications. Because our findings suggest associations between augmented mortality and PRN prescription of *any* psychotropic, each of the preceding concerns anticipates overestimation of mortality.

The third interpretation relates to adherence. Anyone with work experience in LTCH settings knows that adherence to drug regimens is problematic. Residents that put pills into their mouths do not necessarily swallow them. Instead, some residents chose to hide their pills, others throw them away. Previous findings show that nonadherence to antidepressant medication has unfavorable implications for mortality [19]. Findings from psychiatry show frequent low adherence to antipsychotic medication [29]. That study reports rates of nonadherence to antipsychotic medication by psychiatric patients as high as 40% within a year. Because low adherence results in intermittent use of antipsychotic medication, the consequences in LTCH residents could well include excessive mortality.

Our scientific journey progressed past milestones that indicate consistency in findings with alternative indices of mortality and control of confounding variables. At the end of the journey, the metaphorical villain is no longer daily prescription of psychotropic medication but PRN prescription. Although relatively few residents receive PRN prescriptions on a per drug basis, one resident in eight (12.5%) has at least one such prescription. Although residents prescribed PRN medication have high mortality risk, as measured by the CHESS, **Figure 6** shows elevated mortality rates at every level of mortality risk.

Issues that arise from our research include reasons for the high mortality associated with PRN prescriptions and implications for health care practice and policy. However, before such discussion, here are some words of caution.

The present research design is correlational rather than experimental. Only the latter assigns individuals randomly to the various conditions. Despite agreement that correlational designs provide less-compelling evidence about causality than experimental designs, the majority of studies on the effects of psychotropic medications are correlational. For example, most recent studies of the effects of antipsychotic medication on mortality have correlation designs that compare residents prescribed a given drug with residents without prescription or prescribed an alternative medication [6]. However, even in experimental studies, which are invariably of short duration [5], any differences in mortality between conditions do not necessarily imply direct causation. Such effects may arise because of changes

to health stability or changes in likelihood of adverse health events. We make these points to warn against simplistic interpretation of complex phenomena.

Efforts within epidemiology to facilitate appropriate causal inferences include procedures to identify *confounding by indication*, which “refers to a situation where patient characteristics, rather than the intervention, are independent predictors of outcome” ([30], p. 841). The present analyses encompass procedures used to evaluate confounding by indication, which include, but are not limited to, the following. Covariate adjustment in which potential confounders are added to the list of fixed effects in modeling (e.g., age, gender, and functional measures). “Propensity” scores were used, which relate to the likelihood of intervention (e.g., high CHES scores increase the likelihood of PRN prescription). The use of instrumental variables presumed to substitute for unmeasured confounders (e.g., LTCH and properties of LTCH as random and fixed effect variables, respectively). Although other research reports differences in causal direction depending on the kind of analysis [30], the present findings indicate directional consistency in relationships between mortality and PRN prescribing before (**Figures 1–5**) and after adjustment of variables from all three classes of confound.

However, our analyses clearly omit control for unmeasured sources of confounding. Also, our research lacks the rigor that random assignment brings to experimental forms of design. Consequently, we strongly recommend that future randomized controlled trials evaluate the relationships we report here.

Our cautious interpretation of effects on mortality associated with daily and PRN prescription of psychotropic medication rests heavily on findings from the final analysis. These findings indicate that PRN prescription overturns any protective effects associated with daily prescription, whereas daily prescription lowers adverse consequences of PRN prescribing. These findings suggest a mutually antagonistic relationship between daily and PRN prescriptions with respect to their effects on mortality. The clinical rationale for daily prescription is the alleviation of disturbance to a resident’s equilibrium, as exemplified by aggression, depression, pain, anxiety and insomnia. Successful treatment results in regained equilibrium after the resident adapts to regular ingestion of the drug. Conversely, the reasoning behind PRN prescription is to alleviate disturbances to equilibrium thought to be temporary. However, irregularity of ingestion is antagonistic to adaptation and may exacerbate instability through toxicity rather than help restore equilibrium. This interpretation appears to be consistent with our findings. Practical implications for health care practices and policy are consistent with current trends. Such trends include the de-prescribing of psychotropic medications for older people, with such medications to be used only for short durations and as a last resort [5, 6]. Similarly, a recent rewrite of Medicaid Long Term Care rules in the USA states that LTCH residents must not be prescribed antipsychotic, antidepressant, anxiolytic or hypnotic medications unless necessary to treat a specific condition diagnosed and documented in the clinical record. The new rules also normally limit PRN prescriptions to 14 days. Any extension requires an attending physician or prescribing practitioner to document the rationale in the resident’s medical record [31]. We especially applaud these latter rules, which tackle an issue hitherto neglected in health care practice and policy.

3. Conclusion

PRN prescriptions of psychotropic medications have more aversive effects on the mortality of LTCH residents than daily prescriptions. These findings apply to all types of psychotropic medication after control for major confounding variables. The findings also suggest that daily prescription may ameliorate effects on mortality associated the PRN prescriptions, whereas PRN prescriptions exacerbate effects on mortality associated with daily prescription.

Acknowledgements

All the authors contributed to the research and manuscript preparation, and verified their authorship of this chapter. The authors wish to thank the editors, Robert Reynolds and Steven Day, for very helpful comments on an earlier draft.

Conflict of interest

No author has any conflict of interest.

Author details

Michael J. Stones*, Sarah Worobetz, Jason Randle, Carlina Marchese,
Shauna Fossum, Dane Ostrom and Peter Brink
Lakehead University, Thunder Bay, Ontario, Canada

*Address all correspondence to: mstones@lakeheadu.ca

IntechOpen

© 2019 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] Kozman MN, Wattis J, Curran S. Pharmacological management of behavioural and psychological disturbance in dementia. *Human Psychopharmacology: Clinical and Experimental*. 2006;**21**(1):1-2. DOI: 10.1002/hup.745
- [2] Cerejeira J, Lagarto L, Mukaetova-Ladinska E. Behavioral and psychological symptoms of dementia. *Frontiers in Neurology*. 2012;**3**:73. DOI: 10.3389/fneur.2012.00073
- [3] Kapur S, Mamo D. Half a century of antipsychotics and still a central role for dopamine D2 receptors. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2003;**27**(7):1081-1090. DOI: 10.1016/j.pnpbp.2003.09.004
- [4] Prakash S, Masand MD. Side effects of antipsychotics in the elderly. *The Journal of Clinical Psychiatry*. 2000;**61**:43-49
- [5] Banerjee S. The Use of Antipsychotic Medication for People with Dementia: Time for Action. London: Department of Health, UK Government; 2009. Available from:<http://psychrights.org/research/digest/nlps/banerjeereportongeriatric> Ralph SJ, Espinet AJ. Increased all-cause mortality by antipsychotic drugs: Updated review and meta-analysis in dementia and general mental health care. *Journal of Alzheimer's Disease Reports*. 2018;**2**(1):287-312. DOI: 10.3233/ADR-170042
- [6] Brink P, Stewart S, Stones MJ. Institutional reactions to verbally abusive behaviour by residents of long-term care facilities. In: *Proceedings of the Annual Conference of the Ontario Network for the Prevention of Elder Abuse*. Toronto, ON; 2005
- [7] Jones RN, Marcantonio ER, Rabinowitz T. Prevalence and correlates of recognized depression in US nursing homes. *Journal of the American Geriatrics Society*. 2003;**51**(10):1404-1409. DOI: 10.1046/j.1532-5415.2003.51458.x
- [8] Neufeld E, Freeman S, Joling K, Hirdes JP. "When the golden years are blue" Changes in depressive symptoms over time among older adults newly admitted to long-term care facilities. *Clinical Gerontologist*. 2014;**37**(3):298-315. DOI: 10.1080/07317115.2014.885919
- [9] Hirdes JP, Poss JW, Mitchell L, Korngut L, Heckman G. Use of the interRAI CHES scale to predict mortality among persons with neurological conditions in three care settings. *PLoS One*. 2014;**9**(6):e99066. DOI: 10.1371/journal.pone.0099066
- [10] Worobetz S. Effects of antipsychotic medications on older adults with dementia in Canadian complex and long-term care facilities [thesis]. Thunder Bay: Lakehead University; 2014
- [11] Stasinopoulos J, Bell JS, Ryan-Atwood TE, Tan EC, Ilomäki J, Cooper T, et al. Frequency of and factors related to pro re nata (PRN) medication use in aged care services. *Research in Social and Administrative Pharmacy*. 2018;**14**(10):964-967. DOI: 10.1016/j.sapharm.2017.11.004
- [12] La Frenais FL, Bedder R, Vickerstaff V, Stone P, Sampson EL. Temporal trends in analgesic use in long-term care facilities: A systematic review of international prescribing. *Journal of the American Geriatrics Society*. 2018;**66**(2):376-382. DOI: 10.1111/jgs.15238
- [13] Holmerová I, Auer SR, Beránková A, Höfler M, Ratajczak P, Štefl M. Cognitive status and use of analgesics and anxiolytics in residents of nursing homes in the Czech Republic. *Clinical Interventions in Aging*. 2018;**13**:2511. DOI: 10.2147/CIA.S18860

- [14] Bhattacharjee S, Oh YM, Reiman EM, Burke WJ. Prevalence, patterns, and predictors of depression treatment of community-dwelling elderly individuals with dementia in the United States. *The American Journal of Geriatric Psychiatry*. 2017;**25**(7):803-813. DOI: 10.1016/j.jagp.2017.03.003
- [15] Enache D, Fereshtehnejad SM, Kareholt I, Cermakova C, et al. Antidepressants and mortality risk in a dementia cohort: Data from SveDem, the Swedish Dementia Registry. *Acta Psychiatrica Scandinavica*. 2016;**134**: 430-440. DOI: 10.1111/acps.12630
- [16] Zivin K, Kim HM, Yosef M, Maust DT, et al. Antidepressant medication treatment and risk of death. *Journal of Clinical Psychopharmacology*. 2016;**36**(5):445-452. DOI: 10.1097/JCP.0000000000000545
- [17] Bali V, Chatterjee S, Johnson ML, Chen H, et al. Risk of mortality in elderly nursing home patients with depression using paroxetine. *Pharmacotherapy*. 2017;**37**(3):287-296. DOI: 10.1007/s11920-018-
- [18] Krivoy A, Stubbs B, Balicer RD, Weizman S, et al. Low adherence to antidepressants is associated with increased mortality risk: A large nationally representative cohort study. *European Neuropsychopharmacology*. 2017;**27**:970-976
- [19] Biffi A, Scotti L, Rea F, Lucenteforte E, et al. Adherence to antidepressants and mortality in elderly patients with cardiovascular disease. *Clinical Drug Investigation*. 2018;**38**:593-602. DOI: 10.1080/17425255.2019.1561860
- [20] Andreescu C, Varon D. New research on anxiety disorders in the elderly and an update on evidence-based treatments. *Current Psychiatry Reports*. 2015;**17**:53. DOI: 10.1007/s11920-015-0595-8
- [21] Hwang Y, Chen T, Wen Y, Liou H. Does the prescription of anxiolytic and hypnotic drugs increase mortality in older adults? *Journal of the American Geriatrics Society*. 2015;**63**(6):1263-1265. DOI: 10.1111/jgs.13466
- [22] Weich S, Pearce HL, Croft P, Singh S, Crome I, Bashford J, et al. Effect of anxiolytic and hypnotic drug prescriptions on mortality hazards: Retrospective cohort study. *BMJ*. 2014;**2014**:348. DOI: 10.1136/bmj.g1996
- [23] Usher K, Holmes C, Lindsay D, Luck L. PRN psychotropic medications: The need for nursing research. *Contemporary Nurse*. 2003;**14**(3):248-257. DOI: 10.5172/conu.14.3.248
- [24] Lindsey PL. Psychotropic medication use among older adults: What all nurses need to know. *Journal of Gerontological Nursing*. 2009;**35**(9):28-38. DOI: 10.3928/00989134-20090731-01
- [25] Stokes JA, Purdie DM, Roberts MS. Factors influencing PRN medication use in nursing homes. *Pharmacy World & Science*. 2004;**26**(3):148-154. DOI: 10.1023/B:PHAR.0000026803.89436.a8
- [26] Wright S, Stewart D, Bowers L. Psychotropic PRN Medication in Inpatient Psychiatric Care: A Literature Review. London: Section of Mental Health Nursing, Institute of Psychiatry; 2012. Available from: <https://www.kcl.ac.uk/ioppn/depts/hspr/archive/mhn/projects/PRN-Medication>
- [27] Hirdes J, Poss JW, Caldarelli H, Fries BE, Morris JN, Teare GF, et al. An evaluation of data quality in Canada's continuing care reporting system (CCRS): Secondary analyses of Ontario data submitted between 1996 and 2011. *BMC Medical Informatics and Decision Making*. 2013;**13**:27. Available from: <http://www.biomedcentral.com/1472-6947/13/27>

[28] Perkins DO. Adherence to antipsychotic medications. *The Journal of Clinical Psychiatry*. 1999;**60**(Suppl 21): 25-30. Available from: <https://europepmc.org/abstract/med/10548139s>

[29] Cnossen MC, van Essen TA, Ceyisakar IE, Polinder S, Andriessen TM, van der Naalt J, et al. Adjusting for confounding by indication in observational studies: A case study in traumatic brain injury. *Clinical Epidemiology*. 2018;**10**:841-852. DOI: 10.2147/CLEP.S154500

[30] Barlas S. Medicare adds new long-term-care pharmacy rules: Agency passes again on pharmacist Independence requirements. *Pharmacy and Therapeutics*. 2016;**41**(12):762-764