Chapter

Effects of Antipsychotic Medication on Mortality in Long-Term Care Home Residents

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Abstract

This chapter examines mortality in long-term care home (LTCH) residents as associated with the use antipsychotic medication when combined with other psychotropic medications. The data at census-level pertain to all new admissions to long-term care homes (LTCH) in Ontario, Canada, during a given financial year (i.e., over 20,000 LTCH residents). The observations include comprehensive assessment upon admission and at quarterly intervals thereafter for a maximal period of 1-year after the initial assessment. The mortality data derive from three linked databases, with mortality classified as death within 90 days of the final assessment. The findings indicate that combinations of concurrent daily usage of antipsychotic medication with daily usage of other psychotropic medications (particularly antidepressants and analgesics) are associated with relatively low mortality, whereas intermittent usage (e.g. *pro re nata*; as needed) is associated with relatively high mortality.

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

1. Introduction

This chapter builds upon findings from retrospective studies described in a previous chapter by Stones, Worobetz, Randle, Marchese, Fossum, Ostrum and Brink [1]. Those studies examine associations between mortality in long-term care home (LTHC) residents in the Canadian province of Ontario and the reported use of psychotropic medications. Regulations in Section 155 of the Canadian province of Ontario's *Long-Term Care Homes Act* of 2007 specifies that the residents of LTCH should be (1) 18+ years of age; (2) insured under the *Health Insurance Act*; (3) in need of 24-hours on-site nursing care, or (4) frequent daily assistance with activities of daily living (ADL), or (5) on-site monitoring or supervision in order to ensure safety and well-being. Alternative terms for LTCH in other dominions and countries include nursing homes and homes for the aged. Such homes contrast with supportive housing and continuing care hospitals that respectively provide lesser or greater levels of health care provision.

The impetus for what became our research program concerns the allegedly harmful effects of antipsychotic medication on mortality and medical conditions

that potentially precipitate mortality. Although the research we describe in this chapter relates specifically to the effects of antipsychotics, our overall research program evolved to focus more generally on associations between mortality and the reported usage of any type of psychotropic medication. The latter includes not only antipsychotics but also anxiolytics, analgesics, antidepressants and hypnotics. The primary instrumentation deployed in these studies is the Resident Assessment Instrument 2.0 (RAI 2.0). This tool provides standardized clinical assessment and good data quality [2], with widespread adoption throughout the world. The measure of psychotropic usage on the RAI 2.0 is the number of days of delivery during the week preceding an assessment.

The findings described in the earlier chapter indicate strongest associations with mortality for intermittent usage of 1–6 days per week when compared with no use or daily use. These findings are significant for each type of psychotropic medication in both univariate and multivariate analyses, where the latter attempts to control for potentially confounding effects and interactions. We refer to intermittent prescribing as *pro re nata* (PRN, or 'as needed') prescription in order to be consistent with recent regulatory initiatives to curb hazardous effects associated with 'as needed' prescribing practices [3].

In contrast to augmented mortality with PRN prescribing, our earlier findings indicate lower mortality associated with daily usage of antidepressant and antipsychotic medications when compared to an absence of usage. The findings on daily usage of antipsychotic medication depart from expectations in the existing literature of its hazardous effects on mortality. This finding is also surprising because the database is among the most all-encompassing of any used in previous studies. It includes consensus level, yearly incidence data on all new admissions to all LTCHs in Ontario (i.e., over 20,000 new admissions to over 600 LTCHs during a given year, with each resident followed up for 1-year). The purpose of the research in this chapter is to explore reasons for this discrepancy.

1.1 Caregiving for behavioral and psychological symptoms of dementia

The context of our research concerns caregiving for residents of long-term care homes with behaviors that generally fall under the rubric of behavioral and psychological symptoms of dementia (BPSD). A consensus conference of the International Psychogeriatric Association in 1976 defined BPSD as "symptoms of disturbed perception, thought content, mood or behavior that frequently occur in patients with dementia" [4]. These symptoms include physical aggression, loud vocalization, restlessness, agitation, wandering, anxiety, depressive mood, hallucinations, and delusions [5]. Not all residents with dementia exhibit such symptoms, which usually emerge during the middle and later stages of the illness. Previous estimates indicate that BPSD characterizes nearly 40% of residents in Ontario's LTCHs [1].

By far the most frequent treatment for residents of LTCHs is chemical management. Of the five types of psychotropic medication, the main purposes are to alleviate pain and discomfort (i.e., analgesics), depression (i.e., antidepressants), anxiety (i.e., anxiolytics), sleeplessness (i.e., hypnotics) and BPSD (i.e., antipsychotics). The two categories of antipsychotic medication are termed *typical* and *atypical*. The latter were introduced in attempt to intent reduce adverse side-effects associated with the former [6].

The first columns in **Figure 1**, which is adapted from our previous chapter [1], shows more than double the usage of antipsychotic medication for male and female LTCH residents with than without diagnosed dementia. The findings for no other form of psychotropic medication approach this level of discrepancy. Consequently, antipsychotic medication is the most frequently used psychotropic medication

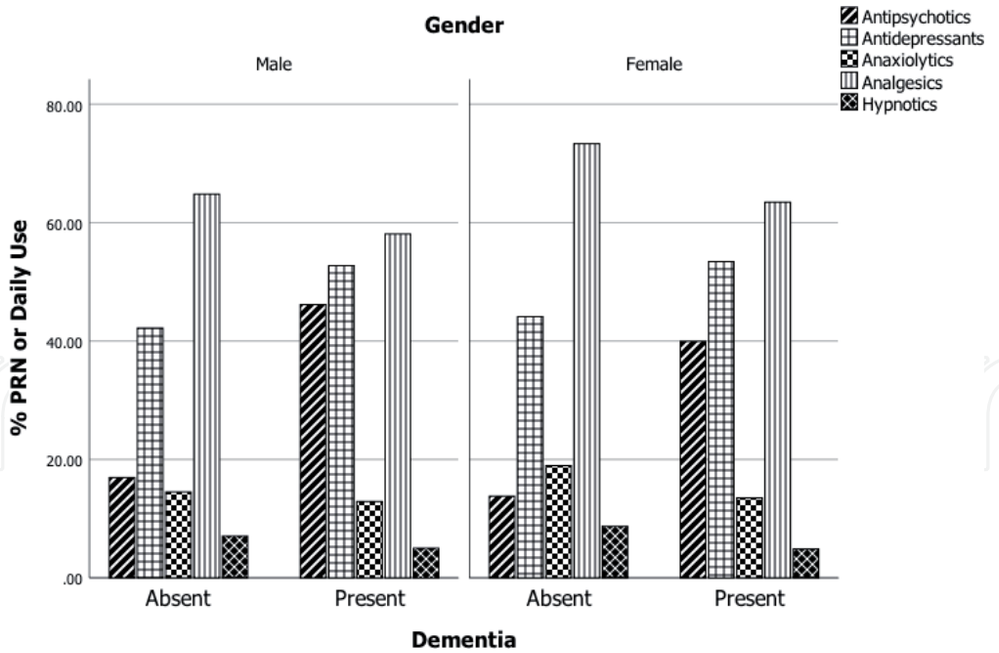

Figure 1.
Percentage of PRN or daily use of psychotropic medications for residents with or without diagnosed dementia.

specifically used with demented individuals, which is a conclusion consistent with that reported in previous publications [7].

Concerns arose early in this millennium about adverse effects associated with the use of antipsychotic medications for the management of dementia. Such effects include cardiovascular and cerebrovascular events, cardiac arrythmia, cognitive decline, extrapyramidal symptoms, falls, fractures, pneumonia and elevated mortality [8]. Levels of the preceding for people with antipsychotic prescriptions exceed those among elderly people in general, people with dementia but without antipsychotic prescriptions, and those exhibiting BPSD without antipsychotic prescriptions [9].

From 2002 onwards, manufacturers of antipsychotic medications issued warnings about health and mortality risks when prescribed for elderly people. In 2005, the USA's Federal Food and Drug Administration required "black box" warnings on packages of atypical antipsychotics, which in 2008 was extended to typical antipsychotics. This warning reads: "WARNING: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death." Health authorities in other countries subsequently issued comparable warnings.

Recent meta-analysis [10] and scoping reviews [11] draw the following conclusions about mortality and antipsychotic usage in elderly people. The mortality risks are comparable between typical and atypical antipsychotics, and approximately twice that of people without such usage. The risks are comparable between individuals with or without dementia; they increase with dosage, and are highest during with first month(s) of usage. The latter suggests to authors of the scoping review [11] that factors other than antipsychotic medication may contribute to findings of elevated mortality. The authors of the meta-analytic study [10] recommend restriction and de-prescribing of antipsychotics with older people.

1.2 Methodology of retrospective studies of antipsychotic-mortality relationships

The findings discussed in our earlier chapter [1] indicate that, after control for variables that include gender, age, activities of daily living, level of cognition and

mortality risk, mortality was (1) significantly elevated with PRN use for each type of psychotropic medication (2) significantly attenuated with daily use of antipsychotic and antidepressant medications, (3) significantly elevated for combinations of psychotropic medications that include PRN use and (4) significantly attenuated for combinations of psychotropic medications that include their daily use. These findings are consistent with and build upon unpublished thesis research on antipsychotic medication use by Worobetz [12]. Differences and confounds that might relate to discrepancies between our findings and previous reports of excessive mortality associated with antipsychotic medication use include the following.

First, the analyses in our chapter use generalized linear mixed modeling (GLMM) procedures. Such modeling includes a random variable that encompasses clustering of observations within that variable. This structure is appropriate for the analysis of LTCH data, with the individual homes assumed to be a random variable (i.e., the homes are independent and uncorrelated entities). In contrast, observations of residents living within a given home have commonalities because of localized admission practices, treatment preferences that differ in content and/or frequency from those in other homes, the mutual interactions of residents, etc. Traditional regression and survival analyses fail to account for such commonalities, thereby violating assumptions of independence of observations of residents, which adds to correlated error, potentially with adverse implications for the correctness of analytic outcomes. Unfortunately, it appears that the majority of studies of LTCH residents fail to address this problem. The specific form of mixed modeling used in our earlier [1] and present studies is interval censored survival (i.e., a binomial distribution with a complementary log–log link), which is appropriate for analysis of clustered observations, some of which are without a terminal event.

Second, the majority of studies of relationships between antipsychotic medication and mortality report the type and dosage of medication but not the frequency of usage [11]. Although a few studies treat PRN use as an exclusionary criterion [11], it is more likely grouped with daily use in the majority of studies. The implications of such inclusion include augmented mortality beyond that associated with daily use.

Third, our earlier study indicates augmented mortality associated with PRN use of any psychotropic but ameliorated mortality associated with daily use of certain psychotropics (e.g., antidepressants) [1]. Consequently, combinations that include PRN or daily use of other psychotropics have respective implications for increased or decreased mortality levels associated with antipsychotic use.

Fourth, compliance and adherence to medication regimens are problematic among older people with chronic illness [13]. Anyone with work experience in long-term care settings knows that "residents who put pills into their mouths do not necessarily swallow them" [1]. Some residents chose to hide those pills, others throw them away. In effect, such 'hidden' non-compliance transforms daily prescriptions to intermittent usage, potentially with adverse effects on the estimated risk of mortality.

2. The present study

The motivation that underlies the present research is to explain our earlier finding that daily use of antipsychotic medication ameliorates mortality, which contradicts conclusions reported in the majority of previous studies [9–11]. The research that follows analyzes the same database as our earlier chapter [1] to answer

questions about the frequencies of concurrent combinations of antipsychotic with other psychotropic usage and their associations with subsequent mortality. As in the earlier study, the target variable is mortality within 90 days following the final RAI 2.0 assessment. The reason for this duration is that successive RAI 2.0 assessments occur at approximately 90-day intervals.

To simplify the presentation of results, we limit the control variables in analyses of mortality to the *Changes in Health, End-Stage Disease, Signs, and Symptoms Scale* (CHESS), which is an established indicator of mortality risk [14]. Although preliminary analyses also included demographic measures of age, gender and objective scales from the RAI 2.0 that include the Cognitive Performance Scale, the Activities of Daily Living Hierarchy and the Aggressive Behavior Scale (ABS), their inclusion fails to add appreciably to an interpretation of effects associated with the primary predictor variable. The latter is represented in **Table 1** by concurrent combinations of antipsychotic use and other psychotropic use.

The 1st and 2nd columns in **Table 1** represent combinations of concurrent usage of antipsychotic and other psychotropic medications. The frequencies for antipsychotics include no use, PRN use and daily use. The inclusive frequencies all other types of psychotropic are no use, PRN and daily use, only PRN use and only daily use. The 3rd, 4th, 5th and 6th columns represent possible combinations of antipsychotics with antidepressant, analgesic, anxiolytic or hypnotic medications, respectively. The possible frequencies for each of the latter are no use, PRN use and daily use.

The main hypotheses derive from our previous findings that, after control of the major risk factor for mortality, daily use of psychotropic medication ameliorates risk, whereas PRN use exacerbates risk. Consequently, we anticipate that combinations of antipsychotics with the daily use of other psychotropics ameliorate mortality to levels below that associated with absence of psychotropic use. In contrast, we predict augmented mortality associated with combinations of antipsychotic and other psychotropics that involve PRN use.

Antipsychotic prescription	**Prescriptions for other psychotropics**				
	All psychotropics	**Antidepressant**	**Analgesic**	**Anxiolytic**	**Hypnotic**
None	None	None	None	None	None
None	PRN & Daily	.	.	.	.
None	PRN	PRN	PRN	PRN	PRN
None	Daily	Daily	Daily	Daily	Daily
PRN	None	None	None	None	None
PRN	PRN & Daily	.	.	.	.
PRN	PRN	PRN	PRN	PRN	PRN
PRN	Daily	Daily	Daily	Daily	Daily
Daily	None	None	None	None	None
Daily	PRN & Daily	.	.	.	.
Daily	PRN	PRN	PRN	PRN	PRN
Daily	Daily	Daily	Daily	Daily	Daily

Table 1.
Antipsychotic prescription frequencies combined with frequencies for other antipsychotic medications on the final assessment.

2.1 Participants and measures

The participants are all new admissions, aged 65 years and older, to LTCHs in the Canadian province of Ontario during the financial year April 1st 2010 to March 31st 2011. They include 20,414 residents from 631 LTCHs. The distribution of men to women is 33.6% to 66.4%. The mean age of men is 83.03 years with a standard deviation of 7.37 years. The mean age of women is 85.29 years with a standard deviation of 7.19 years.

The main assessment tool used here is the RAI 2.0, which, to the authors' knowledge, (1) is used in more countries, (2) has a more thorough psychometric evaluation, and (3) is more comprehensive than any other geriatric assessment tool. The RAI 2.0 requires trained heath care professionals to score quantifiable assessment items relevant to medical diagnoses, levels of functioning, behavioral and emotional problems, forms of treatment, etc. The information is from medical records, clinical observations, and communication with residents, their family members and the facility's staff members. As already indicated, the RAI also contains objective scales that are evaluated against 'gold standard' measures from the relevant literature. The measures in the present analyses are the CHESS and items on antipsychotic, analgesic, antidepressant, anxiolytic and hypnotic medication use. The latter items record the number of days of usage during the week preceding an assessment. We report here on three usage categories: no use, PRN (i.e., intermittent) use, and daily use.

The RAI 2.0 also provides information on the mortality of residents in a LTCH. Other databases linked to the RAI 2.0 are the Discharge Abstract Database (DAD) and the National Ambulatory Care Reporting System (NACRS). The DAD reports mortality data for hospital discharges and the NACRS reports mortality in settings for emergency and ambulatory care. Consequently, our data encompasses mortality throughout the health care system. We are grateful to the Canadian Institute for Health Information (CIHI) for the provision of the data with encrypted personal and facility level identifiers.

Residents receive RAI 2.0 assessments upon admission and thereafter at quarterly intervals. The maximal follow-up period in the present study is 1-year. We report here on data from the final assessment, with mortality indexed by its absence or presence during 90 days following that assessment (i.e., a period that precedes the scheduled date of any subsequent assessment).

2.2 Statistical analyses

The statistical analyses relate to three issues. The first concerns the types of concurrent combination of usage frequencies between antipsychotics with other psychotropics. These analyses begin graphic and tabular statistics that relate to concurrent relationships between frequencies antipsychotic usage with frequencies for other types of psychotropic usage. Then follows findings from *Statistical Package for the Social Sciences* (SPSS Version 25) GLMM multinomial analysis of frequencies of antipsychotic usage (i.e., the target variable) against corresponding frequencies for each other psychotropic (i.e., the fixed effect variables). The random variable for this and every subsequent GLMM analysis are LTCHs.

The second issue concerns mortality within 90 days of the final assessment. The primary analysis is a GLMM interval censored survival model (i.e., a binomial distribution with a complementary log–log link). The CHESS (i.e., centered on its grand mean) and concurrent combinations of frequencies for antipsychotic and other psychotropic usage comprise the fixed effects. Then follows GLMM interval censored survival models that attempt to clarify implications of the preceding by analyzing

summative categories that respectively relate to antipsychotic use and other psychotropic use. Next, we analyze models that examine combinations of antipsychotics with each type of psychotropic. The purpose is to ascertain the types of antipsychotic that may ameliorate of exacerbate risk of mortality at different levels of usage. All the latter models include the CHESS as a measure of mortality risk.

The final issue concerns the effects on mortality of changes in health condition and prescribing practices from the penultimate to final assessment. This GLMM analysis examines whether changes in the CHESS and PRN prescriptions have independent implications for survival. In contrast, an alternative hypothesis suggests that changes in PRN prescription are a consequence of changes in health condition, with the former having with no direct implications for survival.

2.2.1 Analyses of psychotropic combinations

The following graph and table illustrate relationships between frequencies of usage for antipsychotic medication with corresponding usage of all other psychotropic medications. **Figure 2** shows 95% confidence intervals for the totality of any other psychotropic use against no use, PRN, and daily use for antipsychotic medication. The mean use of other psychotropic medication is significantly lower with no use of antipsychotic medication than for PRN and daily use, as evidenced by non-overlapping confidence intervals. **Table 2** shows percentages of residents with a given frequency of antipsychotic medication combined with the use of 1, 2, 3 or 4 other psychotropic medications. The statistical mode (i.e., the most frequent value) within columns of this table indicates that residents without antipsychotics most frequently receive one other psychotropic, whereas those with PRN and daily antipsychotic use most frequently use two other psychotropic medications.

The following figures illustrate frequencies of use of specific psychotropics that accompany no, PRN or daily use of antipsychotics. **Figure 3** shows findings associated with antidepressant medication. The findings indicate that approximately 60% of residents with daily antipsychotics and just over 40% of those with no antipsychotics receive antidepressants on a daily basis. Of those residents with PRN use of antipsychotics, the majority show either PRN (18%) or daily (35%) use of antidepressants.

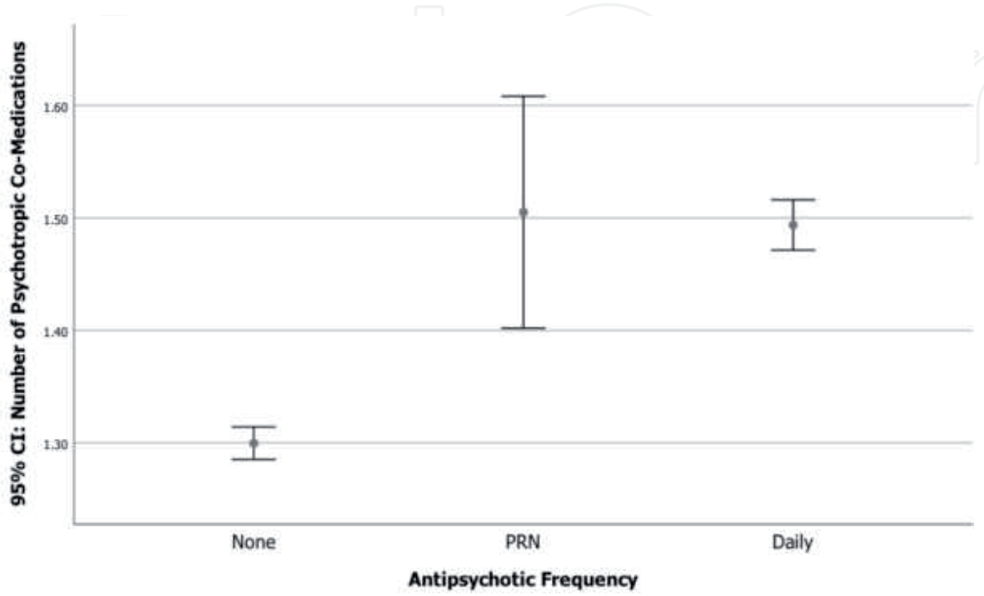

Figure 2.
95% confidence intervals for summative Co-medication frequencies for other psychotropics against frequencies for antipsychotic medication.

Number of other of psychotropics	Percentage of residents		
	Antipsychotic use		
	None	PRN	Daily
0	18.6%	13.6%	13.2%
1	41.4%	35.6%	36.6%
2	31.8%	38.6%	38.9%
3	7.7%	11.2%	10.4%
4	0.5%	1.0%	1.0%

Table 2.
Percentage of residents with No, PRN or daily use of antipsychotics 1, 2, 3 or 4 other psychotropics.

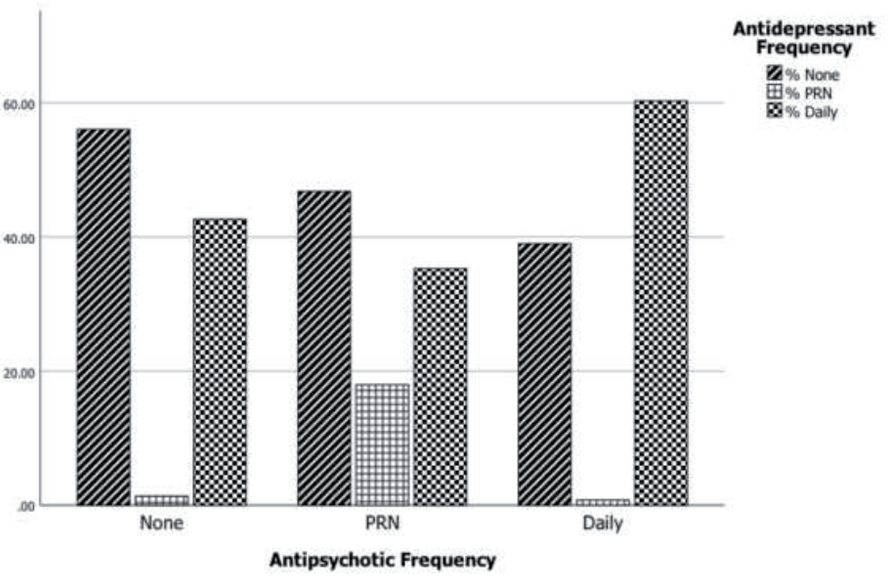

Figure 3.
Percentage antidepressant frequency against antipsychotic frequency.

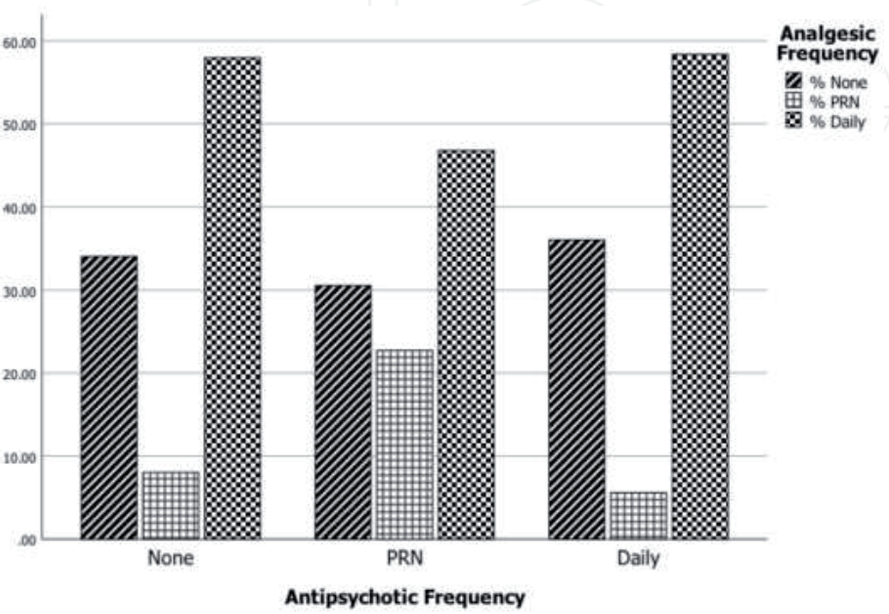

Figure 4.
Percentage analgesic frequency against antipsychotic frequency.

Levels of analgesic medication are uniformly high. **Figure 4** shows PRN or daily use among approximately 65–70% of residents regardless of frequency of usage of antipsychotic medication. Consistent with finding for antidepressants and anxiolytics (see below), the highest PRN use of analgesics corresponds with PRN use antipsychotic medication (approximately, 22%).

Figure 5 indicates a low overall use of anxiolytic medication. The levels of daily use are approximately 7–10% regardless of frequency of use for antipsychotics. However, among residents with PRN use of antipsychotics, PRN use of anxiolytics is approximately 14%, which is considerably higher than daily use for this subgroup of residents.

Figure 6 shows hypnotic use to be lower than for any of other psychotropic (i.e., approximately 6.3% of residents). The highest PRN use of hypnotics occurs

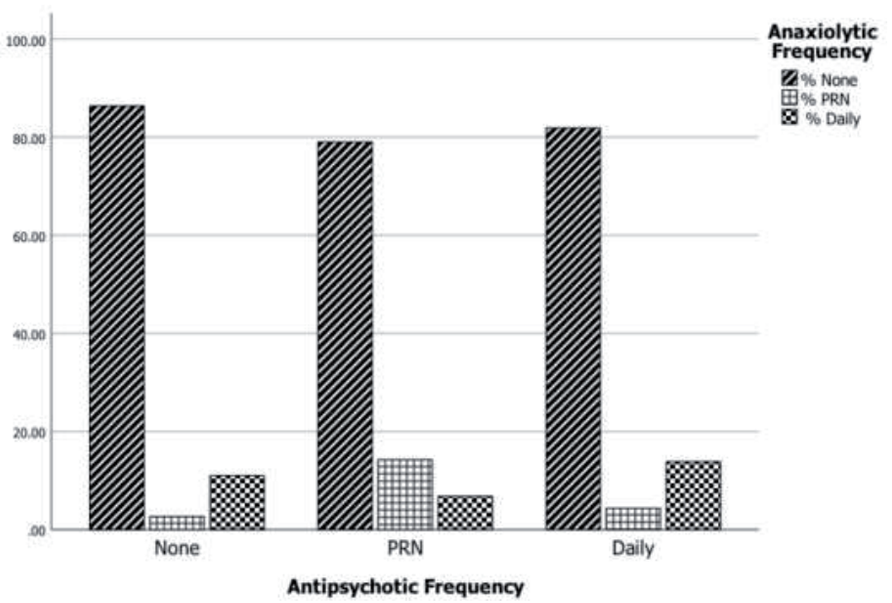

Figure 5.
Percentage Anaxiolytic frequency against antipsychotic frequency.

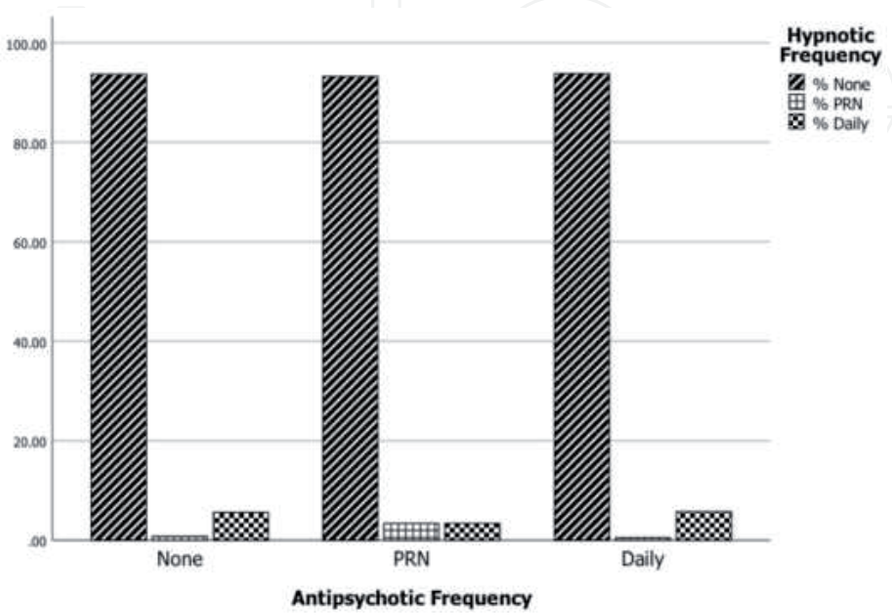

Figure 6.
Percentage hypnotic frequency against antipsychotic frequency.

Antipsych. frequency	Model term	Coefficient	Std. error	Sig.	95% confidence interval		Exponential coefficient
					Lower	Upper	
Daily	Intercept	−1.119	.0372	.000	−1.192	−1.046	.327
	Antidepress. Daily	.682	.0329	.000	.617	.746	1.977
	Antidepress. PRN	−.242	.1705	.155	−.576	.092	.785
	Antidepress. None	0	.	.	.	.	1.00
	Analgesic Daily	−.134	.0347	.000	−.201	−.066	.875
	Analgesic PRN	−.384	.0701	.000	−.521	−.246	.681
	Analgesic None	0	.	.	.	.	1.00
	Anxiolytic Daily	.207	.0484	.000	.112	.302	1.230
	Anxiolytic PRN	.561	.0863	.000	.392	.730	1.753
	Anxiolytic None	0	.	.	.	.	1.00
	Hypnotic Daily	−.033	.0694	.634	−.169	.103	.967
	Hypnotic PRN	−.302	.2145	.160	−.722	.119	.740
	Hypnotic None	0	.	.	.	.	1.00
PRN	Intercept	−4.151	.1246	.000	−4.395	−3.907	.016
	Antidepress. Daily	.054	.1330	.683	−.206	.315	1.056
	Antidepress. PRN	2.378	.1898	.000	2.006	2.750	10.788
	Antidepress. None	0	.	.	.	.	1.00
	Analgesic Daily	−.120	.1398	.389	−.394	.154	.887
	Analgesic PRN	.703	.1777	.000	.355	1.052	2.020
	Analgesic None	0	.	.	.	.	1.00
	Anxiolytic Daily	−.312	.2373	.188	−.777	.153	.732
	Anxiolytic PRN	1.399	.1907	.000	1.025	1.773	4.050
	Anxiolytic None	0	.	.	.	.	1.00
	Hypnotic Daily	−.392	.3289	.234	−1.036	.253	.676
	Hypnotic PRN	.986	.3710	.008	.259	1.713	2.680
	Hypnotic None	0	.	.	.	.	1.00

Table 3.
Fixed effects coefficients and odds ratios for prediction of antipsychotic frequency by frequencies of all other antipsychotic categories.

in combination with PRN use of antipsychotics. Daily use of hypnotics has approximately similar levels among residents with no of daily use of antipsychotic medication.

Inferences from the preceding graphs and table include the following. First, residents with PRN or daily use of antipsychotics have higher concurrent use of other psychotropic medications than those without antipsychotic use. **Table 2** shows that over 80% of residents without antipsychotic use receive at least one other psychotropic. The psychotropics that appear most frequently in these combinations are antidepressants and analgesics, which have the highest overall frequency of usage. Second, PRN use of antipsychotics combines with the highest PRN in each other psychotropic category. This finding suggests a clustering of PRN prescribing that encompasses all types of psychotropic medication.

The final analysis this section is a GLMM multinomial analysis. This analysis includes LTCHs as a random variable and fixed effect predictors that evaluate the independent contributions by other psychotropics to frequencies of antipsychotic use. The target and predictor variables are on nominal scales of no use, PRN use and daily use, respectively, with the former designated as reference category.

The findings in **Table 3** include the regression coefficients, standard errors, levels of statistical significance and 95% confidence intervals. **Table 3** also includes derivative exponential coefficient for readers that prefer odds ratios over regression coefficients. Positive or negative regression coefficients respectively indicate mean values above or below those associated with the reference category, with odds ratios greater or less than unity having comparable meaning. The overall findings for the model include significant random effects of LTCHs at $p < .001$. Findings for the fixed effect terms are as follows.

Daily antidepressants, daily anxiolytics and PRN anxiolytics are all positive predictors of daily antipsychotic use (all $p < .001$). Daily analgesics and PRN analgesics are negative predictors (both $p < .001$). These findings suggest that psychotropics purportedly relevant to mood improvement and anxiety reduction are likely to accompany daily antipsychotic use, whereas medications purportedly relevant to pain relief are less likely to occur in combination with daily antipsychotic medication.

PRN use of antidepressants ($p < .001$), anxiolytics ($p < .001$), analgesics ($p < .001$) and hypnotics ($p < .001$) are positive predictors of PRN use of antipsychotics. There are no significant relationships between daily use of other psychotropics and PRN use of antipsychotics. These findings indicate a clustering of PRN prescribing.

2.2.2 Survival analyses

Mortality during the 1-year follow-up period of data collection is 18.1% overall. The mortality rates for men and women are 21.1% and 16.3% respectively. The distribution of mortality across assessments indicates that 45% of residents died within 90 days of the admission assessment, with a decreasing proportion of deaths at each subsequent assessment.

The primary interval censored survival analysis shows a significant random effect for LTCHs $p < .001$. Because the same level of significance is present in all subsequent GLMM analyses, we need not report them henceforth. **Table 4** shows findings for the fixed effects. Unsurprisingly, the positive coefficient for the CHESS indicates higher mortality for residents at greater risk of mortality. The reference category for combinations of medications is the daily use of both antipsychotics and other psychotropics, which numerically is associated with the lowest level of mortality. This combination has significantly lower mortality ($p < .005$ or beyond) than any other combination except for those that combine no antipsychotics with daily psychotropics and PRN use of antipsychotics with daily psychotropics.

Fixed effects	Coefficient	Std. error	Sig.	95% Confidence interval		Exponential coefficient
				Lower	Upper	
Intercept	−1.938	.0412	.000	−2.019	−1.858	.14
CHESS	.569	.0136	.000	.543	.596	1.77
AP, None: PT, None	.366	.0600	.000	.248	.483	1.44
AP, None: PT, Mixed	.552	.0776	.000	.400	.704	1.74
AP, None: PT, PRN	.643	.0782	.000	.490	.797	1.90
AP, None: PT, Daily	.084	.0459	.066	−.005	.174	1.09
AP, PRN: PT, None	.999	.2851	.000	.441	1.558	2.72
AP, PRN: PT, Mixed	.818	.2480	.001	.332	1.304	2.27
AP, PRN: PT, PRN	.910	.1978	.000	.522	1.298	2.48
AP, PRN: PT, Daily	.346	.1739	.047	.005	.687	1.41
AP, Daily: PT, None	.273	.0944	.004	.088	.458	1.31
AP, Daily: PT, Mixed	.421	.1036	.000	.218	.624	1.52
AP, Daily: PT, PRN	.549	.1537	.000	.248	.850	1.73
AP, Daily: PT, Daily	0	.	.	.	.	1.00

Table 4.
Fixed effect coefficients for the CHESS and combinations of antipsychotic (AP) and other psychotropic (PT) frequencies in prediction of mortality.

Fixed effects	Coefficient	Std. error	Sig.	95% Confidence interval		Exponential coefficient
				Lower	Upper	
Intercept	−1.846	.0355	.000	−1.915	−1.776	.16
CHESS	.577	.0134	.000	.550	.603	1.78
No Antipsychotics	.113	.0380	.003	.039	.188	1.12
PRN Antipsychotics	.566	.1095	.000	.352	.781	1.76
Daily Antipsychotics	0	.	.	.	.	1.00

Table 5.
Fixed effect coefficients for combined categories of antipsychotic frequencies with other psychotropic medications.

An implication is that daily use of psychotropics ameliorates mortality associated with antipsychotics to levels below that associated with no use of the latter.

A Bonferroni multiple comparison with the combination that includes neither antipsychotic nor any other psychotropic provides further support for this inference. The only other combination with significantly lower mortality than zero use of any psychotropic is that of no antipsychotics but daily use of other psychotropics ($p < .001$). Consequently, the latter ameliorates mortality below the level associated with zero psychotropic medications.

The next two analyses condense the preceding array of combinations into those associated with antipsychotic use (i.e., none, PRN and daily) and other psychotropic use, respectively (i.e., none, mixed, PRN and daily). Both analyses include the CHESS, with daily use as the reference category for the combinational variable.

Fixed effects	Coefficient	Std. error	Sig.	95% Confidence interval		Exponential coefficient
				Lower	Upper	
Intercept	−1.879	.0262	.000	−1.930	−1.827	.15
CHESS	.572	.0135	.000	.546	.598	1.77
No Psychotropics	.294	.0455	.000	.205	.383	1.34
Mixed Psychotropics	.457	.0578	.000	.344	.570	1.58
PRN Psychotropics	.589	.0626	.000	.466	.712	1.80
Daily Psychotropics	0	.	.	.	.	1.00

Table 6.
Fixed effect coefficients for combined categories of other psychotropic medication use with antipsychotic use.

The findings in **Table 5** show the findings from the analysis of psychotropic use. In addition to significance for the CHESS, daily use of antipsychotics is associated with significantly lower mortality than no use or PRN use ($p < .005$ or beyond). Moreover, a Bonferroni multiple comparison shows that no use has a significantly lower level of mortality than PRN use. These findings replicate the trends for antipsychotic use reported in our earlier publication [1].

Table 6 shows findings from the analysis of the use of other psychotropics. With daily use as the reference category, no use, mixed use and PRN use are associated with higher levels of mortality ($p < .005$ or beyond). Sequential Bonferroni multiple comparisons of no, mixed and PRN use reveal higher mortality for PRN than no use ($p < .001$), with no comparison that involves mixed use significant at $p < .01$ level. These findings suggest that daily use of other psychotropics has ameliorative effects on mortality. **Figure 7** provides a graphic portrayal of the combined finding from last two analyses, indicating inverted-V or inverted-U structures corresponding to frequencies of no, mixed, PRN and daily use, with lowest frequencies associated with daily use of other psychotropics.

Fixed effects	Coefficient	Std. error	Sig.	95% Confidence interval		Exponential coefficient
				Lower	Upper	
Intercept	−1.984	.0464	.000	−2.075	−1.893	.14
CHESS	.575	.0135	.000	.549	.601	1.78
AP, None: AD, None	.370	.0510	.000	.270	.470	1.45
AP, None: AD, PRN	.718	.1374	.000	.448	.987	2.05
AP, None, AD, Daily	.069	.0547	.207	−.038	.176	1.07
AP, PRN: AD, None	.819	.1541	.000	.517	1.121	2.27
AP, PRN: AD, PRN	1.040	.2203	.000	.608	1.472	2.83
AP, PRN, AD, Daily	.301	.2127	.157	−.116	.718	1.35
AP, Daily: AD, None	.320	.0647	.000	.193	.447	1.38
AP, Daily: AD, PRN	.625	.2955	.034	.046	1.204	1.87
AP, Daily, AD, Daily	0	.	.	.	.	1.00

Table 7.
Fixed effect coefficients for the CHESS and combinations of antipsychotic (AP) and antidepressant (AD) use in prediction of mortality.

Fixed Effects	Coefficient	Std. Error	Sig.	95% Confidence Interval		Exponential Coefficient
				Lower	Upper	
Intercept	−1.891	.0450	.000	−1.979	−1.803	.15
CHESS	.573	.0136	.000	.546	.599	1.77
AP, None: AN, None	.225	.0551	.000	.117	.333	1.25
AP, None: AN, PRN	.566	.0714	.000	.426	.706	1.76
AP, None, AN, Daily	.055	.0501	.276	−.044	.153	1.06
AP, PRN: AN, None	.701	.2015	.001	.306	1.096	2.02
AP, PRN: AN, PRN	.721	.2139	.001	.302	1.140	2.06
AP, PRN, AN, Daily	.510	.1579	.001	.200	.819	1.67
AP, Daily: AN, None	.012	.0705	.860	−.126	.151	1.01
AP, Daily: AN, PRN	.546	.1117	.000	.327	.764	1.73
AP, Daily, AN, Daily	0	.	.	.	.	1.00

Table 8.
Fixed effect coefficients for the CHESS and combinations of antipsychotic (AP) and analgesic (AN) use in prediction of mortality.

Fixed effects	Coefficient	Std. error	Sig.	95% Confidence interval		Exponential coefficient
				Lower	Upper	
Intercept	−1.925	.0886	.000	−2.099	−1.751	.15
CHESS	.574	.0134	.000	.548	.601	1.78
AP, None: AX, None	.199	.0898	.027	.023	.375	1.22
AP, None: AX, PRN	.537	.1322	.000	.278	.797	1.71
AP, None, AX, Daily	.042	.1078	.695	−.169	.254	1.04
AP, PRN: AX, None	.546	.1503	.000	.251	.840	1.73
AP, PRN: AX, PRN	1.143	.2503	.000	.652	1.633	3.14
AP, PRN, AX, Daily	.649	.4058	.110	−.146	1.444	1.91
AP, Daily: AX, None	.081	.0941	.390	−.104	.265	1.08
AP, Daily: AX, PRN	.302	.1580	.056	−.007	.612	1.35
AP, Daily, AX, Daily	0	.	.	.	.	1.00

Table 9.
Fixed effect coefficients for the CHESS and combinations of antipsychotic (AP) and anxiolytic (AX) use in prediction of mortality.

The following GLMM interval censored survival analyses examine combinations of antipsychotic with separate types of other psychotropic. These combinations correspond to frequencies of usage outlined in last four columns of **Table 1**. All these analyses include the CHESS among the fixed effects, with daily usage of both

Fixed effects	Coefficient	Std. error	Sig.	95% Confidence interval		Exponential coefficient
				Lower	Upper	
Intercept	−1.707	.1230	.000	−1.948	−1.466	.18
CHESS	.576	.0134	.000	.550	.602	1.78
AP, None: HY, None	−.027	.1237	.828	−.269	.216	.97
AP, None: HY, PRN	.657	.2081	.002	.249	1.065	1.93
AP, None, HY, Daily	−.123	.1495	.411	−.416	.170	.88
AP, PRN: HY, None	.450	.1633	.006	.130	.770	1.57
AP, PRN: HY, PRN	.001	.5223	.999	−1.023	1.025	1.00
AP, PRN, HY, Daily	.350	.5583	.531	−.744	1.444	1.42
AP, Daily: HY, None	−.149	.1264	.239	−.397	.099	.86
AP, Daily: HY, PRN	−.009	.4182	.982	−.829	.810	.99
AP, Daily, HY, Daily	0	.	.	.	.	1.00

Table 10.
Fixed effect coefficients for the CHESS and combinations of antipsychotic (AP) and hypnotic (HY) use in prediction of mortality.

an antipsychotic and the other specified psychotropic as the reference category for combinations.

Tables 7–10 show fixed effect findings for combinations that include antidepressants, analgesics, anxiolytics and hypnotics respectively. **Tables 7** and **8** show coefficients for the combinations that include the most frequently used psychotropics. **Table 7** shows significantly lower mortality for a combination of daily antipsychotic with antidepressant use than for two of three combinations without antipsychotics ($p < .001$); the exception being a combination of no antipsychotics with daily antidepressants. **Table 8** shows comparable findings for the combination of daily antipsychotics with analgesic use. Also, every combination that includes PRN use of an antipsychotic and/or another psychotropic has significantly higher mortality than the reference category.

Tables 9 and **10** show findings for combinations of antipsychotic use with anxiolytic and hypnotic use, respectively. Neither psychotropic has a high prevalence of usage in LTCHs. The findings mainly indicate non-significant differences in mortality against the reference category. The significant differences include higher mortality than for the reference category for combinations that include PRN use of antipsychotic or another psychotropic ($p < .001$).

A final analysis in this section relates mortality to the duration of residence in a LTCH. Because previous reviews indicate higher mortality during the beginning phase of antipsychotic use, we would be remiss not to examine such effects [10, 11]. We report at the beginning of this section that nearly half the deaths occurred within 90 days of the admission assessment. Consequently, the following GLMM multinomial analysis uses as the target variable categories of (1) death after the admission assessment, (2) death after subsequent assessments, with (3) absence of mortality as the reference category. Findings in **Table 11** for death after the initial assessment indicate significantly lower mortality for the daily antipsychotic with other psychotropic use combination than for any other combination ($p < .005$ and beyond). Bonferroni multiple comparison also shows that the no antipsychotic but other daily psychotropic use combination has lower mortality than the combination with neither antipsychotic nor other

Assessment	Model term	Coefficient	Std. error	Sig	95% Confidence interval		Exponential coefficient
					Lower	Upper	
Initial	Intercept	−2.932	.0717	.000	−3.072	−2.791	.053
	CHESS	.557	.0230	.000	.512	.602	1.745
	AP, None: PT, None	.906	.0961	.000	.717	1.094	2.474
	AP, None: PT, Mixed	1.211	.1223	.000	.971	1.450	3.356
	AP, None: PT, PRN	1.423	.1187	.000	1.190	1.655	4.148
	AP, None: PT, Daily	.420	.0802	.000	.263	.577	1.522
	AP, PRN: PT, None	2.079	.3858	.000	1.323	2.835	7.995
	AP, PRN: PT, Mixed	1.605	.4089	.000	.803	2.406	4.977
	AP, PRN: PT, PRN	1.714	.3130	.000	1.100	2.327	5.549
	AP, PRN: PT, Daily	.819	.2808	.004	.268	1.369	2.268
	AP, Daily: PT, None	.688	.1474	.000	.399	.977	1.991
	AP, Daily: PT, Mixed	.839	.1701	.000	.506	1.172	2.314
	AP, Daily: PT, PRN	.768	.2735	.005	.232	1.304	2.156
	AP, Daily: PT, Daily	0	.	.	.	.	1.00
Subsequent	Intercept	−2.315	.0558	.000	−2.424	−2.206	.099
	CHESS	.773	.0214	.000	.731	.815	2.166
	AP, None: PT, None	.006	.0908	.949	−.172	.184	1.006
	AP, None: PT, Mixed	.152	.1253	.225	−.094	.397	1.164
	AP, None: PT, PRN	.015	.1361	.912	−.252	.282	1.015
	AP, None: PT, Daily	−.140	.0636	.028	−.265	−.015	.869
	AP, PRN: PT, None	.206	.5757	.720	−.922	1.334	1.229
	AP, PRN: PT, Mixed	.626	.4299	.145	−.216	1.469	1.871
	AP, PRN: PT, PRN	.882	.3216	.006	.252	1.513	2.416
	AP, PRN: PT, Daily	.058	.2753	.834	−.482	.597	1.059
	AP, Daily: PT, None	.075	.1397	.589	−.198	.349	1.078
	AP, Daily: PT, Mixed	.331	.1522	.030	.033	.629	1.392
	AP, Daily: PT, PRN	.483	.2271	.033	.038	.928	1.621
	AP, Daily: PT, Daily	0	.	.	.	.	1.00

Table 11.
Fixed effect coefficients for the CHESS and combinations of antipsychotic (AP) and other psychotropic (PT) frequencies in the prediction of mortality after the first and later assessments.

psychotropic use ($p < .001$). These findings are comparable to those reported for mortality over the full range of assessments. However, the findings for mortality after the admission assessment show no significant effects. We conclude, therefore, that effects associated with the medicinal combinations are stronger for mortality that occurs shortly after the admission assessment.

2.2.3 Survival analysis against measures of change

The preceding analyses relate mortality to CHESS scores and prescription profiles on the final assessment. Questions raised in our preceding chapter concern issues about causality with respect to relationships between health and medicinal

Model term	Coefficient	Std. error	Sig	95% Confidence interval		Exponential coefficient
				Lower	Upper	
Intercept	−2.249	.0308	.000	−2.309	−2.188	.053
CHESS Preceding, High	1.958	.2346	.000	1.499	2.418	1.745
CHESS Preceding, Low	0	.	.	.	.	2.474
CHESS Change, Worse	2.015	.0756	.000	1.867	2.163	3.356
CHESS Change, Better	−1.052	.2904	.000	−1.621	−.482	4.148
CHESS Change, None	0	.	.	.	.	1.522
PRN Preceding, Present	.349	.1005	.001	.152	.545	7.995
PRN Preceding, Absent	0	.	.	.	.	4.977
PRN Change, Increase	.648	.0731	.000	.505	.791	5.549
PRN Change, Decrease	−.123	.1247	.325	−.367	.122	2.268
PRN Change, None	0	.	.	.	.	1.00

Table 12.
Fixed effect coefficients for the CHESS and PRN levels on penultimate assessment and their changes from the penultimate to final assessments in the prediction of mortality after the final assessment.

prescriptions, with potential implications for subsequent mortality [1]. One hypothesis is that changes toward higher PRN prescribing explains both worsening in health condition and subsequent mortality.

A second hypothesis is that worsening of health condition results in higher PRN prescribing and subsequent mortality, such that any relationship between PRN and mortality is artifactual rather than actual. A third hypothesis is that changes toward higher PRN prescribing and changes in health conditions make independent contributes to levels of mortality.

The following GLMM analysis tests these hypotheses with the data necessarily restricted to the penultimate and final assessments among residents with two or more assessments. With mortality as the target variable, the fixed effects include binary scores of (1) high-risk scores *versus* low risk on the CHESS (i.e., high risk scores are 4 or 5 on a 5-point scale) (2) the presence or absence of any PRN prescription on the penultimate assessment; and (3) changes in the CHESS index and (4) the PRN index from the penultimate to final assessment. **Table 12** shows the findings.

Levels of mortality are significantly higher for high risk scores on the CHESS and the presence of PRN prescription. Changes on the CHESS toward worsening health are associated with significantly higher mortality, whereas changes toward lower risk scores are associated with significantly lower mortality, when compared an absence of change on the CHESS index. Compared to no change on the PRN index, an increased frequency of PRN prescription is associated with significantly increased mortality. Consequently, the findings indicate that detrimental levels and detrimental changes on the CHESS and PRN indexes contribute independently to higher levels of mortality.

2.3 Discussion

Our previous research with this database [1] includes a number of resident-level and facility-level control variables from the RAI 2.0. The analyses reported here simplify the presentation of results by inclusion of only the CHESS as a control variable. The justification is that unreported analyses, which included a wider range of fixed effect predictors of mortality, did not substantially alter the present findings. We should also mention findings from unreported analyses with Cox regression, which is a common form of survival analysis that takes no account for correlated error in SPSS 25. Despite this limitation, the findings with Cox regression are otherwise comparable to those reported here.

The present findings indicate that approximately 30% of residents are in receipt of antipsychotic medication, with more than 99% of those residents in receipt of at least one other psychotropic medication. The most frequently used among the latter are antidepressants and analgesics. The GLMM analysis in **Table 3** indicates that psychotropics with positive effects on mood and anxiety are frequently combined with daily use of antipsychotics, whereas analgesics are more frequent in residents without antipsychotic usage. PRN use of other types of psychotropic significantly predicts PRN use of antipsychotics, which indicates that residents typically receive PRN prescription for multiple types of psychotropic medication.

To our knowledge, the study presented here is the first to examine how concurrent prescriptions of other psychotropics can affect elevated mortality among the elderly, which is attributed in many previous studies to the use of antipsychotics. Although limitations in present data includes absence of information on the types and dosages of psychotropics, a limitation common to previous studies is an absence of information on the frequencies of usage. Although prior evidence indicates the good overall quality of RAI 2.0 data [2], a limitation for present purposes is an absence of information about medicinal use prior to admission. A consequence is uncertainty about whether high mortality shortly after admission reflects effects associated with short-term antipsychotic use, relocation to a LTCH, or other unknown effects. However, the findings reported in **Table 12** on residents with at least two RAI 2.0 assessments indicate that changes in prescribing practices do have effects on mortality beyond those associated with changes in high risk health conditions measured by the CHESS. Consequently, we conclude that the relationship between PRN usage and mortality is one of primary determination, rather than secondary to the relationship between declining health and mortality.

The overall findings on mortality support our hypotheses that daily use of other psychotropics may ameliorate mortality levels associated with antipsychotic use, whereas PRN use of other psychotropics augments that mortality. **Figure 7** provides a cogent illustration of the supportive findings. The specific psychotropics that support amelioration with daily use are antidepressants and analgesics, whereas concurrent PRN use of analgesics, anxiolytics and hypnotics are associated with augmented mortality. However, despite the high percentage of death among LTCH residents with PRN prescriptions on the final assessment, it must be remembered that only 12.9% are in receipt of such prescription.

Implications of the findings are that retrospective studies may incorrectly estimate the mortality associated with antipsychotic prescriptions by failure to take account of the deleterious effects of PRN usage and the beneficial effects of daily usage of other psychotropics. We reasoned in our previous chapter that the clinical rationale for psychotropic prescription is to renormalize disturbances to a resident's equilibrium (e.g., aggression, depression, pain, anxiety, insomnia), with

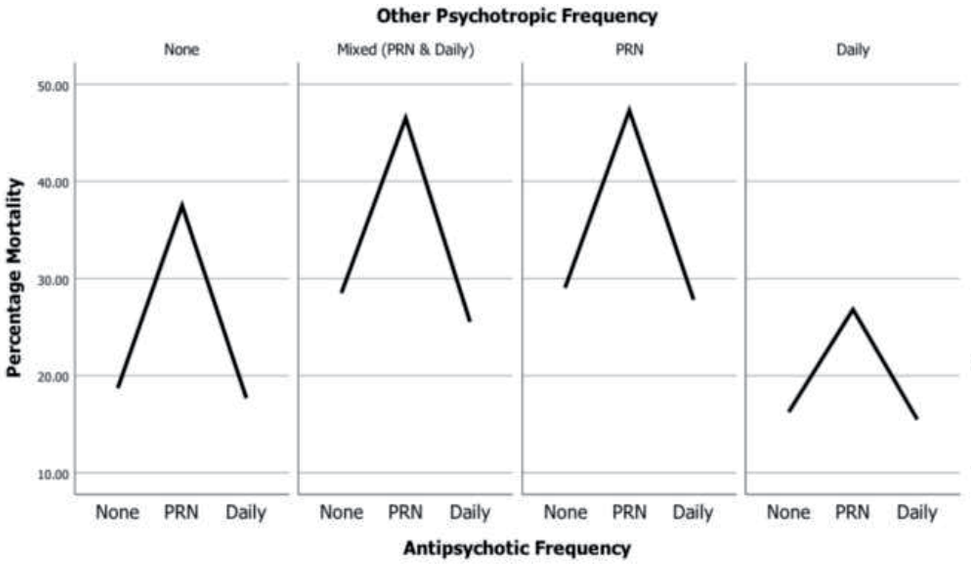

Figure 7.
Percentage mortality for frequency combinations of antipsychotic with other psychotropic medication.

such disequilibrium considered a risk to wellbeing and mortality [1]. Successful treatment is associated with regained equilibrium after adaptation to regular prescription of the requisite medication. However, intermittent medication usage is antagonistic to adaptation, may exacerbate disequilibrium, with an elevation of mortality risk. Consequently, implications for caregiving of residents with BPSD may include daily antipsychotic and other daily psychotropic usage if non-pharmaceutical intervention fails to bring relief, but should avoid PRN usage of any form of psychotropic medication.

3. Conclusions

Behavioral disturbance is common among residents with dementia in LTCH. Such disturbance is associated with poor quality of life, caregiver burden and adverse health care outcomes. Although non-pharmacological procedures are recommended as the first line of treatment [15], the usual treatment in LTCHs includes the use of antipsychotics despite limited evidence for effectiveness and health outcomes reported to include elevated mortality. The research described here suggests that daily use of antipsychotics with daily use of other psychotropics (particularly antidepressants and analgesics) attenuate mortality whereas concurrent combinations that include PRN usage exacerbate mortality. The implications for caregiving include avoidance of PRN prescriptions of psychotropic medications.

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Conflict of interest

No author has any conflict of interest.

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