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Fracture Risk among Nursing Home Residents Initiating Antipsychotic Medications

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Abstract

Objectives—to determine whether antipsychotic medication initiation is associated with subsequent fracture in nursing home residents, whether fracture rates differ between first-generation versus second-generation antipsychotic use, and whether fracture rates differ among users of haloperidol, risperidone, olanzapine, and quetiapine.

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Design—time-to-event analyses were conducted in a retrospective cohort using linked Medicaid, Medicare, Minimum Data Set and Online Survey, Certification and Reporting data sets.

Setting and Participants—nursing home residents aged ≥ 65 years in CA, FL, MO, NJ and PA.

Measurements—fracture outcomes (any fracture; hip fracture) in first-versus second-generation antipsychotic users, and specifically among users of haloperidol, risperidone, olanzapine and quetiapine. Comparisons incorporated propensity scores that included patient-level variables (demographics, comorbidity, diagnoses, weight, fall history, concomitant medications, cognitive performance, physical function, aggressive behavior) and facility-level variables (nursing home size, ownership factors, staffing levels).

Results—Among 8,262 subjects (within 4,131 pairs), 4.3% suffered any fracture during observation with 1% having a hip fracture during an average follow up period of 93 ± 71 days; range 1 to 293 days). Antipsychotic initiation was associated with any fracture (hazard ratio (HR) 1.39, $p=0.004$) and with hip fracture (HR 1.76, $p=0.024$). The highest risk was found for hip fracture when antipsychotic use was adjusted for dose (HR=2.96; $p=0.008$). However, no differences in time-to-fracture were found in first-versus second-generation agents or across competing individual drugs.

Conclusion—Antipsychotic initiation is associated with fracture in nursing home residents, but risk does not differ across commonly used antipsychotics.

Keywords

fracture; antipsychotic; nursing home

INTRODUCTION

Hip fractures negatively impact survival and health status.¹⁻³ Hip fracture is four times more common in nursing home (NH) residents than in community-dwelling older adults.⁴ Psychotropic medications are associated with fall-related fractures in older adults.⁵ Along with sedating effects and orthostatic hypotension, first-generation antipsychotics (FGAP) have extrapyramidal side effects that may reduce gait stability. Second-generation antipsychotics (SGAP) have fewer extrapyramidal side effects and thus have been widely presumed to be safer for gait stability than FGAP. This distinction between FGAP and SGAP has been a central theme in the rapid transition in antipsychotic prescribing practices in the United States.⁶ In 2001, only seven years after the introduction of risperidone to market, SGAPs accounted for more than 90% of all antipsychotic use in NH residents.⁷

However, the widely-held notion that SGAPs are safer for gait stability and must therefore pose less fracture risk than FGAPs has not been shown in randomized clinical trials (RCTs). Fractures are relatively uncommon events that do not occur in sufficient numbers for evaluation during typical short-term RCTs that are designed to test drug efficacy. Published observational studies to date have reached varying conclusions from different populations, study designs, available variables and AP use measures.⁸⁻¹³

Despite Food and Drug Administration (FDA) safety warnings and regulatory scrutiny of antipsychotic (AP) use in NHs, one in five NH residents still receive APs.¹⁴ Among residents with cognitive impairment and behavioral problems, the rate of AP use in 2010 was 39%.¹⁴ Because of the paucity of other pharmacologic alternatives, knowledge of the comparative safety across competing APs remains important for the foreseeable future.

Our goal was to use existing observational data to examine the association between AP use and fracture outcomes in NH residents, using propensity-based matching to control for patient-level and facility-level confounding factors.

METHODS

Cohort Formation

We conducted a retrospective cohort study with a new-user design in dually Medicaid- and Medicare-eligible NH residents in California, Florida, Missouri, New Jersey and Pennsylvania. Data from 1999 were selected because more recent years did not provide sufficient observations of FGAP use, owing to rapidly changing prescribing patterns. We purchased data from the Centers for Medicare and Medicaid Services (CMS) and linked Medicaid, Medicare, and Minimum Data Set (MDS) nursing home data at the individual level. We incorporated facility-level characteristics from the Online Survey, Certification and Reporting (OSCAR) database.¹⁵

We required all subjects to have Medicare parts A and B in order to capture both inpatient and outpatient fractures. Exclusion criteria included age <65 years, NH use for <100 days, history of psychiatric hospitalization or severe mental illness, or a diagnosis of schizophrenia or bipolar mood disorder. Other pragmatic exclusions were residence in multiple states or multiple NHs, lack of a baseline MDS assessment prior to AP initiation, or lack of required data elements needed for the calculation of propensity scores or drug exposure measures. We also excluded subjects who did not have at least 60 days of observable time in the data set without AP use, in order to assure an observed ‘wash out’ period prior to AP initiation.

Exposure and Outcome Measures—National drug codes (NDC) were extracted from Medicaid pharmacy claims and converted to specific medications and doses using the Multum drug data base.¹⁶ FGAPs included haloperidol, thioridazine, chlorpromazine, fluphenazine, perphenazine, thiothixene, loxapine, trifluoperazine, mesoridazine, molindone, pimozide and promazine. SGAPs included risperidone, olanzapine, and quetiapine; we excluded clozapine because of its narrow indications. AP-users who received only a single AP agent throughout observation were classified as either FGAP or SGAP users, and were further assigned into individual drug groups (risperidone, quetiapine, olanzapine, haloperidol or ‘other’). Persons who switched APs during observation were included in the AP-use versus non-use analyses but excluded from drug-drug comparisons.

The primary explanatory variable was use or non-use of any AP, but we also characterized AP exposure by regularity of use over time and dosing intensity. Use over time was described by the ‘proportion of days covered’ (PDC), a measure of medication persistence.¹⁷ We allowed a seven day gap length between prescriptions and assumed that APs were continued during periods of hospitalization.¹⁸ Doses were standardized across APs of different potencies by converting average daily doses to a ‘chlorpromazine equivalent.’¹⁹

Fracture outcomes were captured from diagnosis and procedure codes within Medicare data using published methods.²⁰⁻²³ Hip fracture was defined by a new inpatient claim for hip fracture. Non-hip fractures were deemed present according to a previously published algorithm that required a set of confirmatory imaging and physician service codes.²³

Propensity Score Development and Matching—Propensity score models were developed to describe the likelihood of each person to have been an AP-user, and then used in matching as described below.²⁴ Candidate variables for propensity score modeling were

based on published literature regarding patient-level and facility-level predictors of AP use and fracture in NH residents.^{5,7,12,22,25-28} These variables were derived from the baseline MDS record which was defined as the MDS assessment closest to but still preceding the onset of observed follow up time (i.e., prior to AP initiation among AP-users.) Demographic factors included state, gender, age, race/ethnicity and rural/urban residence. Disease burden was characterized by a claims-based version of the Charlson comorbidity index and by the total number of medications used. Dementia diagnoses and Parkinson's disease were identified through a combination of claims, MDS markers, and tracer medications (e.g., cholinesterase inhibitor to indicate dementia). From the MDS, we identified the occurrence of a fall in the last 180 days, body mass index, urinary incontinence, and use of anxiolytic, antidepressant or hypnotic medications. Widely-used, validated MDS scales were used to characterize cognitive performance (the MDS Cognitive Performance Score),²⁹ activities of daily living (the MDS hierarchical Activities of Daily Living Score),³⁰ aggressive behavior (the MDS Aggressive Behavior Score)³¹ and mortality risk (the MDS CHES mortality risk score which incorporates medical activity and treatments along with other domains).³² Scores were converted to categorical variables by severity-based groupings. Facility-level variables included ownership factors, number of beds, hours of certified nursing assistant care and total nursing hours of care per bed per day.

To derive propensity scores, we used bivariate analyses to evaluate the balance of measured covariates between AP-users and non-users. We then used unconditional logistic regression to derive models predicting AP use as a function of these explanatory factors, with propensity scores being the resulting predicted probabilities. A propensity model with all possible two-way interaction terms was selected due to its superior performance, and the Hosmer-Lemeshow goodness-of-fit test was conducted.³³

These propensity scores were then used to create 1:1 matched pairs of AP-users and similar non-users, using the greedy matching algorithm of Parsons.³⁴ Matching was conducted within state, age group, and gender strata so the pairs were perfectly balanced on these three measures. AP-users were discarded if an appropriate non-user match could not be found. After matching, the AP-User and non-user groups were re-evaluated to assure equalization of the previous differences between groups.²⁴

For drug-drug comparisons in AP users only, we used the same variables to calculate a new propensity score that modeled the likelihood for any individual AP user to have received a SGAP. These propensity scores were incorporated into fracture outcome analyses for purposes of covariate adjustment among AP users.

Outcome Analyses—Matched 1:1 AP-user/non-user pairs were followed in a time-to-event analysis, starting from the first day of an AP prescription (i.e., the Index Date) after the required washout period. Non-users were also required to have a similar period of observed time prior to the start date, in order to assure that both members of the pair had a similar opportunity to contribute follow-up time. Subjects were followed until a first fracture event and were right-censored if they died, were hospitalized for 30 days for reasons other than fracture, were discharged from the NH, ceased to be Medicaid or Medicare eligible, or if the AP-user in the pair stopped receiving AP medication for at least one month.

McNemar's test was used to evaluate whether the fracture rate was greater among AP-users than among non-users. Kaplan-Meier curves were generated to visually examine time-to-fracture data. Stratified Cox proportional hazards models were used to analyze survival endpoints, using the propensity-matched pairs as the strata for adjustment for confounding.²⁴ Hazard ratios were derived from these models. Cox proportional hazards

regression models were also used to examine the impact of PDC and dose on fracture outcomes among AP users.

Fracture outcomes were also analyzed by drug class. We derived adjusted hazard ratios for fracture outcomes in SGAP users as compared to FGAP users, adjusted for the propensity to have been an SGAP user. Similarly adjusted models were used to compare fracture outcomes across individual drug groups (risperidone, olanzapine, quetiapine, haloperidol), using haloperidol as the reference group. These analyses were carried out only in subjects who stayed on the same specific AP throughout observation.

Finally, we considered the possibility of barriers to medication ascertainment in subjects who used skilled nursing facility (SNF) days during their observation period; if drugs were provided by Medicare during post-acute care, AP use would not have been ascertainable via Medicaid claims during that time. We conducted a sensitivity analysis by excluding subjects using SNF services during their period of observation, and then repeating all outcome analyses described above.

All data management and analyses were performed using SAS version 9.1.3 (2002-2003, SAS Institute Inc., Cary, NC).

This project was approved by the Institutional Review Board of The University of Kansas Medical Center. The Centers for Medicare & Medicaid Services provided data under Data Use Agreement #16798.

RESULTS

Sample Characteristics

Data files could be linked across all three data sets for 224,764 persons. After application of initial demographic and clinical inclusion/exclusion criteria, 197,514 persons remained. Of these, 130,309 persons had all required data elements needed to calculate a propensity score. The propensity model predicting AP use had a c-statistic of 0.739 with no evidence to suggest problems with goodness of fit ($p=0.136$). After additional exclusions due to prevalent AP use, lack of the necessary washout period prior to AP initiation, and/or lack of a baseline MDS assessment prior to AP initiation, there remained 44,898 persons with complete data. This group was comprised of 4,545 AP-users and 40,353 non-users from which we drew the matched pairs. We excluded 9% (414 out of 4,545) of AP-users for whom no match could be found. The final sample consisted of 4,131 matched 1:1 pairs of AP-users and non-users (total $n=8,262$).

Table 1 demonstrates differences between AP-user and non-user groups prior to matching and shows resolution of those differences after matching. The final AP-users and non-users within the 4,131 matched pairs were similar in demographic, clinical, cognitive, functional, behavioral and NH factors.

Antipsychotic Medication Use

As shown in Table 1, 46% of persons in the matched pairs were aged ≥ 85 years. Women comprised 72% of the sample, and most were cognitively and functionally impaired. Among AP users, 54% received risperidone, 15% received olanzapine, 11% received haloperidol, and 4% received quetiapine. The remaining 16% switched APs during observation or took a variety of rarely used, older FGAPs.

Fracture Outcomes in Matched Pairs—Any fracture occurred in 342 (4.3%) of subjects, with 79 (1%) having a hip fracture. Fractures were associated with AP-use. Any

fracture occurred in 204 AP-users whose matched non-user did not have any fracture; in contrast, any fracture occurred in 138 non-users whose matched AP-user did not have any fracture (McNemar's test, $p < 0.001$). Hip fracture occurred in 52 AP-users whose matched non-user did not have a hip fracture; in contrast, hip fracture occurred in 27 non-users whose matched AP-user did not have a hip fracture (McNemar's test, $p = 0.005$).

Table 2 shows results of the stratified Cox regression models. AP use, compared to non-use, was associated with a hazard ratio (HR) of 1.39 ($p = 0.004$) for any fracture, with higher HRs found when AP exposure was characterized by regularity of use over time (by PDC) or dosage (in chlorpromazine equivalents). A similar pattern was seen for hip fracture (HR=1.76; $p = 0.024$). The highest risk was found for AP use characterized by dosage (HR=2.96; $p = 0.008$), with this HR reflecting the increased risk for hip fracture associated with every 100 mg dose increase in chlorpromazine equivalents.

Fracture Outcomes in Comparator Drug Groups—As shown in Table 3, we found no difference in propensity-adjusted time-to-fracture between FGAP and SGAP users for any fracture (adjusted hazard ratio=1.016; $p = 0.9399$) or for hip fracture (adjusted hazard ratio=0.79; $p = 0.529$). Similarly, no differences were detected in propensity-adjusted time-to-fracture for users of haloperidol, risperidone, olanzapine or quetiapine (overall test across four drugs: $p = 0.825$ for any fracture; $p = 0.529$ for hip fracture). Table 3 also shows individual drug-drug comparisons using haloperidol as the reference group.

Sensitivity Analysis

Finally, the pattern of these results was not altered by the exclusion of subjects who used SNF services (data not shown); this occurred in 13% of the matched pairs.

DISCUSSION

We found that risk for any fracture is ~40% higher among NH residents initiating an AP, compared to otherwise similar persons not taking an AP, when matched on a comprehensive group of confounding factors. For hip fracture specifically, the risk is ~80% higher in AP users than in non-users. Persons with ongoing regular AP use are at even greater risk, as are persons receiving higher AP doses. For each 100 mg increase in chlorpromazine equivalents, there is a ~3-fold increased risk of hip fracture. To place this in clinical context, such a dose increase equates to 2 mg of risperidone, 2 mg of haloperidol, 5 mg of olanzapine, or 75 mg of quetiapine.³⁵

Importantly, we did not detect a difference in fracture rate between FGAP versus SGAP users or among users of the four most commonly used individual APs in propensity-adjusted analyses. These results do not support the widely held clinical notion that SGAPs are safer than FGAPs for fall/fracture risk reduction in NH residents.

Other investigators have studied associations between AP use and fracture using varied study samples, data sources and designs. Cohort studies from NH settings are most relevant. Huybrechts et al found that hip fracture occurred more often during FGAP use than in SGAP use in NH residents in British Columbia; however, functional, cognitive and behavioral data were not available for that analysis.¹² Huybrechts et al also examined numerous important outcomes (hip fracture, myocardial infarction, stroke, bacterial infection, and overall mortality) associated with FGAP and SGAP use in a large cohort study of U.S. nursing homes from 2001-2005, using the same data sources incorporated here.^{36,37} Although the point estimate suggested a trend toward a higher rate of hip fracture in FGAP users as compared to SGAP users (hazard ratio 1.29; CI 0.95-1.76), this finding did not reach statistical significance.³⁷

Other investigators have conducted case-control studies using similar data sources. Liperoti et al used the Systematic Assessment of Geriatric Drug Use via Epidemiology (SAGE) data base to identify a 35-37% increased risk of hip fracture with both SGAP use and FGAP use.¹⁰ Jalbert et al used Medicaid and MDS data to identify an overall 26% increased risk of hip fracture with any AP use, with higher risk associated with longer periods of use.¹¹ Among prevalent AP users, they found an association between hip fracture and SGAP use but a similar trend for FGAP use did not reach statistical significance.

Although each aforementioned paper has methodological strengths, none to date has incorporated all these elements simultaneously, as this study does : a) inclusion of cognitive, functional, and behavioral data, along with facility-level factors; b) a cohort design using propensity-matched AP users and comparable non-users; c) characterization of drug persistence over time; d) a 'new user' design to reduce bias inherent in prevalent user samples; e) standardization of AP dose equivalency across drugs; f) capture of fall-related non-hip fractures in addition to hip fractures; g) sufficient observations of haloperidol use to support its analysis as an individual drug group. This final point is important because haloperidol is the least sedating FGAP and the most likely candidate among FGAPs for use in older adults.

Taken together, the existing literature and the results presented here reaffirm that fracture is associated with AP use but provide no convincing evidence that fracture rates differ meaningfully across APs when detailed cognitive, functional and behavioral person-level data from the MDS are incorporated into the analysis.

LIMITATIONS

Treatment selection bias impacts all observational pharmacoepidemiologic studies. However, when assessing relatively rare events or populations that are difficult to enroll in RCTs, rigorous observational studies constitute essential evidence.^{38,39} We addressed treatment selection bias by incorporating numerous confounders and achieving elimination of measurable differences between AP users and non-users by propensity-based matching. However, unmeasured confounding can never be completely eliminated. Although some investigators advocate the use of high-density propensity scores derived from all available data, we preferred to use literature-based guidance to select variables for inclusion. Recognizing that the quality of MDS variables for research purposes is variable, we chose only variables that were adequately supported by the literature. Differences between the results of this traditional method of propensity score development and that of the newer high-density propensity scores are modest.⁴⁰

An additional limitation is that comorbidity and other adjustment variables were measured only at baseline but are not static measures. Certain clinically important factors could not be captured in these data sources. Although we lacked bone density data, osteoporosis afflicts 85% of 85-year-old women NH residents⁴¹ and would have been unlikely to be differentially distributed among AP-users and non-users. We had no direct measurement of gait and balance, but did use fall history to provide a directly relevant balance-related fracture risk measure.

Our study population was limited to dually-eligible Medicare and Medicaid beneficiaries, but such persons account for more than 50% of the NH population in the United States.¹⁴ Finally, the older age of these 1999 data presents limitations. These APs may be prescribed differently at present than they were in 1999, and newer SGAPs (e.g., ziprasidone, aripiprazole) were not available during our study timeframe.

Clinical Relevance

These results contribute to changing perspectives about the relative risks of FGAPs versus SGAPs. A decade ago, it seemed a foregone conclusion that SGAPs were safer than FGAPs for older adults who required AP treatment.⁶ Subsequently, newer data on adverse metabolic effects of SGAPs began to temper this view. A number of additional AP-associated risks, including increased mortality, cerebrovascular and cardiovascular morbidity, and pneumonia now complicate AP-related prescribing decisions.⁴⁰ The FDA has issued warnings for both FGAPs and SGAPs about increased mortality and morbidity with AP use in older adults with dementia, emphasizing that all such use is off-label.⁴² Despite these risks, a subgroup of NH residents with dementia will require pharmacotherapy to manage distressing psychosis, in the face of limited medication alternatives.

The risk of fracture must be part of this complex prescribing decision because antipsychotic initiation is indeed associated with increased fracture risk in NH residents. However, these results suggest that fracture risk does not differ according to drug class or across the four most commonly used APs. On the other hand, fracture risk does increase with higher dose and with greater regularity of use. Prescribers should use minimal AP doses for the shortest durations possible when non-pharmacologic approaches have failed to manage dementia-related psychosis.

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Table 1

Antipsychotic Users & Non-Users Before and After Propensity-based Matching

		Non-User Pool for potential matching (n=40,353) Column %	Antipsychotic- User Pool for potential matching (n=4,545) Column %	p-value for bivariate test of unmatched groups	Non-User Subjects retained and paired during matching process (n=4,131) Column %	Antipsychotic Users retained and paired during matching process (n=4,131) Column %	p-value for bivariate test of 1:1 Matched groups
		<i>BEFORE MATCHING</i>			<i>AFTER MATCHING</i>		
State		<0.001					*1.0
	CA	32.1	23.8		24.1	24.1	
	FL	21.7	25.3		25.0	25.0	
	MO	10.0	10.9		11.2	11.2	
	NJ	12.7	12.8		12.8	12.8	
	PA	23.5	27.2		26.9	26.9	
Gender	Women	74.5	71.3	<0.001	72.1	72.1	*1.0
Age Group		<0.001					*1.0
	65-69	5.3	5.2		5.2	5.2	
	70-74	9.4	10.3		9.8	9.8	
	75-79	16.1	16.2		15.9	15.9	
	80-84	21.2	23.0		23.5	23.5	
	85-89	23.6	24.8		24.7	24.7	
	90+	24.5	20.5		21.0	21.0	
Race/ethnicity		0.04					0.15
	Black	11.1	10.4		10.8	10.4	
	Other	5.9	5.3		4.3	5.2	
	White	82.9	84.3		84.9	84.4	
Rural/urban		0.03					0.80
	Large metro	61.7	60.2		60.1	60.4	
	Small metro	26.3	27.0		27.4	26.9	
	Non metro	12.0	12.9		12.5	12.8	
Number of comorbidities		<0.001					0.74
	0-1	27.9	22.1		22.6	22.4	
	2-3	37.9	39.8		40.6	39.9	
	4-5	24.1	27.0		26.5	26.6	
	6	10.2	11.2		10.3	11.0	
CHESS mortality risk score		<0.001					0.69
	0	36.9	34.1		35.0	34.1	
	1	32.9	32.9		32.4	32.9	
	2	30.2	33.1		32.6	33.0	
ADL Score		<0.001					0.23
	0-2	32.1	35.8		37.1	35.4	

		Non-User Pool for potential matching (n=40,353) Column %	Antipsychotic- User Pool for potential matching (n=4,545) Column %	p-value for bivariate test of unmatched groups	Non-User Subjects retained and paired during matching process (n=4,131) Column %	Antipsychotic Users retained and paired during matching process (n=4,131) Column %	p-value for bivariate test of 1:1 Matched groups
		<i>BEFORE MATCHING</i>			<i>AFTER MATCHING</i>		
	3-4	30.1	37.9		36.0	37.4	
	5-6	37.8	26.3		26.9	27.2	
Cognitive Performance Score				<0.001			0.52
	0-1	30.2	18.8		19.8	19.2	
	2-3	39.9	51.5		51.5	51.1	
	4	29.8	29.7		28.6	29.7	
Aggressive Behavior Score				<0.001			0.20
	0	78.30	53.3		56.2	54.8	
	1-2	13.9	25.2		24.6	25.2	
	3	7.8	21.5		19.2	20.1	
Dementia diagnosis (yes/no)		47.1	62.1	<0.001	61.2	61.3	0.85
Parkinson's disease (yes/no)		7.3	7.5	0.65	6.9	7.5	0.26
Fell in last 180 days (yes/no)		31.7	41.8	<0.001	41.0	41.5	0.66
Body Mass Index category				<0.001			0.82
	<18.5 (underweight)	14.2	10.8		11.4	10.9	
	18.5-24.9 (normal)	49.7	51.8		51.3	51.8	
	25-29.9 (overweight)	23.4	24.4		24.0	24.4	
	>=30 (obese)	12.8	13.1		13.3	12.9	
Occasional urinary incontinence (yes/no)		5.6	7.3	<0.001	7.4	7.3	0.77
Number of medications				<0.001			0.31
	<5	25.2	21.8		23.2	21.9	
	5-7	30.4	30.4		29.5	30.6	
	8-10	24.2	25.9		24.9	25.8	
	>=11	20.3	22.0		22.4	21.6	
Anxiolytic use				<0.001			0.66
	0 days per week	88.9	76.6		77.6	78.0	
	1-6 days per week	2.5	5.3		4.7	5.0	
	7 days per week	8.6	18.1		17.7	17.0	
Antidepressant use				<0.001			0.64
	0 days per week	72.7	57.4		57.4	58.3	
	1-6 days per week	1.8	2.6		2.4	2.5	
	7 days per week	25.4	40.0		40.2	39.2	
Hypnotic use				0.14			0.25
	0 days per week	95.0	94.7		95.3	94.8	
	1-6 days per week	2.3	2.1		2.1	2.1	

	Non-User Pool for potential matching (n=40,353) Column %	Antipsychotic- User Pool for potential matching (n=4,545) Column %	p-value for bivariate test of unmatched groups	Non-User Subjects retained and paired during matching process (n=4,131) Column %	Antipsychotic Users retained and paired during matching process (n=4,131) Column %	p-value for bivariate test of 1:1 Matched groups
	<i>BEFORE MATCHING</i>			<i>AFTER MATCHING</i>		
7 days per week	2.7	3.2		2.6	3.2	
Type of NH control			0.04			0.88
For profit	70.5	68.7		68.8	69.2	
Government owned	8.2	9.2		9.0	8.8	
Not for profit	21.3	22.2		22.3	22.0	
Multi-facility ownership	58.3	57.6	0.35	57.7	58.0	0.80
Change in facility ownership	46.7	44.5	0.01	43.7	45.3	0.14
Number of beds in facility			<0.001			0.31
<102	25.7	21.8		21.6	22.1	
102-123	24.0	24.6		25.1	24.6	
124-180	26.4	27.0		25.9	27.3	
181	23.9	26.5		27.5	26.1	
3 or more hours per day of certified nurse assistant time per bed (yes/no)	18.4	17.8	0.36	17.2	16.9	0.72
Hours of total nursing staff time per resident per day			0.80			0.79
<3.2	23.6	23.8		23.5	24.3	
3.2-<3.7	25.3	24.6		25.2	24.9	
3.7-<4.2	26.0	26.3		26.9	26.4	
>4.2	25.1	25.2		24.5	24.4	

* After finding all potential matches who shared the same state, gender and age group, we then selected the single non-user whose propensity score was closest to that of each antipsychotic-user, thus creating matched 1:1 pairs.

Table 2

Hazard Ratios for Any Fracture and Hip Fracture in Antipsychotic Users versus Non-Users

	Any Fracture			Hip Fracture		
	Hazard Ratio	95% Confidence Interval	p-value	Hazard Ratio	95% Confidence Interval	p-value
Matched AP Users versus Non-Users	1.39	1.11-1.75	0.004	1.76	1.08-2.87	0.024
Antipsychotic Use characterized by proportion of days covered (PDC) *	1.54	1.17-2.02	0.002	2.31	1.30-4.12	0.005
Antipsychotic Dosage as standardized 'chlorpromazine equivalents' **	1.45	1.12-1.88	0.004	2.96	1.33-6.57	0.008

Hazard ratios and corresponding p-values were generated from stratified Cox proportional hazards regression models. Antipsychotic-users were pair-matched with non-users based on the propensity to be an antipsychotic user in order to adjust for patient-level and facility-level factors.

* Hazard ratio reflects the risk of fracture for a PDC=1 (reflecting daily AP use) as compared to 0 (reflecting non-use).

** Hazard ratio reflects the risk of fracture associated with every 100 mg increase in chlorpromazine equivalents.³⁵

Table 3

*Adjusted Hazard Ratios for Any Fracture and Hip Fracture in Users of Different Antipsychotic Medications

	Any Fracture			Hip Fracture		
	*Adjusted Hazard Ratio	95% Confidence Interval	p-value	*Adjusted Hazard Ratio	95% Confidence Interval	P-value
By Drug Class:						
First-generation ('typical') antipsychotic	Reference Group			Reference Group		
Second-generation ('atypical') antipsychotic	1.02	0.67-1.53	0.940	0.79	0.39-1.63	0.529
By Individual Medications:						
Haloperidol	Reference Group			Reference Group		
Risperidone	0.91	0.56-1.49	0.713	0.59	0.23-1.34	0.205
Olanzapine	1.03	0.58-1.83	0.916	0.77	0.29-2.02	0.591
Quetiapine	1.20	0.54-2.67	0.658	1.02	0.26-3.94	0.980

* Hazard ratios and corresponding p-values were generated from Cox proportional hazards regression models, adjusted for the propensity for second-generation antipsychotic medication use, based upon demographic factors (state, age, gender, rural/urban residence, race/ethnicity), clinical factors (comorbidity, number of medications, dementia, Parkinson's disease, fall history, body mass index, urinary incontinence, use of anxiolytic, antidepressant, and/or hypnotic medications, cognitive performance, activities of daily living score, aggressive behavior score, and mortality risk score), and nursing home factors (type of nursing home control, multi-facility ownership, change in ownership, number of beds, hours of certified nursing care per bed per day, and total nursing hours per bed per day).