THE GERONTOLOGICAL SOCIETY OF AMERICA®

*Journals of Gerontology: Medical Sciences*
cite as: *J Gerontol A Biol Sci Med Sci*, 2017, Vol. 72, No. 5, 695–702
doi:10.1093/gerona/glw095
Advance Access publication May 31, 2016

OXFORD

Research Article

# Fall and Fracture Risk in Nursing Home Residents With Moderate-to-Severe Behavioral Symptoms of Alzheimer's Disease and Related Dementias Initiating Antidepressants or Antipsychotics

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Received September 27, 2015; Accepted May 10, 2016

**Decision Editor:** Stephen Kritchevsky, PhD

## Abstract

**Background:** Both antidepressants and antipsychotics are used in older adults with behavioral symptoms of Alzheimer's disease and related dementias. Despite the prevalent use of these agents, little is known about their comparative risks for falls and fractures.
**Methods:** Using 2007–2009 Medicare claims data linked to Minimum Data Set 2.0, we identified new users of antidepressants and antipsychotics among nursing home residents with Alzheimer's disease and related dementias who had moderate-to-severe behavioral symptoms. Separate discrete-time survival models were used to estimate risks of falls, fractures, and a composite of both among antidepressant group versus antipsychotic group.
**Results:** Compared to antipsychotic users, antidepressant users experienced significantly higher risk for fractures (adjusted hazard ratio = 1.35, 95% confidence interval = 1.10–1.66). The overall risk of falls or fractures remained significant in the antidepressant versus antipsychotic group (adjusted hazard ratio = 1.16, 95% confidence interval = 1.02–1.32).
**Conclusions:** Antidepressants are associated with higher fall and fracture risk compared to antipsychotics in the management of older adults with Alzheimer's disease and related dementias who experience moderate-to-severe behavioral symptoms. Clinicians need to assess the ongoing risks/benefits of antidepressants for these symptoms especially in light of the increasingly prevalent use of these agents.

**Keywords:** Falls—Fractures—Antipsychotics—Antidepressants—Alzheimer's disease and related dementia

Each year over two thirds of older adults residing in nursing homes (NHs) receive at least one psychopharmacological medication, notably antipsychotics and antidepressants (1). Prevalent use is due to an increasing number of residents with psychiatric and/or mental illness (1,2), as well as increased prescribing for a broad spectrum of psychiatric and behavioral conditions beyond those approved by the Food and Drug Administration yet considered acceptable by clinical guidelines (2–4). For instance, after a thorough assessment of underlying causes of behavioral symptoms associated with Alzheimer's disease and related dementia (ADRD), antipsychotics and antidepressants are considered viable pharmacological options when nonpharmacological approaches have failed (5–7).

Although beneficial, the use of antidepressants and antipsychotics often presents unintended safety risks, such as falls and fractures. A large body of literature has indicated a strong correlation between psychopharmacological medication use and increased risk of falls or fractures (8–11). Underlying mechanisms for medication-induced falls/fractures remain unclear, but may be mediated through

the influence of medication side effects, including extrapyramidal effects, confusion, sedation, arrhythmia, and/or orthostatic hypotension (8,11). Psychopharmacological medication dose–response and duration–response relationships also are well established in fall/fracture risks, with risks rising with increased doses of antipsychotics (12,13) or antidepressants (9,14), and highest in the first month of medication initiation (9,14,15).

In addition, risks of falls and fractures have been examined between subclasses and across individual agents within antipsychotics or antidepressants. The study results were mixed, with some supporting a fall/fracture risk variation among medication agents or classes (16–18), and others suggesting the contrary (12,13,19).

Although the link between use of antidepressants and antipsychotics and risk for falls/fractures among older adults has been well documented, the comparative risk between these two psychopharmacological classes remains unclear, particularly among ADRD patients with behavioral symptoms, such as aggression, agitation, and psychosis (20). With evidence of increased mortality and morbidity associated with use of antipsychotics (21–23), all psychopharmacological agents are typically reserved for ADRD patients who had moderate-to-severe behavioral symptoms that pose life-threatening danger and cannot be addressed by nonpharmacological strategies (24). Recent reviews of randomized controlled trials suggest that antidepressants provide more benefits and fewer risks than do antipsychotics in the management of behavioral symptoms in patients with dementia. Compared to antipsychotics, antidepressants may be more efficacious in alleviating agitation and aggression symptoms associated with dementia (6,7), have fewer side effects (eg, extrapyramidal symptoms) (6,7), and are associated with reduced risk of mortality (23). Although the clinical evidence favors antidepressants over antipsychotics, the relative risk for major adverse health events, such as falls/fractures, is not well understood between these two classes. Due to the extensive utilization of these medications in this population, there is an increasing need for head-to-head studies that compare their safety profiles.

Using population-based data, this study aims to compare the incidence of falls, fractures, and a composite of both adverse outcomes associated with antipsychotics and antidepressants among NH residents with moderate-to-severe behavioral symptoms associated with ADRD. We focused on moderate-to-severe behavioral symptoms, including verbally abusive, physically abusive, and/or socially inappropriate/disruptive behaviors among individuals with ADRD. These behavioral disturbances may pose a danger to residents or others even with nonpharmacological interventions and, thereby, are considered acceptable conditions for treatment with antidepressants and antipsychotics (24). We seek to provide greater information on the comparative safety profile of antipsychotics and antidepressants in treating behavioral symptoms of ADRD in order to assist prescribers in the optimal use.

## Methods

### Study Design and Source

This retrospective, longitudinal cohort study used a 5% random sample of Medicare beneficiaries with administrative claims data linked to Minimum Data Set (MDS) 2.0 files from 2007 to 2009. Medicare administrative data include claims for Parts A (inpatient), B (physician/supplier), and D (prescription drug) services. MDS 2.0, a federally mandated assessment tool for residents living in Medicare- and/or Medicaid-certified NHs, collects demographic and clinical information, including cognitive and behavioral symptoms, physical functioning, and diagnoses. Each resident receives an MDS assessment at admission, discharge, quarterly intervals, and upon major changes in status (25). The University of Maryland Baltimore Institutional Review Board approved this study.

### Study Sample

The study sample included beneficiaries who (i) resided in a NH for a long stay of ≥101 consecutive days and had evidence of ADRD (*International Classification of Disease, Ninth Revision, Clinical Modification* [ICD-9-CM] codes of 290.0–290.4, 331.0–33.2, 331.7, 797) between 2007 and 2009; (ii) initiated antipsychotic or antidepressant agents (Supplementary Table 1); and (iii) had moderate-to-severe behavioral symptoms in the 6 months before or 3 months after the date of antidepressant or antipsychotic initiation (index date). Moderate-to-severe behaviors symptoms were determined by the presence of ≥4 days of any of three MDS-measured behaviors: verbally abusive (question identifier E4ba), physically abusive (question identifier E4ca), and/or socially inappropriate (question identifier E4da) (26). These behavioral symptoms may pose a threat to individuals and remain so after nonpharmacological interventions. Therefore, these conditions are suggested as appropriate for antidepressant and antipsychotic treatment based on the Centers for Medicare and Medicaid Services guidance for unnecessary medications (24).

To identify long-stay NH residents, we relied on an algorithm that utilized both Medicare claims and MDS 2.0 data and identified a higher proportion of long-stay residents than Medicare claims data alone, when compared to MDS data only (27). This algorithm has been used in several studies (1,28). In this study, we also utilized 2006 Medicare data to determine whether residents discharged in January–March of 2007 qualified as long-stay residents, as well as to ascertain eligibility of pre-NH stay Medicare enrollments among residents whose earliest long-stay NH admission was on January 1, 2007. Residents with a short NH stay (<101 days) were excluded due to lack of Part D prescription data which are bundled into Part A payments (29).

To ensure the completeness of diagnosis and prescription data, residents were excluded if they had discontinuous Medicare Parts A, B, and D enrollment or had Medicare Advantage/Health Maintenance Organization insurance during the 6 months prior to the index date and thereafter until the date of outcome event (fall or fracture) or the end of study period (death, discharge from a NH, or December 31, 2009). Finally, to ascertain incident cases during the follow-up period, we excluded patients who had diagnoses of falls or fractures within 6 months prior to the index date. Based on these inclusion and exclusion criteria, 6,644 eligible beneficiaries were selected from the 5% random sample of national Medicare data.

### Outcome Measure

The primary outcomes of interest were incident fractures, accidental falls, and a composite outcome of a fracture or fall event requiring inpatient or outpatient (eg, physician visit, emergency room visit) care. The composite outcome was assessed because both fracture and fall events are strongly associated with use of psychopharmacological medications (8,10), are important causes of morbidity (9), and their relationship is intertwined and recursive (30). For example, patients who fall may also experience serious injury, such as bone fractures, and bone fractures further put patients at high risk of falls. Our composite measure may reflect the overall risk of falls and fractures associated with antidepressants versus antipsychotics, which provides integrated information for patients, their caregivers and clinicians when making decisions on psychopharmacological treatment for behavioral symptoms of ADRD.

Fall or fracture outcomes were measured using Medicare claims data show a high accuracy of detecting cases with these outcomes, compared to medical records (31,32). We refrained from using MDS files to ascertain outcomes due to the under-reporting of fall cases in such data (33). Fractures were defined as having inpatient or outpatient claims with ICD-9-CM codes of 808.xx (pelvic fracture), 820.xx (upper femur fracture), 821.xx (lower femur fracture), or 733.1x (pathological fracture). We focused on hip/pelvic and lower femur fractures because they were highly associated with psychopharmacological medication use (17). We combined pelvic with hip fractures as a category because pelvic factures occur in the bones that make up the hip area. Accidental falls were defined as inpatient or outpatient claims with ICD-9-CM codes of E880.xx–E889.x.

### Identification of Antipsychotics and Antidepressants

A total of 22 distinct antipsychotics and 29 antidepressants were captured through the Part D prescription drug event file using National Drug Codes (Supplementary Table 1). To perform a head-to-head comparison of two active psychopharmacological medications, we identified two mutually exclusive comparative user groups who received antipsychotics as monotherapy only and antidepressants as monotherapy only.

### Covariates

Baseline covariates measured in the 6 months prior to the index date of medication of interest (ie, baseline) included sociodemographics, comorbidities, indicators of functional, cognitive, and frailty status, hospitalization (yes/no), skilled NH stay (yes/no), and use of anxiolytics and/or sedative-hypnotics (yes/no); we also controlled for pre-index antidepressant and antipsychotic dose and duration of therapy. Sociodemographics included age, sex, race/ethnicity, geographic region, and low-income subsidy status (yes/no). We measured the number of comorbid conditions using Centers for Medicare and Medicaid Services—Hierarchical Condition Categories Risk-adjustment model (34). This risk adjuster produces a person-specific risk score by summing the total count of conditions from 189 diagnostic categories. To control for potential confounding by indication, we measured disease status of delirium, depression, and severe mental illness at baseline. Delirium was identified based on ICD-9-CM diagnostic codes (290.11, 290.3, 290.41, 291.0, 292.81, 293.0, 293.1) and/or MDS assessment items (question identifier B5a-B5f, VA01a) for delirium. Following the prior studies, we defined depressed patients if they had diagnostic codes of depression *or* MDS 2.0 diagnosis plus a Depression Rating Scale score of ≥3 (1,35). Severe mental illness was defined using diagnostic codes of schizophrenia, schizoaffective disorder, and bipolar disorder.

We measured users' physical function, cognitive function, and relevant signs and symptoms with three MDS scales: Activities of Daily Living dependence, MDS Cognition Scale, and Changes in Health, End-stage disease and Symptoms and Signs (MDS-CHESS) scale, respectively. Use of anxiolytics/sedative-hypnotics also was controlled because of their association with increased risk of falls and fractures in older adults (10). Dose and duration of antipsychotic or antidepressant use were measured as time-varying covariates assessed monthly. We operationalized dose exposure using modified standardized daily dose, which compares the mean daily dose of each individual medication against its maximum allowable geriatric dose (1). The dose was then dichotomized as ≤1 or >1, with the latter group being considered above the recommended dose. In the duration measurement, Part A covered hospital and skilled nursing facility days were excluded because prescription claims data during these periods were unobservable.

### Data Analysis

Baseline demographic and clinical characteristics of users of antipsychotics and antidepressants were presented. Differences in characteristics were examined between the user groups using *t* tests (continuous variables) and the chi-squared tests (categorical variables). We also described types of medication classes and medication agents among the users.

To control for time-varying dose and duration exposure, we constructed interval-censored data where medication use and fall/fracture events were assessed for each user and each month of follow-up. Each user contributed the user-months at risk from medication initiation until the occurrence of the first fall or fracture outcome or the end of the follow-up. Patients who experienced both an incident fall and a fracture during the follow-up would contribute person months in the analyses of all three outcomes of interest (ie, falls, fractures, and the composite of outcome measure). For the composite outcome, a fall or a fracture was counted only once, whichever occurred first. To handle time-varying covariates and interval-centered data, we used discrete-time survival regression models with a complementary log–log link to estimate hazard ratios and 95% confidence intervals for outcomes between users with antipsychotics (reference) and antidepressants (36). Separate models were performed for falls, fractures, and overall risk of either adverse outcome. All analyses were performed using SAS 9.2 (SAS Institute, Cary, NC). Statistical significance was set at $p < .05$, and all tests were two tailed.

## Results

Characteristics of monotherapy antipsychotic users and monotherapy antidepressant users were different in most respects in this study cohort (Table 1). Compared to antipsychotic users, antidepressant users tended to be older, female, white race/ethnicity, non-low-income subsidy recipients, and have depressive symptoms and unstable health (MDS-CHESS ≥ 2). However, antidepressant monotherapy users were less likely to have severe mental illness, delirium, cognitive impairment (MDS Cognition Scale ≥ 7), functional impairment (activities of daily living dependence ≥ 22), skilled nursing stays, and use of anxiolytics/sedative-hypnotics at baseline. In addition, in any given month, antidepressant users had a longer duration of medication use and tended to receive medication dose within recommended maximum thresholds for older adults, compared with antipsychotic users.

Nearly 90% of users who initiated antipsychotics used atypical agents; of these, over one-third used either quetiapine or risperidone (Table 2). Most users who initiated antidepressants as monotherapy used selective serotonin reuptake inhibitor agents, followed by alpha antagonists and tricyclic antidepressants.

Among residents with moderate-to-severe behavioral symptoms of ADRD, there were 1,040 fall and 529 fracture events during the follow-up period (Table 3). The multivariate regression results showed that compared to residents initiating antipsychotics, those starting antidepressants had a higher but nonsignificant risk of falls (adjusted hazard ratios = 1.12, 95% confidence interval = 0.97–1.29), but experienced a significantly increased risk of incident fractures (adjusted hazard ratios = 1.35, 95% confidence interval = 1.10–1.66). When considering overall risk of either falls or fractures, a similar result was observed with a higher risk

**Table 1.** Characteristics of New Users of Antipsychotic Monotherapy and Antidepressant Monotherapy Among Alzheimer's Disease and Related Dementia Patients With Moderate-to-Severe Behavioral Symptoms

| Baseline* Characteristics | Total Sample | Antipsychotic Monotherapy Users | | Antidepressant Monotherapy Users | | *p* Value† |
|---|---|---|---|---|---|---|
| Sample Size | *N* | *n* | % | *n* | % | |
| | 6,644 | 1,964 | 100 | 4,680 | 100 | |
| Age | | | | | | |
| Mean, SD | 82.9 (8.9) | 82.7 (9.4) | | 83.0 (8.7) | | |
| ≤64 | 210 | 81 | 4.1 | 129 | 2.8 | |
| 65–74 | 775 | 229 | 11.7 | 546 | 11.7 | |
| 75–84 | 2,476 | 745 | 38.4 | 1,721 | 36.8 | |
| 85+ | 3,184 | 900 | 45.8 | 2,284 | 48.8 | .008 |
| Female sex | 4,847 | 1,385 | 70.5 | 3,462 | 74.0 | .004 |
| Race | | | | | | |
| White | 5,330 | 1,481 | 75.5 | 3,849 | 82.2 | |
| Black | 1,031 | 388 | 19.8 | 643 | 13.7 | |
| Others‡ | 283 | 95 | 4.8 | 188 | 4.0 | <.001 |
| Region | | | | | | |
| Northeast | 1,460 | 413 | 21.0 | 1,047 | 22.4 | |
| North Central | 1,854 | 543 | 27.7 | 1,311 | 28.0 | |
| South | 2,657 | 793 | 40.4 | 1,864 | 39.8 | |
| West | 673 | 215 | 11.0 | 458 | 9.8 | .370 |
| Low-income subsidy | 5,702 | 1,22 | 87.7 | 3,980 | 85.0 | .005 |
| Number of comorbid conditions (Mean, *SD*) | 3.6 (3.4) | 3.4 (3.4) | | 3.7 (3.4) | | .696 |
| Depression | 2,152 | 449 | 22.9 | 1,703 | 36.4 | <.001 |
| Severe mental illness | 1,523 | 693 | 35.3 | 830 | 17.7 | <.001 |
| Delirium | 1,814 | 604 | 30.8 | 1,210 | 25.9 | <.001 |
| MDS Cognition Scale | | | | | | |
| 0–3 | 353 | 58 | 3.0 | 295 | 6.3 | |
| 4–6 | 4,726 | 1,301 | 66.2 | 3,425 | 73.2 | |
| 7–10 | 1,565 | 605 | 30.8 | 960 | 20.5 | <.001 |
| Activities of daily living dependence | | | | | | |
| 0–7 | 950 | 290 | 14.8 | 660 | 14.1 | |
| 8–14 | 1,301 | 403 | 20.5 | 898 | 19.2 | |
| 15–21 | 2,541 | 695 | 35.4 | 1,846 | 39.4 | |
| 22–28 | 1,852 | 576 | 29.3 | 1,276 | 27.3 | .021 |
| MDS-CHESS scale | | | | | | |
| 0 | 285 | 98 | 5.0 | 187 | 4.0 | |
| 1 | 4,065 | 1,222 | 62.2 | 2,843 | 60.8 | |
| 2–5 | 2,294 | 644 | 32.8 | 1,650 | 35.3 | .047 |
| Any hospitalization | 3,400 | 979 | 49.9 | 2,421 | 51.7 | .161 |
| Any skilled nursing stay | 3,207 | 1,003 | 51.1 | 2,204 | 47.1 | .003 |
| Any AXSH use | 608 | 183 | 9.3 | 425 | 9.1 | .760 |
| Monthly medication dose | | | | | | |
| mSDD ≤ 1 | 6,020 | 1,625 | 82.7 | 4,395 | 93.9 | |
| mSDD > 1 | 624 | 339 | 17.3 | 285 | 6.1 | <.001 |
| Days of medication use per month (mean, *SD*) | 18 (9) | 16 (9) | | 19 (8) | | <.001 |

*Notes:* AXSH = anxiolytics and sedative-hypnotics; CHESS = Changes in Health, End-stage disease and Symptoms and Signs; MDS = Minimum data set; mSDD = Modified standardized daily dose.

*Baseline = 6 months prior to the date of the first recorded antipsychotics or antidepressants.

†Differences between antipsychotic and antidepressant users.

‡Other included Hispanic, Asian, the natives of North American, and individuals with other or unknown races and ethnicities.

in the antidepressant versus antipsychotic group (adjusted hazard ratios = 1.16, 95% confidence interval = 1.02–1.32).

## Discussion

Using data from 2007 to 2009 Medicare claims linked to MDS 2.0, this study assessed the comparative safety of two commonly used psychopharmacological medications—antipsychotics and antidepressants—in Medicare long-stay NH residents with ADRD-related behavioral symptoms. Our findings suggest use of antidepressants may be associated with higher risk of fractures, compared to antipsychotic use. The overall risk of fractures and falls was higher in the antidepressant group. To our knowledge, this study is among the first to address this important clinical issue.

The mechanisms for higher risk of fractures or injurious accidental falls with antidepressants among ADRD patients with moderate-to-severe behavioral symptoms are unclear. Although both psychopharmacological medication classes share several similar adverse effects contributing to falls/fractures (eg, sedation, orthostatic hypotension, and cardiac arrhythmia), at least one recent study suggests these side

**Table 2.** Patterns of Antipsychotic and Antidepressant Treatment Among the Study Sample

| Antipsychotic Monotherapy, *n* = 1,964 (100%) | | Antidepressant Monotherapy, *n* = 4,680 (100%) | |
|---|---|---|---|
| Any typical agents | 414 (21.1) | Any selective serotonin reuptake inhibitors | 2,894 (61.8) |
| Haloperidol | 346 (83.6) | Escitalopram | 942 (32.6) |
| Others | 73 (17.7) | Sertraline | 779 (26.9) |
| Any atypical agents | 1,748 (89.0) | Paroxetine | 224 (7.7) |
| Quetiapine | 783 (44.8) | Fluoxetine | 214 (7.4) |
| Risperidone | 758 (43.4) | Others | 7 (0.2) |
| Olanzapine | 287 (16.4) | Any alpha antagonists (mirtazapine) | 1,677 (35.8) |
| Others | 162 (9.3) | Any tricyclic antidepressants | 1,128 (24.0) |
| | | Clomipramine | 987 (87.5) |
| | | Amitriptyline | 75 (6.7) |
| | | Others | 87 (7.7) |
| | | Any serotonin antagonists | 480 (10.2) |
| | | Trazodone | 480 (10.0) |
| | | Any other agents | 505 (10.8) |

effects may be more pronounced with antidepressants than antipsychotics (8). A meta-analysis showed the odds ratios of fractures ranged from 1.71 to 1.94 for antidepressant users, as opposed to 1.30–1.68 for antipsychotic users (both compared to nonusers) among older adults (8). These studies, however, did not directly compare antidepressants and antipsychotics, likely due to the differences in disease conditions for which the two psychopharmacological classes are prescribed. In our study, we were able to make a head-to-head comparison among ADRD patients with moderate-to-severe behavioral symptoms managed by antipsychotics or antidepressants.

Our study noted significant differences in several characteristics between antipsychotic and antidepressant users. Compared to residents taking antipsychotic monotherapy, those with antidepressant monotherapy were more likely to be older, white, female, and suffer from depression and unstable health, features that may put them at risk for falls/fractures. On the other hand, antipsychotic monotherapy users tended to be low-income recipients with severe mental illness and delirium, poor cognitive and physical function, and high antipsychotic dose exceeding the clinical recommended level. These factors also contribute to fall/fracture risk in antipsychotic users. After adjusting for the differences in baseline characteristics, our study concluded that antidepressant use was associated with a higher risk of falls and fractures, compared to antipsychotic use for moderate-to-severe behavioral symptoms of ADRD.

Our study possessed several elements essential for comparative safety research. First, we selected new medication users and followed new fall/fracture events, an optimal approach that minimizes residual effects of prior medication use and outcome event on subsequent medication use and outcomes. Although this design inevitably limits generalizability to new antipsychotic or antidepressant users who had a long stay in Medicare- and/or Medicaid-certified NH facilities, it preserves the internal validity of our comparative findings. As well, we adjusted for antidepressant and antipsychotic dose and their duration of use, which are often ignored in other studies. We further controlled for use of anxiolytics and sedative-hypnotics covered by the Part D plans, as these are highly associated with an increased risk of falls/fractures (10). That said, some noncovered Part D medications (eg, benzodiazepines) were unable to be identified and controlled in the study. In addition, we controlled several conditions clinically indicated for treatment by psychopharmacological medications and which also are established risk factors for falls/fractures, in an effort to reduce potential bias from confounding by indication. Finally, we used a novel approach where time to the first fall/facture was monthly interval censored. This method allows for assessing and including time-varying confounders (eg, medication dose/duration) in the regression models, and thus provides more accurate estimates of the parameters of interest. Future research is needed to explore the comparative safety of combinations of psychopharmacological medications to better understand the risk profiles of these medications.

Our findings provide new information on the comparative safety of the psychopharmacological treatment options available for NH residents suffering from behavioral symptoms that often occur with ADRD. Several psychopharmacological medications, including antipsychotics and antidepressants, are recommended when patients' behavioral and psychological symptoms persist and fail to be addressed by nonpharmacological therapy (5–7). To our understanding, no guidelines have provided specific guidance on which psychopharmacological agents to use for which specific behaviors in dementia patients. The general rule to decide whether to use one therapeutic agent over another depends on a clinical evaluation of underlying conditions and an assessment of benefits and risks of the treatment in the individual patient (3,4).

To better understand the comparative safety and efficacy of psychopharmacological treatment, many clinical studies have been undertaken. Recent reviews of clinical trials concluded that antidepressants appear more efficacious and better tolerated than antipsychotics in managing the behavioral symptoms in dementia patients (6,7). Despite the potential clinical benefits, use of these medications has been implicated for increased risk of falls and fractures, with antidepressants potentially having a poorer safety profile, as suggested by our study findings. Given that antipsychotics have been under federal warnings and scrutiny (37–39), antidepressants may be considered as an alternative in the management of patients with neuropsychiatric symptoms of dementia (40). Nevertheless, our study suggests that antidepressant medications may pose a higher risk for falls and fractures than antipsychotics. The risks of both antidepressants and antipsychotics should be carefully weighed against their potential treatment benefits.

This study shares several limitations common in observation studies, especially those using administrative data. First, the problem of confounding by indication is persistent in pharmacoepidemiology studies. To minimize this potential bias, we restricted our study population to those with moderate-to-severe behavioral symptoms of ADRD only. The majority of the study sample presented more than one of the three studied behavioral disturbances (ie, exhibited verbally abusive, physically abusive, and/or socially inappropriate/disruptive behaviors) and were treated by antipsychotics or antidepressants, both

**Table 3.** Incident Fracture Events, Accidental Falls, or a Composite of Either Events Associated With Antidepressant Monotherapy, Compared With Antipsychotic Monotherapy

| Outcomes | Total Sample ($n$ = 6,644 users) | | | Antipsychotic Monotherapy ($n$ = 1,964 users) | | | | | Antidepressant Monotherapy ($n$ = 4,680 users) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Number of Events | User-months | Rate per 1,000 User-months | Number of Events | User-months | Rate per 1,000 User-months | Hazard Ratio (95% CI) | | Number of Events | User-months | Rate per 1,000 User-months | Hazard Ratio (95% CI) | |
| | | | | | | | Unadjusted | Adjusted* | | | | Unadjusted | Adjusted* |
| Falls | 1,040 | 83,105 | 12.5 | 296 | 24,419 | 12.1 | 1.00 | 1.00 | 744 | 58,686 | 12.7 | 1.05 (0.91–1.20) | 1.12 (0.97–1.29) |
| Fractures | 529 | 87,206 | 6.1 | 136 | 25,629 | 5.3 | 1.00 | 1.00 | 393 | 61,577 | 6.4 | 1.20 (0.99–1.46) | 1.35 (1.10–1.66) |
| Falls or fractures | 1,287 | 80,578 | 16.0 | 355 | 23,745 | 14.9 | 1.00 | 1.00 | 932 | 56,833 | 16.4 | 1.10 (0.97–1.24) | 1.16 (1.02–1.32) |

*Notes:* CI = confidence interval.
*Adjusted covariates are listed in Table 1.

of which are recommended by clinical guidelines to treat these behavioral symptoms. Because all psychopharmacological medications can be used for all symptoms without restriction to specific behaviors, medication choice is less likely due to patients' behaviors. The selection of the medications, however, may be more related to factors, such as patients' underlying conditions (eg, depression), and depression is also a risk factor of falls and fractures. To address this concern, we have adjusted several potential indications, including depression and delirium, which might confound our study findings.

The second limitation of this study is that early discontinuation or nonadherence to medication regimens may affect the treatment effect, thereby introducing bias to our results. In general, adherence to medications is high in NHs, with contracted pharmacies providing drug supplies only upon written physician orders, administration only by staff, and citations and possible fines for infractions (41). We examined the proportion of antipsychotic or antidepressant users who stopped these medications between cohort months and found it to be very small (<1%). Third, serious fall/fracture events may be under-ascertained if not recorded in Medicare claims data. Nevertheless, the accuracy of claims data for capturing falls/fractures is high when compared to medical records (31,32). Fourth, residual confounding may remain due to claims data lacking information on potential confounders, such as disease severity, medication tolerability and treatment failure. These omitted variables can potentially bias our estimates either toward or away from the null, depending upon the relationship of these confounders to medication exposure and outcomes. Lastly, our study that measured fall and fracture events at the monthly, rather than daily level and, as such, was unable to examine the acute risk of falls or fractures within a few weeks of antipsychotic or antidepressant initiation. Previous NH studies have suggested that a psychopharmacological medication initiation or change may signal an acute period of heightened risk for falls (42,43). Future studies that investigate the acute risk of falls or fractures between different psychopharmacological classes are warranted.

In conclusion, monotherapy antidepressant use is associated with higher risk of fractures and falls, compared to monotherapy antipsychotic use, among NH residents with ADRD who had moderate-to-severe behavioral symptoms. Clinicians need to assess the ongoing risks/benefits of antidepressants for moderate-to-severe behavioral symptoms of ADRD especially in light of their increasingly prevalent use. This study like others indicates the need for additional research to look at the ongoing dilemmas with the new as well as chronic use of psychopharmacological medications in older adults.

## Supplementary Material

Supplementary material can be found at: http://biomedgerontology.oxfordjournals.org/

## Funding

This research was funded by the Research Retirement Foundation (Contract Grant no. 2011-107). The funding agency has no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

## Acknowledgments

The authors gratefully acknowledge Christine Franey and Lori Walker of the Pharmaceutical Research Computing Center at the University of Maryland

School of Pharmacy for their assistance in constructing analytic files and providing technical assistance.

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