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Non-benzodiazepine sleep medications and hip fractures in nursing home residents

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Abstract

Background—It is important to understand the relationship between sleep medications and injurious falls in nursing home residents. We conducted a case-crossover study to estimate the association between non-benzodiazepine hypnotic drugs (zolpidem, eszopiclone, zaleplon) and risk of hip fracture among a nationwide sample of long-stay nursing home residents, overall and stratified by functional and facility level characteristics.

Methods—Participants included 15,528 long-stay U.S. nursing home residents aged ≥ 50 years with a hip fracture (7/1/2007–12/31/2008) in fee-for-service Medicare Parts A & D. Odds ratios (ORs) of hip fracture were estimated using conditional logistic regression models by comparing possession of non-benzodiazepine hypnotic drugs during the 0–29 days before the hip fracture (hazard period) with possession during the 60–89 and 120–149 days before the hip fracture (control periods). Analyses were stratified by individual and facility characteristics.

Results—Among participants, 1,715 (11%) were prescribed a non-benzodiazepine hypnotic before the hip fracture, with 927 exposure-discordant pairs included in the analyses. Mean age was 81 years (± 10 years), and 78% were female. Risk of hip fracture was elevated among users of a non-benzodiazepine hypnotic (OR 1.66; 95% CI 1.45, 1.90). The association between non-benzodiazepine hypnotics and hip fracture was somewhat greater in new users (OR 2.20; 95% CI 1.76, 2.74) and in residents with mild versus moderate-severe impairment in cognition (OR 1.86 vs. 1.43; p=0.06), moderate versus severe functional impairment (OR 1.72 vs. 1.16; p=0.11), limited versus full assistance with transfers (OR 2.02 vs. 1.43; p=0.02), or in a facility with fewer Medicaid beds (OR 1.90 vs. 1.46; p=0.05).

Conclusions—Risk of hip fracture is elevated among nursing home residents using a non-benzodiazepine hypnotic. New-users and residents with mild-moderate cognitive impairment or requiring limited assistance with transfers may be most vulnerable to these drugs. Caution should be used when prescribing sleep medications to nursing home residents.

Background

In 2006 Medicare Part D instituted a restrictive policy that excluded benzodiazepines from mandatory drug coverage. Following Medicare's restriction of benzodiazepine coverage, non-benzodiazepine sleep medications, such as zolpidem, have been increasingly used to manage insomnia in U.S. nursing homes.[1] Although initially believed to be safer than

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benzodiazepines with respect to fall risk, a case-control study demonstrates that use of non-benzodiazepine hypnotics is associated with a 2-fold increased risk of hip fracture,[2] and a retrospective cohort study suggests that non-benzodiazepine hypnotic initiation is associated with a 1.7–2.2 times greater risk of fracture as compared with short-acting benzodiazepines.[3]

Despite the suggestion of harm from these studies, it is possible that these results can be partly explained by intrinsic differences between persons prescribed a sleep medication as compared with persons without a sleep medication. It is important to understand whether sleep medications themselves are associated with an increased risk of fracture because withholding hypnotics may also have detrimental consequences: in a large cohort study of nursing home residents there was a stronger association between untreated insomnia and falls as compared with insomnia effectively treated with a hypnotic drug.[4]

In order to address these uncertainties, we examined the association between non-benzodiazepine hypnotics and risk of hip fracture using a *self-controlled*, case-crossover study design among 15,528 national long-stay nursing home residents. We additionally stratified analyses by individual characteristics (i.e., cognitive performance, functional status, ability to transfer, urinary incontinence, and restraint use) and facility level characteristics (i.e., high resident to staff ratio and % Medicaid beds) in order to identify subgroups that are at greatest risk for hip fracture when using a non-benzodiazepine hypnotic.

Methods

Subjects

For our source population, Medicare Part A and Part D claims were linked to nursing home resident assessments using unique, individual identifiers.[5] Among more than 9 million patients identified with a Medicare Fee-for-service Part A claim (7/1/2007 – 12/31/2008), we identified 127,917 with the diagnosis of hip fracture (Figure 1). Of those patients, 127,253 (99%) were enrolled in Medicare for a minimum of 6 months, and 23,882 resided in a nursing home during the 6 months before the diagnosis of hip fracture. Included in our sample were 15,626 participants (65%) who were enrolled in Medicare Part D with complete prescription drug information. We additionally excluded 98 participants aged < 50 years for a final sample size of 15,528 participants.

Case-Crossover Study Design

The case-crossover design was specifically developed to assess the effects of a transient exposure on an acute event.[6] Exposure during a relevant period of time preceding the event (hazard period) is compared with exposure during periods of time without an event (control period) *in the same individual*. In our study, we compared exposure (i.e., possession of non-benzodiazepine hypnotic drugs) during the 0–29 days before the hip fracture (hazard period) with exposure during the 60–89 and 120–149 days before the hip fracture (control periods) *for each participant* (Figure 2). By comparing subjects to themselves, the potential effects of time-fixed, unmeasured confounders between participants using and not using the drug are eliminated. It remains possible that a change in severity of illness within a person (i.e., worsening insomnia) contributed to both dispensing of the drug and risk of hip fracture.

Hip fracture

Hip fractures were ascertained through Medicare Part A claims data, and defined as the first hospitalization with ICD-9 diagnosis of 820.xx (fracture of the neck of femur) or 733.14 (pathologic fracture of neck of femur) in the presence of a procedure code for surgical repair

during hospitalization.[7] The estimated positive predictive value using this definition is 98%, and similar definitions have yielded a sensitivity of 96%.[8]

Non-benzodiazepine sedative use

Dispensings of a non-benzodiazepine hypnotic drug (i.e., zolpidem, eszopiclone, zaleplon) were ascertained using Medicare Part D pharmacy claims. For the primary analysis, we defined possession if the date of dispensing of the hypnotic drug plus the days supplied fell within the hazard or control periods.

We also considered the effect of "new use" of a non-benzodiazepine hypnotic drug on risk of hip fracture. "New use" was defined as a drug dispensing that occurred without drug possession in the preceding 60 days, but with more remote possession possible. Although use of non-benzodiazepine hypnotics was intermittent for all subjects who contributed to the estimation of odds ratios, only a subset of patients were "new users" during the hazard or control period.

Resident characteristics

The Minimum Data Set is an instrument designed to measure quality and assess the individual needs of nursing home residents.[9] The federal government mandates completion of the MDS for all residents in a Medicare or Medicaid certified nursing facility at the time of admission, and then quarterly thereafter. The MDS is generally considered to be reliable and valid.[10–11]

All resident characteristics, including those to define subgroupings, were ascertained from the MDS assessment (version 2.0) closest to and preceding the control periods. Cognitive performance was ascertained using the validated Cognitive Performance Scale[12] and categorized as normal or mild impairment (0–2) versus moderate to severe impairment (3–6). Functional status was ascertained using the validated ADL long scale[13] and categorized as mild (score 0–7), moderate (score 8–20), or severe impairment (score 21–28). Ability to transfer was categorized as independent (score 0), requiring supervision or limited assistance (score 1–2), or requiring extensive or full assistance with transfers (score 3–4, 8). Residents who were always continent or always incontinent of urine were grouped together versus residents that were intermittently incontinent. Bed restraint use was considered as any use of a bed or side rail in the past 7 days.

Facility characteristics

The Online Survey, Certification, and Reporting database (OSCAR) contains facility characteristics as obtained by a Department of Public Health surveyor. Estimates of facility characteristics using OSCAR are similar to data from the 1995 National Nursing Home Survey.[14] For our study, facility level characteristics were obtained using the OSCAR measure closest to and preceding the control periods and included the following characteristics categorized as above or below the national median: resident to staff ratio [total of registered nursing (RN), licensed practical nurse (LPN), and certified nursing assistant (CAN) hours per resident per day] and percent Medicaid beds.

Statistical analysis

In the analysis of case-crossover studies, subjects that are exposed in either the hazard or control periods, but not during both periods, contribute to the estimate of the odds ratio.[6] We used conditional logistic regression models (SAS version 9.2, SAS Institute, Cary, N.C.) to estimate odds ratios (OR) and 95% confidence intervals (CIs) of the risk of hip fracture in the 30 days following possession of a non-benzodiazepine hypnotic drug, as compared with

periods of time without possession of a non-benzodiazepine hypnotic drug. The resulting odds ratio is interpretable as an incidence rate ratio.

Because results of the case-crossover method can be sensitive to the classification of exposure, we considered an alternative, pre-specified hazard period (0–14 days before the hip fracture), with corresponding control periods of 30–44 and 60–74 days before the hip fracture.

We performed analyses overall, and stratified by individual and facility level characteristics. For comparison of OR within subgroups, we used the difference in the log odds ratio between strata to calculate a Z-score and p-values.

Sensitivity analyses

We conducted two sensitivity analyses to test the validity of our findings. First, we addressed the concern that drugs that affect the risk of hip fracture (e.g., antidepressants) could be co-prescribed more often with non-benzodiazepine hypnotics as compared with non-use.[15] To determine the degree of confounding that can be present by concomitant use of an antidepressant,[16] we estimated the prevalence of exposure to non-benzodiazepine hypnotics from our data (15%), the prevalence of antidepressant use in the source data (38%, state-level median),[17] and we identified the association between antidepressant use (SSRIs) and the risk of hip fracture from the literature (OR: 2.0).[18]

Second, the case-crossover method will provide spurious ORs when the prevalence of the exposure (i.e., non-benzodiazepine hypnotic drug use) changes over the observation period, as might occur when use of the drug increases in the general population. To understand the potential impact of this concern, we estimated the daily dispensing prevalence of non-benzodiazepine hypnotics among patients without a hip fracture who otherwise met eligibility criteria. These patients were assigned an index date sampled from index dates across calendar time in the case series. We then estimated the mean prevalence of use of non-benzodiazepine hypnotics during the index hazard and control periods for each resident without a hip fracture, and calculated the mean difference of the prevalence estimates between hazard and control periods for each case.

Results

Of the 15,528 long-stay nursing home residents with hip fracture, 1,715 (11.0%) were dispensed a non-benzodiazepine hypnotic. Characteristics of participants that used a non-benzodiazepine hypnotic in the hazard or control periods, but not in both periods, are shown in Table 1. The mean age of participants was 81.0 yrs (± 9.7 yrs), and 77.6% were female. There was a high prevalence of selected comorbidities, ranging from 6.8% for anemia to 49.9% for depression. Nearly 40% of participants had moderate to severe cognitive impairment, and 65.4% had moderate impairment in ADLs. The mean number of RN/LPN/CNA hours per resident per day was 3.4 (± 1.2 hours).

The risk of hip fracture within 30 days of possessing a non-benzodiazepine hypnotic was elevated (OR: 1.66, 95% CI 1.45, 1.90; Table 2). This elevated risk was similar when the hazard period was shortened to 15 days (OR: 1.47, 95% CI 1.24, 1.74). When new-users of a non-benzodiazepine hypnotic were considered separately, risk of hip fracture was greatest in the first 15 days (OR: 2.2, 95% CI 1.76, 2.74).

There was a trend towards an increased risk of hip fracture among non-benzodiazepine hypnotic users with normal or mild impairment in cognition (Table 3; OR: 1.86, 95% CI 1.56, 2.21) compared to residents with moderate to severe impairment (OR: 1.43, 95% CI

1.15, 1.77; p=0.06 for comparison). Residents with moderate impairment in ADLs (OR: 1.71, 95% CI 1.44, 2.02) tended to be at greater risk for hip fracture when using a hypnotic drug compared to residents with severe ADL impairment (OR: 1.16, 95% CI 0.75, 1.79; p=0.11 for comparison). Residents who used a hypnotic and required limited assistance with transfers (OR: 2.02, 95% CI 1.65, 2.48) tended to be at greater risk for hip fracture as compared to residents who were independent (OR: 1.46, 95% CI 1.06, 2.01; p=0.09 for comparison) or required full assistance with transfers (OR: 1.43, 95% CI 1.14, 1.79; p=0.02 for comparison). There was no difference in the risk of hip fracture among hypnotic users when stratified by bladder incontinence or bed restraint use.

Residents using a non-benzodiazepine hypnotic in a facility with fewer Medicaid beds (OR: 1.90, 95% CI 1.57, 2.31) were at a greater risk of hip fracture compared with residents in a facility with more Medicaid beds (OR: 1.46, 95% CI 1.20, 1.77; p=0.05 for comparison). There was little difference in the risk of hip fracture among hypnotic users when stratified by resident to staff ratio.

Sensitivity analysis

Under the assumptions described in the methods, for confounding by time-dependent use of antidepressants to explain the primary effect of non-benzodiazepine hypnotics on hip fracture (OR: 1.66), antidepressants must have been >10 times more commonly used during periods of non-benzodiazepine hypnotic drug use relative to periods of non-use. Given the high baseline prevalence of antidepressant use (median 38%), this difference across time periods is implausible, and confounding by antidepressant use could not explain the observed OR.

As shown in Figure 3, there were no temporal trends in non-benzodiazepine hypnotic use across the source population (Panel B), while there was an increase in the prevalence of hypnotic use in the 30 days prior to the hip fracture date (Panel A). Thus, temporal trends in hypnotic drug use could not explain the observed OR.

Discussion

Our results from a large sample of U.S. long-stay nursing home residents demonstrate a 66% increased risk of hip fracture within 30 days of using a non-benzodiazepine hypnotic drug. The risk of hip fracture appears to be greatest in the first 15 days among new-users. Residents requiring limited assistance with transfers appear to be particularly vulnerable to hypnotic drug use with respect to risk of hip fracture. Although not statistically significant, residents with normal or mild impairment in cognition and residents with moderate functional impairment also appear to be more vulnerable to these drugs.

Our results are consistent with prior studies. In a case-control study, use of zolpidem was associated with nearly a 2-fold increased risk of hip fracture (OR: 1.95, 95% CI 1.09, 3.51).[2] In a cohort study, risk of non-vertebral fracture or dislocation was greatest in the 16–30 days following drug initiation (RR: 3.58, 95% CI 1.90, 6.75).[3] These studies acknowledge that the risk of fracture associated with hypnotic use may have been somewhat overestimated given their inability to completely account for between-person confounding. Our study utilized a self-controlled, case-crossover design in an effort to minimize this type of confounding, and we found that the risk of hip fracture associated with non-benzodiazepine hypnotic use was similar (OR: 1.66).

In our study, 11% of nursing home residents with a hip fracture used a non-benzodiazepine hypnotic drug, and we estimate that 15% of all nursing home residents used a non-benzodiazepine hypnotic drug during the study period. This is comparable or even slightly

greater than the proportion of nursing home residents that used a benzodiazepine in the 2004 National Nursing Home Survey (13%).[19] Given the additional cost and similar unfavorable side effect profile of the newer drugs, restrictive policies on benzodiazepines that may have unintentionally caused an increase in non-benzodiazepine hypnotic use in the nursing home should be carefully considered.

Our study adds to the existing literature on hypnotic drug use and risk of hip fracture as we explored vulnerable subgroups. Because non-benzodiazepine hypnotics acutely affect memory, attention, and balance,[20–21] we hypothesized that residents with cognitive and functional impairment would be at greater risk for hip fracture when using these drugs. Interestingly, our results suggest that residents using hypnotic drugs with mild impairment in cognition are at greater risk of hip fracture. More cognitively impaired residents may be less mobile and require more assistance with care. Previous studies have found that the ability to ambulate and transfer independently is associated with an increased risk of fracture in frail community-dwellers and nursing home residents[22–23] Our study also suggests that nursing home residents requiring limited assistance with transfers are more vulnerable to hypnotic drugs with respect to fracture risk.

Many falls in the nursing home occur at night in the setting of toileting,[24] and urinary continence[25] or intermittent urinary incontinence[23] is a risk factor for hip fracture in nursing home residents. Restraint use, including bed and side rails, may also increase the risk of injurious falls.[26] We hypothesized that hypnotic drug users who are intermittently incontinent of urine or using bed restraints would be at greatest risk for hip fracture, yet surprisingly, we did not find a differential effect of hypnotic drug use on risk of hip fracture based on these factors.

Facility level characteristics, including a high resident to staff ratio, have been associated with higher fall rates in some studies,[27] and we expected to find a differential effect of hypnotics on risk of hip fracture by these factors. We found no difference in the association of hypnotics based on resident to staff ratio, but we found residents using hypnotics in a facility with fewer Medicaid beds were at greater risk for hip fracture when using these drugs. It is possible that this finding could be explained by chance.

Our study is the first to use a self-controlled, case-crossover study design to determine the effects of non-benzodiazepine hypnotic drug use on risk of hip fracture. Additional strengths include a large sample of U.S. nursing home residents with prescription drug data and functional characteristics available.

This study also has limitations. First, we did not consider dosage, and residents using higher doses may be at greater risk. Second, because traditional benzodiazepines are covered under Medicaid services, we are unable to consider whether interactions with benzodiazepines further increase the risk of fracture. Third, our study excluded 35% of residents that otherwise met eligibility criteria but were not enrolled in Medicare Part D. Residents not enrolled in Part D were more likely to be male (30 vs. 22%), have normal or mild impairment in cognition (62 vs. 47%), and require full assistance with transfers (43 vs. 37%) as compared with study participants. We do not expect that these differences would affect the generalizability of our results to residents without Part D coverage given that we performed stratified analyses.

Finally, we are unable to completely separate the effects of the hypnotic drug from the associated medical condition (i.e., insomnia) or a worsening in the medical condition with respect to risk of hip fracture. This form of confounding by indication or time-dependent confounding is not unique to our study, but rather it applies to all observational pharmacoepidemiologic studies.[28] Our sensitivity analysis of antidepressant users suggests

that at least unmeasured, time-varying confounders, such as depressive symptoms and antidepressant use, are unlikely to explain our results. Regardless of our ability to tease out whether it is the underlying medical illness or sleep medication resulting in an increased risk of hip fracture, the implications of our findings remain: nursing home residents using non-benzodiazepine hypnotic drugs should be closely monitored for falls and screened for osteoporosis in an effort to prevent fractures in the nursing home setting.

In summary, nursing home residents are at an increased risk of hip fracture when using non-benzodiazepine hypnotic drugs. Given the high prevalence of hypnotic drugs in this setting (15%) the moderate increase in the risk of fracture is of clinical significance. Nursing home residents that may be the most vulnerable to non-benzodiazepine hypnotic drugs include new users and residents with mild impairment in cognition and residents requiring limited assistance with transfers. Caution should be used when prescribing a non-benzodiazepine hypnotic to nursing home residents.

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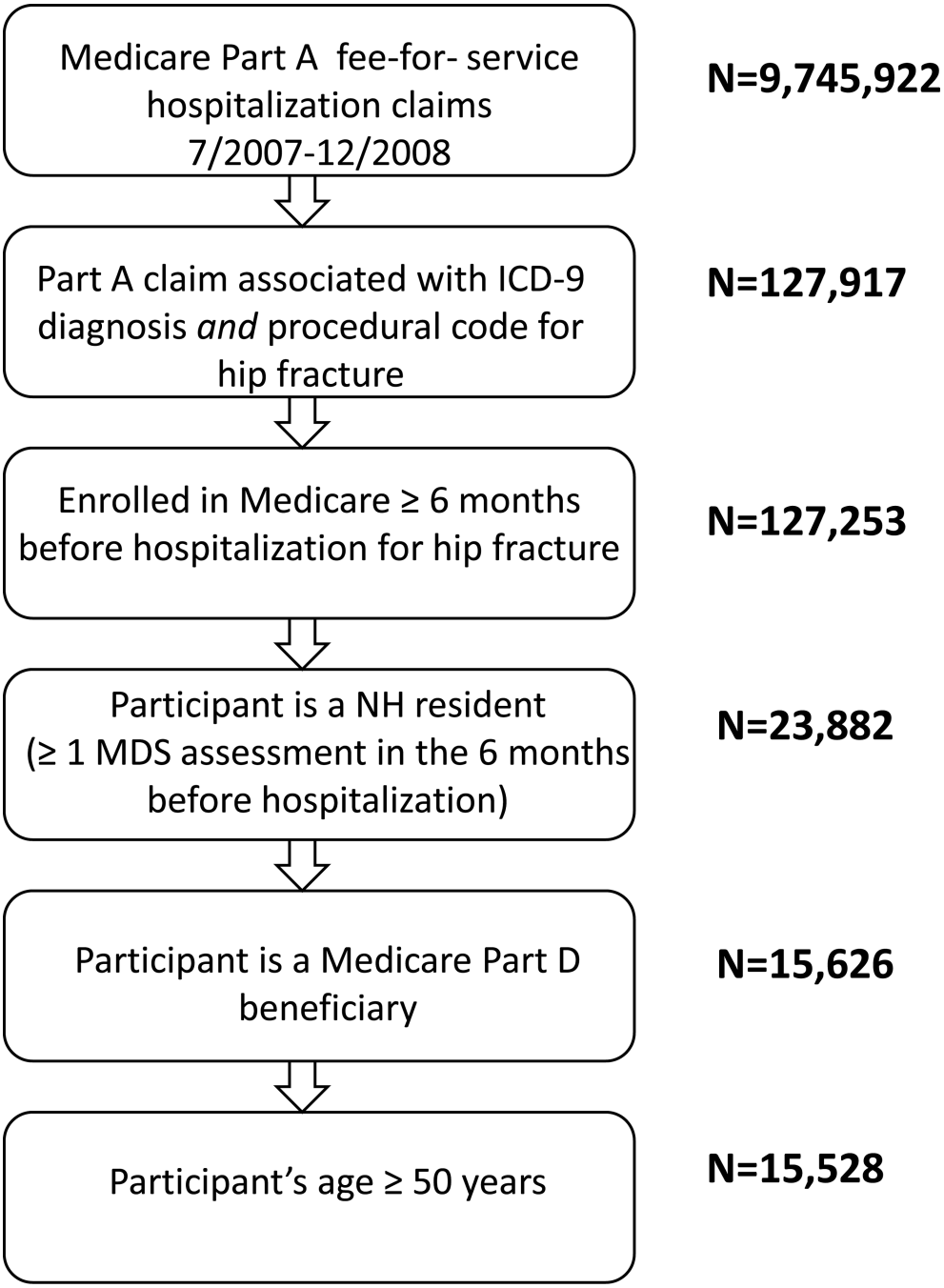

Figure 1.
Diagram of the selection process for participants in a case-crossover study of hypnotics and hip fracture

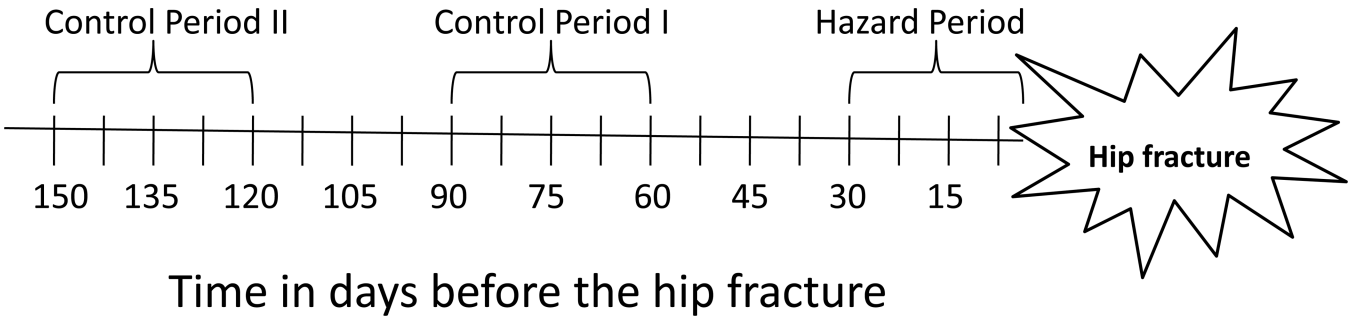

Figure 2.
Diagram of the case-crossover study design. We compared possession of non-benzodiazepine hypnotic drugs during the 0–29 days before the hip fracture (hazard period) with possession during the 60–89 and 120–149 days before the hip fracture (control periods).

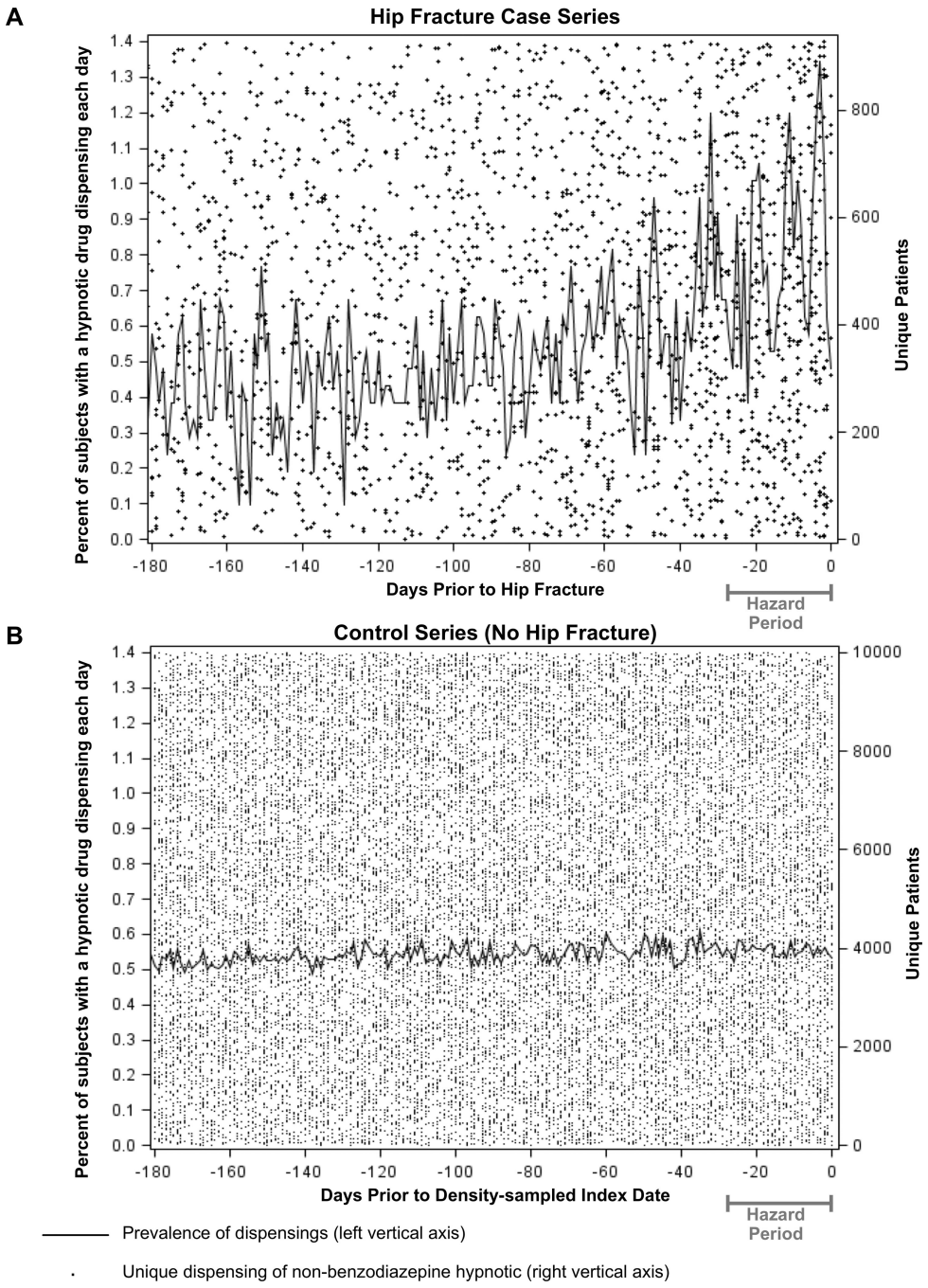

Figure 3.

Density and daily prevalence of dispensings of non-benzodiazepine hypnotics in the 180 days prior to the hip fracture date for the case series (Panel A) and the 180 days prior to a density-sampled index date for 10,000 non-cases (Panel B).

Table 1

Characteristics of 927 nursing home residents with a hip fracture and discordant exposure to non-benzodiazepine hypnotic drugs across hazard and control periods (2007–2009)

Individual characteristics (%, unless otherwise specified)	
Age *	81.0 ± 9.7
Female	77.6
Ethnicity	
White, not Hispanic	89.7
Black, not Hispanic	3.3
Hispanic	4.5
Other	2.6
Comorbidities	
Anemia	6.8
Arthritis	8.9
Congestive Heart Failure	20.7
Depression	49.9
Diabetes	31.7
Stroke	15.2
Cognitive status	
Intact or mild impairment (CPS 0–1)	60.4
Moderate to severe impairment (CPS 2–6)	39.6
Functional Status	
Mild impairment (score 0–7)	24.6
Moderate impairment (score 8–20)	65.4
Total or severe dependence (score 21–28)	10.0
Transfers	
Independent	18.1
Requires supervision or limited assistance	45.2
Requires extensive or full assistance	36.7
Urinary incontinence	
Always continent or always incontinent	63.5
Intermittently incontinent	36.5
Bed restraints used	23.3
Facility characteristics	
Number of RN/LPN/CNA hours per resident per day *	3.4 ± 1.2
% Medicaid beds *	58.6 ± 21.9

* mean ± standard deviation

Table 2

Effect of non-benzodiazepine hypnotic drug use on the risk of hip fracture in a case-crossover study of nursing home residents

Hazard period	Number of exposed participants	Odds ratio	95% Confidence intervals
Any hypnotic drug use			
0–15 days before the hip fracture	622	1.47	1.24, 1.74
0–30 days before the hip fracture	927	1.66	1.45, 1.90
New hypnotic drug use			
0–15 days before the hip fracture	366	2.20	1.76, 2.74
0–30 days before the hip fracture	564	1.90	1.60, 2.26

Table 3

Effect of non-benzodiazepine hypnotic drugs on the risk of hip fracture as stratified by the following individual and facility level characteristics

	Number of exposed participants*	Odds ratio	95% confidence intervals	p-value
Individual characteristics				
Cognitive status				
Intact or mild impairment	558	1.86	1.56, 2.21	0.06
Moderate to severe impairment	366	1.43	1.15, 1.77	
Functional status				
Mild impairment	227	1.84	1.40, 2.42	0.65†
Moderate impairment	604	1.71	1.44, 2.02	
Total or severe dependence	92	1.16	0.75, 1.79	0.11†
Transfers				
Independently	167	1.46	1.06, 2.01	0.09‡
Supervision or mild assistance	417	2.02	1.65, 2.48	
Extensive or full assistance	339	1.43	1.14, 1.79	0.02‡
Urinary incontinence				
Always continent or always incontinent	587	1.70	1.43, 2.01	0.79
Intermittently incontinent	337	1.63	1.30, 2.04	
Bed restraints				
No bed rails or side rails	709	1.65	1.41, 1.93	0.78
Bed or side rails used	215	1.73	1.30, 2.31	
Facility characteristics				
Hi resident to staff ratio	463	1.87	1.52, 2.27	0.11
Low resident to staff ratio	457	1.50	1.23, 1.82	
Hi Medicaid bed use	453	1.46	1.20, 1.77	0.05
Low Medicaid bed use	468	1.90	1.57, 2.31	

*30 day hazard period

†Moderate functional impairment is the reference group

‡Mild assistance with transfers is the reference group