Effects of anticholinergic and sedative medication use on fractures: A self-controlled design study

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Abstract

Background/Objectives: Unintentional falls are a leading cause of injury for older adults, and evidence is needed to understand modifiable risk factors. We evaluated 1-year fall-related fracture risk and whether dispensing of medications with anticholinergic/sedating properties is temporally associated with an increased odds of these fractures.

Design: A retrospective cohort study with nested self-controlled analyses conducted between January 1, 2014, and December 31, 2016.

Setting: Twenty percent nationwide, random sample of US Medicare beneficiaries.

Participants: New users of medications with anticholinergic/sedating properties who were 66+ years old and had Medicare Parts A, B, and D coverage but no claims for medications with anticholinergic/sedating properties in the year before initiation were eligible.

Measurements: We followed new users of medications with anticholinergic/sedating properties until first non-vertebral, fall-related fracture (primary outcome), Medicare disenrollment, death, or end of study data. We estimated the 1-year risk with corresponding 95% confidence intervals (CIs) of first fracture

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after new use. We applied the self-controlled case-crossover and case-time-control designs to estimate odds ratios (ORs) and 95% CIs by comparing anticholinergic and/or sedating medication exposure (any vs. none) during a 14-day hazard period preceding the fracture to exposure to these medications during an earlier 14-day control period.

Results: A total of 1,097,989 Medicare beneficiaries initiated medications with anticholinergic/sedating properties in the study period. The 1-year cumulative incidence of fall-related fracture, accounting for death as a competing risk, was 5.0% (95% CI: 5.0%–5.0%). Using the case-crossover design (n = 41,889), the adjusted OR for the association between anticholinergic/sedating medications and fractures was 1.03 (95% CI: 0.99, 1.08). Accounting for the noted temporal trend using the case-time-control design (n = 209,395), the adjusted OR was 1.60 (95% CI: 1.52, 1.69).

Conclusion: Use of anticholinergic/sedating medication was temporally associated with an increased odds of fall-related fractures. Patients and their healthcare providers should consider pharmacologic and non-pharmacologic treatments for the target condition that are safer.

KEYWORDS

aging, bone fracture, cholinergic antagonists, hypnotics and sedatives, inappropriate prescribing

INTRODUCTION

Falls are one of the most common and burdensome adverse events for older adults (aged ≥65 years).[1,2] One in four older adults experiences an unintentional fall annually, and fall-related injuries among older adults account for 2.8 million emergency department (ED) visits and 800,000 hospitalizations each year.[1,3] For older adults residing in the United States, fractures comprise 35% of nonfatal fall-related injuries and account for 61% of the nonfatal fall-related injury medical costs.[4] Hip fractures, 95% of which are attributed to falls, frequently result in reduced long-term mobility and nursing home admission.[2,5] Older adults who experience a hip fracture remain at an elevated risk for premature death for several years following the index fracture.[6]

Although many studies have identified medications associated with increased fall risk, fall-prevention interventions have mainly focused on exercise and vitamin D supplementation.[7–12] Therefore, the US Preventive Services Task Force (USPSTF) has identified medication management interventions as a research need in its 2018 Recommendation Statement regarding interventions for fall prevention in community-dwelling older adults.[13]

Key Points

- Among older adults in the United States, we report a short-term increase in fall-related fractures associated with anticholinergic/sedating medication use.

Why Does this Paper Matter?

These results support efforts to promote safer pharmacologic and non-pharmacologic approaches to reduce fall risk among older adults.

The literature on the association between medication use and fall risk has been progressively synthesized descriptively (i.e., systematic reviews) and statistically (i.e., meta-analyses) since the 1990s.[10–12,14,15] However, the dearth of sufficiently high-quality observational studies of certain medication classes and groups makes it difficult to synthesize the literature conclusively.[10–12] Specifically, there is a need for studies to (1) establish clear temporal relationships between medication exposure and health outcomes, (2) focus on chemical

properties rather than broad pharmacologic groups (such as antihypertensives), (3) improve confounding control, and (4) expand medication ascertainment by incorporating longitudinal prescription data.[10,11,16,17]

To guide future medication management interventions, we sought to generate high-quality evidence regarding medication use and temporally associated fall-related fracture risk using a large, nationwide random sample of Medicare patients. We focused on older adults initiating use of medications with anticholinergic/sedating properties because of the high burden of polypharmacy among community-dwelling older adults and the associated downstream drug-related adverse events.[18,19] This is also an identifiable population for whom fall-prevention interventions could feasibly be implemented. Among this population, our objectives were to (1) evaluate the 1-year risk of fall-related fractures and (2) examine the effect of transient exposure to medications with anticholinergic/sedating properties on fall-related fractures.

METHODS

Data source and study population

We obtained a 20% nationwide, random sample of Medicare beneficiaries through a data use agreement between the Centers for Medicaid and Medicare Services (CMS) and the University of North Carolina at Chapel Hill (UNC-CH). We conducted a retrospective study of Medicare beneficiaries who initiated use of medications with anticholinergic and/or sedating properties during 2014–2016, where medication use was defined by claims for dispensed prescriptions. This time frame was chosen because Medicare Part D did not cover benzodiazepines (BZDs), a major class of medications with sedating properties, from 2006 to 2012.[20] We required that each beneficiary have Medicare Parts A, B, and D coverage (with a 1 month grace period allowed) and no Part D claims for medications with anticholinergic/sedating properties for at least 1 year before initiation. The index date was the date of first dispensing of a medication with anticholinergic/sedating properties. Patients were required to be ≥66 years at the index date because beneficiaries who receive coverage before age 65 are eligible based on disability or advanced disease. Although patients could potentially meet the initiation definition more than once, we restricted the cohort to the first new use period and followed individuals from the index date until the first of the following events: first non-vertebral fracture (because vertebral fractures are more likely related to osteoporosis rather than to falls), disenrollment in Medicare Parts A, B, or D, death, or end of study data (December 31, 2016) (Figure S1).

Outcome assessment

Fall-related fractures were identified using diagnosis and procedure codes in Medicare Parts A and B claims using a modified Medicare-based algorithm for fracture identification.[21] An orthopedic physical therapist and injury epidemiologist (YMG) helped modify the original algorithm to capture fall-related fractures by removing codes unlikely to be fall-related (e.g., related to motor vehicle crashes or violence). We required a fracture-related diagnosis code and a corresponding (i.e., same fracture site) procedure code (e.g., diagnostic imaging, cast application) up to 7 days after the diagnosis code. Fractures having a motor vehicle crash diagnosis code on the same day as the diagnosis code were excluded. A forward–backward mapping approach was used to convert the ICD-9-CM codes in the original algorithm for the ICD-10-CM era.[22] Codes are provided in Supplementary Table S2.

Exposure assessment

Two geriatric pharmacists (MJP and JCB) reviewed all unique medication generic names listed in the Part D claims and classified each as having anticholinergic or sedating effects, both, or neither (Supplementary Table S1), as previously described.[23] For our primary exposure definition, we defined exposure to medications with anticholinergic/sedating properties dichotomously (any vs. none), and exposure was assessed by identifying continuous periods of use based on the days' supply of the prescription. Overlapping prescriptions were shifted to account for forward stockpiling. Additional details are provided in the Supplementary Material.

Covariate assessment

We assessed covariates during the 12 months before initiation using Medicare Part A, B, and D claim files. Demographic characteristics included age, race (black, white, Asian, Hispanic, Native American, other, unknown), and sex (male, female). Dichotomous (any, none) proxy measures for socioeconomic status included: partial low-income subsidy, full low-income subsidy, and state buy-in Parts A and B coverage during the 12 months before

initiation. We estimated a proxy measure for frailty using the validated Faurot Medicare claims-based algorithm that incorporated predictors of activities of daily living dependency.[24–26] Beneficiaries' predicted probabilities of being frail were categorized as follows: low (0% to < 10%), low/intermediate (10% to < 20%), intermediate/high (20% to <50%), and high (≥50%).[27] We estimated the Gagne combined comorbidity score.[28] We examined several healthcare utilization indicators including: number of unique dispensed medications (count by generic name), number of outpatient visits, number of ED visits, and number of hospital admissions. For time-varying confounder control during the control and hazard windows, we adjusted for dispensing of medication classes associated with increased fall risk (analgesics, antipsychotics, anticonvulsants, BZDs, antihypertensives, cardiac medications, antiarrhythmics, antidepressants, diuretics), as defined by the Agency for Healthcare Research and Quality (AHRQ).[29] We did not adjust for use of AHRQ-defined medications with anticholinergic/sedating properties within the control and hazard windows because these medications were included in our primary exposure definition.

Statistical analysis

New user cohort

We described cohort characteristics using covariates assessed in the year before initiation and examined the most common anticholinergic/sedating medications initiated among these beneficiaries. We then estimated the 1-year first fracture rate and corresponding 95% confidence intervals (CIs), and the 1-year risk of first fracture following anticholinergic/sedating medication initiation with death as a competing event with bootstrapped 95% CIs (100 repetitions) using the Aalen–Johansen estimator.[30]

Nested self-controlled analyses

To assess the transient effects of anticholinergic/sedating medication dispensing on fall-related fractures, we implemented two self-controlled study designs: the case-crossover and the case-time-control designs, nested within the new user cohort (Figure S2). These designs control for time-fixed and slowly time-varying confounders because each beneficiary serves as their own control. Therefore, these designs help eliminate confounding by factors that do not change over a short time interval (e.g., prior history of falls/fractures). [31] The case-crossover design is restricted to individuals who experienced the event (i.e., cases) (Figure 1A).[32] Each case's person-time is subset into two windows (or periods): (1) a hazard period, or an "at risk" period, which immediately precedes the first event, and (2) a control period, which has the same length as the hazard period (to enable a matched analysis) but does not overlap with it.[32,33] A washout period separates these two observation periods in which the exposure of interest is assessed. Only beneficiaries with discordant exposures (e.g., any exposure in the hazard period but no exposure in the control period or vice versa) contribute to the analysis. For an exposure to cause a transient increase in risk of the event, it ought to be more common in the hazard period than in the control period.

Both study designs were nested within our new user cohort. For the primary analyses, the control and hazard periods were each 14 days, and the washout period was 30 days. These exposure windows are biologically plausible because the use of these medications is anticipated to elevate fall risk in the short term; fall-increasing medications whose use results in falls in the inpatient setting are typically prescribed between 24 h and 7 days before the associated fall.[34] Because this study was conducted among individuals in the non-acute setting (rather than an inpatient setting) and we studied a more severe outcome, we extended the control and hazard periods.

To estimate the matched (on case) odds ratio (OR) using the case-crossover design, we compared exposure frequencies during the control and hazard periods.[32] This exposure OR, estimated using conditional logistic regression, estimates the incidence rate ratio that we would have obtained were we to study a full cohort.[31] Although time-fixed (and slow-varying) covariates (e.g., race, chronic conditions, exercise) were controlled for by design, we included dispensing (any vs. none) of each of the AHRQ-defined medication classes associated with fall risk (described above), measured during the control and hazard windows, in the adjusted models.

Since population-level temporal trends in exposure (e.g., increases in uptake of a new medication) and the existence of only certain exposure patterns in the population (persistent user bias) may bias case-crossover results, we also applied a case-time-control design, which has been demonstrated to account for these biases in simulations.[35,36] This design had the same structure as the case-crossover, but also included matched controls (Figure 1B).[37] Four controls were matched per case based on attained age (in days) and sex, where each control had at least the same amount of follow-up time as the case to which they were matched and did not become a case themselves subsequently.[37] We compared the case-crossover results for the cases (i.e., an exposure OR in the

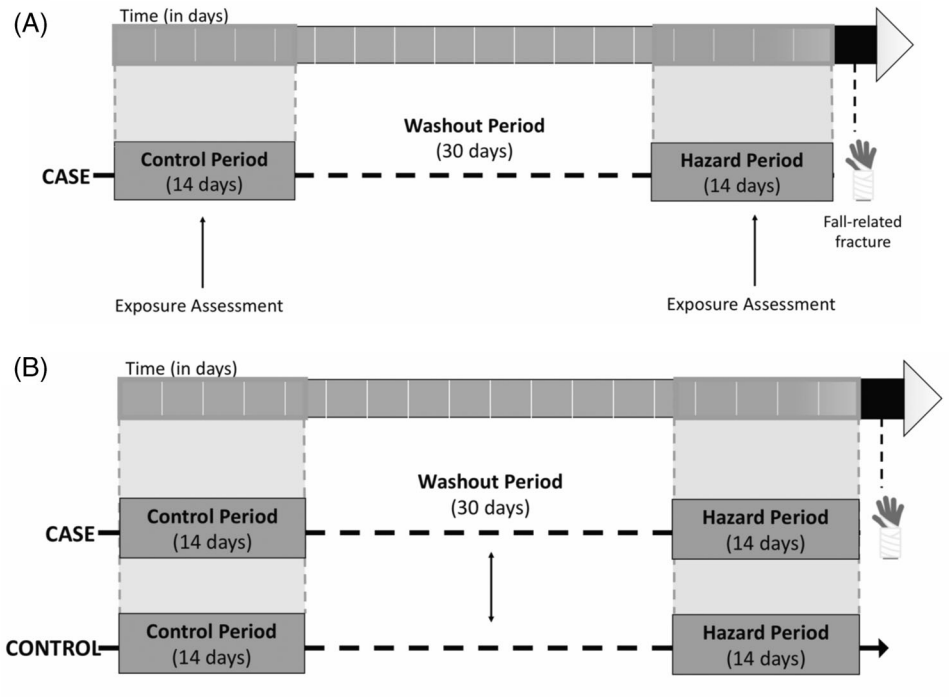

FIGURE 1 Self-controlled study design schematics for the main analysis. (A) Case-crossover design, (B) Case-time-control design

cases) to the case-crossover results for the controls (i.e., an exposure OR in the controls) by dividing the cases' exposure OR by the controls' exposure OR to obtain the case-time-control OR.[38]

Sensitivity analyses

We conducted sensitivity analyses to assess the robustness of our results. First, we examined both shorter (7-day) and longer (21-day) control and hazard windows. Second, since concurrent use of multiple prescriptions with anticholinergic/sedating properties may be indicated under certain circumstances, we used a less conservative approach that did not shift overlapping prescriptions but did account for days' supply. Third, since patients who are hospitalized, in a nursing facility, or in hospice care may not use their Part D benefits, we restricted to patients not in these settings during the control and/or hazard windows. Fourth, to account for the potential for weakness induced by a recent inpatient stay, we adjusted for being in one of these settings during the control and/or hazard windows. Fifth, to better understand the drivers of the associations, we considered several alternative exposure definitions as sensitivity analyses: we defined exposure to (1) medications with sedating properties dichotomously (any vs. none) and (2) both properties (any vs. none). We also conducted analyses restricted to several of the most common prescription medications with sedating properties and both properties during the hazard and control windows.

The UNC-CH Institutional Review Board approved this research (Study #18-2999). Statistical analyses were conducted using SAS Statistical Software, version 9.3 (Cary, NC).

RESULTS

Patient characteristics

The analysis population included 1,097,989 Medicare beneficiaries who initiated the use of an anticholinergic/sedating medication during 2014–2016. The most commonly initiated medications tended to be sedatives only (initiated as a single drug): combination medications containing hydrocodone (24%), tramadol (11%), and combination medications containing oxycodone (7%)) (Table 1). Of the medications containing anticholinergic properties initiated as a single drug, meclizine was most common (4%). Furthermore, 6% of patients initiated multiple drugs simultaneously. Table 2 describes the population characteristics stratified by whether the patient initiated one drug with sedating only properties, one drug with both properties, or multiple drugs. Patients were 76 years of age on average, 56% identified as women, and 85% identified as white. Patients initiating a single drug tended to have more similar characteristics, whereas those initiating multiple drugs tended to be younger, have more healthcare utilization in acute settings, and higher frailty probability.

TABLE 1 Most common anticholinergic/sedating medications initiated among medicare beneficiaries (2014–2016), stratified by medication property

A sedating drug only (n = 849,410)	**No. (%)**	**A drug with both properties only (n = 183,441)**	**No. (%)**	**Multiple drugs (n = 65,138)**	**No. (%)**	**Overall (n = 1,097,989)**	**No. (%)**
Combination[a] with hydrocodone	262,454 (31)	Meclizine	45,435 (25)	Cyclobenzaprine, combination with hydrocodone	2210 (3)	Combination with hydrocodone	262,545 (24)
Tramadol	118,021 (14)	Cyclobenzaprine	18,735 (11)	Combination with hydrocodone, tramadol	1888 (3)	Tramadol	118,021 (11)
Combination with oxycodone	74,277 (9)	Oxybutynin	15,146 (8)	Diazepam, combination with hydrocodone	1823 (3)	Combination with oxycodone	74,277 (7)
Combination with codeine	61,473 (7)	Dicyclomine	10,743 (6)	Gabapentin, combination with hydrocodone	1444 (2)	Multiple drugs	65,138 (6)
Gabapentin	48,294 (6)	Tizanidine	9893 (5)	Gabapentin, tramadol	1345 (2)	Combination with codeine	61,473 (6)
Alprazolam	36,399 (4)	Combination with atropine	9678 (5)	Cyclobenzaprine, tramadol	1203 (2)	Gabapentin	48,294 (4)
Lorazepam	27,308 (3)	Hydroxyzine	9101 (5)	Combination with hydrocodone, promethazine	978 (2)	Meclizine	45,435 (4)
Zolpidem	22,149 (3)	Prochlorperazine	7978 (4)	Oxycodone, tramadol	925 (1)	Alprazolam	36,399 (3)
Oxycodone	21,894 (3)	Promethazine	6349 (4)	Diazepam, combination with oxycodone	879 (1)	Lorazepam	27,308 (2)
Sertraline	18,339 (2)	Quetiapine	5422 (3)	Lorazepam, morphine	837 (1)	Zolpidem	22,149 (2)

[a]Combination refers to combination medications (i.e., medications with more than one active ingredients).

TABLE 2 Patient characteristics of anticholinergic and/or sedating medication initiators among medicare beneficiaries (2014–2016), stratified by medication initiated

Patient characteristic[a]	No. (%)			
	A sedating drug only (n = 849,410)	A drug with both properties only (n = 183,441)	Multiple drugs (n = 65,138)	Total (n = 1,097,989)
Age, mean (SD)	75.9 (7.64)	76.4 (7.71)	75.0 (7.80)	75.9 (7.67)
Sex, male	381,374 (44.9%)	70,576 (38.5%)	28,286 (43.4%)	480,236 (43.7%)
Race				
White	725,067 (85.4%)	152,518 (83.1%)	55,952 (85.9%)	933,537 (85.0%)
Black	63,364 (7.5%)	14,338 (7.8%)	4670 (7.2%)	82,372 (7.5%)
Other	17,818 (2.1%)	4527 (2.5%)	1273 (2.0%)	23,618 (2.2%)
Asian	18,840 (2.2%)	6397 (3.5%)	1326 (2.0%)	26,563 (2.4%)
Hispanic	14,695 (1.7%)	3831 (2.1%)	1172 (1.8%)	19,698 (1.8%)
Unknown	9626 (1.1%)	1830 (1.0%)	745 (1.1%)	12,201 (1.1%)
Healthcare utilization				
Outpatient office visits, mean (SD)	7.8 (6.30)	7.9 (6.43)	6.9 (6.18)	7.8 (6.32)
Hospital adm, mean (SD)	0.4 (0.92)	0.3 (0.81)	0.7 (1.32)	0.4 (0.94)
ED visits, mean (SD)	0.6 (1.16)	0.5 (1.09)	0.7 (1.39)	0.6 (1.17)
Rx fills in last 30 days, mean (SD)	1.5 (1.47)	1.5 (1.47)	1.2 (1.46)	1.5 (1.47)
Polypharmacy[b]	33,979 (4.0%)	7204 (3.9%)	2153 (3.3%)	43,336 (3.9%)
SES				
Any parts and B state buy-in	123,503 (14.5%)	29,618 (16.1%)	12,040 (18.5%)	165,161 (15.0%)
Any low-income subsidy	24,284 (2.9%)	5260 (2.9%)	2093 (3.2%)	31,637 (2.9%)
Health status indicators				
Frailty probability[c]				
Low	731,633 (86.1%)	159,016 (86.7%)	51,466 (79.0%)	942,115 (85.8%)
Low/middle	59,281 (7.0%)	12,511 (6.8%)	5319 (8.2%)	77,111 (7.0%)
Middle/high	38,999 (4.6%)	7893 (4.3%)	4986 (7.7%)	51,878 (4.7%)
High	19,497 (2.3%)	4021 (2.2%)	3367 (5.2%)	26,885 (2.4%)
GCS,[d] mean (SD)	1.4 (2.48)	1.3 (2.44)	1.8 (2.93)	1.4 (2.51)

Abbreviations: ED, emergency department; SES, socioeconomic status.
[a]Assessed in the year before initiation of anticholinergic/sedating drugs.
[b]Assessed in the last 30 days and defined as ≥5 fill.
[c]Defined as low (0% to <10%), low/middle (10% to <20%), middle/high (20% to <50%), high (≥50%).
[d]Gagne Comorbidity Score.

Fall-related fractures and all-cause mortality

During the first year after medication initiation, 49,601 beneficiaries experienced a first, fall-related fracture (accounting for 51,893 fracture sites). The most common fracture sites were: radius (n = 10,922 [22.0%]), hip (n = 9266 [18.7%]), and humerus (n = 7898 [15.9%]). The fall-related first fracture rate in the first year since medication initiation was 577 per 10,000 person-years (95% CI: 577–577). Fifty-nine thousand and four of the beneficiaries died in the first year since medication initiation. The 1-year cumulative incidence of fall-related fracture, accounting for death as a competing risk, was 5.0% (95% CI: 5.0%, 5.0%) (Figure 2), whereas the 1-year cumulative incidence of mortality was 6.2% (95% CI: 6.1%, 6.2%).

Transient exposure to medications with anticholinergic/sedating properties and fall-related fractures

The self-controlled, case-crossover 14-day period analysis included 41,889 beneficiaries who experienced a fall-related

fracture following initiation of a medication with anticholinergic/sedating properties during 2014–2016. Beneficiaries experiencing a fall-related fracture in the first 58 days were excluded because there would not have been enough time to observe a 14-day control window, a 14-day hazard window, and a 30-day washout period between the two. We found that beneficiaries with any anticholinergic/sedating medication exposure (assessed by claims) during the hazard period did not have a notable increased odds of fall-related fracture, as compared with those with any exposure in the control period (OR: 1.04 [95% CI: 1.00, 1.09]). Further adjustment for exposure to known fall-increasing medications without anticholinergic/sedating properties had no relevant effect on the estimate (aOR: 1.03 (95% CI: 0.99, 1.08)) (Table 3).

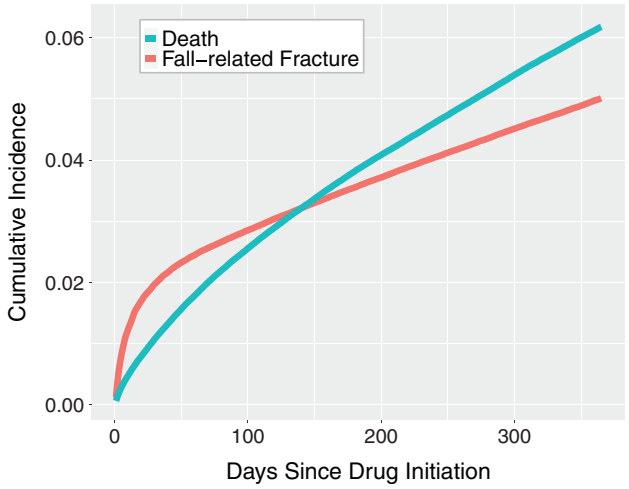

FIGURE 2 Cumulative incidence of fall-related fractures with death as a competing risk

The 14-day self-controlled, case-time-control analysis included the same 41,889 beneficiaries who experienced a fall-related fracture and 167,506 sex- and age-matched controls who did not experience a fall-related fracture during the study period. Among the controls, exposure to medications with anticholinergic/sedating properties was higher in the control period relative to the case period (OR: 0.65 [95% CI: 0.63, 0.67]), suggesting a temporal trend. Accordingly, compared with the case-crossover results, the case-time-control OR estimate was further from the null (matched aOR: 1.60 (95% CI: 1.52, 1.69)) and supported an elevated association between anticholinergic/sedating medication exposure and fall-related fractures.

TABLE 3 Association of anticholinergic/sedating medication exposure and fall-related fractures, medicare beneficiaries (2014–2016)

	Cases			Matched controls				
	No. (%)[b]			No. (%)				
Study design	Hazard period Exposed[c] (A)	Control period (B)	Crude exposure odds ratio (95% CI) (C)	Hazard period Exposed[c] (D)	Control period (E)	Crude exposure odds ratio (95% CI) (F)	Crude odds ratio (95% CI) (C)/(F)	Adj. odds ratio[a] (95% CI) (G)
Primary exposure definition[d]								
Case-crossover study design[e]								
7-day[e]	3559 (8)	3759 (9)	0.95 (0.90, 0.99)					0.94 (0.90, 0.99)
14-day	3691 (9)	3540 (9)	1.04 (1.00, 1.09)					1.03 (0.99, 1.08)
21-day	3762 (9)	3360 (8)	1.12 (1.07, 1.17)					1.11 (1.06, 1.16)
Case-time control study design								
7-day	3559 (8)	3759 (9)	0.95 (0.90, 0.99)	8538 (5)	14,437 (8)	0.59 (0.58, 0.61)	1.60 (1.52, 1.69)	1.60 (1.52, 1.69)
14-day	3691 (9)	3540 (9)	1.04 (1.00, 1.09)	9043 (5)	13,942 (8)	0.65 (0.63, 0.67)	1.61 (1.52, 1.70)	1.60 (1.52, 1.69)
21-day	3762 (9)	3360 (8)	1.12 (1.07, 1.17)	9476 (6)	13,791 (9)	0.69 (0.67, 0.71)	1.63 (1.54, 1.72)	1.62 (1.54, 1.71)

[a]We restricted to participants who could be observed in from the start of the control period to the end of the hazard period, hence for the 7-day period analysis, the case-crossover n = 43,952 and the case-time control n = 219,710. For the 14-day period analysis, the case-crossover n = 41,889, and the case-time control n = 209,395. For the 21-day period analysis, the case-crossover n = 40,252 and the case-time control n = 201,210.

[b]Refers to discordantly exposed patients (i.e., exposed in the hazard period and unexposed in the control period) who contribute to the analysis.

[c]Adjusted for time-varying exposure of dispensing of medication classes associated with increased fall risk, as defined by the AHRQ.[29] Fall risk medications with anticholinergic and/or sedating properties were excluded. Not adjusted for baseline covariates in Table 1.

[d]The primary exposure definition defined a patient as exposed by accounting for continuous periods of use by incorporating the days' supply of the prescription. It also shifted overlapping prescriptions to account for forward stockpiling.

[e]Length of each of the control and hazard periods. The 14-day period was the main analysis.

Sensitivity analyses

In both self-controlled analyses, when we varied the length of the control and hazard periods (examined both a shorter (7-day) and longer (21-day) period), the association was slightly attenuated (or unchanged) and then strengthened, respectively. For example, in the case-time-control analysis, the 7-day adjusted OR was 1.60 (95% CI: 1.52, 1.69) and the 21-day OR was 1.62 (95% CI: 1.54, 1.71) (Table 3). When we applied a less conservative exposure definition that did not shift overlapping prescriptions, the results were qualitatively the same (e.g., adjusted OR for case-time-control was 1.60 [95% CI: 1.51, 1.68]), relative to the primary exposure definition (Table S3). Excluding patients in care settings where they may not be using their Part D benefits during the exposure assessment windows or adjusting for these stays in the windows did not affect the estimates meaningfully (Tables S4 and S5). Examining (1) medications with sedating properties dichotomously (any vs. none) and (2) medications with both properties (any vs. none) separately suggested that the combined results were being driven by the medications with sedating properties (Tables S4 and S5). Additionally, it was noted that the use of specific common medications with sedating properties was more consistently associated with increased short-term odds of fall-related fractures, as compared with use of medications with both properties (Tables S4 and S5).

DISCUSSION

In this nationwide, random sample of Medicare beneficiaries, we found a positive association between anticholinergic/sedating medication use and increased short-term odds of fall-related fractures among beneficiaries who initiated the use of medications with anticholinergic and/or sedating properties when using a case-time-control design. Fall-related fractures were more common shortly after medication initiation, accounting for the competing risk of death, and risk did not appear to mitigate substantially with time since initiation. The most common fracture sites were the radius, hip, and humerus. Initiators of medications with anticholinergic/sedating properties tended to initiate a single medication with only sedating properties, such as a combination medication containing hydrocodone or tramadol.

Given the substantial burden that falls and fall-related fractures impose on the individual and the healthcare system, the strong evidence we provide can help inform the medication management interventions called for by the USPSTF.[13] Although many of the medication classes often associated with fall risk (e.g., BZDs, antipsychotics, opioids, and antiepileptics) have anticholinergic/sedating properties,[10–12,39] few studies have examined these two properties jointly in association with fractures.[40] Our findings build on those of prior observational studies demonstrating positive associations between exposure to anticholinergic/sedating medications and falls[41–44] and hip fractures.[40] This study makes a novel contribution by focusing specifically on new use of medications with anticholinergic/sedating properties. Nesting analyses within a new user cohort helps minimize the bias induced by depletion of patients who are susceptible to medication-related adverse events that can arise when studying prevalent users.[45]

Our self-controlled analyses suggested that, as expected, the cases were more likely to have the discordant exposure pattern in which they were exposed in the hazard window but not in the control window when compared with the controls. However, we also noted a strong temporal trend among the controls, in which exposure to medications with anticholinergic/sedating properties was higher in the control period relative to the hazard period. This might be related to the most common drugs observed in the windows being pain-relief medications, some intended for shorter duration of use. Using a case-time-control design, we accounted for this temporal trend potentially biasing estimates generated from the case-crossover analyses.

Our study has several important strengths. First, self-controlled designs offer a clear advantage for slow and time-invariant confounding control, and have been implemented to examine certain medications with these properties (e.g., non-BZD hypnotics, BZDs) in association with hip fractures or fractures more broadly.[46–49] Our study was the first to leverage this design to examine the association of these two medication properties jointly and separately with fall-related fractures. Second, we paired this design with medication claims data from a large, nationwide healthcare database, which provides rich longitudinal exposure and outcome data but can suffer from inadequate information on time-invariant or slow-varying patient characteristics (e.g., physical activity, smoking, diet), to innovatively address this research question.[31] Third, we developed an updated fall-related fracture algorithm, based on an existing validated fracture identification Medicare-based algorithm.[21] Fall-related fractures are a good proxy for severe falls; however, our definition excludes some very severe falls (such as those that result in traumatic brain injuries or other substantially disabling injuries).

One limitation of applying self-controlled study designs is that they precluded us from capturing early

events because patients were required to have at minimum 58 days between medication initiation and the fall-related fractures. However, these results were only slightly attenuated when we shortened the hazard and control windows to 7 days each. Additionally, although we controlled for the use of other prescription medications known to increase fall risk, the potential for residual confounding by time-varying factors not captured in the data such as over-the-counter (OTC) medications and underlying clinical measures of physical function remains. There is also the potential for confounding by indication in the self-controlled analyses if acute conditions arose or there were changes in chronic condition severity during the 58 days before the fracture that affected subsequent dispensing. Next, although claims are audited and undergo validity checks, they do not capture OTC medications with these properties (e.g., some antihistamines) nor confirm that the patient was actually taking the prescription. We considered two exposure definitions, a more conservative definition that considered days' supply and shifted overlapping prescriptions, and another that did not shift overlapping prescriptions, and both definitions yielded similar results. Nonetheless, nonadherence may lead to bias due to misclassification of exposure. Lastly, our study cannot determine the mechanism of fall-related fractures. These medications have complex effects including psychotropic effects on alertness and attention, and motor effects on movement coordination and balance responses.

CONCLUSIONS

Medication use is an important potentially modifiable risk factor for falls and fall-related fractures among older adults. In this study of Medicare beneficiaries, we observed a 5% cumulative risk of fall-related fracture within 1 year of initiating a medication with anticholinergic/sedating properties. Within this population, we also report an elevated odds of fall-related fracture associated with transient use of anticholinergic/sedating medications. Exploring the effects of cumulative exposure would be an interesting future direction. Patients and their healthcare providers should carefully evaluate whether the use of medications with anticholinergic/sedating properties is appropriate and whether safer alternatives exist. This work also supports close monitoring for falls and near falls among patients initiating these medications. Fall-prevention interventions among older adults should consider the impact of combining exercise-based interventions, which are known to decrease risk,[13] and home visits to assess environmental hazards and recommend modifications (e.g., remove rugs/carpets, install grab bars),[50] with effective medication management strategies.

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CONFLICT OF INTEREST

SS is a consultant for CERobs Consulting, LLC on projects unrelated to the submitted work. TS receives investigator-initiated research funding and support as Principal Investigator (R01 AG056479) from the National Institute on Aging (NIA), and as Co-Investigator (R01 HL118255, R01MD011680), National Institutes of Health (NIH). He also receives salary support as Director of Comparative Effectiveness Research (CER), NC TraCS Institute, UNC Clinical and Translational Science Award (UL1TR002489), the Center for Pharmacoepidemiology (current members: GlaxoSmithKline, UCB BioSciences, Takeda, AbbVie, Boehringer Ingelheim), from pharmaceutical companies (GSK, Amgen, AstraZeneca, Novo Nordisk), and from a generous contribution from Dr. Nancy A. Dreyer to the Department of Epidemiology, University of North Carolina at Chapel Hill. TS does not accept personal compensation of any kind from any pharmaceutical company. He owns stock in Novartis, Roche, and Novo Nordisk. JLL receives research support from the Center for Pharmacoepidemiology (members: GlaxoSmithKline, UCB BioSciences Inc, AbbVie, Boehringer Ingelheim, Takeda and Merck [past member]). JLL also receives salary support from AbbVie, Inc. for an unrelated research study. JLL's spouse is a full-time, paid

employee of and owns stock in GlaxoSmithKline. No potential conflicts of interest were disclosed by the other authors.

AUTHOR CONTRIBUTIONS

Study Concept and Design: Shmuel, Golightly, Hanson, Stürmer, Naumann, Lund. *Acquisition of subjects and/or data*: Shmuel. *Analysis and Interpretation of data*: All authors. *Preparation of the Manuscript*: All authors.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

Appendix S1. Supporting Information

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