Published in final edited form as:

J Am Med Dir Assoc. 2018 April ; 19(4): 328–332.e2. doi:10.1016/j.jamda.2017.09.015.

Age, Sex, and Dose Effects of Non-benzodiazepine Hypnotics on Hip Fracture in Nursing Home Residents

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Abstract

Objective—The FDA recommends a reduced dose of non-benzodiazepine hypnotics in women, yet little is known about the age-, sex-, and dose-specific effects of these drugs on risk of hip fracture, especially among nursing home (NH) residents. We estimated the age-, sex-, and dose-specific effects of non-benzodiazepine hypnotics on the rate of hip fracture among NH residents.

Design and Setting—Case-crossover study in US NHs.

Participants—691 women and 179 men with hip fracture sampled from all U.S. long-stay NH residents.

Measurements—Measures of patient characteristics were obtained from linked Medicare and the Minimum Data Set (2007–2008). The outcome was hospitalization for hip fracture with surgical repair. We estimated rate ratios (RR) and 95% confidence intervals (CI) from conditional logistic regression models for non-benzodiazepine hypnotics (vs. non-use) comparing 0–29 days before hip fracture (hazard period) with 60–89 and 120–149 days before hip fracture (control periods). We stratified analyses by age, sex, and dose.

Results—The average RR of hip fracture was 1.7 (95% CI 1.5 to 1.9) for any use. The RR of hip fracture was higher for residents aged ≥90 years vs. <70 years (2.2 vs. 1.3); however, the CIs overlapped. No differences in the effect of the hypnotic on risk of hip fracture were evident by sex. Point estimates for hip fracture were greater with high-dose versus low-dose hypnotics (RR 1.9 vs. 1.6 for any use), but these differences were highly compatible with chance.

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Conclusions—The rate of hip fracture in NH residents due to use of non-benzodiazepine hypnotics was greater among older patients than among younger patients and, possibly, with higher doses than with lower doses. When clinicians are prescribing a non-benzodiazepine hypnotic to any NH resident, doses of these drugs should be kept as low as possible, especially among those with advanced age.

Keywords

Non-benzodiazepine hypnotics; hip fracture; nursing home; pharmacoepidemiology; case-crossover study

Introduction

On January 10, 2013, the US Food and Drug Administration (FDA) notified healthcare professionals and consumers about the risk of next-morning psychomotor impairment after the use of zolpidem, a non-benzodiazepine hypnotic.¹ The risk of psychomotor impairment appeared highest for extended-release versions of zolpidem and among women, leading the FDA to recommend reductions in doses for women.^{1–4} Other data point to higher rates of psychomotor impairment with hypnotic drugs among elderly patients, raising questions about whether dosage modifications are also indicated for older persons.⁵

Although many frail, older persons do not drive, it is likely that the impairment observed with non-benzodiazepine hypnotic use and driving tests translates to an increased risk of other adverse psychomotor effects, such as falls and bone fractures. In a meta-analysis on the safety of hypnotic use in the elderly, fractures resulting from falls occurred more frequently than motor vehicle accidents.⁶ Hip fractures are catastrophic in elderly patients, with a case fatality rate of 24% at one year.⁷ Although studies have confirmed the relationship between non-benzodiazepine hypnotics and fractures^{8–13}, the results for sex-specific effects have been inconclusive.¹¹ Moreover, little data are available for frail older persons.

Identifying the appropriate dose of potentially harmful medications is a problem faced by nearly all physicians. Furthermore, sleep disorders in older persons residing in the nursing home (NH) are common, and data on important outcomes plays a critical role in prescribing decisions.¹⁴ This topic is especially important given that prior publications showed that the benefit of non-benzodiazepine hypnotics relative to placebo is modest.^{15,16} With only modest benefits of treatment, there is often little tolerance by clinicians and patients for important adverse effects.

Therefore, we examined the age-, sex- and dose-specific effects of non-benzodiazepine hypnotics on the rate of hip fractures among long-stay U.S. nursing home (NH) residents—a population potentially at the highest risk of psychomotor impairment from non-benzodiazepine hypnotics due to a high baseline burden of frailty and cognitive impairment.

Methods

Data Sources

The Brown University Institutional Review Board approved this study. Details of the data and study population have been previously reported.⁹ We linked data from Medicare Part A (inpatient) and Part D (prescription drug) claims to NH Minimum Data Set (MDS) resident assessments. The Medicare claims data provided information on demographics, Medicare eligibility, hospitalizations, and dispensing of prescription drugs for each patient. Medicare Part D provided information on drug name, dosage, route of administration, formulation, quantity dispensed, and days supplied. Approximately 81% of NH residents were enrolled in Part D in 2006.¹⁷ The MDS is a federally mandated health assessment tool that captures information on cognitive, physical, and psychosocial functioning; active clinical diagnoses and health conditions; and services. NH staff assess each resident at least annually for all MDS measures, at 3-month intervals for many measures, and at any time that a significant change in resident status occurs.¹⁸ We used the MDS 2.0, which has been found generally reliable and valid for measuring domains when used by trained staff.¹⁹

Study Population

Among more than 9 million patients identified with a Medicare Fee-for-service Part A hospital inpatient claim between 7/1/2007 and 12/31/2008, we identified 127,917 beneficiaries who had a hip fracture, of whom 127,253 (99%) were enrolled in Part A for 6 months and 23,882 resided in a NH for 100 consecutive days prior to the date of their hip fractures (long-stay residents). After requiring continuous enrollment in Part D and age 65 years, the final sample size was 15,528 participants. A description of non-benzodiazepine hypnotic use in the source population can be found in Appendix Tables A1 and A2.

Study Design

This was a unidirectional case-crossover study.²⁰ Non-benzodiazepine hypnotics are good candidates for this study design because they are intended for intermittent or short-term use.²¹ Similarly, the risk of hip fracture is highest immediately following use of zolpidem.¹⁰ With the case-crossover design, the prevalence of exposure is measured during the etiologically relevant period of time preceding the event (hazard period) and during periods of time without an event (control period)—with comparisons made within individuals (Appendix Figure A1). By comparing participants to themselves, the potential effects of unmeasured time-invariant confounders between participants using and not using the drug are eliminated. We compared the prevalence of non-benzodiazepine hypnotic possession (as a proxy for consumption) 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. Periods of 30 days were selected because a non-benzodiazepine prescription often lasts for approximately this long in clinical practice. Washout periods (from 30–59 days and 90 to 119 days) were used to minimize carry-over effects between the hazard period and control periods.

Measurement of Hip Fracture

We defined hip fractures as the first hospitalization with an International Classification of Diseases, 9th Edition (ICD-9) diagnosis code of 820.xx (fracture of the neck of femur) or 733.14 (pathologic fracture of neck of femur) with a concomitant procedure code for surgical repair of the fracture.²² The estimated positive predictive value of this definition is 98%, and similar definitions have an estimated sensitivity of 96%.²³

Measurement of Non-benzodiazepine Hypnotic Exposure

Non-benzodiazepine hypnotics included zolpidem, eszopiclone, and zaleplon. Hypnotic use was identified using National Drug Codes in Medicare Part D claims. We defined possession of a hypnotic according to the date of dispensing of the hypnotic drug plus the recorded days supply. If this dispensing period overlapped with the hazard or control periods, we categorized the beneficiary as exposed during that period. We separately restricted the analysis to apparent new users of non-benzodiazepine hypnotics (no drug possession in preceding 60 days) because the aforementioned exposure definition potentially includes long-term users who may not be at the same elevated risk of hip fracture from hypnotic use.²⁴ High-dose formulations were defined as zolpidem >6.25 mg, eszopiclone 3 mg, and zaleplon 10 mg.

Measurement of Covariates

Covariates and their definitions were the same as in our earlier work.⁹ We used the most recent MDS assessment prior to the earliest control period when ascertaining covariates.

Statistical Analysis

We used conditional logistic regression models (SAS version 9.3, SAS Institute, Cary, N.C.) to estimate the effect as odds ratios, which can be interpreted as incidence rate ratios (RR).²⁰ Estimates were thus the RRs and 95% CIs of the rate 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.²⁰ A 95% CI excluding 1 denoted a significant association between non-benzodiazepine hypnotic use and hip fracture. To ensure that residents remained in the NH throughout their control period, we used only the 60–89 day control window for comparison in a sensitivity analysis.

We performed analyses stratified by age categories, sex, and dose. For comparison of RRs across subgroups, we used the difference in the log odds ratio between strata to calculate a Z-score and its associated p-value.

Results

Characteristics of the Case Series

Nearly 80% of the hip fracture case series were women, 46% were between 80 and 89 years of age, and 19% were 90 years old (Table 1). The prevalence of comorbidities ranged from 6% for anemia to 30% for diabetes mellitus. More than one-half of the population reported some pain, and 82% required some assistance with transfers. The majority had some cognitive impairment and 76% had moderate or severe functional impairment (activities of

daily living long-scale score 8).²⁵ Zolpidem use accounted for 86% of all non-benzodiazepine hypnotic use in the case series. 60% were prescribed zolpidem 10 mg and 26% zolpidem 5 mg. Men were more likely than women to use high-dose, immediate-release zolpidem (10 mg), but not higher doses of eszopiclone or zaleplon.

Rate Ratios of Hip Fracture

The average RR of hip fracture was 1.7 (CI 1.5–1.9) for any use and 1.9 (CI 1.6–2.4) among new users (Figure 1A). When using only the 60–89 day control window for comparison, the average RR for any use was 1.5 (CI 1.3–1.7). The point estimates increased as age increased, but there was some overlap in the confidence intervals. For example, the RR was 1.7 times higher for persons ≥90 years old relative to persons <70 years old (2.2 vs. 1.3); however, the CIs overlapped. In women, the point estimates increased with increasing age, from an RR of 1.1 (CI 0.6–2.1) for age<70 years to 2.0 (CI 1.4–2.8) for age ≥90 years. In men, the trend was similar, although confidence intervals were wide given the small number of hip fractures in men.

With respect to dose effects, the point estimates for higher doses of non-benzodiazepine hypnotics were consistently elevated for high-dose formulations relative to lower doses and there was some, but not complete separation in the CIs (Appendix Figure A2). The estimates were more precise for lower doses, reflecting the higher number of users of these formulations. The dose-specific results were similar for new users of non-benzodiazepine hypnotics relative to any use (Appendix Figure A2). Exact values of the RR and CI are in Appendix Table A3.

Discussion

We observed a consistently elevated rate of hip fracture in association with use of non-benzodiazepine hypnotics among all long-stay NH residents in the U.S. with Medicare Part D. Additionally, we observed a suggestion of a dose-response relationship, particularly among the oldest residents. We cannot rule out the possibility this apparent difference is due to chance given smaller numbers in the subgroup analyses with overlapping confidence intervals. In contrast to concerns raised by the FDA, there was no apparent modification of the drug effect by sex.¹

In prior published work, patients with mild-moderate cognitive impairment and those requiring limited assistance with transfers were potentially at highest risk of hypnotic-triggered fractures.⁹ The dose-specific and sex-specific analyses of this paper are novel. Although other studies have found an association between non-benzodiazepine hypnotics and the increased risk of hip fracture, our work is important as we evaluated a population for whom the previous studies may not have generalized.^{8,10,11} The extremely sick and frail long-stay NH resident population has a number of identifiable risk factors for adverse drug events that may not be present in the elderly population at large.²⁶ In addition to a possible dose-response relationship, this study found that older residents appeared to have higher risk of drug-induced harm—a phenomenon that may worsen with larger doses. Our data support the observations of FDA and prior studies that certain subgroups of the population may be at higher risk of psychomotor impairment from non-benzodiazepine hypnotics.^{1–4}

We were surprised to find that older men, rather than women, may be more susceptible to hip fracture while using these drugs. It is possible that this reflects the increased burden of co-morbidities and frailty among older male compared with female NH residents. Three (12.5%) of the 24 p-values calculated for individual comparisons across categories of age were <0.05 (8 were 0.2), numbers higher than expected by chance alone. However, no single trend was apparent across all categories of age and there was no clear modification of the RR by sex.

Although the low dose of immediate release zolpidem made up the majority of non-benzodiazepine hypnotic dispensings (62.4%), 23.2% of residents received high-dose, immediate-release zolpidem and 4.8% an extended-release formulation of these drugs. We found the high proportion of residents using these drugs to be surprising given that these drugs appear to have a similar adverse event profile to benzodiazepines. It is unclear whether the use of high-dose hypnotics has decreased since the FDA warning in 2013 that recommended against the use of more than 5mg immediate release zolpidem and more than 6.25mg extended release zolpidem. Our findings that both low and high dose hypnotics were used frequently in the nursing home raises the question of whether more should be done to reduce use of non-benzodiazepine hypnotics in this setting. This is especially true given that in 2015, the American Geriatrics Society updated the Beers Criteria to unambiguously recommend avoiding non-benzodiazepine hypnotics without consideration of duration of use (due to their associated harms and minimal efficacy in treating insomnia) rather than just avoiding long-term use of 90 days or more.²⁷

Several limitations of this study deserve discussion. First, we addressed the possibility of time-dependent confounding only indirectly. Other drugs that affect the risk of hip fracture (e.g., antidepressants or benzodiazepines) could be co-prescribed for insomnia with non-benzodiazepine hypnotics. In a previous quantitative sensitivity analysis,²⁸ we found that for confounding by time-dependent use of antidepressants to explain the primary effect of non-benzodiazepine hypnotics on hip fracture (RR 1.7), antidepressants must have been >10 times more commonly used during periods of non-benzodiazepine hypnotic 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 RR.²⁸ We were unable to examine non-prescription treatments like melatonin because they are unobservable in the Medicare Part D claims. Second, the indication for using hypnotics is not recorded in our data. Although we expect that the majority of use is for insomnia, there exists the possibility of co-indications or modifiers of the severity of insomnia that vary over time (e.g., physical activity) and, thus, may induce confounding. Third, the case-crossover method can be sensitive to the classification of exposure, though results were similar when using alternative hazard and control periods.⁹ However, results were similar when using alternative hazard and control periods.⁹ Our classification intervals were also sufficiently short to minimize exposure misclassification.²⁹ Fourth, our data are relatively old (2007–2008). However, the biological mechanisms of the relationship between hypnotic use and hip fracture are likely to be time invariant. Further, non-benzodiazepine hypnotics are still commonly prescribed in the NH according to more recent data.^{30,31} Finally, although it would be helpful to examine whether

outcomes differ for residents who use non-benzodiazepine hypnotics every night versus those who use them intermittently, our data did not permit us to undertake such an analysis.

Conclusion

In summary, we found that the elevated risk of hip fracture that results from non-benzodiazepine hypnotic use may be worsened by advanced age and higher doses of the drugs, but sex was a less important modifier of this effect. Absences of differences by sex were perhaps due to the small sample size from the crossover study design. We recommend that when clinicians are prescribing a non-benzodiazepine hypnotic to any NH resident, doses of these drugs should be kept as low as possible, especially among those with advanced age.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was partially funded through research grants from the National Institute on Aging (5P01AG027296-05, K23AG033204, and 5R01AG045441). A.R.Z. is supported by an Agency for Healthcare Research and Quality award (5K12HS022998). The authors thank Joshua J. Gagne, PharmD, ScD for comments on a previous version of this manuscript.

Conflict of Interest Disclosures

V.M.'s research is in a related area to that of several different paid activities. V.M. also periodically serves as a paid speaker at national conferences where he discusses trends and research findings in long term and post-acute care. V.M. holds stock of unknown value in PointRight, Inc. an information services company providing advice and consultation to various components of the long term care and post-acute care industry, including suppliers and insurers. PointRight sells information on the measurement of nursing home quality to nursing homes and liability insurers. V.M. was a founder of the company but has subsequently divested much of his equity in the company and relinquished his seat on board. In addition, V.M. Chairs the Independent Quality Committee for HRC Manor Care, Inc., a nursing home chain, for which he receives compensation in the \$20,000–\$40,000 range. V.M. also serves as chair of a Scientific Advisory Committee for NaviHealth, a post-acute care service organization, for which he also receives compensation in the \$20,000–40,000 per year range. V.M. serves as a Technical Expert Panel member on several Centers for Medicare/Medicaid quality measurement panels. V.M. is a member of the board of directors of Tufts Health Plan Foundation; Hospice Care of Rhode Island; and The Jewish Alliance of Rhode Island.

D.D.D. is an employee of Optum and stockholder in UnitedHealth Group, Optum's parent company.

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Figure 1.
Relative Rate of Non-benzodiazepine Hypnotic Use on the Occurrence of Hip Fracture
Relative to Non-use among US Long-stay Nursing Home Residents, 2007–2008.

Table 1

Characteristics of long-stay Nursing Home residents with a Hip Fracture and Discordant Exposure to Non-benzodiazepine Hypnotic Drugs across Hazard and Control Periods (2007–2008).

	Women (N=691)		Men (N=179)	
	n	%	n	%
Age				
<70	47	6.8	18	10.1
70–79	185	26.8	50	27.9
80–89	321	46.5	82	45.8
90	138	20.0	29	16.2
Race/ethnicity				
White, not of Hispanic origin	625	90.4	153	85.5
Hispanic	28	4.1	<11 [*]	5.0
Black, non-Hispanic	20	2.9	<11 [*]	3.9
Other	18	2.6	<11 [*]	5.6
Comorbidities				
Anemia	42	6.1	13	7.3
Arthritis	64	9.3	14	7.8
Heart failure	137	19.8	46	25.7
Stroke	102	14.8	24	13.4
Diabetes mellitus	205	29.7	57	31.8
Urinary Incontinence				
Always continent or always incontinent	431	62.4	115	64.2
Intermittently incontinent	260	37.6	64	35.8
Pain Frequency				
No pain	303	43.8	106	59.2
Pain less than daily	212	30.7	48	26.8
Pain daily	176	25.5	25	14.0
Transfers				
Independent	120	17.4	32	17.9
Requires supervision or limited assistance	309	44.7	89	49.7
Requires extensive or full assistance	262	37.9	58	32.4
Bed rails used	161	23.3	43	24.0
Functional status				
No or mild impairment (score 0–7)	169	24.5	36	20.1
Moderate impairment (score 8–20)	444	64.3	133	74.3
Total or severe dependence (score 21–28)	78	11.3	<11 [*]	5.6
Cognitive Status				
Intact or mild impairment (CPS [†] 0–1)	287	41.5	67	37.4
Moderate or severe impairment (CPS 2–6)	404	58.5	112	62.6

^{*} The Center for Medicare and Medicaid Services prohibits showing exact counts for cell sizes under 11.

[†]CPS, cognitive performance scale

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