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Original Study

Age, Sex, and Dose Effects of Nonbenzodiazepine Hypnotics on Hip Fracture in Nursing Home Residents

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A B S T R A C T

Objective: The Food and Drug Administration recommends a reduced dose of nonbenzodiazepine 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 nonbenzodiazepine hypnotics on the rate of hip fracture among NH residents.
Design and Setting: Case-crossover study in US NHs.
Participants: A total of 691 women and 179 men with hip fracture sampled from all US 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 (RRs) and 95% confidence intervals (CIs) from conditional logistic regression models for nonbenzodiazepine hypnotics (vs nonuse) comparing 0 to 29 days before hip fracture (hazard period) with 60 to 89 and 120 to 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 1.5–1.9) 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.
Conclusions: The rate of hip fracture in NH residents due to use of nonbenzodiazepine hypnotics was greater among older patients than among younger patients and, possibly, with higher doses than with lower doses. When clinicians are prescribing a nonbenzodiazepine hypnotic to any NH resident, doses of these drugs should be kept as low as possible, especially among those with advanced age.

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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 to $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 to $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. No other conflicts of interest to disclose.

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On January 10, 2013, the US Food and Drug Administration (FDA) notified health care professionals and consumers about the risk of next-morning psychomotor impairment after the use of zolpidem, a nonbenzodiazepine 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 nonbenzodiazepine 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 1 year.[7] Although studies have confirmed the relationship between nonbenzodiazepine hypnotics and fractures,[8–13] the results for sex-specific effects have been inconclusive.[11] Moreover, few 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 play a critical role in prescribing decisions.[14] This topic is especially important given that prior publications showed that the benefit of nonbenzodiazepine 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 nonbenzodiazepine hypnotics on the rate of hip fractures among long-stay US NH residents: a population potentially at the highest risk of psychomotor impairment from nonbenzodiazepine 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 July 1, 2007, and December 31, 2008, we identified 127,917 beneficiaries who had a hip fracture, of whom 127,253 (99%) were enrolled in Part A for $\geq$6 months and 23,882 resided in a NH for $\geq$100 consecutive days before the date of their hip fractures (long-stay residents). After requiring continuous enrollment in Part D and age $\geq$65 years, the final sample size was 15,528 participants. A description of nonbenzodiazepine 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] Nonbenzodiazepine 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 nonbenzodiazepine hypnotic possession (as a proxy for consumption) during the 0 to 29 days before the hip fracture (hazard period) with exposure during the 60 to 89 and 120 to 149 days before the hip fracture (control periods) for each participant. Periods of 30 days were selected because a nonbenzodiazepine 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 carryover 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, Ninth 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 Nonbenzodiazepine Hypnotic Exposure

Nonbenzodiazepine 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 nonbenzodiazepine 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 before the earliest control period when ascertaining covariates.

Statistical Analysis

We used conditional logistic regression models (SAS version 9.3; SAS Institute, Cary, NC) to estimate the effect as odds ratios, which