A 5-Year Prospective Assessment of the Risk Associated with Individual Benzodiazepines and Doses in New Elderly Users

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OBJECTIVES: To determine the risk of injury associated with the new use of individual benzodiazepines and dosage regimens in the elderly.

DESIGN: Prospective database cohort study with 5 years of follow-up.

SETTING: Quebec, Canada.

PARTICIPANTS: Two hundred fifty-three thousand two hundred forty-four persons aged 65 and older who were nonusers of benzodiazepines in the year before follow-up.

MEASUREMENTS: Population-based hospitalization and prescription and medical services claims databases were used to compare the risk of injury during periods of benzodiazepine use with those of nonuse. Periods of use were measured for 10 insured benzodiazepines by drug and dose as time-dependent covariates. Injury was defined as the first occurrence of a nonvertebral fracture, soft-tissue injury, or accident-related hospital admission. Patient age, sex, previous injury history, concomitant medication use, and comorbidity were measured as fixed and time-dependent confounders. Cox proportional hazards models were used to estimate the risk of injury with benzodiazepine use and to determine the extent to which patient characteristics, differences in dosage, or in the effect of increasing dosage for individual drugs explained differences between drugs.

RESULTS: More than one-quarter (27.6%) of 253,244 elderly were dispensed at least one prescription for a benzodiazepine, and 17.7% of elderly were treated for at least one injury during follow-up, of which fractures were the most common. Patient characteristics, systematic differences in the risk of injury in elderly prescribed different benzodiazepines, and differences in dosage prescribed for individual drugs confounded the risk of injury with benzodiazepine use. The risk of injury with increasing dosage varied by drug from a hazard ratio of 0.92 (95% confidence interval (CI) = 0.60, 1.42) for alprazolam to 2.20 (95% CI = 1.39, 3.47) for flurazepam per 1 standardized adult dose increase.

CONCLUSION: The risk of injury varied by benzodiazepine, independent of half-life, as did the risk associated with increasing dosage for individual products. Higher doses of oxazepam, flurazepam, and chlordiazepoxide are associated with the greatest risk of injury in the elderly. **J Am Geriatr Soc 53:233–241, 2005.**

Key words: benzodiazepine; injury; elderly

The elderly, particularly women,[1–5] commonly use benzodiazepines. Prevalence of use ranges from 10% to 30% per annum in elderly, compared with 2% to 5% in younger adults.[1,3–5] Because injuries are also common in the elderly,[6,7] particularly fall-related fractures in women,[8] extensive epidemiological investigations have been conducted to determine the risk of injury that may be associated with benzodiazepines.[9–11] Most studies have shown that the use of benzodiazepines is associated with an increased risk of falls, hip fractures, and motor vehicle accidents,[12–18] but there is inconsistent evidence about the specific drug regimens that may increase injury risk. More recent research[19–25] has challenged prior reports that concluded that only long-acting benzodiazepines were problematic and short-acting products were safe.[15,16]

Several investigators have provided possible explanations for this inconsistency.[19–21] One reported that benzodiazepines with sedative indications were associated with a higher risk of injury (relative risks (RRs) of 2.3–4.0) than benzodiazepine tranquilizers (RRs of 1.6–2.5).[20] Yet, the meaning of these findings is unclear because benzodiazepines are often prescribed for a variety of indications.[26,27] Another tested the hypothesis that age-related decline in hepatic oxidation would increase the risk of hip fracture with the use of oxidative-metabolized benzodiazepines but found that the use of nonoxidative metabolized benzodiazepines conferred the greatest risk of injury.[21]

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Post hoc analysis of individual drugs has provided the most interesting insights. One study found that temazepam, a short-half-life hypnotic benzodiazepine, was associated with an increased risk of hip fracture in the elderly (odds ratio = 3.78, 95% confidence interval (CI) = 1.6–8.9), whereas long-half-life products such as diazepam or those used for similar hypnotic indications were not associated with any increase in risk.[22] The most intriguing results reported suggested that the risk of hip fracture was associated with the benzodiazepine prescribed and differences in the effect of increasing dose between drugs.[19] For example, low and high doses of lorazepam were associated with five times the risk of fracture. In contrast, temazepam was associated with three times in the risk of fracture but only at higher doses, whereas nitrazepam use was not significantly associated with a greater risk of hip fracture at low or higher doses.[19]

Inadequate study power has primarily hampered elucidation of the risks associated with specific benzodiazepines and drug-specific dose regimens. Individual studies have an insufficient number of users of specific benzodiazepines and too few events to provide a precise estimate of the risk associated with individual drugs and dosage regimens. As a result, it has been difficult to evaluate the risk associated with individual drugs, control for confounding related to differences in dose prescribed, or test the potential drug-specific dose effects as suggested by one study.[19]

Clinical indication and prevalent user biases represent additional problems that may explain apparent differences in risk associated with use of drug-specific benzodiazepine regimens. Indication biases are probable because elderly patients with a greater risk of injury are more likely to be prescribed smaller doses and short-acting products.[5,27] Prevalent users[25] include those who have switched from one benzodiazepine to another (approximately 29% of elderly[28]), and persons who switch medication in a given class have been shown to have a higher risk of adverse events.[29]

Because guidelines for benzodiazepine use currently advise physicians to avoid long-acting benzodiazepines in the elderly in favor of short-acting drugs,[30,31] the risks associated with specific drugs and dose regimens need to be identified to guide physician practice. The current study was designed to estimate the risk of injury in the elderly associated with specific benzodiazepines and drug-specific dose regimens within a population-based sample of community-dwelling elderly. Limitations in prior research were addressed by restricting the study to new benzodiazepine use by all elderly patients over a 5-year period and by using analytic methods that were able to account for systematic differences between users and nonusers and dosage regimens.

METHODS

Context and Data Sources

This study was conducted in Quebec, a Canadian province that provides public insurance coverage for medical and hospital care for all residents and insured prescription drug coverage for all persons aged 65 and older. Information from Quebec insurance plan databases was used to assemble the study cohort, assess prescription drug use, and determine the occurrence of injuries. The beneficiary demographic database provided data on age, sex, and date of death. The prescription claims database, previously validated,[32] provided data on each prescription dispensed from community-based pharmacies, including the drug, quantity, date, and duration of each prescription. The physician claims database provided information on the date, type, diagnosis, procedure, and location of service delivery, for all services, provided on a fee-for-service basis, including those for injury treatment. The hospitalization database provided the cause of accident-related admissions and primary and secondary *International Classification of Diseases, Ninth Revision* (ICD-9) diagnostic codes for all hospital discharges in Quebec.

Design and Study Population

A cohort of community-dwelling Quebec elderly who did not use benzodiazepines in the baseline year (1989) was assembled by first retrieving a random sample of 517,450 who were aged 65 and older on January 1, 1989, from the beneficiary database. All prescriptions and medical services and hospitalization records were retrieved for the sample from the prescription claims, physician claims, and hospitalization database for the baseline and follow-up period (January 1, 1990 to December 31, 1994). Persons who were dispensed prescriptions for benzodiazepines in 1989 (n = 211,474, 40.9%), died in 1989 (n = 18,257, 3.5%) or were institutionalized for the entire follow-up period (n = 34,475, 6.7%) were excluded, resulting in a cohort of 253,244 persons who were nonusers of benzodiazepines at the start of the follow-up period.

Benzodiazepine Use

All prescriptions dispensed for each person in the cohort were assessed over the 5-year follow-up period. Ten benzodiazepines, insured through the provincial program, were studied: three with short elimination half-life (10 hours: triazolam, oxazepam, temazepam), four with intermediate half-life (11–47 hours: alprazolam, nitrazepam, bromazepam, lorazepam), and three with long half-life (48 hours: chlordiazepoxide, flurazepam, diazepam).[10,11] Time-dependent measures of benzodiazepine use were created using the start and end dates of each prescription to minimize misclassification errors.[33] For each follow-up day, individuals were classified as current users of a specific benzodiazepine, using 10 binary indicator variables to represent each drug. During periods of use, daily dosage was measured by first determining the prescribed number of tablets to be taken each day (number of tablets dispensed divided by prescription duration) and multiplying daily quantity by the strength of each tablet. Standardized daily dosages were created by dividing the prescribed dose by the World Health Organization (WHO) recommended daily dose for adults[34] to permit comparisons among drugs.

A new record characterizing benzodiazepine usage was generated each time individuals changed their exposure status, defined as a change in drug dosage, or a change to nonuse status determined by the end-date of the prescription. Overlaps and gaps of less than 3 days in filling prescriptions for the same drug and dosage were ignored because the insurer permits refills within 3 days of the expiry date of a prescription. Drugs dispensed during periods of hospitalization were not recorded in the prescription

claims files. To minimize measurement error, the patient was temporarily removed from the risk set during days spent in the hospital. To adjust for systematic but unmeasured differences in treatment indication or injury risk associated with the choice of benzodiazepine prescribed by a physician,[2] 10 cumulative indicator variables were created, each indicating the prescription of a specific benzodiazepine. Initially, all subjects were assigned a 0-value for all cumulative indicators, but the day the subject first started using a benzodiazepine, the value of the corresponding cumulative indicator was permanently changed to 1. Thus, on each day of follow-up, a particular cumulative indicator identified those subjects who had been prescribed a given product at any time up to that day, regardless of their current exposure status.

Injury Occurrence

Four categories of injuries were assessed: (1) nonvertebral fractures (fractures of the upper and lower extremity, hip, pelvis, skull, and thorax), (2) soft-tissue injuries (laceration, subluxation), (3) fall-related hospital admissions (E codes: 880–888), and (4) other accident-related hospital admissions for which the cognitive and psychomotor side effects of benzodiazepines could have increased injury risk (transportation accidents in which the individual was the driver (E codes: 810.0.2.6.7–825.0.2.6.7), accident caused by fire (E codes: 890–899), and poisoning (E codes: 850–869)). Diagnostic and treatment procedure codes (e.g., procedure code 2584: pelvis fracture, open reduction) recorded in medical services claims were used to measure fractures and soft-tissue injuries, in accordance with previously validated algorithms.[35] In the elderly, approximately 80% of fractures and soft-tissue injures are fall related.[35] The sensitivity of using diagnostic and treatment procedure codes to assess these injuries in Quebec is greater than 80%.[35] In addition, accident-related hospital admissions that were not associated with fractures and soft-tissue injuries were identified by inspection of the admission E code field for each subject in the hospitalization database.

Potential Confounders

Fixed and time-varying covariates were used to measure relevant patient and treatment characteristics.[7–9,15,16,22,36,37] Age, sex, and prior injury were assessed in the baseline year and were treated as fixed covariates. Prior injury was assessed using the same approach as outlined for injury assessment during follow-up. Concurrent use of drugs that may increase (neuroleptics, antidepressants, opioid analgesics, anticonvulsants, other sedative-hypnotics)[6,15,16,22] or diminish (thiazide diuretics, estrogen replacement)[22,37] the risk of injury was represented as time-varying covariates. Comorbid conditions that are associated with a greater risk of fall-related injuries[6,36] were identified in the baseline year and follow-up period using validated ICD-9 diagnostic codes in the medical services[38] and hospitalization database as well as by use of disease-specific medication in the prescription claims database. These conditions included visual impairment (ICD-9 360–379, antiglaucoma drugs), stroke (ICD-9 430–431, 434, 436), Parkinson's disease (ICD-9 332–333, antiparkinsonian drugs), dementia (ICD-9 290, 291, 294, 331–335), epilepsy (ICD-9 345, anticonvulsant medication), and lower extremity arthritis (ICD-9 710–719, 724, 725, 726.1, 726.6, 726.7, 727.1, 274), as well as treatment codes for hip or knee arthroplasty.

Analysis

To assess the effect of benzodiazepines use on the risk of injury, Cox proportional hazards model with time-dependent covariates was used.[39] Time to event was defined as the days elapsed between the cohort inception, on January 1, 1990, and the first injury. Individuals who did not have any injury recorded during follow-up were censored at the end of the study or on the date of benzodiazepine switch/addition, a move out of the province, institutionalization, or death. Follow-up was truncated after a benzodiazepine switch/addition because subjects who have been switched from another drug may be at systematically higher risk than new users of the same product.[21,24,29]

Four models were estimated, each using a different combination of time-dependent variables (TDVs) to represent current use, prior use, and dosage of a given benzodiazepine. All models included the same baseline and time-dependent measures of potential confounders that were found to be statistically significant in at least one model.

The first model estimated the risk associated with current use of individual benzodiazepines, irrespective of dose, by including 10 binary on-off TDVs, each indicating current use of a specific benzodiazepine, relative to periods of nonuse, with never users assigned a value of 0. In the second model, the 10 cumulative indicator variables were added to the model that included TDVs for current use to assess whether unmeasured patient characteristics, related to a physician's choice of drug, confounded the risk estimates for individual benzodiazepines. The cumulative indicators represented the risk of injury during periods of nonuse relative to persons who were not prescribed a benzodiazepine. This model allowed for the separation of the risk associated with current use from systematic, but unmeasured, differences between elderly prescribed different drugs. The resulting estimate of the hazard ratio (HR) for current use represented the risk associated with periods of use compared with periods of nonuse in persons previously prescribed the same benzodiazepine. The third model assessed whether systematic differences in the doses prescribed confounded comparisons between individual benzodiazepines. A single TDV for standardized dosage was added to a model that included the 10 TDV current-use indicators. To permit a meaningful interpretation of the current-use indicators, a centered dose was created for each person by subtracting the mean standardized dose for all benzodiazepines prescribed during the follow-up period from the standardized dose on each day of use.[40] The estimated HRs for indicators of current use represented the risk associated with the current use at a common mean dose, relative to nonuse, assuming a common dose-response relationship for all benzodiazepines. The fourth model assessed whether the effect of increasing dose on the risk of injury may differ between benzodiazepines as suggested previously.[19] To permit separate estimates of the dose-response for each drug, the 10 binary indicators of current use were replaced with 10 corresponding quantitative measures of standardized

dose for each product. The HRs estimated in this model represented the risk associated with increasing the current dose of a given drug from 0% to 100% of the recommended daily adult dose.

The use of several time-dependent covariates resulted in more than 10 million records for 253,244 individuals. The resources required for Cox regression analyses of a data set of this size exceeded the available memory capacities by a factor of about seven. Therefore, a method based on pooling separate HR estimates from independent data sets was employed.[41] First, the entire study population was randomly divided into seven mutually exclusive subsets. The four models were then estimated separately for each subset. The pooled overall HR estimate, together with 95% CIs, were estimated using the method proposed by Parmar.[41] Akaike information criterion,[42] based on pooled log likelihood, was employed to compare the goodness of fit of alternative models while accounting for differences in degrees of freedom.

RESULTS

At the start of the follow-up period, the average age of persons in the cohort was 73.4 years; 52.4% were female, and 4.8% had been treated or hospitalized for injuries in the previous year (Table 1). Between 1990 and 1994, 27.6% (69,791) received at least one benzodiazepine prescription. New benzodiazepine users were more likely than nonusers to use antidepressant and other sedative hypnotic medication in the baseline year but otherwise were similar to nonusers with respect to the prevalence of chronic illness that would increase the risk of fall-related injuries, mortality, and prior hospitalization (Table 1). The majority of new users were

Table 1. Characteristics of the Study Population in the Baseline Year (1989) Before the Start of Follow-Up—Overall and by Benzodiazepine Use Status During Follow-Up

		Benzodiazepine Use During Follow-Up (1990–1994)	
Baseline Cohort Characteristic	Overall (N = 253,244)	New Users (n = 69,791)	Never Users (n = 183,453)
Patient demographics			
Age, mean ± SD	73.4 ± 6.0	73.8 ± 5.7	73.6 ± 6.1
Female, %	52.4	55.5	51.1
Comorbidity that increases the risk of falls, %			
Visual impairment	21.9	22.7	21.7
Lower extremity arthritis	11.2	12.6	10.7
Stroke	1.2	1.0	1.2
Parkinson's disease	1.3	1.5	1.3
Dementia	1.3	1.2	1.4
Epilepsy	1.1	0.9	1.2
Medications that may increase the risk of falls, %			
Psychotropics			
Antidepressants	2.8	4.3	2.3
Antipsychotics	1.4	1.6	1.3
Other sedatives	3.1	4.2	2.7
Other drugs			
Cardiac drugs	27.3	30.5	26.1
Antihypertensives	12.5	13.9	12.0
Vasodilators	13.9	16.6	12.9
Nonthiazide diuretics	11.2	12.1	10.8
Opiate antagonists	0.7	0.8	0.6
Medications that may reduce the risk of fractures, %			
Estrogen	0.1	0.1	0.1
Thiazide diuretics	6.6	7.2	6.4
General health status measures			
Number of medical visits, mean ± SD	9.2 ± 10.9	10.0 ± 10.9	8.9 ± 10.8
Number of hospitalizations, mean ± SD	0.2 ± 0.7	0.2 ± 0.6	0.2 ± 0.7
Injury in the baseline year			
Fracture-, soft tissue-, or accident-related admissions, %	4.8	4.5	4.9

SD = standard deviation.

Table 2. Characteristics of Benzodiazepine Use During Follow-Up (1990–1994) for the 69,791 New Users

Characteristic	N	%
Starting year		
1990	25,191	36.1
1991	16,197	23.2
1992	11,772	16.9
1993	9,519	13.6
1994	7,112	10.2
Drug type		
Short half-life (≤10 hours)		
Triazolam	2,174	3.1
Temazepam	3,699	5.3
Oxazepam	14,084	20.2
Intermediate half-life (11 to ≤48 hours)		
Alprazolam	3,743	5.4
Nitrazepam	1,369	2.0
Bromazepam	3,686	5.3
Lorazepam	30,507	43.7
Long half-life (>48 hours)		
Chlordiazepoxide	828	1.2
Flurazepam	4,993	7.1
Diazepam	4,708	6.7
Duration of first period of uninterrupted use, days		
≤15	13,108	18.8
16–30	15,926	22.8
31–60	32,002	45.8
61–90	3,685	5.3
91–180	3,103	4.4
181–360	1,342	1.9
>360	625	0.9
Standardized dose in first period of uninterrupted use, %		
≤50	42,544	61.0
51–100	20,812	29.8
>100	6,435	9.2

initially prescribed less than half of the recommended adult dose, and most were started on lorazepam (43.7%) (Table 2).

In the 5-year follow-up period, 44,753 (17.7%) persons in the cohort sustained at least one injury requiring medical treatment, and 5,336 (2.1%) were treated for multiple injuries at the time of their first event (Table 3). Fractures were the most common injury, followed by lacerations.

The injury rate during periods of nonuse was 46.2 per 1,000 person-years, whereas rates during benzodiazepine use ranged from 46.6 (diazepam) to 86.7 (flurazepam) per 1,000 person-years, indicating a 1% to 88% unadjusted increase in risk (Table 4, column 4). Model 1 (Table 4, column 5) shows the relative risks associated with the current use of a given benzodiazepine compared with periods of nonuse pooled from past users and never users, with adjustment for baseline risk factors, concurrent use of other drugs, and morbidity. Comparison of columns 4 and 5 of Table 4 shows that these adjustments produced modest changes in the estimated HRs, except for chlordiazepoxide, for which there was a substantial and statistically significant increase in risk of injury with current use. Temazepam, oxazepam, lorazepam, and flurazepam were also associated with statistically significant increases in injury risk. For triazolam ($P = .07$) and nitrazepam ($P = .07$), the risks associated with current use were of similar magnitude but were marginally nonsignificant because of smaller sample sizes.

Model 2 (Table 4, column 6) additionally adjusted the effects of current use for the 10 cumulative indicators of previous use of specific benzodiazepines that indirectly accounted for possible systematic differences in unmeasured patient characteristics between users of different benzodiazepines. Accordingly, these estimates allowed the risk of injury during periods of use versus nonuse of all persons prescribed a specific benzodiazepine to be compared. These additional adjustments produced substantive reductions in the estimated risk for oxazepam, nitrazepam, lorazepam, flurazepam, and chlordiazepoxide (Model 2, Table 4, column 6). This is because persons who were started on oxazepam (HR = 1.10, 95% CI = 1.04–1.18), nitrazepam (HR = 1.27, 95% CI = 1.05–1.52), lorazepam (HR = 1.06,

Table 3. Characteristics of the First Injury Event During Follow-Up (1990–1994) for the 253,244 Persons in the Study Population

Injury Occurrence	N	%
No injury	208,491	82.3
Any injury	44,753	17.7
Single injury	39,417	15.6
Multiple injuries sustained at first event	5,336	2.1
Injury frequency by type		
Single injury (n = 39,417)*		
Any fracture	19,506	49.5
Upper extremity fracture	6,356	16.1
Lower extremity fracture	5,603	14.2
Hip fracture	3,674	9.3
Other fracture (e.g., skull, thorax, pelvis)	3,873	9.8
Any soft-tissue injury	17,403	44.2
Laceration	16,040	40.6
Subluxation	1,363	3.5
Fall-related accidents	2,114	5.4
Other accidents	394	0.9
Multiple injuries at first event (n = 13,555) injuries†		
Any fracture	9,223	68.0
Upper extremity fracture	2,506	18.5
Lower extremity fracture	3,413	25.2
Hip fracture	2,079	15.3
Other fracture (e.g. skull, thorax, pelvis)	1,225	9.0
Any soft-tissue injury	1,646	12.1
Laceration	1,163	8.6
Subluxation	483	3.6
Fall-related accidents	2,463	18.2
Other accidents	223	1.6

* Percentage refers to percentage of single injuries.
† Percentage refers to percentage of multiple injuries.

Table 4. The Risk of Injury Associated with Periods of Benzodiazepine Use by Drug During the Follow-Up Period (1990–1994)* in the Study Population of 253,244 Elderly in Quebec

	Injury Rate by Use and Type of Benzodiazepine			Hazard Ratio (95% CI)		
				Unadjusted	Adjusted	
Benzodiazepine Exposure	Number of Events (1)	Person-Years (2)	Injury Rate/ 1,000 per Year (3)	Current Use (4)	Current Use‡ (Model 1) (5)	Effect of Current Use Adjusted for Past Use§ (Model 2) (6)
Nonuse periods†	43,043	930,939	46.2	Reference	Reference	Reference
Periods of benzodiazepine use						
Short half-life products						
Triazolam	42	742	56.6	1.22 (0.90–1.66)	1.32 (0.98–1.79)	1.34 (0.95–1.90)
Temazepam	94	1,429	65.8	1.42 (1.16–1.74)	1.26 (1.03–1.55)	1.29 (1.01–1.65)
Oxazepam	392	5,673	69.1	1.49 (1.35–1.65)	1.24 (1.12–1.36)	1.14 (1.01–1.28)
Intermediate half-life products						
Alprazolam	72	1,377	52.3	1.13 (0.90–1.43)	1.10 (0.87–1.38)	1.10 (0.84–1.42)
Nitrazepam	38	569	66.8	1.44 (1.05–1.99)	1.34 (0.97–1.84)	1.12 (0.77–1.63)
Bromazepam	60	1,236	48.5	1.05 (0.82–1.35)	1.03 (0.80–1.32)	1.08 (0.81–1.43)
Lorazepam	830	13,699	60.6	1.31 (1.22–1.40)	1.20 (1.12–1.29)	1.15 (1.06–1.24)
Long half-life products						
Chlordiazepoxide	12	199	60.4	1.31 (0.74–2.30)	1.83 (1.04–3.22)	1.55 (0.83–2.90)
Flurazepam	113	1,303	86.7	1.88 (1.56–2.26)	1.78 (1.48–2.14)	1.61 (1.31–1.99)
Diazepam	57	1,222	46.6	1.01 (0.78–1.31)	0.99 (0.76–1.28)	1.01 (0.77–1.33)

* Cohort observed from January 1, 1990 (baseline), until first injury, loss to follow-up, switch to/addition of another benzodiazepine, or December 31, 1994.

† Periods of nonuse combine nonuse periods for past users and never users.

‡ Model 1 adjusted for fixed covariates in the baseline year (age at baseline, sex, history of injury) and time-dependent measures of visual impairment, stroke, arthritis, Parkinson/dementia, and concurrent psychotropic drug use. This model compares injury risk during current use with injury risk during nonuse periods for never users and noncurrent users of benzodiazepines.

§ Model 2 compared the estimated risk of injury associated with current use with that of nonuse for past users of a given benzodiazepine. Ten indicator variables, representing the benzodiazepine started by the individual, for new users were included in the model that included patient demographics and comorbidity (see footnote (†)). This model estimated the risk of injury with use of a specific drug by comparing periods of use and nonuse for all persons started on the same benzodiazepine. Persons who were started on oxazepam (hazard ratio (HR) = 1.10; 95% confidence interval (CI) = 1.04–1.18), nitrazepam (HR = 1.27, 95% CI = 1.05–1.52), lorazepam (HR = 1.06, 95% CI = 1.01–1.10), and flurazepam (HR = 1.12, 95% CI = 1.01–1.24) had a significantly higher risk of injury during nonuse periods than persons who were not prescribed a benzodiazepine, suggesting that the population prescribed these drugs had unmeasured risk factors for injury.

Table 5. The Risk of Injury Associated with Periods of Benzodiazepine Use by Drug, Adjusting for Average Dose and Estimating Dose-Response Effects by Drug

		Standardized Dose	Adjusted Hazard Ratio (95% Confidence Interval)		
Benzodiazepine Exposure*	WHO-Defined Daily Dose mg[†]	Mean ± SD[‡]	Effect of Current Use Adjusted for Past Use[§] (Model 2)	Effect of Current Use Adjusted for Past Use+Dose[‖] (Model 3)	Drug-Specific Effect of Current Dose Adjusted for Past Use[¶] (Model 4)
	(1)	(2)	(3)	(4)	(5)
Short half-life products					
Triazolam	0.25	0.92 ± 0.38	1.34 (0.95–1.90)	1.31 (0.93–1.85)	1.20 (0.85–1.70)
Temazepam	20	1.04 ± 0.45	1.29 (1.01–1.65)	1.22 (0.94–1.57)	1.23 (1.01–1.51)
Oxazepam	50	0.41 ± 0.25	1.14 (1.01–1.28)	1.19 (1.05–1.35)	1.46 (1.17–1.81)
Intermediate half-life products					
Alprazolam	1	0.54 ± 0.36	1.10 (0.84–1.42)	1.13 (0.87–1.47)	0.92 (0.60–1.42)
Nitrazepam	5	1.29 ± 0.52	1.12 (0.77–1.63)	1.02 (0.69–1.49)	1.06 (0.81–1.38)
Bromazepam	10	0.44 ± 0.26	1.08 (0.81–1.43)	1.14 (0.86–1.52)	1.29 (0.79–2.11)
Lorazepam	2.5	0.49 ± 0.29	1.15 (1.06–1.24)	1.19 (1.09–1.30)	1.29 (1.14–1.46)
Long half-life products					
Chlordiazepoxide	30	0.65 ± 0.51	1.55 (0.83–2.90)	1.55 (0.83–2.90)	2.20 (1.39–3.47)
Flurazepam	30	0.74 ± 0.31	1.61 (1.31–1.99)	1.62 (1.31–1.99)	1.93 (1.53–2.44)
Diazepam	10	0.63 ± 0.45	1.01 (0.77–1.33)	1.03 (0.78–1.36)	1.03 (0.71–1.48)

* Periods of benzodiazepine use relative to periods of nonuse among past users of the same drug.
† The World Health Organization (WHO)-Defined Daily Dose (DDD) for each benzodiazepine was used to standardize the measurement of dose to permit comparisons between drug products. For example, the DDD for triazolam was 0.25 mg, and the average standardized dose prescribed during periods of use was 0.92, or 0.23 mg (0.92 mg × 0.25 mg) in the original dosage units.
‡ The mean standardized dose represents the mean of daily doses for all persons using a given drug during periods of use.
§ Results are replicated from Table 4, column 6, to permit comparisons between dose-adjusted (Table 5, column 4) and dose-unadjusted models (Table 5, column 3).
‖ Model 3 assumes that the dose-response effect is equivalent for all benzodiazepines.
¶ In Model 4, 10 quantitative measures of standardized dose for each drug replaced binary indicator variables, representing periods of use versus nonuse for each benzodiazepine. The hazard ratio estimated in Model 4 represents the risk of increasing the dose of a given product from 0% to 100% of the standardized adult dose for the respective product.

95% CI = 1.01–1.10), chlordiazepoxide (HR = 1.10, 95% CI = 0.88–1.37), and flurazepam (HR = 1.12, 95% CI = 1.01–1.24) had a higher risk of injury during nonuse periods than persons who were not prescribed a benzodiazepine, suggesting that the population prescribed these drugs has unmeasured risk factors for injury.

The average standardized dose prescribed for different benzodiazepines varied from 0.41 of the WHO-defined daily dose of 50 mg for oxazepam (i.e., an average dose of 0.41 × 50 = 20.5 mg) to 1.29 of the defined daily dose of 5 mg for nitrazepam (Table 5, column 2). To avoid possible confounding by differences in dose, Model 3 (Table 5, column 4) shows the effects of current use, adjusted for the time-dependent covariate representing current dose. Dose, when added to the model, was associated with a 20% risk increase, with a change from 0 to the recommended defined daily dose for adults (HR = 1.20, 95% CI = 1.04–1.38). Although, as expected, the estimated HRs increased for benzodiazepines prescribed at lower average doses, and diminished for those prescribed at higher doses, adjustment for dose did not remove the differences in estimated effect of individual benzodiazepines (Table 5, column 4 vs column 3). Oxazepam, lorazepam, and flurazepam use continued to be associated with a statistically significant greater risk in contrast to the absence of effect for diazepam and nitrazepam (Table 5, column 4).

Whereas Model 3 implicitly assumes that dose has the same effect on all benzodiazepines, Model 4 estimates a separate effect of dose for each drug. Indeed, when binary indicators of benzodiazepine use were replaced with quantitative measures of benzodiazepine-specific standardized doses, there was an improvement in model fit as judged by the Akaike information criterion compared with Model 3. Model 4 yielded statistically significant increases in the risk associated with increasing dose for temazepam, oxazepam, lorazepam, chlordiazepoxide, and flurazepam (Table 5, column 5). In contrast, there was a lack of any dose-response effect for drugs such as alprazolam, nitrazepam, and diazepam. The dose-response effects for the long-acting benzodiazepines varied substantially by drug. For chlordiazepoxide (HR = 2.20), and flurazepam (HR = 1.93), the estimated increase of injury risk associated with an increase from 0 to the recommended adult dose was about double, whereas there was no effect for diazepam (HR = 1.03).

DISCUSSION

This study confirmed the hypothesis that the risk of injury in elderly persons varies by benzodiazepine, independent of half-life. Baseline injury risk in persons prescribed different benzodiazepines, differences in the average dose prescribed for different benzodiazepines, and differences in the effect

of increasing dose for individual drugs on the risk of injury explained part of the differences between drugs. Moreover, even after adjusting for these differences, there were substantial differences in estimated risk of injury in the new users of three long-acting benzodiazepines. Current use of flurazepam and chlordiazepoxide was associated with a 50% to 60% increase in injury risk, in contrast to diazepam, which had no significant increase in risk with use or dose. Although this study was conducted using data from the early 1990s, benzodiazepines that were commonly used in this cohort of elderly persons continue to be the most commonly prescribed benzodiazepines in North America,[43] and thus the estimated relative risks of injury associated with these medications are applicable to current practice.

The strengths of this study were that it was possible to prospectively follow a large, population-based cohort of elderly persons over a 5-year period and examine the risks associated with the new use of individual benzodiazepines using comprehensive and validated information on prescription drug use and injury occurrence.[32,35] With the availability of a large sample of new users, and time-dependent assessment of exposure,[33] it was possible to isolate the contributions of the individual drug, dosage, and differences in the dose-response relationship between benzodiazepines to the risk of injury. Bias in comparisons between drugs was reduced through the novel employment of cumulative drug indicator variables, which adjusted for systematic unmeasured differences in the risk of injury in persons started on different benzodiazepines. Using incident users, adjusting for differences in injury history, and using time-varying covariates to represent changes over time in the concurrent use of other relevant medications further reduced risk of bias in comparisons between drugs. By estimating different multivariable models, it was possible to gain insight into how different aspects of drug use and confounders affected risk estimates. For example, the risk associated with nitrazepam use was reduced from 44% to 34% when adjusted for potential confounding and to 12% when adjusted for unmeasured risk factors (the cumulative use indicator). The higher risk of injury in persons prescribed nitrazepam than in those prescribed other benzodiazepines likely represents confounding by unmeasured clinical indications. Dose was also a major confounder, because nitrazepam was prescribed at a higher mean dose than other benzodiazepines. Adjustment for dose reduced the risks associated with nitrazepam from 12% to 2%. When a separate effect of dose for each benzodiazepine was estimated, important differences in the strength of the dose-response relationship across drugs were evident. An increase from 0 to the maximum adult dose for nitrazepam and diazepam was associated with increased risk of injury of 6% and 3%, respectively, whereas the same increase in dose for flurazepam was associated with twice the risk.

Although comprehensive linked population databases provide many advantages, these data sources have limitations that need to be considered in the interpretation of the results. Drug exposure assessment is based on prescription refills and not direct measurement of drug use. Accurate assessment of benzodiazepine use has proved to be challenging because self-report has been shown to underestimate use by as much as 40% when compared with urine and blood analysis.[44] Prescription refills have been shown to provide a reasonably accurate measure of drug use with many medications,[45,46] but when benzodiazepines are prescribed on an as-needed (PRN) basis for problems such as insomnia,[1,47] refill measurement could misclassify current drug use and dose, likely leading to an attenuation of the estimated effect of drug use on the risk of injury. In the few studies that have compared the risk associated with PRN and non-PRN benzodiazepine prescriptions, the risk of falls and hip fracture was similar or even modestly higher for PRN prescriptions.[21]

The cause of the injury was not ascertained in this study, yet prior validation studies showed that the primary mechanism for most injuries in the elderly is related to falls.[35] A subset of possible injuries that would more likely be related to the side effects of benzodiazepine use was selected,[9–11] but random errors in relevant injury ascertainment will likely lead to modest attenuation of relative risk estimates, although this should not vary from one drug to another.

In prior research, benzodiazepines have been treated as a homogeneous class of products or grouped by half-life, oxidative pathway, or approved indication. Based on established variations in prescribing patterns,[27,28,48,49] one would expect that the particular mix of products, and the doses at which they were prescribed, would vary from one study to another. In the current study, the mean dose for some of the benzodiazepines prescribed exceeded the WHO defined daily dose, even though lower doses than the maximum adult dose are generally recommended in the elderly.[10] Differences in the drugs and doses prescribed within a broader classification of benzodiazepines, as well as potential biases related to the inclusion of prevalent users and unmeasured confounders, may explain inconsistency in results across studies.

Higher doses of flurazepam, chlordiazepoxide, and oxazepam appear to be associated with the greatest risk of injury in the elderly. Until confirmatory evidence is provided through experimental studies, these benzodiazepines should be avoided in the elderly, particularly at higher doses. Future research needs to investigate the possible reasons for differences in injury risk between medications. Differences in drug potency, the affinity of a benzodiazepine for its receptors, may be one explanation for dose-related differences between drugs. Potency has been noted to vary between benzodiazepines independent of half-life[27,50] but the investigation of pharmacological potency in the elderly, where age-related changes in receptors may influence therapeutic effects, is only beginning to emerge[50] and should be addressed in subsequent research to establish parameters for safe and effective benzodiazepine use in this vulnerable population.

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