ORIGINAL RESEARCH ARTICLE

Drug Safety 2005; 28 (12): 1141-1150
0114-5916/05/0012-1141/$34.95/0

Effect of Concomitant Use of Benzodiazepines and Other Drugs on the Risk of Injury in a Veterans Population

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Abstract

Background: Benzodiazepines comprise a class of drugs that when used as monotherapy are generally acknowledged to pose a risk for injury by increasing the likelihood of falls, fall-related injuries, adverse drug events and car accidents. Benzodiazepines may also be used concomitantly with other high risk medications that may further exacerbate the risk of injury. The aim of this study is to examine the occurrence of the concomitant use of benzodiazepines and other drugs and then quantify the indirect effect of these drug combinations on the likelihood of an injury-related healthcare episode.

Methods: A multivariate model was specified that included outpatient prescription data and inpatient/outpatient medical utilisation records for 13 745 patients at a Veterans Administration hospital system over a 3-year period (1999–2001). We analysed 133 872 outpatient benzodiazepine prescriptions and >1.5 million non-benzodiazepine prescriptions for the study population. Micromedex software was used to identify combinations of benzodiazepines and other drugs that are likely to result in 'major' interactions. We then further restricted our focus to the use of these drug combinations within a 30-day period prior to an injury-related medical event. The adjusted odds ratio on a variable characterising concomitant use of a benzodiazepine and another drug within this period was used to quantify the relative risk of injury. The principal outcome was the estimated risk of an injury-related healthcare episode within a 30-day period when taking both a benzodiazepine and another drug with a 'major' severity rating as defined by Micromedex. The risk of injury was adjusted for comorbidities, hospital discharges, marital status, age, mean arterial pressure and body mass index, as well as the dose of benzodiazepine (converted to diazepam equivalents) and duration of benzodiazepine treatment.

Results: Of the 1110 unique individuals who experienced an injury, 790 (71.2%) patients had used a benzodiazepine in combination with another drug. Furthermore, only 4.3% (320/7522) of the patients taking benzodiazepines who did not have concomitant drug use experienced an injury. The occurrence of this concom-

itant use increased the odds of an injury >2-fold in the model. Dose and duration of benzodiazepine use, as well as certain comorbidities, were also associated with an increased risk for injury, whereas being married reduced the risk.
Conclusions: This is the first large-scale study to quantify the impact of concomitant use of benzodiazepines and other drugs on the risk of injury in a population of Veterans Administration patients. It demonstrates the utility of expanding the focus of inappropriate medication usage to include analyses that link potentially inappropriate drug use with healthcare utilisation for injuries.

Background

Certain medications increase the risk of injury and other adverse health events, which in turn increase healthcare utilisation and costs. Even when used as monotherapy, the use of medications such as antidepressants, antihypertensives, some analgesics, hypnosedatives and anxiolytics has been identified as a significant risk factor in falls, fall-related injuries, adverse drug events and car accidents.[1-11] Such risks are raised still more when these medications are used in combination.[12-19] In order to minimise risk and ensure appropriate use, clinicians and policy makers alike have a stake in fully understanding the extent to which certain drugs and drug combinations influence injury risk in various patient populations.

Benzodiazepines are an important case in point. These medications have been shown in several studies to be independent risk factors in fall-related and other serious injuries in community dwelling elders.[9-11,20-24] In a previous multivariate analysis,[25] we found that benzodiazepine dose and duration each significantly raised the risk of an injury episode of care in a population of patients treated at a single Veterans Administration (VA) health facility. Controlling for comorbidities and demographic factors, our analysis estimated that injury risk increased by approximately 6% for each unit increase in dose and another 4% per unit increase in duration of use.

The findings of previous analyses of benzodiazepines, including our own, referred exclusively to the direct effects of the medication on the risk of injury. It is quite likely, however, that benzodiazepines are taken with other high-risk drugs and the combination or concomitant use of these medications may produce indirect or interaction effects that substantially increase the risk of an injury beyond the direct impacts of benzodiazepine dose and duration alone.[26,27] To illustrate, benzodiazepines and opioid analgesics are used concomitantly in short- and long-term pain and substitution therapy.[28,29] Muscle relaxants and barbiturates may also be taken at the same time.[26,30] Although it is generally understood that the use of benzodiazepines with certain other drugs poses an additional risk for injuries, the extent to which the concomitant use of benzodiazepines and specific other drugs actually elevate such risk is unclear at present. We were, for instance, unable to find any empirical estimates of the magnitude of such risks in the published literature. This gap in the knowledge base has crucial implications for clinical practice and public policy, and immediate efforts are needed to narrow it.

The main aim of this article is to prepare clinical and policy-relevant estimates of the increased risk of injury attributable to the concomitant use of benzodiazepines and other drugs, controlling for the confounding influences of other factors. The next section briefly sets out the analytical framework and data used to estimate the relative risk (multivariate-adjusted odds ratio [OR]) of the concomitant use of benzodiazepines and other drugs on the likelihood of an injury-related episode of healthcare, net of the elevated risk of such an episode attributable to the dose and duration of benzodiazepine use alone. The empirical results of the analysis and a discussion of their significance are then set out in turn.

Materials and Methods

Sources of Data

We drew upon Veteran Health Administration (VHA) data from the pharmacy benefit management (PBM) system for three calendar years (1999–2001)

for the James A. Haley Veterans Administration Hospital, Tampa, Florida, USA. The study population encompasses all VA patients who received at least one outpatient benzodiazepine prescription at some point over the 3-year study period. In order to examine the concomitant use of benzodiazepines and other drugs in this population, all outpatient prescriptions recorded for each patient at any and all points over the study period were entered into the study database. The PBM system records information on the strength of the drug, prescribed daily amount, fill date and quantity supplied for each patient; it also includes a unique patient identifier. Using these unique patient identifiers, the pharmacy data were then merged with calendar year (1999–2001) VHA healthcare utilisation data. The inpatient and outpatient data extracts from the centralised VHA National Patient Care Database included detailed information on patient demographics, injuries and diagnoses. Thus, the working data set used in the empirical analysis reported here included detailed profiles of all outpatient prescriptions coupled to equally detailed information on health-related events and medical care utilisation for each subject in the study population.

Variable Construction

The dependent variable in the model was an injury, constructed in reference to our previously published benzodiazepine study.[25] It refers to an injury or adverse event that occurred within a specified period of time after benzodiazepines had been prescribed. Injuries and adverse events were identified using the International Classification of Diseases (9th Edition)-Clinical Modification (ICD-9-CM) coding for injuries and poisoning (800–999) and then associated with an injury episode of care. These diagnosis codes include physical injuries such as sprains, strains and fractures, as well as adverse events associated with medications. We did not include spinal cord injuries in our study because of coding anomalies in the VHA datasets. We also did not include adverse events associated with medical care, such as complications due to surgery or medical devices. These injuries and adverse events correspond to the Agency for Healthcare Research and Quality's Clinical Classification Software (CCS) for selected injuries and adverse events (i.e. CCS category 225–226, 228–236, 239–244 and 253), as used in our recent article.[25] Injuries were identified for each individual by linking data on inpatient and outpatient encounters, in order to avoid double counting. To simplify matters, only the first injury encounter was used in the construction of the injury risk variable, i.e. multiple injury events for patients with more than one event were excluded from further consideration. Thus, the outcome or dependent variable of interest is cast as a dichotomous measure taking the value of 'one' if an individual had a first injury episode while receiving benzodiazepines as an outpatient and a value of 'zero' otherwise.

The main effects of benzodiazepine use are represented by both dose and duration variables, each again constructed in reference to our earlier analysis.[25] The dose variable was converted to a homogenous measure that captured differences in strength and overall effect of each different benzodiazepine in terms of diazepam equivalents (Valium® [1] 10mg).[31] The duration variable, constructed in reference to fill dates, is measured in weeks. The squared value of duration was also included in the analysis to account for nonlinear effects of the length of use on the risk of an injury. Patients may initially be at higher risk for injury when they are new users of benzodiazepines, whereas long-term users may have lower risks for injury because they are better acquainted with the adverse effects of this class of medications.[23]

The indirect effects of concomitant drug use are represented by the 'concomitant use of benzodiazepines and other drugs' (CUBZDD) variable. This measure requires a somewhat more detailed explanation here because it was not included in our previous analysis[25] and, correspondingly, is the principal focus of the present study. Variable construction began with Micromedex software that categorises a drug combination based on potential adverse event severity ('minor', 'moderate' and 'major'), onset and documentation.[27] We limited combinations to those with a severity rating of 'major' as defined by Micromedex. We did so for two reasons: (i) we wanted to capture the combinations that are most

1 The use of trade names is for product identification purposes only and does not imply endorsement.

likely to pose a risk for a serious injury; and (ii) we wanted to avoid analytical and conceptual problems in the specification of the CUBZDD variable, such as multicollinearity and the mixture of combinational subgroupings. It should be noted that all 'major' severity-rated drugs used in the James A. Haley Veterans Hospital outpatient setting were systemic in nature, i.e. those oral and transdermal medications that are absorbed systemically. Topical medications excluded from the analysis included azole-antifungal creams and shampoos.

Given the Micromedex 'major' categories of medications, we constructed the CUBZDD variable by linking drug fill dates and durations with the timing of injury-related healthcare encounters. Concomitant use of a benzodiazepine and one of these other drugs was indicated by overlapping fill dates and duration. We then constrained these pair-wise combinations of medications to just those being used within the 30-day period prior to the date of the healthcare encounter for the injury. Thus, the CUBZDD variable takes the value of 'one' if a patient used a benzodiazepine concurrently with any one of the other listed drugs within 30 days of an injury-related health encounter and a value of 'zero' otherwise.

Finally, we constructed a set of other covariates designed to control for the confounding influences of demographic characteristics (age and marital status as proxy for social support[32]). We examined the distribution of ages and determined that categorising age into a 4-fold vector of dummy variables corresponding to age quartiles (with AgeQ4, the oldest quartile, as the reference or omitted group) reduced the linear dependence with other variables. Additionally, we controlled for selected physiological indicators (mean arterial pressure as proxy for orthostatic hypotension[33] and body mass index for weight-related health risks[34]) and health-related history or status (hospital discharges as measure for well being[35] and selected Elixhauser comorbidities[36,37]) on the risk of injury.

We used the Elixhauser methodology as a means of controlling for patient comorbidities that could impact the risk for an injury. The Elixhauser methodology is a well established health services research method that uses specific inpatient ICD-9-CM diagnoses codes in the discharge data to identify comorbidities. Under the Elixhauser methodology, a secondary diagnosis was considered to be a comorbidity only when it did not relate directly to the principal diagnosis, screened through a diagnosis related group (DRG). For example, secondary diagnosis codes that are used to identify cardiac arrhythmias as comorbid conditions are excluded when the DRG for a patient indicates that the principal diagnosis is a cardiac disease-related illness. In addition, diagnosis codes that represent potential complications are excluded as indicators of comorbid illness from our analyses.

We overlapped the 1999–2001 drug data with a 1-year look-back period (1998) for historical comorbidities.[38] Our preliminary analyses, based on all 30 Elixhauser comorbidity categories, were biased by multicollinearity. This was probably because of the fact that many of the comorbidities were diseases of the same organ system or were encompassed in the same DRG, as modified by admission diagnosis. After reviewing the literature and discussing the issue with clinical experts, we reduced the 30 comorbid conditions down to the 11 that most likely pose serious injury risk and excluded the remaining 19. It should be noted that four of the 11 comorbid conditions that we kept are recognised to increase the risk of injuries or adverse events under the newly revised Beers criteria (see table I).[39]

Statistical Analysis

The effect of the concomitant use of benzodiazepines and other drugs on the risk of an injury, controlling for dose and duration of benzodiazepine use and other covariates, was estimated by means of a generalised linear model with general estimation equations (GEE) [all analyses were conducted with SAS version 8.2].[40] The GEE technique was used because of the clustered nature of the data set with 133 872 benzodiazepine prescriptions for 13 745 patients. Conventional logit analysis ignores clustering and potential correlations among observations, and would thus yield biased estimates. Because GEE handles problems associated with clustering, it yields consistent parameter estimates and robust standard errors. In order to facilitate the interpretation of the multivariate results, all GEE parameter estimates were exponentiated and presented thereby as estimated ORs; 95% confidence intervals are also

Table I. Descriptive statistics by variable and the concomitant use of benzodiazepines and other drugs (CUBZDD) category

Variables[a]	CUBZDD		All
	Yes (n = 1)	No (n = 0)	
Sample no.	6223	7522	13 745
Dependent variable means			
Injury[b]	0.127 (790/6223)	0.043 (320/7522)	0.081 (1110/13745)
Independent variable means			
Dose (diazepam equivalents)	2.11	1.81	2.00
Benzodiazepine duration (wk)	48	24	34
Age (y) [Q1,[b] Q2,[b] Q3[b]]	58	61	60
Mean arterial pressure (mm Hg)	77.52	80.38	79.07
Body mass index	30.27	29.55	29.87
Hospital discharges	0.47	0.40	0.43
Married[b]	0.59	0.62	0.61
Alcohol abuse[b]	0.06	0.05	0.05
Cardiac arrhythmias[b,c]	0.05	0.03	0.04
Deficiency anaemia[b]	0.07	0.05	0.06
Diabetes, complicated[b]	0.02	0.01	0.02
Drug abuse[b]	0.03	0.02	0.03
Fluid and electrolyte disorders[b]	0.08	0.04	0.06
Hypertension, complicated[b,c]	0.23	0.16	0.19
Hypothyroidism[b]	0.03	0.02	0.02
Other neurological disorders[b,c]	0.02	0.01	0.02
Pulmonary circulation disorders[b,c]	0.05	0.03	0.03
Rheumatoid arthritis[b]	0.01	<0.01	<0.01

a See the methods section for definitions of variables.

b Binary variable (= 1 presence, = 0 absence).

c Beers criteria diseases.

presented testing the (null) hypothesis that the true OR equals 'one'. This study was reviewed by all relevant institutional review boards and complied with human subjects protection standards.

Results

Table I, table II and table III summarise key descriptive characteristics of the study population over the course of the 3-year study period. Table II presents the list of specific benzodiazepine prescriptions written for the study population by strength and diazepam equivalents. It also sets out the frequency distribution of these prescriptions over the period 1999–2001. Table III presents the Micromedex 'major' combinations of benzodiazepines and other unique drugs within drug classes by number of prescriptions and unique patients. There were a total of 54 591 prescriptions involving the concomitant use of benzodiazepines and other drugs for 6223 unique patients. It is clear that many patients had multiple prescriptions that included the concomitant use of benzodiazepines and other drugs. Furthermore, 45.3% of all benzodiazepine patients (6223/13 745) had a CUBZDD variable that was classified as 'major' during the 3-year study period. Table I summarises the salient characteristics of the study population divided by dependent and independent variables and CUBZDD classification over the course of the study period. Overall, the mean of benzodiazepine dose and duration was 2.00 diazepam equivalents and 34 weeks, respectively. The mean age was 60 years, with the youngest patient being 21 years of age and the oldest 97 years of age, and 60% were married.

There were 1110 unique injury diagnoses and 71.2% (790/1110) of injured patients had a major CUBZDD. In total, 12.7% (790/6223) of the unique patients with concomitant use of benzodiazepines and other drugs had an injury or adverse event, as compared with 4.3% (320/7522) of the patients tak-

Table II. Prescribed benzodiazepines by strength and frequency, study population (n = 13 745), 1999–2001[a]

Drug name	Dose (mg)	Diazepam equivalent[b]	Frequency	Percent
Alprazolam	0.25	0.5	10 371	7.75
	0.5	1	15 385	11.49
	1	2	8493	6.34
	7.5	1	56	0.04
Chlordiazepoxide	5	0.2	734	0.55
	10	0.4	2960	2.21
	25	1	1836	1.37
Clonazepam	0.5	1	9704	7.25
	1	2	8544	6.38
Diazepam	2	0.2	2618	1.96
Dipotassium clorazepate	3.75	0.5	91	0.07
	5	0.5	19 526	14.59
	10	1	11 220	8.38
Flurazepam	15	1	7	0.01
	30	2	19	0.01
Lorazepam	0.5	0.5	359	0.27
	1	1	2130	1.59
	2	2	306	0.23
Oxazepam	10	1	7737	5.78
	15	1.5	8889	6.64
	30	3	2107	1.57
Temazepam	15	0.75	9816	7.33
	30	1.5	10 875	8.12
Triazolam	0.25	0.5	89	0.07
All Prescriptions			133 872	100.00

a Corrected frequencies from previously published analyses.[25]

b One diazepam equivalent = Valium® 10mg.

ing benzodiazepines who did not have concomitant drug use (see table I).

Table IV presents the main results of the multivariate estimates of the effects of the concomitant use of benzodiazepines and other drugs as well as of benzodiazepine dose and duration on injury risk. Model fit was confirmed with a deviance score of 0.68 and a non-significant Pearson statistic (= 0.95, p = 1.0, degrees of freedom = 13E4). As expected, the occurrence of the concomitant use of benzodiazepines and other drugs was associated with an increased risk for an injury. The occurrence of the concomitant use of benzodiazepines and other drugs increases the odds for an injury by >2-fold. The effect of increasing the benzodiazepine dose by one diazepam equivalent resulted in a 6% increase in the odds of an injury. Increasing duration by 1 week was also associated with an odds increase of approximately 3%.

Discussion

The goal of this study was to quantify the effect of an increase in the risk of an injury when benzodiazepines are prescribed concomitantly with other medications that are recognised as having a 'major' interaction with benzodiazepines. Roughly 3.4% of the >1.5 million outpatient prescriptions were identified as a 'major' interaction. We found that 45.3% (6223/13 745) of the outpatients receiving benzodiazepine in our study population also had a major interaction. These patients had a marginally higher average benzodiazepine dose (2.11 vs 1.81 diazepam equivalents), much longer treatment duration (48 vs 24 weeks) and more comorbidities than those patients without concomitant use of benzodiazepines and other drugs (table I). Furthermore, 71.2% (790/1110) of those patients with injuries were receiving benzodiazepines with other concomitant drugs, which suggests that the combination

use of a benzodiazepine and another drug may have been a significant contributory factor for the injury.

When looking at the association of patient co-morbidities on the risk of an injury (table IV), the strongest relationship was found for the patients with a neurological disorder (OR 2.81, 95% CI 2.56, 3.09) and this represents one of the revised Beers criteria diseases. Patients with pre-existing neurological conditions, such as stroke or Parkinson's disease, frequently have gait and balance problems and their functional performance and fall risk may be further negatively influenced when given a benzodiazepine alone or with other centrally acting drugs, such as muscle relaxants and opioids. This increases their risk of injury.

Surprisingly, advancing age was associated with decreased injury risk (table IV). However, we had no means to assess or measure the activity level of our population. It is possible that older individuals had lower activity levels leading to less exposure

Table III. Hospital outpatient medications with Micromedex 'major' combinations of benzodiazepine and other drug use, 1999–2001

Drug name	Unique patients (n)	Prescriptions [n (%)]
Azole antifungals		
Clotrimazole	70	170 (20.63)
Fluconazole	166	337 (40.90)
Itraconazole	20	68 (8.25)
Ketoconazole	92	249 (30.22)
Subtotal	*318*[a]	*824 (1.51)*[b]
Babiturates		
Phenobarbital[c]	33	321 (39.00)
Primidone[c]	80	502 (61.00)
Subtotal	*113*	*823 (1.51)*[b]
Centrally acting muscle relaxants		
Carisoprodol[c]	53	740 (7.83)
Chlorzoxazone[c]	4	15 (0.16)
Cyclobenzaprine[c]	967	2286 (24.19)
Methocarbamol[c]	1221	6050 (64.01)
Tizanidine	94	360 (3.81)
Subtotal	*2009*[a]	*9451 (17.31)*[b]
Opioid analgesics		
Codeine	2120	6356 (14.63)
Dextropropoxyphene[c]	2194	11 185 (25.75)
Fentanyl	50	217 (0.50)
Hydrocodone	1	1 (0.00)
Hydromorphone	22	84 (0.19)
Methadone	59	231 (0.53)
Morphine	766	6003 (13.82)
Oxycodone	3216	18 946 (43.62)
Pentazocine[c]	53	288 (0.66)
Pethidine[c]	34	123 (0.28)
Subtotal	*5541*[a]	*43 434 (79.56)*[b]
Other		
Chloral hydrate	7	59 (100.00)
Subtotal	*7*	*59 (0.10)*[b]
Total	**6223**[d]	**54 591**

a Unique patient numbers may not add up because some patients had prescriptions for more than one drug in this class of drugs.

b Percentage of total prescriptions.

c Beers criteria drugs.[39]

d Unique patient numbers may not add up because some patients had prescriptions for more than one class of drugs.

Table IV. Model estimates

Variable	Odds ratio	95% CI	p-Value > χ^2
CUBZDD	2.31	(2.20, 2.41)	<0.0001
Benzodiazepine dose	1.06	(1.04, 1.07)	<0.0001
Benzodiazepine duration	1.03	(1.01, 1.05)	<0.0012
Benzodiazepine duration squared	0.99	(0.98, 1.00)	<0.4925
AgeQ1 (quartiles)	2.37	(2.22, 2.52)	<0.0001
AgeQ2	1.39	(1.31, 1.49)	<0.0001
AgeQ3	1.10	(1.03, 1.17)	<0.0028
Married	0.90	(0.87, 0.93)	<0.0001
Body mass index	1.01	(1.00, 1.01)	<0.0016
Mean arterial pressure	0.98	(0.98, 0.99)	<0.0001
Hospital discharges	1.04	(1.03, 1.05)	<0.0001
Alcohol abuse	1.82	(1.71, 1.94)	<0.0001
Cardiac arrhythmias	2.12	(1.97, 2.29)	<0.0001
Deficiency anaemia	1.57	(1.47, 1.68)	<0.0001
Diabetes, complicated	1.19	(1.06, 1.33)	<0.0030
Drug abuse	1.40	(1.30, 1.51)	<0.0001
Fluid and electrolyte disorders	1.12	(1.31, 1.53)	<0.0001
Hypertension, complicated	1.83	(1.78, 1.95)	<0.0001
Hypothyroidism	1.06	(0.96, 1.16)	<0.2585
Other neurological disorders	2.81	(2.56, 3.09)	<0.0001
Pulmonary circulation disorders	0.97	(0.89, 1.07)	<0.5411
Rheumatoid arthritis	0.98	(0.85, 1.14)	<0.7718

CUBZDD = concomitant use of benzodiazepines and other drugs.

and a lowered risk of injury.[25] Being married had a small protective effect, which provides further confirmation of earlier findings that social support may improve functional status and decrease the risk for an injury.[32]

As expected, injury risk was increased in patients with coded comorbidities for alcohol abuse (OR 1.82, 95% CI 1.71, 1.94) or drug abuse (OR 1.40, 95% CI 1.30, 1.51). CUBZDD was associated with, and significantly increased, the risk of injury requiring medical care (OR 2.31, 95% CI 2.20, 2.41). The use of muscle relaxants and opioids with benzodiazepines was very common in our population comprising 17% and 79% of total benzodiazepine and other drug prescriptions, respectively (table III). The approximately 2-fold increase in the risk of injury associated with the concomitant use of benzodiazepines and other drugs, suggests the need for better patient and provider education on the potentially negative effects of combining certain drugs. It also emphasises the need for close patient monitoring when these drugs are used together. Additionally, this underscores the need for a thorough benefit-risk assessment when prescribing these drugs in combination. These findings further demonstrate the potentially negative effects of benzodiazepines on gait and balance.[6,41] The negative effect of benzodiazepines on gait and balance and injury risk might be potentiated when used in combination with other CNS-acting drugs.[11,14,15]

We should note some limitations of our study. Our study population consists of predominantly older and overwhelmingly male veterans. Many veterans are eligible for VA, Medicare, Medicaid or other healthcare benefits. Since we evaluated only VHA data, we may not have captured injuries that were treated outside the VHA. It is possible that the number of injuries we captured may under-report the actual number.

Our analysis only included dose and duration for benzodiazepine medications. No dose and duration analyses were conducted for the other medications. Patients with more than one injury associated with the concomitant use of benzodiazepines and other drugs were only included once in the analysis. We did not analyse multiple combinations of drug use-associated injuries for patients in our model. Future analyses will examine such injury patterns.

In our analyses, we did not include drugs, nutritional supplements or foods that are known to reduce, as opposed to increase, the concentration of benzodiazepines. We analysed benzodiazepines as a group and did not analyse the individual benzodiazepine medications' impact on injury risk. We recognise that different medications have different pharmacokinetics and pharmacodynamics, which might also affect the injury risk. In the elderly, certain biotransformation pathways, e.g. via cytochrome P450 enzymes, can also change with age. Future research will examine individual medications and their potential impact on injury risk. The results of these studies could lead to recommendations for selecting safer medications or medication combinations in vulnerable populations.

Conclusions

This study is the first large-scale analysis to quantify the impact of the concomitant use of benzodiazepines and other drugs on the risk of injury in veterans. This study demonstrates the utility of expanding the focus of inappropriate medication usage to include analyses that link potentially inappropriate drug use with healthcare utilisation for injuries. Studies of inappropriate prescribing in the elderly have been controversial, with clinicians and healthcare systems questioning the clinical efficacy and cost effectiveness.[39] Our study used the Micromedex classification scheme, which is widely used in the VHA. There is not necessarily agreement between different classification lists.[42]

Recently, an update of the Beers criteria for potentially inappropriate prescribing in the elderly emphasised the importance of including drug-drug and drug-disease interactions in studies of the appropriateness of medication use.[39] Fick et al.[39] noted that the criteria for identifying potentially inappropriate medication usage relies on specific lists of drugs and does not include other issues such as under use and drug interactions in the elderly. They noted that rigorous, well controlled prospective research studies are needed to demonstrate that adhering to the Beers criteria makes a difference in patient outcomes. Our present retrospective study is nevertheless responsive to the research question of the association of the concomitant use of benzodiazepines and other drugs as a risk factor for injuries. Future patient injury risk models must incorporate complex aspects of medication usage, such as dose and duration, as well as the concomitant use of drugs linked to adverse outcomes.

Acknowledgements

The research reported here was supported by the Department of Veterans Affairs, Veterans Health Administration (VHA), VISN-8. The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs. The authors have no conflicts of interest that are directly relevant to the content of this study.

References

1. Ebly EM, Hogan DB, Fung TS. Potential adverse outcomes of psychotropic and narcotic drug use in Canadian seniors. J Clin Epidemiol 1997; 50: 857-63
2. Kohn LT, Corrigan JM, Donaldson MS, editors. To err is human: building a safer health system committee on quality of health care in America. Washington, DC: Institute of Medicine, 2000
3. Castle SC. High risk medications and falls: a practical approach to risk management. Presented at the 3rd Annual Evidence-Falls Conference; 2002 Mar 5; Tampa (FL): VA Patient Safety Center, 2002
4. Smith RG. Fall-contributing adverse effects of the most frequently prescribed drugs. J Am Podiatr Med Assoc 2003; 93: 42-50
5. Morrissey EFR, McElnay JC, Scott M, et al. Influence of drugs, demographics and medical history on hospital readmission of elderly patients: a predictive model. Clin Drug Invest 2003; 23: 119-28
6. Evans JG. Drugs and falls in later life [letter]. Lancet 2003; 361: 448
7. Rizzo JA, Friedkin R, Williams CS, et al. Health care utilization and costs in a Medicare population by fall status. Med Care 1998; 36: 1174-88
8. Fick DM, Waller JL, Maclean JR, et al. Potentially inappropriate medication use in a medicare managed care population: association with higher costs and utilization. J Manag Care Pharm 2001; 7: 407-13
9. Neutel CI. Risk of traffic accident injury after a prescription for a benzodiazepine. Ann Epidemiol 1995; 5: 239-44
10. Barbone F, McMahon AD, Davey PG, et al. Association of road-traffic accidents with benzodiazepine use. Lancet 1998; 24: 1331-6
11. Oster G, Huse DM, Adams SF, et al. Benzodiazepine tranquilizers and the risk of accidental injury. Am J Public Health 1990; 80: 1467-70
12. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis. Part I and part II. J Am Geriatr Soc 1999; 47: 30-50
13. Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly: an update. Arch Intern Med 1997; 157: 1531-6
14. Weiner DK, Hanlon JT, Studenski SA. Effects of central nervous system polypharmacy on falls liability in community dwelling elderly. Gerontology 1998; 44: 217-21
15. Schwab M, Roder F, Aleker T, et al. Psychotropic drug use, falls and hip fracture in the elderly. Aging (Milano) 2000; 12: 234-9

16. Liu GG, Christensen DB. The continuing challenge of inappropriate prescribing in the elderly: an update of the evidence. J Am Pharm Assoc 2002; 42: 847-57
17. Zhan C, Sangl J, Bierman AS, et al. Potentially inappropriate medication use in the community-dwelling elderly: findings from the 1996 Medical Expenditures Panel Survey. JAMA 2001; 286: 2823-9
18. Hanlon JT, Fillenbaum G, Kuchibhatla M, et al. Inappropriate drug use, functional status decline, and mortality among community dwelling elderly [letter]. Gerontologist 2000; 40: 37
19. Gandhi TK, Weingart SN, Borus J, et al. Adverse drug events in ambulatory care. N Engl J Med 2003; 348: 1556-64
20. Tinetti ME, Liu WL, Claus EB. Predictors and prognosis of inability to get up after falls among elderly persons. JAMA 1993; 269: 65-70
21. Cumming RG. Epidemiology of medication-related falls and fractures in the elderly. Drugs Aging 1998; 12: 43-53
22. Koski K, Luukinen H, Laippala P, et al. Physiological factors and medications as predictors of injurious falls by elderly people: a prospective population-based study. Age Ageing 1996; 25: 29-38
23. Neutel CI, Hirdes JP, Maxwell CJ, et al. New evidence on benzodiazepine use and falls: the time factor. Age Ageing 1996; 25: 273-8
24. Grad R, Tamblyn R, Holbrook AM, et al. Risk of a new benzodiazepine prescription in relation to recent hospitalization. J Am Geriatr Soc 1999; 47: 184-8
25. French DD, Campbell R, Spehar A, et al. Benzodiazepines and injury: a risk adjusted model. Pharmacoepidemiol Drug Saf. Epub 2004 Apr 23 2005; 14: 17-24
26. Tillement JP, Albengres E, Cottin D, et al. The risk of falling due to benzodiazepine administration, alone or in combination, in elderly subjects. Therapie 2001; 56: 435-40
27. Thomson MICROMEDEX® Health Series 1974-2004 Vol. 119 [online]. Available from URL: http://www.micromedex.com [accessed 2005 Oct 12]
28. Megarbane B, Gueye P, Baud F. Interactions between benzodiazepines and opioids. Ann Med Interne (Paris) 2003; 154: S64-72
29. Maurer PM, Bartkowski RR. Drug interactions of clinical significance with opioid analgesics. Drug Saf 1993; 8: 30-48
30. Moreno MR, Rojas CO, Gilbert-Rahola J, et al. Drug interactions of methadone with CNS-active agents. Actas Esp Psiquiatr 1999; 27: 103-10
31. Aston H. Guidelines for the rational use of benzodiazepines: when and what to use. Drugs 1994; 48: 25-38
32. Jenice GS, Sohn L, Harada ND. Living alone and outpatient care use by older veterans. J Am Geriatr Soc 2004; 52: 617-22
33. Tinetti ME, McAvay G, Claus E. Does multiple risk factor reduction explain the reduction in fall rate in the Yale FICSIT trial? Frailty and injuries cooperative studies of intervention techniques. Am J Epidemiol 1996; 144: 389-99
34. Wei TS, Hu CH, Wang SH, et al. Fall characteristics, functional mobility and bone mineral density as risk factors of hip fracture in the community-dwelling ambulatory elderly. Osteoporos Int 2001; 12: 1050-5
35. Pope GC. Diagnostic cost group hierarchical condition category models for medicare risk adjustment. Final Report to the US Health Care Financing Administration under Contract No. 500-95-048. Waltham (MA): Health Economics Research Inc., 2000 Dec
36. Elixhauser A, Steiner C, Harris DR, et al. Comorbidity measures for use with administrative data. Med Care 1998; 36: 8-27
37. Johnston JA, Wagner DP, Timmons S, et al. Impact of different measures of comorbid disease on predicted mortality of intensive care unit patients. Med Care 2002; 40: 929-40
38. Stukenborg GJ, Wagner DP, Connors AF. Comparison of the performance of two comorbidity measures, with and without information from prior hospitalizations. Med Care 2001; 39: 727-39
39. Fick DM, Cooper JW, Wade WE, et al. Updating the Beers criteria for potentially inappropriate medication use in older adults. Arch Intern Med 2003; 163: 2716-24
40. SAS Language: reference, version 8. Cary (NC): SAS Institute, 2001
41. Eto F, Saotome I, Furuichi T, et al. Effects of long-term use of benzodiazepine on gait and standing balance in the elderly. Ann N Y Acad Sci 1998; 860: 543-5
42. Abarca J, Malone DC, Armstrong EP, et al. Concordance of severity ratings provided in four drug interaction compendia. J Am Pharm Assoc 2004; 128: 131-4

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