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National outpatient medication profiling: medications associated with outpatient fractures in community-dwelling elderly veterans

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What is already known about this subject
- Polypharmacy, to include a subissue of potentially inappropriate prescribing, in community-dwelling elderly is widespread.
- The objective of this study was to identify the magnitude of problematic outpatient drug prescribing and its potential association as a risk factor for injuries.

What this study adds
- This is the first national study of outpatient injuries in elderly veterans.
- The results are consistent with previous published literature highlighting the risks associated with prescribing central nervous system drugs in the elderly.

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Aims
The primary objective of this retrospective case–control study in an elderly veteran population was to assess the impact of specific medications with recognized side-effects that increase the risk of a fall and were prescribed prior to fractures treated in the outpatient setting compared with patients treated for nonspecific chest pain.

Methods
Two national Veterans Health Administration (VHA) databases were used to identify 17 273 unique patients, aged ≥65 years, treated in outpatient settings with a fracture in fiscal year 2005, and for whom we could link to all of their outpatient prescriptions (809 536). For comparison, we identified other elderly patients with outpatient clinic visits for nonspecific chest pain ($N = 62\,331$) for whom we could link with their 2 987 394 outpatient prescriptions. We categorized the fall-related medications as drugs that primarily affect the cardiovascular (CVS), the central nervous (CNS) or the muscular skeletal system (MSS).

Results
Significant differences in the two patient groups occurred in the CNS category. Approximately 41% of the patients with fracture-coded encounters were prescribed CNS drugs compared with 31% of the patients in the comparison group ($P < 0.0003$). Finally, the use of muscle relaxants in the MSS category was significantly higher in the fracture group than in the nonspecific chest pain group.

Conclusions
Studies using administrative data can foster the development of more proactive pharmacovigilance systems and assist in formulary refinement, particularly in countries with national healthcare systems that have integrated patient data. Particular attention and monitoring of elderly patients taking CNS medications may be important for injury prevention.

Introduction

Fractures are the most prevalent nonfatal unintentional injury associated with falls in the elderly [1–5]. Fall-related injuries themselves are the leading nonfatal cause of injury hospitalizations in the elderly, dwarfing the second leading cause (car crash injuries) by 60-fold [3]. Of the elderly who fall, 20–30% suffer moderate to severe injuries such as hip fractures or other skeletal events. Some studies put the fall fracture rate as high as 95% [3, 4, 6].

Previous studies have found associations between certain medications and the risk of a fall. Medications such as antidepressants, antihypertensives, antipsychotics, cholinesterase inhibitors, anti-Parkinson's, some analgesics, sedative hypnotics and anxiolytics have been identified as significant risk factors for falls [7–19]. Meta-analysis of 40 studies of psychotropics (e.g. neuroleptics, hypnotics, antidepressants and benzodiazepines) has also found a relationship between their use and falls [20]. Another meta-analysis of 29 studies found certain cardiac and analgesic drugs increased the risk of falls [21]. In addition, taking four or more medications or any psychoactive medications also increases the risk of a fall [22].

Previous studies of outpatient medications analysed certain medication categories [e.g. cardiovascular system (CVS), central nervous system (CNS), muscular skeletal system (MSS)] or specific classes of drugs (e.g. β-blockers, antidepressants, muscle relaxants) that have been linked to injuries or adverse events [15–19]. These studies have identified the importance of CNS medications in fall risk assessment. Fall risk assessments are an important requirement of the current Joint Commission on Accreditation of Healthcare Organizations (JCAHO) patient safety goals focusing on reducing the risk of patient harm resulting from falls in all healthcare settings. This JCAHO goal requires healthcare providers to implement and evaluate patient fall risk reduction programmes, which include medication reviews [23]. At the present time, no fall-related medication studies of elderly outpatient fractures have been done on a national scale in the USA.

The Veterans Health Administration (VHA) has unique datasets which allow the linkage of outpatient prescriptions to fall-related healthcare. The primary goal of the present study was to examine specific medications within recognized major problematic drug categories that increase the risk of a fall and were prescribed prior to the fracture. In order to provide some clinical relevance to the study results, medication profiles for fracture patients were compared with medication profiles of patients with nonspecific chest pain.

A secondary objective of this study was to demonstrate the potential usefulness of a proactive surveillance system that links national data on outpatient medications to health outcomes of interest and costs for both improved pharmacovigilance and a future business case for patient safety initiatives [24, 25]. This may be particularly useful to researchers and policy makers in countries with national healthcare systems such as Canada, Australia, the UK and other European Union countries that have national integrated patient data which can be analysed for such initiatives.

Materials and methods

Sources of data

Data were obtained from the national VHA Ambulatory Event database [2, 26]. This database contains ambulatory encounters occurring in all hospital outpatient departments, as well as smaller satellite facilities and community clinics. The database contains information on diagnoses, procedures, type of clinic visited, demographic characteristics of patients and a unique encrypted patient identifier. In fiscal year (FY) 2005 the database included data from all of the 21 Veterans Integrated Service Networks (VISN) for over 5 million unique patients with approximately 75 million outpatient encounters.

Using the unique encrypted patient identifiers, the encounter data were merged with outpatient pharmacy data from the VHA Decision Support System (DSS) for FY 2005. The DSS pharmacy data provided prescription information on the drug, the fill date and the quantity supplied, dispensing cost, drug product cost and ordering provider type. The working dataset included detailed information on all patients with fracture outpatient encounters coupled to detailed information on the patients' drug utilization [27].

Identifying fracture patients and the comparison patient groups

All VHA patients, community dwelling (non-nursing home) patients aged ≥65 years with at least one outpatient prescription, who had a primary diagnosis (DXLSF) of a fracture for the outpatient encounter in FY 2005 were defined as the fracture patients. We excluded patients who had inpatient treatment associated with the fractures. These outpatient fracture cases were identified using the Agency for Healthcare Research and Quality (AHRQ) Clinical Classification Software (CCS), which aggregates the ICD-9-CM codes into 260 mutually exclusive diagnosis categories [28]. The CCS groups of interest were CCS '229-upper limb fracture' ($N = 4365$),

'230-lower limb fracture' ($N = 5008$), '231-other fracture' ($N = 7900$) primarily treated in the outpatient setting.

We identified a comparison group of community-dwelling patients aged ≥65 years without a CCS 229, 230 or 231 code and with a primary diagnosis CCS code of '102-nonspecific chest pain' ($N = 62\,331$). We chose the nonspecific chest pain patients as the comparison group because nonspecific chest pain ranks as one of the most common reasons for visits to the outpatient setting and is an important symptom in cardiovascular disease [29]. There are three ICD-9-CM codes in the AHRQ's classification for CCS code 102 that identifies patients with nonspecific chest pain (i.e. 786.50 chest pain NOS, 786.51 precordial pain, 786.59 chest pain NEC). Additionally, recent data on the VHA population for outpatient fall injury visits showed that nonspecific chest pain ranked among the most frequent co-morbidities for a fall ambulatory care visit [2].

Some patients may have had multiple outpatient encounters over our study period (FY) 2005, therefore we examined only their first encounter. Our final study groups included 17 273 unique patients with a fracture and their 809 536 prescriptions, and 62 331 patients with nonspecific chest pain and their 2 987 394 prescriptions.

Healthcare and medication costs

We obtained national costs data for the outpatient fracture treatments from the Decision Support System National Data Extract (DSS-NDE). A patient can have multiple encounters and phases of care; these costs are not encompassing and do not capture an episode of care or follow-up treatment but only aspects of the initial visit or encounter with the healthcare system. The average cost for fracture treatment was derived by adding the total costs for the initial encounter for the three CCS fracture groups and then dividing by the total number of unique fracture patients for those groups [VHA report, *DSS-NDE Outpatient Report by CCS-FY05,* VHA intranet KLF Menu (available at: http://KLFmenu.med.va.gov/, last accessed: 11 October 2006)]. The cost of treatment for the nonspecific chest pain was derived in a similar manner.

Total pharmacy costs were calculated for all medications dispensed for both groups for one fiscal year, 2005. The cost of the individual prescription was based on the sum of DSS dispensing costs (DISPCOST), which includes the direct labour plus any mailing costs associated with dispensing the prescription and drug product costs (VSCOST), which is the cost of the drug plus the cost of other supplies to produce the drug [27]. We summed the cost of each individual prescription for each of the two study groups to obtain the total annual pharmaceutical costs. It is important to note that these drug costs are reflective of national contracts between the VHA and the various pharmaceutical companies, which are typically much lower than purchasing at an individual or private rate in the USA because of volume.

Outpatient medication profiles and temporal alignment

The medication list for this study and in our previously published work [15–17] included medications from the Canadian Safety Council's fall risk assessment tool as well as selected Beers criteria medications, cross referenced to the VHA national formulary [30–32]. This list organizes medications that potentially increase the risk of falls and injuries into drug categories and classes [30]. This medication list includes over 200 specific medications identified by the national drug code [15].

Time constraints were specified to account for the temporal relationships between use of prescribed medications and outpatient healthcare encounters. For the purposes of this study, a medication associated with a fracture or nonspecific chest pain outpatient encounter was of interest if it was actively prescribed up to the time of the initial encounter. By using the drug fill date, days' supply and date of encounter, we programmed two inequalities:

$$\text{If drug fill date} \geq \text{encounter date, then delete} \quad (1)$$

$$\text{If drug fill date} + \text{days supplied} \geq \text{encounter date, then output} \quad (2)$$

The first inequality eliminated all outpatient medications prescribed after the time of the outpatient encounter. This was important, because a patient might have been prescribed a medication after the initial outpatient encounter, but not before the encounter, and it therefore could not be a potentially contributing risk factor. On the other hand, the second inequality retained the potentially problematic medications for which there was a sufficient supply prescribed up to the time of a healthcare encounter. Finally, using bivariate statistics (comparing fracture to nonspecific chest pain groups), we analysed the drug categories and specific drug classes. Since that analysis incorporated a large number of χ^2 tests, we employed a Bonferroni adjustment to control for experimental type 1 errors [33]. All analyses were conducted with SAS version 9.1 (SAS Inc., Cary, NC, USA) [34]. This study was reviewed and approved by the University of South Florida Institutional Review Board (FWA 00001669) and the James A. Haley Research and Development Committee for compliance with human subject protection standards.

Results

The patient characteristics and costs for the two groups are presented in Table 1 and medication usages in Table 2. The groups were similar in terms of the average number of prescriptions, gender, marital status and age (Table 1). Comparing medication profiles of the two groups (Table 2), we found the use of CVS medications in the fracture group was significantly less than in the nonspecific chest pain group (62.87% *vs.* 72.01%), with specific classes of angiotensin II receptor antagonists, ACE inhibitors, β-blockers, calcium channel blockers, vasodilators, diuretics and antiarrhythmics used more in the nonspecific chest pain group ($P < 0.0003$).

Comparing use of CNS medications between the two groups, we found large differences in the CNS drug category, with 41.31% usage in the fracture group compared with 31.04% usage in the nonspecific chest pain group ($P < 0.0003$). The most notable differences were in the drug classes of anticonvulsants/barbiturates, antidepressants, antihistamine/antinauseants, antipsychotics and cholinesterase inhibitors, opioid analgesics/narcotics and anti-Parkinson's, with more usage in the fracture group compared with the nonspecific chest pain group ($P < 0.0003$).

In the MSS category we found statistically significant differences between the two groups, with 9.23% usage in the fracture group compared with 7.88% in the nonspecific chest pain group ($P < 0.0003$). The use of muscle relaxants was higher in the fracture group compared with the nonspecific chest pain group, but there were no statistically significant differences in the use of nonsteroidal anti-inflammatory drugs between the two groups.

The average encounter cost per patient treated was $594.59 (£313.04) for a fracture and $453.57 (£238.85) for the nonspecific chest pain group (Table 1). These costs represent only the first encounter with the healthcare system. Patients may have had multiple phases of treatment and therefore these are not reflective of an episode of care.

Since elderly patients are often on a large number of medications for their chronic conditions, we wanted to compare these two groups for their overall number of prescriptions and medication costs on an annual basis. For FY 2005 there were 809 536 total prescriptions that were filled for the fracture group, an average of 46.90 prescriptions per person per year, compared with 2 987 394 prescriptions filled for the nonspecific chest

Table 1
General demographic and cost information

	Fracture ($N = 17\,273$)	Nonspecific chest pain ($N = 62\,331$)
Mean age, years (minimum, maximum)	75.95 (65 104)	74.60 (65 105)
Standard deviation of age	6.79	6.30
Percent married	55.85	61.21
Percent male	95.28	97.63
Average encounter cost per patient, $* (£)	594.59 (313.27)	453.57 (238.99)
Total annual prescriptions filled (all drugs)†	809 536	2 987 394
Average number of prescriptions (annually)	46.90	47.90
A. Annual drug product cost, $† (£)	22 511 179 (11 862 668)	79 567 015 (41 928 357)
B. Annual dispensing cost, $† (£)	4 916 711 (2 590 893)	16 864 533 (8 886 837)
C. Annual drug product and dispensing, $† (£)	27 427 890 (14 452 621)	96 431 548 (50 812 391)
D. Average annual drug cost per patient, $† (£)	1 588 (836)	1 547 (815)

**Based on fiscal year (FY) 2005 Decision Support System (DSS) National Data Extracts (NDE) single encounter and not an episode of care. †Based on FY 2005 DSS National Outpatient Pharmacy Extract.*

Table 2
Outpatient fracture patients and nonspecific chest pain patients (≥65 years old): percentage of patients prescribed selected medications by drug categories (CVS, CNS, MSS) and classes

Drug categories/classes	Fracture (*N* = 17 273) *n* (%)	Nonspecific chest pain (*N* = 62 331) *n* (%)
Cardiovascular system (CVS)†	10 860 (62.87)	44 886 (72.01)*
Antihypertensives		
Angiotensin II receptor antagonists	797 (4.61)	3 516 (5.64)*
ACE Inhibitors	4 682 (27.11)	19 898 (31.92)*
α-Blockers	541 (3.13)	2 278 (3.65)
β-Blockers	2 977 (17.23)	13 647 (21.94)*
Calcium channel blockers	2 587 (14.98)	10 828 (17.37)*
Vasodilators	3 328 (19.27)	17 771 (28.51)*
Diuretics	4 542 (26.30)	18 163 (29.14)*
Antiarrhythmics	2 768 (16.03)	12 412 (19.91)*
Blood modifiers	83 (0.48)	355 (0.57)
Platelet aggregation inhibitors	48 (0.28)	199 (0.32)
Central nervous system (CNS)†	7 135 (41.31)*	19 349 (31.04)
Psychotropics		
Anticonvulsants/barbiturates	1 339 (7.75)*	3 457 (5.55)
Antidepressants	3 209 (18.58)*	9 373 (15.04)
SSRI	2 180 (12.62)*	5 590 (8.97)
TCA	486 (2.81)	1 622 (2.60)
Other	995 (5.76)*	2 987 (4.79)
Antihistamines/antinauseants	165 (0.96)	637 (1.02)
Antipsychotics	516 (2.99)*	1 322 (2.12)
Atypical	454 (2.63)*	1 138 (1.83)
Typical	76 (0.44)	226 (0.36)
Benzodiazepines	1 218 (7.05)	4 245 (6.81)
Cholinesterase inhibitors	588 (3.40)*	1 331 (2.14)
Opioid analgesics, narcotics	3 155 (18.27)*	6 797 (10.90)
Hypnotics	71 (0.41)	208 (0.33)
Anti-Parkinson's	363 (2.10)*	789 (1.27)
Muscular skeletal system (MSS)†	1 595 (9.23)*	4 910 (7.88)
Muscle relaxants	547 (3.17)*	1 395 (2.24)
Nonsteroidal anti-inflammatory drugs‡	1 142 (6.61)	3 764 (6.04)

**P-value of <0.0003 interpreted as statistically significant based on Bonferroni adjustment of nominal P-value of 0.01 and 29 independent χ^2 tests, comparing fracture patients with nonspecific chest pain. †Percentages may not add up because some patients had prescriptions of more than one drug. ‡Includes: Celecoxib, Diclofenac, Etodolac, Idomethacin, Ketorolac, Nabumetone, Naproxen, Oxaprozin, Piroxicam, Rofecoxib, Suldinac, Tolmetin. Excludes: Paracetanol, Aspirin and Ibuprofen because they do not require a prescription.*

pain group with an annual average of 47.90 prescriptions. The total annual outpatient medication costs were $27 427 890 (£14 443 342) for the fracture group and $96 431 548 (£50 790 877) for the nonspecific chest pain group. On average this amounts to $1588 (£836) total annual medication costs per patient for the fracture group compared with $1547 (£815) for the nonspecific chest pain group.

Discussion

This was the first national veterans study to examine selected outpatient medication usage temporally aligned with outpatient treatment for a fracture. The goal of this study was to provide insight into the use of medications that may be associated with these fractures. Polypharmacy and certain specific medications in the elderly have been linked to increased risk of falls and fall-

related injuries, especially fractures [1–22]. In this study, a comparison group was used to determine if there were any important differences in the medication profile between these two outpatient treatment groups. An analysis centred on the average number of prescriptions as a risk factor for injurious falls in this study does not provide any insight into clinically meaningful differences between the groups (approximately 47 prescriptions per year, per group). Therefore, it is especially important to analyse carefully the qualitative differences in the types of medication prescribed to a patient at a specific point in time (i.e. their medication profile) associated with healthcare outcomes of interest (i.e. outpatient treatment for a fracture or nonspecific chest pain).

Not surprisingly, the nonspecific chest pain group had significantly more CVS medications prescribed in virtually every instance than the fracture group. However, using highly conservative measures of statistical significance ($P < 0.0003$), the fracture patients had higher levels of drug usage than the nonspecific chest pain patients in seven of 12 CNS medication classes and muscle relaxants in the MSS. This is consistent with our previous findings [15–19] and other recently published research [35]. While benzodiazepines were not statistically significant at very conservative levels, we cannot conclude from this analysis that they are not a risk factor for fractures since we did not assess dose, duration or concomitant use of other medications in a more sophisticated model [18, 19].

We have been able temporally to link selected medications associated with an increased risk of falls to specific outpatient healthcare utilization. We also examined the treatment costs of the initial visit or encounter and annual prescription costs for the two patient groups. From a system perspective, these costs take on significance by allowing more refined future analyses of outcomes related to costs, quality, efficiency, productivity and patient safety. This analysis was possible because of the large-scale national datasets available in the VHA. In fiscal year 2005, the VHA maintained detailed national healthcare data on nearly 76 million outpatient encounters for over five million unique patients and approximately 118 million outpatient prescriptions.

This study has several limitations. Our population was composed largely of elderly male veterans. While some of the medications examined have been linked by researchers to the risk of fractures, we recognize that our findings do not necessarily imply causation but are descriptive and demonstrate the potential usefulness of administrative data for hypothesis generation in pharmacovigilance studies. We did not include other important clinical information such as dose, duration, comorbidities or laboratory and other vital data in these analyses. We also did not identify the specific mechanism of injury (E-codes) for the fractures in this study. These are generally underreported in administrative datasets [2]. However, fractures in the elderly are typically due to falls and motor vehicle accidents [3].

Conclusion

Studies using administrative data can foster the development of more proactive pharmacovigilance systems and assist in formulary refinement, particularly in countries with national healthcare systems that have comprehensive integrated patient data. Particular attention and monitoring of patients taking CNS medications may be important for injury prevention. Future studies which include detailed costs associated with health outcomes and medication profiles will allow a more refined and compelling business case to be made for patient safety initiatives.

Competing interests: None declared.

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