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Patterns of Prescription Drug Use Before and After Fragility Fracture

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IMPORTANCE Patients who have a fragility fracture are at high risk for subsequent fractures. Prescription drugs represent 1 factor that could be modified to reduce the risk of subsequent fracture.

OBJECTIVE To describe the use of prescription drugs associated with fracture risk before and after fragility fracture.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study conducted between February 2015 and March 2016 using a 40% random sample of Medicare beneficiaries from 2007 through 2011 in general communities throughout the United States. A total of 168 133 community-dwelling Medicare beneficiaries who survived a fracture of the hip, shoulder, or wrist were included. Cohort members were required to be enrolled in fee-for-service Medicare with drug coverage (Parts A, B, and D) and to be community dwelling for at least 30 days in the immediate 4-month postfracture period.

EXPOSURES Prescription drug use during the 4-month period before and after a fragility fracture.

MAIN OUTCOMES AND MEASURES Prescription fills for drug classes associated with increased fracture risk were measured using Part D retail pharmacy claims. These were divided into 3 categories: drugs that increase fall risk; drugs that decrease bone density; and drugs with unclear fracture risk mechanism. Drugs that increase bone density were also tracked.

RESULTS A total of 168 133 patients with a fragility fracture (141 569 women; 84.2%) met the inclusion criteria for this study; 91.8% were white. Across all fracture types, the mean (SD) age was 80.0 (7.7) years, and 53.2% of the fracture cohort was hospitalized at the time of the index fracture, although this varied significantly depending on fracture type (100% of hip fractures, 8.2% of wrist fractures, and 15.0% of shoulder fractures). The frequency of discharge to an institution for rehabilitation following hospitalization also varied by fracture type, but the mean (SD) duration of acute rehabilitation did not: 28.1 (19.8) days. Most patients were exposed to at least 1 nonopiate drug associated with increased fracture risk in the 4 months before fracture (77.1% of hip, 74.1% of wrist, and 75.9% of shoulder fractures). Approximately 7% of these patients discontinued this drug exposure after the fracture, but this was offset by new users after fracture. Consequently, the proportion of the cohort exposed following fracture was unchanged (80.5%, 74.3%, and 76.9% for hip, wrist, and shoulder, respectively). There was no change in the average number of fracture-associated drugs used. This same pattern of use before and after fracture was observed across all 3 drug mechanism categories. Use of drugs to strengthen bone density was uncommon (≤25%) both before and after fracture.

CONCLUSIONS AND RELEVANCE Exposure to prescription drugs associated with fracture risk is infrequently reduced following fragility fracture occurrence. While some patients eliminate their exposure to drugs associated with fracture, an equal number initiate new high-risk drugs. This pattern suggests there is a missed opportunity to modify at least one factor contributing to secondary fractures.

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Fragility fractures among the elderly population are a source of substantial morbidity and mortality and are associated with annual direct costs of over $16 billion.[1,2] With morbidity, mortality, and financial burdens of fragility fractures projected to increase as the US population ages, there is an urgent need to identify individuals at risk for fracture and to promote use of interventions that reduce fracture occurrence.[1,3,4] One clearly defined high-risk population is survivors of a first fragility fracture. Not only are such patients at significantly increased risk of experiencing a second fracture, the incidence is highest in the first 6 months after a first fracture, highlighting the importance of identifying modifiable risk factors and interventions that can be implemented immediately after an index fragility fracture.[5-13]

Prescription drugs represent a potentially modifiable risk factor for a second fragility fracture. In recent years, many studies have linked commonly prescribed drugs to increased fracture risk, either by increasing the risk of falls or by lowering bone density.[14-32] Other drugs, primarily bisphosphonates, have been shown to increase bone density and decrease the risk of subsequent fractures.[16,33-35] Several research teams,[36-39] including our own,[38] have shown that the use of bisphosphonates among fracture survivors is low. Meanwhile, Sjöberg and colleagues[40] describe a very high rate of use of drugs associated with falls both before and after fracture among 100 consecutive patients at a single institution in Sweden. This suggests that prescription drugs associated with increased fracture risk could represent a critical risk factor for secondary prevention. To our knowledge, the extent to which opportunities exist to decrease exposure to fracture-promoting drugs among older Americans has not previously been studied. We therefore designed this study to explore the use of drugs associated with fracture risk before and after a fracture of the hip, wrist, or shoulder to determine (1) the prevalence of prescription drug use as a potentially modifiable risk factor for secondary fracture prevention among a large cohort of fracture survivors in the United States and (2) whether an index fracture event modifies the prescribing behavior of physicians with respect to drugs that either increase or decrease fracture risk.

Key Points

Question Does a fragility fracture lead to a change in the use of prescription drugs that increase the risk of fracture?

Findings In this cohort study of 168 133 Medicare beneficiaries who survived a fragility fracture, three-quarters of patients were using at least 1 drug that increases the risk of fracture at the time of the fracture. This proportion did not change following the fracture event.

Meaning There is a missed opportunity to reduce the risk of a second fragility fracture through modification of exposure to prescription drugs.

Methods

Study Cohort

The study was approved by the Committee for the Protection of Human Subjects at Dartmouth College, waiving written informed consent. The study cohort consisted of US Medicare beneficiaries who sustained a fracture of the hip (proximal femur), shoulder (proximal humerus), or wrist (distal radius) from 2007 through 2011. Fractures were identified using *International Classification of Diseases, Ninth Revision* codes and had to be accompanied by an appropriate surgical procedure code (Current Procedural Terminology code) in the case of hip fracture, or a code for a radiology examination within 7 days of the diagnosis of an shoulder or wrist fracture and indication of immobilization or fixation. Complete details of cohort selection and the database used for this study have been previously published.[41] To be included in the cohort, beneficiaries had to be enrolled in Medicare Parts A and B for at least 12 months and in Part D for 4 months prior to the index fracture and for the duration of follow-up. Beneficiaries were also required to be community dwelling at the time of the fracture and for at least 30 days within the 4 months following the fracture. This requirement was implemented to ensure that retail pharmacy fills would be captured in the database and to focus attention on patients cared for outside of the nursing home setting. Patients who were enrolled in hospice, who were discharged to a nursing home or rehabilitation facility without returning to the community after fracture, and who did not fill at least 1 prescription for a drug of any kind during the observation period were excluded.

Study Period

The date of the first Medicare claim indicating a fracture was used as the index date. To ensure the index date represented a new fracture, we examined the prior 12 months of claims for codes identifying a previous fracture at the same site. A 120-day lookback window from the index date was used to define prescription drug use prior to the fracture. To determine prescription drug use after the index fracture, we analyzed patient records from the index date forward 120 days. This allowed us to capture any outpatient prescription fills after the index fracture, including those with a 3-month supply filled just prior to the fracture.

Prescription Drug Use

We identified 21 drug classes that have been associated in the literature with increased fracture risk. These drugs were examined as a single group and then subdivided into those drugs thought to increase fracture risk by increasing risk of falls, those that decrease bone density, and those with unclear fracture risk mechanism (**Table 1**). We also analyzed opiate drugs separately to avoid inflating our postfracture drug use measures by including potentially appropriate pain control following a fracture event. We excluded opiate fills in the 7 days prior to a fracture to avoid misclassifying exposure for those patients treated for pain associated with the fracture event before the fracture was diagnosed. We used retail pharmacy claims from the Part D Prescription Drug Event file to identify prescriptions filled by patients in the community setting. Beneficiaries were considered exposed prior to fracture if they had at least 1 fill for a drug on the list of fracture-associated drugs in the

120 days prior to the fracture event. Similarly, patients were considered exposed after the index fracture if they had at least 1 prescription fill for a drug of interest in the 120 days following the index date. Prefracture use of intravenous bisphosphonates was assessed using Part B records. Because intravenous bisphosphonate use was uncommon (observed in 2.2% of the cohort prior to fracture) and because prefracture use automatically determined postfracture use by virtue of annual dosing in most cases, we reported only oral bisphosphonate use in our analyses.

We then identified a subset of drugs that we hypothesized would be most likely to be discontinued after a fracture event based on the quality of existing evidence. To select drugs associated with fall risk, we used the meta-analysis of Woolcott et al,[42] who analyzed data available at the time of our study cohort. This study identified sedative/hypnotic medications, antipsychotics, and antidepressants as the drugs with the strongest association with fracture. To this list of 3 drug classes, we also added drug classes with either numerous studies linking them to fracture risk (oral steroids), or at least 1 high-quality and widely publicized study establishing a link to fracture risk (proton pump inhibitors and thiazolidinediones).

Statistical Analysis

The primary outcome was the proportion of fracture survivors who were exposed to any potentially fracture-promoting drug (excluding opiates) in the 120 days following an index fracture event. This was then compared with the proportion exposed prior to the fracture event using the McNemar test, which effectively compares the frequency of those who stop previous use of a drug after the index fracture to those who start a drug not previously used prior to the index fracture. Similar comparisons were made for each subgroup of fracture-promoting drugs. The proportions of patients using oral bisphosphonates and other drugs associated with increased bone density were also compared. To determine how often the fracture event modified physician prescribing behavior, we calculated the proportion of patients who had filled a drug of interest prior to fracture but who did not fill it after the fracture (users who became nonusers), and the proportion of patients who were nonusers prior to the fracture event who then filled a prescription for a drug of interest after the fracture event (new starters). These analyses were also repeated for drugs that increase bone density. Finally, to ensure that our dichotomous outcome did not misclassify a reduction in the total burden of drug exposure, we used *t* tests to compare the mean number of fracture-promoting drugs used prior to fracture with the number used after fracture.

Three sensitivity analyses were then performed. First, we repeated the primary analysis for each drug class included in our subset of drugs most strongly supported by existing literature. A second sensitivity analysis was then performed, excluding patients who were discharged to any acute rehabilitation facility (skilled nursing facility, inpatient rehabilitation facility, or swing bed) prior to returning to the community. The intent was to evaluate the potential effect of missing data because medication prescriptions are not captured in Medicare Part D data during these stays. A third sensitivity analysis was performed that quantified the use of drugs that increase bone density stratified on whether patients used drugs that increase the risk of fracture. This analysis was designed to explore whether physicians consistently attempt to attenuate the risk of fracture when patients are prescribed drugs that increase fracture risk.

Table 1. Drugs Associated With Increased Risk of Fracture by Proposed Mechanism

Proposed Mechanism of Increased Fracture Risk	Cohort Use Prior to Fracture, %
Increased Risk of Falls	
Benzodiazepines	2.8
Barbiturates	1.2
Sedative-hypnotics (nonbenzodiazepine)[a]	10.8
Opiates	35.5
Selective serotonin reuptake inhibitors[a]	26.4
Tricyclic antidepressants	4.8
Anti-Parkinson disease drugs	5.6
Centrally acting antihypertensives	3.9
Nitrates	8.6
Nonnitrate anti-anginal agents	1.4
Thiazide diuretics	23.4
Thiazide-like diuretics	2.9
Decreased Bone Density	
Inhaled glucocorticoids	7.0
Oral glucocorticoids[a]	9.8
Proton pump inhibitors[a]	25.6
H2 receptor antagonists	5.6
Thiazolidinediones[a]	5.7
Anticonvulsants	9.3
Unclear Primary Mechanism	
Atypical antipsychotics[a]	5.2
Early-generation antipsychotics	1.8
Loop diuretics	21.0

[a] Subset of drugs with a risk of fracture most strongly supported by existing literature.

Results

A total of 168 133 patients with a fragility fracture met the inclusion and exclusion criteria for this study. The demographics, comorbidities, fracture type, and discharge destination after fracture are summarized in **Table 2**. Across all fracture types, the mean (SD) age was 80.0 (7.7) years; 84.2% were women; and 91.8% were white. At the time of the index fracture, 53.2% of the cohort was hospitalized, although this varied substantially depending on fracture type (100% of hip fractures, 8.2% of wrist fractures, and 15.0% of shoulder fractures). The frequency of discharge to an institution for rehabilitation following hospitalization also varied by fracture type, but the mean (SD) duration of acute rehabilitation did not: 28.1 (19.8) days.

Table 2. Baseline Characteristics of Medicare Beneficiaries Who Sustained a Fragility Fracture and Returned to the Community Within 120 Days of the Index Fragility Fracture[a]

Characteristic	Total	Location of Fracture		
		Hip	Wrist	Shoulder
Total	168 133 (100)	80 508 (47.9)	60 930 (36.2)	26 695 (15.9)
Age at fracture, mean (SD), y	80.0 (7.7)	81.9 (7.5)	78.2 (7.5)	78.5 (7.5)
Age at fracture, y				
65-69	18 079 (10.8)	5198 (6.5)	9183 (15.1)	3698 (13.9)
70-74	27 805 (16.5)	9700 (12.0)	12 606 (20.7)	5499 (20.6)
75-79	32 621 (19.4)	14 337 (17.8)	12 777 (21.0)	5507 (20.6)
80-84	38 310 (22.8)	19 666 (24.4)	12 824 (21.0)	5820 (21.8)
≥85	51 318 (30.5)	31 607 (39.3)	13 540 (22.2)	6171 (23.1)
Female sex	141 569 (84.2)	64 672 (80.3)	54 056 (88.7)	22 841 (85.6)
Race				
Black	5015 (3.0)	2574 (3.2)	1764 (2.9)	677 (2.5)
Hispanic	8805 (5.2)	3685 (4.6)	3860 (6.3)	1260 (4.7)
White and other	154 313 (91.8)	74 249 (92.2)	55 306 (90.8)	24 758 (92.7)
Low-income subsidy recipient	52 494 (31.2)	25 687 (31.9)	18 738 (30.8)	8069 (30.2)
Count of Charlson comorbidities				
0	63 346 (37.7)	22 361 (27.8)	30 060 (49.3)	10 925 (40.9)
1	31 737 (18.9)	17 598 (21.9)	9760 (16.0)	4379 (16.4)
2	35 228 (21.0)	17 292 (21.5)	11 992 (19.7)	5944 (22.3)
3	19 126 (11.4)	11 171 (13.9)	5116 (8.4)	2839 (10.6)
≥4	18 696 (11.1)	12 086 (15.0)	4002 (6.6)	2608 (9.8)
Total prescription drugs active at index fracture, mean (SD)	7.0 (4.2)	7.0 (4.1)	6.8 (4.3)	7.3 (4.3)
Hospitalized at index fracture	89 491 (53.2)	80 508 (100.0)	4983 (8.2)	4000 (15.0)
Discharge to inpatient rehabilitation[b]	57 081 (63.8)	53 976 (67.0)	1570 (31.5)	1535 (38.4)
Days spent in inpatient rehabilitation after discharge, mean (SD)	28.1 (19.8)	28.0 (19.7)	29.5 (21.0)	29.5 (21.0)

[a] Unless otherwise noted, data are reported as number (percentage) of participants.

[b] Skilled nursing facility, inpatient rehabilitation facility, or swing bed facility.

Use of Fracture-Promoting Drugs Prior to Fracture

More than three-quarters (76%) of fragility fracture patients were exposed to at least 1 nonopiate drug associated with an increased risk of fracture in the 120 days prior to their index event (**Table 3**). This finding was consistent across all fracture types (77.1% for hip, 74.1% for wrist, and 75.9% for shoulder). More than half (55.7%) of patients were taking at least 1 drug that increases fall risk prior to the index fracture, while slightly less than half (42.2%) were taking at least 1 drug that decreases bone density. Again, we observed very little variation in these values across fracture types.

Use of Fracture-Promoting Drugs After Fracture

In the 120 days following a fragility fracture, we observed very similar numbers of patients who were exposed to at least 1 nonopiate drug associated with increased fracture risk (80.5% for hip, 74.3% for wrist, and 76.9% of shoulder). This represents a total change in the absolute proportion exposed by fracture type of +3.4%, +0.2%, and +1.0% for hip, wrist, and shoulder, respectively. As Table 3 details, there were similarly small changes in the proportion exposed to drugs that increase fall risk and drugs that decrease bone density across all fracture types. Our sensitivity analysis limited to only those patients who returned directly to the community after the index fracture revealed very similar results (eTable 2 in the Supplement).

When we further examined prefracture and postfracture drug use, we observed a group of patients who stopped taking fracture-promoting drugs after fracture; however, this group was offset by other patients who initiated therapy with a high-risk drug after fracture (**Figure**). This pattern was also observed in our analysis of those drugs most clearly associated with fracture risk in the literature (**Table 4**). While almost one-quarter of users of sedatives, antipsychotics, and thiazolidinediones and almost half of oral corticosteroid users discontinued use after fracture, a similar or greater number of nonusers initiated treatment with these drugs after the fracture. The end result was that use of corticosteroids and thiazolidinediones decreased only slightly in the population as a whole, while use of the other 4 drug types increased after fracture.

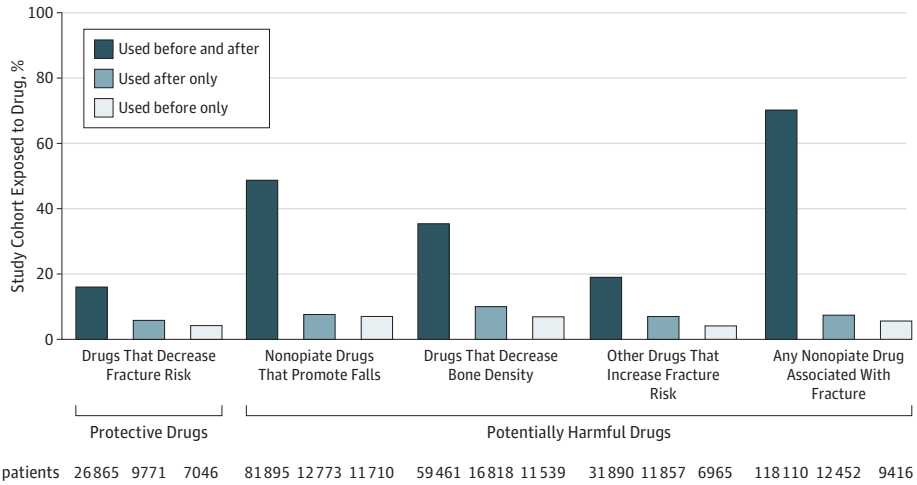
We also found that the total number of drugs per person associated with fracture risk did not change meaningfully after the fracture event (Table 3). Most patients continued to fill the same number of prescriptions for high-risk, nonopiate drugs after their index fracture (eTable 1 in the Supplement). At the same time, more patients increased than decreased the number of fracture-promoting drug fills, suggesting that the

Table 3. Use Before and After a Fragility Fracture of Drugs That Affect Fracture Risk

Fracture Location and Drug Type	Users Before Fracture		Users After Fracture	
	No. (%)	Drugs Used, Median No.	No. (%)	Drugs Used, Median No.
Hip (n = 80 508)				
Any drug that increases fracture risk	64 923 (80.6)	2	71 904 (89.3)[a]	2
Nonopiate drugs that increase fracture risk	62 098 (77.1)	1	64 779 (80.5)[a]	2
Nonopiate drugs that increase fall risk	44 930 (55.8)	1	45 837 (56.9)[a]	1
Drugs that decrease bone density	34 087 (42.3)	0	39 073 (48.5)[a]	0
Other fracture-promoting drugs	20 436 (25.4)	0	24 202 (30.1)[a]	0
Opiates	21 137 (26.3)	0	44 371 (55.1)[a]	1
Drugs that increase bone density	15 444 (19.2)	0	17 163 (21.3)[a]	0
Wrist (n = 60 930)				
Any drug that increases fracture risk	49 817 (81.8)	2	51 810 (85.0)[a]	2
Nonopiate drugs that increase fracture risk	45 175 (74.1)	1	45 262 (74.3)	1
Nonopiate drugs that increase fall risk	33 859 (55.6)	1	33 840 (55.5)	1
Drugs that decrease bone density	25 393 (41.7)	0	25 512 (41.9)	0
Other fracture-promoting drugs	12 302 (20.2)	0	12 771 (21.0)[a]	0
Opiates	23 332 (38.3)	0	31 002 (50.9)[a]	1
Drugs that increase bone density	13 689 (22.5)	0	14 466 (23.7)[a]	0
Shoulder (n = 26 695)				
Any drug that increases fracture risk	23 110 (86.6)	2	23 862 (89.4)[a]	2
Nonopiate drugs that increase fracture risk	20 253 (75.9)	1	20 521 (76.9)[a]	2
Nonopiate drugs that increase fall risk	14 816 (55.5)	1	14 991 (56.2)	1
Drugs that decrease bone density	11 520 (43.2)	0	11 694 (43.8)	0
Other fracture-promoting drugs	6117 (22.9)	0	6774 (25.4)[a]	0
Opiates	13 821 (51.8)	1	16 740 (62.7)[a]	1
Drugs that increase bone density	4778 (17.9)	0	5007 (18.8)[a]	0

[a] $P<.001$ for use after fracture vs use before fracture.

Figure. Use of Drugs That Affect Fracture Risk Before and After Fracture



binary classification we used to define our primary outcome did not mask a significant decline in the overall burden of potentially harmful prescribing.

Use of Drugs That Decrease Fracture Risk

The use of drugs that may reduce fracture risk was uncommon at the time of the index fracture (Table 3). Across fracture types, less than one-quarter of patients in the study cohort had filled a prescription for a drug that increases bone density in the 120 days prior to the fracture event. Following the fracture, the total numbers increased only slightly (Table 3 and Figure). Further analysis yielded a similar pattern to that seen with drugs that increase fracture risk: approximately 1 in 5 current users discontinued therapy after fracture, while a nearly identical number of nonusers at the time of fracture initiated treatment. Finally, when we

Table 4. Use of Select Drugs Associated With Fracture Risk Before and After a Fragility Fracture

Drug[a]	Users Prior to Fracture, No.	Users Who Stopped After Fracture, No. (%)	Nonusers Who Started After Fracture, No. (%)	Users After Fracture, No.
Oral steroids	16559	7221 (43.6)	6589 (4.3)	15 927
Proton pump inhibitors	43 114	3724 (8.6)	13 181 (10.5)	52 571
Thiazolidinediones	9632	2366 (24.6)	1168 (0.7)	8434
Hypnotics	18 107	3786 (20.9)	8672 (5.8)	22 993
SSRI	44 349	2640 (6.0)	7268 (5.9)	48 977
Antipsychotics	9678	2110 (21.8)	3767 (2.4)	11 335

Abbreviation: SSRI, selective serotonin reuptake inhibitor.

[a] Drugs selected as having the highest-quality evidence supporting a risk of fracture (see Methods section for further details).

examined whether drugs that decrease fracture risk might be targeted to patients taking drugs that increase fracture risk, we found a small effect. The use of drugs to decrease fracture risk was only slightly higher (22.7% vs 21.1%; $P < .001$) among users of fracture-promoting drugs than among those who were not using high-risk drugs (eFigure in the Supplement).

Discussion

This study has 3 primary findings. First, most Medicare beneficiaries who experience a fragility fracture are users of at least 1 drug that has been shown to increase fracture risk. This suggests that prescription drugs may be an important modifiable risk factor for primary fracture prevention. Second, a fragility fracture does not consistently serve as a sentinel event to decrease the total burden of exposure to drugs associated with increased fracture risk. An almost identical number of patients are exposed to drugs that are associated with increased fracture risk in the 4 months following a fracture as in the period preceding the index event. Third, a fracture event does result in modified exposure for a minority of patients, but in both directions: some patients no longer fill fracture-associated drug prescriptions after their fracture, while an almost equal number initiate exposure. This pattern was observed even among the subset of drugs most widely and convincingly recognized to cause fractures. The fact that some patients in our study cohort had decreased exposure to fracture-associated drugs following a fracture supports the feasibility of more effective medication review at the time of a fracture event.

The very high prevalence of fracture-associated drug use in this cohort (76%) is consistent with the findings of Sjöberg et al,[40] who found that nearly all of 100 elderly patients with fracture in a single institution cohort in Sweden were using a drug that could increase fall risk at the time of the fracture event. Although these authors used a broader definition of drugs that could increase fall risk, our findings are also consistent with their report that the same proportion was using fall-promoting drugs in the 6 months following fracture. In addition, our study confirms prior work demonstrating that the use of bisphosphonates and other fracture-prevention drugs is uncommon at the time of fracture and does not increase during follow-up. In fact, many patients who were taking drugs to increase bone density discontinued treatment with these medications after the fracture, a finding that may indicate that physicians consider a fragility fracture evidence that the drugs are ineffective.

The fact that these treatment patterns are apparent in this large, US cohort suggests that prescription drug use may be an effective target for secondary fracture prevention. Three caveats to this conclusion must be acknowledged. First, many of these drugs have important indications that may preclude discontinuation in response to a fracture event. Other drugs, however, are less clearly indicated, and emerging evidence suggests that there are many missed opportunities for reduction of prescription drug therapy among elderly patients in whom the risks of therapy likely outweigh the benefits.[43] Patients in whom a fracture may be in part the result of drug exposure should at least be considered for such reduction of therapy. So while it is not realistic to eliminate exposure to drugs that increase fracture risk in all cases, reductions in that risk through evaluation of medication use and selective discontinuation after fracture appear achievable.

A second caveat is that the magnitude of the risk associated with many prescription drugs remains uncertain among fracture survivors. Observational data have demonstrated the link between exposure and primary fracture risk,[14-32] but the precision of these estimates is often poor, and most studies have not been conducted to address the question of secondary prevention. Published studies also do not address the complexities of drug combinations that may have additive or synergistic effects on fracture risk. This leaves unanswered questions concerning the magnitude of benefit that could be achieved through concerted efforts to modify exposure to fracture-associated drugs after a fragility fracture.

Third, the mechanism to improve prescribing practices after fracture is not clearly developed. Patients go through a process of medication reconciliation at hospital admission, which should include a review of all potentially hazardous drugs; however, our data indicate that this process does not reduce high-risk drug use even among patients with hip fracture, all of whom were hospitalized. This may reflect a reluctance to modify chronic drug regimens on the part of physicians who manage an acute event but are not involved in the long-term management of multiple comorbid conditions. It may also reflect a knowledge gap among physicians with respect to known associations between prescription drugs and fracture risk. Automated decision support in the electronic medical record focused on fracture risk could be

developed to address the second concern,[44,45] but this will not change the need for effective communication between hospitalist physicians, orthopedic surgeons, and community primary care physicians regarding the risk-benefit tradeoffs of long-term medications.

Strengths of our study include the sample size and geographic representation of the study cohort as well as the comprehensive drug exposure information afforded by Part D data. Our study also has important limitations. The data include only Part D enrollees, who tend to have more comorbid conditions and higher overall prescription drug utilization rates than nonenrollees.[46] Our results may not therefore be generalizable to other populations. We used a 4-month lookback period to focus on prescription drugs that were likely to be currently in use at the time of the fracture event and could therefore be modified by the fracture event. This lookback window does not capture prescription drug use prior to that time, which may misclassify exposure to drugs that affect bone density long after use is discontinued. If anything, however, this decision will cause our results to underestimate exposure prior to fracture. After fracture, retail pharmacy claims captured in Part D data do not include drugs dispensed in a skilled nursing facility after discharge. Our decision to require cohort members to have at least 30 days of community dwelling time after fracture mitigates these missing data, and our sensitivity analyses demonstrate that patterns of use were nearly identical among those discharged directly home. In addition, most benzodiazepine use was excluded from Part D coverage until after the last year of the study cohort. Consequently, our data underrepresent this drug class. Finally, our data only extend to 2011, leaving open the possibility that current prescribing practices are not accurately reflected in our analysis.

Conclusions

The use of drugs that can contribute to elevated fracture risk is common among Medicare beneficiaries who experience a fragility fracture, and the fracture event does not consistently lead to a reduction in use of these drugs. This suggests that at least some secondary fragility fractures may be preventable through a more concerted effort to manage high-risk drugs around a primary fracture event. Additional research is needed to quantify the possible benefits associated with modifying postfracture drug exposure in this high-risk population.

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REFERENCES

1. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. *J Bone Miner Res*. 2007;22(3):465-475.

2. Ray NF, Chan JK, Thamer M, Melton LJ III. Medical expenditures for the treatment of osteoporotic fractures in the United States in 1995: report from the National Osteoporosis Foundation. *J Bone Miner Res*. 1997;12(1):24-35.

3. Bone Health and Osteoporosis. *A Report of the Surgeon General*. Rockville, MD: US Department of Health and Human Services; 2004.

4. Omsland TK, Magnus JH. Forecasting the burden of future postmenopausal hip fractures. *Osteoporos Int*. 2014;25(10):2493-2496.

5. Berry SD, Samelson EJ, Hannan MT, et al. Second hip fracture in older men and women: the Framingham Study. *Arch Intern Med*. 2007;167(18):1971-1976.

6. Colón-Emeric C, Kuchibhatla M, Pieper C, et al. The contribution of hip fracture to risk of subsequent fractures: data from two longitudinal studies. *Osteoporos Int*. 2003;14(11):879-883.

7. Egan M, Jaglal S, Byrne K, Wells J, Stolee P. Factors associated with a second hip fracture: a systematic review. *Clin Rehabil*. 2008;22(3):272-282.

8. Kanis JA, Johnell O, De Laet C, et al. A meta-analysis of previous fracture and subsequent fracture risk. *Bone*. 2004;35(2):375-382.

9. Lauritzen JB, Schwarz P, McNair P, Lund B, Transbøl I. Radial and humeral fractures as predictors of subsequent hip, radial or humeral fractures in women, and their seasonal variation. *Osteoporos Int*. 1993;3(3):133-137.

10. Riley RL, Carnes ML, Gudmundsson A, Elliott ME. Outcomes and secondary prevention strategies for male hip fractures. *Ann Pharmacother*. 2002;36(1):17-23.

11. Ryg J, Rejnmark L, Overgaard S, Brixen K, Vestergaard P. Hip fracture patients at risk of second hip fracture: a nationwide population-based cohort study of 169,145 cases during 1977-2001. *J Bone Miner Res*. 2009;24(7):1299-1307.

12. Schrøder HM, Petersen KK, Erlandsen M. Occurrence and incidence of the second hip fracture. *Clin Orthop Relat Res*. 1993;(289):166-169.

13. Wolinsky FD, Fitzgerald JF. Subsequent hip fracture among older adults. *Am J Public Health*. 1994;84(8):1316-1318.

14. De Vries F, Bracke M, Leufkens HG, Lammers JW, Cooper C, Van Staa TP. Fracture risk with intermittent high-dose oral glucocorticoid therapy. *Arthritis Rheum*. 2007;56(1):208-214.

15. Dormuth CR, Carney G, Carleton B, Bassett K, Wright JM. Thiazolidinediones and fractures in men and women. *Arch Intern Med*. 2009;169(15):1395-1402.

16. Ensrud KE, Blackwell TL, Mangione CM, et al; Study of Osteoporotic Fractures Research Group. Central nervous system-active medications and risk for falls in older women. *J Am Geriatr Soc*. 2002;50(10):1629-1637.

17. Guo Z, Wills P, Viitanen M, Fastbom J, Winblad B. Cognitive impairment, drug use, and the risk of hip fracture in persons over 75 years old: a community-based prospective study. *Am J Epidemiol*. 1998;148(9):887-892.

18. Hubbard R, Tattersfield A, Smith C, West J, Smeeth L, Fletcher A. Use of inhaled corticosteroids and the risk of fracture. *Chest*. 2006;130(4):1082-1088.

19. Hugenholtz GW, Heerdink ER, van Staa TP, Nolen WA, Egberts AC. Risk of hip/femur fractures in patients using antipsychotics. *Bone*. 2005;37(6):864-870.

20. Johannes CB, Schneider GA, Dube TJ, Alfredson TD, Davis KJ, Walker AM. The risk of nonvertebral fracture related to inhaled corticosteroid exposure among adults with chronic respiratory disease. *Chest*. 2005;127(1):89-97.

21. Kahn SE, Zinman B, Lachin JM, et al; Diabetes Outcome Progression Trial (ADOPT) Study Group. Rosiglitazone-associated fractures in type 2 diabetes: an Analysis from A Diabetes Outcome Progression Trial (ADOPT). *Diabetes Care*. 2008;31(5):845-851.

22. Lee TA, Weiss KB. Fracture risk associated with inhaled corticosteroid use in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2004;169(7):855-859.

23. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis, I: psychotropic drugs. *J Am Geriatr Soc*. 1999;47(1):30-39.

24. Ray WA, Griffin MR, Schaffner W, Baugh DK, Melton LJ III. Psychotropic drug use and the risk of hip fracture. *N Engl J Med*. 1987;316(7):363-369.

25. Ray WA, Thapa PB, Gideon P. Benzodiazepines and the risk of falls in nursing home residents. *J Am Geriatr Soc*. 2000;48(6):682-685.

26. Richards JB, Papaioannou A, Adachi JD, et al; Canadian Multicentre Osteoporosis Study Research Group. Effect of selective serotonin reuptake inhibitors on the risk of fracture. *Arch Intern Med*. 2007;167(2):188-194.

27. Schneeweiss S, Wang PS. Association between SSRI use and hip fractures and the effect of residual confounding bias in claims database studies. *J Clin Psychopharmacol*. 2004;24(6):632-638.

28. Shorr RI, Griffin MR, Daugherty JR, Ray WA. Opioid analgesics and the risk of hip fracture in the elderly: codeine and propoxyphene. *J Gerontol*. 1992;47(4):M111-M115.

29. Takkouche B, Montes-Martínez A, Gill SS, Etminan M. Psychotropic medications and the risk of fracture: a meta-analysis. *Drug Saf*. 2007;30(2):171-184.

30. van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Oral corticosteroids and fracture risk: relationship to daily and cumulative doses. *Rheumatology (Oxford)*. 2000;39(12):1383-1389.

31. Vestergaard P, Rejnmark L, Mosekilde L. Anxiolytics, sedatives, antidepressants, neuroleptics and the risk of fracture. *Osteoporos Int*. 2006;17(6):807-816.

32. Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA*. 2006;296(24):2947-2953.

33. Wells G, Cranney A, Peterson J, et al. Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. *Cochrane Database Syst Rev*. 2008;(1):CD004523.

34. Wells G, Cranney A, Peterson J, et al. Etidronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. *Cochrane Database Syst Rev*. 2008;(1):CD003376.

35. Wells G, Cranney A, Peterson J, et al. Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. *Cochrane Database Syst Rev*. 2008;(1):CD001155.

36. Elliot-Gibson V, Bogoch ER, Jamal SA, Beaton DE. Practice patterns in the diagnosis and treatment of osteoporosis after a fragility fracture: a systematic review. *Osteoporos Int*. 2004;15(10):767-778.

37. Giangregorio L, Papaioannou A, Cranney A, Zytaruk N, Adachi JD. Fragility fractures and the osteoporosis care gap: an international phenomenon. *Semin Arthritis Rheum*. 2006;35(5):293-305.

38. Liu SK, Munson JC, Bell JE, et al. Quality of osteoporosis care of older Medicare recipients with fragility fractures: 2006 to 2010. *J Am Geriatr Soc*. 2013;61(11):1855-1862.

39. Solomon DH, Finkelstein JS, Katz JN, Mogun H, Avorn J. Underuse of osteoporosis medications in elderly patients with fractures. *Am J Med*. 2003;115(5):398-400.

40. Sjöberg C, Bladh L, Klintberg L, Mellström D, Ohlsson C, Wallerstedt SM. Treatment with fall-risk-increasing and fracture-preventing drugs before and after a hip fracture: an observational study. *Drugs Aging*. 2010;27(8):653-661.

41. Bynum JP, Bell JE, Cantu RV, et al. Second fractures among older adults in the year following hip, shoulder, or wrist fracture. *Osteoporos Int*. 2016;27(7):2207-2215.

42. Woolcott JC, Richardson KJ, Wiens MO, et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Arch Intern Med*. 2009;169(21):1952-1960.

43. Sussman JB, Kerr EA, Saini SD, et al. Rates of Deintensification of Blood Pressure and Glycemic Medication Treatment Based on Levels of Control and Life Expectancy in Older Patients With Diabetes Mellitus. *JAMA Intern Med*. 2015;175(12):1942-1949.

44. Niehoff KM, Rajeevan N, Charpentier PA, Miller PL, Goldstein MK, Fried TR. Development of the Tool to Reduce Inappropriate Medications (TRIM): a clinical decision support system to improve medication prescribing for older adults. *Pharmacotherapy*. 2016;36(6):694-701.

45. Peterson JF, Kripalani S, Danciu I, et al. Electronic surveillance and pharmacist intervention for vulnerable older inpatients on high-risk medication regimens. *J Am Geriatr Soc*. 2014;62(11):2148-2152.

46. Munson JC, Morden NE, Goodman DC, Valle LF, Wennberg JE. *The Dartmouth Atlas of Medicare Prescription Drug Use*. Lebanon, NH: The Dartmouth Institute for Health Policy and Clinical Practice; 2013.