Published in final edited form as:

JAMA Intern Med. 2016 October 1; 176(10): 1531–1538. doi:10.1001/jamainternmed.2016.4814.

Patterns of prescription drug use before and after fragility fracture in the United States

Jeffrey C Munson, MD, MSCE^{1,2}, Julie PW Bynum, MD, MPH^{1,3}, John-Erik Bell, MD, MS^{1,4}, Robert Cantu, MD, MS⁴, Christine McDonough, PT, PhD⁵, Qianfei Wang, MS¹, Tor Tosteson, ScD^{1,3}, and Anna NA Tosteson, ScD^{1,3}

¹The Dartmouth Institute for Health Policy and Clinical Practice, Lebanon, NH

²Department of Medicine, Geisel School of Medicine at Dartmouth, Lebanon, NH

³Department of Community and Family Medicine, Geisel School of Medicine at Dartmouth, Lebanon, NH

⁴Department of Orthopaedic Surgery, Geisel School of Medicine at Dartmouth, Lebanon, NH

⁵Boston University School of Public Health, Boston, MA

Abstract

Importance—Patients who suffer a fragility fracture are at high risk for subsequent fractures. Prescription drugs represent one 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—Retrospective cohort study using a 40% random sample of Medicare claims from 2007–2011.

Setting—General communities throughout the United States

Participants—168,133 community-dwelling Medicare beneficiaries who survived a fracture of the hip, upper arm or wrist. Cohort members were required to be enrolled in Medicare fee-for-service with drug coverage (Parts A, B and D) and to be community-dwelling for at least 30 days in the immediate 4 month post-fracture period.

Exposure—The 4 month periods before and after a fragility fracture.

Outcome Measures—Prescription fills for drug classes associated with increased fracture risk were measured using Part D retail pharmacy claims. These were divided into three categories: drugs that increase fall risk; drugs that decrease bone density; and drugs whose primary mechanism of increased fracture risk is unclear. Drugs that increase bone density were also tracked.

Results—Most patients were exposed to at least one non-opiate drug associated with increased fracture risk in the 4 months before fracture (77.1% of hip, 74.1% of wrist, and 75.9% of upper arm fractures). Approximately 7% of these patients discontinued exposure after fracture; however, 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% 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 three 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.

Background

Fragility fractures among the elderly are a source of significant morbidity and mortality and are associated with annual direct costs of over 16 billion dollars.^{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 six 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. Over 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} Our group and others have previously shown that the use of bisphosphonates among fracture survivors is low, arguing that this alone is not an effective strategy for secondary fracture prevention.^{36–39} Meanwhile, Sjöberg and colleagues described 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.⁴⁰ This suggests that prescription drugs associated with increased fracture risk could represent a critical risk factor for secondary prevention. 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 upper arm 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.

Methods

Study cohort

The study cohort consisted of US Medicare beneficiaries who sustained a fracture of the proximal femur, humerus or distal radius between the years of 2007–2011. Fractures were identified using ICD-9 codes and had to be accompanied by an appropriate surgical procedure code (CPT code) in the case of hip fracture, or a code for a radiology examination within 7 days of the diagnosis of an upper arm 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 fracture and for at least 30 days within the 4 months following 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 one prescription drug of any kind during the observation period were excluded.

Study period

The date a fracture was first coded in Medicare claims 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 followed patients 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 with increased fracture risk in the existing literature. These drugs were examined as a single group, and then subdivided into those drugs whose mechanism of fracture risk is thought to be due to increased falls, those that decrease bone density, and those whose primary mechanism of fracture risk is unclear (Table 1). We also analyzed opiate drugs separately to avoid inflating our post-fracture drug use measures by including potentially appropriate pain control following a fracture event. We also 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 one 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 one prescription fill for a drug of interest in the 120 days following the index date. Pre-fracture use of intravenous bisphosphonates was assessed using Part B records. Because IV bisphosphonate use was

uncommon (observed in 2.2% of the cohort prior to fracture) and because pre-fracture use automatically determined post-fracture 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 which 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 published using data available at the time of our study cohort.⁴² This study identified sedative/hypnotic medications, antipsychotics, and antidepressants as the drugs with the strongest association with fracture. To this list of three drug classes, we also added drug classes with either numerous studies linking them to fracture risk (oral steroids), or at least one 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 to the proportion exposed prior to the fracture event using McNemar's test, which effectively compares the frequency of those who stop previous use of a drug after the index fracture to those that 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 after fracture (users who became non-users), and the proportion of patients who were non-users prior to the fracture event who filled a drug of interest after the fracture event (new starters). These analyses were also repeated for drugs that increase bone density. Finally, to ensure our dichotomous outcome didn't misclassify a reduction in the total burden of drug exposure, we used Student's t-test 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 impact 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.

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 displayed in Table 2. Across all fracture types, the average age was 80.0 years (SD 7.7 yrs), 84.2% were women, and 91.8% were white. 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% of upper arm fractures). The frequency of discharge to an institution for rehabilitation following hospitalization also varied by fracture type, but the duration of acute rehabilitation did not (total mean 28.1 days, SD 19.8).

Use of fracture-promoting drugs prior to fracture

More than three-quarters (76%) of fragility fracture patients were exposed to at least one non-opiate 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 upper arm). More than half (55.7%) of patients were taking at least one drug that increases fall risk prior to the index fracture, while slightly less than half (42.2%) were taking at least one 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 one non-opiate drug associated with increased fracture risk (80.5% for hip, 74.3% for wrist, and 76.9% of upper arm). This represents a total change in the absolute proportion exposed by fracture type of +3.4%, +0.2%, and +1.0% respectively. As Table 3 shows, 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).

When we further examined pre- and post-fracture use, we observed a group of patients who stopped fracture promoting drugs after fracture; however, this group was offset by other patients who initiated therapy with a high-risk drug after fracture (Figure 1). 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 these drugs. The end result was that use of corticosteroids and thiazolidinediones decreased only slightly in the population as a whole, while use of the other four drugs 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.) The majority of patients continued to fill the same number of high-risk, non-opiate drugs after their index fracture (eTable 1). At the same time, more patients increased than decreased the number of fracture-promoting

drug fills, suggesting the 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 1). Further analysis yielded a similar pattern to that seen with drugs that increase fracture risk: approximately one in five current users discontinued therapy after fracture while a nearly identical number of non-users at the time of fracture initiated treatment. Finally, when we 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%, $p<0.001$) among users of fracture-promoting drugs than among those who were not using high-risk drugs (eFigure 1).

Discussion

This study identified three primary findings. First, the majority of Medicare beneficiaries who suffer a fragility fracture are users of at least one 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 four 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 drugs after their fracture event, 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 Sjoberg et al who found that nearly all of 100 elderly fracture patients in a single institution cohort in Sweden were using a drug that could increase fall risk at the time of the fracture event.⁴⁰ 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. Additionally, 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 these medications after fracture, a finding which 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 there are many missed opportunities for de-intensification 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 de-escalation 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} however 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 which 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 on 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 will not change the need for effective communication between hospitalist physicians, orthopedic surgeons, and community primary care physicians regarding the risk-benefit tradeoffs of chronic medications.

Strengths of our study include the sample size and geographic representation of the study cohort as well as the comprehensive drug exposure data 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 than non-enrollees.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 impact 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 this missing data, and our sensitivity analyses demonstrate that patterns of use were nearly identical among those discharged directly home. Additionally, most benzodiazepine use was excluded from Part D coverage until after the last year of the study cohort. Consequently, our data under-represent 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.

Conclusion

The use of drugs that can contribute to elevated fracture risk is common among Medicare beneficiaries who suffer 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 post-fracture drug exposure in this high-risk population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References Cited

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.* Mar; 2007 22(3):465–475. [PubMed: 17144789]
2. Ray NF, Chan JK, Thamer M, Melton LJ 3rd. Medical expenditures for the treatment of osteoporotic fractures in the United States in 1995: report from the National Osteoporosis Foundation. *J Bone Miner Res.* Jan; 1997 12(1):24–35. [PubMed: 9240722]
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.* Oct; 2014 25(10):2493–2496. [PubMed: 24980184]
5. Berry SD, Samelson EJ, Hannan MT, et al. Second hip fracture in older men and women: the Framingham Study. *Arch Intern Med.* Oct 8; 2007 167(18):1971–1976. [PubMed: 17923597]
6. Colon-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.* Nov; 2003 14(11):879–883. [PubMed: 14530910]
7. Egan M, Jaglal S, Byrne K, Wells J, Stolee P. Factors associated with a second hip fracture: a systematic review. *Clin Rehabil.* Mar; 2008 22(3):272–282. [PubMed: 18057086]
8. Kanis JA, Johnell O, De Laet C, et al. A meta-analysis of previous fracture and subsequent fracture risk. *Bone.* Aug; 2004 35(2):375–382. [PubMed: 15268886]
9. Lauritzen JB, Schwarz P, McNair P, Lund B, Transbol I. Radial and humeral fractures as predictors of subsequent hip, radial or humeral fractures in women, and their seasonal variation. *Osteoporos Int.* May; 1993 3(3):133–137. [PubMed: 8481589]
10. Riley RL, Carnes ML, Gudmundsson A, Elliott ME. Outcomes and secondary prevention strategies for male hip fractures. *Ann Pharmacother.* Jan; 2002 36(1):17–23. [PubMed: 11816248]
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.* Jul; 2009 24(7):1299–1307. [PubMed: 19257816]

12. Schroder HM, Petersen KK, Erlandsen M. Occurrence and incidence of the second hip fracture. *Clin Orthop Relat Res*. Apr.1993 (289):166–169. [PubMed: 8472408]
13. Wolinsky FD, Fitzgerald JF. Subsequent hip fracture among older adults. *Am J Public Health*. Aug; 1994 84(8):1316–1318. [PubMed: 8059894]
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*. Jan; 2007 56(1):208–214. [PubMed: 17195223]
15. Dormuth CR, Carney G, Carleton B, Bassett K, Wright JM. Thiazolidinediones and fractures in men and women. *Arch Intern Med*. Aug 10; 2009 169(15):1395–1402. [PubMed: 19667303]
16. Ensrud KE, Blackwell TL, Mangione CM, et al. Central nervous system-active medications and risk for falls in older women. *J Am Geriatr Soc*. Oct; 2002 50(10):1629–1637. [PubMed: 12366615]
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*. Nov 1; 1998 148(9):887–892. [PubMed: 9801019]
18. Hubbard R, Tattersfield A, Smith C, West J, Smeeth L, Fletcher A. Use of inhaled corticosteroids and the risk of fracture. *Chest*. Oct; 2006 130(4):1082–1088. [PubMed: 17035441]
19. Hugenholtz GW, Heerdink ER, van Staa TP, Nolen WA, Egberts AC. Risk of hip/femur fractures in patients using antipsychotics. *Bone*. Dec; 2005 37(6):864–870. [PubMed: 16111927]
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*. Jan; 2005 127(1):89–97. [PubMed: 15653967]
21. Kahn SE, Zinman B, Lachin JM, et al. Rosiglitazone-associated fractures in type 2 diabetes: an Analysis from A Diabetes Outcome Progression Trial (ADOPT). *Diabetes Care*. May; 2008 31(5): 845–851. [PubMed: 18223031]
22. Lee TA, Weiss KB. Fracture risk associated with inhaled corticosteroid use in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. Apr 1; 2004 169(7):855–859. [PubMed: 14711795]
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*. Jan; 1999 47(1):30–39. [PubMed: 9920227]
24. Ray WA, Griffin MR, Schaffner W, Baugh DK, Melton LJ 3rd. Psychotropic drug use and the risk of hip fracture. *N Engl J Med*. Feb 12; 1987 316(7):363–369. [PubMed: 2880292]
25. Ray WA, Thapa PB, Gideon P. Benzodiazepines and the risk of falls in nursing home residents. *J Am Geriatr Soc*. Jun; 2000 48(6):682–685. [PubMed: 10855607]
26. Richards JB, Papaioannou A, Adachi JD, et al. Effect of selective serotonin reuptake inhibitors on the risk of fracture. *Arch Intern Med*. Jan 22; 2007 167(2):188–194. [PubMed: 17242321]
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*. Dec; 2004 24(6): 632–638. [PubMed: 15538126]
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*. Jul; 1992 47(4):M111–115. [PubMed: 1624693]
29. Takkouche B, Montes-Martinez A, Gill SS, Etminan M. Psychotropic medications and the risk of fracture: a meta-analysis. *Drug Saf*. 2007; 30(2):171–184. [PubMed: 17253881]
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)*. Dec; 2000 39(12):1383–1389. [PubMed: 11136882]
31. Vestergaard P, Rejnmark L, Mosekilde L. Anxiolytics, sedatives, antidepressants, neuroleptics and the risk of fracture. *Osteoporos Int*. 2006; 17(6):807–816. [PubMed: 16520889]
32. Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA*. Dec 27; 2006 296(24):2947–2953. [PubMed: 17190895]
33. Wells G, Cranney A, Peterson J, et al. Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. *Cochran Database of Systematic Reviews*. 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. *Cochran Database of Systematic Reviews*. 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. *Cochran Database of Systematic Reviews*. 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*. Oct; 2004 15(10):767–778. [PubMed: 15258724]
37. Giangregorio L, Papaioannou A, Cranney A, Zytaruk N, Adachi JD. Fragility fractures and the osteoporosis care gap: an international phenomenon. *Semin Arthritis Rheum*. Apr; 2006 35(5): 293–305. [PubMed: 16616152]
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*. Nov; 2013 61(11):1855–1862. [PubMed: 24219186]
39. Solomon DH, Finkelstein JS, Katz JN, Mogun H, Avorn J. Underuse of osteoporosis medications in elderly patients with fractures. *The American journal of medicine*. Oct 1; 2003 115(5):398–400. [PubMed: 14553876]
40. Sjoberg C, Bladh L, Klintberg L, Mellstrom 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*. Aug 1; 2010 27(8):653–661. [PubMed: 20658793]
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*. Feb 24.2016
42. Woolcott JC, Richardson KJ, Wiens MO, et al. MEta-analysis of the impact of 9 medication classes on falls in elderly persons. *Archives of Internal Medicine*. 2009; 169(21):1952–1960. [PubMed: 19933955]
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 internal medicine*. Dec; 2015 175(12):1942–1949. [PubMed: 26502220]
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*. Apr 3.2016
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*. Nov; 2014 62(11):2148–2152. [PubMed: 25366414]
46. Munson, JC.; Morden, NE.; Goodman, DC.; Valle, LF.; Wennberg, JE. *The Dartmouth Atlas of Medicare Prescription Drug Use*. The Dartmouth Institute for Health Policy and Clinical Practice; 2013.

Figure 1.
Use of drugs that impact fracture risk before (top) and after (bottom) fracture.

Table 1

Drugs associated with increased risk of fracture by proposed mechanism

Drugs that increase the risk of falls	% of study cohort using prior to fracture
Benzodiazepines	2.8
Barbiturates	1.2
Sedative-hypnotics (non-benzodiazepine) *	10.8
Opiates	35.5
Selective serotonin reuptake inhibitors (SSRI) *	26.4
Tricyclic antidepressants	4.8
Antiparkinson's Disease drugs	5.6
Centrally acting antihypertensives	3.9
Nitrates	8.6
Non-nitrate anti-anginals	1.4
Thiazide diuretics	23.4
Thiazide like diuretics	2.9
Drugs that decrease bone density	
Inhaled glucocorticoids	7.0
Oral glucocorticoids *	9.9
Proton pump inhibitors (PPI) *	25.6
H2 receptor antagonists	5.6
Thiazolidinediones *	5.7
Anticonvulsants	9.3
Drugs with an unclear primary mechanism of increased risk	
Atypical antipsychotics *	5.2
Early generation antipsychotics	1.8
Loop diuretics	21.0

* Subset of drugs with a risk of fracture most strongly supported by existing literature

Table 2

Baseline characteristics of Medicare beneficiaries who sustain a fragility fracture and return to the community within 120 days of the index fragility fracture

	Total	Hip	Wrist	Humerus
N	168,133 (100.0)	80,508 (47.9)	60,930 (36.2)	26,695 (15.9)
Age at fracture (mean, SD)	80.0 (7.7)	81.9 (7.5)	78.2 (7.5)	78.5 (7.5)
Age at fracture (N, %)				
65–69	18,079 (10.8)	5,198 (6.5)	9,183 (15.1)	3,698 (13.9)
70–74	27,805 (16.5)	9,700 (12.0)	12,606 (20.7)	5,499 (20.6)
75–79	32,621 (19.4)	14,337 (17.8)	12,777 (21.0)	5,507 (20.6)
80–84	38,310 (22.8)	19,666 (24.4)	12,824 (21.0)	5,820 (21.8)
85+	51,318 (30.5)	31,607 (39.3)	13,540 (22.2)	6,171 (23.1)
Sex (female)	141,569 (84.2)	64,672 (80.3)	54,056 (88.7)	22,841 (85.6)
Race				
black	5,015 (3.0)	2,574 (3.2)	1,764 (2.9)	677 (2.5)
hispanic	8,805 (5.2)	3,685 (4.6)	3,860 (6.3)	1,260 (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)	8,069 (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)	9,760 (16.0)	4,379 (16.4)
2	35,228 (21.0)	17,292 (21.5)	11,992 (19.7)	5,944 (22.3)
3	19,126 (11.4)	11,171 (13.9)	5,116 (8.4)	2,839 (10.6)
4+	18,696 (11.1)	12,086 (15.0)	4,002 (6.6)	2,608 (9.8)
Number of 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)	4,983 (8.2)	4,000 (15.0)
Discharge to Inpatient Rehab Setting *	57,081 (63.8)	53,976 (67.0)	1,570 (31.5)	1,535 (38.4)
Days spent in Inpatient Rehab after discharge (mean, SD)	28.1 (19.8)	28.0 (19.7)	29.5 (21.0)	29.5 (21.0)

* Skilled nursing facility, In-patient rehabilitation facility, or Swing Bed

Table 3

Use before and after a fragility fracture of drugs that impact fracture risk

	Users before fracture		Users after fracture	
	N (%)	Number of drugs in category used (median)	N (%)	Number of drugs in category used (median)
Hip (N=80,508)				
Any drug that increases fracture risk	64,923 (80.6)	2	71,904 (89.3) *	2
Non-opiate drugs that increase fracture risk	62,098 (77.1)	1	64,779 (80.5) *	2
Non-opiate drugs that increase fall risk	44,930 (55.8)	1	45,837 (56.9) *	1
Drugs that decrease bone density	34,087 (42.3)	0	39,073 (48.5) *	0
Other fracture-promoting drugs	20,436 (25.4)	0	24,202 (30.1) *	1
Opiates	21,137 (26.3)	0	44,371 (55.1) *	1
Drugs that increase bone density	15,444 (19.2)	0	17,163 (21.3) *	0
Wrist (N=60,930)				
Any drug that increases fracture risk	49,817 (81.8)	2	51,810 (85.0) *	2
Non-opiate drugs that increase fracture risk	45,175 (74.1)	1	45,262 (74.3)	1
Non-opiate 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) *	0
Opiates	23,332 (38.3)	0	31,002 (50.9) *	1
Drugs that increase bone density	13,689 (22.5)	0	14,466 (23.7) *	0
Humerus (N=26,695)				
Any drug that increases fracture risk	23,110 (86.6)	2	23,862 (89.4) *	2
Non-opiate drugs that increase fracture risk	20,253 (75.9)	1	20,521 (76.9) *	2
Non-opiate 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	6,117 (22.9)	0	6,774 (25.4) *	0
Opiates	13,821 (51.8)	1	16,740 (62.7) *	1
Drugs that increase bone density	4,778 (17.9)	0	5,007 (18.8) *	0

*
p<0.0001 for use after fracture vs use before fracture

Table 4

Use of select* drugs associated with fracture risk before and after a fragility fracture.

Drug	Users prior to fracture	N (%) of users who stopped after fracture	N (%) of non-users who started after fracture	Users after fracture
Oral steroids	16,559	7,221 (43.6)	6,589 (4.3)	15,927
Proton pump inhibitors	43,114	3,724 (8.6)	13,181 (10.5)	52,571
Thiazolidinediones	9,632	2,366 (24.6)	1,168 (0.7)	8,434
Hypnotics	18,107	3,786 (20.9)	8,672 (5.8)	22,993
SSRI	44,349	2,640 (6.0)	7,268 (5.9)	48,977
Anti-psychotics	9,678	2,110 (21.8)	3,767 (2.4)	11,335

* Drugs selected as having the highest quality evidence supporting a risk of fracture (see methods for further details)