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Opioid Analgesics and the Risk of Fractures Among Older Adults with Arthritis

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Abstract

Objectives—To compare the risk of fracture associated with initiating opioids vs. non-steroidal anti-inflammatory drugs (NSAIDs), and the variation in risk by opioid dose, duration of action, and duration of use.

Design—Retrospective Cohort Study.

Setting—Enrollees in two statewide pharmaceutical benefit programs for persons aged 65 and older.

Participants—12,436 initiators of opioids and 4,874 initiators of NSAIDs began treatment between 1/1/1999 and 12/31/2006. The mean age at initiation of analgesia was 81 years, 85% were female, and all had arthritis.

Measurements—Cox proportional hazard models, adjusted for several potential confounders, quantified fracture risk. Study outcomes were fractures of the hip, humerus/ulna, or wrist, identified by a combination of diagnosis (CD-9CM codes) and procedure (CPT codes).

Results—There were 587 fracture events among the patients initiating opioids (120 fractures per 1,000 person-years) and 38 fracture events among patients initiating NSAIDs (25 fractures per 1,000 person-years), hazard ratio [HR], 4.9 [95% CI, 3.5 to 6.9]. Fracture risk increased with opioid dose. Risk was higher for short-acting opioids (HR, 5.1, [CI, 3.7 to 7.1]) than for long-acting opioids (HR, 2.6, [CI, 1.5 to 4.4]), even among patients taking equianalgesic doses, with differential fracture risk apparent for the first two weeks after starting opioids, but not thereafter.

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Conflict of Interest

No other authors have disclosures to make.

Author Contributions

Drs Miller, Azrael, Sturmer and Solomon all contributed to the conception of the design of the study, interpretation of analyses, and grant writing to obtain funding. Matthew Miller wrote the paper. Drs Azrael, Sturmer and Solomon critically reviewed and contributed to the shaping and writing of the paper throughout its several iterations. Raisa Levin constructed the cohort and conducted statistical analyses under Dr Solomon's supervision.

Conclusion—Older patients with arthritis who initiate therapy with opioids are more likely to suffer a fracture, compared with patients who initiate NSAIDs. For the first two weeks after initiating opioid therapy, but not thereafter, short-acting opioids are associated with a higher risk of fracture than are long-acting opioids.

Keywords

fractures; opioids; arthritis; elderly

Introduction

Opioids are commonly prescribed to older Americans.[1, 2] One large nationally representative survey found that 5% of respondents over 65 years of age report having used prescription opioids in the past month[2] Among older adults with arthritis, opioid use appears to be even more common. In one study[3] of low-income older adults with arthritis approximately 10% of patients with osteoarthritis and almost 20% of patients with rheumatoid arthritis filled prescriptions for opioids in the past 12 months; among those with rheumatoid arthritis, 5% were prescribed opioids for at least 6 months of continuous use in any given calendar year.[3]

Experimental studies on young adults have found that opioids impair cognition, balance, coordination and judgement.[4–7] Comparable data for older adults is lacking, but age-related comorbidities and physiological changes (e.g., renal insufficiency and lower lean body mass relative to total body mass) may make older adults more susceptible to opioid-related cognitive and psychomotor effects,[8] many of which are risk factors for falls.[9–13] In addition, older adults are more likely to be seriously injured when they fall and to die from common fall-related injuries (e.g., hip fractures).[14–18] Unfortunately, few rigorous studies provide clinicians useful data about the risk of fall-related injuries when prescribing opioids or about whether some opioid formulations are safer than others. Indeed, the 2009 AGS guidelines on preventing falls[19] is silent on the risks of opioid use in older adults, even though it recommends explicitly that several other broad classes of medications that can affect sensory-motor and cognitive function should be minimized or withdrawn, if possible (including sedative hypnotics, anxiolytics, antidepressants, and antipsychotics).[19]

Randomized clinical trials of opioid treatment have been too small to assess the risk of fractures associated with opioid use. Observational studies large enough to address this issue have produced inconsistent findings.[14, 15, 20–28] Moreover, most observational studies have failed to account for several sources of potential confounding, including the underlying indication for prescribing analgesic medication, physician channeling bias, and potentially important features of opioid exposure (e.g., dose, duration of action, and duration of use).

A limitation shared by all but two studies[24, 28] is that subjects included prevalent users of opioids. Including prevalent users can underestimate drug-related risk (i.e., prevalent user bias), especially, but not only, if the risk is greatest soon after starting the medication.[29] The first study to use an incident user design[28] examined fracture risk among older ambulatory adults in Saskatchewan, Canada, between 1977 and 1985, and found that subjects prescribed codeine or propoxyphene were twice as likely to fracture their hip, compared with those not prescribed opioids, RR 2.2 (1.7–2.8). The relative risk of hip fracture among prevalent users of opioids, RR 1.3 (1.0–1.6) was lower than among incident users of opioids, suggesting that prevalent user bias can result in spurious underestimates of fracture risk attributable to opioids. No difference in fracture risk was observed when users of codeine were compared with users of propoxyphene, or when users of fewer than 30 mg of codeine/day were compared with users of more than 30 mg codeine/day. More than a decade later, a U.S.

study of Medicare-eligible active and retired employees with employer-sponsored supplemental plans[24] found that the risk of hip fracture among recent starters of opioids was twice that compared with non-analgesic controls. Risk did not differ between users of propoxyphene and users of an aggregated group of other opioids, or between users of non-selective NSAIDs and non-analgesic controls. Unlike the Canadian study, the U.S. study found a positive relationship between dose and the risk of subsequent fracture (HR 2.1 for users of >260 mg of propoxyphene vs. HR 1.5 for users of <260 mg). Dose effects were not explored further.

To our knowledge, the current study is the first to examine whether the risk of fracture among incident users of opioids varies by duration of opioid action (i.e., short vs. long-acting agents). We pursue this aim in a cohort of Medicare beneficiaries with arthritis who initiated analgesic therapy with either an NSAID or an opioid.

METHODS

Patients and Data source

The study population consists of Medicare beneficiaries with osteoarthritis or rheumatoid arthritis who initiated monotherapy with a NSAID or an opioid between 1/1/1999 and 12/31/2006. All subjects were both Medicare beneficiaries and beneficiaries of a state sponsored drug benefit program -- the New Jersey Pharmaceutical Assistance Program for the Aged and Disabled (PAAD) or the Pennsylvania Assistance Contract for the Elderly (PACE). These programs cover all prescription medication expenses, including expenses for NSAIDs, for low-income elderly in New Jersey and Pennsylvania.

Using unique individual-level identifiers, Medicare data were linked to pharmacy data. Medicare data include information on all inpatient and outpatient health care utilization. This comprises all diagnoses, procedures, and admissions. Pharmacy data include all prescriptions, dosages, days supply and quantity dispensed for each medication, and the date dispensed. The linked data allowed us to construct a picture of a given individual's acute and chronic medical conditions; the out-patient, emergency department, and in-patient care received; how a given condition had been treated pharmacologically; and the chronology of disease, treatment and injury. These data included injuries seen in out-patient, emergency or hospital settings.

To be eligible for inclusion in our cohort, subjects must have had recorded diagnoses for osteoarthritis or rheumatoid arthritis on two separate visits at least one week apart (see **Appendix I** for diagnosis codes used to identify these subjects). After their second diagnosis, subjects became eligible to enter the cohort on their index date (i.e., first new analgesic prescription dispensing).

Initiating opioids or NSAIDs was defined as filling an opioid or NSAID prescription without having filled one in the preceding 180 days. Patients may have had an opioid or an NSAID prescription prior to this 6-months "wash-out" period and thus are not necessarily drug-naïve. Patients initiating therapy with more than one analgesic agent or with a preparation that combined an opioid with a non-opioid analgesic were excluded (to keep comparisons as rigorous as possible), as were those diagnosed with malignancy, admitted to a nursing home, or who had used hospice services in the year prior to their index date. To demonstrate consistent health care system use prior to their index date, all patients were required to have a health care or pharmacy claim in each of the four three-month periods before the start of an analgesic.

Opioid medication exposure

We included the four single agent oral opioids prescribed most commonly to our cohort (hydrocodone, oxycodone, propoxyphene and codeine), as well as transdermal fentanyl, an opioid delivered topically by patch in ambulatory patients. We included the ten single agent oral NSAIDs most commonly prescribed to our cohort (Diclofenac, etodolac, flurbiprofen, ketorolac, Ibuprofen, indomethacin, meloxicam, naproxen, piroxicam, sulindac). Exposure status was assigned based on the initiated medication.

Ongoing exposure to opioids and NSAIDs was based on days supplied for each consecutive prescription dispensed. When a new dispensing occurred before the previous prescription for the same opioid should have run out, we assumed that patients continued to use the medication from the old prescription until they ran out, then started using the medication from the new prescription. Thus, use of the new prescription was assumed to begin the day after the end of the old prescription.

Subjects contributed information from their index date forward until they experienced a fracture, died, became ineligible for the pharmaceutical assistance programs, or reached the end of their exposure time, whichever came first. Each patient's exposure time ended when they had been without an opioid supply (for opioid initiators) or a NSAID supply (for NSAID initiators) for 14 days. Subjects were allowed to enter analyses once only. If a second type of analgesic was received (opioids for NSAID users or NSAIDs for opioid users), the subject was censored without any extension.

Duration of action—Short- and long- acting opioids were defined, respectively, as agents with duration of action of less than 8 hours and with duration of action of 8 hours or longer. Most of the orally administered forms of opioids were short-acting agents. Fentanyl, ER-oxycodone (i.e., Oxycontin), and SR Hydrocodone were considered long-acting opioids.

Dosage—Daily dose levels were recorded for all opioid prescriptions. To assess the possible effects of opioid dose as well as to control for dose in analyses of duration of action, we converted all opioid use to milligram equivalents of codeine. The distribution of doses was divided into three groups: >0–75, 76–225, and >225 mg equivalents of codeine/day. We categorized dosage based on the initial prescription of opioid preparation.

Duration of use—Days supply is a calculated variable based on the number of pills dispensed and the number of doses per day. For PRN orders, we assumed the drug dispensed was taken as if always needed on schedule, but also include a 15 grace period, as described below. Days supply data from the index date forward were used as an estimate of days of continuous opioid and NSAID use. Continuous use was defined as having no interruption of 15 days or more.

Study endpoints

Study outcomes were fractures of the hip, humerus/ulna, or wrist, identified by a combination of diagnosis (CD-9CM codes) and procedure (CPT codes) (see Appendix)[30] that have been previously found to have high positive predictive values.[31] All fractures that occurred on the index date of drug fill were censored, as some fractures may have occurred before the prescription was filled.

Other covariates

Patient characteristics were assessed at each patient's index date and were based on medical claims during the year preceding cohort entry. Covariates, listed in Table 1, were selected to control for many of the potential confounders identified in the literature.[14, 15, 20–28, 32–41]

Statistical analyses

Incidence rates with 95% confidence intervals (CIs)[42] were calculated for all fracture events for each of our exposures. We summed person-days and fractures for each category of exposure, divided person-days by 365 and expressed crude incidence rates as number of fractures per 1,000 person-years.

Cox proportional hazards regressions were used to estimate the risk of fracture. NSAID users were the referent group. Models adjusted for the baseline covariates in Table 1. Analyses were as treated with respect to opioids and NSAIDs, but based on first dose and duration of action carried forward. Sensitivity analyses compared initiators of opioids to initiators of NSAIDs after matching opioid and NSAID initiators on their propensity to be treated with NSAIDs. Propensity scores were estimated based on variables that can be measured in claims data (see **Appendix** for variables and codes). We used 5 to 1 digit matching without replacement to find an NSAIDs initiator for every opioid initiator with a similar propensity score: starting with a very narrow caliper of +/− 0.000005 we gradually increased the width of the caliper up to +/− 0.05 if no match could be found.[43] We also conducted stratified analyses by duration of continuous opioid use, guided by inspection of Kaplan-Meier survival curves, and subgroup analyses that excluded patients with a history of a fracture and patients with a diagnosis of osteoporosis and/or who were on osteoporosis medications at baseline. This study was approved by the Partners Healthcare System Human Research Committee at Brigham and Women's Hospital. Funding sources had no role in the study.

RESULTS

Most subjects were white women; 90% had osteoarthritis, the rest had rheumatoid arthritis (Table 1). The mean age was 81 years for opioid users and 80 years for NSAIDs users. Our sample consisted of 4,874 patients who started NSAIDs and 12,436 who started opioids. Most opioid users in our study initiated use with propoxyphene (5,552), hydrocodone (3,805), or oxycodone (2,476). There were 371 users of codeine and 232 users of fentanyl. A greater proportion of opioid initiators, compared with NSAID initiators, were exposed to benzodiazepines, antidepressants, proton pump inhibitors, and oral corticosteroids before their index analgesic prescription date. A comparable proportion of opioid and NSAIDs patients used thiazide diuretics and osteoporosis medications. Compared with NSAID initiators, a greater proportion of opioid initiators suffered a fracture or had fallen in the year prior to the index analgesic prescription date. Opioid initiators also used a greater total number of medications, made more out-patient visits to physicians, were more frequently hospitalized, were more likely to have renal impairment, and had higher Charlson comorbidity scores, compared with NSAIDs initiators. Compared with initiators of long-acting opioids, initiators of short-acting opioids were more likely to have a history of diabetes, falls, and fractures, and less likely to have osteoporosis or to have used glucocorticoids in the year prior to starting opioids.

There were 587 fracture events among patients initiating opioids and 38 fracture events among patients initiating NSAIDs (Table 2). Fracture incidence among initiators of NSAIDs was 25 per 1,000 person-years (95% CI 17-- 34) and among opioid initiators it was 120 per 1,000 person-years (95% CI 111-- 130). Higher opioid dose was associated with higher fracture rates. Fracture incidence was significantly higher among users of short-acting opioids, 128 per 1,000 person-years (95% CI 118--138), than among users of long-acting opioids, 53 per 1,000 person-years (95% CI 34--79). This pattern was evident in stratified analyses of structurally identical opioids (e.g. 129 per 1,000 person-years (95% CI 110--151) among users of immediate release hydrocodone vs. 46 per 1,000 person-years (95% CI 24--79) among users of sustained release hydrocodone).

Fracture incidence was greatest during the first two weeks after initiating therapy (Figure 1, Table 3), especially for users of short-acting opioids, as seen by a steeper slope for short compared with long-acting opioids for the first two-weeks after initiating therapy, but similar slopes thereafter (Figure 1). The incidence of fracture for the first two weeks after starting short-acting opioids, 902 per 1,000 person-years (95% CI 813--998), was significantly greater than the incidence of fracture thereafter, 46 per 1,000 person-years (95% CI 39--53) and approximately seven-fold higher than the risk of fracture among users of long-acting opioids during the first two weeks of therapy, 121 per 1,000 person-years (95% CI 33—310), but not thereafter, 47 per 1,000 person-years (95% CI 28—75) (Table 3). Two-thirds of all fracture events (65%) observed among patients who initiated opioids (and 45% among NSAID initiators) occurred between days 1–14 of continuous use (Table 3). Three percent of patients who used an opioid suffered a fracture within the first 14 days after initiating opioids (n=382), compared with 0.4% of those initiating NSAIDS (n=17). Over 90% of fracture events over the study period occurred within the first year after initiating analgesic therapy (98% of all fractures among NSAID users, 96% among users of short-acting opioids, and 93% among users of long-acting opioids).

After adjustment for demographic and clinical variables, health care utilization, co-medication and comorbidities, the risk of fracture among patients initiating opioids remained significantly higher than the risk among patients initiating NSAIDs (HR 4.9, 95% CI 3.5 – 6.9). Higher doses of opioids were associated with higher fracture risk. For users of less than 75 milligram equivalents of codeine/day, the hazard ratio was 2.2, 95% CI 0.9 -- 5.2; for users of 76–225 milligram equivalents of codeine/day, the HR was 4.6, 95% CI 3.2 -- 6.6; and for users of greater than 225 milligram equivalents of codeine/day, the HR was 5.1, 95% CI 3.7 -- 7.2.

For the study period as a whole, compared with initiators of NSAIDs, the relative risk of fracture for users of short-acting opioids (HR 5.1, 95% CI 3.7 -- 7.1) was higher than for users of long-acting opioids (HR 2.6, 95% CI 1.5 -- 4.4) (Table 2). Because long-acting opioids were prescribed predominantly at high doses, we ran additional analyses restricted to patients prescribed high doses of opioids. Among high-dose opioid users, the risk of fracture (relative to risk among NSAID users) was greater among initiators of short-acting opioids (HR 6.4, 95% CI 4.6 -- 8.9), than among initiators of long-acting opioids (HR 2.8, 95% CI 1.6 -- 4.7). A direct comparison of initiators of high-dose-short-acting opioids to initiators of high-dose-long-acting opioids found that users of short-acting opioids were twice as likely as were users of long-acting opioids to experience a fracture, even after controlling for exact dose as a continuous variable (HR 2.1, 95% CI 1.3 -- 3.5).

Figure 3 shows results from additional sensitivity analyses. The estimated hazards ratio for fractures among opioid users (relative to users of NSAID) derived from analyses that controlled for confounding using propensity score matching, HR 4.9, 95% CI 3.5 -- 7.0, and the hazards ratio derived from conventional multivariable outcome regression techniques, HR 4.9, 95% CI 3.5-- 6.9, were virtually identical. Excluding patients with prior fractures or osteoporosis at baseline did not change our findings. Compared with initiators of NSAIDs, the risk of fracture among patients who started short-acting opioids was significantly greater than the risk among patients starting long-acting opioids for the first two weeks after initiation, HR 8.0, 95% CI 4.9 -- 13.0 vs. HR 1.3, 95% CI 0.4 -- 3.8, but not thereafter, HR 2.6, 95% CI 1.6 -- 4.1 vs. HR 2.8, 95% CI 1.5 -- 5.4.

DISCUSSION

We observed higher fracture risk among patients who started an opioid analgesic, compared with those starting a NSAID. Higher opioid dose was associated with higher fracture risk.

Moreover, during the first two weeks after initiating opioid therapy (but not thereafter), the risk of fracture was significantly higher among patients initiating short-compared with long-acting opioids, even after controlling for several potential confounders including age, sex, comorbidity, comedication, duration of use, and opioid dose. Findings were consistent within subgroups defined by several subject characteristics and in analyses restricted to subjects matched on their propensity for treatment with NSAIDs.

Our finding that fracture risk was twice as high for initiators of short-acting opioids, compared with initiators of long-acting opioids, has not been reported previously. Long-acting opioids provide more prolonged and consistent plasma concentrations of drug, perhaps reducing the frequency and severity of breakthrough musculoskeletal pain,[44] an established risk factor for falls in older adults.[45] The relatively infrequent administration schedule required by long- (vs. short-) acting opioids might also have allowed for more restful nights (uninterrupted by the need to take a dose) and, consequently, less daytime somnolence[46] (itself a risk factor for fall-related injuries).[15, 47] It is also possible that the more abrupt fluctuations in plasma opioid levels seen with short-acting opioids resulted in more frequent and severe psychomotor impairment. Alternatively, the association we observed between duration of action and fracture risk could have occurred if physicians preferentially prescribed short- rather than long-acting opioids to patients at greater risk of fracture. However, we account for several important confounders in our analyses and, within strata of these important confounders, have no reason to expect that physicians would preferentially prescribe short- over long-acting opioids to patients at higher fracture risk.

The hazards ratios we observed for fracture risk among users of opioids (relative to users of NSAIDs) is larger than the relative risk estimates reported for opioids in most other studies.[14, 15, 20–28] It is unclear whether and to what extent this discrepancy is due to differences in unmeasured confounders, study populations, reference groups, exposure definitions, and covariate adjustment. Perhaps clinicians treating our patients prescribed opioids, rather than NSAIDs, to patients who were more likely to fall and/or to patients who were more likely to fracture when they fall. Although we restricted our cohort to patients with arthritis and non-malignant pain and adjusted for several measures of chronic illness and other medications taken, it is still possible that such residual confounding may bias our findings.[48]

Our risk estimates could be higher than prior reports if arthritis exacerbates opioid-induced fracture risk, or because all opioid users in our study were incident users, whereas most prior studies included prevalent users of opioids in their exposure group. It is possible that we observed higher opioid-related fracture risk than prior incident user studies because our patients were, on average, prescribed higher doses of opioids. Consistent with this possibility, the hazards ratio we observed for low dose opioid users, relative to NSAID users, was similar to that observed for patients initiating comparably low doses in prior reports (i.e., compared with users of <30 mg of codeine[24] or <260 mg of propoxyphene[28]). It is also possible that we observed higher relative risk estimates for opioid initiators because we specified duration of exposure more precisely. For example, whereas Shorr[24] assumed a 30-day supply of opioids for all subjects, many of whom may have had opioids prescribed for shorter courses, we had information about the exact number of days that were prescribed and defined continuous use more stringently.

Our findings concerning other risk factors for fracture are consistent with previous reports,[21, 23, 27, 39, 47, 49–54] and results of our sensitivity analyses (Figure 2) were similar to our primary findings, providing face validity for our results. Nevertheless, our observations should be interpreted in light of several potential limitations. First, residual confounding, especially by unmeasured differences in functional status across exposure groups, may have

distorted our findings. We were also unable to adjust for other potentially important confounders including pain severity and extent of pain relief, body mass index, and use of tobacco, alcohol, aspirin, and over the counter NSAIDs.

Second, misclassification of exposure and endpoints may also have biased our results. For example, subjects may not have used analgesics as prescribed and they may have used over-the-counter agents not accounted for in our dataset (e.g., acetaminophen). Although the direction and extent of such bias in our analysis is uncertain, relative risk estimates are typically biased toward the null when misclassification of exposure is random.

Third, members of our cohort were predominantly older white women with osteoarthritis. Generalization to younger adults, to men, or to patients with different underlying reasons for chronic pain may not be warranted. Fourth, requiring eligible subjects to have made claims for medications and non-drug services may have caused them to be frailer than subjects not eligible for inclusion, further limiting generalizability. Fifth, even though all of our subjects had arthritis, we do not know that arthritis per se was the indication for which the analgesic was prescribed.

Lastly, our long-acting opioid preparations (i.e., CR oxycodone, fentanyl) are formulations of opioids with intrinsically short elimination half-lives that have been engineered to be released into the body so as to provide long lasting analgesia. It is possible, therefore, that our findings might not generalize to opioids that have intrinsically long elimination half-lives (e.g., methadone). Similarly, because our study excluded formulations that combine opioid and non-opioid analgesics into a single product, our findings may not generalize to combination agents.

Despite these limitations, our findings indicate that opioid use increases the risk of fractures among older patients with arthritis and suggests that clinicians should be alert to the possibility that short-acting opioids pose a significantly greater risk of fracture among older adults than do equianalgesic doses of long-acting opioids, especially during the first two-weeks after initiating therapy. Recent evidence suggests that controlled release opioid preparations can be used as effectively and efficiently as immediate release formulations for rapid titration to stable analgesia,[55, 56] and that long-acting preparations may provide more reliable relief for chronic non-cancer pain.[57] Our findings, if borne out in other databases, could help inform safer prescribing practices consonant with the latest AGS guidelines on the pharmacological management of pain in older persons,[58] which recommend that all patients with moderate-severe pain, pain-related functional impairment, or diminished quality of life due to pain should be considered for opioid therapy.

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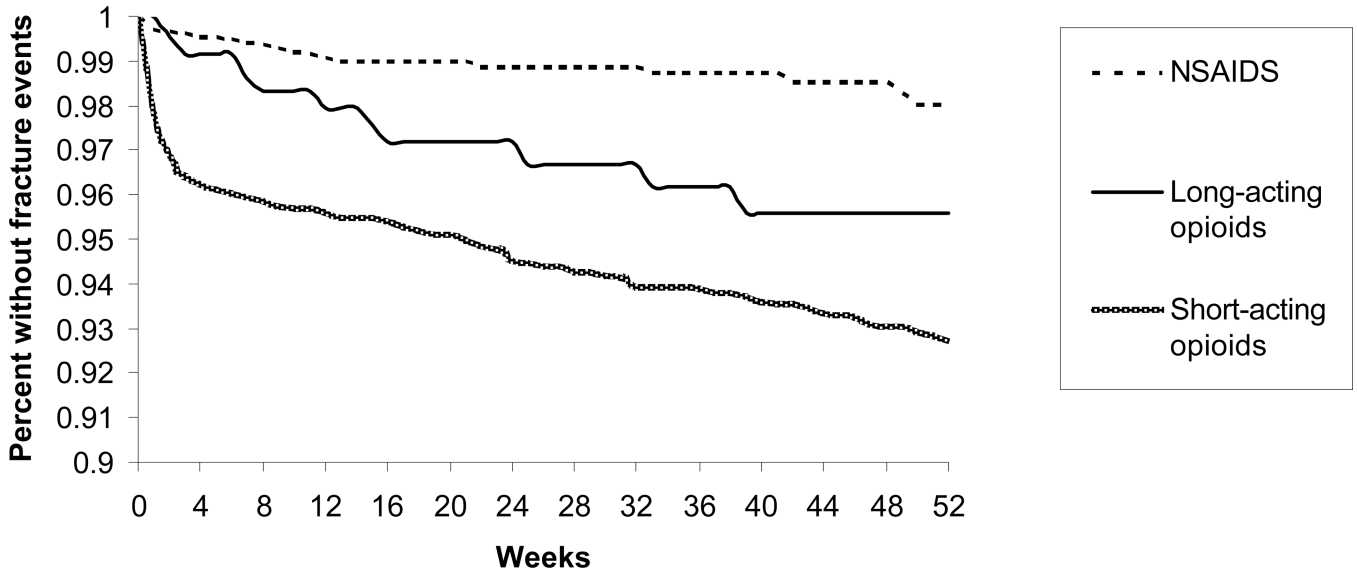

Figure 1.
Kaplan-Meier Survival Curves Showing Fracture-free Survival for the First 52 Weeks After Initiating NSAIDs vs. Short-acting Opioids vs. Long-acting Opioids, Among Medicare Beneficiaries with Arthritis

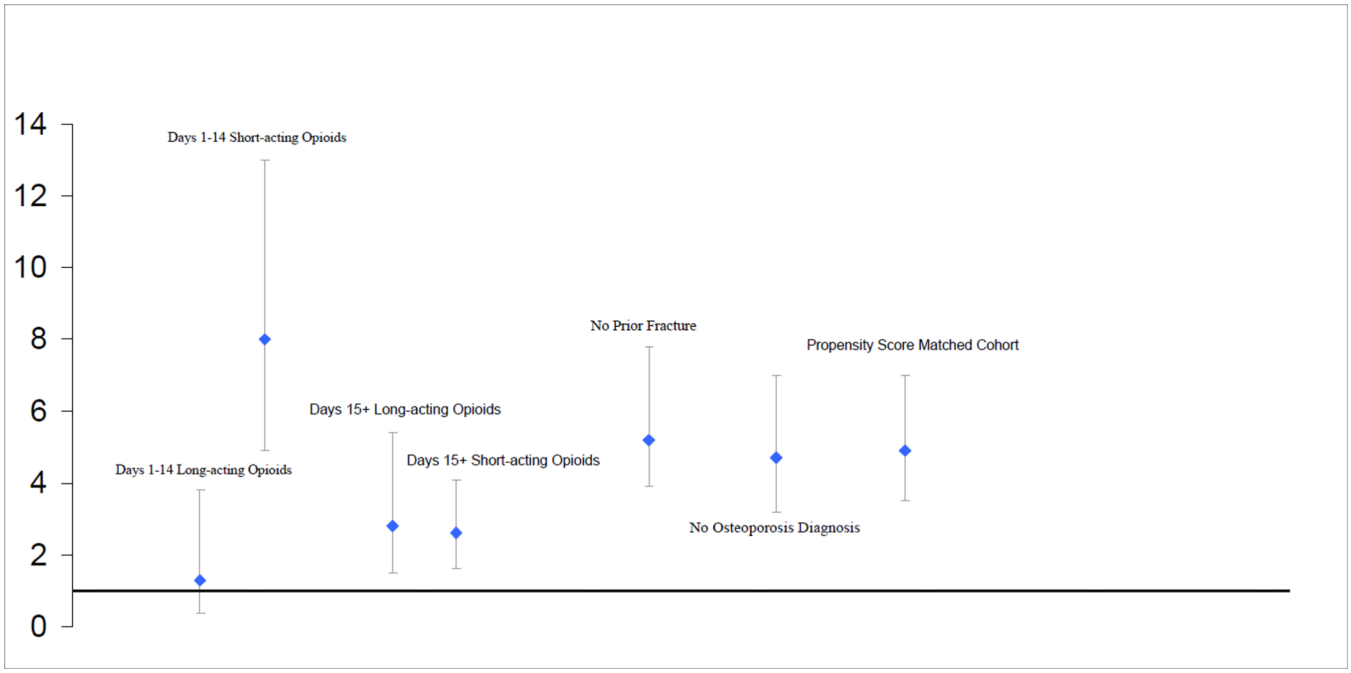

Figure 2.

Hazard Ratios* (95% Confidence intervals) for Fracture Risk Comparing Users of Opioids vs. NSAIDs among Medicare Beneficiaries with Arthritis Initiating Analgesic Medications, by Subgroup

*All hazards ratios are multivariate adjusted, with non-propensity score models including as independent variables all the characteristics in Table 1

Table 1

Baseline Characteristics of Medicare Beneficiaries with Arthritis Initiating a Prescription Analgesic

	NSAIDs (n=4,874)	Any Opioid (n=12,436)	Short-Acting Opioids (n=11,549)	Long –Acting Opioids (n=887)
	N (%) or mean (±SD)			
Osteoarthritis	4,382 (89.9%)	11,206 (90.1%)	10,415 (90.2%)	791 (89.2%)
Rheumatoid arthritis	492 (10.1%)	1,230 (9.9%)	1,134 (9.8%)	96 (10.8%)
Age, years	79.7 (±7.0)	81.1 (±7.2)	81.1 (±7.1)	81.5 (±7.7)
Gender, female	4,094 (84.0%)	10,452 (84.1%)	9,704 (84.0%)	748 (84.3%)
Race, white	4,124 (84.6%)	11,490 (92.4%)	10,691 (92.6%)	799 (90.1%)
Number of physician visits	8.7 (±6.3)	10.1 (±7.1)	10.1 (±7.1)	9.8 (±7.4)
Number of different drugs	8.3 (±4.7)	9.7(±5.7)	9.7 (±5.3)	10.4 (±5.8)
Acute care hospital days	1.9 (±6.9)	4.1 (±9.3)	4.1 (±9.3)	3.7 (±9.0)
Comorbidity index	1.6 (±1.5)	2.2 (±1.8)	2.2 (±1.8)	2.1 (±1.7)
Diabetes	1,612 (33.1%)	4,423 (35.6%)	4,141 (35.9)	282 (31.8)
Hypertension	3,445 (70.7)	8,958 (72.0)	8,336 (72.2)	622 (70.1)
Hyperlipidemia	3,215 (66.0%)	7,860 (63.2%)	7311 (63.3%)	549 (61.9%)
Myocardial Infarction	254 (5.2%)	1,182 (9.5%)	1109 (9.6%)	73 (8.23%)
Stroke	740 (15.2%)	2,677 (21.5%)	2,491 (21.6)	186 (21.0)
Angina	309 (6.3%)	1,141(9.2%)	1068 (9.3%)	73 (8.2%)
Coronary re-vascularization	51 (1.1%)	302 (2.4%)	289 (2.5%)	12 (1.5%)
Upper gastrointestinal disease	123 (2.5%)	466 (3.8%)	442 (3.83%)	24 (2.7%)
Use of a proton pump inhibitor	1,105 (22.7%)	3,619 (29.1%)	3,344 (29.0%)	275 (31.0%)
Use of an H_2-receptor antagonist	411 (8.4%)	1,447 (11.6%)	1,354 (11.7%)	93 (10.5%)
Alzheimer's disease	472 (9.7%)	1,390 (11.2%)	1,276 (11.1%)	114 (12.9%)
Parkinson's disease	124 (2.5%)	443 (3.6%)	415 (3.6%)	28 (3.2%)
Fractures	317 (6.5%)	1,695 (13.6%)	1,600 (13.9%)	95 (10.7%)
Osteoporosis	1,430 (29.3%)	3,897 (31.3%)	3,586 (31.1%)	311(35.1%)
Falls	110 (2.3%)	592 (4.8%)	574 (5.0%)	18 (2.0%)
Bone mineral density testing	499 (10.2%)	1,061 (8.5%)	990 (8.6%)	71 (8.0%)
Chronic liver disease	182 (3.7%)	543 (4.4%)	496 (4.3%)	47 (5.3%)
Acute Renal Failure	60 (1.2%)	432 (3.5%)	393 (3.4%)	39 (4.4%)
Loop diuretic use	1,039 (21.3%)	3882 (31.2%)	3597 (31.2%)	285 (32.1%)
Chronic back pain	1,393 (28.6%)	4,085 (32.9%)	3826 (33.1%)	259 (29.2%)
Gout	319 (6.5%)	645 (5.2%)	603 (5.2%)	42 (4.7%)
Use of anti-thrombotic therapy	703 (14.4%)	3,449 (27.7%)	3210 (28.0%)	239 (27.9%)
Use of benzodiazepines	1,003 (20.6%)	3,035 (24.4%)	2810 (24.3%)	225 (25.4%)
Use of selective serotonin reuptake inhibitors	589 (12.1%)	1,935 (15.6%)	1792 (15.5%)	143 (16.1%)
Use of beta-blockers	1,823 (37.4%)	5,232 (42.1%)	4876 (42.2%)	356 (40.1%)
Use of ACE inhibitors	1,289 (26.4%)	3,668 (29.5)	3420 (30.0%)	248 (28.0%)
Use of angiotensin receptor blockers	644 (13.2%)	1,768 (14.2%)	1,649 (14.3%)	119 (13.4%)
Use of thiazide diuretics	717 (14.7%)	1,834 (14.8%)	1706 (14.8%)	128 (14.4%)

	NSAIDs (n=4,874)	Any Opioid (n=12,436)	Short-Acting Opioids (n=11,549)	Long –Acting Opioids (n=887)
Use of oral glucocorticoids	379 (7.8%)	1,396 (11.2%)	1286 (11.1%)	110 (12.4%)
Use of anti-convulsants	262 (5.4%)	829 (6.7%)	763 (6.6%)	66 (7.4%)

Notes: Definitions for each covariate are given in **Appendix I**. All baseline characteristics were assessed during the 12 months preceding the subjects' first analgesic prescription in the study period. We identified patients with acute renal failure (ARF) with the following administrative codes: presence of ICD-9-CM codes 584.5, 584.6, 584.7, 584.8, or 584.9 in any of the listed diagnoses. ARF was also identified by the additional presence of any of the following ICD-9-CM codes for hemodialysis: Procedure code 39.95 (hemodialysis) or diagnosis codes V45.1 (renal dialysis status), V56.0 (extracorporeal dialysis), or V56.1 (fitting and adjustment of dialysis catheter).

Table 2

Distribution of Fracture Events, Incidence of Fractures per 1,000 Person-years (95% Confidence Interval) after Initiating Analgesic Medications, and Adjusted Hazards Ratio (95% confidence interval), among Medicare Beneficiaries with Arthritis

		Events	Person-Years (P-Y)	Incidence Rate (per 1,000 P-Y)	95% CI	Hazards Ratio*	95% CI
NSAIDs		38	1,546	25	17, 34	Ref	.
All Opioids		587	4,877	120	111, 130	4.9	3.5, 6.9
Opioid Dose	Low dose of opioid	6	114	53	20, 111	2.2	0.9, 5.2
	Med dose of opioid	146	1,265	115	98, 134	4.6	3.2, 6.6
	High dose of opioid	435	3,441	126	115, 138	5.1	3.7, 7.2
Opioid Duration of Action	Long acting opioids†	22	414	53	34, 79	2.6	1.5, 4.4
	Short acting opioids	565	4,407	128	118, 138	5.1	3.7, 7.1

*Adjusted for characteristics in table 1.

†Long-acting agents include Fentanyl (n=232), Extended Release Oxycodone (n=100), and Sustained Release Hydrocodone (n=555). The 22 fracture events among users of long-acting were distributed as follows: 5 among users of Fentanyl, 4 among users of ER Oxycodone, and 13 among users of SR Hydrocodone

Table 3

Distribution of Fracture Events, Incidence of Fractures per 1,000 Person-years (95% Confidence Interval) after Initiating Analgesic Medications, by Duration of Analgesic Use, Among Medicare Beneficiaries with Arthritis

		< 15 days of analgesic use						15+ days of analgesic use					
		Number of Initiators	**Person-Years**	**Fracture events**	**Incidence Rate**	**95% CI**		**Number of Initiators**	**Person-Years**	**Fracture events**	**Incidence Rate**	**95% CI**	
NSAIDs		4,874	180	17	90	55	151	7,501	1,347	21	16	10	24
All Opioids		12,432	451	382	847	764	936	16,881	4,426	205			
Opioid Dose	Low dose of opioid	306	11	3	272	56	797	468	102	3	29	6	86
	Med dose of opioid	3,136	114	89	781	627	961	4,309	1,159	57	49	37	64
	High dose of opioid	8,990	326	290	890	790	998	12,104	3,165	145	46	39	54
Opioid Duration of Action	Long acting opioids	887	33	4	121	33	310	1,305	381	18	47	28	75
	Short acting opioids	11,545	419	378	902	813	998	15,576	4,044	187	46	39	53

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