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Commonly Initiated Opioids and Risk of Fracture Hospitalizations in United States Nursing Homes

Jacob N. Hunnicutt¹, Anne L. Hume^{2,3}, Shao-Hsien Liu¹, Christine M. Ulbricht¹, Jennifer Tjia¹, Kate L. Lapane¹

¹Department of Quantitative Health Sciences, University of Massachusetts Medical School, 55 Lake Road North, Worcester, MA 01655, USA

²Department of Family Medicine, Alpert Medical School, Brown University, Memorial Hospital of Rhode Island, Providence, RI, USA

³Department of Pharmacy Practice, College of Pharmacy, University of Rhode Island, Kingston, RI, USA

Abstract

Objectives—The aim of this study was to estimate the comparative safety of initiating commonly used opioids among older, long-stay United States nursing home residents with fracture hospitalizations.

Methods—We conducted a new-user retrospective cohort study of nursing home residents initiating short-acting oxycodone, hydrocodone, or tramadol by merging the 2011–2013 Minimum Data Set 3.0 to Medicare hospitalization and pharmacy claims. Residents (> 65 years, no cancer or hospice use) contributed treatment episodes (> 120 days with no prior opioid claims) and were followed for 180 days until incident fracture hospitalization (hip, femur, humerus, pelvis, radius/ulna), death (competing risk), treatment changes (e.g., discontinuation), or administrative censoring. Competing risks models with inverse probability of treatment weighting were used to estimate subdistribution hazard ratios (HR_{SD}) and 95% confidence intervals (CI).

Results—Overall, 110,862 residents contributed 134,432 treatment episodes: 14,373 oxycodone; 69,182 hydrocodone; and 50,877 tramadol initiators. The incidences of fracture hospitalizations per 100 person-years were 9.4 (95% CI 7.5–11.7) for oxycodone, 7.9 (95% CI 7.1–8.8) for hydrocodone, and 5.0 (95% CI 4.3–5.7) for tramadol initiators. In weighted models, oxycodone initiators had a similar rate of fractures to hydrocodone initiators (HR_{SD} 1.08, 95% CI 0.79–1.48). Tramadol initiators had lower fracture rates than hydrocodone initiators (HR_{SD} 0.67, 95% CI 0.56–0.80).

Kate L. Lapane, kate.lapane@umassmed.edu.

Conflict of interest JNH, ALHSHL, CMU, JT and KLL have no conflicts of interest to declare.

Ethical approval This study used routinely collected administrative and claims data and was approved by the University of Massachusetts Medical School Institutional Review Board.

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Conclusions—The lower rate of fractures that we documented among tramadol initiators compared with hydrocodone initiators is consistent, albeit attenuated compared with prior studies among community-dwelling older adults. However, overall fracture rates were lower than in community settings, potentially due to the limited risk of falling in this population with limited mobility.

1 Introduction

Globally, prescription opioid use in long-term care facilities has increased over time [1], with one-third of older United States (US) nursing home residents prescribed an opioid during 2011–2012 to manage their non-malignant pain [2, 3]. Fifteen percent of US nursing home residents were prescribed opioids long-term [2], more than two-fold the prevalence documented in community settings [4, 5]. Acute and long-term opioid use may be necessary in this vulnerable population given the high burden of painful comorbidities and concerns of the consequences of undertreating pain [6–8]. Further, these practices are consistent with 2009 American Geriatrics Society guidelines recommending that “all patients with moderate to severe pain, pain-related functional impairment, or diminished quality of life due to pain should be considered for opioid therapy”. However, these strong recommendations are supported by limited evidence to guide clinical decision-making on which opioids to initiate, particularly among older, medically complex nursing home residents.

Short-acting formulations of oxycodone, hydrocodone, and tramadol are prescribed to > 80% of residents initiating opioids in US nursing homes [3]. These medications have varying pharmacokinetic and pharmacodynamic profiles including affinity for μ -opioid receptors, metabolic pathways, bio-availability, and elimination half-lives [9–11]. Such differences may affect time to onset of effect, potency, duration of analgesia, and ultimately the risk of safety events such as fractures (e.g., by impairing cognition, coordination, and balance leading to falls). In community-dwelling older adults, persons initiating tramadol had lower fracture risk compared with hydrocodone initiators, especially in the first 30 days [12]. Oxycodone initiators had similar fracture risk to hydrocodone initiators [12]. It is unclear if such findings extend to older nursing home residents due to differences in age, disease burden, complex drug regimens, and overall frailty in comparison with community-dwelling adults [13–16]. Yet, fractures are common and have devastating consequences in nursing homes. Three percent of long-stay residents will experience a hip fracture within 2 years [17], with survivors suffering from pressure ulcers and infections, functional decline, and mortality [18–21]. Other fracture hospitalizations may also be devastating but have been understudied in this care setting.

Given the wide use of opioids in nursing homes and residents’ increased risk of adverse drug events including fractures, understanding the comparative safety of commonly used opioids in nursing homes is critical. Therefore, we conducted this study to evaluate the risk of major fracture hospitalizations following the initiation of short-acting oxycodone, hydrocodone, or tramadol.

2 Methods

The University of Massachusetts Medical School Institutional Review Board approved this study.

2.1 Data Sources

We conducted a retrospective cohort study using 2011–2013 Minimum Data Set (MDS) 3.0 merged to the Master Beneficiary Summary File (MBSF; contains Medicare enrollment and death information), Medicare Part A hospitalization claims, and Part D pharmacy claims (including generic drug names, fill date, days' supply, and dosage strength). The MDS 3.0 is a federally required assessment of all US nursing residents living in US Medicare- and/or Medicaid-certified nursing homes (~ 96% of all homes). Registered nurses conduct comprehensive assessments at admission, annually, and whenever there is a change in clinical status, and condensed quarterly assessments (with a subset of items) at 90-day intervals. Nurses collect information by reviewing residents' medical record and interviewing residents with validated instruments to collect information on comorbidities, cognitive and physical functioning, pain, mood, and other measures [22–24]. MDS 3.0 measures have demonstrated validity and reliability [22].

2.2 Treatment Groups and Study Population

Our study cohort included Medicare beneficiaries who were long-stay nursing home residents (≥ 120 consecutive days in facility) and who initiated short-acting oral formulations of hydrocodone, oxycodone, or tramadol between March 31, 2011 and December 31, 2013. Initiation was defined as being prescribed a study drug with no prior prescriptions of any opioid in the 120 days before the initiating fill date (index date; see Supplementary Tables 1, 2 in the electronic supplementary material [ESM] for further information on study and non-study opioids). We focused on these medications because they were the three most commonly used short-acting opioids in US nursing homes during the study period [2], though they differed in drug scheduling (oxycodone: schedule II, hydrocodone: schedule III, tramadol: unscheduled). Eligible residents had Medicare Part A, B, and D coverage and no Medicare Advantage plan in the 4 months before initiating the aforementioned drugs; these criteria were implemented to reduce concerns of incomplete (i.e., missing) hospitalization claims [25].

The unit of analysis was a treatment episode. As such, residents could contribute multiple treatment episodes if they met our inclusion/exclusion criteria. We excluded treatment episodes with no MDS assessment (quarterly or comprehensive) in the 120 days preceding opioid initiation or no comprehensive assessment in the prior year; those who were recently hospitalized and/or received skilled nursing facility care within 120 days preceding opioid initiation; those living in provider-based facilities and free-standing skilled nursing facilities; treatment episodes where the resident was < 65 years old at initiation or were comatose, had cancer, received hospice care, or had missing data on potential confounders; and those initiating unusually high opioid doses > 180 mg of oral morphine equivalents (OME) [26, 27]. In addition, states/districts contributing < 100 treatment episodes to the analysis (Alaska, Washington DC) and states where < 2% of treatment episodes were oxycodone

(Illinois, Michigan, Texas) were also excluded. Further details on inclusion/exclusion criteria and study design overview are displayed in Supplementary Appendix 1 and Supplementary Fig. 1 in the ESM, respectively.

2.3 Opioid Use: Initiating Dose and Follow-up

2.3.1 Initiating Dose—Average daily dose of the oxycodone, hydrocodone, or tramadol prescriptions initiated on the index date was calculated by multiplying dosage strength in OME and quantity dispensed and then dividing by days' supply. Oral morphine conversion factors used for oxycodone, hydrocodone, and tramadol were 1.0, 1.5, and 0.1, respectively [28]. Doses were categorized as < 25 mg, 25–49 mg, and ≥ 50 mg OME/day. Although unconventional, these categorizations were chosen because most residents initiate lower doses than community-dwelling adults [3, 29, 30]. Doses ≥ 50 mg OME/day are considered potentially inappropriate in persons initiating opioids for chronic non-cancer pain outside of the context of palliative or end-of-life care [31].

2.3.2 Follow-up—We were interested in estimating the as-treated effect of commonly initiated opioids on fracture hospitalizations within 180 days of opioid initiation. Residents contributed follow-up time to analyses based on the number of days from the prescription fill date and the earliest of the following: experiencing the study outcome of interest (incident fracture hospitalizations); death (a competing event, described below); changes in opioid treatment including discontinuation, switching treatment groups, or initiating a non-study opioid; enrolling in Medicare Advantage; reaching end of follow-up (December 31, 2013); or 180 days of treatment. Residents were assumed to take opioids as prescribed from the fill date through to the end of the prescription days' supply. We allotted a 7-day grace period between prescription fills (in which a resident was still at risk for the outcome). If a resident filled a subsequent prescription before the calculated end date of the previous prescription, we assumed the new prescription began after the calculated end date of the old prescription. Residents who discontinued initial treatment could re-enter (and change treatment groups) if a later treatment episode met eligibility criteria.

2.4 Fracture Hospitalizations

The outcome of interest was fracture hospitalizations within 180 days of treatment initiation. We used Part A hospitalization claims diagnosis codes to create a composite outcome for major fracture hospitalizations, including femur, hip, humerus, pelvis, or radius/ulna fractures. Although certain fractures (e.g., radius/ulna) may be less likely to result in hospitalization than others (e.g., hip), they are all clinically significant and are among the most common injuries leading to hospitalizations in older adults [32]. External validation studies were used to define fractures using International Classification of Diseases, 9th edition codes (positive predictive value for hip fractures = 87%; see Supplementary Table 3 [see ESM] for specific definitions used for each fracture type) [33, 34]. Except for hip fractures, we did not use procedure codes to identify the study outcome because we did not have outpatient claims available. If during a treatment episode a resident had multiple fracture hospitalizations, only the first hospitalization was included in the analysis.

2.5 Competing Risks

Traditional survival analysis techniques such as Kaplan–Meier curves and Cox proportional hazards models assume that censored study participants have the same survival experience as those remaining in the study [35]. Competing risks violate this assumption because they are events that preclude the study outcome [36], and analyses that ignore competing risks will overestimate cumulative incidence (the complement of the survival curve). Because residents who die cannot be hospitalized for fractures, we treated death as a competing event, measured using the date of death in the MBSF.

2.6 Potential Confounders

We adjusted for variables that we thought might be confounders based on clinical expertise (JT, ALH) and prior literature identifying risk factors for fractures in US nursing homes [37]. Potential confounders were ascertained from Part D claims and the most recent MDS assessment in the 120 days preceding opioid initiation [37]. Because certain chronic comorbidities (e.g., arthritis, osteoporosis) were not included on quarterly assessments, the most recent comprehensive assessment within 365 days preceding opioid initiation was used for these conditions.

Prior MDS assessments provided information about state of residence [38]; resident demographics (age [included as a continuous variable and quadratic term], gender, race/ethnicity); cognitive impairment [39] and other measures of cognitive functioning (attention, disorganized thinking); physical functioning [40] including the MDS Activities of Daily Living Self-performance hierarchy and specific measures of physical functioning for transferring between surfaces, locomotion on unit, and locomotion off unit; self- or staff-assessed pain; behaviors (rejecting care, wandering); urinary and bowel incontinence; mobility device use (wheelchairs, cane/walker); oxygen use; unplanned weight loss; comorbidities associated with falls or fractures (e.g., dementia; history of falls); and anxiolytic and hypnotic use (because benzodiazepines were not covered by Medicare during 2011–2012).

Part D data was used to identify overall medications prescribed in the 120 days before opioid initiation and other medications that may be associated with fractures either directly or as proxies for medical conditions associated with fractures. This includes psychotropic medications (e.g., antipsychotics), pain adjuvants (e.g., skeletal muscle relaxants), cardiovascular medications (e.g., beta blockers), diabetic medications (e.g., sulfonylureas), gastric medications (e.g., proton pump inhibitors), dementia medications (e.g., cholinesterase inhibitors), osteoporosis medications, and Parkinson's medications. See Supplementary Table 4 in the ESM for further detail on specific resident characteristics included as potential confounders.

2.7 Statistical Analysis

We examined the distribution of potential confounders across the three treatment groups and calculated standardized mean differences (SMDs), first by calculating each pairwise treatment contrast and then averaging all three treatment contrasts. SMDs measure the differences in means/proportions between treatment groups in units of pooled standard

deviation and are uninfluenced by sample size; covariates with SMDs > 0.1 are generally considered meaningfully imbalanced [41].

To adjust for potential confounders, we estimated propensity scores generalized to multiple treatment groups and implemented with inverse probability of treatment (IPT) weighting [42, 43]. A propensity score is the probability of treatment given measured covariates and was estimated using a multinomial model that included main terms for state of residence and potential resident confounders. We estimated stabilized IPT weights for each treatment episode by dividing the overall probability of treatment by the resident's propensity score of being prescribed the treatment they received [44]. Our IPT-weighting standardized the distribution of measured confounders within each treatment group to that of the entire study population [45]. We evaluated our IPT weights by comparing the propensity score distributions of initiating each study drug before and after weighting and comparing the SMDs of the potential baseline confounder in the crude and weighted sample [41].

We fit Poisson models to estimate crude and weighted incidence rates of fracture hospitalizations per 100-person years by treatment group. We then fit Fine and Gray competing risks models to estimate crude and weighted cumulative risks and subdistribution hazards ratios (HR_{SD}) for initiating commonly used opioids on fracture hospitalization risk within 180 days of treatment initiation [46]. For HR_{SD} , robust 95% confidence intervals (CIs) were used to account for weighting and clustering of multiple treatment episodes within residents. We determined that the proportional sub-distribution hazards assumption was satisfied after examining the log(-log) transformation of the crude and weighted nonparametric cumulative incidence function [36]. In all analyses, hydrocodone was chosen as the referent treatment because it is the most commonly prescribed opioid in nursing homes and facilitated comparison to prior studies [2, 12]. In secondary analyses, we estimated HR_{SD} and cumulative risk over progressively longer periods of follow-up to understand how risk may vary as length of opioid use increased (1–30 days, 1–60 days, 1–90 days) [47].

We conducted stratified analyses by prescribed dosage strength to examine whether the primary associations were modified by initiating dose. Because the specific opioid and dose are simultaneously initiated, we reweighted the data for these analyses as the product of the stabilized treatment IPT weights (described above) and stabilized dose IPT weights [48]. Stabilized dose IPT weights were estimated as the probability of being prescribed the specific dose initiated (< 25 mg, 25–49 mg, or 50 mg OME/day) given treatment in the numerator and the probability of initiating the specific dose given treatment and previously described confounders in the denominator. We formally tested for additive interaction by estimating the relative excess risk due to interaction (RERI) [49].

We conducted several sensitivity analyses to examine the robustness of our findings: (1) examining the intention-to-treat effect of initiating different opioids on fracture hospitalization risk within 180 days of treatment initiation; (2) restricting the outcome to hip fracture hospitalizations to potentially enhance the sensitivity and specificity of the outcome definition; (3) restricting to states where 10% of treatment episodes were oxycodone because study medications may be more exchangeable in these regions; (4) excluding

residents with physical dependence or wheelchair use to examine fracture risk in physically mobile residents; (5) excluding residents with no previously documented pain on the most recent MDS assessment to mitigate concerns of confounding by pain severity; (6) excluding residents with osteoporosis who may be at increased risk for fractures unrelated to opioid use; and (7) bias analyses to examine the minimum strength an unmeasured confounder would need to have with exposure and outcome on the risk ratio scale to completely explain our primary study results [50, 51].

Our statistical estimates will have a causal interpretation under the following assumptions: consistency (i.e., our treatment groups are well defined and the observed outcome for the treatment received is equal to their counterfactual outcome for that treatment [52, 53]); no unmeasured confounding, selection bias, or measurement error; positivity (i.e., there is a nonzero probability of receiving every treatment for every combination of potential confounders [53]); and correct specification of the weights and outcome model. Although these assumptions are likely violated in practice, we believe this framework provides useful guidance for evaluating our results and the extent to which they can be interpreted causally [54].

All analyses were conducted in SAS 9.4 (SAS Institute, Inc., Cary, NC, USA) and R version 3.4 (R Foundation for Statistical Computing, Vienna, Austria).

3 Results

We identified 110,862 long-stay residents (of 1,345,693 long-stay residents who were Medicare beneficiaries) who met inclusion criteria and contributed 134,432 treatment episodes to our analysis. Ten percent of initiation episodes were oxycodone, 51.4% were hydrocodone, and 37.9% were tramadol; see Supplementary Table 5 in the ESM for further detail on the inclusion and exclusion of initiation episodes by treatment group for each study criteria.

Table 1 shows selected unadjusted baseline characteristics and overall IPT-weighted characteristics of the cohort; see Supplementary Table 4 in the ESM for a complete summary of baseline characteristics in the unweighted and IPT-weighted cohort at baseline. More than half (55.5%) of initiators were 85 years old, 47.1% had moderate or severe cognitive impairment, three-quarters required extensive assistance to manage their activities of daily living or were physically dependent, 29.5% had self- or staff-reported pain at their most recent MDS assessment, and 32.1% were prescribed two or more psychotropic medications prior to opioid initiation. Before IPT-weighting, oxycodone initiators were on average younger, more likely to be men, with a lower burden of moderate and severe cognitive impairment, but more physical dependence than tramadol or hydrocodone initiators. IPT-weighting reduced imbalances between groups at baseline by standardizing the distribution of potential measured confounders to that of the entire study cohort. All measured confounders had SMDs 0.1 after IPT-weighting. See Supplementary Fig. 2 in the ESM for information on the distribution of propensity scores before and after IPT-weighting. See Supplementary Figs. 3 and 4 in the ESM for detail on SMDs of potential confounders pre- and post-weighting.

Table 2 shows the crude incidence rates of major fracture hospitalizations per hundred person-years were 9.4 for oxycodone initiators (77 fractures, 821 person-years; 95% CI 7.5–11.7), 7.9 for hydrocodone initiators (336 fractures, 4232 person-years; 95% CI 7.1–8.8), and 5.0 for tramadol initiators (209 fractures, 4197 person-years; 95% CI 4.3–5.7). Nearly half the hospitalizations were for hip fractures. All-cause mortality during follow-up was common. The crude incidence rate of death among oxycodone initiators (60.9 per 100 person-years, 95% CI 55.7–66.8) was nearly two-fold that of hydrocodone (31.7 per 100 person-years, 95% CI 30.1–33.4) or tramadol initiators (29.1 per 100 person-years, 95% CI 27.5–30.8), with 9.7% of initiation episodes within 90 days of death.

Using IPT-weighting to reduce differences in baseline confounders between treatment groups, the cumulative risk of fracture hospitalizations during 180 days of follow-up was 1.8, 1.6, and 1.1 for oxycodone, hydrocodone, and tramadol initiators, respectively (Table 3). The IPT-weighted HR_{SD} of fracture hospitalizations during 180 days of follow-up was 1.08 for oxycodone initiation versus hydrocodone (95% CI 0.79–1.48); weighted HR_{SD} estimates were similar when restricting follow-up to shorter time periods. Tramadol was associated with a lower subdistribution hazard of fractures relative to hydrocodone during 180 days of follow-up (HR_{SD} 0.67, 95% CI 0.56–0.80); these results were consistent when restricting follow-up to shorter time periods.

Oxycodone initiators were more often prescribed doses ≥ 50 mg OME/day (20.2%; mean dose mg OME/day: 39.2; median dose mg OME/day: 32.1) than hydrocodone (6.2%; mean dose mg OME/day: 25.2; median dose mg OME/day: 21.4) or tramadol initiators (1.2%; mean dose mg OME/day: 18.3; median dose mg OME/day: 18.8). When stratifying by dose, the IPT-weighted HR_{SD} for oxycodone versus hydrocodone (< 25 mg OME/day: HR_{SD} 1.36, 95% CI 0.82–2.28; 25–49 mg OME/day: HR_{SD} 0.89, 95% CI 0.56–1.41) differed qualitatively, but there was limited evidence of effect modification on the additive scale (RERI 0.45, 95% CI –0.31 to 1.21). Dose-stratified HR_{SD} for tramadol versus hydrocodone (< 25 mg OME/day: HR_{SD} 0.66, 95% CI 0.53–0.82; 25–49 mg OME/day: HR_{SD} 0.81) were qualitatively similar with limited evidence of additive effect measure modification (RERI –0.19, 95% CI –0.83 to 0.45). We did not test for effect measure modification in the highest dose strata due to the low number of fracture hospitalizations among oxycodone and tramadol initiators.

Alternative analytic approaches were largely consistent with our primary analyses (Table 4), though the HR_{SD} between tramadol and fracture hospitalizations relative to hydrocodone was attenuated in the intention-to-treat analyses (HR_{SD} 0.86, 95% CI 0.76–0.97). When restricting to residents who were not physically dependent or wheelchair users, the IPT-weighted cumulative risk and incidence rates during 180 days of as-treated follow-up increased relative to our primary analysis, especially among oxycodone initiators (cumulative risk 4.7%; 21.3 fracture hospitalizations per 100 person-years, 95% CI 11.9–38.2; HR_{SD} in comparison with hydrocodone: 1.55, 95% CI 0.85–2.85).

In sensitivity analyses examining the robustness of our primary findings to unmeasured confounding, we found that the HR_{SD} between tramadol and fracture hospitalizations during 180 days of as-treated follow-up versus hydrocodone initiation of 0.67 could be explained

away by an unmeasured confounder associated with both specific opioid initiated and fracture hospitalization by a risk ratio of 2.35. See Supplementary Figs. 5 and 6 in the ESM for a range of exposure–confounder and confounder–disease associations needed to explain the results of our primary analysis.

4 Discussion

Fracture risk may be important to residents and their caregivers when determining which opioid to initiate given their devastating sequelae, including reduced quality of life [20], functional decline [20], and death [20, 21]. In this new-user, IPT-weighted retrospective cohort study of long-stay nursing home residents, we found that initiating tramadol was associated with reduced fracture hospitalization rates during 180 days of as-treated follow-up, whereas oxycodone initiators had similar rates of fracture hospitalizations to hydrocodone initiators. These results are largely consistent with a prior study of the comparative safety of opioids in community-dwelling older adults [12]. Yet, we observed a reduced fracture rate among residents initiating opioids relative to what has been documented in community-dwelling populations [12, 56, 57]. We believe this work provides further context for weighing the risks when initiating commonly used opioids, though we also note the limitations of our study and directions for future research.

Our results are consistent with, albeit less pronounced than Solomon and colleagues' study, which found that community-dwelling elders initiating tramadol had 0.32 times the rate of fractures as matched hydrocodone initiators, and oxycodone initiators had 1.02 times the rate of fractures as hydrocodone initiators [12]. Solomon et al.'s study population had a higher rate of fractures among hydrocodone (26 per 100 person-years), oxycodone (25 per 100 person-years), and tramadol initiators (7 per 100 person-years) than our study population. Although some of this difference may be due to how fractures were operationalized (e.g., hospitalization claims alone [current study] versus outpatient and hospitalization claims), the limited mobility of long-stay nursing home residents may modify and lower the potential risk of fractures following opioid initiation in comparison with community-dwelling older adults [55], especially if the primary mechanism of action between opioids and fractures among older adults is through acute neurological effects [12, 56, 57] rather than hypogonadism or lowering bone mineral density [58, 59]. This was supported by the heightened rates of fracture hospitalizations that we observed in analyses restricted to residents without total physical dependence or wheelchair use who had fracture hospitalization rates per 100 person-years ranging from 7.3 (tramadol; HR_{SD} versus hydrocodone 0.74, 95% CI 0.57–0.99) to 21.3 (oxycodone; HR_{SD} versus hydrocodone 1.55; 95% CI 0.85–2.85). Mobility may matter when evaluating opioid and fracture risk in nursing homes, with higher physical dependence inversely associated with fractures in some [37, 60, 61] but not all previous studies [62].

Tramadol is commonly prescribed in nursing homes to manage pain [2, 3] and produces analgesia through two mechanisms—weak μ -opioid receptor affinity and serotonin and norepinephrine reuptake inhibition [9]. Because of this unique dual mechanism of action, residents initiating tramadol may on average have lower somnolence, dizziness, and fall risk compared with hydrocodone or oxycodone initiators. However, few head-to-head trials of

these commonly used opioids have been conducted to provide further detail on how they may influence fracture risk, particularly among older adults [63, 64]. Although tramadol has a similar safety profile to hydrocodone in terms of somnolence and dizziness in younger populations treated for acute pain [65, 66], it is unclear if these findings extend to older adults with chronic pain. Further work is needed to elucidate potential mechanisms by which tramadol and other commonly used opioids may cause adverse events among older nursing home residents.

All opioid initiators in our study had a higher rate of fracture hospitalizations (2.8 [tramadol]–3.8 [oxycodone] hip fractures per 100 person-years) than previously reported among long-stay nursing home residents overall (2.3 hip fractures per 100 person-years) [17]. This higher rate among opioid initiators versus non-users is consistent with prior work in community settings and should be kept in mind when initiating any opioid regardless of treatment setting [67–69]. However, the risks of other adverse events must also be considered. For example, tramadol is associated with rare but potentially life-threatening adverse drug events including serotonin syndrome and hypoglycemia [70, 71]. Finally, nursing home residents are at increased risk of dying compared with community-dwelling adults and may have different goals of care that mitigate concerns of fractures in favor of analgesia or pain relief. Hydrocodone and tramadol initiators died at slower rates (29.1–31.7 deaths per 100 person-years) than the overall long-stay nursing home population (37.5 per 100 person-years) [17]. However, oxycodone initiators were dying at a faster rate (60.9 per 100 person-years); further work is needed to understand whether oxycodone increases mortality risk relative to other opioids as has been documented in community settings [12].

This study has several unique strengths. We used an active comparator, new-user design to compare three commonly used treatments in nursing homes. This design reduces concerns of confounding by indication and selection bias introduced by comparing incident and prevalent users [72, 73]. Compared with prior studies examining fracture risk in older adults [12, 56, 57, 67], we had enhanced information from the MDS 3.0 on potential confounders including pain, cognitive impairment, and physical functioning that are not normally available in studies relying on Medicare claims alone. Using IPT-weighting, we achieved good balance of measured baseline confounders; such analytic strategies are not always used despite their advantages when the outcome is rare and there are many potential confounders [56, 68, 74].

This study has several limitations that may limit the causal interpretation of our effect estimates. Although we were able to adjust for confounders not normally available in observational research (e.g., physical functioning), we cannot rule out unmeasured confounding. Further, we did not adjust for potential facility-level and other environmental characteristics that may affect fracture risk. In bias analyses, a measured confounder with a risk ratio of 2.35 with both tramadol and fracture hospitalizations would be needed to attenuate our primary finding. This is above and beyond the strength of measured resident- and facility-level confounders with opioids and fractures in this and other studies, but is still possible [3, 37, 75]. We likely undercounted fractures (i.e., reduced sensitivity) by focusing solely on hospitalizations. Our estimates of overall cumulative fracture risk are thus conservative. Our HR_{SD} estimates are expected to be biased towards the null assuming

nondifferential misclassification. We assumed that loss to follow-up was nondifferential across treatment groups. We focused only on the most commonly initiated opioids in nursing homes and cannot comment on the comparative safety of initiating other opioids [3, 76]. We measured opioids using claims data and could not distinguish between as-needed (pro re nata) or scheduled use. Such limitations may be addressable in future research using electronic medication administration records to more accurately measure daily opioid use. Our effect measure modification analyses were underpowered. Finally, we assumed that propensity score models and outcome models were correctly specified, though we flexibly parameterized potential confounders (including several categories rather than dichotomizing variables, including higher-order terms for continuous variables) to mitigate these concerns.

In conclusion, we found that initiating tramadol relative to hydrocodone was associated with lower fracture hospitalization risk among older adults living in nursing homes. This may be of particular relevance for persons at heightened risk for falls or who are otherwise concerned about falling. Although this finding is consistent with prior work among community-dwelling older adults, the overall risk of fractures was lower than previously documented in community settings. Further work is needed to elucidate potential mechanisms between opioids and fracture hospitalization risk, as well as whether initiating opioids is associated with other adverse events (e.g., mortality).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. La Frenais FL, Bedder R, Vickerstaff V, Stone P, Sampson EL. Temporal trends in analgesic use in long-term care facilities: a systematic review of international prescribing. *J Am Geriatr Soc*. 2018;66:376–82. [PubMed: 29274247]
2. Hunnicutt JN, Chrysanthopoulou SA, Ulbricht CM, Hume AL, Tjia J, Lapane KL. Prevalence of long-term opioid use in long-stay nursing home residents. *J Am Geriatr Soc*. 2018;66:48–55. [PubMed: 28940193]
3. Hunnicutt JN, Baek J, Alcusky M, Hume AL, Liu SH, Ulbricht CM, Tjia J, Lapane KL. Geographic variation in the initiation of commonly used opioids and dosage strength in United States nursing homes. *Med Care*. 2018 (in press).
4. Kuo Y, Raji M, Chen N, Hasan H, Goodwin JS. Trends in opioid prescriptions among Part D Medicare recipients from 2007 to 2012. *Am J Med*. 2016;129:221.e21–30.
5. Campbell C, Weisner C, Leresche L, Ray GT, Saunders K, Sullivan MD, Banta-Green CJ, Merrill JO, Silverberg MJ, Boudreau D, Satre DD, Von Korff M. Age and gender trends in long-term opioid analgesic use for noncancer pain. *Am J Public Health*. 2010;100:2541–7. [PubMed: 20724688]
6. Won A, Lapane K, Gambassi G, Bernabei R, Mor V, Lipsitz LA. Correlates and management of nonmalignant pain in the nursing home. SAGE Study Group. Systematic Assessment of Geriatric drug use via Epidemiology. *J Am Geriatr Soc*. 1999;47:936–42. [PubMed: 10443853]
7. Lapane K, Quilliam B, Chow W, Kim M. The association between pain and measures of well-being among nursing home residents. *J Am Med Dir Assoc*. 2012;13:344–9. [PubMed: 21450246]

8. Cadogan M, Edelen MO, Lorenz KA, Jones M, Yosef J, Hascall T, et al. The relationship of reported pain severity to perceived effect on function of nursing home. *J Gerontol A Biol Sci Med Sci*. 2008;63:969–73. [PubMed: 18840802]
9. Smith HS. Opioid metabolism. *Mayo Clin Proc*. 2009;84(7):613–24. [PubMed: 19567715]
10. McLachlan AJ, Bath S, Naganathan V, Hilmer SN, Le Couteur DG, Gibson SJ, Blyth FM. Clinical pharmacology of analgesic medicines in older people: impact of frailty and cognitive impairment. *Br J Clin Pharmacol*. 2011;71:351–64. [PubMed: 21284694]
11. Naples JG, Gellad WF, Hanlon JT. The role of opioid analgesics in geriatric pain management. *Clin Geriatr Med*. 2016;32:725–35. [PubMed: 27741966]
12. Solomon D, Rassen JA, Glynn RJ, Garneau K, Levin R, Lee J, Schneeweiss S. The comparative safety of opioids for nonmalignant pain in older adults. *Arch Intern Med*. 2010;170(22):1979–86. [PubMed: 21149754]
13. Freedman VA, Spillman BC. The residential continuum from home to nursing home: size, characteristics and unmet needs of older adults. *J Gerontol B Psychol Sci Soc Sci*. 2014;69:S42–50. [PubMed: 25342822]
14. Cigolle CT, Langa KM, Kabeto MU, Tian Z, Blaum CS. Geriatric conditions and disability: the health and retirement study. *Ann Intern Med*. 2007;147(3):156–64. [PubMed: 17679703]
15. Jokanovic N, Tan EC, Dooley MJ, Kirkpatrick CM, Bell JS. Prevalence and factors associated with polypharmacy in long-term care facilities: a systematic review. *J Am Med Dir Assoc*. 2015;16:535.e1–12.
16. Kojima G. Prevalence of frailty in nursing homes: a systematic review and meta-analysis. *J Am Med Dir Assoc*. 2015;16:940–5. [PubMed: 26255709]
17. Berry S, Lee Y, Zullo AR, Kiel DP, Dosa D, Mor V. Incidence of hip fracture in US nursing homes. *J Gerontol A Biol Sci Med Sci*. 2016;71:1230–4. [PubMed: 26980299]
18. Berry SD, Samelson EJ, Bordes M, Broe K, Kiel DP. Survival of aged nursing home residents with hip fracture. *J Gerontol Ser A Biol Sci Med Sci*. 2009;64:771–7. [PubMed: 19414511]
19. Baumgarten M, Margolis DJ, Orwig DL, Shardell MD, Hawkes WG, Langenberg P, et al. Pressure ulcers in elderly patients with hip fracture across the continuum of care. *J Am Geriatr Soc*. 2009;57:863–70. [PubMed: 19484841]
20. Beaupre LA, Jones CA, Johnston DWC, Wilson DM, Majumdar SR. Recovery of function following a hip fracture in geriatric ambulatory persons living in nursing homes: prospective cohort study. *J Am Geriatr Soc*. 2012;60:1268–73. [PubMed: 22702238]
21. Neuman M, Silber J, Magaziner JS, Passarella MA, Mehta S, Werner RM. Survival and functional outcomes after hip fracture among nursing home residents. *JAMA Intern Med*. 2014;174:1273–80. [PubMed: 25055155]
22. Saliba D, Buchanan J. Development and validation of a revised nursing home assessment tool: MDS 3.0. Santa Monica: Rand Corp; 2008.
23. Saliba D, Buchanan J. Making the investment count: revision of the Minimum Data Set for nursing homes, MDS 3.0. *J Am Med Dir Assoc*. 2012;13:602–10. [PubMed: 22795345]
24. Saliba D, Jones M, Streim J, Ouslander J, Berlowitz D, Buchanan J. Overview of significant changes in the Minimum Data Set for nursing homes version 3.0. *J Am Med Dir Assoc*. 2012;13:595–601. [PubMed: 22784698]
25. Virnig B. Sources and use of medicare enrollment information-<https://www.resdac.org/sites/resdac.umn.edu/files/Sources> and Use of Medicare Enrollment Information %28Slides%29.pdf. Accessed 30 Jul 2018.
26. Ballantyne J, Mao J. Opioid therapy for chronic pain. *N Engl J Med*. 2003;349:1943–53. [PubMed: 14614170]
27. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Prescription of long-acting opioids and mortality in patients with chronic noncancer pain. *JAMA*. 2016;315(22):2415–23. [PubMed: 27299617]
28. Centers for Disease Control and Prevention. Opioid morphine equivalent conversion factors. 2015 <https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Opioid-Morphine-EQ-Conversion-Factors-March-2015.pdf>. Accessed 20 Jan 2018.

29. Jeffery MM, Hooten WM, Hess EP, Meara ER, Ross JS, Henk HJ, et al. Opioid prescribing for opioid-naïve patients in emergency departments and other settings: characteristics of prescriptions and association with long-term use. *Ann Emerg Med*. 2018;71:326–36. [PubMed: 28967517]
30. Shah A, Hayes CJ, Martin BC. Factors Influencing long-term opioid use among opioid naïve patients: an examination of initial prescription characteristics and pain etiologies. *J Pain*. 2017;18:1374–83. [PubMed: 28711636]
31. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *JAMA*. 2016;315(15):1624–45. [PubMed: 26977696]
32. Russo C, Owens P, Stocks C. Common injuries that result in hospitalization, 2004: statistical brief #19. <https://www.ncbi.nlm.nih.gov/books/NBK63503>. Accessed 10 Aug 2017.
33. Hudson M, Avina-Zubieta A, Lacaille D, Bernatsky S, Lix L, Jean S. The validity of administrative data to identify hip fractures is high—a systematic review. *J Clin Epidemiol*. 2013;66:278–85. [PubMed: 23347851]
34. Sing CW, Woo YC, Lee ACH, Lam JKY, Chu JKP, Wong ICK, et al. Validity of major osteoporotic fracture diagnosis codes in the Clinical Data Analysis and Reporting System in Hong Kong. *Pharmacoepidemiol Drug Saf*. 2017;26:973–6. [PubMed: 28371079]
35. Kleinbaum D, Klein M. *Survival analysis: a self-learning text*. 3rd ed New York: Springer; 2012.
36. Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiologic data. *Am J Epidemiol*. 2009;170:244–56. [PubMed: 19494242]
37. Berry SD, Zullo AR, Lee Y, Mor V, McConeghy KW, Banerjee G, et al. Fracture risk assessment in long-term care (FRAiL): development and validation of a prediction model. *J Gerontol Ser A*. 2018;73:763–9.
38. Banerjee G, Zullo AR, Berry SD, Lee Y, McConeghy K, Kiel DP, et al. Geographic variation in hip fracture among United States long-stay nursing home residents. *J Am Med Dir Assoc*. 2016;17:865.e1–3. [PubMed: 27461867]
39. Thomas KS, Dosa D, Wysocki A, Mor V. The minimum data Set 3.0 cognitive function scale. *Med Care*. 2017;55:e68–72. [PubMed: 25763665]
40. Morris JN, Fries BE, Morris SA. Scaling ADLs within the MDS. *J Gerontol A Biol Sci Med Sci*. 1999;54(11):M546–53. [PubMed: 10619316]
41. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med*. 2015;34:3661–79. [PubMed: 26238958]
42. Rosenbaum P, Rubin D. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983;70:41–55.
43. Imbens GW. The role of the propensity score in estimating dose-response functions. *Biometrika*. 2000;87:706–10.
44. Cole S, Hernán M. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol*. 2008;168:656–64. [PubMed: 18682488]
45. Sato T, Matsuyama Y. Marginal structural models as a tool for standardization. *Epidemiology*. 2003;14:680–6. [PubMed: 14569183]
46. Fine J, Gray R. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat*. 1999;94(496–509):46.
47. Hernán MA. The hazards of hazard ratios. *Epidemiology*. 2010;21:13–5. [PubMed: 20010207]
48. VanderWeele TJ, Vansteelandt S, Robins JM. Marginal structural models for sufficient cause interactions. *Am J Epidemiol*. 2010;171:506–14. [PubMed: 20067916]
49. Li R, Chambless L. Test for additive interaction in proportional hazards models. *Ann Epidemiol*. 2007;17:227–36. [PubMed: 17320789]
50. Ding P, VanderWeele TJ. Sensitivity analysis without assumptions. *Epidemiology*. 2016;27:368–77. [PubMed: 26841057]
51. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Ann Intern Med*. 2017;167:268–74. [PubMed: 28693043]
52. Hernán MA. Does water kill? A call for less casual causal inferences. *Ann Epidemiol*. 2016;26:674–80. [PubMed: 27641316]

53. Cole SR, Frangakis CE. The consistency statement in causal inference: a definition or an assumption? *Epidemiology*. 2009;20:3–5. [PubMed: 19234395]
54. Petersen M, van der Laan M. Causal models and learning from data: integrating causal modeling and statistical estimation. *Epidemiology*. 2014;25:506–14.
55. Keyes K, Galea S. What matters most: quantifying an epidemiology of consequence. *Ann Epidemiol*. 2015;25:305–11. [PubMed: 25749559]
56. Miller M, Stürmer T, Azrael D, Levin R, Solomon DH. Opioid analgesics and the risk of fractures in older adults with arthritis. *J Am Geriatr Soc*. 2011;59(3):430–8. [PubMed: 21391934]
57. Solomon DH, Rassen JA, Glynn RJ, Lee J, Levin R, Schneeweiss S. The comparative safety of analgesics in older adults with arthritis. *Arch Intern Med*. 2010;170:1968–76. [PubMed: 21149752]
58. Katz N, Mazer NA. The impact of opioids on the endocrine system. *Clin J Pain*. 2009;25(2):170–5. [PubMed: 19333165]
59. Yoshida K, Yu Z, Greendale GA, Ruppert K, Lian Y, Tedeschi SK, et al. Effects of analgesics on bone mineral density: a longitudinal analysis of the prospective SWAN cohort with three-group matching weights. *Pharmacoepidemiol Drug Saf*. 2018;27:182–90. [PubMed: 29230890]
60. Girman CJ, Chandler JM, Zimmerman SI, Martin AR, Hawkes W, Hebel JR, et al. Prediction of fracture in nursing home residents. *J Am Geriatr Soc*. 2002;50:1341–7. [PubMed: 12164989]
61. Colon-Emeric CS, Biggs DP, Schenck AP, Lyles KW. Risk factors for hip fracture in skilled nursing facilities: who should be evaluated? *Osteoporos Int*. 2003;14:484–9. [PubMed: 12730734]
62. Dobnig H, Piswanger-Sölkner JC, Obermayer-Pietsch B, Tiran A, Strele A, Maier E, et al. Hip and nonvertebral fracture prediction in nursing home patients: role of bone ultrasound and bone marker measurements. *J Clin Endocrinol Metab*. 2007;92:1678–86. [PubMed: 17311861]
63. Papaleontiou M, Henderson CR Jr, Turner BJ, Moore AA, Olkhovskaya Y, Amanfo L, Reid MC. Outcomes associated with opioid use in the treatment of chronic noncancer pain in older adults: a systematic review and meta-analysis. *J Am Geriatr Soc*. 2010;58(7):1353–69. [PubMed: 20533971]
64. Chou R, Turner JA, Devine EB, Hansen RN, Sullivan SD, Blazina I, Dana T, Bougatsos C, Deyo RA. The effectiveness and risks of long-term opioid treatment of chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med*. 2015;162(4):276–86. [PubMed: 25581257]
65. Fricke JR, Karim R, Jordan D, Rosenthal N. A double-blind, single-dose comparison of the analgesic efficacy of tramadol/acetaminophen combination tablets, hydrocodone/acetaminophen combination tablets, and placebo after oral surgery. *Clin Ther*. 2002;24:953–68. [PubMed: 12117085]
66. Hewitt DJ, Todd KH, Xiang J, Jordan DM, Rosenthal NR, CAPSS-216 Study Investigators. Tramadol/acetaminophen or hydrocodone/acetaminophen for the treatment of ankle sprain: a randomized, placebo-controlled trial. *Ann Emerg Med*. 2007;49:468. e2–480.e2. [PubMed: 17113683]
67. Saunders KW, Dunn KM, Merrill JO, Sullivan M, Weisner C, Braden JB, et al. Relationship of opioid use and dosage levels to fractures in older chronic pain patients. *J Gen Intern Med*. 2010;25:310–5. [PubMed: 20049546]
68. Li L, Setoguchi S, Cabral H, Jick S. Opioid use for noncancer pain and risk of fracture in adults: a nested case-control study using the general practice research database. *Am J Epidemiol*. 2013;178:559–69. [PubMed: 23639937]
69. Vestergaard P, Rejnmark L, Mosekilde L. Fracture risk associated with the use of morphine and opiates. *J Intern Med*. 2006;260:76–87. [PubMed: 16789982]
70. Boyer EW, Shannon M. The serotonin syndrome. *N Engl J Med*. 2005;352:1112–20. [PubMed: 15784664]
71. Fournier JP, Azoulay L, Yin H, Montastruc JL, Suissa S. Tramadol use and the risk of hospitalization for hypoglycemia in patients with noncancer pain. *JAMA Intern Med*. 2015;175:186–93. [PubMed: 25485799]
72. Ray W. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol*. 2003;158:915–20. [PubMed: 14585769]

73. Lund JL, Richardson DB, Stürmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. *Curr Epidemiol Rep.* 2015;2:221–8. [PubMed: 26954351]
74. Cepeda MS, Boston R, Farrar JT, Strom BL. Comparison of logistic regression versus propensity score when the number of events is low and there are multiple confounders. *Am J Epidemiol.* 2003;15:280–7.
75. Zullo AR, Zhang T, Banerjee G, Lee Y, McConeghy KW, Kiel DP, et al. Facility and state variation in hip fracture in US nursing home residents. *J Am Geriatr Soc.* 2018;66:539–45. [PubMed: 29336024]
76. Hunnicutt JN, Hume AL, Ulbricht CM, Tjia J, Lapane KL. Long-acting opioid initiation in US nursing homes. *Pharmacoepidemiol Drug Saf.* 2018;. 10.1002/pds.4568.

Key Points

In this new-user retrospective cohort study of long-stay nursing home residents initiating short-acting oxycodone, hydrocodone, or tramadol, crude fracture hospitalization rates ranged from 5 (tramadol) to 9 (oxycodone) per 100 person-years.

In inverse probability of treatment weighted competing risk analyses, initiating tramadol versus hydrocodone was associated with reduced fracture hospitalization rates during 180 days of as-treated follow-up (subdistribution hazard ratios [HR_{SD}] 0.67, 95% confidence interval [CI] 0.56–0.80). Oxycodone initiators had similar fracture hospitalization rates compared with hydrocodone initiators (HR_{SD} 1.08, 95% CI 0.79–1.48).

Baseline characteristics of nursing home residents in the 120 days before initiating oxycodone, hydrocodone, or tramadol ($N = 110,862$ residents; 134,432 treatment episodes)

Characteristic	Crude, stratified by opioid initiated			Overall, IPT-weighted ^a
	Oxycodone	Hydrocodone	Tramadol	
Number of treatment episodes ^b	14,373	69,182	50,877	134,357
Demographics				
Age in years, mean(standard deviation)	83.7 (8.8)	84.3 (8.6)	85.5 (8.4)	84.7 (8.5)
Women, %	72.2	74.5	79.0	76.1
Non-Hispanic White, %	81.0	83.5	84.5	84.1
Married, %	17.5	17.2	15.6	16.7
Behavior, %				
Rejects care	10.2	10.1	9.9	10.0
Wandering	5.0	6.4	6.4	6.2
Cognitive impairment, ^c %				
Moderately impaired	33.6	38.1	37.2	37.0
Severely impaired	10.3	10.1	9.2	9.6
Physical functioning, ^d %				
Requires extensive assistance	55.1	53.1	53.9	53.7
Physical dependence	23.8	21.2	19.5	20.7
Pain, ^e %				
Any self-reported pain	28.1	25.3	25.4	26.1
Any staff-assessed pain	3.8	4.1	3.3	3.7
Urinary incontinence, always %	35.0	31.9	27.7	30.5
Bowel incontinence, always %	29.8	28.0	27.7	26.5
Mobility devices normally used, %				
Cane/walker	45.0	44.0	48.4	46.0
Wheelchair	79.4	75.6	73.9	75.4
Comorbidities, %				
History of falls	21.0	23.4	23.1	23.1

Characteristic	Crude, stratified by opioid initiated			Overall, IPT-weighted ^a
	Oxycodone	Hydrocodone	Tramadol	
Previous fracture	3.9	2.9	2.7	3.0
Parkinson's disease	6.8	7.4	7.2	7.3
Seizures/epilepsy	8.2	8.2	6.1	7.4
Osteoporosis	18.5	18.5	19.6	18.9
Arthritis	30.2	30.1	33.5	31.7
Pressure ulcers	5.5	3.9	3.3	3.9
Congestive heart failure	21.5	21.0	20.7	21.1
Stroke	17.6	17.6	16.7	17.2
Diabetes	35.0	34.5	31.5	33.5
Depression	57.2	56.6	55.2	56.4
Number of medications prescribed, median (P25-P75) Psychotropic medications, %	9 (7-13)	9 (7-13)	9 (6-12)	9(6-13)
2 psychotropic medications prescribed ^f	32.2	33.1	30.9	32.3
Antipsychotics	25.1	26.7	25.8	26.2
Antidepressants ^g	64.6	62.7	61.2	62.5
Anxiolytics ^h	20.1	21.3	19.6	20.7
Hypnotics ^h	5.6	5.7	5.1	5.6
Pain adjuvant medications, %				
Anticonvulsants	18.8	15.8	14.1	15.7
Systemic corticosteroids	8.7	7.7	7.9	8.0
Nonsteroidal anti-inflammatory drugs	11.7	11.9	13.1	12.5
Skeletal muscle relaxants	5.6	4.3	3.8	4.4

ESM electronic supplementary material. IPT inverse probability of treatment, P25-P75 25th to 75th percentiles

^aStabilized IPT-weights (mean 1.00, minimum 0.16, maximum 8.65) were used to standardize the distribution of potential confounders to that of the entire study population. See Supplementary Table 4 in the ESM for the IPT-weighted distribution of potential confounders by opioid initiated. See Supplementary Figs. 2, 3 and 4 in the ESM for further detail on the overall distribution of propensity scores and standardized mean differences before and after IPT-weighting

^b110,862 residents contributed 134,432 treatment initiation episodes (17.0% of residents contributed > 1 treatment episode [range 2-6]). Treatment switching was uncommon: 2.4% and 0.01% of residents initiated 2 or 3 different treatments, respectively

^cCognitive impairment was defined using the Cognitive Function Scale (CFS; range 0-3): cognitively intact (0), mild impairment (1), moderate impairment (2), and severe impairment

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^dPhysical limitations were defined using the Activities of Daily Living Self-Performance Hierarchy (range: 0–6): no/mild limitations (0–2), extensive limitations (3–4), and physical dependence (5–6)

^eResident pain in the 5 days preceding the most recent Minimum Data Set (MDS) assessment before treatment initiation was based on self-report when the resident was able to and staff assessment otherwise

^fBased on antipsychotics, antidepressants, anxiolytics, and hypnotics

^gSee Supplementary Table 4 in the ESM for further detail on specific classes of antidepressants prescribed (e.g., tricyclics) by study drug initiated

^hAnxiolytics and hypnotics were measured in the 7 days before the most recent MDS assessment because benzodiazepines were not covered by Part D in 2011–2012

Table 2

Crude incidence of first major fracture hospitalizations per 100-person years among nursing home residents initiating oxycodone, tramadol, or hydrocodone; 180 days of as-treated follow-up ($N = 110,862$ residents; 134,432 treatment episodes)

Endpoint	Oxycodone		Hydrocodone		Tramadol	
	No. of events	Incidence rate ^a (95% CI)	No. of events	Incidence rate ^a (95% CI)	No. of events	Incidence rate ^a (95% CI)
Major fracture hospitalization ^b	77	9.4 (7.5–11.7)	336	7.9 (7.1–8.8)	209	5.0 (4.3–5.7)
Hip	35	4.3 (3.1–5.9)	162	3.8 (3.3–4.5)	118	2.8 (2.3–3.4)
Femur	16	1.9 (1.2–3.2)	59	1.4 (1.1–1.8)	30	0.7 (0.5–1.0)
Humerus	18	2.2 (1.4–3.5)	54	1.3 (1.0–1.7)	24	0.6 (0.4–0.9)
Pelvis	— ^c	— ^c	48	1.1 (0.9–1.5)	30	0.7 (0.5–1.0)
Radius/ulna	— ^c	— ^c	26	0.6 (0.4–0.9)	15	0.4 (0.2–0.6)
Competing risk: death	500	60.9 (55.7–66.8)	1343	31.7 (30.1–33.4)	1220	29.1 (27.5–30.8)

^aOxycodone initiators contributed 821 person-years of as-treated follow-up (median follow-up: 14 days; 25th–75th percentiles [P25–P75]: 11–21 days), hydrocodone initiators contributed 4232 person-years (median: 14 days; P25–P75: 12–22 days), and tramadol initiators contributed 4197 person-years (median: 15; P25–P75: 12–26)

^bThe total number of specific fracture events exceeds the number of major fracture hospitalizations because 25 initiators were simultaneously hospitalized for 2 major fractures

^cRates are suppressed in accordance with Centers for Medicare and Medicaid Service's cell size suppression policy because there were < 11 events

Fracture hospitalizations by opioid initiated among older nursing home residents during as-treated follow-up ($N = 110,862$ residents; 134,432 treatment episodes)

Table 3

Treatment group No. of episodes	Crude		IPT-weighted		
	Cumu-lative risk, %	Incidence rate ^a (95% CI)	HR _{SD} (95% CI)	Cumu-lative risk, %	Incidence rate ^a (95% CI)
Primary analysis: 1–180 days					
Hydrocodone	69,182	1.5	Referent	1.6	8.1 (7.2–9.0)
Oxycodone	14,373	1.7	1.13 (0.88–1.44)	1.8	9.6 (7.1–12.8)
Tramadol	50,877	1.1	0.76 (0.64–0.90)	1.1	4.5 (3.9–5.2)
Secondary analyses Restricted follow-up: 1–30 days					
Hydrocodone	69,182	0.6	Referent	0.6	9.4 (8.4–10.6)
Oxycodone	14,373	0.7	1.11 (0.86–1.44)	0.6	10.3 (9.6–13.9)
Tramadol	50,877	0.4	0.72 (0.60–0.87)	0.4	5.1 (4.4–6.0)
Restricted follow-up: 1–60 days					
Hydrocodone	69,182	0.8	Referent	0.8	9.3 (8.3–10.5)
Oxycodone	14,373	0.9	1.14 (0.88–1.46)	0.9	10.6 (7.9–14.3)
Tramadol	50,877	0.6	0.74 (0.62–0.88)	0.5	5.3 (4.6–6.2)
Restricted follow-up: 1–90 days					
Hydrocodone	69,182	1.0	Referent	1.1	8.1 (7.2–9.0)
Oxycodone	14,373	1.1	1.15 (0.90–1.48)	1.2	9.6 (7.1–12.8)
Tramadol	50,877	0.7	0.74 (0.62–0.89)	0.7	4.5 (3.9–5.2)
Dose stratified: < 25 mg OME/day					
Hydrocodone	36,246	1.5	Referent	1.6	6.9 (5.9–8.0)
Oxycodone	4098	2.0	1.33 (0.91–1.95)	2.2	9.1 (5.6–14.9)
Tramadol	40,899	1.1	0.74 (0.60–0.91)	1.1	4.1 (3.5–4.9)
Dose stratified: 25–49 mg OME/day ^b					
Hydrocodone	28,616	1.6	Referent	1.7	11.0 (9.1–13.3)
Oxycodone	7372	1.7	1.06 (0.73–1.53)	1.5	9.1 (6.0–13.9)
Tramadol	9374	1.3	0.85 (0.58–1.23)	1.4	8.7 (6.1–14.5)
Dose stratified: 50 mg OME/day ^b					
Hydrocodone	28,616	1.6	Referent	1.7	11.0 (9.1–13.3)
Oxycodone	7372	1.7	1.06 (0.73–1.53)	1.5	9.1 (6.0–13.9)
Tramadol	9374	1.3	0.85 (0.58–1.23)	1.4	8.7 (6.1–14.5)

Treatment group	No. of episodes	Crude		IPT-weighted			
		Cumu-lative risk, %	Incidence rate ^a (95% CI)	HR _{SD} (95% CI)	Cumu-lative risk, %	Incidence rate ^a (95% CI)	HR _{SD} (95% CI)
Hydrocodone	4320	0.7	9.4 (5.1–17.6)	— ^c	1.3	7.5 (4.2–13.3)	— ^c
Oxycodone	2903	— ^c	— ^c	— ^c	— ^c	— ^c	— ^c
Tramadol	604	— ^c	— ^c	— ^c	— ^c	— ^c	— ^c

CI confidence interval, *HR_{SD}* subdistribution hazards ratio, *IPT* inverse probability of treatment, *OME* oral morphine equivalent

^aFracture hospitalizations per 100 person-years

^bWe found no evidence that higher doses (25–49 mg OME/day vs < 25 mg OME/day) increased the subdistribution hazard of fracture risk on the additive scale for hydrocodone and oxycodone (Relative Excess Risk due to Interaction [RERI] = 0.45, 95% CI –0.31 to 1.21) or hydrocodone and tramadol (RERI = – 0.19, 95% CI –0.83 to 0.45). We did not compare those initiating doses 50 mg OME/day due to the low number of fracture hospitalizations in this group

^cSuppressed in accordance with Centers for Medicare and Medicaid Service's cell size suppression policy because there were < 11 events

Table 4

Sensitivity analyses

Treatment group No. of episodes		Crude	IPT-weighted				
		Cumu-lative risk, %	Incidence rate ^a (95% CI)	HR _{SD} (95% CI)	Cumu-lative risk, %	Incidence rate ^a (95% CI)	HR _{SD} (95% CI)
Intention-to-treat analysis ^b							
Hydrocodone	56,375	1.4	3.1 (2.9–3.4)	Referent	1.4	3.2 (2.9–3.4)	Referent
Oxycodone	12,273	1.5	3.6 (3.1–4.2)	1.11 (0.94–1.31)	1.6	3.8 (3.1–4.7)	1.17 (0.93–1.47)
Tramadol	42,214	1.2	2.8 (2.6–3.1)	0.90 (0.80–1.01)	1.2	2.7 (2.5–3.0)	0.86 (0.76–0.97)
Restricting outcome to hip fractures							
Hydrocodone	69,182	0.9	3.8 (3.3–4.5)	Referent	1.0	3.9 (3.3–4.6)	Referent
Oxycodone	14,373	0.9	4.3 (3.1–5.9)	1.05 (0.73–1.51)	1.0	4.6 (3.0–7.1)	1.08 (0.68–1.71)
Tramadol	50,877	0.7	2.8 (2.3–3.4)	0.86 (0.68–1.09)	0.7	2.5 (2.1–3.1)	0.75 (0.59–0.97)
Excluding states where < 10% of treatment episodes were oxycodone ^c							
Hydrocodone	15,815	1.1	8.0 (6.4–9.9)	Referent	1.2	7.9 (6.3–10.0)	Referent
Oxycodone	9298	1.3	9.4 (7.1–12.3)	1.12 (0.79–1.59)	1.4	10.0 (7.4–13.4)	1.18 (0.81–1.71)
Tramadol	15,782	0.9	4.9 (3.8–6.1)	0.76 (0.56–1.05)	0.9	4.5 (3.5–5.8)	0.72 (0.51–1.01)
Excluding residents with physical dependence or wheelchair use							
Hydrocodone	14,422	3.1	13.1 (10.9–15.7)	Referent	3.1	12.5 (10.3–15.1)	Referent
Oxycodone	2518	4.2	19.4 (13.1–28.5)	1.36 (0.89–2.08)	4.7	21.3 (11.9–38.2)	1.55 (0.85–2.85)
Tramadol	11,982	2.4	8.5 (6.8–10.5)	0.76 (0.57–1.00)	2.2	8.0 (6.4–10.0)	0.74 (0.57–0.99)
Excluding residents without documented pain							
Hydrocodone	20,350	1.4	4.7 (3.7–6.0)	Referent	1.4	4.9 (3.8–6.4)	Referent
Oxycodone	4593	1.6	5.7 (3.5–9.3)	1.17 (0.68–2.0)	1.6	6.8 (3.2–10.3)	1.11 (0.64–1.93)
Tramadol	14,619	1.1	3.5 (2.6–4.7)	0.83 (0.56–1.23)	1.1	3.3 (2.4–4.5)	0.75 (0.51–1.12)
Excluding residents with osteoporosis							
Hydrocodone	56,397	1.4	7.8 (6.9–8.8)	Referent	1.6	8.0 (7.1–9.1)	Referent
Oxycodone	11,718	1.7	9.6 (7.4–12.2)	1.17 (0.89–1.53)	1.8	9.8 (7.1–13.6)	1.12 (0.85–1.47)
Tramadol	40,918	1.1	4.9 (4.2–5.7)	0.76 (0.62–0.92)	1.1	4.5 (3.8–5.3)	0.67 (0.55–0.82)

CI confidence interval, HR_{SP}subdistribution hazards ratio, IPT[†]inverse probability of treatment^aFracture hospitalizations per 100 person-years

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The sample for the intention-to-treat analysis was restricted to the first initiation episode ($n = 110,862$ residents)

^cRestricted to the following states: Arizona, Colorado, Connecticut, Delaware, Massachusetts, Maryland, Maine, Minnesota, North Carolina, North Hampshire, New Jersey, New Mexico, Nevada, New York, Oregon, Pennsylvania, Rhode Island, Vermont, Washington