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Opioid and non-opioid analgesic regimens after fracture and risk of serious opioid-related events

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ABSTRACT

Background Non-opioid analgesics are prescribed in combination with opioids among patients with long bone fracture to reduce opioid prescribing needs, yet evidence is limited on whether they reduce the risk of serious opioid-related events (SOREs). We compared the risk of SOREs among hospitalized patients with long bone fracture discharged with filled opioid prescriptions, with and without non-opioid analgesics.

Design We identified a retrospective cohort of analgesic-naïve adult patients with a long bone fracture hospitalization using the Merative MarketScan Commercial Database (2013–2020). The exposure was opioid and non-opioid analgesic (gabapentinoids, muscle relaxants, non-steroidal anti-inflammatory drugs, acetaminophen) prescriptions filled in the 3 days before through 42 days after discharge. The outcome was the development of new persistent opioid use or opioid use disorder during follow-up (day 43 through day 408 after discharge). We used Cox proportional hazards regression with inverse probability of treatment weighting with overlap trimming to compare outcomes among those that filled an opioid and a non-opioid analgesic to those that filled only an opioid analgesic. In secondary analyses, we used separate models to compare those that filled a prescription for each specific non-opioid analgesic type with opioids to those that filled only opioids.

Results Of 29 489 patients, most filled an opioid prescription alone (58.4%) or an opioid and non-opioid (22.0%). In the weighted proportional hazards regression model accounting for relevant covariates and total MME, filling both a non-opioid analgesic and an opioid analgesic was associated with 1.63 times increased risk of SOREs compared with filling an opioid analgesic only (95% CI 1.41 to 1.89). Filling a gabapentin prescription in combination with an opioid was associated with an increased risk of SOREs compared with those that filled an opioid only (adjusted HR: 1.84 (95% CI1.48 to 2.27)).

Conclusions Filling a non-opioid analgesic in combination with an opioid was associated with an increased risk of SOREs after long bone fracture.

Level of evidence Level III, prognostic/epidemiological.

Study type Retrospective cohort study.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Though non-opioid analgesics are increasingly prescribed after traumatic injuries to reduce overall opioid prescribing needs, there is growing evidence that the concomitant prescribing of non-opioid analgesics in combination with opioids is associated with an increased risk of persistent opioid use and opioid use disorder.

WHAT THIS STUDY ADDS

⇒ In this retrospective cohort study, compared with those filling an opioid analgesic prescription only, those that filled a non-opioid analgesic prescription had an elevated risk of developing persistent opioid use or an opioid use disorder after adjusting for all relevant covariates, include total MME dose. The elevated risk was highest for those filling a gabapentin prescription in combination with opioids.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Clinical guidelines regarding postsurgery analgesia should indicate that caution may be warranted when prescribing multimodal or high-dose opioid medications as they may increase the risk of serious opioid-related harms.

INTRODUCTION

The quadrupling of opioid prescriptions since 1999 has coincided with the increase in opioid-related harms globally, including over 100 000 overdose deaths in the USA.[1–3] Opioid prescribing after surgical procedures and traumatic injuries, especially at high doses, has been associated with increased risk of subsequent opioid-related harms, including development of persistent opioid use and opioid use disorder (OUD) as well as opioid-related overdoses and deaths.[4–7] Though intraoperative (eg, spinal and regional anesthesia) and postoperative pain management (eg, ketorolac administration) strategies during hospitalization have shown potential benefits at reducing subsequent opioid-related harms, beneficial outpatient pain management strategies remain less well understood.[8 9]

Long bone fracture is a common and costly traumatic injury requiring hospitalization in the USA.[10] Patients hospitalized for long bone fracture often require opioid use for appropriate pain management, which could potentially lead to a higher risk for experiencing serious opioid-related harms compared with non-trauma patients.[10–12] Risk factors for opioid-related harms after traumatic injury include male sex, preoperative opioid use, payer type, American Society of Anesthesiologists

score and injury severity score.[13–19] The use of multimodal analgesia (ie, opioid and non-opioid analgesics) is one potential strategy to reduce risk through the reduction in postdischarge opioid requirements or by lowering perceived pain in certain surgical populations.[2 20–24] However, it remains unclear whether the use of non-opioid analgesics, alone or in combination with opioids, protects against the development of serious opioid-related events (SORE) after traumatic injury.

We sought to compare the risk of developing SOREs (including persistent opioid use, coded diagnosis or treatment for OUD, or opioid-related hospitalization) among previously analgesic naïve patients hospitalized for long bone fracture that filled opioid analgesics in combination with at least one non-opioid analgesic prescription (muscle relaxants, gabapentin, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen) at discharge compared with patients who filled only an opioid analgesic prescription.

METHODS

Data sources and study cohort

We identified opioid naïve patients aged 18–65 years hospitalized for long bone fracture in the USA from July 1, 2013, through December 31, 2019, using the Merativ MarketScan Commercial Database. We focused solely on long bone fracture to limit confounding due to different pain management guidelines and potential differences in the underlying risks for SOREs for different injury types. The Merative MarketScan Commercial Database encompasses deidentified enrollment data, inpatient and outpatient claims and outpatient filled prescription drug claims for a population of more than 215 million individuals with employer-sponsored private insurance health plans, including employees, covered spouses and dependents. The study was approved by the authors' institutional review board.

We identified patients hospitalized with evidence of a long bone fracture based on a primary or secondary diagnosis claim of humerus (ICD9: 812.00–812.59; ICD10: S42.201-S42.929), femur (ICD9: 820.00–821.39; ICD10: S72.001-S72.929) or tibia fracture (ICD9: 823.00–824.99; ICD10: S82.101-S82.929). Patients entered the cohort on day 43 after discharge (t_0) if they were continuously enrolled (no gaps >30 days) in the health plan at least 6 months before through 42 days after discharge (figure 1). We excluded patients with evidence of OUD (coded diagnosis, opioid-related hospitalization or use of medication-assisted therapy (online supplemental appendix table 1)) during baseline. To focus on patients who were analgesic-naïve prior to hospitalization, we excluded patients with evidence of outpatient prescriptions for opioids, gabapentinoids, muscle relaxants, NSAIDs and acetaminophen in the 6 months prior to admission through 3 days prior to discharge. We also excluded patients with severe injuries hospitalized for longer than 14 days.

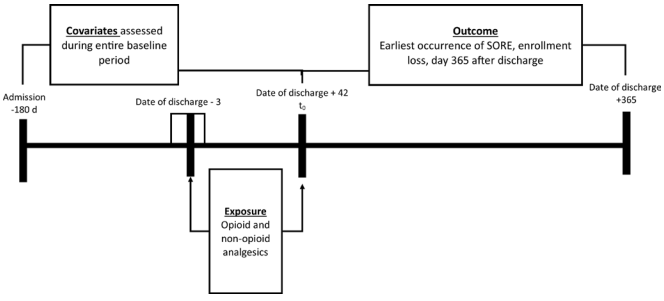

Figure 1 Study design overview. SORE, serious opioid-related event.

Hospitalizations with a one calendar day gap or less between discharge and subsequent readmission were considered the same hospitalization. We also did not include any hospitalizations for the same individual that occurred during the follow-up period (eg, additional injuries, removal of hardware, revision) to remove overlapping follow-up periods for the same individual and to reduce correlated observations within the same individual. For the primary analysis, we restricted the study population to only those individuals who received at least one discharge opioid prescription in the 3 days before through 42 days after discharge from the fracture hospitalization to remove potential bias from including those that did not fill any analgesic in the exposure period.

Patient follow-up continued from day 43 after discharge through the earliest of the following: day 408 after discharge (365 days after day 42 after discharge), loss of enrollment, death, or evidence of a SORE (figure 1).

Exposure

We identified use of opioids and non-opioid analgesics using National Drug Classification codes for filled prescriptions 3 days before through 42 days after discharge. The Merative Marketscan Commerical Database does not include information on inpatient analgesic administration and dosing and so was not assessed. Opioid-combination drugs, (eg, hydrocodone-acetaminophen, oxycodone-acetaminophen) were classified as opioid prescriptions only. Non-opioid analgesics included single-entity prescriptions for muscle relaxants, gabapentin, NSAIDs and acetaminophen. We excluded combined-entity prescriptions for NSAIDs and acetaminophen intended to manage symptoms of cold, influenza or allergies (eg, acetaminophen-dextromethorphan, acetaminophen phenylephrine, ibuprofen-pseudoephedrine). We further calculated the total dose of all opioids filled in this period as the total morphine milligram equivalents (MME) filled (MME=strength per tablet × quantity × MME conversion factor) to be accounted for as a covariate in the model (see below). In the primary analysis among individuals filling an opioid prescription, the exposure of interest was the filling of any non-opioid analgesic prescription compared with the opioid only group as reference. Secondary analyses focused specifically on individual non-opioid analgesic prescriptions (eg, gabapentin, muscle relaxants, NSAIDs, acetaminophen) compared with the opioid only group as reference.

Serious opioid-related events

The primary SORE outcome was a composite measure identified on the earliest date either of the following was detected: (1) persistent opioid use, defined as the earliest date a patient fills a greater than 90-day supply of opioids within a 180-day window,[25–27] (2) evidence of OUD based on coded diagnoses for OUD, (3) opioid-related hospitalization or (4) use of medication-assisted therapy (online supplemental appendix table 1). Importantly, only opioid prescriptions filled on or after t_0 (day 43 after discharge) were included in the determination of persistent opioid use during follow-up.

Covariates

We identified covariates *a priori* as potential confounders in the association between postdischarge analgesic use and SOREs. We identified patient demographics from the trauma hospitalization, including study year, age at admission, health plan type (employer, health plan), sex (male, female), employee classification (union/non-union/other), employee status (full-time,

part-time, retiree, COBRA/long-term disability, other) and US geographic region of residence. We further identified characteristics of the trauma hospitalization, including length of stay, surgery during the hospitalization, fracture type (primary fracture, secondary fracture, more than one fracture type), evidence of multiple traumas as identified by the diagnosis-related group, and the number of readmissions from discharge through day 42 after discharge. Furthermore, we identified comorbidities among patients in the baseline period using coded diagnoses, including back pain, headache, musculoskeletal pain, psychogenic pain, neuropathic pain, sickle cell/hemolytic anemia, arthritis pain, depression, frailty and malignancy. We further calculated each patient's Elixhauser comorbidity index using inpatient hospitalization data in the baseline period, excluding conditions measured separately (eg, depression).

Statistical analysis

For descriptive analyses of demographics and baseline covariates, we categorized opioid-exposure groups based on the median MME among opioid users (eg, no opioid, opioid only with total MME≤675, opioid only with total MME>675, both non-opioid and opioid with total MME≤675, non-opioid and opioid-with total MME>675). For the primary analysis, we used Cox proportional hazard regression with inverse probability of treatment weighting (IPTW) with overlap trimming to compare outcomes among those that filled an opioid and a non-opioid analgesic to those that filled only an opioid analgesic. Those that did not fill a discharge opioid were not included in the primary analysis. The probability of filling a non-opioid was calculated using a logistic regression model including all relevant covariates, including total opioid dose (using restricted cubic splines).[27–29] We then calculated an adjusted HR (aHR) with 95% CIs using robust SEs comparing opioid and non-opioid users to opioid only users. In preplanned secondary analyses, we used separate Cox proportional hazard regression models with separate IPTW to compare those that filled each non-opioid analgesic type (gabapentin, muscle relaxants, NSAIDs, acetaminophen) with opioids to those that filled opioids without that specific non-opioid type. The use of the other non-opioid analgesics was subsequently included in IPTW model as a covariate for each secondary analysis. We also conducted a post hoc comparison among those that filled an opioid and one of the two most common muscle relaxant prescriptions (cyclobenzaprine, methocarbamol). Statistical analyses were completed using SAS Enterprise Guide, V.8.2.9.4 (SAS Institute, Cary, North Carolina) and Stata statistical software (release V.17.0; Stata-Corp LLC, College Station, Texas).

RESULTS

We identified 29 489 patients aged 18–65 years with evidence of a long bone fracture that met all inclusion and exclusion criteria (2013–2020) (figure 2). Of these patients, 76.1% were identified with a primary diagnosis for at least one long bone fracture type while 23.9% were identified with a secondary diagnosis (table 1).

The most common discharge pain regimen was opioids only with total MME ≤675 (30.1%), followed by opioid only with total MME >675 (28.3%), no analgesic (18.2%), both opioid and non-opioid analgesics with MME >675 (13.1%) and MME ≤675 (8.9%) and non-opioids only (1.5%). Muscle relaxants were the most prescribed non-opioid analgesic (12.9%), followed by gabapentin (8.6%), NSAIDs (7.3%) and acetaminophen

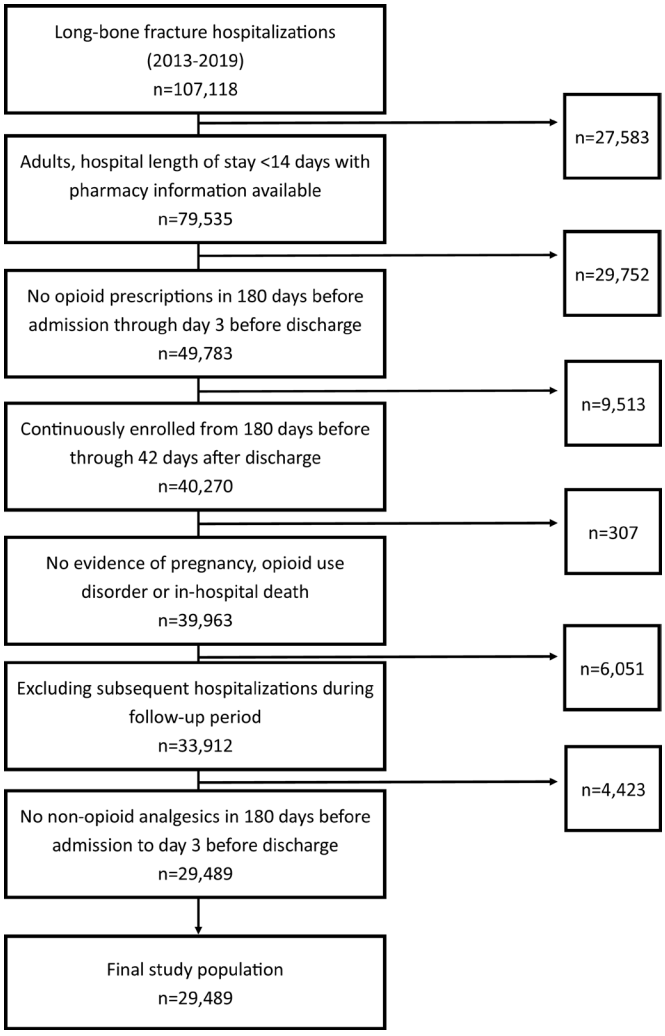

Figure 2 Population flow diagram.

(0.1%), while 5.0% filled a prescription for more than one non-opioid analgesic.

The crude rate for SOREs was highest in those filling a non-opioid analgesic in combination with an opioid analgesic with a total dose >675 MME (13.37 per 100 person-years) and lowest in those filling an opioid only with a total dose ≤675 MME (0.93 per 100 person-years) (table 2). Among the 1039 patients with SOREs during the period, the earliest SORE was persistent opioid use for 849 patients and evidence of OUD for 190 patients (table 2). In the unadjusted Cox proportional hazard model, filling a non-opioid analgesic with an opioid was associated with a 2.58 times increased risk of SORE compared with filling an opioid only (95% CI 2.26 to 2.95). In the weighted proportional hazard regression model accounting for all relevant covariates and total MME (with standardized differences <0.024 for all covariates (online supplemental appendix table 2)), filling a non-opioid analgesic with an opioid analgesic was associated with 1.63 times increased risk of SORE compared with filling an opioid analgesic only (95% CI 1.41 to 1.89).

In drug-specific comparisons among only individuals that filled an opioid analgesic, filling a gabapentin prescription was associated with a higher risk compared with those that did not in the unadjusted (HR: 3.25 (95% CI 2.80 to 3.79) and adjusted models (aHR: 1.84 (95% CI 1.48 to 2.27)). We observed similar findings for filling a muscle relaxant (crude HR: 2.42 (95% CI

Table 1 Baseline and follow-up characteristics of adult patients discharged to home after hospitalization for long bone fracture, stratified by discharge pain regimen type, Merative MarketScan Commercial Database (2013–2020), n=29 489

	No analgesic	Non-opioid only	Opioid only—low dose	Opioid only—high dose	Opioid and non-opioid—low opioid dose	Opioid and non-opioid—high opioid dose
	n=5358	n=427	n=8882	n=8347	n=2617	n=3858
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Demographics						
Sex, female	2820 (53%)	208 (49%)	4578 (52%)	3885 (47%)	1157 (44%)	1566 (41%)
Health plan type						
Employer	3764 (70%)	348 (81%)	6939 (78%)	5990 (72%)	2006 (77%)	2917 (76%)
Health plan	1594 (30%)	79 (19%)	1943 (22%)	2357 (28%)	611 (23%)	941 (24%)
Employee type						
Union	2034 (38%)	174 (41%)	3975 (45%)	3307 (40%)	1137 (43%)	1626 (42%)
Non-union	879 (16%)	81 (19%)	1388 (16%)	1260 (15%)	379 (14%)	609 (16%)
Other/unknown	2445 (46%)	172 (40%)	3519 (40%)	3780 (45%)	1101 (42%)	1623 (42%)
Employee status						
Active	2671 (50%)	283 (66%)	5359 (60%)	4827 (58%)	1773 (68%)	2478 (64%)
Retiree	962 (18%)	50 (12%)	1389 (16%)	1018 (12%)	244 (9%)	321 (8%)
COBRA/LTD	205 (4%)	23 (5%)	311 (4%)	278 (3%)	88 (3%)	160 (4%)
Other/unknown	1520 (28%)	71 (17%)	1823 (21%)	2224 (27%)	512 (20%)	899 (23%)
Hospitalization characteristics						
Surgery during hospitalization	2139 (40%)	165 (39%)	4713 (53%)	4742 (57%)	1251 (48%)	1983 (51%)
Type of fracture						
Primary fracture—one type	3534 (66%)	247 (58%)	6835 (77%)	6425 (77%)	1809 (69%)	2642 (68%)
Secondary fracture—one type	967 (18%)	87 (20%)	1060 (12%)	1002 (12%)	406 (16%)	642 (17%)
Primary fracture ->one type	176 (3%)	26 (6%)	198 (2%)	241 (3%)	119 (5%)	195 (5%)
Secondary fracture ->one type	681 (13%)	67 (16%)	789 (9%)	679 (8%)	283 (11%)	379 (10%)
Discharge prescribing characteristics						
Muscle relaxants	0 (0%)	170 (40%)	0 (0%)	0 (0%)	1340 (51%)	2297 (60%)
Gabapentin	0 (0%)	159 (37%)	0 (0%)	0 (0%)	900 (34%)	1483 (38%)
NSAIDs	0 (0%)	178 (42%)	0 (0%)	0 (0%)	966 (37%)	1012 (26%)
Acetaminophen	0 (0%)	2 (0%)	0 (0%)	0 (0%)	7 (0%)	19 (74%)
Opioid type						
Any hydrocodone	0 (0%)	0 (0%)	3467 (39%)	3817 (46%)	822 (31%)	1607 (42%)
Any oxycodone	0 (0%)	0 (0%)	5073 (57%)	5804 (70%)	1659 (63%)	2913 (76%)
Any other opioid	0 (0%)	0 (0%)	1064 (12%)	2339 (28%)	473 (18%)	1462 (38%)
Baseline comorbidities†						
Back pain	742 (14%)	67 (16%)	1000 (11%)	992 (12%)	412 (16%)	664 (17%)
Dental pain	23 (0%)	3 (1%)	21 (0%)	45 (0%)	15 (0%)	21 (0%)
Headache	241 (4%)	19 (4%)	329 (4%)	333 (4%)	140 (5%)	193 (5%)
Musculoskeletal pain	3906 (73%)	313 (73%)	5895 (66%)	5556 (67%)	1892 (72%)	2829 (73%)
Psychogenic pain	1499 (28%)	134 (31%)	2397 (27%)	2351 (28%)	870 (33%)	1405 (36%)
Neuropathic pain	601 (11%)	47 (11%)	607 (7%)	565 (7%)	272 (10%)	434 (11%)
Sickle cell/hemolytic anemia	11 (0%)	0 (0%)	16 (0%)	12 (0%)	2 (0%)	6 (0%)
Arthritis pain	212 (4%)	8 (2%)	167 (2%)	138 (2%)	38 (1%)	49 (1%)
Depression	654 (12%)	54 (13%)	796 (9%)	772 (9%)	235 (9%)	362 (9%)
Frailty	1730 (32%)	96 (22%)	1651 (19%)	1984 (24%)	438 (17%)	856 (22%)
Malignancy	381 (7%)	28 (7%)	397 (4%)	342 (4%)	122 (5%)	164 (4%)
Multiple trauma-related diagnosis	462 (9%)	64 (15%)	484 (5%)	592 (7%)	355 (14%)	578 (15%)
Year of admission						
2013	519 (10%)	18 (4%)	663 (7%)	940 (11%)	115 (4%)	266 (7%)
2014	1130 (21%)	37 (9%)	1793 (20%)	2108 (25%)	266 (10%)	710 (18%)
2015	814 (15%)	40 (9%)	1345 (15%)	1728 (21%)	231 (9%)	652 (17%)
2016	780 (15%)	53 (12%)	1287 (14%)	1493 (18%)	310 (12%)	735 (19%)
2017	684 (13%)	66 (15%)	1265 (14%)	1083 (13%)	400 (15%)	670 (17%)
2018	744 (14%)	110 (26%)	1315 (15%)	621 (7%)	590 (23%)	505 (13%)
2019	687 (13%)	103 (24%)	1214 (14%)	374 (4%)	705 (27%)	320 (8%)

Continued

Table 1 Continued

	No analgesic	Non-opioid only	Opioid only—low dose	Opioid only—high dose	Opioid and non-opioid—low opioid dose	Opioid and non-opioid—high opioid dose
	n=5358	n=427	n=8882	n=8347	n=2617	n=3858
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Region						
Northeast	1237 (23%)	78 (18%)	1905 (21%)	1161 (14%)	406 (16%)	412 (11%)
North Central	1107 (21%)	77 (18%)	1879 (21%)	1920 (23%)	500 (19%)	785 (20%)
South	1780 (33%)	153 (36%)	3038 (34%)	2975 (36%)	1048 (40%)	1686 (44%)
West	827 (15%)	77 (18%)	1345 (15%)	1433 (17%)	368 (14%)	611 (16%)
Other	407 (8%)	42 (10%)	715 (8%)	858 (10%)	295 (11%)	364 (9%)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Mean (SD) for continuous variables						
Age at admission (years)	49.3 (14.6)	47.1 (14.7)	46.8 (15.0)	44.9 (14.5)	42.7 (15.3)	41.7 (14.1)
Length of initial hospital stay, days	4.5 (3.2)	4.8 (3.3)	3.2 (2.4)	3.4 (2.4)	3.9 (2.9)	4.5 (3.2)
Total MME in 42 days after discharge	0.0 (0.0)	0.0 (0.0)	382.4 (170.2)	3965.9 (43083.4)	385.9 (172.2)	4098.4 (35363.4)
MME per day in 42 days after discharge	0.0 (0.0)	0.0 (0.0)	53.2 (28.1)	240.2 (2288.9)	50.9 (26.0)	180.3 (1738.6)
Elixhauser comorbidity score	0.3 (1.0)	0.2 (0.8)	0.1 (0.5)	0.1 (0.4)	0.1 (0.6)	0.1 (0.5)
Hospitalizations between discharge and cohort entry	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Hospitalization days between discharge and cohort entry	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Follow-up, days	277.4 (123.7)	286.7 (121.1)	297.3 (113.1)	291.1 (116.6)	294.1 (114.2)	273.3 (125.5)

*Patients could only enter cohort starting 1 July 2013.
†Baseline comorbidities measured over entirety of baseline period (day 180 before admission through day 42 after discharge).
‡Elixhauser comorbidity score[42] only calculated from inpatient hospitalization encounters during the baseline period.
COBRA, Consolidated Omnibus Budget Reconciliation Act; LTD, long-term disability; MME, morphine milligram equivalent; NSAIDs, non-steroidal anti-inflammatory drugs.

2.09 to 2.80) and aHR: 1.37 (95% CI 1.15 to 1.62)) or NSAID prescription (crude HR: 2.41 (95% CI 2.09 to 2.79) and aHR: 1.36 (95% CI 1.08 to 1.71)) compared with those that did not. In the post hoc comparison by muscle relaxant type, we did not observe a significant difference among those that filled an opioid with cyclobenzaprine versus an opioid with methocarbamol (aHR: 0.92; 95% CI 0.68 to 1.24). The low number of individuals (n=28) that filled a non-combination acetaminophen prescription precluded a secondary analysis in this subgroup. The log–log survival plots indicated no major deviations from parallel for each exposure group.

DISCUSSION

Summary of findings

We observed a significantly elevated risk of SOREs associated with filling a non-opioid analgesic in combination with an opioid analgesic compared with those that filled an opioid analgesic only, even after accounting total opioid dose (and other relevant covariates). Importantly, the highest risk was associated with the concomitant filling of gabapentin and opioid prescriptions, though significantly elevated risks were associated with the filling of muscle relaxant and NSAID prescriptions as well.

Table 2 Serious opioid-related events (SORE)1 associated with opioid and non-opioid pain regimens filled after discharge from trauma hospitalization, Merative MarketScan (2013–2020)

Pain regimen	N	SORE	Follow-up, years	SORE/100 py	95% CI	Persistent use*	MOUD/OUD diagnosis	Loss of enrollment
						N (%)	N (%)	N (%)
No opioid or non-opioid	5358	154	4069	3.78	3.23 to 4.43	112 (2.09)	42 (0.78)	5204 (97.13)
Non-opioid only	427	6	335	1.79	0.8 to 3.98	5 (1.17)	1 (0.23)	421 (98.59)
Opioid only								
Total dose≤650 MME	8882	67	7229	0.93	0.73 to 1.18	48 (0.54)	19 (0.21)	8815 (99.25)
Total dose>650 MME	8347	385	6652	5.79	5.24 to 6.4	330 (3.95)	55 (0.66)	7962 (95.39)
Opioid and non-opioid								
Total dose≤650 MME	2617	41	2107	1.95	1.43 to 2.64	28 (1.07)	13 (0.5)	2576 (98.43)
Total dose>650 MME	3858	386	2887	13.37	12.1 to 14.77	326 (8.45)	60 (1.56)	3472 (89.99)

*Persistent opioid use (>90 days' supply in 180-day window), opioid use disorder diagnosis or buprenorphine/methadone prescription fill or evidence of opioid overdose diagnosis.
MOUD, medication for opioid use disorder; OUD, opioid use disorder; PY, person-years.

Prior literature has demonstrated that opioid prescribing after surgical procedures is associated with SOREs. For example, several studies have demonstrated that patients filling prescriptions for higher initial opioid doses after cesarean delivery have a higher risk of SOREs compared with patients who filled prescriptions for opioids at low doses or who did not fill an opioid prescription at all.[25 27 30] In a meta-analysis by Lawal *et al* including 33 different studies, the authors reported that approximately 1 in 10 patients with a surgical procedure subsequently develop prolonged opioid use.[16] Specific to patients with traumatic injury, Alghnam and Castillo showed that patients with traumatic injuries are approximately 1.4 times more likely to become persistent opioid users compared with those without a traumatic injury.[11]

Due to the recognized risk of SOREs among patients using high-dose opioids after surgery or traumatic injury, increased prescribing of non-opioid analgesic medications has been observed and recommended as an option to reduce overall opioid prescribing in these populations.[21 31–36] These recommendations were based on prior work that has demonstrated equivocal perceived pain intensity and decreased opioid use among patients receiving multimodal analgesia. For example, Hamrick *et al* demonstrated that the total prescribed opioid dose among adult trauma ICU patients was reduced with the implementation of a multimodal order set without any change to overall pain scores before and after multimodal treatment.[21] Additionally, Elia *et al* performed a meta-analysis that showed that multimodal treatment reduced the use of morphine and the intensity of pain in a surgery population.[20] Cramer *et al* evaluated the use of opioids in combination with non-opioids and showed that the use of multimodal analgesia was more effective in postoperative pain control than that of an opioid regimen.[1] Additionally, the conclusions from the meta-analysis by Lawal *et al* were that patients at risk for prolonged opioid use should transition to non-opioid interventions.[16]

Though these updated recommendations have led to decreased opioid prescribing and increased non-opioid prescribing in the USA, there is a growing concern that the concomitant use of opioid and non-opioid analgesics, though intended to reduce prescribed opioids, could potentially increase the risk of SOREs after surgery or traumatic injury. In a population-based case–control study among opioid users in Canada (1997–2013), the coprescribing of gabapentin and opioids was associated with a nearly twofold increased odds of opioid-related death compared with the prescribing of opioids alone.[37] Similarly, in a nested case–control study among Medicare beneficiaries (2013–2016), at least one overlapping day of gabapentin and opioid use was associated with an increased odds of opioid-related overdose (aOR:1.74; 95% CI 1.25 to 2.41) compared with those with opioid use alone.[38] Additionally, a recent examination of 62 652 overdose deaths reported to the State Unintentional Drug Overdose Reporting System, which found a near doubling in the absolute number of drug overdose deaths for which gabapentin was detected in 2020 compared with 2019.[39 40] Thus, our study contributes to the growing concerns around concomitant opioid and gabapentin use, as we found that the coprescribing of opioids with non-opioids (including gabapentin) after long bone fracture hospitalization was not associated with a lower risk of SOREs, but rather a potentially elevated risk for developing persistent opioid use, OUD and opioid-related overdose. Importantly, this association was observed even after accounting for the total opioid dose in the 42-day baseline postdischarge period.

Strengths/limitations

The findings from our retrospective study should be considered in the context of several strengths and limitations. We used the Merative MarketScan Commercial Database to have sufficient power to detect significant differences in the risk of SOREs among patients with different discharge analgesic regimens. However, this likely reduces the generalizability of our findings to the entire population of patients with traumatic injury in the USA. Furthermore, we are unable to detect potentially fatal opioid-related overdose events, nor do we have inpatient hospitalization data to account for the severity of the injury. However, we attempt to account for the severity of injury by restricting to patients with a length of stay <14 days, identifying any evidence of surgical procedures during the hospitalization, and controlling for total opioid dose prescribed in the discharge period. Additionally, we required continuous enrollment during baseline and follow-up to allow for complete ascertainment of covariates, exposure groups and outcomes but recognize the potential for bias due to differential loss to follow-up in our study population despite the use of Cox proportional hazards regression.

We implemented a definition for persistent opioid use that has been used in prior work to study serious opioid-related harms in other populations but recognize our study findings may differ with the use of a different definition of persistent opioid use. Importantly, the algorithm used to identify medication for OUD treatment as evidence of OUD diagnosis did not distinguish between buprenorphine and methadone administered for pain and OUD treatment. Although we adjusted for many *a priori* confounders, we cannot rule out potential misclassification of certain key covariates in the study population due to the use of a 6-month baseline period and the inability to consider information not captured in the claims record. As this study is retrospective, despite our attempt to account for a long list of possible confounders using IPTW, we cannot rule out the possibility of unmeasured confounding.

Finally, though pharmacy fill data have reliably been used to identify opioid use in prior retrospective cohort studies, we recognize we were unable to measure actual analgesic use in our study, including drugs paid for out of pocket and the misuse of illicit opioids. Beaulieu-Bonneau *et al* identified significant alcohol and recreational drug use at 8 and 12 months following admission for TBI, many of whom also met criteria for substance use disorder.[41] To address this concern, we excluded all individuals with prior opioid use or evidence of OUD at baseline, whereas the development of OUD in the year after admission was a component of composite outcome. However, it is possible that we underestimated non-prescribed or illicit opioid use during the baseline period. Similarly, we were unable to account for differences in the use of other over the counter analgesics (eg, acetaminophen, NSAIDs). Importantly, many prescription drug plans do not cover acetaminophen, leading many patients to purchase acetaminophen over the counter, a practice that may explain why so few individuals had evidence of a filled single-entity acetaminophen prescription during the exposure period. Furthermore, as it is difficult to separate the therapeutic benefit of acetaminophen and opioids in combination, and since our exposure of interest was filling a standalone non-opioid prescription in addition to an opioid-analgesic prescription (single-entity or combination), we classified combination opioid-acetaminophen drugs as opioids only in our analysis. An additional limitation is that Merative MarketScan Commercial Database does not include information on inpatient analgesic administration and

dosing and so we were unable to account for inpatient analgesic use in the analysis.

CONCLUSION

Compared with those that filled only an opioid analgesic prescription after a long bone fracture hospitalization, patients who filled both opioid and non-opioid analgesics in the discharge period were at an increased risk of developing a SORE. Thus, the concomitant prescribing of non-opioid analgesics with opioids did not lower the risk of subsequent SOREs.

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REFERENCES

1 Cramer JD, Barnett ML, Anne S, Bateman BT, Rosenfeld RM, Tunkel DE, Brenner MJ. Multimodal analgesia as first-line therapy after otolaryngology operations: primer on nonsteroidal anti-inflammatory drugs (NSAIDs). *Otolaryngol Head Neck Surg* 2021;164:712–9.
2 Jivraj NK, Raghavji F, Bethell J, Wijeysundera DN, Ladha KS, Bateman BT, Neuman MD, Wunsch H. Persistent postoperative opioid use: a systematic literature search of definitions and population-based cohort study. *Anesthesiology* 2020;132:1528–39.
3 Tanz LJ, Dinwiddie AT, Mattson CL, O'Donnell J, Davis NL. Drug overdose deaths among persons aged 10-19 years - United States, July 2019-December 2021. *MMWR Morb Mortal Wkly Rep* 2022;71:1576–82.
4 Brummett CM, Waljee JF, Goesling J, Moser S, Lin P, Englesbe MJ, Bohnert ASB, Kheterpal S, Nallamothu BK. New persistent opioid use after minor and major surgical procedures in US adults. *JAMA Surg* 2017;152:e170504.
5 Dunn LK, Taylor DG, Smith SJ, Skojec AJ, Wang TR, Chung J, Hanak MF, Lacomis CD, Palmer JD, Ruminski C, *et al*. Persistent post-discharge opioid prescribing after traumatic brain injury requiring intensive care unit admission: a cross-sectional study with longitudinal outcome. *PLoS One* 2019;14:e0225787.
6 Peahl AF, Dalton VK, Montgomery JR, Lai Y-L, Hu HM, Waljee JF. Rates of new persistent opioid use after vaginal or cesarean birth among US women. *JAMA Netw Open* 2019;2:e197863.
7 Sun EC, Darnall BD, Baker LC, Mackey S. Incidence of and risk factors for chronic opioid use among opioid-naive patients in the postoperative period. *JAMA Intern Med* 2016;176:1286–93.
8 Badin D, Ortiz-Babilonia CD, Gupta A, Leland CR, Musharbash F, Parrish JM, Aiyer AA. Prescription patterns, associated factors, and outcomes of opioids for operative foot and ankle fractures: a systematic review. *Clin Orthop Relat Res* 2022;480:2187–201.
9 Kwok AK, O'Hara NN, Pollak AN, O'Hara LM, Herman A, Welsh CJ, Slobogean GP. Are injured workers with higher rehabilitation service utilization less likely to be persistent opioid users? A cross-sectional study. *BMC Health Serv Res* 2019;19:32.
10 Hornik ES, Thode HC, Singer AJ. Analgesic use in ED patients with long-bone fractures: a national assessment of racial and ethnic disparities. *Am J Emerg Med* 2023;69:11–6.
11 Alghnam S, Castillo R. Traumatic injuries and persistent opioid use in the USA: findings from a nationally representative survey. *Inj Prev* 2017;23:87–92.
12 Gossett TD, Finney FT, Hu HM, Waljee JF, Brummett CM, Walton DM, Holmes JR. New persistent opioid use and associated risk factors following treatment of ankle fractures. *Foot Ankle Int* 2019;40:1043–51.
13 Anoushiravani AA, Kim KY, Roof M, Chen K, O'Connor CM, Vigdorchik J, Schwarzkopf R. Risk factors associated with persistent chronic opioid use following THA. *Eur J Orthop Surg Traumatol* 2020;30:681–8.
14 Graves JM, Mackelprang JL, Moore M, Abshire DA, Rivara FP, Jimenez N, Fuentes M, Vavilala MS. Rural-urban disparities in health care costs and health service utilization following pediatric mild traumatic brain injury. *Health Serv Res* 2019;54:337–45.
15 Inacio MCS, Hansen C, Pratt NL, Graves SE, Roughead EE. Risk factors for persistent and new chronic opioid use in patients undergoing total hip arthroplasty: a retrospective cohort study. *BMJ Open* 2016;6:e010664.
16 Lawal OD, Gold J, Murthy A, Ruchi R, Bavry E, Hume AL, Lewkowitz AK, Brothers T, Wen X. Rate and risk factors associated with prolonged opioid use after surgery: a systematic review and meta-analysis. *JAMA Netw Open* 2020;3:e207367.
17 Liu S, Genel F, Harris IA, Patanwala AE, Adie S, Stevens J, Hassett G, Luckie K, Penm J, Naylor J. Effectiveness of pharmacological-based interventions, including education and prescribing strategies, to reduce subacute pain after total hip or knee arthroplasty: a systematic review of randomized controlled trials. *Pain Med* 2022;23:1476–88.
18 Seal KH, Bertenthal D, Barnes DE, Byers AL, Gibson CJ, Rife TL, Yaffe K, Chronic Effects of Neurotrauma Consortium Study Group. Traumatic brain injury and receipt of prescription opioid therapy for chronic pain in Iraq and Afghanistan veterans: do clinical practice guidelines matter. *J Pain* 2018;19:931–41.
19 von Oelreich E, Eriksson M, Brattström O, Sjölund K-F, Discacciati A, Larsson E, Oldner A. Risk factors and outcomes of chronic opioid use following trauma. *Br J Surg* 2020;107:413–21.
20 Elia N, Lysakowski C, Tramèr MR. Does Multimodal analgesia with acetaminophen, nonsteroidal antiinflammatory drugs, or selective cyclooxygenase-2 inhibitors and patient-controlled analgesia morphine offer advantages over morphine alone? Meta-analyses of randomized trials. *Anesthesiology* 2005;103:1296–304.
21 Hamrick KL, Beyer CA, Lee JA, Cocanour CS, Duby JJ. Multimodal analgesia and opioid use in critically ill trauma patients. *J Am Coll Surg* 2019;228:769–75.
22 Polomano RC, Fillman M, Giordano NA, Vallerand AH, Nicely KLW, Jungquist CR. Multimodal analgesia for acute postoperative and trauma-related pain. *Am J Nurs* 2017;117:S12–26.
23 Gedda C, Nygren J, Garpenbeck A, Hoffström L, Thorell A, Soop M. Multimodal analgesia bundle and postoperative opioid use among patients undergoing colorectal surgery. *JAMA Netw Open* 2023;6:e2332408.
24 Murphy PB, Kasotakis G, Haut ER, Miller A, Harvey E, Hasenboehler E, Higgins T, Hoegler J, Mir H, Cantrell S, *et al*. Efficacy and safety of non-Steroidal anti-inflammatory drugs (NSAIDs) for the treatment of acute pain after orthopedic trauma: a practice management guideline from the Eastern Association for the Surgery of Trauma and the Orthopedic Trauma Association. *Trauma Surg Acute Care Open* 2023;8:e001056.
25 Osmundson SS, Min JY, Wiese AD, Hawley RE, Mitchel E, Patrick SW, Samuels LR, Griffin MR, Grijalva CG. Opioid prescribing after childbirth and risk for serious opioid-related events: a cohort study. *Ann Intern Med* 2020;173:412–4.
26 Wiese AD, Osmundson SS, Mitchel E, Adgent M, Phillips S, Patrick SW, Horn A, Samuels LR, Griffin MR, Grijalva CG. Prescription opioid dose after vaginal delivery and the risk of serious opioid-related events: a retrospective cohort study. *Womens Health Issues* 2021;31:376–83.
27 Wiese AD, Osmundson SS, Mitchel E, Adgent M, Phillips S, Patrick SW, Spieker AJ, Grijalva CG. The risk of serious opioid-related events associated with common opioid prescribing regimens in the postpartum period after cesarean delivery. *Am J Obstet Gynecol MFM* 2021;3:100475.
28 Jenkner C, Lorenz E, Becher H, Sauerbrei W. Modeling continuous covariates with a "spike" at zero: bivariate approaches. *Biom J* 2016;58:783–96.
29 Lorenz E, Jenkner C, Sauerbrei W, Becher H. Modeling variables with a spike at zero: examples and practical recommendations. *Am J Epidemiol* 2017;185:650–60.
30 Bateman BT, Franklin JM, Bykov K, Avorn J, Shrank WH, Brennan TA, Landon JE, Rathmell JP, Huybrechts KF, Fischer MA, *et al*. Persistent opioid use following cesarean delivery: patterns and predictors among opioid-naïve women. *Am J Obstet Gynecol* 2016;215:353.

31 Bohnert ASB, Guy GP, Losby JL. Opioid prescribing in the United States before and after the centers for disease control and prevention's 2016 opioid guideline. *Ann Intern Med* 2018;169:367–75.
32 Encinosa W, Bernard D, Selden TM. Opioid and non-opioid analgesic prescribing before and after the CDC's 2016 opioid guideline. *Int J Health Econ Manag* 2022;22:1–52.
33 Ahmadi A, Bazargan-Hejazi S, Heidari Zadie Z, Euasobhon P, Ketumarn P, Karbasfrushan A, Amini-Saman J, Mohammadi R. Pain management in trauma: a review study. *J Inj Violence Res* 2016;8:89–98.
34 Gardner WT, MacDonald DRW, Kennedy MJ, Faulkner AC, McIntyre JR, Forget P, Aitken SA, Stevenson IM, On Behalf Of The Score Collaborative. Opioid prescription following wrist and ankle fracture fixation in Scotland-tradition prevails. *J Clin Med* 2022;11:468.
35 Karamchandani K, Klick JC, Linskey Dougherty M, Bonavia A, Allen SR, Carr ZJ. Pain management in trauma patients affected by the opioid epidemic: a narrative review. *J Trauma Acute Care Surg* 2019;87:430–9.
36 Rajput K, Shergill S, Chow RM, Vadivelu N, Kaye AD. Enhanced recovery after surgery: opioid sparing strategies after discharge: a review. *Curr Pain Headache Rep* 2022;26:93–102.
37 Gomes T, Juurlink DN, Antoniou T, Mamdani MM, Paterson JM, van den Brink W. Gabapentin, opioids, and the risk of opioid-related death: a population-based nested case-control study. *PLoS Med* 2017;14:e1002396.
38 Olopoenia A, Camelo-Castillo W, Qato DM, Adekoya A, Palumbo F, Sera L, Simoni-Wastila L. Adverse outcomes associated with concurrent gabapentin, opioid, and benzodiazepine utilization: a nested case-control study. *Lancet Reg Health Am* 2022;13:100302.
39 Kuehn BM. Growing role of gabapentin in opioid-related overdoses highlights misuse potential and off-label prescribing practices. *JAMA* 2022;328:1283.
40 Mattson CL, Chowdhury F, Gilson TP. Notes from the field: trends in Gabapentin detection and involvement in drug overdose deaths - 23 States and the District of Columbia, 2019-2020. *MMWR Morb Mortal Wkly Rep* 2022;71:664–6.
41 Beaulieu-Bonneau S, St-Onge F, Blackburn MC, Banville A, Paradis-Giroux AA, Ouellet MC. Alcohol and drug use before and during the first year after traumatic brain injury. *J Head Trauma Rehabil* 2018;33:E51–60.
42 van Walraven C, Austin PC, Jennings A, Quan H, Forster AJ. A modification of the Elixhauser Comorbidity measures into a point system for hospital death using administrative data. *Medical Care* 2009;47:626–33.