Identification and quantification of prescription opioid-related drug-drug interactions in electronic healthcare data

HARVARD UNIVERSITY

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DISSERTATION ACCEPTANCE CERTIFICATE

The undersigned, appointed by the
Committee on Higher Degrees in Population Health Sciences,
have examined a dissertation entitled

"Identification and Quantification of Prescription Opioid-Related Drug-Drug Interactions in Electronic Healthcare Data"

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Abstract

Identification and Quantification of Prescription Opioid-Related Drug-Drug Interactions in Electronic Healthcare Data

Polypharmacy is common among patients taking prescription opioids long-term, and the co-dispensing of interacting medications may further increase opioid overdose risk. To identify non-opioid medications that may increase opioid overdose risk in this population, we conducted a case-crossover-based screening of electronic claims data from IBM® MarketScan® and Optum© Clinformatics® Data Mart spanning 2003 through 2019. Eligible patients were 18 years of age or older and had at least 180 days of continuous enrollment and 90 days of prescription opioid use immediately before an opioid overdose resulting in an emergency room visit or hospitalization. The main analysis quantified the odds ratio (OR) between opioid overdose and each non-opioid medication dispensed in the 90 days immediately before the opioid overdose date after adjustment for prescription opioid dosage and benzodiazepine co-dispensing. Additional analyses restricted to patients without cancer diagnoses and individuals who used only oxycodone for 90 days immediately before the opioid overdose date. The false discovery rate (FDR) was used to account for multiple testing. We identified 24,866 individuals who experienced opioid overdose. Baclofen (OR 1.56; FDR < 0.01; 95% confidence interval (CI), 1.29 to 1.89), lorazepam (OR 1.53; FDR < 0.01; 95% CI, 1.25 to 1.88), and gabapentin (OR 1.16; FDR = 0.09; 95% CI, 1.04 to 1.28), among other non-opioid medications, were associated with opioid overdose. Similar patterns

were observed in non-cancer patients and individuals who used only oxycodone. Interventions may focus on prescribing safer alternatives when a potential for interaction exists.

The concomitant use of prescription opioids and skeletal muscle relaxants has been associated with opioid overdose. Little data exist on the head-to-head safety of these drug combinations. Our objective was to compare the risk of opioid overdose among patients on long-term opioid therapy who concurrently initiate skeletal muscle relaxants. We conducted a new user, active comparator cohort study spanning data from 2000 to 2019. The primary analysis quantified opioid overdose risk across seven prescription opioid-skeletal muscle relaxant therapies and a negative control outcome (sepsis) to assess potential confounding by unmeasured illicit opioid use. Secondary analyses evaluated two- and five-group comparisons in patients with similar baseline characteristics; individuals without prior recorded substance abuse; and subgroups stratified by baseline opioid dosage, benzodiazepine co-dispensing, and oxycodone or hydrocodone use. We used healthcare utilization data from four US commercial and public insurance databases. Individuals were required to have at least 180 days of continuous enrollment and at least 90 days of continuous prescription opioid use immediately before and on the date of skeletal muscle relaxant initiation. Exposures included the concomitant use of prescription opioids and skeletal muscle relaxants. The main outcomes and measures were the hazard ratio (HR) and bootstrapped 95% confidence interval (CI) of opioid overdose resulting in an emergency visit or hospitalization. The weighted HR of opioid overdose relative to cyclobenzaprine was 2.52 (95% CI 1.29-4.90) for baclofen; 1.64 (95% CI 0.81-3.34) for carisoprodol; 1.14

(95% CI 0.53-2.46) for chlorzoxazone/orphenadrine; 0.46 (95% CI 0.17-1.24) for metaxalone; 1.00 (95% CI 0.45-2.20) for methocarbamol; and 1.07 (95% CI 0.49-2.33) for tizanidine in the 30-day intention-to-treat analysis. Findings were similar in the as-treated analysis, two- and five-group comparisons, and in patients without prior recorded substance abuse. None of the therapies relative to cyclobenzaprine were associated with sepsis, and no subgroups indicated increased risk of opioid overdose. Concomitant use of prescription opioids and baclofen relative to cyclobenzaprine is associated with opioid overdose. Clinical interventions may focus on prescribing alternatives in the same drug class or providing access to opioid antagonists if treatment with both medications is necessary for pain management.

The concomitant use of prescription opioids and select antibiotics has been associated with opioid overdose. It is unclear whether this increased risk persists after accounting for underlying infection. Our objective was to compare the risk of opioid overdose among patients who concurrently initiate antibiotics on long-term opioid therapy. We conducted a new user, active comparator cohort study spanning data from 2000 to 2019. The primary analysis quantified the relative risk of opioid overdose between sulfamethoxazole/trimethoprim, nitrofurantoin, and fluoroquinolones among patients diagnosed with urinary tract infection (UTI). Matching weights were used to adjust for confounding, and intention-to-treat analyses were conducted with a maximum follow-up of 30 days immediately after antibiotic initiation. Secondary analyses evaluated the comparative risk of sepsis as a negative control outcome to account for unmeasured confounding; subgroups stratified by baseline opioid dosage; and patients without prior recorded substance abuse. We used healthcare utilization data from four

US commercial and public insurance databases. Individuals were required to have at least 180 days of continuous enrollment and 90 days of continuous prescription opioid use immediately before and on the date of antibiotic initiation. Diagnosis for UTI was required within three days prior to or on the antibiotic dispensing date. Exposures included the concomitant use of prescription opioids and antibiotics. The main outcomes and measures were the weighted hazard ratio (HR) and 95% bootstrapped confidence interval (CI) for emergency department visits or hospitalizations for opioid overdose. We identified 555,183 UTI patients across the three treatment groups who contributed to the weighted analysis. The mean age at antibiotic initiation was 65 years, and 93% were female in the weighted population. Co-prescription of opioids and nitrofurantoin relative to sulfamethoxazole/trimethoprim was unassociated with opioid overdose (pooled weighted HR 1.06, 95% CI 0.77-1.46). Results were similar for fluoroquinolones relative to sulfamethoxazole/trimethoprim. Nitrofurantoin co-prescription relative to sulfamethoxazole/trimethoprim was associated with sepsis (pooled weighted HR 1.18, 95% CI 1.07-1.30), which persisted in patients without prior recorded substance abuse. No increased risk of opioid overdose was observed for patients prescribed high opioid dosages. Additional studies are needed to disentangle drug-drug interactions from underlying infection in potentially increasing opioid overdose risk.

Table of Contents

Co-prescription of opioids with other medications and risk of opioid overdose

Background

Despite appropriate use of prescription opioids, patients on long-term opioid therapy may be at high risk of opioid overdose.[1] The growing prevalence of polypharmacy among those on long-term opioid therapy may also predispose patients to drug-drug interactions that increase opioid overdose risk.[2-4] Among long-term prescription opioid users who overdosed between 2015 and 2017, 74% were taking four or more non-opioid medications in addition to an average of 2.5 prescription opioids at the time of opioid overdose (**Figure S1.1**). The most commonly co-dispensed non-opioid medications included gabapentin, alprazolam, and clonazepam, which cause central nervous system (CNS) depression and may increase opioid overdose risk (**Table S1.1**).[5,6]

Over the last 20 years, opioid overdose deaths involving other drug classes have also increased; most commonly, benzodiazepines were involved in 33% of all prescription opioid overdose deaths in 2017.[7,8] Gabapentinoids and muscle relaxants have also been prescribed with opioids to optimize pain relief, but concurrent use has been associated with opioid overdose.[9-13] Aside from these CNS-depressing medications, little evidence is available regarding the clinical relevance of interactions involving other drug combinations that may increase opioid overdose risk.[14] In addition to contributing to CNS depression, concurrent use of other medications could lead to changes in opioid plasma concentration that may trigger an opioid overdose event.

The objective of this study was to identify non-opioid medications that may increase the risk of opioid overdose in patients on long-term opioid therapy.

Methods

Data Source

We used data spanning January 1, 2003 to December 31, 2018 from the IBM® MarketScan® Database and January 1, 2004 to December 31, 2019 from Optum© Clinformatics® Data Mart. Both databases contain longitudinal, de-identified administrative pharmacy and medical claims for a large commercially insured population across all 50 states, including data for retirees with Medicare supplemental insurance paid by employers.

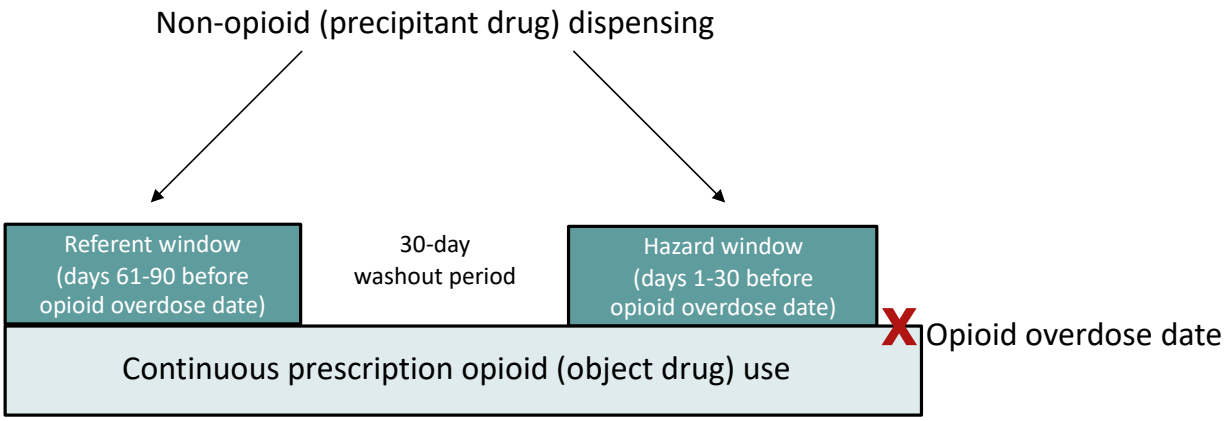
This study was approved by the Institutional Review Board at Brigham and Women's Hospital.

Study Design

This screening approach was based on the case-crossover design, which intended to identify non-opioid (precipitant) drugs that may lead to opioid overdose when taken with a drug that is affected by the interaction (object drug – i.e., opioids).[15] The design retrospectively evaluates patients who had the event by comparing exposure during a hazard window immediately before the event to that during a referent window in the past.[16] Data collection was restricted to patients who experienced their first eligible opioid overdose in the database and compared exposure to each potential precipitant

drug in a 30-day hazard window (days 1-30 before the opioid overdose date) to that in an earlier 30-day referent window (days 61-90 before the opioid overdose date) (**Figure 1.1**).[16]

Figure 1.1 Case-crossover-based screening framework to identify prescription opioid-related drug-drug interactions associated with opioid overdose.



Caption: Patients who experienced opioid overdose immediately following at least 90 days of continuous prescription opioid use were evaluated with respect to non-opioid medication dispensings in a 30-day hazard window and 30-day referent window.

Windows of 30 days were selected to capture most chronically and acutely taken drugs while focusing on medications that may have triggered an interaction within a short time period before opioid overdose.[15] A 30-day washout between the hazard and referent windows was incorporated to prevent autocorrelation in precipitant drug exposure and potential carryover effects.[15,17] Since each case serves as his/her own control, the case-crossover design accounts for between-individual and within-individual confounding by characteristics that remain constant over the 90-day observation period.[18] The 30-day hazard and referent windows within close proximity also limit the

magnitude of confounding by factors that change over the long term.[19] This screening approach was previously evaluated in other test cases and identified known drug-drug interactions without generating false positive signals.[15]

Study Population

We identified patients by their first eligible opioid overdose at age 18 years or older with at least 180 days of continuous health plan enrollment immediately preceding the opioid overdose date. The study population was further restricted to patients with 90-day continuous prescription opioid use to mitigate confounding by indication for opioids.[15] Continuous use was defined by dispensing dates with any dosage and days' supply that covered each of 90 consecutive days immediately before and on the opioid overdose date (**Table S1.2**). Grace periods of up to 14 days were incorporated between the end of one prescription and beginning of the subsequent prescription. Patients were allowed to switch between different prescription opioids in the primary analysis.

Exposure Assessment

Exposure to each potential precipitant drug was defined based on fill dates corresponding to at least one dispensing that occurred within the 30-day hazard and/or referent windows. We evaluated all prescriptions dispensed within the windows as potential precipitant drugs except other opioid-containing products, dietary supplements, devices, irrigation solutions, and powder and topical formulations. Screening was performed at the generic drug name level.

Outcome Assessment

Opioid overdose was defined using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes for an episode resulting in hospitalization or an emergency room visit (**Table S1.3**).[20] ICD-9-CM codes used to define opioid overdose, together with codes for poisoning by heroin, have been found to have a sensitivity of 25.0%, specificity of 99.9%, positive predictive value of 84.6%, and negative predictive value of 99.0%.[21] The ICD-10-CM codes for poisoning involving opioids other than heroin have a positive predictive value of 79.4%.[22]

Patient Characteristics

We assessed the following characteristics over the 180 days immediately before and on the opioid overdose date: demographic characteristics (age on the opioid overdose date and sex); diagnosis of opioid dependence; diagnosis of opioid abuse; other comorbidities, including anxiety, bipolar disorder, and depression; and diagnoses of pain conditions.

Statistical Analyses

We used methods for matched data to estimate the odds ratio (OR) for the association between each potential precipitant drug and opioid overdose.[17] In a case-crossover design, the Mantel-Haenszel OR can be calculated as the ratio of opioid overdose cases who were exposed in the hazard window and unexposed in the referent window to opioid overdose cases who were unexposed in the hazard window and exposed in

the referent window.[17] We used McNemar's test for matched data to obtain the p-value for the null hypothesis of no association. Only non-opioid medications with at least 100 patients with discordant exposure across the windows were analyzed to avoid statistically unstable estimates.

P-values were adjusted for multiple testing using the false discovery rate (FDR).[23] The FDR controls the average proportion of rejected tests that are false positives and is preferred to more conservative methods for type I error control in exploratory analyses.[23,24] Specifically, the FDR minimizes false negatives relative to other multiple testing adjustment approaches and may be preferred in a screening setting to identify as many true positives as possible with sufficient statistical power.[23,24] We ranked p-values for all potential precipitant drugs in ascending order and calculated FDR q-values by dividing each p-value by its rank number and multiplying by the total number of comparisons.[23] Screening results were evaluated in ascending order to identify non-opioid medications associated with opioid overdose (OR > 1).

A limitation of the case-crossover design is potential confounding by factors that change over time within an individual in a way that is associated with the exposure of interest and are associated with the outcome. Two possible sources of within-individual time-varying confounding in this setting include changes in prescription opioid dosage and benzodiazepine co-dispensing, which may contribute to opioid overdose.[25] To account for changes in prescription opioid dosage over the 90-day observation period, we quantified patient-level available morphine milligram equivalents (MMEs) based on

prescription opioids dispensed to patients in the 30-day hazard and referent windows.[26] Screening was restricted to patients with absolute changes of ≤ 300 MMEs between the hazard and referent windows. This amounts to a ≤ 10 MME/day change in opioid dosage over a 30-day period, on average, which was considered a small enough increase to avoid substantial confounding by prescription opioid dosage. We accounted for benzodiazepine co-dispensing by measuring exposure based on dispensing dates that occurred within each window. Conditional logistic regression was used to obtain ORs additionally adjusted for benzodiazepine co-dispensing and Wald chi-square p-values for each potential precipitant drug.

Secondary Analyses

We conducted two pre-specified additional analyses. Individuals diagnosed with cancer and who may be at the end of life could initiate prescriptions for certain conditions (e.g., pain or anxiety), which may lead to bias for non-opioid medications used for the treatment of these indications.[27] We restricted screening to patients without diagnosis codes for cancer to limit bias associated with time-varying prognosis. Additionally, therapeutic class-based evaluation of pharmacodynamic drug interactions in the primary analysis may not detect pharmacokinetic interactions that are drug-specific since different opioids are metabolized by different liver enzymes.[28] Switching to more potent prescription opioids during the observation period in the primary analysis may also contribute to opioid overdose, which could cause confounding if switching is associated with the use of other medications of interest. To address these issues, we conducted a

sensitivity analysis restricted to patients who continuously used only oxycodone during the 90-day observation period and opioid overdose date.

Results

We identified 24,866 patients who experienced their first opioid overdose following at least 90 days of continuous prescription opioid use (**Figure S1.2**). The mean age at opioid overdose was 56.5 years, 63% were female, and 94% had a diagnosis code for at least one chronic pain condition. One in four patients had either opioid dependence or abuse codes recorded in the 180 days immediately before or on the opioid overdose date. Patients were dispensed an average of 5.2 (standard deviation: 3.5) non-opioid medications in addition to their prescription opioids in the 90 days immediately before the event (**Table 1.1**).

Table 1.1 Characteristics of individuals who experienced opioid overdose on long-term opioid therapy, 2003-2019 (n = 24,866)

Characteristic	**No. (%)**
Age, mean years (SD)	56.53 (13.31)
Female	15,597 (62.72)
Male	9,268 (37.27)
Unknown	1 (< 0.10)
Comorbidities	
Opioid abuse	1,601 (6.44)
Opioid dependence	5,037 (20.26)
Alcohol abuse	2,806 (11.28)
Anxiety	10,102 (40.63)
Bipolar disorder	3,184 (12.80)
Cancer	2,398 (9.64)
Chronic renal insufficiency	3,498 (14.07)
Congestive heart failure	4,005 (16.11)
Dementia	2,362 (9.50)
Depression	12,367 (49.73)

Table 1.1 (Continued)

Characteristic	No. (%)
Comorbidities	
Liver disease	3,603 (14.49)
Psychosis	2,983 (12.00)
Pain diagnoses	
Back and neck pain	19,035 (76.55)
Diabetic neuropathy	2,409 (9.69)
Fibromyalgia	4,516 (18.16)
Osteoarthritis	7,653 (30.78)
Rheumatoid arthritis	1,465 (5.89)
Postherpetic neuralgia	118 (0.47)
Other arthritis	16,332 (65.68)
Other neuropathic pain	11,253 (45.25)

Overall, 63.4% and 61.4% of patients were dispensed four or more distinct non-opioid prescriptions in the hazard and referent windows, respectively (**Table S1.4**). Individuals were commonly co-dispensed gabapentin, alprazolam, and zolpidem, among other non-opioid medications, in the hazard and referent windows (**Table S1.5**).

From 822 candidate drugs, we evaluated 179 non-opioid medications as potential precipitant drugs after exclusion of medications with fewer than 100 patients with discordant exposure across the windows in the unadjusted analysis and 114 non-opioid drugs following the same exclusion in the adjusted analysis. In the unadjusted analyses, baclofen (OR 1.52; FDR < 0.01; 95% confidence interval (CI), 1.34 to 1.71), alprazolam (OR 1.31; FDR < 0.01; 95% CI, 1.19 to 1.43), clonazepam (OR 1.53; FDR < 0.01; 95% CI, 1.37 to 1.71), and lorazepam (OR 1.41; FDR < 0.01; 95% CI, 1.26 to 1.59) were among several non-opioid medications associated with opioid overdose. After exclusion of patients with large changes in prescription opioid dosage and adjustment for benzodiazepine co-dispensing, baclofen (OR 1.56; FDR < 0.01; 95% CI,

1.29 to 1.89), alprazolam (OR 1.38; FDR < 0.01; 95% CI, 1.19 to 1.61), clonazepam (OR 1.51; FDR < 0.01; 95% CI, 1.26 to 1.81), lorazepam (OR 1.53; FDR < 0.01; 95% CI, 1.25 to 1.88), and sulfamethoxazole/trimethoprim (OR 1.47; FDR < 0.01; 95% CI, 1.20 to 1.79) were highly ranked with OR > 1. Other non-opioid medications associated with opioid overdose in the adjusted analysis included escitalopram (OR 1.40; FDR = 0.05; 95% CI, 1.12 to 1.73), cephalexin (OR 1.30; FDR = 0.08; 95% CI, 1.08 to 1.57), gabapentin (OR 1.16; FDR = 0.09; 95% CI, 1.04 to 1.28), prednisone (OR 1.22; FDR = 0.08; 95% CI, 1.05 to 1.40), and propranolol (OR 1.60; FDR = 0.10; 95% CI, 1.12 to 2.28) (**Table 1.2**).

Table 1.2 Potentially interacting non-opioid medications by ascending p-value of the adjusted odds ratio for the association with opioid overdose > 1 in individuals on long-term opioid therapy (n = 24,866)

Rank	Potential precipitant drug	Number of patients with discordant exposure	Unadjusted			Number of patients with discordant exposure	Adjusted*		
			Odds ratio	P-value	FDR q-value		Odds ratio	P-value	FDR q-value
1	Baclofen	1,092	1.52	< 0.01	< 0.01	454	1.56	< 0.01	< 0.01
2	Alprazolam	1,897	1.31	< 0.01	< 0.01	713	1.38	< 0.01	< 0.01
3	Clonazepam	1,306	1.53	< 0.01	< 0.01	478	1.51	< 0.01	< 0.01
4	Lorazepam	1,175	1.41	< 0.01	< 0.01	392	1.53	< 0.01	< 0.01
5	Sulfamethoxazole/ trimethoprim	1,001	1.21	< 0.01	0.04	410	1.47	< 0.01	< 0.01
6	Escitalopram	883	1.12	0.09	0.28	341	1.40	< 0.01	0.05
7	Cephalexin	1,176	1.14	0.02	0.13	458	1.30	0.01	0.08
8	Gabapentin	3,497	1.15	< 0.01	< 0.01	1,430	1.16	0.01	0.09
9	Prednisone	1,888	1.17	< 0.01	0.01	765	1.22	0.01	0.08
10	Propranolol	290	1.18	0.16	0.36	130	1.60	0.01	0.10

Among the 22,468 patients without diagnosis codes for cancer, similar non-opioid medications were associated with opioid overdose. After exclusion of patients with large changes in prescription opioid dosage and adjustment for benzodiazepine co-dispensing, alprazolam (OR 1.39, FDR < 0.01; 95% CI, 1.19 to 1.63), clonazepam (OR 1.48; FDR < 0.01; 95% CI, 1.23 to 1.79), lorazepam (OR 1.61; FDR < 0.01; 95% CI, 1.30 to 2.00), baclofen (OR 1.47; FDR < 0.01; 95% CI, 1.21 to 1.79), and sulfamethoxazole/trimethoprim (OR 1.51; FDR < 0.01; 95% CI, 1.22 to 1.86) were highly ranked with OR > 1. Additional non-opioid medications associated with opioid overdose in the adjusted analysis included cephalexin (OR 1.38; FDR = 0.02; 95% CI, 1.13 to 1.67), propranolol (OR 1.77, FDR = 0.04; 95% CI, 1.21 to 2.58), gabapentin (OR 1.17, FDR = 0.05; 95% CI, 1.05 to 1.31), prednisone (OR 1.23; FDR = 0.08; 95% CI, 1.06 to 1.43), and ondansetron (OR 1.28; FDR = 0.08; 95% CI, 1.06 to 1.54) (**Table 1.3**).

Table 1.3 Potentially interacting non-opioid medications by ascending p-value of the adjusted odds ratio for the association with opioid overdose > 1 in individuals without cancer diagnoses (n = 22,468)

Rank	Potential precipitant drug	Number of patients with discordant exposure	Unadjusted			Number of patients with discordant exposure	Adjusted*		
			Odds ratio	P-value	FDR q-value		Odds ratio	P-value	FDR q-value
1	Alprazolam	1,703	1.29	< 0.01	< 0.01	658	1.39	< 0.01	< 0.01
2	Clonazepam	1,207	1.50	< 0.01	< 0.01	451	1.48	< 0.01	< 0.01
3	Lorazepam	992	1.43	< 0.01	< 0.01	350	1.61	< 0.01	< 0.01
4	Baclofen	985	1.48	< 0.01	< 0.01	418	1.47	< 0.01	< 0.01
5	Sulfamethoxazole/ trimethoprim	884	1.20	0.01	0.07	369	1.51	< 0.01	< 0.01
6	Cephalexin	1,060	1.16	0.01	0.11	420	1.38	< 0.01	0.02
7	Propranolol	267	1.28	0.04	0.19	118	1.77	< 0.01	0.04
8	Gabapentin	3,113	1.14	< 0.01	0.01	1,302	1.17	< 0.01	0.05
9	Prednisone	1,655	1.16	< 0.01	0.03	682	1.23	0.01	0.08
10	Ondansetron	1,214	1.28	< 0.01	< 0.01	468	1.28	0.01	0.08

When screening was restricted to the 4,030 patients who used only oxycodone during the 90-day observation period and opioid overdose date, furosemide (OR 1.31; FDR = 0.53; 95% CI, 0.97 to 1.77), gabapentin (OR 1.21; FDR = 0.38; 95% CI, 0.97 to 1.51), and cyclobenzaprine (OR 1.31; FDR = 0.61; 95% CI, 0.89 to 1.94) were among the top-ranked non-opioid medications associated with opioid overdose in the adjusted analysis. However, the estimates were generally underpowered due to the smaller number of patients with discordant exposure to each potential precipitant drug.

Discussion

In this case-crossover-based screening of two large administrative claims databases in the US, we identified several non-opioid medications associated with opioid overdose among patients using prescription opioids long-term. Certain muscle relaxants, benzodiazepines, antibiotics, and gabapentinoids were among the top-ranked potential precipitant drugs after exclusion of patients with large changes in prescription opioid dosage and adjustment for benzodiazepine co-dispensing. We observed similar results in patients without cancer diagnosis codes and individuals who used only oxycodone continuously in the 90 days immediately before and on the opioid overdose date.

Several benzodiazepines were among the top-ranked non-opioid medications in our screening study and are known to increase the risk of opioid overdose in patients taking opioids. Between 2011 and 2016, nearly 30% of fatal overdoses in the US implicated opioids and benzodiazepines, which are suspected to cause additive respiratory depression.[29,30] The Centers for Disease Control and Prevention (CDC) published

guidelines in 2016 recommending that clinicians avoid prescribing opioids with benzodiazepines or provide access to opioid antagonists when both medications are necessary.[31] Gabapentin was also associated with opioid overdose among long-term opioid users in the adjusted analysis. A number of population-based studies suggest that additive respiratory depression is probable with concomitant use of opioids and gabapentinoids, and the US Food and Drug Administration (FDA) has issued drug safety communications advising against the co-prescribing of these medications.[5,6,9,10] The ORs in this study may have been smaller than associations observed in other studies due to potential differences in designs and analyses, concomitant therapy that may have been well managed by treating clinicians, or greater surveillance of patients taking these drug combinations with respect to opioid overdose risk.

Our screening also identified non-opioid medications that have been recently evaluated as potential precipitant drugs that increase opioid overdose risk. Baclofen has been increasingly co-prescribed with opioids for the management of pain conditions.[12,13] A population-based cohort study using claims data from 2005 to 2015 found that concomitant use of prescription opioids and muscle relaxants was associated with opioid overdose, particularly among prevalent opioid users and patients dispensed baclofen or carisoprodol.[11] Another claims-based screening study found that concomitant use of certain prescription opioids and muscle relaxants was associated with unintentional traumatic injury.[14] As CNS depressants, muscle relaxants may exacerbate breathing difficulty when taken with opioids and lead to clinically significant adverse events.[5] Since our results suggest that co-dispensing of baclofen is associated

with opioid overdose after confounding adjustment, this medication may be a potential precipitant drug that should be investigated in follow-up studies.

Certain antibiotics were identified as potential precipitant drugs in our screening study, though these results may be confounded by changes in opioid exposure or other treatment associated with underlying infection. Sulfamethoxazole/trimethoprim was highly ranked and is known to result in adverse events when taken with other medications, but the mechanism of drug interaction with opioids is unclear. The large number of top-ranked antibiotics with OR > 1, including cephalexin and ciprofloxacin, may suggest that underlying infection could predispose long-term opioid users to an opioid overdose event. However, our exploratory results should be evaluated further to identify specific factors associated with opioid overdose in patients with infection.

Escitalopram, prednisone, and propranolol are not known to interact with opioids, but their association with opioid overdose may reflect changes in other factors over the observation period to treat unresolved pain. The dispensing of these non-opioid medications may also serve as proxies for increased symptoms of comorbid conditions that could further contribute to opioid overdose. Future studies should account for illicit opioid use, alcohol intake, hospitalizations, emergency department visits, non-opioid medication dosage, and dispensing of multiple CNS-depressing medications that may contribute to changing drug utilization patterns over the observation period immediately preceding the opioid overdose date. Observational cohort studies may also be

warranted in this setting to account for confounding by indication and identify true drug-drug interactions using a new-user, active comparator approach.

Our findings were similar when we evaluated potential precipitant drugs in the subgroup of patients without diagnosis codes for cancer. Since any attenuation in the ORs was small and the potential precipitant medications identified were not substantially different from those in the primary analysis, the bias from time-varying prognosis did not appear to fully explain our results. The oxycodone-specific analysis aimed to evaluate drug interactions involving non-opioid medications that may affect the cytochrome P450 3A4 (CYP3A4) or 2D6 (CYP2D6) isoenzymes responsible for metabolizing oxycodone, assess potential pharmacodynamic interactions, and account for switching between different prescription opioids in the main analysis. The findings in this subgroup did not identify any known medications that may interact pharmacokinetically with oxycodone. It is possible that CYP-mediated drug-drug interactions do not lead to opioid overdose events, the concomitant therapy was well managed by treating clinicians, or we were underpowered to detect an increase in risk due to the smaller numbers of patients exposed to these drug combinations.

Although exploratory, our findings have important implications for future research and clinical practice. Identified drugs should be further evaluated in hypothesis-testing studies to determine whether therapeutic alternatives may be associated with lower rates of overdose when used concomitantly with opioids. Nevertheless, even if the observed associations are not causal, the identified drug combinations may be markers

of other risk factors for experiencing an overdose event. Since multiple medication use is common in this patient population, frequent encounters with prescribers and pharmacists may provide opportunities to discuss the risks of concomitant drug use and treatment regimen modification, if warranted. Dispensing of naloxone is recommended for patients co-prescribed opioids and benzodiazepines,[31] and it may be warranted to expand guidelines to include patients also taking muscle relaxants or gabapentinoids. Our study has several limitations. Although we considered patients to be continuously exposed to prescription opioids based on dispensing dates and days' supply, we could not determine whether patients actually consumed these medications continuously over the 90-day observation period and opioid overdose date. We also could not determine whether patients dispensed a non-opioid medication consumed both the potential precipitant and opioid medications concurrently. We were additionally unable to account for changes in underlying health status or other sources of drug exposure inadequately captured in claims data, including family member prescriptions, illicit opioids, and over-the-counter medications. While we attempted to adjust for changes in prescription opioid dosage by restricting to patients with absolute changes of $\leq$ 300 MMEs between the hazard and referent windows, there may be confounding by smaller changes in prescription opioid dosage. The outcome definition does not distinguish between prescription and illicit opioid-related overdose events, and the data are limited to opioid overdoses that resulted in an emergency room visit or hospitalization. It is possible that our study excludes fatal events that did not make it to the emergency room or hospital, which may lead to selection bias if included opioid overdose cases do not represent all eligible cases with respect to non-opioid medication exposure. We

assumed that opioid overdose events triggered by drug-drug interactions have the same fatality rate as events that are unrelated to drug-drug interactions. Outcome misclassification due to the lack of sensitivity of the outcome definition is also unlikely to bias results for relative measures of association since the outcome definition has high specificity (99.9%).[21,32] Nevertheless, the medication combinations identified in this screening should be evaluated in follow-up studies as drug-drug interactions that may increase opioid overdose risk.

The results of this case-crossover-based screening of electronic healthcare data suggest that co-dispensing of certain muscle relaxants, benzodiazepines, antibiotics, and gabapentinoids may increase the risk of opioid overdose in patients on long-term opioid therapy. Several implicated precipitant drugs, such as benzodiazepines and gabapentinoids, have been previously identified as potentially interacting with opioids. Baclofen and other muscle relaxants have been recently evaluated as possible precipitant drugs and should be investigated in follow-up studies. Clinicians should be aware of drug-drug interactions when treating patients with opioids and consider prescribing safer alternatives or opioid antagonists when a potential for interaction exists. Expanding guidelines regarding opioid antagonists to patients taking opioids with these medications may also be warranted to prevent severe complications of opioid overdose.

Comparative risk of opioid overdose with concomitant use of prescription opioids and skeletal muscle relaxants

Background

Overdose deaths involving prescription opioids have quadrupled over the last 20 years in the US.[33] From 1999 to 2018, more than 232,000 people died from overdose related to opioid prescriptions.[33,34] Over the same time period, opioid overdose deaths involving other drug classes have increased. In 2016, the US Food and Drug Administration (FDA) warned against the combined use of prescription opioids with central nervous system (CNS) depressants due to the increased risk of sedation and other adverse events.[5] However, there are few studies that have quantified these risks or identified alternatives for patients who require treatment with opioids and other CNS depressants.

Skeletal muscle relaxants are among the most commonly co-prescribed medications with opioids for pain management.[13] Between 2005 and 2016, 67.2% (95% confidence interval (CI) 62.0%-72.5%) of office visits with a continuing skeletal muscle relaxant prescription also recorded concomitant use of an opioid.[13] Although the mechanism of drug-drug interaction has not been fully elucidated, co-prescription of baclofen and carisoprodol has been associated with opioid overdose and unintentional traumatic injury due to potential additive CNS depression.[14,35] It is unclear whether all skeletal muscle relaxants, when used in combination with opioids, have the same degree of

opioid overdose risk or whether there may be alternatives for patients who require treatment with both medications.

The objective of this study was to evaluate the comparative safety of skeletal muscle relaxants when used concomitantly with prescription opioids. We specifically focused on the risk of opioid overdose among patients on long-term opioid therapy.

Methods

We conducted a new user, active comparator cohort study to quantify the comparative risk of opioid overdose for seven prescription opioid and skeletal muscle relaxant combination therapies.

Data Sources

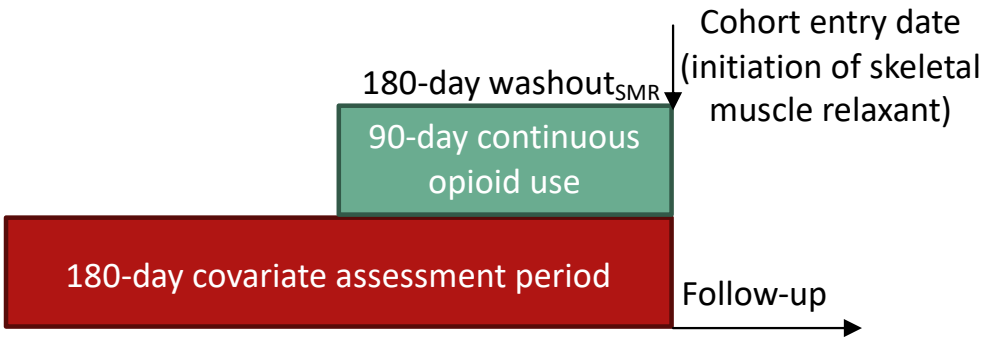
We used data spanning January 1, 2000 to December 31, 2014 from Medicaid Analytic eXtract (MAX); January 1, 2012 to December 31, 2017 from a Medicare fee-for-service cohort of beneficiaries with diabetes, heart failure, and/or stroke; January 1, 2004 to December 31, 2019 from Optum© Clinformatics® Data Mart; and January 1, 2003 to December 31, 2018 from IBM® MarketScan® Research Database. The databases contain de-identified and longitudinal administrative pharmacy and medical claims for commercially insured individuals (Optum© Clinformatics® Data Mart and IBM® MarketScan® Research Database), publicly insured individuals under the age of 65 (Medicaid), and beneficiaries aged 65 and older or younger than 65 with disabilities and/or end stage renal disease (Medicare) across the US. Patient-level ZIP codes in

Medicaid were linked to the 2017 American Community Survey from the US Census Bureau to assess measures of socioeconomic status.[36] ZIP codes were also linked to the 2013 rural-urban continuum codes from the US Department of Agriculture Economic Research Service to distinguish between metropolitan and nonmetropolitan areas.[37]

Study Population

Eligible individuals were identified based on their first dispensing for a skeletal muscle relaxant at age 18 or older (cohort entry date) immediately following at least 180 days of continuous health plan enrollment with no prior skeletal muscle relaxant dispensing and 90 days of continuous prescription opioid use (**Figure 2.1**).

Figure 2.1 New user and active comparator cohort study design to quantify comparative risk of opioid overdose for prescription opioid and skeletal muscle relaxant therapies



Caption: Patients with continuous prescription opioid use for at least 90 days immediately proceeded by initiation of a skeletal muscle relaxant following a 180-day washout period are eligible for study inclusion.

The skeletal muscle relaxants under study included baclofen, carisoprodol, cyclobenzaprine, metaxalone, methocarbamol, tizanidine, and chlorzoxazone or orphenadrine (evaluated as a single group). Continuous opioid use was defined by prescription fills for opioids with days' supply that covered the 90 days immediately before and on the cohort entry date. Grace periods of up to 14 days were incorporated between opioid prescriptions to account for inaccuracies in the days' supply estimation. Patients who experienced opioid overdose prior to or on the cohort entry date were excluded.

Outcome Assessment and Follow-Up

Opioid overdose was defined using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and ICD, Tenth Revision, CM (ICD-10-CM) codes for an opioid overdose episode resulting in hospitalization or an emergency room visit. ICD-9-CM codes used to define opioid overdose, together with codes for poisoning by heroin, have a specificity of 99.9%.[9] The ICD-10-CM algorithm for opioid overdose unrelated to heroin poisoning has a positive predictive value of 79.4%.[21,22]

We used sepsis as a negative control outcome to evaluate potential confounding by illicit opioid use, which is under-captured in claims data. Patients who use illicit opioids may be more likely to be prescribed certain opioid-skeletal muscle relaxant therapies, and intravenous drug use associated with illicit opioids may lead to sepsis. Different rates of sepsis across the seven treatment strategies could suggest that illicit opioid use may have biased the findings in the primary outcome analyses.

We performed a 30-day intention-to-treat analysis to evaluate the acute risk of opioid overdose following initiation of concomitant therapy. Follow-up began the day after cohort entry until outcome occurrence, end of continuous enrollment, death, nursing home admission, or end of the 30-day period immediately after the cohort entry date. In the as-treated analysis, patients could contribute follow-up time beyond 30 days but were additionally censored at prescription opioid discontinuation, skeletal muscle relaxant discontinuation, initiation of a skeletal muscle relaxant from another group, or end of the 365-day period immediately following the cohort entry date. We allowed grace periods of up to 14 days between prescriptions for both opioids and skeletal muscle relaxants, and the medication discontinuation date was defined as 14 days following the final prescription's days' supply.

Covariates

We assessed demographic information, comorbidities, pain conditions, other prescription fills, prior prescription opioid utilization, and healthcare utilization over the 180 days immediately before and on the cohort entry date. We also used patient-level ZIP codes in Medicaid to capture socioeconomic status variables and type of metropolitan area.

Statistical Analyses

We utilized matching weights, an extension of propensity score-based weighting approaches, to adjust for covariates in this multigroup setting. Within each database, a multinomial logistic regression model was used to estimate the probability of treatment

for each prescription opioid-skeletal muscle relaxant therapy as a function of the covariates. Each patient was subsequently assigned a matching weight, which is a ratio of the smallest conditional probability of treatment (of all probabilities estimated) and the conditional probability of receiving the treatment actually received.[38] The estimand of this weighting method (i.e., the subgroup of patients that would theoretically be eligible to receive any of the combination therapies under study) is asymptotically equivalent to that of 1:1 propensity score matching across the treatment groups provided that common support holds.[38]

Within each database, we fit a Cox proportional hazards model weighted by matching weights to estimate the hazard ratios (HRs) and bootstrapped 95% CIs of opioid overdose for each treatment relative to a common reference group (i.e., cyclobenzaprine). To estimate a common HR of opioid overdose for each treatment group across all databases, we fit a Cox proportional hazards model stratified by database in the pooled data and weighted by matching weights. This approach allows the baseline hazard of opioid overdose to vary by database and assumes that the HR is constant across the databases.

Secondary Analyses

We conducted several additional analyses. Although in the same drug class, skeletal muscle relaxants have different indications for treatment. Baclofen is approved for spasticity (e.g., resulting from spinal cord diseases), while the other skeletal muscle relaxants are approved for muscle spasm (e.g., acute musculoskeletal conditions), and

tizanidine is approved for both indications in the US.[39] We also observed that tizanidine initiators tended to be more similar to the baclofen initiators relative to the initiators of other skeletal muscle relaxants, and initiators of other skeletal muscle relaxants were quite similar to each other. We therefore conducted two subgroup analyses comparing: 1) baclofen and tizanidine and 2) carisoprodol, cyclobenzaprine, chlorzoxazone/orphenadrine, metaxalone, and methocarbamol. From the seven-group comparison, we also carried out a subgroup analysis restricted to patients without prior substance abuse as recorded by ICD codes for opioid dependence, opioid abuse, alcohol abuse, tobacco use, and other drug abuse in the baseline period to reduce potential confounding by unmeasured illicit opioid use. We separately stratified our analyses by baseline benzodiazepine use (binary); median MMEs (above or equal to median (high) or below median (low) MMEs); oxycodone dispensing (binary); and hydrocodone dispensing (binary) on the cohort entry date to identify subgroups with an increased risk of opioid overdose. In Medicaid, we adjusted for socioeconomic status measures and rural-urban area to account for residual confounding that may not be captured by other demographic variables. We fit multinomial logistic regression models for each analysis to re-estimate matching weights for each subgroup.

Results

Study population

We identified 136,650 baclofen initiators; 117,633 carisoprodol initiators; 32,152 chlorzoxazone/orphenadrine initiators; 552,649 cyclobenzaprine initiators; 67,435 metaxalone initiators; 124,662 methocarbamol initiators; and 214,838 tizanidine

initiators across the four databases. The mean age at skeletal muscle relaxant initiation was 53 years (standard deviation: 14.3 years), and 62% were female in the weighted population (**Table 2.1**).

Table 2.1 Select characteristics of individuals who initiated concomitant prescription opioid and skeletal muscle relaxant therapy pooled across four databases (post-matching weights)

	Baclofen	Carisoprodol	Chlorzoxazone/ orphenadrine	Cyclobenzaprine	Metaxalone	Methocarbamol	Tizanidine	SMD
n	24330	24694	24825	24800	24765	24759	24647	
Demographic information (n (%))								
Age (mean (SD))	52.65 (14.58)	53.05 (13.96)	53.12 (14.52)	53.12 (14.14)	52.88 (14.31)	53.12 (14.43)	52.43 (14.20)	0.022
Sex								0.005
Unknown	5 (0.0)	6 (0.0)	4 (0.0)	6 (0.0)	5 (0.0)	7 (0.0)	6 (0.0)	
Male	9244 (38.0)	9297 (37.7)	9410 (37.9)	9424 (38.0)	9317 (37.6)	9388 (37.9)	9345 (37.9)	
Female	15082 (62.0)	15391 (62.3)	15411 (62.1)	15370 (62.0)	15444 (62.4)	15364 (62.1)	15295 (62.1)	
Race								0.015
Unknown	17475 (71.8)	17593 (71.2)	17735 (71.4)	17702 (71.4)	17657 (71.3)	17669 (71.4)	17637 (71.6)	
Asian	68 (0.3)	84 (0.3)	83 (0.3)	78 (0.3)	83 (0.3)	78 (0.3)	76 (0.3)	
Black	771 (3.2)	858 (3.5)	888 (3.6)	905 (3.7)	853 (3.4)	889 (3.6)	863 (3.5)	
White	5723 (23.5)	5805 (23.5)	5771 (23.2)	5783 (23.3)	5830 (23.5)	5795 (23.4)	5759 (23.4)	
Other	294 (1.2)	354 (1.4)	348 (1.4)	332 (1.3)	342 (1.4)	327 (1.3)	312 (1.3)	
Ethnicity								0.009
Unknown	17638 (72.5)	17784 (72.0)	17910 (72.1)	17877 (72.1)	17834 (72.0)	17833 (72.0)	17802 (72.2)	
Hispanic	113 (0.5)	141 (0.6)	151 (0.6)	134 (0.5)	141 (0.6)	139 (0.6)	124 (0.5)	
Non-Hispanic	6580 (27.0)	6769 (27.4)	6764 (27.2)	6789 (27.4)	6790 (27.4)	6787 (27.4)	6720 (27.3)	
Comorbidities (n (%))								
Opioid dependence	793 (3.3)	788 (3.2)	769 (3.1)	755 (3.0)	768 (3.1)	786 (3.2)	781 (3.2)	0.005
Opioid abuse	80 (0.3)	74 (0.3)	77 (0.3)	76 (0.3)	69 (0.3)	68 (0.3)	75 (0.3)	0.004
Anxiety	4381 (18.0)	4304 (17.4)	4317 (17.4)	4336 (17.5)	4353 (17.6)	4376 (17.7)	4391 (17.8)	0.007
Bipolar disorder	920 (3.8)	932 (3.8)	919 (3.7)	916 (3.7)	926 (3.7)	950 (3.8)	933 (3.8)	0.003
Cancer	1395 (5.7)	1401 (5.7)	1364 (5.5)	1387 (5.6)	1379 (5.6)	1389 (5.6)	1352 (5.5)	0.005
COPD/asthma/oxygen	4290 (17.6)	4335 (17.6)	4396 (17.7)	4356 (17.6)	4297 (17.3)	4449 (18.0)	4281 (17.4)	0.007
Depression	5153 (21.2)	5113 (20.7)	5085 (20.5)	5056 (20.4)	5146 (20.8)	5029 (20.3)	5117 (20.8)	0.009
Intentional self-harm	15 (0.1)	14 (0.1)	14 (0.1)	15 (0.1)	13 (0.1)	15 (0.1)	17 (0.1)	0.002
Musculoskeletal injury	2305 (9.5)	2338 (9.5)	2349 (9.5)	2332 (9.4)	2303 (9.3)	2370 (9.6)	2324 (9.4)	0.003
Pneumonia	824 (3.4)	820 (3.3)	826 (3.3)	817 (3.3)	822 (3.3)	850 (3.4)	812 (3.3)	0.003
Renal dysfunction	1740 (7.2)	1763 (7.1)	1796 (7.2)	1793 (7.2)	1772 (7.2)	1837 (7.4)	1710 (6.9)	0.006

Table 2.1 (Continued)

	Baclofen	Carisoprodol	Chlorzoxazone/ orphenadrine	Cyclobenzaprine	Metaxalone	Methocarbamol	Tizanidine	SMD
n	24330	24694	24825	24800	24765	24759	24647	
Pain conditions (n (%))								
Back and neck pain	17426 (71.6)	17129 (69.4)	17232 (69.4)	17221 (69.4)	17185 (69.4)	17269 (69.7)	17276 (70.1)	0.018
Fibromyalgia	3833 (15.8)	3671 (14.9)	3624 (14.6)	3555 (14.3)	3671 (14.8)	3585 (14.5)	3794 (15.4)	0.017
Osteoarthritis	5555 (22.8)	5703 (23.1)	5752 (23.2)	5736 (23.1)	5638 (22.8)	5745 (23.2)	5583 (22.7)	0.006
Rheumatoid arthritis	1155 (4.7)	1202 (4.9)	1194 (4.8)	1193 (4.8)	1191 (4.8)	1182 (4.8)	1172 (4.8)	0.002
Postherpetic neuralgia	69 (0.3)	57 (0.2)	59 (0.2)	64 (0.3)	69 (0.3)	63 (0.3)	64 (0.3)	0.004
Other unspecified pain	8694 (35.7)	8464 (34.3)	8492 (34.2)	8496 (34.3)	8443 (34.1)	8575 (34.6)	8572 (34.8)	0.013
Other prescription fills (n (%))								
Antibiotics	14598 (60.0)	14926 (60.4)	14969 (60.3)	14952 (60.3)	14962 (60.4)	14969 (60.5)	14866 (60.3)	0.004
Antidepressants, SSRIs	6826 (28.1)	6948 (28.1)	6947 (28.0)	6941 (28.0)	6942 (28.0)	6905 (27.9)	6952 (28.2)	0.003
Antidepressants, SNRIs	3983 (16.4)	3981 (16.1)	3920 (15.8)	3916 (15.8)	3995 (16.1)	3932 (15.9)	4057 (16.5)	0.009
Antidepressants, TCAs	2710 (11.1)	2697 (10.9)	2614 (10.5)	2595 (10.5)	2624 (10.6)	2562 (10.3)	2660 (10.8)	0.011
Antidepressants, other	4149 (17.1)	4262 (17.3)	4154 (16.7)	4132 (16.7)	4196 (16.9)	4117 (16.6)	4195 (17.0)	0.008
Benzodiazepines	10855 (44.6)	10842 (43.9)	10768 (43.4)	10761 (43.4)	10818 (43.7)	10764 (43.5)	10894 (44.2)	0.011
CNS stimulants	903 (3.7)	923 (3.7)	900 (3.6)	893 (3.6)	908 (3.7)	883 (3.6)	940 (3.8)	0.006
Gabapentinoids	6862 (28.2)	6685 (27.1)	6570 (26.5)	6588 (26.6)	6630 (26.8)	6531 (26.4)	6750 (27.4)	0.017
NSAIDs	10796 (44.4)	11197 (45.3)	11110 (44.8)	11101 (44.8)	11099 (44.8)	11134 (45.0)	11048 (44.8)	0.007
Prescription opioid utilization (n (%))								
Total dispensed MMEs per interval (days) (mean (SD))								
(Index - 180) to (index - 151)	1959.86 (3195.34)	1902.29 (3036.60)	1810.27 (2974.34)	1813.23 (3103.42)	1840.48 (3088.81)	1826.03 (3125.36)	1893.27 (3064.74)	0.021
(Index - 150) to (index - 121)	2024.76 (3203.60)	1971.67 (3054.14)	1878.02 (3021.94)	1877.00 (3143.77)	1909.88 (3133.64)	1896.89 (3182.06)	1961.03 (3124.42)	0.021
(Index - 120) to (index - 91)	2194.19 (3288.79)	2123.62 (3102.39)	2020.50 (3085.97)	2024.16 (3200.77)	2057.54 (3229.48)	2043.34 (3283.71)	2115.51 (3153.22)	0.024
(Index - 90) to (index - 61)	2183.92 (3208.45)	2123.40 (3096.32)	2023.00 (3101.10)	2027.45 (3187.39)	2061.22 (3192.00)	2037.90 (3217.93)	2115.54 (3152.78)	0.023
(Index - 60) to (index - 31)	2209.64 (3313.17)	2132.25 (3096.40)	2040.21 (3129.95)	2041.79 (3215.06)	2076.80 (3218.49)	2054.64 (3256.91)	2128.21 (3175.75)	0.023
(Index - 30) to index	2631.41 (3778.28)	2537.68 (3538.30)	2415.82 (3721.36)	2416.39 (3801.31)	2449.88 (3767.53)	2425.86 (3794.14)	2532.62 (3612.86)	0.026

Table 2.1 (Continued)

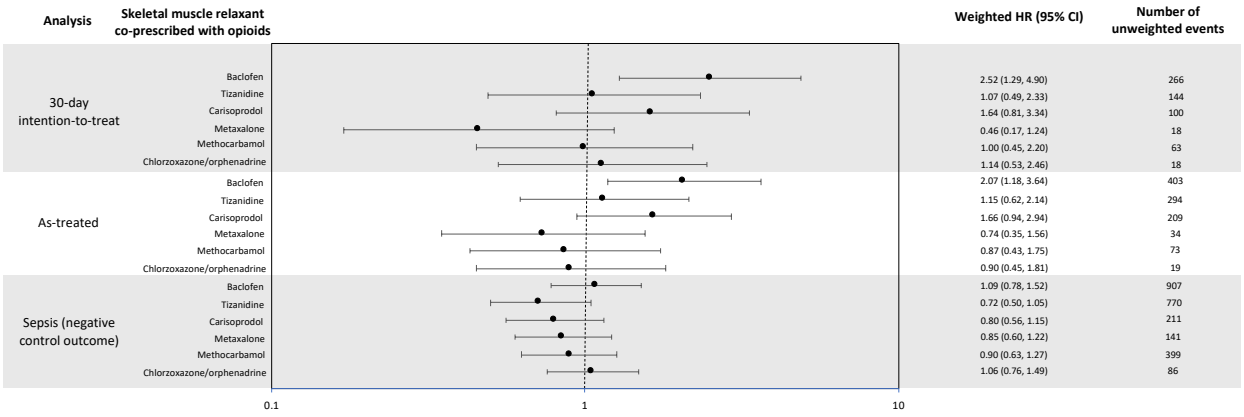
	Baclofen	Carisoprodol	Chlorzoxazone/ orphenadrine	Cyclobenzaprine	Metaxalone	Methocarbamol	Tizanidine	SMD
n	24330	24694	24825	24800	24765	24759	24647	
Healthcare utilization (mean (SD))								
Number of physician visits	8.80 (7.16)	8.65 (7.37)	8.61 (7.25)	8.60 (7.24)	8.64 (7.18)	8.65 (7.15)	8.71 (7.10)	0.011
Number of distinct prescribed medications	12.47 (6.25)	12.53 (6.45)	12.42 (6.29)	12.40 (6.28)	12.46 (6.31)	12.46 (6.24)	12.44 (6.32)	0.008
Number of hospitalizations	0.21 (0.64)	0.21 (0.62)	0.21 (0.68)	0.21 (0.62)	0.22 (0.64)	0.22 (0.60)	0.21 (0.65)	0.005
Number of hospitalization days	1.16 (5.33)	1.11 (4.81)	1.10 (4.05)	1.11 (4.30)	1.13 (4.03)	1.15 (4.28)	1.12 (4.69)	0.006

Prior to weighting, demographic characteristics varied between initiators of baclofen and tizanidine and those of other skeletal muscle relaxants. In the unweighted population, the baclofen and tizanidine groups tended to be older with a mean age of 59 years (standard deviation: 14.8 years) relative to the other treatment groups. The baclofen group also included more patients from California compared to other skeletal muscle relaxants, which was most pronounced in Medicaid and persisted across all databases before weighting. Comorbidities, pain conditions, other prescription fills, prior prescription opioid use, and healthcare utilization were otherwise similar across the treatment groups before and after weighting.[40]

Intention-to-treat analysis

In the first 30 days of follow-up, 887 opioid overdose events requiring emergent care occurred across the seven treatment groups. The highest absolute number of events occurred in the cyclobenzaprine (n = 278) and baclofen (n = 266) groups across the four databases. The crude incidence rate (IR) of opioid overdose varied by database but was high among baclofen initiators (e.g., crude IR of opioid overdose for baclofen ranged from 14.91 events per 1,000 person-years (95% CI 11.02-20.18) in IBM® MarketScan® Research Database to 45.78 events per 1,000 person-years (95% CI 38.70-54.16) in Medicare). After adjustment, the pooled weighted HR for opioid overdose relative to cyclobenzaprine was 2.52 (95% CI 1.29-4.90) for baclofen; 1.64 (95% CI 0.81-3.34) for carisoprodol; 1.14 (95% CI 0.53-2.46) for chlorzoxazone/orphenadrine; 0.46 (95% CI 0.17-1.24) for metaxalone; 1.00 (95% CI 0.45-2.20) for methocarbamol; and 1.07 (95% CI 0.49-2.33) for tizanidine (**Figure 2.2**).

Figure 2.2 Weighted hazard ratio of opioid overdose for concomitant prescription opioid and skeletal muscle relaxant therapies pooled across four databases



Caption: Forest plot of weighted hazard ratio and 95% confidence interval of opioid overdose for each prescription opioid and skeletal muscle relaxant treatment strategy by analysis type.

As-treated analysis

A total of 1,420 opioid overdose events were captured across the seven treatment groups in the as-treated analysis, with most occurring in the baclofen (n = 403) and cyclobenzaprine (n = 388) groups. Median length of follow-up varied by treatment group and database, ranging from 23 days for chlorzoxazone/orphenadrine initiators (interquartile range: 24 days) to 43 days for baclofen (interquartile range: 40 days), carisoprodol (interquartile range: 72 days), and tizanidine initiators (interquartile range: 43 days). After adjustment, the pooled weighted HR for opioid overdose relative to cyclobenzaprine was 2.07 (95% CI 1.18-3.64) for baclofen; 1.66 (95% CI 0.94-2.94) for carisoprodol; 0.90 (95% CI 0.45-1.81) for chlorzoxazone/orphenadrine; 0.74 (95% CI

0.35-1.56) for metaxalone; 0.87 (95% CI 0.43-1.75) for methocarbamol; and 1.15 (95% CI 0.62-2.14) for tizanidine.

Negative control outcome analysis

In the first 30 days of follow-up, 4,324 sepsis events occurred across the seven treatment groups. The highest absolute number of events occurred among cyclobenzaprine (n = 1,810) and baclofen (n = 907) initiators across the four databases. Following adjustment, the pooled weighted HR for sepsis relative to cyclobenzaprine was 1.09 (95% CI 0.78-1.52) for baclofen; 0.80 (95% CI 0.56-1.15) for carisoprodol; 1.06 (95% CI 0.76-1.49) for chlorzoxazone/orphenadrine; 0.85 (95% CI 0.60-1.22) for metaxalone; 0.90 (95% CI 0.63-1.27) for methocarbamol; and 0.72 (95% CI 0.50-1.05) for tizanidine.

Secondary analyses

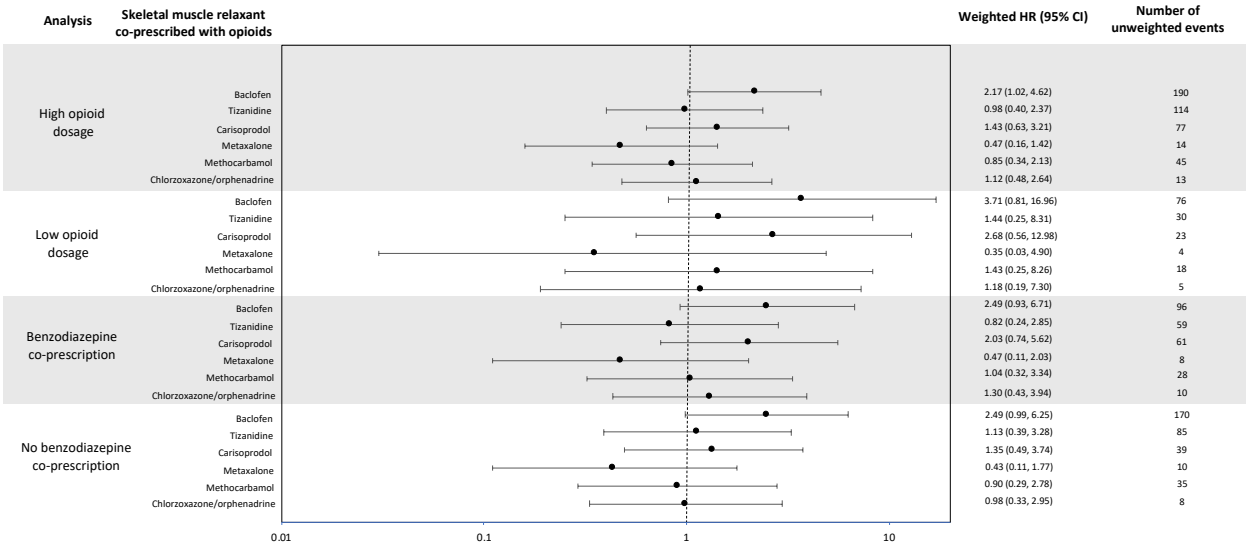
In the two-group comparison, baclofen relative to tizanidine was associated with opioid overdose in the weighted analysis (pooled weighted HR 2.50, 95% CI 1.95-3.21). In the five-group comparison, none of the skeletal muscle relaxants relative to cyclobenzaprine were associated with opioid overdose after adjustment. In a separate analysis of patients without prior recorded substance abuse, baclofen relative to cyclobenzaprine was associated with opioid overdose in the weighted analysis (pooled weighted HR 2.48, 95% CI 1.02-6.04), while the other skeletal muscle relaxants relative to cyclobenzaprine were unassociated with opioid overdose (**Table 2.2**).

Table 2.2 Hazard ratio of opioid overdose for concomitant prescription opioid and skeletal muscle relaxant therapies in patients without prior recorded substance abuse (by database and pooled)

Database	Skeletal muscle relaxant co-prescribed with opioids	Number of unweighted events	Number of individuals	Crude HR (95% CI)	Weighted HR (95% CI)
Medicaid Analytic eXtract (MAX)	Baclofen	19	19,685	2.79 (1.54, 5.04)	2.95 (0.38, 23.02)
	Tizanidine	11	14,760	2.10 (1.04, 4.24)	2.07 (0.24, 17.79)
	Carisoprodol	19	17,585	3.03 (1.68, 5.47)	2.30 (0.28, 19.00)
	Metaxalone	5	10,427	1.34 (0.52, 3.49)	1.47 (0.15, 14.34)
	Methocarbamol	6	14,472	1.18 (0.49, 2.87)	1.66 (0.18, 15.47)
	Chlorzoxazone/orphenadrine	2	6,298	0.89 (0.21, 3.75)	0.97 (0.08, 11.89)
	Cyclobenzaprine	26	73,381	Ref	Ref
Medicare (diabetes, heart failure, and stroke)	Baclofen	69	27,608	3.80 (2.55, 5.67)	2.78 (0.41, 18.82)
	Tizanidine	23	34,691	0.96 (0.57, 1.61)	0.80 (0.07, 9.28)
	Carisoprodol	6	8,078	1.06 (0.45, 2.50)	0.75 (0.06, 8.92)
	Metaxalone	1	3,303	0.45 (0.06, 3.27)	0.21 (< 0.01, 10.70)
	Methocarbamol	8	13,312	0.88 (0.41, 1.89)	1.19 (0.13, 10.92)
	Chlorzoxazone/orphenadrine	1	2,247	0.65 (0.09, 4.71)	0.31 (0.01, 8.82)
	Cyclobenzaprine	37	54,513	Ref	Ref
Optum© Clinformatics® Data Mart	Baclofen	20	25,973	2.56 (1.47, 4.48)	1.32 (0.09, 18.75)
	Tizanidine	28	51,494	1.78 (1.07, 2.96)	1.52 (0.12, 19.81)
	Carisoprodol	18	23,332	2.52 (1.41, 4.49)	3.31 (0.34, 32.40)
	Metaxalone	1	10,514	0.31 (0.04, 2.28)	0.30 (< 0.01, 19.52)
	Methocarbamol	8	21,668	1.22 (0.56, 2.64)	1.02 (0.06, 17.01)
	Chlorzoxazone/orphenadrine	3	4,805	2.04 (0.63, 6.67)	2.74 (0.27, 28.23)
	Cyclobenzaprine	32	105,100	Ref	Ref
IBM® MarketScan® Research Database	Baclofen	29	29,519	3.56 (2.28, 5.56)	2.52 (0.69, 9.16)
	Tizanidine	17	60,895	1.00 (0.58, 1.72)	0.65 (0.11, 3.70)
	Carisoprodol	20	48,980	1.47 (0.88, 2.44)	1.42 (0.34, 5.90)
	Metaxalone	7	34,026	0.74 (0.34, 1.62)	0.56 (0.09, 3.44)
	Methocarbamol	11	47,342	0.84 (0.44, 1.59)	0.75 (0.14, 3.95)
	Chlorzoxazone/orphenadrine	3	12,844	0.84 (0.26, 2.68)	0.93 (0.19, 4.45)
	Cyclobenzaprine	58	208,552	Ref	Ref
Pooled	Baclofen	137	102,785	3.34 (2.64, 4.22)	2.48 (1.02, 6.04)
	Tizanidine	79	161,840	1.28 (0.98, 1.69)	1.06 (0.37, 2.97)
	Carisoprodol	63	97,975	1.92 (1.43, 2.57)	1.70 (0.66, 4.36)
	Metaxalone	14	58,270	0.75 (0.44, 1.30)	0.61 (0.18, 2.06)
	Methocarbamol	33	96,794	0.98 (0.67, 1.43)	1.04 (0.37, 2.97)
	Chlorzoxazone/orphenadrine	9	26,194	1.01 (0.52, 1.98)	1.06 (0.37, 3.00)
	Cyclobenzaprine	153	441,546	Ref	Ref

We did not observe increased risks of opioid overdose among patients prescribed high opioid dosages at baseline; among individuals co-prescribed benzodiazepines; among individuals on oxycodone therapy on the cohort entry date; or among individuals on hydrocodone therapy on the cohort entry date (**Figure 2.3**).

Figure 2.3 Weighted hazard ratio of opioid overdose for select subgroup analyses pooled across four databases



Caption: Forest plot of weighted hazard ratio and 95% confidence interval of opioid overdose for each prescription opioid and skeletal muscle relaxant treatment strategy by subgroup analysis.

In a sensitivity analysis, we adjusted for measures of socioeconomic status and rural-urban area using individual-level ZIP codes in Medicaid. Patients initiating baclofen were of higher socioeconomic status and more likely to live in metropolitan areas compared to initiators of other skeletal muscle relaxants before weighting. Adjustment for these variables did not substantially change the HRs and 95% CIs of opioid overdose relative to the primary analysis in the Medicaid database.

Discussion

In this comparative safety study of seven skeletal muscle relaxants used concomitantly with prescription opioids, baclofen relative to cyclobenzaprine was associated with an increased risk of opioid overdose. Other skeletal muscle relaxants relative to cyclobenzaprine were unassociated with opioid overdose in the 30-day intention-to-treat and as-treated analyses. We observed similar results in patients without prior recorded substance abuse and in the two- and five-group comparisons among patients with similar baseline characteristics. None of the skeletal muscle relaxants relative to cyclobenzaprine were associated with sepsis, which may suggest a lower risk of unmeasured confounding by illicit opioid use in our head-to-head comparison of the seven medication combinations. No increased risk of opioid overdose was observed across subgroups stratified by baseline opioid dosage, benzodiazepine co-prescription, or oxycodone or hydrocodone therapy on the cohort entry date.

Our cohort study evaluated a potentially harmful medication combination that has recently been associated with adverse events in other settings. In two claims-based screening studies of administrative claims data, baclofen in particular increased the risks of opioid overdose and unintentional traumatic injury when co-dispensed with opioids.[14,35] A separate population-based cohort study using claims data from 2005 to 2015 found that patients co-prescribed baclofen (HR 1.83, 95% CI 1.11-3.04) or carisoprodol (HR 1.84, 95% CI 1.34-2.54) had an increased risk of opioid overdose compared to patients prescribed opioids alone, particularly among prevalent opioid users.[11] Our results are in line with previous findings in a larger study population of

commercially and publicly insured individuals in the US. We also used an active comparator design that evaluates the comparative safety of prescription opioid-skeletal muscle relaxant therapies to identify alternatives when both medications are necessary for treatment. This approach allows for improved adjustment of measured and unmeasured confounding as well as other sources of bias that are frequent in observational studies using claims data.[41]

In our stratified analyses, high prescription opioid dosages, concomitant benzodiazepine use, and oxycodone or hydrocodone therapy on the cohort entry date did not suggest an increased risk of opioid overdose for the skeletal muscle relaxant groups. Prior studies have identified elevated risks of opioid overdose with high versus low opioid dosages and separately with benzodiazepine co-prescription relative to prescription opioid use alone.[8,42,43] We may not have observed similar results due to limited power to detect these associations, particularly in stratified analyses with small numbers of events. The findings for the oxycodone and hydrocodone subgroups may also indicate lack of power or no true change in risk between users and non-users based on dispensings on the cohort entry date.

Although we cannot determine the cause of each opioid overdose event, our findings have important implications for clinical practice. Greater awareness among clinicians about the adverse effects of these medications is necessary to encourage prescribing of alternatives within the same drug class, especially in the absence of evidence suggesting another advantage to choosing one skeletal muscle relaxant over another.

Since individuals on long-term opioid therapy tend to take multiple medications, discussions with patients may be warranted to evaluate the risks of concomitant medication use and modify treatment strategies. For patients who require treatment with prescription opioids and baclofen, clinicians may consider providing access to opioid antagonists to prevent complications of opioid overdose.

Our study has several limitations. We defined concomitant use of prescription opioids and skeletal muscle relaxants based on dispensing dates and days' supply, but we were unable to assess if patients took these medications concurrently. We also could not determine whether opioid overdose events were due to true drug-drug interactions, an increase in the number of prescription opioid pills taken, illicit opioid use, or other factors. Based on the findings from the negative control outcome analysis, subgroup of patients without prior recorded substance abuse, and sensitivity analysis adjusting for socioeconomic status measures and metropolitan area in Medicaid, substantial confounding due to illicit opioid use may be unlikely in our primary analyses. The outcome definition includes opioid overdoses that required emergent care, and it is possible that fatal events or events treated with naloxone outside of hospitals were not recorded. However, the lack of sensitivity is unlikely to bias our relative measures of association due to the high specificity of the ICD code algorithm (99.9%).[21] We were likely underpowered to detect clinically relevant changes in opioid overdose risk, particularly in the stratified analyses, due to the small numbers of patients concurrently taking these medications. Larger follow-up studies are needed to investigate additional

risk factors that may predispose patients to opioid overdose while on skeletal muscle relaxant therapy.

Conclusions

The results of this large, nationwide US cohort study in four large administrative claims databases suggest that concomitant use of baclofen while on prescription opioids may increase the risk of opioid overdose relative to cyclobenzaprine. Greater awareness among clinicians about the risks of concomitant baclofen use may motivate discussions regarding prescribing of alternatives or ensuring access to opioid antagonists in patients for whom baclofen is the only option available.

Comparative risk of opioid overdose with concomitant use of prescription opioids and antibiotics

Background

Prescription opioid overdose events involving other drug classes are common in the US. Among patients who experienced opioid overdose while on long-term opioid therapy between 2015-2017, 74% were taking four or more non-opioid medications in addition to an average of 2.5 prescription opioids at the time of the event.[44] The high prevalence of polypharmacy may predispose patients to drug-drug interactions that increase the risk of adverse events.[2,4] Indeed, two separate screening studies of administrative claims data identified associations between co-prescription of opioids and antibiotics, including sulfamethoxazole/trimethoprim, and opioid overdose and unintentional traumatic injury, respectively.[14,44]

Antibiotics are one of the most frequently prescribed drug classes in the US and account for a large proportion of adverse drug events requiring emergent care.[45-48] Between 2013 and 2014, antibiotics were involved in 16% of emergency department visits and were implicated in more adverse events than any other drug class among patients under 50 years of age.[45-48] However, evidence for drug-drug interactions with opioids is limited to potential pharmacokinetic interactions involving specific fluoroquinolones that may inhibit the cytochrome P450 3A4 (CYP3A4) isoenzymes responsible for metabolism of certain opioids.[49,50] While previous screening studies did not detect potential safety signals for fluoroquinolones, co-prescription of

sulfamethoxazole/trimethoprim was associated with adverse events, though the mechanism of interaction with opioids is unclear.[14,44] Prior results may be at least partially attributable to the underlying infection, which could predispose patients to adverse drug events, or changes in other factors that affect prescription and/or illicit opioid use.[14,44] The safety of concomitant opioid and antibiotic therapy has not been assessed after accounting for these factors from the previous screening analyses.

The objective of this study was to evaluate the comparative safety of select antibiotic use on opioid overdose among patients on long-term opioid therapy.

Methods

We conducted a new user, active comparator cohort study to quantify the relative risk of opioid overdose for concomitant prescription opioid and antibiotic therapies. All analyses were conducted among patients diagnosed with urinary tract infection (UTI), one of the most common infections preceding opioid overdose based on International Classification of Disease (ICD) diagnosis codes in a previous screening assessment.[44] The antibiotics under study included sulfamethoxazole/trimethoprim, fluoroquinolones, and nitrofurantoin to investigate the safety of concurrent opioid and sulfamethoxazole/trimethoprim therapy relative to comparable antibiotics based on findings from two prior screening studies of administrative claims data.[14,44]

Data Sources

We used administrative pharmacy and medical claims data from four US commercial and public insurance databases, including Medicaid Analytic eXtract (January 1, 2000 to December 31, 2014); a Medicare fee-for-service cohort of beneficiaries with diabetes, heart failure, and/or stroke (January 1, 2012 to December 31, 2018); Optum© Clinformatics® Data Mart (January 1, 2004 to December 31, 2019); and IBM® MarketScan® Research Database (January 1, 2003 to December 31, 2018). The databases contain de-identified and patient-level demographic information, health plan enrollment status, inpatient and outpatient medical encounters, and pharmacy dispensings for a commercially insured population (Optum© Clinformatics® Data Mart and IBM® MarketScan® Research Database), publicly insured individuals under the age of 65 years (Medicaid), and beneficiaries aged 65 years and older or younger than 65 years with disabilities and/or end stage renal disease (Medicare).

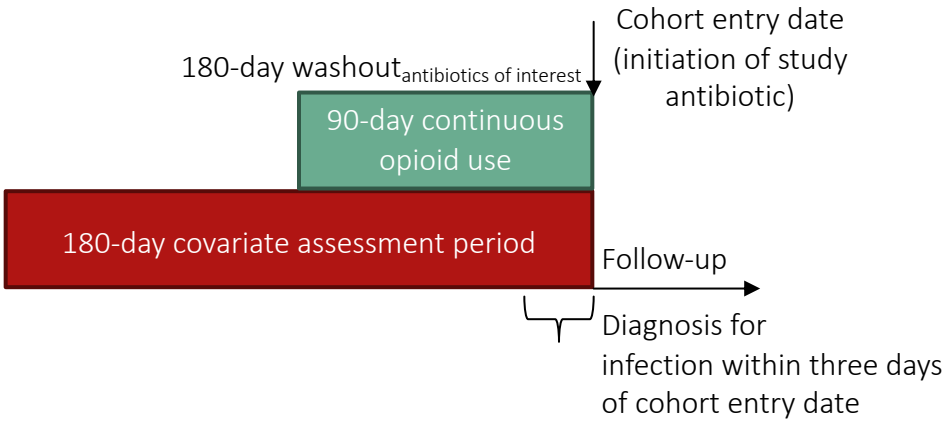
This study was approved by the Institutional Review Board at Brigham and Women's Hospital.

Study Population

We identified eligible individuals based on their first dispensing for a study antibiotic at age 18 years or older (cohort entry date) immediately preceded by at least 180 days of continuous health plan enrollment with no dispensing for the study antibiotic or comparator drugs. Patients were required to have at least 90 days of continuous opioid use immediately before and on the cohort entry date, which was defined by dispensing

dates and days' supply with grace periods of up to 14 days between opioid prescriptions. We further restricted to patients with at least one ICD, Ninth Revision, Clinical Modification (ICD-9-CM) and/or ICD, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis code for UTI within three days prior to or on the cohort entry date (**Figure 3.1**). Patients who experienced opioid overdose resulting in an emergency room visit or hospitalization at any time prior to or on the cohort entry date were excluded from the study population.

Figure 3.1 New user and active comparator cohort study design to quantify comparative risk of opioid overdose for prescription opioid and antibiotic therapies



Caption: Patients with continuous prescription opioid use for at least 90 days immediately proceeded by initiation of a study antibiotic following a 180-day washout period are eligible for study inclusion.

Outcome Assessment and Follow-Up

Opioid overdose was defined using ICD-9-CM and ICD-10-CM codes for an episode resulting in an emergency department visit or hospitalization during follow-up. ICD-9-CM codes used to define opioid overdose, together with codes for poisoning by heroin, have been found to have a sensitivity of 25.0%, specificity of 99.9%, positive predictive value of 84.6%, and negative predictive value of 99.0%.[21] The ICD-10-CM algorithm for opioid overdose unrelated to heroin poisoning has a positive predictive value of 79.4%.[22]

We performed intention-to-treat analyses with a maximum follow-up of 30 days to emulate the case-crossover-based screening framework in which concomitant exposure to prescription opioids and antibiotics was assessed in the 30 days immediately before an opioid overdose event.[44] Patients were followed until outcome occurrence or censored on the date of health plan disenrollment, death, nursing home admission, or end of the 30-day period.

Covariates

Several patient characteristics were assessed in the 180 days immediately before and on the cohort entry date. These included demographic information (e.g., age, sex, state of residence), comorbidities (e.g., opioid dependence or opioid abuse), pain conditions (e.g., back and neck pain or osteoarthritis), other prescription fills (e.g., non-study antibiotics or benzodiazepines), prior prescription opioid utilization (e.g., morphine milligram equivalents (MMEs) in the 30-day interval immediately before and on the

cohort entry date), and healthcare utilization (e.g., number of hospitalizations or number of physician visits).

Statistical Analyses

We used matching weights to adjust for baseline confounding. Within each database, we fit a multinomial logistic regression model to estimate the probability of treatment conditional on baseline covariates for each therapy. The estimated probabilities were used to calculate and assign a matching weight to each patient, which is a ratio of each individual's smallest conditional probability of treatment (of all probabilities estimated) and the conditional probability of receiving the treatment actually received. Matching weights are analogous to 1:1 propensity score matching across all treatment groups but preserve statistical efficiency by assigning each individual a weight proportional to the amount of information contributed to the weighted analysis.[38]

We fit database-specific Cox proportional hazards models weighted by matching weights to estimate the hazard ratios (HRs) and bootstrapped 95% confidence intervals (CIs) of opioid overdose for each treatment relative to sulfamethoxazole/trimethoprim. We additionally pooled the data and fit a Cox proportional hazards model stratified by database and weighted by matching weights to estimate a single HR and 95% CI of opioid overdose for each treatment group. This approach allows the baseline hazard of opioid overdose to vary by database but assumes that the HR is constant across the databases. The crude 30-day risk and 95% CI of opioid overdose for each treatment were estimated using the Kaplan-Meier method.

Secondary Analyses

We conducted several additional analyses. A three-day window between infection diagnosis and antibiotic initiation may include patients who used the study antibiotics for non-UTI infections. Analyses were restricted to patients diagnosed with the infection on the antibiotic dispensing date to provide greater assurance that study antibiotic use was intended for the treatment of UTI. In separate analyses, we stratified by baseline opioid dosage to evaluate whether patients dispensed high opioid dosages may be at increased risk of opioid overdose. Based on the MMEs dispensed in the 30 days immediately before and on the antibiotic initiation date, we calculated the median MMEs dispensed in each database. Patients dispensed MMEs equal to or above the database-specific median were classified as taking high opioid dosages, while those dispensed MMEs less than the database-specific median were classified as taking low opioid dosages. We also evaluated the comparative safety of these medications in a subgroup of patients without prior evidence of substance abuse based on ICD codes for opioid dependence, opioid abuse, alcohol abuse, tobacco use, or other drug abuse during the baseline period.

To address potential unmeasured confounding in the primary analysis, we quantified the association between each treatment group and sepsis as a negative control outcome. Patients using illicit opioids may be more likely to be prescribed certain study antibiotics, and intravenous drug use associated with illicit opioids may lead to sepsis. A different risk of sepsis for each study antibiotic could suggest that illicit opioid use may have biased the findings in the primary analysis. Observed associations with the negative

control outcome may additionally capture other sources of unmeasured confounding, such as differential severity of underlying infection, to the extent that it impacts opioid overdose. We also conducted this analysis in the subgroup of patients without prior evidence of substance abuse to evaluate potential residual confounding in a population that is less likely to use illicit opioids based on select ICD codes.

Results

Across the four databases, we identified 321,937 fluoroquinolone initiators; 105,598 nitrofurantoin initiators; and 127,648 sulfamethoxazole/trimethoprim initiators among patients diagnosed with UTI. The mean age at study antibiotic initiation was 65 years (standard deviation: 17 years), and 93% of patients were female in the weighted population. Comorbidities, pain conditions, other prescription fills, prior prescription opioid use, and healthcare utilization were similar across the treatment groups based on standardized mean differences below the conventional 0.1 threshold before and after weighting (**Table 3.1**).[40]

Table 3.1 Select characteristics of patients diagnosed with urinary tract infection who initiated concomitant prescription opioid and antibiotic therapy pooled across four databases (post-matching weights)

	Fluoroquinolones	Nitrofurantoin	Sulfamethoxazole/ trimethoprim	SMD
n	93771.75	93990.64	93884.25	
Demographic information (n (%))				
Age (mean (SD))	64.53 (16.81)	64.49 (17.00)	64.46 (16.90)	0.003
Sex				0.003
Unknown	17.5 (0.0)	17.5 (0.0)	18.1 (0.0)	
Male	6852.9 (7.3)	6849.7 (7.3)	6941.4 (7.4)	
Female	86901.4 (92.7)	87123.5 (92.7)	86924.8 (92.6)	
Race				0.002
Unknown	27041.7 (28.8)	27089.7 (28.8)	27051.4 (28.8)	
Asian	461.0 (0.5)	468.2 (0.5)	455.2 (0.5)	
Black	7729.8 (8.2)	7767.1 (8.3)	7803.9 (8.3)	
White	55150.2 (58.8)	55253.2 (58.8)	55162.4 (58.8)	
Other	3389.1 (3.6)	3412.5 (3.6)	3411.4 (3.6)	
Ethnicity				0.001
Unknown	35815.4 (38.2)	35929.9 (38.2)	35923.3 (38.3)	
Hispanic	2806.1 (3.0)	2807.5 (3.0)	2798.6 (3.0)	
Non-Hispanic	55150.2 (58.8)	55253.2 (58.8)	55162.4 (58.8)	
Comorbidities (n (%))				
Opioid dependence	3525.7 (3.8)	3543.1 (3.8)	3520.9 (3.8)	0.001
Opioid abuse	279.6 (0.3)	276.2 (0.3)	270.6 (0.3)	0.001
Anxiety	23594.9 (25.2)	23648.8 (25.2)	23586.5 (25.1)	0.001
Bipolar disorder	4407.5 (4.7)	4400.5 (4.7)	4422.8 (4.7)	0.001
Cancer	7489.3 (8.0)	7487.9 (8.0)	7440.0 (7.9)	0.002

Table 3.1 (Continued)

	Fluoroquinolones	Nitrofurantoin	Sulfamethoxazole/ trimethoprim	SMD
n	93771.75	93990.64	93884.25	
COPD/asthma/oxygen	24419.7 (26.0)	24420.5 (26.0)	24348.5 (25.9)	0.002
Dementia	11301.1 (12.1)	11302.8 (12.0)	11232.3 (12.0)	0.002
Depression	26473.5 (28.2)	26472.0 (28.2)	26384.9 (28.1)	0.002
Intentional self-harm	72.3 (0.1)	72.7 (0.1)	73.9 (0.1)	<0.001
Musculoskeletal injury	7308.9 (7.8)	7313.4 (7.8)	7266.1 (7.7)	0.001
Renal dysfunction	15778.9 (16.8)	15773.6 (16.8)	15725.0 (16.7)	0.001
Pain conditions (n (%))				
Back and neck pain	56155.1 (59.9)	56294.1 (59.9)	56341.8 (60.0)	0.002
Fibromyalgia	12871.6 (13.7)	12886.3 (13.7)	12890.7 (13.7)	<0.001
Osteoarthritis	33870.8 (36.1)	33891.5 (36.1)	33777.9 (36.0)	0.002
Rheumatoid arthritis	6142.7 (6.6)	6162.5 (6.6)	6115.5 (6.5)	0.001
Postherpetic neuralgia	390.7 (0.4)	384.8 (0.4)	389.0 (0.4)	0.001
Other unspecified pain	46654.3 (49.8)	46697.1 (49.7)	46631.9 (49.7)	0.001
Other prescription fills (n (%))				
Other antibiotics	51007.2 (54.4)	50953.3 (54.2)	50744.7 (54.1)	0.005
Antidepressants, SSRIs	30367.8 (32.4)	30385.2 (32.3)	30338.3 (32.3)	0.001
Antidepressants, SNRIs	17014.5 (18.1)	17087.0 (18.2)	17033.1 (18.1)	0.001
Antidepressants, TCAs	9316.3 (9.9)	9339.1 (9.9)	9331.4 (9.9)	<0.001
Antidepressants, other	18836.3 (20.1)	18887.5 (20.1)	18853.2 (20.1)	<0.001
Benzodiazepines	37976.5 (40.5)	37985.3 (40.4)	37939.9 (40.4)	0.001

Table 3.1 (Continued)

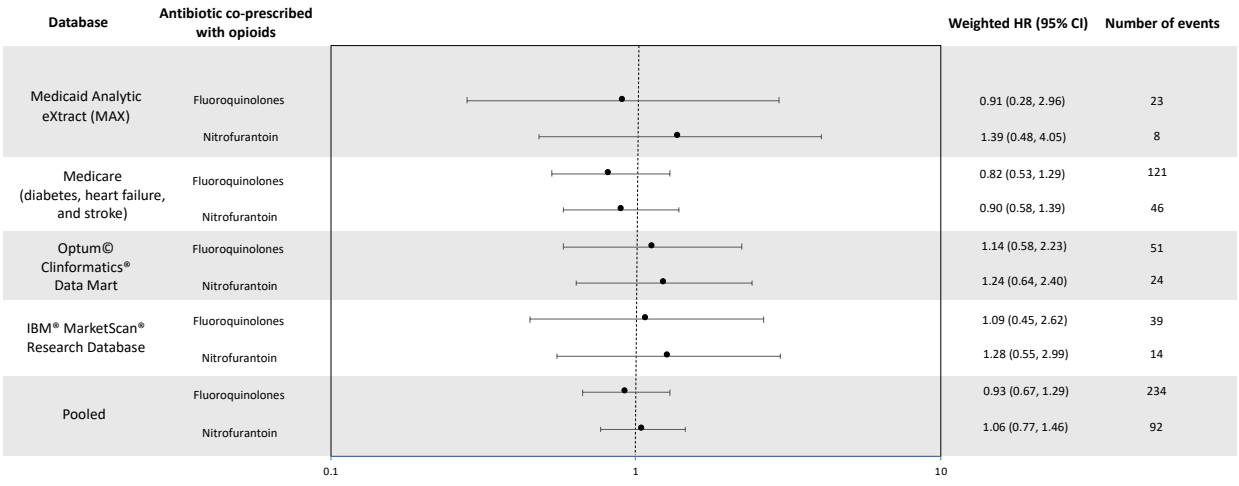
	Fluoroquinolones	Nitrofurantoin	Sulfamethoxazole/ trimethoprim	SMD
n	93771.75	93990.64	93884.25	
CNS stimulants	2153.7 (2.3)	2176.8 (2.3)	2187.0 (2.3)	0.001
Gabapentinoids	31444.8 (33.5)	31512.4 (33.5)	31442.3 (33.5)	0.001
NSAIDs	29903.0 (31.9)	30037.3 (32.0)	30058.8 (32.0)	0.002
Prior prescription opioid utilization (n (%))				
Total dispensed MMEs per interval (days) (mean (SD))				
(Index - 180) to (index - 151)	1625.84 (2606.52)	1626.19 (2641.83)	1632.56 (2619.17)	0.002
(Index - 150) to (index - 121)	1662.42 (2613.43)	1662.72 (2618.42)	1667.67 (2627.76)	0.001
(Index - 120) to (index - 91)	1782.28 (2679.59)	1780.80 (2666.43)	1786.19 (2677.39)	0.001
(Index - 90) to (index - 61)	1782.86 (2647.71)	1782.78 (2675.36)	1787.30 (2660.89)	0.001
(Index - 60) to (index - 31)	1794.60 (2668.50)	1795.33 (2660.28)	1800.70 (2707.05)	0.002
(Index - 30) to index	1916.05 (2885.14)	1916.76 (2922.82)	1921.91 (2887.40)	0.001
Healthcare utilization (mean (SD))				
Number of physician visits	10.58 (8.34)	10.57 (8.15)	10.51 (8.46)	0.005
Number of distinct prescribed medications	13.93 (5.79)	13.92 (5.80)	13.90 (5.86)	0.004

Table 3.1 (Continued)

	Fluoroquinolones	Nitrofurantoin	Sulfamethoxazole/ trimethoprim	SMD
n	93771.75	93990.64	93884.25	
Number of hospitalizations	0.30 (1.49)	0.30 (1.82)	0.30 (1.93)	0.001
Number of hospitalization days	1.48 (5.28)	1.46 (5.69)	1.45 (5.67)	0.003

In the first 30 days of follow-up, 420 opioid overdose events requiring emergent care occurred across the three treatment groups. The crude 30-day risk of opioid overdose for each treatment group was low and varied by database; as examples, the crude 30-day outcome risk for sulfamethoxazole/trimethoprim ranged from 0.04% (95% CI 0.02%-0.06%) in IBM® MarketScan® Research Database to 0.12% (95% CI 0.09%-0.15%) in Medicare. After adjustment, the pooled weighted HR for opioid overdose was 0.93 (95% CI 0.67-1.29) comparing fluoroquinolones to sulfamethoxazole/trimethoprim and 1.06 (95% CI 0.77-1.46) comparing nitrofurantoin to sulfamethoxazole/trimethoprim (**Figure 3.2**). Results were similar when analyses were restricted to patients diagnosed with UTI on the antibiotic initiation date.

Figure 3.2 Hazard ratio of opioid overdose for concomitant prescription opioid and antibiotic therapies among patients diagnosed with urinary tract infection



Caption: Forest plot of weighted hazard ratio and 95% confidence interval of opioid overdose for each prescription opioid and antibiotic treatment strategy by database.

In subgroup analyses stratified by baseline opioid dosage, 92 opioid overdose events occurred among patients prescribed low opioid dosages, and 328 events occurred among those prescribed high opioid dosages. There was no increased risk of opioid overdose with co-prescription of fluoroquinolones relative to sulfamethoxazole/trimethoprim among patients prescribed high opioid dosages (pooled weighted HR 0.97, 95% CI 0.67-1.41) compared to those prescribed low opioid dosages (pooled weighted HR 0.92, 95% CI 0.45-1.90). Similar results were observed for co-prescription of nitrofurantoin relative to sulfamethoxazole/trimethoprim (**Table 3.2**).

Table 3.2 Hazard ratio of opioid overdose for concomitant prescription opioid and antibiotic therapies among patients diagnosed with urinary tract infection and with low or high opioid dosage (by database and pooled)

		Low opioid dosage			High opioid dosage		
Database	Antibiotic co-prescribed with opioids	Number of events	Number of individuals	Weighted HR (95% CI)	Number of events	Number of individuals	Weighted HR (95% CI)
Medicaid Analytic eXtract (MAX)	Fluoroquinolones	7	17,178	1.90 (0.16, 22.96)	16	18,147	0.76 (0.20, 2.95)
	Nitrofurantoin	3	4,687	3.20 (0.32, 32.34)	5	4,619	1.03 (0.30, 3.60)
	Sulfamethoxazole/ trimethoprim	2	10,595	Ref	12	9,697	Ref
Medicare (diabetes, heart failure, and stroke)	Fluoroquinolones	24	63,108	0.78 (0.28, 2.21)	97	70,849	0.86 (0.52, 1.41)
	Nitrofurantoin	11	20,679	1.15 (0.45, 2.95)	35	23,145	0.86 (0.52, 1.41)
	Sulfamethoxazole/ trimethoprim	9	22,184	Ref	40	25,471	Ref
Optum© Clinformatics ® Data Mart	Fluoroquinolones	13	35,084	1.09 (0.27, 4.42)	38	35,729	1.21 (0.55, 2.63)
	Nitrofurantoin	4	13,093	0.99 (0.24, 4.13)	20	12,566	1.37 (0.64, 2.93)
	Sulfamethoxazole/ trimethoprim	4	13,689	Ref	15	13,746	Ref

		Low opioid dosage			High opioid dosage		
Database	Antibiotic co-prescribed with opioids	Number of events	Number of individuals	Weighted HR (95% CI)	Number of events	Number of individuals	Weighted HR (95% CI)
IBM® MarketScan ® Research Database	Fluoroquinolones	7	40,535	0.74 (0.11, 4.96)	32	41,307	1.27 (0.47, 3.48)
	Nitrofurantoin	5	13,551	1.70 (0.36, 8.12)	9	13,258	1.21 (0.44, 3.35)
	Sulfamethoxazole/ trimethoprim	3	16,227	Ref	9	16,039	Ref
Pooled	Fluoroquinolones	51	155,905	0.92 (0.45, 1.90)	183	166,032	0.97 (0.67, 1.41)
	Nitrofurantoin	23	52,010	1.33 (0.68, 2.57)	69	53,588	1.02 (0.71, 1.47)
	Sulfamethoxazole/ trimethoprim	18	62,695	Ref	76	64,953	Ref

For the negative control outcome, 4,755 sepsis events occurred across the three treatment groups. In the unadjusted analysis, co-prescription of nitrofurantoin relative to sulfamethoxazole/trimethoprim was associated with sepsis (pooled HR 1.19, 95% CI 1.09-1.30). After adjustment, the increased risk of sepsis persisted for this comparison (pooled weighted HR 1.18, 95% CI 1.07-1.30). Fluoroquinolone co-prescription relative to sulfamethoxazole/trimethoprim was unassociated with sepsis in the crude analysis (pooled HR 1.06, 95% CI 0.98-1.14) and after adjustment (pooled weighted HR 0.96, 95% CI 0.86-1.06) (**Table 3.3**).

Table 3.3 Hazard ratio of sepsis for concomitant prescription opioid and antibiotic therapies among patients diagnosed with urinary tract infection (by database and pooled)

Database	Antibiotic co-prescribed with opioids	Number of events	Number of individuals	Crude HR (95% CI)	Weighted HR (95% CI)
Medicaid Analytic eXtract (MAX)	Fluoroquinolones	136	35,325	1.93 (1.36, 2.74)	1.24 (0.71, 2.18)
	Nitrofurantoin	41	9,306	2.21 (1.43, 3.40)	1.85 (1.10, 3.12)

Table 3.3 (Continued)

Database	Antibiotic co-prescribed with opioids	Number of events	Number of individuals	Crude HR (95% CI)	Weighted HR (95% CI)
Medicaid Analytic eXtract (MAX)	Sulfamethoxazole/ trimethoprim	41	20,292	Ref	Ref
Medicare (diabetes, heart failure, and stroke)	Fluoroquinolones	1,579	133,957	0.97 (0.88, 1.06)	0.90 (0.79, 1.03)
	Nitrofurantoin	621	43,824	1.18 (1.05, 1.32)	1.17 (1.03, 1.33)
	Sulfamethoxazole/ trimethoprim	580	47,655	Ref	Ref
Optum© Clinformatics® Data Mart	Fluoroquinolones	691	70,813	1.32 (1.13, 1.54)	1.25 (1.01, 1.54)
	Nitrofurantoin	249	25,659	1.31 (1.09, 1.57)	1.36 (1.11, 1.67)
	Sulfamethoxazole/ trimethoprim	203	27,435	Ref	Ref
IBM® MarketScan® Research Database	Fluoroquinolones	347	81,842	0.87 (0.72, 1.05)	0.72 (0.55, 0.96)
	Nitrofurantoin	109	26,809	0.83 (0.65, 1.06)	0.85 (0.65, 1.11)
	Sulfamethoxazole/ trimethoprim	158	32,266	Ref	Ref
Pooled	Fluoroquinolones	2,753	321,937	1.06 (0.98, 1.14)	0.96 (0.86, 1.06)
	Nitrofurantoin	1,020	105,598	1.19 (1.09, 1.30)	1.18 (1.07, 1.30)
	Sulfamethoxazole/ trimethoprim	982	127,648	Ref	Ref

Among 440,033 patients without prior recorded substance abuse, 245 opioid overdose events occurred across the three treatment groups. After adjustment, neither co-prescription of fluoroquinolones nor nitrofurantoin relative to sulfamethoxazole/trimethoprim was associated with opioid overdose. In this subgroup,

co-prescription of nitrofurantoin relative to sulfamethoxazole/trimethoprim was associated with sepsis in the weighted analysis (pooled weighted HR 1.23, 95% CI 1.10-1.38). No association with sepsis was observed comparing fluoroquinolones to sulfamethoxazole/trimethoprim after adjustment (pooled weighted HR 0.99, 95% CI 0.88-1.12).

Discussion

In this comparative safety study of select prescription opioid and antibiotic combination therapies, we found that co-prescription of fluoroquinolones or nitrofurantoin relative to sulfamethoxazole/trimethoprim did not increase opioid overdose risk in patients diagnosed with UTI. The crude 30-day risk of opioid overdose for sulfamethoxazole/trimethoprim ranged from 0.04% (95% CI 0.02%-0.06%) in IBM® MarketScan® Research Database to 0.12% (95% CI 0.09%-0.15%) in Medicare, though this likely underestimates the true incidence since the outcome definition only captured events resulting in emergent care. Results were similar in patients diagnosed with UTI on the antibiotic dispensing date and in individuals without prior recorded substance abuse, and no increased risk of opioid overdose was observed for patients prescribed high opioid dosages. Co-prescription of nitrofurantoin relative to sulfamethoxazole/trimethoprim was associated with sepsis in the full study population and in the subgroup of patients without prior recorded substance abuse, which may suggest potential unmeasured confounding in the primary analysis.

Our cohort study was prompted by findings from two separate screening studies that intended to identify non-opioid medications that may increase the risk of adverse events when taken concurrently with prescription opioids.[14,44] In the first study, a case-crossover-based framework was used to screen two commercial claims databases and quantify the association between each non-opioid medication dispensed in the 90 days immediately before the event and opioid overdose.[44] This approach identified an increased risk of opioid overdose for sulfamethoxazole/trimethoprim (odds ratio (OR) 1.47, 95% CI 1.20-1.79). Fluoroquinolones, such as ciprofloxacin (OR 1.22, 95% CI 1.02-1.45) and levofloxacin (OR 1.05, 95% CI 0.88-1.26), and nitrofurantoin (OR 1.11, 95% CI 0.85-1.47) were marginally associated or unassociated with opioid overdose.[44] In the second study, the authors conducted a self-controlled case series design to screen one commercial claims database to identify signals for prescription opioid drug-drug interactions that may lead to unintentional traumatic injury.[14] The screening approach identified associations with co-prescription of hydrocodone and sulfamethoxazole (rate ratio (RR) 1.35, 95% CI 1.15-1.58), hydrocodone and trimethoprim (RR 1.34, 95% CI 1.14-1.57), tramadol and sulfamethoxazole (RR 2.02, 95% CI 1.63-2.52), and tramadol and trimethoprim (RR 2.00, 95% CI 1.61-2.48).[14] No associations were observed with co-prescription of opioids and fluoroquinolones or nitrofurantoin and unintentional traumatic injury.[14]

Although the findings from the screening studies suggest potential differences in the risk of adverse events for the study antibiotics, these self-controlled approaches for screening are vulnerable to time-varying confounding by changes in underlying health

status or worsening of infection to the extent that these factors impact adverse event risk.[14,44] Potential time-varying confounding could at least partially explain why antibiotics often appear as safety signals in claims-based screening studies, as their co-prescription may be associated with variables that are also unmeasured risk factors for the outcome.[14,15,44] Our study intended to address these biases by evaluating medication combinations in a cohort design that more explicitly accounts for confounding by indication via a new user, active comparator approach restricted to patients with specific indications for antibiotic use. However, a null finding for the use of fluoroquinolones or nitrofurantoin relative to sulfamethoxazole/trimethoprim may be at least partially attributable to unmeasured confounding based on findings from the negative control outcome analyses.

Sepsis was selected as a negative control outcome since it likely captures similar sources of bias that may be present in the primary analysis. A higher risk of sepsis for nitrofurantoin relative to sulfamethoxazole/trimethoprim was intended to reflect differences in illicit opioid use between the treatment groups that may confound the hazard ratio of opioid overdose in the primary analysis. However, this association with sepsis persisted in a subgroup of patients who are less likely to use illicit opioids based on evidence of prior substance abuse. The ICD codes used to define this subgroup may have poor sensitivity and likely under-capture risk factors for illicit opioid use such that the results from the negative control outcome analysis could still reflect unmeasured confounding by this variable. Alternatively, other factors could explain these findings that are unique to the study of antibiotics. While antibiotics do not cause

sepsis and are expected to produce a null result in accordance with an appropriate negative control outcome, an observed association may indicate differential antibiotic effectiveness in preventing sepsis. This may lead to differences in underlying severity of infection between the treatment groups, which may be an additional source of unmeasured confounding to the extent that it impacts opioid overdose risk. An unexpected association with the negative control outcome may also reflect unmeasured confounding for antibiotics and sepsis that is not present in the primary analysis; as a result, we may observe a non-null association with sepsis even if the analysis with opioid overdose is unconfounded.[51] To address this limitation, it may be warranted to adjust for confounders of antibiotics and sepsis or select additional negative control outcomes that share identical common causes as those of the primary treatment and outcome and are unlikely to be caused by treatment.[51]

Aside from potential unmeasured confounding in the primary analysis, our study could not rule out drug-drug interactions between opioids and antibiotics. Pharmacokinetic interactions have been reported between particular opioids, such as oxycodone, and specific fluoroquinolones, including ciprofloxacin, which are likely mediated by potent CYP3A4 inhibition.[49,50] While prior screening studies assessed each non-opioid medication individually or by active ingredient in association with opioid-related adverse events, we evaluated opioids and fluoroquinolones on the drug class level to preserve statistical power. As a result, the potential effects of pharmacokinetic interactions in particular may have been diluted in the primary analysis. Future studies may seek to quantify the relative risk of opioid overdose for specific medication combinations to

evaluate the clinical relevance of potential pharmacokinetic drug-drug interactions between opioids and antibiotics.

Our subgroup analyses suggested that the comparative risks of opioid overdose across the study antibiotics are similar for patients prescribed high versus low opioid dosages. Other studies have identified a dose-response relationship between prescription opioids and risk of opioid overdose.[42] However, it is possible that we did not detect a similar relationship if prescription opioid dosage does not have a clinically relevant impact on the comparative safety of opioid and antibiotic therapies with respect to opioid overdose. We may also have been underpowered to evaluate these subgroups due to the small number of opioid overdose events, particularly among patients prescribed low opioid dosages at baseline.

While we could not determine the cause of opioid overdose for each patient who experienced an event, our findings have important implications for future research. Further study is needed to identify an additional negative control outcome with regards to the study of antibiotics and opioid overdose or to quantify associations with sepsis after adjustment for confounders of antibiotics and this negative control outcome. Larger studies may be warranted to evaluate potential pharmacokinetic, pharmacodynamic, and other mechanisms of drug-drug interactions between opioids and antibiotics to investigate the comparative safety of these medication combinations with respect to adverse event risk. Future studies should also elucidate the role of the underlying infection in potentially predisposing patients to an opioid overdose event,

which our current study was not designed to address. Diagnosis and severity of infection may suppress immune response and increase vulnerability to adverse events, yet this hypothesis has not been evaluated in a clinical setting. Occurrence of infection may necessitate guidance for modifications to prescription opioid dosage, opioid utilization, or dispensing of opioid antagonists that warrants further investigation.

Our study has several limitations. Although we defined concomitant use of prescription opioids and antibiotics based on concurrent dispensing and/or overlapping days' supply on the cohort entry date, we could not evaluate if patients took these medications together over the duration of follow-up or whether patients may have modified their opioid consumption patterns in the context of infection. We similarly could not determine if opioid overdose events were due to drug-drug interactions, illicit opioid use, an acute increase in prescription opioid dosage, or other factors that may predispose patients to an event. Our outcome definition only captures events that result in an emergency department visit or hospitalization; however, this is unlikely to lead to bias due to the high specificity of the ICD code algorithm.[21] We evaluated opioids as a drug class and were underpowered to detect potential pharmacokinetic interactions between specific opioids and antibiotics due to the small numbers of patients with prescription fills for these particular medications. The comparative safety of these combination therapies should be evaluated in larger studies to identify potential risk factors for opioid overdose.

Conclusions

The findings from this cohort study of administrative claims data spanning a 20-year period do not rule out the differential safety of concomitant prescription opioid and antibiotic therapies with respect to opioid overdose risk. In addition to addressing the limitations of our negative control outcome analysis, further studies are needed to evaluate the clinical relevance of potential drug-drug interactions between opioids and antibiotics and the role of underlying infection in potentially predisposing patients to adverse drug events.

Bibliography

1. Baldini A, Von Korff M, Lin EH. A Review of Potential Adverse Effects of Long-Term Opioid Therapy: A Practitioner's Guide. Prim Care Companion CNS Disord 2012;14.

2. Bain KT, Knowlton CH. Role of Opioid-Involved Drug Interactions in Chronic Pain Management. J Am Osteopath Assoc 2019;119:839-847.

3. Medicare Payment Advisory Commission. Report to the Congress: Medicare and the Health Care Delivery System. Chapter 5: Polypharmacy and opioid use among Medicare Part D enrollees. https://www.medpac.gov/docs/default-source/reports/chapter-5-polypharmacy-and-opioid-use-among-medicare-part-d-enrollees-june-2015-report-.pdf?sfvrsn=0. June 2015. Accessed January 22, 2020.

4. Pergolizzi JV, Jr., Labhsetwar SA, Puenpatom RA, Joo S, Ben-Joseph RH, Summers KH. Prevalence of exposure to potential CYP450 pharmacokinetic drug-drug interactions among patients with chronic low back pain taking opioids. Pain Pract 2011;11:230-239.

5. US Food and Drug Administration. FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning. https://www.fda.gov/media/99761/download. August 2016. Accessed January 22, 2020.

6. US Food and Drug Administration. FDA warns about serious breathing problems with seizure and nerve pain medicines gabapentin (Neurontin, Gralise, Horizant) and pregabalin (Lyrica, Lyrica CR) when used with CNS depressants or in patients with lung problems. https://www.fda.gov/media/133681/download. December 2019. Accessed January 22, 2020.

7. National Institute on Drug Abuse. Overdose death rates. https://www.drugabuse.gov/drug-topics/trends-statistics/overdose-death-rates. 2020. Accessed January 22, 2020.

8. Tori ME, Larochelle MR, Naimi TS. Alcohol or Benzodiazepine Co-involvement With Opioid Overdose Deaths in the United States, 1999-2017. JAMA Netw Open 2020;3:e202361.

9. Gomes T, Greaves S, van den Brink W, et al. Pregabalin and the Risk for Opioid-Related Death: A Nested Case-Control Study. Ann Intern Med 2018;169:732-734.

10. 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.

11. Li Y, Delcher C, Wei YJ, et al. Risk of Opioid Overdose Associated With Concomitant Use of Opioids and Skeletal Muscle Relaxants: A Population-Based Cohort Study. Clin Pharmacol Ther 2020;108:81-89.

12. Reynolds K, Kaufman R, Korenoski A, Fennimore L, Shulman J, Lynch M. Trends in gabapentin and baclofen exposures reported to U.S. poison centers. Clin Toxicol (Phila) 2020;58:763-72.

13. Soprano SE, Hennessy S, Bilker WB, Leonard CE. Assessment of Physician Prescribing of Muscle Relaxants in the United States, 2005-2016. JAMA Netw Open 2020;3:e207664.

14. Leonard CE, Brensinger CM, Pham Nguyen TP, et al. Screening to identify signals of opioid drug interactions leading to unintentional traumatic injury. Biomed Pharmacother 2020;130:110531.

15. Bykov K, Schneeweiss S, Glynn RJ, Mittleman MA, Gagne JJ. A Case-Crossover-Based Screening Approach to Identifying Clinically Relevant Drug-Drug Interactions in Electronic Healthcare Data. Clin Pharmacol Ther 2019;106:238-44.

16. Maclure M, Mittleman MA. Should we use a case-crossover design? Annu Rev Public Health 2000;21:193-221.

17. Mostofsky E, Coull BA, Mittleman MA. Analysis of Observational Self-matched Data to Examine Acute Triggers of Outcome Events with Abrupt Onset. Epidemiology 2018;29:804-816.

18. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. Am J Epidemiol 1991;133:144-153.

19. Mittleman MA, Mostofsky E. Exchangeability in the case-crossover design. Int J Epidemiol 2014;43:1645-1655.

20. Cauley CE, Anderson G, Haynes AB, Menendez M, Bateman BT, Ladha K. Predictors of In-hospital Postoperative Opioid Overdose After Major Elective Operations: A Nationally Representative Cohort Study. Ann Surg 2017;265:702-708.

21. Rowe C, Vittinghoff E, Santos GM, Behar E, Turner C, Coffin PO. Performance Measures of Diagnostic Codes for Detecting Opioid Overdose in the Emergency Department. Acad Emerg Med 2017;24:475-483.

22. Slavova S, Quesinberry D, Costich JF, et al. ICD-10-CM-Based Definitions for Emergency Department Opioid Poisoning Surveillance: Electronic Health Record Case Confirmation Study. Public Health Rep 2020;135:262-269.

23. Benjamini Y and Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. Journal of the Royal Statistical Society 1995;57:289-300.

24. Glickman ME, Rao SR, Schultz MR. False discovery rate control is a recommended alternative to Bonferroni-type adjustments in health studies. J Clin Epidemiol 2014;67:850-857.

25. Algera MH, Olofsen E, Moss L, et al. Tolerance to Opioid-Induced Respiratory Depression in Chronic High-Dose Opioid Users: A Model-Based Comparison With Opioid-Naive Individuals. Clin Pharmacol Ther 2021;109:637-645.

26. Von Korff M, Saunders K, Thomas Ray G, et al. De facto long-term opioid therapy for noncancer pain. Clin J Pain 2008;24:521-527.

27. Wang SV, Gagne JJ, Glynn RJ, Schneeweiss S. Case-crossover studies of therapeutics: design approaches to addressing time-varying prognosis in elderly populations. Epidemiology 2013;24:375-378.

28. Cascorbi I. Drug interactions--principles, examples and clinical consequences. Dtsch Arztebl Int 2012;109:546-555.

29. National Institute on Drug Abuse. Benzodiazepines and Opioids. https://www.drugabuse.gov/drugs-abuse/opioids/benzodiazepines-opioids. 2020. Accessed January 22, 2020.

30. Hedegaard H, Bastian BA, Trinidad JP, Spencer M, Warner M. Drugs Most Frequently Involved in Drug Overdose Deaths: United States, 2011–2016. *Natl Vital Stat Rep*. 2018;67:1-13.

31. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. *MMWR Recomm Rep*. 2016;65:1-49.

32. Kelsey JL, Whittemore AS, Evans AS, Thompson WD. Methods in Observational Epidemiology. 2nd Ed. 1996. New York, NY.

33. Centers for Disease Control and Prevention. Prescription opioids overview. 2021. Available at https://www.cdc.gov/drugoverdose/data/prescribing/overview.html.

34. McClure FL, Niles JK, Kaufman HW, Gudin J. Concurrent Use of Opioids and Benzodiazepines: Evaluation of Prescription Drug Monitoring by a United States Laboratory. J Addict Med 2017;11:420-426.

35. Khan NF, Bykov K, Glynn RJ, Barnett ML, Gagne JJ. Co-prescription of opioids with other medications and risk of opioid overdose. Clin Pharmacol Ther 2021.

36. Agency for Healthcare Research and Quality. Race, Ethnicity, and Language Data: Standardization for Health Care Quality Improvement. 2018. Available at https://www.ahrq.gov/research/findings/final-reports/iomracereport/reldata3.html.

37. US Department of Agriculture Economic Research Service. Rural-Urban Continuum Codes. 2020. Available at https://www.ers.usda.gov/data-products/rural-urban-continuum-codes.aspx.

38. Yoshida K, Hernandez-Diaz S, Solomon DH, et al. Matching Weights to Simultaneously Compare Three Treatment Groups: Comparison to Three-way Matching. Epidemiology 2017;28:387-395.

39. Witenko C, Moorman-Li R, Motycka C, et al. Considerations for the appropriate use of skeletal muscle relaxants for the management of acute low back pain. P T 2014;39:427-435.

40. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behav Res 2011;46:399-424.

41. Franklin JM, Schneeweiss S. When and How Can Real World Data Analyses Substitute for Randomized Controlled Trials? Clin Pharmacol Ther 2017;102:924-933.

42. Coyle DT, Pratt CY, Ocran-Appiah J, Secora A, Kornegay C, Staffa J. Opioid analgesic dose and the risk of misuse, overdose, and death: A narrative review. Pharmacoepidemiol Drug Saf 2018;27:464-472.

43. Sun EC, Dixit A, Humphreys K, Darnall BD, Baker LC, Mackey S. Association between concurrent use of prescription opioids and benzodiazepines and overdose: retrospective analysis. BMJ 2017;356:j760.

44. Khan NF, Bykov K, Glynn RJ, Barnett ML, Gagne JJ. Co-prescription of opioids with other medications and risk of opioid overdose. Clin Pharmacol Ther 2021.

45. Linder JA. Editorial commentary: antibiotics for treatment of acute respiratory tract infections: decreasing benefit, increasing risk, and the irrelevance of antimicrobial resistance. Clin Infect Dis 2008;47:744-746.

46. Shehab N, Lovegrove MC, Geller AI, Rose KO, Weidle NJ, Budnitz DS. US Emergency Department Visits for Outpatient Adverse Drug Events, 2013-2014. JAMA 2016;316:2115-2125.

47. Shehab N, Patel PR, Srinivasan A, Budnitz DS. Emergency department visits for antibiotic-associated adverse events. Clin Infect Dis 2008;47:735-743.

48. Centers for Disease Control and Prevention. Adverse Drug Events from Specific Medicines. 2019. Available at https://www.cdc.gov/medicationsafety/adverse-drug-events-specific-medicines.html.

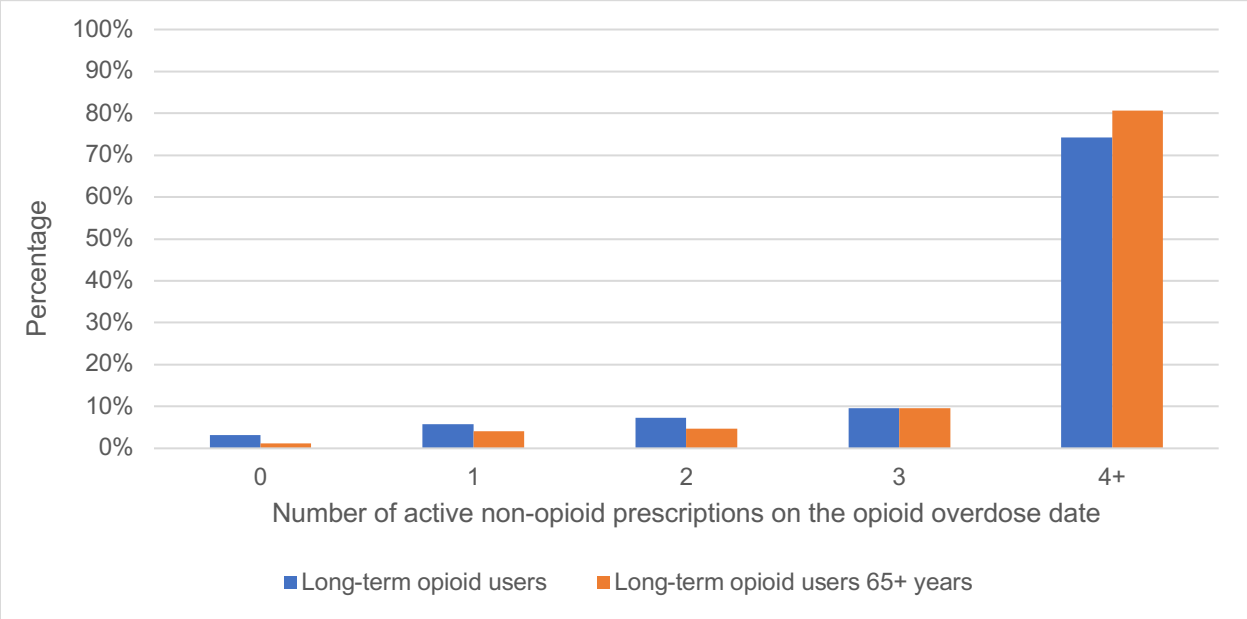
49. Methadone and cipro interaction. AIDS Patient Care STDS 2001;15:175.

50. Herrlin K, Segerdahl M, Gustafsson LL, Kalso E. Methadone, ciprofloxacin, and adverse drug reactions. Lancet 2000;356:2069-2070.

51. Lipsitch M, Tchetgen Tchetgen E, Cohen T. Negative controls: a tool for detecting confounding and bias in observational studies. Epidemiology 2010;21:383-388.

Supplemental Material

Figure S1.1 Number of active non-opioid prescriptions on the opioid overdose date in patients on long-term opioid therapy between 2015-2017 in IBM® MarketScan® (n = 2,295)



[a]Prescriptions were considered active on the opioid overdose date if the dispensing date and days' supply overlapped with the event date.

Figure S1.2 Eligibility criteria for inclusion in case-crossover-based screening framework

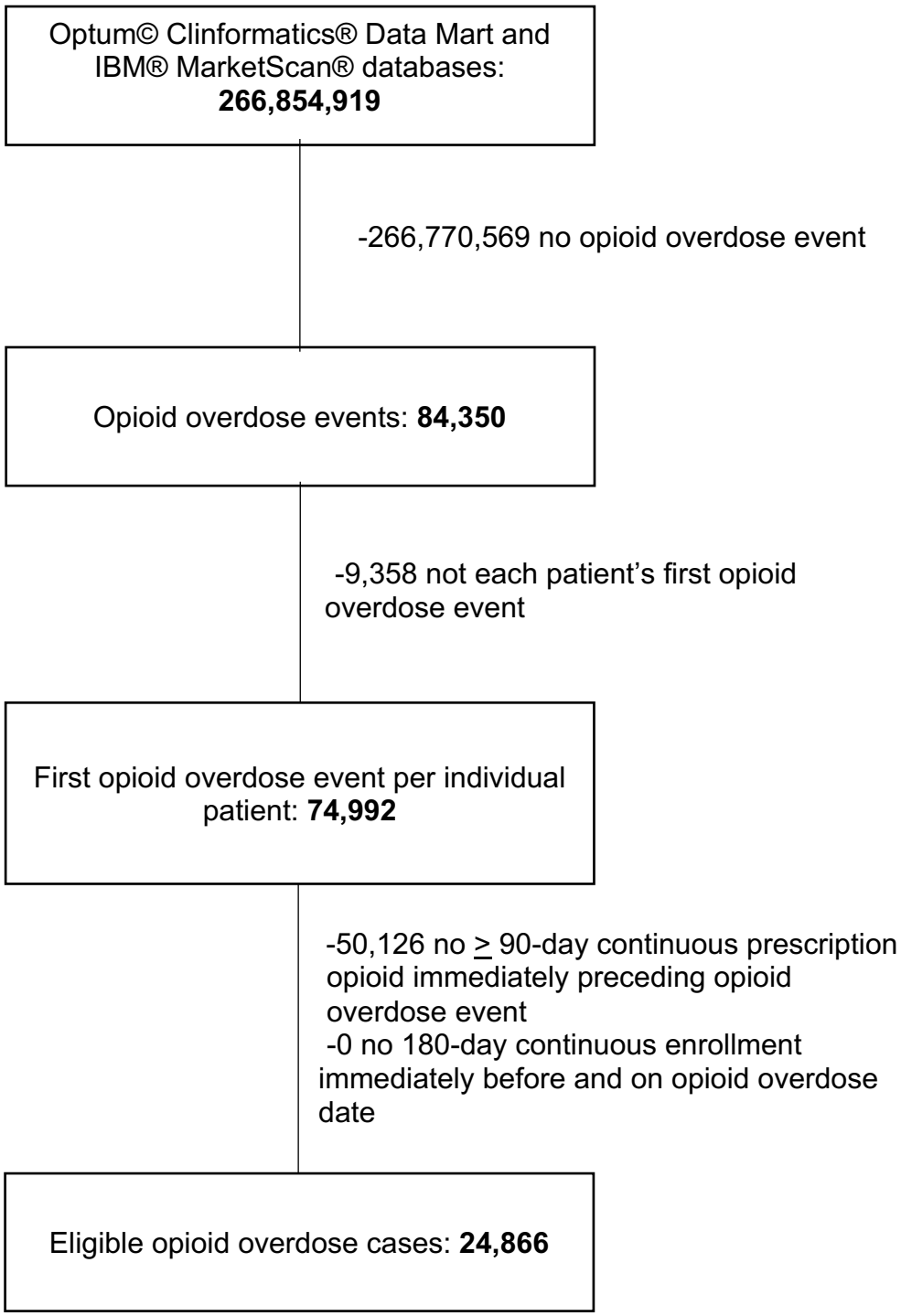


Table S1.1 Most commonly dispensed opioid and non-opioid prescriptions active on the opioid overdose date in patients on long-term opioid therapy between 2015-2017 in IBM® MarketScan® (n = 2,295)

	Opioid prescriptions		Non-opioid prescriptions	
Rank	**Generic drug name**	**No. (%)**	**Generic drug name**	**No. (%)**
1	Oxycodone	1,178 (51.3)	Gabapentin	700 (30.5)
2	Hydrocodone	721 (31.4)	Alprazolam	476 (20.7)
3	Morphine	429 (18.7)	Duloxetine	354 (15.4)
4	Fentanyl	353 (15.4)	Levothyroxine	344 (15.0)
5	Tramadol	250 (10.9)	Clonazepam	300 (13.1)
6	Hydromorphone	160 (7.0)	Lisinopril	296 (12.9)
7	Methadone	117 (5.1)	Metoprolol	290 (12.6)
8	Oxymorphone	99 (4.3)	Zolpidem	283 (12.3)
9	Codeine	87 (3.8)	Omeprazole	266 (11.6)
10	Tapentadol	55 (2.4)	Atorvastatin	256 (11.2)

[a]Prescriptions were considered active on the opioid overdose date if the dispensing date and days' supply overlapped with the event date.
[b]Categories are not mutually exclusive.
[c]Other opioid prescriptions active on the opioid overdose date: Buprenorphine [18 (0.8)], butorphanol [5 (0.2)], meperidine [3 (0.1)], pentazocine [3 (0.1)], opium [2 (0.1)], dihydrocodeine [(1 (< 0.1)], levorphanol [1 (< 0.1)].

Table S1.2 Prescription opioids used to define long-term use

Generic drug name	Included combinations
Butorphanol	• Butorphanol tartrate
Codeine	• Acetaminophen/codeine phosphate • Aspirin/codeine phosphate • Butalbital/acetaminophen/caffeine/codeine phosphate • Carisoprodol/aspirin/codeine phosphate • Codeine phosphate/aspirin/caffeine/butalbital • Codeine phosphate • Codeine sulfate
Dihydrocodeine	• Acetaminophen/caffeine/dihydrocodeine bitartrate • Dihydrocodeine bitartrate/aspirin/caffeine
Fentanyl	• Fentanyl • Fentanyl citrate
Hydrocodone	• Hydrocodone bit/acetaminophen • Hydrocodone bitartrate/acetaminophen/dietary supplement #11 • Hydrocodone bitartrate • Hydrocodone bitartrate/acetaminophen • Hydrocodone/ibuprofen
Hydromorphone	• Hydromorphone hcl • Hydromorphone hcl/bupivacaine hcl/sodium replacement 0.9%/pf
Levorphanol	• Levorphanol tartrate
Meperidine	• Meperidine hcl • Meperidine hcl/promethazine hcl
Methadone	• Methadone hcl
Morphine	• Morphine sulfate • Morphine sulfate/naltrexone hcl
Opium	• Opium • Opium tincture • Opium/belladonna alkaloids
Oxycodone	• Ibuprofen/oxycodone hcl • Oxycodone hcl • Oxycodone hcl/acetaminophen • Oxycodone hcl/oxycodone terephthalate/aspirin • Oxycodone hcl/aspirin

Table S1.2 (Continued)

Generic drug name	• Included combinations
Oxymorphone	• Oxymorphone hcl
Pentazocine	• Pentazocine hcl/naloxone hcl • Pentazocine hcl/acetaminophen
Tapentadol	• Tapentadol hcl
Tramadol	• Tramadol hcl • Tramadol hcl/acetaminophen • Tramadol hcl/dietary supplement,misc. cb.11

Table S1.3 ICD-9-CM and ICD-10-CM code definitions for opioid overdose in claims data

ICD-9-CM definition		ICD-10-CM definition (ending in A, D, or S)	
965.00	Poisoning by opium (alkaloids) unspecified	T40.0X1x T40.0X2x T40.0X3x T40.0X4x	Poisoning by opium
965.02	Poisoning by methadone	T40.2X1x T40.2X2x T40.2X3x T40.2X4x	Poisoning by other opioids
965.09	Poisoning by other opiates and related narcotics	T40.3X1x T40.3X2x T40.3X3x T40.3X4x	Poisoning by methadone
E850.1	Accidental poisoning by methadone	T40.4X1x T40.4X2x T40.4X3x T40.4X4x	Poisoning by other synthetic narcotics
E850.2	Accidental poisoning by other opiates and related narcotics	T40.601x T40.602x T40.603x T40.604x	Poisoning by unspecified narcotics
		T40.691x T40.692x T40.693x T40.694x	Poisoning by other narcotics

Table S1.4 Number of distinct non-opioid prescriptions dispensed per patient in the hazard and referent windows among patients who experienced opioid overdose on long-term opioid therapy (n = 24,866)

Hazard window		Referent window	
Number of distinct non-opioid prescriptions dispensed per patient	No. (%)	Number of distinct non-opioid prescriptions dispensed per patient	No. (%)
0	1,293 (5.2)	0	1,347 (5.4)
1	2,136 (8.6)	1	2,329 (9.4)
2	2,727 (11.0)	2	2,853 (11.5)
3	2,955 (11.9)	3	3,076 (12.4)
≥ 4	15,755 (63.4)	≥ 4	15,261 (61.4)

Table S1.5 Most common non-opioid prescriptions dispensed in the hazard and referent windows among patients on long-term opioid therapy who experienced opioid overdose (n = 24,866)

	Hazard window		Referent window	
Rank	**Generic drug name**	**No. (%)**	**Generic drug name**	**No. (%)**
1	Gabapentin	5,479 (22.0)	Gabapentin	5,238 (21.1)
2	Alprazolam	5,025 (20.2)	Alprazolam	4,774 (19.2)
3	Zolpidem	3,256 (13.1)	Zolpidem	3,228 (13.0)
4	Clonazepam	2,928 (11.8)	Clonazepam	2,656 (10.7)
5	Duloxetine	2,502 (10.1)	Duloxetine	2,474 (9.9)
6	Carisoprodol	2,451 (9.9)	Levothyroxine	2,431 (9.8)
7	Levothyroxine	2,351 (9.5)	Carisoprodol	2,399 (9.6)
8	Furosemide	2,272 (9.1)	Trazodone	2,241 (9.0)
9	Trazodone	2,269 (9.1)	Lisinopril	2,229 (9.0)
10	Diazepam	2,266 (9.1)	Furosemide	2,175 (8.7)

[a]Categories are not mutually exclusive. The same patient could be dispensed multiple distinct non-opioid prescriptions in the hazard and referent windows, respectively.