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Associations between naloxone prescribing and opioid overdose among patients with acute and chronic pain conditions

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ABSTRACT

Aims To assess whether naloxone prescribing in clinical contexts targeted pain patients most at risk for opioid overdose. **Design** A retrospective cohort study using data from the Health Facts Database. **Setting** Over 600 United States healthcare facilities. **Participants** Three patient groups were followed for 2 years during 2009 to 2017: individuals with shoulder or long bone fractures (n = 252 424), chronic pain syndrome (CPS) (n = 76 141), or non-traumatic low back pain (n = 792 956) who received an opioid prescription. Groups were chosen based on previous work. **Measurements** The outcome was opioid overdose identified by International Classification of Diseases codes (ICDs) and the primary predictor was number of naloxone prescriptions identified by National Drug Codes (NDCs). **Findings** Opioid overdoses occurred among 0.16% of fracture patients (average follow-up time to overdose [AFU] = 240 days), 1.28% of CPS patients (AFU = 244 days), and 0.30% low back pain patients (AFU = 264 days). A total of 58 083 bone fracture patients received naloxone prescriptions, and naloxone prescription was associated with subsequent opioid overdose (hazard ratio [HR] = 1.87, 95% CI = 1.68–2.09), and number of subsequent overdoses (incidence rate ratio [IRR] = 1.89, 95% CI = 1.69–2.12). A total of 19 529 CPS patients received naloxone prescriptions, and naloxone prescription was associated with subsequent opioid overdose (HR = 1.69, 95% CI = 1.61–1.78) and number of subsequent overdoses (IRR = 1.74, 95% CI = 1.67–1.83). A total of 110 608 low back pain patients received naloxone prescriptions, and naloxone prescription was associated with subsequent opioid overdose (HR = 1.33, 95% CI = 1.27–1.40) and number of subsequent overdoses (IRR = 1.35, 95% CI = 1.29–1.41). **Conclusions** Receiving a naloxone prescription appears to be associated with increased risk of subsequent opioid overdose among patients with acute and chronic pain, suggesting prescribers often identify patients most in need of naloxone.

Keywords Acute pain, chronic pain, harm reduction, naloxone, opioids, overdose, prescribing.

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INTRODUCTION

The United States (US) government authorities such as the Substance Abuse and Mental Health Services Administration [1] and the Office of the Surgeon General [2] support naloxone distribution for preventing opioid overdose deaths. Naloxone is an opioid antagonist that temporarily reverses respiratory depression and sedation, and dramatically reduces opioid overdose fatalities [3]. It was largely used in the United States by emergency medical personnel until harm reduction advocates pushed for wider availability, including via pharmacies [4]. US pharmacy-based naloxone dispensing has increased significantly, especially since 2015 [5]. Co-prescription of naloxone and opioids has been recommended by the US Department of Health and Human Services since late 2018 and recent laws in some states have subsequently required naloxone co-prescription for patients at risk of overdose [6,7]. Analyses of naloxone prescribing behaviors have largely examined the effects of naloxone policies on prescribing practices [6,8], characteristics of patients prescribed naloxone [9,10], or provider attitudes [11,12], however less is known about subsequent outcomes among patients co-prescribed naloxone in US clinical contexts.

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Although there appears to be growing acceptance and uptake of naloxone among some classes of prescribers [13], especially among those receiving naloxone training [11,14], barriers to effective overdose education and naloxone prescribing remain. Logistical barriers include time pressure during visits [13,15], uncertainty regarding billing [15,16], and limited knowledge of how to identify patients from target populations and best practices for overdose education [13]. Attitudes among providers may also affect acceptance and prescribing. Provider fears of offending patients [15,17] and concerns that naloxone may provide tacit approval of risky substance use [13,15,18] also can pose barriers. The majority of peer-reviewed studies contradict these concerns and show significant improvements among populations served by community overdose prevention and naloxone programs, such as reduced overdose deaths [3,19], increased knowledge of how to prevent overdose [20], reduction in frequency of heroin use [20], and fewer opioid-related emergency department visits [21].

In light of community naloxone program success and calls for physicians to co-prescribe naloxone with opioids to patients most at risk for overdose [22], this study uses national US data to (i) estimate whether naloxone co-prescribed with opioids in clinical settings is associated with subsequent opioid overdose among patients with acute or chronic pain conditions; and (ii) estimate whether naloxone prescription is associated with a greater number of subsequent overdoses among acute or chronic pain patients. These analyses will assist in determining whether recent increases in naloxone prescribing among health professionals outside of dedicated harm reduction programs are appropriately targeting the highest risk patients.

METHODS

Study sample

Data were drawn from the Health Facts database, which includes electronic health records (EHR) for over 62 million unique patients from over 600 hospitals/clinics using the Cerner EHR system. EHR from 2009 through 2017 were used in the analyses. International Classification of Diseases (ICD)-9 and ICD-10 codes were used to identify patients with either long bone or shoulder fracture (ICD-9: 812, 813, 821, 823 and ICD-10: S42, S52, S72, S82), chronic pain syndrome (ICD-9: 338.4 and ICD-10: G89.4), or non-traumatic low back pain (ICD-9: 724 and ICD-10: M54.5) as their primary reason for visit. Because of the size of the Health Facts database, obtaining manageable sample sizes for analysis requires data queries to target particular procedures, prescriptions, health conditions, or other defined parameters. Long bone and shoulder fractures were selected as a query parameter because of its use in previous opioid research as an example of an acute pain condition with defined duration [23,24]. Two chronic pain conditions were also selected because previous research shows such conditions with uncertain prognoses affect opioid prescribing [25]. Both non-traumatic low back pain and chronic pain syndrome (CPS) were top primary reasons for visit involving chronic pain, for which opioids are prescribed in the database. Patients were selected for the sample if they had an encounter documented in the EHR during which their primary reason for visit was long bone or shoulder fracture, CPS, or non-traumatic low back pain and the patient received an opioid prescription. Finally, patients under 15 years of age were excluded from the final sample data. The resulting patient samples includes charts from 252 424 unique fracture patients, 76 141 unique CPS patients, and 792 956 unique low back pain patients using Cerner hospitals/clinics from 2009 to 2017. There was some overlap across patient samples. Although unique individuals are only represented once within each of the CPS, low back pain, and fracture samples, a proportion of individuals are represented in multiple samples as shown in Fig. 1. Stratified analysis by type of diagnosis (i.e. long bone or shoulder fracture, CPS, and non-traumatic low back pain) was conducted because of the crude interaction effect of total number of naloxone prescriptions and type of diagnosis on the odds of subsequent opioid overdose ($\chi^2 = 48.63$, d.f. = 2, $P < 0.0001$) which is represented in Fig. 2. This illustrates that the association between the number of naloxone prescriptions and subsequent overdose depends on the type of diagnosis, therefore separate analyses were conducted among each pain diagnosis group so that these effects are not diluted.

Study design

This is a retrospective cohort study with 2 years of follow-up using the Health Facts database from the study period January 1, 2009 through December 31, 2016 for patient baseline data. At baseline, exposed patients were identified if they had opioid and naloxone prescriptions in the same encounter as a diagnosis for long bone or shoulder fracture, CPS, or low back pain. Non-exposed patients were identified if they had an opioid prescription in the same encounter as a diagnosis for long bone or shoulder fracture, CPS, or low back pain, but did not receive a naloxone prescription. All patients were followed for 2 years from baseline until the occurrence of an opioid overdose (for the Cox proportional hazard analysis) or until the end of the 2 years (for the Quasi-Poisson analysis) counting all opioid overdoses. Patients were only included and followed in each pain sample once. Although the majority of the sample included individuals with baseline data in the 2009–2015 period, therefore allowing for a full

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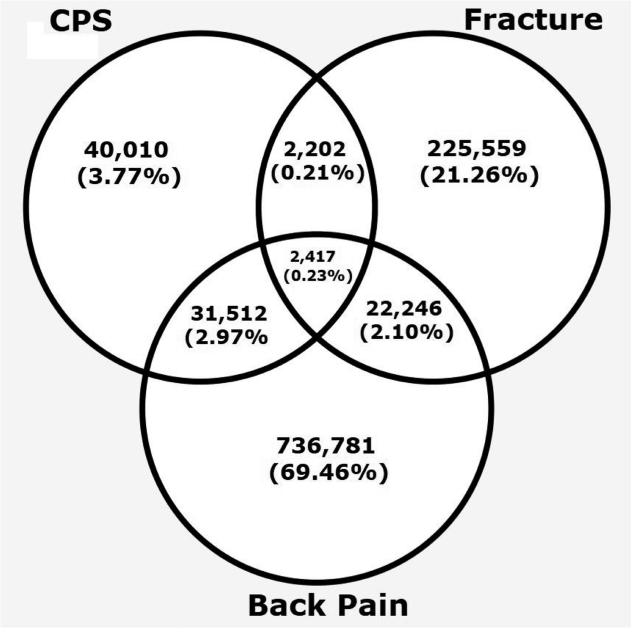

Figure 1 Chronic pain syndrome (CPS), low back pain, and fracture samples.

2-year follow-up (the data are through 2017), with rises in opioid overdoses and expansion of naloxone prescribing in later years of these data, individuals with baselines in 2016 were also included in the sample. Our sensitivity analysis showed that including patients with incomplete follow-up (i.e. <2years) did not change the conclusions of this study (changes in the results were observed only at the third decimal point) nor undermined its strength, because it allowed us to gain more statistical power.

Measures

Outcomes

For the Cox proportional hazard model, the dependent variable is composed of two parts including (i) time to opioid overdose (i.e. interval of risk); and (ii) event status, which records if the event of interest (i.e. opioid overdose) occurred or not. Opioid overdose events were identified using ICD codes (ICD-9: 965.00–09, E850.0–2 and ICD-10: T40.0–4, T40.6; defined in Supporting information Data S1, Table A). For the Quasi-Poisson regression model, the outcome is the count of opioid overdoses.

Key predictor

The primary exposure is the total number of naloxone prescriptions recorded in the EHR (i) during the baseline encounter, in which the primary reason for visit is one of the three pain conditions and the patient received an opioid prescription; and (ii) subsequent encounters before observing an opioid overdose within the 2-year follow-up window. Patients who received a prescription for naloxone were identified using National Drug Codes (NDCs) for all drugs categorized as naloxone hydrochloride (49 unique NDCs listed in Supporting information Data S1, Table B) [26].

Covariates

In the analyses, we controlled for whether patients had an outpatient opioid prescription, and if so, whether the prescription was for a low dose (<50 morphine milligram equivalents [MME]) or high dose (≥50 MME), as defined by Centers for Disease Control (CDC) guideline for prescribing opioids for chronic pain [27]. Outpatient opioid MME was calculated as dose quantity × Strength per Unit × MME conversion factor where the dose quantity is defined as the number of units to be administered to the patient. Strength per Unit and MME conversion factors were obtained for each NDC code from multiple sources using CDC databases linking NDCs with drug characteristics [28–31]. Opioids typically prescribed in inpatient settings, as well as injectable and intravenous opioids were categorized as "inpatient opioids" per CDC recommendations for analyses using MME to estimate prescription strength. These include: fentanyl in solution, buprenorphine in solution, alfentanil, sufentanil, opioids in powder, dezocine, remifentanil, apomorphine HCl, hexafluorenium, alphaprodine HCl, tincture of opium, topical tramadol, midazolam, and all opioids in solutions and delivered by injection and/or i.v. [32].

Analyses also controlled for histories of several health conditions, including whether the patient ever had a previous opioid overdose, mental health condition, chronic

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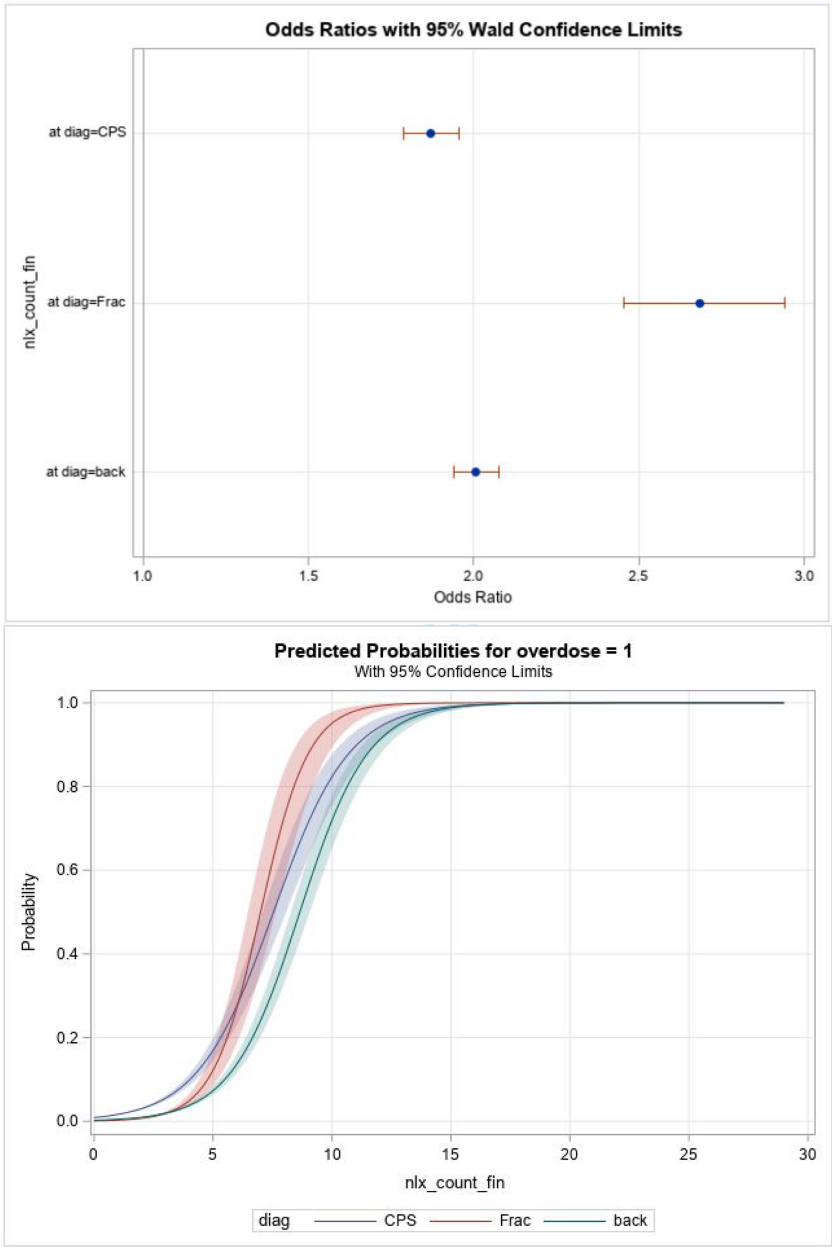

Figure 2 Top panel: The crude association between an increase of one prescription of naloxone and the odds of a subsequent opioid overdose by type of diagnosis (OR = 1.87, 2.69, 2.01; and 95% CI = 1.79–1.96, 2.45–2.94, and 1.94–2.08, respectively for CPS, fracture, and back pain); Bottom panel: The predicted probability of a subsequent overdose by the crude interaction effect of total number of naloxone prescriptions and type of diagnosis ($\chi^2 = 48.63$, d.f. = 2, $P < 0.0001$).

obstructive pulmonary disease (COPD), or sleep apnea recorded in the EHR any time before (or during) the baseline encounter. Additional controls included whether the patient had a benzodiazepine prescription up to 1 year before (or during) the baseline encounter, or whether they had been diagnosed with a non-opioid substance use disorder (SUD) or an opioid use disorder (OUD) up to 2 years before (or during) the baseline encounter. Patients with SUDs, OUDs, mental health conditions, COPD, and sleep apnea were identified using ICD-9 and ICD-10 codes (Supporting information Data S1, Table C). Benzodiazepine and opioid prescriptions were identified using NDCs (Supporting information Data S1, Tables D and E) (US Food and Drug Administration, n.d.). Models also controlled for patient sex, age, race/ethnicity, insurance type, and marital status, and hospital/clinic site information including geography and census region, and year to account for changes over time in naloxone prescribing trends [33].

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Data analysis

Two analysis approaches were used to evaluate the association between the number of naloxone prescriptions a patient received and the patient experiencing a subsequent opioid overdose. The first approach uses Cox proportional hazard models to estimate the hazard ratio (HR) of a subsequent opioid overdose after an opioid prescription among patients who received a naloxone prescription while adjusting for the independent variables described above. The Cox proportional hazard model estimates the time to a first opioid overdose event after 24 hours of receiving an opioid prescription during a visit where fracture, CPS, or low back pain were the primary reason for visit and within 2 years of that encounter. The starting point for follow-up was chosen as 24-hours after the patient's first naloxone prescription to assure a subsequent opioid overdose recorded in the EHR was not at the same encounter where naloxone was provided. The 2-year end period was chosen because 24 months is the approximate shelf life for naloxone. All patients who did not experience an opioid overdose within the 2 years of follow-up were right censored. The Cox proportional hazard analysis allowed for possible heterogeneity across hospitals/clinic sites by using the maximum likelihood estimates (MLEs) with sandwich variance estimate after considering observations with the same hospital identification number coming from the same cluster. These analyses were implemented in the PHREG procedure using the SAS 9.4 system (SAS Institute) by invoking the COVS (AGGREGATE) option and specifying the proper variable in the ID statement that distinguishes clusters in adopting a generalized estimating equations (GEE)-like marginal approach [34,35]. Overall goodness of fit for models was assessed by the Cox-Snell residuals [36], and the proportional hazards assumption was evaluated by the Schoenfeld residuals [37]. The three models for fracture, CPS, and low back pain achieved satisfactory overall goodness of fit and established the proportional hazards assumption as shown in Supporting information Data S1, Figs. S1, S2, and S3.

The second analysis approach uses Quasi-Poisson regressions to estimate the incidence rate ratio (IRR) of subsequent opioid overdoses after an opioid prescription among patients while adjusting for the same independent variables listed above. Quasi-Poisson modeling was used to account for overdispersion (i.e. violation of the equal mean and variance assumption). Overall goodness of fit was assessed by examining if the deviance followed a χ^2 distribution with degrees of freedom equal to the model residual. The three models in Table 4 achieved such assessment. GEE estimates with empirical standard error using the exchangeable correlation structure were used while considering observations with the same hospital ID coming from the same cluster. The Quasi-Poisson models determined whether there is an association between the number of naloxone prescriptions a patient received and the number of subsequent overdose events experienced by the patient in the same 2-year time period described above in the Cox proportional hazard models. These analyses were implemented using the SAS GENMOD procedure with the SCALE = PEARSON option, the REPEATED statement with SUBJECT = Hospital ID, and CORR = EXCH.

To determine whether the association between naloxone prescription and subsequent overdose varied among patients with pain caused by different conditions, separate Quasi-Poisson and Cox proportional hazard models were fit for each diagnosis: (i) for those with long bone and shoulder fracture; (ii) for those with CPS; and (iii) for those with low back pain, resulting in a total of six regressions. HRs and IRRs are deemed significant if their corresponding 95% CIs do not overlap with 1.00. Logistic regression modeling was also provided in supplemental results (see Supporting information Data S1, Table H) to illustrate odds of the event occurring during the 2-year window without considering the time to event.

To compare balance in the characteristics of fracture, CPS, and low back pain patients by status of naloxone prescription, the χ^2 test for independence was used for categorical variables and Wilcoxon rank sum test was used for skewed numeric variables. To assess effect sizes, Cohen's d and h were used for means and proportions, respectively, where ES = 0.20 indicates small effect, ES = 0.50: medium effect, and ES = 0.80: large effect. All statistical tests were completed in SAS 9.4 (SAS Institute) and were considered to be statistically significant if their *P*-values are <0.05. The primary research question of the study and analysis plan were not pre-registered on a publicly available platform and the results should be considered exploratory.

RESULTS

Descriptive statistics

The demographic characteristics of the study samples are presented in Table 1. Inpatient opioids were prescribed to 22.07% of long bone and shoulder fracture patients, 20.52% of CPS patients, and 35.23% of back pain patients (Supporting information Data S1, Table F). Opioids commonly prescribed for outpatient use were prescribed to 77.93% of fracture patients, 79.48% of CPS patients, and 64.77% of back pain patients. Naloxone was co-prescribed to 23.01% of fracture patients (n = 58 083), 25.65% of CPS patients (n = 19 529), and 13.95% of low back pain patients (n = 110 608) (Table 3). The average follow-up time for those who experienced an overdose after baseline is 240 days for long bone and shoulder fracture patients (234 days for those with naloxone and 247 for those without naloxone), 244 days for CPS patients (229 days for those with naloxone and 261 for those

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Table 1 Characteristics of long bone and shoulder fracture, chronic pain syndrome (CPS), and low back pain patients (2009–2017) by naloxone prescription status (%[a] = column percentage).

	Fracture				*CPS*				*Low back pain*			
	No naloxone n (%[a])	*Yes naloxone* n (%[a])	*ES*	*Total* n (%[a])	*No naloxone* n (%[a])	*Yes naloxone* n (%[a])	*ES*	*Total* n (%[a])	*No naloxone* n (%[a])	*Yes naloxone* n (%[a])	*ES*	*Total* n (%[a])
Total	194 341 (76.99)	58 083 (23.01)	NA	252 424 (100.00)	56 612 (74.35)	19 529 (25.65)	NA	76 141 (100.00)	682 348 (86.05)	110 608 (13.95)	NA	792 956 (100.00)
Mean age (±SD)	57.32 (±22.51)	63.54 (±20.85)	0.29	58.75 (±22.29)	56.43 (±15.59)	56.69 (±14.76)	0.02	56.50 (±15.38)	50.65 (±18.51)	56.81 (±17.64)	0.34	51.51 (±18.51)
Sex												
Female	112 283 (57.78)	35 594 (61.28)	0.07	147 877 (58.58)	34 921 (61.68)	12 254 (62.75)	0.02	47 175 (61.96)	396 405 (58.09)	66 751 (60.35)	0.05	463 156 (58.41)
Male	82 058 (42.22)	22 489 (38.72)		104 547 (41.42)	21 691 (38.32)	7275 (37.25)		28 966 (38.04)	285 943 (41.91)	43 857 (39.65)		329 800 (41.59)
Race/ethnicity												
African American	18 341	3927	0.10	22 268	5672	1732	0.04	7404	109 250	11 438	0.17	120 688
	(9.44)	(6.76)		(8.82)	(10.02)	(8.87)		(9.72)	(16.01)	(10.34)		(15.22)
Asian/Pacific Islander	3147	706	0.03	3853	315	118	0.01	433	8137	1047	0.02	9184
	(1.62)	(1.22)		(1.53)	(0.56)	(0.60)		(0.57)	(1.19)	(0.95)		(1.16)
Hispanic	1820	411	0.03	2231	280	110	0.01	390	9153	883	0.05	10 036
	(0.94)	(0.71)		(0.88)	(0.49)	(0.56)		(0.51)	(1.34)	(0.80)		(1.27)
Missing	4900	1070	0.05	5970	970	243	0.04	1213	14 249	1788	0.03	16 037
	(2.52)	(1.84)		(2.37)	(1.71)	(1.24)		(1.59)	(2.09)	(1.62)		2.02
Native American	3192	731	0.03	3923	525	238	0.03	763	8397	1508	0.01	9905
	(1.64)	(1.26)		(1.55)	(0.93)	(1.22)		(1.00)	(1.23)	(1.36)		1.25
Other	8678	1875	0.06	10 553	1443	496	0.00	1939	35 373	4010	0.08	39 383
	(4.47)	(3.23)		(4.18)	(2.55)	(2.54)		(2.55)	(5.18)	(3.63)		(4.97)
Non-Hispanic White	154 263	49 363	0.15	203 626	47 407	16 592	0.03	63 999	497 789	89 934	0.20	587 723
	(79.38)	(84.99)		(80.67)	(83.74)	(84.96)		(84.05)	(72.95)	(81.31)		(74.12)
Marital status												
Divorced/separated	18 201	5650	0.01	23 851	10 930	3581	0.02	14 511	88 755	14 171	0.01	102 926
	(9.37)	(9.73)		(9.45)	(19.31)	(18.34)		(19.06)	(13.01)	(12.81)		(12.98)
Missing	6159	2073	0.02	8232	1109	300	0.03	1409	16 100	2403	0.01	18 503
	(3.17)	(3.57)		(3.26)	(1.96)	(1.54)		(1.85)	(2.36)	(2.17)		(2.33)
Single	65 920	15 014	0.18	80 934	14 595	4701	0.04	19 296	234 867	27 453	0.21	262 320
	(33.92)	(25.85)		(32.06)	(25.78)	(24.07)		(25.34)	(34.42)	(24.82)		(33.08)
Widowed	33 950	13 083	0.13	47 033	7038	2158	0.04	9196	59 390	12 353	0.08	71 743
	(17.47)	(22.52)		(18.63)	(12.43)	(11.05)		(12.08)	(8.70)	(11.17)		(9.05)
Married/partnered	70 111	22 263	0.05	92 374	22 940	8789	0.09	31 729	283 236	54 228	0.15	337 464

(*Continues*)

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Table 1. (Continued)

	Fracture				*CPS*				*Low back pain*			
	No naloxone n (%[a])	*Yes naloxone n (%[a])*	*ES*	*Total n (%[a])*	*No naloxone n (%[a])*	*Yes naloxone n (%[a])*	*ES*	*Total n (%[a])*	*No naloxone n (%[a])*	*Yes naloxone n (%[a])*	*ES*	*Total n (%[a])*
	(36.08)	(38.33)		(36.59)	(40.52)	(45.00)		(41.67)	(41.51)	(49.03)		(42.56)
Insurance type												
Medicaid	18 839	3962	0.10	22 801	8079	2564	0.03	10 643	98 057	13 224	0.07	111 281
	(9.69)	(6.82)		(9.03)	(14.27)	(13.13)		(13.98)	(14.37)	(11.96)		(14.03)
Medicare	66 410	28 542	0.30	94 952	25 653	9682	0.09	35 335	175 958	42 716	0.28	218 674
	(34.17)	(49.14)		(37.62)	(45.31)	(49.58)		(46.41)	(25.79)	(38.62)		(27.58)
Missing	29 248	6213	0.13	35 461	5450	1597	0.05	7047	94 459	12 168	0.09	106 627
	(15.05)	(10.70)		(14.05)	(9.63)	(8.18)		(9.26)	(13.84)	(11.00)		(13.45)
Other	31 530	7861	0.08	39 391	5821	1667	0.06	7488	113 381	13 866	0.12	127 247
	(16.22)	(13.53)		(15.61)	(10.28)	(8.54)		(9.83)	(16.62)	(12.54)		(16.05)
Uninsured	17 760	2861	0.17	20 621	3256	663	0.11	3919	81 302	4965	0.28	86 267
	(9.14)	(4.93)		(8.17)	(5.75)	(3.39)		(5.15)	(11.92)	(4.49)		(10.88)
Private	30 554	8644	0.02	39 198	8353	3356	0.07	11 709	119 191	23 669	0.10	142 860
	(15.72)	(14.88)		(15.53)	(14.75)	(17.18)		(15.38)	(17.47)	(21.40)		(18.02)

[a]The χ^2 test for independence was used for categorical variables and Wilcoxon rank sum test was used for numeric variables (i.e. age). All variables were significantly associated with naloxone status at the 5% significance level. However, all effect sizes (Cohen's d for age, and Cohen's h for all other categorical variables) were small. Effect size, ES = 0.20: small effect, ES = 0.50: medium effect, ES = 0.80: large effect.

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without naloxone), and 264 days for low back pain patients (244 days for those with naloxone and 276 for those without naloxone). The prevalence of a subsequent opioid overdose among fracture patients who were prescribed naloxone is 0.36%, whereas 0.10% of fracture patients who did not receive a prescription experienced a subsequent opioid overdose. Among CPS patients, 2.70% of those who received a naloxone prescription experienced a subsequent opioid overdose, compared to 0.79% of CPS patients who did not receive a prescription. Finally, 0.81% of low back pain patients who received a naloxone prescription experienced a subsequent overdose, compared to 0.22% of low back pain patients who did not receive a prescription (Supporting information Data S1, Table F).

Inferential statistics

The Cox proportional hazard models controlling for confounding variables demonstrate variation in the magnitude of the association between naloxone prescription and subsequent opioid overdose (Table 2). Among fracture patients, an additional naloxone prescription was associated with 87% greater risk for experiencing a subsequent opioid overdose (HR = 1.87, 95% CI = 1.68–2.09), whereas CPS patients were at 69% greater risk for a subsequent overdose (HR = 1.69, 95% CI = 1.61–1.78) and low back pain patients were at 33% greater risk for a subsequent overdose (HR = 1.33, 95% CI = 1.27–1.40) for each one prescription increase in naloxone.

The primary analyses included all forms of naloxone, including generic and brand name formulations. Because EHR data do not indicate whether a prescription is for a drug administered during the encounter or a drug prescribed for outpatient use, we restricted a sub-analysis to only brand name formulations most typically prescribed on an outpatient basis. This sub-analysis used Cox proportional hazard models in which the key naloxone predictor only counted Narcan and Evzio prescriptions while controlling for the same covariates as the primary model. The results of the primary and sub-analysis models were similar, although slightly magnified with the sub-analysis approach: for each one prescription increase in a brand name naloxone formulation, fracture patients were at 183% greater risk (HR = 2.83, 95% CI = 1.80–4.47) for a subsequent opioid overdose, and patients with CPS and low back pain were at 160% (HR = 2.60, 95% CI = 1.90–3.57) and 46% (HR = 1.46, 95% CI = 1.11–1.91) greater odds of a subsequent overdose compared to those who did not receive brand name naloxone, respectively (see Supporting information Data S1, Table I for complete results). An additional sub-analysis also further restricted the data to only those with encounters during or after 2013, when outpatient naloxone prescribing became more commonplace [5], which resulted in even greater magnification of the primary analysis results: for each one prescription increase in brand name naloxone formulations during or after 2013, patients with fractures were at 246% greater risk (HR = 3.46, 95% CI = 1.89–6.36) for subsequent opioid overdose, patients with CPS were at 312% greater risk (HR = 4.12, 95% CI = 2.88–5.89) and those with low back pain were at 105% greater risk (HR = 2.05, 95% CI = 1.44–2.91) compared to patients who did not receive brand name naloxone. Restricting this sub-analysis further to only those individuals both co-prescribed an outpatient opioid and those with a history of an OUD or other SUD (i.e. groups at higher risk for opioid overdose) the results again indicate greater risk for subsequent overdose among patients prescribed brand name naloxone (fracture HR = 2.58, 95% CI = 1.93–3.44; CPS HR = 2.64, 95% CI = 1.62–4.29; low back pain HR = 1.47, 95% CI = 1.00–2.18).

The distribution of the number of subsequent opioid overdoses and the frequency of naloxone prescriptions among patients in each of the three pain condition samples are presented in Table 3. Quasi-Poisson models adjusting for the same confounding variables also demonstrated significant association between the number of naloxone prescriptions and higher numbers of subsequent opioid overdoses experienced by a patient (Table 4). Fracture patients had the greatest incidence of subsequent opioid overdose (IRR = 1.89, 95% CI = 1.69–2.12), followed by CPS patients (IRR = 1.74, 95% CI = 1.67–1.83), and low back pain patients (IRR = 1.35, 95% CI = 1.29–1.41).

There was some overlap between patient samples, in which patients were represented in the fracture sample, low back pain sample, and CPS sample, or a combination of overlap involving two samples (Fig. 1). Although 94.49% of individuals in the total study sample were only represented once, 5.51% of patients were represented more than once, therefore appearing in multiple models (see Supporting information Data S1, Table G). In a sub-analysis, the Cox proportional hazard models and Quasi-Poisson models were restricted to patients appearing only once across the three samples to determine if the results of the primary models were altered. The sub-analysis demonstrated results consistent with the primary analyses: patients only represented in the fracture sample (n = 225 559) exhibited both greater hazard of subsequent opioid overdose for an additional naloxone prescription (HR = 1.98, 95% CI = 1.71–2.28) and a greater number of subsequent overdoses (IRR = 1.89, 95% CI = 1.58–2.27). Similarly, patients only represented in the CPS sample (n = 40 010) also exhibited greater risk for subsequent overdose (HR = 1.84, 95% CI = 1.71–1.98) and a greater number of overdoses (IRR = 1.95, 95% CI = 1.79–2.13) for an additional naloxone prescription. Patients only represented in the low back pain sample (n = 736 781) also

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Table 2 Adjusted HRs for an opioid overdose (2009–2017).

Variable	*Bone fracture model*[a] *n = 252 424 HR (95% CI)*[b]	*Chronic pain syndrome model*[a] *n = 76 141 HR (95% CI)*[b]	*Low back pain model*[a] *n = 792 956 HR (95% CI)*[b]
No. of naloxone prescriptions (1-unit increment)	**1.87**[c] (1.68–2.09)	**1.69** (1.61–1.78)	**1.33** (1.27–1.40)
Opioid prescription			
Outpatient (≥50 MME)	**2.68** (1.51–4.78)	**1.38** (1.06–1.80)	**1.92** (1.60–2.31)
Outpatient (<50 MME)	1.08 (0.81–1.45)	**1.25** (1.01–1.55)	1.03 (0.93–1.14)
Inpatient opioid	Ref = 1	Ref = 1	Ref = 1
Benzodiazepine prescription			
Yes	**1.31** (1.03–1.67)	**1.33** (1.05–1.68)	**1.31** (1.18–1.46)
No	Ref = 1	Ref = 1	Ref = 1
OUD			
Yes	*1.57*[d] (0.94–2.61)	1.09 (0.91–1.3)	**1.57** (1.28–1.93)
No	Ref = 1	Ref = 1	Ref = 1
Race			
African American	**0.40** (0.23–0.70)	**0.57** (0.42–0.78)	**0.70** (0.58–0.85)
Asian/Pacific Islander	0.28 (0.05–1.70)	0.95 (0.45–2.02)	0.98 (0.60–1.61)
Hispanic	0.53 (0.12–2.34)	0.35 (0.09–1.39)	0.72 (0.49–1.07)
Missing	0.97 (0.43–2.19)	0.63 (0.28–1.43)	**0.66** (0.47–0.93)
Native American	1.18 (0.78–1.79)	0.87 (0.42–1.82)	**0.67** (0.47–0.96)
Other	0.79 (0.46–1.37)	**0.51** (0.28–0.92)	**0.67** (0.52–0.86)
Non-Hispanic White	Ref = 1	Ref = 1	Ref = 1
Sex			
Male	0.90 (0.73–1.10)	0.99 (0.86–1.15)	*1.08* (0.99–1.19)
Female	Ref = 1	Ref = 1	Ref = 1
Age (10-y increment)	**0.80** (0.75–0.86)	**0.91** (0.87–0.97)	**0.89** (0.85–0.92)
Marital status			
Divorced/separated	**1.52** (1.13–2.04)	**1.40** (1.21–1.63)	**1.52** (1.37–1.68)
Missing	0.67 (0.34–1.29)	0.79 (0.39–1.58)	0.77 (0.45–1.33)
Single	0.98 (0.72–1.33)	1.13 (0.94–1.36)	**1.19** (1.06–1.34)
Widowed	0.95 (0.67–1.35)	**1.34** (1.07–1.67)	**1.33** (1.13–1.58)
Married/partnered	Ref = 1	Ref = 1	Ref = 1
Insurance			
Medicaid	*1.54* (0.98–2.42)	**1.43** (1.03–1.99)	**1.89** (1.54–2.32)
Medicare	**1.89** (1.26–2.85)	**1.60** (1.21–2.12)	**1.90** (1.55–2.33)
Missing	1.15 (0.74–1.80)	1.04 (0.73–1.48)	**1.33** (1.04–1.70)
Other	1.33 (0.85–2.09)	**1.44** (1.05–1.99)	**1.42** (1.15–1.75)
Uninsured	1.38 (0.85–2.25)	**1.72** (1.16–2.53)	**1.86** (1.50–2.31)
Private	Ref = 1	Ref = 1	Ref = 1
Urban/rural status			
Rural	1.03 (0.77–1.37)	0.85 (0.68–1.08)	0.91 (0.72–1.16)
Urban	Ref = 1	Ref = 1	Ref = 1
Census region			
Midwest	0.81 (0.58–1.13)	0.77 (0.56–1.07)	**0.65** (0.53–0.80)
Northeast	*0.75* (0.56–1.02)	**0.62** (0.49–0.78)	**0.67** (0.51–0.88)
South	0.87 (0.65–1.18)	**0.74** (0.61–0.90)	**0.67** (0.55–0.82)
West	Ref = 1	Ref = 1	Ref = 1
Year (1-y increment)	**0.90** (0.85–0.95)	**0.86** (0.83–0.90)	**0.87** (0.84–0.89)
SUD (excluding OUD)			
Yes	**2.28** (1.64–3.16)	**1.69** (1.43–2.00)	**2.19** (1.86–2.58)
No	Ref = 1	Ref = 1	Ref = 1
Mental health diagnosis			
Yes	**2.93** (2.28–3.77)	**1.80** (1.52–2.12)	**2.44** (2.19–2.71)
No	Ref = 1	Ref = 1	Ref = 1
COPD			
Yes	**1.44** (1.12–1.84)	**1.40** (1.22–1.61)	**1.58** (1.42–1.76)
No	Ref = 1	Ref = 1	Ref = 1

(***Continues***)

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Table 2. (Continued)

Variable	*Bone fracture model*[a] *n = 252 424 HR (95% CI)*[b]	*Chronic pain syndrome model*[a] *n = 76 141 HR (95% CI)*[b]	*Low back pain model*[a] *n = 792 956 HR (95% CI)*[b]
Sleep apnea			
Yes	**2.01** (1.47–2.74)	1.11 (0.95–1.29)	1.04 (0.89–1.21)
No	Ref = 1	Ref = 1	Ref = 1
History of overdose			
Yes	**6.82** (4.54–10.26)	**4.11** (3.42–4.95)	**6.52** (5.45–7.81)
No	Ref = 1	Ref = 1	Ref = 1

CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; OUD = opioid use disorder; SUD = substance use disorder. [a]Model satisfied overall goodness of fit according to the Cox-Snell residuals, and achieved the proportional hazards assumption according to the Schoenfeld residuals. [b]Maximum likelihood estimates with sandwich variance estimate considering observations with the same hospital ID from the same cluster. [c]Bold indicates statistical significance at the 5% significance level. [d]Italic indicates being on the boundary of statistical significance (i.e. $0.05 < P$ value < 0.10).

Table 3 The distribution of opioid overdoses and naloxone prescriptions among unique patients within each pain condition sample (frequency and column percentages) from 2009–2017 for individuals age 15 or older.

	Frequency	*Fracture patients*	*CPS patients*	*Low back pain patients*
Opioid overdose, *n* (%)	None	252 020 (99.84)	75 167 (98.72)	790 544 (99.70)
	Once	214 (0.08)	485 (0.64)	1222 (0.15)
	Twice	153 (0.06)	353 (0.46)	894 (0.11)
	Three times	23 (0.01)	72 (0.09)	152 (0.02)
	Four times	9 (0.00)	33 (0.04)	83 (0.01)
	Five times	1 (0.00)	17 (0.02)	29 (0.00)
	Six times or more	4 (0.00)	14 (0.02)	32 (0.00)
Total no. of unique patients with at least one opioid overdose		404 (0.16)	974 (1.28)	2412 (0.30)
Naloxone prescription, *n* (%)	None	194 341 (76.99)	56 612 (74.35)	682 348 (86.05)
	Once	50 424 (19.98)	14 519 (19.07)	89 701 (11.31)
	Twice	6884 (2.73)	3824 (5.02)	16 918 (2.13)
	Three times	645 (0.26)	747 (0.98)	2763 (0.35)
	Four times	80 (0.03)	247 (0.32)	771 (0.10)
	Five times	36 (0.01)	107 (0.14)	248 (0.03)
	Six times or more	14 (0.01)	85 (0.11)	207 (0.03)
Total no. of unique patients with at least one naloxone prescription		58 083 (23.01)	19 529 (25.65)	110 608 (13.95)

exhibited greater opioid overdose risk (HR = 1.33, 95% CI = 1.25–1.41) and greater numbers of overdoses (IRR = 1.35, 95% CI = 1.28–1.43).

DISCUSSION

These analyses show naloxone prescriptions in clinical contexts are associated with increased risk for subsequent overdose and greater numbers of subsequent overdoses among patients prescribed opioids with long bone and shoulder fracture, non-traumatic low back pain, and CPS. These findings suggest prescribers often correctly identify the chronic and acute pain patients at highest risk for overdose. Even after controlling for relevant clinical risk factors captured in EHR, patients with forms of chronic and acute pain who are prescribed naloxone exhibit greater risk for subsequent overdose, which may mean prescribers also solicit additional information about overdose risk factors during clinical interactions that is not captured in health records, but influences their prescribing practices. Our analysis controls for many known overdose risk factors, such as history of overdose or SUDs and high dose opioid prescriptions [38], but it is possible that additional considerations known to affect overdose risk are revealed in clinical interactions. These may include social factors such as homelessness [39] and physical signs of injection drug use [40]. Although the Institute of Medicine has called for improved documentation of social and behavioral

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Table 4 Adjusted IRRs for opioid overdoses (2009–2017).

Variable	*Bone fracture model*[a] *n = 252 424 IRR (95% CI)*[b]	*Chronic pain syndrome model*[a] *n = 76 141 IRR (95% CI)*[b]	*Low back pain model*[a] *n = 792 956 IRR (95% CI)*[b]
No. of naloxone prescriptions (1-unit increment)	**1.89**[c] (1.69–2.12)	**1.74** (1.67–1.83)	**1.35** (1.29–1.41)
Opioid prescription			
Outpatient (≥50 MME)	**2.89** (1.59–5.25)	**1.44** (1.12–1.85)	**1.89** (1.56–2.29)
Outpatient (<50 MME)	1.13 (0.84–1.52)	**1.37** (1.10–1.69)	1.01 (0.91–1.11)
Inpatient opioid	Ref = 1	Ref = 1	Ref = 1
Benzodiazepine prescription			
Yes	**1.36** (1.05–1.74)	**1.39** (1.07–1.82)	**1.29** (1.18–1.42)
No	Ref = 1	Ref = 1	Ref = 1
OUD			
Yes	1.47 (0.86–2.49)	1.05 (0.86–1.28)	**1.49** (1.18–1.87)
No	Ref = 1	Ref = 1	Ref = 1
Race			
African American	**0.37** (0.20–0.68)	**0.56** (0.40–0.79)	**0.67** (0.54–0.84)
Asian/Pacific Islander	0.35 (0.06–2.09)	0.74 (0.33–1.68)	0.97 (0.61–1.54)
Hispanic	0.65 (0.15–2.81)	**0.21** (0.06–0.71)	**0.62** (0.39–0.97)
Missing	0.86 (0.38–1.96)	0.65 (0.28–1.50)	**0.58** (0.42–0.80)
Native American	1.43 (0.91–2.26)	0.72 (0.38–1.36)	0.66 (0.38–1.15)
Other	0.87 (0.48–1.60)	0.47 (0.19–1.17)	**0.66** (0.51–0.85)
Non-Hispanic White	Ref = 1	Ref = 1	Ref = 1
Sex			
Male	0.90 (0.70–1.14)	0.97 (0.85–1.11)	*1.08*[d] (0.99–1.19)
Female	Ref = 1	Ref = 1	Ref = 1
Age (10-y increment)	**0.78** (0.73–0.84)	*0.94* (0.88–1.01)	**0.90** (0.87–0.94)
Marital status			
Divorced/separated	**1.70** (1.13–2.57)	**1.52** (1.29–1.79)	**1.50** (1.34–1.68)
Missing	0.74 (0.37–1.48)	0.78 (0.38–1.60)	0.74 (0.41–1.33)
Single	1.04 (0.73–1.47)	**1.33** (1.08–1.63)	**1.22** (1.10–1.37)
Widowed	1.14 (0.77–1.69)	**1.40** (1.08–1.82)	**1.33** (1.12–1.59)
Married/partnered	Ref = 1	Ref = 1	Ref = 1
Insurance			
Medicaid	1.41 (0.92–2.17)	*1.33* (0.95–1.86)	**1.75** (1.40–2.18)
Medicare	**1.75** (1.18–2.61)	**1.53** (1.19–1.98)	**1.76** (1.44–2.16)
Missing	1.04 (0.63–1.71)	0.90 (0.62–1.29)	1.20 (0.92–1.56)
Other	1.20 (0.70–2.07)	**1.50** (1.06–2.14)	**1.27** (1.04–1.57)
Uninsured	1.15 (0.67–1.96)	**1.62** (1.11–2.36)	**1.70** (1.35–2.16)
Private	Ref = 1	Ref = 1	Ref = 1
Urban/rural status			
Rural	1.00 (0.71–1.43)	0.94 (0.72–1.22)	1.02 (0.8–1.29)
Urban	Ref = 1	Ref = 1	Ref = 1
Census region			
Midwest	0.86 (0.57–1.30)	*0.68* (0.44–1.04)	**0.65** (0.51–0.83)
Northeast	**0.69** (0.49–0.97)	**0.59** (0.46–0.76)	**0.57** (0.43–0.76)
South	0.80 (0.56–1.14)	**0.77** (0.60–0.99)	**0.63** (0.49–0.81)
West	Ref = 1	Ref = 1	Ref = 1
Year (1-y increment)	**0.85** (0.80–0.91)	**0.82** (0.78–0.87)	**0.82** (0.79–0.85)
SUD (excluding OUD)			
Yes	**2.30** (1.57–3.37)	**1.73** (1.43–2.10)	**2.15** (1.79–2.59)
No	Ref = 1	Ref = 1	Ref = 1
Mental health diagnosis			
Yes	**2.90** (2.21–3.8)	**1.80** (1.49–2.17)	**2.44** (2.19–2.71)
No	Ref = 1	Ref = 1	Ref = 1
COPD			
Yes	**1.56** (1.18–2.05)	**1.44** (1.24–1.67)	**1.72** (1.48–2.01)

(***Continues***)

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Table 4. (Continued)

Variable	*Bone fracture model*[a] *n = 252 424 IRR (95% CI)*[b]	*Chronic pain syndrome model*[a] *n = 76 141 IRR (95% CI)*[b]	*Low back pain model*[a] *n = 792 956 IRR (95% CI)*[b]
No	Ref = 1	Ref = 1	Ref = 1
Sleep apnea			
Yes	**1.99** (1.41–2.80)	1.14 (0.95–1.37)	1.02 (0.88–1.19)
No	Ref = 1	Ref = 1	Ref = 1
History of overdose			
Yes	**6.48** (4.08–10.29)	**4.02** (3.07–5.25)	**7.15** (5.81–8.81)
No	Ref = 1	Ref = 1	Ref = 1

COPD = chronic obstructive pulmonary disease; IRR = Incident rate ratio; OUD = opioid use disorder; SUD = substance use disorder. [a]Quasi-Poisson Model satisfied overall goodness of fit (deviance follows a χ^2 distribution with degrees of freedom equal model residual). [b]GEE estimates with empirical standard error using the exchangeable correlation structure considering observations with the same hospital ID from the same cluster. [c]Bold indicates statistical significance at the 5% significance level. [d]Italic indicates being on the boundary of statistical significance (i.e. $0.05 < P$ value < 0.10).

factors like housing insecurity in EHR systems [41], the recommendations are not included in the EHR for available Health Facts data years. Previous research indicates patient race/ethnicity is also associated with naloxone prescription rates in ways that do not clearly match patient risk profiles [42], therefore research using more detailed data is needed to understand provider naloxone prescription decisions. The role of clinical interactions and social/behavioral factors would be better investigated using a different database, or through the collection of primary data.

Previous research has grappled with naloxone concerns and objections among providers because of fears of "risk compensation," [13,15,18] or instances when safety policies designed to prevent or lessen injury unintentionally encourage unsafe behavior by reducing perceptions of risk. This idea is resoundingly rejected by public health authorities as a factor that should limit distribution of, or access to naloxone [43,44]. Not only do public health authorities emphasize the primacy of reduced mortality as the goal of naloxone distribution regardless of increases in substance use [45], but scant evidence of risk compensation exists. These findings do not weigh in on risk compensation debates, as such an analysis would require a study design allowing for causal inference (this study only tests associations) and such a study should also consider the primary public health goal of net reduction in mortality among patients prescribed naloxone [45,46]. The increases in overdose exhibited among patients in the sample data are difficult to interpret without also being able to control for factors like regional increases in illicit fentanyl entering US drug markets. Therefore, this analysis cannot determine whether naloxone prescribing influences subsequent patient behavior, or if prescribers simply are responding to existing community and patient-level risk factors. Therefore, our findings do not contradict research showing reduction in overdose and risky substance use among people who use drugs and are enrolled in community overdose education and naloxone distribution programs. Such programs offer higher levels of patient education and support for naloxone distribution than the majority of clinical settings [20,47]. In fact, this study is best interpreted both as a sign that naloxone prescribing is appropriately targeting high risk patients and as a call for clinical settings offering naloxone prescriptions to also offer enhanced harm reduction support, as has been suggested in previous research of naloxone distribution in treatment settings [48].

Research suggests adapting and integrating elements of community naloxone and harm reduction programs into outpatient clinical contexts is both feasible and can contribute to improved patient outcomes. The Veteran's Health Administration (VHA) launched a national overdose education and naloxone distribution program that sought to mimic successes in small-scale community programs in a system-based approach. This program used a multi-stage process that developed standard naloxone kits and added these to the national formulary, identified target patient populations as those with OUDs and those prescribed opioids, drafted policies and clinician guidance for using risk assessment tools and issuing naloxone, trained staff in providing overdose education, and drafted educational resources for patients [49]. Almost 40 000 patients were prescribed naloxone in the first year of implementation, including to 55.8% of people prescribed opioids through the VHA. Over time, VHA sites that exposed all prescribers to the educational components of the intervention had more than five times the rate of naloxone prescribing compared to VHA sites where no providers were exposed to the intervention [50]. More piecemeal approaches to integrating community overdose education and naloxone distribution models have also been tested among facilities in less centralized healthcare systems. One study trained primary care teams in naloxone prescribing, including instruction in identifying high risk patients, using non-stigmatizing language, and improving knowledge of insurance coverage for naloxone. Primary

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care clinics were further supported by study staff that helped prescribers navigate logistical barriers to naloxone. Patients who received naloxone from trained teams experienced significant reductions in opioid-related emergency department visits [21]. Another intervention added therapists to an emergency department who offered overdose education (although no direct naloxone access) through motivational interviewing. This approach yielded similarly promising results in terms of lessened overdose risk behaviors and illicit opioid use over time among patients [51]. Peer support for people with OUDs is another common harm reduction practice that is growing in popularity among emergency departments as part of overdose response [52,53]. Expansion of peer support to patients using hospitals for chronic and acute pain may further assist patients with preventing subsequent overdose by providing patients a point of contact to discuss behavior change, safer substance use, and treatment.

The data used in these analyses only capture prescribing practices recorded in EHR and cannot indicate whether a prescription was filled and received by a patient. This and other limitations related to EHR data must be considered. The EHR data used in this study may reflect naloxone prescriptions that were never received by a patient. Naloxone varies in cost depending on generic versus brand name formulation and patient insurance coverage, and such costs may be prohibitive for patients, resulting in unfilled prescriptions. However, the focus of this study is on prescriber behavior, which is adequately captured in EHR. Insurance claims databases that indicate whether a patient actually received a prescription drug may be used in future research to examine whether insured patients who fill prescriptions for naloxone exhibit risk for subsequent overdose, however these data would also exclude uninsured patients who are captured in the data used in this study. EHR data also cannot capture non-prescription naloxone distributed by harm reduction programs, overdoses that occur outside of healthcare settings, whether an overdose was fatal or non-fatal, or details about prescriber education with patients, which may or may not include overdose prevention education. EHR data are limited in their ability to fully capture all patient healthcare encounters, and therefore, fully account for complete medical histories, because patients may use multiple clinics/hospitals, some of which may not use the EHR system from which the database draws patient records. However, many of the model predictors capturing relevant components of medical history, such as sleep apnea and SUDs, are generally chronic conditions, and therefore would be unlikely to change across the study window. Finally, EHR data rely on accurate diagnostic codes, and can suffer from coding errors, which may affect the measurement of the covariates used in the analyses. Despite these limitations, this study provides large sample sizes for an array of patients who come in contact with healthcare facilities, and therefore, still offers insight into the association between naloxone prescribing and opioid overdose.

CONCLUSIONS AND IMPLICATIONS

This study addresses the limited knowledge of opioid overdose among pain patients prescribed opioids and naloxone in clinical contexts. By showing there is a significant association between naloxone prescription and subsequent opioid overdose, these findings indicate prescribers correctly identify pain patients most in need of naloxone. The increased risk for overdose among acute and chronic pain patients also suggests that clinical settings may need to integrate harm reduction services, such as peer support and evidence-based approaches to safer substance use and overdose education, into their practices. Coordination with harm reduction programs that have long track records of successfully reducing risky substance use may be a key strategy for integrating such services into clinics and hospitals treating chronic and acute pain patients. Such programs may offer harm reduction training for clinical staff, and facilities may direct staff to refer patients to these community services. The findings of this research should be interpreted as an opportunity to increase targeted harm reduction support services among acute and chronic pain patients who are prescribed opioids and naloxone instead of a call for cessation of naloxone distribution. Future research may evaluate how such institutional policies and protocols linking chronic and acute pain patients at risk of overdose to additional harm reduction resources may affect substance use and overdose outcomes.

Declaration of Interests

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Author contributions

Fares Qeadan: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; software; supervision; validation;

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visualization. **Erin Madden:** Conceptualization; investigation; methodology; project administration.

References

1. SAMHSA. Naloxone [Internet]. 2016 [cited 2018 Feb 16]. Available from: https://www.samhsa.gov/medication-assisted-treatment/treatment/naloxone
2. Adams J. M. Increasing naloxone awareness and use: the role of health care practitioners. *JAMA* 2018; **319**: 2073–4.
3. Walley A. Y., Xuan Z., Hackman H. H., Quinn E., Doe-Simkins M., Sorensen-Alawad A., *et al*. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. *BMJ* 2013; **346**: f174.
4. Hanson B. L., Porter R. R., Zöld A. L., Terhorst-Miller H. Preventing opioid overdose with peer-administered naloxone: findings from a rural state. *Harm Reduct J* 2020; **17**: 4.
5. Guy G. P., Haegerich T. M., Evans M. E., Losby J. L., Young R., Jones C. M. Vital signs: pharmacy-based naloxone dispensing — United States, 2012–2018. *Morb Mortal Wkly Rep* 2019; **68**: 8.
6. Green T. C., Davis C., Xuan Z., Walley A. Y., Bratberg J. Laws mandating Coprescription of naloxone and their impact on naloxone prescription in five US states, 2014–2018. *Am J Public Health* 2020; **110**: 881–7.
7. Haffajee R. L., Cherney S., Smart R. Legal requirements and recommendations to prescribe naloxone. *Drug Alcohol Depend* 2020; **209**: 107896.
8. Smart R., Pardo B., Davis C. S. Systematic review of the emerging literature on the effectiveness of naloxone access laws in the United States. *Addiction* 2021; **116**: 6–17.
9. Follman S., Arora V. M., Lyttle C., Moore P. Q., Pho M. T. Naloxone prescriptions among commercially insured individuals at high risk of opioid overdose. *JAMA Netw Open* 2019; **2**: e193209–e193209.
10. Lin L. (Allison), Brummett CM, Waljee JF, Englesbe MJ, Gunaseelan V, Bohnert ASB. Association of Opioid Overdose Risk Factors and Naloxone Prescribing in US adults. *J Gen Intern Med* 2020; **35**: 420–7.
11. Behar E., Rowe C., Santos G.-M., Coffa D., Turner C., Santos N. C., *et al*. Acceptability of naloxone co-prescription among primary care providers treating patients on long-term opioid therapy for pain. *J Gen Intern Med* 2017; **32**: 291–5.
12. Muzyk A., Smothers Z. P. W., Collins K., MacEachern M., Wu L.-T. Pharmacists' attitudes toward dispensing naloxone and medications for opioid use disorder: a scoping review of the literature. *Subst Abus* 2019; **40**: 476–83.
13. Behar E., Bagnulo R., Coffin P. O. Acceptability and feasibility of naloxone prescribing in primary care settings: a systematic review. *Prev Med* 2018; **114**: 79–87.
14. Appel G., Avery J. J., Ho K., Livshits Z., Rao R. B., Avery J. Improved emergency medicine physician attitudes towards individuals with opioid use disorder following naloxone kit training. *Am J Emerg Med* 2020; **38**: 1039–41.
15. Binswanger I. A., Koester S., Mueller S. R., Gardner E. M., Goddard K., Glanz J. M. Overdose education and naloxone for patients prescribed opioids in primary care: a qualitative study of primary care staff. *J Gen Intern Med* 2015; **30**: 1837–44.
16. Salvador J. G., Sussman A. L., Takeda M. Y., Katzman W. G., Moya Balasch M., Katzman J. G. Barriers to and recommendations for take-home naloxone distribution: perspectives from opioid treatment programs in New Mexico. *Harm Reduct J* 2020; **17**: 31.
17. Green T. C., Case P., Fiske H., Baird J., Cabral S., Burstein D., *et al*. Perpetuating stigma or reducing risk? Perspectives from naloxone consumers and pharmacists on pharmacy-based naloxone in 2 states. *J Am Pharm Assoc JAPhA* 2017; **57**: S19–S27.e4.
18. Winograd R. P., Davis C. S., Niculete M., Oliva E., Martielli R. P. Medical providers' knowledge and concerns about opioid overdose education and take-home naloxone rescue kits within veterans affairs health care medical treatment settings. *Subst Abus* 2017; **38**: 135–40.
19. Katzman J. G., Takeda M. Y., Bhatt S. R., Moya Balasch M., Greenberg N., Yonas H. An innovative model for naloxone use within an OTP setting: a prospective cohort study. *J Addict Med* 2018; **12**: 113–8.
20. Seal K. H., Thawley R., Gee L., Bamberger J., Kral A. H., Ciccarone D., *et al*. Naloxone distribution and cardiopulmonary resuscitation training for injection drug users to prevent heroin overdose death: a pilot intervention study. *J Urban Health* 2005; **82**: 303–11.
21. Coffin P. O., Behar E., Rowe C., Santos G.-M., Coffa D., Bald M., *et al*. Non-randomized intervention study of naloxone co-prescription for primary care patients on long-term opioid therapy for pain. *Ann Intern Med* 2016; **165**: 245–52.
22. Giroir AdmBP. Spotlight on Naloxone Co-Prescribing [Internet]. HHS.gov. 2020 [cited 2020 Oct 28]. Available from: https://www.hhs.gov/blog/2020/08/31/spotlight-naloxone-co-prescribing.html
23. Fuentes E. F., Kohn M. A., Neighbor M. L. Lack of association between patient ethnicity or race and fracture analgesia. *Acad Emerg Med* 2002; **9**: 910–5.
24. Tamayo-Sarver J. H., Hinze S. W., Cydulka R. K., Baker D. W. Racial and ethnic disparities in emergency department analgesic prescription. *Am J Public Health* 2003; **93**: 2067–73.
25. Anderson K. O., Green C. R., Payne R. Racial and ethnic disparities in pain: causes and consequences of unequal care. *J Pain* 2009; **10**: 1187–204.
26. U.S. Food and Drug Administration. National Drug Code Directory [Internet]. [cited 2018 Oct 2]. Available from: https://www.accessdata.fda.gov/scripts/cder/ndc/
27. Centers for Disease Control and Prevention. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. MMWR Recomm Rep [Internet]. 2016 [cited 2019 May 9];65. Available from: https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm
28. CDC Injury Center. Data Resources: Drug Overdose [Internet]. 2020 [cited 2020 Oct 30]. Available from: https://www.cdc.gov/drugoverdose/resources/data.html
29. New York State Department of Health. National Drug Code MME Conversion Factor and Strength Per Unit [Internet]. 2020. Available from: https://health.ny.gov/professionals/narcotic/docs/ndc_mme_table.xNewlsx
30. Oregon Health Authority. Oral Morphine Milligram Equivalent Conversion Factors [Internet]. 2017. Available from: https://www.oregon.gov/oha/HPA/DSI/QIDocs/Opioid-Class-40-Drug-List.xlsx
31. World Health Information Science Consultants. Master Opioids LIst [Internet]. n.d. Available from: http://whiscon.com/uploads/3033-2_Master_Opioids_2019.09.06.xlsx
32. National Center for Injury Prevention and Control *CDC compilation of benzodiazepines, muscle relaxants, stimulants, zolpidem,*

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and opioid analgesics with oral morphine milligram equivalent conversion factors, 2017 version [Internet]. Atlanta, GA: Centers for Disease Control and Prevention; 2017 Available from: https://www.cdc.gov/drugoverdose/resources/data.html
33. Centers for Disease Control and Prevention. U.S. Opioid Prescribing Rate Maps [Internet]. 2018 [cited 2019 Feb 25]. Available from: https://www.cdc.gov/drugoverdose/maps/rxrate-maps.html
34. Gharibvand L. & Liu L. Analysis of Survival Data with Clustered Events [Internet]. 2009. (SAS Global Forum 2009 Statistics and Data Analysis). Available from: http://citeseerx.ist.psu.edu/viewdoc/download%3Fdoi%3D10.1.1.176.2418%26rep%3Drep1%26type%3Dpdf
35. Zeger S. L., Liang K.-Y. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 1986; **42**: 121–30.
36. Xue Y., Schifano E. D. Diagnostics for the cox model. *Commun Stat Appl Methods* 2017; **24**(6):583–604. https://doi.org/10.29220/csam.2017.24.6.583
37. Schoenfeld D. Partial residuals for the proportional hazards regression model. *Biometrika* 1982; **69**(1):239–41. https://doi.org/10.1093/biomet/69.1.239
38. Coffin P. O., Tracy M., Bucciarelli A., Ompad D., Vlahov D., Galea S. Identifying injection drug users at risk of nonfatal overdose. *Acad Emerg Med* 2007; **14**: 616–23.
39. O'Driscoll P. T., McGough J., Hagan H., Thiede H., Critchlow C., Alexander E. R. Predictors of accidental fatal drug overdose among a cohort of injection drug users. *Am J Public Health* 2001; **91**: 984–7.
40. Lin L., Hosanagar A., Park T. W., Bohnert A. Opioid overdose: risk assessment and mitigation in outpatient treatment. *J Addict Med* 2016; **10**: 382–6.
41. Institute of Medicine. Capturing Social and Behavioral Domains in Electronic Health Records: Phase 1 [Internet]. Washington (DC): National Academies Press (US); 2014 [cited 2018 Jul 23]. (The National Academies Collection: Reports funded by National Institutes of Health). Available from: http://www.ncbi.nlm.nih.gov/books/NBK195994/
42. Madden E. F., Qeadan F. Racial inequities in U.S. naloxone prescriptions. *Subst Abus* 2019; **0**: 1–13.
43. American Public Health Association. Prevention and Intervention Strategies to Decrease Misuse of Prescription Pain Medication [Internet]. 2015 Nov [cited 2018 Jul 18]. Report No.: Policy number 20154. Available from: https://www.apha.org/policies-and-advocacy/public-health-policy-statements/policy-database/2015/12/08/15/11/prevention-and-intervention-strategies-to-decrease-misuse-of-prescription-pain-medication
44. World Health Organization. Information sheet on opioid overdose [Internet]. WHO. 2014 [cited 2018 Jul 18]. Available from: http://www.who.int/substance_abuse/information-sheet/en/
45. Tas B., Humphreys K., McDonald R., Strang J. Should we worry that take-home naloxone availability may increase opioid use? *Addiction* 2019; **114**: 1723–5.
46. Frank R. G., Humphreys K. & Pollack H. A. Does Naloxone Availability Increase Opioid Abuse? The Case For Skepticism. Health Affairs Blog [Internet]. 2018 Mar 19 [cited 2021 Feb 18]; Available from: https://www.healthaffairs.org/do/10.1377/hblog20180316.599095/full/
47. Wagner K. D., Valente T. W., Casanova M., Partovi S. M., Mendenhall B. M., Hundley J. H., *et al*. Evaluation of an overdose prevention and response training programme for injection drug users in the skid row area of Los Angeles, CA. *Int J Drug Policy* 2010; **21**: 186–93.
48. Katzman J. G., Greenberg N. H., Takeda M. Y., Moya Balasch M., Katzman Joanna G., Greenberg Nina H., Takeda Mikiko Y. & Moya Balasch M. Characteristics of patients with opioid use disorder associated with performing overdose reversals in the community: An opioid treatment program analysis. *J. Addict. Med.* 2019;**13**(2):131–8. https://doi.org/10.1097/adm.0000000000000461
49. Oliva E. M., Christopher M. L. D., Wells D., Bounthavong M., Harvey M., Himstreet J., *et al*. Opioid overdose education and naloxone distribution: development of the veterans health Administration's national program. *J Am Pharm Assoc* 2017; **57**: S168–S179.e4.
50. Bounthavong M., Devine E. B., Christopher M. L. D., Harvey M. A., Veenstra D. L., Basu A. Implementation evaluation of academic detailing on naloxone prescribing trends at the United States veterans health administration. *Health Serv Res* 2019; **54**: 1055–64.
51. Bohnert A. S. B., Bonar E. E., Cunningham R., Greenwald M. K., Thomas L., Chermack S., *et al*. A pilot randomized clinical trial of an intervention to reduce overdose risk behaviors among emergency department patients at risk for prescription opioid overdose. *Drug Alcohol Depend* 2016; **163**: 40–7.
52. McGuire A. B., Powell K. G., Treitler P. C., Wagner K. D., Smith K. P., Cooperman N., *et al*. Emergency department-based peer support for opioid use disorder: emergent functions and forms. *J Subst Abuse Treat* 2020; **108**: 82–7.
53. Waye K. M., Goyer J., Dettor D., Mahoney L., Samuels E. A., Yedinak J. L., *et al*. Implementing peer recovery services for overdose prevention in Rhode Island: an examination of two outreach-based approaches. *Addict Behav* 2019; **89**: 85–91.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1 Supporting information.

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