Association of Opioid Overdose Risk Factors and Naloxone Prescribing in US Adults

Lewei (Allison) Lin, M.D., M.S.^{1,2,3}, Chad M. Brummett, M.D.^{3,4},
Jennifer F. Waljee, M.D., M.P.H., M.S.^{3,5}, Michael J. Englesbe, M.D.^{3,5},
Vidhya Gunaseelan, M.B.A., M.S., M.H.A.^{3,5}, and Amy S. B. Bohnert, Ph.D., M.H.S.^{1,2,3}

¹Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA; ²VA Center for Clinical Management Research (CCMR), VA Ann Arbor Healthcare System, Ann Arbor, MI, USA; ³Michigan Opioid Prescribing Engagement Network, Ann Arbor, MI, USA; ⁴Department of Anesthesiology, University of Michigan, Ann Arbor, MI, USA; ⁵Department of Surgery, University of Michigan, Ann Arbor, MI, USA.

BACKGROUND: Prescribing naloxone to patients is a key strategy to prevent opioid overdoses, but little is known about the reach of naloxone prescribing.

OBJECTIVE: Determine patient factors associated with receiving naloxone and trends over time in patients with key overdose risk factors.

DESIGN: Retrospective observational study.

PARTICIPANTS: Using the Clinformatics DataMart, a US-wide health insurance claims dataset, we compared adults who received opioids and naloxone (opioid+naloxone) from January 2014 to June 2017 with adults who received opioids without naloxone (opioids only), matched on gender, age $\pm$ 5 years, month/year of opioid fill, and number of opioid claims.

MAIN MEASURES: Key patient-level opioid overdose risk factors included receipt of high-dosage opioids, concurrent benzodiazepines, history of opioid and other substance use disorders, and history of opioid overdose.

RESULTS: We included 3963 opioid+naloxone and 19,815 opioid only patients. Key factors associated with naloxone fills included high opioid daily dosage (50 to < 90 morphine milligram equivalents (MME): AOR = 2.43, 95% CI 2.15–2.76 and $\geq$ 90 MME: AOR = 3.94, 95% CI 3.47–4.46; reference: < 50 MME), receiving concurrent benzodiazepines (AOR = 1.27, 95% CI 1.16–1.38), and having a diagnosis of opioid use disorder (AOR = 1.56, 95% CI 1.40–1.73). History of opioid overdose was not associated with naloxone (AOR = 0.92, 95% CI 0.74–1.15). The percent of patients receiving naloxone increased, yet less than 2% of patients in any of the key overdose risk factor groups received naloxone by the last 6 months of the study period.

CONCLUSIONS: Naloxone prescribing has increased and was more likely to be co-prescribed to patients with some risk factors for overdose. However, overall prescribing remains minimal. Additional efforts are needed across health systems to increase naloxone prescribing for patients at risk for opioid overdose.

KEY WORDS: overdose prevention; naloxone; opioids; opioid use disorder.

J Gen Intern Med 35(2):420–27

DOI: 10.1007/s11606-019-05423-7

© Society of General Internal Medicine (This is a U.S. government work and not under copyright protection in the U.S.; foreign copyright protection may apply) 2019

INTRODUCTION

Despite ongoing efforts to curb opioid-associated risks in the USA, opioid overdose mortality continues to rise.¹ Naloxone is a rapid-acting opioid antagonist medication that can reverse opioid overdose if administered in a timely way, and is a critical tool to prevent opioid overdose deaths. Historically, naloxone is often used by emergency medical services personnel to effectively reverse suspected opioid overdoses.² In recent years, particularly with the availability of easy-to-use formulations,³ providing naloxone to patients at risk for overdose and their family members to hasten time from overdose to naloxone administration has become a key strategy for overdose prevention.⁴ Primary care and other medical settings where opioids are routinely prescribed are a particularly important setting to prioritize naloxone prescribing. Naloxone prescribing in primary care to patients receiving opioids has been associated with reductions in ED visits and is an acceptable overdose prevention strategy to patients and providers.^{5,6}

In April 2018, the Surgeon General issued the “Advisory on Naloxone and Opioid Overdose,” which encourages healthcare providers to identify patients with risk factors for opioid overdose and prescribe naloxone to those patients to prevent overdose.^{7,8} Naloxone prescribing was also emphasized in the 2016 CDC Guideline for Prescribing Opioids for Chronic Pain, which specifically recommends “considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages ($\geq$ 50 MME/day), or concurrent benzodiazepine use are present.”⁹ These are key risk factors identified through prior studies of overdose.^{10–14}

However, the degree to which naloxone has been prescribed in recent years, and whether naloxone is being prescribed to patients at increased risk for overdose, remains poorly understood. Prior studies of naloxone have focused on distribution of naloxone within community-based programs,^{15,16} populations often

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s11606-019-05423-7>) contains supplementary material, which is available to authorized users.

Published online December 9, 2019

covered under Medicaid or are uninsured. However, there has been much less work examining naloxone in the commercially insured population or in general medical settings, which may be critical to reach a broader population at risk for overdose.

In this study, we examined patient factors associated with being prescribed naloxone among patients receiving opioids and trends in naloxone receipt among patient groups at high risk for overdose. We hypothesized that well-established risk factors for opioid overdose emphasized in the CDC Guidelines, which include prior history of overdose, history of opioid use disorder, higher opioid dosages, and benzodiazepine co-prescribing, are associated with naloxone prescribing. Naloxone receipt among these patients would indicate clinicians are appropriately prioritizing patients at risk for overdose. Understanding who is being prescribed naloxone helps elucidate the current scope of naloxone use, identify where gaps exist, and indicate if any patient populations should be further prioritized to receive naloxone.

METHODS

Study Design and Data Source

We analyzed data from Clinformatics® DataMart (OptumInsight, Eden Prairie, MN), a national insurance claims database that captures 30.6 million (19%) of the commercially insured population and 3.2 million (19%) of the Medicare Advantage population of the USA, including members in all 50 states, though with higher prevalence of covered lives in the Midwest, while lower in the South and West.¹⁷ This database includes patient-level data on enrollment, demographics, outpatient pharmacy fills, and treatment utilization. The University of Michigan human subjects review committee determined this study to be exempt from review based on the use of de-identified data.

We examined patient characteristics associated with naloxone receipt in a sample including all patients receiving naloxone and an opioid (opioid+naloxone) and a matched comparison group receiving an opioid without naloxone (opioid only). In a secondary analysis, we also described trends in the prevalence of naloxone fills in different patient populations at high risk for overdose including patients receiving high-dosage opioids, receiving concurrent benzodiazepines, having a diagnosis of opioid use disorder, and having a history of opioid overdose.

Sample

Patients were eligible for inclusion if they were age 18 and older, filled either an opioid or naloxone prescription from January 1, 2014 to June 30, 2017. Patients receiving opioid and naloxone were eligible for inclusion if they filled a naloxone prescription from January 1, 2014 to June 30, 2017, were age 18 and older, and filled the naloxone prescription within 30 days of an opioid prescription. We examined patient characteristics prior to the first naloxone fill during the study time period. We defined the index opioid fill as the date of the last opioid fill prior to the naloxone fill. To capture diagnoses and treatment data, patients must be

continuously enrolled in the insurance plan from at least 1 year prior to, and 1 month after, the index opioid fill. Limiting naloxone fills to 30 days after opioid prescription was chosen to allow us to capture as complete a sample of patients receiving naloxone as possible given the continuous enrollment criteria.

Opioid+naloxone patients were compared with opioid only patients during the study period. We matched patients who received both naloxone and opioids to patients receiving opioids without naloxone using a 1:5 matching ratio on the following: gender, age $\pm$ 5 years, number of opioid fills in the 12 months prior to the index opioid fill, and month and year of the index opioid fill. We matched on month and year of the index date to account for the changing trends in opioid prescribing during the study period.¹⁸

Measures

Data on patient demographics (age, gender, race/ethnicity, region of residence) available in enrollment files were included. Demographic information that was missing was coded as unknown. Receiving naloxone was the primary outcome of interest and was defined as patients receiving an outpatient fill for a naloxone prescription. Naloxone formulations included Evzio®, Narcan®, and naloxone HCl (in pre-filled syringes, sometimes used with a nasal spray adapter).¹⁹

Receiving opioids was defined as patients filling an outpatient prescription for an opioid analgesic (see Appendix Table 3 for included opioids). We excluded naloxone and opioid prescriptions that did not specify type of opioid, date of fill, days supply, or quantity. Opioid prescriptions filled in the 3 months prior to the index opioid fill were used to calculate average daily dosage. Morphine milligram equivalents (MME) were calculated for each opioid prescription and aggregated to determine the average daily MME over the 3 months.²⁰ Prescriptions in the 3 months prior to the index opioid fill were examined for receipt of long-acting opioids and for concurrent benzodiazepine fills (see Appendix Table 3 for included benzodiazepines).⁹ Concurrent benzodiazepines were defined as a benzodiazepine fill with days supply of medication that overlapped with the index date opioid fill by seven or more days.

History of overdose, substance use disorders, and other medical conditions were assessed using the International Classification of Disease (ICD-9-CM and ICD-10) diagnosis codes (Appendix Table 4). Mental health disorders were categorized based on the Agency for Healthcare and Quality Clinical Classification System (Appendix Table 5). We included medical and mental health disorders previously associated with opioid overdose in numerous studies.^{10,12,21,22} Diagnosis codes within 12 months prior to the index opioid fill were considered to determine history of overdose and all other comorbid conditions.

Primary Analyses

First, characteristics of opioid+naloxone patients were compared with opioid only patients using χ^2 tests. We then used conditional logistic regression to account for matching and

estimated adjusted odds ratios for individual patient characteristics and receipt of naloxone using robust standard errors. We included only characteristics that were significantly different between the two groups in the bivariate analysis.

Secondary Analysis

Across 6-month time periods from January 2014 through June 2017, we also examined trends in the percent of patients with naloxone receipt among separate patient populations considered high risk for opioid overdose (i.e., separate denominators of patients) including patients with receipt of high-dosage opioids (≥ 50 MME and ≥ 90 MME), receipt of a concurrent benzodiazepine, history of opioid use disorder, and history of opioid overdose. Patients must be continuously enrolled in the insurance plan but could fill naloxone at any time during each 6-month period.

All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and Stata version 14.2 (StataCorp). p values were 2-tailed and p values < 0.05 were considered statistically significant.

RESULTS

Overall Patients Receiving Naloxone

A total of 7151 patients filled 7813 naloxone prescriptions and 6,811,685 patients filled 35,398,892 opioid prescriptions during the study period. Among those who filled naloxone, 94.3% ($n = 6746$) were among patients who had received an opioid during the study period. Among those, 5803 patients filled naloxone within 30 days of filling an opioid prescription (Fig. 1).

Patient Characteristics Associated with Naloxone Fills

Table 1 describes patient characteristics comparing opioid+naloxone patients with opioid only patients. A higher percentage of opioid+naloxone patients had each of the key risk factors for overdose including the following: received high dosages of opioids, received concurrent benzodiazepines, had history of opioid and other substance use disorders, and had history of opioid overdose. Patients who received opioid+naloxone differed from opioid only patients in race and geographic region of residence. People who received opioid+naloxone had higher prevalence of nicotine dependence and mental health disorders and higher prevalence of all pain conditions and other comorbid medical conditions. A higher proportion of these patients also received long-acting opioids.

In conditional logistic regression analyses (Table 2), African American race (AOR = 1.52, 95% CI 1.35–1.70), receipt of long-acting opioids (AOR = 1.78, 95% CI 1.59–1.98), having a mood disorder (AOR = 1.30, 95% CI 1.19–1.41), and having a nicotine use disorder (AOR = 1.19, 95% CI 1.10–1.29) were associated with opioid+naloxone. Midwest (AOR = 0.44, 95% CI 0.39–0.49), Northeast (AOR = 0.59, 95% CI 0.50–0.71), and living in an unknown region (AOR = 0.34, 95% CI 0.20–0.60) were associated with lower likelihood of receiving opioid+naloxone. Sleep apnea (AOR = 1.36, 95% CI 1.23–1.50), HIV/AIDS (AOR = 1.63, 95% CI 1.03–2.60), back/neck pain (AOR = 2.01, 95% CI 1.80–2.23), and other pain conditions (AOR = 1.15, 95% CI 1.06–1.25) were also associated with opioid+naloxone.

Among the key overdose risk factors, higher dosages of opioids demonstrated the largest association with

Figure 1 Patient sample flow diagram.

Table 1 Characteristics of Opioid+naloxone Patients Compared with Opioid Only Patients

Patient characteristics	Opioid+naloxone % (n) (N = 3963)	Opioid only % (n) (N = 19,815)	Total % (n) (N = 23,778)	p value
Gender				
Female	59.7% (2366)	59.7% (11,830)	59.7% (14,196)	1.000
Male	40.4% (1597)	40.3% (7985)	40.3% (9582)	
Age				
18–29	1.0% (40)	1.0% (199)	1.0% (239)	0.005
30–49	16.5% (655)	17.3% (3434)	17.2% (4089)	
50–64	50.4% (1999)	47.4% (9385)	47.9% (11,384)	
≥ 65	32.0% (1269)	34.3% (6797)	33.9% (8066)	
Race				
Caucasian	65.0% (2577)	64.5% (12,786)	64.6% (15,363)	< 0.001
African American	14.3% (568)	10.9% (2167)	11.5% (2735)	
Asian	0.7% (28)	0.9% (183)	0.9% (211)	
Hispanic	6.6% (260)	7.4% (1466)	7.2% (1726)	
Unknown	13.4% (530)	16.2% (3213)	15.7% (3743)	
Geographic region				
Midwest	10.1% (400)	21.6% (4285)	19.7% (4685)	< 0.001
Northeast	5.0% (197)	6.9% (1373)	6.6% (1570)	
South	57.8% (2289)	49.6% (9819)	50.9% (12,108)	
West	26.8% (1062)	21.0% (4164)	22.0% (5226)	
Unknown	0.4% (15)	0.9% (174)	0.8% (189)	
Key overdose risk factors				
Average daily opioid dose				
< 50 MME	35.4% (1404)	66.2% (13,123)	61.1% (14,527)	< 0.001
50 to < 90 MME	15.9% (630)	12.3% (2427)	12.9% (3057)	
≥ 90 MME	48.7% (1929)	21.5% (4265)	26.1% (6194)	
Concurrent benzodiazepine	41.5% (1644)	31.7% (6278)	33.3% (7922)	< 0.001
Opioid use disorder	23.2% (918)	11.3% (2243)	13.3% (3161)	< 0.001
Alcohol and other substance use disorders	15.9% (629)	10.7% (2127)	11.6% (2756)	< 0.001
History of overdose	4.2% (167)	2.2% (443)	2.6% (610)	< 0.001
Receipt of long-acting opioid	52.8% (2094)	25.6% (5077)	30.2% (7171)	< 0.001
Mental health and other behavioral conditions				
Nicotine dependence	44.2% (1752)	36.4% (7209)	37.7% (8961)	< 0.001
Anxiety disorder	45.8% (1813)	36.4% (7207)	37.9% (9020)	< 0.001
Mood disorder	48.7% (1930)	37.0% (7325)	38.9% (9255)	< 0.001
Other mental health disorders [†]	20.3% (806)	16.3% (3221)	16.9% (4027)	< 0.001
Other medical conditions [‡]				
HIV/AIDS	0.9% (36)	0.5% (96)	0.6% (132)	0.001
Liver disease	9.2% (365)	7.7% (1518)	7.9% (1883)	0.001
Renal failure	14.1% (557)	13.4% (2659)	13.5% (3216)	0.285
Sleep apnea	22.5% (890)	15.2% (3013)	16.4% (3903)	< 0.001
Arthritis pain	84.6% (3353)	80.9% (16,034)	81.5% (19,387)	< 0.001
Back or neck pain	87.0% (3446)	72.9% (14,450)	75.3% (17,896)	< 0.001
Other pain conditions	58.8% (2329)	49.0% (9716)	50.7% (12,045)	< 0.001

MME, morphine milligram equivalents

[†]See Appendix Table 5 for list of included conditions[‡]See Appendix Table 4 for list of International Classification of Disease (ICD-9-CM and ICD-10) diagnosis codes

opioid+naloxone (50 to < 90 MME: AOR = 2.43, 95% CI 2.15–2.76 and ≥ 90 MME: AOR = 3.94, 95% CI 3.47–4.46). Concurrent benzodiazepines (AOR = 1.27, 95% CI 1.16–1.38) and history of opioid use disorder (AOR = 1.56, 95% CI 1.40–1.73) were also associated with receiving opioid+naloxone, albeit with comparatively small effect sizes. However, history of opioid overdose (AOR = 0.92, 95% CI 0.74–1.15) and other substance use disorders (AOR = 1.04, 95% CI 0.93–1.17) were not associated with opioid+naloxone in the adjusted analysis.

Naloxone in High-risk Groups

Naloxone fills increased modestly across all patient populations who should be considered for naloxone, as recommended by the CDC Guideline for Prescribing Opioids for Chronic Pain (Fig. 2).⁹ By January to June of 2017, highest prevalence of naloxone receipt occurred among those receiving opioid dosages ≥ 90 MME (1.6%, *n* = 1776 among 111,482), while 1.1% (*n* = 2271 among 211,927)

of those receiving opioid dosages ≥ 50 MME filled naloxone (see Appendix Table 6 for counts of naloxone fills). Among 8638 individuals with history of opioid overdose, 1.6% (*n* = 137) filled naloxone. Among 44,681 individuals with opioid use disorder, 1.4% (*n* = 637) filled naloxone, and among 232,110 individuals who received a benzodiazepine concurrently with an opioid, only 0.6% (*n* = 1402) received naloxone. Thus, across high-risk groups, naloxone prescription fills were still quite rare. Examining naloxone receipt in the last 6 months of the study period, 85% of patients receiving naloxone had at least one of the CDC recommended risk criteria with over 40% having more than one risk factor. The most common risk factor was high opioid dosage.

DISCUSSION

In this study examining a national sample of commercially insured adults, naloxone fills among those receiving opioids

Table 2 Conditional Logistic Regression Examining Patient Characteristics Associated with Opioid+Naloxone Versus Opioid Only

	Adjusted odds ratio	p value	95% confidence interval
Race (ref group: Caucasian)			
African American	1.52	< 0.001	1.35, 1.70
Asian	0.78	0.289	0.50, 1.23
Hispanic	0.87	0.081	0.75, 1.02
Unknown	0.81	< 0.001	0.72, 0.91
Region (ref group: South)			
Midwest	0.44	< 0.001	0.39, 0.49
Northeast	0.59	< 0.001	0.50, 0.71
West	1.09	0.063	1.00, 1.20
Unknown	0.34	< 0.001	0.20, 0.60
Key overdose risk factors			
Average daily opioid dose (ref group: < 50 MME)			
50 to < 90 MME	2.43	< 0.001	2.15, 2.76
≥ 90 MME	3.94	< 0.001	3.47, 4.46
Concurrent benzodiazepine	1.27	< 0.001	1.16, 1.38
Opioid use disorder	1.56	< 0.001	1.40, 1.73
Other substance use disorders	1.04	0.490	0.93, 1.17
History of overdose	0.92	0.471	0.74, 1.15
Receipt of long-acting opioid	1.78	< 0.001	1.59, 1.98
Mental health and other behavioral conditions			
Nicotine dependence	1.19	< 0.001	1.10, 1.29
Anxiety disorder	1.08	0.103	0.98, 1.18
Mood disorder	1.30	< 0.001	1.19, 1.41
Other mental health disorders [†]	1.09	0.099	0.98, 1.21
Comorbid medical conditions [‡]			
HIV/AIDS	1.63	0.038	1.03, 2.60
Liver disease	1.08	0.245	0.95, 1.24
Sleep apnea	1.36	< 0.001	1.23, 1.50
Arthritis pain	1.02	0.654	0.92, 1.14
Back or neck pain	2.01	< 0.001	1.80, 2.23
Other pain conditions	1.15	0.001	1.06, 1.25

MME, morphine milligram equivalents

[†]See Appendix Table 5 for list of included conditions[‡]See Appendix Table 4 for list of International Classification of Disease (ICD-9-CM and ICD-10) diagnosis codes

increased from January 2014 through June 2017, but were still very low by the end of the study period. These results are consistent with recent studies that have shown general increases in naloxone dispensing.^{19,23} However, the current study further shows, despite increases in overall dispensing, the actual prevalence of naloxone fills by patients with even the greatest risk factors for overdose remains minimal in absolute terms.

Recent studies suggest naloxone prescribing by clinicians may be feasible and acceptable in outpatient care settings,^{5,24} but it is critical to assess which patient populations are being reached by efforts to increase naloxone. With 94% of patients receiving naloxone also receiving prescription opioids, our results suggest that naloxone is primarily being prescribed to

people who are concurrently receiving opioids, and among those, especially patients receiving high dosages of opioids. Further studies are needed to examine effectiveness of naloxone receipt among different patient populations at risk for overdose. Recent studies have examined the development of overdose risk prediction tools among patients receiving prescription opioids.^{21,22} These models are a valuable tool to inform which patients may benefit most from naloxone, but will also need to be updated continuously with changes in overdose trends. For example, there is increasing presence of illicit synthetic opioids mixed with cocaine and other illicit stimulants.²⁵ We did not find an association between non-opioid substance use disorder and receipt of naloxone, but this may be an important patient population to prioritize for naloxone prescribing.

A potentially concerning finding from this study is that a history of opioid overdose, which was identified in claims data, was not associated with naloxone fill. People who experience a non-fatal opioid overdose often experience a repeat overdose in the subsequent year, and history of overdose is a particularly important risk factor for overdose prevention.²⁶ It is unclear to what extent providers are aware of a patient's history of overdose. However, the availability of this information within claims data suggests that this may be an important risk factor that should be further highlighted in overdose prevention efforts and one that should be emphasized as a key risk factor for providers to identify.

Although many patient risk factors associated with overdose were also associated with naloxone receipt, perhaps more importantly, the overall prevalence of naloxone prescription fills remains minimal in populations at risk for opioid overdose. Focusing on opioid overdose risk factors emphasized in the CDC Guideline for Prescribing Opioids for Chronic Pain,⁹ only 1.6% of all adults who received average opioid dosages ≥ 90 MME filled naloxone. An even smaller percent of patients filled naloxone in other high-risk categories, including patients with history of overdose or with a diagnosed opioid use disorder. Some patients may receive naloxone from other sources including community naloxone distribution programs. However, there is likely still a substantial under-utilization of naloxone even among patient populations at the highest risk for overdose.

There are likely numerous health system, patient, and clinician barriers contributing to the low levels of naloxone fills. Knowledge and comfort with naloxone use and opioid overdose prevention are major barriers for both patients and clinicians to using naloxone.^{27–29} Specifically for clinicians, there is uncertainty about which patients they should prescribe naloxone to, and in some cases, there may be perceptions that prescribing naloxone may lead to increases in overdose behaviors.²⁸ Educational interventions can substantially improve both patient and clinician knowledge and increase use of naloxone,^{5,30} but additional efforts are needed to implement educational efforts more widely.³¹ However, additional policy changes are also key to increasing naloxone prescribing.

As of 2017, 48 states and the District of Columbia have enacted naloxone access laws.³² In particular, standing order policies,

Figure 2 Trends in percentage of patients filling naloxone among categories of patients at high risk for overdose (i.e., separate denominators of patients). †See Appendix Table 6 for counts of naloxone fills across each high-risk group.

which allow pharmacists to dispense naloxone without a patient-specific prescription from a prescriber, have been associated with increased naloxone use.³³ From 2014 to 2016, the number of states with standing order laws increased from 16 to 42. However, the overall impact may still be limited. Recent studies have examined early adopter states,^{34,35} including a study of pharmacies in California, which found less than a quarter indicated they could dispense naloxone without a prescription.³⁵ Furthermore, only 60% of these pharmacies correctly reported that insurance companies can be billed for naloxone obtained from the standing order policies.³⁵ These findings suggest policies alone focused on decreasing barriers for naloxone access may not be sufficient to increasing use. Policies further specifying which patient populations should receive naloxone and mandating co-prescribing or encouraging default prescribing of naloxone among patients at high risk for overdose may be more effective. Virginia and Vermont became the first two states to mandate naloxone co-prescription in patients at high risk for overdose in 2017, and a recent study found these policies were associated with a substantially increased number of naloxone prescriptions.³⁶

There are several important limitations of this study. Our dataset may not capture patients obtaining naloxone from other sources, including from community distribution programs. However, in this study, we utilized a large claims dataset with members across all 50 states and we focus specifically on outpatient naloxone fills among patients who have received an opioid, a group of patients whose overdose risk should be assessed by their outpatient clinicians. Also, the data are from patients with commercial insurance, and the findings may not be representative of other patient populations, including Medicaid

and uninsured populations, who may experience higher prevalence of sociodemographic and other clinical risk factors associated with overdose. However, opioid overdose remains a tremendous challenge in the commercially insured population and risky opioid prescriptions, other risk factors for opioid overdose and low rates of treatment for those with opioid use disorders are all common in the commercially insured population.^{37–39} Costs and copay of naloxone may differ across insurance plans. Although demand for naloxone seems to depend less on price compared with other medications,⁴⁰ future studies are needed to examine the impact of different copays and prices on naloxone use. Finally, we examined prescription fills for naloxone, which underestimates the total prescriptions for naloxone due to patients choosing not to fill prescriptions in some cases.

In conclusion, we find a growing prevalence of naloxone fills among insured US adults receiving opioids, but overall prevalence of naloxone prescribing remains extremely low. Key risk factors associated with opioid overdose risk were also associated with receiving naloxone, except for history of opioid overdose. Increasing naloxone availability is one of the most promising interventions to reduce opioid overdose.⁴ These findings suggest there is substantial further work needed to increase naloxone for patients at risk for opioid overdose.

Corresponding Author: Lewei (Allison) Lin, M.D., M.S.; Department of Psychiatry University of Michigan, Ann Arbor, MI, USA (e-mail: leweil@med.umich.edu).

Funding Information This work was supported by Precision Health at the University of Michigan, National Institute on Drug Abuse (grant R01 DA042859), and Substance Abuse and Mental Health Services

Administration and Michigan Department of Health and Human Services. Dr. Lin was supported in part by a Career Development Award (CDA 18-008) from the US Department of Veterans Affairs Health Services Research & Development Service.

Compliance with Ethical Standards:

Conflict of Interest: Dr. Brummett reported holding a patent for peripheral perineural dexmedetomidine licensed to the University of Michigan, being a consultant for Recro Pharma and Heron Therapeutics, and receiving research funding from Neuros Medical. All remaining authors declare that they do not have a conflict of interest.

Disclaimer: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, and approval of the manuscript and decision to submit the manuscript for publication.

REFERENCES

- Hedegaard H., Minino A.M., Warner M. Drug Overdose Deaths in the United States, 1999-2017. NCHS Data Brief, no 329. Hyattsville, MD: National Center for Health Statistics; 2018.
- Chou R, Korthuis PT, McCarty D, et al. Management of suspected opioid overdose with naloxone in out-of-hospital settings: a systematic review. *Ann Intern Med.* 2017;167(12):867-875. <https://doi.org/10.7326/M17-2224>.
- Dunn KE, Barrett FS, Bigelow GE. Naloxone formulation for overdose reversal preference among patients receiving opioids for pain management. *Addict Behav.* 2018. <https://doi.org/10.1016/j.addbeh.2018.03.011>.
- Pitt AL, Humphreys K, Brandeau ML. Modeling health benefits and harms of public policy responses to the US opioid epidemic. *Am J Public Health.* 2018;108(10):1394-1400. <https://doi.org/10.2105/AJPH.2018.304590>.
- Behar E, Bagnulo R, Coffin PO. Acceptability and feasibility of naloxone prescribing in primary care settings: a systematic review. *Prev Med.* 2018;114:79-87. <https://doi.org/10.1016/j.ypmed.2018.06.005>.
- Coffin PO, Behar E, Rowe C, et al. nonrandomized intervention study of naloxone coprescription for primary care patients receiving long-term opioid therapy for pain. *Ann Intern Med.* 2016;165(4):245-252. <https://doi.org/10.7326/M15-2771>.
- Office of the Surgeon General; US Department of Health and Human Services. Surgeon General's Advisory on Naloxone and Opioid Overdose. <http://www.surgeongeneral.gov>. Accessed August 23, 2019.
- Adams JM. Increasing naloxone awareness and use: the role of health care practitioners. *JAMA.* 2018;319(20):2073-2074. <https://doi.org/10.1001/jama.2018.4867>.
- Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016. *JAMA.* 2016;315(15):1624-1645. <https://doi.org/10.1001/jama.2016.1464>.
- Park TW, Lin LA, Hosanagar A, Kogowski A, Paige K, Bohnert ASB. Understanding risk factors for opioid overdose in clinical populations to inform treatment and policy. *J Addict Med.* 2016;10(6):369-381. <https://doi.org/10.1097/ADM.0000000000000245>.
- Bohnert ASB, Ilgen MA, Ignacio RV, McCarthy JF, Valenstein M, Blow FC. Risk of death from accidental overdose associated with psychiatric and substance use disorders. *Am J Psychiatry.* 2012;169(1):64-70. <https://doi.org/10.1176/appi.ajp.2011.10101476>.
- Bohnert ASB, Valenstein M, Bair MJ, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA.* 2011;305(13):1315-1321. <https://doi.org/10.1001/jama.2011.370>.
- Park TW, Saitz R, Ganoczy D, Ilgen MA, Bohnert ASB. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. *BMJ.* 2015;350:h2698.
- Paulozzi LJ. Prescription drug overdoses: a review. *J Safety Res.* 2012;43(4):283-289. <https://doi.org/10.1016/j.jsr.2012.08.009>.
- Clark AK, Wilder CM, Winstanley EL. A systematic review of community opioid overdose prevention and naloxone distribution programs. *J Addict Med.* 2014;8(3):153-163. <https://doi.org/10.1097/ADM.0000000000000034>.
- McDonald R, Strang J. Are take-home naloxone programmes effective? Systematic review utilizing application of the Bradford Hill criteria. *Addiction.* 2016;111(7):1177-1187. <https://doi.org/10.1111/add.13326>.
- Optum. https://www.optum.com/content/dam/optum/resources/productSheets/5302_Data_Assets_Chart_Sheet_ISPOR.pdf. Accessed August 23, 2019.
- Guy GP, Zhang K, Bohm MK, et al. Vital signs: changes in opioid prescribing in the United States, 2006-2015. *MMWR Morb Mortal Wkly Rep.* 2017;66(26):697-704. <https://doi.org/10.15585/mmwr.mm6626a4>.
- Freeman PR, Hankosky ER, Lofwall MR, Talbert JC. The changing landscape of naloxone availability in the United States, 2011 - 2017. *Drug Alcohol Depend.* 2018;191:361-364. <https://doi.org/10.1016/j.drugalcdep.2018.07.017>.
- Centers for Disease Control and Prevention. Opioid Morphine Equivalent Conversion Factors. <https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Opioid-Morphine-EQ-Conversion-Factors-March-2015.pdf>. Accessed August 23, 2019.
- Glanz JM, Narwaney KJ, Mueller SR, et al. Prediction model for two-year risk of opioid overdose among patients prescribed chronic opioid therapy. *J Gen Intern Med.* 2018. <https://doi.org/10.1007/s11606-017-4288-3>.
- Oliva EM, Bowe T, Tavakoli S, et al. Development and applications of the Veterans Health Administration's Stratification Tool for Opioid Risk Mitigation (STORM) to improve opioid safety and prevent overdose and suicide. *Psychol Serv.* 2017;14(1):34-49. <https://doi.org/10.1037/ser0000099>.
- Jones CM, Lurie PG, Compton WM. Increase in naloxone prescriptions dispensed in US retail pharmacies since 2013. *Am J Public Health.* 2016;106(4):689-690. <https://doi.org/10.2105/AJPH.2016.303062>.
- Behar E, Rowe C, Santos G-M, et al. Acceptability of naloxone coprescription among primary care providers treating patients on long-term opioid therapy for pain. *J Gen Intern Med.* 2017;32(3):291-295. <https://doi.org/10.1007/s11606-016-3911-z>.
- Kariisa M, Scholl L, Wilson N, Seth P, Hoots B. Drug overdose deaths involving cocaine and psychostimulants with abuse potential - United States, 2003-2017. *MMWR Morb Mortal Wkly Rep.* 2019;68(17):388-395. <https://doi.org/10.15585/mmwr.mm6817a3>.
- Olsson M, Wall M, Wang S, Crystal S, Blanco C. Risks of fatal opioid overdose during the first year following nonfatal overdose. *Drug Alcohol Depend.* 2018;190:112-119. <https://doi.org/10.1016/j.drugalcdep.2018.06.004>.
- Kirane H, Ketteringham M, Bereket S, et al. Awareness and attitudes toward intranasal naloxone rescue for opioid overdose prevention. *J Subst Abuse Treat.* 2016;69:44-49. <https://doi.org/10.1016/j.jsat.2016.07.005>.
- Binswanger IA, Koester S, Mueller SR, Gardner EM, Goddard K, Glanz JM. Overdose education and naloxone for patients prescribed opioids in primary care: a qualitative study of primary care staff. *J Gen Intern Med.* 2015;30(12):1837-1844. <https://doi.org/10.1007/s11606-015-3394-3>.
- Winograd RP, Davis CS, Niculete M, Oliva E, Martielli RP. Medical providers' knowledge and concerns about opioid overdose education and take-home naloxone rescue kits within Veterans Affairs health care medical treatment settings. *Subst Abuse.* 2017;38(2):135-140. <https://doi.org/10.1080/08897077.2017.1303424>.
- Ashrafioun L, Gamble S, Herrmann M, Baciewicz G. Evaluation of knowledge and confidence following opioid overdose prevention training: A comparison of types of training participants and naloxone administration methods. *Subst Abuse.* 2016;37(1):76-81. <https://doi.org/10.1080/08897077.2015.1110550>.
- Kerensky T, Walley AY. Opioid overdose prevention and naloxone rescue kits: what we know and what we don't know. *Addict Sci Clin Pract.* 2017;12. <https://doi.org/10.1186/s13722-016-0068-3>.
- PDAPS - Naloxone Overdose Prevention Laws. <http://pdaps.org/datasets/laws-regulating-administration-of-naloxone-1501695139>. Accessed August 23, 2019.
- Gertner AK, Domino ME, Davis CS. Do naloxone access laws increase outpatient naloxone prescriptions? Evidence from Medicaid. *Drug Alcohol Depend.* 2018;190:37-41. <https://doi.org/10.1016/j.drugalcdep.2018.05.014>.
- Guadamuz JS, Alexander GC, Chaudhri T, Trotzky-Sirr R, Gato DM. Availability and Cost of Naloxone Nasal Spray at Pharmacies in Philadelphia, Pennsylvania, 2017. *JAMA Netw Open.* 2019;2(6). <https://doi.org/10.1001/jamanetworkopen.2019.5388>.
- Puzantian T, Gasper JJ. Provision of naloxone without a prescription by California pharmacists 2 years after legislation implementation. *JAMA.* 2018;320(18):1933-1934. <https://doi.org/10.1001/jama.2018.12291>.

36. **Sohn M, Talbert JC, Huang Z, Lofwall MR, Freeman PR.** Association of naloxone coprescription laws with naloxone prescription dispensing in the United States. *JAMA Netw Open.* 2019;2(6):e196215. <https://doi.org/10.1001/jamanetworkopen.2019.6215>.
37. **Larochelle MR, Liebschutz JM, Zhang F, Ross-Degnan D, Wharam JF.** Opioid prescribing after nonfatal overdose and association with repeated overdose: a cohort study. *Ann Intern Med.* 2016;164(1):1-9. <https://doi.org/10.7326/M15-0038>.
38. **Wollschlaeger BA, Willson TM, Montejano LB, Ronquest NA, Nadipelli VR.** Characteristics and treatment patterns of US commercially insured and Medicaid patients with opioid dependence or abuse. *J Opioid Manag.* 2017;13(4):207-220. <https://doi.org/10.5055/jom.2017.0389>.
39. **Ali MM, Tehrani AB, Mutter R, et al.** Factors associated with potentially problematic opioid prescriptions among individuals with private insurance and medicaid. *Addict Behav.* 2019;98:106016. <https://doi.org/10.1016/j.addbeh.2019.06.005>.
40. **Murphy SM, Morgan JR, Jeng PJ, Schackman BR.** Will converting naloxone to over-the-counter status increase pharmacy sales? *Health Serv Res.* 2019. <https://doi.org/10.1111/1475-6773.13125>.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.