The Journal of Emergency Medicine, Vol. 79, No. C, pp. 111–122, 2025

https://doi.org/10.1016/j.jemermed.2025.04.022
0736-4679/$ - see front matter

Selected Topics: Toxicology

Use of Multiple Naloxone Administrations in the Emergency Department: A Retrospective Claims-Based Analysis

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□ **Abstract—Background: Potent synthetic opioids such as fentanyl and its analogues now account for most opioid overdose deaths in the United Stated (US). To help combat this development, Food and Drug Administration (FDA)-approved doses of the opioid overdose reversal agent naloxone and use of multiple naloxone administrations by emergency medical services (EMS) have increased. Objectives: To determine whether use of multiple naloxone administrations was similarly increasing in emergency departments (EDs) by investigating recent trends in ED naloxone use. Methods: A retrospective claims-based cohort study using data from the Merative MarketScan® and the National Emergency Department Sample (NEDS) databases was conducted. The percentage of patients who received multiple naloxone administrations during their first ED visit in the analysis period (MarketScan) and percentage of ED visits with multiple naloxone administrations (NEDS) were calculated with 95% confidence intervals. Time trends were analyzed by 2-sided Cochran-Armitage trend tests. Results: Among MarketScan patients who received naloxone in the ED, the percentage who received multiple naloxone administrations was 14.7% across the years 2016 to 2022 and increased 72.8% from 10.1% to 17.4%. ($p < 0.01$). Similarly, the percentage of NEDS ED visits with multiple naloxone administrations among visits where naloxone was administered was 6.3% in 2016 to 2021 and increased 146.7% from 3.0% to 7.3% ($p < 0.01$). Conclusions: A small but growing percentage of ED patients require multiple naloxone administrations, highlighting the need to monitor this trend and the ongoing adequacy of current treatment options for managing opioid intoxication.**

□ **Keywords—antagonists, narcotic; emergency service, hospital; fentanyl; naloxone; opiate overdose; poisoning**

Introduction

The opioid overdose epidemic in the United States (US) is a significant and worsening crisis. Today, major contributors to opioid-related deaths are potent synthetic opioids such as illicitly manufactured fentanyl and its analogs (1–4). Between 2013 and 2022, the rate of fatal overdoses involving synthetic opioids increased by more than 2,200%, with more than 90% of opioid overdose deaths in 2022 involving synthetic opioids (5,6).

The Centers for Disease Control and Prevention (CDC) describes the rise in opioid overdose deaths as 3 distinct waves (7): increased prescription opioid overdose deaths beginning in the 1990s; rapid increases in overdose deaths involving heroin beginning in 2010; and substantial increases in overdose deaths involving synthetic opioids, particularly illicitly manufactured fentanyl and its analogs, since 2013. In the current landscape, many opioid overdose deaths also involve other drugs. In 2022, among a sub-set of jurisdictions, nearly 43% of drug over-

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RECEIVED: 15 January 2025; FINAL SUBMISSION RECEIVED: 13 March 2025;
ACCEPTED: 29 April 2025

dose deaths involved both opioids and stimulants. An examination of trends showed that synthetic opioid deaths surpassed heroin sometime in 2016 (5,6).

Standard of care for reversing opioid overdoses by emergency medical services (EMS) and in the emergency department (ED) is the opioid receptor antagonist naloxone, which can be administered intranasally, intramuscularly, or intravenously. An analysis of US National Emergency Medical Services Information System (NEMSIS) data showed that the proportion of EMS encounters in which naloxone was administered increased by 75% between 2012 and 2016 (8), coinciding with the start of the third (synthetic opioid) wave of the epidemic. Another NEMSIS study showed that the Northeast census region had the highest per capita increase in EMS administration of naloxone between 2013 and 2016 (9), paralleling the increase in fatal synthetic opioid overdoses observed in that region (10) and suggesting a connection between the high prevalence of synthetic opioid toxicity and the need to administer naloxone in the community.

In addition to the general increase in use of naloxone in the community, use of multiple naloxone administrations by prehospital health care professionals to reverse opioid overdoses has also increased. Based on analyses of NEMSIS data, the percentage of individuals receiving multiple administrations of naloxone from EMS personnel doubled from 14% in 2012 to 28% in 2020 (9,11). The increase in multiple naloxone administrations might suggest that naloxone is less effective in treating the symptoms of fentanyl toxicity compared to heroin toxicity, but some have speculated that the observed increase is an artifact borne primarily of increased naloxone availability to EMS personnel (12). Regardless, the increase in multiple naloxone administrations arguably highlights the need to monitor both this trend and the adequacy of current treatment options for managing opioid intoxication.

Use of naloxone in EDs has been less reported compared to use by EMS (13). In this study, we used US claims data to evaluate naloxone use in the ED and to document any changes in the frequency of multiple naloxone administrations. A documented increase in the administration of multiple naloxone doses would be a strong indicator of the adequacy (or otherwise) of current treatments and serve as a foundation for expanding research on the need for alternative treatment options.

Materials and Methods

Data Sources

This was a retrospective claims-based cohort study of opioid overdose in the US. Data were from Merative MarketScan® and NEDS. MarketScan data were from the Commercial Claims and Encounters (CCAE), Medicare Supplemental (MDCR), and Medicaid Multi-State (MDCD) databases. The CCAE database contains data for fully adjudicated medical and pharmaceutical claims. The MDCR database contains claims data for Medicare-eligible retirees with employer-sponsored Medicare supplemental plans, while the MDCD database contains pooled Medicaid data from 8 to 12 geographically dispersed states (depending on the year). NEDS contains ED discharge data from nearly 1,000 hospitals across the US and is the largest all-payer ED database in the country.

In compliance with the Health Insurance Portability and Accountability Act, only de-identified patient data were used in this study. As there was no possibility to identify individual patients, this study was exempt from institutional review board review under 45 CFR 46.101(b)(2).

Study Population

Four study cohorts were created: 2 based on MarketScan data and 2 on NEDS data. Members of each cohort had at least 1 ED claim for opioid abuse (International Classification of Diseases, Tenth Revision [ICD-10] F11.1), opioid dependence (F11.2), unspecified opioid use (F11.9), or poisoning or adverse effects due to heroin (T40.1), other opioids (T40.2), methadone (T40.3), other synthetic narcotics (T40.4), or other and unspecified narcotics (T40.6). Naloxone use was identified based on Healthcare Common Procedure Coding System (HCPCS) code J2310 (injection, naloxone hydrochloride); no other HCPCS codes exist for other routes administered in the ED. Both MarketScan cohorts comprised adults ($\geq$18 years) with complete age and sex data and with an ICD-10 code for an opioid overdose between January 1, 2016, and December 31, 2022. The cohorts were: (a) all patients; and (b) patients who received naloxone during any of their opioid overdose ED visits. For the MarketScan cohorts, only the first ED claim for each patient was used in the analyses, which facilitated an examination of patient comorbidities and the impact of these comorbidities on outcomes. The NEDS cohorts comprised ED visits for adults with complete age and sex data with an ICD-10 code for an opioid overdose between January 1, 2016, and December 31, 2021: (a) all ED visits; and (b) ED visits where naloxone was administered. The start date for all cohorts was chosen to coincide with the year in which deaths due to synthetic opioids first outnumbered deaths due to heroin (14). All data available at the time of the analyses were included.

A further cohort consisting of patients who received naloxone and had continuous insurance enrollment for 6 months prior to the index date was created from the Mar-

ketScan data in order to conduct a sensitivity analysis that used patient comorbidities as covariates.

Outcomes

The primary MarketScan outcome was the percentage of patients who received multiple naloxone administrations during their first ED visit for an opioid overdose, among patients who received naloxone. The primary NEDS outcome was the percentage of ED visits when naloxone was administered multiple times, among ED visits where naloxone was administered at least once. Neither MarketScan nor NEDS includes data on administered naloxone dose strengths or cumulative doses. Percentages of MarketScan patients and NEDS visits where heroin or "other synthetic narcotics" was recorded as the overdose substance were also calculated. The overdose substance(s) recorded within these claims databases were not necessarily validated by laboratory testing.

Statistical Analysis

Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC). Descriptive statistics were calculated for patient characteristics. Percentages of patients who received naloxone were computed with 95% confidence intervals (CIs). For those patients who received naloxone, percentages who received multiple (2 or more) naloxone administrations were calculated. Time trends in the use of naloxone and multiple naloxone administrations were analyzed by 2-sided Cochran-Armitage trend test (15,16). To further measure the association between time and use of multiple naloxone administrations, multivariable logistic regression models were calculated using time as the main effect. The models were adjusted for age, sex, and insurance type. For the cohort of MarketScan patients with continuous enrollment for 6 months prior to the index date, the model was additionally adjusted for baseline comorbidities as a sensitivity analysis. Odds ratios (ORs) and 95% CIs were calculated.

Results

Data Attrition

The MarketScan data included 335,846 eligible patients with at least 1 ED claim for opioid overdose between 2016 and 2022. Among these patients, 27,742 (8.3%) received naloxone during at least 1 of their ED encounters. NEDS included 2,087,492 eligible ED visits for opioid overdose in 2016–2021. Naloxone was administered during 50,791 (2.4%) of these ED visits for opioid overdose.

Patients

The mean age was 41 years in the all-patients MarketScan cohort and 39 years for patients who received naloxone in the ED (Table 1). For the NEDS cohorts, mean age was 46 years overall and 41 years for patients who attended ED visits during which naloxone was administered. In the all-patients MarketScan cohort, numbers of men and women were comparable (Table 1). In the naloxone-treated MarketScan cohort and both NEDS cohorts, there were more men than women. Data describing race or ethnicity were only available from the MarketScan MDCD database. Most Medicaid patients in the MarketScan cohorts (66–68%) were classified as White. Insurance types in the all-patient MarketScan cohort consisted primary of Medicaid (75%) and commercial/private insurance (22%). In the all-visit NEDS cohort, insurance type was more evenly balanced among Medicaid (41%), Medicare (26%), commercial/private insurance (16%), and self-pay (14%) (Table 1).

Overdose Substance

In the all-patients MarketScan and all-visits NEDS cohorts, the overdose substance was recorded as unknown in most cases (61% for MarketScan, 69% for NEDS) (Table 1). The most frequently recorded overdose substance for patients who received naloxone in the ED was heroin for both MarketScan (32%) and NEDS (39%); "other synthetic narcotics" (which include fentanyl and its analogs) was recorded in 5% or less of such overdoses. Between 2016 and 2022, the percentage of patients in the overall MarketScan cohort with heroin recorded as the overdose substance decreased from 14.6% to 4.6% (Figure 1). During the same time interval, recording of "other synthetic narcotics" as the overdose substance increased from 2.4% to 7.4%. Similar albeit more modest trends were observed for NEDS ED visits between 2016 and 2021. Nonetheless, all 4 trend lines were significant ($p < 0.05$).

Naloxone use in the ED

Time trends of naloxone use

The proportion of MarketScan patients who received naloxone at their first ED visit increased from 5.8% in 2016 to 9.3% in 2022 – a 60.5% increase (Figure 2). Although the percentage peaked in 2020 at 10.5%, the overall time trend indicated a significant increase ($p < 0.01$). The proportion of NEDS ED visits where naloxone was administered increased from 1.9% in 2016 to 2.9% in 2021 – a 49.9% increase (Figure 2), with a significant increase over time ($p < 0.01$). Among MarketScan patients, the unadjusted OR for receiving at least 1 administration

Table 1. Demographics and Clinical Characteristics of the Overdose Cohorts

	MarketScan		NEDS	
	All patients ($N = 335,846$)	Patients who received naloxone ($N = 27,742$)	All visits ($N = 2,087,492$)	Visits where naloxone was administered ($N = 50,791$)
Age at index visit (years)				
Mean	41	39	46	41
Median	38	37	43	37
Age group (years), n (%)				
18–29	87,668 (26)	7,445 (27)	406,048 (19)	13,532 (27)
30–39	94,415 (28)	8,712 (31)	502,838 (24)	14,374 (28)
40–49	60,053 (18)	4,964 (18)	344,728 (17)	8,165 (16)
50–64	72,783 (22)	5,428 (20)	528,400 (25)	11,007 (22)
≥65	20,927 (6)	1,193 (4)	305,478 (15)	3,641 (7)
Sex, n (%)				
Female	168,900 (50)	11,721 (42)	932,447 (45)	18,138 (36)
Male	166,946 (50)	16,021 (58)	1,155,045 (55)	32,581 (64)
Reported overdose substance(s) [a], n (%)				
Heroin	37,157 (11)	8,739 (32)	178,231 (9)	19,864 (39)
Other opioids	40,269 (12)	4,348 (16)	252,072 (12)	8,687 (17)
Methadone	1,585 (0)	218 (1)	12,601 (1)	626 (1)
Other synthetic narcotics	12,401 (4)	1,378 (5)	51,194 (2)	1,871 (4)
Other and unspecified narcotics	19,818 (6)	4,227 (15)	136,891 (7)	8,758 (17)
More than one opioid[b]	19,471 (6)	4,811 (17)	12,030 (1)	643 (1)
Unknown	205,145 (61)	4,021 (14)	1,444,473 (69)	10,270 (20)
Geographic region, n (%)				
Midwest	-	-	431,661 (21)	18,590 (37)
Northeast	-	-	498,212 (24)	9,104 (18)
South	-	-	708,068 (34)	20,475 (40)
West	-	-	449,551 (22)	2,550 (5)
Insurance type, n (%)				
Commercial/ private	74,355 (22)	3,364 (12)	324,338 (16)	7,303 (14)
Medicare	8,783 (3)	312 (1)	545,548 (26)	7,340 (14)
Medicaid	252,708 (75)	24,066 (87)	849,161 (41)	20,670 (41)
Self-pay	-	-	287,096 (14)	13,149 (26)
Other	-	-	63,079 (3)	1,697 (3)
Missing/unknown	-	-	18,270 (1)	560 (1)
Race/ethnicity[c]				
n	252,708	24,066	-	-
White, n (%)	167,022 (66)	16,281 (68)	-	-
Black, n (%)	35,575 (14)	3,077 (13)	-	-
Hispanic, n (%)	9,437 (4)	990 (4)	-	-
Other, n (%)	7,617 (3)	612 (3)	-	-
Missing/unknown, n (%)	33,057 (13)	3,106 (13)	-	-

NEDS = National Emergency Department Sample.

[a] Not necessarily based on laboratory testing.

[b] Two or more of the following ICD-10 codes: T40.1, T40.2, T40.3, T40.4, and T40.6.

[c] Only available for patients identified in the MarketScan Medicaid database. The classification system combining race and ethnicity is the 1 used by MarketScan.

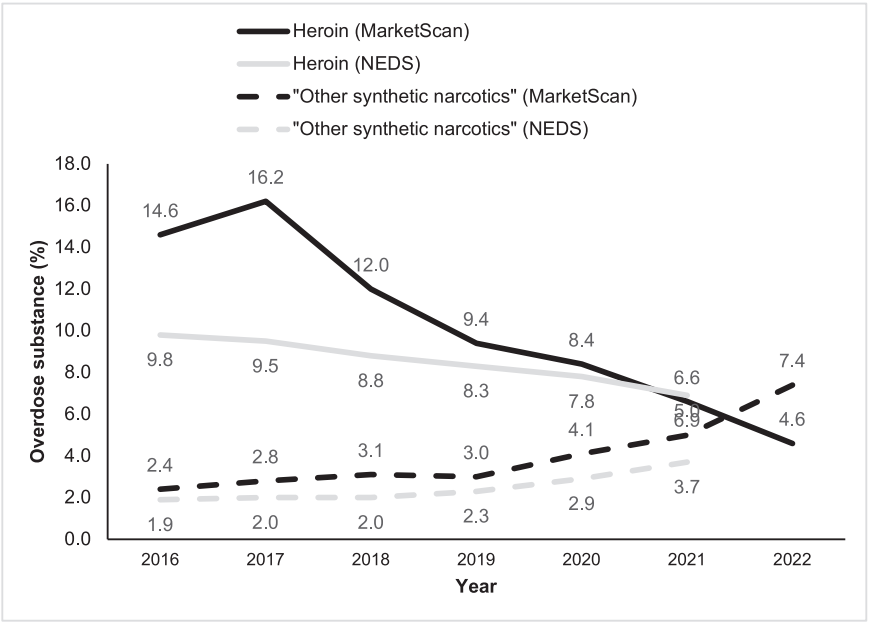

Figure 1. Temporal trends in ED reporting of overdose substances for opioid overdose patients. For MarketScan, data are the percentages of patients where heroin or "other synthetic narcotics" was recorded as the overdose substance during their index ED visit for opioid overdose. For NEDS, data are the percentage of ED visits where these narcotics were recorded as the overdose substance. ED = emergency department; NEDS = National Emergency Department Sample.

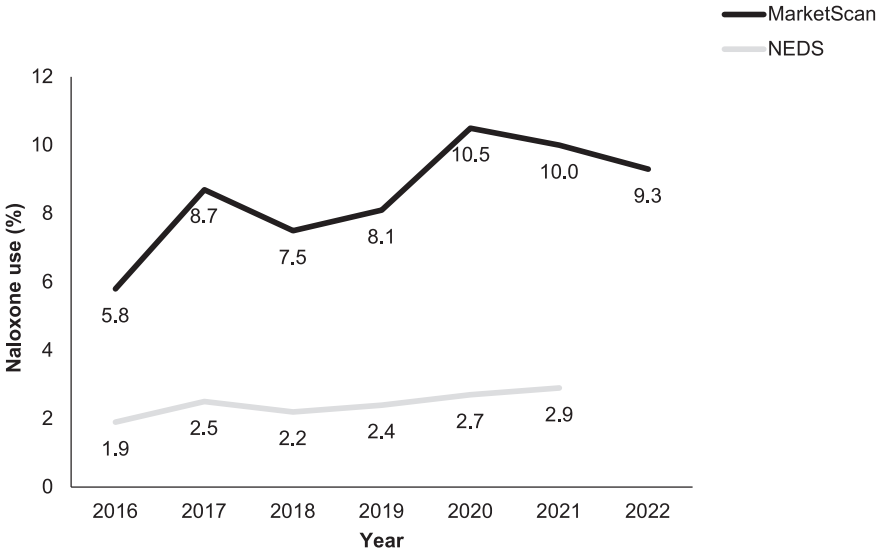

Figure 2. Temporal trends in administration of naloxone (overall cohort). For MarketScan, data are the percentage of patients who received naloxone during their index ED visit for opioid overdose. For NEDS, data are the percentage of ED visits for opioid overdose during which naloxone was administered. ED = emergency department; NEDS = National Emergency Department Sample.

of naloxone during the first ED visit was 1.03 (95% CI: 1.03, 1.04) for each 1-year increase in time. In an analysis adjusted for age, sex, and insurance type, the OR for receiving naloxone was 1.02 (95% CI: 1.02, 1.03). For NEDS ED visits, the unadjusted OR for receiving at least 1 naloxone administration was 1.07 (95% CI: 1.06, 1.07) for each 1-year increase in time. When the analysis was adjusted for age, sex, and insurance type, the OR for receiving naloxone was also 1.07 (95% CI: 1.06, 1.07).

Multiple naloxone administrations

Of the MarketScan patients who received naloxone in the ED, 14.7% (95% CI:14.3, 15.1) received multiple

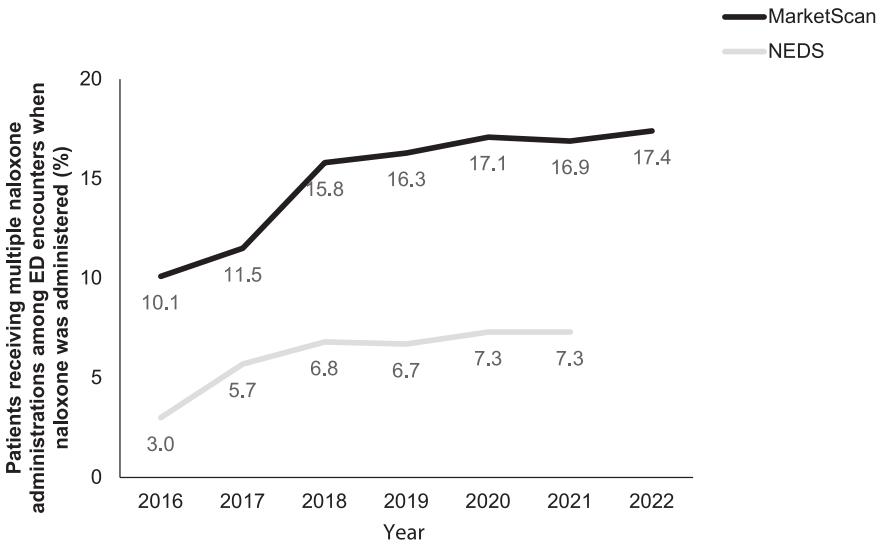

Figure 3. Temporal trends in multiple naloxone administrations. ED = emergency department; NEDS = National Emergency Department Sample.

administrations. Specifically, 11.1% received 2 administrations, and 3.6% received 3 or more administrations. Multiple naloxone administrations were registered during 6.3% (95% CI: 6.1, 6.5) of NEDS ED visits during which naloxone was administered. Two administrations of naloxone were used during 5.3% of such ED visits, and 3 or more administrations of naloxone were used during 1.0% of such visits.

Time trends of multiple naloxone administrations

Use of multiple naloxone administrations increased over time during the analysis period. For MarketScan, the percentage of naloxone-treated patients who received multiple naloxone administrations increased from 10.1% in 2016 to 17.4% in 2022 – a 72.8% increase (Figure 3). The time trend was significant ($p < 0.01$). The percentage of ED visits with multiple naloxone administrations in the NEDS cohort more than doubled between 2016 and 2021, increasing by 146.7% from 3.0% to 7.3% of visits where naloxone was administered ($p < 0.01$ for trend) (Figure 3). Among MarketScan patients who received naloxone in the ED, the unadjusted OR for receiving multiple naloxone administrations was 1.11 (95% CI: 1.09, 1.13) for each 1-year increase in time. In an analysis adjusted for age, sex, and insurance type, the OR for receiving multiple administrations of naloxone was 1.10 (95% CI: 1.09, 1.12). For NEDS ED visits during which naloxone was administered, the unadjusted OR for receiving multiple naloxone administrations was 1.13 (95% CI: 1.10, 1.15) for each 1-year increase in time. When the analysis was adjusted for age, sex, and insurance type, the OR for receiving multiple naloxone administrations was 1.13 (95% CI: 1.11, 1.16).

Sensitivity analysis

Among patients in the naloxone-treated MarketScan cohort, 21,393 (77.1%) had continuous insurance coverage for 6 months prior to the index date. The most frequent comorbidities occurring in these patients were substance use disorder (55%), anxiety disorder (34%), major depressive disorder (30%), hypertension (26%), cardiac arrhythmias (cardiac dysrhythmias) (17%), alcohol dependence (alcohol use disorder) (16%), bipolar disorder (15%), chronic obstructive pulmonary disease (11%), and post-traumatic stress disorder (10%). Trends of naloxone use for this cohort were similar as for the main naloxone-treated MarketScan cohort. Considering all ED visits by patients, 11.8% of patients received 2 naloxone administrations, and 3.7% received at least 3 administrations. The unadjusted OR for receiving multiple administrations of naloxone was 1.09 (95% CI: 1.07, 1.11) for each 1-year increase in time. When the analysis was adjusted for age, sex, insurance type, and comorbidities, the OR for receiving multiple naloxone administrations was 1.09 (95% CI: 1.06, 1.11).

Discussion

In this retrospective analysis of data from the period between 2016 and 2022, the adjusted odds of receiving multiple naloxone administrations in the ED increased by approximately 10% to 13% each year. Multiple naloxone administrations in MarketScan increased 73% from 2016 to 2022, while multiple naloxone administrations in NEDS increased 147% from 2016 to 2021. These changes are similar to a previously reported change in the percentage of individuals receiving multiple administrations of

naloxone from EMS personnel, which doubled from 14% in 2012 to 28% in 2020 (9,11).

The proportion of patients receiving naloxone in the ED increased 61% between 2016 and 2022 in MarketScan, and the proportion of ED visits where naloxone was administered increased 50% between 2016 and 2021 in NEDS. Overall proportions of patients receiving naloxone in the ED may appear low, but many patients will have received naloxone in a pre-hospital setting. The claims data analyzed in this study cannot link pre-hospital treatment to treatments received in the ED. Therefore, numbers of naloxone administrations received pre-hospital and their impact on subsequent administrations in the ED is unknown. However, recent analyses of NEMSIS data showed an increasing number of patients receiving naloxone from EMS (9). Viewed together with the current study results, these NEMSIS data suggest that the number of people needing naloxone treatment is increasing in both pre-ED and ED settings.

The observed increase in naloxone use may be driven in part by an overall increase in illicit drug use, exacerbated by social isolation and stress during the COVID-19 pandemic (17–19). It also coincides with the dramatic increase in toxicity due to illicitly manufactured fentanyl (20). Fentanyl is extremely potent, with a very high affinity for mu-opioid receptors, which accounts for the profound central nervous system and respiratory depression it causes and its high lethality (21). While fentanyl is recognized as having a rapid onset of action and generally a short duration of therapeutic effect, its high lipid solubility leads to its rapid redistribution from plasma to adipose tissue. After large or multiple smaller doses, fentanyl may accumulate in adipose tissue to such an extent that redistribution is ineffective at removing fentanyl from its site of action (22). Slow release into the plasma results in an elimination half-life of approximately 3 to 8 hours (22)—longer than the half-life of naloxone (30 minutes to 2 hours) (23,24). Long half-lives and durations of action have also been described with some fentanyl analogs, including sufentanil and carfentanil (half-life approximately 6 hours for both) (25,26). This suggests that some patients could experience rebound opioid toxicity after initial reversal by naloxone (27).

Directly linking increases in fentanyl exposure to the increased use of multiple naloxone administrations is challenging with currently available data. Studies examining non-fatal overdoses do not systematically report on the specific opioid(s) involved (28–30). In the current study, there was a high degree of missing data for reported overdose substance(s), implying that healthcare providers routinely administer naloxone to address suspected opioid toxicity without confirmatory testing. Moreover, overdose substances were often identified by patient or bystander recall, which raises questions about their accuracy (30). Even when hospitals attempt to confirm overdose substances via toxicology screening, most hospitals' routine drugs of abuse panel uses a standard opiate screening test that is not sensitive to fentanyl or its analogs (31), thus fentanyl use may be missed or under-detected in non-fatal cases. Notwithstanding these challenges, the rise in multiple naloxone administrations found in our analyses coincides with an increase in deaths attributed to synthetic opioids, as reported by the Centers for Disease Control and Prevention (32), suggesting that these phenomena are related.

The increased use of illicitly made fentanyl and presence of even more potent synthetic opioids such as nitazenes in overdoses (33) means that it is important to monitor the adequacy of current opioid overdose antidotes. Some have already classified the observed increases in multiple naloxone administrations by EMS as clinically meaningless or artifacts of increased naloxone availability, concluding that no changes are needed to current naloxone administration practices (12,34,35). Although a single naloxone administration continues to reverse overdoses for the majority of people who receive it in the ED, the ongoing epidemic of opioid overdoses necessitates continued exploration of novel technologies and approaches for treating overdoses. These include covalent naloxone nanoparticles, serotonin (5-HT)1A receptor agonists, and fentanyl-binding cyclodextrin scaffolds (36). In addition, early findings from an exploration of intravenous buprenorphine for the reversal of methadone-induced respiratory depression suggest that buprenorphine may be a useful antidote for opioid-induced respiratory depression (37). However, the authors noted the need for further studies to determine optimal dosing that can consistently reverse respiratory depression without precipitating withdrawal. Moreover, the higher-dose injectable and intranasal naloxone products that received Food and Drug Administration (FDA) approval in 2021 (38,39)—together with injectable and nasal forms of the more potent (23,40) and longer-acting (23,41) opioid antagonist nalmefene, recently approved by the FDA for the management of opioid overdose (42–44)—provide additional treatment options for opioid overdose.

With the availability of higher-dose opioid antagonists and increased use of reversal agents in community settings and by laypersons, the potential for serious adverse effects is worth mentioning. While prospective studies are lacking, retrospective studies describing opioid antagonist doses and their association with adverse events have generally found that higher doses administered in ED or prehospital settings are associated with higher rates of precipitated opioid withdrawal and pulmonary complications in opioid-dependent patients (45–48). As such, there is a need to raise awareness of these risks, educate the public to appreciate that these opioid antag-

onists are not a substitute for emergency medical care, and conduct further real-world research to better understand the relationship between use of opioid antagonists and the likelihood of these complications. findings should be considered in view of the study's limitations. Claims data do not routinely include causes of opioid toxicity, thus the analyses cannot demonstrate that multiple administrations of naloxone were directly linked to fentanyl toxicity, only that both increased in frequency during the study period (2016 to 2022). Compared to NEDS claims, MarketScan claims were more likely to come from Medicaid. Moreover, the MarketScan sample was a few years younger on average and more evenly gender balanced compared to the NEDS sample. These differences may have contributed to the observed lower rates of naloxone administration in NEDS compared to MarketScan. However, more germane to the study conclusions is that time trends of naloxone administration and multiple naloxone administrations showed significant increases in both the MarketScan and NEDS cohorts. Claims data do not include complete information on pre-hospital administration of naloxone or the precise timing of administrations within the ED. Therefore, these data do not discriminate multiple administrations in response to an insufficient initial dose from multiple administrations in response to opioid toxicity that lasts longer than the duration of action of the opioid antagonist. Claims data also do not capture naloxone dose strengths, route of administration, or whether naloxone is administered by continuous intravenous infusion. Intravenous infusion of naloxone is commonly recommended for patients who are intoxicated with opioids that are long-acting or have high opioid receptor affinity, or who have recurrent respiratory depression (49,50). However, it is unclear how naloxone infusions are captured or recorded in patient records—as a single dose, multiple doses, or otherwise. This gap begs additional nuance in interpreting naloxone dosing in the current overdose landscape and further complicates analysis of trends in ED naloxone use. As recently outlined by Stolbach et al., Taylor and Lasser, and Infante et al. (51–53), additional clinical practice and real-world research is needed to determine optimal doses of naloxone and nalmefene to achieve desired patient outcomes, compare effectiveness between routes of administration, and determine the appropriate timing of repeat administrations, particularly in community settings where treatments are administered by bystanders and non-medically trained first responders (51–53). Given the increased involvement of longer-acting synthetic opioids in overdoses, the potential need for prolonged clinical care or observation after opioid antagonist administration should also be explored.

While our cross-sectional dataset was large and had good geographic coverage, it may not have been fully representative of EDs across the US. Moreover, naloxone use in the ED may not always be recorded in claims data, so the changes in naloxone use reported here might be magnified if the entire population could be captured. Also, we did not assess differences between first and subsequent ED visits. An analysis of these differences would provide useful information, as patients hospitalized for opioid overdose are at high risk of dying or being readmitted to hospital following discharge (54–56). However, a comparison of first and subsequent ED visits would not have been possible in NEDS, as data are recorded at the ED visit level, rather than at the patient level. Finally, the most recent data available at the time of the analyses were from 2022. The above-mentioned higher-dose naloxone products were introduced after that date, and trends for the post-pandemic era are not analyzable at this time. Additional analyses are planned when newer claims data are available.

Conclusions

Increases in fatal and non-fatal opioid toxicities involving fentanyl have been accompanied by increased use of naloxone in the ED. While a single naloxone administration appears to address the needs of most ED patients, a small but growing percentage of ED patients require multiple naloxone administrations. This finding highlights the need to more accurately characterize the changing nature of the current opioid toxicity crisis (through expanded ED-based urine drug screening that includes fentanyl testing); to monitor the continued adequacy of current treatments; and to analyze real-world data for recently approved longer-acting and higher-dose opioid antagonists.

Funding

This work was supported by Purdue Pharma.

Data Statement

The authors' ability to share unanalyzed data is limited by our contractual agreements with the database owners.

CRediT authorship contribution statement

Rachael Rzasa Lynn: Writing – review & editing, Methodology. **Jeffrey Galinkin**: Writing – review & editing, Methodology. **Monica McClain**: Writing – review & editing, Validation, Resources, Methodology, Investigation, Formal analysis, Data curation. **Thomas Alfieri**: Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

RRL has received grants from the Department of Defense Congressionally Directed Medical Research Programs, National Institute on Drug Abuse, and National Center for Complementary and Integrative Health, and has served as President of the Colorado Pain Society. JG has received financial support from Purdue Pharma for work on this manuscript; has received consulting fees from Adamis Pharmaceuticals, Purdue Pharma, and US Worldmeds; and serves on the Drug Safety Medical Board of Kyowa Kirin. MM is a former employee of Genesis Research, which was paid by Purdue for work relating to this study. TA is an employee of Purdue, which sponsored this study.

CRediT authorship contribution statement

Rachael Rzasa Lynn: Writing – review & editing, Methodology. **Jeffrey Galinkin:** Writing – review & editing, Methodology. **Monica McClain:** Writing – review & editing, Validation, Resources, Methodology, Investigation, Formal analysis, Data curation. **Thomas Alfieri:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Acknowledgements

Medical writing support was provided in accordance with Good Publication Practice guidelines by Stephen Gilliver (PPD clinical research business of Thermo Fisher Scientific) and was paid for by Purdue Pharma. Data analytic support was provided by Steven Wang, Xin Zhao, and Tiange Yu of Genesis Research and was paid for by Purdue Pharma.

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Article Summary

1. Why is this topic important?

Today, most opioid-related deaths in the US involve illicitly manufactured opioids such as fentanyl and its analogs. For an increasing number of opioid overdoses, emergency medical services are using multiple doses of the opioid receptor antagonist naloxone.

2. What does this study attempt to show?

This real-world study aimed to determine whether use of multiple naloxone administrations is also increasing in the emergency department (ED). The objective was to help inform the ongoing discussion surrounding the adequacy of current treatment options for reversing overdoses involving potent synthetic opioids.

3. What are the key findings?

Using MarketScan data, we found that the percentage of naloxone-treated patients who received multiple naloxone administrations increased from 10.1% in 2016 to 17.4% in 2022. Similarly, the percentage of NEDS (National Emergency Department) ED visits with multiple naloxone administrations increased from 3.0% of visits where naloxone was administered in 2016 to 7.3% in 2021. During the analysis period, the adjusted odds of receiving multiple naloxone administrations in the ED increased by approximately 10%–3% each year.

4. How is patient care impacted?

The increasing use of multiple naloxone doses in the ED highlights the need to continue monitoring the adequacy of current treatment options for opioid intoxication. Additional real-world research should determine optimal doses of naloxone and other opioid receptor antagonists to meet the evolving needs of patients in the dynamic opioid toxicity landscape.