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RESEARCH REPORT

ADDICTION SSA

Healthcare costs and use before and after opioid overdose in Veterans Health Administration patients with opioid use disorder

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Abstract

Aims: To compare healthcare costs and use between United States (US) Veterans Health Administration (VHA) patients with opioid use disorder (OUD) who experienced an opioid overdose (OD cohort) and patients with OUD who did not experience an opioid overdose (non-OD cohort).

Design: This is a retrospective cohort study of administrative and clinical data.

Setting: The largest integrated national health-care system is the US Veterans Health Administration's healthcare systems.

Participants: We included VHA patients diagnosed with OUD from October 1, 2017 through September 30, 2018. We identified the index date of overdose for patients who had an overdose. Our control group, which included patients with OUD who did not have an overdose, was randomly assigned an index date. A total of 66 513 patients with OUD were included for analysis (OD cohort: n = 1413; non-OD cohort: n = 65 100).

Measurements: Monthly adjusted healthcare-related costs and use in the year before and after the index date. We used generalized estimating equation models to compare patients with an opioid overdose and controls in a difference-in-differences framework.

Findings: Compared with the non-OD cohort, an opioid overdose was associated with an increase of $16 890 [95% confidence interval (CI) = $15 611–18 169; P < 0.001] in healthcare costs for an estimated $23.9 million in direct costs to VHA (95% CI = $22.1 million, $25.7 million) within the 30 days following overdose after adjusting for baseline characteristics. Inpatient costs ($13 515; 95% CI = $12 378–14 652; P < 0.001) reflected most of this increase. Inpatient days (+6.15 days; 95% CI, = 5.33–6.97; P < 0.001), inpatient admissions (+1.01 admissions; 95% CI = 0.93–1.10; P < 0.001) and outpatient visits (+1.59 visits; 95% CI = 1.34–1.84; P < 0.001) also increased in the month after opioid overdose. Within the overdose cohort, healthcare costs and use remained higher in the year after overdose compared with pre-overdose trends.

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Conclusions: The US Veterans Health Administration patients with opioid use disorder (OUD) who have experienced an opioid overdose have increased healthcare costs and use that remain significantly higher in the month and continuing through the year after overdose than OUD patients who have not experienced an overdose.

KEYWORDS

Economics, healthcare costs, opiate overdose, opioid-related disorders, Unites States, utilization, veterans

INTRODUCTION

The opioid crisis is a national public health emergency in the United States [1,2]. The National Survey on Drug Use and Health, which is known to significantly underestimate the prevalence of opioid use disorder (OUD), reported that 2.7 million Americans had OUD in 2020 [3,4]. Opioid-related overdose deaths from prescription opioids, heroin and synthetic opioids, such as fentanyl, have increased in tandem with OUD, accumulating to a tragic 78 000 deaths in 2021 [5]. The US Department of Veterans Affairs (VA) Veterans Health Administration (VHA) is the largest integrated national healthcare system and the largest single provider of substance use disorder treatment in the US [6]. The risk for OUD and subsequent overdose deaths among veterans is higher compared with non-veterans, in part due to higher rates of comorbidities such as chronic pain, major depression and post-traumatic stress disorder, as well as the population being predominantly male [7–9].

Understanding the costs of treatment and other services that precede and follow an opioid-related overdose can help VHA and other decision-makers with planning and resource allocation. Studies have estimated that the economic burden associated with opioid-related overdose is substantial [10–13]. Maeng and colleagues reported that healthcare expenditures remained higher after an opioid overdose among those with non-fatal overdose [13]. However, these studies focused on the general population, and the marginal cost of opioid overdose among veterans with OUD within VHA remains unknown. Therefore, we sought to describe and compare healthcare cost and utilization trends among VHA patients with OUD who did and did not experience an opioid overdose from the perspective of VHA.

METHODS

Study design and data source

This retrospective cohort study evaluated the healthcare costs and utilization trends among VHA patients with OUD who experienced an opioid overdose (OD cohort) and those who did not (non-OD cohort). OUD diagnoses, as well as patient demographics, outpatient and inpatient visits, comorbidities, and pharmacy claims, associated with both VA and non-VA care paid for by VA, were pulled from the VHA Corporate Data Warehouse (CDW). Data from October 2015 through September 2019 were analyzed. Approval to perform the study was obtained from the Stanford Institutional Review Board (no. 43725).

Cohort selection

Our study included two groups of VHA patients with OUD: (1) those who experienced an opioid overdose event during the study time-frame ('OD cohort') and (2) those who did not ('non-OD cohort'). VHA patients aged 18 years or older, with valid birth and (if applicable) death dates, who were diagnosed with OUD from October 2017 through 30 September 2018 (FY18) were included. OUD diagnosis was defined as the first documented International Classification of Diseases (ICD-10-CM) code F11 (opioid-related disorders) found in the CDW during the time-frame.

For our OD cohort, we defined the index date as the date of overdose and excluded VHA patients with an overdose within the previous 360 days or with more than one overdose after the index date. We defined the opioid overdose event as the first opioid-related overdose ICD-10-CM code found in either the inpatient or outpatient CDW data sets between 1 October 2017 through 30 September 2018. Inpatient codes were limited to those present on admission; outpatient codes were limited to those generated by urgent care visits, emergency department visits or ambulance records. We excluded those diagnosed with cancer or who received palliative or hospice care. To minimize confounding because of differences in baseline characteristics, we established a control cohort (non-OD cohort), in which we randomly assigned patients with OUD but without overdose to an index date in FY18 and applied the same exclusion criteria. Random assignment avoids pitfalls that have been raised with other methods, such as matching [14]. We also excluded patients who had died prior to the randomly assigned index date. We used a monthly time interval and defined the index month as the 30-day period inclusive of the index date. Figure 1 summarizes our inclusion and exclusion criteria. Of 71 471 patients diagnosed with OUD in FY18, 66 513 (93.1%) met the criteria for study inclusion. The final OD cohort included 1413 patients; the non-OD cohort included 65 100 patients. See Supporting information A for details.

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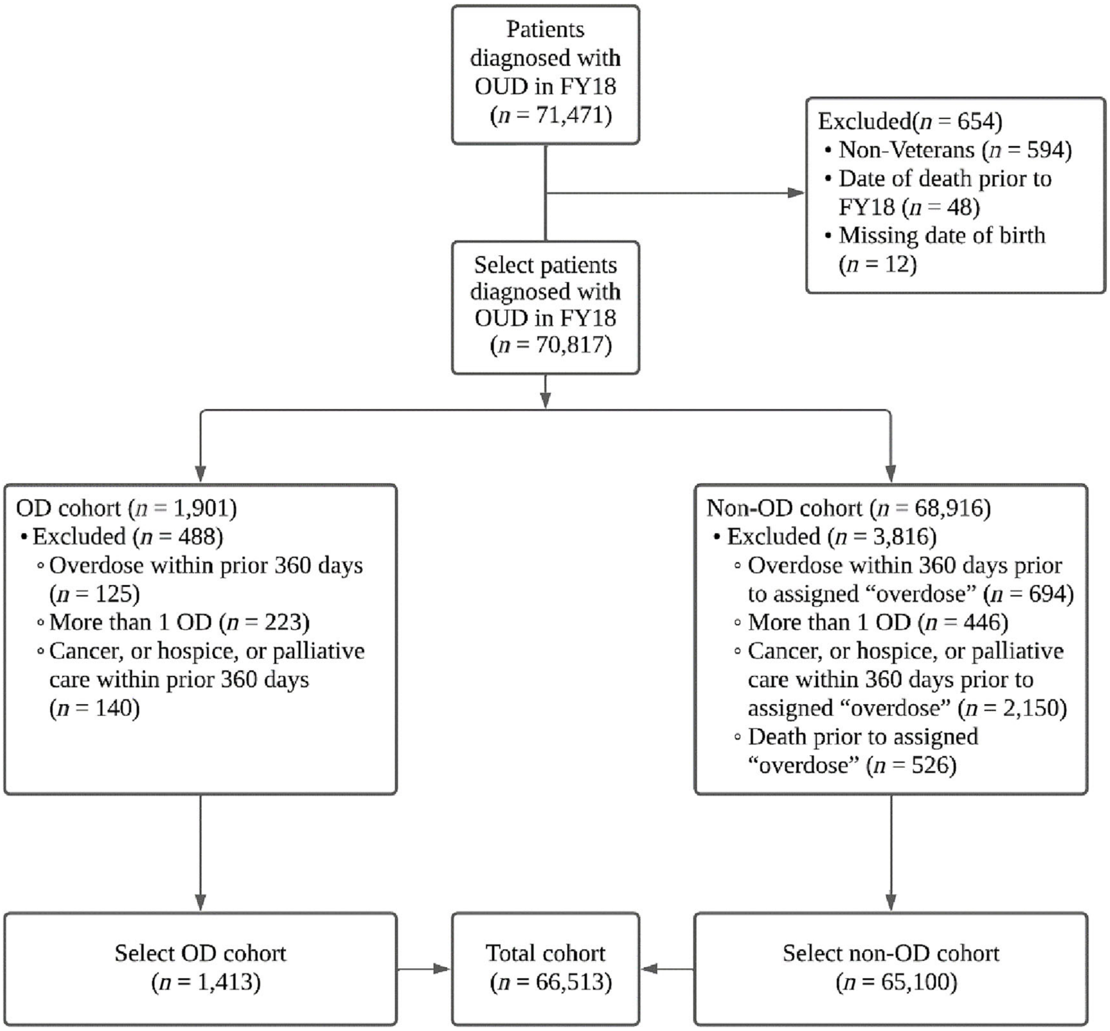

FIGURE 1 Flow-chart showing patient inclusion and exclusion.

Study variables

Our primary outcomes of interest were total healthcare costs and utilizations following an opioid overdose. We identified inpatient and outpatient costs using VA Managerial Cost Accounting System inpatient treating specialty and outpatient data files, as well as the cost of non-VA care paid for by VA using Fee Basis and Program Integrity Tool (PIT) files. We grouped VA and purchased care cost data into three broad categories (inpatient, outpatient and other) using several codes (VA inpatient treating specialty, outpatient clinic stop, Fee purpose of visit and PIT place of service). We also grouped VA inpatient and outpatient cost data into mutually exclusive categories: medical/surgical, pharmacy (outpatient only), psychiatry/mental health, substance use treatment, mental health residential rehabilitation treatment program and other.

We captured the healthcare costs and utilizations among those with multiple opioid-related overdoses. Patients with multiple overdoses were grouped as having either one or two or more overdoses.

We obtained baseline demographic and clinical characteristics reflecting 360 days prior to the index date. Demographic variables included age, sex, race, ethnicity, marital status, geographic region and VA service-connected disability greater than 50%. We also identified Elixhauser comorbidities in the 360 days prior to the index date, such as mental health conditions (e.g. depression), chronic pulmonary disease, tobacco use disorder and sleep apnea, and created a simple summary of comorbidities [15]. Medications examined included prescription opioids as well as antidepressants, benzodiazepines, stimulants and muscle relaxants. Finally, we calculated the Risk Index for Overdose and Serious Opioid-Induced Respiratory Depression (RIOSORD) using data from the 180 days prior to the index date for all patients in our cohort. RIOSORD is a validated score that estimates the likelihood of overdose or serious opioid-induced respiratory depression [16]. Additional details are available in Supporting information B and C.

Analysis

We compared demographic characteristics between the groups using standardized differences (fewer than 10% considered not

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TABLE 1 Patient characteristics for FY18 Veterans Health Administration patients with opioid use disorder with and without opioid overdose (*n* = 66 513).

Characteristic	OD cohort (*n* = 1413)	Non-OD cohort (*n* = 65 100)	Standardized difference
Demographics[a]			
Sex, *n* (%)			
Female	108 (7.6)	5007 (7.7)	0.002
Age at overdose, mean (SD)	51.6 (15.1)	52.4 (14.3)	0.053
Race, *n* (%)			
Black	249 (17.6)	12 140 (18.6)	0.027
White	1086 (76.9)	48 941 (75.2)	0.039
Other	44 (3.1)	2070 (3.2)	0.004
Ethnicity, Hispanic, *n* (%)	78 (5.5)	3759 (5.8)	0.011
Marital status, *n* (%)			
Never married	373 (26.5)	15 042 (23.5)	0.068
Married	401 (28.5)	20 819 (32.6)	0.090
Separated	108 (7.7)	4968 (7.8)	0.004
Divorced	469 (33.3)	20 980 (32.9)	0.009
Widowed	56 (4)	1979 (3.1)	0.047
Geographic region, *n* (%)			
Urban	1085 (77)	47 125 (72.9)	0.095
Rural	318 (22.6)	17 018 (26.3)	0.087
Highly rural	7 (0.5)	536 (0.83)	0.041
Territory	0 (0)	6 (0.01)	0.014
≥ 50% VA service-connected disability, *n* (%)	703 (49.9)	28 420 (43.9)	0.120
Clinical			
Elixhauser comorbidities, mean (SD)	5.6 (3.3)	4 (2.7)	−0.543
RIOSORD Risk Index Score, mean (SD)	40.4 (16)	26 (16.1)	−0.895
RIOSORD class, *n* (%)			
1 (0–24)	241 (17.1)	32 595 (50.1)	0.746
2 (25–32)	151 (10.7)	9990 (15.3)	0.139
3 (33–37)	166 (11.7)	6389 (9.8)	0.062
4 (38–42)	195 (13.8)	5500 (8.4)	0.171
5 (43–46)	151 (10.7)	3062 (4.7)	0.226
6 (47–49)	98 (6.9)	1909 (2.9)	0.186
7 (50–54)	164 (11.6)	2640 (4.1)	0.284
8 (55–59)	106 (7.5)	1625 (2.5)	0.231
9 (60–66)	81 (5.7)	934 (1.4)	0.233
10 (≥ 67)	60 (4.2)	456 (0.7)	0.230
Alcohol abuse	644 (45.8)	23 233 (36.7)	0.185
Chronic kidney disease	142 (10)	3163 (4.9)	0.199
Chronic hepatitis or cirrhosis	457 (32.3)	12 980 (19.9)	0.285
Chronic pulmonary disease	506 (35.8)	12 929 (19.9)	0.362
Tobacco use	1135 (80.3)	45 277 (69.5)	0.251
Bipolar disorder or manic episodes	229 (16.2)	7921 (12.2)	0.116
Schizophrenia or schizoaffective disorder	90 (6.4)	2861 (4.4)	0.088
Sleep apnea	267 (18.9)	9910 (15.2)	0.098
Prescription drugs			
Opioid use, by formulation			

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TABLE 1 (Continued)

Characteristic	OD cohort (*n* = 1413)	Non-OD cohort (*n* = 65 100)	Standardized difference
Immediate-release only	392 (27.7)	22 193 (34.1)	0.138
Extended-release/long-acting only	47 (3.3)	1684 (2.6)	0.044
Both	117 (8.3)	3006 (4.6)	0.150
Average total daily morphine milligram equivalents, *n* (%)			
< 50	1225 (86.7)	59 872 (92)	0.171
50 to < 100	97 (6.9)	3038 (4.7)	0.094
≥ 100	91 (6.4)	2190 (3.4)	0.143
Select non-opioid drugs, n (%)			
Antidepressant	823 (58.2)	33 469 (51.4)	0.138
Benzodiazepine	158 (11.2)	5033 (7.7)	0.118
Stimulant	49 (3.5)	2223 (3.4)	0.003
Muscle relaxant	285 (20.2)	10 302 (15.8)	0.113

Note: 'Other' race includes American Indian or Alaska Native, Asian, Multiple, Native Hawaiian or Other Pacific Islander. There were 1949 (3%) with decline toanswer/unknown/or missing race data in the no overdose group and 34 (2.4%) with decline to answer/unknown/or missing race data in the overdosegroup. There were 948 (1.5%) with multiple/decline to answer/unknown/or missing ethnicity data in the no overdose group and 22 (1.6%) with multiple/decline to answer/unknown/or missing ethnicity data in the overdose group. There were 1312 (2%) with missing marital status data in the no overdose group and six (0.4%) with missing marital status data in the overdose group. There were 415 (0.6%) missing rurality in the no overdose group and three (0.2%) with missing rurality in the overdose group. There were 307 (0.5%) with missing disability in the no overdose group and three (0.2%) with missing disability in the overdose group.
Abbreviations: SD = standard deviation; RIOSORD = Risk Index for Overdose and Serious Opioid-Induced Respiratory Depression.

meaningfully different) [17]. Due to the large sample size fallacy, conventional bivariate analyses were not used to compare the demographics between the groups, and practical significance using standardized differences were applied [18]. Continuous data were presented as mean with standard deviation and categorical data were presented as frequency with proportion.

In the unadjusted analyses, we evaluated the trends in healthcare costs and utilizations by categorizing and summarizing data per patient per monthly (30-day) period for the 12 months before the index date and 12 months after the index date. Bivariate analyses were performed to compare the differences in average healthcare costs and utilizations at the index month using the Mann–Whitney *U*-test for non-parametric data. Results were presented as the mean with standard deviation for each healthcare expenditure category.

A difference-in-differences (DiD) framework was used to compare healthcare costs and utilizations 12 months before and after the index date between VHA patients with OUD who experienced an opioid overdose and those who did not. DiD is a quasi-experimental design that uses longitudinal data to estimate a causal effect. This technique is useful when randomization is not possible and is often used to evaluate the effect of a treatment or intervention by comparing changes in outcomes over time between the intervention and control groups [19,20]. Healthcare costs included the total overall costs, total inpatient costs and total outpatient costs. Healthcare utilization included the length of stay, number of inpatient admissions and number of outpatient visits (excluding non-VA care paid for by VA). Wilcoxon's signed rank test was used to compare the average monthly healthcare costs and utilizations before and after the overdose. For the healthcare costs, adjusted analyses were performed by constructing generalized estimating equation (GEE) models using a linear structure with autoregressive correlation adjusting for baseline characteristics, which included patients' age, sex, ethnicity, marital status, VA service-connected disability status, total number of Elixhauser comorbidities, morphine equivalent dose, nicotine use, rural status, chronic pulmonary disorder, chronic kidney disease, hepatitis and medication history 90 days prior to the index date [16] (note: the RIOSORD was not included in the GEE model due to multicollinearity with the individual factors that make up its calculation). For healthcare utilization (length of stay, number of inpatient admissions and number of outpatient visits), GEE models with a negative binomial distribution were constructed. Robust standard errors were estimated by clustering on the patient. Model selection was assessed using the quasi-information criterion (QIC) [21]. Results were presented as the marginal effects with their corresponding 95% confidence interval (CI) at different values of time [22].

For our sensitivity analysis, we evaluated the change in the average monthly healthcare costs and utilization before and after the opioid overdose among those with subsequent overdoses. Wilcoxon signed rank test was used to compare the average monthly healthcare costs and utilization before and after the opioid overdose within each stratum: having one additional overdose or two or more overdoses after the index month.

If a patient did not use care in a 30-day period, their costs were set to zero. If a patient died during one of the post-index date periods, we included cost and utilization data of the period when the death occurred and assigned subsequent period costs and utilization to missing, effectively removing this person from the analysis after

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death. All costs were adjusted using the Consumer Price Index for 2020. We followed the 2022 Consolidated Health Economic Evaluation Reporting Standards (CHEERS II) task force guidelines on good reporting practices for economic evaluations (see Supporting information F) [23]. 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. All analyses were performed in SAS Enterprise Guide 8.2 (SAS Institute, Cary, NC, USA) and Stata MP version 17 (StataCorp, College Station, TX, USA).

RESULTS

Of the patients who met our inclusion criteria, 1413 (2.1%) patients with OUD had an opioid overdose, with an estimated $23.9 million ($16 890 × 1413 patients) in direct costs to VHA (95% CI = $22.1 million, $25.7 million) within the 30 days following overdose. Patient characteristics are described in Table 1. Mean age at overdose/randomly assigned index date, sex, race, ethnicity and geographic region were similar across groups (standardized difference ≤ 0.10). Patients with overdose had a higher proportion of VA service-connected disability (49.9 versus 43.9%, standardized difference = 0.12), a higher RIOSORD risk index score (40.4 versus 26.0, standardized difference = −0.89), and were more likely to have several comorbidities reported within the prior 360 days including chronic pulmonary disease (35.8 versus 19.9%, standardized difference = 0.36). Immediate-release opioid use in the prior 90 days was lower in patients with overdose (27.7 versus 34.1%, standardized difference = 0.14) and average total daily morphine milligram equivalents was higher (≥ 100, 6.4 versus 3.4%, standardized difference = 0.14). Antidepressant use was also higher in those with overdose in FY18 (58.2 versus 51.4%, standardized difference = 0.14).

Unadjusted trend analyses

Figure 2 and Supporting information E illustrate the unadjusted healthcare costs for total, inpatient and outpatient categories. Throughout all cost categories, costs increased in the first 30 days after an opioid overdose occurred for the OD cohort. Increased costs were not observed in the non-overdose cohort after the index period. The average total costs for the opioid overdose and non-overdose cohorts during the index month (days 0–30) were $21 686 [standard deviation (SD) = $24 806] and $3341 (SD = $9780) (2020 US dollars) ($P < 0.001$), respectively (Table 2; see Supporting information, Table D1 for medians and interquartile ranges). This increase was driven by inpatient costs, which accounted for most of the difference. The total inpatient cost for the OD cohort was $15 929 (SD = $21 910) compared to $1542 (SD = $8713) for the non-OD cohort ($P < 0.001$). Similarly, average outpatient cost was higher for the OD cohort compared to the non-OD cohort; the total outpatient costs for the OD and non-OD cohorts were $5542 (SD = $11 411) and $1746 (SD = $3650), respectively ($P < 0.001$).

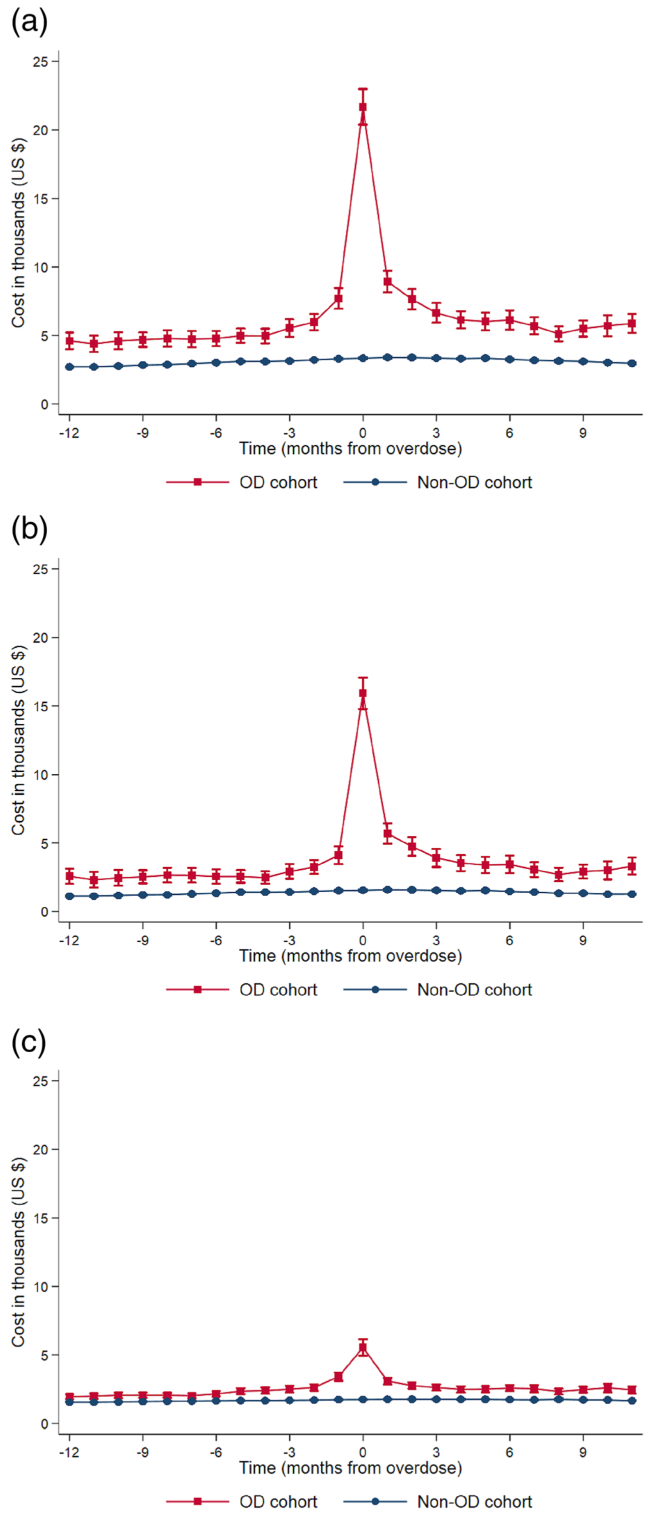

FIGURE 2 (a) Unadjusted average monthly total healthcare costs 12 months before and after overdose, by cohort*. *Both the opioid overdose (OD) and non-OD cohorts' average monthly costs include the 95% confidence intervals. (b) Unadjusted average monthly inpatient healthcare costs 12 months before and after overdose, by cohort*. *Both the OD and non-OD cohorts' average monthly costs include the 95% confidence intervals. (c) Unadjusted average monthly outpatient healthcare costs 12 months before and after overdose, by cohort*. *Both the OD and non-OD cohorts' average monthly costs include the 95% confidence intervals.

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TABLE 2 Comparison of unadjusted average costs 0–30 days after the index date between the overdose and non-overdose cohorts (2020 US dollars).

Types of costs	Opioid OD cohort (*n* = 1413)	Non-opioid OD cohort (*n* = 65 100)	*P*-value
Total costs ($), mean (SD)	21 686 (24 806)	3341 (9780)	< 0.001
Inpatient cost categories ($), mean (SD)			
Total inpatient costs	15 929 (21 910)	1542 (8713)	< 0.001
Medical/surgical	8244 (17 846)	435 (6660)	< 0.001
Psychiatry/mental health	3465 (8606)	359 (2945)	< 0.001
Substance use treatment	838 (3604)	125 (1404)	< 0.001
Mental health residential rehabilitation treatment program	731 (3399)	378 (2596)	< 0.001
Other	1393 (8133)	155 (2619)	< 0.001
Outpatient cost categories ($), mean (SD)			
Total outpatient costs	5542 (11 411)	1746 (3650)	< 0.001
Medical/surgical	1370 (1702)	457 (1254)	< 0.001
Psychiatry/mental health	572 (970)	286 (720)	< 0.001
Substance use treatment	346 (912)	194 (621)	< 0.001
Pharmacy	345 (1074)	305 (1331)	< 0.001
Mental health residential rehabilitation treatment program	40 (238)	9 (98)	< 0.001
Other	1525 (10 005)	330 (1187)	< 0.001

Note: Of 1413 patients in our opioid overdose (OD) cohort, 148 (10.5%) died within the year after overdose. Of 65 100 patients in our non-OD cohort, 1999 (3.1%) died within the year after the index date. If a patient died during one of the post-index date periods, we assigned subsequent period costs to missing. Mann–Whitney *U*-tests were performed for non-parametric data.
Abbreviation: SD = standard deviation.

Adjusted cost analyses

In the regression model, total healthcare costs were significantly higher by $16 890 (95% CI = $15 611, $18 169) in the first 30 days after the opioid overdose, adjusting for baseline characteristics (Table 3). Table 3 contains the abbreviated results for the 90 days prior to and after the index date (full results, including 360 days prior to and after the index date, are available in Supporting information, Tables D2a,b and Supporting information, Figs E12–17). The marginal increase in costs between the OD and the non-OD cohorts in the first 30 days after the opioid overdose was mostly driven by an increase in inpatient costs ($13 515; 95% CI = $12 378, $14 652); outpatient costs were also significantly higher ($3247; 95% CI = $2648, $3845). Overdose was associated with a marginal increase in mean length of stay (6.15 days; 95% CI = 5.33, 6.97) in the first 30 days after the opioid overdose. Moreover, the average length of stay remained significantly higher for the OD cohort compared to the non-OD cohort for up to 360 days after the opioid overdose. Similarly, the marginal increase in total inpatient admissions was 1.01 (95% CI = 0.93, 1.10), which remained significantly higher in the OD cohort compared to the non-OD cohort for up to 360 days after the opioid overdose. The marginal increase in outpatient visits was 1.59 (95% CI = 1.34, 1.84) in the first 30 days after the opioid overdose and remained significantly higher for up to 120 days after the index month.

Pre-trend analyses

The DiD analysis provides causal inference on the effect of the overdose when the pre-trends are similar between cases and controls. However, we report violations of this assumption for the total, inpatient and outpatient costs and utilization pre-trends (Table 3). Total, inpatient and outpatient costs were significantly higher in the OD cohort compared to the non-OD cohort 90 days before the index month; inpatient mental health residential rehabilitation treatment program costs were significantly lower among those with OD in the 30 days prior to overdose. The length of stay and number of inpatient admissions were significantly higher in the OD cohort compared to the non-OD cohort 90 days before the index month. Similarly, the number of outpatient visits was significantly higher in the OD cohort compared to the non-OD cohort 30 days before the index month.

More than one overdose event

Of 223 patients with multiple overdose events, 180 patients had one additional overdose after the index month and 43 had two or more overdoses (Table 4; see Supporting information, Table D3 for medians and interquartile ranges). Those with two or more additional opioid overdoses had the most pronounced differences in costs and admissions. Average monthly total, inpatient and outpatient costs were

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TABLE 3 Marginal adjusted costs and utilizations of the overdose and the non-overdose groups at 90 days before and up to 90 days after the index date (2020 US dollars).

Types of costs	−90 to −61 days	−60 to −31 days	−30 to −1 days	0–30 days	31–60 days	61–90 days
All costs ($), mean (95% CI)	915 (299, 1531)**	1241 (667, 1815)***	2908 (2171, 3645)***	16 890 (15 611, 18 169)***	3970 (3218, 4722)***	2784 (2067, 3502)***
Inpatient categories ($), mean (95% CI)						
Total inpatient costs	611 (82, 1141)*	856 (346, 1366)**	1686 (1046, 2325)***	13 515 (12 378, 14 652)***	3118 (2399, 3837)***	2281 (1608, 2955)***
Medical/surgical	292 (−37, 622)	509 (202, 817)**	1215 (694, 1736)***	7522 (6594, 8450)***	589 (188, 989)**	555 (155, 956)**
Psychiatry/mental health	180 (−42, 402)	108 (−94, 310)	320 (99, 541)**	2884 (2437, 3330)***	536 (253, 819)***	259 (32, 485)*
Substance use treatment	69 (−34, 172)	−24 (−96, 47)	17 (−79, 113)	671 (482, 859)***	242 (110, 374)***	158 (51, 266)**
Mental health residential rehabilitation treatment program	−89 (−225, 47)	−78 (−226, 70)	−242 (−341, −143)***	230 (52, 407)*	681 (424, 938)***	591 (337, 844)***
Other	116 (−117, 350)	164 (−79, 408)	114 (−98, 325)	1098 (673, 1524)***	766 (385, 1148)***	431 (118, 744)**
Outpatient categories ($), mean (95% CI)						
Total outpatient costs	240 (6, 475)*	352 (122, 582)**	1116 (815, 1418)***	3247 (2648, 3845)***	775 (535, 1015)***	454 (226, 682)***
Medical/surgical	72 (−16, 160)	106 (35, 178)**	402 (284, 520)***	756 (669, 842)***	141 (76, 205)***	99 (11, 188)*
Psychiatry/mental health	−10 (−54, 34)	−16 (−54, 22)	61 (2, 120)*	224 (173, 274)***	52 (5, 100)*	20 (−20, 59)
Substance use treatment	14 (−22, 51)	33 (−8, 75)	20 (−16, 56)	135 (87, 182)***	146 (94, 197)***	86 (44, 128)***
Pharmacy	−119 (−175, −62)***	−76 (−136, −15)*	−35 (−143, 72)	−58 (−115, −0.1)*	−29 (−100, 42)	22 (−88, 132)
Mental health residential rehabilitation treatment program	−0.6 (−5, 4)	0.1 (−5, 5)	10 (3, 17)**	28 (15, 40)***	20 (9, 31)***	9 (2, 16)*
Other	80 (0.6, 160)*	181 (45, 317)**	354 (242, 466)***	1070 (545, 1595)***	221 (131, 311)***	171 (70, 271)**
Resource utilization, mean (95% CI)						
Length of stay (days)	0.29 (0.04, 0.54)*	0.30 (0.06, 0.54)*	0.45 (0.23, 0.68)***	6.15 (5.33, 6.97)***	2.26 (1.74, 2.77)***	1.61 (1.16, 2.06)***
Inpatient admissions (no.)	0.04 (0.01, 0.07)**	0.05 (0.03, 0.08)***	0.10 (0.07, 0.13)***	1.01 (0.93, 1.10)***	0.19 (0.15, 0.23)***	0.14 (0.11, 0.18)***
Outpatient visits (no.)	−0.15 (−0.37, 0.06)	0.002 (−0.22, 0.22)	0.23 (0.01, 0.45)*	1.59 (1.34, 1.84)***	0.78 (0.52, 1.03)***	0.42 (0.17, 0.67)**

Abbreviation: CI = confidence interval.

*< 0.05; **< 0.01; ***< 0.001.

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TABLE 4 Pre- and post-event outcomes for those with subsequent overdoses among the opioid overdose cohort (2020 US dollars).

One additional opioid overdose after the index date				
Type of costs/expenditures, mean (95% CI)	**Before the index event (*n* = 180)**	**On or after the index event (*n* = 180)**	**difference**	***P*-value**
Total costs ($)	6410 (5219, 7602)	11 057 (9109, 13 005)	4647 (2746, 6547)	<0.001
Total inpatient costs ($)	3692 (2694, 4689)	7745 (6007, 9484)	4054 (2246, 5861)	< 0.001
Total outpatient costs ($)	2511 (2102, 2920)	2984 (2606, 3362)	473 (87, 859)	< 0.001
Length of stay (days)	2.16 (1.55, 2.78)	3.72 (2.94, 4.51)	1.56 (0.67, 2.45)	<0.001
Inpatient admission (*n*)	0.33 (0.25, 0.40)	0.58 (0.49, 0.68)	0.26 (0.15, 0.36)	< 0.001
Outpatient visits (*n*)	4.60 (4.11, 5.08)	4.69 (4.17, 5.20)	0.09 (−0.36, 0.54)	0.656
Two or more additional opioid overdose after the index date				
Type of costs/expenditures, mean (95% CI)	**Before the index event (*n* = 43)**	**On or after the index event (*n* = 43)**	**Difference**	***P*-value**
Total costs ($)	6844 (4887, 9000)	12 802 (9693, 15 912)	5958 (2888, 8828)	< 0.001
Total inpatient costs ($)	4063 (2477, 5649)	8474 (6075, 10 873)	4411 (1752, 7070)	< 0.001
Total outpatient costs ($)	2406 (1801, 3012)	3930 (2999, 4860)	1523 (700, 2347)	<0.001
Length of stay (days)	2.22 (1.10, 3.34)	3.24 (2.07, 4.42)	1.03 (−0.59, 2.64)	0.208
Inpatient admission (*n*)	0.40 (0.23, 0.57)	0.68 (0.49, 0.87)	0.28 (0.08, 0.49)	0.002
Outpatient visits (*n*)	4.85 (3.85, 5.86)	5.43 (4.36, 6.51)	0.58 (0.34, 1.50)	0.217

Note: Wilcoxon's signed rank tests were used for non-parametric paired data.
Abbreviation: CI = confidence interval.

significantly higher after the index month by $5958 (95% CI = $2888–8828; $P < 0.001$), $4411 (95% CI = $1752–7070; $P < 0.001$) and $1523 (95% CI = $700–2347; $P < 0.001$), respectively. Additionally, the average monthly number of inpatient admissions was significantly higher after the index month by 0.28 (95% CI = 0.08–0.49; $P = 0.002$) admissions.

DISCUSSION

Our analysis found that the total overall cost of an opioid overdose was substantial, with a marginal increase of $16 890 in the first 30 days following overdose. With 2.1% of the OUD population experiencing an opioid-related overdose, the economic burden was estimated to be approximately $23.9 million to the VHA within the first 30 days post-overdose. Increases in costs at the month of the event were driven mainly by inpatient expenditures and less so by outpatient expenditures; these increases continued for the 360 days after the event. Our study is the first to empirically analyze opioid-related overdose healthcare costs and utilization patterns among VHA patients with OUD.

Previous studies have reported that opioid overdoses can have a significant impact on healthcare costs and utilization. Florence and colleagues reported that fatal opioid overdose accounted for approximately $260 million in healthcare costs in the United States (2017 dollars) [12]. Stevens and colleagues reported that an opioid-related intensive care unit admission cost hospitals $92 408 in 2015 dollars [24]. However, these studies focused on the general population instead of veterans within VHA, who are at increased risk for drug overdose mortality. Moreover, few previous studies reported on the trends before and after an opioid overdose—helpful in understanding the impact of opioid overdose on the healthcare system. VA has implemented policies to increase access to harm reduction interventions and treatments including naloxone and pharmacotherapy for OUD (e.g. buprenorphine, naltrexone and methadone) to address the opioid epidemic [25,26]. Understanding the trends in healthcare costs and utilization among VHA patients with OUD who experience an opioid-related overdose may provide insight into the effects of these policies on overall expenditures.

Policies such as improving access to naloxone and medications for OUD (MOUD, e.g. buprenorphine, naltrexone and methadone) were modeled by the Stanford–Lancet Commission on the North American Opioid Crisis to reduce mortality and morbidity [27]. Based on the present analysis, such policies are also likely to have an impact on the overall total healthcare costs and utilization among patients with OUD who have an opioid-related overdose. Understanding these economic consequences should stimulate much-needed policy reform to reduce barriers to treatment and to improve retention among those who are treated with MOUD, both of which have beneficial economic consequences. Fairley and colleagues reported that patients with OUD who are provided MOUD will yield net present per-person savings of $100 000 for methadone, $60 000 for buprenorphine and $40 000 for naltrexone over the life-time of the patient [28]. Despite these benefits, we recognize that some MOUD patients do not stay in treatment. Among VHA patients, buprenorphine retention rates dropped from 68.1% at 1 year to 31.8% at

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3 years [29]. To realize the clinical and economic benefits of treatment, policies will need to reduce the burden to access and improve retention of MOUD use.

Further investigation for those with multiple non-fatal overdoses should focus upon increased risk and potential expenditures and whether appropriate post-overdose follow-up care is implemented or prescribed. In our study, minimal additional outpatient encounters observed post-overdose may suggest opportunities for enhancing engagement in effective substance use disorder treatments after an overdose. The literature on post-overdose follow-up care is limited, and best practices are not clearly defined. We know, however, that patients with previous overdoses are at greater risk for future overdoses [16]. Given this risk, and to improve post-overdose care, VHA recently mandated reporting of all overdose events using national standardized documentation templates with overdose events reviewed by interdisciplinary teams [30]. Post-overdose care in the emergency department setting is one potential avenue for action. Other avenues include peer recovery coaching and pilot frameworks—all of which may provide much-needed relief in the opioid crisis [31,32]. Future research should examine whether there are pre- and/or post-overdose treatment-related costs that can help with preventing other high costs. It is well documented that medications for OUD are highly cost-effective. Identifying the extent to which other post-overdose treatments prevent other high costs could help to inform post-overdose programming.

In our study, 11.7% of patients in our original OD cohort had multiple opioid-related overdoses after the index date. Moreover, these patients continued to have higher healthcare costs and utilization 360 days after their first reported opioid overdose compared to those with OUD who did not experience an overdose as identified by clinical healthcare data. Prevention of overdose and subsequent overdoses will not only reduce morbidity and mortality, but will also reduce the economic consequences of uncontrolled opioid dependency. As a chronic disease, OUD requires medication for treatment, behavioral counseling and harm reduction with naloxone [33]. There is an expectation that resources will need to be pooled to treat and manage OUD. However, these costs are necessary to avoid future increases due to subsequent non-fatal opioid overdoses.

Healthcare cost and utilization patterns suggest that there may be signals that occur prior to the opioid-related overdose. In the 90 days leading up to the event, healthcare cost and utilization were significantly elevated among the OD cohort with marginal increases that were higher compared to those with OUD who did not experience an overdose. Inpatient costs were driven by medical/surgical and psychiatry/mental health services costs. These patterns are similar to a previous study by Maeng and colleagues that reported pre-event patterns of healthcare costs and utilization increasing as early as 2 years prior to the overdose [13]. These signals may be informative for healthcare policy makers in developing early opioid overdose prevention strategies; however, whether these early increases in healthcare cost and utilization are indicators for a future opioid overdose requires further investigation.

Limitations

There were several limitations with our analysis. First, we recognize that, at baseline, the OD cohort had a different comorbidity profile than the non-OD cohort (e.g. more likely to have chronic kidney disease among other potentially interacting comorbidities). Also, unobserved factors may be confounding the cost differences. We mitigated potential bias by selecting patients with OUD, employing the same inclusion and exclusion criteria as the OD cohort, and controlling for baseline characteristics in the regression models. Secondly, the significant increases in healthcare costs and utilizations in the pre-trends violate the parallel trends assumption of the DiD framework, which would bias the estimates upwards [34]. Thirdly, cost and resource utilization data were based on data from both VA and non-VA claims paid for by VA. Non-VA files have not been validated and require extensive data cleaning to make the data usable. We mitigated chances for error by performing several sensitivity analyses such as inclusion and exclusion of non-VA data from our analysis. There were no meaningful differences in total costs; however, there were differences by categories of care for each group. Fourthly, we were unable to determine the reasons for the increase in costs and utilization several months prior to the opioid overdose. We recommend that a future study investigate these potential signals and inform and possibly improve future risk models to predict and prevent opioid overdoses. Fifthly, RIOSORD was developed using a VHA cohort with at least one opioid pharmacy record. We applied the algorithm to the entire OUD cohort despite the possibility that patients did not receive prescription opioids in the 180 days immediately prior to the index date. Also, because our study was limited to examining patients with OUD who had an overdose event, it misses patients for whom an overdose event is the first time an OUD is identified. Next, despite VA's policy of mandatory reporting for all overdose events, there is the potential for missing data; patients may be reluctant to report that they experienced an overdose, particularly when the overdose events occurred in the community and not within the VA healthcare system. Hence, the reported number in this report only reflects the available overdose events as documented within the VHA electronic health record and should be considered an underestimate. Lastly, this study was performed among patients with OUD receiving care within VHA and may not be generalizable to other populations. Unlike most payers, VHA is a large, integrated national healthcare system that provides healthcare, supplies and benefits to veterans. Cost and utilization patterns among patients with OUD are unlikely to be identical to those that occur in other populations. Nonetheless, the results of our study will be informative for stakeholders who are planning to measure the impact of the opioid epidemic on their population of interest.

CONCLUSIONS

The opioid epidemic has strained healthcare resources nation-wide, and VA is no exception. This cohort study estimated the costs for VHA patients with OUD who experienced an opioid-related overdose.

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We found much higher costs before and especially after the overdose when compared to opioid using VHA patients who never experienced an opioid overdose. Stakeholders can use this information when planning strategies to support overdose avoidance efforts.

AUTHOR CONTRIBUTIONS

Vilija R. Joyce: Data curation (lead); formal analysis (lead); investigation (supporting); methodology (lead); project administration (lead); software (lead); supervision (lead); validation (lead); visualization (supporting); writing—original draft (lead); writing—review and editing (lead). **Elizabeth M. Oliva:** Conceptualization (supporting); resources (lead); writing—review and editing (supporting). **Carla C. Garcia:** Project administration (supporting); writing—review and editing (supporting). **Jodie Trafton:** Conceptualization (supporting); resources (supporting); writing—review and editing (supporting). **Steven M. Asch:** Conceptualization (supporting); writing—review and editing (supporting). **Todd H. Wagner:** Conceptualization (supporting); methodology (supporting); writing—review and editing (supporting). **Keith Humphreys:** Conceptualization (supporting); supervision (supporting); writing—review and editing (supporting). **Douglas K. Owens:** Conceptualization (lead); funding acquisition (lead); investigation (lead); writing—review and editing (supporting). **Mark Bounthavong:** Conceptualization (supporting); data curation (supporting); formal analysis (supporting); investigation (supporting); methodology (supporting); software (supporting); visualization (lead); writing—original draft (supporting); writing—review and editing (supporting).

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DECLARATION OF INTERESTS

E.O. is a Data and Safety Monitory Board Member for National Institute on Drug Abuse Center for the Clinical Trials Network (NIDA CTN). J.T. is an employee, speaker, member of the board of directors and developer of written continuing medical education materials for the Institute for Brain Potential, a non-profit continuing education provider that focuses on neuroscience and clinical evidence-based training for behavioral health. T.W. received the National Institutes of Health, US Department of Veterans Affairs, Robert Wood Johnson Foundation, and Agency Healthcare Research and Quality grants and is a Data and Safety Monitory Board Member for National Institutes of Health and US Department of Veterans Affairs. K.H. is the Deputy Editor-in-Chief of *Addiction*. The other authors declare no competing interests.

DATA AVAILABILITY STATEMENT

Author elects to not share data.

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