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Title: Early buprenorphine-naloxone initiation for opioid use disorder reduces opioid overdose, emergency room visits and healthcare cost compare to late initiation

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Abstract:

Background: Although the effectiveness of buprenorphine-naloxone (BUP-NX) has been established, real-world evidence on the benefits of early treatment initiation is limited.

Objective: To evaluate the association between early BUP-NX initiation and health-related outcomes among insured adults with opioid use disorder (OUD).

Methods: We conducted a cross-sectional analysis using the Optum's de-identified Clinformatics® Data Mart Database from 2010 to 2018. Patients who initiated BUP-NX within 30 days of OUD diagnosis were classified as early initiators. Patients who initiated BUP-NX later, but within the one-year follow-up, were defined as late initiators. Outcomes included opioid overdose, opioid overdose-related emergency department (ED) visits, and all-cause healthcare cost during the year after OUD diagnosis. We employed generalized linear models to compare outcomes between early and late initiators, adjusting for baseline covariates and accounting for missing information for covariates using multiple imputation.

Results: A total of 8,388 patients with OUD were identified; mean age was 39.9 years; 36% were female; and 67.6% were early initiators. Early initiators had an estimated 42% lower rate of opioid overdose (adjusted rate ratio (aRR) = 0.58; 95% confidence interval (CI): 0.52, 0.64); 51% lower rate of opioid overdose-related ED visits (aRR = 0.49; 95% CI: 0.44, 0.55); and 31%

lower total healthcare cost (adjusted cost ratio = 0.69; 95% CI: 0.66, 0.72), compared to late initiators.

Conclusion: Compared to late BUP-NX initiation, early initiation was associated with a lower risk of opioid overdose and opioid overdose-related ED visits, and reduced total healthcare cost among insured adult patients with OUD.

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Introduction

The U.S. Department of Health and Human Services declared opioid use disorder (OUD) a national public health crisis in 2015 (1, 2), attracting renewed scientific interest in identifying implementation strategies to address the opioid epidemic. Several studies have shown that OUD is associated with elevated morbidity, overdose-related mortality, and other adverse health conditions (3-5). A systematic review and meta-analysis of 58 cohort studies of people living with OUD found a pooled all-cause crude mortality rate of 20.9 per 1000 person-years and a pooled standard mortality ratio of 14.7, with opioid overdose being the most common cause of death (6). This crisis is exacerbated by the presence of the COVID-19 pandemic (7-9). Based on the available data, drug overdose deaths started to increase from 2020 March and the predicted count of 12 month drug overdose death was 95,230 by the first month of 2021 based on avaible data on 2021 August 1st (10, 11).

There are more than an estimated 2 million people living with OUD in the US and the total cost of the opioid crisis including, direct, indirect, and lost productivity, has been rising dramatically. For example, the total cost of OUD care increased from 43.2 billion in 2009, 78.5 billion in 2013, and $471 billion in 2017 (12-14). The increased cost of OUD and opioid-related overdose deaths in the US has drawn more attention to the need to expand access to medications for opioid use disorder (MOUD). The US Food and Drug Administration (FDA) has approved buprenorphine (with/without naloxone), methadone, and injectable naltrexone for the treatment of OUD (15). The American Society of Addiction Medicine's updated national practice guidelines

recommends the use of one of these three medications for OUD care (16). Although long-term treatment of OUD has shown great promise in curbing the opioid overdose crisis, and patients are initiated or maintained on long-term treatment after diagnosis. For example, from 2009 to 2013, only 1 in 5 patients living with OUD received any form of treatment (17). As a result, access to MOUD continues to be limited for many people living with OUD due to provider, pharmacy, geographic, regulatory, and financial barriers (18-21).

Of the three medications (buprenorphine, naltrexone, methadone) approved for OUD, buprenorphine-naloxone (BUP-NX) is widely viewed as offering the greatest opportunity for expanding access to medication treatment. Naltrexone initiation often requires detoxification and an opioid-free period (22, 23), and higher induction failure rates have been observed compared to buprenorphine (with or without naloxone) (24). Furthermore, a recent cohort study showed that all-cause and opioid-related mortality rates during the first four-week after treatment initiation were higher among patients treated with methadone as compared to those who received buprenorphine (with or without naloxone): adjusted all-cause mortality RR: 2.17, 95% CI: 1.29, 3.76; adjusted opioid-related mortality RR: 7.61, 95% CI: 1.80, 31.94 (25). In addition, maintaining methadone treatment requires frequent provider and counseling visits, which places an additional burden on patients, particularly for patients who live in rural areas. One study showed that people who lived in the rural census areas of Indiana, Kentucky, Ohio, Virginia, and West Virginia had longer drive times than patients who lived in urban places of the same five states (median drive time to methadone dispensing provider for rural versus urban:

16.1 versus 48.4 minutes in 2018) (26). In the current OUD clinical management guidelines, BUP-NX is the recommended treatment (27, 28).

Several studies have investigated the relationship between MOUD and all-cause mortality, but very few have examined the association between timely initiation of treatment and health-related outcomes. A 2018 observational study found that timely initiation of MOUD (i.e., within 3-month after OUD diagnosis) was associated with a higher rate of retention on treatment compared to the use of behavioral health services alone among youths (ages 13 -22) with OUD (29). One randomized clinical trial compared immediate BUP-NX initiation in the emergency department (ED) with brief behavioral intervention and/or referral without initiating MOUD (30). Initiation of BUP-NX in the ED reduced self-reported illicit drug use and use of inpatient services during a 30-day follow-up period, compared to patients who only received the brief behavioral intervention and/or referral for treatment. In another small randomized trial, early treatment with buprenorphine (initiated after randomization) resulted in significant reductions in illegal opioid use compared to those who initiated treatment later at 4, 8, and 12 weeks, respectively (31). These studies suggest that early initiation of BUP-NX may be a successful OUD management strategy for many patients (16). However, the relationship between early BUP-NX initiation and health-related outcomes (e.g., opioid overdose episodes, healthcare utilization, and cost) has not yet been well studied. This study examined the association between early BUP-NX initiation and health-related outcomes, including opioid overdose, opioid overdose-related ED visits, and total healthcare cost, among insured adult patients living with OUD in the United States from 2010 to 2018.

Methods

We conducted a cross-sectional study using healthcare claims from the Optum's de-identified Clinformatics® Data Mart Database (OptumInsight, Eden Prairie, MN) (32). The data spanned the period from January 1, 2010 through December 31, 2018. This study was approved by the Institutional Review Board of the University of Rhode Island. The requirement for consent was waived for deidentified claims data. To create the study sample, the following eligibility criteria were applied to identify all adults with a diagnosis of OUD: 1) at least two separate outpatient claims within 3 months of each other or one inpatient claim for OUD as the primary or secondary diagnosis using the *International Classification of Diseases,* 9th and 10th Revision, Clinical Modification (ICD-9/10-CM) code (Supplemental Table 1) (29, 33, 34); 2) at least one year of continuous enrollment before the first eligible OUD diagnosis (index date); 3) at least one year of continuous follow-up after the index date; 4) at least 18 years old as of the index date; 5) initiate BUP-NX during the one-year following the index OUD diagnosis. The baseline period was used to ascertain demographic and medical information. We defined the date of the first observed OUD diagnosis in the database as the start of follow-up. Both the exposure and the outcome were ascertained from the one-year follow-up period (Figure 1). The flowchart for this study is shown in Figure 2.

Receipt of BUP-NX was identified using pharmacy claims by brand or generic names. Mono-ingredient buprenorphine was not considered as exposure. Because there was no information

available for either the formulation or the indication, and we were not able to distinguish whether the single ingredient buprenorphine was prescribed for pain or OUD management. Early BUP-NX initiation was defined as receipt of BUP-NX within 30 days after the index date. Patients who initiated BUP-NX after 30 days of the index OUD diagnosis during the follow-up were classified as late initiators.

The study included four main outcomes: 1) the number of opioid overdose-related ED visits; 2) any occurrence of opioid overdose; 3) counts of opioid overdose episodes, and 4) total healthcare cost (including inpatient, outpatient, and prescription cost) during the one-year period following OUD diagnosis. The occurrence of an opioid overdose was measured in terms of the number of opioid overdoses episodes and as a binary indicator of whether a patient experienced at least one opioid overdose during follow-up. Opioid overdose was identified using ICD-9/10 codes in inpatient and outpatient claims. Opioid overdose claims separated by at least 7 days were considered different overdose episodes (Supplemental Table 1). To identify ED visits, we used the Yale ED identification algorithm, which utilizes the Healthcare Common Procedure Coding System (HCPCS) codes, revenue codes, and place of service codes in the database (35, 36). Total healthcare costs in the year following the index date were defined and computed as the sum of the standard price of provider services for all inpatient and outpatient medical claims and outpatient pharmacy files. The cost was adjusted for inflation to the 2018 US dollar using the Consumer Price Index inflation calculator from the Bureau of Labor Statistics (37).

Sociodemographic covariates included age at OUD diagnosis, gender, type of insurance (commercial or Medicare Advantage), type of health plan, and self-reported socioeconomic status (SES). Clinical baseline covariates included history of opioid overdose, history of opioid utilization, opioid polypharmacy, Charlson comorbidity index (CCI), receipt of methadone and/or naltrexone, daily morphine milligram equivalent (MME), history of chronic obstructive pulmonary diseases, depression, receipt of antidepressants, history of alcohol use disorder, and total healthcare cost during the baseline period (4). Opioid prescription information was converted to daily MME using standard conversion factors provided by the Centers for Disease Control and Prevention (CDC) (38). Paitents who had not received any prescription opioid would have daily MME equal to zero. The CCI included 17 different conditions, such as myocardial infarction and chronic obstructive pulmonary diseases, and it is widely used as a measure of disease burden (39). Self-reported SES included race, house ownership, educational level, household income level, household net worth, poverty level, and presence of a child in the household. Some of the SES covariates were missing and only 58.4% of patients had complete information (n = 4,899), and the missing pattern was not monotone (i.e., there was not a natural ordering of variables, where for a given patient once one variable starts to have missing value, all subsequent variables were also missing for that patient) (Supplemental Table 2). All baseline comorbidities were identified using ICD-9/10-CM from both inpatient and outpatient records (Supplemental Table 1) (40).

Statistical Methods

Baseline characteristics were summarized by the BUP-NX initiation group. Descriptive statistics were calculated as mean with standard deviation (SD) for continuous variables and frequency and proportion for categorical variables. We employed a generalized linear model (GLM) to compare the outcomes between early BUP-NX initiation and late initiation groups. The log link with a Poisson distribution was used for count outcomes with adjustment for overdispersion (i.e., number of opioid overdose episodes and number of ED visits); the log link with a gamma distribution for cost outcome (i.e., total healthcare cost); and the logit link with a binomial distribution for the binary outcome (i.e., any occurrence of opioid overdose) (41).

We first fit an unadjusted model on the full study sample. Due to the missing data in self-reported SES, we conducted an adjusted comparison among complete cases adjusting for SES, comorbidities, and concomitant medications. There was no evidence of collinearity among baseline variables. To account for missing data in the SES variable, we employed multiple imputation with a fully conditional specification (FCS), an imputation approach for continuous and categorical variables. Twenty imputed datasets with complete information were generated using multiple imputation by FCS. The exposure status, baseline information, and the outcome were included in the imputation model. The coefficients estimated by GLM from twenty imputed datasets were combined, and the confidence intervals were calculated using Rubin's estimator of the variance (42-44). Because the results from the imputation may depend on the sequence in which variables are imputed (45), we conducted a sensitivity analysis with two imputation sequences: 1) starting from variables that had the most missing value to the ones that had the least; 2) starting from variables had the least missing value to the most. We also

conducted a sensitivity analysis with different definitions of early initiation: initiation within 15 and initiation within 45 days. We also evaluated the impact of the calendar year (i.e., the possible impact of policy changing across the study period) on our result by adding it as a categorical variable into models. All statistical analyses were conducted using SAS, version 9.4 (SAS Institute, Cary, NC), and statistical tests were two-sided and conducted at the 0.05 significance level.

Results

Overall, 8,388 adult patients were diagnosed with OUD during the study period and were prescribed BUP-NX sometime during the year following their diagnosis, 5,667 (67.6%) received BUP-NX within 30 days of their OUD diagnosis (i.e., early BUP-NX initiators), while 2,721 (32.4%) were late initiators (Table 1 and Figure 2, and Supplemental Table 3). Almost two-thirds of the patients were male (64%), and the mean age was 39.9 years (SD = 14.74). More than two-thirds of the patients were enrolled in commercial health insurance (77.5%), and the rest were enrolled in Medicare Advantage (22.5%). Based on the available self-reported SES information, most patients had a bachelor's degree or less (85.6%), a majority were white (84.8%), and about half had a household income of less than $75,000 (50.3%). Most patients were homeowners (82.7%) and about two-thirds had a net worth of less than $250,000 (67.8%). Furthermore, most patients were living above 400% federal poverty line (FPL) (74.8%), and most living in a childless home (77.9%) (Supplemental Table 2). The average CCI at baseline was 0.03 (SD = 1.04), but half of the patients had a history of chronic pain (49.9%); less than one-

third had depression (30.1%); 6.9% had chronic obstructive pulmonary disease; 6.0% had a documented history of alcohol use disorder; and 2.9% had a history of opioid overdose. More late initiators (32.6%) had received benzodiazepine dispensing prior to the OUD diagnosis than early initiators (28.6%). Usage of benzodiazepine and/or alcohol could delay the initiation of BUP-NX (46). The average total healthcare utilization cost during the baseline period was $27,100 (SD = $59,380) (Table 1). Less than 5% of patients had received naltrexone or methadone for OUD during the follow-up.

Overall descriptively in the study, 314 (3.7%) out of 8,388 patients in the study experienced at least one opioid overdose during the one-year following their OUD diagnosis. Among the early BUP-NX initiation group, 144 (2.5%) patients had in total 206 opioid overdose episodes (3.64 per 100 person-year). Table 2 shows, among the late BUP-NX initiation group, 170 patients (6.3%) had a total of 220 opioid overdose episodes (8.09 per 100 person-year). The opioid overdose-related inpatient visit rate among early initiators was 1 per 100 person-year and 2 per 100 person-year among late initiators. The average opioid overdose-related inpatient stay length was 4.58 and 4.42 days per year for early and late initiators, respectively. For all-cause healthcare utilization, the early initiators had 26.7 outpatient visits per year (SD = 23.60), 0.56 inpatient admissions per year (SD = 1.55), 10.91 days inpatient stay per year (SD = 17.20), and 2.07 ED visits per year (SD = 5.06). Among the late initiators, the average number of outpatient visits per year was 35.59 (SD=29.98), the average number of inpatient admissions per year was 1.22 (SD = 1.92), the average days of inpatient stay per year was 14.34 (SD = 18.57), and the average number of ED visits per year was 3.02 (SD = 6.41) (Table 2).

Table 3 shows unadjusted average annual costs. The average annual cost of BUP-NX among early initiators and the late initiators was $3,637 (SD = $2,987) and $2,320 (SD= $2,280), respectively. The average opioid overdose-related spending during follow-up among early and late initiators was $289 (SD = $3,557) and $605 (SD = $4643), respectively. For all-cause spending, the average annual prescription medication cost was $7,125 (with 51% was due to BUP-NX) for the early initiators and $5,803 (with 40% was due to BUP-NX) for the late initiators. The average annual total healthcare utilization cost among the early and late initiators was $34,316 (SD = $63,867) and $55,485 (SD = $84,874), respectively.

We compared the adjusted healthcare utilization between early BUP-NX initiators and late initiators by the generalized linear model combined with multiple imputation. Compared to the late initiators, the early BUP-NX initiators had a 42% reduction in the rate of opioid overdose (adjusted relative risk (aRR) = 0.58, 95% confidence interval (CI): 0.52, 0.64); 51% reduction in the rate of opioid overdose-related ED visit (aRR = 0.49, 95% CI: 0.44, 0.55); 48% reduction in the odds of opioid overdose (adjusted odds ratio= 0.52, 95% CI: 0.41, 0.66); and 31% less total healthcare cost (adjusted cost ratio (aCR) = 0.69, 95% CI: 0.66, 0.72) (Table 4). The results from sensitivity analyses were comparable across different definitions of early treatment initiation (Supplemental Table 4). The point estimate and the 95% confidence interval were comparable, regardless of the imputation sequence (Supplemental Table 5). Furthermore, the results were also consistent across different calendar years (Supplemental Table 6).

Discussion

This cross-sectional study used a large national administrative claim dataset of more than 50 million insured patients in the United States from 2010 to 2018. The results provide evidence that buprenorphine-naloxone (BUP-NX) treatment initiation for OUD within 30 days of the initial OUD diagnosis is associated with clinical and cost benefits for the patient and the healthcare system. Early BUP-NX initiation was associated with a lower risk of opioid overdose, a lower rate of overdose-related ED visits, and reduced total healthcare cost during the year following an initial OUD diagnosis, after adjusting for baseline sociodemographic and medical characteristics.

Our findings are consistent with results from other previous studies. For example, Morgan et al. (47) had shown that active buprenorphine (with or without naloxone) treatment versus interrupted treatment was associated with a lower hazard of overdose among commercially insured patients with OUD in the US (adjusted hazard ratio = 0.40; 95% CI: 0.35, 0.46). Furthermore, Baser et al. (48) found that patients who received MOUD had lower total healthcare utilization costs during the 6-month window after treatment initiation compared to patients with OUD who did not initiate treatment. With the evidence supporting the benefit of MOUD, a treatment cascade for diagnosis and treatment of OUD management was established by Williams et al (49). However, access to medication treatment remains limited. In our study, among the eligible adult patients with OUD (n= 55,608), only 15.1% (n = 8,388) received at least one buprenorphine-naloxone dispensing during the year after the OUD diagnosis (Figure 2).

These matches findings from other recent studies. After the Comprehensive Addiction and Recovery Act passed by the U.S. Congress, there were only 10-20% of patients with OUD received medications for OUD by estimation (19). During 2009-2013, 21.5% (95% CI: 19.1, 24.0) patients with OUD had received any type of treatment for OUD (medication or non-pharmacological) during the previous 12 months (50).

Our study addresses a critical gap in knowledge for OUD treatment and some limitations identified in prior studies. We successfully identified early initiators from claims data and evaluated the association between timely BUP-NX initiation and opioid overdose, healthcare utilization, and cost among insured adult patients with OUD. This study provides preliminary evidence supporting timely BUP-NX treatment initiation. Our study also addressed the concern about unmeasured confounding due to SES variables, a known risk factor for overdose, by including available information in generalized linear models with multiple imputation. We employed generalized linear models with multiple imputation to account for missing data, leveraging important variables to control for possible imbalances between exposure groups. We also conducted a series of sensitivity analyses to explore the impact of different exposure definitions and the imputation approaches on the results.

We found that less opioid overdose-related cost was incurred among the early initiators compared to the late initiators. However, BUP-NX treatment cost per patient was higher among the early initiators. Overall, the unadjusted total healthcare utilization cost, including prescription and in/outpatient cost regardless of disease, was much lower among the early

BUP-NX initiators than late initiators, $34,316 and $55,485, respectively. Baser et al. (48) also found that the cost of detoxification/rehabilitation and/or provider visits was 29% higher among untreated patients compared to those who received MOUD. In another study, immediate BUP-NX initiation in ED was more cost effective than a brief behavioral intervention and referral among adult patients with OUD (51).

Our study has some limitations that are common in observational studies using administrative claims data. Because the exposure was not randomly assigned, patient sociodemographic information and medical history may not be balanced between the two groups. To address this issue, we used the generalized linear models to adjust for possible confounders measured at baseline, including gender, SES variables, and comorbidities. However, we did not have information about the severity of OUD, illegal drug use, patient lifestyle, or community distribution of naloxone and we could not ascertain whether the indexed OUD was the first one during their lifetime. Although we used commonly employed codes from the literature, the sensitivity and specificity of some of the diagnosis codes have not yet been validated. The treatment initiation group and the outcomes were assessed during the same period. As a result, the temporal sequence of exposure and outcomes was not guaranteed. Because of this type of cross-sectional design, the results in this paper do not confer any causal interpretations, even though patients were followed longitudinally. Lastly, we did not have information on mortality, and the study population was restricted to patients with commercial insurance or Medicare Advantage, which limits the generalizability of the findings.

Conclusion

Initiation of buprenorphine-naloxone within 30 days of opioid use disorder diagnosis was associated with a reduced occurrence of opioid overdose and a significant decrease in total healthcare utilization and cost during the one-year period following the OUD diagnosis compared to later initiation. These findings should be considered by clinicians when assessing potential risks and clinical benefits of initiating BUP-NX among adults with OUD in routine medical practice. Longitudinal cohort studies that ensure a temporal ordering between exposure and outcomes, avoid conditioning on post-baseline variables, and use appropriate methods to address confounding are warranted.

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Table 1 Descriptive summary of baseline medication and comorbidity information of the analytical sample

	Early initiators (n = 5,667)	Late initiators (n = 2,721)	Total (n = 8,388)
Gender, n (%)[1]			
Female	2004 (35.4)	1012 (37.2)	3016 (36.0)
Male	3663 (64.6)	1709 (62.8)	5372 (64.0)
Age (years) at OUD dx, Mean (SD)	40.78 (14.54)	38.07 (15.00)	39.90 (14.74)
Type of insurance, n (%)[1]			
Commercial	4351 (76.8)	2152 (79.1)	6503 (77.5)
Medicare Advantage	1316 (23.2)	569 (20.9)	1885 (22.5)
Type of health plan, n (%)[1]			
Exclusive provider organization	570 (10.1)	239 (8.8)	809 (9.6)
Health maintenance organization	821 (14.5)	429 (15.8)	1250 (14.9)
Point of service	3312 (58.4)	1636 (60.1)	4948 (59.0)
Preferred provider organization	263 (4.6)	168 (6.2)	431 (5.1)
Indemnity or others[2]	701 (12.4)	249 (9.2)	950 (11.3)
Medical conditions, n (%)			
Chronic pain	2807 (49.5)	1381 (50.8)	4188 (49.9)
Depression	1610 (28.4)	914 (33.6)	2524 (30.1)
Alcohol use disorder	284 (5.0)	216 (7.9)	500 (6.0)
History of opioid overdose	137 (2.4)	107 (3.9)	244 (2.9)
Chronic pulmonary disease	389 (6.9)	189 (6.9)	578 (6.9)
CCI at baseline, Mean (SD)	0.30 (1.06)	0.30 (0.99)	0.30 (1.04)
90 days prior to OUD dx, n (%)			
Benzodiazepine	1618 (28.6)	886 (32.6)	2504 (29.9)
Anti-depressants	2119 (37.4)	1102 (40.5)	3221 (38.4)
180 days prior to OUD dx, n (%)			
Multiple opioids Rx	1398 (24.7)	755 (27.7)	2153 (25.7)
Any opioid Rx	2743 (48.4)	1436 (52.8)	4179 (49.8)
Mean daily MME 180 days prior to OUD dx, Mean (SD) [3]	27.5 (52.7)	34.0 (59.4)	29.6 (55.0)
Daily MME among patients received prescription opioid 180 days prior to OUD dx, Mean (SD)[3]	56.8 (63.9)	64.4 (68.7)	59.4(65.7)
Medications during the follow-up, n (%)			
Naltrexone	140 (2.5)	195 (7.2)	335 (4.0)
Methadone[2]	14 (0.2)	<11	<26
Baseline cost ($), Mean (SD)			
Outpatient cost	16086 (41823)	19963 (38887)	17344 (40931)
Inpatient cost	4283 (21339)	5366 (22457)	4634 (21713)
Medication cost	5490 (13452)	4354 (9371)	5121 (12289)
ED visit cost	3976 (11113)	5231 (13593)	4383 (11981)
Total healthcare cost	25859 (59473)	29683 (59115)	27100 (59380)

[1] Values of polytomous variables might not sum to 100% due to rounding

[2] Categories were combined, or number was masked due to small cell count

[3] Single-ingredient buprenorphine was included in the MME calculation

rx: prescription; dx: diagnosis; MME: morphine milligram equivalent

Table 2 Descriptive summary of opioid overdose-related and all-cause healthcare utilization

Healthcare utilization during the one-year period following opioid use disorder diagnosis	Early initiators (n = 5,667)	Late initiators (n = 2,721)	Total (n = 8,388)
Number of opioid overdose episodes, Mean (SD)	0.04 (0.28)	0.08 (0.35)	0.05 (0.30)
Number of patients who had at least one opioid overdose, n (%)	144 (2.5)	170 (6.2)	314 (3.7)
Number of opioid overdose episodes among patients who had at least one opioid overdose, Mean (SD)	1.43 (1.06)	1.29 (0.85)	1.36 (0.84)
Opioid overdose-related healthcare utilization, Mean (SD)			
Number of inpatient visits	0.01 (0.10)	0.02 (0.14)	0.01 (0.11)
Length of inpatient stay (day)*	4.58 (4.29)	4.42 (6.15)	4.51 (5.19)
Number of outpatient visits	0.06 (0.60)	0.11 (0.61)	0.07 (0.61)
Number of ED visits	0.03 (0.25)	0.08 (0.42)	0.04 (0.31)
All-cause healthcare utilization, Mean (SD)			
Number of inpatient visits	0.56 (1.55)	1.22 (1.92)	0.77 (1.71)
Length of inpatient stay (day)*	10.91 (17.20)	14.34 (18.57)	12.52 (17.94)
Number of outpatient visits	26.74 (23.60)	35.59 (29.98)	29.61 (26.17)
Number of ED visits	2.07 (5.06)	3.02 (6.41)	2.38 (5.55)

ED: emergency department.

* The average length of inpatient stay was calculated among patients who had at least one inpatient admission.

Table 3 Descriptive summary of opioid-related and all-cause healthcare cost per patient

Cost of different healthcare utilization during one-year following opioid use disorder diagnosis	Early initiators (n = 5,667)	Late initiators (n = 2,721)	Total (n = 8,388)
Opioid overdose-related cost in US dollars, Mean (SD)			
ED visit cost	54 (539)	194 (1308)	100 (869)
Inpatient visit cost	74 (1227)	138 (2045)	95 (1541)
Outpatient visit cost	215 (2585)	467 (2984)	297 (2723)
Total cost	289 (3557)	605 (4643)	391 (3945)
Buprenorphine-naloxone cost, Mean (SD)	3637 (2987)	2320 (2281)	3210 (2845)
All-cause healthcare cost in US dollars, Mean (SD)			
ED visit cost	3653 (10455)	5516 (12831)	4257 (11314)
Prescription cost	7125 (11577)	5803 (9638)	6696 (11002)
Inpatient visit cost	6657 (28325)	14125 (34937)	9080 (30823)
Outpatient visit cost	20538 (42623)	35575 (57314)	25416 (48396)
Total cost	34316 (63867)	55485 (84874)	41183 (72043)

ED: emergency department.

Table 4 Comparison of outcomes between early buprenorphine-naloxone initiation group and late initiation group during the one-year period following the OUD diagnosis

Outcomes	Unadjusted	Adjusted with complete records	Adjusted with MI
Count of opioid overdose episodes (RR with 95% CI)	0.45 (0.41, 0.49)	0.52 (0.46, 0.59)	0.58 (0.52, 0.64)
Count of opioid overdose-related ED visit (RR with 95% CI)	0.36 (0.32, 0.40)	0.43 (0.37, 0.49)	0.49 (0.44, 0.55)
Opioid overdose (OR with 95% CI)	0.39 (0.31, 0.49)	0.44 (0.32, 0.61)	0.52 (0.41, 0.66)
Total healthcare cost (CR with 95% CI)	0.62 (0.59, 0.65)	0.68 (0.64, 0.72)	0.69 (0.66, 0.72)

RR: risk ratio; CI: Confidence Interval; OR: odds ratio; CR: cost ratio.

Figure 1 Schematic of the cross-sectional study design

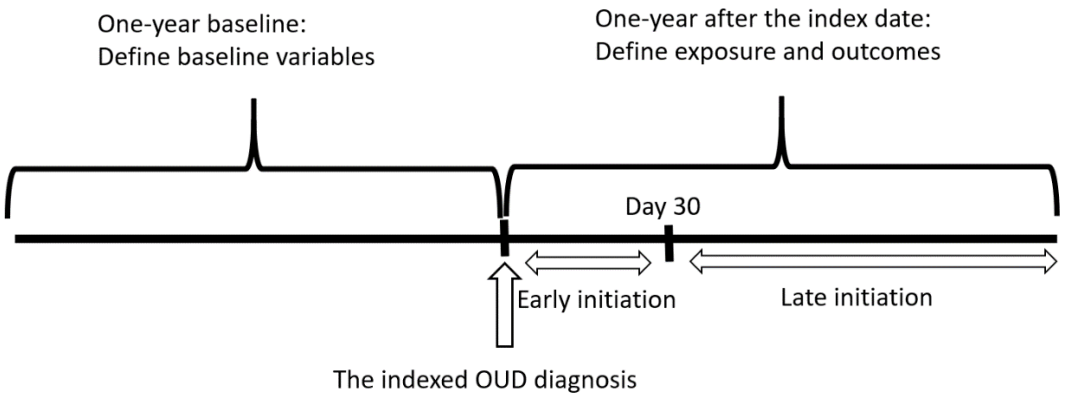

Figure 2 Flowchart of cohort building based on in/exclusion criteria for a study of insured adult patients with opioid use disorder in the United States, 2010 – 2018