



Original Investigation | Substance Use and Addiction

# Comparative Effectiveness of Different Treatment Pathways for Opioid Use Disorder

Sarah E. Wakeman, MD; Marc R. Larochelle, MD, MPH; Omid Ameli, MD, MPH; Christine E. Chaisson, MPH; Jeffrey Thomas McPheeters, BA; William H. Crown, PhD; Francisca Azocar, PhD; Darshak M. Sanghavi, MD

## Abstract

**IMPORTANCE** Although clinical trials demonstrate the superior effectiveness of medication for opioid use disorder (MOUD) compared with nonpharmacologic treatment, national data on the comparative effectiveness of real-world treatment pathways are lacking.

**OBJECTIVE** To examine associations between opioid use disorder (OUD) treatment pathways and overdose and opioid-related acute care use as proxies for OUD recurrence.

**DESIGN, SETTING, AND PARTICIPANTS** This retrospective comparative effectiveness research study assessed deidentified claims from the OptumLabs Data Warehouse from individuals aged 16 years or older with OUD and commercial or Medicare Advantage coverage. Opioid use disorder was identified based on 1 or more inpatient or 2 or more outpatient claims for OUD diagnosis codes within 3 months of each other; 1 or more claims for OUD plus diagnosis codes for opioid-related overdose, injection-related infection, or inpatient detoxification or residential services; or MOUD claims between January 1, 2015, and September 30, 2017. Data analysis was performed from April 1, 2018, to June 30, 2019.

**EXPOSURES** One of 6 mutually exclusive treatment pathways, including (1) no treatment, (2) inpatient detoxification or residential services, (3) intensive behavioral health, (4) buprenorphine or methadone, (5) naltrexone, and (6) nonintensive behavioral health.

**MAIN OUTCOMES AND MEASURES** Opioid-related overdose or serious acute care use during 3 and 12 months after initial treatment.

**RESULTS** A total of 40 885 individuals with OUD (mean [SD] age, 47.73 [17.25] years; 22 172 [54.2%] male; 30 332 [74.2%] white) were identified. For OUD treatment, 24 258 (59.3%) received nonintensive behavioral health, 6455 (15.8%) received inpatient detoxification or residential services, 5123 (12.5%) received MOUD treatment with buprenorphine or methadone, 1970 (4.8%) received intensive behavioral health, and 963 (2.4%) received MOUD treatment with naltrexone. During 3-month follow-up, 707 participants (1.7%) experienced an overdose, and 773 (1.9%) had serious opioid-related acute care use. Only treatment with buprenorphine or methadone was associated with a reduced risk of overdose during 3-month (adjusted hazard ratio [AHR], 0.24; 95% CI, 0.14-0.41) and 12-month (AHR, 0.41; 95% CI, 0.31-0.55) follow-up. Treatment with buprenorphine or methadone was also associated with reduction in serious opioid-related acute care use during 3-month (AHR, 0.68; 95% CI, 0.47-0.99) and 12-month (AHR, 0.74; 95% CI, 0.58-0.95) follow-up.

*(continued)*

## Key Points

**Question** What is the real-world effectiveness of different treatment pathways for opioid use disorder?

**Findings** In this comparative effectiveness research study of 40 885 adults with opioid use disorder that compared 6 different treatment pathways, only treatment with buprenorphine or methadone was associated with reduced risk of overdose and serious opioid-related acute care use compared with no treatment during 3 and 12 months of follow-up.

**Meaning** Methadone and buprenorphine were associated with reduced overdose and opioid-related morbidity compared with opioid antagonist therapy, inpatient treatment, or intensive outpatient behavioral interventions and may be used as first-line treatments for opioid use disorder.

## + Supplemental content

Author affiliations and article information are listed at the end of this article.

**Open Access.** This is an open access article distributed under the terms of the CC-BY-NC-ND License.

Abstract (continued)

**CONCLUSIONS AND RELEVANCE** Treatment with buprenorphine or methadone was associated with reductions in overdose and serious opioid-related acute care use compared with other treatments. Strategies to address the underuse of MOUD are needed.

JAMA Network Open. 2020;3(2):e1920622. doi:10.1001/jamanetworkopen.2019.20622

## Introduction

The increasing burden of opioid use disorder (OUD) has resulted in increased opioid-related morbidity and mortality, with 47 600 overdose deaths in 2017 alone.<sup>1-3</sup> From 2002 to 2012, hospitalization costs attributable to opioid-related overdose increased by more than \$700 million annually.<sup>4</sup> Associated health complications, such as hepatitis C infection, HIV infection, and serious injection-related infections, are also increasing.<sup>5-7</sup> In addition, as rates of opioid-related death have increased despite decreases in prescription opioid supply, there is an increasing recognition that greater attention must be paid to improving access to effective OUD treatment.<sup>8,9</sup>

Medication for opioid use disorder (MOUD) is effective and improves mortality, treatment retention, and remission, but most people with OUD remain untreated.<sup>10-15</sup> Many parts of the United States lack access to buprenorphine prescribers, and only a few addiction treatment programs offer all forms of MOUD.<sup>16-18</sup> This lack of access has resulted in a treatment gap of an estimated 1 million people with OUD untreated with MOUD annually.<sup>19</sup>

Nationally representative, comparative effectiveness studies of MOUD compared with nonpharmacologic treatment are limited. One prior study<sup>12</sup> compared MOUD with psychosocial treatments but was limited to a Massachusetts Medicaid population. Studies<sup>20-23</sup> examining OUD treatment among nationally representative populations have examined trends in MOUD initiation, patterns of OUD treatment, and effectiveness of different types of MOUD at reducing overdose using Medicaid and commercial claims data. However, none of those studies<sup>20-23</sup> compared the effectiveness of MOUD with nonpharmacologic treatments in a national sample. Despite better access to medical care, only a few commercially insured patients are treated with MOUD, and psychosocial-only treatments continue to be common, suggesting that greater understanding of the comparative effectiveness of these different treatments is needed.<sup>21</sup>

In this study, we used a large, nationally representative database of commercially insured and Medicare Advantage (MA) individuals to evaluate the effectiveness of MOUD compared with nonpharmacologic treatment. This retrospective comparative effectiveness study was designed to inform treatment decisions made by policy makers, insurers, practitioners, and patients.

## Methods

We conducted a comparative effectiveness research study using the OptumLabs Data Warehouse, which includes medical, behavioral health, and pharmacy claims for commercial and MA enrollees.<sup>24</sup> The database represents a diverse mixture of ages, races/ethnicities, and geographic regions across the United States. Our analysis used deidentified administrative claims data. The window for identification of OUD for this study was January 1, 2015, to September 30, 2017. The study used claims data from October 3, 2014, to December 31, 2017, to allow for a 90-day period to ensure a nonopioid clean period and a minimum of 90 days of follow-up for all individuals with diagnosed OUD. Data analysis was performed from April 1, 2018, to June 30, 2019. Because this study involved analysis of preexisting, deidentified data, the Chesapeake Institutional Review Board deemed it exempt from institutional review board approval. This study followed the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) reporting guideline.<sup>25</sup>

## Cohort Selection

We defined OUD as 1 or more inpatient or 2 or more outpatient claims for *International Classification of Diseases, Ninth Revision (ICD-9)* or *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* diagnosis codes for opioid dependence that occurred within 3 months of each other; 1 or more claims for diagnosis codes for opioid dependence, opioid use, or opioid abuse plus diagnosis codes for an encounter related to opioid overdose or an injection-related infection, opioid-related inpatient detoxification or residential services; or claims for MOUD or detoxification (eFigure 1 in the [Supplement](#)). Cohort inclusion required presence of OUD and age of 16 years or older; commercial or MA medical, pharmacy, and behavioral coverage; and continuous enrollment for 3 months before and after OUD treatment initiation date. For those in the no treatment group, a treatment initiation index date was selected at random that matched the treated groups (eAppendix 1 in the [Supplement](#)).

## Treatment Pathways

We examined treatments received in the 3 months after OUD diagnosis during the first 90 days after cohort entry to identify patterns of treatment (eFigure 2 in the [Supplement](#)). We categorized individuals into 1 of 6 mutually exclusive pathway designations based on initial treatment: (1) no treatment, (2) inpatient detoxification or residential services, (3) intensive behavioral health (intensive outpatient or partial hospitalization), (4) buprenorphine or methadone, (5) naltrexone, and (6) only nonintensive behavioral health (outpatient counseling) (eAppendix 2 in the [Supplement](#)). In addition, we examined mean duration of MOUD treatment in days.

Classification of treatment pathways was informed by detailed exploration of the sequence of treatment modalities provided to patients using medical and pharmacy claims (eFigure 3 in the [Supplement](#)). For this study, consistent with an intent-to-treat design, patients were assigned to the initial treatment received.

## Outcomes

Our primary outcomes were overdose or serious opioid-related acute care use, defined as an emergency department or hospitalization with a primary opioid diagnosis code. Overdose was identified based on diagnosis codes from claims for health care encounters. These encounters may include both fatal and nonfatal overdose (lack of mortality data preclude that determination). For actively treated individuals, the index date was the date of first treatment. For untreated individuals, the index date was set randomly based on the distribution of time to first treatment among actively treated individuals. Risk for adverse outcomes started 1 day after the index date; however, because the time sequence for adverse events that occurred during an initial inpatient treatment could not be reliably established, risk of adverse outcomes started 1 day after inpatient discharge. Time to event was calculated as (event date - index date + 1), which is consistent with an intent-to-treat analysis for all treatment pathways. Individuals were censored at the earlier outcome, health plan disenrollment, or 12 months. We selected overdose and opioid-related acute care use as negative clinical outcomes, which likely indicate recurrence of OUD. These outcomes may underestimate the prevalence of OUD recurrence because they represent severe consequences of ongoing use.

A secondary outcome was admission to inpatient detoxification or readmission for those who initiated treatment with inpatient detoxification or residential services. All outcomes were evaluated for 3 months and 12 months after treatment initiation. In the absence of an event, patients were followed up until the earliest date of health plan disenrollment or end of the respective period.

## Statistical Analysis

We used Cox proportional hazards regression models to estimate the hazard ratios (HRs) for primary and secondary outcomes, adjusting for age, sex, race/ethnicity, insurance type, baseline cost rank, mental health and medical comorbidities, and injection-related infections or overdose at study inclusion. For medical comorbidities, we used a modified Elixhauser index that excluded mental

health subcomponents because they were classified separately.<sup>26</sup> All analyses were conducted using an intent-to-treat approach that attributed patient outcomes to their initial treatment category. We conducted a subanalysis of patients who received methadone or buprenorphine, stratifying by duration of MOUD treatment as 1 to 30 days, 31 to 180 days, or more than 180 days.

For the secondary outcome of admission to inpatient detoxification, we conducted a subanalysis in which patients in the no treatment and nonintensive behavioral health groups were removed from the sample. These 2 treatment pathways were, by definition, required to not have any treatment (no treatment group) or any treatment other than outpatient behavioral health treatment (nonintensive behavioral health group) in the first 3 months of follow-up, which made them systematically different from the other pathways evaluated for this outcome.

Analysis of survival for all outcomes was performed using unadjusted Kaplan-Meier curves and adjusted Cox proportional hazards regression (PHREG procedure, SAS Enterprise Guide, version 7.13 [SAS Institute Inc]) under both 3-month and 12-month time windows to examine potential survivorship bias and informative censoring. For the unadjusted analysis, the log-rank test is reported; 95% Wald CIs are reported for the adjusted HRs (AHRs). The proportionality assumption was assessed visually and tested by including treatment pathway as a time-dependent covariate in the Cox proportional hazards regression model. Hazards appeared to be proportional during 3 months, but there was evidence of nonproportionality for the behavioral health outpatient pathway during the 12-month time window.

---

## Results

### Cohort Characteristics

A total of 40 885 individuals with OUD (mean [SD] age, 47.73 [17.25] years; 22 172 [54.2%] male; 30 332 [74.2%] white) were identified. A total of 23 636 (57.8%) were commercially insured, and 17 249 (42.2%) were enrolled in MA plans. Of those with MA, 10 322 (25.2%) were younger than 65 years. Non-substance use disorder mental health comorbidities in the 3 months before the index date were found in 10 942 individuals (45.1%) in the cohort. Depression (9733 [23.8%]) and anxiety (10 704 [26.2%]) were most common (**Table 1**).

The most common treatment pathway was nonintensive behavioral health (24 258 [59.3%]), followed by inpatient detoxification or residential services (6455 [15.8%]) and buprenorphine or methadone (5123 [12.5%]). Not receiving any treatment was more common (2116 [5.2%]) than naltrexone (963 [2.4%]) or intensive behavioral health (1970 [4.8%]). Mean (SD) length of stay in inpatient detoxification or residential services was 7.47 (10.35) days. For the 5048 in that group who had at least 6 months of continuous enrollment, mean (SD) length of stay was 7.56 (10.99) days. For the 3098 in that group who had at least 12 months of continuous enrollment, mean (SD) length of stay was 7.64 (12.24) days.

Maintaining continuous commercial health insurance was challenging in this cohort; 19 685 (48.1%) were disenrolled by 12 months after the index date. Individuals receiving nonintensive behavioral health had the lowest disenrollment (11 037 [45.5%]), and those receiving MOUD treatment with buprenorphine or methadone (2755 [53.8%]) and MOUD treatment with naltrexone (520 [54.0%]) had the highest disenrollment rates. No differences were found between those who maintained enrollment and those who were disenrolled with regard to race/ethnicity, comorbidities, or markers of severity of OUD, including those with a history of an injection-related infection, hepatitis C infection, or overdose. It was not possible to distinguish disenrollment attributable to death from disenrollment for other reasons (eg, health insurance options offered by employers). Details on demographic characteristics and comorbidities by treatment group for individuals who were disenrolled are provided in the eTable in the [Supplement](#).

**Recurrence Outcomes**

During the 3-month follow-up period, 707 participants (1.7%) experienced an overdose, and 773 (1.9%) had a serious opioid-related acute care use episode. Only individuals receiving MOUD treatment with buprenorphine or methadone were less likely to experience an overdose compared with those receiving no treatment (AHR, 0.24; 95% CI, 0.14-0.41) (Table 2 and Figure 1A). Inpatient detoxification or residential services (AHR, 0.82; 95% CI, 0.57-1.19), naltrexone (AHR, 0.59; 95% CI, 0.29-1.20), nonintensive behavioral health services (AHR, 0.92; 95% CI, 0.67-1.27), or intensive

**Table 1. Patient Characteristics<sup>a</sup>**

Characteristic	Total	No Treatment	MOUD				
			Inpatient Detoxification or Residential Services	BH IOP	Buprenorphine or Methadone	Naltrexone	BH Other
Total sample	40 885 (100)	2116 (5.2)	6455 (15.8)	1970 (4.8)	5123 (12.5)	963 (2.4)	24 258 (59.3)
Age, mean (SD), y	47.73 (17.25)	44.85 (18.66)	39.22 (15.38)	31.28 (12.19)	42.58 (13.93)	38.10 (14.01)	53.05 (16.36)
Follow-up duration, mean (SD), d	293.2 (91.3)	285.0 (93.9)	284.3 (96.1)	291.1 (93.2)	281.8 (94.7)	282.5 (94.5)	299.3 (88.1)
Age group, y							
16-25	5978 (14.6)	437 (20.7)	1837 (28.5)	948 (48.1)	578 (11.3)	247 (25.6)	1931 (8.0)
26-34	5350 (13.1)	354 (16.7)	1124 (17.4)	404 (20.5)	1194 (23.3)	197 (20.5)	2077 (8.6)
35-44	6070 (14.8)	332 (15.7)	1089 (16.9)	290 (14.7)	1172 (22.9)	206 (21.4)	2981 (12.3)
45-54	7208 (17.6)	300 (14.2)	1059 (16.4)	188 (9.5)	995 (19.4)	167 (17.3)	4499 (18.5)
54-64	8897 (21.8)	318 (15.0)	983 (15.2)	117 (5.9)	817 (15.9)	108 (11.2)	6554 (27)
≥65	7382 (18.1)	375 (17.7)	363 (5.6)	23 (1.2)	367 (7.2)	38 (3.9)	6216 (25.6)
Sex							
Female	18 713 (45.8)	797 (37.7)	2482 (38.5)	662 (33.6)	1971 (38.5)	387 (40.2)	12 414 (51.2)
Male	22 172 (54.2)	1319 (62.3)	3973 (61.5)	1308 (66.4)	3152 (61.5)	576 (59.8)	11 844 (48.8)
Insurance type							
Commercial	23 636 (57.8)	1299 (61.4)	5062 (78.4)	1889 (95.9)	3630 (70.9)	841 (87.3)	10 915 (45)
Medicare Advantage							
Age <65 y	10 322 (25.2)	457 (21.6)	1067 (16.5)	63 (3.2)	1147 (22.4)	91 (9.4)	7497 (30.9)
Age ≥65 y	6927 (16.9)	360 (17.0)	326 (5.1)	18 (0.9)	346 (6.8)	31 (3.2)	5846 (24.1)
Race/ethnicity							
White	30 332 (74.2)	1485 (70.2)	4976 (16.4)	1552 (78.8)	4044 (78.9)	791 (82.1)	17 484 (72.1)
Hispanic	3388 (8.3)	192 (9.1)	511 (15.1)	158 (8.0)	338 (6.6)	47 (4.9)	2142 (8.8)
Black	4991 (12.2)	317 (15.0)	628 (12.6)	161 (8.2)	468 (9.1)	68 (7.1)	3349 (13.8)
Other or unknown	2174 (5.3)	122 (5.8)	340 (15.6)	99 (5.0)	273 (5.3)	57 (5.9)	1283 (5.3)
Elixhauser index score excluding mental health, mean (SD)							
Any mental health diagnosis	18 218 (44.6)	585 (27.6)	3078 (47.7)	933 (47.4)	2060 (40.2)	620 (64.4)	10 942 (45.1)
Depression	9733 (23.8)	270 (12.8)	1670 (25.9)	552 (28.0)	965 (18.8)	398 (41.3)	5878 (24.2)
Anxiety	10 704 (26.2)	274 (12.9)	1921 (29.8)	554 (28.1)	1329 (25.9)	391 (40.6)	6235 (25.7)
ADHD	1774 (4.3)	33 (1.6)	402 (6.2)	159 (8.1)	272 (5.3)	77 (8.0)	831 (3.4)
PTSD	1462 (3.6)	41 (1.9)	245 (3.8)	104 (5.3)	153 (3.0)	69 (7.2)	850 (3.5)
Alcohol	4166 (10.2)	174 (8.2)	961 (14.9)	471 (23.9)	225 (4.4)	496 (51.5)	1839 (7.6)
Bipolar disorder	3138 (7.7)	102 (4.8)	556 (8.6)	183 (9.3)	290 (5.7)	146 (15.2)	1861 (7.7)
Psychosis	1526 (3.7)	76 (3.6)	268 (4.2)	76 (3.9)	87 (1.7)	40 (4.2)	979 (4)
IDU infection	5556 (13.6)	249 (11.8)	330 (5.1)	66 (3.4)	151 (2.9)	31 (3.2)	4729 (19.5)
Hepatitis C	2018 (4.9)	64 (3.0)	181 (2.8)	<29 (<1.7)	121 (2.4)	<11 (<1.1)	1623 (6.7)
Opioid overdose	2135 (5.2)	249 (11.8)	267 (4.1)	84 (4.3)	86 (1.7)	27 (2.8)	1422 (5.9)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BH IOP, intensive behavioral health (intensive outpatient or partial hospitalization); BH other, only nonintensive behavioral health (outpatient counseling); IDU, injection drug use; MOUD, medication for opioid use disorder; PTSD, posttraumatic stress disorder.

<sup>a</sup> Data are presented as number (percentage) of patients unless otherwise indicated.

behavioral health services (AHR, 0.81; 95% CI, 0.50-1.32) were not significantly associated with overdose.

MOUD treatment with buprenorphine or methadone was also protective against serious opioid-related acute care use during the 3-month follow-up period (AHR, 0.68; 95% CI, 0.47-0.99) (Table 2 and Figure 1B). Inpatient detoxification or residential services treatment, naltrexone, and intensive behavioral health services were not significantly associated with serious opioid-related acute care use during 3 months (inpatient detoxification or residential services: AHR, 1.05; 95% CI, 0.76-1.45; naltrexone: AHR, 1.15; 95% CI, 0.69-1.92; intensive behavioral health: AHR, 0.84; 95% CI, 0.54-1.30).

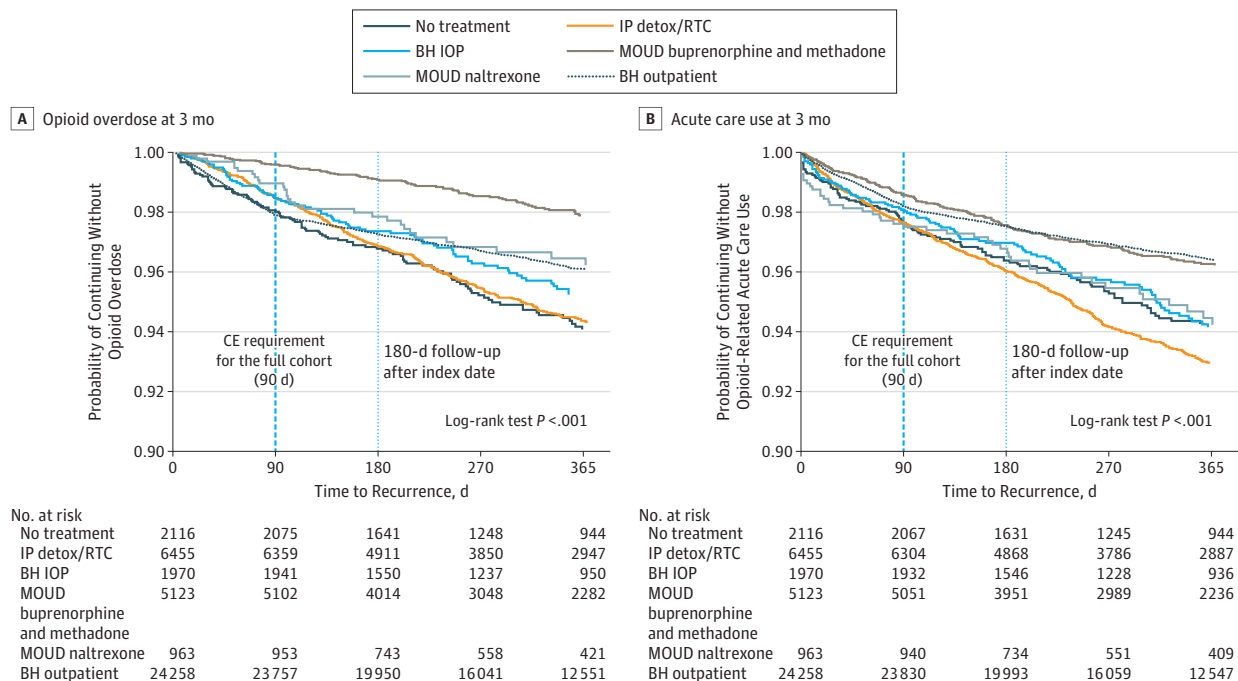
**Table 2. Adjusted Hazard Ratios for Overdose and Serious Opioid-Related Acute Care Use by Initial Treatment Group Compared With No Treatment<sup>a</sup>**

Variable	Adjusted Hazard Ratio (95% CI)	
	3 Months	12 Months
<b>Overdose</b>		
No treatment	1 [Reference]	1 [Reference]
Inpatient detoxification or residential services	0.82 (0.57-1.19)	1 (0.79-1.25)
BH IOP	0.81 (0.50-1.32)	0.75 (0.56-1.02)
MOUD treatment with buprenorphine or methadone	0.24 (0.14-0.41)	0.41 (0.31-0.55)
MOUD treatment with naltrexone	0.59 (0.29-1.20)	0.73 (0.48-1.11)
BH other	0.92 (0.67-1.27)	0.69 (0.56-0.85)
<b>ED or inpatient stay</b>		
No treatment	1 [Reference]	1 [Reference]
Inpatient detoxification or residential services	1.05 (0.76-1.45)	1.20 (0.96-1.50)
BH IOP	0.84 (0.54-1.30)	0.90 (0.67-1.20)
MOUD treatment with buprenorphine or methadone	0.68 (0.47-0.99)	0.74 (0.58-0.95)
MOUD treatment with naltrexone	1.15 (0.69-1.92)	1.07 (0.75-1.54)
BH other	0.59 (0.44-0.80)	0.60 (0.48-0.74)

Abbreviations: BH IOP, intensive behavioral health (intensive outpatient or partial hospitalization); BH other, only nonintensive behavioral health (outpatient counseling); ED, emergency department; MOUD, medication for opioid use disorder.

<sup>a</sup> The hazard ratios were adjusted for age, sex, race/ethnicity, insurance type, baseline medical (modified Elixhauser index score) and mental health comorbidities (depression, anxiety, posttraumatic stress disorder, and attention-deficit/hyperactivity disorder), evidence of overdose or infections related to intravenous drug use, and cost rank.

**Figure 1. Probability of Opioid Overdose and Acute Care Use During the 3-Month Follow-up Period**



BH indicates behavioral health; CE, continuing education; BH IOP, intensive behavioral health (intensive outpatient or partial hospitalization); IP detox/RTC, inpatient detoxification or residential services; and MOUD, medication for opioid use disorder.

Nonintensive behavioral health services were associated with a reduction in serious opioid-related acute care use (AHR, 0.59; 95% CI, 0.44-0.80). Receiving MOUD treatment with buprenorphine or methadone continued to be protective against overdose (AHR, 0.41; 95% CI, 0.31-0.55) and serious opioid-related acute care use (AHR, 0.74; 95% CI, 0.58-0.95) at 12 months.

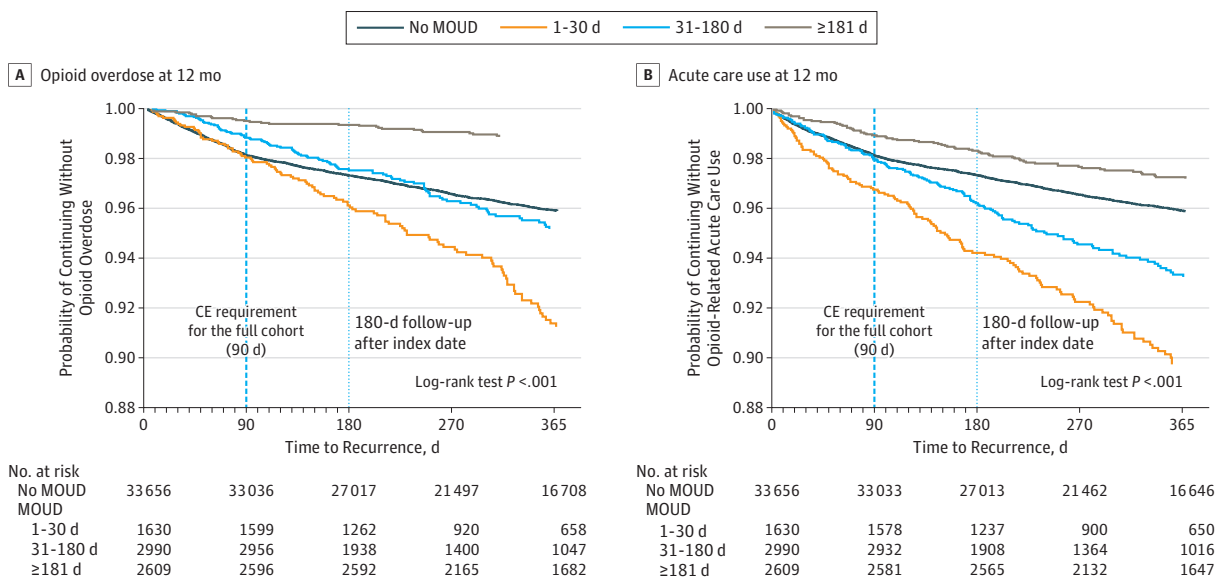
Compared with MOUD treatment with buprenorphine or methadone, all treatment groups were more likely to have a posttreatment admission to inpatient detoxification. Patients who initiated treatment with inpatient detoxification or residential services were most likely to return within 3 months (AHR, 3.76; 95% CI, 2.98-4.74) and 12 months (AHR, 3.48; 95% CI, 3.02-4.01). However, treatment with naltrexone or intensive behavioral health services was also associated with a higher risk of subsequent detoxification admission during the 3-month (naltrexone: AHR, 2.64; 95% CI, 1.84-3.78; intensive behavioral health: AHR, 2.19; 95% CI, 1.63-2.96) and 12-month (naltrexone: AHR, 1.98; 95% CI, 1.55-2.52; intensive behavioral health: AHR, 2.08; 95% CI, 1.73-2.50) follow-up periods.

### MOUD Treatment Duration

Treatment duration for MOUD was relatively short. During 12 months, the mean (SD) treatment duration for naltrexone was 74.41 (70.15) days and 149.65 (119.37) days for buprenorphine or methadone. Individuals who received longer-duration MOUD treatment with buprenorphine or methadone had lower rates of overdose (Figure 2A) or serious opioid-related acute care use (Figure 2B).

At the end of 12 months, 1198 (3.6%) of those who received no MOUD had an overdose, and 1204 (3.6%) had serious opioid-related acute care use; 105 (6.4%) of those who received MOUD treatment with buprenorphine or methadone for 1 to 30 days had an overdose, and 133 (8.2%) had serious opioid-related acute care use; 101 (3.4%) of those who received MOUD treatment with buprenorphine or methadone for 31 to 180 days had an overdose, and 148 (5.0%) had serious opioid-related acute care use; and 28 (1.1%) of those who received MOUD treatment with buprenorphine or methadone for more than 180 days had an overdose, and 69 (2.6%) had serious opioid-related acute care use.

Figure 2. Probability of Opioid Overdose and Acute Care Use During the 12-Month Follow-up Period



CE indicates continuing education; MOUD, medication for opioid use disorder.

## Discussion

In a national cohort of 40 885 insured individuals between 2015 and 2017, MOUD treatment with buprenorphine or methadone was associated with a 76% reduction in overdose at 3 months and a 59% reduction in overdose at 12 months. To our knowledge, this was the largest cohort of commercially insured or MA individuals with OUD studied in a real-world environment with complete medical, pharmacy, and behavioral health administrative claims.

Treatment with buprenorphine or methadone was associated with a 32% relative rate of reduction in serious opioid-related acute care use at 3 months and a 26% relative rate of reduction at 12 months compared with no treatment. In contrast, detoxification, intensive behavioral health, and naltrexone treatment were not associated with reduced overdose or serious opioid-related acute care use at 3 or 12 months.

Despite the known benefit of MOUD treatment with buprenorphine or methadone, only 12.5% initiated these evidence-based treatments. Most individuals in this cohort initiated treatment with psychosocial services alone or inpatient detoxification, both of which are less effective than MOUD. It is possible that individuals accessed public sector treatments that were not captured in our data, particularly for methadone, which was not covered by Medicare and may not have been covered without co-payment for all commercial plans during this time. Low rates of MOUD use among an insured population highlight the need for strategies to improve access to and coverage for MOUD treatment.

Our results demonstrate the importance of treatment retention with MOUD. Individuals who received methadone or buprenorphine for longer than 6 months experienced fewer overdose events and serious opioid-related acute care use compared with those who received shorter durations of treatment or no treatment. These findings are consistent with prior research<sup>11,15,27-29</sup> demonstrating high rates of recurrent opioid use if MOUD treatment is discontinued prematurely. Despite the benefit of MOUD in our study, treatment duration was relatively short. Given the chronic nature of OUD and the evidence that longer treatment duration may be associated with improved outcomes, patient-centered MOUD treatment models explicitly focused on engagement and retention are needed. Low-threshold treatment, which aims to reduce barriers to entry and is tailored to the needs of high-risk populations,<sup>30</sup> may be a strategy to improve retention; however, to our knowledge, no rigorous studies have evaluated these models to date.<sup>31,32</sup> In addition, patient-centered MOUD care, which allows participants to determine the services they need rather than requirements, such as mandatory counseling, are noninferior to traditional treatment.<sup>32</sup>

Numerous barriers limit sustained engagement in MOUD, including a lack of access to waived practitioners, high co-payments, prior authorization requirements, and other restrictions on use. Previous studies<sup>33,34</sup> have demonstrated that restrictions on use for MOUD are associated with limited access and harm. Addiction treatment programs in states that require Medicaid prior authorizations for buprenorphine are less likely to offer buprenorphine, and the more restrictions on use in state Medicaid programs, the fewer treatment programs that offer buprenorphine.<sup>33</sup> Requiring prior authorization for higher doses of buprenorphine may also result in increased recurrence rates among patients.<sup>34</sup> Our finding that MOUD treatment with buprenorphine or methadone was associated with lower overdose and serious opioid-related acute care use supports expanded coverage of these medications without restrictions on use.

Our findings are also consistent with analyses showing that MOUD treatment with buprenorphine or methadone is significantly associated with reduced overdose and recurrence of opioid use compared with no treatment or non-MOUD treatment. A previous cohort study<sup>15</sup> of individuals in Massachusetts demonstrated a reduction in overdose-related mortality associated with treatment with buprenorphine (AHR, 0.62; 95% CI, 0.41-0.92) or methadone (AHR, 0.41; 95% CI, 0.24-0.70), results that are similar to our finding of an AHR of 0.41 (95% CI, 0.31-0.55) for overdose at 12 months for methadone or buprenorphine. A large meta-analysis<sup>11</sup> examining mortality when individuals were in or out of treatment with buprenorphine or methadone similarly showed



decreased overdose mortality during treatment. A study<sup>12</sup> examining proxies for recurrent OUD among Massachusetts Medicaid enrollees found that treatment with buprenorphine or methadone was associated with lower recurrence rates and costs. No studies, to our knowledge, have examined the effect of different OUD treatment pathways on overdose and serious opioid-related acute care use among a national sample of commercially insured and MA enrollees.

Our finding that MOUD treatment with naltrexone was not protective against overdose or serious opioid-related acute care use is consistent with other studies<sup>15,35</sup> that found naltrexone to be less effective than MOUD treatment with buprenorphine. The mean (SD) treatment duration for naltrexone in this cohort was longer than prior observational studies at 74.41 (70.15) days.

The findings that nonintensive behavioral health treatment was associated with a reduced risk of overdose at 12 months but not 3 months and a reduced risk of opioid-related acute care use was surprising. Although we attempted to control for differences among various treatment groups, individuals referred to nonintensive behavioral health may represent a less complex patient population than those who receive MOUD treatment or are referred to intensive behavioral health or inpatient treatment.

### Strengths and Limitations

Specifically, we identified a research question a priori that was meaningful, had clinical and policy implications, and was concise and unambiguous. Our study design's strengths are the large, nationally representative sample and complete claims data, which allowed us to adequately identify appropriate patients and interventions. In addition, we used a conservative definition of OUD and of proxies for OUD recurrence to limit inclusion of individuals who did not have OUD or of outcomes that did not represent clinically significant recurrence.

This study has limitations. The limitations of our study design include the lack of clinical information in claims data or outcomes that occurred outside a health care encounter (eg, fatal overdoses or active use without medical complication). As with any observational study, there is the possibility that unmeasured patient characteristics were associated with treatment assignment and outcomes, possibly biasing estimates of outcomes associated with MOUD treatment groups. It is also possible that individuals selected for different treatments differed by characteristics that were also associated with the outcomes. We were able to control for many patient characteristics, such as race/ethnicity, sex, insurance type, and comorbidities, but selection bias is possible. Another limitation is the degree of sample attrition during the 12-month follow-up period. However, we attempted to assess potential bias from informative censoring in 2 ways.<sup>36</sup> First, we compared the baseline characteristics of censored and uncensored cases. These distributions were similar, suggesting that, at least on the basis of observable characteristics, censored cases were not statistically different from uncensored cases. Second, we examined the proportionality of HRs. Visual inspection of the HRs indicated that they were proportional for the 3-month period but could not be assumed to be proportional for the 12-month period. Another limitation is the risk of immortal time bias by requiring 3-month enrollment for inclusion; however, we believed it was important to require 3 months of follow-up to adequately measure outcomes. In addition, assessment of community mortality with claims data is characterized by high degrees of measurement error. Traditional instrumental variable methods for addressing immortal time bias cannot be applied to survival models because of their nonlinear functional form.

### Conclusions

In a national sample of commercial insurance and MA enrollees with OUD, treatment with buprenorphine or methadone was associated with reductions in overdose and serious opioid-related acute care use, but only a few individuals were treated with these medications. These findings suggest that opportunities exist for health plans to reduce restrictions on use for MOUD and the need for treatment models that prioritize access to and retention of MOUD treatment.

## ARTICLE INFORMATION

**Accepted for Publication:** December 12, 2019.

**Published:** February 5, 2020. doi:10.1001/jamanetworkopen.2019.20622

**Open Access:** This is an open access article distributed under the terms of the [CC-BY-NC-ND License](#). © 2020 Wakeman SE et al. *JAMA Network Open*.

**Corresponding Author:** Sarah E. Wakeman, MD, Division of General Internal Medicine, Department of Medicine, Massachusetts General Hospital, 55 Fruit St, Founders 880, Boston, MA 02114 ([swakeman@partners.org](mailto:swakeman@partners.org)).

**Author Affiliations:** Division of General Internal Medicine, Department of Medicine, Massachusetts General Hospital, Boston (Wakeman); Department of Medicine, Harvard Medical School, Boston, Massachusetts (Wakeman); Clinical Addiction Research and Education Unit, Boston Medical Center, Boston, Massachusetts (Larochelle); Department of Medicine, Boston University School of Medicine, Boston, Massachusetts (Larochelle); Integrated Programs, OptumLabs Inc, Cambridge, Massachusetts (Ameli, Chaisson); Department of Research, OptumLabs, Minnetonka, Minnesota (McPheeters); Department of Research, OptumLabs, Cambridge, Massachusetts (Crown); Department of Research, Optum Behavioral Health, Cambridge, Massachusetts (Azocar); Department of Medicare and Retirement, United Healthcare, Minnetonka, Minnesota (Sanghavi).

**Author Contributions:** Drs Wakeman and Sanghavi had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Concept and design:** Wakeman, Larochelle, Ameli, Chaisson, Crown, Azocar, Sanghavi.

**Acquisition, analysis, or interpretation of data:** Wakeman, Larochelle, Ameli, Chaisson, MCPheeters, Crown, Azocar.

**Drafting of the manuscript:** Wakeman, Ameli, Crown, Azocar.

**Critical revision of the manuscript for important intellectual content:** Wakeman, Larochelle, Ameli, Chaisson, MCPheeters, Crown, Sanghavi.

**Statistical analysis:** Ameli, MCPheeters, Crown.

**Administrative, technical, or material support:** Chaisson, MCPheeters, Azocar.

**Supervision:** Chaisson, Sanghavi.

**Conflict of Interest Disclosures:** Dr Wakeman reported receiving personal fees from OptumLabs during the conduct of the study. Dr Ameli reported receiving grants from OptumLabs during the conduct of the study. Ms Chaisson, Mr MCPheeters, and Dr Azocar reported receiving salary support from OptumLabs during the conduct of the study. Dr Azocar also reported receiving salary support from United Health Group outside the submitted work. Dr Sanghavi reported being an employee of United Health Group. No other disclosures were reported.

**Funding/Support:** This study was supported by grant K23DA042168 from Boston Medical Center, grant 1UL1TR001430 from the National Institute on Drug Abuse and the National Center for Advancing Translational Sciences, National Institutes of Health, grant U01CE002780 from the Centers for Disease Control and Prevention, grant HHSF22320091000061 from the US Food and Drug Administration, grant G1799ONDCP06B from the Office of National Drug Control Policy/University of Baltimore, a Boston University School of Medicine Department of Medicine Career Investment Award (Dr Larochelle) and by Massachusetts General Hospital, grant 1R01DA044526-01A1 from the National Institutes of Health, grant 3UG1DA015831-17S2 from the National Institute on Drug Abuse, grant 1H79TI081442-01 from the Substance Abuse and Mental Health Services Administration, and the Laura and John Arnold Foundation (Dr Wakeman).

**Role of the Funder/Sponsor:** The funding sources reviewed the manuscript but had no role in the design and conduct of the study; interpretation of the data; preparation, or approval of the manuscript; and decision to submit the manuscript for publication.

## REFERENCES

1. Scholl L, Seth P, Kariisa M, Wilson N, Baldwin G. Drug and opioid-involved overdose deaths—United States, 2013–2017. *MMWR Morb Mortal Wkly Rep*. 2018;67(5152):1419–1427. doi:10.15585/mmwr.mm675152e1
2. Robinson WT, Kazbour C, Nassau T, et al. Brief report: nonfatal overdose events among persons who inject drugs: findings from seven national HIV behavioral surveillance cities 2009 & 2012. *J Acquir Immune Defic Syndr*. 2017;75(suppl 3):S341–S345. doi:10.1097/QAI.0000000000001426
3. Burnett JC, Broz D, Spiller MW, Wejnert C, Paz-Bailey G. HIV infection and HIV-associated behaviors among persons who inject drugs—20 cities, United States, 2015. *MMWR Morb Mortal Wkly Rep*. 2018;67(1):23–28. doi:10.15585/mmwr.mm6701a5
4. Hsu DJ, McCarthy EP, Stevens JP, Mukamal KJ. Hospitalizations, costs and outcomes associated with heroin and prescription opioid overdoses in the United States 2001–12. *Addiction*. 2017;112(9):1558–1564. doi:10.1111/add.13795

5. Zibbell JE, Asher AK, Patel RC, et al. Increases in acute hepatitis C virus infection related to a growing opioid epidemic and associated injection drug use, United States, 2004 to 2014. *Am J Public Health*. 2018;108(2):175-181. doi:10.2105/AJPH.2017.304132
6. Cranston K, Alpren C, John B, et al; Amy Board. Notes from the field: HIV diagnoses among persons who inject drugs—Northeastern Massachusetts, 2015–2018. *MMWR Morb Mortal Wkly Rep*. 2019;68(10):253-254. doi:10.15585/mmwr.mm6810a6
7. Weir MA, Slater J, Jandoc R, Koivu S, Garg AX, Silverman M. The risk of infective endocarditis among people who inject drugs: a retrospective, population-based time series analysis. *CMAJ*. 2019;191(4):E93-E99. doi:10.1503/cmaj.180694
8. Chen Q, Laroche MR, Weaver DT, et al. Prevention of prescription opioid misuse and projected overdose deaths in the United States. *JAMA Netw Open*. 2019;2(2):e187621. doi:10.1001/jamanetworkopen.2018.7621
9. Ciccarone D. The triple wave epidemic: supply and demand drivers of the US opioid overdose crisis. *Int J Drug Policy*. 2019;71:183-188. doi:10.1016/j.drugpo.2019.01.010
10. The National Academies of Science, Engineering, and Medicine. Medications for opioid use disorder save lives. March 20, 2019. <http://www.nationalacademies.org/hmd/Reports/2019/medications-for-opioid-use-disorder-save-lives.aspx>. Accessed March 26, 2019.
11. Sordo L, Barrio G, Bravo MJ, et al. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. *BMJ*. 2017;357:j1550. doi:10.1136/bmj.j1550
12. Clark RE, Baxter JD, Aweh G, O'Connell E, Fisher WH, Barton BA. Risk factors for relapse and higher costs among Medicaid members with opioid dependence or abuse: opioid agonists, comorbidities, and treatment history. *J Subst Abuse Treat*. 2015;57:75-80. doi:10.1016/j.jsat.2015.05.001
13. Hser YI, Evans E, Huang D, et al. Long-term outcomes after randomization to buprenorphine/naloxone versus methadone in a multi-site trial. *Addiction*. 2016;111(4):695-705. doi:10.1111/add.13238
14. Weiss RD, Potter JS, Griffin ML, et al. Long-term outcomes from the National Drug Abuse Treatment Clinical Trials Network Prescription Opioid Addiction Treatment Study. *Drug Alcohol Depend*. 2015;150:112-119. doi:10.1016/j.drugalcdep.2015.02.030
15. Laroche MR, Bernson D, Land T, et al. Medication for opioid use disorder after nonfatal opioid overdose and association with mortality: a cohort study. *Ann Intern Med*. 2018;169(3):137-145. doi:10.7326/M17-3107
16. Abraham AJ, Adams GB, Bradford AC, Bradford WD. County-level access to opioid use disorder medications in Medicare Part D (2010-2015). *Health Serv Res*. 2019;54(2):390-398. doi:10.1111/1475-6773.13113
17. Andrilla CHA, Moore TE, Patterson DG, Larson EH. Geographic distribution of providers with a DEA waiver to prescribe buprenorphine for the treatment of opioid use disorder: a 5-year update. *J Rural Health*. 2019;35(1):108-112. doi:10.1111/jrh.12307
18. Mojtabai R, Mauro C, Wall MM, Barry CL, Olfson M. Medication treatment for opioid use disorders in substance use treatment facilities. *Health Aff (Millwood)*. 2019;38(1):14-23. doi:10.1377/hlthaff.2018.05162
19. Jones CM, Campopiano M, Baldwin G, McCance-Katz E. National and state treatment need and capacity for opioid agonist medication-assisted treatment. *Am J Public Health*. 2015;105(8):e55-e63. doi:10.2105/AJPH.2015.302664
20. Hadland SE, Wharam JF, Schuster MA, Zhang F, Samet JH, Laroche MR. Trends in receipt of buprenorphine and naltrexone for opioid use disorder among adolescents and young adults, 2001-2014. *JAMA Pediatr*. 2017;171(8):747-755. doi:10.1001/jamapediatrics.2017.0745
21. Morgan JR, Schackman BR, Leff JA, Linas BP, Walley AY. Injectable naltrexone, oral naltrexone, and buprenorphine utilization and discontinuation among individuals treated for opioid use disorder in a United States commercially insured population. *J Subst Abuse Treat*. 2018;85:90-96. doi:10.1016/j.jsat.2017.07.001
22. Wollschlaeger BA, Willson TM, Montejano LB, Ronquest NA, Nadipelli VR. Characteristics and treatment patterns of US commercially insured and Medicaid patients with opioid dependence or abuse. *J Opioid Manag*. 2017;13(4):207-220. doi:10.5055/jom.2017.0389
23. Morgan JR, Schackman BR, Weinstein ZM, Walley AY, Linas BP. Overdose following initiation of naltrexone and buprenorphine medication treatment for opioid use disorder in a United States commercially insured cohort. *Drug Alcohol Depend*. 2019;200:34-39. doi:10.1016/j.drugalcdep.2019.02.031
24. OptumLabs. *OptumLabs and OptumLabs Data Warehouse (OLDW) Descriptions and Citation*. Cambridge, MA: OptumLabs; May 2019.

25. Berger ML, Mamdani M, Atkins D, Johnson ML. Good research practices for comparative effectiveness research: defining, reporting and interpreting nonrandomized studies of treatment effects using secondary data sources: the ISPOR Good Research Practices for Retrospective Database Analysis Task Force Report, part I. *Value Health*. 2009;12(8):1044-1052. doi:10.1111/j.1524-4733.2009.00600.x
26. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43(11):1130-1139. doi:10.1097/01.mlr.0000182534.19832.83
27. Sees KL, Delucchi KL, Masson C, et al. Methadone maintenance vs 180-day psychosocially enriched detoxification for treatment of opioid dependence: a randomized controlled trial. *JAMA*. 2000;283(10):1303-1310. doi:10.1001/jama.283.10.1303
28. Weiss RD, Potter JS, Fiellin DA, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial. *Arch Gen Psychiatry*. 2011;68(12):1238-1246. doi:10.1001/archgenpsychiatry.2011.121
29. Fiellin DA, Schottenfeld RS, Cutter CJ, Moore BA, Barry DT, O'Connor PG. Primary care-based buprenorphine taper vs maintenance therapy for prescription opioid dependence: a randomized clinical trial. *JAMA Intern Med*. 2014;174(12):1947-1954. doi:10.1001/jamainternmed.2014.5302
30. Mofizul Islam M, Topp L, Conigrave KM, Day CA. Defining a service for people who use drugs as 'low-threshold': what should be the criteria? *Int J Drug Policy*. 2013;24(3):220-222. doi:10.1016/j.drugpo.2013.03.005
31. Edland-Gryt M, Skatvedt AH. Thresholds in a low-threshold setting: an empirical study of barriers in a centre for people with drug problems and mental health disorders. *Int J Drug Policy*. 2013;24(3):257-264. doi:10.1016/j.drugpo.2012.08.002
32. Schwartz RP, Kelly SM, Mitchell SG, et al. Patient-centered methadone treatment: a randomized clinical trial. *Addiction*. 2017;112(3):454-464. doi:10.1111/add.13622
33. Andrews CM, Abraham AJ, Grogan CM, Westlake MA, Pollack HA, Friedmann PD. Impact of Medicaid restrictions on availability of buprenorphine in addiction treatment programs. *Am J Public Health*. 2019;109(3):434-436. doi:10.2105/AJPH.2018.304856
34. Clark RE, Baxter JD, Barton BA, Aweh G, O'Connell E, Fisher WH. The impact of prior authorization on buprenorphine dose, relapse rates, and cost for Massachusetts Medicaid beneficiaries with opioid dependence. *Health Serv Res*. 2014;49(6):1964-1979. doi:10.1111/1475-6773.12201
35. Lee JD, Nunes EV Jr, Novo P, et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. *Lancet*. 2018;391(10118):309-318. doi:10.1016/S0140-6736(17)32812-X
36. Siannis F, Copas J, Lu G. Sensitivity analysis for informative censoring in parametric survival models. *Biostatistics*. 2005;6(1):77-91. doi:10.1093/biostatistics/kxh019

#### SUPPLEMENT.

**eAppendix 1.** Cohort Selection

**eAppendix 2.** Supplementary Methods

**eFigure 1.** Definition of OUD

**eFigure 2.** Cohort Inclusion and Timeline

**eFigure 3.** Alluvial Flow of OUD Treatment Pathways in the Initial Cohort

**eTable.** Censoring by Baseline Characteristics