Drug and Alcohol Dependence 273 (2025) 112679

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Receipt of addiction treatment after nonfatal opioid overdose and risk of subsequent overdose: A retrospective cohort study

Benjamin A. Howell [a,b,*], Anne Black [a], Hsiu-Ju Lin [c,d], Mark A. Liberatore [e], Christina R. Greene [f], Gail D'Onofrio [g], Robert Heimer [h], Lauretta E. Grau [h], Kathryn Hawk [b,g], David A. Fiellin [a,b,h], William C. Becker [a,b]

[a] Section of General Medicine, Yale School of Medicine, New Haven, CT, United States
[b] Program in Addiction Medicine, Yale School of Medicine, New Haven, CT, United States
[c] Connecticut Department of Mental Health and Addiction Services, Hartford, CT, United States
[d] School of Social Work, University of Connecticut, Hartford, CT, United States
[e] Office of New Drugs, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, United States
[f] Division of Epidemiology (DEPI-II), Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, United States
[g] Department of Emergency Medicine, Yale School of Medicine, New Haven, CT, United States
[h] Yale School of Public Health, New Haven, CT, United States

ARTICLE INFO

Keywords:
Opioid overdose, opioid agonist treatment
Medications for opioid use disorder
Medically supervised withdrawal
Inpatient addiction treatment
Addiction health services research

ABSTRACT

Background: Opioid overdose survivors are at high risk for subsequent overdose. There are few evaluations using real-world data to compare overdose risk after receipt of different addiction treatment modalities.
Objective: To assess the association between receipt of different addiction treatment modalities and risk of subsequent opioid overdose among opioid overdose survivors.
Design: Survival analysis comparing time-to-subsequent overdose within a cohort of opioid overdose survivors using a linked state-wide individual level data of different addiction treatment modalities: opioid agonists treatments (OAT, i.e., methadone or buprenorphine) and non-medication based inpatient addiction treatments (medically supervised opioid withdrawal and extended inpatient treatment).
Subjects: Opioid-involved overdose survivors (N = 4089) admitted to a hospital or emergency department in Connecticut between May 2016 and December 2017
Main measures: Time-to-subsequent overdose (fatal or non-fatal) and time-to-subsequent fatal overdose
Key results: Following the index overdose, 467 (11.4 %) experienced another overdose event within 12 months (87 fatal and 380 non-fatal), 35 % received OAT (25 % buprenorphine and 13 % methadone), and 21 % received inpatient addiction treatment (19 % medically supervised opioid withdrawal and 8 % extended inpatient treatment). In survival analyses adjusted for demographics, incarceration, and receipt of non-OAT opioids or benzodiazepines, receipt of methadone (aHR 0.41, 95 % CI: 0.26–0.66) or buprenorphine (aHR 0.72, 95 % CI: 0.53–0.98) was associated with a decreased risk of subsequent overdose compared to no receipt of methadone or buprenorphine, respectively. Neither medically supervised opioid withdrawal (aHR 1.08, 95 % CI: 0.77–1.50) nor extended inpatient treatment (aHR 0.90, 95 % CI: 0.53–1.54) was associated with reduced risk of subsequent overdose. Neither OAT nor non-medication based inpatient treatment modalities were associated with a change in risk of subsequent fatal overdose; benzodiazepine exposure was associated with increased risk (aHR 2.65, 95 % CI: 1.66–4.23).
Conclusion: Using statewide data, our findings underscore the importance of OAT to reduce risk of subsequent overdose following a non-fatal opioid overdose.

* Correspondence to: SEICHE Center for Health and Justice, Yale School of Medicine, 60 Temple St, Suite 5C, New Haven, CT 06510, United States.
E-mail address: benjamin.howell@yale.edu (B.A. Howell).

https://doi.org/10.1016/j.drugalcdep.2025.112679
Received 3 October 2024; Received in revised form 13 March 2025; Accepted 15 April 2025
Available online 13 May 2025

1. Background

In the United States, fatal opioid overdoses have increased 200 % since 2010 and are now a leading cause of preventable death (Rudd et al., 2016). Over 100,000 people died due to drug overdose in 2022, driven mostly by rising opioid overdoses (Provisional Data Shows U.S.S.S, 2023). Connecticut's experience has been similar, with over 1400 people dying due to drug overdoses in 2022, making it the state's leading cause of accidental death (Drug Overdose Monthly Report, 2023).

Non-fatal opioid overdose is a predictor of fatal opioid overdose and is associated with 5 % mortality at one year (Caudarella et al., 2016; Larochelle et al., 2019, 2016; Chen et al., 2019; Saloner et al., 2020). Exposure to addiction treatment following a non-fatal opioid overdose can impact the risk of a subsequent opioid overdose. Addiction treatment modalities available for opioid use disorder (OUD) include opioid agonist treatments (OAT), including methadone and buprenorphine, opioid antagonists, namely naltrexone, and non-medication based inpatient addiction treatments, such as medically supervised opioid withdrawal and extended inpatient treatment. There is likely heterogeneity in the impact of different treatment modalities on the risk of a subsequent opioid overdose. As policy makers and public health professionals make decisions with limited funding about which treatment modalities to emphasize it is important to understand different modalities are associated with risk of subsequent overdose.

Methadone, a full mu-opioid receptor agonist, and buprenorphine, a partial mu-opioid receptor agonist, are OAT approved by the U.S. Food and Drug Administration (FDA) for the treatment of OUD. Clinical trial data demonstrate that use of these medications can improve OUD treatment outcomes: increased treatment retention, decreased risk of relapse, and decreased risk of overdose (Mattick et al., 2009, 2014). Observational data also show that use of OAT is associated with reduced all-cause and overdose mortality (Larochelle et al., 2018). Naltrexone, an opioid antagonist, is also approved by the FDA for the long-term treatment of OUD (Tetrault and Fiellin, 2012).

Other modalities of addiction treatment include medically supervised opioid withdrawal (detoxification or "detox") and extended inpatient treatment (rehabilitation or "rehab"). The data on the effectiveness of these modalities in preventing relapse and subsequent opioid overdose is limited compared to OAT, yet 30 % of individuals with OUD access them, alone or in combination with medication-based OUD treatment (Saloner et al., 2022; de Andrade et al., 2019). Increasing access to medically supervised opioid withdrawal and extended inpatient treatment is often emphasized by the lay public and policymakers as a response to reduce morbidity and mortality related to opioid addiction (Tetrault and Fiellin, 2018; Strach et al., 2020; Stein et al., 2015; Nayak et al., 2021; Beetham et al., 2021).

A study in Massachusetts from 2012 to 2014 showed that only 30 % of people used medications for opioid use disorder (including methadone, buprenorphine, or naltrexone) in the year following an opioid overdose, and use of these medications, especially methadone or buprenorphine, was associated with lower risk of all-cause and opioid-related mortality (Larochelle et al., 2018). This study found that 22 % of people in the cohort accessed medically supervised opioid withdrawal and 16 % accessed extended inpatient treatment, though it did not assess risk of subsequent mortality following these exposures (Larochelle et al., 2018). Another study, using the same data source in Massachusetts but not focused on opioid overdose survivors, showed that individuals exposed to medically supervised opioid withdrawal for OUD had a higher risk of opioid-involved overdose compared to those released from extended inpatient treatment (Morgan et al., 2020). For this study, we aimed to replicate and supplement these prior studies using data from Connecticut using linked data from hospital and emergency department claims, addiction treatment, prescription drug monitoring program, and overdose deaths (Howell et al., 2023; Becker et al., 2021).

2. Methods

2.1. Study design

We conducted a retrospective cohort study of individuals who survived an opioid overdose in Connecticut using a novel multi-source, linked administrative data set. We used data from the Connecticut Hospital Association (CHA), Connecticut Department of Mental Health and Addiction Services (DMHAS), Connecticut Department of Consumer Protection (DCP), the Office of the Chief Medical Examiner (OCME), and the Connecticut Department of Correction (DOC). Our process of obtaining and linking these data sets has been described in detail elsewhere (Becker et al., 2021). We included data between May 1, 2016, and December 31, 2017; the time period for which there was complete coverage from all five data sources.

We used ChimeData, a dataset maintained by CHA that includes dates of admission/discharge and discharge diagnoses of inpatient admissions, hospital-based outpatient surgeries, and emergency department (ED) visits in Connecticut. Data on the use of addiction treatment services (excluding services, such as buprenorphine for the treatment of OUD, provided through office-based practices) from all entities that received state funds or federal block grants, as required by law, (Treatment Episode Data Set, 2021) were provided by DMHAS. The DCP provided data on prescriptions filled for controlled substances—including buprenorphine— in outpatient pharmacies collected via the Connecticut Prescription Monitoring and Reporting System (CPMRS), the state's prescription drug monitoring program (Drug Laws and Regulations, 2021). Finally, OCME provided data regarding opioid-involved overdose deaths, including cause of death for cases involving suspected unnatural causes, except suspected homicides, suicides, and deaths associated with a therapeutic procedure (Examiner OoCM,.).

2.2. Cohort selection

We included all individuals, age $\geq$ 18 years old, who experienced a nonfatal opioid-involved overdose in the state between May 1, 2016, and December 31, 2017 using ChimeData. Opioid overdoses were determined by ICD-9/ICD-10-coded discharge diagnoses for any inpatient admissions or emergency department visits (ICD-9/ICD-10 codes included in Supplementary Table 1) (Larochelle et al., 2016; Green et al., 2017; Dunn et al., 2010). The first nonfatal overdose event occurring during the target period was defined as the "index event" and the date of discharge was used as the "time zero" for our analyses.

2.3. Exposures

Our primary exposure of interest was receipt of addiction treatment within the 12 months following hospital or emergency department discharge after experiencing a non-fatal opioid overdose. We categorized treatment exposures as non-exclusive, time-updated receipt of methadone, buprenorphine, medically supervised opioid withdrawal, or extended inpatient addiction treatment. In descriptive tables and a secondary analysis, we combined receipt of either methadone or buprenorphine as OAT receipt, and combined receipt of either medically supervised opioid withdrawal or extended inpatient treatment as inpatient addiction therapy. Naltrexone is not captured in the datasets included in this study, precluding inclusion in our analyses (Morgan et al., 2018).

We coded exposure variables as dichotomous time-updated indicators of receipt of treatment modality in each of the 12 months following discharge after the index event. To identify receipt of buprenorphine-containing products we used CPMRS data, restricting to receipt of formulations indicated for OUD. We identified methadone receipt via DMHAS treatment episode data. By federal law, methadone for OUD can only be provided via opioid-treatment programs that report

Table 1
Baseline demographics of individuals experiencing a non-fatal overdose in Connecticut, May 2016-December 2017 by treatment received within 12 months of discharge after index event.

Characteristic, N(%)	Full Cohort (N = 4089)	No exposure (N = 2277)	Opioid Agonist Therapy (OAT)			Inpatient addiction treatment			Both OAT and Inpatient[a] (N = 511)
			Methadone[a] (N = 526)	Buprenorphine[a] (N = 1013)	Any OAT[a] (N = 1445)	Medically supervised opioid withdrawal[a] (N = 788)	Extended inpatient treatment[a] (N = 340)	Any inpatient treatment[a] (N = 878)	
Male	2430 (59.4)	1199 (52.7)	322 (61.2)	768 (75.8)	1022 (70.7)	515 (65.4)	226 (66.5)	573 (65.3)	367 (71.8)
Female	1333 (32.6)	843 (37.0)	178 (33.8)	231 (22.8)	385 (26.6)	211 (26.8)	84 (24.7)	234 (26.7)	127 (24.9)
Missing Sex	326 (8.0)	235 (10.3)	26 (4.9)	14 (1.4)	38 (2.6)	62 (7.9)	30 (8.8)	71 (8.1)	17 (3.3)
Age, mean (SD)	40.6 (14.4)	43.5 (15.6)	39.6 (12.2)	36.0(11.4)	37.3 (11.9)	35.0 (10.7)	34.85 (10.1)	35.06 (10.6)	34.67 (10.0)
Race and Ethnicity									
White, non-Hispanic	3046 (74.5)	1674 (73.5)	401 (76.2)	762 (75.2)	1089 (75.4)	610 (77.4)	265 (77.9)	675 (76.9)	392 (76.7)
Black, non-Hispanic	304 (7.4)	194 (8.5)	30 (5.7)	56 (5.5)	83 (5.7)	47 (6.0)	17 (5.0)	52 (5.9)	25 (4.9)
Hispanic	611 (14.9)	336 (14.8)	77 (14.6)	165 (16.3)	228 (15.8)	108 (13.7)	49 (14.4)	124 (14.1)	77 (15.1)
Other/ unknown	128 (3.1)	73 (3.2)	18 (3.4)	30 (3.0)	45 (3.1)	23 (2.9)	9 (2.6)	27 (3.1)	17 (3.3)
Covariate exposures									
Benzodiazepine	1237 (30.2)	746 (32.8)	191 (36.3)	243 (24.0)	405 (28.0)	200 (25.4)	67 (19.7)	218 (24.8)	132 (25.8)
Non-OAT opioid	1681 (41.1)	1094 (48.1)	193 (36.7)	271 (26.8)	447 (30.9)	267 (33.9)	106 (31.2)	290 (33.0)	150 (29.4)
Incarceration	291 (7.1)	148 (6.5)	48 (9.1)	66 (6.5)	107 (7.4)	74 (9.4)	31 (9.1)	81 (9.2)	45 (8.8)

[a] Exposure defined as receipt of that treatment modality in any month in the 12 months following discharge after index overdose event; treatment categories are not exclusive of each other

data to DMHAS, therefore methadone dispensed for pain treatment via pharmacy (as captured in CPMRS data) was not included in our definition. We used DHMAS data to identify receipt of inpatient addiction treatment services, categorized as either medically supervised opioid withdrawal episodes or extended inpatient treatment.

2.4. Outcomes

Our primary outcome was fatal or non-fatal opioid-involved overdose within 12 months following discharge after the index event. We identified opioid-involved overdose deaths using OCME data where opioid exposure was identified as a contributing cause of death. We identified subsequent non-fatal overdoses using ChimeData. For a secondary analysis, we limited the outcome to opioid-involved overdose deaths.

2.5. Covariates

To control for confounders, we included measures of age at time of index event, race and ethnicity, and the following secondary time-updated exposure indicators for each of the 12 months following the index event: receipt of non-OAT opioid analgesics, benzodiazepines, and incarceration. We did not compare groups by sex given a high rate of missing data for that variable.

2.6. Statistical analysis

First, we generated tables describing the distribution of demographic variables and covariates across both the non-exclusive treatment exposure groups and experience of the outcomes of interest. Treatment exposure groups included the following: no addiction treatment; receipt of methadone, buprenorphine, and any OAT; receipt of medically supervised opioid withdrawal, extended inpatient, and any inpatient addiction treatment; and receipt of both OAT and inpatient addiction treatment. In this table, treatment groups were non-exclusive reflecting the potential for individuals to access any combination of treatments following the index overdose event. We compared distribution of demographics and treatment receipt across groups experiencing our outcomes of interest using ANOVA and chi-squared tests.

Second, we conducted survival analyses using unadjusted and adjusted Cox proportional hazards modeling of time to first overdose over the 12 months following discharge after the index event. The risk of experiencing a first post-nonfatal overdose in each month (given no prior post non-fatal overdose) was modeled as a function of post-non-fatal overdose treatment exposure in that month (i.e., monthly exposure indicators of buprenorphine, methadone, medically supervised opioid withdrawal, and extended inpatient treatment). For these models, time-updated treatment receipt was not exclusive, and individuals could have received any combination of treatments, or none, within each month. Although this approach entailed a trade-off versus creating mutually exclusive exposure groups, it reflects the real-world exposures of individuals after overdose and mirrored the approach taken in similar analyses (Larochelle et al., 2018).

We performed several secondary analyses. First, we reran our model with exclusive time-updated monthly treatment indicators: methadone receipt only, buprenorphine receipt only, medically supervised opioid withdrawal only, extended inpatient treatment only, and receipt of any two or more forms of treatment. Second, we reran our model using exclusive time-updated monthly treatment indicators: any OAT (buprenorphine or methadone), any inpatient treatment (medically supervised withdrawal or extended inpatient treatment), and both OAT and inpatient treatment. Third, we performed a secondary analysis in which we limited the outcome to fatal opioid-involved overdoses following the same procedures.

Prior to analyses, we tested the proportionality assumption by visual inspection of plotted cumulative hazard functions, and by Wald test of month by exposure interaction terms. Models adjusted for differences in age at index event, race (white vs. other), and time-updated exposure to benzodiazepines, non-OAT opioids, and incarceration. The use of time-updated exposure indicators minimized the risk of immortal time bias (Shintani et al., n.d.; Yadav and Lewis, 2021).

The Connecticut Department of Mental Health and Addiction

Table 2
Demographic, covariates, and treatment exposure characteristics of individuals by any subsequent overdose and subsequent fatal overdose within 12 months of discharge after index overdose event.

Baseline Characteristic, N (%)	No subsequent overdose (N = 3622)	Any subsequent overdose (N = 467)	Subsequent fatal overdose (N = 87)
Male	2138 (59.0)	289 (61.9)	59 (67.8)
Female	1246 (34.4)	89 (19.1)	28 (32.2)
Missing Sex	238 (6.6)	89 (19.1)	0 (0.0)
Age, mean (SD)	41.1 (14.6)	36.5 (12.4)	41.7 (13.0)
Race and Ethnicity			
White, non-Hispanic	2687 (74.2)	359 (76.9)	76 (87.4)
Black, non-Hispanic	284 (7.8)	20 (4.3)	5 (5.8)
Hispanic	543 (15.0)	68 (14.6)	3 (3.5)
Other/unknown	108 (3.0)	20 (4.3)	3 (3.5)
Treatment Exposure			
No treatment	2002 (55.3)	275 (58.9)	58 (66.7)
Opioid Agonist Therapy (OAT)			
Buprenorphine[a]	893 (24.7)	120 (25.7)	15 (17.2)
Methadone[a]	493 (13.6)	33 (7.1)	7 (8.1)
Any OAT[a]	1297 (35.81)	148 (31.69)	22 (25.29)
Inpatient addiction treatment			
Medically supervised opioid withdrawal[a]	704 (19.4)	84 (18.0)	15 (17.2)
Extended Inpatient Treatment[a]	302 (8.3)	38 (8.1)	9 (10.3)
Any inpatient treatment[a]	786 (21.7)	92 (19.70)	17 (19.54)
Both OAT and inpatient[a]	463 (12.78)	48 (10.28)	10 (11.49)

[a] Exposure defined as receipt of listed treatment modality in any month in the 12 months following discharge after index overdose event; treatment categories are not exclusive of each other

Services (DMHAS) and Yale University IRBs approved this project. We maintained Memoranda of Understanding and Data Use Agreements with all participating state agencies. This research was supported by a grant (1U01FD005938) from the FDA Office of Regulatory Science and Innovation via the Yale-Mayo Clinic Centers of Excellence in Regulatory Science and Innovation. Subject matter experts from the FDA participated in design of the study, provided input on interpretation of study findings, and feedback on manuscript drafting. We performed all analyses using SAS (version 9.4)

3. Results

A total of 4089 individuals survived an index opioid-involved overdose between May 2016 through December 2017. In this group 65 % of those with known sex were male, the average age at time of index event was 41 years old, and 74 % identified as non-Hispanic, white. Within the 12 months following discharge following the index event or prior to the subsequent opioid overdose, whichever happened first, 2277 (56 %) individuals received no addiction treatment, 35 % received OAT within at least one month (25 % buprenorphine and 13 % methadone) and 21 % received inpatient addiction treatment within at least one month (19 % admitted for medically supervised opioid withdrawal and 8 % for extended inpatient treatment) (Table 1). A total of 41 % of individuals received a non-OAT opioid, 30 % received a benzodiazepine, and 7 % were incarcerated.

In the 12 months following discharge for the index event, 467 individuals (11.4 %) experienced a subsequent fatal or non-fatal opioid-involved overdose (87 fatal [2.1 %]; 380 non-fatal [9.3 %]). People who experienced any subsequent opioid-involved overdose, compared to those who did not, were more likely to be male, non-Hispanic white, and younger (Table 2), and were less likely to have received methadone ($p < 0.001$). There was no difference between groups in the probability

Table 3
Unadjusted and adjusted primary survival analysis of time-to-any subsequent overdose (non-fatal or fatal) within 12 months of discharge after index overdose event.

	Unadjusted Models HR (95 % CI)	p-value	Adjusted Model aHR (95 % CI)	p-value
Treatment exposure[a]				
Methadone	0.44 (0.27 – 0.71)	< 0.001	0.41 (0.26 – 0.66)	< 0.001
Buprenorphine	0.82 (0.60 – 1.12)	0.21	0.72 (0.53 – 0.98)	0.04
Medically supervised opioid withdrawal	1.22 (0.87 – 1.71)	0.25	1.08 (0.77 – 1.50)	0.67
Extended inpatient treatment	0.96 (0.56 – 1.64)	0.88	0.90 (0.53–1.54)	0.71
Covariates				
Age	N/A		0.98 (0.97 – 0.99)	< 0.001
White, non-Hispanic	N/A		1.02 (0.82 – 1.28)	0.83
Non-OAT opioid	N/A		0.58 (0.41 – 0.81)	0.001
Benzodiazepine	N/A		1.47 (1.15 – 1.86)	0.002
Incarceration	N/A		1.24 (0.66 – 2.31)	0.52

[a] Treatment exposures coded as monthly time-updating indicator variables of receipt of that treatment modality. Reference group for hazards ratio for each treatment exposure is no receipt of that treatment modality.

between the two groups of having received buprenorphine, medically supervised opioid withdrawal, or extended inpatient treatment (data not shown).

3.1. Receipt of addiction treatment and time-to-subsequent overdose

In unadjusted Cox proportional hazards models, we observed lower risk of an opioid-involved overdose for those exposed to methadone (HR 0.44, 95 % CI 0.27–0.71) compared to those who were not exposed to methadone. We observed no difference in risk of subsequent opioid-involved overdose for those exposed to buprenorphine (HR 0.82, 95 % CI 0.60–1.12), medically supervised opioid withdrawal (HR 1.22, 95 % CI 0.87–1.71) or extended inpatient treatment (HR 0.96, 95 % CI 0.56–1.64) compared, respectively, to individuals who did not receive those treatment modalities.

In adjusted models, those exposed to either methadone or buprenorphine had significantly lower risk of subsequent overdose (methadone aHR 0.41, 95 % CI 0.26–0.66; buprenorphine aHR 0.72 95 % CI 0.53, 0.98) compared to those who did not receive those treatment modalities. Like unadjusted models, neither exposure to medically supervised opioid withdrawal (HR 1.08, 95 % CI 0.77–1.50) nor extended inpatient treatment (HR 0.90, 95 % CI 0.53–1.54) was independently associated with risk of subsequent overdose. Among covariates, non-OAT opioid exposure (HR 0.58, 95 % CI: 0.41–0.81) was associated with lower risk for subsequent overdose whereas exposure to benzodiazepines (HR 1.47, 95 % CI: 1.15–1.86) was associated with greater risk. Complete results of the unadjusted and adjusted models are reported in Table 3.

In our first secondary analysis, modeling addiction treatment within month as mutually exclusive exposures (methadone only, buprenorphine only, etc.), results were consistent with our primary analysis. Receipt of methadone only was associated with lower risk of subsequent opioid-involved overdose (aHR 0.36, 95 % CI 0.20–0.63) and non-medication-based treatments were not associated with a change in risk (medically supervised withdrawal only: aHR 1.19, 95 % CI 0.83–1.72;

Table 4
Unadjusted and adjusted secondary survival analysis of time-to-any subsequent overdose (non-fatal or fatal) within 12 months of discharge after index overdose event.

	Unadjusted Models		Adjusted Model	
	HR (95 % CI)	p-value	aHR (95 % CI)	p-value
Treatment Exposure[a]				
OAT (methadone or buprenorphine)	0.69 (0.51 – 0.92)	0.01	0.61 (0.45 – 0.81)	< 0.001
Inpatient treatment (medically supervised opioid withdrawal or extended inpatient)	1.27 (0.91 – 1.76)	0.16	1.08 (0.77 – 1.51)	0.65
Both OAT and inpatient treatment	0.67 (0.37–1.23)	0.20	0.57 (0.31–1.03)	0.06
Covariates				
Age	N/A		0.98 (0.97 – 0.99)	< 0.001
White, non-Hispanic	N/A		1.02 (0.82 – 1.28)	0.84
Non-OAT opioid	N/A		0.58 (0.41 – 0.81)	0.002
Benzodiazepine	N/A		1.46 (1.15 – 1.86)	0.002
Incarceration	N/A		1.22 (0.65 – 2.29)	0.53

[a] Treatment exposures coded as monthly time-updating indicator variables of receipt of that treatment modality. Reference group for hazards ratio for each treatment exposure is no receipt of that treatment modality.

extended inpatient treatment only: aHR 0.82, 95 % CI 0.44–1.53). Receipt of any combination of two or more treatment modalities[1] in a month was associated with reduced risk of subsequent opioid-involved overdose (aHR 0.57, 95 % CI: 0.31–1.03). Although the point estimate for buprenorphine in the secondary model was similar to the primary model, it was not statistically significant (aHR 0.77, 95 % CI: 0.55–1.07). Full results are reported in Supplementary Table 1.

In our second secondary analysis, modeling time-updated addiction treatment receipt as mutually exclusive exposures and combining OAT and non-medication based treatment modalities (OAT, inpatient treatment, or both OAT and inpatient treatment), led to similar results regarding the association between receipt of OAT and risk of subsequent opioid overdose (aHR 0.61, 95 % CI 0.45–0.81), and no association between the outcome and receipt of inpatient treatment (aHR 1.08, 95 % CI 0.77–1.51). Exposure to both OAT and inpatient treatment within the same month demonstrated a trend towards being associated with lower risk of subsequent overdose (aHR 0.57, 95 % CI: 0.31–1.03). Full results are presented in Table 4.

3.2. Results of secondary survival analysis of time-to-fatal overdose

In secondary analysis focused on risk of fatal opioid-involved overdose, none of the addiction treatments were associated with the outcome in the unadjusted model. Infrequent exposures (incarceration) precluded estimation of the full adjusted model, and we reduced the model to include age, race, benzodiazepine, and non-OAT exposures only. In this reduced adjusted model, no addiction treatment modality was significantly associated with risk for subsequent fatal opioid-involved overdose. Among covariates in the adjusted model, receiving non-OAT opioids (aHR 0.47 95 % CI: 0.24–0.93) was associated with lower risk whereas white race (aHR 2.16, 95 % CI: 1.14, 4.11) and benzodiazepine exposure (aHR 2.65, 95 % CI: 1.66, 4.23) was associated with greater risk for fatal opioid overdose (Table 5). To assess whether our findings were due to limited statistical power, we reran this model using mutually exclusive treatment combinations as described above, but results from this analysis were similar to the model with separate non-mutually exclusive treatment categories: (OAT aHR 0.74, 95 % CI: 0.40–1.38; inpatient treatment aHR 1.29, 95 % CI: 0.58–2.83; both OAT and inpatient treatment aHR 0.32 95 % CI: 0.04, 2.28) (Supplemental Table 2).

4. Discussion

In this cohort of over 4000 individuals who experienced a non-fatal opioid-involved overdose between May 2016 and December 2017, over 11 % experienced another opioid overdose within 12 months, including 2.1 % experiencing a fatal opioid-involved overdose. Following a non-fatal opioid-involved overdose, over one-third of individuals accessed methadone or buprenorphine for the treatment of OUD within 12 months and 1 in 5 received inpatient addiction treatment. Consistent with data from clinical trials and similar work using real-world epidemiological data, receipt of OAT for OUD was associated with decreased risk of subsequent overdose, with methadone associated with lower risk than buprenorphine for any overdose. In addition, we found that use of inpatient addiction treatments, supervised opioid withdrawal or extended inpatient treatment, in the context of all other treatments, was not associated with risk of subsequent overdose. We did not find any modality of addiction treatment, whether OAT or inpatient treatment, to be associated with risk for fatal overdose, but this was likely due to lack of statistical power because of the small number of fatal overdose events observed. Interestingly, receipt of non-OAT opioids (e.g., oxycodone, hydrocodone, etc.) after surviving an opioid-involved overdose was associated with lower risk of any overdose and of a fatal overdose. Consistent with prior literature, receipt of benzodiazepines was associated with increased risk of any opioid-involved overdose and of fatal opioid overdose specifically.

Our analysis builds on evidence from other studies using observational data to examine the association between receipt of addiction treatment following an overdose and risk of subsequent overdose. These results reveal a mixed picture of medical system interactions following a

Table 5
Unadjusted and adjusted survival analysis of time-to-subsequent fatal overdose within 12 months of discharge after index overdose event.

	Unadjusted Models		Adjusted Model	
	HR (95 % CI)	p-value	aHR (95 % CI)	p-value
Treatment Exposure[a]				
Methadone	0.64 (0.26, 1.60)	0.34	0.56 (0.23 – 1.40)	0.22
Buprenorphine	0.79 (0.38, 1.65)	0.53	0.71 (0.34–1.49)	0.37
Medically supervised opioid withdrawal	0.84 (0.35, 2.02)	0.70	0.85 (0.35 – 2.05)	0.72
Extended inpatient treatment	1.56 (0.54, 4.50)	0.41	1.70 (0.59 – 4.95)	0.33
Covariates[b]				
Age	N/A		1.01 (0.99 – 1.02)	0.56
White, non-Hispanic	N/A		2.16 (1.14 – 4.11)	0.02
Non-OAT opioid	N/A		0.47 (0.24 – 0.93)	0.03
Benzodiazepine	N/A		2.65 (1.66 – 4.23)	< 0.001
Incarceration	N/A		N/A	N/A

[a] Treatment exposures coded as monthly time-updating indicator variables of receipt of that treatment modality. Reference group for hazards ratio for each treatment exposure is no receipt of that treatment modality.

[b] Due to model constraints incarceration was not included in fatal overdose model

[1] Treatment variable includes receipt of any combination of medication or non-medication-based treatment modalities.

non-fatal opioid-involved overdose. Compared to earlier studies of access to OAT following an overdose, specifically those using similar data sources in Massachusetts during an earlier time period, (Larochelle et al., 2016, 2018; Wakeman et al., 2020; Walley et al., 2020) our study revealed a similar percentage of individuals accessed these medications in Connecticut following a nonfatal opioid overdose. Our analysis cannot explore the reasons these percentages have not increased despite increased public health expenditures to increase access to OAT. Further study is needed to explore interventions to increase OAT utilization, especially among overdose survivors. Our results, which mirror the associations seen in other observational studies and the effect seen in clinical trials of OAT, (Mattick et al., 2009, 2014; Tetrault and Fiellin, 2012) show evidence of the benefit of OAT, either methadone or buprenorphine, to avert subsequent opioid-involved overdose in real-world settings.

Our study also highlights that inpatient addiction treatment, which does not focus on initiation of OAT, appears, on average, to have no independent association on risk of subsequent overdose in overdose survivors. While similar results have been described in other observational research, (Wakeman et al., 2020) given lack of clinical trials to support this association inferences on treatment effects should be made with caution. Our analysis cannot rule out whether individuals accessing these treatments had a different underlying risk of subsequent overdose, unrelated to the treatment effect, which confounded the observed association. Regardless, although often preferred by patients, (Stein et al., 2015) families, (Nayak et al., 2021) and policymakers, (Beetham et al., 2021) given the limited data supporting their efficacy in averting overdoses and often high out-of-pocket cost, (Beetham et al., 2021) they may not be ideal as first line treatment for OUD in the absence of OAT. If inpatient treatment modalities are offered, our results highlight that they should be offered in conjunction, and not in lieu of, OAT. It is also unclear if the receipt of inpatient treatment in conjunction with OAT was associated with a reduction in overdose risk beyond the receipt of OAT alone, as the estimate of the hazard ratio was similar, and we cannot rule out an additive effect. More research is needed to help inform the role of inpatient addiction treatment following a non-fatal overdose.

Our study also highlights how other interactions with medical providers following an opioid-involved overdose may alter risk of a subsequent opioid-involved overdose. Over 40 % of individuals received a prescribed opioid or benzodiazepine after experiencing a non-fatal opioid-involved overdose, although we do not know if prescribers were alerted of these events or how it impacted clinical decision making regarding subsequent prescribing. Contrary to clinical guidance that non-OAT opioid agonists should be prescribed with caution in people at risk for overdose (including overdose survivors and those with OUD), (Larochelle et al., 2016; Dowell et al., 2022) our findings showed that receipt of non-OAT opioids was associated with a lower risk of subsequent opioid-involved overdose. There are several explanations for this unanticipated result. First, it may reflect clinical decision making by prescribers who accurately assessed risk of subsequent overdose and may limit prescribing opioids to patients already deemed to be at lower risk of subsequent overdose. Second, receipt of non-OAT opioids may reflect engagement in treatment, reflecting underlying differences in overdose risk in these individuals on subsequent risk of overdose independent of receipt of non-OAT opioids. In contrast, it may reflect the high prevalence of high potency synthetic opioids in the drug market, dominated by fentanyl, (Howell et al., 2023) where receipt of a regulated, prescribed opioid may limit use of unprescribed, unregulated opioids in the illicit market. This possible explanation is suggested both by cohort studies on heroin initiation following opioid discontinuation (Binswanger et al., 2020) and by qualitative research describing the experience of individuals entering the illicit opioid market following abrupt discontinuation of a prescription opioid (Dickson-Gomez et al., 2022). Although any inferences from this finding are limited, it does suggest more research is warranted regarding effects of prescribing or discontinuing non-OAT opioids in individuals at high risk for opioid overdose, including opioid overdose survivors.

In contrast to the outcomes related to non-OAT opioid, we found higher risk of subsequent opioid-involved overdose in individuals prescribed a benzodiazepine. Despite both opioids and benzodiazepines containing a boxed warning cautioning prescribers of the serious risk of combined use (New Safety Measures Announced for Opioid Analgesics, 2024) relatively less public health attention is focused on the role of prescribed benzodiazepines in the ongoing opioid overdose crisis, where many opioid-involved overdoses involve multiple substances, including benzodiazepines. This finding, along with studies documenting a high prevalence of benzodiazepines found in post-mortem toxicology results following opioid-involved overdoses, (Howell et al., 2023; Freeman et al., 2023) highlights a need for more research and for greater attention to the role of benzodiazepine prescribing in the current opioid overdose crisis.

4.1. Limitations

There are several limitations to our study. First, this is an observational study with risk for selection bias. Although we adjusted for baseline characteristics using multivariable regression, we cannot account for all factors that may differentiate patients who accessed these treatment modalities versus those who do not, and residual confounding is likely present due to inherent differences in these populations. Similarly, as an observational study of real-world treatment use there was heterogeneity in time-to-initiation, duration of treatment, and crossover between treatments, leading us to opt for a survival analysis using time-updating variables, which, although consistent with other similar work, (Larochelle et al., 2018) limits our ability to compare unconditional treatment exposures to no treatment in assessing associations with our outcomes (Dekker et al., 2008). In our analysis, we also included incarceration as a time-varying exposure as a covariate. The role of incarceration on treatment exposure and overdose risk is complex (Joudrey et al., 2019) and therefore this approach runs the risk of controlling for a mediating factor between our primary exposures and outcomes of interest. Second, we used a hospital-based system for capturing non-fatal opioid-involved overdoses during the study period, and that would miss non-fatal opioid-involved overdoses that did not lead to a hospital or emergency department presentation. However, these events capture interactions with the healthcare system and were thus more likely to lead to addiction treatment, which is the primary goal of our study. This approach is also reliant on accurate coding of hospital and emergency department diagnoses, which could lead to misclassification of events; both potential for underreporting and overreporting of OUD-related events (Green et al., 2017; Howell et al., 2021; Lagisetty et al., 2021; Becker et al., 2020). Similarly, we relied on OCME investigations and data to capture fatal opioid-involved overdoses, though the OCME has wide discretion to investigate all accidental deaths in the state. Third, we were limited to fewer than two years of data because of data restrictions from the CT DCP, which manages CPMRS. This led to smaller number of individuals who experienced outcomes of interest (especially fatal opioid-involved overdose) or were exposed to treatment modalities reducing power to observe some associations. Nevertheless, we included a cohort of over 4000 individuals with a large number who experienced the primary outcome.

Given data limitations mentioned above, we could not measure the receipt of naltrexone or its association with risk of subsequent overdose. Extended-release naltrexone is FDA-approved for the treatment of opioid use disorder, although previous studies have found it make up a small proportion of treatment receipt (<5 %) both overall and relative to other modalities and has not been associated with a change in risk of overdose (Larochelle et al., 2018; Morgan et al., 2018). We also did not account for potential temporal variation (seasonal or otherwise) in the opioid market or overdose risk that could have confounded our observed association though our analysis covered a relatively short period of time

(20 months) and visual inspection of overdose trends did not demonstrate seasonal variation. Finally, our data cannot account for individuals who had exposures (addiction treatment, controlled substance prescriptions, etc.) and outcomes (non-fatal and fatal opioid overdoses) that occurred outside of Connecticut. This analysis, limited to events that occurred in Connecticut, which has a relatively high opioid-related mortality, may not be generalizable to other states, though our findings are generally consistent with similar analyses in other states (Larochelle et al., 2016, 2018; Wakeman et al., 2020). Our data also reflect the experience of overdose survivors occurring over six years ago and given changes in the illicit drug market and overdose epidemiology since then, may not be generalizable to the current moment.

5. Conclusions

We found, using a state-wide linked dataset of exposures to different addiction treatment modalities following a non-fatal opioid-involved overdose, that OAT is associated with reduced risk of overdose following a non-fatal opioid-involved overdose, but that a minority of individuals access these medications. In addition, our findings demonstrate that inpatient addiction treatment alone, whether medically supervised opioid withdrawal or extended inpatient treatment, is not associated with reduced risk of subsequent opioid-involved overdose. Further public health and policy interventions to increase use of OAT in this high-risk population are needed to curb the worsening opioid overdose crisis.

CRediT authorship contribution statement

Fiellin David A.: Writing – review & editing, Supervision. **Becker William C.:** Writing – review & editing, Supervision. **Howell Benjamin A:** Writing – original draft, Methodology, Formal analysis, Conceptualization. **Black Anne:** Writing – review & editing, Methodology, Formal analysis. **Lin Hsiu-ju:** Writing – review & editing, Data curation. **Liberatore Mark:** Writing – review & editing. **Greene Christina R.:** Writing – review & editing. **D'Onofrio Gail:** Writing – review & editing. **Heimer Robert:** Writing – review & editing. **Grau Lauretta E:** Writing – review & editing. **Hawk Kathryn:** Writing – review & editing.

Funding

This publication was supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award [U01FD005938] totaling $388,163 with 100 percent funded by FDA/HHS. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA/HHS, or the US Government. Dr. Howell was supported by National Institute on Drug Abuse Grant No. 5K12DA033312.

Declaration of Competing Interest

The authors have no financial conflicts of interest to disclose.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.drugalcdep.2025.112679.

References

de Andrade, D., Elphinston, R.A., Quinn, C., Allan, J., Hides, L., 2019. The effectiveness of residential treatment services for individuals with substance use disorders: a systematic review. Drug Alcohol Depend. 201, 227–235. https://doi.org/10.1016/j.drugalcdep.2019.03.031.

Becker, W.C., Gordon, K.S., Edelman, E.J., et al., 2020. Are we missing opioid-related deaths among people with HIV? Drug Alcohol Depend. 212, 108003. https://doi.org/10.1016/j.drugalcdep.2020.108003.

Becker, W.C., Heimer, R., Dormitzer, C.M., et al., 2021. Merging statewide data in a public/university collaboration to address opioid use disorder and overdose. Addict. Sci. Clin. Pract. 16 (1), 1. https://doi.org/10.1186/s13722-020-00211-9.

Beetham, T., Saloner, B., Gaye, M., Wakeman, S.E., Frank, R.G., Barnett, M.L., 2021. Admission practices and cost of care for opioid use disorder at residential addiction treatment programs In The US. Health Aff. 40 (2), 317–325. https://doi.org/10.1377/hlthaff.2020.00378.

Binswanger, I.A., Glanz, J.M., Faul, M., et al., 2020. The association between opioid discontinuation and heroin use: a nested case-control study. Drug Alcohol Depend. 217, 108248. https://doi.org/10.1016/j.drugalcdep.2020.108248.

Caudarella, A., Dong, H., Milloy, M.J., Kerr, T., Wood, E., Hayashi, K., 2016. Non-fatal overdose as a risk factor for subsequent fatal overdose among people who inject drugs. Drug Alcohol Depend. 162, 51–55. https://doi.org/10.1016/j.drugalcdep.2016.02.024.

Chen, Q., Larochelle, M.R., Weaver, D.T., et al., 2019. Prevention of prescription opioid misuse and projected overdose deaths in the United States. JAMA Netw. Open 2 (2), e187621. https://doi.org/10.1001/jamanetworkopen.2018.7621.

Dekker, F.W., de Mutsert, R., van Dijk, P.C., Zoccali, C., Jager, K.J., 2008. Survival analysis: time-dependent effects and time-varying risk factors. Kidney Int. 74 (8), 994–997. https://doi.org/10.1038/ki.2008.328.

Dickson-Gomez, J., Krechel, S., Spector, A., et al., 2022. The effects of opioid policy changes on transitions from prescription opioids to heroin, fentanyl and injection drug use: a qualitative analysis. Subst. Abus. Treat., Prev., Policy 17 (1), 55. https://doi.org/10.1186/s13011-022-00480-4.

Dowell, D., Ragan, K.R., Jones, C.M., Baldwin, G.T., Chou, R., 2022. CDC clinical practice guideline for prescribing opioids for pain—United States, 2022. MMWR Recomm. Rep. 71 (3), 1.

Drug Laws and Regulations. Connecticut Department of Consumer Protection. Accessed December 15, 2021, ⟨https://portal.ct.gov/DCP/Drug-Control-Division/Drug-Control/Drug-Laws-and-Regulations⟩

Drug Overdose Monthly Report. Connecticut Department of Public Health. Accessed 2023, 2023. ⟨https://portal.ct.gov/-/media/DPH/Injury-and-Violence-Prevention/Opioid-Overdose-Data/Monthly-Death-Reports/2019-March-2023_Drug-Overdose-Deaths-Monthly-Report_Connecticut_updated-on-4-18-2023_Final.pdf⟩

Dunn, K.M., Saunders, K.W., Rutter, C.M., et al., 2010. Overdose and prescribed opioids: associations among chronic non-cancer pain patients. Ann. Intern. Med. 152 (2), 85.

Examiner OoCM. Regulations of the commission on medicolegal investigations. ⟨https://portal.ct.gov/-/media/OCME/Policies-and-Regulations/19a401COMLIregscodifiedto10302006pdf.pdf⟩

Freeman, P.R., McAninch, J., Dasgupta, N., et al., 2023. Drugs involved in Kentucky drug poisoning deaths and relation with antecedent controlled substance prescription dispensing. Subst. Abus. Treat., Prev., Policy 18 (1), 53. https://doi.org/10.1186/s13011-023-00561-y.

Green, C.A., Perrin, N.A., Janoff, S.L., Campbell, C.I., Chilcoat, H.D., Coplan, P.M., 2017. Assessing the accuracy of opioid overdose and poisoning codes in diagnostic information from electronic health records, claims data, and death records. Pharmacoepidemiol Drug Saf. 26 (5), 509–517. https://doi.org/10.1002/pds.4157.

Howell, B.A., Abel, E.A., Park, D., Edmond, S.N., Leisch, L.J., Becker, W.C., 2021. Validity of incident opioid use disorder (OUD) diagnoses in administrative data: a chart verification study. J. Gen. Intern. Med. 36 (5), 1264–1270. https://doi.org/10.1007/s11606-020-06339-3.

Howell, B.A., Black, A.C., Grau, L.E., et al., 2023. Concordance between controlled substance receipt and post-mortem toxicology in opioid-detected overdose deaths: a statewide analysis. Drug Alcohol Depend. 244, 109788. https://doi.org/10.1016/j.drugalcdep.2023.109788.

Joudrey, P.J., Khan, M.R., Wang, E.A., et al., 2019. A conceptual model for understanding post-release opioid-related overdose risk. Addict. Sci. Clin. Pr. 14 (1), 17. https://doi.org/10.1186/s13722-019-0145-5.

Lagisetty, P., Garpestad, C., Larkin, A., et al., 2021. Identifying individuals with opioid use disorder: validity of international classification of diseases diagnostic codes for opioid use, dependence and abuse. Drug Alcohol Depend. 221, 108583. https://doi.org/10.1016/j.drugalcdep.2021.108583.

Larochelle, M.R., Bernson, D., Land, T., et al., 2018. Medication for opioid use disorder after nonfatal opioid overdose and association with mortality: a cohort study. Ann. Intern Med 169 (3), 137–145. https://doi.org/10.7326/m17-3107.

Larochelle, M.R., Bernstein, R., Bernson, D., et al., 2019. Touchpoints - Opportunities to predict and prevent opioid overdose: a cohort study. Drug Alcohol Depend. 204, 107537. https://doi.org/10.1016/j.drugalcdep.2019.06.039.

Larochelle, M.R., Liebschutz, J.M., Zhang, F., Ross-Degnan, D., Wharam, J.F., 2016. Opioid prescribing after nonfatal overdose and association with repeated overdose: a cohort study. Ann. Intern Med 164 (1), 1–9. https://doi.org/10.7326/m15-0038.

Mattick, R.P., Breen, C., Kimber, J., Davoli, M., 2009. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database Syst. Rev. ;2009 (3), Cd002209. https://doi.org/10.1002/14651858.CD002209.pub2.

Mattick, R.P., Breen, C., Kimber, J., Davoli, M., 2014. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst. Rev. (2), Cd002207. https://doi.org/10.1002/14651858.CD002207.pub4.

Morgan, J.R., Schackman, B.R., Leff, J.A., Linas, B.P., Walley, A.Y., 2018. 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. Abus. Treat. 85, 90–96. https://doi.org/10.1016/j.jsat.2017.07.001.

Morgan, J.R., Wang, J., Barocas, J.A., et al., 2020. Opioid overdose and inpatient care for substance use disorder care in Massachusetts. J. Subst. Abus. Treat. 112, 42–48. https://doi.org/10.1016/j.jsat.2020.01.017.

Nayak, S.M., Huhn, A.S., Bergeria, C.L., Strain, E.C., Dunn, K.E., 2021. Familial perceptions of appropriate treatment types and goals for a family member who has opioid use disorder. Drug Alcohol Depend. 221, 108649. https://doi.org/10.1016/j.drugalcdep.2021.108649.

New Safety Measures Announced for Opioid Analgesics, Prescription Opioid Cough Products, and Benzodiazepines. U.S. Food and Drug Administration. Accessed February 28, 2024, 2024. ⟨https://www.fda.gov/drugs/information-drug-class/new-safety-measures-announced-opioid-analgesics-prescription-opioid-cough-products-and⟩

Provisional Data Shows U.S. Drug Overdose Deaths Top 100,000 in 2022. NCHS: a blog of the National Center for Health Statistics blog. May 18, 2023, 2023. ⟨https://blogs.cdc.gov/nchs/2023/05/18/7365/⟩

Rudd, R.A., Aleshire, N., Zibbell, J.E., Gladden, R.M., 2016. Increases in Drug and Opioid Overdose Deaths–United States, 2000-2014. MMWR Morb. Mortal. Wkly Rep. 64 (50-51), 1378–1382. https://doi.org/10.15585/mmwr.mm6450a3.

Saloner, B., Chang, H.Y., Krawczyk, N., et al., 2020. Predictive modeling of opioid overdose using linked statewide medical and criminal justice data. JAMA Psychiatry 77 (11), 1–9. https://doi.org/10.1001/jamapsychiatry.2020.1689.

Saloner, B., Li, W., Bandara, S.N., McGinty, E.E., Barry, C.L., 2022. Trends in the use of treatment for substance use disorders, 2010–19. Health Aff. 41 (5), 696–702. https://doi.org/10.1377/hlthaff.2021.01767.

Shintani A.K., Girard Td Fau - Eden S.K., Eden Sk Fau - Arbogast P.G., Arbogast Pg Fau - Moons K.G.M., Moons Kg Fau - Ely E.W., Ely E.W. Immortal time bias in critical care research: application of time-varying Cox regression for observational cohort studies. (1530-0293 (Electronic))

Stein, M.D., Anderson, B.J., Bailey, G.L., 2015. Preferences for aftercare among persons seeking short-term opioid detoxification. J. Subst. Abus. Treat. 59, 99–103. https://doi.org/10.1016/j.jsat.2015.07.002.

Strach, P., Zuber, K., Pérez-Chiqués, E., 2020. Why policies fail: the illusion of services in the opioid epidemic. J. Health Polit. Policy Law 45 (2), 341–364. https://doi.org/10.1215/03616878-8004910.

Tetrault, J.M., Fiellin, D.A., 2012. Current and potential pharmacological treatment options for maintenance therapy in opioid-dependent individuals. Drugs 72 (2), 217–228. https://doi.org/10.2165/11597520-000000000-00000.

Tetrault, J.M., Fiellin, D.A., 2018. More beds or more chairs? Using a science-based approach to address the opioid epidemic. Ann. Intern Med 1, 73–74.

Treatment Episode Data Set. Substance Abuse and Mental Health Services Administration. Accessed December 15, 2021, ⟨https://www.samhsa.gov/data/data-we-collect/teds-treatment-episode-data-set⟩

Wakeman, S.E., Larochelle, M.R., Ameli, O., et al., 2020. Comparative effectiveness of different treatment pathways for opioid use disorder. JAMA Netw. Open 3 (2), e1920622. https://doi.org/10.1001/jamanetworkopen.2019.20622.

Walley, A.Y., Lodi, S., Li, Y., et al., 2020. Association between mortality rates and medication and residential treatment after in-patient medically managed opioid withdrawal: a cohort analysis. Addiction 115 (8), 1496–1508. https://doi.org/10.1111/add.14964.

Yadav, K., Lewis, R.J., 2021. Immortal time bias in observational studies. JAMA 325 (7), 686–687. https://doi.org/10.1001/jama.2020.9151.