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Receipt of opioid use disorder treatments prior to fatal overdoses and comparison to no treatment in Connecticut, 2016–17

Robert Heimer [a,*], Anne C. Black [b,d], Hsiuju Lin [c], Lauretta E. Grau [a], David A. Fiellin [a,b], Benjamin A. Howell [b], Kathryn Hawk [a,b], Gail D'Onofrio [a,b], William C. Becker [b,d]

[a] Yale School of Public Health, New Haven, CT, United States
[b] Yale School of Medicine, New Haven, CT, United States
[c] University of Connecticut School of Social Work, Hartford, CT, United States
[d] VA Connecticut Healthcare System, West Haven, CT, United States

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ABSTRACT

Objective: To determine the relative risk of death following exposure to treatments for OUD compared to no treatment.
Methods: In this retrospective cohort study we compiled and merged state agency data on accidental and undetermined opioid overdose deaths in 2017 and exposures to OUD treatment in the prior six months to determine incidence rates following exposure to different treatment modalities. These rates were compared to the estimated incidence among those exposed to no treatment to determine relative risk of death for each treatment exposure.
Results: Incidence rates for opioid poisoning deaths for those exposed to treatment ranged from 6.06±1.40 per 1000 persons exposed to methadone to 17.36±3.22 per 1000 persons exposed to any non-medication treatment. The estimated incidence rate for those not exposed to treatment was 9.80±0.72 per 1000 persons. With no exposure to treatment as referent, exposure to methadone or buprenorphine reduced the relative risk by 38% or 34%, respectively; the relative risk of non-medication treatments was equal to or worse than no exposure to treatment (RR = 1.27–1.77).
Principal conclusions: Exposure to non-MOUD treatments provided no protection against fatal opioid poisoning whereas the relative risk was reduced following exposures to MOUD treatment, even if treatment was not continued. Population level efforts to reduce opioid overdose deaths need to focus on expanding access to agonist-based MOUD treatments and are unlikely to succeed if access to non-MOUD treatments is made more available.

1. Introduction

The opioid crisis contributes to declining life expectancy in many parts of the U.S. (Case and Deaton, 2015; Beseran et al., 2022). Treatment options for opioid use disorder (OUD) can be divided into those that provide agonist medications, methadone and buprenorphine with or without psychosocial assistance (MOUD), those that provide antagonist medication, generally long-acting formulations of naltrexone, and those that forgo longer-term medication-based treatment (non-MOUD). Non-MOUD approaches include short-term opioid "detoxification," with or without short-term opioid assistance, and longer-term, non-MOUD "rehabilitation." The decision on which treatment approach is optimal should consider how to minimize the likelihood of relapse, of which opioid-involved death is the most catastrophic result. While buprenorphine, methadone, and naltrexone are the three FDA-approved medications to treat opioid use disorder, the agonist medications buprenorphine and methadone are demonstrably more effective and are on the WHO's Essential Medication's List (World Health Organization, 2021). The evidence for the benefit from agonist MOUD is well established within the framework of clinical trials (Mattick et al., 2009, 2014; Sordo et al., 2017; National Academies of Sciences, Engineering, and Medicine, 2019; Santo et al., 2021) and these are now considered the standard of care by the U.S. National Institute on Drug Abuse, and the World Health Organization (NIDA, 2021; World Health Organization, 2021). Recent studies in the U.S., using data in real-world scenarios outside the realm of clinical trials, have demonstrated that agonist

* Correspondence to: Yale School of Public Health, 60 College Street, New Haven, CT 06520-8034, United States.
E-mail address: robert.heimer@yale.edu (R. Heimer).

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MOUD out-performs other forms of treatment when considering outcomes including overdose and serious acute care complications of opioid use (Larochelle et al., 2018; Morgan et al., 2018; Wakeman et al., 2020). What remains unclear is the effectiveness of agonist MOUD and non-MOUD treatment, in an environment where both are available, compared to no exposure to treatment.

The state of Connecticut is an appropriate location for analyzing the influence of OUD treatment exposure on fatal opioid overdoses since it has been heavily affected by the opioid crisis. The annual number of opioid-associated overdose deaths has quadrupled since 2010, and Connecticut has been consistently on the list of the ten states with the highest overdose death rates (CDC Wonder, 2018). The changes in Connecticut in the types of opioids found in individuals dying of an opioid overdose mirror national trends. Initially, the majority of deaths involved pharmaceutical opioids. After 2012, the increase predominantly involved heroin and then, beginning in 2016, fentanyl replaced heroin as the most common narco-trafficked opioid detected in fatal overdoses nationally (Ciccarone, 2021; Volkow, 2021). In Connecticut, the increase has been spread across the state, sparing only two of the state's 169 municipalities, with evidence of spatial clustering only for illicit fentanyl as it emerged during the latter half of the decade (Lu et al., 2023).

In 2016, then Governor Dannel Molloy convened an expert panel to enumerate evidence-based strategies that could, if implemented, be expected to reduce the adverse impact of opioids, including the number of opioid-related deaths (Fiellin et al., 2016). Two of the six major strategy recommendations were expanding agonist MOUD treatment and using existing data from state agencies to better understand and help control the spiraling rate of overdose deaths. To inform the implementation of the evidence-based treatment strategies, we merged datasets from state and federal agencies to identify the timing, type, and duration of OUD treatment received by individuals who subsequently experienced a fatality in which an opioid was detected (Becker et al., 2021). In this report, we use the merged data to compare those with no evidence of treatment exposure in the six months leading up to the fatal overdose to those receiving different forms of OUD treatment. This analysis reveals the potential mortality benefit of the different treatment modalities as part of our efforts to inform the decisions of patients, families, clinicians, and policy-makers by providing local data regarding the risk of death associated with OUD treatment options (Tetrault and Fiellin, 2018).

2. Data sources and methods

The rationale and method for data merging have been published (Becker et al., 2021). Most of the data for this study were obtained through data use agreements and memoranda of understanding between the research team at Yale and state agencies; some of the denominators used in the analysis have been estimated. The sources for opioid-detected accidental and undetermined deaths and for all treatment exposures are summarized in Table 1. This study was ruled exempt from human subjects review because linkages of protected individual level data were condcuted behind state agencies' firewalls.

2.1. Poisonings listing an opioid as a cause of death

In Connecticut, suspected poisoning deaths are investigated by the Office of the Chief Medical Examiner (OCME) as part of their assessment of all unanticipated deaths in the state. The OCME investigations determine the cause and manner of death and can include toxicological testing. For this study, we included as an opioid poisoning death only those that occurred among CT residents in 2017 in which one or more opioids was listed in the cause of death and ruled "accidental" or "undetermined" (see Table 1). For cases in which toxicological tests were available and detected in quantifiable amounts, we obtained data on the specific compounds or their metabolites. In addition to opioids, toxicology data included but not limited to detection of alcohol, benzodiazepines, and cocaine. For cases without toxicological testing, the substances listed in the cause of death, identified by the medical examiner during the investigation, were used. Additional demographic information abstracted from the OCME records included sex, date of birth, and race. Locations of the injury and death and of decedents' residence were recorded.

Table 1
Data sources for outcomes and exposures.

Outcome		
Fatal Opioid Overdose	Office of the Chief Medical Examiner provided data on all deaths in which an opioid was listed as a cause of death. One author (LEG) reviewed source documents to confirm that the manner of death was accidental or undetermined.	
Exposures	Numerator (Deaths within 6 Months of Exposure)	Denominator (Total Exposed in 6 Month Window)
Methadone Treatment	CT Department of Mental Health and Addiction Services	CT Department of Mental Health and Addiction Services
Buprenorphine Treatment	CT Department of Consumer Protection	Estimated from DEA ARCOS data and the published literature on buprenorphine dosing and treatment duration (see Methods for details)
Short-term non-MOUD Treatments	CT Department of Mental Health and Addiction Services	CT Department of Mental Health and Addiction Services
Short-term non-MOUD Treatments	CT Department of Mental Health and Addiction Services	CT Department of Mental Health and Addiction Services
None		Estimated from the published literature (see Methods for details)

2.2. Treatment for opioid use disorder

Treatment episodes at substance use treatment facilities accredited by the state and supported with state funding are recorded by the CT Department of Mental Health and Addiction Services (DMHAS). These include short-term non-MOUD treatment of 14 or fewer days, longer-term non-MOUD treatment of 21 days or more, and methadone for ongoing MOUD treatment. Having set a window of six months for treatment exposure prior to opioid-detected deaths in 2017, treatment data were obtained for the period July 1, 2016 through December 31, 2017. The number of unique individuals receiving each treatment modality for OUD specifically or for any substance use problem during the window period was provided by DMHAS. Individuals receiving multiple forms of treatment were deduplicated to yield a roster of people diagnosed with OUD receiving any treatment for during this period.

Data on treatment with buprenorphine formulations were based on pharmacy prescription fill records collected in the CT Prescription Monitoring and Reporting System (CPMRS) maintained by the Connecticut Department of Consumer Protection. Due to limitations in the memorandum of understanding, CPMRS data were used only for the purpose of matching decedents to individuals with prescriptions for seven days or more of medications. Of note, as it is not a controlled substance, CPMRS does not track prescription fills for naltrexone, and exposure to this treatment modality for OUD could not be ascertained.

The denominator for buprenorphine exposure, i.e., the number of people being treated with buprenorphine for OUD during the 2016–2017 exposure window, was estimated, starting with pharmacy sales data compiled by the Drug Enforcement Administration in their Automated Reports and Consolidated Ordering System (ARCOS), in which manufacturers and distributors report their controlled substances transactions. To convert the ARCOS data reported in grams into an estimate of the number of people prescribed buprenorphine, we assumed a daily dose of 20 mg/day and mean duration of treatment of four months

for an estimated total per person treated of 2.44 g.(Mattick et al., 2014; Gordon et al., 2015; Thomas et al., 2017; Olfson et al., 2020; Landis et al., 2022) Opioid treatment programs in the state have begun to increase the number of patients prescribed buprenorphine as part of MOUD treatment, and these are included in the ARCOS dataset since the prescriptions are filled at a pharmacy (DEA Division of Diversion Control, 2022). Programs that administer buprenorphine in decreasing doses as part of short-term non-MOUD treatment are not captured in the ARCOS pharmacy dataset. Conversely, the ARCOS dataset contains pharmacy sales for buprenorphine formulations prescribed for pain management. Therefore, the estimate of the number of patients filling buprenorphine prescriptions as part of MOUD treatment is an upper bound. Between July 1, 2016, and December 31, 2017, pharmacies in Connecticut dispensed 83,138 g of buprenorphine, and each patient received an estimated 2.44 g during their 4-month MOUD treatment period. This volume of buprenorphine was estimated to treat 34,073 individuals during the 18-month exposure window.

The total number of people exposed to each treatment during a six-month window period was estimated based on the annual number of people treated and the average duration that an individual is treated (Table 2). For buprenorphine and non-MOUD treatments, the average treatment period was less than six months, so the number of individuals exposed to treatment was half the annual number, assuming that initiation of treatment occurred at an essentially constant rate throughout the year. For methadone, the average treatment period was set at eight months since some of the larger opioid treatment programs in the state report that retention at six months exceeded 85% and 74% at one year (Madden et al., 2018; Anonymous, 2022). Thus, the number of people with exposure in a six-month window would be two-thirds of the annual total.

2.3. Estimating the number of people with OUD not exposed to treatment

The number of people with OUD not exposed to treatment within a six-month window was estimated using two complementary approaches. The first relied on an analysis of the 2015–17 National Survey on Drug Use and Health. Jones and McCance-Katz (2019) reported that 34.5% of individual nationwide reporting OUD had a treatment exposure. The cumulative number of people receiving one or more treatment types in our six-month window would therefore comprise 34.5% of the total treatment need, and the proportion untreated would constitute the remainder. The second approach used data from a recent estimate of the U.S. population with OUD. Using two separate multiplier methods, Keyes et al. (2022) established point estimates of 6.7 and 7.6 million. We used the average of the two, multiplied by the proportion of the U.S. population 18–65 years of age that live in Connecticut (1.08% of the total U.S. population), and adjusted the product by the ratio of overdose deaths in Connecticut compared to the U.S. as a whole to estimate the number of people with OUD in the state. For the first approach, based on treatment data, our estimate was 97,258; for the second, based on people with OUD, our estimate was 109,652. Averaging these two, we settled on an estimate of 103,455 as the number of people with OUD in Connecticut and, by deducting the unique individuals known to be exposed to any form of treatment, the number of people not exposed to treatment in a six-month window as 72,586.

Table 2
OUD treatment exposure in a six-month window, July 1, 2016 through December 31, 2017.

Treatment Modality	Individuals Receiving Treatment, Total for 7/16–12/17	Treatment Duration	Individuals Receiving Treatment, 6 months
Methadone	23,102	8 months average	11,551
Buprenorphine	34,073	4 months average	11,358
All non-MOUD	19,005	≤6 months	6335
Short-term	17,079	≤14 days	5693
Long-term	5625	15 days – 6 months	1875

Exposure calculations are described in detail in the text. Numbers of unique individuals were ascertained from state agency data for methadone and non-MOUD treatment modality and were estimated for buprenorphine treatment episodes.

2.4. Merging of the datasets

Linking opioid-detected accidental and undetermined deaths to treatment exposures in the six months prior to death was done behind DMHAS and Department of Consumer Protection firewalls by one member of the research team (H. L.). Linkage between exposure and death used Link King, a public domain software program that uses both probabilistic and deterministic matching algorithms and can achieve a high degree of linking accuracy with sensitivity and positive predictive values greater than 90% (Campbell et al., 2008). All available demographic and geographic information in the exposure and OCME records were assessed, applying a set of established criteria, to ascertain whether record pairs matched or did not match. This approach using Connecticut state agency databases has been described previously (Becker et al., 2021).

The treatment exposure closest in time to the date of death was determined by reviewing admission and discharge dates for the various treatments. If an individual had more than one category of treatment exposure during the 6-month window and the treatment periods – based on admission and discharge dates – appeared to have overlapped, the last exposure was determined based solely on admission date.

2.5. Analysis of the merged data

Deaths involving one or more opioids were matched to treatment records to determine if the decedent had been exposed, in the six months prior to their death, to one of four treatment modalities in two contrasting groups: for non-MOUD, short and longer-term treatments; and for MOUD, methadone and buprenorphine. If multiple treatment modalities were accessed within the six-month window, the most recent modality was considered the exposure of interest. Treatment could have commenced before or during the six-month exposure period and could have terminated before or on the date of death. Decedents without matches to a treatment exposure were considered unexposed to treatment.

2.5.1. Characteristics of decedents

Data from OCME records were abstracted to determine the characteristics of decedents, which included age, biological sex, race (limited to African-American or White), opioid(s) and other drugs involved, location of injury, and history of incarceration.

2.5.2. Incidence and relative risk of opioid-involved overdose death

The incidence rate was calculated by dividing the deaths for each exposure category by the total exposures throughout the state during a six-month period. Relative risk was determined using the incidence in the unexposed population as the referent. The z-statistic, 95% confidence intervals, and p-value were calculated manually using standard approaches (Aschengrau and Seage, 2008).

3. Results

In 2017, there were 965 accidental or undetermined poisoning among the residents of Connecticut in which at least one opioid was detected. Using the last exposure as the exposure of interest, we found that 69 decedents had been exposed to methadone, 72 to buprenorphine, 71 to short-term non-MOUD treatments, and 26 to longer term

Table 3
Characteristics of unintentional opioid-involved decedents as a function of exposure to treatment for OUD in the six months prior to death.

	Exposure Categories					
	All Decedents[1]	Short-term non-MOUD	Longer-term non-MOUD	Methadone	Buprenorphine Prescription	No Exposure
Number of Decedents	**965**	**71**	**26**	**69**	**72**	**711**
Mean age ± sd	41.15 (12.2)	37.7 (10.6)	36.58 (10.2)	39.81 (11.4)	39.9 (11.9)	42.1 (12.4)
Sex: % female	235 (24.4)	17 (23.9)	7 (26.9)	25 (36.2)	16 (22.2)	167 (23.5)
Race[2]						
White	874 (90.6)	62 (87.3)	24 (92.3)	65 (94.2)	68 (94.4)	641 (90.2)
African-American	79 (8.2)	8 (11.3)	1 (3.9)	4 (5.8)	3 (4.2)	63 (8.9)
Missing	12 (1.2)	1 (1.4)	1 (3.9)	0 (0)	1 (1.4)	7 (1.0)
Location of Death						
Own Residence	513 (53.2)	31 (43.7)	10 (38.5)	39 (56.2)	32 (44.4)	393 (55.3)
Other's Residence	75 (7.8)	5 (7.0)	2 (7.7)	1 (1.4)	5 (6.9)	62 (8.7)
Automobile	18 (1.9)	0	0	2 (2.9)	3 (4.2)	13 (1.8)
Indoor Public	321 (33.3)	30 (42.3)	12 (46.2)	27 (39.1)	28 (38.9)	216 (30.4)
Outdoor Public	23 (2.4)	5 (7.0)	1 (3.8)	0	4 (5.6)	13 (1.8)
Incarceration						
within 5 years of death	304 (31.5)	40 (56.3)	12 (46.2)	15 (21.7)	29 (40.3)	200 (29.1)
within 1 years of death	172 (17.8)	25 (35.2)	7 (26.9)	9 (13.0)	11 (15.3)	118 (16.6)
Opioids Involved						
Heroin	486 (50.4)	46 (64.8)	10 (38.5)	34 (49.3)	41 (56.9)	346 (48.7)
Fentanyl and analogs	676 (70.1)	57 (80.3)	23 (88.5)	39 (56.5)	58 (80.6)	488 (68.6)
Methadone	100 (10.4)	4 (5.6)	1 (3.9)	43 (62.3)	3 (4.2)	45 (6.3)
Buprenorphine	24 (2.5)	0 (0)	0 (0)	0 (0)	14 (19.4)	10 (1.4)
Pharmaceutical Opiates[3]	263 (27.3)	17 (23.9)	2 (7.7)	17 (24.6)	16 (22.2)	205 (28.8)
>1 Opioid Involved						
Other Drugs Involved	507 (52.5)	48 (67.6)	10 (38.5)	32 (46.4)	46 (63.9)	362 (50.9)
Cocaine	335 (34.7)	26 (36.6)	11 (42.3)	21 (30.4)	26 (36.11)	244 (34.3)
Benzodiazepines	345 (35.8)	26 (36.6)	2 (7.7)	33 (47.8)	30 (41.7)	248 (34.9)
Alcohol	316 (32.8)	21 (29.6)	9 (34.6)	17 (24.6)	17 (23.6)	248 (34.9)

Categorial data are presented as number (and percentage) within each exposure category.
Notes:
1. Exposure to treatment most proximal to fatal opioid overdose could not be determined for 16 decedents (1.7%).
2. Ethnicity is not routinely reported by the CT Office of the Chief Medical Examiner.
3. The category of pharmaceutical opioids excludes buprenorphine and methadone.

non-MOUD treatments. We could not establish an unambiguous sequence for 13 decedents were exposed to a non-MOUD treatment, so a total of 110 decedents were classified as exposed to a non-MOUD treatment. A total of 711 opioid-detected poisoning deaths occurred among individuals with no record of receiving treatment for OUD within six months of death.

3.1. Characteristics of decedents

Characteristics of the decedents, as whole and by exposure category, appear in Table 3. There are some significant differences in characteristics across the different exposure categories. In terms of demographics, women were significantly over-represented among those exposed to methadone (36.2%) compared to 23.7% for the other exposures and 23.5% for those with no exposure ($p = 0.018$). An indoor, public space for the poisoning death was more common for individuals exposed to non-MOUD (43.3%) compared to 31.8% of those with exposure to MOUD or with no exposure ($p = 0.023$). Individuals with exposure to non-MOUD treatments were twice as likely as all other decedents to have been incarcerated in the year prior to death (33.0–16.3%, $p < 0.001$).

There were significant differences in opioids associated with the fatal poisonings across exposure categories. Decedents exposed to methadone or buprenorphine were more likely to have those medications identified through toxicology or OCME investigation. Among those exposed to methadone, 43 (62.3%) were found to have methadone, compared to all others 57 (6.8%) ($p<0.001$). Among those exposed to buprenorphine, 14 (19.4%) were found to have buprenorphine; for all others the prevalence of methadone or buprenorphine was 1.1% ($p<0.001$). The presence of benzodiazepines was much less common in decedents exposed to longer-term MOUD treatment (7.7%) compared to all others (36.8%) ($p=0.005$). Nearly half of decedents exposed to methadone (47.8%) also had benzodiazepines identified in the toxicology or OCME investigation report, significantly different from all the other groups ($p = 0.029$).

3.2. Incidence of fatal opioid poisoning

To determine the mortality rate among individuals with OUD, we calculated the denominator as the number of individuals exposed to each form of treatment in a six-month period (Table 2) and the number of individuals not exposed to treatment. The annual rate of opioid-detected accidental and undetermined fatalities ranged from 6.06 per 1000 individuals exposed to methadone to 13.87 per 1000 for individuals exposed to longer-term non-MOUD treatment (Table 4). Incidence rates were 6.52 deaths per 1000 for those last exposed to buprenorphine treatment and 12.47 deaths per 1000 for individuals exposed to short-term non-MOUD treatment. Combining all individuals with any non-MOUD exposure, including those with ambiguous discharge dates, the incidence rate rose to 17.36 per 1000 individuals. Among those with no treatment exposure, the estimated mortality rate in 2017 was 9.80 per 1000. The 95% confidence interval around each point estimate is reported in Table 4.

3.3. Relative risk of fatal opioid poisoning

The risk of death for each treatment modality was compared to that for individuals not exposed to any treatment captured in state agency data (Table 4, top). Exposure to methadone or to buprenorphine was protective, with relative risks of 0.619 (95% CI, 0.484 – 0.844; $p < 0.001$) and 0.662 (95% CI, 0.524 – 0.844; $p < 0.001$), respectively. The

Table 4
Incidence rate and relative risk for exposures to most recent treatment for OUD within 6 months of fatal opioid-involved overdose.

Treatment Exposure	Number of Fatal ODs among those Exposed	Number of People Exposed in a 6-Month Period	Incidence per 1000 People Exposed (±s.d.)	Relative Risk (95% Confidence Interval)	p-value
Methadone	70	11,551	6.06 (±1.40)	0.619 (0.484 – 0.790)	0.0002
Buprenorphine	74	11,358	6.52 (±1.44)	0.662 (0.524 – 0.844)	0.0008
Short-Term non-MOUD	71	5693	12.47 (±2.90)	1.272 (0.999 – 1.623)	0.0509
Longer-Term non-MOUD	26	1875	13.87 (±5.29)	1.416 (0.960 – 2.088)	0.0796
Any non-MOUD*	110	6335	17.36 (±3.22)	1.773 (1.453 – 2.163)	<0.0001
No Treatment Exposure	711	72,586	9.80 (±0.72)	ref	
Methadone	70	11,551	6.06 (±1.40)	ref	
Short-Term non-MOUD	71	5693	12.47 (±2.90)	2.058 (1.482 – 2.859)	<0.0001
Longer-Term non-MOUD	26	1875	13.87 (±5.29)	2.288 (1.428 – 3.577)	0.0003
Any non-MOUD*	110	6335	17.36 (±3.22)	2.865 (2.127 – 3.860)	<0.0001

We were able to match 949 of 965 individuals who experienced a fatal opioid-involved overdose unambiguously to one of the categories and another 13 to a non-MOUD treatment.
* Any non-MOUD includes those decedents in which the distinguishing between whether the last exposure was short- or longer-term was not possible. This adds 13 opioid overdose deaths to the sum of short-term and longer-term non-MOUD exposures.

relative risk of death was higher for the non-MOUD treatment approaches individually and in sum. Compared to no treatment, risk of death in the group exposed to longer-term non-MOUD (RR = 1.416; 95% CI, 0.960, 2.088; p = 0.080) and to short-term MOUD (RR = 1.272; 95% CI, 0.999 – 1.623; p = 0.051) was higher, but the small number of events in each group prevented the relative risk from being significant. However, the risk of death was significantly higher when combining all non-MOUD exposures (RR = 1.773; 95% CI, 1.453 – 2.163, p < 0.001).

A sub-analysis was conducted that was restricted to the cases in which we could obtain both death and total exposure from state agency databases. This covered methadone and both short- and longer-term non-MOUD treatments (Table 3, bottom). In this analysis, the mortality among those exposed to methadone was the referent category. The relative rates of mortality after exposure to short-term, longer-term treatment, and any non-MOUD treatment were 2.058 (95% CI: 1.482 – 2.859), 2.288 (95% CI: 1.428 – 3.577), and 2.865 (95% CI: 2.127 – 3.860), respectively.

4. Discussion

The findings revealed that exposures to MOUD, even if not continued throughout the six-month exposure period was associated with reduced risk of a fatal poisoning compared to non-MOUD forms of treatment and no treatment exposure. It is also clear that risk of death associated with exposure to non-MOUD forms of treatment was no less than that for no treatment; indeed, non-MOUD treatment might have produced worse outcomes than no treatment. Comparing the relative risk for the treatments for which agency-based numbers are available revealed that any exposure to methadone in the six months prior to death in 2017 was associated with 65% reduced relative risk of fatal opioid poisoning compared to exposure to any non-MOUD treatment recorded in the DMHAS database. Even more apparent, based on the available data from 2017, the relative risk of fatal opioid death in the six months following exposure to non-MOUD treatments ranged from 1.5 to 1.74 compared to no treatment. This is an unacceptably high probability for treatments that are purported to benefit patients with OUD and likely to be paid for by public tax revenues. In fact, it seems likely, based on our estimates of the number of people with OUD not exposed to treatment, that non-MOUD treatments were inferior to no treatment.

There is a century of data demonstrating that non-MOUD treatment is followed by a high rate of relapse to opioid use – especially for morphine and heroin – approaching 90% at six months (Musto, 1999; Broers et al., 2000; Heimer et al., 2019). Relapse rates for those regularly using fentanyl may be even higher (Stone et al., 2018). There is ample evidence from the U.S. and elsewhere that longer-term non-MOUD treatments place those who relapse at an especially high risk of opioid overdose and death (Strang et al., 2003; Wakeman et al., 2020). There is also compelling evidence that agonist MOUD decreases opioid-involved and all-cause mortality (Santo et al., 2021), and nearly thirty years of evidence that methadone reduces HIV-related mortality (Fugelstad et al., 1995; Parashar et al., 2016; Sordo et al., 2017). Our analysis was based on exposures to treatment, not their completion or retention, therefore our findings indicate that exposures to agonist MOUD treatment convey more benefit that non-MOUD even if the treatment is incompletely adhered to or terminated.

4.1. Strengths and limitations

The analytic approach and the results demonstrate the strengths and weaknesses of using state agency data to explore the relationships between treatment for OUD and opioid-detected fatalities. A major strength is that the data come from real-world treatment exposure, not clinical trials, and thus provide assurance that our findings are representative of how treatment is delivered to most individuals who seek it. While such databases can yield firm numbers for many of the parameters needed for a thorough analysis, some important numbers could only be estimated. At least one of these estimates, the number of people exposed to buprenorphine treatment, could be replaced with a firmer number if a more comprehensive data use agreement had been crafted between the academic research team and one of the state agencies. But other values would remain estimates including the number of people obtaining non-MOUD treatment from programs not reporting to CT DMHAS (e.g., programs outside the state), and, more importantly, the number of people with OUD and those not exposed to treatment. Nevertheless, we can feel confident that some firm conclusions can be drawn from the available data.

As noted above, there are limitations to our study. Some of the numbers, especially regarding the denominators for calculating incidence are estimates. We were granted access to only 18 months of data on buprenorphine for matching filled prescriptions and fatal opioid overdoses at the individual level. Expanding our access to these sources can only improve our estimates, and we are working with these agencies to gain such access.

We were unable to obtain data on exposure to naltrexone. Neither data with personal identifiers for matching to overdose deaths nor the numbers of people receiving naltrexone treatment are captured in state agency data. Thus, we have a less-than-complete understanding of the relationship between treatment exposure and opioid-related deaths.

Another limitation is confounding that might occur if the severity of OUD differed for individuals seeking different types of treatment. If individuals seeking non-MOUD treatment had greater addiction severity, that could explain why their relative risk was found to be higher.

However, it does seem that the stigma associated with MOUD, and especially with methadone, would make it more plausible that individuals would seek non-MOUD initially and then consider agonist MOUD if non-MOUD treatments fail them (Mackey et al., 2020).

4.2. Conclusions

The findings presented in this report can inform individuals with OUD and their loved ones regarding treatment exposure choices. Furthermore, these findings should be considered by state agencies and organizations involved in the regulation of OUD treatment facilities, including those involved in payment and quality. Similar processes should take place nationally; this will become increasingly important as states make decision on spending opioid settlement funds. We are hopeful that our analysis, from which we conclude that exposure to methadone or buprenorphine in the past 6 months was associated with a reduced rate of fatal overdose, will inform decisions that will decrease the number of opioid overdose deaths nationally.

Declaration of Competing Interest

The authors have no conflicts of interest to declare. The authors also state that the work described has not been published previously nor is under consideration for publication elsewhere.

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Author contributions

Robert Heimer, conceived the study design, assigned with data collection, matching, and analysis, drafted and circulated versions of the manuscript, and prepared the final for submission.

Anne C. Black conducted some of the matching of opioid fatalities to treatment data behind the firewall of the CT Department of Mental Health and Addiction Services, conducted the final statistical analysis, assisted with editing the manuscript, and approved the final draft.

Hsiuju Lin provided guidance on categorizing non-medication treatment exposures as reported to CT Department of Mental Health and Addiction Services, conducted most of the matching of opioid fatalities to treatment data behind the firewall of the CT Department of Mental Health and Addiction Services, assisted with editing the manuscript, and approved the final draft.

Lauretta E. Grau curated the opioid overdose poisoning data at the Office of the Chief Medical Examiner, assisted with matching of decedents to treatment exposures, assisted with editing the manuscript, and approved the final draft.

David A. Fiellin led the research team that has conducted a series of studies collecting and matching data from multiple state agencies to better understand the scope of and response to the opioid crisis in Connecticut, provided guidance on estimating the number of individuals exposed to buprenorphine, assisted with editing the manuscript, and approved the final draft.

Benjamin A. Howell assisted with matching datasets, reviewed analysis of match results, assisted with editing the manuscript, and approved the final draft.

Kathryn Hawk assisted in developing the design of the study, reviewed analysis of match results, assisted with editing the manuscript, and approved the final draft.

Gail D'Onofrio assisted in developing the design of the study, reviewed analysis of match results and epidemiological analysis, assisted with editing the manuscript, and approved the final draft.

William C. Becker produced a preliminary analysis leading to the elaboration of the study design, assisted in further developing the design, reviewed analysis of match results and epidemiological analysis, assisted with editing the manuscript, and approved the final draft.

All authors have approved the final article as submitted to Drug and Alcohol Dependence.

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