doi:10.1111/add.14964

Association between mortality rates and medication and residential treatment after in-patient medically managed opioid withdrawal: a cohort analysis

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ABSTRACT

Background and aim Medically managed opioid withdrawal (detox) can increase the risk of subsequent opioid overdose. We assessed the association between mortality following detox and receipt of medications for opioid use disorder (MOUD) and residential treatment after detox. **Design** Cohort study generated from individually linked public health data sets. **Setting** Massachusetts, USA. **Participants** A total of 30 681 opioid detox patients with 61 819 detox episodes between 2012 and 2014. **Measurements** Treatment categories included no post-detox treatment, MOUD, residential treatment or both MOUD and residential treatment identified at monthly intervals. We classified treatment exposures in two ways: (a) 'on-treatment' included any month where a treatment was received and (b) 'with-discontinuation' individuals were considered exposed through the month following treatment discontinuation. We conducted multivariable Cox proportional hazards analyses and extended Kaplan–Meier estimator cumulative incidence for all-cause and opioid-related mortality for the treatment categories as monthly time-varying exposure variables. **Findings** Twelve months after detox, 41% received MOUD for a median of 3 months, 35% received residential treatment for a median of 2 months and 13% received both for a median of 5 months. In on-treatment analyses for all-cause mortality compared with no treatment, adjusted hazard ratios (AHR) were 0.34 [95% confidence interval (CI) = 0.27–0.43] for MOUD, 0.63 (95% CI = 0.47–0.84) for residential treatment and 0.11 (95% CI = 0.03–0.43) for both. In with-discontinuation analyses for all-cause mortality, compared with no treatment, AHRs were 0.52 (95% CI = 0.42–0.63) for MOUD, 0.76 (95% CI = 0.59–0.96) for residential treatment and 0.21 (95% CI = 0.08–0.55) for both. Results were similar for opioid-related overdose mortality. **Conclusions** Among people who have undergone medically managed opioid withdrawal, receipt of medications for opioid use disorder, residential treatment or the combination of medications for opioid use disorder and residential treatment were associated with substantially reduced mortality compared with no treatment.

Keywords Detox, medically managed withdrawal, medication for opioid use disorders, mortality, residential treatment, overdose.

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Submitted 6 July 2019; initial review completed 16 September 2019; final version accepted 6 January 2020

INTRODUCTION

In the United States, there were 47 600 opioid-involved overdose deaths in 2017, a 12% increase from 2016 [1]. The link between underlying opioid use disorder (OUD) and opioid overdose death is strong [2–4]. Individuals with OUD often seek treatment through in-patient medically managed withdrawal programs, also known as 'detox' programs. Detox programs also treat individuals with alcohol use disorder in a similar fashion, but using medications for alcohol withdrawal symptoms. Individuals with OUD entering detox are offered either an opioid agonist, such as methadone or buprenorphine, or a combination of non-opioid alternatives, such as clonidine, anti-cholinergics, non-steroidal anti-inflammatory medications and benzodiazepines to treat the symptoms of withdrawal.

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These programs typically conform to the characteristics of Level 3.7 and higher of the American Society of Addiction Medicine's (ASAM) criteria [5]. Medications are tapered over 5–10 days as withdrawal symptoms subside, resulting in a reduction in physical dependence. Concomitantly there is a reduction in opioid tolerance. Optimally, detox is followed by further treatment with additional in-patient treatment, psychotherapy and/or medications for opioid use disorders (MOUD). However, linkage to further treatment often does not occur, even though most individuals are interested [6–10].

Because detox without further treatment only addresses physical dependence in the short term, but does not address the underlying chronic disease, relapse to opioid use is common [11–13], and because tolerance is reduced by detox, at the time of relapse the risk for overdose and death is high [4,14–18]. In Massachusetts in 2014, the age- and gender-standardized mortality ratio for opioid detox patients was extremely high at 66, and the population-attributable fraction for detox patients and opioid overdose death was 0.19 [19]. MOUD, including methadone, buprenorphine and naltrexone, are Food and Drug Administration (FDA)-approved and demonstrated to reduce opioid use, increase engagement in other treatment and, for methadone and buprenorphine, are associated with reduced opioid overdose and all-cause mortality risk [20–25]. Thus, the traditional detox episode presents an irony to patients and providers—while the intention is to engage individuals into treatment, only 13–36% of detox patients are linked to further treatment, resulting in high risk for relapse and overdose [7,26,27]. Further in-patient treatment, which typically includes less medically intensive clinical stabilization and transitional support programs and long-term residential programs that facilitate the progressive re-engagement in work and community life (halfway houses), may provide the opportunity for patients to engage in cognitive behavioral relapse prevention therapy, stabilize in recovery and address socio-economic challenges. A 2008 study of Medicaid billing data from 10 states showed that, among patients with a substance use disorder (SUD) who were discharged from either in-patient hospitalization or detox treatment, post-discharge MOUD and in-patient treatment were both associated with reduced hospital or detox re-admission for SUD or mental health condition [26]. An Italian study showed reduced overdose rates among patients in therapeutic communities, a type of residential care, that was limited to the time in treatment [16].

In order to understand more clearly the causes and potential solutions to rising deaths among people using opioids, we used a linked state-wide population-level data set from Massachusetts to: (1) describe medication and in-patient treatment for OUD after in-patient medically managed opioid withdrawal (detox) and (2) determine the association between receiving these treatments for OUD after detox and opioid-related and all-cause and opioid mortality. We hypothesized that MOUD and further in-patient treatment after opioid detoxification-treatment would be associated with reduced risk of opioid-related and all-cause mortality.

METHODS

Study design and data source

We conducted a retrospective cohort study using the Massachusetts Public Health Data Warehouse (PHD). This data warehouse was established initially as part of a Massachusetts (MA) legislative mandate and is overseen by the Massachusetts Department of Public Health. PHD includes data between 2011 and 2015 on residents aged 11 years or older with health insurance as reported in the MA All-Payer Claims Database (APCD), representing more than 98% of MA residents. Data from APCD were linked at the individual level with records from other data sets using a multi-stage deterministic linkage technique, as described elsewhere [28]. This work was mandated by Massachusetts law and conducted by a public health authority where no institutional review board (IRB) review was required. The Boston University Medical Campus IRB also determined that this study was not human subjects research. The primary research question and analysis plan were not pre-registered on a publicly available platform, and thus the results should be considered exploratory.

Cohort selection

We included individuals in the Bureau of Substance Addiction Services (BSAS) data set with an opioid-related in-patient medically managed withdrawal treatment (detox) episode between January 2012 and December 2014, allowing 12 months observation prior to and following the first recorded detox episode. BSAS is the licensing and regulating agency for addiction treatment services in Massachusetts and contracts with programs to treat the uninsured and to cover services not offered by other payers including Medicaid (i.e. long-term residential). BSAS-contracted in-patient medically managed withdrawal programs, clinical stabilization, transitional support and long-term residential programs are required to report patient-level data to BSAS for each treatment episode. These data include an indicator variable of the primary substance which we used to determine whether the detox episodes were opioid-related. In order to ensure that these episodes were distinct, we excluded recurrent detox episodes within 30 days. We restricted the cohort to people aged 18 years and older because medically managed withdrawal and MOUD treatment access is substantially different in adolescents compared with adults [29]. We

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excluded individuals with evidence of cancer at any time in the 5-year study period of the PHD due to high competing mortality risk. Cancer was identified using ICD-9 diagnosis codes in APCD (Supporting information) or entry in the state-based cancer registry. We also excluded individuals with unknown date of birth or sex.

Recurrent detox and censoring

Recurrent detox episodes on the same individual were common. Therefore, we included up to the first five qualifying detox episodes for each individual, which accounted for 93% of the detox episodes within the window. For each detox episode, follow-up started at month of detox and ended at the earliest date of death, recurrent detox episode or 12 months after detox. Those who were censored at a recurrent detox episode were re-entered into the cohort as a new episode.

Exposure definition

The exposure of interest in our main analysis was a categorical variable with four mutually exclusive and time-varying event categories: (i) no treatment, (ii) MOUD, (iii) residential treatment and (iv) concomitant MOUD and residential treatment in each month after detox. Because methadone and residential treatment episodes were only available at monthly intervals, we identified MOUD and residential treatment episodes in monthly intervals, meaning if treatment was received for 1 day or more in a month, the month was a treatment month. MOUD included treatment with methadone, buprenorphine or naltrexone in a month. We identified exposure to methadone maintenance treatment in two ways: a medical claim from APCD for methadone administration via Healthcare Common Procedure Coding System code H0020 or a record of treatment with methadone from BSAS data. Treatment with buprenorphine was identified via dispensing in the prescription monitoring program (PMP) for buprenorphine or buprenorphine/naloxone. Naltrexone was identified via a pharmacy claim for injectable or oral naltrexone in the APCD. Residential treatment included post-detoxification short-term residential and long-term residential recorded in the BSAS treatment data. To describe the cohort at the individual level, we classified individuals into four mutually exclusive categories of OUD treatment in the 12 months following the index overdose: never received any treatment, ≥ 1 months of MOUD and no in-patient treatment, ≥ 1 months of in-patient treatment and no MOUD and ≥ 1 months each of MOUD and in-patient treatment.

Outcome

The outcomes of interest that were examined in separate analyses were all-cause and opioid-related mortality, as identified in death files. Classification of opioid-related death was based on medical examiner determination or standardized assessment by Massachusetts Department of Public Health (Supporting information).

Confounders

We recorded the following potentially confounding variables at or in the 12 months before the index detox episode: sex, age (18–29, 30–44 and ≥ 45 years) and diagnosis of anxiety or depression defined using ICD-9/ICD-10 diagnosis codes from APCD (Supporting information), race/ethnicity (Hispanic, white non-Hispanic, black non-Hispanic and other non-Hispanic) from the BSAS treatment data set, monthly dispensing of opioids and benzodiazepines from the PMP, non-fatal overdoes episode (an ambulance encounter for overdose in the Massachusetts Ambulance Trip Record Information System or hospital encounter in case mix) and release from incarceration in either the Department of Correction or House of Correction data sets. For homelessness, we used a previously defined dichotomous variable in the PHD (Supporting information) [9].

Statistical analysis

To describe individual-level cohorts, we compared characteristics recorded at the index detox episode using χ^2 tests. We also calculated the proportion of individuals receiving MOUD and in-patient treatment before and after the index in-patient detox episode, as well as the median time in months spent on each of these treatments after detox episodes.

Extended Kaplan–Meier cumulative incidence was estimated using follow-up after each detox episode where the exposure variable was the four mutually exclusive and time-varying OUD categories [30]. To account for follow-up intervals defined by multiple detox episodes on the same individuals, we fitted a Cox proportional hazards discrete time model in which the time zero was reset to zero at each new detox episode and stratified by prior number of detox episodes [31,32].

To ensure that there was no substantial interdependence across successive episodes, we ran separate models for each detox episode and found no substantive changes or trends in the parameter estimates across different episodes. The model was adjusted for the confounders defined above, as well as MOUD or residential treatment within 12 months before the index detox episode. Receipt of prescription opioids and benzodiazepines in each month after discharge from detox were included as time-varying covariates.

We defined the time-varying exposure variable in two different ways (Supporting information, Fig. S1). In our

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primary approach we defined the 'on-treatment' exposure variable, in which we considered individuals exposed to OUD treatment only in months that OUD treatment was received. Several studies have demonstrated an increased risk of all-cause and opioid-related mortality during the 4-week period immediately following MOUD discontinuation [16,24,25]. Thus, as a sensitivity analysis, we also defined a 'with-discontinuation' classification to attribute any impact of discontinuation to the last OUD treatment. For the 'with-discontinuation' classification, we attributed the mortality outcomes that occurred during the first month with 'no treatment' to the treatment category received in the prior month.

We calculated the E-value to identify how strong an unmeasured confounder would need to be associated with the treatment and outcome to explain observed associations between OUD treatment and mortality [33]. The PHD requires cell suppression of any counts between 1 and 10 to reduce the risk that data will be attributable to particular individuals. We used SAS Studio version 3.6 (SAS Institute, Cary, NC, USA) for analyses.

RESULTS

Baseline characteristics

The database included 79 043 detox episodes among 31 861 individuals. Among these, 1940 individuals had six or more detox episodes which were excluded, and 57 deaths occurred after these detox episodes which were not included. After exclusions (Fig. 1), the analytical cohort consisted of 61 819 detox episodes among 30 681 adult Massachusetts residents who were treated in in-patient detox programs for opioid withdrawal between 2012 and 2014. Two-thirds (20 944) were male, 86% (26 311) were aged less than 45 years, 81% (24 710) were white and 23% (6900) were homeless (Table 1).

Receipt of OUD treatment before and after in-patient detox episodes

For most of the year prior to a detox episode, 16% of individuals were receiving MOUD. At the month before the detox episode, MOUD dropped to 14%. After detox, the proportion of patients receiving MOUD per month climbed to from 15% in the month of discharge to 25% in month 12. Residential treatment minimally increased from 5.3% during the 12 months prior to the detox episode until the month of the detox episode, when it surged to 17% and then decreased monthly for the next 12 months to 3.3%. Treatment with concomitant MOUD and residential treatment was particularly uncommon before the detox episode at 1%, then increased to almost 3.0% around the time of the detox episode and regressed to 0.8% (Fig. 2).

Regarding specific MOUD, methadone treatment frequency decreased before the detox episode from 7.6 to 5.4% and subsequently climbed to 14%. Buprenorphine treatment climbed steadily from 8.4 to 11% throughout the 12 months before and after detox, with a dip the month before and month of detox. Naltrexone treatment was 0.54% and flat before detox, with a bump to 2.4% at the time of detox, and then decreased during the subsequent year. Treatment with opioid pain medication dropped from 8.1 to 5.3%, whereas benzodiazepine remained at 6.1% before and 6.2% after the detox episode (Fig. 3).

After the detox episode, 41% individuals received any MOUD within 12 months, with buprenorphine being the most common medication (21%). Methadone was the medication with the most median time on-treatment at 5 months, and thus the highest cumulative proportion were receiving methadone at 12 months (Fig. 3). The median time on naltrexone was 1 month. The median time in further in-patient treatment was 2 months for 35% of the cohort. Thirteen per cent of the cohort received both

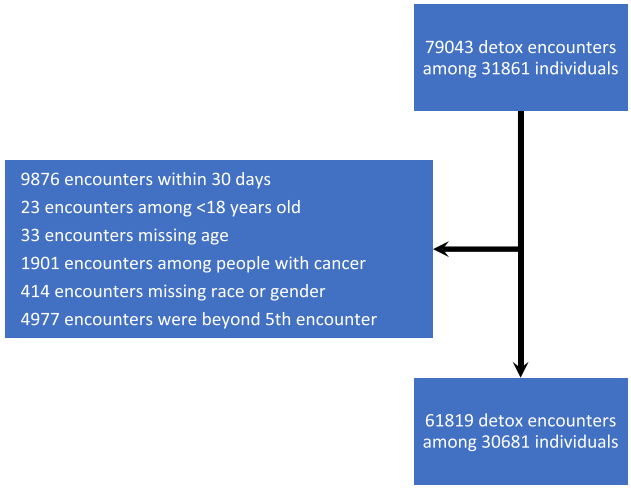

Figure 1 Cohort exclusions for detox episodes, Massachusetts, 2012–14. [Colour figure can be viewed at wileyonlinelibrary.com]

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Table 1 Patient characteristics prior to index detox episode by receipt of subsequent in-patient treatment or medication for opioid use disorder (MOUD) following initial detox program—Massachusetts 2012–14.

		MOUD and in-patient treatment in the 12 months following index detox episode[a]			
Baseline characteristics[b]	*Full cohort (n = 30 681)*	*No treatment (n = 9386)*	*MOUD (n = 9990)*	*Further in-patient (n = 5829)*	*Both in-patient and MOUD*[d] *(n = 5476)*
Male	68% (20 944)	74% (6966)	65% (6511)	71% (4123)	61% (3344)
Age (years)					
18–29	46% (14 084)	43% (4027)	43% (4335)	49% (2841)	53% (2881)
30–44	40% (12 227)	39% (3661)	43% (4252)	38% (2222)	38% (2092)
≥ 45	14% (4370)	18% (1698)	14% (1403)	13% (766)	9.2% (503)
Race/ethnicity					
White, non-Hispanic	81% (24 710)	77% (7190)	82% (8205)	90% (4669)	85% (4646)
Black, non-Hispanic	4.1% (1249)	5.7% (536)	2.7% (269)	5.4% (312)	2.4% (132)
Asian/Pacific Islander non-Hispanic	0.39% (121)	0.54% (51)	0.30% (30)	0.41% (24)	0.29% (16)
Hispanic	12% (3781)	15% (1399)	13% (1261)	11% (636)	8.9% (485)
American Indian or Other	2.7% (820)	2.2% (210)	2.3% (225)	3.2% (188)	3.6% (197)
Homeless	23% (6900)	18% (1684)	17% (1716)	28% (1631)	34% (1869)
Anxiety diagnosis before detox	9.0% (2748)	7.4% (692)	9.7% (973)	7.8% (456)	12% (627)
Depression diagnosis before detox	11% (3370)	9.2% (863)	12% (1210)	9.9% (576)	13% (721)
Incarceration before detox	6.0% (1825)	5.2% (484)	4.7% (471)	7.5% (434)	8.0% (436)
Non-fatal overdose before detox	5.3% (1621)	4.5% (420)	4.4% (441)	6.4% (370)	7.1% (390)
Treatment before detox					
Methadone maintenance treatment	13% (3954)	6.6% (616)	19% (1868)	7.8% (457)	19% (1013)
Buprenorphine	21% (6383)	9.9% (933)	31% (3050)	12% (689)	31% (1711)
Naltrexone	3.5% (1064)	2.3% (212)	3.1% (314)	4.2% (243)	5.4% (295)
Detox treatment	22% (6821)	17% (1573)	18% (1804)	29% (1709)	32% (1735)
Short-term residential[c]	9.2% (2821)	4.5% (420)	4.7% (465)	17% (984)	17% (952)
Long-term residential	8.2% (2510)	4.4% (409)	4.2% (422)	14% (841)	15% (838)
Opioid prescription	36% (11030)	35% (3326)	40% (3961)	31% (1829)	35% (1914)
Benzodiazepine prescription	19% (5857)	16% (1472)	23% (2282)	15% (876)	22% (1227)

[a]$P < 0.001$ for χ^2 comparison of each baseline characteristic category [except receipt of opioid prescription ($P = 0.003$)] by five post-overdose MOUD receipt categories. [b]Received respective diagnosis, medication or service in one or more months in the 12 months preceding the index in-patient detox episode. [c]Clinical Stabilization/Step Down Services (CSS) or Transitional Support Services (TSS). [d]MOUD and in-patient at some point 12 months after in-patient detox, not necessarily at the same time.

MOUD and further in-patient treatment for a median of 5 months (Table 2).

Mortality, cumulative incidence and adjusted hazards on treatment analyses

For those receiving no further treatment, the crude mortality rates were 2.04 [95% confidence interval (CI) = 1.9–2.2] all-cause deaths per 100 person-years and 1.42 (95% CI = 1.3–1.6) overdose deaths per 100 person-years in the on-treatment analyses. In extended Kaplan–Meier estimator for time-varying exposure to OUD treatment, the cumulative incidence for all-cause and opioid mortality at 12 months was lower for time receiving MOUD, further in-patient treatment or both than time receiving no treatment (see Figs 4a, 5a and Table 3. (a)). In the multivariable Cox proportional hazards models for the on-treatment analyses, all-cause mortality was reduced with MOUD [adjusted hazard ratio (AHR) = 0.34, 95% CI = 0.27–0.43], further in-patient (AHR = 0.63, 95% CI = 0.47–0.84) and combined MOUD and further in-patient (AHR = 0.11, 95% CI = 0.03–0.43). Opioid mortality was similar with

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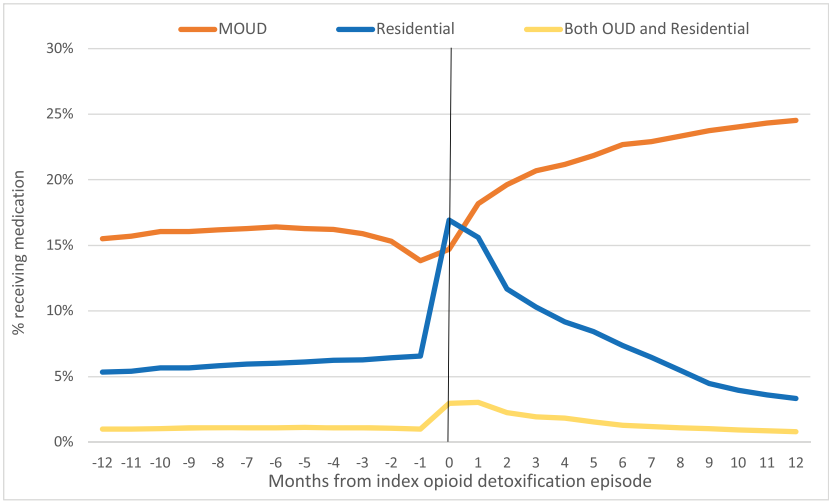

Figure 2 Receipt of treatment for opioid use disorder (OUD) before and after the detox episode—Massachusetts 2012–14 (*n* = 61 819). [Colour figure can be viewed at wileyonlinelibrary.com]

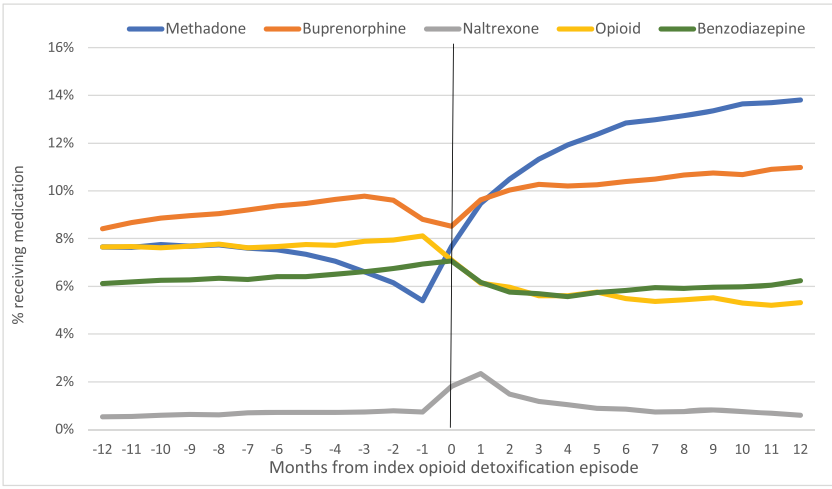

Figure 3 Receipt of medication for opioid use disorder (OUD) before and after detox episode—Massachusetts 2012–14 (*n* = 61 819). [Colour figure can be viewed at wileyonlinelibrary.com]

Table 2 Proportion of detox episodes (*n* = 61 819) followed by medication and/or further in-patient treatment after in-patient detox episode and median months on treatment (not mutually exclusive)—Massachusetts, 2012–14.

	Proportion receiving treatment within at least 1 month	*Median months on treatment (25th and 75th percentiles)*
Both MOUD and residential[a]	13%	5 (3, 9)
Any MOUD	41%	3 (1, 8)
Methadone	18%	5 (2, 10)
Buprenorphine	21%	3 (1, 6)
Naltrexone	7.2%	1 (1, 2)
Any further residential	35%	2 (1, 4)

[a]Medication for opioid use disorder (MOUD), and in-patient at some point 12 months after in-patient detox, not necessarily at the same time.

MOUD (AHR = 0.31, 95% CI = 0.23–0.41), further in-patient (AHR = 0.69, 95% CI = 0.50–0.94) and combined MOUD and further in-patient (AHR = 0.14, 95% CI = 0.03–0.55). For all-cause mortality, E-value estimates (confidence limit) were 5.91 (4.31), 2.26 (1.32), and 13.77 (3.04) for MOUD, further in-patient treatment and both MOUD and in-patient treatment, respectively, with similar results for opioid mortality.

Mortality, cumulative incidence and adjusted hazards with discontinuation analyses

For those receiving no further treatment, the crude mortality rates were 1.94 (95% CI = 1.8–2.1) all-cause deaths per 100 person-years and 1.35 (95% CI = 1.2–1.5) overdose deaths per 100 person-years in with-discontinuation

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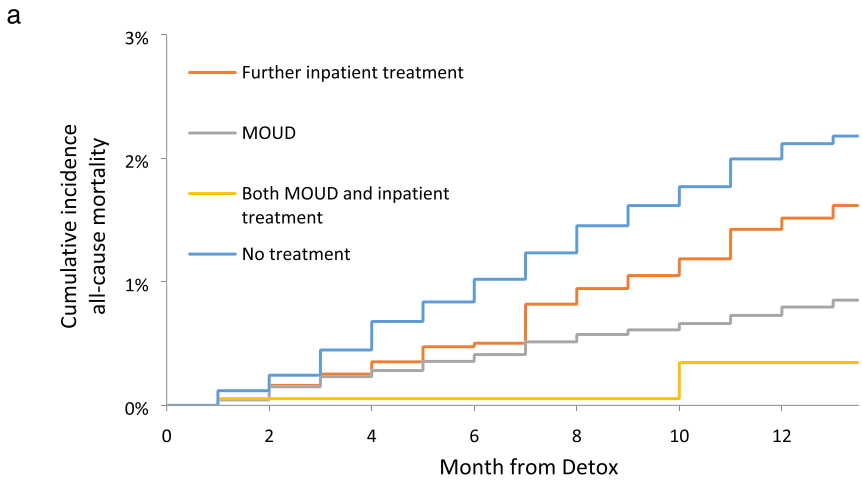
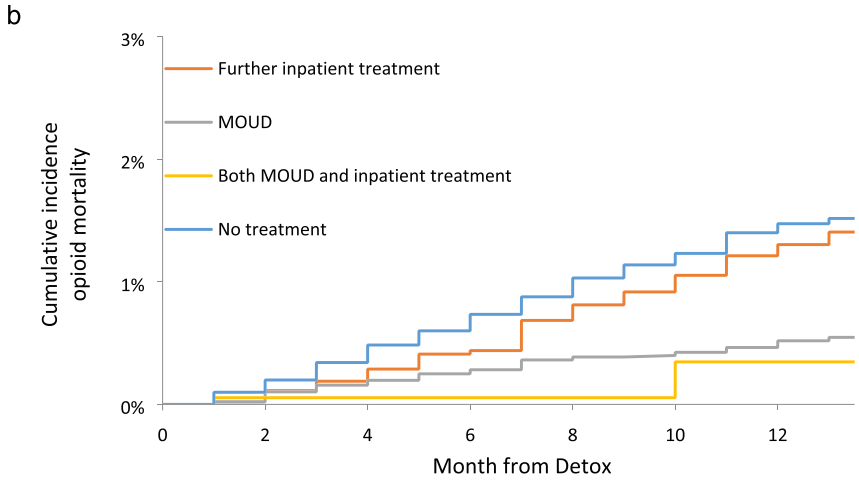


Episodes of further inpatient treatment	10465	6539	4083	2832	1881	1241	964
Episodes of MOUD	9100	10976	9418	8715	8028	7537	7091
Episodes of both MOUD and inpatient treatment	1836	1254	810	494	379	290	232
Number surviving No treatment	40418	37131	30155	26389	24112	22290	20620



Episodes of further inpatient treatment	10465	6539	4083	2832	1881	1241	964
Episodes of MOUD	9100	10976	9418	8715	8028	7537	7091
Episodes of both MOUD and inpatient treatment	1836	1254	810	494	379	290	232
Episodes of no treatment	40418	37131	30155	26389	24112	22290	20620

Figure 4 (a) Cumulative incidence of all-cause mortality, on treatment analyses—Massachusetts 2012–14. (b) Cumulative incidence of opioid-related mortality, on treatment analyses—Massachusetts 2012–14, medication for opioid use disorder (MOUD). [Colour figure can be viewed at wileyonlinelibrary.com]

analyses. In extended Kaplan–Meier estimator for time-varying exposure to OUD treatment, cumulative incidence for all-cause and opioid mortality at 12 months was attenuated for receiving MOUD, further in-patient treatment or both than time receiving no treatment (see Figs 4b, 5b and Table 3. (b)). In multivariable Cox proportional hazards models for the with-discontinuation analyses, associations were similar. There was a reduction in all-cause mortality with MOUD (AHR = 0.52, 95% CI = 0.42–0.63) for MOUD, further in-patient (AHR = 0.75, 95% CI = 0.59–0.96) and combined MOUD and further in-patient (AHR = 0.21, 95% CI = 0.08–0.55). Opioid mortality was similar for MOUD

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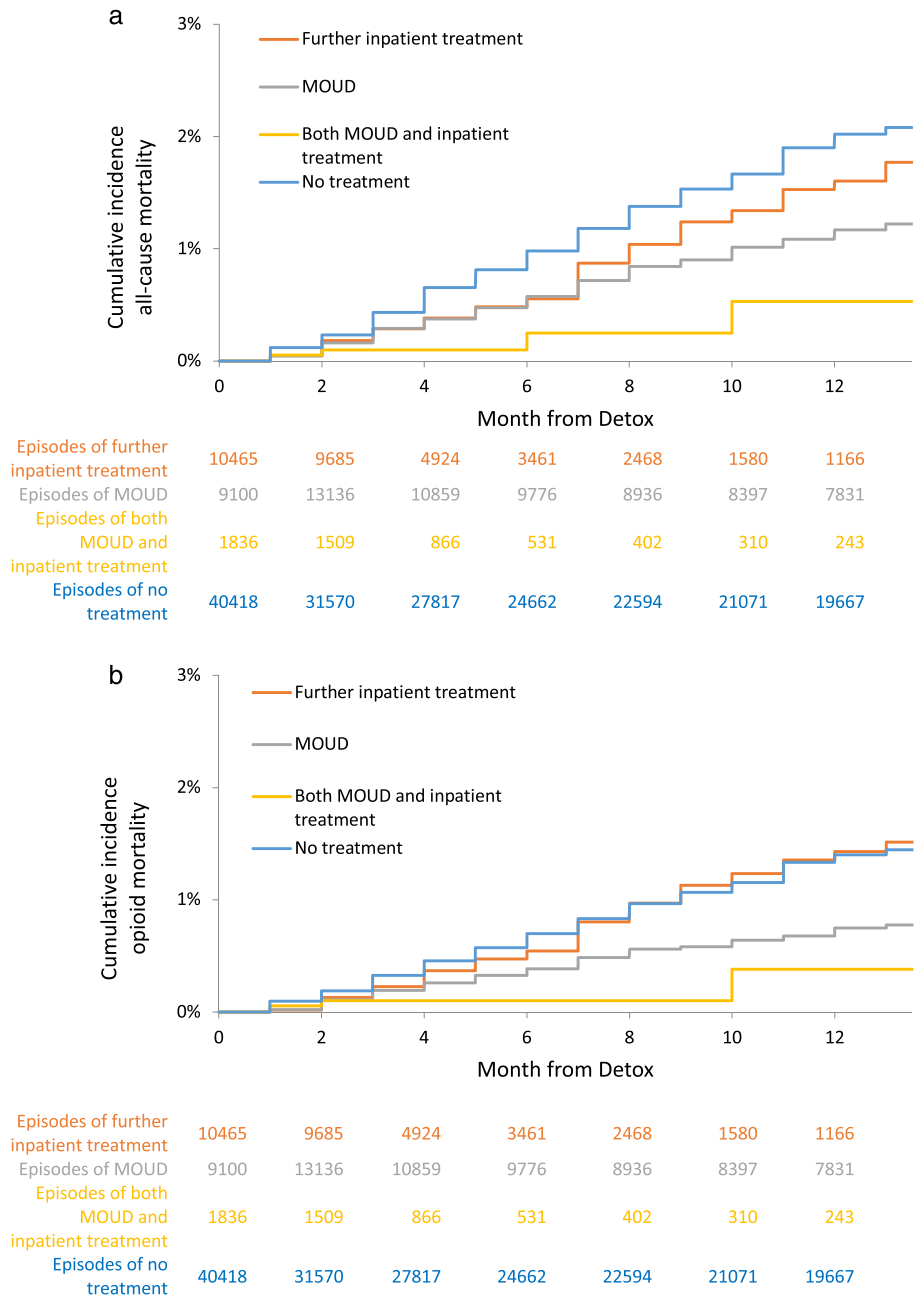

Figure 5 (a) Cumulative incidence of all-cause mortality, with discontinuation analysis—Massachusetts 2012–14. (b) Cumulative incidence of opioid-related mortality, with discontinuation analysis—Massachusetts 2012–14, medication for opioid use disorder (MOUD). [Colour figure can be viewed at wileyonlinelibrary.com]

(AHR = 0.46, 95% CI = 0.36–0.59) and combined MOUD and further in-patient (AHR = 0.20, 95% CI = 0.06–0.62). For all-cause mortality, E-value estimates (confidence limit) were 3.27 (2.78), 1.67 (1.43), and 9.47 (2.61) for MOUD, further in-patient treatment and both MOUD and in-patient treatment, respectively, with similar results for opioid mortality. For further in-patient and overdose mortality, the hazard ratio was not statistically significant (AHR = 0.84, 95% CI = 0.64–1.10) (full models in Supporting information, Table S3).

DISCUSSION

Among a population cohort of adults aged mainly under 45 years and treated for opioid withdrawal in in-patient detox programs, all-cause and opioid mortality were very high in the next 12 months, particularly among those who received no further treatment. During the subsequent 12 months, 41% of detox patients received an FDA-approved medication for OUD and 35% received any further in-patient treatment. As has been shown in other

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Table 3. (a) Crude incidence rates and multivariable Cox proportional hazards analyses for all-cause and opioid-related death by receipt of medications for opioid use disorder (MOUD) and further in-patient addiction treatment, on-treatment—Massachusetts, 2012–14.

	OUD treatment in 12 months following in-patient detox episode[a]			
Exposure classification—on-treatment[a]	*No treatment*	*MOUD*	*Further in-patient treatment*	*Both MOUD and in-patient treatment*
Person-years exposure	30 893.5	9550.3	4254.3	815.6
All-cause mortality				
Number of deaths	629	77	54	≤ 10‖
Crude incidence rate per 100 person-years (95% CI)	2.04 (1.9, 2.2)	0.81 (0.63, 0.99)	1.27 (0.93, 1.6)	≤ 1.23‖
Adjusted hazard ratio[b] (95% CI)	1.0 (Ref)	**0.34 (0.27, 0.43)**	**0.63 (0.47, 0.84)**	**0.11 (0.03, 0.43)**
E-value, estimate (confidence limit)[c]	NA	5.33 (4.08)	2.66 (1.67)	17.67 (4.08)
Opioid-related mortality				
Number of deaths	440	50	45	≤ 10‖
Crude mortality rate (95% CI)	1.42 (1.3, 1.6)	0.52 (0.38, 0.67)	1.06 (0.75, 1.4)	≤ 1.23‖
Adjusted hazard ratio[b] (95% CI)	1.0 (Ref)	**0.31 (0.23, 0.41)**	**0.69 (0.50, 0.94)**	**0.14 (0.03, 0.55)**
E-value, estimate (confidence limit)[c]	NA	5.91 (4.31)	2.26 (1.32)	13.77 (3.04)

[a]MOUD and in-patient treatment variables are binary time-varying monthly indicators of receipt of treatment. Exposure is limited to months treatment is received. [b]Results of multivariable Cox proportional hazards models adjusting for: age, sex, race/ethnicity, homelessness, anxiety diagnoses, depression diagnoses, opioid and benzodiazepine prescriptions, non-fatal overdose episode, release from incarceration, MOUD or residential treatment within 12 months prior to index in-patient detox encounter, and time-varying receipt of opioid prescription, benzodiazepine prescription. (full model results included in Supporting information, Appendix Table S3). All values are adjusted hazard ratios with 95% confidence intervals (CI). NA = not available. [c]The E-value represents the minimum strength of association between an unmeasured confounder with both the treatment and outcome to explain observed associations between MOUD and mortality. E-values presented for the adjusted hazard ratio (AHR) and 95% confidence limit closest to the null. If the CI includes the null, the E-value is 1. ‖Data suppressed due to small cell size: < 10 indicates a count of 1–9 for that cell. Other cells suppressed to prevent calculation of small cells. [a]Index in-patient detox encounter defined as an individual's first opioid-related in-patient detox encounter between January 2012 and December 2014.

cohorts, MOUD was strongly associated with 49% or more reduction in all-cause and opioid mortality rates [24,25]. Individuals who received further residential treatment had reduced mortality while in that treatment, and were treated for a median of 2 months. Few patients received combined treatment with MOUD and in-patient treatment but, when they did, their risk of all-cause and opioid mortality was reduced by 80–90% compared to no treatment.

While our study is unprecedented in its use of a state population cohort that links MOUD, in-patient addiction treatment and mortality, our findings of high all-cause mortality rates without further treatment of approximately 2 per 100 person-years are consistent with previous research on detoxification and mortality. A study among 137 detoxification patients in England found that 2.2% (three of 137) died of overdose within 4 months after release [14]. A study of 10 454 Italian people who inject drugs recruited in treatment found one overdose death per 100 person-years overall, but 2.3 overdose deaths per 100 person-years among those in the 30 days after leaving treatment [16]. A study that followed 32 322 people in California with opioid dependence initiating either detoxification or maintenance treatment found 0.80 drug-related deaths per 100 person-years among those who left treatment compared to 0.23 drug-related deaths per 100 person-years among those during maintenance treatment [4].

People seeking care for opioid withdrawal through in-patient detoxification programs are a high-risk group because of the severity of their opioid use disorder, high risk of opioid relapse and probable reduced opioid tolerance if MOUD is not initiated or continued. While some transition from detox to further treatment with MOUD or in-patient care, most do not [6,7,26,27]. In a Massachusetts study that analyzed addiction treatment episodes between 1996 and 2002, multiple detox admissions without further treatment was the most common utilization pattern among people who injected drugs [6]. Methadone treatment or out-patient counseling after detox was much less common. Our findings of improved survival among high-risk individuals who receive MOUD echo similar findings from our study of Massachusetts residents at another health-care encounter, those who survive an opioid overdose [25]. In-patient detox episodes are high-yield health system encounters during which much is to be gained by initiating and engaging patients in evidence-based care. These system encounters are opportunities to mobilize our best treatments and harm reduction efforts for the highest-risk individuals. At the patient–provider level, detox programs and their providers have the responsibility

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Table 3. (b) Crude incidence rates and multivariable Cox proportional hazards analyses for all-cause and opioid-related death by receipt of medications for opioid use disorder (MOUD) and further in-patient addiction treatment, with discontinuation—Massachusetts, 2012–14.

	OUD treatment in 12 months following in-patient detox episode[d]			
Exposure classification—with-discontinuation[a]	*No treatment*	*MOUD*	*Further in-patient treatment*	*Both MOUD and in-patient treatment*
Person-years exposure	28 527.7	10 799.2	5300.5	886.3
All-cause mortality				
Number of deaths	553	126	79	≤ 10
Crude cumulative incidence per 100 person-years (95% CI)	1.94 (1.80, 2.10)	1.17 (0.96, 1.37)	1.49 (1.16, 1.82)	≤ 1.13
Adjusted hazard ratio[b] (95% CI)	1.0 (Ref)	**0.52 (0.42, 0.63)**	**0.75 (0.59, 0.96)**	**0.21 (0.08, 0.55)**
E-value, estimate (confidence limit)[c]	NA	3.26 (2.55)	2.00 (1.25)	8.99 (3.04)
Opioid-related mortality				
Number of deaths	386	81	67	≤ 10
Crude mortality rate (95% CI)	1.35 (1.22, 1.49)	0.75 (0.59,0.91)	1.26 (0.96,1.57)	≤ 1.23
Adjusted hazard ratio[b] (95% CI)	1.0 (Ref)	**0.46 (0.36, 0.59)**	0.84 (0.64, 1.10)	**0.20 (0.06, 0.62)**
E-value, estimate (confidence limit)[c]	NA	3.27 (2.78)	1.67 (1.43)	9.47 (2.61)

[a]MOUD and in-patient treatment variables are binary time-varying monthly indicators of receipt of medication. Exposure extends through the month after treatment discontinuation. [b]Results of multivariable cox proportional hazards models adjusting for: age, sex, race/ethnicity, baseline anxiety diagnosis, depression diagnosis, opioid and benzodiazepine prescriptions in 12 months prior to index in-patient detox encounter, and time-varying receipt of opioid prescription, benzodiazepine prescription (full model results included in Supporting information, Appendix Table S2a). All values are adjusted hazard ratios (AHR) with 95% confidence intervals (CI). NA = not available. [c]The E-value represents the minimum strength of association between an unmeasured confounder with both the treatment and outcome to explain observed associations between MOUD and mortality. E-values presented for the AHR and 95% confidence limit closest to the null. If the CI includes the null, the E-values is 1. Data suppressed due to small cell size: < 10 indicates a count of 1–9 for that cell. Other cells suppressed to prevent calculation of small cells. [d]Index in-patient detox encounter defined as an individual's first opioid-related in-patient detox encounter between January 2012 and December 2014.

to educate their patients and solicit informed consent about the elevated mortality risk when patients do not access further treatment. Overdose education and naloxone rescue kit distribution should be included in every medically managed withdrawal care episode for individuals with OUD. A promising reform would be to convert opioid 'detox' programs to programs focused on the initiation and retention on MOUD where, rather than 'opting in' to further treatment[34], detox patients would have to 'opt out' of further treatment. Recent randomized controlled trials have demonstrated reduced opioid use among patients initiating buprenorphine or naltrexone during initial in-patient opioid use disorder treatments [22,23,35]. The survival benefits of MOUD are limited to the time retained on MOUD [16,24,25]. Thus, intervention development should focus both on how to initiate detox patients on MOUD and how to increase retention on MOUD.

In this cohort, the median duration of residential treatment was shorter than MOUD and associated with less reduction in mortality than MOUD, but when combined with MOUD the reduction in risk may be synergistically reduced. Therefore, for high-risk individuals for whom MOUD is not sufficient treatment, combining it with further residential treatment is warranted. Individuals who are neither interested in nor have access to MOUD probably benefit from further residential treatment while participating, but residential treatment is time-limited. Thus, overall overdose morality risk reduction from further residential treatment alone may be marginal; discontinuation analyses for opioid mortality did not achieve statistical significance.

Factors other than OUD treatment were included in the mortality models to reduce confounding (Supporting information, Table S3). As expected, younger age was associated with reduced hazard of all-cause mortality, but it was also associated with reduced hazard of overdose mortality. Previous treatment with methadone maintenance, baseline anxiety or depression diagnoses and prescriptions for opioids for pain and benzodiazepines either before or after the index detox episode were associated with either increased overdose mortality or both overdose and all-cause mortality. Previous non-fatal overdose and incarceration were both associated with increased mortality. Concomitant mental illness and exposure to prescription opioids and benzodiazepines are known risks for overdose and indicators of worse overall health, and thus higher all-cause mortality. However, pre-detox episode methadone maintenance may mark a special group of individuals who are either recently discharged from methadone maintenance treatment (MMT) or being treated with methadone but are not doing well.

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Detox patients who are homeless may be particularly likely to benefit from further in-patient treatment. Individuals who are homeless are at high risk of overdose mortality [36]. Homelessness is more common among residential treatment than out-patient treatment patients [37]. Detox patients who are homeless have a stronger preference for further in-patient care than non-homeless patients [9]. Among detox patients, persistent homelessness is a strong risk factor for subsequent mortality [38]. However, in our models homelessness was unexpectedly associated with lower all-cause and overdose mortality in the adjusted models. Our measure of homelessness was specific, with face validity, but it did not distinguish chronic from acute homelessness and we could not analyze it as a time-varying exposure variable. More study is warranted in a cohort with more detail about homelessness to understand the interplay between homelessness, MOUD, in-patient treatment and mortality among people with OUD.

Our analyses had strengths and limitations. We employed a first-of-its-kind data set that drew from the almost complete population of one state with universal healthcare coverage. The data set individually linked multiple state-wide databases allowing for the identification of the state population cohort with in-patient opioid detoxification-treatment, the tracking of exposures before and after treatment episodes and the determination of opioid overdose and all-cause mortality. A limitation in any observational study is the potential for confounding, and in particular confounding by indication where individuals who receive different treatment modalities have inherent differences in their risk for the outcome. We controlled for several known confounders, including demographic, medical, mental health and addiction treatment variables, but the potential for unmeasured confounding persists. Calculated E-values were 3 or greater for the MOUD treatment exposures and approximately 2 or greater for the residential treatment exposures, indicating that unmeasured confounders would need to be highly associated with the exposure and outcome to account for these findings. We also note the potential for misclassification bias with exposures and outcomes. Only treatment episodes reported by state-licensed and contracted treatment facilities were included. While these facilities probably include a majority of detox and residential treatment programs in Massachusetts, some programs might have not been included. Further work is needed to clarify how many programs or treatment episodes were not captured in our data. Missing episodes of detox would have resulted in fewer individuals being included in the study. Missing residential treatment would have resulted in some individuals being misclassified as not receiving residential treatment when they did, which would probably have resulted in biasing results towards the null hypothesis. Methadone treatment classification also relied on this BSAS data, but we bolstered the methadone data by crossing and merging it with APCD data. Buprenorphine from the PMP and naltrexone from the APCD were complete, because they represent prescription filling at the dispensing pharmacy. Because methadone, naltrexone and residential treatment exposure was only measurable at the month level, analyses were conducted using monthly rather than daily exposure. Finally, claims for naltrexone in this data set did not distinguish between oral and injectable naltrexone, so we were not able to analyze these formulations separately.

CONCLUSIONS

This study demonstrated that, among a state population cohort of individuals treated with in-patient opioid detox, the mortality rate was high. Treatment with MOUD or further in-patient care was accessed by fewer than half, rarely combined and typically not sustained. Those who were treated with MOUD or further residential treatment had better survival while receiving those treatments. Our best understanding of the evidence is that patients treated in in-patient detox should not be 'detoxed', but should be started on an MOUD that they are likely to continue and connected with further residential treatment. The combination of MOUD and residential may be particularly protective.

Declaration of interests

None.

Acknowledgements

This study was funded by grant no. 1UL1TR001430 from the National Center for Advancing Translational Sciences of the National Institutes of Health. M.R.L. was supported by award K23 DA042168 from the National Institute on Drug Abuse and a Boston University School of Medicine Department of Medicine Career Investment Award and by the Office of National Drug Control Policy's Combatting Opioid Overdose through Community-level Intervention grant program through a subcontract with University of Baltimore (G1799ONDCP06B). The authors acknowledge Ryan Bernstein for his data management work on earlier aspects of this study and Mary Tomanovich for formatting the manuscript. We acknowledge the Massachusetts Department of Public Health for creating the unique, cross-sector database used for this project and for providing technical support for the analysis.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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