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Medication for Opioid Use Disorder After Nonfatal Opioid Overdose and Association With Mortality

A Cohort Study

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Background: Opioid overdose survivors have an increased risk for death. Whether use of medications for opioid use disorder (MOUD) after overdose is associated with mortality is not known.

Objective: To identify MOUD use after opioid overdose and its association with all-cause and opioid-related mortality.

Design: Retrospective cohort study.

Setting: 7 individually linked data sets from Massachusetts government agencies.

Participants: 17 568 Massachusetts adults without cancer who survived an opioid overdose between 2012 and 2014.

Measurements: Three types of MOUD were examined: methadone maintenance treatment (MMT), buprenorphine, and naltrexone. Exposure to MOUD was identified at monthly intervals, and persons were considered exposed through the month after last receipt. A multivariable Cox proportional hazards model was used to examine MOUD as a monthly time-varying exposure variable to predict time to all-cause and opioid-related mortality.

Results: In the 12 months after a nonfatal overdose, 2040 persons (11%) enrolled in MMT for a median of 5 months (interquartile range, 2 to 9 months), 3022 persons (17%) received buprenorphine for a median of 4 months (interquartile range, 2 to 8 months), and 1099 persons (6%) received naltrexone for a median of 1 month (interquartile range, 1 to 2 months). Among the entire cohort, all-cause mortality was 4.7 deaths (95% CI, 4.4 to 5.0 deaths) per 100 person-years and opioid-related mortality was 2.1 deaths (CI, 1.9 to 2.4 deaths) per 100 person-years. Compared with no MOUD, MMT was associated with decreased all-cause mortality (adjusted hazard ratio [AHR], 0.47 [CI, 0.32 to 0.71]) and opioid-related mortality (AHR, 0.41 [CI, 0.24 to 0.70]). Buprenorphine was associated with decreased all-cause mortality (AHR, 0.63 [CI, 0.46 to 0.87]) and opioid-related mortality (AHR, 0.62 [CI, 0.41 to 0.92]). No associations between naltrexone and all-cause mortality (AHR, 1.44 [CI, 0.84 to 2.46]) or opioid-related mortality (AHR, 1.42 [CI, 0.73 to 2.79]) were identified.

Limitation: Few events among naltrexone recipients preclude confident conclusions.

Conclusion: A minority of opioid overdose survivors received MOUD. Buprenorphine and MMT were associated with reduced all-cause and opioid-related mortality.

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The United States is in the midst of a crisis of opioid-related harms (1). Some efforts to address this crisis focus on expanding access to effective treatment of opioid use disorders (OUDs) (2). Prior nonfatal opioid overdose is a known risk factor for subsequent nonfatal and fatal overdoses (3–7), and engaging persons in treatment who survive an overdose may be effective in limiting subsequent fatalities. However, data on the association between treatment of OUD and mortality after a nonfatal overdose are limited to a single retrospective cohort study that analyzed enrollment in methadone maintenance treatment (MMT) at a single time point and found no association (3).

The 3 medications for OUD (MOUD) approved by the U.S. Food and Drug Administration are methadone, buprenorphine, and naltrexone. Randomized controlled trials of these medications have shown consistent benefits across many outcomes, including increased treatment retention and suppression of illicit opioid use (8–10). A recent systematic review and meta-analysis of 19 observational cohort studies identified substantial reductions in all-cause and overdose mortality for methadone and buprenorphine (11). However, the mortality benefit in this analysis was limited to time actively retained in treatment, and the 4-week period after discontinuation was associated with an especially high risk for death. The few studies that examined mortality among patients receiving naltrexone show an unclear effect (12–15).

Massachusetts has been particularly affected by the opioid crisis: Opioid overdose deaths more than tripled between 2010 and 2016 (16). Through Chapter 55 of the Acts of 2015, the state legislature permitted individual-level linkage of data from 16 Massachusetts government agencies to gain a deeper understanding of the circumstances that influence fatal and nonfatal opioid overdoses (17). For this analysis, we identified a cohort of persons in the Chapter 55 data set who survived an opioid overdose and described any episodes of treatment with MOUD before and after that overdose. Specifically, we sought to determine whether

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treatment with MOUD, including receipt of MMT, buprenorphine, or naltrexone, was associated with reduced risk for all-cause and opioid-related mortality.

METHODS

Study Design and Data Source

We did a retrospective cohort study using the Massachusetts Chapter 55 data set, which includes data between 2011 and 2015 on residents aged 11 years or older with health insurance (as reported in the Massachusetts All-Payer Claims Database [APCD]) and represents more than 98% of Massachusetts residents. Data from APCD were linked at the individual level with records from other data sets using a multistage deterministic linkage technique described elsewhere (18). For this study, we used 7 linked Massachusetts databases: APCD, the Registry of Vital Records and Statistics, the prescription monitoring program, the Acute Hospital Case Mix, the Ambulance Trip Record Information System, the Bureau of Substance Addiction Services licensed treatment encounters, and the cancer registry. This work was mandated by Massachusetts law and conducted by a public health authority that required no institutional board review. The Boston University Medical Campus Institutional Review Board also determined that this study was not human subjects research.

Cohort Selection

We identified persons who had had a nonfatal opioid overdose between January 2012 and December 2014 to allow 12 months of observation before and after the overdose. We restricted the cohort to persons aged 18 years or older because access to OUD treatment substantially differs in adolescents versus adults (19). We identified opioid overdose in 2 ways. First, we identified emergency department, observation, or inpatient encounters with a medical claim containing a diagnosis code for opioid poisoning from the International Classification of Diseases, Ninth Revision, Clinical Modification (codes 965.00, 965.01, 965.02, 965.09, E850.0, E850.1, and E850.2). A study validated these codes by showing positive predictive values of 81% for identifying fatal or nonfatal opioid overdose and 94% for an opioid overdose or opioid-related adverse event (20). Second, we identified persons with an ambulance encounter for opioid overdose (available in 2013 and 2014 only). In collaboration with the Centers for Disease Control and Prevention, the Massachusetts Department of Public Health created and refined an algorithm to use with emergency medical services data to identify opioid-related overdoses; this algorithm was previously validated against internal emergency medical services data on opioid overdose events (**Supplement**, available at Annals.org).

We examined the first qualifying event (nonfatal opioid overdose) for each person, hereafter called the index overdose. Of 20 155 persons with an event, we excluded 1203 who died within 30 days after the overdose using dates of death from the Registry of Vital Records and Statistics. We excluded 1338 persons with evidence of cancer at any time in the 5 years of Chapter 55 data because of high competing risk for death. Cancer was identified using International Classification of Diseases, Ninth Revision, diagnosis codes in APCD (**Supplement**) or entry in the state-based cancer registry. We also excluded 46 persons whose age or sex was unknown, yielding a final cohort of 17 568 persons.

Key Variables

We identified exposure to MOUD in monthly intervals. Exposure to MMT was identified in 2 ways: a medical claim from APCD for methadone administration via Healthcare Common Procedure Coding System code H0020 or a record of treatment with methadone in data from the Bureau of Substance Addiction Services. We used the prescription monitoring program to identify dispensing of buprenorphine or buprenorphine and naloxone combined. Naltrexone was identified via a pharmacy claim for injectable or oral naltrexone in APCD. We examined 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 the Massachusetts Department of Public Health (**Supplement**).

We examined potential confounding variables. We obtained patient sex and age from APCD and categorized age as 18 to 29 years, 30 to 44 years, or 45 years or older. We identified monthly dispensings of opioid analgesics and benzodiazepines from the prescription monitoring program. We identified diagnosis of anxiety or depression using International Classification of Diseases, Ninth and Tenth Revisions, diagnosis codes from APCD (**Supplement**). We identified OUD treatment services, including inpatient detoxification episodes and postdetoxification treatment in short- and long-term residential facilities, through the Bureau of Substance Addiction Services.

Statistical Analysis

To compare baseline characteristics by receipt of MOUD, we developed the following 5 categories of MOUD receipt in the 12 months after the index overdose: no MOUD during follow-up, 1 or more months of buprenorphine, 1 or more months of methadone, 1 or more months of naltrexone, and 1 or more months of 2 or 3 MOUDs combined. We compared baseline characteristics among these mutually exclusive treatment groups using χ^2 tests.

We did time-to-event analyses for all-cause and opioid-related mortality using MOUD as a monthly time-varying exposure variable. We used 2 dichotomous classifications for MOUD exposure, "with discontinuation" and "on treatment." Several studies have shown an increased risk for all-cause and opioid-related mortality in the 4 weeks immediately after MOUD discontinuation (11, 21). Thus, we defined a "with discontinuation" exposure variable, which we considered the primary classification, to attribute any effect of MOUD discontinuation on mortality to the MOUD. For this classification, persons were considered exposed to MOUD in any month in which they received it and in the month after last receipt. We defined an "on treatment" exposure variable as the sec-

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ondary classification, in which persons were considered exposed to MOUD only in months in which they received it (Figure 1).

We used an extended Kaplan–Meier estimator allowing for time-varying exposure to MOUD to generate cumulative incidence curves (Supplement) (22). We developed a multivariable Cox regression model of time to all-cause and opioid-related mortality. The predictors of interest were monthly receipt of MMT, buprenorphine, and naltrexone as time-varying exposure variables. Covariates were age; sex; monthly time-varying receipt of prescription opioids, benzodiazepines, and OUD treatment services; baseline characteristics, including mental health diagnoses; and prior receipt of medication or OUD treatment services. We calculated the E-value to identify the minimum strength of association that an unmeasured confounder would need to have with both treatment and outcome, conditional on the measured covariates, to explain away the observed associations between MOUD and mortality (23). We used SAS Studio, version 3.5 (SAS Institute), for analyses (Supplement).

To examine the effect of prior experience with MOUD, we did an exploratory subgroup analysis stratified by receipt of MOUD in the 12 months before the index nonfatal overdose.

Role of the Funding Source

This project was supported by the National Center for Advancing Translational Sciences, the National Institute on Drug Abuse, the Boston University School of Medicine Department of Medicine, and the GE Foundation. The funding sources had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

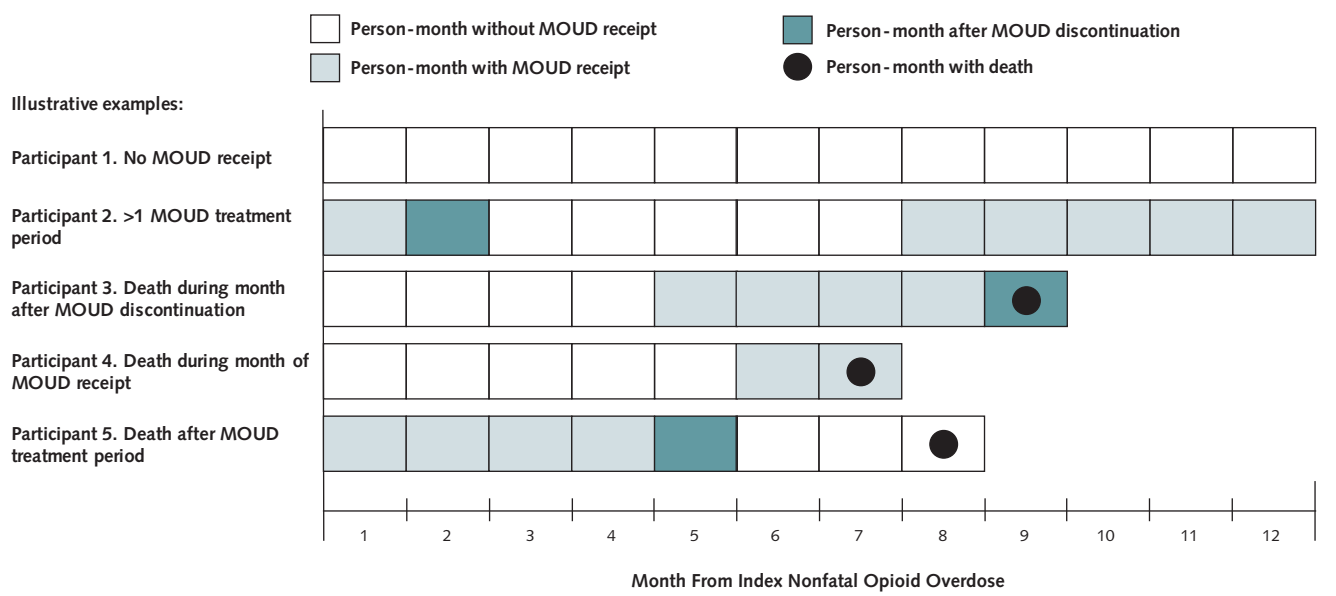
RESULTS

Baseline Characteristics

We identified 17 568 persons meeting inclusion criteria who had 1 or more nonfatal opioid overdoses between 2012 and 2014 in Massachusetts; 62% were male, and 69% were younger than 45 years. In the 12 months before the index overdose, 26% received 1 or more types of MOUD, 41% received prescriptions for opioid analgesics, and 28% received prescriptions for benzodiazepines. Twenty-two percent had an episode of opioid detoxification treatment (Table 1).

In the 12 months after the index overdose, 30% of participants (n = 5273) received any MOUD, 8% (n = 1416) received MMT, 13% (n = 2228) received buprenorphine, 4% (n = 772) received naltrexone, and 5% (n = 857) received more than 1 MOUD. Baseline characteristics and treatment history differed for persons who received MOUD after the index overdose (Table 1). Patients receiving MOUD were more likely to be younger than 45 years, to have a diagnosis of anxiety or depression, and to have received detoxification treatment in the past 12 months. Nearly half of patients who received MMT or buprenorphine in the period after the index overdose had received the same treatment in the

Figure 1. MOUD exposure classification.



For the primary classification (with discontinuation), MOUD exposure extends through the month after discontinuation (light and dark-green months). For the secondary classification (on treatment), exposure is limited to months in which treatment is received (light-green months only). In the illustrative examples, participant 1 is not exposed to MOUD through follow-up; participant 2 is exposed in months 1–2 and 7–12 for the primary classification and months 1 and 7–12 for the secondary classification. In the month of death, participant 3 would be considered exposed in the primary classification only, participant 4 would be considered exposed in both primary and secondary exposure classifications, and participant 5 would be considered not exposed to MOUD. MOUD = medication for opioid use disorder.

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Table 1. Baseline Patient Characteristics Before and Treatments After Index Nonfatal Opioid Overdose*

Baseline Characteristic†	Full Cohort (*n* = 17 568)	MOUDs in the 12 Months After Index Nonfatal Opioid Overdose‡				
		No MOUDs (*n* = 12 295)	Enrollment in MMT (*n* = 1416)	Buprenorphine (*n* = 2228)	Naltrexone (*n* = 772)	Multiple MOUDs (*n* = 857)
Male	10 955 (62)	7633 (62)	831 (59)	1479 (66)	500 (65)	512 (60)
Age						
18–29 y	6147 (35)	3943 (32)	540 (38)	883 (40)	389 (50)	392 (46)
30–44 y	5915 (34)	3781 (31)	592 (42)	913 (41)	271 (35)	358 (42)
≥45 y	5506 (31)	4571 (37)	284 (20)	432 (19)	112 (15)	107 (12)
Anxiety	3034 (17)	1799 (15)	322 (23)	492 (22)	212 (27)	209 (24)
Depression	3676 (21)	2287 (19)	347 (25)	557 (25)	255 (33)	230 (27)
Any MOUD before index overdose	4492 (26)	1587 (13)	866 (61)	1229 (55)	283 (37)	527 (61)
MMT	1817 (10)	594 (5)	691 (49)	233 (10)	55 (7)	244 (28)
Buprenorphine	2635 (15)	842 (7)	257 (18)	1052 (47)	127 (16)	357 (42)
Naltrexone	757 (4)	356 (3)	54 (4)	118 (5)	148 (19)	81 (9)
Detoxification	3872 (22)	1949 (16)	561 (40)	684 (31)	323 (42)	355 (41)
Residential treatment						
Short-term§	1658 (9)	850 (7)	213 (15)	288 (13)	162 (21)	145 (17)
Long-term	1284 (7)	668 (5)	148 (10)	207 (9)	127 (16)	134 (16)
Opioid prescription	7185 (41)	5039 (41)	598 (42)	917 (41)	265 (34)	366 (43)
Benzodiazepine prescription	4871 (28)	3237 (26)	427 (30)	743 (33)	179 (23)	285 (33)

MMT = methadone maintenance treatment; MOUD = medication for opioid use disorder.
* Values are numbers (percentages). "Index nonfatal opioid overdose" was defined as a participant's first ambulance or hospital encounter for opioid overdose between January 2012 and December 2014 without death in the subsequent 30 d.
† Participants received these diagnoses, medications, or services in ≥1 of the 12 mo preceding the index nonfatal opioid overdose.
‡ $P < 0.001$ for χ^2 comparison of each baseline characteristic category (except receipt of opioid prescription [$P = 0.003$]) by 5 postoverdose MOUD receipt categories.
§ Clinical stabilization/step-down or transitional support services.

12 months before that overdose, compared with 19% of those who received naltrexone.

Receipt of Treatments and Services After the Index Overdose

In the 12 months after the index overdose, 11% of participants (*n* = 2040) received MMT for a median of 5 months (interquartile range, 2 to 9 months), 17% (*n* = 3022) received buprenorphine for a median of 4 months (interquartile range, 2 to 8 months), and 6% (*n* = 1099) received naltrexone for a median of 1 month (interquartile range, 1 to 2 months). The proportion of persons receiving methadone changed from 6% to 4% during the 12 months before the index overdose and gradually increased to 7% over 12 months of follow-up (Figure 2, *top*). The proportion of persons receiving buprenorphine was steady at 6% for the 12 months before the index overdose and then changed gradually, reaching 8% in the final month of follow-up. Fewer than 1% of participants received naltrexone in each of the 12 months before the index overdose, 2% received it in the first month after that overdose, and 1% received it in the subsequent months.

In 12 months of follow-up, 34% of participants received 1 or more prescriptions for opioid analgesics and 26% received prescriptions for benzodiazepines. During the month of the index overdose, 15% received opioid analgesics and 15% benzodiazepines; these proportions changed to 10% and 11%, respectively, at the end of the 12-month follow-up (Figure 2, *middle*). Nine percent of persons were treated in detoxification units during the month of the index overdose, and 4% were served in short-term residential facilities in the month after that overdose. Treatment at long-term residential facilities reached and held relatively constant at 3% after the third month after the index overdose (Figure 2, *bottom*).

All-Cause and Opioid-Related Mortality

Over 12 months of follow-up, 807 participants died of any cause and 368 died of an opioid-related overdose. Crude incidence rates per 100 person-years were 4.7 deaths (95% CI, 4.4 to 5.0 deaths) for all-cause mortality and 2.1 deaths (CI, 1.9 to 2.4 deaths) for opioid-related mortality.

Primary Exposure Classification

In unadjusted survival analyses for time-varying exposure to MOUD, cumulative incidence of all-cause mortality at 12 months was 4.9% (CI, 4.5% to 5.3%) for persons not receiving MOUD, 2.5% (CI, 1.6% to 3.3%) for those enrolled in MMT, 3.0% (CI, 2.2% to 3.9%) for those receiving buprenorphine, and 4.7% (CI, 2.1% to 7.4%) for those receiving naltrexone (Figure 3, *A*). Cumulative incidence of opioid-related mortality at 12 months was 2.2% (CI, 1.9% to 2.4%) for those not receiving MOUD, 1.4% (CI, 0.7% to 2.0%) for those enrolled in MMT, 2.0% (CI, 1.3% to 2.7%) for those receiving buprenorphine, and 3.0% (CI, 0.8% to 5.1%) for those receiving naltrexone (Figure 3, *C*).

In the multivariable Cox proportional hazards models, we observed a reduction in all-cause mortality with MMT (adjusted hazard ratio [AHR], 0.47 [CI, 0.32 to 0.71]) and buprenorphine (AHR, 0.63 [CI, 0.46 to 0.87]). For naltrexone, wide CIs precluded confident conclusions (AHR, 1.44 [CI, 0.84 to 2.46]). Findings for opioid-related mortality were similar: AHRs were 0.41 (CI, 0.24 to

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0.70) for MMT, 0.62 (CI, 0.41 to 0.92) for buprenorphine, and 1.42 (CI, 0.73 to 2.79) for naltrexone (Table 2).

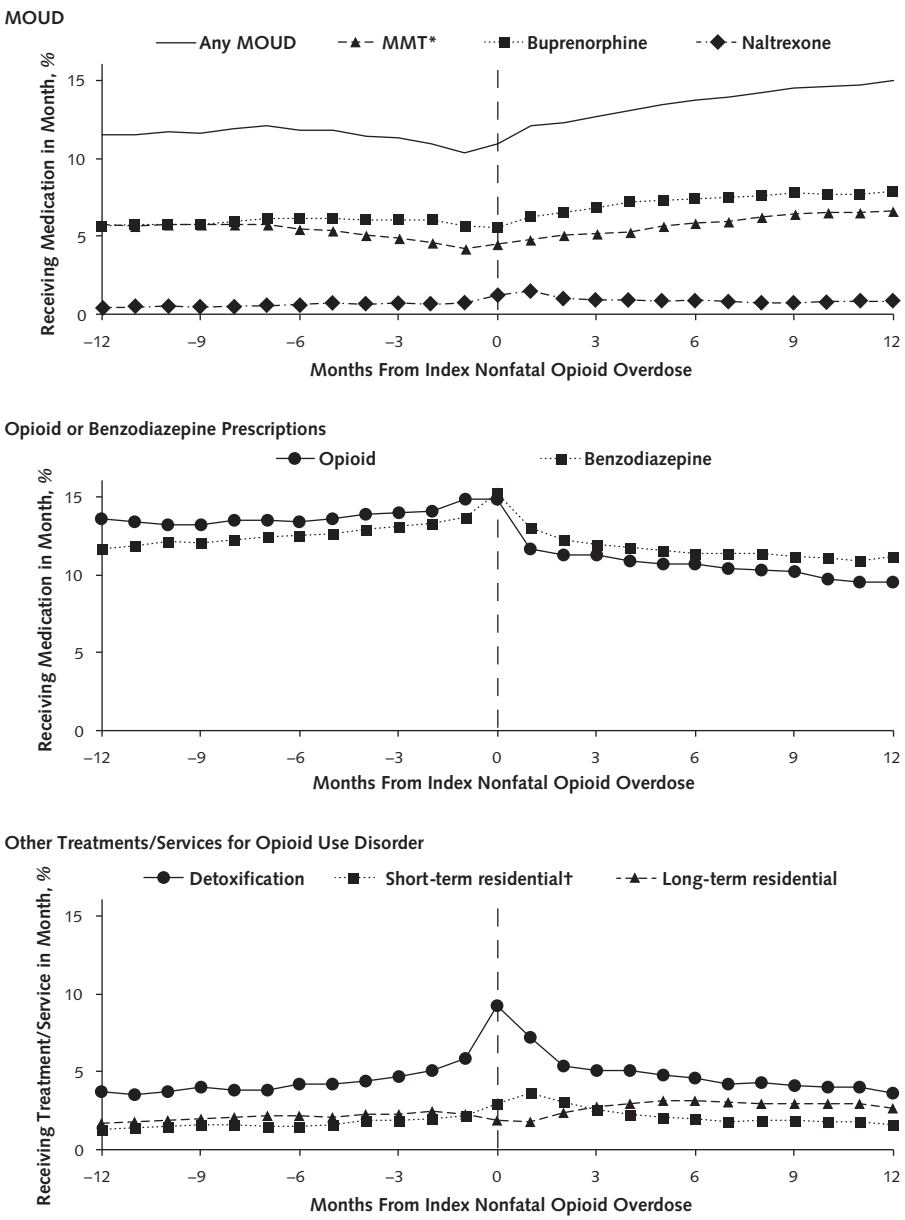
Secondary Exposure Classification

When we classified MOUD exposure as only months in which MOUD was received, the unadjusted cumulative incidence of all-cause mortality at 12 months was 5.0% (CI, 4.7% to 5.4%) for persons not receiving MOUD, 2.0% (CI, 1.2% to 2.9%) for those enrolled in MMT, 1.8% (CI, 1.1% to 2.5%) for those receiving buprenorphine, and 1.0% (CI, 0.0% to 2.7%) for those receiving naltrexone (Figure 3, *B*). In the multivariable Cox proportional hazards models, we observed a reduction in all-cause mortality with MMT (AHR, 0.37 [CI, 0.24 to 0.59]) and buprenorphine (AHR, 0.35 [CI, 0.23 to 0.53]) but not naltrexone (AHR, 0.34 [CI, 0.08 to 1.34]) (Table 2). The relative effect of MOUD on cumulative incidence and adjusted hazard of opioid-related mortality was similar (Figure 3, *D*, and Table 2).

Stratification by Baseline Receipt of MOUD

We identified 12 453 participants (71%) who did not receive MOUD in the 12-month baseline period. Of these, 1745 (14%) received 1 or more months of

Figure 2. Monthly receipt of treatments/services, by cohort.



In the 12 mo before and after index opioid overdose, Massachusetts, 2012–2014 (*n* = 17 568). MMT = methadone maintenance treatment; MOUD = medication for opioid use disorder.
* Enrollment in MMT.
† Clinical stabilization/step-down or transitional support services.

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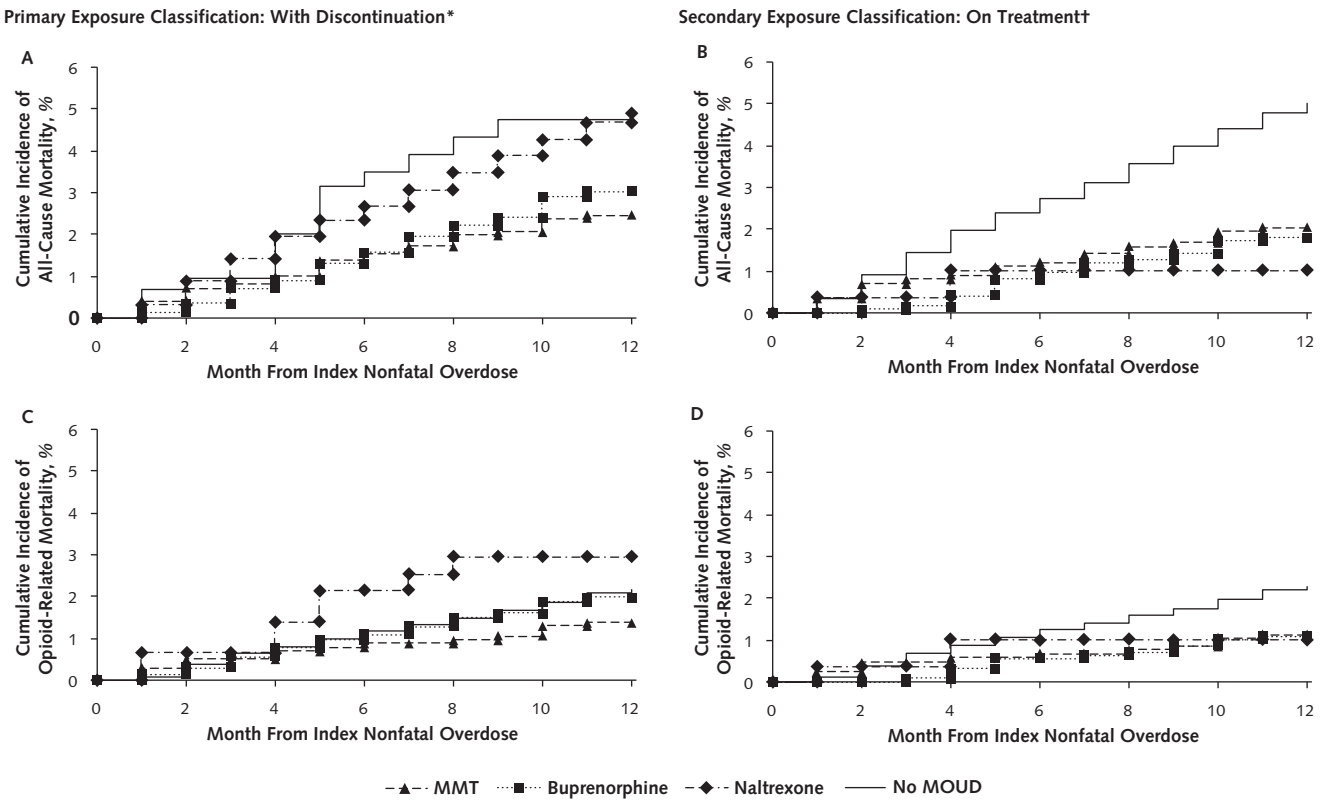
Figure 3. Extended Kaplan–Meier cumulative incidence of all-cause mortality (*A* and *B*) and opioid-related mortality (*C* and *D*), by monthly exposure to MOUD after index overdose.



Massachusetts, 2012–2014 (*n* = 17 568). MMT = methadone maintenance treatment; MOUD = medication for opioid use disorder.
* MOUD exposure extends through the month of discontinuation.
† Exposure is limited to months in which treatment was received.

MOUD in the 12-month follow-up. For comparison, 2905 (65%) of the 4492 participants who received MOUD in the baseline period also received it during follow-up. Opioid-related mortality was higher in the subgroup with prior MOUD experience: 3.0 deaths (CI, 2.6 to 3.6 deaths) per 100 person-years versus 1.8 deaths (CI, 1.6 to 2.1 deaths) per 100 person-years (**Supplement Table 3**, available at Annals.org). Multivariable Cox proportional hazards models stratified by receipt of MOUD before the index overdose yielded hazard ratios for all-cause and opioid-related mortality with overlapping 95% CIs for each MOUD (**Supplement Table 4**, available at Annals.org).

DISCUSSION

In a cohort of more than 17 000 persons who had a nonfatal opioid overdose between 2012 and 2014 in Massachusetts, all-cause mortality at 12 months was 4.7 deaths per 100 person-years. For comparison, opioid-related mortality in Massachusetts increased from 0.011 to 0.020 deaths per 100 residents per year between 2012 and 2014 (16). Fewer than a third of participants received MOUD in the 12 months after a nonfatal opioid overdose. Buprenorphine and MMT were associated with reductions in all-cause and opioid-related mortality.

To our knowledge, this is the first study to examine the association between MOUD and mortality after a nonfatal opioid overdose and the first U.S.-based study to examine the association between all 3 treatments approved by the U.S. Food and Drug Administration and mortality in any setting. The associations with methadone and buprenorphine observed in this study are consistent with results of past observational cohort studies. A recent meta-analysis found that pooled all-cause mortality rates in and out of treatment were 1.1 and 3.6 deaths per 100 person-years, respectively, for methadone and 0.43 and 0.95 deaths per 100 person-years, respectively, for buprenorphine (11). The higher overall all-cause mortality in our study likely reflects the higher risk associated with restricting our cohort to persons who recently survived an opioid overdose.

Two previous studies examined treatment patterns after a nonfatal opioid overdose. The first examined a large U.S. population with commercial insurance receiving long-term opioid therapy before an overdose and found that 7% of participants received buprenorphine after the overdose (24). Of note, the time frame (2000 to 2012) spanned approval for opioid use disorder of buprenorphine in 2002 and intramuscular naltrexone in 2010. The study did not find evidence about MMT, which commercial insurers rarely paid for during

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that period. In a second study among opioid overdose survivors in Pennsylvania Medicaid claims, rates of MOUD treatment before and after overdose were similar to those observed in this Massachusetts cohort (25).

Median duration of treatment was less than 6 months for all 3 MOUDs and particularly low for naltrexone, which most patients received for a single month. Randomized controlled trials of oral and injectable naltrexone yielded retention rates greater than 50% at 6 months, which likely reflect the special characteristics of persons qualifying for these trials (8, 13). Observational studies have shown lower retention rates: In some, only 50% to 60% of participants received a second injection, and fewer than 10% received a fifth monthly injection (26, 27). Of note, a recent open-label randomized trial comparing intramuscular naltrexone versus buprenorphine initiation during voluntary inpatient admissions for detoxification found significantly higher induction failures for naltrexone (28% vs. 6%) (28).

The period after MOUD discontinuation, and in particular the first 4 weeks, has been associated with increased risk for overdose death. A recent meta-analysis that compared overdose death rates in the 4 weeks before and after discontinuation found an increase from 2.0 to 4.0 deaths per 1000 person-years for MMT and 1.5 to 10.8 deaths per 1000 person-years for buprenorphine (11). Similar data are not available for intramuscular naltrexone; however, a study from Australia found that the overdose death rate on treatment discontinuation was 8 times higher for oral naltrexone than for opioid agonist treatments, including MMT and buprenorphine (29). By considering persons exposed to MOUD through the month after last receipt, our primary exposure classification attributes any increased risk from discontinuation to the MOUD itself.

Buprenorphine and MMT remained associated with reductions in opioid-related and all-cause mortality when we accounted for the effect of treatment discontinuation. We cannot draw conclusions about the effect of naltrexone given uncertainty in estimates, which reflects the relatively small number of persons exposed to naltrexone for brief durations. Of note, we could not distinguish oral from intramuscular naltrex-

Table 2. Crude Incidence Rates and Multivariable Cox Proportional Hazards Analyses for All-Cause and Opioid-Related Mortality, by Receipt of Treatments

Variable*	Receipt of MOUDs in the 12 Months After Index Nonfatal Opioid Overdose†			
	No MOUDs	**Enrollment in MMT**	**Buprenorphine**	**Naltrexone**
Primary exposure classification: with discontinuation‡				
Exposure, *person-months*	172 791	13 324	17 955	3310
All-cause mortality				
Deaths, *n*	724	27	46	14
Crude incidence per 100 person-years (95% CI)	5.0 (4.7–5.4)	2.4 (1.7–3.5)	3.1 (2.3–4.1)	5.1 (3.0–8.6)
Adjusted hazard ratio (95% CI)§	1.00 (reference)	0.47 (0.32–0.71)	0.63 (0.46–0.87)	1.44 (0.84–2.46)
Estimated E-value (confidence limit)‖	NA	3.7 (2.2)	2.6 (1.6)	2.2 (1)
Opioid-related mortality				
Deaths, *n*	Suppressed¶	15	30	<10 (suppressed)¶
Crude incidence per 100 person-years (95% CI)	Suppressed¶	1.4 (0.8–2.2)	2.0 (1.4–2.9)	Suppressed¶
Adjusted hazard ratio (95% CI)§	1.00 (reference)	0.41 (0.24–0.70)	0.62 (0.41–0.92)	1.43 (0.73–2.79)
Estimated E-value (confidence limit)‖	NA	4.3 (2.2)	2.7 (1.4)	2.2 (1)
Secondary exposure classification: on treatment**				
Exposure, *person-months*	178 418	12 025	15 045	1892
All-cause mortality				
Deaths, *n*	Suppressed¶	20	23	<10 (suppressed)¶
Crude incidence per 100 person-years (95% CI)	Suppressed¶	2.0 (1.3–3.1)	1.8 (1.2–2.8)	Suppressed¶
Adjusted hazard ratio (95% CI)§	1.00 (reference)	0.37 (0.24–0.59)	0.35 (0.23–0.53)	0.34 (0.08–1.34)
Estimated E-value (confidence limit)‖	NA	4.8 (2.8)	5.2 (3.2)	5.3 (1)
Opioid-related mortality				
Deaths, *n*	Suppressed¶	11	14	<10 (suppressed)¶
Crude incidence per 100 person-years (95% CI)	Suppressed¶	1.1 (0.6–2.0)	1.1 (0.7–1.9)	Suppressed¶
Adjusted hazard ratio (95% CI)§	1.00 (reference)	0.32 (0.17–0.59)	0.31 (0.18–0.54)	0.52 (0.13–2.08)
Estimated E-value (confidence limit)‖	NA	5.7 (2.8)	5.9 (3.1)	3.3 (1)

MMT = methadone maintenance treatment; MOUD = medication for opioid use disorder; NA = not applicable.
* MOUD variables are binary, time-varying monthly indicators of receipt of medication.
† Defined as a participant's first ambulance or hospital encounter for opioid overdose between January 2012 and December 2014 without death in the subsequent 30 d.
‡ MOUD exposure extended through the month after discontinuation.
§ Results of multivariable Cox proportional hazards models adjusted for age; sex; baseline anxiety diagnosis; depression diagnosis; receipt of methadone, buprenorphine, opioid, and benzodiazepine prescriptions in the 12 mo before index nonfatal opioid overdose; and time-varying receipt of opioid prescriptions, benzodiazepine prescriptions, detoxification episode, and short- and long-term residential treatments (**Appendix Table 2** [available at Annals.org] shows full model results).
‖ Represents the minimum strength of association between an unmeasured confounder and both the treatment and outcome to explain observed associations between MOUDs and mortality, conditional on the measured covariates. These values are presented for the adjusted hazard ratio and 95% confidence limit closest to the null. If the CI includes the null, the E-value is 1.
¶ Data were suppressed because of small cell size; values <10 indicate a value of 1–9 for that cell. Other cells were suppressed to prevent calculation of small cells.
** Exposure was limited to the months in which treatment was received.

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one in this study. Intramuscular naltrexone has shown improved efficacy in randomized controlled trials (30, 31). Further work is needed with larger samples of persons treated with naltrexone to identify its potential association with opioid-related and all-cause mortality. Given the low level of opioid overdose and all-cause mortality reported in randomized controlled trials, these findings highlight the value of observational data, such as those used in this study.

Our study has several limitations. First, our observational data are subject to selection bias. We noted differences by each baseline characteristic between persons who did and did not receive MOUD, as well as differences by which treatment was received. We attempted to control for these differences using multivariable regression; however, residual confounding remained likely. Second, key cohort, exposure, and outcome variables may have been misclassified through either lack of capture or linkage error. We used a conservative definition of nonfatal opioid overdose that excluded any death within 30 days of the overdose encounter. Monthly time resolution of variables prevented us from determining the order of events when MOUD receipt and the index nonfatal overdose occurred in the same month. The optimal window between overdose and death to distinguish nonfatal from fatal overdoses warrants further study. Although not all overdose survivors have an opioid use disorder with a MOUD indication, a subgroup analysis showed high opioid-related mortality in those who had never received MOUD at the time of the overdose. Linkage error or incomplete data that resulted in misclassification of MOUD exposure would bias observed associations toward the null. Third, our findings may have limited generalizability outside Massachusetts, which has higher opioid-related mortality and higher prevalence of insurance coverage than the U.S. average; these factors may translate to higher treatment rates.

Our analysis has several strengths based on the number of persons represented in the Chapter 55 data set. We report the population experience with MOUD in Massachusetts among persons who have survived an overdose. Our primary analyses attributed the mortality risk in the month of discontinuation to the MOUD episode to account for the known increased risk after treatment discontinuation. In the same analysis, we examined not only all 3 MOUDs but also other treatment factors, including exposure to prescription opioids, benzodiazepines, detoxification, and residential services.

Our data confirm that nonfatal opioid overdose is an opportunity to identify persons at high risk for death and engage them in treatment. Of note, rates of treatment initiation are inversely proportional to the lag between being offered and being able to start treatment (32). New models that offer treatment initiation and linkage to care from emergency department and inpatient settings have demonstrated increased treatment engagement (33–35). Our findings also show that treatment initiation without retention undermines benefits. We need to improve delivery systems that improve treatment retention, especially with naltrexone.

A minority of persons who survive an opioid overdose receive MOUD. Buprenorphine and MMT were associated with reduced all-cause and opioid-related mortality. These findings suggest meaningful opportunities to improve engagement and retention in treatment of opioid use disorders after a nonfatal overdose.

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