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RESEARCH REPORT

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Duration of medication treatment for opioid-use disorder and risk of overdose among Medicaid enrollees in 11 states: a retrospective cohort study

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Abstract

Background and aims: Medication for opioid use disorder (MOUD) reduces harms associated with opioid use disorder (OUD), including risk of overdose. Understanding how variation in MOUD duration influences overdose risk is important as health-care payers increasingly remove barriers to treatment continuation (e.g. prior authorization). This study measured the association between MOUD continuation, relative to discontinuation, and opioid-related overdose among Medicaid beneficiaries.

Design: Retrospective cohort study using landmark survival analysis. We estimated the association between treatment continuation and overdose risk at 5 points after the index, or first, MOUD claim. Censoring events included death and disenrollment.

Setting and participants: Medicaid programs in 11 US states: Delaware, Kentucky, Maryland, Maine, Michigan, North Carolina, Ohio, Pennsylvania, Virginia, West Virginia and Wisconsin. A total of 293 180 Medicaid beneficiaries aged 18–64 years with a diagnosis of OUD and had a first MOUD claim between 2016 and 2017.

Measurements: MOUD formulations included methadone, buprenorphine and naltrexone. We measured medically treated opioid-related overdose within claims within 12 months of the index MOUD claim.

Findings: Results were consistent across states. In pooled results, 5.1% of beneficiaries had an overdose, and 67% discontinued MOUD before an overdose or censoring event within 12 months. Beneficiaries who continued MOUD beyond 60 days had a lower relative overdose hazard ratio (HR) compared with those who discontinued by day 60 [HR = 0.39; 95% confidence interval (CI) = 0.36–0.42; $P < 0.0001$]. MOUD continuation was associated with lower overdose risk at 120 days (HR = 0.34; 95% CI = 0.31–0.37; $P < 0.0001$), 180 days (HR = 0.31; 95% CI = 0.29–0.34; $P < 0.0001$), 240 days (HR = 0.29; 95% CI = 0.26–0.31; $P < 0.0001$) and 300 days (HR = 0.28; 95% CI = 0.24–0.32; $P < 0.0001$). The hazard of overdose was 10% lower with each additional 60 days of MOUD (95% CI = 0.88–0.92; $P < 0.0001$).

For affiliations refer to page 3086.

Conclusions: Continuation of medication for opioid use disorder (MOUD) in US Medicaid beneficiaries was associated with a substantial reduction in overdose risk up to 12 months after the first claim for MOUD.

KEYWORDS
Distributed research network, landmark survival analysis, Medicaid, medication, opioid use disorder, opioid-related overdose

INTRODUCTION

The United States is confronted with a rise in opioid use disorder (OUD) and associated harms, most recently exacerbated by the COVID-19 pandemic [1]. Medication for opioid use disorder (MOUD), including formulations of methadone, buprenorphine and naltrexone, are the gold standard treatment for OUD [2–9]. While engaged in care, patients receiving MOUD reduce illicit opioid use, mortality, criminal activity, health-care costs and high-risk behaviors and experience improvement in their quality of life; these benefits diminish after treatment cessation [10–16]. Thus, retention in treatment is an important clinical practice goal [17]. However, there is no consensus regarding the optimal duration of MOUD [18–20]. Expert recommendations range from a minimum of 6 months with no prescribed maximum [21] to 'as long as it provides a benefit' [22]. It is important to understand how variation in MOUD duration affects patient outcomes to inform clinical decision-making, educate and support patient treatment choices and set meaningful performance targets for health systems.

Experimental research indicates that a longer duration of MOUD tapering, following a brief stabilization period, yields a greater likelihood of opioid abstinence during follow-up periods of 1–3 months in duration [23–25]. Additionally, 20 years of prospective and retrospective studies have shown reduced risk of overdose and mortality and improved quality of life associated with MOUD treatment [26–28]. Among studies that have compared acute health-care use or overdose outcomes among cohorts defined by their duration in MOUD treatment, the most consistent finding is a lower likelihood of a hospital-based care associated with longer treatment duration [29–31]. The preponderance of this research also demonstrates a protective association between duration of treatment and risk of overdose [30–33]. However, this type of comparison may be biased. Assignment to the treatment cohort requires that subjects remain observed and without the outcome under study for long enough to meet the treatment cohort criterion (e.g. 180 days' MOUD duration), thereby giving this group a 'survival' advantage and introducing immortal time bias.

This study builds upon the existing evidence base. First, we study Medicaid beneficiaries. Medicaid is the single largest payer for MOUD [34]. However, most research that examines MOUD duration and overdose risk concerns individuals with commercial or Medicare insurance coverage [33], patients in opioid treatment programs [32] and those with a prior overdose [35]. Evidence specific to Medicaid beneficiaries remains limited [29–31]. We evaluate MOUD duration and overdose risk among Medicaid enrollees from 11 states that vary in population demographic characteristics, the scope and severity of the opioid epidemic, substance use policy and treatment availability. We pooled administrative data across Medicaid programs, and estimated the hazard of overdose during a 12-month follow-up period among enrollees with OUD who continued MOUD relative to those who did not at 6, 120, 180, 240 and 300 days after the initial MOUD claim.

METHOD

Design

In this retrospective cohort study, we implemented landmark survival analysis to estimate the association between treatment continuation and overdose risk at the time-points noted above. Landmark survival analysis mitigates immortal time bias [36], thereby improving the comparability of the study groups compared to conventional survival analysis.

Data

We obtained Medicaid enrollment, medical and pharmacy claims data from 2016 to 2018 for a census of enrollees from 11 states (Delaware, Kentucky, Maryland, Maine, Michigan, North Carolina, Ohio, Pennsylvania, Virginia, West Virginia and Wisconsin) that participate in the Medicaid Outcomes Distributed Research Network (MODRN) [37]. MODRN represents a research network of state partnerships between the state Medicaid agency and at least one state university in the state. In this study, participating states account for 16.3 million Medicaid beneficiaries (22% of enrollees nationally) including six of the 10 states with highest drug overdose death rates in 2018 [37]. Each university obtained claims and enrollment data for a census of enrollees from its state's Medicaid agency and transformed these data into a common data model with uniform structure and data elements that the MODRN had previously developed. The study's coordinating center distributed an identical statistical software code to each university for application to its state's Medicaid data. The universities returned aggregate results to the coordinating center for analysis following previously validated methods [38]. Each university received an exempt determination from their institutional review board.

Sample

We identified Medicaid enrollees, aged 18–64 years, enrolled in one of the 11 states' full-benefit Medicaid programs at any time between January 2016 and December 2018 and who were not dually enrolled in Medicare. We selected all individuals who received MOUD and had a diagnosis of OUD within 6 months before or after a MOUD encounter (Table 1). We identified receipt of MOUD using pharmacy claims with National Drug Codes (NDC) for formulations (oral and injectable) of buprenorphine and naltrexone indicated by the US Food and Drug Administration for OUD, or professional or outpatient facility claims with a procedure code for administration of formulations of methadone, buprenorphine and naltrexone for Medicaid enrollees with OUD (Supporting information, eAppendix 1). We identified enrollees with an OUD diagnosis (using ICD-10 codes F11.xx) appearing on an inpatient or outpatient facility claim or professional claim. We excluded women who were pregnant at any point during the study period because of pregnancy-specific treatment guidelines that differ from the non-pregnant adult population [39]. Additionally, we excluded individuals for whom the first observed MOUD claim, the index MOUD claim, occurred after 31 December 2017 to allow for up to 12 months of follow-up. We did not require any minimum duration of Medicaid enrollment for study inclusion to reduce the risk of selection bias and strengthen the generalizability of results.

Measures

The study outcome, medically treated opioid-related overdose, took on a value of 1 if we observed an inpatient, outpatient or professional claim with an ICD-10 diagnosis of opioid-related poisoning [40, 41] during the 12 months following the index MOUD claim and before any other censoring event (Supporting information, eAppendix 2). Censoring events included disenrollment or death. We defined disenrollment as a gap in Medicaid enrollment of ≥ 60 days.

We defined the key independent variable as continuation of MOUD beyond the selected time-point relative to the index MOUD claim, 60, 120, 180, 240 and 300 days. This relatively short interval between time-points supports an inductive approach to understanding the association between MOUD continuation and overdose risk. We initially implemented 30-day intervals but found that the cell sizes were too small for some states and time-points to support multivariate comparisons. We defined discontinuation as ≥ 30 days without any MOUD. The first day of that gap is the MOUD discontinuation date (Supporting information, eAppendix 1). In the absence of a gold standard to define MOUD discontinuation (e.g. 14, 30, 32, ≥ 90 days, etc.) [42–48] we sought to balance the possibility of underestimating the association between discontinuation and overdose risk (by using short treatment gaps) and overestimating that association (by using long treatment gaps).

Covariates for all regression analyses included the year of index MOUD; age in 5-year increments; sex; race/ethnicity (non-Hispanic white and all others, which included non-Hispanic black, Hispanic and other); rural or urban residence [49]; and Medicaid eligibility category (disabled adults and all other others). Additionally, we included three categories of comorbidities, infectious disease [i.e. hepatitis B virus (HBV), hepatitis C virus (HCV), HIV], mental illness and other substance use disorders, and medical complications of injection drug use (i.e. intracranial and intraspinal abscess, osteomyelitis, endocarditis and soft skin tissue infection), based on a diagnosis code recorded in the follow-up period (Supporting information, eAppendix 3). We aggregated our covariates to the groupings described above, because the cell sizes obtained when using more granular categories were too small for some states and time-points to implement multivariate comparisons.

We assessed type of MOUD at index and report those summary statistics; however, we did not include this variable in our main regression models because a small subset of the states did not offer all types of MOUD during the study period.

Statistical analysis

We aimed to estimate the association between the duration of MOUD and risk of an opioid-related overdose. To do so, we implemented landmark survival analysis [50] which combats a

TABLE 1 Sample flow-chart

Order	Description	Total *N*	% Changed from the previous step
1	Non-elderly adult enrollees with a first, or index, MOUD claim between 2016 and 2018 and a diagnosis of opioid use disorder	432 011	
2	Exclude enrollees with an index date after 31 December 2017, to allow up to 12 months of follow-up	335 611	−22.3%
3	Exclude enrollees who were pregnant at any point 2016–18	295 395	−12.0%
4	Exclude enrollees with survival time < 0 day, i.e. due to data error	293 907	−0.5%
5	Exclude enrollees with any missing value for covariates	293 180	−0.2%

MOUD = medication for opioid use disorder.

common source of bias in traditional survival analysis: immortal time bias [36]. Immortal time bias arises when treatment assignment at t_0 depends upon a behavior or exposure after t_0 when the outcomes are assessed. For example, one might compare the hazard of overdose from t_0 to 12 months for a treatment group and a comparison group that are defined by MOUD duration from t_0 forward (e.g. ≥ 120 days and < 120 days). Treatment subjects have a survival advantage, or 'immortal time' of 120 days because, by design, they cannot develop the outcome before receiving the treatment.

Landmark survival analysis mitigates immortal time bias by identifying treatment or comparison group status independent of the subject's exposure to MOUD during the outcome assessment period and allowing study group status to vary within person over time. Specifically, for each subject we defined their treatment group (i.e. continuing MOUD), comparison group (i.e. discontinued MOUD) or censored status at each landmark time-point, t_n, relative to the index MOUD date. For each landmark time-point, we implemented a separate Cox proportional hazard model to assess the relative hazard of overdose among those who continued MOUD beyond t_n relative to those who discontinued by t_n. The analytical sample for each model included only subjects who had not experienced the outcome and remained eligible for treatment or comparison status up to that landmark time-point. In other words, the comparison and treatment group subjects at each landmark time-point had comparable immortal time. This approach improved the exchangeability of study groups, because all subjects, whether identified as treated or comparison at t_n, were equally likely to continue as participants to t_n.

We used a two-stage procedure to conduct these analyses. First, all states ran identical analytical SAS code (version 9.4; SAS Institute, Inc., Cary, NC, USA) on their respective data that had been standardized according to the MODRN common data model. We excluded subjects with missing data for rural/urban living area from the analytical sample.

In the second stage, we conducted random-effects meta-analyses to pool the state-specific estimates and generate global estimates adopting methods validated in similar settings and previously deployed in the MODRN [37, 50, 51]. We generated global estimates of the hazard ratio (HR) of MOUD continuation relative to discontinuation at each landmark time-point by averaging the model estimates from each state weighted by the inverse of their variances to account for differences in population size. We used Cochran's Q to measure and test the statistical significance of between-state heterogeneity in the estimates. To construct valid 95% confidence intervals (CIs) for the global estimate we used the Hartung–Knapp–Sidik–Jonkman method to estimate between-state variances [52]. We tested whether the global estimate equaled 1 using a two-sided adjusted t-test and a significance threshold of 0.05 [53]. We allowed for between-state variation in the effect of MOUD continuation because we had only a selection of states, but wished to extend our inference to similar states outside of our sample. To do so, we constructed 90% prediction intervals [54]. The prediction intervals convey state-to-state variability denoting the range within which the HR would fall for 90% of the states if we drew a different sample of states (Supporting information, eAppendix 4). For this reason, prediction intervals remain relatively stable to the number of states included in the pooled analysis, providing an objective measurement of uncertainty, while CIs (i.e. from fixed-effect pooling) would continue to decrease as more states were included.

We conducted a test for trend during the 12-month follow-up period in the global HR estimates using random-effects meta-analysis with the inclusion of time. The landmark time-point was included as a linear fixed-effect, and a random effect of state was also included.

We tested the sensitivity of our results to the inclusion of the type of MOUD at index by re-estimating the analyses including the states that offered all MOUD types throughout the study period. Finally, we estimated the E-values for our main results [55], the global HR estimates, to explore the degree to which our main estimates could be explained by unobserved confounding variables. Finally, we explored the moderating role of MOUD type in the association between MOUD continuation and overdose risk. We implemented stratified analyses in the four states that covered all MOUD types in all years and had sufficient sample sizes to compare overdose risk among continuers and discontinuers by MOUD type at all time-points. The study's analytical plan was not pre-registered.

RESULTS

Characteristics of study participants

The sample included 293 180 Medicaid beneficiaries with OUD who received at least 1 day of MOUD treatment during the study period (Table 2). On average, subjects were 36.9 years of age. More than half of enrollees, 54.7%, were male, and 80.1% were non-Hispanic white. Adults without disabilities comprised 85.3% of the sample. The most common type of MOUD at index was formulations of buprenorphine at 59.2% of the sample followed by methadone at 27.6%. Approximately 26.2% of the sample resided in a rural location. The sample had relatively stable Medicaid enrollment, including an average of 11.4 months within the 360-day study period from index MOUD to 12 months. We observed diagnoses for infectious diseases among 16.8% of the sample, other mental illness or substance use disorders among 67.3% of the sample, and other medical complications among 13.4% of the sample.

Frequency of opioid-related overdose and MOUD discontinuation

During the 12-month follow-up period, 196 485 beneficiaries (67%) discontinued MOUD before an overdose or censoring event (Table 2). An additional 5% of beneficiaries discontinued MOUD after an overdose or censoring event during the 12-month period following the

TABLE 2 Adult Medicaid beneficiaries with opioid use disorder who received medication for opioid use disorder, 2016–17 (n = 293 180)

	Mean/ percentage	Range of mean/ percentage
Age (mean)	36.9	(35.6–39.8)
Male (%)	54.7	(33.2–59.4)
Race/ethnicity (%)		
Non-Hispanic white	80.1	(60.7–92.9)
All other race/ethnicity	19.9	(7.1–39.3)
Eligibility group (%)		
Adults without disabilities	85.3	(68.8–94.3)
Adults with disabilities	14.7	(5.7–31.2)
Living area (%)		
Urban	73.8	(31.6–96.4)
Rural	26.2	(3.6–68.4)
Index year (%)		
2016	67.9	(48.9–81.2)
2017	32.1	(18.8–51.1)
Type of index MOUD (%)		
Buprenorphine or buprenorphine/naloxone	59.2	(38.1–89.7)
Methadone	27.6	(0–56.6)
Naltrexone, oral	5.9	(1.6–9.3)
Naltrexone, intramuscular injection	7.3	(0.3–12.7)
Comorbidities (%)		
Infectious diseases	16.8	(9–20.1)
Mental illness or non-opioid substance use disorder	67.3	(62.9–97.2)
Medical complications associated with injection drug use	13.4	(10.1–15.1)
Medicaid-enrolled months from date of index MOUD through 12 months (mean)	11.4	(10.9–11.7)
Follow-up months from date of index MOUD until overdose, censoring event or study conclusion (mean)	9.5	(8.7–10.3)
Discontinued MOUD before an overdose or censoring event (%)	67	(37.5–80.6)
Overdose any time from date of index MOUD to 12 months follow-up (%)	5.1	(1.6–7.7)

Authors' calculations from Medicaid enrollment and health-care claims data from the 11 participating states. Adults with disabilities includes adults eligible for Medicaid through participation in the Supplemental Security Income program. MOUD = medication for opioid use disorder. The index MOUD date is the date of the first observed MOUD claim.

index MOUD claim. A total of 14 903 beneficiaries (5.1%) had an overdose between the date of the MOUD index claim and the end of the 12-month follow-up period (Table 2).

Analytical sample for landmark regression analysis

For each time-point, the number of subjects included and excluded from the regression analysis are shown in Table 3. For example, to analyze the likelihood of overdose during the follow-up period among those continuing MOUD beyond 60 days and those who discontinued on or before 60 days, there were 280 186 subjects, of whom 203 074 (72.5%) were still receiving MOUD and 77 112 (27.5%) who had discontinued. The 60-day analysis excluded the 12 994 subjects who had an overdose or a censoring event on or before the 60-day landmark time-point. Among the analytical sample of 280 186 subjects, 4.1% had an overdose during the 12-month follow-up period.

Association between MOUD continuation and overdose

The black line in Figure 1 illustrates the global estimates from the meta-analyses. Global and state-specific point estimates are shown in Table 4. On average across the study states, enrollees who continued MOUD beyond 60 days after the index MOUD date had a significantly lower hazard of an opioid-related overdose within the 12-month follow-up period than those who discontinued on or before day 60 [HR = 0.39; 95% CI = 0.36–0.42; P < 0.0001; 90% prediction interval (PI) = 0.34–0.45]. We can interpret the HR of 0.39 as a 61% lower likelihood of overdose conditional on still being at risk for an overdose in the immediate prior period (i.e. days 1–60 after the index MOUD). We observed a significant protective association between MOUD continuation and risk of overdose at each subsequent landmark time-point. The PIs are not much wider than the CIs at each landmark time-point, indicating the consistency of HR estimates across states. The results from Cochran's Q test suggested non-significant deviation from homogeneity at all landmark time-points except day 60 (Table 4). Complete results of the meta-analyses are included in Supporting information, eTable 1.

Test of trend

We found the hazard of an overdose event as 0.90 times lower (95% CI = 0.88–0.92; P < 0.0001) with each additional 60 days of MOUD continuation from our test for trend regression analysis. This represents a 10% risk reduction with each additional 60 days of MOUD. Complete results for the trend test appear in Supporting information, eTable 2.

Sensitivity analyses

Our results were robust to the inclusion of the type of MOUD at index in the regression model (Supporting information, eFigure 1). Results from our estimation of E-values for the global HR estimates indicate that the magnitude of unmeasured confounding would need to be very large (i.e. an HR of 0.22) to explain away the observed association between continuation and overdose risk (Supporting information, eTable 3). The results of our analysis of the moderating

TABLE 3 Analytical sample for landmark regression analyses

	Landmark time-point (days since index MOUD)				
	60	120	180	240	300
Included in analytical sample	280 186	253 447	227 873	206 357	187 055
Discontinued MOUD, *n*	77 112	88 900	87 010	83 272	76 756
Continued MOUD, *n*	203 074	164 547	140 863	123 085	110 299
Excluded from analytical sample (cumulative)	12 994	39 733	65 307	86 823	106 125
Percentage of analytical sample with an overdose within the 12-month follow-up period (*n*)	4.1% (11450)	3.2% (8022)	2.3% (5184)	1.5% (3076)	0.7% (1311)

A separate Cox proportional hazard regression was estimated for each landmark time-point, including only those subjects who remained at risk for the outcome through that time-point. Each column describes the composition of the analytical sample, including those who discontinued MOUD on or before that time-point and those who continued. The number of subjects excluded from each analytical sample is also noted; individuals were excluded if they experienced an overdose or disenrollment on or before the time-point. Once excluded, subjects did not re-enter the analytical sample.
MOUD = medication for opioid use disorder.

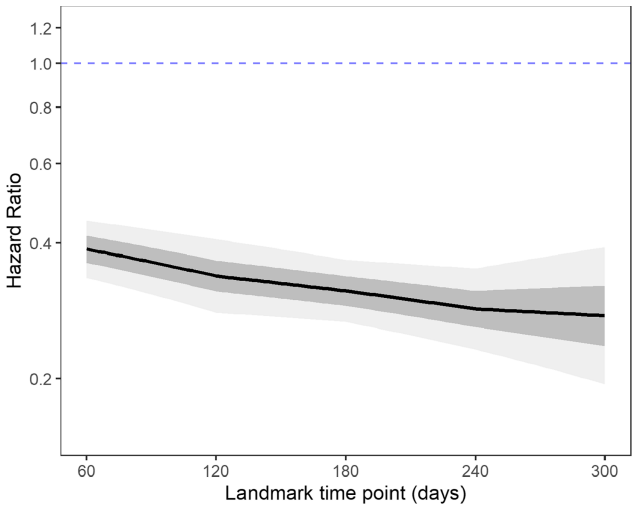

FIGURE 1 Relative hazard of opioid-related overdose among Medicaid beneficiaries who continued compared to those who discontinued medication for opioid use disorder. Authors' calculations from Medicaid claims and enrollment data. The bold line intersects the global hazard ratio estimates from the meta-analysis of state specific results. The dark grey region represents the 95% confidence interval for the global estimate, and the light grey region represents the 90% prediction interval for the global estimate [Color figure can be viewed at wileyonlinelibrary.com]

role of MOUD type were consistent in the four states where the analysis was feasible (Supporting information, eFigure 2). Risk of overdose was lower, and statistically significantly different from 1, for those continuing versus discontinuing with either buprenorphine or methadone. For naltrexone, the magnitude of the protective association was smaller, and generally not statistically significantly different from 1.

DISCUSSION

In the largest study of MOUD continuity among Medicaid enrollees with OUD, we estimated a substantial relative reduction in risk of medically treated overdose for enrollees who continued compared to those who discontinued MOUD at every observed time-point during a 12-month period. We found a consistent association between MOUD duration and reduction in overdose across states that varied in demographics [56], Medicaid policy [57], opioid epidemic severity [58] and substance use disorder treatment capacity [59]: all factors that may affect OUD treatment and overdose. The robustness of our findings in such diverse settings and populations increases our confidence in the relationship. Furthermore, our estimates indicated that the magnitude of the risk reduction increased during the 12-month period. These results highlight the importance of policies and interventions to support patients' continuation of MOUD.

There is room for improvement. This study team previously reported a flat trend from 2014 to 2018 in the prevalence of Medicaid beneficiaries with OUD from 11 states who received at least 180 days of MOUD [37]. A growing body of research examines the effectiveness of multiple approaches to improve MOUD treatment retention that may alter this trend. Inclusion of peer recovery coaches within the medical team is associated with MOUD treatment and opioid abstinence [60]. Recent research within a US Veteran population found that telehealth encounters for SUD, relative to in-person visits, are associated with lower rates of MOUD discontinuation during a 12-month period [61]. Looking ahead, a new multi-site clinical trial will test the effectiveness of alternative interventions to improve MOUD treatment retention [17]. A critical next step will be to engage Medicaid programs in the adoption of these strategies, as well as the reduction in policies that may impose limits on treatment duration [62].

Our findings suggest caution in the use of quality measures that specify a single treatment duration to assess health system performance such as the National Qualify Forum endorsed measure of 180 days' MOUD duration [21]. The adoption of a single cut-point ignores the benefits associated with treatment durations that fall short of 180 days and those that exceed it. Indeed, the technical documentation defining the measure notes the absence of evidence to identify the effectiveness of MOUD treatment for fewer than

TABLE 4 Hazard of overdose among those who continued through each time-point relative to those who discontinued: results from random-effects meta-analysis and state-specific Cox proportional hazard regression

	Landmark time-point				
	Global estimates				
	60	120	180	240	300
Hazard ratio	0.39[c]	0.34[c]	0.31[c]	0.29[c]	0.28[c]
(95% CI)	(0.36, 0.42)	(0.31, 0.37)	(0.29, 0.34)	(0.26, 0.31)	(0.24, 0.32)
[90% PI]	[0.34, 0.45]	[0.28, 0.41]	[0.27, 0.42]	[0.26, 0.31]	[0.19, 0.39]
P-value for Cochran's *Q* test	0.0135	0.237	0.376	0.634	0.576
State, hazard ratio (95% CI)	State-specific estimates				
A	0.33[c] (0.29, 0.38)	0.29[c] (0.24, 0.35)	0.27[c] (0.21, 0.35)	0.25[c] (0.18, 0.36)	0.26[c] (0.15, 0.46)
B	0.39[c] (0.35, 0.43)	0.37[c] (0.33, 0.42)	0.37[c] (0.32, 0.42)	0.32[c] (0.27, 0.38)	0.33[c] (0.25, 0.44)
C	0.36[c] (0.32, 0.4)	0.32[c] (0.28, 0.37)	0.28[c] (0.24, 0.33)	0.33[c] (0.27, 0.41)	0.28[c] (0.2, 0.38)
D	0.36[c] (0.27, 0.49)	0.44[c] (0.31, 0.62)	0.38[c] (0.25, 0.56)	0.35[c] (0.2, 0.6)	0.46[a] (0.22, 0.95)
E	0.41[c] (0.38, 0.43)	0.34[c] (0.31, 0.36)	0.3[c] (0.27, 0.33)	0.27[c] (0.23, 0.31)	0.27[c] (0.21, 0.34)
F	0.45[c] (0.42, 0.49)	0.36[c] (0.33, 0.4)	0.31[c] (0.27, 0.35)	0.28[c] (0.23, 0.33)	0.21[c] (0.15, 0.28)
G	0.31[c] (0.2, 0.48)	0.29[c] (0.17, 0.48)	0.3[c] (0.16, 0.55)	0.2[c] (0.08, 0.5)	0.37 (0.09, 1.52)
H	0.39[c] (0.32, 0.49)	0.33[c] (0.25, 0.42)	0.31[c] (0.22, 0.43)	0.22[c] (0.14, 0.36)	0.3[b] (0.15, 0.63)
I	0.37[c] (0.29, 0.46)	0.28[c] (0.2, 0.37)	0.3[c] (0.2, 0.45)	0.27[c] (0.16, 0.46)	0.31[b] (0.14, 0.65)
J	0.4[c] (0.31, 0.52)	0.38[c] (0.28, 0.52)	0.34[c] (0.23, 0.5)	0.3[c] (0.18, 0.51)	0.17[c] (0.06, 0.46)
L	0.38[b] (0.21, 0.69)	0.28[c] (0.15, 0.5)	0.42[a] (0.21, 0.87)	0.2[c] (0.08, 0.48)	0.16[a] (0.04, 0.68)

Global hazard ratio (HR) is from the random-effects meta-analysis, adjusting for the covariates shown in Table 2; 95% confidence interval (CI) was generated using the Hartung–Knapp–Sidik–Jonkman method.
Two-sided *P*-value was reported.
[a]*P*-value < 0.05;
[b]*P*-value < 0.01;
[c]*P*-value < 0.001.
The 90% prediction interval (PI) is constructed following the approach in Supporting information, eAppendix 4. It can be interpreted as denoting the range within which the prevalence ratios would fall for 90% of states if a different sample of states were to be drawn. It estimates the between-state variability of the true prevalence ratios of the state populations. Cochran's *Q* tests the statistical significance of the observed state-level variability. State-specific HRs are from Cox proportional hazard regressions, adjusting for the covariates shown in Table 2.

3 months or any upper duration limit [21]. We found a strong association between MOUD treatment and reduced risk of overdose at durations as short as 60 days among Medicaid beneficiaries with a diagnosis of OUD. Moreover, when we tested for a trend in the global estimates across time-points, we found an incremental benefit associated with each additional 60 days of treatment; specifically, a 10% relative reduction in risk of overdose. In other words, MOUD treatment appeared increasingly protective at each 60-day treatment duration observed up to 12 months following the index claim. Performance metrics that encourage health systems to increase retention in MOUD treatment rather than to meet one duration threshold may better serve patients.

Limitations

This observational study has limitations. First, unobserved differences in the treatment and comparison cohorts related to MOUD duration and risk of overdose may bias study findings. For example, we cannot observe care-seeking preferences, factors related to Medicaid disenrollment or health conditions and overdose events that preceded the study period. However, the estimated E-values for our results suggest that the magnitude of association between an unobserved confounder and MOUD duration and overdose would need to be very large to explain away the study results. Secondly, our results reflect Medicaid programs and populations in 2016–18 which may not generalize to 2021, given the dynamic nature of the opioid epidemic and treatment landscape. Thirdly, we observed Medicaid-paid claims and may have underestimated MOUD duration or misclassified MOUD discontinuation, if individuals obtained treatment from other sources. Fourthly, our outcome measure included opioid-related overdose cases observed in a health-care setting and will thus underestimate all overdose events in the population. Finally, our study population reflects a subset of Medicaid programs, and may not generalize to all Medicaid populations or programs in the country.

CONCLUSION

Longer is better. Our findings align with research supporting the benefits of longer duration of MOUD episodes of care [23–25] and add to the existing evidence by quantifying how even relatively small increases in treatment duration are associated with reductions in risk of overdose in a population that continues to be disproportionately affected by the opioid epidemic. After a year in which opioid-related overdose deaths have climbed dramatically [1], there is yet greater urgency to identify and implement effective opioid-related overdose prevention strategies. This study finds that for Medicaid beneficiaries, supporting continuity of MOUD probably represents one such strategy.

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DECLARATION OF INTERESTS

None.

AUTHOR CONTRIBUTIONS

Marguerite Burns: Conceptualization; formal analysis; funding acquisition; investigation; methodology; project administration; resources; supervision; validation. **Lu Tang:** Formal analysis; methodology; software. **Chung-Chou Chang:** Methodology; validation. **Joo Yeon Kim:** Data curation; formal analysis; methodology; software. **Katherine Ahrens:** Data curation; formal analysis; funding acquisition; project administration; software. **Lindsay Allen:** Conceptualization. **Adam Gordon:** Conceptualization; funding acquisition; investigation. **Marian Jarlenski:** Conceptualization; investigation; validation. **Peter Cunningham:** Writing – review & editing-Equal. **Paul Lanier:** Data curation; investigation; project administration; supervision. **Rachel Mauk:** Data curation; project administration; software; validation. **Mary Joan McDuffie:** Formal analysis. **Shamis Mohamoud:** Software. **Jeffery Talbert:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation; visualization. **Kara Zivin:** Project administration. **Julie Donohue:** Conceptualization; funding acquisition; investigation; project administration; resources; supervision.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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