7-11-2022

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Jason M. Glanz

Ingrid A. Binswanger

Christina L. Clarke

Anh P. Nguyen

Morgan A. Ford

See next page for additional authors

Recommended Citation

Glanz JM, Binswanger IA, Clarke CL, Nguyen AP, Ford MA, Ray GT, Xu S, Hechter RC, Yarborough BJH, Roblin DW, Ahmedani B, Boscarino JA, Andrade SE, Rosa CL, and Campbell CI. The association between buprenorphine treatment duration and mortality: a multi-site cohort study of people who discontinued treatment. Addiction 2022.

Authors

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Received: 3 November 2021 | Accepted: 22 June 2022

DOI: 10.1111/add.15998

RESEARCH REPORT

ADDICTION SSA

The association between buprenorphine treatment duration and mortality: a multi-site cohort study of people who discontinued treatment

Jason M. Glanz[1,2] | Ingrid A. Binswanger[1,3,4,5] | Christina L. Clarke[1] | Anh P. Nguyen[1] | Morgan A. Ford[1] | G. Thomas Ray[6] | Stanley Xu[7] | Rulin C. Hechter[7] | Bobbi Jo H. Yarborough[8] | Douglas W. Roblin[9] | Brian Ahmedani[10,11] | Joseph A. Boscarino[12] | Susan E. Andrade[13] | Carmen L. Rosa[14] | Cynthia I. Campbell[6]

[1]Institute for Health Research, Kaiser Permanente Colorado, Aurora, CO, United States

[2]Colorado School of Public Health, Aurora, CO, United States

[3]Colorado Permanente Medical Group, Aurora, CO, United States

[4]Division of General Internal Medicine, Department of Medicine, University of Colorado School of Medicine, Aurora, CO, United States

[5]Department of Health System Sciences, Kaiser Permanente Bernard J. Tyson School of Medicine, Pasadena, CA, United States

[6]Division of Research, Kaiser Permanente Northern California, Oakland, CA, United States

[7]Department of Research & Evaluation, Kaiser Permanente Southern California, Pasadena, CA, United States

[8]Center for Health Research, Kaiser Permanente Northwest, Portland, OR, United States

[9]Mid-Atlantic Permanente Research Institute, Kaiser Permanente Mid-Atlantic States, Rockville, MD, United States

[10]Center for Health Policy and Health Services Research, Henry Ford Health System, Detroit, MI, United States

[11]Department of Behavioral Health Services, Henry Ford Health System, Detroit, MI, United States

Abstract

Background and aims: Buprenorphine is an effective medication for opioid use disorder that reduces mortality; however, many patients are not retained in buprenorphine treatment, and an optimal length of treatment after which patients can safely discontinue treatment has not been identified. This study measured the association between buprenorphine treatment duration and all-cause mortality among patients who discontinued treatment. Secondary objectives were to measure the association between treatment duration and drug overdose and opioid-related overdoses.

Design: Multi-site cohort study.

Setting: Eight US health systems.

Participants: Patients who initiated and discontinued buprenorphine treatment between 1 January 2012 and 31 December 2018 (n = 6550). Outcomes occurring after patients discontinued buprenorphine treatment were compared between patients who initiated and discontinued treatment after 8–30, 31–90, 91–180, 181–365 and > 365 days.

Measurements: Covariate data were obtained from electronic health records (EHRs). Mortality outcomes were derived from EHRs and state vital statistics. Non-fatal opioid and drug overdoses were obtained from diagnostic codes. Four sites provided cause-of-death data to identify fatal drug and opioid-related overdoses. Adjusted frailty regression was conducted on a propensity-weighted cohort to assess associations between duration of the final treatment episode and outcomes.

Findings: The mortality rate after buprenorphine treatment was 1.82 per 100 person-years (n = 191 deaths). In regression analyses with > 365 days as the reference group,

Jason M. Glanz and Ingrid A. Binswanger Co-first authors, having contributed equally to this manuscript.

[12]Department of Population Health Sciences, Geisinger Clinic, Danville, PA, United States

[13]Meyers Primary Care Institute, Worcester, MA, United States

[14]National Institute on Drug Abuse, Bethesda, MD, United States

Correspondence
Jason M. Glanz PhD, Senior Investigator, Institute for Health Research, Kaiser Permanente Colorado, 2550 South Parker Road, Suite 200, Aurora, CO 80014, USA.
Email: jason.m.glanz@kp.org

Funding information
This study was supported by a grant from the National Institute on Drug Abuse (NIDA) (UG1DA040314, CTN Protocol ID: CTN-0084-A-1). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

treatment duration was not associated with all-cause mortality and drug overdose ($P > 0.05$ for both). However, compared with > 365 days of treatment, 91–180 days of treatment was associated with increased opioid overdose risk (hazard ratio = 2.94, 95% confidence interval = 1.11–7.79).

Conclusions: Among patients who discontinue buprenorphine treatment, there appears to be no treatment duration period associated with a reduced risk for all-cause mortality. Patients who discontinue buprenorphine treatment after 91–180 days appear to be at heightened risk for opioid overdose compared with patients who discontinue after > 365 days of treatment.

KEYWORDS
Buprenorphine, cohort, mortality, opioid, opioid use disorder, overdose

INTRODUCTION

Buprenorphine is an effective treatment for opioid use disorder (OUD) that reduces the risk of recurrence of opioid use, overdose and death [1–5]. People who discontinue treatment are at increased risk for overdose and all-cause mortality, particularly in the first 4 weeks after ceasing treatment [1, 6]. As a result, the American Society of Addiction Medicine and the Substance Abuse and Mental Health Services Administration do not recommend a limit on the time patients remain on buprenorphine treatment [7, 8]. Retaining patients on buprenorphine treatment, however, is difficult [2, 9–12]. At treatment onset, more than a quarter of patients report that they do not want to stay on buprenorphine treatment for more than 6 months [13], and approximately 40% of patients who initiate treatment discontinue within 6 months [14, 15]. Patients may voluntarily discontinue because of other life obligations or dissatisfaction with the medication, or they may be involuntarily discontinued because of conflicts with program staff, difficulty adhering with program requirements, substance use or incarceration [13].

At present, a time-period after which patients can safely discontinue buprenorphine treatment has not been established. Treatment durations of greater than a year have been associated with reduced emergency department (ED) and inpatient utilization [16], but the effect of treatment duration on mortality risk is not known. Randomized clinical trials could help to identify an optimal duration of buprenorphine treatment, but such studies may face ethical challenges and enroll participants who do not necessarily represent the overall population of patients indicated for treatment. To address this gap in research, we conducted a multi-site cohort study to examine the association between duration of buprenorphine treatment and mortality among patients who discontinued treatment. Participating sites represent a diverse group of health systems that provide care for commercially insured, Medicaid and Medicare populations. A propensity score analytical approach with inverse probability weighting was used to control for confounding. We hypothesized that mortality risk after buprenorphine discontinuation would increase with shorter buprenorphine treatment duration prior to discontinuation. As secondary objectives, we examined associations between buprenorphine treatment duration and risks of fatal and non-fatal opioid and drug overdoses (also called poisonings) after treatment discontinuation. We followed reporting guidelines from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

METHODS

Study settings, data sources and data elements

The study (CTN-0084A1) was conducted using data from the Opioid Registry (CTN-0084) of the Health Systems Node, a multi-site collaboration funded by the National Institute on Drug Abuse, National Drug Abuse Treatment Clinical Trials Network (CTN). The following eight health system sites participated in the study: Geisinger Health System (Pennsylvania); the Henry Ford Health System (HFHS, Michigan); Kaiser Permanente Colorado (KPCO); Kaiser Permanente Mid-Atlantic States (KPMAS, Maryland, Virginia, and Washington, DC); Kaiser Permanente Northern California (KPNC); Kaiser Permanente Northwest (KPNW, Oregon); Kaiser Permanente Southern California (KPSC); and Meyers Primary Care Institute (MPCI, for Fallon Health, Massachusetts). Each health system site represented an integrated health insurance plan and care delivery system serving between approximately 270 000 and 4.7 million patients among multiple clinics, pharmacies and hospitals. Each site delivered OUD treatment through internal or contracted specialty addiction treatment programs

and, in some cases, primary care. All sites provided sublingual buprenorphine or buprenorphine/naloxone (hereafter referred to as buprenorphine), oral and intramuscular naltrexone, and referrals to externally licensed methadone treatment programs.

Each site created standardized data sets derived from the Opioid Registry, a harmonized, distributed registry maintained locally at each health system site. The Opioid Registry includes electronic health record (EHR), automated pharmacy records, membership/enrollment and mortality data tables. All patients with at least one opioid dispensation or a diagnosis of OUD between 2012 and 2018 were included in the registry. The following data elements were used for study eligibility, covariates and outcomes: demographic variables (sex, age, race and ethnicity); types of insurance (commercial, Medicare and Medicaid); insurance enrollment dates; medical encounters in the outpatient, inpatient and ED settings; and outpatient dispensed medications including dose and days' supply. National drug codes (NDC) were used to identify buprenorphine, antidepressants, gabapentin, zolpidem, eszopiclone, zaleplon and benzodiazepines. Procedure claims codes were used to identify methadone treatment (Supporting information, Table S2 lists procedure codes used) because methadone for opioid use disorder treatment occurs in externally licensed treatment centers. Naltrexone was identified with both NDC and procedure codes. Diagnoses were identified using International Classification of Disease (ICD)-9 and -10 codes (Supporting information, Table S1 lists ICD codes used) or tumor registries. All sites provided data on death and date of death recorded in the EHR, including deaths that occurred in the ED or hospital or that were reported to the treating physician, health system or insurance plan (fact of death). For a subset of health systems (KPCO, KPNW, KPNC and Henry Ford), state vital statistics offices supplemented EHR-based vital records with cause-of-death data. The other four sites were not able to contribute cause of death data due to privacy policies.

Approval to conduct this study was granted by the KPNC Institutional Review Board (IRB), with each of the other sites' IRBs ceding oversight to the KPNC IRB.

Study design and population

We conducted a retrospective cohort study of patients aged 18 years and older who had initiated and discontinued buprenorphine treatment. We first identified patients who had initiated treatment between 1 January 2012 and 31 December 2017. These patients had to have at least 90 days of continuous insurance enrollment prior to their first buprenorphine dispensing and at least 1 day of insurance enrollment after discontinuing buprenorphine. Requiring 90 or more days of enrollment helped to ensure adequate capture of covariate data and to ensure an accurate assignment of the treatment start date, as patients could enter the health plan already receiving buprenorphine treatment. Patients with self-funded insurance or insurance without pharmacy coverage were excluded. Patients were followed from inclusion in the study sample until 31 December 2018. We then limited the cohort to patients who had discontinued buprenorphine treatment at some point throughout the follow-up. Patients who were still receiving treatment at the end of 2018 were not included.

Buprenorphine treatment during the study period was categorized into treatment episodes. Distinct treatment episodes were separated by buprenorphine dispensing gaps of 28 days or more [17]. Patients could have multiple treatment episodes throughout the follow-up. Treatment episodes of fewer than 8 days were excluded, as these patients probably had an unsuccessful induction onto buprenorphine. We also excluded treatment episodes interrupted by disenrollment from the health plan, death, hospice or a cancer diagnosis.

The ending date of a buprenorphine treatment episode—the date when the patient discontinued buprenorphine treatment—was considered the index date. Patients with multiple treatment episodes separated by 28 or more days had multiple index dates. For patients with multiple treatment episodes, the primary analysis focused upon the final treatment episode during the study period; time on treatment was not summed across treatment episodes unless the gap was less than 28 days. We analyzed the final treatment episode during the study period to avoid biasing results in favor of shorter treatment episodes. For example, among the patients with more than one treatment episode the initial episode, was on average, 30 days shorter than the final treatment episode. These patients probably required multiple treatment episodes to treat their opioid use disorder because the earlier episodes were not fully effective. Patients with multiple treatment episodes also could not have died between treatment episodes during the study period. Including earlier treatment episodes in the analysis could therefore bias the results by underestimating the mortality rate following shorter treatment durations [17].

After buprenorphine discontinuation, follow-up started the day after the index date and ended on the earliest occurrence of either death, disenrollment, a switch to methadone or naltrexone treatment or 31 December 2018. We censored follow-up at a switch to methadone or naltrexone treatment because they are known to affect mortality risk among patients with an opioid use disorder [5, 18].

Although the primary analysis focused on the final treatment episode during the study period, it is possible that this could introduce a bias favoring longer treatment episodes. We therefore conducted a sensitivity analysis that included all treatment episodes during the study period.

Exposure groups, outcomes and covariates

Patients who initiated and discontinued buprenorphine treatment were divided into five groups based on clinically relevant durations of time on buprenorphine treatment: 8–30, 31–90, 91–180, 181–365 and > 365 days. These time-periods were selected to capture the evolving intensity of clinical monitoring over time on treatment. Early in treatment, programs may provide more frequent visits (e.g. weekly), request more frequent urine drug toxicology and provide smaller supplies of medication, whereas, after patients appear stable, programs may provide less frequent visits, request less frequent toxicology and

provide longer medication supplies [7, 19]. The periods were also selected to ensure that we captured early treatment discontinuation, as the median length of treatment observed was 36 days [interquartile range (IQR) = 19, 137].

Outcomes were assessed in the post-discontinuation follow-up time (i.e. after the index date). For our primary outcome, we examined all-cause mortality in all eight sites using deaths identified in each site's opioid registry. As secondary outcomes, we examined non-fatal and fatal opioid overdoses and fatal and non-fatal drug overdoses in a subset of four sites that had cause-of-death data available (see Supporting information, Table S1 for ICD codes). Person-time was censored at the first overdose event after the last treatment episode; patients could not experience multiple overdoses after the episode.

We considered covariates that were either known to be associated with buprenorphine retention based on prior studies or thought to impact upon whether or not a patient was discontinued from treatment [15, 20–22]. Demographic covariates included age, race and ethnicity. We assessed several medication exposures as covariates, including dispensing of antidepressants, gabapentin, zolpidem, eszopiclone, zaleplon and benzodiazepines in the 6 months prior to and including the first day of the final buprenorphine treatment episode. We also considered prescription opioid dispensing in the 30 days prior to and including the first day of the final treatment episode, and the total number of prior buprenorphine treatment episodes. The following clinical covariates were measured in the 6 months prior to and including the first day of the final treatment episode: medical comorbidity (captured with the Quan modification of the Charlson Comorbidity Index) [23], number of prior ED visits, prior drug overdose, severity of OUD diagnosis (mild/moderate, severe and unknown), infections associated with injection drug use (e.g. infective endocarditis, hepatitis B, abscess, cellulitis) [24], alcohol use disorder, non-opioid drug use disorders [9, 10, 14, 20] and mental health conditions (schizophrenia and psychotic disorder, mood disorders including bipolar, major depressive disorder and adjustment disorder with depressed mood, anxiety and post-traumatic stress disorder, personality disorders and attention deficit hyperactivity disorders). We also assessed the maximum dispensed buprenorphine dose (milligrams per day) during the final treatment episode; due to secular changes in OUD treatment practices, we considered the calendar year that patients started their final treatment episode.

Analysis

Propensity score

To account for the imbalance of covariates among the five buprenorphine treatment duration groups, we conducted a propensity score analysis and applied stabilized weighting. Stabilized weighting is an improved version of inverse probability weighting (IPTW) that reduces the impact of observations with extreme IPTW values [25, 26]. Among the covariates under consideration, we included those that were associated with both treatment duration and all-cause mortality (i.e. potential confounders). To determine which covariates were associated with treatment duration, we conducted univariate multinomial logistic regressions with the five treatment duration categories as the dependent variable and each covariate as the independent variable. For all-cause mortality, we conducted univariate Cox proportional hazard regressions, with death as the dependent variable and each covariate as the independent variable. To calculate the propensity scores and stabilized weights, covariates with $P < 0.10$ in both univariate regression analyses were included in a single multivariable multinomial logistic regression model, with treatment duration group as the dependent variable. The weights were applied to the cohort, and covariate balance across treatment groups was assessed with population standardized mean differences (PSD) before and after propensity score weighting and with diagnostic plots. To calculate the PSDs, we set up separate bivariate comparisons for each covariate within each of the five treatment groups (e.g. treatment duration of 8–30 days versus pooled population), resulting in five different comparisons for each covariate [27]. For a given covariate, a PSD of less than 0.10 was considered adequate balance [28].

A time-to-event analysis was conducted on the propensity-weighted cohort to assess the association between treatment duration and primary and secondary outcomes. A buprenorphine treatment duration of > 365 days served as the referent group for the five-level treatment duration variable. Frailty models were used to estimate adjusted hazard ratios (aHRs) and 95% confidence intervals (CI) [29]. A frailty model is an extension of a Cox proportional hazards model that incorporates random effects to account for the clustering of observations. Study site was included in the models as a random effect, and the maximum dispensed dose of buprenorphine (mg/day) was included in the model as a covariate. Variables from the propensity score analysis with PSDs greater than 0.10 across two or more of the treatment comparisons were included as covariates to account for residual confounding [28]. In *post-hoc* analyses, pairwise comparisons were conducted between the treatment duration groups without an adjustment for multiple comparisons. We conducted two-sided statistical tests with a $P < 0.05$ cut-off for statistical significance. The proportional hazards assumption was evaluated with scaled Schoenfield residuals plots and a global goodness-of-fit test. For age, the assumption of linearity in the log hazard was assessed with a Kolmogorov-type supremum test in which a *P*-value was calculated based on a sample of 1000 residual patterns [30]. A *P*-value < 0.05 indicates a departure from linearity.

Published studies have documented higher mortality in the first 4 weeks off treatment [5]; therefore, Kaplan–Meier curves for all-cause mortality were generated to visually examine the survival probabilities across groups over time. We examined the first 180 days off treatment to visualize differences that occur early after treatment discontinuation.

As a sensitivity analysis, all treatment episodes during the study period were assessed in a frailty model. Individual patients were included in the model as a random effect, which accounted for the clustering of treatment episodes among individuals who had more than one episode. All-cause mortality, and fatal and non-fatal

overdose rates were calculated between treatment episodes and after the final episode. For fatal and nonfatal overdose, person-time was censored at the fatal overdose, but individuals could experience recurrent non-fatal overdoses between multiple treatment episodes. Site was included in the frailty model as a strata variable, and all the variables described in the primary analysis were assessed as time-varying covariates at or prior to each treatment episode.

All analyses were conducted using SAS® Studio Software version 3.8 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient characteristics

We identified 6550 patients who initiated and discontinued buprenorphine treatment between 1 January 2012 and 31 December 2017, and had at least 1 day of health plan enrollment after discontinuing treatment (Figure 1). The number of buprenorphine treatment episodes ranged from one to 17 (median 1), but a majority of patients (*n* = 4897, 74.8%) had a single treatment episode. The mean and median times on treatment were 181.4 days [standard deviation (SD) = 289.6] and 60 days (IQR = 27–203), respectively. Among those with multiple treatment episodes, the mean times on treatment for the initial and final episodes were 109.5 days (SD = 169.5) and 139.6 days (SD = 237.3), respectively. The median times on treatment for initial and final episodes were 42 days (IQR = 22–126) and 40 days (IQR = 21–141), respectively. The mean time between treatment episodes was 264 days (SD = 298), and the median time between episodes was 147 (IQR = 64–351). Approximately 46% of patients (*n* = 3014) discontinued buprenorphine between 8 and 30 days after initiating the final treatment episode.

The mean age of the cohort was 36.8 years (SD = 14.7); 39.2% of the patients were female, 72.5% were non-Hispanic white and 12.9% were Hispanic (Table 1). Approximately 29% may have transitioned from opioid analgesic use, based on receiving opioid dispensings in the month prior to starting buprenorphine. Most (82.3%) had moderate-to-severe OUD diagnoses, and a majority (54.7%) had mental health diagnoses.

Among all eight health systems, 191 cohort members died after discontinuing buprenorphine treatment (1.82 per 100 person-years; Table 2). The highest crude mortality rate was among patients who received buprenorphine for 91 to 180 days (2.92 per 100 person-years). Among the sites with complete cause-of-death information (*n* = 3934) the rate of fatal and non-fatal drug overdose was 5.55 per 100 person-years (*n* = 327), and approximately one-third were noted to be opioid-related (*n* = 109, 1.78 per 100 person-years). Among the 109 opioid overdoses from the four sites with cause-of-death data, 80 (73.4%) were non-fatal and 29 (26.6%) were fatal. Similar to all-cause mortality, the highest overdose rates occurred among people who were treated from 91 to 180 days (drug = 6.63 per 100 person-years; opioid = 2.76 per 100 person-years).

Propensity score weighting

In the univariate regression analyses, the following variables were associated with both treatment and all-cause mortality ($P < 0.10$): age,

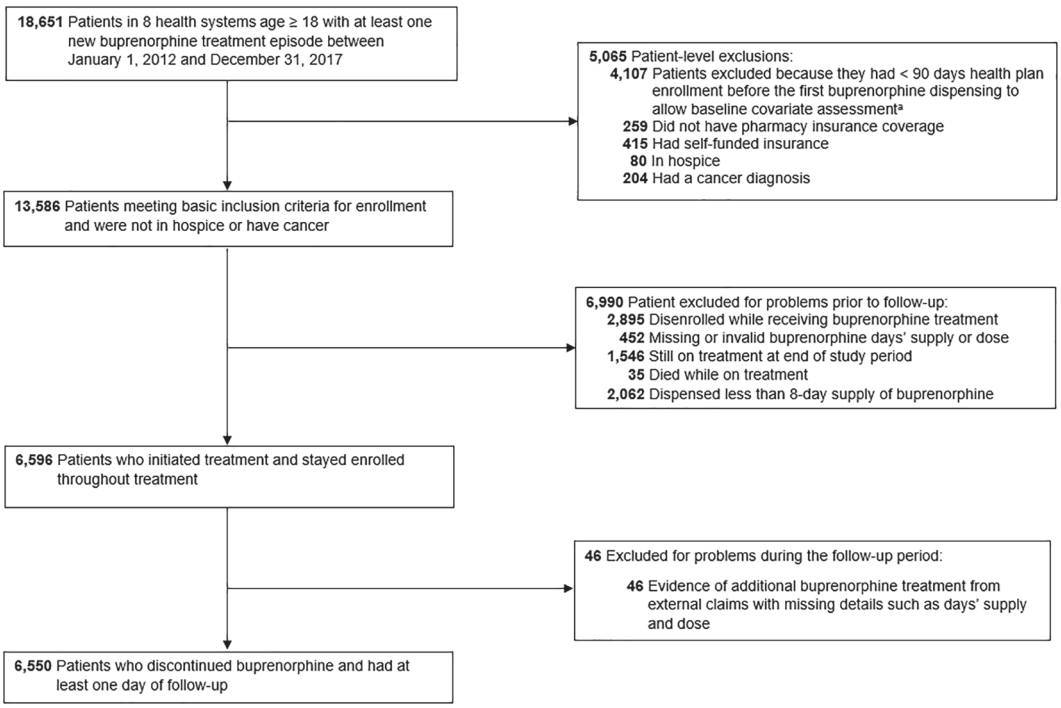

FIGURE 1 Cohort diagram. [a]2228 (54%) also had at least one other exclusion criterion

TABLE 1 Unweighted characteristics of patients in eight health systems who discontinued buprenorphine between 2012 and 2018, by buprenorphine treatment episode duration[a]

	Buprenorphine treatment duration						
Characteristic	**All ≥ 8 days (*N* = 6550)**	**8–30 days (*n* = 3014)**	**31–90 days (*n* = 1426)**	**91–180 days (*n* = 768)**	**181–365 days (*n* = 622)**	**≥ 366 days (*n* = 720)**	***P*-value**
Age, mean (SD)	36.8 (14.7)	37.1 (15.5)	35.2 (13.8)	35.5 (13.5)	37.2 (13.8)	39.5 (14.6)	< 0.0001
Gender, *n* (%)							0.3941
Female	2568 (39.2)	1157 (38.4)	550 (38.5)	312 (40.6)	247 (39.7)	302 (41.9)	
Male	3982 (60.8)	1857 (61.6)	876 (61.4)	456 (59.4)	375 (60.3)	418 (58.1)	
Race/ethnicity, *n* (%)							< 0.0001
Black, non-Hispanic	337 (5.1)	181 (6.0)	59 (4.1)	35 (4.6)	25 (4.0)	37 (5.1)	
Hispanic	848 (12.9)	449 (14.9)	186 (13.0)	75 (9.8)	68 (10.9)	70 (9.7)	
Asian, Pacific Islander, Native American and Other non-Hispanic	221 (3.4)	106 (3.5)	46 (3.2)	22 (2.9)	30 (4.8)	17 (2.4)	
Unknown[b]	395 (6.0)	165 (5.5)	108 (7.6)	61 (7.9)	36 (5.8)	25 (3.5)	
White, non-Hispanic	4749 (72.5)	2113 (70.1)	1027 (72.0)	575 (74.9)	463 (74.4)	571 (79.3)	
Year treatment episode started,[a] *n* (%)							0.0028
2012	789 (12.0)	361 (12.0)	192 (13.5)	91 (11.8)	64 (10.3)	81 (11.3)	
2013	1063 (16.2)	485 (16.1)	233 (16.3)	118 (15.4)	91 (14.6)	136 (18.9)	
2014	1072 (16.4)	500 (16.6)	211 (14.8)	123 (16.0)	102 (16.4)	136 (18.9)	
2015	1138 (17.4)	535 (17.8)	249 (17.4)	123 (16.0)	109 (17.5)	122 (16.9)	
2016	1237 (18.9)	557 (18.5)	250 (17.5)	156 (20.3)	118 (19.0)	156 (21.7)	
2017	1251 (19.1)	576 (19.1)	291 (20.4)	157 (20.4)	138 (22.2)	89 (12.4)	
Opioid dispensed in 30 days prior to buprenorphine treatment episode,[a] *n* (%)	1915 (29.2)	893 (29.6)	405 (28.4)	221 (28.8)	178 (28.6)	218 (30.3)	0.8617
Medications dispensed in 6 months prior to buprenorphine treatment episode[a]							
'Z' medications,[c] *n* (%)	315 (4.8)	141 (4.7)	68 (4.8)	42 (5.5)	27 (4.3)	37 (5.1)	0.8587
Antidepressants, *n* (%)	3139 (47.9)	1394 (46.3)	700 (49.1)	370 (48.2)	321 (51.6)	354 (49.2)	0.0934
Gabapentin, *n* (%)	1083 (16.5)	476 (15.8)	216 (15.1)	159 (20.7)	122 (19.6)	110 (15.3)	0.0013
Benzodiazepines, *n* (%)	2106 (32.2)	957 (31.8)	483 (33.8)	256 (33.3)	197 (31.7)	213 (29.6)	0.3050
Diagnoses in 6 months prior to buprenorphine treatment episode[a]							
Opioid use disorder severity, *n* (%)[d]							
No severity indicated	1032 (15.8)	603 (20.0)	181 (12.7)	82 (10.7)	78 (12.5)	88 (12.2)	< 0.0001
Mild	126 (1.9)	44 (1.5)	29 (2.0)	12 (1.6)	15 (2.4)	26 (3.6)	
Moderate/severe	5392 (82.3)	2367 (78.5)	1216 (85.3)	674 (87.8)	529 (85.0)	606 (84.2)	
Alcohol use disorder, *n* (%)	1208 (18.4)	514 (17.1)	268 (18.8)	159 (20.7)	115 (18.5)	152 (21.1)	0.0409
Injection drug use Infection,[e] *n* (%)	292 (4.5)	130 (4.3)	75 (5.3)	43 (5.6)	24 (3.9)	20 (2.8)	0.0452
Mental health disorder, *n* (%)	3582 (54.7)	1638 (54.3)	798 (55.9)	422 (54.9)	333 (53.5)	391 (54.3)	0.8418
Diagnoses any time prior to the final buprenorphine treatment episode							
Drug use disorder,[f] *n* (%)	4249 (64.9)	1923 (63.8)	952 (66.8)	535 (69.7)	395 (63.5)	444 (61.7)	0.0042
Drug overdose, *n* (%)	684 (10.4)	322 (10.7)	144 (10.1)	106 (13.8)	57 (9.2)	55 (7.6)	0.0023
Emergency department visits in 6 months prior to treatment episode, median number [interquartile range (IQR)]	0 (0, 1)	0 (0, 1)	0 (0, 1)	0 (0, 0)	0 (0, 1)	0 (0, 1)	0.0204
Charlson Comorbidity Index, median (IQR)	0 (0, 1)	0 (0, 1)	0 (0, 1)	0 (0, 1)	0 (0, 1)	0 (0, 1)	0.1526

(Continues)

TABLE 1 (Continued)

Characteristic	Buprenorphine treatment duration						
	All ≥ 8 days (*N* = 6550)	8–30 days (*n* = 3014)	31–90 days (*n* = 1426)	91–180 days (*n* = 768)	181–365 days (*n* = 622)	≥ 366 days (*n* = 720)	*P*-value
Buprenorphine treatment episodes, median number (IQR)	1 (1, 2)	1 (1, 2)	1 (1, 2)	1 (1, 2)	1 (1, 2)	1 (1, 2)	0.1940
Maximum buprenorphine dose prescribed in final episode, median mg/day (IQR)	12 (8, 16)	8 (6, 16)	12.6 (8, 16)	16 (8, 20.6)	16 (8.2, 22)	16 (12, 24)	< 0.0001
Switched to naltrexone or methadone after buprenorphine treatment episode, *n* (%)[g]	713 (10.9)	317 (10.5)	164 (11.5)	98 (12.8)	79 (12.7)	55 (7.6)	0.0090

[a]If individuals had more than one treatment episode, the final one between 2012 and 2018 is described.
[b]Unknown race was treated as a separate race/ethnicity category in the propensity score.
[c]Includes zolpidem, eszopiclone and zaleplon.
[d]Opioid severity was assessed in the 6 months prior to the final buprenorphine treatment episode, including the first day of the final treatment episode. ICD-9 codes of 304.0, 304.7 or an ICD-10 code of F11.2 indicated moderate/severe opioid use disorder; ICD-9 code of 305.5 or ICD-10 code of F11.1, F11.9 indicated mild opioid use disorder.
[e]Includes skin or soft tissue infections, bacteremia or sepsis and osteomyelitis.
[f]Alcohol, opioid abuse and tobacco were not included.
[g]Patients were censored at the time they switched to naltrexone or methadone after stopping buprenorphine. SD = standard deviation.

TABLE 2 Crude death and overdose rates after last buprenorphine treatment episode between 2012 and 2018, overall and by treatment episode duration

Outcome event	Total person-years after stopping final treatment episode	Number of outcome events after each buprenorphine treatment duration prior to discontinuation (crude event rate per 100 person years)					
		8–30 days	31–90 days	91–180 days	181–365 days	≥ 366 days	Overall[a]
All-cause mortality	10471.48	88 (1.60)	48 (2.10)	32 (2.92)	10 (1.21)	13 (1.72)	191 (1.82)
Non-fatal and fatal drug overdose[b–d]	5891.89	160 (5.79)	75 (5.75)	49 (6.63)	19 (3.43)	24 (4.56)	327 (5.55)
Non-fatal and fatal opioid overdose[b,c,e,f]	6111.70	54 (1.88)	23 (1.70)	21 (2.76)	6 (1.06)	5 (0.91)	109 (1.78)

[a]If individuals had more than one treatment episode between 2012 and 2018, the final one is analyzed.
[b]Limited to the four sites with cause-of-death data (*n* = 3934).
[c]Person-time censored at first overdose event; patients could not experience more than one overdose in the analysis.
[d]There were 281 patients who had a non-fatal drug overdose, and 46 who had a fatal drug overdose.
[e]Opioid overdoses include heroin and pharmaceutical opioid overdoses and are a subset of drug overdoses.
[f]There were 80 patients who had a non-fatal opioid overdose and 29 who had a fatal opioid overdose.

race/ethnicity, antidepressant use, gabapentin use, drug overdose prior to treatment initiation, intravenous drug use infections, alcohol use disorder, substance use disorder diagnosis, calendar year of final treatment and prior ED visits (Supporting information, Table S3). These variables were included in a multivariable multinomial logistic regression model, with treatment duration group as the dependent variable to calculate the propensity scores and stabilized weights. After applying the weights and calculating PSDs, age had a PSD > 0.10 in two of the five treatment group comparisons, and was therefore included in the adjusted Cox regression models (Supporting information, Figures S1–S5). Based on the diagnostic plots, the covariates appeared to be evenly balanced across the treatment groups.

Analysis of primary and secondary outcomes

In the fully adjusted and propensity-weighted model, no statistically significant association between the final buprenorphine treatment length and all-cause mortality was observed, with > 365 days as the reference group (Figure 2). The aHRs were above 1.00 and increased incrementally for treatment durations of 8–30 days (aHR = 1.25; 95% CI = 0.68–2.31), 31–90 days (aHR = 1.59; 95% CI = 0.85–2.98) and 91–180 days (aHR = 1.93; 95% CI = 1.00–3.71), and then dropped to below 1.00 for 181–365 days (aHR = 0.79; 95% CI = 0.35–1.82). The pairwise comparisons revealed two statistically significant associations indicating higher risk with shorter treatment durations: treatment duration 31–90 days compared to

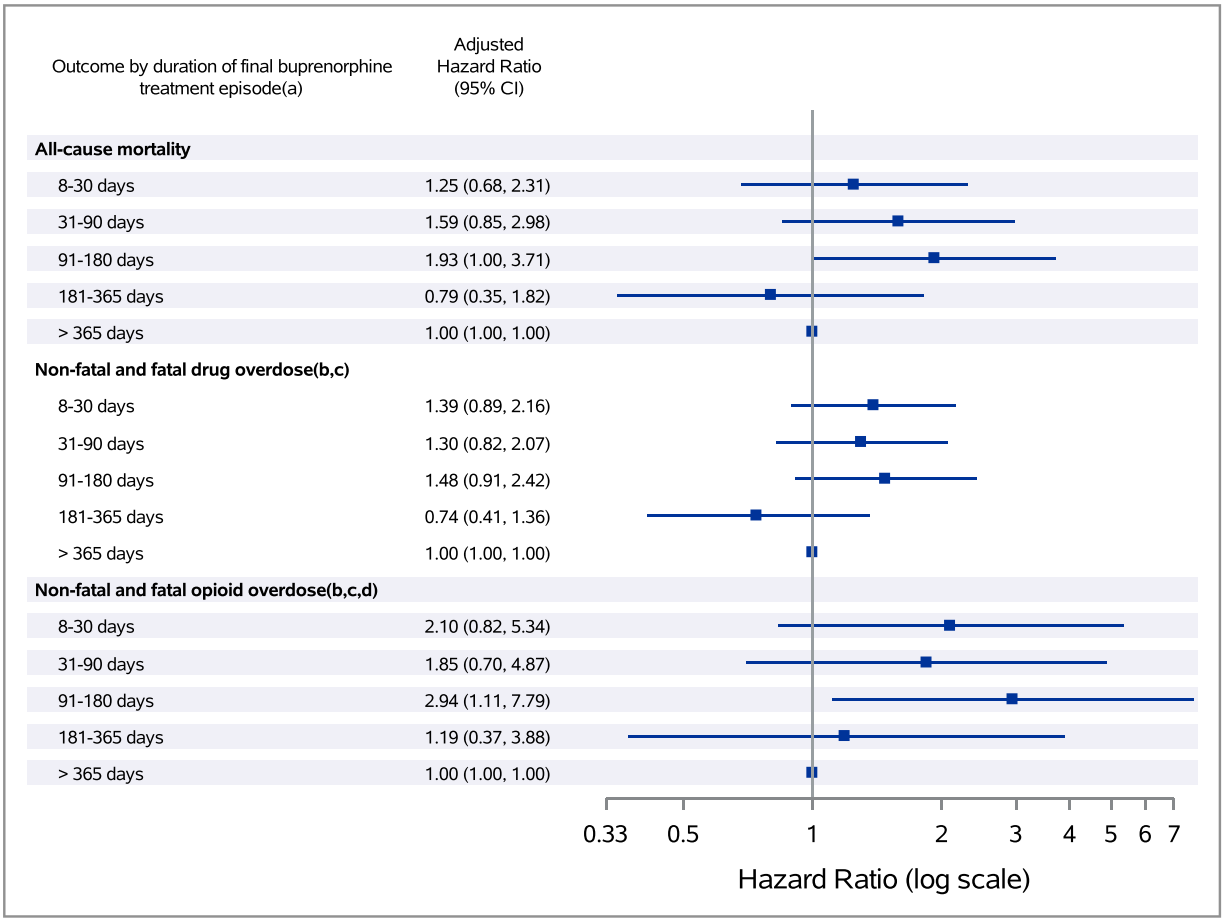

FIGURE 2 Adjusted hazard ratios representing the association between duration of buprenorphine treatment and all-cause mortality, drug overdose or opioid overdose after the final treatment episode. [a]If individuals had more than one treatment episode, the final one between 2012 and 2018 is analyzed. [b]Limited to the four sites with cause-of-death data (n = 3934). [c]Person-time censored at first overdose event after the final treatment episode; patients could not experience more than one overdose in the analysis. [d]Opioid overdoses include heroin and pharmaceutical opioid overdoses and are a subset of drug overdoses. CI = confidence interval

181–365 days (aHR = 2.00; 95% CI = 1.01–3.98) and 91–180 days compared to 181–365 days (aHR = 2.42; 95% CI = 1.19–4.95; Table 3). Based on the Kolmogorov-type supremum test, the assumption of linearity in the log hazard for age did not appear to be violated (P = 0.422).

Similar patterns were observed for the secondary outcomes of fatal and non-fatal drug and opioid overdoses (Figure 2). For fatal and non-fatal drug overdose, the aHRs were above 1.00 for 8–30 days (aHR = 1.39; 95% CI = 0.89–2.16), 31–90 days (aHR = 1.30; 95% CI = 0.82–2.07) and 91–180 days (aHR = 1.48, 95% CI, 0.91–2.42), and then dropped below 1.00 for 181–365 days (aHR = 0.74; 95% CI = 0.41–1.36). The pairwise comparisons revealed three statistically significant associations for drug overdose: treatment duration 8–30 days compared to 181–365 days (aHR = 1.86; 95% CI = 1.14–3.04), 31–90 days compared to 181–365 days (aHR = 1.75; 95% CI = 1.05–2.91) and 91–180 days compared to 181–365 days (aHR = 1.99; 95% CI = 1.17–3.40) (Table 3).

For fatal and non-fatal opioid overdose, the aHRs were above 1.00 for 8–30 days (aHR = 2.10; 95% CI = 0.82–5.34), 31–90 days (aHR = 1.85; 95% CI = 0.70–4.87), 91–180 days (aHR = 2.94; 95% CI, 1.11–7.79) and 181–365 days (aHR = 1.19; 95% CI = 0.37–3.88). None of the pairwise comparisons were statistically significant (Table 3).

Kaplan–Meier survival curves (Supporting information, Figure S6) demonstrate that people treated for 365 days or more had a steeper drop in survival during the first 30 days after treatment, whereas the patients treated for 91–180 days had lower survival than other groups after 120 days.

In the sensitivity analysis that included all treatment episodes, there were no statistically significant associations between buprenorphine treatment length and all-cause mortality, fatal and non-fatal drug overdose or fatal and non-fatal opioid overdose (Table 4). For all-cause mortality, the aHRs demonstrated a similar pattern to that of the primary analysis, but the associations were attenuated by approximately 12 to 16%.

TABLE 3 *Post-hoc* analyses showing adjusted pairwise comparisons between different buprenorphine treatment durations with all-cause mortality, drug overdose or opioid overdose after discontinuing buprenorphine

	Adjusted hazard ratio (95% CI)		
Days of treatment prior to discontinuation[a]	All-cause mortality	Non-fatal and fatal drug overdose[b,c]	Non-fatal and fatal opioid overdose[b–d]
8–30 versus 31–90	0.79 (0.55, 1.13)	1.07 (0.80, 1.41)	1.14 (0.69, 1.87)
8–30 versus 91–180	0.65 (0.42, 1.01)	0.93 (0.67, 1.31)	0.71 (0.42, 1.21)
8–30 versus 181–365	1.57 (0.80, 3.08)	1.86 (1.14, 3.04)	1.76 (0.75, 4.16)
31–90 versus 91–180	0.83 (0.52, 1.31)	0.88 (0.61, 1.27)	0.63 (0.35, 1.14)
31–90 versus 181–365	2.00 (1.01, 3.98)	1.75 (1.05, 2.91)	1.55 (0.63, 3.82)
91–180 versus 181–365	2.42 (1.19, 4.95)	1.99 (1.17, 3.40)	2.47 (0.99, 6.14)

[a]If individuals had more than one treatment episode between 2012 and 2018, the final one is analyzed.
[b]Limited to the four sites with cause-of-death data (n = 3934).
[c]Person-time censored at first overdose event after the final treatment episode; patients could not experience more than one overdose in the analysis.
[d]Opioid overdoses include heroin and pharmaceutical opioid overdoses and are a subset of drug overdoses. CI = confidence interval.

TABLE 4 Adjusted hazard ratios for associations between buprenorphine treatment duration and all-cause mortality, drug overdose, and opioid overdose after discontinuing buprenorphine, using all buprenorphine treatment episodes

Outcome by duration of buprenorphine treatment episode (days)	Adjusted hazard ratio for all treatment episodes (95% CI)[a]
All-cause mortality[b]	
8–30	1.07 (0.57, 2.02)
31–90	1.40 (0.73, 2.68)
91–180	1.65 (0.84, 3.25)
181–365	0.66 (0.28, 1.55)
> 365	1.00 (1.00, 1.00)
Non-fatal and fatal drug overdose[c,d]	
8–30	1.55 (0.99, 2.43)
31–90	1.30 (0.81, 2.08)
91–180	1.45 (0.89, 2.37)
181–365	1.02 (0.59, 1.78)
> 365	1.00 (1.00, 1.00)
Non-fatal and fatal opioid overdose[c–e]	
8–30	2.19 (0.86, 5.60)
31–90	1.96 (0.74, 5.15)
91–180	2.55 (0.95, 6.82)
181–365	2.46 (0.87, 6.96)
> 365	1.00 (1.00, 1.00)

[a]If individuals had more than one treatment episode of 8 days or longer during the study period, all episodes 8 days or longer are analyzed.
[b]There were 9135 episodes of treatment across all sites.
[c]Limited to the four sites with cause-of-death data (n = 5509 episodes).
[d]Person-time censored at first overdose event after each treatment episode; patients could not experience more than one overdose after each treatment episode.
[e]Opioid overdoses include heroin and pharmaceutical opioid overdoses and are a subset of drug overdoses.

DISCUSSION

In this multi-site cohort study, we examined the association between different lengths of buprenorphine treatment and all-cause mortality among patients who discontinued treatment. Mortality risks for treatment durations of 8–30, 31–90, 91–180 and 181–365 days were not significantly different to treatment durations of greater than 365 days. In pairwise comparisons, treatment durations of 31–90 and 91–180 days were associated with increased risks compared to longer treatment durations of 181–365 days. These findings do not support time limits on buprenorphine treatment.

In *post-hoc* analyses, when compared to treatment durations of 6–12 months, treatment durations of 3–6 months were unexpectedly associated with an increased incidence of all-cause mortality, drug overdose and opioid overdose—findings that should be replicated in future studies. If confirmed, future research should aim to understand why people discontinue treatment after 3–6 months and why this may be a period of heightened risk. One possible explanation is that, after 3 months of treatment, patients may resume opioid use in new, unfamiliar environments, which is thought to reduce tolerance and increase the risk for overdose [7, 31]. Another possible explanation may relate to the evolving intensity of clinical monitoring and support in the early phases of treatment. For example, some subgroups of patients may be enrolled in intensive outpatient treatment during the first 30–90 days of treatment. If they continue to require more intensive support due to polysubstance use or psychiatric reasons, they may be at increased risk for adverse outcomes after intensive outpatient treatment ends.

In this study, we were not able to determine why patients stopped buprenorphine treatment. However, some patients may have been involuntarily discontinued because they were subjected to contracts and policies requiring frequent and costly urine toxicology monitoring, psychotherapy and follow-up visits. Given our mortality findings, health systems should consider updating their

policies on buprenorphine management, reducing patient treatment costs, implementing medication first principles [32] and adopting low treatment threshold practices [33] to encourage treatment retention. For patients who choose to discontinue treatment, providers should make them aware of the risks of overdose and death, educate them about the risks and benefits of methadone and extended-release injectable naltrexone, and prescribe them naloxone [7].

This study included eight diverse integrated health systems that cared for commercially insured, Medicaid and Medicare patient populations. This both increases the study's representativeness and provides an advantage over other large, commercially available healthcare databases. It is possible that different health systems have varying treatment practices and policies that determine who, when and for how long patients receive buprenorphine treatment. If these factors are also associated with outcomes, such as overdose and death, failing to control for health system site could lead to biased results.

Another key strength of this study was the ability to analyze mortality and ascertain the cause of death in four of the health system sites. This is particularly important when studying opioid overdose due to its high case fatality rate. In our prior research on risk of opioid overdose among patients prescribed chronic opioid therapy we found that approximately 27% of opioid overdoses were fatal [34]. To accommodate mortality as an outcome, we did not require more than 1 day of post-treatment insurance enrollment for cohort inclusion because doing so could create an immortal time bias. For example, requiring 6 months of post-treatment enrollment implies that the patient had to be alive for the entire time-period and could not have experienced the outcome.

Although we used a rigorous propensity score weighting approach to control for bias, this study had limitations. Treatment episodes past 2018 were not captured in the opioid registry, and we were not able to discern between maintenance and withdrawal management treatment approaches. We were unable to assess cause of death from all sites, and data on overdoses in EHRs and vital statistics databases are subject to variability and error throughout health systems, counties and states [35]. Despite these limitations, the mortality rates we observed were within the range of those observed among studies of people with opioid dependence who are not in treatment [5]. In addition, there were probably several different reasons why patients discontinued buprenorphine treatment, and we were not able to determine which patients stopped because they resumed opioid use.

These findings did not identify an optimal period after which patients can safely discontinue buprenorphine treatment. Although our results suggest that patients should remain on buprenorphine treatment for at least 6 months, observational data show that greater than 50% of patients who initiate treatment discontinue within 6 months [36]. Future clinical and research efforts should continue to focus upon how to minimize discontinuation and retain patients in treatment.

ACKNOWLEDGEMENTS

We wish to thank Jennifer Sawyer at Kaiser Permanente Colorado and Andrea Altschuler at Kaiser Permanente Northern California for their contributions and support.

DECLARATION OF INTERESTS

I.A.B. is employed by the Colorado Permanente Group, which provides treatment to individuals with substance use disorders. The following co-authors have, within the past 3 years, received funding from pharmaceutical companies paid to their institutions for unrelated research: R.C.H. (Gilead Sciences, Inc.); J.A.B. (Gilead Sciences, Inc., Pfizer, Purdue Pharma); and S.E.A. (GlaxoSmithKline, Pfizer). In addition, R.C.H., B.J.H.Y., B.A., J.A.B., S.E.A. and C.I.C. are involved with research on risks of long-term prescription opioid use which is being conducted as part of a Food and Drug Administration post-marketing requirement for extended-release and long-acting opioid analgesics, with funding through their institutions from the Opioid Postmarketing Requirements (PMR) Consortium.

AUTHOR CONTRIBUTIONS

Ingrid A. Binswanger: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; supervision; validation; visualization. **Christina L. Clarke:** Data curation; formal analysis; investigation; methodology; validation; visualization. **Anh P. Nguyen:** Formal analysis; methodology; validation. **Morgan A. Ford:** Project administration; resources. **G. Thomas Ray:** Data curation; formal analysis; project administration; resources; validation. **Stanley Xu:** Formal analysis; investigation; methodology; validation. **Rulin C. Hechter:** Investigation; resources; validation. **Bobbi Jo H. Yarborough:** Investigation; resources; validation. **Douglas W. Roblin:** Investigation; resources; validation. **Brian Ahmedani:** Investigation; resources; validation. **Joseph A. Boscarino:** Investigation; resources; validation. **Susan E. Andrade:** Investigation; resources; validation. **Carmen L. Rosa:** Conceptualization; funding acquisition; investigation; project administration; resources; supervision. **Cynthia I. Campbell:** Conceptualization; formal analysis; funding acquisition; investigation; methodology; project administration; resources; supervision; validation.

ORCID

Jason M. Glanz https://orcid.org/0000-0002-1950-7034
Ingrid A. Binswanger https://orcid.org/0000-0001-8862-8078

REFERENCES

1. Cornish R, Macleod J, Strang J, Vickerman P, Hickman M. Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK general practice research database. BMJ. 2010;341:c5475.
2. Hickman M, Steer C, Tilling K, Lim AG, Marsden J, Millar T, et al. The impact of buprenorphine and methadone on mortality: a primary care cohort study in the United Kingdom. Addiction. 2018;113:1461–76.
3. Larochelle MR, Bernson D, Land T, Stopka TJ, Wang N, Xuan Z, et al. Medication for opioid use disorder after nonfatal opioid overdose

and association with mortality: a cohort study. Ann Intern Med. 2018; 169:137–45.
4. Mattick RP, Breen C, Kimber J, Davoli M, Cochrane Drugs and Alcohol Group. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2014;2:CD002207.
5. Sordo L, Barrio G, Bravo MJ, Indave BI, Degenhardt L, Wiessing L, et al. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. BMJ. 2017; 357:j1550.
6. Santo T Jr, Clark B, Hickman M, Grebely J, Campbell G, Sordo L, et al. Association of opioid agonist treatment with all-cause mortality and specific causes of death among people with opioid dependence: a systematic review and meta-analysis. JAMA Psychiatry. 2021;78: 979–93.
7. American Society of Addiction Medicine (ASAM). The ASAM National Practice Guideline for the treatment of opioid use disorder: 2020 focused update. J Addict Med. 2020;14:1–91.
8. Substance Abuse and Mental Health Services Administration. Medications for Opioid Use Disorder—For Healthcare and Addiction Professionals, Policymakers, Patients, and Families. TIP 63. Washington, DC: US Department of Health and Human Services; 2021.
9. Manhapra A, Agbese E, Leslie DL, Rosenheck RA. Three-year retention in buprenorphine treatment for opioid use disorder among privately insured adults. Psychiatr Serv. 2018;69:768–76.
10. Manhapra A, Petrakis I, Rosenheck R. Three-year retention in buprenorphine treatment for opioid use disorder nationally in the Veterans health administration. Am J Addict. 2017;26:572–80.
11. Pinto H, Maskrey V, Swift L, Rumball D, Wagle A, Holland R. The SUMMIT trial: a field comparison of buprenorphine versus methadone maintenance treatment. J Subst Abuse Treat. 2010;39: 340–52.
12. Timko C, Schultz NR, Cucciare MA, Vittorio L, Garrison-Diehn C. Retention in medication-assisted treatment for opiate dependence: a systematic review. J Addict Dis. 2016;35:22–35.
13. Gryczynski J, Mitchell SG, Jaffe JH, O'Grady KE, Olsen YK, Schwartz RP. Leaving buprenorphine treatment: patients' reasons for cessation of care. J Subst Abuse Treat. 2014;46:356–61.
14. Gryczynski J, Mitchell SG, Jaffe JH, Kelly SM, Myers CP, O'Grady KE, et al. Retention in methadone and buprenorphine treatment among African Americans. J Subst Abuse Treat. 2013;45:287–92.
15. Stein MD, Cioe P, Friedmann PD. Buprenorphine retention in primary care. J Gen Intern Med. 2005;20:1038–41.
16. Williams AR, Samples H, Crystal S, Olfson M. Acute care, prescription opioid use, and overdose following discontinuation of long-term buprenorphine treatment for opioid use disorder. Am J Psychiatry. 2020;177:117–24.
17. Suissa S. Immortal time bias in pharmaco-epidemiology. Am J Epidemiol. 2008;167:492–9.
18. Molero Y, Zetterqvist J, Binswanger IA, Hellner C, Larsson H, Fazel S. Medications for alcohol and opioid use disorders and risk of suicidal behavior, accidental overdoses, and crime. Am J Psychiatry. 2018; 175:970–8.
19. Crotty K, Freedman KI, Kampman KM. Executive summary of the focused update of the ASAM national practice guideline for the treatment of opioid use disorder. J Addict Med. 2020;14:99–112.
20. Samples H, Williams AR, Olfson M, Crystal S. Risk factors for discontinuation of buprenorphine treatment for opioid use disorders in a multi-state sample of Medicaid enrollees. J Subst Abuse Treat. 2018; 95:9–17.
21. Shcherbakova NTG, Tereso G, Spain J, Roose RJ. Treatment persistence among insured patients newly starting buprenorphine/naloxone for opioid use disorder. Ann Pharmacother. 2018;52:405–14.
22. Weinstein ZM, Kim HW, Cheng DM, Quinn E, Hui D, Labelle CT, et al. Long-term retention in office based opioid treatment with buprenorphine. J Subst Abuse Treat. 2017;74:65–70.
23. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005;43:1130–9.
24. Tookes H, Diaz C, Li H, Khalid R, Doblecki-Lewis S. A cost analysis of hospitalizations for infections related to injection drug use at a county safety-net hospital in Miami, Florida. PLOS ONE. 2015;10:e0129360.
25. Faries DZX, Kadziola Z, Siebert U, Kuehne F, Obenchain RL, Haro JM. Real World Health Care Data Analysis: Causal Methods and Implementation Using SAS® Cary, NC: SAS Institute, Inc.; 2020.
26. Xu S, Ross C, Raebel MA, Shetterly S, Blanchette C, Smith D. Use of stabilized inverse propensity scores as weights to directly estimate relative risk and its confidence intervals. Value Health. 2010;13: 273–7.
27. Li F, Li F. Propensity score weighting for causal inference with multiple treatments. Ann Appl Stat. 2019;13:2389–415.
28. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med. 2009;28:3083–107.
29. Nguyen TL, Collins GS, Spence J, Daures JP, Devereaux PJ, Landais P, et al. Double-adjustment in propensity score matching analysis: choosing a threshold for considering residual imbalance. BMC Med Res Methodol. 2017;17:78.
30. Lin DY, Wei LJ, Ying Z. Checking the Cox model with cumulative sums of martingale-based residuals. Biometrika. 1993;80:557–72.
31. Gerevich J, Bacskai E, Farkas L, Danics Z. A case report: Pavlovian conditioning as a risk factor of heroin 'overdose' death. Harm Reduct J. 2005;2:11.
32. Winograd RP, Presnall N, Stringfellow E, Wood C, Horn P, Duello A, et al. The case for a medication first approach to the treatment of opioid use disorder. Am J Drug Alcohol Abuse. 2019;45: 333–40.
33. Kourounis G, Richards BD, Kyprianou E, Symeonidou E, Malliori MM, Samartzis L. Opioid substitution therapy: lowering the treatment thresholds. Drug Alcohol Depend. 2016;161:1–8.
34. Glanz JM, Narwaney KJ, Mueller SR, Gardner EM, Calcaterra SL, Xu S, et al. Prediction model for two-year risk of opioid overdose among patients prescribed chronic opioid therapy. J Gen Intern Med. 2018;33:1646–53.
35. Green CA, Perrin NA, Janoff SL, Campbell CI, Chilcoat HD, Coplan PM. Assessing the accuracy of opioid overdose and poisoning codes in diagnostic information from electronic health records, claims data, and death records. Pharmacoepidemiol Drug Saf. 2017;26: 509–17.
36. Meinhofer A, Williams AR, Johnson P, Schackman BR, Bao Y. Prescribing decisions at buprenorphine treatment initiation: do they matter for treatment discontinuation and adverse opioid-related events? J Subst Abuse Treat. 2019;105:37–43.

SUPPORTING INFORMATION

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

How to cite this article: Glanz JM, Binswanger IA, Clarke CL, Nguyen AP, Ford MA, Ray GT, et al. The association between buprenorphine treatment duration and mortality: a multi-site cohort study of people who discontinued treatment. Addiction. 2022. https://doi.org/10.1111/add.15998