Check for updates

Received: 13 March 2025 | Accepted: 1 September 2025

DOI: 10.1111/add.70211

RESEARCH REPORT

ADDICTION SSA

Evaluating the optimal duration of medication treatment for opioid use disorder

Corey J. Hayes[1,2,3,4] | Rebecca A. Raciborski[4,5,6] | Mahip Acharya[3,7] | Nahiyan Bin Noor[3] | Edward V. Nunes[8] | T. John Winhusen[9,10]

[1]Division of Pharmaceutical Evaluation and Policy, College of Pharmacy, University of Arkansas for Medical Sciences, Little Rock, AR, USA

[2]Department of Biomedical Informatics, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, USA

[3]Institute for Digital Health and Innovation, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, USA

[4]Center for Mental Healthcare and Outcomes Research, Central Arkansas Veterans Healthcare System, North Little Rock, AR, USA

[5]Behavioral Health Quality Enhancement Research Initiative, Central Arkansas Veterans Healthcare System, North Little Rock, AR, USA

[6]Evidence, Policy, and Implementation Center, Central Arkansas Veterans Healthcare System, North Little Rock, AR, USA

[7]Department of Obstetrics and Gynecology, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, USA

[8]Division on Substance Use Disorders, Department of Psychiatry, Columbia University Irving Medical Center, New York, NY, USA

[9]Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine, Cincinnati, OH, USA

[10]Center for Addiction Research, University of Cincinnati College of Medicine, Cincinnati, OH, USA

Correspondence

Corey J. Hayes, Division of Pharmaceutical Evaluation and Policy, College of Pharmacy, University of Arkansas for Medical Sciences, 4301 W. Markham Street, Slot 782, Little Rock, AR 72205, USA.
Email: cjhayes@uams.edu

Rebecca A. Raciborski, Center for Mental Healthcare and Outcomes Research, Central

Abstract

Background and aims: Clinicians have little guidance on the ideal length of time patients should remain on medication treatment for opioid use disorder (MOUD) before being able to safely discontinue MOUD. This study estimated how the risk of all-cause mortality changes with the duration of MOUD, controlling for patient characteristics that change the risk profile independent of duration of therapy.

Design, setting and participants: Retrospective cohort study using electronic health record data from the US Veterans Healthcare Administration. Veterans initiating MOUD with buprenorphine, methadone or extended-release naltrexone from October 2010 to September 2020. Our analytic sample included 19 666 buprenorphine initiators, 8675 methadone initiators and 4007 extended-release naltrexone initiators.

Measurement: Duration of MOUD was measured in days. Discontinuation was defined as a gap in any MOUD coverage exceeding 28 days, regardless of MOUD type initiated. The primary outcome was all-cause mortality. We estimated multistate survival models allowing for the modeling of multiple states (i.e. on and off MOUD, death) without having to consider censoring or competing events, while adjusting for sociodemographic, clinical, prescription and facility and provider characteristics.

Findings: We observed approximately 226 000 person-years of time at risk for discontinuation or pre-discontinuation death, during which we observed 26 841 discontinuations (118.9 discontinuations per 1000 person-years). We similarly observed a total of about 106 000 person-years of post-discontinuation follow-up, during which we observed 3251 deaths (3.1 deaths per 1000 person-years). We found the largest marginal gain in probability of 6-year survival from an additional year on MOUD appears to occur around 2 years, as compared to 6 months on MOUD. Statistically significant gains continued through approximately 4–5 years of MOUD retention relative to 6-month MOUD retention. After 4–5 years, the marginal gain from one additional year of MOUD was not statistically significant.

Conclusions: Among US veterans, the benefit of retention on medication treatment for opioid use disorder (MOUD) towards overall survival continues through at least 4 years

Corey J. Hayes and Rebecca A. Raciborski are co-corresponding and first authors.

Arkansas Veterans Healthcare System, North 4300 West 7th Street, Little Rock, AR 72205, USA.
Email: rebecca.raciborski@va.gov

Funding information
This work was supported by the National Institute on Drug Abuse of the National Institutes of Health (UG1DA013732-23S3) under the CTN-0142 protocol. C.J.H. was also supported by a VA Health Services Research and Development Career Development Award-2 (IK2HX003358) and by funding from the UAMS Vice Chancellor for Research and Innovation and the Arkansas Biosciences Institute.

of MOUD treatment. Quality metrics based on 6-month MOUD retention may be insufficient.

KEYWORDS
duration of therapy, medication treatment for opioid use disorder, mortality, multistate survival analysis, opioid use disorder, veterans

INTRODUCTION

Opioid use disorder (OUD) reduces quality of life [1], increases risks to human life including overdose [2, 3] and infectious disease [4] and imposes higher societal costs [5]. Medications for opioid use disorder (MOUD) (buprenorphine, methadone and naltrexone) are effective at improving outcomes for persons with OUD. People with OUD who receive MOUD have fewer drug cravings, improved social functioning and better quality of life than those who do not [6–17]. Although clinical practice guidelines from several organizations [18–20] advocate for universal, first line access to MOUD, there is conflicting advice about the optimal duration of therapy. MOUD treatment exceeding a year is associated with reduced emergency department visits, inpatient utilization and overdose, although risk of such adverse events remains high [18–20]. Yet, standards of care specify only 6 months as the minimum target for treatment duration [21, 22].

Clinicians are left with unclear guidance about when to counsel patients that it is safe to discontinue treatment. The American Society of Addiction Medicine National Practice Guideline for the treatment of OUD calls for further research on the optimal length of treatment with each type of MOUD [23]. The ambiguity may hinder patients' ability to fully participate in treatment plans. Only 50% to 60% of patients remain on MOUD for the current recommended minimum of 6 months following treatment initiation [24–28], with more than 25% saying they want even shorter durations [29]. Better information about potential differences in expected outcomes as treatment duration varies may help patients make more informed decisions about their care.

This study's objective was to quantify the relationship between MOUD therapy duration and risk of death among patients initiating MOUD. We estimated how the risk of all-cause mortality changes with MOUD duration while controlling for patient characteristics that change the risk profile independent of duration of therapy (e.g. age). We, then, identified how survival probability increases with increased treatment duration for each type of MOUD initiated. The results of this study provide insights about optimizing treatment duration for clinicians and patients through empirical evidence about relative benefits and when improvements in survival are no longer expected with increased MOUD duration.

METHODS

Study design, setting and participants

Using electronic health record data, this retrospective cohort study was set in the Veterans Health Administration (VHA) of the United States (US) Department of Veterans Affairs (VA) from 1 October 2010 to 30 September 2020. Our target population was community-dwelling US veterans diagnosed with OUD undergoing treatment with any MOUD. To be included, veterans had to have an OUD diagnosis and MOUD initiation during the study period and be 18 years or older at the diagnosis date. OUD diagnosis was identified using International Classification of Diseases (ICD) 9 and 10 codes, from a previous study [30]. Initiation was defined as first MOUD use following the OUD diagnosis that qualified them for the study and with no MOUD use in the prior 180 days, similar to previous studies [31, 32]. They entered the study at the initiation date (t = 0) and were followed until death or censoring at the end of study follow-up, with assessment of whether they were still on any MOUD type or had discontinued at the time of death or censoring. We required neither a minimum duration of therapy nor a minimum follow-up time as a criterion for inclusion, but the survival data methods used in our study precluded participants from initiating on the last day of the study where follow-up time is zero days.

Participants who were not US residents, not users of VA at the time of initiation or no longer US residents at the time of discontinuation were considered out of scope for the study. User of VA was defined as having at least 2 visits to or paid for by the VA in the 365 days before the reference date, inclusive. Veterans were also excluded if they received MOUD from a non-VA pharmacy, had a diagnosis for metastatic cancer, resided in a nursing home or were admitted to hospice care at any time during the study period. We also made two incidental exclusions of participants for whom we could not obtain a full year of history for baseline: those without a VA enrollment date, who enrolled less than a year before their first post-diagnosis MOUD prescription or who filled their first post-diagnosis prescription before 1 October 2011.

The study was approved by the Central Arkansas Veterans Healthcare System Institutional Review Board and uses the Strengthening the Reporting of Observational Studies (STROBE) reporting guidelines for cohort studies [33]. The analysis plan for this study was not pre-registered; therefore, the findings should be considered exploratory.

Variables and data sources

We extracted study data from the VHA Corporate Data Warehouse (CDW), which includes electronic medical records, socio-demographic characteristics and linked mortality data. All-cause mortality was selected as the outcome instead of overdose mortality because OUD may increase the risk of death from other health conditions [34]. Death date was obtained from the VHA Mortality Data Repository. Duration of initial episode of MOUD therapy was the exposure of interest. Duration was measured as the time between initiation and discontinuation. Discontinuation was defined as in prior research [35, 36] to be a treatment gap greater than 28 days, where 'gap' is time between the last covered day from a previously documented fill or administration and the next documented receipt of any MOUD type. Switching to another MOUD type was not considered a discontinuation unless there was a treatment gap.

The type of MOUD initiated was included in the model as a categorical covariate. We did not explicitly capture exposure to additional types of MOUD (e.g. transitioning MOUD type after initiation). Other MOUD initiation characteristics were initiating location, prescribing provider specialty and prescribing provider credential. Socio-demographic and geographic variables, including age, sex, race, ethnicity, Census region, rurality [37], employment status, marital status, VA priority group, social vulnerability index (SVI) scores [38], homelessness and justice-involvement were assessed using information collected in a 365-day review period at baseline and, except for sex, race and ethnicity again for discontinuation. Rurality and SVI were obtained by linking to veterans' ZIP codes. Comorbidity [39] and health service use also were assessed with a 365-day review period, while prescription medications were assessed with a 30-day review period because it is likely more recent medication exposure better indicates active treatment of the participant's comorbidities. Only the following had values that changed at discontinuation: age, marital status, employment status, VA priority group [40], rurality and social risk. All other covariates used values measured only at baseline.

Statistical analyses

Descriptive statistics were computed overall and for the subsets of the sample that experienced each state during follow-up. Naïve and age-sex adjusted Kaplan–Meier curves were constructed to illustrate the survival probabilities that would be computed when death is treated as a censoring event for discontinuation and likewise discontinuation as a censoring event when examining death after initiation as the outcome.

All other analyses were conducted using an illness-death modelling framework, a simplified version of multi-state survival models [41, 42]. Unlike the more common Cox proportional hazard model [43, 44], multi-state survival models allow us to model different events a

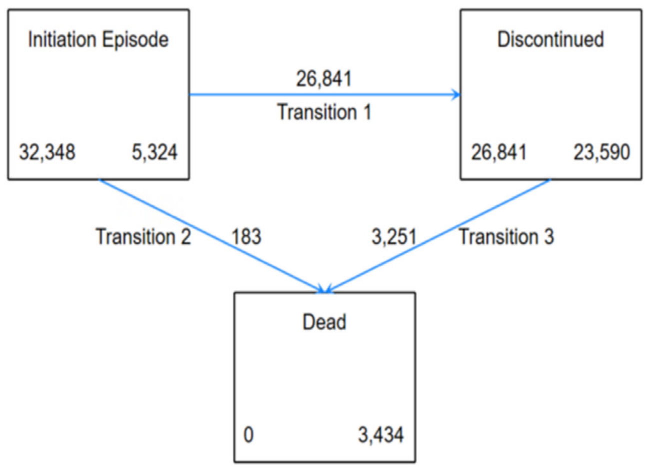

FIGURE 1 Observed transitions for veterans initiating medications for opioid use disorder (MOUD). This figure depicts the number of participants who started in the given state along with their transitions. For example, 32 348 initiated MOUD (as shown in the bottom left of the 'initiation episode' box) while 5324 remained on MOUD without transitioning to either the 'discontinued' or 'dead' states (32 348 participants initiating MOUD – 26 841 participants who discontinued MOUD – 183 participants who died before discontinuing MOUD). Numbers of the other states can be interpreted similarly.

participant may experience without treating them as censoring or competing events. Further, these models do not require us to restrict our sample to participants who discontinued, avoiding the risk from immortal time bias that occurs when requiring one event to be observed before another and removing the need to use statistical corrections like inverse probability weighting to adjust for the probability that a subject survived to long enough to be observed in our sample. Because the model in this article is estimated parametrically, it does not carry the proportional hazards assumption. Instead, it has the usual parametric survival assumption that the functional form is correct and, as parameterized in this work, the additional semi-Markovian assumption that transition probabilities in the future depend only on time spent in the current state [45]. The former assumption was checked during the model selection process described in Data S1. The latter assumption is untestable, but our specification of the model relaxes the full Markovian 'memory-lessness' assumption that the future depends only on the present state with no reference to time in state.

Our model was conceptualized with three states and permits participants to transition into each state a maximum of one time (Figure 1). All participants started in the 'initiation episode' state and could transition directly to either the 'discontinued' state (transition 1; discontinuation) or 'dead' state (transition 2; pre-discontinuation death). Participants could also transition to dead through discontinued (transition 3; post-discontinuation death). Parametric models for the transitions were selected using a pre-defined process to determine an appropriate functional form for the baseline hazard and covariates in the models. Transitions were modeled separately to accommodate different hazard distributions for each transition. The model was fit using a clock-forward approach for follow-up time (i.e. all transitions share a common time zero at initiation). Details of the full process to fit and select our model may be found in Data S1.

Coefficient estimates for a multi-state model are not directly interpretable. Instead, they are interpreted via post-estimation predictions. This requires selecting covariate values to compute predictions at, for instance, 'reference' participants. We present predictions for four reference participants that were selected to capture expected mortality risk by age and sex: 30- and 50-year-old male and 30- and 50-year-old female. We present stratified results to minimize the effect of systematic differences by age and sex between the veteran and non-veteran US population. Because the type of medication that a person initiated on was parameterized as a categorical variable and could alter their baseline risk, we assigned each drug covariate a value equal to its proportion within the sample to capture the treatment mix when performing our post-estimation calculations.

In our post-estimation analysis, we created stacked transition probability plots, which show the probability that a participant assessed at time 0 will be in one of the three states as of time t. We, then, predicted relative survival at increasing duration of treatment to identify if, and where, continuing MOUD no longer yields additional survival benefit. We made these predictions for treatment durations of 6 months and for 1 to 6 years in 3 month increments and then computed relative expected post-discontinuation survival at 1 through 6 years with 95% CI. The 6-year prediction horizon was selected after reviewing sample descriptives because 95% of participants had 6 or fewer years of follow-up after discontinuation, and we did not want to use sparse data for the predictions. These survival predictions incorporate information from all transition models and so better capture the rich variation in experiences across groups that single-equation models can only model with an interaction term. Predictions are presented graphically. Full model output is available on request.

Sensitivity analyses

The primary factor governing survival predictions is the estimated shape of the hazard function. We, therefore, conducted simplified sensitivity analyses that determined if the shape of the hazard was expected to change with modifications to the sample to confirm the robustness of the primary analysis. First, we excluded participants who switched MOUD type in their initiation episode. We, then, excluded participants who resumed MOUD to determine if the post-discontinuation transition model was substantively different.

RESULTS

Our final analytic sample was 19 666 buprenorphine initiators, 8675 methadone initiators and 4007 extended-release naltrexone initiators (Figure S1). Figure 1 shows the number of observed transitions between states ('initiation episode', 'discontinued', 'dead') and Table 1 summarizes characteristics as measured at initiation for veterans by state experience. Of all study-eligible veterans, 60.8% initiated buprenorphine, 26.8% initiated methadone and 12.4% initiated extended-release naltrexone. Regardless of state experience, veterans in the study were middle age (means between 49.2 and 53.4 years) and predominantly male (>92%), resided in urban areas (>85%), frequently had chronic physical and mental health conditions (e.g. >84% chronic pain, >52% anxiety, >67% depression). Overall, approximately 85% of participants had a year or more of post-initiation follow-up and 84% had at least a year post-discontinuation. We observed approximately 226 000 person-years at risk for discontinuation or pre-discontinuation death for participants in the analytic sample, during which we observed 26 841 discontinuations (118.9 discontinuations per 1000 person years) and 183 pre-discontinuation deaths (0.81 deaths per 1000 person-years). We similarly observed a total of approximately 106 000 person-years of post-discontinuation follow-up, during which we observed 3251 deaths (3.1 deaths per 1000 person-years).

Our selected multi-state models use a generalized gamma distribution for the discontinuation transition and log-logistic distribution for the two transitions to the dead state. The models provided overall good fit for the data (Figure S2), with typical deviations at longer follow-up as data becomes sparse. The stacked transition probability plots shown in Figure 2 show that, for example, males and females both have a higher probability of remaining in the 'on MOUD' state when initiating at 50 years old compared initiating at 30 years old. Other states and cross-characteristic comparisons may be interpreted similarly. See Figure S3 for Kaplan–Meier plots.

Figure 3 plots the relative survival probability for the reference participants by different MOUD durations. As computed here, relative predicted survival probability is the ratio of the predicted probability of surviving to 6 years if a patient is treated for 1 year instead of 6 months, 2 years instead of 6 months and so on. They indicate that longer time on therapy increases expected relative survival, with larger gains in longer time horizons. Taking the highest-risk reference participant (50-year-old male) as an example, continuing MOUD for 2 years is associated with a survival probability of 1.04. This means that the expected 6-year survival probability is 4% greater than that of similar patients treated only 6 months, a 4% increase in the expected 6-year survival probability. By contrast, our lowest-risk reference participant (30-year-old female) is not projected to achieve a 4% greater survival probability until approximately 5 years of MOUD duration. Additionally, for the lowest risk reference participant, the marginal gains, improvements in relative survival for each additional year of therapy, start to diminish as duration increases, with no statistically discernible difference beyond 4 years. Similar plots showing relative predicted survival to 3 months and 1 year are shown in Figure S4.

Our sensitivity analyses excluded 1045 participants (3.2%) who switched MOUD type and separately excluded 13 664 participants (42.2%) who resumed therapy after discontinuation. These analyses indicate that the finding of increased relative survival with longer MOUD duration is not substantively changed by our treatment of switches and resumptions. The results are presented in the Sensitivity Analyses section of Data S1.

TABLE 1 Characteristics of participants at initiation of medication treatment for opioid use disorder by experience of states: initiation, discontinuation and death.[a]

	State		
Characteristics	**Initiation of MOUD, *n* = 32 348**	**MOUD discontinuation, *n* = 26 841**	**Death, *n* = 3434**
Type of MOUD initiated (*n*, %)			
Buprenorphine	19 666 (60.8)	14 683 (54.7)	1797 (52.3)
Methadone	8675 (26.8)	8333 (31.0)	1339 (39.0)
Extended-release naltrexone	4007 (12.4)	3825 (14.3)	298 (8.7)
Age (y; mean, SD)	49.39 (14.09)	49.15 (14.09)	53.35 (13.55)
Sex (*n*, %)			
Male	29 901 (92.4)	24 581 (92.6)	3293 (95.9)
Self-identified race and ethnicity (*n*, %)			
American Indian or Alaska Native	299 (0.9)	247 (0.9)	26 (0.8)
Black or African American	6164 (19.1)	5614 (20.9)	762 (22.2)
Asian, Native Hawaiian or other Pacific Islander	258 (0.8)	212 (0.8)	25 (0.7)
White, Hispanic or Latino	1236 (3.8)	1052 (3.9)	101 (2.9)
White, not Hispanic or Latino	22 026 (68.1)	17 735 (66.1)	2297 (66.9)
More than one race	285 (0.9)	239 (0.9)	29 (0.8)
Declined to answer	1273 (3.9)	1074 (4.0)	83 (2.4)
Unknown by patient	620 (1.9)	512 (1.9)	58 (1.7)
Not recorded	187 (0.6)	156 (0.6)	53 (1.5)
Marital status (*n*, %)			
Never married	8179 (25.3)	7001 (26.1)	859 (25.0)
Married	9395 (29.0)	7340 (27.3)	802 (23.4)
Separated	2573 (8.0)	2222 (8.3)	283 (8.2)
Divorced	11 106 (34.3)	9360 (34.9)	1343 (39.1)
Widowed	986 (3.0)	838 (3.1)	132 (3.8)
Unknown	109 (0.3)	80 (0.3)	15 (0.4)
Employment status (*n*, %)			
Employed for self or others	6011 (18.6)	4640 (17.3)	382 (11.1)
Other than employed	26 337 (81.4)	22 201 (82.7)	3052 (88.9)
Priority group[b] (*n*, %)			
1	13 841 (42.8)	11 414 (42.5)	1223 (35.6)
2–3	5285 (16.3)	4354 (16.2)	516 (15.0)
4	2056 (6.4)	1850 (6.9)	385 (11.2)
5	8785 (27.2)	7380 (27.5)	1128 (32.8)
6	441 (1.4)	349 (1.3)	26 (0.8)
7A and 7C	452 (1.4)	353 (1.3)	39 (1.1)
8A–8G	1488 (4.6)	1141 (4.3)	117 (3.4)
US Census region residence (*n*, %)			
Northeast	6660 (20.6)	5679 (21.2)	794 (23.1)
South	11 885 (36.7)	9675 (36.0)	1132 (33.0)
Midwest	6696 (20.7)	5636 (21.0)	796 (23.2)
West	7107 (22.0)	5851 (21.8)	712 (20.7)
Residential rurality (*n*, %)			
Urban	27 539 (85.1)	23 156 (86.3)	3012 (87.7)
Large rural city/town	2834 (8.8)	2177 (8.1)	255 (7.4)
Isolated small rural town	1975 (6.1)	1508 (5.6)	167 (4.9)

TABLE 1 (Continued)

Characteristics	State: Initiation of MOUD, *n* = 32 348	MOUD discontinuation, *n* = 26 841	Death, *n* = 3434
SVI score[c] (mean, SD)			
Socio-economic status	0.44 (0.24)	0.44 (0.24)	0.44 (0.24)
Household characteristics	0.36 (0.26)	0.35 (0.26)	0.34 (0.26)
Racial and ethnic minority status	0.73 (0.25)	0.74 (0.25)	0.75 (0.24)
Housing type and transportation	0.64 (0.24)	0.65 (0.24)	0.66 (0.23)
Composite SVI	0.54 (0.24)	0.55 (0.24)	0.55 (0.24)
Prior year social risk (*n*, %)			
Justice involved	3754 (11.6)	3357 (12.5)	394 (11.5)
Unhoused	12 742 (39.4)	11 464 (42.7)	1569 (45.7)
Prior year health service use (mean, SD)			
Emergency department visits	2.51 (4.26)	2.69 (4.41)	3.45 (4.97)
Psychiatric admissions	0.71 (1.35)	0.78 (1.42)	0.86 (1.59)
Inpatient admissions	1.18 (1.93)	1.29 (2.01)	1.72 (2.35)
Psychotherapy visits	11.45 (18.20)	12.81 (19.10)	12.03 (18.56)
Prior year overdose history (*n*, %)			
Opioid	1046 (3.2)	878 (3.3)	171 (5.0)
Other, non-opioid	1972 (6.1)	1734 (6.5)	278 (8.1)
Elixhauser comorbidities[d] (mean, SD)	4.31 (2.46)	4.42 (2.47)	5.50 (2.93)
Prior year substance use history (*n*, %)			
Alcohol use disorder	15 698 (48.5)	13 785 (51.4)	1804 (52.5)
Tobacco use disorder	19 331 (59.8)	16 463 (61.3)	2231 (65.0)
Other drug use disorder	18 809 (58.1)	16 497 (61.5)	2134 (62.1)
Prior year mental health history (*n*, %)			
Anxiety disorder	19 948 (61.7)	16 538 (61.6)	1791 (52.2)
Bipolar disorder	5021 (15.5)	4454 (16.6)	595 (17.3)
Depression	21 794 (67.4)	18 618 (69.4)	2507 (73.0)
PTSD	14 947 (46.2)	12 709 (47.3)	1475 (43.0)
Psychotic disorder	3109 (9.6)	2838 (10.6)	434 (12.3)
Prior year medical history (*n*, %)			
Pain-related health conditions	27 010 (83.5)	22 494 (83.8)	2963 (86.3)
Hepatitis C	6390 (19.8)	5707 (21.3)	1172 (34.1)
Hepatitis B	290 (0.9)	265 (1.0)	61 (1.8)
Endocarditis	195 (0.6)	160 (0.6)	51 (1.5)
HIV	488 (1.5)	450 (1.7)	82 (2.4)
Prior year opioid treatment history (mean, SD)			
Average opioid dose (MME)	19.34 (53.13)	19.64 (56.43)	26.34 (51.36)
Prior month prescription history (*n*, %)			
Antidepressant	17 060 (52.7)	14 471 (53.9)	1901 (55.4)
Benzodiazepine	2887 (8.9)	2350 (8.8)	414 (12.1)
Non-benzodiazepine hypnotics	2850 (8.8)	2402 (8.9)	354 (10.3)
Other, non-opioid analgesics	11 026 (34.1)	9348 (34.8)	1341 (39.1)
Skeletal muscle relaxants	4691 (14.5)	3860 (14.4)	490 (14.3)

(Continues)

TABLE 1 (Continued)

Characteristics	State Initiation of MOUD, *n* = 32 348	MOUD discontinuation, *n* = 26 841	Death, *n* = 3434
Provider and facility characteristics			
Provider credential (*n*, %)			
MD/DO	19 961 (61.7)	15 547 (57.9)	1908 (55.6)
PA/NP	1795 (5.5)	1352 (5.0)	103 (3.0)
PharmD	465 (1.4)	412 (1.5)	32 (0.9)
Other/undetermined	10 127 (31.3)	9530 (35.5)	1391 (40.5)
Provider specialty (*n*, %)			
Behavioral/mental health	18 538 (57.3)	14 643 (54.6)	1788 (52.1)
Primary care/internal medicine	1837 (5.7)	1274 (4.7)	136 (4.0)
Emergency medicine/hospitalist	286 (0.9)	211 (0.8)	27 (0.8)
Other/unknown	11 687 (36.1)	10 713 (39.9)	1483 (43.2)
Facility type (*n*, %)			
VA medical center	29 355 (90.7)	24 701 (92.0)	3208 (93.4)
Outpatient health facility[e]	2131 (6.6)	1455 (5.4)	153 (4.5)
Other outpatient services	324 (1.0)	206 (0.8)	13 (0.4)
Other	538 (1.7)	479 (1.8)	60 (1.7)
OTP clinic (*n*, %)	7356 (22.7)	7123 (26.5)	1099 (32.0)

Abbreviations: MD/DO, medical doctor or doctor of osteopathy; MME, morphine milligram equivalents; MOUD, medication treatment for opioid use disorder; OTP, opioid treatment program; PA/NP, physician assistant or nurse practitioner; PharmD, doctor of pharmacy; PTSD, post-traumatic stress disorder; SVI, Social Vulnerability Index; US, United States; VA, Veterans Affairs.

[a]Values in the table are shown as either (*n*, %) to designate the number of participants in the column along with the percentage of all participants in the column this represents or as (mean, SD) to designate the value as the mean with the corresponding SD.

[b]VA priority group status is a multi-faceted measure of health and social need, determined by factors such as military service history, disability rating, income level and Medicaid eligibility. For example, priority groups 1 and 4 have high levels of disability (the former because of service-connected injuries and the latter otherwise having catastrophic injuries preventing work). VA priority group status also helps to determine the co-payments that veterans pay.

[c]The SVI uses 16 US Census variables from the 5-year American Community Survey to identify communities that may need support before, during or after disasters. The SVI has four themed measures of area risk: (1) socio-economic status, (2) household characteristics, (3) racial and ethnic minority status and (4) housing type and transportation.

[d]Elixhauser comorbidities are 38 different conditions that can be identified from administrative data and are used for severity adjustment.

[e]Outpatient health facilities include Veteran Health Administration health care centers and community-based outpatient clinics.

DISCUSSION

In a large, national sample of veterans initiating one of three MOUD types, we estimated the relationship between treatment duration and expected medium-term survival probability, adjusting for patient characteristics that alter risk. Several MOUD retention metrics endorsed by the National Quality Forum [46] and the OUD Cascade of Care [21, 47] suggest a minimum MOUD duration of 6 months. Yet, this is not empirically derived and in the presence of increased risk of opioid-related adverse patient outcomes seen after MOUD discontinuation [18, 19, 48, 49], some have recommended against MOUD discontinuation at any time point [50]. Our aim with this study was to identify, if possible, the point beyond which additional days of treatment did not provide significant survival benefits.

Using potential therapy durations of up to 6 years, we found that the suggested 6-month minimum MOUD is likely insufficient, regardless of the patient's individual mortality risk. This is a clinically critical finding. Even for our reference participants that represent patients at low mortality risk, we demonstrated a potential benefit up to 4 years of therapy over the 6 years examined, but with the gain in relative survival decreasing with each additional year of therapy. For the higher baseline risk groups, we did not observe a levelling, but there also does not appear to be a statistically significant difference in gain in relative survival past 4 years. This may be due, in part, to the small number of participants who had treatment duration longer than 4 years, limiting our ability to make more accurate predictions at the upper end of treatment duration. We found no point at which additional years of MOUD resulted in lower survival probability compared to the current standard of care. Our predictions were made for reference participants who had no additional health risk factors (e.g. comorbid substance use disorders), so predicted survival probability tended to be high regardless of MOUD duration. Therefore, we expect these are conservative estimates of potential survival benefit from longer MOUD duration.

Additionally, the largest survival benefit from longer MOUD duration accrued to the highest risk group we examined. This finding

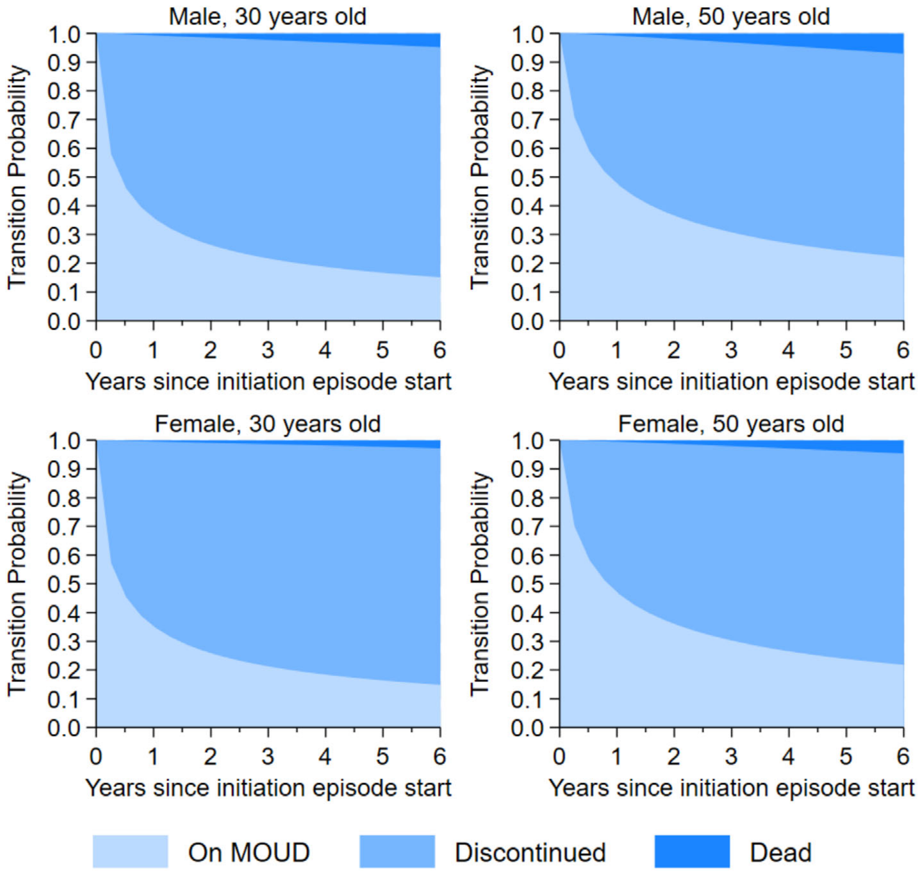

FIGURE 2 Stacked transition probabilities for initiation episodes from 'on MOUD' to 'discontinued' or 'dead' for 30- and 50-year-old male and female reference participants. *Note*: A 'reference' participant is a participant who serves as a point of comparison or benchmark within a study. In this figure, we have 4 reference participants, males who are 30 and 50 years of age (top two graphs) and females who are 30 and 50 years of age (bottom two graphs). Each of these reference participants have no other mortality risk factors (e.g. comorbid substance use disorders) beyond opioid use disorder. MOUD, medication for opioid use disorder.

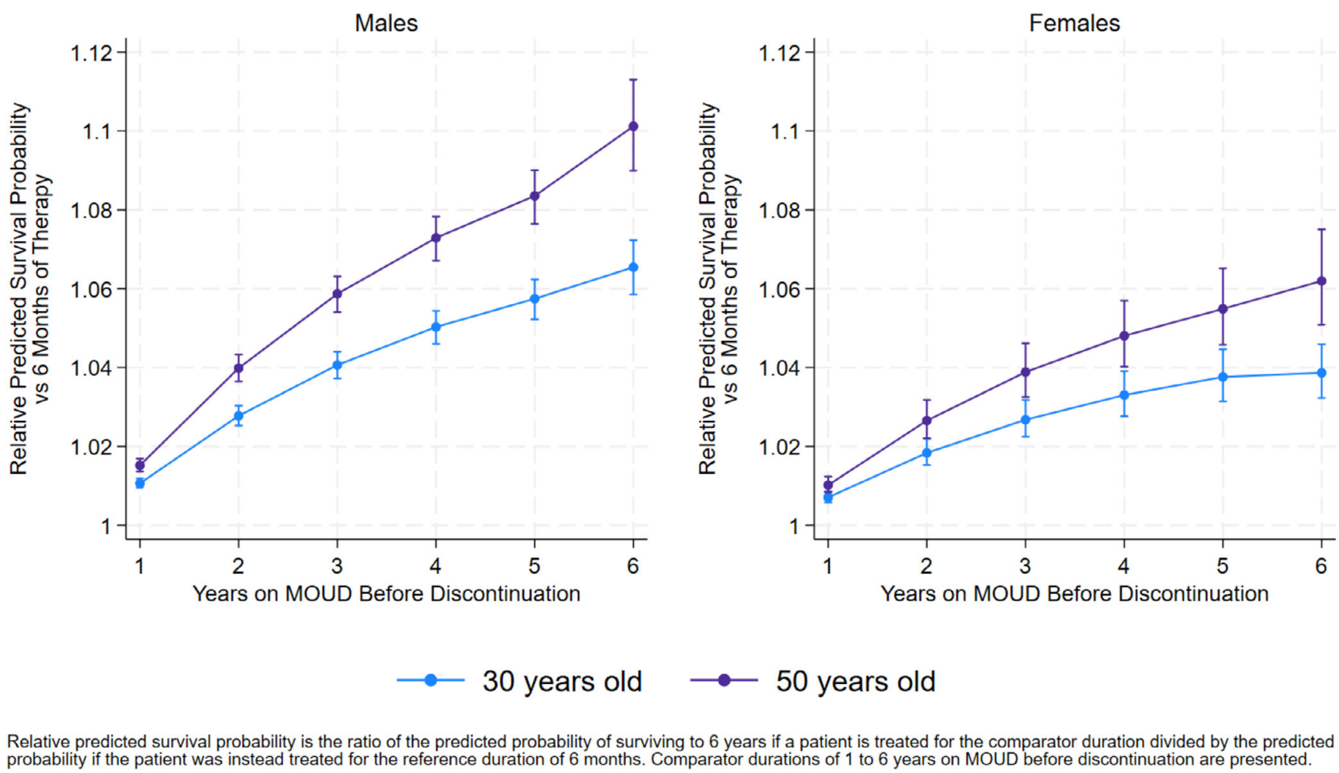

FIGURE 3 Relative predicted 6-year survival probability by treatment duration for 30- and 50-year-old male and female reference participants.

indicates patients at high mortality risk may benefit from MOUD treatment of much longer duration, possibly beyond the 6 years we examined. This offers promise that mortality gaps could be closed by targeting patients at high mortality risk for longer MOUD duration and merits future study with other populations known to be at high risk. Currently, we have treated risk factors only as adjustments to baseline risk, thereby implicitly assuming that the effect of time is constant once baseline differences are accounted for. Future work should evaluate other heterogeneous treatment effects that may moderate the relationship between MOUD duration and survival, such as individual- (e.g. comorbidities) and geographic-level (e.g. SVI) factors.

Because our intent was to fit models that could inform the clinician treating a patient at the start of MOUD, when duration of therapy would not yet be known we made several study design decisions that deviate from the existing literature. We did not impose a minimum treatment duration. Neither did we restrict our sample to only participants who had discontinued therapy. The ability to be more inclusive with the sample was a result of our novel application of a multi-state survival model to MOUD duration, the first application we are aware of in the substance abuse literature. We also allowed switching between different MOUD types in this analysis, a choice we examined in a sensitivity analysis that did not result in substantive differences in conclusions. Further work should explore the characteristics of patients with especially short durations of therapy. Finally, our large sample with available follow-up over many years allowed us to look at differences in outcomes relative to 6 months of MOUD for durations longer than 18 months, previously the longest horizon examined.

With 50% to 60% of patients discontinuing MOUD by 6 months [24–28], the current 90% retention goal is already difficult to achieve [21]. If the recommended duration is increased from 6 months, it may be tempting to conclude that meeting performance standards will only become more challenging. However, this supposition ignores potential improvements by increasing shared decision-making with patients. Some patients already have a strong commitment to continuing MOUD therapy because of their own health beliefs, for example, fear of relapse to illicit opioid use [51]. Other patients may focus decision-making more on health system barriers (e.g. logistical hurdles), medication adverse effects, lack of efficacy in treating chronic pain or a belief that ‘drug free’ is the only true recovery and so MOUD is a bridge to that goal [52]. By providing patients with better information about increased expected relative survival time, our findings can be used to guide discussions about expected benefits with longer MOUD duration that patients can incorporate in their own value system.

Limitations

The veteran population presented in this study is quite different from the general US population with OUD. Most notably veterans are disproportionately male and older, and they also face a higher risk of death from other causes. The way in which we have presented results here is designed to minimize any effect on generalizability. Our results are stratified by age and sex, and we set all risk factors to zero when computing predictions. Further, we have reported results as relative gains in survival within age and sex group rather than absolute gains.

As with any study relying on pharmaceutical records, we can only approximately measure the discontinuation date from the prescription runout date. Because of this, we may have misclassified some patients as being on therapy when they had already discontinued. Fills of buprenorphine within VA had to be 30 days or less up until the coronavirus disease 2019 pandemic, a period largely omitted from this study. Therefore, if we have misclassified veterans as being on therapy, it is likely by no more than 30 days for durations of therapy measured at up to 6 years. Although we excluded veterans who initiated therapy outside of VA, we were not able to capture veterans who continued therapy with a payer other than VHA. Therefore, some veterans may have been misclassified as being discontinued when they had simply changed payers. Veterans covered by VA receive their prescription medications for a co-payment of no more than $5, and most of the veterans in our sample are covered at a benefit level that provides for free prescriptions from VA. We believe it is unlikely that many of the discontinuations in our sample were misclassified because veterans would have little incentive to choose an alternate payer for their medications.

Unfortunately, the results here do not establish that additional days of therapy cause improvements in survival because of the inherent limitations of the observational design. Although our models adjust for a wide array of observable risks that may affect the relationship between MOUD duration and survival, many factors are unmeasurable in electronic health record data (e.g. motivation). We also made no attempt to account for non-random treatment assignment to different MOUD types, a limitation offset by the choice to not model the MOUD types as separate cohorts and compare differential survival by type.

Despite these limitations, our findings are consistent with other literature favoring treatment durations longer than the current 6-month guideline from authors who examined associations with reduced emergency department visits, inpatient utilization and overdose [18–20]. Our findings, regardless of the observational design limitations, are of vital significance given ethical concerns associated with randomizing participants to shorter MOUD durations.

CONCLUSIONS

The findings of this study support others who have concluded that the current minimum needs to be revisited. The benefit of MOUD retention toward overall survival continues through at least 4 years of MOUD treatment. However, gains in survival with each additional year appear to diminish, or at least become not statistically discernible, somewhere between 4 and 5 years of MOUD retention.

Patients and providers will value these gains differently and our work can help guide discussions on how to optimally choose duration of therapy based on expected survival while accommodating individual values.

AUTHOR CONTRIBUTIONS

Corey J. Hayes: Conceptualization (lead); funding acquisition (lead); investigation (lead); methodology (equal); project administration (equal); resources (lead); supervision (lead); visualization (equal); writing—original draft (lead); writing—review and editing (equal). **Rebecca A. Raciborski:** Conceptualization (equal); formal analysis (lead); methodology (lead); project administration (equal); supervision (equal); visualization (lead); writing—review and editing (equal). **Mahip Acharya:** Data curation (equal); methodology (equal); software (equal); writing—review and editing (equal). **Nahiyan Bin Noor:** Data curation (lead); software (lead); writing—review and editing (supporting). **Edward V. Nunes:** Conceptualization (supporting); methodology (supporting); supervision (supporting); validation (supporting); writing—review and editing (equal). **T. John Winhusen:** Conceptualization (lead); funding acquisition (lead); investigation (lead); project administration (supporting); resources (supporting); supervision (supporting); writing—review and editing (equal).

ACKNOWLEDGMENTS

This material is the result of work supported by the US Department of Veterans Affairs Office of Research and Development's VA Informatics and Computing Infrastructure (VINCI) resources, VA ORD 22-D4V.

DECLARATION OF INTERESTS

None.

DISCLAIMER

The content does not represent the views of the US Department of Veterans Affairs, the National Institutes of Health or the US Government.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Veterans Health Administration. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the Veterans Health Administration with the permission of the Veterans Health Administration.

ORCID

Corey J. Hayes https://orcid.org/0000-0002-7776-6157
Rebecca A. Raciborski https://orcid.org/0000-0002-4135-9074
Edward V. Nunes https://orcid.org/0000-0002-2055-3425
T. John Winhusen https://orcid.org/0000-0002-3364-0739

REFERENCES

1. PubMed. Introduction to the opioid epidemic: the economic burden on the healthcare system and impact on quality of life. https://pubmed.ncbi.nlm.nih.gov/29851449/. Accessed 12 August 2024
2. Wei YJJ, Chen C, Fillingim R, Wei YJ, Schmidt SO, Winterstein AG. Trends in prescription opioid use and dose trajectories before opioid use disorder or overdose in US adults from 2006 to 2016: A cross-sectional study. PLoS Med. 2019;16(11):e1002941. https://doi.org/10.1371/journal.pmed.1002941
3. Webster LR. Risk factors for opioid-use disorder and overdose. Anesth Analg. 2017;125(5):1741–8. https://doi.org/10.1213/ANE.0000000000002496
4. Perlman DC, Jordan AE. The Syndemic of opioid misuse, overdose, HCV, and HIV: structural-level causes and interventions. Curr HIV/-AIDS Rep. 2018;15(2):96–112. https://doi.org/10.1007/s11904-018-0390-3
5. Birnbaum HG, White AG, Schiller M, Waldman T, Cleveland JM, Roland CL. Societal costs of prescription opioid abuse, dependence, and misuse in the United States. Pain Med. 2011;12(4):657–67. https://doi.org/10.1111/j.1526-4637.2011.01075.x
6. 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;2014(2):CD002207. https://doi.org/10.1002/14651858.CD002207.pub4
7. Volkow ND, Frieden TR, Hyde PS, Cha SS. Medication-assisted therapies — tackling the opioid-overdose epidemic. N Engl J Med. 2014;370(22):2063–6. https://doi.org/10.1056/NEJMp1402780
8. Volkow ND, Collins FS. The role of science in addressing the opioid crisis. N Engl J Med. 2017;377(4):391–4. https://doi.org/10.1056/NEJMsr1706626
9. Thomas CP, Fullerton CA, Kim M, Montejano L, Lyman DR, Dougherty RH, et al. Medication-assisted treatment with buprenorphine: assessing the evidence. Psychiatr Serv. 2014;65(2):158–70. https://doi.org/10.1176/appi.ps.201300256
10. Clausen T, Anchersen K, Waal H. Mortality prior to, during and after opioid maintenance treatment (OMT): a national prospective cross-registry study. Drug Alcohol Depend. 2008;94(1-3):151–7. https://doi.org/10.1016/j.drugalcdep.2007.11.003
11. Tkacz J, Volpicelli J, Un H, Ruetsch C. Relationship between buprenorphine adherence and health service utilization and costs among opioid dependent patients. J Subst Abuse Treat. 2014;46(4):456–62. https://doi.org/10.1016/j.jsat.2013.10.014
12. Barajas-Nava L. Oral substitution treatment of injecting opioid users for prevention of HIV infection. J Assoc Nurses AIDS Care. 2017;28(5):832–3. https://doi.org/10.1016/j.jana.2017.05.009
13. Degenhardt L, Clark B, Macpherson G, Leppan O, Nielsen S, Zahra E, et al. Buprenorphine versus methadone for the treatment of opioid dependence: a systematic review and meta-analysis of randomised and observational studies. Lancet Psychiatry. 2023;10(6):386–402. https://doi.org/10.1016/S2215-0366(23)00095-0
14. Giacomuzzi SM, Riemer Y, Ertl M, Kemmler G, Rössler H, Hinterhuber H, et al. Buprenorphine versus methadone maintenance treatment in an ambulant setting: a health-related quality of life assessment. Addiction. 2003;98(5):693–702. https://doi.org/10.1046/j.1360-0443.2003.00352.x
15. Ponizovsky AM, Grinshpoon A. Quality of life among heroin users on buprenorphine versus methadone maintenance. Am J Drug Alcohol Abuse. 2007;33(5):631–42. https://doi.org/10.1080/00952990701523698
16. Ponizovsky AM, Margolis A, Heled L, Rosca P, Radomislensky I, Grinshpoon A. Improved quality of life, clinical, and psychosocial outcomes among heroin-dependent patients on ambulatory buprenorphine maintenance. Subst Use Misuse. 2010;45(1-2):288–313. https://doi.org/10.3109/10826080902873010
17. 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. Ann Intern Med. 2018;169(3):137–45. https://doi.org/10.7326/M17-3107

18. 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. 2019;177:117–24. https://doi.org/10.1176/appi.ajp.2019.19060612
19. 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. 2023;118(1):97–107. https://doi.org/10.1111/add.15998
20. Samples H, Williams AR, Crystal S, Olfson M. Impact of long-term buprenorphine treatment on adverse health care outcomes in Medicaid. Health Aff. 2020;39(5):747–55. https://doi.org/10.1377/hlthaff.2019.01085
21. Williams AR, Johnson KA, Thomas CP, Reif S, Socías ME, Henry BF, et al. Opioid use disorder Cascade of care framework design: A roadmap. Subst Abus. 2022;43(1):1207–14. https://doi.org/10.1080/08897077.2022.2074604
22. HHS, CMS, PQMM. Quality ID #468 (NQF 3175): Continuity of Pharmacotherapy for Opioid Use Disorder (OUD)-National Quality Strategy Domain: Effective Clinical Care-Meaningful Measure Area: Prevention and Treatment of Opioid and Substance Use Disorders 2019 COLLECTION TYPE: MIPS CLINICAL QUALITY MEASURES (CQMS) MEASURE TYPE: Process-High Priority.
23. NATIONAL PRACTICE GUIDELINE For the Treatment of Opioid Use Disorder
24. Weinstein LC, Iqbal Q, Cunningham A, Debates R, Landistratis G, Doggett P, et al. Retention of Patients With Multiple Vulnerabilities in a Federally Qualified Health Center Buprenorphine Program: Pennsylvania, 2017-2018. Am J Public Health. 2017;110: 580–6.
25. Hser YI, Saxon AJ, Huang D, Hasson A, Thomas C, Hillhouse M, et al. Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. Addiction. 2014;109(1):79–87. https://doi.org/10.1111/add.12333
26. 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(1):22–35. https://doi.org/10.1080/10550887.2016.1100960
27. 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(6):572–80. https://doi.org/10.1111/ajad.12553
28. 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(7):768–76. https://doi.org/10.1176/appi.ps.201700363
29. 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(3):356–61. https://doi.org/10.1016/j.jsat.2013.10.004
30. Lagisetty P, Garpestad C, Larkin A, Macleod C, Antoku D, Slat S, et al. Identifying individuals with opioid use disorder: validity of international classification of diseases diagnostic codes for opioid use, dependence and abuse. Drug Alcohol Depend. 2021;221:108583. https://doi.org/10.1016/j.drugalcdep.2021.108583
31. Chua KP, Nguyen TD, Zhang J, Conti RM, Lagisetty P, Bohnert AS. Trends in buprenorphine initiation and Retention in the United States, 2016-2022. JAMA. 2023;329(16):1402–4. https://doi.org/10.1001/jama.2023.1207
32. 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. https://doi.org/10.1016/j.jsat.2019.07.010
33. STROBE. Strengthening the reporting of observational studies in epidemiology. https://www.strobe-statement.org/. Accessed 30 September 2024
34. Hser Y-I, Mooney LJ, Saxon AJ, Miotto K, Bell DS, Zhu Y, et al. High mortality among patients with opioid use disorder in a large healthcare system. J Addict Med. 2017;11(4):315–9. https://doi.org/10.1097/ADM.0000000000000312
35. Hayes CJ, Raciborski RA, Nowak M, Acharya M, Nunes EV Jr, Winhusen TJ. Medications for opioid use disorder: Predictors of early discontinuation and reduction of overdose risk in US military veterans by medication type. Addiction. 2024;120(1):138–51. https://doi.org/10.1111/ADD.16659
36. (NIH HEAL Initiative)|National Institute on Drug Abuse (NIDA). Optimizing Retention, Duration, and Discontinuation Strategies for Opioid Use Disorder Pharmacotherapy. https://nida.nih.gov/about-nida/organization/cctn/ctn/research-studies/optimizing-retention-duration-discontinuation-strategies-opioid-use-disorder-pharmacotherapy-nih. Accessed 12 November 2023
37. USDA ERS. Rural-Urban Commuting Area Codes. https://www.ers.usda.gov/data-products/rural-urban-commuting-area-codes/. Accessed 30 October 2024
38. CDC/ATSDR Social Vulnerability Index (SVI). https://www.atsdr.cdc.gov/placeandhealth/svi/index.html. Accessed 19 April 2022
39. Moore BJ, White S, Washington R, Coenen N, Elixhauser A. Identifying increased risk of readmission and in-hospital mortality using hospital administrative data: The AHRQ Elixhauser comorbidity index. Med Care. 2017;55(7):698–705. https://doi.org/10.1097/MLR.0000000000000735
40. VA Priority Groups. https://veteran.com/va-priority-groups/. Accessed 27 November 2023
41. Putter H, Fiocco M, Gekus RB. Tutorial in biostatistics: Competing risks and multi-state models. Stat Med. 2007;26:2389–430.
42. Le-Rademacher JG, Therneau TM, Ou FS. The utility of multistate models: A flexible framework for time-to-event data. Curr Epidemiol Rep. 2022;9:183–9.
43. Burns M, Tang L, Chang CCH, Kim JY, Ahrens K, Allen L, et al. Duration of medication treatment for opioid-use disorder and risk of overdose among Medicaid enrollees in 11 states: a retrospective cohort study. Addiction. 2022;117(12):3079–88. https://doi.org/10.1111/add.15959
44. Morgan JR, Schackman BR, Weinstein ZM, Walley AY, Linas BP. Overdose following initiation of naltrexone and buprenorphine medication treatment for opioid use disorder in a United States commercially insured cohort. Drug Alcohol Depend. 2019;200:34–9. https://doi.org/10.1016/j.drugalcdep.2019.02.031
45. Crowther MJ, Lambert PC. Parametric multistate survival models: flexible modelling allowing transition-specific distributions with application to estimating clinically useful measures of effect differences. Stat Med. 2017;36(29):4719–42. https://doi.org/10.1002/sim.7448
46. Williams AR, Mauro CM, Feng T, Wilson A, Cruz A, Olfson M, et al. Performance measurement for opioid use disorder medication treatment and care retention. Am J Psychiatry. 2022;180: 454–7.
47. Carter E, Schatz D, Isaacs N Garcia J, Henry B, Krawczyk N, et al. Application of an opioid use disorder cascade of care in a large public health system. medRxiv 2023; 2023.10.19.23297271
48. 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. https://doi.org/10.1016/j.jsat.2018.09.001
49. 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. https://doi.org/10.1136/bmj.j1550

50. Zweben JE, Sorensen JL, Shingle M, Blazes CK. Discontinuing methadone and buprenorphine: a Review & Clinical Challenges. J Addict Med. 2021;15(6):454–60. https://doi.org/10.1097/ADM.0000000000000789
51. Bentzley BS, Barth KS, Back SE, Book SW. Discontinuation of buprenorphine maintenance therapy: Perspectives and outcomes. J Subst Abuse Treat. 2014;52:48.
52. Wyse JJ, Eckhardt A, Waller D, Gordon AJ, Shull S, Lovejoy TI, et al. Patients' perspectives on discontinuing buprenorphine for the treatment of opioid use disorder. J Addict Med. 2024;18(3):300–5. https://doi.org/10.1097/ADM.0000000000001292

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: Hayes CJ, Raciborski RA, Acharya M, Noor NB, Nunes EV, Winhusen TJ. Evaluating the optimal duration of medication treatment for opioid use disorder. Addiction. 2026;121(4):922–33. https://doi.org/10.1111/add.70211