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A Retrospective Claims Database Analysis: 2-year Restricted Mean Time in  
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A thesis submitted in partial satisfaction  
of the requirements for the degree Master of Science  
in Epidemiology

by

Zirui Zhou

2024

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## ABSTRACT OF THESIS

### A Retrospective Claims Database Analysis: 2-year Restricted Mean Time in Buprenorphine Treatment Among People with Opioid Use Disorder in the United States

by

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Master of Science in Epidemiology

University of California, Los Angeles, 2024

Professor Marissa J. Seamans, Chair

Buprenorphine is an evidence-based treatment for opioid use disorder, but patient retention is typically low. This retrospective study used the MarketScan claim databases from 2015 to 2019 to examine patient retention in buprenorphine treatment over a two-year follow-up period. We included patients with OUD who started buprenorphine treatment after diagnosis and calculated the restricted mean time on buprenorphine and assessed retention probability under different definitions. Among 53,355 patients, the mean duration of buprenorphine use was 282.5 days (38.7% of the follow-up period). Under the strictest retention definition, only 29.5% of patients were still on buprenorphine after 180 days. The limited retention probability highlights the need for improved strategies for long-term buprenorphine use and provides insight into improving OUD treatment outcomes.

The thesis of Zirui Zhou is approved.

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2024

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## **Background**

Opioid use disorder (OUD) impacts millions of Americans, and buprenorphine is an evidence-based medication for the treatment of OUD [1-3]. However, retention of patients in buprenorphine treatment at 6 months is typically in the 50% or lower range in various trials [4]. The substantial dropout rates from treatment are concerning because discontinuation increases the risk of return to opioid use, which can lead to overdose and death [5, 6].

Varying definitions of retention have been used in the literature to capture durations of treatment needed to improve opioid use outcomes [7, 8]. For instance, the American Society of Addiction Medicine's (ASAM) OUD treatment guidelines suggest that participation in treatment for less than 90 days may be of limited effectiveness, while longer-term treatment is associated with more positive long-term outcomes [9].

The cascade of care framework is proposed as a measure to monitor patient progress through various stages of treatment and can help to evaluate the performance of addiction treatment. For patients with opioid use disorder (OUD), the relevant stages include (1) Diagnosis among those affected with OUD, (2) Linkage to OUD care among those diagnosed, (3) Medication (MOUD) initiation among those entering care, (4) Retention among those initiating MOUD, and (5) Remission or recovery among those retained on MOUD [10, 11].

Because of the high rate of return to opioid use after medication discontinuation, patients with OUD often shift between different stages of the OUD cascade of care. This pattern is analogous to the HIV continuum of care, as people living with HIV (PWH) may fall between adherence and non-adherence to antiretroviral medication. Lesko et al.

presented a novel, patient-centric, longitudinal summary of patient progress through the HIV care continuum to visualize patients' transitions between stages over time [12]. This longitudinal approach is applicable to the OUD cascade of care as a method to examine patients' transitions between OUD treatment stages and describe how patients' time is distributed across the various stages of the OUD cascade of care.

Our aim was to calculate the restricted mean time spent on buprenorphine treatment over a two-year period, both overall and above common retention thresholds. Additionally, we sought to assess how estimates of time spent retained on buprenorphine vary depending on the definition of retention.

## **Methods**

### ***Study sample***

This retrospective study utilized data from the IBM® MarketScan® Research Databases, covering the period from January 1, 2015, to December 31, 2019. These databases contain individual-level, de-identified, healthcare claims information from employers, health plans, hospitals, and Medicare and Medicaid programs. We included patients diagnosed with OUD who received their first buprenorphine prescription after the date of diagnosis and before December 31, 2017, to ensure a minimum two-year follow-up period. The cohort was constructed starting from the stage of MOUD initiation among patients entering care, aligning with the study's aim to analyze the transition and time distribution of buprenorphine use.

Our cohorts were derived from 633,944 individuals in the claims databases who were diagnosed with OUD, which is defined as meeting either of the following criteria:

1) having an International Classification of Diseases, Ninth Edition (ICD-9) or International Statistical Classification of Diseases and Related Health Problems, Tenth Edition (ICD-10) diagnostic code for opioid dependence on one or more inpatient hospital claims or two or more outpatient claims within a three-month period. The date of their diagnosis is the first claim date for dependence; 2) One or more claims with a diagnosis code of opioid dependence, opioid abuse, or opioid use, along with drug claims for medications for opioid use disorder (MOUD) or detoxification, or diagnosis codes of incident related to opioid overdose, or injecting-related infection, opioid-related inpatient detoxification, or hospitalization services. The diagnosis date is defined as the earliest service date [13].

We excluded patients diagnosed prior to July 1, 2015, to ensure they had a minimum of 6 months of continuous enrollment prior to the OUD diagnosis. We restricted to patients who initiated buprenorphine treatment after diagnosis until December 31, 2017, to create an analytic sample of buprenorphine treatment patterns (Figure 1). Buprenorphine use was identified by National Drug Codes (NDC) specifically indicated for opioid use disorder, such as sublingual formulations. Intravenous, intramuscular, and transdermal injections were excluded, as these forms are not commonly used for opioid use disorder.

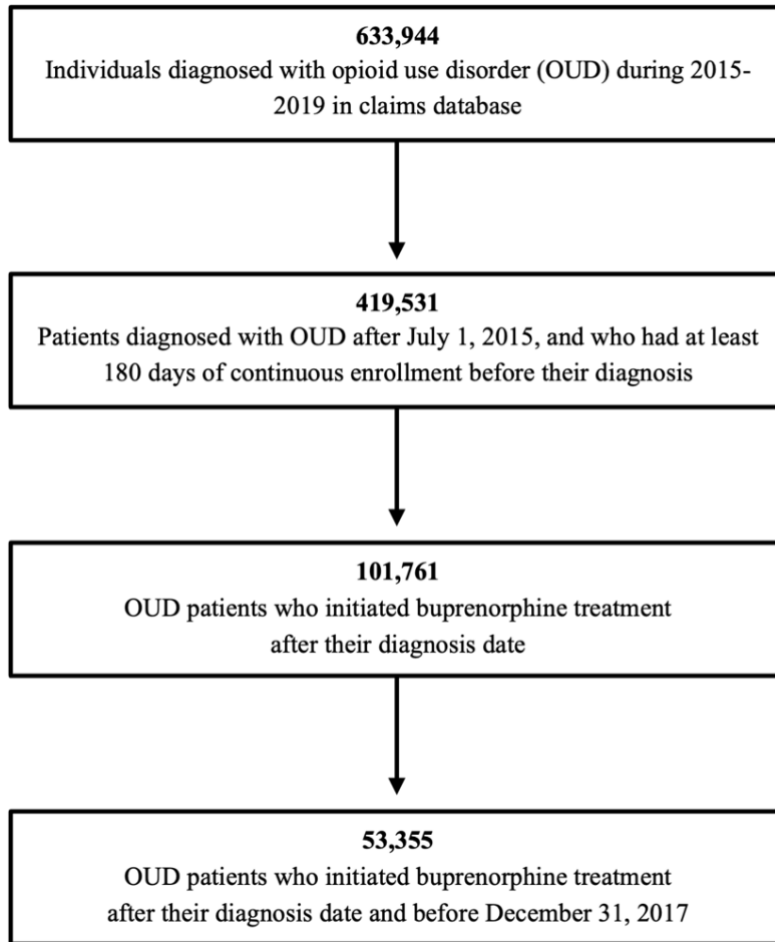


Figure 1. Flowchart of the study cohort

### *Outcome measurement*

As mentioned previously, patients with OUD frequently transition between the different stages of care. Here, we focus on the following buprenorphine treatment stages, as shown in Figure 2: on buprenorphine with treatment duration below and above the retention threshold; off buprenorphine and in follow-up; and loss to follow up (LTFU).

Buprenorphine treatment duration was defined as the consecutive time from the initial prescription start date to the end of the last prescription or prescription gap. Each treatment duration was determined based on the date of service occurrence and days of supply for each buprenorphine claim. When dealing with missing values for days of

supply, we performed multiple imputation using the Markov Chain Monte Carlo (MCMC) method, including days of supply, ingredient costs, measured quantities, and payments as auxiliary variables in the imputation model [14]. Subsequently, four treatment retention definitions were applied to define treatment episodes, with prescription gap thresholds set at 7 days or 30 days, and retention thresholds at 90 days or 180 days.

LTFU was defined as a gap in continuous enrollment for at least 30 days. Patients were considered to have resumed follow-up if they re-enrolled after experiencing LTFU. Because we did not have valid data to ascertain death, LTFU could be due to disenrollment or death.

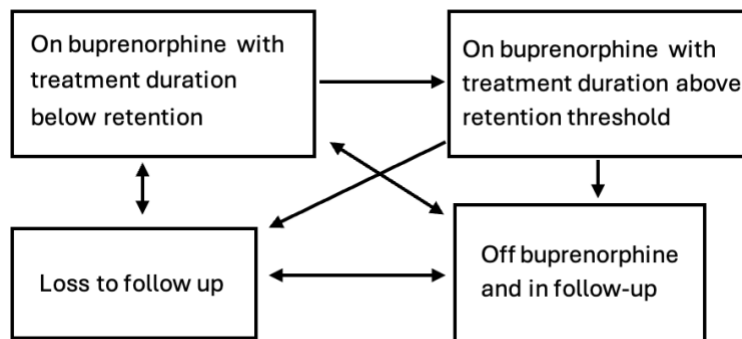


Figure 2. Transition between the different buprenorphine treatment stages

### *Statistical analyses*

We calculated 2-year restricted mean time spent on various states of buprenorphine treatment, including below the retention threshold, above the retention threshold, off buprenorphine and in follow-up, and loss to follow-up for the different retention thresholds (180 days vs. 90 days) and allowable treatment gaps (7 days vs. 30 days). We then calculated the proportion of the study population in each phase at each time point, with the proportion of the population in each of the five phases summing to 1.

The proportions can be represented by a set of stacked curves representing the distribution of the population in the different phases over time. The area under each curve, plotted separately, corresponds to the restricted mean time spent in each buprenorphine treatment stage during the 2-year follow-up period after the initial buprenorphine prescription. All analyses were performed using SAS software, Version 9.4 (SAS Institute, Inc. Cary, NC, USA).

## Results

### *Study sample*

Between July 1, 2015, and December 31, 2017, a total of 53,355 patients initiated buprenorphine treatment following a diagnosis of opioid use disorder (OUD). Of these, 51.2% (n=27,330) identified as female. For patients with Medicaid coverage (n=35,118), 91.0% (n=29,561) identified as non-Hispanic White. Among those with commercial insurance (n=18,237), 45.7% (n=8,338) resided in the southern region. The mean age at the time of OUD diagnosis was 36.6 years (SD 10.7) (Table 1).

Table 1. Demographic of patients with opioid use disorder who initiated buprenorphine, 2015-2017

	<b>N=53,355</b>
Age (SD)	36.6 (10.7)
Sex	
Female	27,330 (51.2)
Male	26,025 (48.8)
Medicaid	35,118 (65.8)
Commercial insurance	18,237 (34.2)
Race (among Medicaid only) *	
Non-Hispanic white	29,561 (91.0)
Non-Hispanic black	2,062 (6.4)
Hispanic	397 (1.2)
Other	460 (1.4)

Region (among Commercial insurance only)	
Northeast	3,951 (21.7)
North Central	3,601 (19.7)
South	8,338 (45.7)
West	2,295 (12.6)
Unknown	52 (0.3)

\*2638 patients have no ethnicity information.

A gap of more than 7 days between prescriptions, indicating a new treatment episode, led to 116,748 buprenorphine treatment episodes, and a gap of more than 30 days resulted in 76,612 buprenorphine treatment episodes. Table 2 provides detailed information on the number of buprenorphine treatments and their duration for each patient.

Table 2. Characteristics of buprenorphine treatment episode with different prescription gap (N=53,355)

	≤ 7 days gap	≤ 30 days gap
Total treatment episodes	116,748	76,612
Treatment episodes per patient, median (IQR)	2 (1, 3)	1 (1, 2)
Treatment episode duration, median (IQR)	53 (22, 154)	95 (30, 307)

### Time spent in each treatment stage

Over the course of two years following initiation, the mean duration on buprenorphine treatment was 282.5 days (SD 259.5), accounting for 38.7% (SD 35.5) of the follow-up period. Patients spent an average of 269.6 days (SD 254.2), or 36.9% (SD 34.8) of the time, off buprenorphine while remaining enrolled, and 177.9 days (SD 235.8), or 24.4% (SD 32.3) of the time, lost to follow-up, with a retention gap defined as 7 days.

Table 3 presents the amount of time spent on buprenorphine above the retention thresholds. Retention definition 1 ( $\geq 180$  days continuous treatment without any gaps  $> 7$  days) was the strictest retention definition and resulted in an average of 113.7 (SD 181.8)

spent retained on buprenorphine. Retention definition 4 ( $\geq 90$  days of continuous treatment without any gaps  $> 30$  days) was the least strict retention definition and resulted in an average of 206.8 (SD 242.9) spent retained on buprenorphine.

Table 3. Average number of days and proportion spent on buprenorphine above retention thresholds based on different retention definitions (N=53,355)

Retention definition	On buprenorphine above retention threshold (days)	Proportion of follow-up time (%)
1. $\geq 180$ days threshold and 7 days as allowable gap	113.7 (181.8)	15.6 (24.9)
2. $\geq 180$ days threshold and 30 days as allowable gap	151.5 (209.3)	20.8 (28.7)
3. $\geq 90$ days threshold and 7 days as allowable gap	169.1 (220.2)	23.2 (30.2)
4. $\geq 90$ days threshold and 30 days as allowable gap	206.8 (242.9)	28.3 (33.3)

### Visualization of time spent in treatment stages

Figure 3 illustrates these data regarding retention definition 1. The area between the curves represents the total time spent in each stage on average by an individual. The interpretation at a given time point is the probability of a person being in each stage. For instance, at the 180-day mark after initiating buprenorphine treatment, the probability of a patient having been on buprenorphine for 180 days or more is 29.5% (highlighted in yellow), gradually decreasing to 15.8% by the end of the second year.



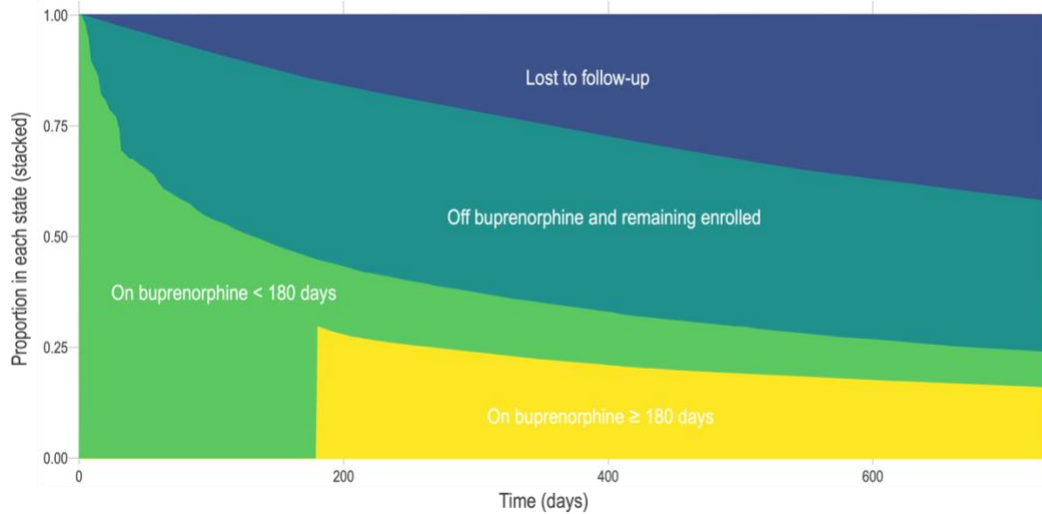


Figure 3. Proportion of patients in each treatment stage in 2 years follow-up with 180 days threshold and 7-day allowable gap

## Discussion

In our study, OUD patients who initiated buprenorphine spent on average only 38.7% of their time on buprenorphine during the two-year follow-up period. With the strictest retention definition, only about 29.5% of patients remained on buprenorphine and crossed the 180-day threshold after their initial prescription. These findings suggest the need for strategies to extend the duration of buprenorphine treatment and improve patient retention [15, 16].

A visual observation of the chart reveals that when the strictest retention criteria are applied, the probability of a patient continuing to use buprenorphine for any given time point from 0.5 to 2 years after initiation of buprenorphine is less than 50%. This observation suggests a significantly lower probability of long-term buprenorphine use. This finding is consistent with results from other studies [17-21].

We assumed that patients lost to follow-up have stopped using buprenorphine, although some may still continue pharmacotherapy due to stockpiled medication or other

sources of payment for their medication. For instance, due to the lack of insurance acceptance by clinicians and insurance restrictions of OUD medications, some patients may pay for their buprenorphine prescriptions in cash, which is not recorded in the claim databases [22-24]. Because the majority of buprenorphine prescriptions dispensed in the United States is paid by insurance, we do not expect cash payments to be a substantial source of bias [25]. However, the average duration and proportion of buprenorphine use above the threshold may be underestimated. Moreover, all cohort patients were given a 30-day grace period to establish 180 days of continuous enrollment before their diagnosis. If the grace period were stricter, the cohort would be smaller but would have better continuous insurance coverage, allowing for more accurate identification of buprenorphine use.

The MarketScan claim databases provide a large sample but has some limitations because it was not specifically designed for research. For example, part of the days of supply data is missing. We tried to address this issue using multiple imputation, where we assume that the days of supply data are at least missing at random. In addition, because of the lack of death information in the databases, some classified as LTFU may have died. We assumed that patients who are LTFU could re-enter different treatment stages, but some may not return because they have died. Developing more efficient and accurate algorithms for identifying deaths could help address this issue. Furthermore, the databases do not include uninsured individuals and small size firms are less represented. As a result, the generalizability of the findings to the entire U.S. population is limited [26].

Despite these limitations, this new method for estimating the duration of OUD treatment phases can enhance our understanding of OUD treatment and factors associated with medication retention. For example, future work could help explore how buprenorphine retention time varies across age groups, comorbidities, or other factors, such as the use of other common medications and patient demographics, on the duration of the treatment phase. This information could inform the development of both individual and public health interventions.

## **Conclusion**

In this retrospective study involving 53,355 OUD patients who initiated buprenorphine, we used a novel approach that accounted for multiple treatment episodes and transitions between treatment phases and observed a significant reduction in buprenorphine retention during a two-year follow-up period. These findings suggest the importance of understanding barriers to retention during OUD treatment.

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