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Predicting buprenorphine adherence among patients with opioid use disorder in primary care settings

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Abstract

Background Medications for opioid use disorder (MOUD), including buprenorphine, are effective treatments for opioid use disorder (OUD) and reduce risk for overdose and death. Buprenorphine can be prescribed in outpatient primary care settings to treat OUD; however, prior research suggests adherence to buprenorphine in these settings can be low. The purpose of this study was to identify the rates of and factors associated with buprenorphine adherence among patients with OUD in the first six months after a new start of buprenorphine.

Methods Data were extracted from the electronic health record (EHR) from a large integrated health system in the upper Midwest. Patients with OUD ($N = 345$; Mean age = 37.6 years, SD 13.2; 61.7% male; 78% White) with a new start of buprenorphine between March 2019 and July 2021 were included in the analysis. Buprenorphine adherence in the first six months was defined using medication orders; the proportion of days covered (PDC) with a standard cut-point of 80% was used to classify patients as adherent or non-adherent. Demographic (e.g., age, sex, race and ethnicity, geographic location), service (e.g., encounters, buprenorphine formulations and dosage) and clinical (e.g., diagnoses, urine toxicology screens) characteristics were examined as factors that could be related to adherence. Analyses included logistic regression with adherence group as a binary outcome.

Results Less than half of patients were classified as adherent to buprenorphine (44%). Adjusting for other factors, male sex (OR = 0.34, 95% CI = 0.20, 0.57, $p < .001$) and having an unexpected positive for opioids on urine toxicology (OR = 0.42, 95% CI = 0.21, 0.83, $p < .014$) were associated with lower likelihood of adherence to buprenorphine, whereas being a former smoker (compared to a current smoker; OR = 1.82, 95% CI = 1.02, 3.27, $p = .014$) was associated with greater likelihood of being adherent to buprenorphine.

Conclusions These results suggest that buprenorphine adherence in primary care settings may be low, yet male sex and smoking status are associated with adherence rates. Future research is needed to identify the mechanisms through which these factors are associated with adherence.

Keywords Substance-related disorders, Adherence, Medications for opioid Use Disorder, Outpatient treatment

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Introduction

More than 109,000 people died from a drug overdose in 2021, with 75% of overdose deaths involving opioids [1]. Given the impact of opioids on overdose deaths, increasing the availability and uptake of efficacious treatments for opioid use disorder (OUD) is critical. Yet, more than 80% of people with OUD do not receive treatment [2]. Medication for OUD (MOUD), including methadone and buprenorphine, have been tremendously successful in decreasing opioid-related mortality and morbidity rates [3] and improving quality of life among people with OUD [4, 5]. Methadone is highly regulated and, when used to treat OUD, can only be dispensed through specialty substance use treatment settings [6]. In contrast, buprenorphine is available by prescription by medical providers with a DEA license regardless of setting (e.g., primary care, emergency department, specialty care) [7–9]. In 2022, Congress eliminated registration (i.e., "waiver") requirements for buprenorphine prescribing allowing medical practitioners to prescribe buprenorphine as they would any other schedule 3 controlled substance, theoretically expanding access to treatment [10].

Although the availability of buprenorphine to patients with OUD is increasing, less is known about how well patients adhere to the medication and what level of adherence is needed for effective treatment [11, 12]. Medication adherence, the extent to which a patient's medication-taking behavior is consistent with their clinician's recommendation [13], is an important behavior in the self-care of chronic illness and enhances treatment outcomes. Adherence is often defined as a ratio of the number of days patients have medication available over the total number of days in a treatment window (using a medication possession ratio or proportion of days covered), with 80% used as a defining threshold [14]. Adherence to medication is a function of factors related to the patient (e.g., the perceived effectiveness, need, harms for taking the medication; health literacy; self-regulation/forgetfulness; sociodemographic; comorbidities), treatment (e.g., side effects, pharmacokinetics/dynamics, polypharmacy), healthcare system (e.g., medication cost; patient engagement in treatment decisions), among many others [15–17].

Mounting evidence suggests that lower adherence to buprenorphine is associated with poor clinical outcomes and higher healthcare costs. For example, patients with lower adherence to buprenorphine are more likely to relapse and be admitted to the hospital and the emergency room [18]. Further, one study demonstrated that patients who were nonadherent to buprenorphine (defined by possessing less than 80% of medication needed to take it as prescribed) incurred approximately $22,194 more in annual healthcare expenditures compared to persons who did not meet this criteria [19]. Thus, it is essential to better understand factors associated with lower adherence and ways to optimize adherence for patients taking buprenorphine.

A narrow section of the literature has examined buprenorphine adherence and factors that are associated with adherence in patients with OUD [20, 21]. Estimates of buprenorphine adherence among various timeframes of patients in clinical settings using administrative claims databases range between 21% and 43% [18]. In contrast, in controlled clinical trials, adherence by self-report and/or electronic monitoring of prescription bottle caps is approximately 70%, with missed dosing being a common reason for non-adherence [22, 23]. Factors associated with adherence in the literature vary from study to study based on adherence measure approach, population, independent variables tested/controlled for, and data source. For example, studies suggest that lower buprenorphine adherence is associated with younger age, poorer health (including co-morbid alcohol use disorder, substance use disorder, depressive disorder, bipolar disorder, or chronic pain), lower average prescribed daily dose of buprenorphine (<12 mg), and tablet compared to the film formulation [18, 19, 24]. One study using EHR data demonstrated that single-daily dosing of buprenorphine v. multiple-daily dosing was not significantly associated with buprenorphine adherence [25]. Thus, although there is preliminary evidence characterizing who may be at risk for non-adherence among patients taking buprenorphine, factors associated with adherence varied across studies. Most studies use prescribing and dispensing information from administrative claims databases, which generally cannot control for important demographic, environmental and social vulnerability, and clinical factors thought to be associated with treatment adherence, retention, outcomes [26, 27]. EHR data also includes information on patients' social determinants of health, including where they live, that may give clues to their levels of income, education, and neighborhood diversity and vulnerability. A minority of studies used clinical data from the EHR, which can capture a wider array of potential demographic and clinical factors than claims data.

Identifying factors associated with non-adherence may help clinicians learn who is most at risk for poor adherence and whether there are modifiable factors that could improve adherence. This may lead to targeting adherence interventions, ultimately leading to improved OUD treatment and outcomes. The overall goal of this project is to examine buprenorphine adherence among primary care patients with OUD using EHR data. The objectives were to: (1) characterize rates of buprenorphine adherence in patients with OUD receiving buprenorphine in primary care settings; and (2) identify factors associated with buprenorphine adherence among these patients.

Methods

Study setting

This secondary analysis was conducted at HealthPartners, the largest consumer-governed nonprofit healthcare organization in the United States. HealthPartners has 55 primary care clinics and cares for more than 1.2 million patients in Minnesota and western Wisconsin. Patients are insured by a mix of insurance types, including Medicaid (12%), Medicare (12%), commercial insurance (60%) and others. Data for this study was taken from index (baseline) visits for a larger clinical trial of a clinical decision support intervention to help PCCs identify and treat patients with OUD [28]. Patients had visits in one of 30 primary care clinics between March 2019 and December 2021, notably a time when waivers were still required to prescribe buprenorphine. This study was reviewed and approved by the HealthPartners Institutional Review Board and data were extracted under a waiver of informed consent.

Patient study population

The study included patients with a diagnosis of OUD (International Classification of Diseases-10th edition codes F11.XX) who were (1) between 18 and 75 years old; (2) had a new start of buprenorphine during the study period (no prescriptions for at least 60 days prior to the first prescription); (3) at least two prescriptions for buprenorphine during the study period; and (4) had at least six months of observation during the study period (started before July 1, 2021). Patients were excluded if they had (1) a cancer diagnosis; (2) lived in hospice or a nursing home; or (3) opted out of research in the health system. Patients were required to have at least two buprenorphine prescriptions to calculate adherence using proportion of days covered (PDC). This threshold was used to establish patients as receiving treatment for OUD from the health system and reduce potential bias of early dropouts from treatment or bridge prescriptions to help patients enter into specialty care [29].

Data source

Data was gathered from the EHR and compiled into an analytic database. The team defined variables of interest in the data dictionary, working with a study programmer who had expertise in compiling multiple sources of electronic automated data.

Measures

Buprenorphine adherence

Buprenorphine adherence in the first 180 days (6 months) of a treatment episode was captured by buprenorphine orders in the EHR. We chose this timeframe because 6 months of continuous MOUD treatment is a quality measure endorsed by the Health Effectiveness and Data Information Set (HEDIS) quality measures [30]. Data based on days' supply were concatenated to create a supply diary for each patient. Similar to prior studies [31], if a prescriber ordered buprenorphine before the end of the days' supply for the previous dispensing, we assumed that use of the new refill began the day after the estimated end date for the prior fill. The PDC was the ratio of the total days' supply divided by the observation period days (180). Patients were categorized as adherent if the PDC$\geq$0.80, and non-adherent if PDC$<$0.80 [14]. The 80% cut point is standard in medication adherence studies and is used in quality measures (e.g., National Committee for Quality Assurance) [14, 28, 29, 31, 32].

Sociodemographic characteristics

Age, sex, race, ethnicity, smoking status, insurance type, and social vulnerability index (SVI) scores were extracted from EHR. Age was calculated using age in years on the date of the index encounter. Biological sex was labeled as either male or female. Race was categorized as Black or African American, Other or Unknown Race (which included American Indian or Alaska Native, Hawaiian or Pacific Islander, Asian, Mixed, Other, or Unknown racial categories), or White. Ethnicity was identified as either Hispanic or Latino/a, Not Hispanic or Latino/o, and Unknown. Insurance was classified as commercial, Medicare, Medicaid, state subsidized, other Insurance, or None.

Finally, the social vulnerability index (SVI) is a CDC-defined measure of social determinants of health based on a patient's neighborhood location [33]. It identifies those census tracts in communities that may benefit from additional resources during emergency events based on 15 social factors. There are 4 sub-indices (socioeconomic percentile, household composition percentile, minority status and language percentile, and housing status percentile) and an overall index score. Scores range from 0 to 1, with higher scores corresponding to greater social vulnerability.

Comorbid diagnoses

Concurrent diagnoses included the presence of comorbid substance use disorders, comorbid mental health disorders, and/or comorbid physical health conditions. Patients were considered to have a comorbid diagnosis if they had at least one International Classification of Diseases-10 (ICD-10) diagnostic code on their EHR problem list or at least one encounter diagnosis in the 18 months prior to their index date. Comorbid substance use disorders were defined as the presence (1) or absence (0) of an alcohol use disorder, cocaine use disorder, or stimulant use disorder. Smoking status was defined as either current smoker, non-smoker, or former smoker. Mental health comorbidities were categorized as presence (2) or

absence (0) of anxiety, depression, personality disorder, post-traumatic stress disorder, or serious mental illness (including bipolar or schizophrenia spectrum disorders). Comorbid physical health conditions were defined as the presence (1) or absence (0) of chronic pain, diabetes, hepatitis C, or hypertension.

Buprenorphine characteristics

Buprenorphine use was characterized by average days' supply, daily dose (in milligrams), and formulation type. Buprenorphine formulation was categorized as either film, tab, or mixed (at least one prescription of both types). The injectable formulation was minimally used (<5 orders) and was excluded from analysis.

Urine toxicology screens

Urine toxicology screens were extracted during the six-month follow-up period. Results were grouped based on substance components and five variables were created: unexpected positive (amphetamines), unexpected positive (benzodiazepines), unexpected positive (cocaine), unexpected positive (opioids), and unexpected negative (buprenorphine). Patients with an unexpected result during the six months of observation were categorized as a 1. If they never had an unexpected result, they were categorized as 0 (including undetermined results).

Encounters

Specialty care encounters were classified by type. If patients ever had an encounter with specialty behavioral health, addiction medicine, or pain medicine during the follow-up period, they were categorized as 1 for each of those variables. Otherwise, they were classified as 0. In addition, if patients had emergency room encounters during the follow-up period, they were categorized by whether (1) or not (0) diagnoses of OUD or overdose were addressed at those encounters.

Analysis

Before analysis, all variables were examined using descriptive statistics to examine distributions, potential outliers, and analysis assumptions. Measures of central tendency (mean) and variability (standard deviation) were used to describe continuous variables overall and across adherence groups. Categorical variables were described using frequencies and percentages. We then assessed univariate associations between potential predictors and adherence groups using logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI). Associations were considered meaningful predictors of adherence based on OR magnitude. Based on univariate results and clinical judgment, we then created a multivariable logistic regression model to determine whether predictors remain associated with outcomes after adjusting for other demographic and clinical factors.

Results

During the study period, a total of 374 patients with OUD had a new start of buprenorphine. Twenty-nine patients only had one buprenorphine order and were excluded from the analysis. Thus, 345 patients with at least two buprenorphine orders were included. We compared those with one buprenorphine order to those with more than one order and found patients with one buprenorphine order were significantly less likely to have chronic pain, $\chi 2\ (1) = 5.19$, $p = .02$, $n = 6$ (20.7%), than patients with more than one order, $n = 146$ (42%); however, the two groups did not significantly differ on any other demographic characteristics or clinical diagnoses. Characteristics of the final sample are described in Table 1. Briefly, patients had an average age of 37.6 (SD = 13.2). The majority were male (61.7%), White (78.0%), not Hispanic or Latino (87.5%), and had Medicaid insurance (58.0%). Notably, the majority were current smokers (57.6%), and two-thirds had a diagnosis of an anxiety disorder (67.3%). Half had diagnoses of depression (49.6%), and many had chronic pain (41.9%).

During the study period, patients had an average of 8.8 buprenorphine orders (SD = 5.4, range 2–27), each covering an average 21-day supply (M = 21.4 days, SD = 8.3). Less than half of patients ($n = 125$; 44%) were classified as adherent on buprenorphine, whereas 193 patients (56%) were classified as non-adherent. A series of univariate logistic regression analyses were used to examine associations between demographic and clinical characteristics and adherence (Table 1). Patients who were older, had commercial insurance, were former smokers (compared to current smokers), had chronic pain, had hypertension, or had a behavioral health encounter were more likely to be adherent to buprenorphine. In addition, those with buprenorphine prescriptions with longer average days' supply were more likely to be adherent. Patients who were male, had Medicaid insurance, had cocaine use disorder, had an unexpected positive drug screen for amphetamines, or an unexpected positive for opioids were less likely to be adherent for buprenorphine.

A series of three multivariable logistic regression models were used to examine predictors of buprenorphine adherence, controlling for other factors (see Table 2). The first model used demographic characteristics, including age, sex, race, ethnicity, and insurance coverage (commercial v. all others and Medicaid vs. all others). In that model, males were 67% less likely to be adherent to buprenorphine than females, and patients who were Black or African American were 62% less likely to be adherent to buprenorphine than patients who were White. None of the other predictors were significantly associated with

Table 1 Characteristics of the entire sample and by adherence/non-adherent groups

Variable	All (*N* = 345)		Non-adherent (*N* = 194; 56%)		Adherent (*N* = 151; 44%)		Univariate logistic regression: Predicting adherence			
	N or M	% or SD	*N* or M	% or SD	*N* or M	% or SD	OR	95% LL	95% UL	*p*
Age	37.6	13.2	36.1	13.3	39.4	12.8	1.02	1.00	1.04	0.021
Sex										
Female	132	38.3	53	40.2	79	59.9	REF			
Male	213	61.7	141	66.2	72	33.8	0.34	0.22	0.54	< 0.001
Race										
Black or African American	44	12.8	33	75.0	11	25.0	0.36	0.18	0.75	0.07
Other or Unknown Race	32	9.3	21	65.6	11	34.4	0.57	0.26	1.23	0.89
White	269	78.0	140	52.0	129	48.0	REF			
Ethnicity										
Hispanic or Latino	12	3.5	9	75.0	3	25.0	0.41	0.11	1.55	0.23
Not Hispanic or Latino	302	87.5	173	56.2	135	43.8	REF			
Unknown	31	9.0	18	58.1	13	41.9	0.89	0.42	1.89	0.51
Social Vulnerability Index										
Socioeconomic %tile	0.34	0.27	0.33	0.26	0.34	0.27	1.10	0.49	2.45	0.83
Household Composition %ile	0.44	0.27	0.43	0.27	0.44	0.26	1.11	0.50	2.49	0.79
Minority Status/Language %ile	0.44	0.26	0.44	0.26	0.45	0.26	1.19	0.52	2.70	0.69
Housing Type/Transportation %ile	0.55	0.29	0.57	0.29	0.53	0.29	0.63	0.31	1.31	0.22
Overall	0.41	0.28	0.42	0.28	0.41	0.30	0.96	0.45	2.02	0.90
Insurance (at index encounter)										
Commercial	119	35.3	55	46.2	64	53.8	1.82	1.16	2.86	0.009
Medicare	44	13.1	24	54.6	20	45.5	1.06	0.56	2.00	0.86
Medicaid	196	58.2	123	62.8	73	37.2	0.51	0.33	0.79	0.003
State subsidized	5	1.5	2	40.0	3	60.0	1.91	0.32	11.59	0.48
Other Insurance	66	19.6	36	54.6	30	45.5	1.00	0.58	1.70	0.99
None	8	2.4	6	75.0	2	25.0	0.41	0.08	2.08	0.28
Smoking status (at index)										< 0.001
Smoker	194	57.6	122	62.9	72	37.1	REF			
Nonsmoker	54	16.0	32	59.3	22	40.7	1.17	0.63	2.16	0.25
Former Smoker	89	26.4	34	38.2	55	61.8	2.74	1.63	4.60	< 0.001
Comorbid Substance Use Disorders										
Alcohol use disorder	46	13.3	28	60.9	18	39.1	0.80	0.43	1.50	0.50
Cocaine use disorder	19	5.5	16	84.2	3	15.8	0.23	0.06	0.79	0.02
Stimulant use disorder	51	14.8	34	66.7	17	33.3	0.60	0.32	1.12	0.11
Comorbid Mental Health Disorders										
Anxiety	232	67.3	123	53.0	109	47.0	1.50	0.95	2.37	0.09
Depression	171	49.6	93	54.4	78	45.6	1.16	0.76	1.78	0.49
Personality disorder	16	4.6	7	43.8	9	56.3	1.69	0.62	4.66	0.31
PTSD	51	14.5	26	51.0	25	49.0	1.28	0.71	2.33	0.41
Serious Mental Illness	45	13	25	55.6	20	44.4	1.03	0.55	1.94	0.92
Comorbid Physical Health Conditions										
Chronic Pain	146	42.3	73	49.7	74	50.3	1.63	1.06	2.51	0.027
Diabetes	23	6.7	15	65.2	8	34.8	0.67	0.28	1.62	0.37
Hepatitis C	17	4.9	12	70.6	5	29.4	0.52	0.18	1.51	0.23
Hypertension	84	24.4	37	44.1	47	56.0	1.92	1.17	3.15	0.01
Buprenorphine										
Average Days Supply	21.4	8.3	18.7	8.1	24.9	6.0	1.12	1.08	1.15	< 0.001
Daily dose (mg)	11.3	6.2	10.8	6.0	12.0	6.4	1.03	1.00	1.07	0.08
Formulation										
All Films	229	66.4	128	55.9	101	44.1	1.04	0.66	1.63	0.86
All Tabs	48	13.9	22	45.8	26	54.2	1.63	0.88	3.00	0.12
Mix formulations	68	19.7	44	64.7	24	35.3	0.64	0.37	1.12	0.12

Table 1 (continued)

Variable	All (*N* = 345)		Non-adherent (*N* = 194; 56%)		Adherent (*N* = 151; 44%)		Univariate logistic regression: Predicting adherence			
	N or M	% or SD	*N* or M	% or SD	*N* or M	% or SD	OR	95% LL	95% UL	*p*
Encounter Types										
Any behavioral health	63	18.3	28	44.4	35	55.6	1.79	1.03	3.10	0.039
Any addiction medicine	10	2.9	8	80.0	2	20.0	0.31	0.07	1.49	0.14
Any pain medicine	65	18.8	35	53.9	30	46.2	1.13	0.66	1.94	0.67
Urine Toxicology Screens										
Unexpected Positive (Amphetamines)	25	7.3	19	76.0	6	24.0	0.38	0.15	0.98	0.045
Unexpected Positive (Benzodiazepines)	18	5.2	11	61.1	7	38.9	0.81	0.31	2.14	0.67
Unexpected Positive (Cocaine)	24	7.0	17	70.8	7	29.2	0.51	0.20	1.25	0.14
Unexpected Positive (Opioids)	58	16.8	43	74.1	15	25.9	0.39	0.21	0.73	0.003
Unexpected Negative (Buprenorphine)	74	21.5	46	62.2	28	37.8	0.73	0.43	1.24	0.25

Note. M = Mean. SD = Standard deviation. OR = Odds Ratio. LL = 95th percentile lower limit. UL = 95th percentile upper limit. REF = Reference group. p = p-value.

Table 2 Logistic regression models predicting adherence to buprenorphine

Variable	Model 1: Demographics				Model 2: Clinical				Model 3: Full Model			
	aOR	95% LL	95% UL	*p*	aOR	95% LL	95% UL	*p*	aOR	95% LL	95% UL	*p*
Age	1.02	1.00	1.03	0.14					0.99	0.97	1.02	0.63
Sex												
Female	REF								REF			
Male	0.33	0.20	0.53	< 0.001					0.34	0.20	0.57	< 0.001
Race												
Black or African American	0.38	0.17	0.82	0.036					0.48	0.21	1.10	0.16
Other or Unknown Race	0.94	0.36	2.47	0.41					0.90	0.32	2.54	0.64
White	REF								REF			
Ethnicity												
Hispanic or Latino	0.41	0.08	2.09	0.37					0.46	0.07	2.91	0.47
Not Hispanic or Latino	REF								REF			
Unknown	0.75	0.34	1.65	0.77					0.84	0.37	1.91	0.73
Insurance												
Commercial	1.62	0.82	3.20	0.16					1.55	0.76	3.17	0.23
Medicaid	0.87	0.44	1.69	0.67					0.88	0.43	1.79	0.72
Smoking status												
Smoker					REF				REF			
Nonsmoker					0.90	0.47	1.71	0.10	0.78	0.39	1.56	0.10
Former Smoker					2.31	1.35	3.95	0.001	1.82	1.02	3.27	0.014
Cocaine use disorder					0.25	0.07	0.92	0.037	0.30	0.08	1.18	0.08
Chronic Pain					1.43	0.88	2.34	0.15	1.26	0.71	2.22	0.44
Hypertension					1.56	0.88	2.77	0.13	1.89	0.96	3.74	0.067
Any behavioral health					1.49	0.83	2.68	0.18	1.50	0.80	2.80	0.20
Unexpected Positive (Amphetamines)					0.46	0.17	1.24	0.13	0.58	0.21	1.62	0.30
Unexpected Positive (Opioids)					0.40	0.20	0.77	0.006	0.42	0.21	0.83	0.014

Note. aOR = Adjusted Odds Ratio. LL = 95th percentile lower limit. UL = 95th percentile upper limit. REF = Reference group. p = p-value

buprenorphine adherence. In Model 2, we examined clinical characteristics associated with adherence, including smoking status; diagnoses of cocaine use disorder, chronic pain, and hypertension; having any visits to specialty behavioral health; and unexpected positive urine toxicology screens for amphetamines and opioids. In that model, being a former smoker (compared to a current smoker) was associated with 2.3 times greater likelihood of being adherent to buprenorphine. Having a cocaine use disorder was associated with a 75% less likelihood of being adherent to buprenorphine, and having an unexpected positive for opioids was associated with a 60% less likelihood of being adherent to buprenorphine.

The final model combined all demographic and clinical characteristics as predictors into the model. In the full model, being male and having an unexpected positive

urine toxicology screen for opioids remained significantly and negatively associated with adherence, whereas being a former smoker was significantly and positively associated with buprenorphine adherence. Specifically, being a former smoker was associated with a 1.82 times greater likelihood of being adherent to buprenorphine. The remaining factors decreased the likelihood that patients were adherent: being male (66%) and having an unexpected opioid positive (58%) after starting buprenorphine.

Discussion

This study used EHR data to examine rates and predictors of buprenorphine adherence among adult primary care patients with OUD for the first six months after a new prescription. Clinical data from the EHR provides a rich source of demographic, social vulnerability, and clinical factors absent from many buprenorphine adherence studies using administrative claims data. Similar to prior studies that used administrative claims, buprenorphine adherence was low (44%) and comorbid cocaine use was a key predictor of nonadherence. However, data also suggested that biological sex and smoking status were associated with buprenorphine adherence, with females and former smokers being more adherent to buprenorphine than men and current smokers, respectively.

We found that less than half (44%) of the patients in this study were adherent to buprenorphine based on medication order data during the study period, which is closer to findings from administrative claims data sources (21–43% adherence rate) [18] than adherence monitoring using prescription cap technology within a randomized controlled trial (71%) [22]. The higher rates in the latter study may reflect an observer effect given patients were aware of more direct, frequent, and proximal monitoring of their medication-taking behavior compared to patients in real world clinical settings. However, the way adherence is defined can influence the rates seen. For example, Gordon et al. [21] defined a buprenorphine course of treatment as consistent medication dispensing without a 30-day gap. Therefore, adherence was much higher in that study (90%) because the course of care was ceased if there was a gap > 30 days.

Consistent with prior research, our findings suggest that buprenorphine adherence is likely lower than adherence to medications for other chronic illnesses, where approximately 50% of medications are not taken as prescribed [34]. Adherence to buprenorphine may be lower than adherence to other medications for chronic diseases for many reasons. Specifically, patients may have more negative perceptions of MOUD (e.g., stigma associated with having a use disorder or replacing one substance for another) than patients taking medications for other chronic illnesses [35]. In addition, patients may be dissatisfied with buprenorphine because of challenging inductions, side effects, bitter taste, and/or long dissolution time [36–39]. Patients with OUD on buprenorphine in primary care settings may also have insufficient support [20, 40–45] and be socially vulnerable [20, 46–48], putting them at greater risk for low adherence. It is important to note that we did not find that neighborhood level social vulnerability was related to adherence in this sample; however, this variable may not fully account for individual level social vulnerabilities that could vary among people with OUD.

Patients who were male, had comorbid cocaine use, or who unexpectedly screened positive for opioid use were more likely to be classified as non-adherent to buprenorphine. Some prospective studies have compared adherence and treatment outcome differences between males and females [49–51]. Although there is strong evidence that buprenorphine is an effective OUD treatment regardless of biological sex [52–54], our results align with other evidence suggesting males are less adherent to buprenorphine than females [46]. These sex differences may be due to differences in buprenorphine pharmacokinetics, which suggest males may have potentially lower therapeutic benefits (e.g., cravings, withdrawal symptoms, analgesia) than females despite identical dosing regimens [55]. Males are also more likely to engage in risky substance use behavior than females [56], reflected by men with OUD being more likely to use illicit fentanyl and co-use stimulants [57]. Cohort studies also show males are less likely to be retained in treatment despite women reporting greater opioid cravings, social vulnerabilities, medical and psychiatric comorbidities, and MOUD access barriers (e.g., stigma) at treatment outset [51, 58–62]. The results reiterate the importance of considering multi-faceted sex-related differences in OUD treatment and buprenorphine adherence and the need for further study in this area.

Although not significantly associated with in our final model, prior studies have demonstrated that comorbid cocaine use is associated with buprenorphine nonadherence [22]. Cocaine use is common among people with OUD [63], with some studies estimating that up to half of individuals taking a MOUD also use cocaine [64], possibly to replace the reduced euphoria from opioids [65]. Additionally, the concurrent use of cocaine with office-based buprenorphine treatment has been associated with lower treatment retention and higher opioid use [66]. However, treating people with comorbid opioid and cocaine use with buprenorphine, even with potential suboptimal adherence, can result in clinically relevant reductions in the substance use [63, 67].

Patients who were nonadherent were more likely to have an unexpected positive for opioids on their urine toxicology screens. A positive screen for opioids is likely

indicative of a relapse, which may be a function of non-adherence (i.e., patients who do not regularly take their buprenorphine may be more likely to relapse or patients may intentionally stop buprenorphine to use opioids). Another interesting finding was that in both groups the average daily dose was lower than recommended to effectively treat opioid withdrawal (10–12 mg/day), and likely not high enough of a dose to manage cravings for stronger opioids like illicit fentanyl, which could lead to relapse and early treatment discontinuation [68]. Thus, it is not clear whether the nonadherence caused or was a consequence of opioid use. Conversely, 18.5% of patients who were classified as adherent had an unexpected negative urine toxicology screen for buprenorphine. There are many possible reasons for this, including that the adherence threshold of at least 80% of days covered allowed for some missed days. Other possibilities include that patients took more than prescribed to manage cravings, left days without coverage near the end of their prescriptions; had buprenorphine but didn't take it (e.g., missed doses); or diversion. Ultimately, the PDC threshold of 80% coverage allowed for some non-adherence in that group.

Many patients (56%) identified as active smokers. However, the smoking rates were lower than in other studies of adults with OUD, which estimated that 83–98% also use tobacco [69]. Nicotine and opioids share a biological pathway (i.e., both activate μ-opioid receptors responsible for producing physical dependence and euphoria), which may contribute to this strong association along with other socioeconomic, personality, and genetic factors [69]. In our study, former smokers were more likely to be adherent to buprenorphine compared to active smokers. Prior studies have also found that active smokers had higher rates of buprenorphine non-adherence [70], and buprenorphine may even increase cigarette smoking [71, 72]. Former smokers also have the experience of quitting one substance (tobacco) and may have greater self-efficacy or access to effective coping skills that help them with their opioid recovery [73]. Our findings support calls for more research on the benefits of co-treatment for OUD and smoking cessation to improve treatment adherence and outcomes for both diseases [74].

Strengths and limitations

The strengths of this study include the use of EHR data, which includes access to a wide number of sociodemographic and clinical characteristics that may be associated with buprenorphine adherence. However, this study also has limitations. First, causality cannot be determined using the retrospective observational study design. In addition, the study was conducted at a single health system in a metropolitan area which may limit generalizability to other health systems or geographic settings. Another limitation was that the study calculated PDC using medication order data, which is a proxy measure of adherence that does not account for medication fills or patient medication-taking behavior. Other indices of adherence (e.g., medication persistence or gaps) may have different results. Additionally, neighborhood level data was used as a proxy for patient-level social vulnerabilities, which may not fully account for adverse effects of sociocultural factors on adherence. Another limitation is that some potential contributing factors were not available in the data (i.e., testing for fentanyl and administration of long-acting injectable buprenorphine, which were rarely used during the study period). It is also not clear how patient factors with low prevalences in our sample (e.g., lack of insurance coverage, comorbid personality disorder or hepatitis C infection) might influence these findings in larger samples with more representation of such patients. In addition, we chose to limit the analyses to patients who had at least two buprenorphine prescriptions because of the way we calculated PDC. This may bias the results towards people who are more likely to return for a follow-up appointment; however, there is an inherent interplay between adherence and retention, in that people who are not retained in treatment will be deemed non-adherent. Another limitation was that patient buprenorphine usage history prior to the study period was unknown; patients with prior buprenorphine treatment episodes may have different patterns of adherence compared to patients for whom this was the first treatment episode. Finally, these data were collected during care in clinics where a larger clinical trial of a clinical decision support intervention to identify and treat people with OUD was active. The goal of that intervention was not to address buprenorphine adherence; however, patients in intervention clinics may have had different patterns of adherence than patients in control clinics.

Conclusion

This study used EHR data to understand rates and predictors of buprenorphine adherence among patients with OUD in a large, integrated health system. Consistent with prior literature, buprenorphine adherence was low and being male or a current smoker or having a comorbid cocaine use disorder were the strongest predictors of nonadherence. Future research should further describe and define different patterns of adherence in buprenorphine treatment and identify strategies to address adherence in outpatient opioid treatment settings.

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Author contributions
SAH and CS conducted the literature review. SK developed the data dictionary and extracted the data from the EHR. SAH conducted the data analysis. SAH, CS, and AWO wrote the first draft of the manuscript. All authors contributed to data interpretation, revised the draft, and approved the final manuscript.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This retrospective data analysis study was approved by the HealthPartners Institute Institutional Review Board. Data were extracted under a waiver of informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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