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Co-occurring psychiatric disorders and disparities in buprenorphine utilization in opioid use disorder: An analysis of insurance claims

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HIGHLIGHTS

- Co-occurring psychiatric disorders are common in people with opioid use disorder (OUD).
- Buprenorphine is underused in people with OUD and co-occurring psychiatric disorders.
- Buprenorphine discontinuation is common in people with OUD and co-occurring psychiatric disorders.

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ABSTRACT

Background: As the overdose crisis continues in the U.S. and Canada, opioid use disorder (OUD) treatment outcomes for people with co-occurring psychiatric disorders are not well characterized. Our objective was to examine the influence of co-occurring psychiatric disorders on buprenorphine initiation and discontinuation.
Methods: This retrospective cohort study used multi-state administrative claims data in the U.S. to evaluate rates of buprenorphine initiation (relative to psychosocial treatment without medication) in a cohort of 236,198 people with OUD entering treatment, both with and without co-occurring psychiatric disorders, grouping by psychiatric disorder subtype (mood, psychotic, and anxiety-and-related disorders). Among people initiating buprenorphine, we assessed the influence of co-occurring psychiatric disorders on buprenorphine retention. We used multivariable Poisson regression to estimate buprenorphine initiation and Cox regression to estimate time to discontinuation, adjusting for all 3 classes of co-occurring disorders simultaneously and adjusting for baseline demographic and clinical characteristics.
Results: Buprenorphine initiation occurred in 29.3 % of those with co-occurring anxiety-and-related disorders, compared to 25.9 % and 17.5 % in people with mood and psychotic disorders. Mood (adjusted-risk-ratio[aRR] = 0.82[95 % CI = 0.82–0.83]) and psychotic disorders (aRR = 0.95[0.94–0.96]) were associated with decreased initiation (versus psychosocial treatment), in contrast to greater initiation in the anxiety disorders cohort (aRR = 1.06[1.05–1.06]). We observed an increase in buprenorphine discontinuation associated with mood (adjusted-hazard-ratio[aHR] = 1.20[1.17–1.24]) and anxiety disorders (aHR = 1.12[1.09–1.14]), in contrast to no association between psychotic disorders and buprenorphine discontinuation.
Conclusions: We observed underutilization of buprenorphine among people with co-occurring mood and psychotic disorders, as well as high buprenorphine discontinuation across anxiety, mood, and psychotic disorders.

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1. Introduction

Against the backdrop of the opioid crisis in the U.S. and Canada, many patients with opioid use disorder (OUD) have unaddressed psychiatric comorbidities.(Humphreys et al., 2022) Unfortunately, the treatment of OUD remains siloed from systems of psychiatric patient care and medical education.(Crowley et al., 2016; DeJong et al., 2022) Previous studies have estimated that over 80 % of patients in substance use treatment settings may meet criteria for psychiatric disorders.(Davis et al., 2022; Lehman et al., 1993; Watkins et al., 2004) With regards to specific psychiatric disorders, OUD is strongly associated with co-occurring psychiatric comorbidities such as anxiety disorders and mood disorders (e.g. depression), and to a lesser extent, with psychotic disorders.(Jones and McCance-Katz, 2019a)

Understanding how the high prevalence of psychiatric comorbidity in OUD impacts buprenorphine utilization may provide crucial clues for the types of targeted interventions needed to curb the ongoing overdose crisis in the U.S. and Canada.(Humphreys et al., 2022; Kariisa et al., 2022) Buprenorphine is a first-line treatment for all people with opioid use disorder, supported by a recent National Academies of Sciences, Engineering, and Medicine report, (NASEM, 2019) as well as the ASAM National Practice Guideline for the Treatment of OUD, including its section on co-occurring psychiatric disorders.(Kampman and Jarvis, 2015) To date, rates of buprenorphine utilization in people with OUD are low in the U.S.(Stein et al., 2012) and Canada,(Gomes et al., 2022; Kestler et al., 2021; Krebs et al., 2021) despite clear evidence of protective effects against overdose and all-cause mortality.(Santo et al., 2022) While access to buprenorphine is promoted by all major U.S. health agencies, only an estimated 1–2 million of 7.6 million individuals with OUD are estimated to receive it in a given year.(Han et al., 2021; Keyes et al., 2022; Saloner et al., 2017) It remains unclear how people with co-occurring psychiatric comorbidity fare with regards to buprenorphine initiation and discontinuation.

Clinical trials evaluating the efficacy of buprenorphine in treating OUD have commonly excluded people with serious psychiatric comorbidity such as psychosis or suicidality.(Dennis et al., 2015) Currently, the relationship between psychiatric comorbidity and OUD treatment outcomes remains poorly characterized and understudied, a barrier to our efforts to boost buprenorphine uptake. Research has been mixed regarding associations of co-occurring psychiatric comorbidity with buprenorphine utilization, with some studies indicating that people with co-occurring mental illness may have worse OUD buprenorphine retention.(Krawczyk et al., 2017; Litz and Leslie, 2017) Other analyses have found improved buprenorphine retention among people with psychiatric comorbidity, which may reflect the greater familiarity people with co-occurring mental illness may have with behavioral health treatment systems.(Tofighi et al., 2015, 2014; Williams et al., 2014)

As psychiatric comorbidity is sometimes treated as a single category, (Jones and McCance-Katz, 2019b; Krawczyk et al., 2017; Novak et al., 2019) research is needed to differentiate between mental illness subtype (anxiety-and-related disorders vs. mood disorders vs. psychotic disorders) and OUD treatment outcomes.(Gonzales et al., 2022) Given these gaps in the literature, our study sought to use multi-state commercial and Medicaid insurance claims in the U.S. to evaluate rates of buprenorphine initiation (relative to psychosocial treatment without medication) in a cohort of people with OUD entering treatment, both with and without co-occurring psychiatric disorders, grouping by psychiatric disorder subtype. Among buprenorphine initiators, we subsequently assessed the influence of co-occurring psychiatric disorders on buprenorphine retention.

2. Materials and methods

2.1. Study design and data source

We conducted a retrospective cohort study using the Merative™ MarketScan® Commercial and Multi-State Medicaid Databases. The MarketScan Databases contain longitudinal data for clinical encounters and filled prescriptions in the U.S., as previously described, spanning both commercial insurance enrollees and Medicaid enrollees.[29] This includes claims for employees and their family members (i.e., dependents, spouses) from multiple large employers and health plans in the commercial database, as well as enrollees from multiple U.S. states (anonymously reported, exact identities unknown) in the Medicaid database. Notably, certain variables such as race/ethnicity are available for Medicaid enrollees only and are missing in the commercial subset of the MarketScan databases. Our data were available from 1/1/2006–12/31/2016 for commercial claims and from 1/1/2011–12/31/2016 for Medicaid claims. We conducted our analyses November 3, 2022 through August 13, 2023.This study was exempt from the Washington University Institutional Review Board because no identifiable private data were used.

2.2. Population

The full derivation of the analytic sample is shown in eTable 1. Our cohort was a group of individuals who initiated OUD treatment with either buprenorphine or psychosocial treatment without MOUD for the first time (i.e. index treatment episode) during the study period.

The cohort of initiators was derived from a larger OUD treatment cohort of 304,676 individuals 12–64 with ICD 9/10- diagnoses for opioid "abuse or dependence," all of whom were *initiating* an episode of OUD treatment (The "abuse or dependence" terms are still used for ICD despite the pejorative and stigmatizing nature of the term "abuse."(Saitz et al., 2021; Volkow et al., 2021) All 304,676 persons were required to have 6 months of continuous medical and prescription drug coverage prior to the start of OUD treatment, which serves as a look-back period for covariate assessment. Because the cohort consisted of people initiating treatment for the first time, they were required to have no prior record of OUD treatment during insurance enrollment(Xu et al., 2021)

Our analytic strategy consisted of two stages. The first part of our analysis evaluated rates of buprenorphine initiation among 250,958 persons initiating OUD treatment with either buprenorphine or psychosocial treatment without medication (reference category). We excluded 53,467 persons initiating naltrexone-PO or naltrexone-extended release and 15,011 initiating methadone resulting in a cohort of 236,198 persons initiating either buprenorphine or psychosocial treatment without medication to treat OUD, for whom we analyzed the association between co-occurring psychiatric diagnoses and buprenorphine initiation. For the second part of our analysis, we analyzed the association between co-occurring psychiatric diagnoses and time to buprenorphine discontinuation; in doing so, we subsequently excluded 134,941 people who were not initiated on buprenorphine. This culminated in a sample of 101,257 people initiated on buprenorphine.

2.3. Variables

The primary predictor variable was co-occurring psychiatric disorders in the 6 months preceding initiation of OUD treatment. We created three general categorical indicators for co-occurring psychiatric disorders: (1) anxiety-and-related disorders (composite of posttraumatic stress disorder, generalized anxiety disorder, panic disorder, obsessive compulsive disorder, social anxiety, anxiety disorder unspecified), (2) mood disorders (major depressive disorders, bipolar disorders), and (3) primary psychotic disorders (schizophrenia, schizoaffective disorders, brief psychotic disorders, schizotypal disorders, delusional disorders, unspecified psychotic disorders). These three categories approximate the classification scheme used in ASAM's assessment criteria which informs patient placement and treatment planning (ASAM, 2023). While the DSM-5 separates between bipolar and depressive disorders, we made the decision to group bipolar and major depressive disorders together in

the same category ("mood disorders") to mitigate misclassification, as under- and misdiagnosis of bipolar disorder as other mood disorders is well-documented.(Phillips and Kupfer, 2013) Likewise, obsessive-compulsive and traumatic disorders were grouped with anxiety-and-related disorders to mitigate risk of misclassification. (Stein et al., 2011, 2010; Stahnke 2021; Tully et al., 2021).

Organic causes of psychosis (i.e., toxic-metabolic encephalopathy, substance-induced psychotic disorders) were not included in the psychotic disorders category. Psychosis secondary to depressive or bipolar disorders were grouped in the mood disorders category, as opposed to the psychotic disorders category given the substantially higher level of disability and cognitive impairment associated with primary psychotic disorders.(Bowie et al., 2010; Green, 2006) ICD 9/10 codes for these disorders are listed in the eTable 2. Each category was coded as a binary (yes/no) variable, and individuals were permitted to have multiple diagnostic categories. In each set of analyses, outcomes for individuals in category 1 were contrasted with those in category 0.

The two primary outcomes were (1) initiation and (2) time to discontinuation of buprenorphine treatment. The unit of analysis was the treatment episode, which was defined by a continuous series of insurance claims for buprenorphine fills without any lapses in medication possession for greater than 45 days. We recognized heterogeneity in thresholds for buprenorphine discontinuation used by previous studies, (Dong et al., 2022) with some analyses using 30-day continuation thresholds (Meinhofer et al., 2019) and other analyses using 60-day thresholds. (Williams et al., 2020) As we were interested in treatment gaps rather than short-term discontinuation of buprenorphine, we elected 45 days as the threshold for discontinuity. We defined the initiation of a new episode of buprenorphine receipt as the first buprenorphine prescription that is followed by a gap of at least 45 days or longer without buprenorphine. We assumed that active prescription fills for buprenorphine were equivalent to medication consumption,(Xu et al., 2021) defining buprenorphine discontinuation as lapses in claims for fills or dispensing exceeding 45 days. Sensitivity analyses specified discontinuation with 30- and 60-day gaps.

Covariates included demographics and co-occurring substance use disorders (alcohol, stimulant, sedative) obtained in the 6-month period preceding and including the date of buprenorphine treatment initiation: age at start of OUD treatment (in years), sex (male vs female), insurance status (Medicaid vs commercial), race/ethnicity (available ***only*** among Medicaid enrollees), as well as Charlson comorbidity index as a proxy for co-occurring medical conditions that may contribute to worse treatment outcomes.

2.4. Statistical analyses

First, we computed descriptive statistics: in addition to evaluating the age, sex, and clinical characteristics of people with and without co-occurring psychiatric disorders in our sample of individuals with OUD who were initiating treatment, we estimated an unadjusted rate of buprenorphine initiation among people with and without co-occurring psychiatric disorders.

For the two outcome variables (buprenorphine initiation and time to discontinuation), we first estimated 3 separate sets of regression models, each focused on a different class of psychiatric disorders. For instance, a separate model estimated anxiety-and-related disorders, another estimated mood disorders, and a third would estimate the association of psychotic disorders with buprenorphine initiation, while adjusting for confounders in each model. We first modeled the classes of psychiatric disorders separately in order to assess for potential confounding among the individual disorders, given significant comorbidity among the disorders. To model buprenorphine initiation, we used Poisson regression with robust standard errors,(Zou, 2004) which are commonly used for the study of outcomes such as medication receipt, (Wright et al., 2021) adjusting for baseline covariates (co-occurring alcohol, sedative, and stimulant use disorders; sex, age (years) at time of treatment initiation; Charlson comorbidity index; insurance status). We subsequently estimated models incorporating all 3 classes of psychiatric disorders simultaneously, because anxiety, mood, and psychotic are known to co-occur.(Huppert and Smith, 2005; Li et al., 2020)

Next, we calculated follow-up time from the first date of buprenorphine receipt to either the date of censoring (loss of coverage or death) or buprenorphine discontinuation, whichever came first. In adjusted analyses, we used Cox regression models to evaluate whether time to buprenorphine discontinuation varied according to presence of co-occurring psychiatric disorders. We first estimated models with each co-occurring psychiatric disorder via 3 separate sets of regressions. Subsequently, we estimated models with all 3 disorders together to evaluate potential confounding among simultaneously occurring disorders.

For all models of buprenorphine initiation and discontinuation, we conducted subgroup analyses adjusting for race/ethnicity, a covariate only available among people with Medicaid coverage. We also conducted sensitivity analyses for psychotic disorders restricting the definition of psychosis to those that had inpatient hospitalization for psychotic illnesses, as admission may increase the likelihood of specialist evaluation and improve the specificity of our psychotic disorders ascertainment. Secondary analyses were conducted that used alternative definitions of buprenorphine continuation thresholds (30-day and 60-day in lieu of 45-day). (Dong et al., 2022)

For all hypotheses testing, we used two-sided p-values with a significance level of 0.05. We conducted all analyses using SAS 9.4 (Cary, NC). RECORD-PE reporting guidelines were followed for all analyses.

3. Results

3.1. Descriptive statistics

As shown in Table 1, the sample included 236,198 people with OUD (mean age 33.6[11.3] years, 48.4 % female) who were initiating buprenorphine or psychosocial treatment without medication for OUD. Co-occurring psychiatric disorders in the 6 months preceding treatment initiation were common with: 37,630 (15.9 %) having anxiety-and-related disorders, 35,392(15 %) mood disorders, and 3616(1.5 %) psychotic disorders. Among people who had psychotic disorders, the majority had co-occurring mood and anxiety disorders (85 %, eTable 2). Approximately half of participants (46.6 %) were Medicaid beneficiaries. Among Medicaid beneficiaries (race/ethnicity data were only available among people enrolled in Medicaid), the majority (83.4 %) were non-Hispanic white (86.7 % anxiety-and-related disorders group; 85.4 % mood disorders group; 74.0 % psychotic disorders group), and 7.4 % were non-Hispanic Black (6.0 % anxiety-and-related disorders, 7.6 % mood disorders; 18.7 % psychotic disorders). Among co-occurring substance use disorders, alcohol use disorder (7.7 % overall) was the highest in prevalence (15.9 % anxiety-and-related disorders; 15.0 % mood disorders; 1.5 % psychotic disorders). Whereas 1 % of the sample overall had a Charlson comorbidity index of 3 or greater (indicating at least moderate severity of medical comorbidity), among people with co-occurring psychotic disorders, this figure was 3.6 % (n = 129), in comparison to 0.9 % in those with anxiety-and-related disorders (n = 1773) and mood disorders (n = 1742).

3.2. Co-Occurring psychiatric disorders and initiation of buprenorphine

In univariate estimates, we found that 101,257(42.9 %) initiated buprenorphine overall (n = 11,042[29.3 %] anxiety-and-related disorders; n = 9159[25.9 %] mood disorders; n = 632 [17.5 %] psychotic disorders). We estimated poisson models assessing the association of buprenorphine initiation, with each of the 3 co-occurring psychiatric disorders in a separate model from one another. Full models are shown in eTable 3. In analyses that adjusted for sex, age, insurance type, co-occurring substance use disorders separately, and charlson

Table 1
Demographic and clinical characteristics by co-occurring psychiatric disorders in the 6 months preceding buprenorphine treatment initiation, $n = 236,198$.

		$n = 236,198$ People with OUD	Co-occurring psychiatric disorders in the 6 months preceding OUD treatment initiation					
			Anxiety-and-related disorders		Mood disorders		Psychotic disorders	
			Yes	No	Yes	No	Yes	No
			37630 (15.9)	198568 (84.1)	35392 (15.0)	200806 (85.0)	3616 (1.5)	232582 (98.5)
Initiated on Buprenorphine (%)		101,257 (42.9)	11,042 (29.3)	90,215 (45.4)	9159 (25.9)	92,098 (45.9)	632 (17.5)	100,625 (43.3)
Female Sex (%)		114,321 (48.4)	22,500 (59.8)	91,821 (46.2)	21,438 (60.6)	92,883 (46.3)	1696 (46.9)	112,625 (48.4)
Mean Age (sd)		33.6 (11.3)	34.3 (10.6)	33.5 (11.4)	34.6 (10.9)	33.4 (11.3)	36.5 (11.3)	33.6 (12.3)
Medicaid (%)		110,064 (46.6)	26,890 (71.5)	83,174 (41.9)	25,929 (73.3)	84,135 (41.9)	3056 (84.5)	107,008 (46.0)
Race, Ethnicity (Among Medicaid Enrollees)	Non-Hispanic White (%)	86,953 (83.4)	21,468 (86.7)	65,485 (82.4)	20,324 (85.4)	66,629 (82.8)	2078 (74.0)	84,875 (83.7)
	Non-Hispanic Black (%)	7714 (7.4)	1477 (6.0)	6237 (7.8)	1803 (7.6)	5911 (7.3)	526 (18.7)	7188 (7.1)
	Hispanic (%)	1269 (1.2)	247 (1.0)	1022 (1.3)	282 (1.2)	987 (1.2)	39 (1.4)	1230 (1.2)
	Other (%)	8340 (8.0)	1565 (6.3)	6775 (8.5)	1386 (5.8)	6954 (8.6)	164 (5.8)	8176 (8.1)
Alcohol Use Disorder (%)		18,076 (7.7)	8947 (23.8)	9129 (4.6)	9171 (25.9)	8905 (4.4)	1347 (37.3)	16,729 (7.2)
Stimulant Use Disorder (%)		15,073 (6.4)	7579 (20.1)	7494 (3.8)	7809 (22.1)	7264 (3.6)	1392 (38.5)	13,681 (5.9)
Sedative Use Disorder (%)		5442 (2.3)	3391 (9.0)	2051 (1.0)	3258 (9.2)	2184 (1.1)	490 (13.6)	4952 (2.1)
Charlson Comorbidity Index*	0 (%)	212,627 (90.0)	31,309 (83.2)	181,318 (91.3)	29,080 (82.2)	183,547 (91.4)	2627 (72.7)	210,000 (90.3)
	1 (%)	17,216 (7.3)	4619 (12.3)	12,597 (6.3)	4564 (12.9)	12,652 (6.3)	671 (18.6)	16,545 (7.1)
	2 (%)	3937 (1.7)	1057 (2.8)	2880 (1.5)	1072 (3.0)	2865 (1.4)	189 (5.2)	3748 (1.6)
	3 or greater (%)	2418 (1.0)	645 (1.7)	1773 (0.9)	676 (1.9)	1742 (0.9)	129 (3.6)	2289 (1.0)

* A Charlson Index score of 1–2 means mild comorbidity, with scores 3 and above indicating at least moderate or severe comorbidity.

comorbidity index, we found that co-occurring mood and psychotic disorders were more strongly associated with decreased likelihood of buprenorphine initiation compared to peers without mood or psychotic disorders: aRR = 0.84[0.83–0.84] (model 1, Table 2) and aRR = 0.91 [0.90–0.92] (model 5, Table 2) respectively. Co-occurring anxiety-and-related disorders were associated with a decreased likelihood of buprenorphine initiation: aRR = 0.98[0.97–0.98] (model 3, Table 2). These findings were robust in analyses limited to Medicaid enrollees (models 2, 4, and 6, Table 2), where we adjusted for race/ethnicity

When we controlled for all 3 co-occurring psychiatric disorders together in the same model (model 7 and 8, Table 2), we observed a positive association between anxiety-and-related disorders and buprenorphine initiation (aRR = 1.06[1.05–1.06]), whereas mood and psychotic disorders remained associated with a decreased likelihood of buprenorphine initiation (aRR = 0.82[0.82–0.83] for mood disorders and aRR = 0.95 [0.94–0.96] for psychotic disorders).

Furthermore, we conducted additional sensitivity analyses (eTable 5) specifying buprenorphine initiation with episode definitions employing 30- and 60- day gaps between episodes; these models did not differ from parent analyses. We also conducted sensitivity analyses that restricted psychotic disorder to people who had at least one inpatient hospitalization for psychosis (eTable 7, $n = 1582$); these analyses showed similar results as the parent analyses.

3.3. *Co-occurring psychiatric disorders and time to discontinuation of buprenorphine*

In Table 3, we present results of adjusted cox proportional hazards models estimating the relationship between time to buprenorphine discontinuation and co-occurring psychiatric disorders, adjusting for sex, age, insurance type, co-occurring substance use disorders, and Charlson comorbidity index. In models that estimated the association between discontinuation and each co-occurring disorder separately, we found that all 3 disorders were associated with increased discontinuation risk: aHR = 1.27[1.24–1.30] for mood disorders (model 1), aHR = 1.20[1.17–1.22] for anxiety-and-related disorders (model 3), and aHR = 1.16[1.07–1.26] for psychotic disorders (model 5). Full models are shown in eTable 4. When we controlled for all 3 co-occurring disorders together in the same model (models 7), the associations between buprenorphine discontinuation and anxiety and mood disorders remained significant: aHR = 1.12[1.09–1.14] and aHR = 1.20 [1.17–1.24] respectively. Interestingly, the association between psychotic disorders and buprenorphine discontinuation was no longer significant in models adjusting for other co-occurring psychiatric disorders (aHR = 1.04[0.96–1.13]).

Analyses of time to buprenorphine discontinuation were robust in subgroup analyses limited to Medicaid enrollees (models 2, 4, 6, and 8, Table 3), allowing for the adjustment for race/ethnicity (otherwise not available in the commercial claims). Findings were also robust in analyses specifying buprenorphine discontinuation with 30- and 60-day gap (eTable 6) definitions and limiting psychotic disorder definitions to people with inpatient admissions for psychosis (eTable 8).

4. Discussion

In this study of multi-state Medicaid and commercial insurance claims data in the U.S., we identified heterogeneity in the association of buprenorphine initiation and retention with co-occurring psychiatric

Table 2
Adjusted models illustrating the association of co-occurring psychiatric disorders and buprenorphine initiation (relative to psychosocial treatment without medication to treat OUD).

			aRR	95 % CI	
Estimating co-occurring psychiatric disorders separately	Model 1, all participants	Anxiety-and-related disorders vs No Anxiety Disorder	0.98	0.97	0.98
	Model 2, limited to Medicaid	Anxiety-and-related disorders vs No Anxiety Disorder	0.91	0.90	0.91
	Model 3, all participants	Mood Disorder vs No Mood Disorder	0.84	0.83	0.84
	Model 4, limited to Medicaid	Mood Disorder vs No Mood Disorder	0.79	0.78	0.79
	Model 5, all participants	Psychotic Disorder vs No Psychotic Disorder	0.91	0.90	0.92
	Model 6, limited to Medicaid	Psychotic Disorder vs No Psychotic Disorder	0.84	0.83	0.85
Estimating co-occurring psychiatric disorders in a single model	Model 7, all participants	Anxiety-and-related disorders vs No Anxiety Disorder	1.06	1.05	1.06
		Mood Disorder vs No Mood Disorder	0.82	0.82	0.83
		Psychotic Disorder vs No Psychotic Disorder	0.95	0.94	0.96
	Model 8, limited to Medicaid	Anxiety-and-related disorders vs No Anxiety Disorder	1.00	1.00	1.01
		Mood Disorder vs No Mood Disorder	0.80	0.79	0.80
		Psychotic Disorder vs No Psychotic Disorder	0.89	0.88	0.90

Full models are shown in eTable 3.
Models 1, 3, 5, and 7: controlling for insurance, sex, age, charlson comorbidity score, co-occurring alcohol use disorder, stimulant use disorder, and sedative use disorder.
Models 2, 4, 6, and 8: controlling for race/ethnicity (thus limited to Medicaid only, because race/ethnicity is not available in the commercial claims), sex, age, charlson comorbidity score, co-occurring alcohol use disorder, stimulant use disorder, and sedative use disorder.

disorders in people initiating treatment for OUD. Mood disorders, like major depressive and bipolar disorders, were consistently associated with decreased buprenorphine initiation and increased discontinuation. While anxiety-and-related disorders were associated with a small increase in initiation rates, they were associated with greater discontinuation.

The association between psychotic disorders and buprenorphine initiation and retention appears to be influenced by confounding, particularly related to co-occurring anxiety and mood disorders. For instance, our descriptive statistics showed that only 17.5 % of people with psychotic disorders initiated buprenorphine in comparison to 25.9 % and 29.3 % of peers with mood and anxiety disorders respectively. However, the magnitude of lower buprenorphine initiation in people with psychotic disorders relative to peers without psychotic disorders was small (adjusted risk ratio of 0.95) in adjusted analyses that controlled for co-occurring mood and anxiety disorders. Furthermore, our adjusted analyses showed that people with psychotic disorders were *as likely* as peers without psychotic disorders to be retained in buprenorphine. In other words, even though buprenorphine initiation and discontinuation may ostensibly appear less favorable in people with co-occurring psychotic disorders, we hierarchically constructed models showing that the worse retention outcomes in people with psychotic disorders were explained for by the burden of co-occurring mood and anxiety disorders, rather than psychotic disorders themselves. Our findings support the need for future investigations into OUD treatment outcomes to incorporate approaches like ours that seek to rigorously evaluate the overlapping biopsychosocial factors common in people with OUD,(Parlier-Ahmad et al., 2022) (Parlier-Ahmad et al., 2021) rather than a 'siloed' approach, to ensure data more accurately reflect the patient experience within the context of systemic and structural factors.

It has been suggested that people with co-occurring serious mental illness, such as schizophrenia, and OUD may experience barriers to engaging in OUD care. Previous literature has depicted a greater burden of OUD severity among those with co-occurring psychiatric disorders, (Morin et al., 2020) and our own data also illustrate that a large percentage of individuals with psychotic disorders also suffered from other co-occurring substance use disorders (37.3 % alcohol use disorder, 38.5 % stimulant use disorders, 13.6 % sedative use disorders), which are known to translate to worse OUD treatment outcomes. (Ford et al., 2021; Lin et al., 2021) Ultimately, our finding that ostensible differences in buprenorphine initiation associated with psychotic disorders is confounded by other co-occurring disorders lends support for past studies that have found comparable buprenorphine discontinuation rates between Medicaid enrollees with and without schizophrenia, (Samples et al., 2018) as well as studies finding comparable rates of treatment discontinuation between people with OUD with and without co-occurring psychotic disorders receiving methadone(Lamont et al., 2020). People with psychiatric conditions seeking medication treatment for OUD may benefit from treatment approaches tailored to their

Table 3
Adjusted models illustrating the association of co-occurring psychiatric disorders and time to buprenorphine discontinuation.

			aHR	95 % CI	
Estimating co-occurring psychiatric disorders separately	Model 1, all participants	Anxiety-and-related disorders vs No Anxiety Disorder	1.20	1.17	1.20
	Model 2, limited to Medicaid	Anxiety-and-related disorders vs No Anxiety Disorder	1.22	1.19	1.22
	Model 3, all participants	Mood Disorder vs No Mood Disorder	1.27	1.24	1.27
	Model 4, limited to Medicaid	Mood Disorder vs No Mood Disorder	1.29	1.25	1.29
	Model 5, all participants	Psychotic Disorder vs No Psychotic Disorder	1.16	1.07	1.16
	Model 6, limited to Medicaid	Psychotic Disorder vs No Psychotic Disorder	1.19	1.09	1.19
Estimating co-occurring psychiatric disorders in a single model	Model 7, all participants	Anxiety-and-related disorders vs No Anxiety Disorder	1.12	1.09	1.12
		Mood Disorder vs No Mood Disorder	1.20	1.17	1.20
		Psychotic Disorder vs No Psychotic Disorder	1.04	0.96	1.04
	Model 8, limited to Medicaid	Anxiety-and-related disorders vs No Anxiety Disorder	1.13	1.10	1.13
		Mood Disorder vs No Mood Disorder	1.21	1.18	1.21
		Psychotic Disorder vs No Psychotic Disorder	1.06	0.98	1.06

Full models are shown in eTable 4.
Models 1, 3, 5, and 7: controlling for insurance, sex, age, charlson comorbidity score, co-occurring alcohol use disorder, stimulant use disorder, and sedative use disorder.
Models 2, 4, 6, and 8: controlling for race/ethnicity (thus limited to Medicaid only, because race/ethnicity is not available in the commercial claims), sex, age, charlson comorbidity score, co-occurring alcohol use disorder, stimulant use disorder, and sedative use disorder.

individual needs, such as with medical or behavioral interventions adjunctive to buprenorphine. Such a personalized medicine approach has been touted as a priority for addictions research and clinical care innovations,(Volkow, 2020) yet the evidence to guide us towards this goal for people with co-morbid OUD and psychiatric conditions is limited. Our findings can equip investigators and public health professionals to take the next steps towards advancing the quality of care for this population. For instance, as individual-level risk scores for return to use in people with OUD are showing increasing promise,(Luo et al., 2023) these data may help guide the development of prediction tools that incorporate baseline psychiatric risk in people with OUD.

Provider- and system-level factors likely contribute to our findings. The framework of intersectionality notes that people's experiences are "embedded within and reflective of multiple, intersecting, and mutually constitutive systems of social, economic, and political power." (Guan et al., 2021; Crenshaw, 2017) In light of this, we cannot rule out unmeasured residual confounding both at the patient level and at unmeasured domains of influence *beyond* the individual level. Amid heterogeneity in the association between buprenorphine uptake and treatment setting type,(Haffajee et al., 2018; Netherland et al., 2009; Ober et al., 2022; Yang et al., 2020) health-systems level research is needed to elucidate whether OUD diagnosis and treatment among people with co-occurring psychiatric disorders is occurring in an emergency/inpatient, outpatient, or specialty treatment settings. In particular, the uptake of buprenorphine among patients in public mental health settings, where many patients with co-occurring psychotic disorders receive care, has been very low, with nearly 80 % having never received treatment for OUD.(Ober et al., 2022) Additionally, we were not able to incorporate measures of social determinants of health into our analyses, due to limitations of our data source. People with OUD and with mental health conditions encounter barriers to addiction treatment more commonly than their counterparts due to variables at the individual, community and societal levels.(Montiel Ishino et al., 2020) Further, race/ethnicity was available for the Medicaid beneficiaries; however, given that race is a social construct, even if we had this variable for all people in our sample, its inclusion would not be sufficient to comprehensively investigate how mental health co-morbidities interplay with factors related to structural and systemic racism to impact OUD outcomes.(Shim, 2021) While research in pharmaco-epidemiologic datasets like the MarketScan databases has traditionally been conducted at the level of the individual patient,(Galea and Hernan, 2020; Jackson and Arah, 2020) future studies evaluating potential targets for OUD treatment intervention among people with co-occurring mental health conditions should incorporate multi-level variables (i.e., metrics of area-based socioeconomic deprivation, accessibility of medical care) that may influence treatment outcomes.(NIMHD, 2018)

Another limitation of our analysis is that we are only able to classify psychiatric diagnoses reflected in claims data which may undercount true prevalence. Only 15 % of our sample had a psychiatric condition diagnosis code, a lower estimate than those reported in other studies of OUD treatment samples.(Campbell et al., 2018) Despite these discrepancies, our findings provide a strong foundation for future research at the patient-level, such as using mixed methods approaches,(Martin, 2023) to elucidate underlying mechanisms of treatment outcome differences among people with OUD and co-morbid mental health conditions. Further, "psychotic disorders" was a single homogenous category, as opposed to differentiating by subtype, cognitive and social deficits, and levels of community functioning. In reality, people with schizophrenia, schizoaffective disorder, and/or other psychotic disorders exhibit tremendous heterogeneity in terms of psychiatric symptoms, levels of substance use, and specific types of deficits over time. While our results did not differ when we limited our definition of psychotic disorders to people who had at least one inpatient admission for psychosis, future studies could provide clinical correlations to the ICD 9/10 diagnostic codes used to identify psychotic disorders in this study (e.g., patient-reported outcomes for functional status, quality of life, etc.), as well as elucidate the settings where these patients were treated. Finally, our sample can be viewed as a "best case scenario" cohort. Our data's age (extending to 2016) precedes recent increases in potency-enhancing use in the United States that have culminated in worsening overdoses, and we urgently need studies to build upon the foundation established by the present analysis. Furthermore, all individuals were required to have received buprenorphine continuously for a minimum of 45 days and have at least 6 months of continuous insurance coverage preceding treatment initiation, which likely excludes vulnerable populations (i.e., people who are uninsured or incarcerated) with impaired social determinants of health and for whom mental illness may be more prevalent. The dual Medicare eligibility status (due to disability) of Medicaid beneficiaries in our dataset is also not known.

5. Conclusions

Our findings illustrate underutilization of buprenorphine among people with co-occurring mood and psychotic disorders, as well as high buprenorphine discontinuation rates across anxiety-and-related disorders, mood disorders, and psychotic disorders. People with OUD and significant co-occurring psychiatric comorbidity have commonly been excluded from important clinical trials investigating the efficacy of evidence-based interventions for OUD, including buprenorphine based treatments. To date, the literature base on the real-world utilization of buprenorphine in people with co-occurring psychiatric comorbidity is limited, and more research is urgently needed to move us towards closing the treatment gap for people with mental illness. Further study is urgently needed to inform risk stratification strategies and care pathways for patients based on pre-existing psychiatric comorbidities at presentation.

Disclosures

Dr. Williams received consulting fees from Ophelia Health, Inc., a telehealth provider for opioid use disorder. Dr Grucza reported receiving grants from the NIH and Arnold Ventures LLC during the conduct of the study, consulting for Janssen Pharmaceuticals, and receiving personal fees for grant reviews from the NIH outside the submitted work.

Data sharing agreement

No additional data available. We intend to provide relevant code on written reasonable request

Dissemination declaration

Dissemination to study participants and or patient organizations is not possible/applicable due to the de-identified nature of our data.

CRediT authorship contribution statement

Kevin Y Xu: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Vivien Huang:** Conceptualization, Investigation, Writing - original draft, Writing - review & editing. **Arthur Robin Williams:** Investigation, Methodology, Writing - review & editing. **Caitlin E Martin:** Investigation, Writing - review & editing. **Alexander R. Bazazi:** Conceptualization, Investigation, Methodology, Writing - review & editing. **Richard A. Grucza:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - review & editing.

Per CADR Data Use Agreement guidelines, Dr. Xu was the only individual who had access to the data and the only one to perform analyses. All of the other authors did not have access to the data, although contributed to the interpretation of data.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Kevin Xu reports financial support was provided by National Institute on Drug Abuse. Arthur Robin Williams reports a relationship with Ophelia Health that includes: consulting or advisory. Dr. Williams received consulting fees from Ophelia Health, Inc., a telehealth provider for opioid use disorder. Dr Grucza reported receiving grants from the NIH and Arnold Ventures LLC during the conduct of the study, consulting for Janssen Pharmaceuticals, and receiving personal fees for grant reviews from the NIH outside the submitted work. This project was funded by R21 DA044744 (PI: Richard Grucza/Laura Bierut). Effort for some personnel was supported by grants NIH K12 DA041449 (Kevin Xu, PI: Laura Bierut, Patricia Cavazos-Rehg), T32 DA015035 (Kevin Xu, PI: Kathleen Bucholz, Jeremy Goldbach), St. Louis University Research Institute Fellowship (Richard Grucza), and R01 DA057566–01 (Arthur Robin Williams), but these grants did not fund the analyses of the Merative™ MarketScan® Commercial and Multi-State Medicaid Database data performed by Dr. Xu. In addition, we acknowledge Matt Keller MS, John Sahrmann MS, Dustin Stwalley MA and the Center for Administrative Data Research (CADR) at Washington University for assistance with data acquisition, management, and storage. CADR is supported in part by the Washington University Institute of Clinical and Translational Sciences via grants UL1 TR002345 (from the National Center for Advancing Translational Sciences of the National Institutes of Health). Dr. Martin is supported by NIDA K23 DA053507 (PI: Caitlin E. Martin).

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dadr.2023.100195.

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