Polysubstance use and association with opioid use disorder treatment in the US Veterans Health Administration

Lewei A. Lin[1,2] (iD), Amy S. B. Bohnert[1,3], Frederic C. Blow[1,2], Adam J. Gordon[4,5], Rosalinda V. Ignacio[1,2], H. Myra Kim[1,6] & Mark A. Ilgen[1,2]

Center for Clinical Management Research (CCMR), VA Ann Arbor Healthcare System, Ann Arbor, MI, USA,[1] Addiction Center, Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA,[2] Department of Anesthesiology, University of Michigan, Ann Arbor, MI, USA,[3] Program for Addiction Research, Clinical Care, Knowledge and Advocacy (PARCKA), Division of Epidemiology, Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City, UT, USA,[4] Informatics, Decision-Enhancement, and Analytic Sciences Center, VA Salt Lake City Health Care System, Salt Lake City, UT, USA[5] and Consulting for Statistics, Computing and Analytics Research (CSCAR), University of Michigan, Ann Arbor, MI, USA[6]

ABSTRACT

Aims To understand the role of comorbid substance use disorders (SUDs), or polysubstance use, in the treatment of opioid use disorder (OUD), this study compared patients with OUD only to those with additional SUDs and examined association with OUD treatment receipt. **Design, setting and participants** Retrospective national cohort study of Veterans diagnosed with OUD ($n = 65\,741$) receiving care from the US Veterans Health Administration (VHA) in fiscal year (FY) 2017. **Measurements** Patient characteristics were compared among those diagnosed with OUD only versus those with one other SUD (OUD + 1 SUD) and with multiple SUDs (OUD + $\geq$ 2 SUDs). The study examined the relationship between comorbid SUDs and receipt of buprenorphine, methadone and SUD outpatient treatment during 1-year follow-up, adjusting for patient demographic characteristics and clinical conditions. **Findings** Among the 65 741 Veterans with OUD in FY 2017, 41.2% had OUD only, 22.9% had OUD + 1 SUD and 35.9% had OUD + $\geq$ 2 SUDs. Common comorbid SUDs included alcohol use disorder (41.3%), cocaine/stimulant use disorder (30.0%) and cannabis use disorder (22.4%). Adjusting for patient characteristics, patients with OUD + 1 SUD [adjusted odds ratio (aOR) = 0.87, 95% confidence interval (CI) = 0.82–0.93] and patients with OUD + $\geq$ 2 SUDs (aOR = 0.65, 95% CI = 0.61–0.69) had lower odds of receiving buprenorphine compared with OUD only patients. There were also lower odds of receiving methadone for patients with OUD + 1 SUD (aOR = 0.91, 95% CI = 0.86–0.97) and for those with OUD + $\geq$2 SUDs (aOR = 0.79, 95% CI = 0.74–0.84). Patients with OUD + 1 SUD (aOR = 1.85, 95% CI = 1.77–1.93) and patients with OUD + $\geq$2 SUDs (aOR = 3.25, 95% CI = 3.103.41) were much more likely to have a SUD clinic visit. **Conclusions** The majority of Veterans in the US Veterans Health Administration diagnosed with opioid use disorder appeared to have at least one comorbid substance use disorder and many have multiple substance use disorders. Despite the higher likelihood of a substance use disorder clinic visit, having a non-opioid substance use disorder is associated with lower likelihood of buprenorphine treatment, suggesting the importance of addressing polysubstance use within efforts to expand treatment for opioid use disorder.

Keywords Buprenorphine, Comorbid substance use disorder, medication treatment, methadone, opioid use disorder, polysubstance.

INTRODUCTION

Opioid overdose mortality continues to rise in the United States and other countries [1–3], but trends have shifted towards overdoses involving illicit opioids and multiple other substances, with the vast majority of opioid overdoses in some areas involving more than one substance [1,4–6]. Having multiple comorbid substance use disorders (SUDs), described as polysubstance use, is one of the most prominent risk factors for opioid overdose [7–9]. Comorbid SUD

is common in patients with opioid use disorder (OUD), with more than 57% of adults with OUD having an additional comorbid SUD among US adults [10]. Beyond the impact on overdose risk, comorbid SUDs among patients with OUD are associated with numerous other negative health and legal consequences and increased health-care utilization [11,12]. Thus, it is important to understand the treatment needs of patients with polysubstance use in order to successfully address the opioid epidemic in the United States and other countries.

Despite the demonstrated benefits of medication treatment for OUD (MOUD) [13,14], including reduced mortality [15], rates of receipt of MOUD remain low in the United States, with fewer than 20–40% of patients with OUD receiving these treatments [16–18]. Clinic and clinician policies and attitudes are key drivers of treatment use, particularly in patients with comorbid SUDs [19,20]. For example, a recent survey study of buprenorphine prescribers in the United States suggested that buprenorphine prescribers may be less willing to initiate buprenorphine in patients with binge alcohol use or misuse of benzodiazepines [20]. However, due to concerns that 'withholding' MOUD treatment may actually worsen outcomes, a 2017 US Food and Drug Administration (FDA) Safety Communication recommended to clinicians that: 'buprenorphine and methadone should not be withheld from patients taking benzodiazepines or other drugs that depress the central nervous system... excluding patients from medication assisted treatment or discharging patients from treatment because of use of benzodiazepines or central nervous system depressants is not likely to stop them from using these drugs together. Instead, the combined use may continue outside the treatment setting, which could result in more severe outcomes [21]'.

However, little is known about polysubstance use within real-world treatment settings for patients with OUD and how treatment patterns may differ between those with and without polysubstance use. We examined the population of Veterans receiving treatment from the Veterans Health Administration (VHA), the largest integrated health system in the United States and the largest single provider of addiction treatment in the United States [22]. The aims of the current study were to: (1) describe the prevalence of specific comorbid SUDs and compare patient characteristics among three categories of patients: patients diagnosed with OUD only versus those with one other SUD (OUD + 1 SUD) and with multiple SUDs (OUD + ≥2 SUDs) and (2) estimate the association of the polysubstance groups with treatment receipt. We hypothesized that patients with a comorbid SUD or greater number of comorbid SUDs would be less likely to receive either buprenorphine or methadone treatment, although these same patients, with their greater burden of illness, would be more likely to access general SUD clinic services.

METHODS

Study design and data source

This study was a retrospective cohort study of Veterans in the United States receiving VHA care. All patient demographic and clinical information are from the VHA Corporate Data Warehouse (CDW), the national repository of VHA electronic medical records. Study protocols were approved by the Veterans Affairs Ann Arbor Healthcare System Institutional Review Board.

Sample

We examined the cohort of Veterans aged 18 and older with at least one VHA inpatient or outpatient encounter at any VHA facility in the United States with a diagnosis of OUD in fiscal year (FY) 2017 (1 October 2016 to 30 September 2017). Diagnoses of OUD were assessed using the International Classification of Disease (ICD-10CM) diagnosis codes (Supporting information, Table S1). Patients were required to have at least one VHA visit (for any health condition) in the prior year to restrict to patients who actively utilized VHA care.

Measures

Outcome variables

The main outcomes of interest were receipt of: (a) methadone, (b) buprenorphine and (c) any outpatient SUD treatment. We focused on buprenorphine and methadone, both opioid agonist medications, which are the most utilized and most effective treatments for OUD [13–15,22, 23]. In contrast, extended-release naltrexone, a newer treatment for OUD, was used by < 1% of VHA patients with OUD in FY 2017 [22]. Outcomes were assessed during the 12-month period after the first visit with a diagnosis of OUD (i.e. latest date possible was 30 September 2018). Receipt of buprenorphine was defined as any VHA filled prescription of oral buprenorphine medication. Similar to prior studies [24–26], clinic 'stop codes' in CDW data, which indicate the clinical setting or type of services received during a specific encounter with VHA providers, were examined to determine receipt of methadone treatment and any SUD treatment (see Supporting information, Table S2). Receipt of methadone for pain diagnosis in the absence of OUD diagnosis was not included. Outpatient SUD treatment included any outpatient treatment in a SUD clinic setting, including individual or group psychotherapy, evaluation, treatment planning and medication visits.

Primary independent variable

The primary predictor of interest was comorbid diagnoses of other SUDs. Specific SUD diagnoses included: alcohol

use disorder, stimulant use disorder, cannabis use disorder, sedative use disorder and other substance use disorders (including hallucinogen, inhalant and other unspecified psychoactive substance use disorders). SUDs were assessed using International Classification of Disease10-CM (ICD10-CM) diagnosis codes (Supporting information, Table S2) during inpatient and outpatient clinical encounters in the 12-month baseline period prior to the first OUD diagnosis in FY 2017. Comorbid SUDs were coded into the following categories: OUD only, OUD plus one other SUD (OUD + 1 SUD) and OUD plus more than one other SUD (OUD + ≥2 SUDs).

Covariates

Demographic characteristics were: age, sex, race, Hispanic ethnicity, rural/urban residence (categorized as urban, large rural, small/isolated rural and unknown) and homelessness. Rurality was categorized using the Rural–Urban Commuting Areas (RUCAs) geographic taxonomy [27]. Homelessness was determined by the presence of ICD-10 codes for housing status or utilization of homeless Veteran services (see Supporting information).

Given prior data indicating differences in receipt of specialty treatment for patients receiving the majority of their care at a large VHA medical center versus smaller community-based outpatient clinics (CBOCs) that are affiliated with VHA medical centers [28,29], a variable indicating whether the patient received > 50% of their primary care visits in a VHA medical center versus CBOC was also included [29]. Additional clinical characteristics reflecting diagnoses made by VHA treatment providers were assessed in the 12-month baseline period prior to first OUD diagnosis in FY 2017. Comorbid mental health diagnoses examined were major depressive disorder, bipolar disorder, post-traumatic stress disorder (PTSD), other anxiety disorders and psychotic disorders (see Supporting information, Table S2). The Charlson comorbidity index was included to indicate severity of comorbid medical conditions [30]. Nicotine use disorder was defined using ICD-10 codes (see Supporting information, Table S2). To control for the effects of unmeasured facility-level differences in the use of OUD treatment, the 130 facilities where patients received their index OUD diagnosis in FY 2017 were included as random effects in the regression model.

Statistical analysis

After descriptively examining the distribution of specific SUD diagnoses in this cohort of VHA patients with OUD, baseline patient demographic and clinical characteristics were compared among the three groups: OUD only, OUD + 1 SUD and OUD +≥ 2 SUDs using χ^2 tests. Generalized linear mixed models for each of the OUD treatment outcomes using binomial distributions with logit link was used to test whether comorbid SUD groups were associated with each OUD treatment. Each model included facilities as random intercepts and was adjusted for all covariates (listed in Table 2). Intraclass correlation coefficient (ICC) for each model was calculated from the intercept-only model using methods for estimating the ICC for categorical outcomes [31].In order to assess the relationship between comorbid SUDs and starting new treatment for OUD, we conducted sensitivity analyses focusing on the subgroup of patients with OUD who did not receive any OUD treatment during the 3 months prior to their first visit with OUD diagnosis in FY 2017. We examined factors associated with newly starting each OUD treatment in this subgroup. All analyses were performed using SAS Enterprise Guide version 7.1. Analyses were not pre-registered, so the results should be considered exploratory.

RESULTS

In FY 2017, 65 843 Veterans receiving VHA care had a diagnosis of OUD. The study excluded patients with missing age ($n = 101$), gender ($n = 100$) or with no VHA visit for any health condition in the prior year ($n = 1$) for a total of 102 patients excluded, leaving a final study cohort of 65 741 Veterans. Among the cohort of patients, 41.2% ($n = 27078$) had OUD only while 22.9% ($n = 15075$) had one other comorbid SUD, and 35.9% ($n = 23588$) had two or more comorbid SUDs (see Table 1). Alcohol use disorder was the most common comorbid SUD followed by stimulant use disorder. Among all patients diagnosed with OUD in FY 2017, 59.4% ($n = 39068$) utilized treatment in an outpatient SUD clinic, but only 16.9% ($n = 11098$) received buprenorphine treatment and 16.9% ($n = 11112$) received treatment in a methadone clinic. The gap between receipt of any outpatient SUD treatment and medication treatment increased with increasing polysubstance use.

Table 2 describes patient characteristics comparing individuals among the three groups: OUD only, OUD + 1 SUD and OUD + ≥2 SUDs. Patients with comorbid SUDs were more likely to be in younger age groups, less likely to be white, more likely to be homeless and more likely to be seen in large VHA medical centers rather than VHA community-based outpatient clinics (CBOCs). The prevalence of all mental health disorders increased as the number of comorbid SUDs increased. The most prevalent mental health disorder was major depressive disorder, which was diagnosed in approximately a third of patients with OUD only, but in almost two-thirds of patients with OUD + ≥2 SUDs.

We examined the association between the substance comorbidity groups with each of the three outcomes, while adjusting for all the patient characteristics and controlling for the random effects of VHA facilities. The intraclass

Table 1 Prevalence of specific substance use disorders (SUDs) across SUD comorbidity groups among patients with an opioid use disorder (OUD) diagnosis.[a]

	Among OUD + 1 other SUD (n = 15 075) % (n)	*Among OUD + ≥ 2 other SUDs* (n = 23 588) % (n)	*Among total OUD cohort* (N = 65 741)
Alcohol use disorder	50.0% (7531)	83.1% (19 592)	41.3% (27 123)
Cannabis use disorder	13.1% (1968)	54.4% (12 728)	22.4% (14 696)
Cocaine/stimulant use disorder	18.7% (2823)	71.7% (16 915)	30.0% (19 738)
Sedative use disorder	6.7% (1010)	23.4% (5509)	9.9% (6519)
Other substance use disorder	11.6% (1743)	47.6% (11 234)	19.7% (12 977)

[a]Mean ± standard deviation (SD) for number of non-alcohol substance use disorders is 0.5 (0.5) in OUD + 1 SUD and 1.97 (0.86) in OUD + ≥ 2 SUDs patients.

correlation coefficient (ICC) from the intercept-only model indicated that 20% of the total variation in buprenorphine treatment was explained by variation among facilities, while only 11% of the variation was explained by facility variation for SUD clinic visits. A number of patient characteristics were associated with lower likelihood of receiving any of the three types of OUD treatment, including: older age, female gender, patients receiving majority of their care in CBOCs, patients with psychotic disorders and patients with Charlson comorbidity index > 1 (see Table 3).

For the primary predictor variable of interest, patients with OUD + 1 SUD and patients with OUD + ≥2 SUDs were less likely to receive buprenorphine and methadone treatment compared to patients with OUD only. In contrast, patients with OUD + 1 SUD and patients with OUD + ≥2 SUDs were much more likely to receive other outpatient SUD treatment.

Sensitivity analyses

Among this cohort, 49.6% of patients with OUD (n = 33 128) were newly initiated on treatment (i.e. not receiving any OUD treatment during the 3 months prior to their first diagnosis in FY 2017). In this subgroup of patients, having OUD + ≥2 SUDs [adjusted odds ratio (aOR) = 0.83, 95% confidence interval (CI) = 0.72, 0.95] was associated with a lower likelihood of receiving buprenorphine treatment compared to patients with OUD only, although the results for the OUD + 1 SUD group was no longer significant (aOR = 1.06, 95% CI = 0.94, 1.19). There were no significant differences in methadone treatment for patients with OUD + 1 SUD (aOR = 0.89, 95% CI = 0.78, 1.02) but patients with OUD + ≥2 SUDs (aOR = 0.73, 95% CI = 0.61, 0.87) were less likely to receive methadone. Similar to the primary analyses, patients with OUD + 1 SUD (aOR = 1.67, 95% CI = 1.56, 1.78) and patients with OUD + ≥2 SUDs (aOR = 2.49, 95% CI = 2.33, 2.66) were much more likely to receive other outpatient SUD treatment.

DISCUSSION

In this study examining treatment receipt among patients with OUD receiving care within the VHA in FY 2017, close to 60% of patients had at least one additional SUD diagnosis and more than a third of patients had multiple comorbid SUDs. The most common comorbid SUD diagnosis was alcohol use disorder, which was present in the majority of those with polysubstance use, followed by cocaine/stimulant use disorder. At the same time, although those with polysubstance use were much more likely to receive outpatient SUD care, they were less likely to receive buprenorphine treatment for OUD. These findings suggest polysubstance use, especially with alcohol and stimulant use disorders, are the norm and not the exception among patients with OUD, but these patients with polysubstance use are less likely to receive buprenorphine and methadone treatment.

There are several potential explanations for this treatment paradox, including lack of models of care within current OUD frameworks for patients with OUD and polysubstance use, patient factors, clinician and system factors. Patients with comorbid SUDs are more likely to receive SUD visits which encompass numerous treatment modalities, including psychotherapy, treatment planning and evaluation, but less likely to receive or initiate medication treatment. These findings are in contrast to the preponderance of studies indicating that patients with a higher burden of other chronic medical conditions are much more likely to receive higher rates of medical and mental health treatment [32–34]. It is possible that patients with comorbid SUDs may perceive lower need for treatment compared to those with OUD only, but the higher utilization of SUD visits suggest there may be additional factors.

Clinicians' attitudes and expectations for patients as requirements for initiating and sustaining treatment may also drive treatment utilization for patients with SUDs. Variations in approaches to SUD treatment among clinicians

Table 2 Demographic, clinical and treatment characteristics across substance use disorder (SUD) comorbidity groups among patients with an opioid use disorder (OUD).[a]

	OUD only n = 27078 (41.2%) % (n)	*OUD + 1 other SUD n = 15075 (22.9%) % (n)*	*OUD + ≥ 2 other SUDs n = 23588 (35.9%) % (n)*	χ^2	*P-value*
Age (years)				2103.35	< 0.001
18–29	5.5% (1487)	7.4% (1109)	9.2% (2170)		
30–64	66.6% (18038)	72.9% (10987)	78.9% (18619)		
65+	27.9% (7553)	19.8% (2979)	11.9% (2799)		
Female	8.3% (2249)	7.1% (1070)	6.9% (1626)	41.20	< 0.001
Race				945.18	< 0.001
White	77.5% (20998)	74.5% (11225)	68.5% (16157)		
Black	14.7% (3989)	18.4% (2771)	25.2% (5954)		
Other/multi-race	1.7% (464)	1.8% (267)	1.7% (406)		
Unknown/missing[b]	5.1% (1384)	4.5% (681)	3.5% (831)		
Hispanic (versus non-)	5.0% (1361)	5.8% (874)	6.2% (1458)	32.91	< 0.001
Residence				186.00	< 0.001
Urban	81.2% (21977)	83.7% (12612)	84.9% (20023)		
Large rural city/town	6.5% (1773)	5.6% (846)	4.8% (1144)		
Small/isolated rural	5.4% (1463)	4.2% (635)	3.6% (841)		
Unknown/missing[c]	6.9% (1865)	6.5% (982)	6.7% (1580)		
Homeless	7.6% (2064)	17.8% (2681)	41.5% (9793)	8621.43	< 0.001
Care location				750.17	< 0.001
CBOC	36.9% (9992)	32.5% (4899)	27.9% (6587)		
VAMC	46.6% (12615)	50.4% (7591)	58.4% (13773)		
Unknown/missing[c]	16.5% (4471)	17.1% (2585)	13.7% (3228)		
Mental health disorders[d]					
Major depression	35.1% (9511)	47.6% (7182)	63.0% (14872)	3939.39	< 0.001
Bipolar disorder	6.2% (1666)	10.8% (1621)	20.4% (4815)	2417.23	< 0.001
PTSD	29.2% (7917)	38.6% (5814)	50.8% (11994)	2474.27	< 0.001
Other anxiety disorder	21.2% (5732)	30.0% (4529)	40.6% (9578)	2260.47	< 0.001
Psychotic disorder	5.2% (1401)	7.6% (1143)	14.5% (3412)	1372.67	< 0.001
Charlson comorbidity index				155.09	< 0.001
= 0	50.5% (13673)	50.9% (7677)	47.0% (11084)		
= 1	20.6% (5589)	21.1% (3182)	24.8% (5854)		
> 1	28.9% (7816)	28.0% (4216)	28.2% (6650)		
Nicotine use disorder	18.2% (4926)	29.5% (4449)	47.0% (11085)	4902.27	< 0.001
Treatments received					
Buprenorphine	18.8% (5104)	17.9% (2698)	14.0% (3296)	227.99	< 0.001
Methadone	17.3% (4689)	17.5% (2639)	16.0% (3784)	19.65	< 0.001
SUD clinic visits	43.4% (11746)	61.5% (9269)	76.5% (18053)	5782.20	< 0.001

[a]All variables from Table 2 were included as covariates across all three models in Table 3 using the same categories depicted, except for the treatment variables which were the outcomes in these models. [b]For race, the 'unknown/missing category' includes those with 'missing', 'blank', 'declined' and 'unknown' by patient. [c]For residence and care location variables, the 'unknown/missing' category represented all missing data. [d]Mean ± standard deviation (SD) for number of mental health disorders is 0.97 (0.99) in OUD only, 1.35 (1.07) in OUD + 1 SUD and 1.89 (1.16) in OUD + ≥ 2 SUDs patients. VAMC = Veterans Affairs Medical Center; CBOC = community-based outpatient clinic; PTSD = post-traumatic stress disorder.

can be characterized using different treatment thresholds [35,36]. Specifically, the expectation of some providers that patients have complete abstinence from all substances as a requirement for medication treatment for OUD may directly contribute to decreased initiation and retention on medications for patients with polysubstance use [37]. Some treatment programs in Canada and many European countries have adopted 'low threshold' models that incorporate harm reduction approaches [38–40], but many treatment programs in the United States still operate under high threshold models. Unfortunately, no data were

available on treatment philosophies of individual clinicians, so it is not possible to directly assess how this influenced the decision to initiate or continue delivery of MOUD. However, the finding that many of the patients at highest risk for negative outcomes (i.e. those with comorbid SUDs) are not receiving medication treatment suggest the need to more clearly understand clinician attitudes in order to improve treatment delivery for these patients.

The high prevalence of these conditions among the OUD patient population indicates the urgent need for treatment models that can deliver evidence-based treatments

Table 3 Generalized linear mixed regression models examining the relationship between SUD comorbidity and receipt of OUD treatment.

Characteristic	Buprenorphine, aOR (95% CI)	Methadone, aOR (95% CI)	SUD clinic visits, aOR (95% CI)
OUD only	Ref.	Ref.	Ref.
OUD + 1 SUD	0.87 (0.82, 0.93)	0.91 (0.86, 0.97)	1.85 (1.77, 1.93)
OUD + ≥2 SUD	0.65 (0.61, 0.69)	0.79 (0.74, 0.84)	3.25 (3.10, 3.41)
Age (years)			
18–29	Ref.	Ref.	Ref.
30–64	0.88 (0.81, 0.95)	0.94 (0.85, 1.03)	0.67 (0.62, 0.72)
> 65	0.45 (0.40, 0.50)	0.77 (0.69, 0.86)	0.36 (0.33, 0.39)
Female	0.85 (0.78, 0.92)	0.84 (0.77, 0.93)	0.78 (0.73, 0.83)
Race			
White	Ref.	Ref.	Ref.
Black	0.54 (0.50, 0.58)	1.12 (1.05, 1.19)	1.23 (1.16, 1.29)
Other/multi-race	0.77 (0.66, 0.88)	1.01 (0.87, 1.18)	0.91 (0.82, 1.02)
Unknown	0.85 (0.76, 0.96)	0.94 (0.84, 1.06)	0.95 (0.87, 1.03)
Hispanic	0.91 (0.81, 1.01)	1.26 (1.13, 1.40)	1.25 (1.15, 1.36)
Location			
Urban	Ref.	Ref.	Ref.
Large rural city/town	1.10 (1.00, 1.21)	0.57 (0.50, 0.66)	0.75 (0.69, 0.82)
Small/isolated rural town	1.07 (0.96, 1.19)	0.51 (0.43, 0.60)	0.80 (0.73, 0.88)
Unknown	0.54 (0.48, 0.60)	0.56 (0.51, 0.63)	0.55 (0.51, 0.60)
Homeless	0.81 (0.77, 0.87)	1.01 (0.95, 1.07)	1.76 (1.68, 1.85)
Care location			
VAMC	Ref.	Ref.	Ref.
CBOC	0.79 (0.75, 0.83)	0.77 (0.72, 0.82)	0.74 (0.71, 0.77)
Unknown	1.03 (0.96, 1.10)	1.11 (1.03, 1.19)	1.32 (1.25, 1.40)
Major depression	0.97 (0.93, 1.02)	0.82 (0.77, 0.86)	0.96 (0.93, 1.00)
Bipolar disorder	0.86 (0.80, 0.92)	0.76 (0.70, 0.83)	0.93 (0.88, 0.99)
Other anxiety	1.19 (1.13, 1.24)	0.98 (0.93, 1.03)	1.18 (1.14, 1.23)
PTSD	0.96 (0.91, 1.01)	0.83 (0.78, 0.88)	0.90 (0.86, 0.94)
Schizophrenia/other psychosis	0.64 (0.58, 0.70)	0.70 (0.64, 0.76)	0.73 (0.69, 0.78)
Charlson comorbidity index			
= 0	Ref.	Ref.	Ref.
= 1	0.82 (0.77, 0.87)	1.03 (0.97, 1.09)	0.81 (0.77, 0.84)
> 1	0.52 (0.49, 0.56)	0.80 (0.75, 0.85)	0.53 (0.50, 0.55)
Nicotine use disorder	1.55 (1.48, 1.64)	1.83 (1.74, 1.93)	1.53 (1.47, 1.59)

OUD = opioid use disorder; SUD =substance use disorder; VAMC = Veterans Affairs Medical Center; CBOC = community-based outpatient clinic; PTSD = post-traumatic stress disorder; aOR = adjusted odds ratio; CI = confidence interval.

for OUD as well as other SUDs. Effective treatments for other SUDs include medications for alcohol use disorder [41,42], but also rely upon evidence-based psychosocial interventions such as cognitive behavioral therapy and contingency management [43–46]. To date, much of the focus to improve treatment of OUD has been on increasing access to and use of medication treatment for patients with OUD. Moving forward, treatment considerations also need to incorporate effective treatments for comorbid SUDs, a group of patients often characterized with worse treatment outcomes, including lower treatment retention, increased legal consequences and poorer health outcomes overall [11,16,47]. Further work is needed to examine treatment strategies that may be particularly effective in patients with polysubstance use; for example, examining the

effectiveness of long-acting naltrexone among patients with comorbid alcohol and opioid use disorder.

In addition, models of care for patients with OUD must also consider how to address the treatment needs of more complex patients with comorbid SUDs. Specialty SUD treatment settings, especially those in the VHA, compared to primary care, may have the capacity to deliver evidence-based psychotherapies for SUDs [48,49], but there is still a dearth of treatment models that incorporate both medication and psychosocial interventions for polysubstance use even within specialty SUD settings. In primary care and other non-specialty care settings, models such as collaborative care and other care management models that can help to deliver effective treatments for multiple substance use disorders may be particularly

promising [50,51]. Future studies should examine effectiveness of different models of care for the large population of patients with polysubstance use found in real-world clinic settings.

There are several important limitations in this study. This study used administrative data to capture treatments for patients with OUD, including buprenorphine, methadone and outpatient visits in SUD clinics, which includes the most effective and commonly used treatments [13,14,16,52]. However, we were not able to further specify the type of outpatient treatment, including individual or group psychotherapy, versus treatment planning and medication visits. It is also possible that increased use of naltrexone and extended-release naltrexone may account for some of the decreased use of buprenorphine and methadone in patients with polysubstance use. Although < 1% of VHA patients with OUD received extended-release naltrexone in 2017 [22], both utilization and effectiveness of naltrexone in patients with OUD and polysubstance use should be examined in future studies. Also, other unmeasured factors (e.g. treatment adherence) may have influenced the present findings, although we found similar results among patients initiating treatment. Furthermore, we did not examine duration or severity of OUD or other SUDs. In addition, patients with polysubstance use may be more likely seen in SUD settings, and those seen in SUD settings are more likely to be diagnosed with additional SUDs. However, this should not alter the finding that polysubstance use was associated with a lower likelihood of receiving buprenorphine treatment, especially because the vast majority of buprenorphine prescribing in the VHA occurs in SUD specialty settings [53]. The study focuses on Veterans, an important population at higher risk for overdose than the general population [54] and with similar prevalence of OUD compared to the non-Veteran population in the United States [55]. However, Veterans obtain medications and other treatments outside the VHA which are not captured by these data, and many patients with OUD do not seek treatment, so there is under-diagnosis of OUD [56]. Finally, the population is predominantly male, which may not generalize to other populations.

Despite these limitations, we found that comorbid SUDs are highly prevalent among patients with OUD but, on average, are associated with a lower likelihood of patients receiving buprenorphine treatments for OUD, but with higher likelihood of patients accessing any outpatient SUD treatment. To date, there have been few studies addressing access to treatment and treatment outcomes for patients with OUD and other comorbid SUDs. Future studies should explore how clinician and other system-level factors may be associated with choice of treatment for patients with polysubstance use and how to more effectively address treatment needs for the majority of patients with OUD who have multiple SUD diagnoses.

Declaration of interests

References

1. Scholl L, Seth P, Kariisa M, Wilson N, Baldwin G. Drug and opioid-involved overdose deaths — United States, 2013–2017. *Morb Mort Wkly Rep* [internet]. 2018. December 21 [cited 2018 Dec 27];67. Available at: https://www.cdc.gov/mmwr/volumes/67/wr/mm675152e1.htm (accessed 31 May 2020).
2. Gomes T., Greaves S., Martins D., Bandola M., Tadrous S., Singh S. *et al. Latest Trends in Opioid-related Deaths in Ontario: 1991–2015.* Toronto: Ontario Drug Policy Research Network; 2017.
3. Larance B., Degenhardt L., Peacock A., Gisev N., Mattick R., Colledge S., *et al.* Pharmaceutical opioid use and harm in Australia: the need for proactive and preventative responses. *Drug Alcohol Rev* 2018; **37**: S203–S205.
4. Seth P., Scholl L., Rudd R. A., Bacon S. Overdose deaths involving opioids, cocaine, and psychostimulants—United States, 2015–2016. *Morb Mort Wkly Rep* 2018; **67**: 349–58.
5. Barocas J. A., Wang J., Marshall B. D. L., LaRochelle M. R., Bettano A., Bernson D., *et al.* Sociodemographic factors and social determinants associated with toxicology confirmed polysubstance opioid-related deaths. *Drug Alcohol Depend* 2019; **200**: 59–63.
6. Hedegaard H., Bastian B. A., Trinidad J. P., Spencer M., Warner M. Drugs Most frequently involved in drug overdose deaths: United States, 2011–2016. *Natl Vital Stat Rep* 2018; **67**: 1–14.
7. Bohnert A. S. B., Ilgen M. A., Ignacio R. V., McCarthy J. F., Valenstein M., Blow F. C. Risk of death from accidental overdose associated with psychiatric and substance use disorders. *Am J Psychiatry* 2012; **169**: 64–70.
8. Betts K. S., McIlwraith F., Dietze P., Whittaker E., Burns L., Cogger S., *et al.* Can differences in the type, nature or amount of polysubstance use explain the increased risk of non-fatal overdose among psychologically distressed people who inject drugs? *Drug Alcohol Depend* 2015; **154**: 76–84.
9. Kerr T., Fairbairn N., Tyndall M., Marsh D., Li K., Montaner J. *et al.* Predictors of non-fatal overdose among a cohort of polysubstance-using injection drug users. *Drug Alcohol Depend* 2007; 87: 39–45.
10. Hassan A. N., Le Foll B. Polydrug use disorders in individuals with opioid use disorder. *Drug Alcohol Depend* 2019; **198**: 28–33.

11. Betts K. S., Chan G., McIlwraith F., Dietze P., Whittaker E., Burns L., *et al.* Differences in polysubstance use patterns and drug-related outcomes between people who inject drugs receiving and not receiving opioid substitution therapies. *Addiction* 2016; **111**: 1214–23.

12. Bhalla I. P., Stefanovics E. A., Rosenheck R. A. Clinical epidemiology of single versus multiple substance use disorders: polysubstance use disorder. *Med Care* 2017; **55**: S24–S32.

13. Nielsen S., Larance B., Lintzeris N. Opioid agonist treatment for patients with dependence on prescription opioids. *JAMA* 2017; **317**: 967–8.

14. Mattick R. P., Breen C., Kimber J., Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev* 2014CD002207.

15. Larochelle M. R., Bernson D., Land T., Stopka T. J., Wang N., Xuan Z. *et al.* Medication for opioid use disorder after nonfatal opioid overdose and association with mortality: a cohort study. *Ann Intern Med* 2018;**169**: 137–145.

16. Morgan J. R., Schackman B. R., Leff J. A., Linas B. P., Walley A. Y. Injectable naltrexone, oral naltrexone, and buprenorphine utilization and discontinuation among individuals treated for opioid use disorder in a United States commercially insured population. *J Subst Abuse Treat* 2018; **85**: 90–96.

17. Lembke A., Chen J. H. Use of opioid agonist therapy for Medicare patients in 2013. *JAMA Psychiatry* 2016; **73**: 990–2.

18. Saloner B., Karthikeyan S. Changes in substance abuse treatment use among individuals with opioid use disorders in the United States, 2004–2013. *JAMA* 2015; **314**: 1515–7.

19. Gryczynski J., Mitchell S. G., Jaffe J. H., O'Grady K. E., Olsen Y. K., Schwartz R. P. Leaving buprenorphine treatment: Patients' reasons for cessation of care. *J Subst Abuse Treat* 2014; **46**: 356–61.

20. Knudsen H. K., Lofwall M. R., Walsh S. L., Havens J. R., Studts J. L. Physicians' decision-making when implementing buprenorphine with new patients: conjoint analyses of data from a cohort of current prescribers. *J Addict Med* 2018; **12**: 31–9.

21. US Food and Drug Administration. FDA urges caution about withhold opioid addiction medications from patients taking benzodiazepines or CNS depressants: careful medication management can reduce risks [internet]. 2017 September. Available at: https://www.fda.gov/media/127688/download (accessed 31 May 2020).

22. Wyse J. J., Gordon A. J., Dobscha S. K., Morasco B. J., Tiffany E., Drexler K. *et al.* Medications for opioid use disorder in the Department of Veterans Affairs (VA) health care system: historical perspective, lessons learned and next steps. *Subst Abuse* 2018; **29**: 139–144.

23. Sordo L., Barrio G., Bravo M. J., Indave B. I., Degenhardt L., Wiessing L., *et al.* Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. *BMJ* 2017; **357**: j1550.

24. Oliva E. M., Harris A. H. S., Trafton J. A., Gordon A. J. Receipt of opioid agonist treatment in the Veterans Health Administration: facility and patient factors. *Drug Alcohol Depend* 2012; **122**: 241–6.

25. Manhapra A., Petrakis I., Rosenheck R. Three-year retention in buprenorphine treatment for opioid use disorder nationally in the Veterans Health Administration. *Am J Addict* 2017; **26**: 572–80.

26. Manhapra A., Quinones L., Rosenheck R. Characteristics of veterans receiving buprenorphine vs. methadone for opioid use disorder nationally in the Veterans Health Administration. *Drug Alcohol Depend* 2016; **160**: 82–9.

27. United States Drug Administration (USDA) ERS—Documentation. 2010 Rural–Urban Commuting Area (RUCA) Codes [internet] [cited 2019 April 21]. Available at: https://www.ers.usda.gov/data-products/rural-urban-commuting-area-codes/documentation/ (accessed 31 May 2020).

28. Malhotra A., Vaughan-Sarrazin M., Charlton M. E., Rosenthal G. E. Comparison of colorectal cancer screening in veterans based on the location of primary care clinic. *J Prim Care Community Health* 2014; **5**: 24–9.

29. Jasuja G. K., Bhasin S., Rose A. J., Reisman J. I., Hanlon J. T., Miller D. R., *et al.* Provider and site-level determinants of testosterone prescribing in the veterans healthcare system. *J Clin Endocrinol Metab* 2017; **102**: 3226–33.

30. Quan H., Sundararajan V., Halfon P., Fong A., Burnand B., Luthi J.-C., *et al.* Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005; **43**: 1130–9.

31. Snijders T. A. B. *Multilevel Analysis: An Introduction To Basic And Advanced Multilevel Modeling, 2nd edn. Thousand Oaks, CA: SAGE Publications Ltd; 2011.*

32. Wu L. T., Kouzis A. C., Leaf P. J. Influence of comorbid alcohol and psychiatric disorders on utilization of mental health services in the National Comorbidity Survey. *Am J Psychiatry* 1999; **156**: 1230–6.

33. van Oostrom S. H., Picavet H. S. J., de Bruin S. R., Stirbu I., Korevaar J. C., Schellevis F. G., *et al.* Multimorbidity of chronic diseases and health care utilization in general practice. *BMC Fam Pract* 2014; **15**: 61.

34. Zulman D. M., Pal Chee C., Wagner T. H., Yoon J., Cohen D. M., Holmes T. H., *et al.* Multimorbidity and healthcare utilisation among high-cost patients in the US veterans affairs health care system. *BMJ Open* 2015; **5**: e007771.

35. Kourounis G., Richards B. D. W., Kyprianou E., Symeonidou E., Malliori M.-M., Samartzis L. Opioid substitution therapy: lowering the treatment thresholds. *Drug Alcohol Depend* 2016; **161**: 1–8.

36. Strike C., Millson M., Hopkins S., Smith C. What is low threshold methadone maintenance treatment? *Int J Drug Policy* 2013; **24**: e51–e56.

37. Bentzley B. S., Barth K. S., Back S. E., Book S. W. Discontinuation of buprenorphine maintenance therapy: perspectives and outcomes. *J Subst Abuse Treat* 2015; **52**: 48–57.

38. Nolan S., Hayashi K., Milloy M.-J., Kerr T., Dong H., Lima V. D., *et al.* The impact of low-threshold methadone maintenance treatment on mortality in a Canadian setting. *Drug Alcohol Depend* 2015; **156**: 57–61.

39. Langendam M. W., van Brussel G. H., Coutinho R. A., van Ameijden E. J. The impact of harm-reduction-based methadone treatment on mortality among heroin users. *Am J Public Health* 2001; **91**: 774–80.

40. Perreault M., Héroux M.-C., White N. D., Lauzon P., Mercier C., Rousseau M. Treatment retention and evolution of clientele in a low threshold methadone substitution treatment program in Montreal. *Can J Public Health/Rev Can Sante Publique* 2007; **98**: 33–6.

41. Jonas D. E., Amick H. R., Feltner C., Bobashev G., Thomas K., Wines R., *et al.* Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. *JAMA* 2014; **311**: 1889–900.

42. Donoghue K., Elzerbi C., Saunders R., Whittington C., Pilling S., Drummond C. The efficacy of acamprosate and naltrexone in the treatment of alcohol dependence, Europe versus the rest of the world: a meta-analysis. *Addiction* 2015; **110**: 920–30.

43. Anton R. F., O'Malley S. S., Ciraulo D. A., Cisler R. A., Couper D., Donovan D. M., *et al.* Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. *JAMA* 2006; **295**: 2003–17.

44. Gates P. J., Sabioni P., Copeland J., Le Foll B., Gowing L. Psychosocial interventions for cannabis use disorder. *Cochrane Database Syst Rev* 2016CD005336.

45. Petry N. M., Alessi S. M., Olmstead T. A., Rash C. J., Zajac K. Contingency management treatment for substance use disorders: how far has it come, and where does it need to go? *Psychol Addict Behav* 2017; **31**: 897–906.

46. Carroll K. M. Recent advances in the psychotherapy of addictive disorders. *Curr Psychiatry Rep* 2005; **7**: 329–36.

47. Samples H., Williams A. R., Olfson M., Crystal S. Risk factors for discontinuation of buprenorphine treatment for opioid use disorders in a multi-state sample of Medicaid enrollees. *J Subst Abuse Treat* 2018; **95**: 9–17.

48. Petry N. M., DePhilippis D., Rash C. J., Drapkin M., McKay J. R. Nationwide dissemination of contingency management: the veterans administration initiative. *Am J Addict* 2014; **23**: 205–10.

49. Moos R. H., Humphreys K., Ouimette P. C., Finney J. Evaluating and improving VA substance abuse patients' care. *Am J Med Qual* 1999; **14**: 45–54.

50. Watkins K. E., Ober A. J., Lamp K., Lind M., Setodji C., Osilla K. C., *et al.* Collaborative care for opioid and alcohol use disorders in primary care: the SUMMIT randomized clinical trial. *JAMA Intern Med* 2017; **177**: 1480–8.

51. Oslin D. W., Lynch K. G., Maisto S. A., Lantinga L. J., McKay J. R., Possemato K., *et al.* A randomized clinical trial of alcohol care management delivered in Department of Veterans Affairs primary care clinics versus specialty addiction treatment. *J Gen Intern Med* 2014; **29**: 162–8.

52. Alderks CE. Trends in the use of methadone, buprenorphine, and extended-release naltrexone at substance abuse treatment facilities: 2003–2015 (update). In: The CBHSQ Report [internet]. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2013 [cited 2019 Sep 30]. Available at: http://www.ncbi.nlm.nih.gov/books/NBK469748/ (accessed 31 May 2020).

53. Valenstein-Mah H., Hagedorn H., Kay C. L., Christopher M. L., Gordon A. J. Underutilization of the current clinical capacity to provide buprenorphine treatment for opioid use disorders within the Veterans Health Administration. *Subst Abuse* 2018; **39**: 286–8.

54. Bohnert A. S. B., Ilgen M. A., Galea S., McCarthy J. F., Blow F. C. Accidental poisoning mortality among patients in the Department of Veterans Affairs Health System. *Med Care* 2011; **49**: 393–6.

55. Rhee T. G., Rosenheck R. A. Comparison of opioid use disorder among male veterans and non-veterans: disorder rates, socio-demographics, co-morbidities, and quality of life. *Am J Addict* 2019; **28**: 92–100.

56. Rhee T. G., Rosenheck R. A. Use of drug treatment services among adults with opioid use disorder: rates, patterns, and correlates. *Psychiatr Serv* 2019; **70**: 992–9.

Supporting Information

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

Table S1. International Classification of Disease-10 (ICD-10) diagnosis codes for mental health and substance use disorders

Table S2. VHA clinic stop codes for treatment received