Prevalence and Medication Treatment of Opioid Use Disorder Among Primary Care Patients with Hepatitis C and HIV

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BACKGROUND: Hepatitis C and HIV are associated with opioid use disorders (OUD) and injection drug use. Medications for OUD can prevent the spread of HCV and HIV.

OBJECTIVE: To describe the prevalence of documented OUD, as well as receipt of office-based medication treatment, among primary care patients with HCV or HIV.

DESIGN: Retrospective observational cohort study using electronic health record and insurance data.

PARTICIPANTS: Adults ≥ 18 years with ≥ 2 visits to primary care during the study (2014–2016) at 6 healthcare systems across five states (CO, CA, OR, WA, and MN).

MAIN MEASURES: The primary outcome was the diagnosis of OUD; the secondary outcome was OUD treatment with buprenorphine or oral/injectable naltrexone. Prevalence of OUD and OUD treatment was calculated across four groups: HCV only; HIV only; HCV and HIV; and neither HCV nor HIV. In addition, adjusted odds ratios (AOR) of OUD treatment associated with HCV and HIV (separately) were estimated, adjusting for age, gender, race/ethnicity, and site.

KEY RESULTS: The sample included 1,368,604 persons, of whom 10,042 had HCV, 5821 HIV, and 422 both. The prevalence of diagnosed OUD varied across groups: 11.9% (95% CI: 11.3%, 12.5%) for those with HCV; 1.6% (1.3%, 2.0%) for those with HIV; 8.8% (6.2%, 11.9%) for those with both; and 0.92% (0.91%, 0.94%) among those with neither. Among those with diagnosed OUD, the prevalence of OUD medication treatment was 20.9%, 16.0%, 10.8%, and 22.3%, for those with HCV, HIV, both, and neither, respectively. HCV was not associated with OUD treatment (AOR = 1.03; 0.88, 1.21), whereas patients with HIV had a lower probability of OUD treatment (AOR = 0.43; 0.26, 0.72).

CONCLUSIONS: Among patients receiving primary care, those diagnosed with HCV and HIV were more likely to have documented OUD than those without. Patients with HIV were less likely to have documented medication treatment for OUD.

KEY WORDS: opioid use disorders; hepatitis C; HIV; buprenorphine; naltrexone.

INTRODUCTION

The USA is experiencing a crisis of opioid use disorders (OUDs). In 2017, there were 47,600 people who died from opioid-related overdoses[1] and an estimated 2.1 million Americans had an OUD, of whom 652,000 had a heroin-involved OUD.[2] Patients with OUD who use pharmaceutical opioids may transition to injection drug use,[3] and up to three-quarters of persons with OUD entering treatment report injecting drugs.[4]

Both hepatitis C virus (HCV) and HIV infection are spread through injection drug use, and these diseases are on the rise in communities affected by the opioid crisis.[5, 6] Hepatitis C is currently the leading cause of infectious disease related death in the USA,[7] surpassing deaths from HIV combined with other infectious causes. Although HCV is now highly curable, directly acting anti-viral treatments are costly and may not be accessible to many patients. To date, HIV remains a chronic disease without cure, and approximately half of Americans living with HIV are not engaged in care and are not virally suppressed.[8]

Medication treatment for OUD has been shown to decrease overall mortality.[9–11] Furthermore, among persons with OUD in addition to HIV and/or HCV, medication treatment of OUD can improve HIV and HCV outcomes. Among persons with HIV, treatments with buprenorphine and extended-release naltrexone are associated with antiretroviral therapy (ART) initiation[12] and HIV viral suppression,[13] respectively. Retention on buprenorphine is associated with enhanced HCV outcomes leading to cure.[14] Treatment of OUD with medications is also associated with lower rates of HCV[15–17] and HIV[18, 19] transmission.

The purpose of this study—conducted across 6 large health systems—was to describe the prevalence of recognized OUDs and office-based medication treatment for OUD among four groups of primary care patients: those with HCV only, HIV only, both HCV and HIV, and neither of these infections. Additionally, we sought to examine whether patients with OUD who had HCV (irrespective of HIV) and HIV (irrespective of HCV) would be more likely to receive office-based medication treatment for OUD compared to patients without.

METHODS

Study Design and Sample

In this cross-sectional study, we ascertained data from the electronic health record (EHR) and insurance claims from six healthcare systems across five states (CO, CA, OR, WA, and MN). The data were collected for Phase 1 of the PRimary care Opioid Use Disorders (PROUD) Study (CTN 0074), a pragmatic trial testing whether a collaborative care model increases OUD medication treatment in primary care. Phase 1 of PROUD was a feasibility study in 11 health systems. Of the 11 sites, only 6 health systems were able to obtain complete phase 1 data needed for this study: HealthPartners (MN), MultiCare (WA), and 4 regions of Kaiser Permanente (WA, CO, Northern CA, Northwest). Of these sites, 5 were integrated health insurance plans and delivery systems with data obtained from both EHRs and insurance claims and linkable dispensed medications from internal pharmacies, and one (MultiCare) was a community healthcare system which provided data only from the EHR. Each health system had linkable data on patient demographics, diagnoses, procedures, and utilization from all settings (e.g., outpatient, inpatient, urgent care, and emergency department), as well as pharmacy dispensing or medication orders. Medication use was determined by pharmacy dispensing data for the five integrated health systems and by medication orders for MultiCare. Diagnoses were based on International Classification of Disease-9th edition (ICD-9-CM; until September 30, 2015) or ICD-10-CM diagnostic codes (starting October 1, 2015).

The study sample included individuals with ≥ 2 visits to primary care who were adults ≥ 18 years of age within fiscal years 2014–2016. Primary care was defined via site of care: it included ambulatory visit encounter type where the department was either family practice, internal medicine, pediatrics, or gerontology. The study was approved by the Kaiser Permanente Washington (KPWA) institutional review board (IRB), and had a waiver of informed consent and HIPAA authorization. The remaining health systems ceded to the KPWA IRB.

Measures

Documented OUD. The primary outcome was a documented OUD diagnosis based on ICD-9 and/or ICD-10 codes (see Appendix) associated with clinical encounters identified from EHRs or insurance claims at any time in the 3-year study period. Codes for "active" or "in remission" OUD were included as providers can differ and use either OUD diagnosis coding (e.g., active vs. remission) when characterizing patients who are receiving medication treatment for OUD. Categories for "active" and "remission" were not mutually exclusive, as status could change during the study period. Patients with no documented ICD code for OUD but a prescription for transmucosal buprenorphine used to treat OUD were also considered to have a documented OUD.

Medication Treatment of OUD. The secondary outcome was receipt of any office-based medication treatment for OUD documented in the EHR or claims, defined as any documented prescription (pharmacy dispensing or order) with buprenorphine, including transmucosal or implanted, with or without naloxone at any time during the 3-year study period

from any prescriber. Buprenorphine transdermal patches, approved by the Food and Drug Administration for pain, were excluded. As a secondary treatment outcome, oral or injectable naltrexone based on a procedure code, medication order, or pharmacy dispensing was considered medication treatment for OUD if patients had a documented OUD diagnosis. This study of office-based medication treatment for OUD did not include methadone, as methadone is not sanctioned for treatment of OUD outside of federally regulated opioid treatment programs (OTPs) in the USA.

HIV/HCV Status. The main independent variable was documentation during the 3-year study of HCV and/or HIV diagnosis based on ICD-9 and/or ICD-10 codes. Patients were placed in one of 4 mutually exclusive groups based on whether they had any diagnosis for HCV and/or HIV documented at least once during the study period: HCV only, HIV only, both HIV and HCV, and neither HCV nor HIV.

Other Covariates. Age, gender, race (white, African American, Asian, Native American/Alaska Native, Hawaiian/Pacific Islander, Multiracial, and Other), ethnicity (Hispanic vs. non-Hispanic), and type of health insurance (Medicare, Private, State-subsidized, and Uninsured) were determined at the time of study entry (i.e., initial primary care visit to a study clinic during the study). Diagnoses were determined by ICD codes in the EHRs or insurance claims during the 3-year study period. Mental health disorder diagnoses included documentation of ICD codes for depression, anxiety, bipolar disorder, and schizophrenia. Substance use disorders (SUDs) included ICD codes for tobacco, alcohol, and other substances, including cannabis, stimulants, and other drugs. ICD codes were used to document any non-cancer pain diagnoses. We defined pain with ICD codes based on a validation study that used chart reviews across 13 primary care sites of a statewide federally qualified health center, and categorized types based on "diagnostic clusters" of pain.[20, 21] Counts of prescription opioids dispensed or ordered during the study period were used to assess opioid use. Acute care during the study period was categorized based on counts of days hospitalized or visits to emergency department, including urgent care (0, 1, 2, and ≥ 3).

Statistical Analysis

We conducted descriptive analyses of demographics and clinical characteristics across the four mutually exclusive HIV/HCV groups. For each of the 4 HCV/HIV groups, the prevalence (95% confidence intervals [CI]) of having an OUD diagnosis documented in the EHR or claims during the 3-year study period, and the prevalence of office-based medication treatment for OUD at any time during the 3-year study among primary care patients were calculated. To assess whether either HCV or HIV was independently associated

with documented office-based medication treatment of OUD among patients with OUD, multivariate logistic regression was performed to examine the adjusted relative odds of receipt of medication treatment for OUD for patients with and without HCV, and with and without HIV. Models included both binary variables (HIV yes/no; HCV yes/no) simultaneously and adjusted for site, age, gender, and race/ethnicity. These analyses were specified a priori. All analyses were conducted using Stata version 15.1 (College Station, TX).

RESULTS

The study sample included 1,368,604 adult primary care patients. Of those, 10,042 (0.73%) were diagnosed with HCV alone, 5821 (0.43%) with HIV alone, 422 (0.03%) with both HCV and HIV, and 1,352, 319 (98.81%) with neither. Those patients diagnosed with HCV and/or HIV were predominantly male, and over 45 years of age and a relatively higher proportion of patients in those groups were African-American compared to the group without HCV and HIV (Table 1). Diagnosed substance use disorders (alcohol, tobacco, cannabis, stimulant, and other), mental health disorders, and non-cancer pain were all more common among persons with HCV and HIV compared to those without.

The prevalence of documented OUD was highest in patients with HCV, both among those with HCV alone and those with HCV and HIV: 11.9% (95% CI: 11.3%, 12.5%) and 8.8% (95% CI: 6.2%, 11.9%), respectively (Table 2). The lowest prevalence of documented OUD was in those with neither HCV nor HIV (0.92%; 95% CI: 0.91%, 0.94%). The prevalence among those with HIV alone was also low (1.6%; 95% CI: 1.3%, 2.0%). Most OUD was characterized by an active diagnosis code (Table 2).

Table 3 describes the prevalence of ordered or dispensed office-based medication treatment for OUD among the sample of patients who had been diagnosed with an OUD for each of the four groups based on HCV and HIV. Buprenorphine was the most frequently prescribed medication treatment for OUD in all groups. Among patients with OUD who were diagnosed with HCV only and patients who were not diagnosed with HCV or HIV, the prevalence of any medication treatment for OUD was 20.9% (95% CI: 18.6%, 23.3%) and 22.3% (95% CI: 21.5%, 23.0%), respectively. The prevalence of medication treatment for OUD was 16.0% (95% CI: 9.2%, 25.0%) in those with OUD and HIV, and 10.8% (95% CI: 3.0%, 25.4%) in those with OUD and both HIV/HCV.

In models adjusted for age, gender, race/ethnicity, and site, those with HIV had \lower relative odds of ordered or dispensed medication treatment for OUD (adjusted odds ratio [aOR] = 0.43; 95% CI: 0.26, 0.72) compared to those without HIV, whereas the relative odds of receiving medication treatment for OUD were no different among persons with HCV (aOR = 1.03; 95% CI (0.88, 1.21)), compared to those without HCV (Appendix). Post hoc analyses excluding patients with

Table 1 Characteristics of Primary Care Patients in 6 Healthcare Systems by HCV and HIV Status

	HCV alone	HIV alone	Both HCV and HIV	Neither HCV nor HIV
Characteristics	n = 10,042 %	n = 5821	n = 422	n = 1352,319
Age, years				
18–25	1.7	4.0	1.2	10.4
26–35	3.5	13.6	5.5	16.0
36–45	7.4	22.2	18.5	16.1
46–55	27.0	34.3	39.3	18.5
56–65	46.3	19.5	30.1	19.3
66–75	10.9	5.7	5.0	12.0
> 75	3.2	0.9	0.5	7.6
Female	42.8	9.8	11.8	57.1
Race				
Hispanic	8.5	14.5	12.8	9.4
White	64.5	62.6	57.1	68.7
African American	13.2	12.0	20.4	5.8
Asian	7.0	4.7	3.3	10.0
Native American/ Alaska Native	1.0	0.4	0.5	0.4
Hawaiian/Pacific Islander	0.4	0.5	0.2	0.5
Multiracial	2.4	2.2	2.1	1.8
Other	0.8	0.3	0.9	0.8
Unknown	2.3	2.8	2.6	2.6
Insurance type				
Medicare	28.7	20.2	30.5	25.1
Private	57.5	74.5	59.9	68.0
State subsidized	12.1	3.9	8.6	5.0
Uninsured	1.7	1.4	1.0	2.0
Tobacco use disorder	50.9	26.2	48.8	16.0
Alcohol use disorder	19.0	7.9	13.0	3.6
Other substance use disorders	19.6	10.4	26.5	2.3
Cannabis	5.9	3.1	5.5	1.1
Stimulant	7.6	6.6	20.6	0.6
Other substances	14.0	5.3	16.1	1.3
Mental health disorder diagnosis†	49.3	47.1	58.3	33.1
Non-cancer pain diagnosis	88.5	71.0	81.0	75.4
Any opioid dispensing				
0 orders	35.5	52.6	36.3	59.6
1–5 orders	34.6	35.1	39.3	32.1
6–11 orders	8.6	4.9	7.6	3.4
12+ orders	21.3	7.5	16.8	4.8
Emergency department visits*				
0	48.7	63.7	40.1	67.3
1	19.4	18.4	23.7	17.7
2	10.3	7.9	10.7	6.9
3+	21.6	9.9	25.5	8.1
Hospitalizations				
0	72.0	85.0	69.2	86.0
1	13.8	8.7	15.9	8.5
2+	5.8	3.0	7.1	3.0
3+	8.4	3.3	7.8	2.5

*Excludes data from Health Partners
**Excludes buprenorphine
†Includes anxiety, depression, bipolar disorder, and schizophrenia

Table 3 Among Primary Care Patients Diagnosed with OUDs in 6 Healthcare Systems, Percentage Office-Based Medications for OUD by HCV and HIV Status

	HCV only (n = 1194)	HIV only (n = 94)	Both HCV and HIV (n = 37)	Neither HCV nor HIV (n = 12,462)
Medication type*	% (95% CI)			
Buprenorphine	19.1 (16.9, 21.4)	11.7 (6.0, 20.0)	10.8 (3.0, 25.4)	20.3 (19.6, 21.0)
Oral naltrexone	1.8 (1.1, 2.7)	3.2 (0.7, 9.0)	0.0 (0.0, 9.5)	2.5 (2.2, 2.8)
Injectable naltrexone	1.1 (0.6, 1.9)	1.1 (0.0, 5.8)	0.0 (0.0, 9.5)	0.9 (0.8, 1.1)
Any office-based medication treatment for OUD	20.9 (18.6, 23.3)	16 (9.2, 25.0)	10.8 (3.0, 25.4)	22.3 (21.5, 23.0)

*The number of patients on individual medications is not mutually exclusive as patients may have been ordered or dispensed more than one medication during the study period

evidence of chronic prescription opioid use—defined as 6 or more prescriptions for opioids during the study period—who might be misdiagnosed as having OUD on the basis of physical dependence alone revealed a similar pattern with prevalence lowest among persons living with HIV, although the prevalence of medications was higher overall in all groups, ranging from 20.0 to 31.6%.

DISCUSSION

Among patients receiving primary care in six large healthcare systems, those diagnosed with HCV and HIV were more likely to have recognized OUD compared to uninfected patients. The prevalence of recognized OUD was low among patients without HCV and HIV (0.92%); persons with HIV had nearly twice the prevalence (1.6%) and persons with HCV had approximately 12-fold higher prevalence (11.9%). Approximately one-fifth of patients diagnosed with OUD received medication treatment for OUD; HCV was not associated with receipt of medication treatment for OUD, but patients with HIV were less likely to receive medication treatment for OUD compared to those without HIV.

No prior study has assessed the prevalence of recognized OUD and OUD treatment among primary care patients with HCV or HIV to the authors' knowledge. A recent study of data

Table 2 Among Primary Care Patients in 6 Healthcare Systems, Percentage with Diagnosed Opioid Use Disorder (OUD) by HCV and HIV Status

	HCV alone (n = 10,042)	HIV alone (n = 5821)	Both HCV and HIV (n = 422)	Neither HCV nor HIV (n = 1,352,319)
% (95% CI)				
Any OUD	11.9 (11.3, 12.5)	1.6 (1.3, 2.0)	8.8 (6.2, 11.9)	0.92 (0.91, 0.94)
Active OUD*	10.6 (10.0, 11.2)	1.5 (1.2, 1.9)	6.9 (4.7, 9.7)	0.86 (0.84, 0.87)
OUD in remission*	4.2 (3.8, 4.6)	0.36 (0.22, 0.55)	3.8 (2.2, 6.1)	0.23 (0.22, 0.24)

*Active and remission OUDs are not mutually exclusive as individuals could have received more than one diagnosis code during the study period

on 830,825 Veterans Health Administration patients who screened positive for unhealthy alcohol use in an outpatient setting observed that 15.6% of patients with HCV had an OUD diagnosis compared to 3.6% of those without HCV,[22] which is higher than what we observed. A study of 10,652 adults with HIV who received screening for substance use at HIV clinics across the USA found that the prevalence of opioid use disorder was 4%.[23]

The finding of higher prevalence of OUD among persons with HCV and HIV in the present study is not surprising given the overlap in risk factors for these diseases. In the USA, HCV is predominantly spread through injection drug use, and in recent years HCV cases have dramatically risen as a result of the growing opioid epidemic.[24] While sexual transmission of HIV is still the primary mode of transmission, approximately 1 in 10 new HIV diagnoses in the USA are attributed wholly or in part to injection drug use,[25] and outbreaks of HIV related to injecting opioids have recently been reported.[26–28] As such, having HCV or HIV is a marker for patients who are at risk for past or current OUD. Another partial explanation for the higher prevalence of OUD among persons with HCV and HIV is that these diseases can lead to painful complications (such as neuropathy and arthritis), which may have resulted in receipt of opioids for pain and subsequent addiction. Chronic pain and chronic use of opioids are common among persons with HCV[29–31] and HIV.[32–34] As our data demonstrate, there is also a higher prevalence of SUD and mental health disorders among persons with HCV and HIV, which are known risk factors for OUD among persons prescribed opioids.[35] Finally, patients with HIV and HCV may have more frequent interactions with healthcare systems due to their infections, and thus have more opportunities for identifying OUD.

The public health significance of treatment of OUD in patients with HCV or HIV might justify specifically targeting these patients for OUD treatment. Untreated addiction may be associated with injection drug use and other high-risk behaviors that can lead to transmission of those infections.[5, 6] Furthermore, medications for OUD can keep patients with HIV and HCV engaged in care resulting in better disease outcomes.[12–14] However, this study found that primary care patients with HCV and HIV are not more likely than those without those infections to receive medication treatment for OUD, and those with HIV were *less* likely.

Our results which demonstrate low rates of receipt of treatment overall are consistent with other studies. National data suggest that less than a fifth of patients with OUD will receive any form of treatment for OUD.[36] A study using Cigna commercial claims from 2014 to 2015 reported that approximately one-quarter of patients with OUD received pharmacotherapy,[37]; and among veterans who had been diagnosed with OUD in 2017, 35% were on medication treatment for OUD.[38] In a community-based sample of persons who injected opioids of which the majority had HCV, past year treatments with methadone and buprenorphine were reported by 27% and 5% respectively.[39] A recent study of national

commercial insurance claims data found that while the overall number of patients diagnosed with OUD increased from 2010 to 2014, the proportion of person-time covered by medications decreased from 25 to 16%.[40]

It is somewhat surprising that patients with OUD who had HIV in this study were less likely to be treated with medication treatment for OUD compared to uninfected patients. The results of the present study are consistent with those of a recently published study of Veterans Affairs patients which demonstrated that persons living with HIV were less likely to receive timely opioid agonist therapy compared to those who did not have HIV.[41] Prior research has demonstrated numerous barriers to implementing buprenorphine treatment in HIV clinics, including workforce and training issues,[42] and an absence of discussions about substance use between patients and HIV providers.[43] It is a limitation of the current study that we were unable to capture OUD treatment with methadone that occurs in OTPs. It is possible persons living with HIV are more likely to be treated with methadone, although data on this are conflicting.[44, 45] Providers might have heightened concerns about polypharmacy, which is a risk in this population,[46] or for hepatotoxicity despite demonstrated safety of medications used to treat OUD.[47, 48] Alternatively, there might be fewer HIV providers who are waivered and prescribe buprenorphine. Integrated models of care have been shown to close gaps in both the OUD and HIV care continuum,[49–51] and such programs only existed within some clinics within these healthcare systems. Further work is needed to explore the barriers to OUD care among persons living with HIV.

There are limitations to the current study. Our results were based on diagnosis codes—we are unable to say what the true prevalence of active OUD is among these patient populations. Studies relying on EHR and claims data will likely underestimate the true prevalence of OUD in primary care as undercoding of behavioral health diagnoses is common.[52–55] However, it is also possible that misclassification could occur in the opposite direction with accidental coding of OUD among patients with physical dependence of opioids due to long-term use. The higher prevalence of OUD in patients with HCV might reflect ascertainment bias. However, it is appropriate for providers to assess for OUD when caring for patients with known HCV and HIV given that injection drug use is an underlying risk factor for both diseases. Our definition of having HCV and HIV is based on diagnosis codes and similarly subject to misclassification: there were undoubtedly patients with those infections who had not been diagnosed, particularly for HCV which is an asymptomatic chronic infection. A study using nationally representative data from 2001 to 2008 found that approximately half of individuals with HCV were not aware of their infection,[56] although more individuals may have been aware at the time of this study given the increased attention to HCV screening. The study did not capture data on medication treatment for OUD obtained outside the five health systems that were also insurers if a claim was not submitted (e.g., self-pay). Care outside the one

community health systems was also not captured regardless of insurance. We are unable to say what fraction of these patients with OUD were receiving methadone and whether that differed by HCV and HIV status. However, the previously mentioned study of commercial claims data found that adding in methadone data only increased the absolute percentage receiving pharmacotherapy for OUD by a few percentage points.[37] The sample of patients with HIV was relatively small, leading to relatively wide confidence intervals for estimates of OUD treatment. Persons living with HIV who received their primary care exclusively within specialty clinics may not be captured in the sample; therefore, results may not be fully representative. Also, this study was conducted among a largely privately insured population limiting generalizability to other populations or settings. Furthermore, whether co-pays or requirements for prior authorization were a barrier to access to OUD treatment is not known. Finally, as this was a cross-sectional study, we cannot infer causality for associations observed between HCV and HIV diagnoses and use of office-based medication treatment for OUD. The timing of these diagnoses relative to diagnoses of OUD was not assessed, as well as continuity of care, both of which could impact medication receipt.

In summary, among patients receiving primary care in 6 large healthcare systems, those who were diagnosed with HCV and HIV were more likely to have documented OUD compared to uninfected patients, with the highest prevalence (11.9%) occurring among patients with HCV. Receipt of medication treatment for OUD was uniformly low for all patients, including those with HCV and HIV, with only up to one-fifth of patients with OUD receiving buprenorphine or naltrexone. The finding that patients with HIV who had OUD were less likely to receive medication treatment for OUD compared to uninfected patients was unexpected and merits further investigation. These results highlight the need for improved access to medications for OUD, particularly from providers caring for patients living with HCV/HIV. Providing effective treatment for OUD is critical for maximizing the health of persons living with HIV and HCV, as well as preventing transmission of these diseases.

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Compliance with Ethical Standards:

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