Association Between Diagnoses of Chronic Noncancer Pain, Substance Use Disorder, and HIV-Related Outcomes in People Living With HIV

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INTRODUCTION

Chronic pain is a common comorbidity in people living with HIV (PLWH). Pain conditions, neuropathic and musculoskeletal pain principally, can affect individuals at any stage of the HIV illness.1 The improvement of combination antiretroviral therapy (ART) has decreased the side effects and notably neuropathic pain.2 However, pain symptoms are still more prevalent in PLWH than general population.3 Psychiatric disorders are also reported more often by PLWH than noninfected individuals.4,5 Recent literature has recognized that chronic pain has a negative impact on HIV care, with a decrease of ART adherence,6 elevated depressive symptoms also correlated with a decrease of ART adherence,7 and an increase of substance use.8 Despite these negative correlations, chronic pain is still undertreated in PLWH probably because of the complexity of ART regimen and potential interactions with pain medication, the higher risks of side effects, and the psychiatric and substance use comorbidities.9,10

Although clinical guidelines for the treatment of chronic pain11 stated that opioid should not be a first-line treatment for chronic pain, opioids have been often prescribed.12,13 In the context of widely diverted and improperly used opioids leading to the current national epidemic of opioid overdoses and opiate use disorders in the United States, prescribing practices for opioids has been questioned. A history of substance use and depression is common among HIV-positive individuals and has been identified as risk factors for opioid medication diversion14 and opiate use disorder.15 Opioid medication has been associated with high risk of injection drug use,16 poorer ART adherence,17 and increased sex risk behavior,17 representing a potential risk of the HIV epidemic. However, little is known on the existence of the opioid prescriptions in clinical settings. Similarly, the prescription patterns of nonopioid medications for pain management have been rarely reported. Furthermore, little is...
known on the impact of pain management and PLWH comorbidities on HIV care in clinical settings.

Routinely collected electronic health records offered the opportunity to examine integrated and real-time health care use and practices in large-scale and diverse samples. Routinely collected electronic health records offered the opportunity to examine integrated and real-time health care use and practices in large-scale and diverse samples. Routinely collected electronic health records offered the opportunity to examine integrated and real-time health care use and practices in large-scale and diverse samples.

The objective of this article was to examine chronic noncancer pain, mental health, and substance use disorder (SUD) diagnoses and to evaluate their associations with HIV-related outcomes in PLWH in HIV care using medical health records.

METHODS

Study Sample

This study, approved by the University of Pennsylvania Institutional Review Board, used deidentified health record database that aggregated electronic medical records of any individual who has ever received care in any of the University of Pennsylvania health system facilities.

In the database, we identified PLWH aged 18 years and older who have received HIV care at one of the outpatient HIV clinics within the University of Pennsylvania health system between 2007 and 2017. Although the database gathered records since 1995, we did not select individuals who have received HIV care before 2007 to limit the bias of the type of care for at least 18 months to only count individuals who have received ART long enough to potentially achieve suppressed viral load (n = 949).

All data have been analyzed using JMP Pro Version 13.2 (SAS Institute, Inc., Cary, NC).

RESULTS

Sample Characteristics

The sample included 3528 individuals, mainly male (73.3%), African American (64.1%), and white (27.6%). The individuals were 41.9 (SD = 13.1) years old on average at their first HIV care encounter visit within the University of Pennsylvania health system. They had an average clinical record history of 1788 days (SD = 1,120, median = 1661, q1 = 682, q3 = 2681) at the HIV clinic.

More than one-third exhibited at least 1 psychiatric disorder (38.1%), mostly mood disorder (29.0%) and SUD (16.8%) (Fig. 1). The type of SUD was unspecified for 23% of the individuals; the others met the following SUDs: cocaine (17.6%), alcohol (17.1%), opiate (14.6%), cannabis (6.6%), amphetamines (3.9%), and sedatives (1.2%).

More than one-third exhibited a chronic noncancer pain diagnosis (35.7%), mostly musculoskeletal chronic pain (33.1%) (Fig. 1). Most of the individuals (84.3%) received a diagnosis of chronic pain after HIV diagnosis. The mean length of time from the first visit at HIV clinic and the pain diagnosis was 951.1 days (SD = 902.3, median = 693.5, q1 = 186.8, q3 = 1519.3). On average, the individuals had 11.2 visits (SD = 17.9, median = 5.0, q1 = 2.0, q3 = 13.0) for pain management.

More than half (57.1%) of the individuals with a diagnosis of chronic pain also met a diagnosis of psychiatric disorder (including SUD). The diagnosis of chronic pain was
made before a mental health disorder (excluding SUD) diagnosis for 30.0%, within the same year for 31.3% and after for 38.7% of the individuals. The diagnosis of chronic pain was made before an SUD diagnosis for 58.7%, within the same year for 23.9% and after for 17.4% of the individuals.

Comorbid diagnoses of SUD and/or mental health disorder to the chronic pain diagnosis were significantly associated with the number of visits for pain management (\(P_{\text{0.0001}}\)), with 10.4 visits (SD = 16.8) for individuals who met chronic pain diagnosis only, 13.4 visits (SD = 21.4) for individuals who met chronic pain diagnosis and SUD diagnosis, 17.7 visits (SD = 21.8) for individuals who met chronic pain diagnosis and mental health disorder diagnosis, and 29.2 visits (SD = 26.5) for individuals who met chronic pain diagnosis and both substance use and mental health disorder diagnoses.

**Treatment of Chronic Noncancer Pain Over the Period 2007–2017**

The majority (93.1%) of the individuals who endorsed a chronic pain diagnosis received more than 1 prescription or a prescription covering 90 days or more of pharmacological treatment for pain management.

Figure 2 displays the type of pharmacological treatment prescribed per year of the chronic pain diagnosis. Opioids have been commonly prescribed (41.4%), followed by NSAIDs (36.1%), anti-anxiety agents (33.2%), gabapentin (13.0%), muscle relaxant (12.5%), antidepressants (11.5%), and antipsychotics (5.4%). There was no change over the past 10 years for opioids (\(P = 0.15\)), gabapentin (\(P = 0.26\)), antidepressants (\(P = 0.41\)), anti-anxiety agents (\(P = 0.54\)), and antipsychotics (\(P = 0.08\)). There was a significant change in NSAIDs (\(P = 0.04\)) and muscle relaxants (\(P < 0.001\)) which became less prescribed after 2009.

**Comparison According to Chronic Pain and SUD Diagnoses**

Table 1 displays the comparison between the 4 groups, i.e., no chronic pain and no SUD (n = 2015), no chronic pain and SUD (n = 255), chronic pain and no SUD (n = 919), and chronic pain and SUD (n = 339).

Although the sample consisted in a majority of men, there were more women in the groups who met chronic pain diagnosis (\(P_{\text{0.0001}}\)). Exhibiting 1 diagnosis of either pain either SUD increased the likelihood to endorse at least 1 psychiatric disorder, while exhibiting a dual diagnosis of pain and SUD increased this likelihood even more for mood (\(P < 0.0001\)), suicide (\(P < 0.0001\)), anxiety (\(P < 0.0001\)), and post-traumatic stress disorder (\(P < 0.0001\)). Opioid prescriptions for pain management have been highly common even in the group that did not meet chronic pain diagnosis, questioning either the need for opioid prescription or the accuracy of the diagnosis. Individuals with a dual diagnosis of chronic pain and SUD received significantly more often an opioid prescription for pain management than individuals who endorsed chronic pain only (87.6% vs. 67.6, \(P < 0.0001\)). Similarly, the dual diagnosis group was more likely to receive NSAID (\(P < 0.0001\)), muscle relaxant (\(P < 0.0001\)), antidepressant (\(P < 0.0001\)), and anti-anxiety agents (\(P < 0.0001\)) for pain management.

**Factors Associated With a Diagnosis of Chronic Noncancer Pain**

The logistic model showed that individuals with a diagnosis of chronic pain were more likely women [odds ratio (OR) = 1.75, 95% confidence interval (CI): 1.18 to 2.59], met at least 1 SUD diagnosis (OR = 1.72, 95% CI: 1.14 to 2.61), met mood disorder diagnosis (OR = 2.03, 95% CI: 1.42 to 2.89), and met anxiety disorder diagnosis (OR = 3.61, 95% CI: 1.34 to 9.71).

**HIV-Related Outcomes**

Individuals who endorsed a chronic pain diagnosis or an SUD diagnosis were significantly less adherent to their HIV care (\(P = 0.004\)).

Among individuals who were enrolled in HIV care and received ART for at least 18 months (n = 949), those with an
unsuppressed viral load were more likely African American (OR = 2.75, 95% CI: 1.73 to 4.60) or another race (OR = 2.50, 95% CI: 1.07 to 5.58) than white and met SUD diagnosis (OR = 1.70, 95% CI: 1.18 to 2.45). A diagnosis of chronic pain was not associated with viral load suppression.

**DISCUSSION**

This study provides a picture of the prevalence and the management of chronic noncancer pain occurring in HIV clinic settings using 10-year PLWH health records of a large health care database. Our findings showed that more than one-third of the PLWH in HIV care met chronic noncancer pain diagnosis, in the 24%–48% range previously reported in the antiretroviral-era literature.\(^7\)\(^{10}\)\(^{19}\)\(^{21}\) Psychiatric comorbidities were prevalent (38%), and 20% met diagnoses for both psychiatric disorder and chronic pain, also consistent with previous literature that found associations between chronic pain and depression,\(^9\)\(^{20}\)\(^{22}\) and history of SUD.\(^9\)\(^{22}\)\(^{24}\) in PLWH.

More than half of the chronic pain diagnoses have been recorded before SUD diagnoses. Previous studies have reported that most opiate use disorder individuals developed the disorder after chronic pain.\(^22\) Almost all the PLWH who have been identified as having chronic pain received a pharmacological treatment for the management of the chronic pain, inconsistent with a literature review that concluded that chronic pain is untreated in PLWH.\(^6\)\(^{24}\) Although short-term course of short-acting and low-dose opioids could be an efficient medication for acute pain, individuals with an history of SUD represent a more vulnerable population to develop SUD.\(^{25}\)\(^{26}\) The most prescribed medications for pain management were opiates, without any change over the 10-year study period, although the guidelines for the management of chronic pain in PLWH highlighted the interaction between opioid medication and ART and stated that opioids should not be the first-line treatment for pain management.\(^11\) These findings are consistent with previous studies showing that opioids are commonly prescribed in PLWH.\(^3\)\(^{13}\)\(^{16}\)\(^{27}\)\(^{28}\) Because of the intertwining opioid prescriptions and opioid epidemic in the United States, states have responded to this crisis through several interventions including new regulations and legislations. Although interventions occurred in Pennsylvania, recent available data showed an increase of opioid prescriptions between 2006 and 2017.\(^{29}\) However, parallel to the opioid prescriptions, nonopioid prescriptions were also common. PLWH with a dual diagnosis of chronic pain and SUD received more often both opioid and nonopioid prescriptions for pain management. Because primary care providers deliver the majority of pain care and they are not typically trained in pain medicine\(^25\) might have explained the high rates of pharmacological medications for pain management.

Interestingly, approximately 25% of the sample received several prescriptions for pain management, although they did not have any recorded chronic pain diagnosis. Other studies have also reported prescription of antidepressants and opiates for pain management in PLWH even without a diagnosis of chronic pain.\(^7\) This could be inherent to the use of electronic medical records. Although the use of health
records provides the most comprehensive individual health histories, but the methodological rigor is weaker than data collected as part of a research study. The data captured in electronic health records is dependent on the physician documentation, and also, medical insurance requirements thus introduced uncontrolled biases. Therefore, the accuracy of the diagnoses is uncertain, and some PWLH may not have been identified as meeting SUDs and chronic pain diagnosis. However, with our query similar to the one used in other studies, we could consider that the mislabeled of chronic pain was very limited but SUDs might have been underreported, as previously stated in other studies. Moreover, when reported, most of the SUD diagnosis has been nonspecified prevented us to explore association between opioid prescription and development of opiate use disorder. Also, as record-based research, we could not have access to PWLH diagnoses outside the university of Pennsylvania health system. Because the University of Pennsylvania health system predominantly serves individuals without private insurance, with Medicare, Medicaid, or no payer as payer sources, the generalizability of the findings could be potentially limited.

Despite these limitations, our study showed that chronic pain diagnosis was associated with SUDs and psychiatric disorders and that SUDs had an impact on the management of chronic pain, leading to an increase of health care service utilization and more visits for pain management, as reported in non-HIV population. SUD has also a negative impact on HIV care and has been found associated with unsuppressed viral load. However, untreated pain increased the incidence of nonmedical use of prescription opioids in HIV non-HIV individuals and has a negative impact on antiretroviral treatment adherence and viral load suppression in PWLH, as well as increased the risk to develop SUDs, including alcohol use disorder. The high rate of chronic pain and co-occurring substance use and psychiatric comorbidities in PLWH in HIV care underscores the need to develop more coordinated care plans integrating the management of pain and psychiatric disorders including SUDs in HIV clinic. The management of pain should align better with the pain management guidelines for PLWH and should minimize the use of opioid prescription, the benefits of which have been questionable in the

### TABLE 1. Characteristic of the Individuals According to the Diagnoses of Noncancer Chronic Pain (Pain) and SUD (n = 3528)

| Characteristic                      | No Pain, No SUD | No Pain, SUD | Pain, No SUD | Pain, SUD     | Test, P  |
|-------------------------------------|-----------------|--------------|--------------|---------------|----------|
| n (% of the sample)                 | 2015 (57.1)     | 255 (7.3)    | 919 (26.0)   | 339 (9.6)     |          |
| Length of observation—days mean (SD)| 1741 (1128)b    | 1385 (1104)c | 1537 (1112)c | 2012 (1150)p  | F(3,3524) = 22.6, P < 0.0001 |
| Sex—men n (%)                       | 1533 (76.1)b    | 203 (79.6)b  | 635 (69.1)a  | 216 (63.7)a   | χ² = 37.4, P < 0.0001 |
| Ethnicity—n (%)                     |                 |              |              |               |          |
| White                               | 564 (28.0)a     | 72 (28.2)a   | 270 (29.4)a  | 66 (19.5)b    | χ² = 35.7, P < 0.0001 |
| African American                    | 1254 (62.2)a    | 169 (66.3)a  | 580 (63.1)a  | 260 (76.7)b   |          |
| Other                               | 197 (9.8)a      | 14 (5.5)a    | 69 (7.5)a    | 13 (3.8)b     |          |
| Psychiatric diagnoses other than SUD—n (%) |            |              |              |               |          |
| At least 1 psychiatric disorder    | 371 (18.4)a     | 128 (50.2)c  | 379 (41.2)b  | 221 (65.4)d   | χ² = 422.4, P < 0.0001 |
| Mood disorder                       | 343 (17.0)a     | 117 (45.9)b  | 348 (37.9)b  | 215 (63.4)c   | χ² = 405.9, P < 0.0001 |
| Suicide attempts or ideation        | 23 (1.1)a       | 31 (12.2)b   | 36 (3.9)b    | 34 (10.3)b    | χ² = 132.5, P < 0.0001 |
| Anxiety disorder                    | 20 (1.0)a       | 18 (7.1)b,c  | 51 (5.6)b    | 36 (10.6)b    | χ² = 108.1, P < 0.0001 |
| PTSD                                | 16 (0.8)a       | 8 (3.1)b,c   | 24 (2.6)b    | 20 (5.9)b     | χ² = 46.2 P < 0.0001 |
| Medications for pain management—n (%) |            |              |              |               |          |
| Prescription opioids                | 500 (24.8)a     | 123 (48.2)b  | 621 (67.6)d  | 297 (87.6)d   | χ² = 772.9, P < 0.0001 |
| NSAIDs                              | 336 (16.7)a     | 104 (40.8)c  | 571 (62.1)f  | 264 (77.9)f   | χ² = 858.1, P < 0.0001 |
| Muscle relaxant                     | 59 (2.9)a       | 14 (5.5)b    | 230 (25.0)b  | 139 (41.0)c   | χ² = 562.8, P < 0.0001 |
| Gabapentin                          | 265 (13.2)      | 43 (16.9)    | 117 (12.7)   | 33 (9.7)      | χ² = 6.7, P = 0.08 |
| Antidepressant                      | 178 (8.8)a      | 30 (11.8)b   | 143 (15.6)b  | 54 (15.9)b    | χ² = 35.6, P < 0.0001 |
| Antianxiety agents                  | 222 (11.0)a     | 64 (25.1)b   | 254 (27.6)b  | 164 (48.4)f   | χ² = 310.4, P < 0.0001 |
| Antipsychotic                       | 88 (7.8)b       | 20 (7.8)b    | 58 (6.3)b    | 26 (7.7)b     | χ² = 12.0, P = 0.007 |
| HIV care (n = 949)*                 |                |              |              |               |          |
| Clinic visits adherence—yes n (%)   | 240 (72.3)a     | 37 (59.7)b   | 189 (60.6)b  | 80 (58.8)b    | χ² = 13.4, P = 0.004 |
| Suppressed viral load—yes n (%)     | 293 (77.7)a     | 48 (70.6)c   | 270 (76.5)a  | 100 (66.2)c   | χ² = 8.9, P = 0.03 |

The Pearson χ² test (χ²) for categorical variables and ANOVA for continuous variables have been performed to evaluate the difference between groups. Superscript labels with different letters reflect significant group differences.

Prescription opioids included medications that content opiates, morphine, codeine, and buprenorphine excluding methadone, buprenorphine, and buprenorphine/naloxone prescribed for opiate use disorder purposes. NSAID included aspirin, diclofenac, ibuprofen, fenoprofen, flurbiprofen, ketoprofen, meloxicam, and naproxen. Muscle relaxant included diazepam, carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol, orphenadrine, and tizanidine. Antidepressant included SNRI (venlafaxine, duloxetine, and milnacipran), SSRI (paroxetine, fluoxetine, and sertraline), and tricyclic (amitriptyline, imipramine, clomipramine, doxepin, nortriptyline, and desipramine). Antianxiety agents included clonazepam, lorazepam, and alprazolam. Antipsychotic agents included olanzapine and quetiapine.

Data on suppressed viral load on individuals who have been at least for 18 months in care for their HIV and receiving antiretroviral therapy (n = 949).

ANOVA, analysis of variance; PTSD, Post-Traumatic Stress Disorder.
management of chronic pain, and better integrate alternative treatments including nonopioid analgesics and non-pharmacologic techniques.

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