Published in final edited form as:

J Addict Med. 2016 ; 10(6): 418–428. doi:10.1097/ADM.0000000000000255.

The Effect of Substance Use Disorders on the Association Between Guideline-Concordant Long-Term Opioid Therapy and All-Cause Mortality

Julie R. Gaither, PhD, MPH, RN^{1,2,3,4}, Joseph L. Goulet, PhD^{2,5}, William C. Becker, MD^{2,6}, Stephen Crystal, PhD⁷, E. Jennifer Edelman, MD, MHS^{4,6}, Kirsha Gordon, MPhil, MS², Robert D. Kerns, PhD^{2,5}, David Rimland, MD^{8,9}, Melissa Skanderson, MSW¹⁰, Amy C. Justice, MD, PhD^{1,2,3,6}, and David A. Fiellin, MD^{1,4,6}

¹Yale School of Public Health, Yale University, New Haven, CT

²VA Connecticut Healthcare System, West Haven, CT

³Yale Center for Medical Informatics, Yale School of Medicine, Yale University, New Haven, CT

⁴Center for Interdisciplinary Research on AIDS, Yale School of Public Health, Yale University, New Haven, CT

⁵Department of Psychiatry, Yale School of Medicine, Yale University, New Haven, CT

⁶Department of Internal Medicine, Yale School of Medicine, Yale University, New Haven, CT

⁷Institute for Health, Health Care Policy, and Aging Research, Rutgers University, New Brunswick, NJ

⁸Division of Infectious Diseases, Emory University School of Medicine, Atlanta, GA

⁹Atlanta VA Medical Center, Decatur, GA

¹⁰VA Pittsburgh Healthcare System, Pittsburgh, PA

Abstract

Objective—Patients with substance use disorders (SUDs) prescribed long-term opioid therapy (LtOT) are at risk for overdose and mortality. Prior research has shown that receipt of LtOT in accordance with clinical practice guidelines has the potential to mitigate these outcomes. Our objective was to determine whether the presence of a SUD modifies the association between guideline-concordant care and 1-year all-cause mortality among patients receiving LtOT for pain.

Corresponding Author: Julie R. Gaither, PhD, MPH, RN, 950 Campbell Avenue, West Haven, Connecticut 06516, Tel: 203-823-8484, Fax: 203-937-4926, julie.gaither@yale.edu.

Disclosure

The content of this paper is solely the responsibility of the authors and does not necessarily reflect the official views of the National Institutes of Health or the Department of Veterans Affairs.

Conflicts of Interest

Dr. Fiellin received an honorarium from Pinney Associates to serve on an external advisory board to monitor the diversion and abuse of buprenorphine. All other authors report no conflicts of interest.

Funding Disclosure: Research reported in this paper was supported by grants from the National Institutes of Health, Agency for Healthcare Quality and Research, and the Department of Veterans Affairs. These organizations had no role in the design, conduct, or reporting of this study.

Methods—Among HIV+ and HIV- patients initiating LtOT (≥ 90d opioids) between 2000 and 2010 as part of the Veterans Aging Cohort Study, we used time-updated Cox regression and propensity-score matching to examine—stratified by SUD status—the association between 1-year all-cause mortality and 3 quality indicators derived from national opioid prescribing guidelines. Specifically, we examined whether patients received: psychotherapeutic co-interventions (≥ 2 outpatient mental health visits), benzodiazepine co-prescriptions (≥ 7d), and SUD treatment (≥ 1 inpatient day or outpatient visit). These indicators were among those found in a previous study to have a strong association with mortality.

Results—Among 17,044 patients initiating LtOT, there were 1,048 (6.1%) deaths during one year of follow-up. Receipt of psychotherapeutic co-interventions was associated with lower mortality in the sample overall and was more protective in patients with SUDs (adjusted hazard ratio [AHR] 0.43, 95% confidence interval [CI] 0.33–0.56 vs. AHR 0.65, 95% CI 0.53–0.81; *P* for interaction = .002). Benzodiazepine co-prescribing was associated with higher mortality in the sample overall (AHR 1.41; 95% CI 1.22–1.63), but we found no interaction by SUD status (*P* for interaction = .11). Among patients with SUDs, receipt of SUD treatment was associated with lower mortality (AHR 0.43; 95% CI 0.33–0.57).

Conclusions—For clinicians prescribing LtOT to patients with untreated SUDs, engaging patients with psychotherapeutic and SUD treatment services may reduce mortality. Clinicians should also avoid, when possible, prescribing opioids with benzodiazepines.

Keywords

Opioid analgesics; practice guideline; quality of healthcare; mortality; substance use disorders

Introduction

Over the past two decades, patients and clinicians have increasingly relied on opioid analgesics to manage chronic non-cancer pain—millions of Americans now receive opioids long term, and are exposed to opioids for months and, frequently, years (Caudill-Slosberg et al., 2004; Korff et al., 2008; Sullivan et al., 2008; Braden et al., 2009; Martin et al., 2011; Volkow et al., 2011; Önen et al., 2012; Edelman et al., 2013; Gaither et al., 2014; Gaither et al., 2016). Although there are anecdotal reports of patients benefitting from extended opioid use (≥ 90 days), the safety and efficacy of long-term opioid therapy (LtOT) is not supported by strong scientific evidence (Korff et al., 2008; Rosenblum et al., 2008; Chou, Ballantyne, et al., 2009; Manchikanti et al., 2011; Von Korff et al., 2011; Chou et al., 2015).

Furthermore, trends in opioid prescribing have coincided with an unprecedented rise in opioid addiction, overdose, and diversion (Centers for Disease Control and Prevention, 2007; Edlund et al., 2007; Hall et al., 2008; Manchikanti & Singh, 2008; Dunn et al., 2010; Bohnert et al., 2011; Centers for Disease Control and Prevention, 2011; Hansen et al., 2011; Office of National Drug Control Policy, 2011; Seal et al., 2012; Centers for Disease & Prevention, 2013; Veldhuizen & Callaghan, 2014; Chou et al., 2015; Dart et al., 2015).

Despite these risks, research (Krebs et al., 2011; Morasco et al., 2011; Starrels et al., 2011; Midboe et al., 2012; Rasu et al., 2013; Gaither et al., 2014; Krebs et al., 2014) suggests that patients prescribed LtOT rarely receive the standard of care outlined in opioid clinical

practice guidelines, which encourage diligent and frequent monitoring in carefully selected patients (American Pain Society/American Academy of Pain Medicine, 1997; US Department of Veterans Affairs/Department of Defense, 2003; Chou, Fanciullo, et al., 2009; US Department of Veterans Affairs/Department of Defense, 2010). For patients who meet the criteria for a current substance use disorder, an even higher standard of care is recommended due to the elevated risk in this population for opioid-related harms, including addiction and overdose (Edlund et al., 2007; Becker et al., 2008; Seal et al., 2012; Morasco, Turk, et al., 2013). Specifically, the guidelines from the Department of Veterans Affairs (VA) state that for patients with a substance use disorder that is not in remission (> 12 months), LtOT should only be initiated if the patient receives concurrent substance use disorder treatment and is stringently monitored for the duration of LtOT (US Department of Veterans Affairs/Department of Defense, 2010). To date, there is little evidence to suggest that these high-risk patients receive this level of care (Braden et al., 2009; Edlund et al., 2010; Morasco et al., 2011; Seal et al., 2012; Edelman et al., 2013; Gaither et al., 2014; Gaither et al., 2016).

In a previous study, we sought to better understand what role guideline-concordant LtOT plays in protecting patients from opioid-related harms (Gaither et al., 2016). Because of the varied risks associated with opioid exposure (Dunn et al., 2010; Saunders et al., 2010; Solomon et al., 2010; Roy et al., 2011; Li et al., 2013; Veldhuizen & Callaghan, 2014) and the inherent challenges in accurately determining underlying cause of death, particularly for overdose deaths (Myers & Farquhar, 1998; Betz et al., 2008; Goldberger et al., 2013; Warner et al., 2013; Huguet et al., 2014; Slavova et al., 2015), we chose as our primary outcome all-cause mortality. We found that patients who received psychotherapeutic co-interventions (i.e., mental health services) had lower mortality, while those receiving benzodiazepine concurrent with opioids had higher mortality (Gaither et al., 2016). Notably, we found that patients with an untreated substance use disorder had a mortality rate more than twice that of those who were engaged in treatment for this disorder (Gaither et al., 2016). It was this finding that prompted the current study, in which we sought to better understand how the presence of a substance use disorder moderated the outcome of all-cause mortality for the remaining indicators (i.e., psychotherapeutic co-interventions and benzodiazepine co-prescribing).

To our knowledge no large national study has yet compared mortality outcomes related to receipt of guideline-concordant LtOT according to substance use disorder status. Additionally, because of the potential clinical implications of our findings related to substance use disorder treatment, we aimed with this study to further examine this outcome using more rigorous statistical models—models better able to control for confounding by indication (Joffe & Rosenbaum, 1999; Pasta, 2001; Schneeweiss et al., 2001; Allison & SAS Institute., 2012).

We examined these aims using the Veterans Aging Cohort Study (VACS): a well-established, validated sample of HIV+ veterans demographically matched to HIV- veterans engaged in care (Fultz et al., 2006; Justice, Dombrowski, et al., 2006; Justice, Erdos, et al., 2006; Lo Re et al., 2011; Justice et al., 2013). This is a robust sample for exploring mortality outcomes associated with LtOT—the mortality rate in both HIV+ patients and veterans is high. In

addition, opioid receipt (including for extended periods and at high doses), chronic pain, and substance use disorders are prevalent in these two patient groups (Seal et al., 2012; Edelman et al., 2013). Patients were followed from the initiation of LtOT to assess for receipt of care during a time when clinicians may be more likely to adhere to clinical practice guidelines. It is also a critical time when the risks for adverse events are thought to be highest (Chou, Fanciullo, et al., 2009).

Given that approximately one in ten patients in primary care and one in three patients in specialty care prescribed LtOT have a current substance use disorder, it is imperative that we gain a better understanding of the benefits of guideline-concordant care in patients at highest risk for opioid-related harms (Morasco et al., 2011; Edelman et al., 2013; Gaither et al., 2014).

Methods

Study Overview

We examined the association between receipt of guideline-concordant LtOT and 1-year all-cause mortality in outpatients initiating LtOT through the VA between 2000 and 2010. To address concerns of confounding by indication, we used a propensity-score design (Pasta, 2001).

Data Source

VACS is a prospective cohort of HIV+ patients matched (1:2) by age, sex, race, and VA site-of-care to HIV- controls (Fultz et al., 2006; Justice, Dombrowski, et al., 2006; Justice, Erdos, et al., 2006). From patients participating in the VACS, we abstracted administrative, clinical, laboratory, and pharmacy data from the VA electronic medical record system.

VACS is HIPAA compliant and is approved by the Review Boards for the VA Connecticut Healthcare System and the Yale School of Medicine. The requirement for informed consent was waived.

Study Population

From the Pharmacy Benefits Management database, we captured outpatient prescriptions for oral and transdermal opioids filled/refilled between fiscal years 2000 (i.e., October 1, 1999) and 2010 (i.e., September 30, 2010). As described in prior research (Edelman et al., 2013; Gaither et al., 2014; Gaither et al., 2016), when considering receipt of LtOT for chronic pain, we included data for methadone prescribed for pain but excluded methadone and buprenorphine prescribed for opioid use disorder. Consistent with previous research, we defined LtOT as receipt of 90 or more days of opioids (Edlund et al., 2007; Korff et al., 2008; Edelman et al., 2013; Gaither et al., 2014; Gaither et al., 2016). Details related to patient inclusion and exclusion criteria are provided in Figure 1. The final analytic sample consisted of 17,044 patients.

A patient was considered to have a substance use disorder if they received a ICD-9-CM (*International Classification of Disease, 9th Revision, Clinical Modification*) code for a alcohol or drug use disorder, inpatient or outpatient substance use disorder treatment (i.e., 1

inpatient bed day or 1 outpatient substance use disorder-specialty clinic visit), or a score of 4 on the AUDIT-C (*Alcohol Use Disorders Identification Test-Consumption*) (Bush et al., 1998).

Indicators of Guideline-Concordant Care

Details on the quality metrics (i.e., indicators) used in this study have been described previously (Gaither et al., 2014; Gaither et al., 2016). In brief, the predictors in this study were indicators of guideline concordance derived from national clinical practice guidelines for the management of LtOT related to receipt of evidenced-based psychotherapeutic co-interventions (i.e., 2 or more outpatient mental health visits) and avoidance of benzodiazepine co-prescriptions (American Pain Society/American Academy of Pain Medicine, 1997; US Department of Veterans Affairs/Department of Defense, 2003; Chou, Fanciullo, et al., 2009; US Department of Veterans Affairs/Department of Defense, 2010). In addition, among patients meeting the criteria for a current substance use disorder (see *Study Population*), we examined receipt of inpatient or outpatient substance use disorder treatment. Unless otherwise noted, we use the term substance use disorder to refer to a *current* substance use disorder diagnosis, as opposed to lifetime history. In Appendix A, we provide the operational definitions for each indicator.

In a previous study using this same sample, we examined the association between all-cause mortality and six indicators of guideline-concordant LtOT (Gaither et al., 2016). In designing the current study, from among these indicators, we chose those showing the strongest associations with mortality as well as those thought to be most relevant to patients with substance use disorders. We considered a patient to have received guideline-concordant care for a particular LtOT indicator if it was received within the first 180 days of initiating LtOT—it is the initial months of opioid therapy that the risks for serious adverse events are thought to be elevated (Chou, Fanciullo, et al., 2009). The surveillance period for guideline concordance began and ended at the same time point for all patients (i.e., LtOT start date through 180 days of treatment). For patients not completing 180 days of LtOT, the surveillance ended when the opioid exposure ended (through death or censoring), which was determined by either the opioid prescription stop date or, when applicable, date of death. Differences in the length of eligibility for receipt of indicators (LtOT duration) were accounted for with time-dependent methods in the analyses (see *Statistical Analyses*) (Suissa, 2007; Allison & SAS Institute., 2010).

Primary Outcome

The primary outcome of interest was 1-year all-cause mortality, which we examined in the sample in its entirety and stratified by substance use disorder status. Through the Beneficiary Identification Records Locator Subsystem Death File (BIRLS), we identified all patient deaths occurring in the 1-year period that began once patients completed the first 90 days of LtOT—BIRLS data have been validated as accurate, complete, and comparable to that of the National Death Index (Fisher et al., 1995; Cowper et al., 2002). The surveillance period of 1 year was chosen because we were interested in deaths occurring in temporal proximity to receipt of guideline-concordant care, which we assessed for a maximum of 180 days (see *Indicators of Guideline-Concordant Care*).

Covariates

To characterize the sample at baseline, we used data from the VA National Patient Care Database, pharmacy data, laboratory results (when applicable), and *ICD-9-CM* codes. To describe and adjust for overall severity of illness, we used the VACS Index, a validated prognostic measure predictive of morbidity and mortality in HIV+ and HIV- patients; higher scores are indicative of greater all-cause mortality risk (Justice et al., 2010; Justice et al., 2013; Tate et al., 2013; Bebu et al., 2014; Brown et al., 2014). The VACS Index is calculated by using age, HIV-1 RNA viral load, CD4 count, hemoglobin, FIB-4, estimated glomerular filtration rate, and hepatitis C status; for HIV- patients, the assumption is made that they have a CD4 count > 500 cells/ μ L and viral load < 20 copies/ml (Akgun et al., 2013). Finally, we used VA clinic and bed section codes to identify treatment variables.

Variables reflecting *current* mental health, pain, and substance use disorder status were based on diagnoses received between LtOT initiation and 180 days of follow-up (or LtOT stop date, when applicable); *lifetime prevalence* (i.e., history) was based on diagnoses received any time prior to LtOT initiation.

Statistical Analyses

We used descriptive statistics to characterize the sample at baseline and according to substance use disorder status—group differences were evaluated using χ^2 -tests for categorical variables and, as appropriate, *t*, ANOVA, or Wilcoxon rank sum tests for continuous variables.

Associations between substance use disorder status and receipt of guideline-concordant LtOT were quantified by odds ratios (ORs) and corresponding 95% confidence intervals (CIs) using unadjusted, multivariable, and propensity-adjusted logistic regression—the results were similar across methods; therefore, we present the multivariable-adjusted results.

To control for confounding by indication (Pasta, 2001), we generated propensity scores to reflect a patient's conditional probability of receiving the treatment of interest (i.e., guideline-concordant care) using separate multivariable logistic regression models. These models included demographic as well as clinical covariates—chosen from an extensive pool of mental health, infectious disease, cardiac, pulmonary, liver, renal, and pain comorbidities—that were associated with both the treatment of interest and the outcome (in all models, we included HIV as a covariate). We also included covariates for body mass index, smoking history, opioid dose (i.e., milligram morphine equivalent daily dose), short- vs. long-acting classification, and controlled substance schedule (e.g., Schedule II opioids). Additionally, we added to the models covariates to adjust for receipt of other LtOT indicators. Finally, we included interactions as necessary to improve the fit of the models. Further details on the use of propensity scores in observational research have been described previously (Joffe & Rosenbaum, 1999).

We used several diagnostics to evaluate the propensity scores generated through the logistic regression models. Specifically, we assessed each model's discrimination and calibration using c-statistics and Hosmer-Lemeshow tests of goodness-of-fit, respectively (see Appendices B–D). Additional diagnostics included an evaluation of histograms by treatment

status and plotting the observed versus expected outcomes from the goodness-of-fit tests (see Appendix B). All logistic regression models were found to have good fit (see Appendix C) (Hosmer & Lemeshow, 2000; Allison & SAS Institute., 2012). The c-statistics for psychotherapeutic co-interventions and substance use disorder treatment were in the excellent range (i.e., .81 and .90, respectively); for benzodiazepine co-prescribing, the c-statistic was in the acceptable range (i.e., .75; see Appendix D) (Schneeweiss et al., 2001). Importantly, for each indicator, to assess the balance of covariates among those who did and did not receive the indicator, we matched patients on the propensity scores using a SAS greedy algorithm macro (Parsons, 2000). Although, we do not present the results here, an analysis of important potential confounders (including all of those shown in Table 1) reveals that patients were well balanced (i.e., P value = .05) on these covariates. Further details on the statistical procedures used in this study to control for confounding by indication (Pasta; Joffe & Rosenbaum, 1999) have been described in detail previously (Gaither et al., 2016).

We then assessed associations between guideline-concordant care and all-cause mortality using propensity-adjusted Cox proportional hazards regression with time-updated covariates. We employed time-updated methods to account for differences in exposure to opioids (i.e., some patients died or discontinued opioids prior to 180 days of therapy, and therefore, had less time to receive guideline-concordant care). With these methods, the time prior to receipt of a particular indicator is classified as the unexposed period; once the indicator is obtained, the time thereafter is correctly classified as the exposed period. Proper estimates can then be obtained upon a patient's death (Suissa, 2007; Allison & SAS Institute., 2010).

All analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC). A two-sided statistical significance level of .05 was applied to all analyses.

Results

Characteristics of the Study Cohort

We identified 17,044 patients initiating LtOT between 2000 and 2010. Demographic and clinical characteristics for the sample overall and according to substance use disorder status are presented in Table 1. In brief, compared to those without a substance use disorder, patients with a disorder ($n=3,329$) were more likely to be black, HIV and hepatitis C positive, and to be current smokers (all $P < .001$). They were also more likely to have a higher VACS Index and to receive a higher average daily opioid dose ($P < .001$).

Guideline-Concordant Care

In the 180 days following LtOT initiation, 68.2% of patients with a substance use disorder received psychotherapeutic co-interventions compared to 23.5% of those without a disorder ($P < .001$; adjusted odds ratio [AOR] 6.88; 95% CI 6.15–7.71). Twenty-one percent of patients in the sample overall received a benzodiazepine co-prescription, and receipt did not differ according to substance use disorder status (21.7% vs. 21.2%; $P = .52$, comparing those with and without a substance use disorder, respectively (AOR 1.00; 95% CI 0.89–1.12). Among those with a current substance use disorder, 50.3% were engaged in substance use disorder treatment.

Guideline-Concordant Care and All-Cause Mortality

Unmatched Analyses—During one year of follow-up, there were 1,048 (6.1%) deaths. The median (interquartile range [IQR]) time-to-death was 227.5 (154.0–328.5) days. In unadjusted analyses, we found that receipt of psychotherapeutic co-interventions was associated with lower all-cause mortality in the sample overall (adjusted hazard ratio [AHR] 0.57; 95% CI 0.49–0.66), and there was evidence of effect measure modification (i.e., interaction) by substance use disorder status (P for interaction = .009): Psychotherapeutic co-interventions were more protective in patients with a substance use disorder (AHR 0.35, 95% CI 0.27–0.44 vs. AHR 0.54, 95% CI 0.44–0.66; all $P < .001$). Benzodiazepine co-prescribing was associated with higher mortality in the sample overall (AHR 1.63; 95% CI 1.43–1.86; $P < .001$), but we found no evidence of effect measure modification by substance use disorder status (P for interaction = .09). Among patients with a substance use disorder, engagement in substance use disorder treatment was associated with a lower mortality rate (AHR 0.38; 95% CI 0.29–0.50; $P < .001$).

Propensity-Adjusted Analyses—Receipt of psychotherapeutic co-interventions was associated with lower all-cause mortality in the sample overall, and this outcome varied by substance use disorder status (P for interaction = .002): Psychotherapeutic co-interventions were more protective in patients with a substance use disorder (adjusted hazard ratio [AHR] 0.43, 95% CI 0.33–0.56 vs. AHR 0.65, 95% CI 0.53–0.81; all $P < .001$). Benzodiazepine co-prescribing was associated with higher mortality in the sample overall (AHR 1.41; 95% CI 1.22–1.63; $P < .001$), but we found no evidence of effect measure modification by substance use disorder status (P for interaction = .11). Among patients with a substance use disorder, engagement in substance use disorder treatment was associated with lower mortality (AHR 0.43; 95% CI 0.33–0.57; $P < .001$). (Figs. 2–4)

Discussion

Among 17,044 patients initiating LtOT over a decade, we found that nearly 20% met the criteria for a current substance use disorder. During one year of follow-up, there were 1,048 (6%) deaths in this sample of patients with a clinically challenging mix of medical, psychiatric, and pain comorbidities. After extensively controlling for potential confounders, we found in patients overall that receipt of psychotherapeutic co-interventions and substance use disorder treatment were protective of mortality, whereas receipt of benzodiazepine co-prescriptions increased mortality. Moreover, we found through stratified analyses and formal tests of interactions that the presence of a substance use disorder modified the mortality outcome related to psychotherapeutic interventions: In patients without a comorbid substance use disorder, the mortality rate for those who did not receive psychotherapeutic co-interventions was 1.5 times that of patients who did. In patients with substance use disorders the rate was nearly 2.5 times that of patients receiving psychotherapeutic co-interventions. For benzodiazepine co-prescriptions, the mortality rate did not differ by substance use disorder status—for the sample overall, those receiving benzodiazepines concurrent with LtOT were nearly 1.5 times more likely to die. Among patients with a substance use disorder, those who received LtOT concurrent with an untreated disorder had

a rate of death 2.6 times that of patients engaged in substance use disorder treatment. Yet only 50% of patients with a current substance use disorder were engaged in treatment.

For receipt of guideline-concordant LtOT according to substance use disorder status, our findings are comparable to previous research demonstrating that few patients, even vulnerable patients—such as those with HIV, serious mental illness, and substance use disorders—receive the standard of care outlined in opioid clinical practice guidelines (Krebs et al., 2011; Morasco et al., 2011; Starrels et al., 2011; Midboe et al., 2012; Morasco, Cavanagh, et al., 2013; Gaither et al., 2014; Gaither et al., 2016). The current study was prompted by findings from a related study, where we examined a broader range of indicators, including multi-modal approaches to pain management, in a sample not stratified by substance use disorder status (Gaither et al., 2016). Mirroring those results, our findings here support recommendations that encourage clinicians prescribing LtOT among patients with substance use disorders to develop a collaborative approach that draws upon the expertise of professionals in mental health services and addiction treatment. Furthermore, our findings support current recommendations that caution against initiating LtOT concurrent with benzodiazepines or untreated substance use disorders (Chou, Fanciullo, et al., 2009; US Department of Veterans Affairs/Department of Defense, 2010). Additionally, for substance use disorder treatment, we replicated our findings from the previous study (Gaither et al., 2016). In the current study, though, we were able to generate propensity scores potentially better able to control for confounding by indication (current c-statistic of .90 vs. .80 in better fitting models).

Our study has several limitations. Although we used accepted statistical approaches to balance potential confounders in patients who did and did not receive guideline-concordant care, residual confounding by indication is still a possibility. Similarly, we did not have the data to address lack of adherence to prescribed guideline-concordant care among patients; nor did we have the data to account for receipt of guideline-concordant care that may have taken place in non-VA settings. However, because the VA offers comprehensive substance use disorder treatment, we believe that the number of patients seeking care for this disorder outside of the VA is likely low (US Department of Veterans Affairs/Veterans Health Administration, 2010). Furthermore, because we limited our sample to patients initiating LtOT—excluding those dying prior to reaching the 90-day threshold for prescribed opioids—deaths occurring in the first 90 days were not included in the analyses; it is during the initial period of opioid exposure when the risks are thought to be greatest (Chou, Fanciullo, et al., 2009). Finally, according to a recent report, prescriptions for opioids decreased slightly in the United States from 2011 to 2013 (Dart et al., 2015). This trend may reflect a broader awareness among clinicians of the risks associated with opioids, which would be in keeping with recently instituted policy and practice initiatives within the VA and other state and federal agencies (Chou et al., 2015; Reuben et al., 2015).

Despite these limitations, we believe our findings have the potential to positively influence clinical practice, especially for patients with substance use disorders, a patient group known to be at increased risk for opioid-related adverse events. Patients receiving LtOT are likely to benefit from care that is delivered in accordance with clinical practice guidelines,

particularly care that addresses the psychological complexities of treating patients with chronic pain.

In summary, as with previous research, our aim with this study was to contribute to the evidence base for opioid clinical practice guidelines. Future studies should examine the association between guideline-concordant LtOT and additional patient outcomes, including cause-specific (e.g. overdose) mortality and long-term survival. Future research is also needed to understand how other recommendations from the guidelines, such as using opioid treatment agreements (Chou, Fanciullo, et al., 2009), influence patient outcomes. Finally, studies are needed to understand the barriers to guideline-concordant care from the perspective of clinicians and patients.

Acknowledgments

Dr. Gaither had full access to all the data in the study and takes responsibility for the integrity of the study and the accuracy of the data analysis. All authors approved the manuscript as submitted.

Funding/Support

Research reported in this paper was supported by grants from the National Institute on Drug Abuse (grant nos. F31DA035567, K12DA033312), National Institute on Alcohol Abuse and Alcoholism (grant nos. U10AA013566; U01AA020790; U24AA020794), National Institute of Mental Health (grant no. P30MH062294), the Agency for Healthcare Research and Quality (grant no. U19HS21112), and the VA Health Services Research and Development Center of Innovation (grant no. CIN13047).

References

- Akgun KM, Tate JP, Pisani M, Fried T, Butt AA, Gibert CL, et al. Medical ICU admission diagnoses and outcomes in human immunodeficiency virus-infected and virus-uninfected veterans in the combination antiretroviral era. *Crit Care Med.* 2013; 41(6):1458–1467. [PubMed: 23507717]
- Allison, PD. SAS Institute. *Survival analysis using the SAS system : a practical guide*, second edition. Cary, NC: SAS Institute; 2010.
- Allison, PD. SAS Institute. *Logistic regression using SAS : theory and application*. 2. Cary, N.C: SAS Pub; 2012.
- American Pain Society/American Academy of Pain Medicine. The use of opioids for treatment of chronic pain. A consensus statement from the American Academy of Pain Medicine and the American Pain Society. *Clin J Pain.* 1997; 13:6–8. [PubMed: 9084947]
- Bebu I, Tate J, Rimland D, Mesner O, Macalino GE, Ganesan A, et al. The VACS Index Predicts Mortality in a Young, Healthy HIV Population Starting Highly Active Antiretroviral Therapy. *J Acquir Immune Defic Syndr.* 2014; 65(2):226–230. [PubMed: 24226058]
- Becker WC, Sullivan LE, Tetrault JM, Desai RA, Fiellin DA. Non-medical use, abuse and dependence on prescription opioids among U.S. adults: psychiatric, medical and substance use correlates. *Drug Alcohol Depend.* 2008; 94(1–3):38–47. [PubMed: 18063321]
- Betz ME, Kelly SP, Fisher J. Death certificate inaccuracy and underreporting of injury in elderly people. *J Am Geriatr Soc.* 2008; 56(12):2267–2272. [PubMed: 19093926]
- Bohnert AS, Valenstein M, Bair MJ, Ganoczy D, McCarthy JF, Ilgen MA, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA.* 2011; 305(13):1315–1321. [PubMed: 21467284]
- Braden JB, Sullivan MD, Ray GT, Saunders K, Merrill J, Silverberg MJ, et al. Trends in long-term opioid therapy for noncancer pain among persons with a history of depression. *Gen Hosp Psychiatry.* 2009; 31(6):564–570. [PubMed: 19892215]
- Brown ST, Tate JP, Kyriakides TC, Kirkwood KA, Holodniy M, Goulet JL, et al. The VACS index accurately predicts mortality and treatment response among multi-drug resistant HIV infected

patients participating in the options in management with antiretrovirals (OPTIMA) study. *PLoS One*. 2014; 9(3):e92606. [PubMed: 24667813]

Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. *Arch Intern Med*. 1998; 158(16):1789–1795. [PubMed: 9738608]

Caudill-Slosberg MA, Schwartz LM, Woloshin S. Office visits and analgesic prescriptions for musculoskeletal pain in US: 1980 vs. 2000. *Pain*. 2004; 109(3):514–519. [PubMed: 15157714]

Centers for Disease, C., & Prevention. Vital signs: overdoses of prescription opioid pain relievers and other drugs among women--United States, 1999–2010. *MMWR Morb Mortal Wkly Rep*. 2013; 62(26):537–542. [PubMed: 23820967]

Centers for Disease Control and Prevention. Unintentional poisoning deaths--United States, 1999–2004. *MMWR Morb Mortal Wkly Rep*. 2007; 56(5):93–96. [PubMed: 17287712]

Centers for Disease Control and Prevention. Vital Signs: Overdoses of Prescription Opioid Pain Relievers--United States, 1999–2008. *MMWR Morb Mortal Wkly Rep*. 2011; 60(43):1487–1492. [PubMed: 22048730]

Chou R, Ballantyne JC, Fanciullo GJ, Fine PG, Miaskowski C. Research gaps on use of opioids for chronic noncancer pain: findings from a review of the evidence for an American Pain Society and American Academy of Pain Medicine clinical practice guideline. *J Pain*. 2009; 10(2):147–159. [PubMed: 19187891]

Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain*. 2009; 2:113–30.

Chou R, Turner JA, Devine EB, Hansen RN, Sullivan SD, Blazina I, et al. The Effectiveness and Risks of Long-Term Opioid Therapy for Chronic Pain: A Systematic Review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med*. 2015

Cowper DC, Kubal JD, Maynard C, Hynes DM. A primer and comparative review of major US mortality databases. *Ann Epidemiol*. 2002; 12(7):462–468. [PubMed: 12377423]

Dart RC, Surratt HL, Cicero TJ, Parrino MW, Severtson SG, Bucher-Bartelson B, et al. Trends in opioid analgesic abuse and mortality in the United States. *N Engl J Med*. 2015; 372(3):241–248. [PubMed: 25587948]

Dunn KM, Saunders KW, Rutter CM, Banta-Green CJ, Merrill JO, Sullivan MD, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. *Ann Intern Med*. 2010; 152(2):85–92. [PubMed: 20083827]

Edelman EJ, Gordon K, Becker WC, Goulet JL, Skanderson M, Gaither JR, et al. Receipt of opioid analgesics by HIV-infected and uninfected patients. *J Gen Intern Med*. 2013; 28(1):82–90. [PubMed: 22895747]

Edlund MJ, Martin BC, Devries A, Fan MY, Braden JB, Sullivan MD. Trends in use of opioids for chronic noncancer pain among individuals with mental health and substance use disorders: the TROUP study. *Clin J Pain*. 2010; 26(1):1–8. [PubMed: 20026946]

Edlund MJ, Steffick D, Hudson T, Harris KM, Sullivan M. Risk factors for clinically recognized opioid abuse and dependence among veterans using opioids for chronic non-cancer pain. *Pain*. 2007; 129(3):355–362. [PubMed: 17449178]

Fisher SG, Weber L, Goldberg J, Davis F. Mortality ascertainment in the veteran population: alternatives to the National Death Index. *Am J Epidemiol*. 1995; 141(3):242–250. [PubMed: 7840098]

Fultz SL, Skanderson M, Mole LA, Gandhi N, Bryant K, Crystal S, et al. Development and verification of a “virtual” cohort using the National VA Health Information System. *Med Care*. 2006; 44(8 Suppl 2):S25–30. [PubMed: 16849965]

Gaither JR, Goulet JL, Becker WC, Crystal S, Edelman EJ, Gordon K, et al. The Association Between Receipt of Guideline-Concordant Long-Term Opioid Therapy and All-Cause Mortality. *J Gen Intern Med*. 2016; 31(5):492–501. [PubMed: 26847447]

Gaither JR, Goulet JL, Becker WC, Crystal S, Edelman EJ, Gordon K, et al. Guideline-concordant management of opioid therapy among human immunodeficiency virus (HIV)-infected and uninfected veterans. *J Pain*. 2014; 15(11):1130–1140. [PubMed: 25152300]

- Goldberger BA, Maxwell JC, Campbell A, Wilford BB. Uniform standards and case definitions for classifying opioid-related deaths: recommendations by a SAMHSA consensus panel. *J Addict Dis.* 2013; 32(3):231–243. [PubMed: 24074189]
- Hall AJ, Logan JE, Toblin RL, Kaplan JA, Kraner JC, Bixler D, et al. Patterns of abuse among unintentional pharmaceutical overdose fatalities. *JAMA.* 2008; 300(22):2613–2620. [PubMed: 19066381]
- Hansen L, Penko J, Guzman D, Bangsberg DR, Miaskowski C, Kushel MB. Aberrant behaviors with prescription opioids and problem drug use history in a community-based cohort of HIV-infected individuals. *J Pain Symptom Manage.* 2011; 42(6):893–902. [PubMed: 21802896]
- Hosmer, DW.; Lemeshow, S. *Applied logistic regression.* 2. New York: Wiley; 2000.
- Huguet N, Kaplan MS, McFarland BH. The effects of misclassification biases on veteran suicide rate estimates. *Am J Public Health.* 2014; 104(1):151–155. [PubMed: 24228669]
- Joffe MM, Rosenbaum PR. Invited commentary: propensity scores. *Am J Epidemiol.* 1999; 150(4):327–333. [PubMed: 10453808]
- Justice AC, Dombrowski E, Conigliaro J, Fultz SL, Gibson D, Madenwald T, et al. Veterans Aging Cohort Study (VACS): Overview and description. *Med Care.* 2006; 44(8 Suppl 2):S13–24. [PubMed: 16849964]
- Justice AC, Erdos J, Brandt C, Conigliaro J, Tierney W, Bryant K. The Veterans Affairs Healthcare System: A unique laboratory for observational and interventional research. *Med Care.* 2006; 44(8 Suppl 2):S7–12. [PubMed: 16849970]
- Justice AC, McGinnis KA, Skanderson M, Chang CC, Gibert CL, Goetz MB, et al. Towards a combined prognostic index for survival in HIV infection: the role of ‘non-HIV’ biomarkers. *HIV Med.* 2010; 11(2):143–151. [PubMed: 19751364]
- Justice AC, Modur SP, Tate JP, Althoff KN, Jacobson LP, Gebo KA, et al. Predictive accuracy of the Veterans Aging Cohort Study index for mortality with HIV infection: a North American cross cohort analysis. *J Acquir Immune Defic Syndr.* 2013; 62(2):149–163. [PubMed: 23187941]
- Korff MV, Saunders K, Thomas Ray G, Boudreau D, Campbell C, Merrill J, et al. De facto long-term opioid therapy for noncancer pain. *Clin J Pain.* 2008; 24(6):521–527. [PubMed: 18574361]
- Krebs EE, Bergman AA, Coffing JM, Campbell SR, Frankel RM, Matthias MS. Barriers to guideline-concordant opioid management in primary care--a qualitative study. *J Pain.* 2014; 15(11):1148–1155. [PubMed: 25179150]
- Krebs EE, Ramsey DC, Milosheff JM, Bair MJ. Primary care monitoring of long-term opioid therapy among veterans with chronic pain. *Pain Med.* 2011; 12(5):740–746. [PubMed: 21481167]
- Li L, Setoguchi S, Cabral H, Jick S. Opioid use for noncancer pain and risk of myocardial infarction amongst adults. *J Intern Med.* 2013; 273(5):511–526. [PubMed: 23331508]
- Lo Re V III, Lim JK, Goetz MB, Tate J, Bathulapalli H, Klein MB, et al. Validity of diagnostic codes and liver-related laboratory abnormalities to identify hepatic decompensation events in the Veterans Aging Cohort Study. *Pharmacoepidemiol Drug Saf.* 2011; 20(7):689–699. [PubMed: 21626605]
- Manchikanti L, Ailinani H, Koyyalagunta D, Datta S, Singh V, Eriator I, et al. A systematic review of randomized trials of long-term opioid management for chronic non-cancer pain. [Review]. *Pain Physician.* 2011; 14(2):91–121. [PubMed: 21412367]
- Manchikanti L, Singh A. Therapeutic opioids: a ten-year perspective on the complexities and complications of the escalating use, abuse, and nonmedical use of opioids. [Review]. *Pain Physician.* 2008; 11(2 Suppl):S63–88. [PubMed: 18443641]
- Martin BC, Fan MY, Edlund MJ, Devries A, Braden JB, Sullivan MD. Long-term chronic opioid therapy discontinuation rates from the TROUP study. *J Gen Intern Med.* 2011; 26(12):1450–1457. [PubMed: 21751058]
- Midboe AM, Lewis ET, Paik MC, Gallagher RM, Rosenberg JM, Goodman F, et al. Measurement of adherence to clinical practice guidelines for opioid therapy for chronic pain. *Transl Behav Med.* 2012; 2(1):57–64. [PubMed: 24073098]
- Morasco BJ, Cavanagh R, Gritzner S, Dobscha SK. Care management practices for chronic pain in veterans prescribed high doses of opioid medications. *Fam Pract.* 2013; 30(6):671–678. [PubMed: 23901065]

- Morasco BJ, Duckart JP, Dobscha SK. Adherence to clinical guidelines for opioid therapy for chronic pain in patients with substance use disorder. *J Gen Intern Med*. 2011; 26(9):965–971. [PubMed: 21562923]
- Morasco BJ, Turk DC, Donovan DM, Dobscha SK. Risk for prescription opioid misuse among patients with a history of substance use disorder. [Research Support, N.I.H., Extramural]. *Drug Alcohol Depend*. 2013; 127(1–3):193–199. [PubMed: 22818513]
- Myers KA, Farquhar DR. Improving the accuracy of death certification. *CMAJ*. 1998; 158(10):1317–1323. [PubMed: 9614825]
- Office of National Drug Control Policy. Epidemic: Responding to America's prescription drug abuse crisis. 2011.
- Önen NF, Barrette EP, Shacham E, Taniguchi T, Donovan M, Overton ET. A review of opioid prescribing practices and associations with repeat opioid prescriptions in a contemporary outpatient HIV clinic. *Pain Pract*. 2012; 12(6):440–448. [PubMed: 22103269]
- Parsons, L. Reducing bias in a propensity score matched-pair sample using greedy matching techniques. Paper presented at the Twenty-Fifth Annual SAS Users Group International Conference, SAS Institute Inc; 2000; Cary, NC. 2000.
- Pasta, DJ. Using Propensity Scores to Adjust for Group Differences: Examples Comparing Alternative Surgical Methods.
- Pasta, DJ. Using Propensity Scores to Adjust for Group Differences: Examples Comparing Alternative Surgical Methods. Paper presented at the Twenty-Sixth Annual SAS Users Group International Conference, SAS Institute Inc; 2001; Cary, NC. 2001.
- Rasu RS, Sohraby R, Cunningham L, Knell ME. Assessing chronic pain treatment practices and evaluating adherence to chronic pain clinical guidelines in outpatient practices in the United States. *J Pain*. 2013; 14(6):568–578. [PubMed: 23578958]
- Reuben DB, AAHA, Ashikaga T, Bogat GA, Callahan CM, Ruffing V, et al. National Institutes of Health Pathways to Prevention Workshop: The Role of Opioids in the Treatment of Chronic Pain. *Ann Intern Med*. 2015
- Rosenblum A, Marsch LA, Joseph H, Portenoy RK. Opioids and the treatment of chronic pain: controversies, current status, and future directions. *Exp Clin Psychopharmacol*. 2008; 16(5):405–416. [PubMed: 18837637]
- Roy S, Ninkovic J, Banerjee S, Charboneau RG, Das S, Dutta R, et al. Opioid drug abuse and modulation of immune function: consequences in the susceptibility to opportunistic infections. *J Neuroimmune Pharmacol*. 2011; 6(4):442–465. [PubMed: 21789507]
- Saunders KW, Dunn KM, Merrill JO, Sullivan M, Weisner C, Braden JB, et al. Relationship of opioid use and dosage levels to fractures in older chronic pain patients. *J Gen Intern Med*. 2010; 25(4):310–315. [PubMed: 20049546]
- Schneeweiss S, Seeger JD, Maclure M, Wang PS, Avorn J, Glynn RJ. Performance of comorbidity scores to control for confounding in epidemiologic studies using claims data. *Am J Epidemiol*. 2001; 154(9):854–864. [PubMed: 11682368]
- Seal KH, Shi Y, Cohen G, Cohen BE, Maguen S, Krebs EE, et al. Association of mental health disorders with prescription opioids and high-risk opioid use in US veterans of Iraq and Afghanistan. *JAMA*. 2012; 307(9):940–947. [PubMed: 22396516]
- Slavova S, O'Brien DB, Creppage K, Dao D, Fondario A, Haile E, et al. Drug Overdose Deaths: Let's Get Specific. *Public Health Rep*. 2015; 130(4):339–342. [PubMed: 26345488]
- Solomon DH, Rassen JA, Glynn RJ, Garneau K, Levin R, Lee J, et al. The comparative safety of opioids for nonmalignant pain in older adults. *Arch Intern Med*. 2010; 170(22):1979–1986. [PubMed: 21149754]
- Starrels JL, Becker WC, Weiner MG, Li X, Heo M, Turner BJ. Low use of opioid risk reduction strategies in primary care even for high risk patients with chronic pain. *J Gen Intern Med*. 2011; 26(9):958–964. [PubMed: 21347877]
- Suissa S. Immortal Time Bias in Observational Studies of Drug Effects. *Pharmacoepidemiol Drug Saf*. 2007; 16(3):241–249. [PubMed: 17252614]

- Sullivan MD, Edlund MJ, Fan MY, Devries A, Brennan Braden J, Martin BC. Trends in use of opioids for non-cancer pain conditions 2000–2005 in commercial and Medicaid insurance plans: the TROUP study. *Pain*. 2008; 138(2):440–449. [PubMed: 18547726]
- Tate JP, Justice AC, Hughes MD, Bonnet F, Reiss P, Mocroft A, et al. An internationally generalizable risk index for mortality after one year of antiretroviral therapy. *AIDS*. 2013; 27(4):563–572. [PubMed: 23095314]
- US Department of Veterans Affairs/Department of Defense. Clinical Practice Guideline for Management of Opioid Therapy for Chronic Pain. 2003.
- US Department of Veterans Affairs/Department of Defense. Clinical Practice Guideline for Management of Opioid Therapy for Chronic Pain. 2010.
- US Department of Veterans Affairs/Veterans Health Administration. [Assessed June 29, 2016] VA Services for Patients with Substance Use Disorders (SUD). 2010. http://www.mentalhealth.va.gov/providers/sud/docs/Fact_Sheet_SUD_final_9-2010.pdf
- Veldhuizen S, Callaghan RC. Cause-specific mortality among people previously hospitalized with opioid-related conditions: a retrospective cohort study. *Ann Epidemiol*. 2014; 24(8):620–624. [PubMed: 25084705]
- Volkow ND, McLellan TA, Cotto JH, Karithanom M, Weiss SR. Characteristics of opioid prescriptions in 2009. *JAMA*. 2011; 305(13):1299–1301. [PubMed: 21467282]
- Von Korff M, Kolodny A, Deyo RA, Chou R. Long-term opioid therapy reconsidered. *Ann Intern Med*. 2011; 155(5):325–328. [PubMed: 21893626]
- Warner M, Paulozzi LJ, Nolte KB, Davis GG, Nelson LS. State variation in certifying manner of death and drugs involved in drug intoxication deaths. *Acad Forensic Pathol*. 2013; 3(2):231–237.

APPENDIX A. Operational Definitions for Indicators of Guideline-Concordant Long-term Opioid Therapy

Guideline Indicators	Operational Definition	Source
Psychotherapeutic Co-Interventions		
Clinicians should avoid relying exclusively on opioids for the management of chronic pain and should routinely take a multidisciplinary approach to pain management that includes the integration of non-opioid pharmacotherapies, rehabilitation or functional restoration, and psychotherapeutic interventions.	Any 2 documented outpatient visits to a VA mental health clinic between LtOT start date and end of 180 d of LtOT (or LtOT stop date).	APS/AAPM ^{28,29} VA/DoD ^{30,31}
Co-Prescription of High-Risk Medications		
Clinicians should avoid co-prescription of sedatives and LtOT.	Pharmacy documentation that patient prescribed benzodiazepines (7 d so as to exclude prescriptions for acute indications [e.g., pre-operative sedation]) between LtOT start date and end of 180 d of LtOT (or LtOT stop date).	VA/DoD ³⁰
High-Risk Patients		
Clinicians should initiate LtOT with caution in patients with a history of a substance use disorder and should never initiate LtOT in patients with a current disorder [§] who are not in substance use disorder treatment.	Among patients with a current substance use disorder, documentation of substance use disorder treatment (1 inpatient bed d or 1 outpatient substance use disorder-specialty clinic visit) between LtOT start and end of 180 d of LtOT (or LtOT stop date).	

Abbreviations: AAPM; American Academy of Pain Medicine; APS, American Pain Society; LtOT, long-term opioid therapy; VA, Veterans Administration.

[§]Substance use disorder diagnosis received between LtOT start date and end of 180 d of LtOT (or LtOT stop date).

APPENDIX B. Goodness-of-Fit Expected vs. Observed Values for Logistic Regression Models

APPENDIX C. Goodness-of-Fit Test Statistics for Logistic Regression Models

Indicator	χ^2	<i>P</i>
Psychotherapeutic Co-Interventions	4.57	.80
Benzodiazepine Co-Prescribing	12.94	.11
Substance Use Disorder Treatment	2.71	.95

APPENDIX D. C-Statistics for Logistic Regression Models

Indicator	<i>C</i>
Psychotherapeutic Co-Interventions	.81
Benzodiazepine Co-Prescribing	.75
Substance Use Disorder Treatment	.90

Figure 1.
Study Flow Diagram

Figure 2.
Propensity-Adjusted Kaplan-Meier Survival Curves for Receipt of Psychotherapeutic Co-Interventions in Patients *with* and *without* a Substance Use Disorder, Respectively

Figure 3. Propensity-Adjusted Kaplan-Meier Survival Curves for Receipt of Benzodiazepine Co-Prescriptions in Patients *with* and *without* a Substance Use Disorder, Respectively

Figure 4.
Propensity-Adjusted Kaplan-Meier Survival Curves for Receipt of Substance Use Disorder Treatment

Table 1

Patient Characteristics at LtOT Initiation According to Substance Use Disorder Status

Characteristic	Substance Use Disorder Yes (n=3,329)	Substance Use Disorder No (n=13,715)	P Value
Age, mean (SD), y	49.4 (7.6)	50.4 (9.7)	< .001
Male Sex, n (%)	3,260 (98)	13,378 (98)	.19
Race, n (%)			< .001
White	1,290 (39)	6,686 (41)	
Black	1,783 (54)	5,607 (41)	
Hispanic	200 (6)	964 (7)	
Other	56 (2)	458 (3)	
HIV, n (%)	1,198 (36)	4,038 (29)	< .001
Hepatitis C, n (%)	1,566 (47)	3,243 (24)	< .001
Diabetes, n (%)	879 (26)	4,201 (31)	< .001
BMI, mean (SD)	26.9 (5.7)	28.8 (6.6)	< .001
Smoking Status, n (%)			< .001
Never	309 (10)	3,239 (25)	
Current	2,656 (82)	7,613 (58)	
Former	257 (8)	2,251 (17)	
Chronic Pain, n (%)	2,293 (69)	7,780 (57)	< .001
Acute Pain, n (%)	703 (21)	1,603 (12)	< .001
Major Depression, n (%)	1,206 (36)	2,485 (18)	< .001
Bipolar Disorder, n (%)	775 (23)	1,218 (9)	< .001
PTSD, n (%)	960 (29)	2,311 (17)	< .001
Psychosis, n (%)	617 (19)	1,248 (9)	< .001
Alcohol Use Disorder, n (%)	2,156 (65)	—	—
Drug Use Disorder, n (%)	1,914 (57)	—	—
VACS Index, median (IQR) *	22.0 (12.0, 39.0)	18.0 (10.0, 33.0)	< .001
CD4 Count, median (IQR) *	333.0 (160.0, 534.0)	365.0 (193.0, 580.0)	< .001
HIV-1 RNA, Log ₁₀ Viral Load, < 500 copies/ml, n (%) *	449 (52)	1,725 (60)	< .001
Average Daily Opioid Dose, Milligrams MEQ, median (IQR)	10.0 (6.1, 20.6)	8.5 (5.0, 16.8)	< .001

Abbreviations: BMI, body mass index; IQR, interquartile range; PTSD, post-traumatic stress disorder; MEQ, morphine equivalents.

* Among HIV-infected patients.