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

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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.

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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., I
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/µL 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 $\chi^2$-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., \( P \text{ value} \geq .05 \)) 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 LIOT 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.

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

<table>
<thead>
<tr>
<th>Guideline Indicators</th>
<th>Operational Definition</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychotherapeutic Co-Interventions</td>
<td>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).</td>
<td>APS/AAPM28,29 VA/DoD30,31</td>
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<tr>
<td>Co-Prescription of High-Risk Medications</td>
<td>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).</td>
<td>VA/DoD30</td>
</tr>
<tr>
<td>High-Risk Patients</td>
<td>Among patients with a current substance use disorder, documentation of substance use disorder treatment (1 inpatient bed day or 1 outpatient substance use disorder-specialty clinic visit) between LtOT start and end of 180 d of LtOT (or LtOT stop date).</td>
<td></td>
</tr>
</tbody>
</table>

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

Footnotes:

5 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

<table>
<thead>
<tr>
<th>Indicator</th>
<th>$\chi^2$</th>
<th>$P$</th>
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<tr>
<td>Psychotherapeutic Co-Interventions</td>
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<tr>
<td>Benzodiazepine Co-Prescribing</td>
<td>12.94</td>
<td>.11</td>
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<tr>
<td>Substance Use Disorder Treatment</td>
<td>2.71</td>
<td>.95</td>
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APPENDIX D. C-Statistics for Logistic Regression Models

<table>
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<th>Indicator</th>
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<tr>
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<tr>
<td>Benzodiazepine Co-Prescribing</td>
<td>.75</td>
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<tr>
<td>Substance Use Disorder Treatment</td>
<td>.90</td>
</tr>
</tbody>
</table>
Figure 1.
Study Flow Diagram

Assessed for cohort (long-term opioid therapy) eligibility (n=26,931)
- Patients receiving ≥ 90 days supply of opioids between October 1, 1999 and September 30, 2010 through the Pharmacy Benefits Database

Excluded patients receiving opioids within prior 90 days (n=8,787)

Patients meeting the criteria for long-term opioid therapy initiation (n=18,144)

Excluded patients with less than 90 days of follow-up (n=1,009)
- Date-of-death within 90 days of starting opioid therapy (n=263)
- Opioid therapy start date after July 4, 2010 (< 90 days remaining in fiscal year 2010) (n=746)

Excluded patients receiving an ICD-9-CM code of V66.7 (i.e., palliative/end-of-life care) on or prior to start of opioid therapy (n=91)

Final analytic sample of patients initiating long-term opioid therapy (n=17,044)
Figure 2.
Propensity-Adjusted Kaplan-Meir Survival Curves for Receipt of Psychotherapeutic Co-Interventions in Patients with and without a Substance Use Disorder, Respectively
Figure 3.
Propensity-Adjusted Kaplan-Meir 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**

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

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

*Among HIV-infected patients.