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Characteristics of Opioid Prescriptions to Veterans with Cirrhosis

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Abstract

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Background & Aims: Despite increased risks for adverse effects in patients with cirrhosis, little is known about opioid prescriptions for this population. We aimed to assess time trends in opioid prescribing and factors associated with receiving opioids among patients with cirrhosis.

Methods: Among Veterans with cirrhosis, identified using national Veterans Health Administration data (2005–2014), we assessed characteristics of patients and their prescriptions for opioids. We calculated the annual proportion of patients receiving any opioid prescription. Among opioid recipients, we assessed prescriptions that were long-term (>90 days' supply), for high doses (>100 MME/day), or involved combinations of opioids and acetaminophen or benzodiazepine. We evaluated patient characteristics independently associated with long-term and any opioid prescriptions using mixed-effects regression models.

Results: Among 127,239 Veterans with cirrhosis, 97,974 (77.0%) received a prescription for an opioid. Annual opioid prescriptions increased from 36% in 2005 to 47% in 2014 ($P<.01$). Among recipients of opioids, the proportions of those receiving long-term prescriptions increased from 47% in 2005 to 54% in 2014 ($P<.01$), and19%–21% received prescriptions for high-dose opioids. Prescriptions for combinations of opioids and acetaminophen decreased from 68% in 2005 to 50% in 2014 ($P<.01$) and for combinations of opioids and benzodiazepines decreased from 24% to 19% over this time ($P<.01$). Greater probability of long-term opioid prescriptions was independently associated with younger age, female sex, white race, hepatitis C, prior hepatic decompensation, hepatocellular carcinoma, mental health disorders, nicotine use disorders, medical comorbidities, surgery, and pain-related conditions.

Conclusion: Among Veterans with cirrhosis, 36%–47% were prescribed opioids in each year. Mental health disorders and hepatic decompensation were independently associated with long-term opioid prescriptions.

Keywords

narcotic; addiction; analgesia; medication safety; chronic

Introduction

Widespread opioid prescribing has resulted in rising numbers of unintentional overdose deaths.[1] As such, addressing the current opioid crisis is a national priority.[2] Not only do prescription opioids create the potential for addiction and abuse,[3] but chronic opioids are likely ineffective in the long-term management of non-malignant pain.4, 5 National initiatives have focused on curbing the use of prescription opioids in general populations.6, 7 These efforts have focused on risky prescribing, including high-dose prescribing, prescribing of opioids with concurrent benzodiazepines, and use of acetaminophen-containing opioids. Opioid prescribing has begun to decline in general populations starting in 2012, particularly in the Veterans Health Administration (VA), where the VA Opioid Safety Initiative has had significant impacts.6, 8, 9 However, patterns of opioid prescribing and their trajectories over time for VA patients with cirrhosis remain unknown.

Opioid prescribing may be both common and particularly risky among patients with cirrhosis compared to the general population. First, chronic pain is reported in up to 79% of patients with cirrhosis,[10] compared to only approximately 14% of general US adults.[11]

Second, while pain is common in this population, the analgesic options for treating pain are limited by the cirrhosis itself. For example, non-steroidal anti-inflammatory drugs (NSAIDS) are the mainstays of analgesia in other populations but are unsafe in the setting of cirrhosis.[12] Third, there may be particular risks with opioids in patients with cirrhosis. Opioid medications have been associated with hepatic encephalopathy,[13] increased hospitalization,[14] post-transplant readmission,[15] and mortality.[16] In fact, liver disease is among the strongest risk factors for opioid-related complications, including overdose, in general populations.17, 18 Thus, while pain is common in cirrhosis and difficult to treat, prescription opioids are highly problematic in this population. However, despite the risks, little existing data describe the time-trends and risk factors for opioid prescribing among patients with cirrhosis.

Given the potential risks of opioids in patients with cirrhosis, it is critical to assess opioid prescribing patterns in this patient population over time. VA cares for one of the largest longitudinal cohorts of individuals with cirrhosis in the US. The objective of this study was to assess the longitudinal trends and predictors of opioid prescribing in a large national sample of Veterans with cirrhosis.

Methods

Cohort definition

This retrospective cohort study was approved as a quality improvement project by the VA Pittsburgh Healthcare System institutional review board and was conducted in partnership with the VA's HIV, Hepatitis, and Related Conditions Program Office. The study population includes all Veterans with cirrhosis, defined as 2 outpatient and/or 1 inpatient International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) codes for cirrhosis or its complications including: cirrhosis with alcoholism (571.2), cirrhosis without mention of alcohol (571.5), esophageal varices with or without bleeding (456.0–456.21), spontaneous bacterial peritonitis (567.23), hepatic encephalopathy (572.2), and hepatorenal syndrome (572.4).[19] VA users meeting these criteria for cirrhosis between 1/1/05–12/31/14 who were in care in a given calendar year were included and followed until death or 12/31/14. "In care" was defined as ≥1 clinical VA encounter in that calendar year. Cohort entry was defined by the first clinical encounter in the study period.

Data Definitions

All study data were extracted from the VA Corporate Data Warehouse (CDW) and included prescription records, demographic information, comorbidities, laboratory values, diagnosis codes, and date of death. Demographics included age, race (defined as White, Black, or Other), sex, homelessness (defined as lack of, or inadequate housing using ICD-9 codes V60.0 and V60.1), and primary location of VA care (VA facility at cohort entry). Period of service was defined as Vietnam vs. other. Marital status was defined as married vs. never married/single vs. divorced/separated/widowed. Mental health comorbidities and substance use disorders were defined using 2 outpatient or 1 inpatient ICD-9 codes for mood disorders, PTSD, schizophrenia, nicotine use disorder, alcohol use disorder (AUD), opioid use disorder (OUD), and other substance use disorders (Appendix 1).

Pain-related conditions were defined using previously-established ICD-9 codes.[20] We defined surgery in each year using the 567 VA Surgical Quality Improvement Program (VASQIP) Current Procedural Terminology (CPT) codes that cover >90% of surgeries in VA. Comorbidities were combined into a Charlson comorbidity score for each year[21] using previously-validated ICD-9-based algorithms.[22] Notably, cancer is included as a comorbidity in this score. Hepatic decompensation was defined in each year using ICD-9 codes (Appendix 1).

Using ICD-9 codes, we classified liver disease etiology as HCV with or without alcohol, alcohol, hepatitis B virus (HBV), autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), or primary sclerosing cholangitis (PSC) and Other. “Other chronic non-alcoholic liver disease” was defined using ICD-9 code 571.8. Patients without codes for the above were listed as “unknown” for etiology. Hepatocellular carcinoma was defined using ICD-9 code 155.0. We calculated Model for End-Stage Liver Disease (MELD) scores for each patient using the first available labs in each year.[23]

Outcome Measures

Our primary outcome was outpatient prescription opioid dispensing.[8] We further categorized prescription opioid use as long-term based on receiving ≥90 calendar days supplied in a calendar year, to allow for short gaps in prescription refills.[24] In order to assess equivalent doses of opioids, the mean and median daily morphine milligram equivalents (MME) were calculated for each patient in each year using standard conversions for all non-liquid opioid medications[25] over the calendar days of opioid prescriptions. We defined high-dose prescriptions as receipt of MME≥100 on any single day in the year, per prior literature.25, 26 We also assessed whether patients received overlapping opioid and benzodiazepine medications, defined as having at least one calendar day of overlap during a given year.[8]

We excluded buprenorphine-naltrexone and methadone in the context of addiction treatment in the definition of prescription opioid use, given our focus on analgesia, as per other studies of prescription opioid use.[26] Methadone treatment for addiction was operationalized as a prescription for methadone with a clinic stop code 523 (opioid substitution clinic) or daily-dosed liquid methadone.

Statistical Analysis

Statistical analyses were conducted using Stata, version 15.[27] We described demographic and clinical characteristics of the cohort at baseline and over time using means and standard deviations for continuous normally distributed variables and medians and interquartile ranges (IQR) for variables that were non-normally distributed. We assessed changes in cohort characteristics over time.

We summarized the proportion of patients prescribed opioids in each year. These proportions were then adjusted for the cohort characteristics for each year using a binary generalized linear model with a logit link. For patients prescribed opioids in each year, we summarized median MME prescribed/day and the percent receiving high-dose prescriptions, benzodiazepine overlap, and acetaminophen-containing opioids. Trends were assessed using Chi-square tests for trend and mixed-effects models as described below.

We assessed the demographic and clinical characteristics associated with receiving any opioids and with receiving long-term (≥90 calendar days prescribed) opioids, first descriptively and then using mixed-effects multivariable logistic regression models, including year and modeling covariates as time-varying, with a one-year lag between exposure and outcomes. For these models, we re-categorized covariates to combine cells with low sample size including collapsing hallucinogen and sedative use disorders into "other drug use disorders" and marital status into married vs. not married. Given the similarities between non-HCV etiologies of liver disease, etiology was reclassified into HCV vs. other/unknown. We assessed collinearity using a pre-specified variance inflation factor of >5. All models clustered patients by facility at cohort entry.

The primary analyses included only patients with complete data. Missingness of data varied by year but in 2014 were <1% for marital status, 10% for race, and 8% for MELD. We assessed the characteristics of patients with and without missing data and fitted models that excluded these variables in order to evaluate the importance of missing data to the stability of our point estimates. When variables with missing values (MELD, marital status, and race) were excluded from the models, there was little change in the point estimates and relationships between the other variables.

Results

We identified 127,239 unique Veterans with cirrhosis from 2005 to 2014 (Table 1). Median follow-up time was 7 years (IQR=4,10). The average age was 58±9 and the median baseline MELD was 9 (IQR 7,12). The most common etiology of liver disease was HCV, with or without alcohol use (51%). Nicotine and alcohol use disorder diagnoses were present in 24% and 32% of the cohort in the baseline year, respectively. In this cohort, 45% of patients had at least 1 pain-related diagnosis in the baseline year and 86% had a pain-related diagnosis over follow-up. From 2005 to 2014 the cohort aged to a mean age of 65±9 and had an increased prevalence of pain-related and mental health conditions (Appendix 2).

Most patients (77%) were prescribed opioid medications at least once over the entire follow-up period, and 41% of the total cohort met the definition of long-term use in at least 1 year. Those patients who had long-term use were prescribed a median of 670 days (IQR=218–1405) of opioids over an average 7.5±3.1 year follow up period. The percentage of patients with cirrhosis receiving opioid medications increased yearly from 36% receiving opioid prescriptions in 2005 to a steady 47% of patients with cirrhosis receiving opioids from 2011–2014 (*P* for trend <.001) (Figure 1).

The proportion of opioid recipients with long-term prescriptions increased from 47% to 54% (*P* for trend <.001) (Table 2). Over this time, the median daily dose ranged from 24 to 29 MME. At the start and end of follow up, 19% of recipients were prescribed ≥100 MME/day. Overlapping prescriptions of opioids and benzodiazepines decreased from 24% in 2005 to 19% in 2014 (*P*<.001). The percentage of opioid recipients prescribed acetaminophen-containing opioids decreased from 68% to 50% (*P*<.001) over follow up.

The most commonly-prescribed opioids were hydrocodone combined with acetaminophen, followed by tramadol and oxycodone. (Figure 2, Appendix 3). Over time, the use of hydrocodone combined with acetaminophen and codeine (with and without acetaminophen) decreased while oxycodone alone and tramadol increased. The percentage of each of the combination opioid-acetaminophen pills decreased from 2005–2014.

We assessed baseline patient-related factors associated with any subsequent opioid prescriptions over follow up. Compared to non-opioid users, those with subsequent any and long-term prescriptions over follow up were younger, more likely to be female, Vietnam era, and white at baseline (Table 3). Mental health comorbidities, HCV, HCC, pain-related conditions, surgery, and higher comorbidity scores were more common among patients with both any and long-term opioid use compared to those with no opioid use over follow up.

In multivariable models that accounted for changes in the covariates and opioid status over time, (Table 4), we found associations between opioid use and year, meaning that any and chronic opioid use significantly increased over time (adjusted odds ratio (AOR)=1.10, 95% confidence interval (CI)= 1.09–1.11 for any opioid and AOR=1.25,CI=1.23–1.27 for chronic opioid use). Opioid use was associated with younger age(AOR/year of increasing age=0.97CI=0.97–0.97), female sex(AOR=1.32,CI=1.20–1.46), White race(AOR for Black race=0.77,CI=0.72–0.84), Vietnam era(AOR=1.22,CI=1.18–1.26), HCV(AOR=1.72,CI=1.64–1.80), HCC(AOR=1.49,CI1.40–1.58), prior hepatic decompensation(AOR=1.09,CI=1.06–1.12), increased comorbidity scores(AOR per point=1.08,CI=1.08–1.09), nicotine use disorders(AOR=1.11,CI=1.08–1.13), mood disorders(AOR=1.13,CI=1.09–1.16), posttraumatic stress disorder(AOR=1.23, CI=1.19–1.27), pain-related conditions(AOR=2.08,CI=2.03–2.13), and surgery(AOR=1.17,CI=1.13–1.21). Those receiving opioids were significantly less likely to have prior opioid use disorders, alcohol use disorders, or other drug use disorders.

The relationships between covariates and long-term opioid prescriptions were similar to those with any opioid prescriptions, except that other race and unmarried status were significantly negatively associated with long-term but not any opioid prescriptions (Table 4).

Discussion

In this first national assessment of opioid prescribing among patients with cirrhosis, opioid prescribing increased between 2005 and 2014, stabilizing at nearly half of Veterans with cirrhosis in VA care receiving opioids in 2014. While the proportion receiving high-dose prescriptions or concurrent benzodiazepines or acetaminophen decreased slightly over time, these high-risk prescribing patterns remained common despite the unique safety risks for patients with cirrhosis. Several factors were independently associated with long-term opioid prescriptions, including some linked to elevated risk of adverse effects from opioids, including mental health disorders and decompensated liver disease.[18] Taken together, our findings demonstrate that patients with cirrhosis frequently receive prescription opioids, often with potentially risky prescribing patterns.

Although opioid prescribing in the general population of Veterans started to decline in 2012 as a result of the system-wide efforts of the VA Opioid Safety Initiative and significant efforts to improve clinician education, pain and addiction management, and risk mitigation nationally 6, 8 we did not observe a similar peak and decline among Veterans with cirrhosis during the study period. However, much of the decline in opioid prescribing in the general population occurred after our study period. More notably, the rates of prescribing in this population of patients with cirrhosis were far higher than the rates in the general VA population of 11–17% over the same time period.[8] The high rate of opioid prescribing in cirrhosis is likely not limited to Veterans - previous research among non-Veterans with cirrhosis found that opioid medications were the most commonly-prescribed form of analgesia and that 56% of patients with Child Class C cirrhosis were prescribed opioids.[28] Based on the consistency of both VA and non-VA reports, widespread opioid prescribing to patients with cirrhosis has likely not been addressed by population-level initiatives such as the Opioid Safety Initiative or other efforts and deserves more attention.

Combination opioid-acetaminophen tablets were used in at least half of the patients who were prescribed opioids. These combination tablets carry a notable risk of unintentional acetaminophen overdose and toxicity,[29] and are particularly dangerous in patients with cirrhosis due to lower thresholds for acetaminophen toxicity.[30] We found that the prescribing rates of opioid-acetaminophen combination pills in this cohort decreased starting in 2011. While there were no VA formulary changes that explain these trends, there was a growing recognition of the importance of avoiding acetaminophen-opioid combination products, including a 2011 FDA warning.[31]

Co-prescription of opioids with benzodiazepines was also common despite recommendations against this practice.[7] The co-prescription rate for patients in this cohort was 19–26% of the group receiving opioids compared to the rate of 7% of Medicaid patients in one study.[32] While these combinations decreased over time, the rates remain higher than ideal. Within VA there are ongoing efforts to address co-prescribing in the overall population, but there may be a need to tailor these initiatives to patients with cirrhosis and focus on combination pills in particular.

While all opioids are potentially problematic in the setting of cirrhosis, some opioids are considered preferable for pharmacologic reasons. For example,[33] while tramadol is considered to be generally less sedating than other opioids, its decreased drug clearance leads to a risk of accumulation, particularly in the context of decompensated hepatic disease.[34] Hydromorphone lacks toxic metabolites and has generally been considered to be the “safest” opioid12, 34 but it was infrequently used in this cohort. Thus, while all opioids carry risk, providers often used theoretically riskier opioids.

Our results indicate opioid prescribing occurs more commonly among patients with HCV, hepatic decompensation, and mental health disorders, consistent with prior finding in non-Veterans with cirrhosis.[28] These associations are concerning because HCV may be a proxy for prior opioid use disorder in this population, and patients with addiction histories have increased risks of prescription opioid-related overdose and death.[18] Moreover, opioid prescriptions are associated with opioid use disorders.[35] The overlap between pain, opioid

use, and mental health issues in this population speaks to the general potential of evidence-based, opioid-sparing approaches to pain that also address underlying mental health. Such approaches include cognitive behavioral therapy[36] exercise therapy[37] and comprehensive pain management programs.38 The finding that more advanced liver disease was associated with increased opioid prescribing is consistent with our prior findings in non-Veterans and concerning given the association between opioids and encephalopathy.

While this is the first national assessment of opioid prescribing in Veterans with cirrhosis, our approach had several limitations. First, we relied on administrative data, which inevitably carries the potential for misclassification. However, in order to maximize the validity of the results, we relied on previously published and validated data definitions.39–41 Second, we were unable to identify the indication for opioid use in our assessment and, in some instances, short-course opioids may be medically indicated (e.g., post-operative, hospice). However, we did include covariates measuring painful conditions, surgeries and comorbidities (including HCC and other cancers) to adjust for these factors. We also intentionally excluded opioid agonist therapy with methadone and buprenorphine from these analyses since these medications are used for substance use disorder treatment and in a distinct population. Third, there were missing data, particularly for MELD and race, but the rates of missingness were similar to other VA studies.[40] and our results did not change significantly when we excluded these variables. Fourth, while we included the last full year of data prior to ICD-10 conversion, these analyses did not extend beyond 2014. Time trends post-2014 will need to be studied, given that the highly-successful VA Opioid Safety Initiatives very well could have impacted the observed trends. Further, while prescription opioids have been previously associated with adverse clinical outcomes, analyses of clinical outcomes like hepatic decompensation or mortality were beyond the scope of this investigation.14, 15, 26 Lastly, we did not assess non-VA sources of opioids,[25] thus resulting in a conservative estimate of opioid use in this population.

In summary, opioid prescribing was common among patients with cirrhosis and prescribing patterns are often high-risk. In particular, patients were often prescribed high doses or co-prescribed benzodiazepines or combination pills with acetaminophen. Future research should address indications for opioid use and the effect of opioids of clinical outcomes. Our findings highlight a need to find opioid-sparing analgesic strategies in the cirrhosis patient population and develop targeted interventions to improve the safety of opioid prescribing specific to this high-risk group.

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Appendix

Appendix 1.

Data Definitions

Variable	ICD-9 Codes
Lack/inadequate housing	V60.0, V60.1
Hepatic decompensation	456.0-456.21, 789.59, 789.5, 572.2, 572.4, 567.23
Nicotine Use Disorder	305.1x
Alcohol Use Disorder	291.x; 303.xx, 305.0x, 291.x, 357.5, 425.5, 535.3; 571.0-571.3, 760.71, 790.3, V11.3
Opioid Use Disorder	304.0x, 305.5x
Other drug use disorders	304.1x-304.9x, 305.1x-305.4x, 305.6x-305.9x, 292.x, 648.3x, 655.5, 760.7x, 779.5, 965.0x
Mood Disorders	296.xx
Schizophrenia	295.xx
PTSD	309.81
HCC	155.0

Appendix

Appendix 2.

Yearly Demographic Characteristics of Veterans with Cirrhosis in VA Care 2005–2014

YEAR	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Characteristic	**n=86,328**	**n=88,773**	**n=89,224**	**n=89,017**	**n=88,915**	**n=87,461**	**n=85,462**	**n=81,880**	**n=76,960**	**n=71,002**
Demographic Characteristics										
Age (mean, sd)	58.7 (9)	59.5 (9)	60.2 (9)	60.8 (9)	61.3 (9)	61.9 (9)	62.6 (9)	63.2 (9)	63.8 (8)	64.5 (8)
Male Sex	84,499 (98)	86,860 (98)	87,283 (98)	87,060 (98)	86,696 (98)	85,482 (98)	83,486 (98)	79,918 (98)	75,051 (98)	69,154 (97)
Race										
Black	14,400 (17)	15,012 (17)	15,250 (17)	15,360 (17)	15,538 (18)	15,256 (17)	15,126 (18)	14,643 (18)	13,828 (18)	12,855 (18)
White	55,537 (64)	59,349 (67)	60,345 (68)	60,696 (68)	61,018 (69)	60,404 (69)	59,138 (69)	56,884 (69)	53,643 (70)	49,685 (70)
Other	2,068 (2)	2,192 (3)	2,238 (3)	2,270 (3)	2,267 (3)	2,289 (3)	2,250 (3)	2,188 (3)	2,082 (3)	1,958 (3)
Missing	14,323 (17)	12,220 (14)	11,391 (13)	10,691 (12)	10,092 (11)	9,512 (11)	8,948 (10)	8,165 (10)	7,407 (10)	6,504 (9)
Marital Status										
Married	33,881 (39)	35,056 (40)	35,410 (40)	35,406 (40)	35,570 (40)	35,180 (40)	34,529 (40)	33,287 (41)	31,408 (41)	29,265 (41)
Never Married/Single	11,200 (13)	11,494 (13)	11,488 (13)	11,455 (13)	11,414 (13)	11,227 (13)	11,040 (13)	10,588 (13)	10,000 (13)	9,278 (13)
Divorced/ Separated/ Widowed	41,163 (48)	42,094 (47)	42,220 (47)	42,059 (47)	41,829 (47)	40,945 (47)	39,776 (47)	37,894 (46)	35,432 (46)	32,331 (46)
Missing/ Unknown	84 (0)	99 (0)	106 (0)	97 (0)	102 (0)	109 (0)	117 (0)	111 (0)	120 (0)	128 (0)

YEAR	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Characteristic	**n=86,328**	**n=88,773**	**n=89,224**	**n=89,017**	**n=88,915**	**n=87,461**	**n=85,462**	**n=81,880**	**n=76,960**	**n=71,002**
Vietnam Era Period of Service	58,158 (67)	59,978 (68)	60,606 (68)	60,669 (68)	60,811 (68)	59,715 (68)	58,292 (68)	55,812 (68)	52,170 (68)	47,958 (68)
Homeless (n,%)	4,048 (5)	4,387 (5)	4,544 (5)	4,678 (5)	5,043 (6)	5,269 (6)	5,604 (7)	5,836 (7)	5,496 (7)	5,113 (7)
Liver-Related Characteristics										
MELD (median, IQR)	9 (7, 12)	9 (7, 12)	9 (7, 12)	9 (7, 12)	9 (7, 12)	9 (7, 12)	9 (7, 12)	9 (8, 12)	9 (8, 12)	9 (8, 12)
Etiology										
Hepatitis C ±alcohol	44,203 (51)	45,567 (51)	46,097 (52)	46,349 (52)	46,601 (52)	46,030 (53)	45,211 (53)	43,441 (53)	40,853 (53)	37,785 (53)
Alcohol	24,062 (28)	24,785 (28)	24,806 (28)	24,601 (28)	24,350 (27)	23,834 (27)	23,113 (27)	22,010 (27)	20,617 (27)	18,859 (27)
Hepatitis B	853 (1)	891 (1)	877 (1)	888 (1)	901 (1)	871 (1)	842 (1)	805 (1)	770 (1)	720 (1)
AIH/PSC/ PBC *	809 (1)	845 (1)	869 (1)	875 (1)	875 (1)	873 (1)	857 (1)	818 (1)	779 (1)	715 (1)
NASH	3,200 (4)	3,400 (4)	3,519 (4)	3,618 (4)	3,763 (4)	3,833 (4)	3,889 (5)	3,855 (5)	3,769 (5)	3,584 (5)
None	13,201 (15)	13,285 (15)	13,056 (15)	12,686 (14)	12,425 (14)	12,020 (14)	11,550 (14)	10,951 (13)	10,172 (13)	9,339 (13)
Hepatocellular carcinoma	1,484 (2)	2,395 (3)	2,918 (3)	3,319 (4)	3,985 (5)	4,639 (5)	5,250 (6)	5,976 (7)	6,425 (8)	6,717 (10)
Hepatic decompensation	9,704 (11)	11,441 (13)	12,379 (14)	12,851 (14)	13,790 (16)	14,905 (17)	15,671 (18)	16,653 (20)	17,343 (23)	18,176 (26)
Co-Morbidities										
Charlson Score (median, IQR)	2 (1, 3)	2 (1, 4)	2 (1, 4)	2 (1, 4)	2 (1, 4)	2 (1, 4)	2 (1, 4)	2 (1, 4)	2 (1, 4)	2 (1, 4)
Nicotine Use Disorder	21,350 (25)	21,179 (27)	25,536 (29)	27,916 (31)	27,932 (31)	27,031 (31)	26,257 (31)	25,103 (31)	23,449 (30)	21,818 (31)
Alcohol Use Disorder	26,787 (31)	29,797 (34)	30,546 (34)	31,233 (35)	31,843 (36)	32,059 (37)	31,632 (37)	30,669 (37)	29,040 (38)	27,320 (38)
Opioid Use Disorder	3,448 (4)	3,628 (4)	3,671 (4)	3,854 (4)	3,977 (5)	3,952 (5)	4,029 (5)	3,883 (5)	3,703 (5)	3,540 (5)
Cocaine Use Disorder	4,868 (6)	5,133 (6)	5,262 (6)	5,357 (6)	5,235 (6)	5,036 (6)	4,847 (6)	4,494 (6)	4,095 (5)	3,786 (5)
Cannabis Use Disorder	2,702 (3)	3,012 (3)	3,199 (4)	3,405 (4)	3,640 (4)	3,874 (4)	3,984 (5)	3,811 (5)	3,783 (5)	3,734 (5)
Other Drug Use Disorders	6,734 (8)	7,244 (8)	7,548 (9)	7,816 (9)	7,873 (9)	7,972 (9)	7,863 (9)	7,462 (9)	7,107 (9)	6,787 (10)
Mood Disorders	9,489 (11)	10,247 (12)	10,863 (12)	11,599 (13)	12,252 (14)	12,555 (14)	12,545 (15)	12,031 (15)	11,666 (15)	11,354 (16)
Schizophrenia	2,991 (4)	3,018 (3)	3,043 (3)	2,998 (3)	2,930 (3)	2,811 (3)	2,707 (3)	2,514 (3)	2,322 (3)	2,137 (3)
Posttraumatic Stress Disorder	11,565 (13)	12,436 (14)	13,007 (15)	13,512 (15)	13,785 (16)	14,037 (16)	14,085 (16)	13,731 (17)	13,037 (17)	12,473 (18)
Pain-Related Conditions	43,241 (50)	48,101 (54)	49,417 (55)	50,519 (57)	51,609 (58)	51,578 (59)	50,970 (60)	49,281 (60)	46,599 (61)	43,892 (62)

YEAR	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Characteristic	**n=86,328**	**n=88,773**	**n=89,224**	**n=89,017**	**n=88,915**	**n=87,461**	**n=85,462**	**n=81,880**	**n=76,960**	**n=71,002**
Surgery	4,049 (5)	5,388 (6)	6,103 (7)	6,457 (7)	6,887 (8)	6,953 (8)	7,438 (9)	7,505 (9)	7,348 (10)	7,117 (10)

*Except where indicated, cell values are n (%); Diagnoses are based on 1 inpatient or 2 outpatient ICD-9 codes from the baseline year in the cohort; MELD=Model for End-Stage Liver Disease; AIH=autoimmune hepatitis, PSC=primary sclerosing cholangitis, PBC=primary biliary cirrhosis; Pain related conditions include established ICD-9 code

Appendix

Appendix 3.

Number of Patients Prescribed Specific Opioids, 2005–2014*

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Any Opioid	30,907	33,827	35,983	37,982	39,638	40,025	39,769	38,439	35,774	33,144
Any Opioid +Acetaminophen*	21,064	22,006	22,878	23,643	25,570	24,451	23,646	21,810	19,412	16,452
Hydrocodone	12,791	14,320	15,913	17,063	18,864	18,806	18,622	17,683	15,733	12,887
Hydrocodone +Acetaminophen	12,772	14,299	15,894	17,049	18,842	18,785	18,601	17,674	15,725	12,879
Tramadol	7,022	8,547	10,199	11,383	12,127	12,074	12,107	12,007	11,586	11,782
Oxycodone	9,907	10,428	10,878	11,704	11,629	12,167	12,562	12,277	11,912	11,995
Oxycodone +Acetaminophen	5,936	5,619	5,292	5,380	6,464	5,061	4,656	3,944	3,507	3,569
Codeine	7,498	7,148	6,694	6,357	6,101	5,367	4,734	3,982	3,478	2,817
Codeine +Acetaminophen	5,605	5,280	4,844	4,408	4,054	3,575	2,969	2,397	1,969	1,554
Morphine	3,821	4,364	4,750	5,512	6,333	5,990	5,882	5,590	5,108	4,541
Methadone	2,364	2,605	2,651	2,654	2,728	2,450	2,262	2,037	1,751	1,457
Fentanyl Patch	644	603	580	547	581	564	562	590	556	502
Hydromorphone	469	608	770	873	1,522	1,301	1,457	1,374	1,268	1,221
Any Other Opioid	37	48	47	38	29	36	38	40	26	29

*combination pills are listed below parent compound and the parent compound total includes the combination and non-combination pills

Abbreviations:

AIH	autoimmune hepatitis
ARRR	adjusted relative rate ratio
AUD	alcohol use disorder
CDW	corporate data warehouse
CI	confidence interval
HBV	hepatitis B virus

HCV	hepatitis C virus
ICD	International Classification of Diseases
MELD	Model for End-Stage Liver Disease
MME	morphine mg equivalents
NAFLD	non-alcoholic fatty liver disease
NSAIDS	non-steroidal anti-inflammatory drugs
OUD	opioid use disorder
PBC	primary biliary cirrhosis
PSC	primary sclerosing cholangitis
PTSD	posttraumatic stress disorder
RRR	relative rate ratio
VA	Department of Veterans Affairs

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Background:

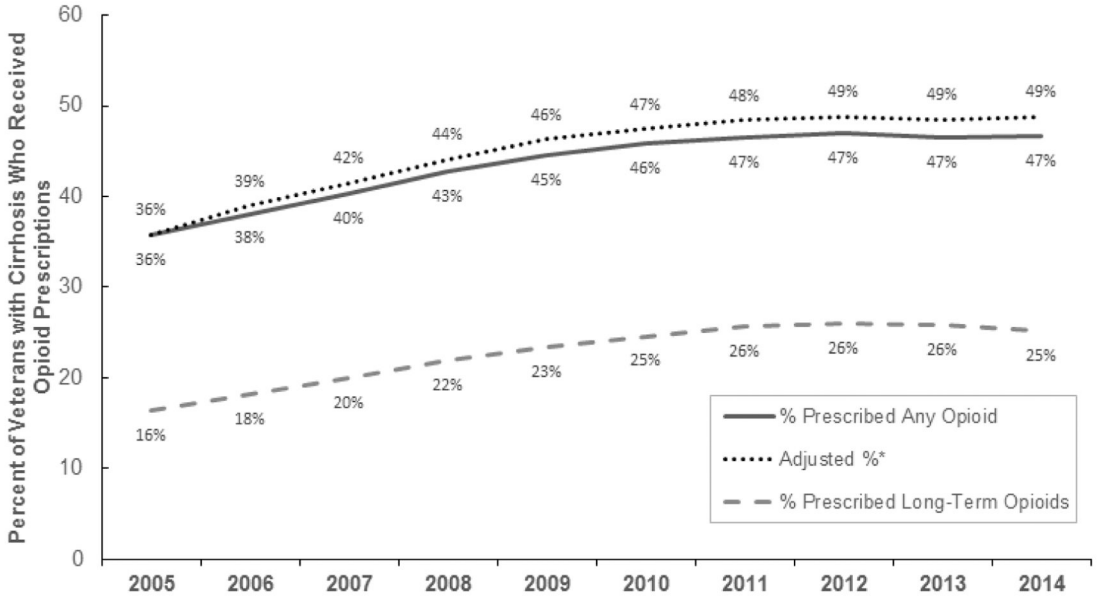
Although cirrhosis is associated with a high risk of prescription opioid-related overdose and death, little is known about how opioids are prescribed to patients with this common condition.

Findings:

Patients with cirrhosis were frequently prescribed opioids and these prescriptions were often high risk (e.g., high-dose, long-term, and associated with other high-risk prescriptions). Patients with co-occurring mental health and substance use disorders were more likely to receive chronic opioid prescriptions.

Implications for patient care:

It is important for clinicians to consider overdose and safety concerns for patients with cirrhosis who are prescribed opioids.



Number Prescribed ≥1 Opioid Medication in the Year	30,907	33,827	35,983	37,982	39,638	40,025	39,769	38,439	35,774	33,144
Number Prescribed Opioid Medications for ≥90 days in the Year	14,066	16,045	17,767	19,447	20,816	21,490	21,843	21,288	19,837	17,863
Total in Cohort	86,328	88,773	89,224	89,017	88,915	87,461	85,462	81,880	79,960	71,002

*percentages are adjusted for the cohort characteristics in each year including comorbidities and demographic and liver-related characteristics; chronic opioid prescriptions were defined as ≥90 days in the year

Figure 1. Observed and adjusted annual percent of Veterans with cirrhosis prescribed opioids and long-term opioids, 2005–2014

The increase in annual opioid prescribing to Veterans with cirrhosis over the study period was statistically significant ($p<0.001$) both before (solid line) and after (dotted line) adjusting for comorbitities and patient- and liver-related characteristics.

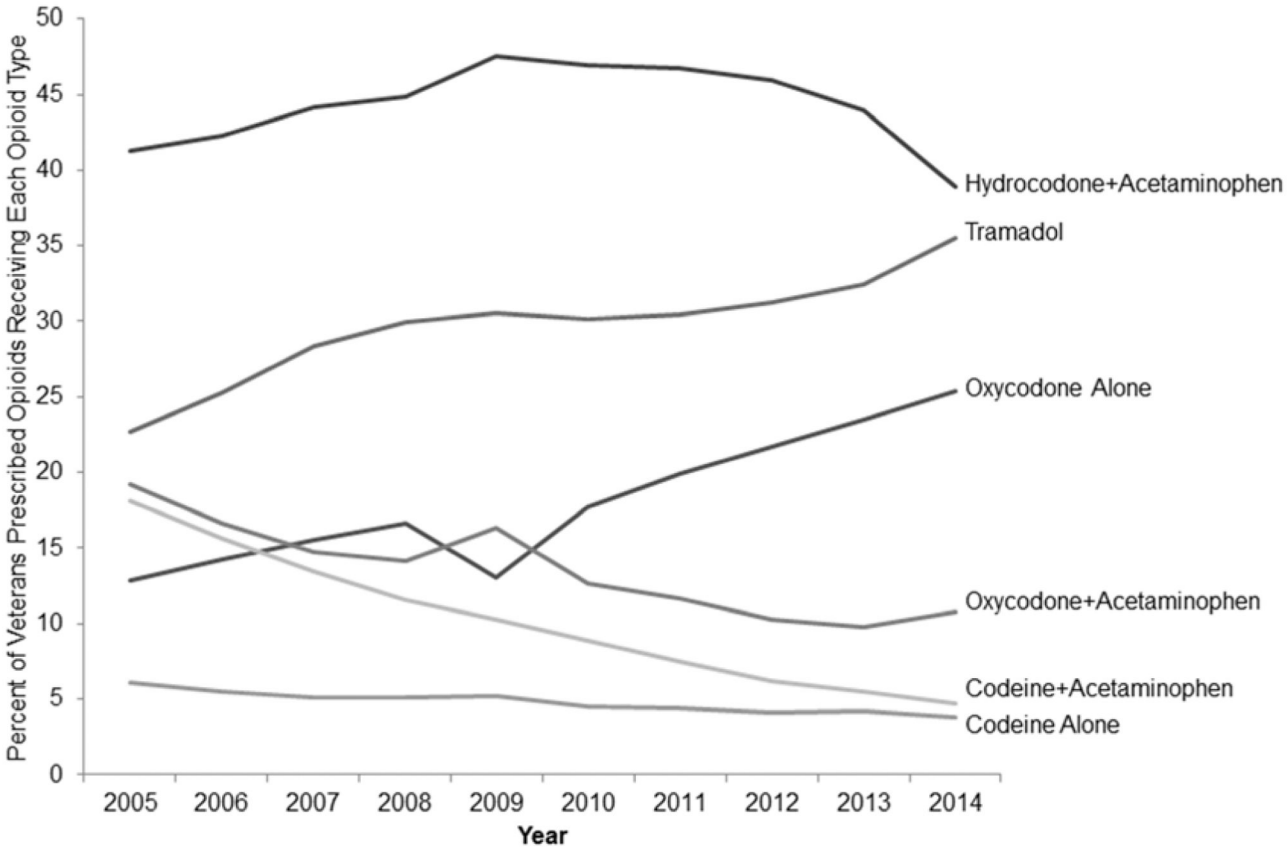


Figure 2.

Proportion of patients prescribed common types of opioid medications alone and in combination with acetaminophen, 2005–2014

Table 1.

Baseline Demographic and Clinical Characteristics of 127,239 Unique Veterans with Cirrhosis 2005–2014*

Baseline Characteristic	N(%)*
Demographic Characteristics	
Age, mean (sd)	58 (9)
Female	2,652 (2)
Race	
White	85,175 (67)
Black	20,127 (16)
Other	3,187 (3)
Missing	18,750 (15)
Marital Status	
Married	50,281 (40)
Never Married/Single	16,552 (13)
Divorced/Separated/Widowed	60,155 (47)
Missing/Unknown	251 (0)
Vietnam era period of service	84,953 (67)
Homeless	6,473 (5)
Liver-Related Characteristics	
MELD, median (IQR)	9 (7, 12)
Etiology	
Hepatitis C±alcohol	65,398 (51)
Alcohol	36,373 (29)
Hepatitis B	1,217 (1)
AIH/PSC/PBC	1,166 (1)
Other non-alcoholic liver disease	4,668 (4)
None of the above	18,417 (14)
Hepatocellular carcinoma	3,026 (2)
Hepatic decompensation	16,831 (13)
Co-Morbidities	
Charlson comorbidity score, median (IQR)	2 (1, 3)
Nicotine Use Disorder	30,936 (24)
Alcohol Use Disorder	40,137 (32)
Opioid Use Disorder	4,400 (4)
Cocaine Use Disorder	6,309 (5)
Cannabis Use Disorder	3,889 (3)
Sedative Use Disorder	510 (0)
Hallucinogen Use Disorder	67 (0)

Baseline Characteristic	**N(%)***
Amphetamine Use Disorder	917 (1)
Other Drug Use Disorders	9,101 (7)
Mood Disorders	12,459 (10)
Post-Traumatic Stress Disorder	14,171 (11)
Pain-Related Conditions	57,708 (45)
Surgery	5,729 (5)

* Except where indicated, cell values are N (%)

Diagnoses are based on 1 inpatient or 2 outpatient ICD-9 codes from the baseline year in the cohort

MELD=Model for End-Stage Liver Disease; IQR=interquartile range; AIH=autoimmune hepatitis, PSC=primary sclerosing cholangitis, PBC=primary biliary cirrhosis; Pain related conditions include established ICD-9 codes; missing data for MELD=13,89

Table 2.

Opioid Prescribing Patterns among Veterans Prescribed Opioids (2005–2014): Chronicity, dosing, and co-prescription with benzodiazepines or acetaminophen*

Prescribing Characteristics	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Total prescribed ≥1 opioid, N	30,907	33,827	35,983	37,982	39,638	40,025	39,769	38,439	35,774	33,144
Long-term opioid prescription	14,066 (46)	16,045 (47)	17,767 (49)	19,447 (51)	20,816 (53)	21,490 (54)	21,843 (55)	21,288 (55)	19,837 (56)	17,863 (54)
MME/day for days taking opioid, median (IQR)	26 (16, 45)	26 (16, 44)	27 (17, 45)	28 (18, 45)	28 (18, 45)	28 (18, 45)	29 (18, 45)	28 (17, 45)	29 (16, 45)	24 (15, 43)
High dose prescription (≥100 MME)	5775 (19)	6420 (19)	7072 (20)	7674 (20)	8278 (21)	8302 (21)	8377 (21)	7955 (21)	7334 (21)	6238 (19)
Co-prescription with benzodiazepine	7479 (24)	8602 (25)	9249 (26)	9384 (25)	9747 (25)	9627 (24)	9270 (23)	9035 (24)	7951 (22)	6425 (19)
At least one opioid prescribed with acetaminophen	21,064 (68)	22,006 (65)	22,878 (64)	23,643 (62)	25,570 (65)	24,451 (61)	23,646 (59)	21,810 (57)	19,412 (54)	16,452 (50)

*Except where indicated, cell values are N (%); all values are for the calendar year

Long-term opioid use defined as ≥90 days in the calendar year; (%) is the % of those prescribed opioids

MME=morphine milligram equivalents

High dose prescriptions are defined as at least one day with a total MME dose ≥100MME

Co-prescriptions with benzodiazepines defined as at least one day with both medications prescribed in the calendar year

Table 3.

Baseline Demographic and Clinical Characteristics by Opioid Status over Follow-up*

Characteristic	No Opioids (n=28,814)	Any Opioids (n=98,425)	Long-term Opioids (n=51,998)
Demographic Characteristics			
Age, mean (sd)	61 (10)	57 (8)	56 (8)
Female Sex	426 (1)	2,226 (2)	1,247 (2)
Race			
White	18,876 (66)	66,299 (67)	35,932 (69)
Black	3,281 (11)	16,846 (17)	8,402 (16)
Other	637 (2)	2,550 (3)	1,316 (3)
Missing	6,020 (21)	12,730 (13)	6,348 (12)
Marital Status			
Married	12,576 (44)	37,705 (38)	19,988 (38)
Not Married	16,125 (56)	60,582 (62)	31,946 (61)
Missing/Unknown	113 (0)	138 (0)	64 (0)
Vietnam Era Period of Service	17,466 (61)	67,487 (69)	36,855 (71)
Homeless	926 (3)	5,547 (6)	3,014 (6)
Liver-Related Characteristics			
MELD, median (IQR) **	10 (8, 14)	9 (7, 11)	8 (7, 11)
Etiology			
Hepatitis C±alcohol	10,524 (37)	54,874 (56)	31,241 (60)
Alcohol	10,552 (37)	25,821 (26)	12,320 (24)
Other/Unknown	7,738 (27)	17,730 (18)	8,437 (16)
Hepatocellular carcinoma	663 (2)	2,323 (2)	1,030 (2)
Hepatic decompensation	5,360 (19)	11,471 (12)	5,418 (10)
Comorbidities			
Charlson comorbidity score, median (IQR)	2 (1, 4)	2 (1, 3)	2 (1, 3)
Nicotine Use Disorder	5,221 (18)	25,715 (26)	14,945 (29)
Alcohol Use Disorder	9,316 (32)	30,821 (31)	16,381 (32)

Characteristic	No Opioids (n=28,814)	Any Opioids (n=98,425)	Long-term Opioids (n=51,998)
Opioid Use Disorder	543 (2)	3,857 (4)	2,401 (5)
Cocaine Use Disorder	715 (2)	5,597 (6)	3,179 (6)
Cannabis Use Disorder	511 (2)	3,378 (3)	1,986 (4)
Other Drug Use Disorders	1,112 (4)	7,989 (8)	4,627 (9)
Mood Disorders	1,650 (6)	10,809 (11)	6,773 (13)
Posttraumatic Stress Disorder	1,845 (6)	12,326 (13)	7,441 (14)
Pain Related Conditions	7,195 (25)	50,513 (51)	31,823 (61)
Surgery	424 (1)	5,305 (5)	3,003 (6)

*Except where indicated, cell values are n (%); covariates are defined during the year of entry; opioid status is defined at any year over follow up; long-term opioid use is defined as ≥90 days in at least 1 year, and is a subset of “any use”

Diagnoses are based on 1 inpatient or 2 outpatient ICD-9 codes from the baseline year in the cohort; surgery is based on CPT codes from VASQIP

**MELD=Model for End-Stage Liver Disease

IQR=interquartile range

Table 4.

Multivariable Mixed-Effects Logistic Regression Models for Associations of Demographic and Clinical Characteristics with Opioid Status

	Any Opioids vs No Opioids* (n=94,990)		Long-term Opioids vs No Opioids* (n=91,827)	
Characteristic	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Year	1.10 (1.09, 1.11)	<.001	1.25 (1.23, 1.27)	<.001
Demographic Characteristics				
Age	0.97 (0.97, 0.97)	<.001	0.94 (0.93, 0.94)	<.001
Female Sex	1.32 (1.20, 1.46)	<.001	1.56 (1.32, 1.83)	<.001
Race				
White	---	---	---	
Black	0.77 (0.72, 0.84)	<.001	0.36 (0.31, 0.41)	<.001
Other	1.00 (0.92, 1.08)	.95	0.82 (0.72, 0.93)	.002
Marital Status				
Married	---		—	
Unmarried	0.98 (0.94,1.01)	.22	0.89 (0.84, 0.94)	<.001
Vietnam Era	1.22 (1.18, 1.26)	<.001	1.82 (1.73, 1.92)	<.001
Homeless	1.04 (1.00,1.09)	0.06	1.01 (0.94, 1.09)	0.81
Liver-Related Characteristics				
MELD	1.00 (1.00,1.00)	0.42	1.00 (1.00, 1.00)	.45
Etiology				
Hepatitis C±alcohol	1.72 (1.64, 1.80)	<.001	3.87 (3.56, 4.20)	<.001
Hepatocellular carcinoma	1.49 (1.40, 1.58)	<.001	1.46 (1.31, 1.64)	<.001
Hepatic decompensation	1.09 (1.06, 1.12)	<.001	1.06 (1.01, 1.12)	.03
Comorbidities				
Charlson comorbidity score	1.08 (1.08,1.09)	<.001	1.12 (1.11, 1.13)	<.001
Nicotine Use Disorder	1.11 (1.08, 1.13)	<.001	1.20 (1.15, 1.25)	<.001
Alcohol Use Disorder	0.98 (0.96, 1.01)	.20	0.97 (0.93, 1.01)	.15
Opioid Use Disorder	0.91 (0.85, 0.98)	.01	0.70 (0.61, 0.79)	<.001
Other Drug Use Disorders	0.95 (0.92, 0.99)	.01	0.85 (0.80, 0.91)	<.001

Characteristic	Any Opioids vs No Opioids* (n=94,990)		Long-term Opioids vs No Opioids* (n=91,827)	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Mood Disorders	1.13 (1.09, 1.16)	<.001	1.19 (1.13, 1.26)	<.001
Posttraumatic Stress Disorder	1.23 (1.19, 1.27)	<.001	1.34 (1.27, 1.42)	<.001
Pain-Related Conditions	2.08 (2.03, 2.13)	<.001	3.99 (3.84, 4.14)	<.001
Surgery	1.17 (1.13, 1.21)	<.001	1.36 (1.30, 1.43)	<.001

*No opioids is the reference group; OR=odds ratio (all ORs are adjusted for other covariates in the model); covariates were modeled as time-varying (except for sex, period of service, marital status, and race)

CI=confidence interval; long-term opioid use is defined as ≥90 days, any opioid use includes those with long-term opioid use