Title

Medication Treatment of Active Opioid Use Disorder in Veterans With Cirrhosis.

Journal

The American journal of gastroenterology, 116(7)

ISSN

0002-9270

Authors

Rogal, Shari
Youk, Ada
Agbalajobi, Olufunso
et al.

Publication Date

2021-07-01

DOI

10.14309/ajg.0000000000001228

Peer reviewed

HHS Public Access

Author manuscript

Am J Gastroenterol. Author manuscript; available in PMC 2022 July 01.

Published in final edited form as:

Am J Gastroenterol. 2021 July 01; 116(7): 1406–1413. doi:10.14309/ajg.0000000000001228.

Medication Treatment of Active Opioid Use Disorder in Veterans with Cirrhosis

Shari Rogal, MD MPH[1,2,3], **Ada Youk, PhD**[1,4], **Olufunso Agbalajobi, MD MPH**[5], **Hongwei Zhang, PhD**[1], **Walid Gellad, MD MPH**[1,6,7], **Michael J. Fine, MD MSc**[1,6], **Pamela Belperio, PharmD MCPS**[8], **Timothy Morgan, MD**[9,10], **Chester B. Good, MD MPH**[1,6,11], **Kevin Kraemer, MD MSc**[1,5]

[1.]Center for Health Equity Research and Promotion, VA Pittsburgh Healthcare System, Pittsburgh, Pennsylvania

[2.]Department of Medicine, Division of Gastroenterology, Hepatology, and Nutrition, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

[3.]Department of Medicine, Division of Transplant Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

[4.]Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

[5.]Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

[6.]Division of General Internal Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

[7.]Center for Pharmaceutical Policy and Prescribing, Health Policy Institute, University of Pittsburgh, Pittsburgh, Pennsylvania.

[8.]Department of Veterans Affairs, Palo Alto Health Care System, Palo Alto, California

[9.]Gastroenterology Section, VA Long Beach Healthcare System, Long Beach, California

[10.]Division of Gastroenterology, Department of Medicine, University of California, Irvine, California

[11.]Centers for Value Based Pharmacy Initiatives and High Value Health Care, UPMC Health Plan Insurance Division, Pittsburgh, PA

Abstract

Objective: Though opioid use disorder (OUD) is common in patients with cirrhosis, it is unclear how medication treatment for OUD (MOUD) is used in this population. We aimed to assess the factors associated with MOUD and mortality in a cohort of Veterans with cirrhosis and OUD.

Corresponding Author: Shari Rogal, MD, MPH, Center for Health Equity Research and Development, VA Pittsburgh Healthcare System, University Drive C (151C), Pittsburgh, PA 15240, Shari.Rogal@va.gov, (412) 360-6177.

Specific author contributions: planning: SR, AY, WG, MF, TM, CB, KK; collecting data: HZ, AY; interpreting data: SR, KK, AY, WG, MF, PB, TM, CB; Drafting the manuscript: SR, OA, and AY; Critical edits to the manuscript: all authors. Authors approved submission

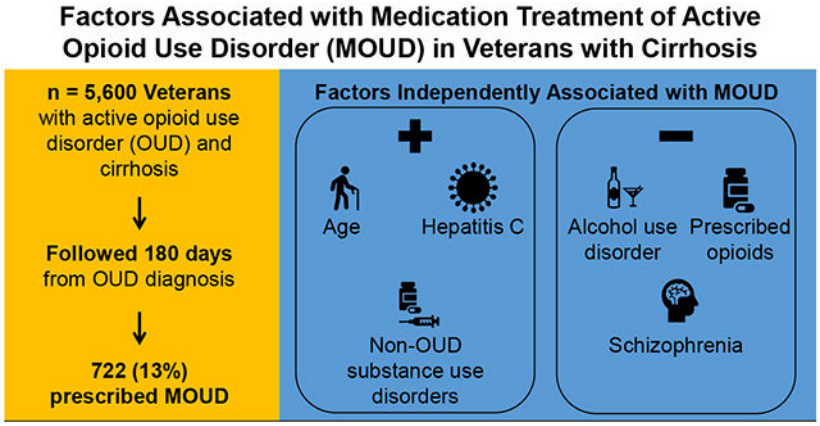
Potential competing interests: None declared

Methods: Within the Veterans Health Administration Corporate Data Warehouse, we developed a cohort of Veterans with cirrhosis and active OUD, using 2 outpatient or 1 inpatient ICD-9 codes from 2011-2015 to define each condition. We assessed MOUD initiation with methadone or buprenorphine over the 180 days following the first OUD ICD code in the study period. We fit multivariable regression models to assess the association of socio-demographic and clinical factors with receiving MOUD and the associations between MOUD and subsequent clinical outcomes, including new hepatic decompensation and mortality.

Results: Among 5,600 Veterans meeting criteria for active OUD and cirrhosis, 722 (13%) were prescribed MOUD over 180 days of follow-up. In multivariable modeling, MOUD was significantly, positively associated with age (Adjusted Odds Ratio (AOR) per year: 1.04, 95% Confidence Interval (CI): 1.01, 1.07), HCV (AOR=2.15, 95% CI=1.37, 3.35), and other substance use disorders (AOR=1.47, 95% CI=1.05, 2.04) negatively associated with alcohol use disorder (AOR=0.70, 95% CI=0.52, 0.95), opioid prescription (AOR=0.51, 95% CI=0.38, 0.70), and schizophrenia (AOR=0.59, 95% CI=0.37, 0.95). MOUD was not significantly associated with mortality (AHR=1.20, 95%CI=0.95-1.52) or new hepatic decompensation (OR=0.57 CI=0.30, 1.09).

Conclusion: Few Veterans with active OUD and cirrhosis received MOUD and those with alcohol use disorder, schizophrenia, and prior prescriptions for opioids were least likely to receive these effective therapies.

Graphical Abstract



Keywords

addiction; alcohol; heroin; drug treatment; hepatitis C; MOUD; methadone; buprenorphine

BACKGROUND

Opioid use disorder (OUD) is common among patients with cirrhosis. In fact the most common causes of cirrhosis, or advanced liver disease, are hepatitis C virus infection and alcohol abuse, which are associated with OUD.(1) In addition to using non-prescribed opioids, individuals with cirrhosis are often prescribed opioid medications for chronic pain, which can lead to subsequent OUD.(2–4)

Medication treatment for OUD (MOUD) is evidence-based and superior to abstinence-based, non-drug therapies.(5–7) There are three US Food and Drug Administration (FDA)-approved medications for MOUD: methadone, buprenorphine, and naltrexone.(7) In general patient populations, methadone and buprenorphine are highly efficacious but markedly underutilized.(8, 9) Naltrexone is more challenging in the general population due to its opioid antagonism mechanism and requirement for total abstinence from opioids before initiation and presents additional challenges for use in cirrhosis due to concerns for drug induced liver injury.(10–14)

There are several reasons why early evidence-based treatment for patients with OUD is particularly critical for patients with cirrhosis. Patients with chronic liver disease, compared to other populations, have more severe addiction and increased risk for dangerous opioid consumption behaviors.(15) MOUD programs can promote HCV treatment adherence and provide infrastructure around directly observed HCV treatment. MOUD treats OUD, which is a contraindication to transplant, the only cure for cirrhosis.(16) Despite the importance of effective OUD treatment for patients with cirrhosis, there are limited data about MOUD receipt in this population and its impact on outcomes. We thus aimed to 1) assess the factors associated with use of MOUD; and 2) determine whether MOUD is associated with hepatic decompensation or mortality in patients with cirrhosis and active OUD.

METHODS

Design and Data Sources

We performed a retrospective cohort study using data from the Veterans Health Administration (VA) Corporate Data Warehouse. We included all Veterans with cirrhosis and active OUD, defining cirrhosis as 2 outpatient and/or 1 inpatient International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) codes for this condition or its complications from 9/30/2011 to 10/31/2015. These validated ICD-9-CM codes included 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).(17) For further inclusion, Veterans were also required to have a diagnosis of OUD, defined as 2 outpatient and/or 1 inpatient validated ICD-9-CM codes for opioid dependence or abuse (304.00-304.02; 304.70-304.72; *305.5*, 305.50-305.52).(18, 19) We used the date of the first diagnostic code within the study time frame to define the OUD index diagnosis date.(20) To ensure that patients had active OUD, we excluded patients already receiving MOUD at their index diagnosis date.(20)

Assessment of MOUD

We used VA pharmacy prescription data and clinic codes to assess whether Veterans received MOUD, defined as any prescription for methadone or buprenorphine or a stop code for opioid replacement therapy (stop code 523) in the 180 days following the OUD index diagnosis. Because naltrexone is generally contraindicated in patients with cirrhosis and was prescribed to only 83 patients in our cohort, it was not considered to be an evidence-based MOUD for purposes of this study.

Covariate Definitions

We assessed covariates using data from the one-year period prior to the OUD index diagnosis. Data definitions are presented in Supplemental Table 1. Demographic information included age and body mass index (BMI) at cohort entry, race and ethnicity, sex, marital status, and homelessness. We defined underlying liver diseases as hepatitis C virus (HCV)-related (with or without other etiology), alcohol-related, or other/unspecified. Among those with HCV, we assessed prior treatment for HCV using VA pharmacy data, including both direct-acting and interferon-based treatments. Prior opioid prescriptions within VA were assessed using pharmacy data in the year prior to cohort entry. We calculated baseline Model for End-Stage Liver Disease (MELD) scores using the closest laboratory values preceding the index diagnosis date.(21) Comorbidities were defined using 2 outpatient or 1 inpatient ICD-9 codes and included mental health disorders (mood disorders, anxiety disorders, schizophrenia, PTSD), substance use disorders (nicotine, alcohol, and other), chronic painful conditions (22), and a composite of 16 individual weighted comorbid conditions operationalized as the Charlson Comorbidity Index that is predictive of all-cause mortality. (23) Opioid prescriptions in the year prior to baseline were also assessed, both overall and by class. Other substance use disorders included cocaine, cannabis, hallucinogens, sedatives, and non-specified disorders (Supplemental Table 1). We assessed for hepatic decompensation in the year prior to the index diagnosis, defined using 2 outpatient or 1 inpatient ICD-9 code for bleeding varices, hepatic encephalopathy, hepatopulmonary syndrome, ascites, spontaneous bacterial peritonitis, or hepatorenal syndrome.(17)

Clinical Outcomes: Hepatic Decompensation and Mortality

We collected all-cause mortality from the VA Corporate Data Warehouse and assessed survival until the end of follow-up (September 30, 2015) among the cohort of patients who were alive 6 months after the initial OUD diagnosis. We excluded patients who died in the first 6 months because this was the period of study for MOUD. Thus, the survival time was defined in days from index diagnosis of OUD+6 months until the end of follow-up or death. We assessed new hepatic decompensation over follow up among patients who did not have baseline decompensation, using the same ICD codes described in “Covariate Definitions.”

Statistical Analyses

We compared the baseline characteristics of the study cohort stratified by receipt of MOUD in the 6-months following index OUD diagnosis, using chi-square statistics for categorical variables and Students t-tests for continuous variables. We fit univariable and multivariable logistic regression models to assess the associations between all baseline patient characteristics and 6-month MOUD initiation, as defined above. We excluded patients who died in the first 180 days, since the primary independent variable of MOUD was defined over this period. Among patients without hepatic decompensation at baseline, we assessed the factors associated with new decompensation using logistic regression. We then fit cox-proportional hazards models to evaluate whether there was an association between MOUD and subsequent time to death, controlling for all covariates and conducted stratified analyses to assess for differences in the relationship between MOUD and mortality by baseline hepatic decompensation status. We used variance inflation factors with a

prespecified cutoff of 5 to assess collinearity in our models and none was found. For all analyses, we used two-tailed tests and a p-value of 0.05 to define statistical significance. We used Stata v15 for all analyses.

RESULTS

Cohort Characteristics

Of 93,612 Veterans with a diagnosis of cirrhosis in VA, 5,600 (6.0%) met study criteria for active untreated OUD and were included in the final cohort. The mean cohort age was 57±7 years, 98% were men, and 83% had HCV as a cause of cirrhosis. The mean MELD score was 10±4, 7% had experienced decompensation events within the past year, and 2% had a history of HCC. Few of the Veterans in this cohort had received HCV treatment (2%) and many were prescribed opioids in the year prior to their OUD diagnosis (52%). (Table 1)

Factors associated with MOUD

Within 180 days of the index OUD diagnosis, 722 patients (13%) received MOUD: 506 (70%) were treated with methadone and 216 (30%) with buprenorphine. In univariate analyses, patients who received MOUD were significantly older and more likely to have HCV and other substance use disorders than those who were not treated (Table 1). Those who received MOUD were significantly less likely to have a pain-related diagnosis or PTSD.

Five patient characteristics were independently associated with receiving MOUD in multivariable models (Table 2). Age (Adjusted Odds Ratio (AOR) per year: 1.04, 95% Confidence Interval (CI): 1.01, 1.07), HCV (AOR=2.25, 95% CI=1.37, 3.35), and other substance use disorders (AOR=1.47, 95% CI=1.05, 2.04) were positively associated with receiving MOUD, whereas alcohol use disorder (AOR=0.70, 95% CI=0.52, 0.95), opioid prescription (AOR=0.51, 95% CI=0.38, 0.70), and schizophrenia (AOR=0.59, 95% CI=0.37, 0.95) were negatively associated with this outcome.

MOUD and new hepatic decompensation

Among Veterans without baseline decompensation (n=5,189, 93%), 302 (6%) had new decompensation events over follow-up. While MOUD was associated with a borderline decrease in decompensation (AOR=0.57, 95% CI=0.30, 1.09), this was not statistically significant (Table 3). The factors associated with increased new decompensation included female gender, HCC, MELD, and AUD.

MOUD and mortality

Since the primary independent variable of MOUD was defined in the first 6 months of follow-up, we excluded the 73 (1%) patients who died in this period from further survival analyses. There were 1,736 deaths over the 5-year study period, excluding the first 6 months; 36% of the patients receiving MOUD vs. 30% of the patients not receiving MOUD died over follow-up. MOUD was not independently associated with survival time in adjusted models (AHR:1.20 95%CI:0.95-1.52, p=0.117) (Table 4). Stratified analyses revealed that age, race, HCC, and AUD were positively, significantly associated with mortality only in the

compensated stratum, and HCV etiology of liver disease was associated with mortality only in the decompensated stratum. MELD and Charlson comorbidity score were associated with death in both strata.

DISCUSSION

In this large cohort of Veterans with OUD and cirrhosis, we found that only a small percentage received MOUD over 6-months of follow-up, despite the efficacy of these medications and the ill effects of untreated OUD. We identified several factors that were positively associated with the receipt of MOUD, including other substance disorders, HCV, and age. In contrast schizophrenia, alcohol use disorder, and prescription opioids were negatively associated with MOUD. While providers and investigators have raised concerns about the safety of MOUD in patients with severe liver disease, we found no significant association between MOUD and increased mortality in this large cohort. There was in fact a trend towards decreased new hepatic decompensation associated with MOUD. This information significantly contributes to the literature, particularly as patients with chronic liver disease, compared to other populations have more severe addiction and are at increased risk for dangerous opioid consumptive behaviors.(15)

We identified three factors positively associated with MOUD in patients with cirrhosis, including other substance use disorders, HCV, and age. Older age has been previously associated with receipt of MOUD in the general Veteran population(24) but not among patients with commercial insurance.(25) While the reasons for these associations remain unclear, initiating MOUD at a younger age is associated with better retention in care, suggesting the need to target the younger population for early intervention.(26) HCV was also associated with MOUD. This may be related to the fact that providers often required OUD treatment before patients could receive interferon-based HCV medications, such that patients seeking HCV treatment may have been more likely to engage in MOUD.(27) In the post-interferon HCV treatment era, providers continue to use HCV treatment as an opportunity to engage patients in MOUD and vice versa.(28) The association between other substance use disorders and MOUD has also been identified in non-Veterans.(25) This association could be related to better documentation of substance use disorders for patients who are being referred to MOUD or could reflect polysubstance increases the likelihood of treatment referral.

It is notable that half of patients with OUD and cirrhosis received prescription opioids prior to cohort entry. This is concerning because opioids are associated with increased hospitalization, disability, and decompensation in patients with cirrhosis.(2, 3, 29–32) Prescription opioids are a common underlying cause of OUD and are more likely to cause overdose and other complications in people with a history of OUD.(33) Moreover, while collinearity precluded inclusion of prescription opioids and chronic pain in the same models, prior use of prescribed opioids was negatively associated with MOUD. This is concerning because it may reflect under-recognition and under-treatment of OUD in patients with chronic pain and chronic prescription opioid use. Further, this finding likely reflects the role of prescription opioids in promoting and exacerbating untreated OUD. Since the time of this study, VA has engaged in concerted opioid safety efforts to curtail opioid prescribing

in high-risk populations. Whether the benefits of these programs have reached patients with cirrhosis is an area of ongoing inquiry.

We found that alcohol use disorder was associated with *decreased* MOUD. This is problematic because the literature suggests that co-use of opioids and alcohol is common and is related to worse outcomes in treatment for either substance.(34) As was found in this cohort, chronic pain frequently co-occurs with use (and co-use) of alcohol and opioids.(34) Patients with OUD and chronic pain who have an additional diagnosis of AUD have significantly increased rates of opioid overdose, accidents, and injury, and higher all-cause health care costs compared with those not diagnosed with AUD.(35) Yet, they were less likely to receive treatment, which is problematic. Likewise, schizophrenia was negatively associated with MOUD in our study population, consistent with prior literature.(24) While this may relate to provider concerns about MOUD adherence, this suggests that there is a need to design approaches for these complex patients. Further research should focus on the co-management of pain, mental health disorders, OUD, and AUD in patients with liver disease.

Low rates of MOUD use are not unique to Veterans with cirrhosis. In fact, only 29-35% of adults with OUD in the general US population receive MOUD (36) and rates of MOUD are low in other Veteran populations.(20, 37) Barriers to MOUD uptake in the general population include regulatory requirements for prescription, lack of perceived patient interest, and lack of education about opioid agonist treatment.(38) Stigma around OUD and its treatment also serves as a significant barrier to treatment initiation and maintenance.(39–41) While insurance coverage of these medications may present barriers outside of VA, cost is less likely to be contributory in our cohort of Veterans with VA care.(42) These known barriers to MOUD implementation likely also apply to patients with cirrhosis and OUD.

While determinants of MOUD adoption in patients with cirrhosis have been understudied, there are several potential barriers that are unique to this population. One barrier may be misperceptions about the comparative harms of prescription opioids, OUD, and MOUD. Clinicians often are not aware of the comparative harms of even common over the counter medications for patients with cirrhosis, let alone more rarely used drugs.(43) Another unique barrier to MOUD in this population may be concerns about transplant eligibility. Transplantation is the only cure for cirrhosis, and one third of transplant programs consider MOUD to be a relative contraindication to transplantation.(44) Even when transplant programs accept candidates who are taking MOUD, historical exclusion of these patients may lead to confusion among referring clinicians. (45–50) Policies requiring discontinuation of methadone in the pre-transplant period contradict the evidence for long-term MOUD and can inadvertently lead to relapse of previously stable patients. While we did not assess transplant eligibility directly, concerns about transplant are likely not the primary driver of low MOUD uptake our cohort with low MELD scores. Patients with cirrhosis also often have acute medical issues which may take precedence over management of OUD management. Moreover, patients with cirrhosis are often comanaged by multiple specialists and there may be diffusion of responsibility regarding OUD management. Given the unique

needs of patients with cirrhosis, it is likely that MOUD implementation in this population will require unique strategies.

We found that there was not a significant association between MOUD and mortality. We thought this was important to address, since one barrier to MOUD in patients with cirrhosis may be drug safety concerns. It is notable that we did excluded the very small number of patients taking naltrexone from these analyses, since this medication is contraindicated in cirrhosis due to the potential for hepatotoxicity.[18] This lack of association between MOUD and mortality is in contrast to our prior finding that alcohol use disorder treatment was associated with reduced mortality in a cohort of Veterans with cirrhosis.(51)

While these data significantly add to the literature regarding OUD management in patients with cirrhosis, our study has several notable limitations. First, we cannot infer causality from these associations, which is a limitation inherent to any observational study. Moreover, the external validity of our findings may be limited because our cohort consisted almost exclusively of male Veterans and the majority had HCV as the etiology of their cirrhosis. Another limitation was the reliance on ICD-9-CM codes to define the cohort and covariates. Relying on codes likely underestimates the true prevalence of OUD in patients with cirrhosis, since OUD is often underdiagnosed and under-coded. This underestimation of the population would have biased towards finding higher, rather than lower, treatment rates. An additional limitation is that the data are from prior to the ICD-10 conversion. However, we anticipate that our findings would be unchanged, based on the slow adoption of MOUD nationally. Another limitation is that, while we included codes for methadone clinics as well as pharmacy data, we could have missed Veterans receiving services outside of the VA system. Moreover, details about the opioid drugs used by the subjects were not available, though it is possible that the treatment recommendations for patients misusing different types of opioids (e.g.; heroin vs. fentanyl vs. misuse of prescription opioids) may be different. A final limitation is that since few patients received MOUDs, we could not compare the relative safety or harms across medication types. Future work should assess the comparative efficacy and harm of MOUDs in patients with cirrhosis. Other data that would be of interest in future studies but were not available in this administrative data include detailed information about cause of death, craving, relapse, and other patient reported outcomes such as quality of life. Despite these limitations, this research brings attention to an important but understudied area of hepatology care.

In conclusion, patients with cirrhosis and OUD rarely receive evidence-based treatment. Patients with OUD and cirrhosis frequently have coexisting mental health and substance use comorbidities and prior opioid prescriptions. We identified a trend towards decreased decompensation and no change in mortality for Veterans with OUD and cirrhosis who received MOUD, suggesting that concerted efforts should be made to diagnose and treat OUD in patients with cirrhosis. Future research should focus on barriers to MOUD uptake, and further assessment of the safest and most efficacious way to implement OUD treatment in patients with cirrhosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Financial support:

AHRQ K12 HS019461; VISN 4 VA Competitive Pilot Project Fund Grant

References

1. Setiawan VW, Stram DO, Porcel J, et al. Prevalence of chronic liver disease and cirrhosis by underlying cause in understudied ethnic groups: The multiethnic cohort. Hepatology 2016;64:1969–1977. [PubMed: 27301913]
2. Rogal SS, Beste LA, Youk A, et al. Characteristics of Opioid Prescriptions to Veterans With Cirrhosis. Clin Gastroenterol Hepatol 2019;17:1165–1174 e3. [PubMed: 30342261]
3. Rogal SS, Bielefeldt K, Wasan AD, et al. Inflammation, psychiatric symptoms, and opioid use are associated with pain and disability in patients with cirrhosis. Clin Gastroenterol Hepatol 2015;13:1009–16. [PubMed: 25460019]
4. Palmer RE, Carrell DS, Cronkite D, et al. The prevalence of problem opioid use in patients receiving chronic opioid therapy: computer-assisted review of electronic health record clinical notes. Pain 2015;156:1208–14. [PubMed: 25760471]
5. Dematteis M, Auriacombe M, D'Agnone O, et al. Recommendations for buprenorphine and methadone therapy in opioid use disorder: a European consensus. Expert Opin Pharmacother 2017;18:1987–1999. [PubMed: 29183228]
6. Veilleux JC, Colvin PJ, Anderson J, et al. A review of opioid dependence treatment: pharmacological and psychosocial interventions to treat opioid addiction. Clin Psychol Rev 2010;30:155–66. [PubMed: 19926374]
7. Bart G Maintenance medication for opiate addiction: the foundation of recovery. J Addict Dis 2012;31:207–25. [PubMed: 22873183]
8. Mattick RP, Breen C, Kimber J, et al. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev 2014:CD002207. [PubMed: 24500948]
9. Wakeman SE, Larochelle MR, Ameli O, et al. Comparative Effectiveness of Different Treatment Pathways for Opioid Use Disorder. JAMA Netw Open 2020;3:e1920622. [PubMed: 32022884]
10. Lee JD, Nunes EV Jr., Novo P, et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. Lancet 2018;391:309–318. [PubMed: 29150198]
11. Reus VI, Fochtmann LJ, Bukstein O, et al. The American Psychiatric Association Practice Guideline for the Pharmacological Treatment of Patients With Alcohol Use Disorder. Focus (Am Psychiatr Publ) 2019;17:158–162. [PubMed: 32021585]
12. Kleber HD, Weiss RD, Anton RF Jr., et al. Treatment of patients with substance use disorders, second edition. American Psychiatric Association. Am J Psychiatry 2007;164:5–123.
13. SAMHSA. Advisory: An Introduction to Extended-Release Injectable Naltrexone for the Treatment of People with Opioid Dependence. 2012 [cited 2020 March 22]; Available from: https://store.samhsa.gov/product/An-Introduction-to-Extended-Release-Injectable-Naltrexone-for-the-Treatment-of-People-with-Opioid-Dependence/SMA12-4682
14. McDonough M. Naltrexone and liver disease. Aust Prescr 2015;38:151. [PubMed: 26648650]
15. Dennis BB, Akhtar D, Cholankeril G, et al. The impact of chronic liver disease in patients receiving active pharmacological therapy for opioid use disorder: One-year findings from a prospective cohort study. Drug Alcohol Depend 2020;209:107917. [PubMed: 32088589]
16. DiMartini A, Crone C, Dew MA. Alcohol and substance use in liver transplant patients. Clin Liver Dis 2011;15:727–51. [PubMed: 22032526]

17. Beste LA, Leipertz SL, Green PK, et al. Trends in burden of cirrhosis and hepatocellular carcinoma by underlying liver disease in US veterans, 2001-2013. Gastroenterology 2015;149:1471–1482 e5; quiz e17-8. [PubMed: 26255044]
18. Harris AH, Ellerbe L, Phelps TE, et al. Examining the Specification Validity of the HEDIS Quality Measures for Substance Use Disorders. J Subst Abuse Treat 2015;53:16–21. [PubMed: 25736624]
19. Harris AH, Reeder RN, Ellerbe LS, et al. Validation of the treatment identification strategy of the HEDIS addiction quality measures: concordance with medical record review. BMC Health Serv Res 2011;11:73. [PubMed: 21481264]
20. Wyse JJ, Robbins JL, McGinnis KA, et al. Predictors of timely opioid agonist treatment initiation among veterans with and without HIV. Drug Alcohol Depend 2019;198:70–75. [PubMed: 30878769]
21. Kamath PS, Kim WR, Advanced Liver Disease Study G. The model for end-stage liver disease (MELD). Hepatology 2007;45:797–805. [PubMed: 17326206]
22. Kaur S, Stechuchak KM, Coffman CJ, et al. Gender differences in health care utilization among veterans with chronic pain. J Gen Intern Med 2007;22:228–33. [PubMed: 17356991]
23. Charlson M, Szatrowski TP, Peterson J, et al. Validation of a combined comorbidity index. J Clin Epidemiol 1994;47:1245–51. [PubMed: 7722560]
24. Oliva EM, Harris AH, Trafton JA, et al. Receipt of opioid agonist treatment in the Veterans Health Administration: facility and patient factors. Drug Alcohol Depend 2012;122:241–6. [PubMed: 22115887]
25. Morgan JR, Schackman BR, Leff JA, et al. Injectable naltrexone, oral naltrexone, and buprenorphine utilization and discontinuation among individuals treated for opioid use disorder in a United States commercially insured population. J Subst Abuse Treat 2018;85:90–96. [PubMed: 28733097]
26. Lander LR, Zheng W, Hustead JD, et al. Long-term treatment retention in West Virginia's comprehensive opioid addiction treatment (COAT) program. J Neurol Sci 2020;411:116712. [PubMed: 32058182]
27. Rogal SS, McCarthy R, Reid A, et al. Primary Care and Hepatology Provider-Perceived Barriers to and Facilitators of Hepatitis C Treatment Candidacy and Adherence. Dig Dis Sci 2017;62:1933–1943. [PubMed: 28523579]
28. Rosenthal ES, Silk R, Mathur P, et al. Concurrent Initiation of Hepatitis C and Opioid Use Disorder Treatment in People Who Inject Drugs. Clin Infect Dis 2020.
29. Acharya C, Betrapally NS, Gillevet PM, et al. Chronic opioid use is associated with altered gut microbiota and predicts readmissions in patients with cirrhosis. Aliment Pharmacol Ther 2017;45:319–331. [PubMed: 27868217]
30. Klinge M, Coppler T, Liebschutz JM, et al. The assessment and management of pain in cirrhosis. Curr Hepatol Rep 2018;17:42–51. [PubMed: 29552453]
31. Rogal SS, Winger D, Bielefeldt K, et al. Healthcare utilization in chronic liver disease: the importance of pain and prescription opioid use. Liver Int 2013;33:1497–503. [PubMed: 23758842]
32. Moon AM, Jiang Y, Rogal SS, et al. Opioid prescriptions are associated with hepatic encephalopathy in a national cohort of patients with compensated cirrhosis. Aliment Pharmacol Ther 2020;51:652–660. [PubMed: 31960985]
33. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain--United States, 2016. JAMA 2016;315:1624–45. [PubMed: 26977696]
34. Witkiewitz K, Vowles KE. Alcohol and Opioid Use, Co-Use, and Chronic Pain in the Context of the Opioid Epidemic: A Critical Review. Alcohol Clin Exp Res 2018;42:478–488. [PubMed: 29314075]
35. Landsman-Blumberg PB, Katz N, Gajria K, et al. Burden of Alcohol Abuse or Dependence Among Long-Term Opioid Users with Chronic Noncancer Pain. J Manag Care Spec Pharm 2017;23:718–724. [PubMed: 28650247]
36. Krawczyk N, Feder KA, Fingerhood MI, et al. Racial and ethnic differences in opioid agonist treatment for opioid use disorder in a U.S. national sample. Drug Alcohol Depend 2017;178:512–518. [PubMed: 28719885]

37. Kraemer KL, McGinnis KA, Fiellin DA, et al. Low levels of initiation, engagement, and retention in substance use disorder treatment including pharmacotherapy among HIV-infected and uninfected veterans. J Subst Abuse Treat 2019;103:23–32. [PubMed: 31229189]
38. Mancher M, Leshner AI, editors. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Sciences Policy; Committee on Medication-Assisted Treatment for Opioid Use Disorders. Medications for Opioid Use Disorders Save Lives. Washington (DC): National Academies Press; 2019.
39. Stringer KL, Baker EH. Stigma as a Barrier to Substance Abuse Treatment Among Those With Unmet Need: An Analysis of Parenthood and Marital Status. J Fam Issues 2018;39:3–27. [PubMed: 29307947]
40. Barry CL, McGinty EE, Pescosolido BA, et al. Stigma, discrimination, treatment effectiveness, and policy: public views about drug addiction and mental illness. Psychiatr Serv 2014;65:1269–72. [PubMed: 25270497]
41. Corrigan PW, Schomerus G, Shuman V, et al. Developing a research agenda for reducing the stigma of addictions, part II: Lessons from the mental health stigma literature. Am J Addict 2017;26:67–74. [PubMed: 27875626]
42. Saloner B, Levin J, Chang HY, et al. Changes in Buprenorphine-Naloxone and Opioid Pain Reliever Prescriptions After the Affordable Care Act Medicaid Expansion. JAMA Netw Open 2018;1:e181588. [PubMed: 30646116]
43. Hong YM, Yoon KT, Heo J, et al. The Prescription Pattern of Acetaminophen and Non-Steroidal Anti-Inflammatory Drugs in Patients with Liver Cirrhosis. J Korean Med Sci 2016;31:1604–10. [PubMed: 27550489]
44. Fleming JN, Lai JC, Te HS, et al. Opioid and opioid substitution therapy in liver transplant candidates: A survey of center policies and practices. Clin Transplant 2017;31.
45. Di Martini A, Weinrieb R. Liver transplantation for methadone-maintained opiate dependents: making the case for cautious optimism. Am J Transplant 2003;3:1183–4. [PubMed: 14510688]
46. Hancock MM, Prosser CC, Ransibrahmanakul K, et al. Liver transplant and hepatitis C in methadone maintenance therapy: a case report. Subst Abuse Treat Prev Policy 2007;2:5. [PubMed: 17270050]
47. Jiao M, Greanya ED, Haque M, et al. Methadone maintenance therapy in liver transplantation. Prog Transplant 2010;20:209–14; quiz 215. [PubMed: 20929104]
48. Kanchana TP, Kaul V, Manzarbeitia C, et al. Liver transplantation for patients on methadone maintenance. Liver Transpl 2002;8:778–82. [PubMed: 12200777]
49. Koch M, Banys P. Liver transplantation and opioid dependence. JAMA 2001;285:1056–8. [PubMed: 11209177]
50. Koch M, Banys P. Methadone is a medication, not an addiction. Liver Transpl 2002;8:783–6. [PubMed: 12200778]
51. Rogal S, Youk A, Zhang H, et al. Impact of Alcohol Use Disorder Treatment on Clinical Outcomes among Patients with Cirrhosis. Hepatology 2019.

What is known?

Opioid use disorder (OUD) is common among patients with cirrhosis. Medication treatment for OUD (MOUD) is evidence-based and superior to abstinence-based non-drug therapies in general populations. However, there is an absence of data about receipt of MOUD in patients with cirrhosis or its impact on outcomes.

What are the new findings?

Patients with cirrhosis were rarely prescribed MOUD, and previous opioid prescriptions, schizophrenia, and alcohol use disorder decreased the likelihood of receiving MOUD. We found no significant association between MOUD and decompensation or mortality.

How might these findings impact clinical practice?

These findings suggest that providers should screen for and treat OUD in patients with cirrhosis. Subsets of patients at risk for non-treatment may require more targeted approaches to increase MOUD adoption.

Table 1.

Baseline Demographic and Clinical Characteristics Overall and Stratified by Medication Treatment of Opioid Use Disorder (MOUD)

Characteristics	Total Cohort	Cohort by MOUD Status		
	N=5600	No MOUD (n=4878)	MOUD (n=722)	p-value
Demographics				
Age (mean, sd)	56.8 (6.6)	56.6 (6.6)	57.8 (6.9)	<0.0001
BMI (mean, sd)*	28.4 (5.8)	28.4 (5.8)	28.2 (6.0)	0.237
Race/Ethnicity (N, %)				<0.0001
Non-Hispanic White	3380 (62.1)	3008 (63.5)	372 (6.9)	
Non-Hispanic Black	1226 (22.5))	1008 (21.3)	218 (31.1)	
Hispanic	582 (10.7)	501 (10.6)	81 (11.5)	
Other Race/ethnicity	255 (4.7)	224 (4.7)	31 (4.4)	
Female (N, %)	138 (2.5)	130 (2.7)	8 (1.1)	0.012
Marital status (N, %)				0.023
Married	1239 (24.5)	1093 (24.8)	146 (22.7)	
Single	1060 (21.0)	899 (20.4)	161 (25.0)	
Divorced/widowed	2761 (54.6)	2425 (54.9)	336 (52.3)	
Homeless (N, %)	800 (14.3)	706 (14.5)	94 (13.0)	0.297
Liver Disease Factors				
Etiology (N, %)				<0.001
Hepatitis C	4619 (82.5)	3954 (81.1)	665 (92.1)	
Alcohol	871 (15.6)	822 (16.9)	49 (6.8)	
Other/unspecified	110 (1.9)	102 (2.1)	8 (1.1)	
Prior decompensation (N, %)	411 (7.3)	363 (7.4)	48 (6.7)	0.445
Hepatocellular carcinoma (N, %)	92 (1.6)	75 (1.5)	17 (2.4)	0.107
Prior hepatitis C treatment	122 (2.2)	110 (2.3)	12 (1.7)	0.308
MELD* (mean, sd)	9.6 (4.0)	9.6 (4.0)	9.8 (4.0)	0.321
Substance Use Disorders				
Nicotine use disorder (N, %)	1719 (30.7)	1476 (30.3)	243 (33.7)	0.065
Alcohol use disorder (N, %)	1779 (31.8)	1589 (32.6)	190 (26.3)	<0.001

Characteristics	Total Cohort	Cohort by MOUD Status		
	N=5600	No MOUD (n=4878)	MOUD (n=722)	p-value
Other substance use disorders (N, %)	1737 (31.0)	1470 (30.1)	267 (37.0)	<0.001
Other Comorbidities				
Pain related diagnosis (N, %)	2930 (52.3)	2600 (53.3)	330 (45.7)	<0.001
Prior prescription opioids (N, %)				
Any opioid	2935 (52.4)	2666 (54.7)	269 (37.3)	<0.001
Hydrocodone	1368 (24.4)	1251 (25.7)	117 (16.2)	<0.001
Oxycodone	1140 (20.4)	1031 (21.1)	109 (15.1)	
Morphine	690 (12.3)	642 (13.2)	48 (6.7)	
Mood disorders (N, %)	2238 (40.0)	1964 (40.3)	274 (38.0)	0.236
Anxiety disorders (N, %)	622 (11.1)	549 (11.3)	73 (10.1)	0.361
Schizophrenia (N, %)	318 (5.7)	283 (5.8)	35 (4.9)	0.301
Post-traumatic stress disorder (N, %)	1055 (18.8)	941 (19.3)	114 (15.8)	0.025
Charlson comorbidity index (mean, sd)	0.82 (1.05)	0.82 (1.05)	0.82 (1.05)	0.961

*BMI=body mass index; MELD=model for end-stage liver disease; sd=standard deviation; missing data: MELD N=3,007, marital status for N=540, and for race N=157; for characteristics with missing data, %s are calculated based on the non-missing total number

Table 2.

Patient characteristics independently associated with MOUD*

Covariate	AOR (95% CI)	p-value
Demographics		
Age (per year)	1.04 (1.01, 1.07)	**0.003**
BMI	1.00 (0.98, 1.02)	0.917
Race/Ethnicity (vs. Non-Hispanic White)		
Non-Hispanic Black	1.35 (0.91, 1.99)	0.135
Hispanic	1.22 (0.66, 2.28)	0.529
Other race/ethnicity	1.07 (0.61, 1.89)	0.806
Female	0.18 (0.02, 1.30)	0.089
Marital status (vs. married)		
Single	1.15 (0.74, 1.76)	0.534
Divorced/widowed	1.06 (0.81, 1.38)	0.688
Homeless	0.85 (0.61, 1.20)	0.352
Liver Disease Factors		
Hepatitis C virus	2.15 (1.37, 3.35)	**0.001**
Prior hepatic decompensation	1.01 (0.69, 1.47)	0.970
Hepatocellular carcinoma	1.30 (0.64, 2.62)	0.471
MELD (per point)	1.00 (0.97, 1.03)	0.882
Prior hepatitis C treatment	0.90 (0.48, 1.70)	0.747
Substance Use Disorders		
Nicotine use disorder	1.24 (0.92, 1.67)	0.161
Alcohol use disorder	0.70 (0.52, 0.95)	**0.020**
Other substance use disorders	1.47 (1.05, 2.04)	**0.024**
Other Comorbidities		
Pain related diagnoses	0.94 (0.69, 1.27)	0.670
Opioid prescription	0.51 (0.38, 0.70)	**<0.001**
Mood disorders	0.98 (0.72, 1.35)	0.918

Covariate	AOR (95% CI)	p-value
Anxiety disorders	1.41 (1.01, 1.98)	**0.046**
Schizophrenia	0.59 (0.37, 0.95)	**0.031**
Post-traumatic stress disorder	0.80 (0.56, 1.14)	0.217
Charlson Comorbidity Index (per point)	1.05 (0.93, 1.19)	0.431

*MOUD=Medication treatment for opioid use disorder; BMI=body mass index; MELD=model for end-stage liver disease; AOR=adjusted odds ratio; CI=confidence interval

Table 3.

Factors associated with new hepatic decompensation

Covariate	AOR (95% CI)	p-value
MOUD	0.53 (0.28, 1.02)	0.059
Demographics		
Age (per year)	1.01 (0.98, 1.04)	0.472
BMI *	1.01 (0.96, 1.06)	0.678
Race/Ethnicity (vs. Non-Hispanic White)		
Non-Hispanic Black	0.38 (0.22, 0.66)	**<0.001**
Hispanic	0.60 (0.29, 1.24)	0.165
Other race/ethnicity	1.28 (0.54, 3.02)	0.581
Female	3.86 (1.65, 9.04)	**0.002**
Marital status (vs. married)		
Single	1.01 (0.58, 1.76)	0.964
Divorced/widowed	0.90 (0.58, 1.40)	0.639
Homeless	0.64 (0.29, 1.42)	0.271
Liver Disease Factors		
Hepatitis C virus	0.82 (0.49, 1.38)	0.456
Hepatocellular carcinoma	3.27 (1.08, 9.93)	**0.036**
MELD (per point)	1.17 (1.12, 1.22)	**<0.001**
Prior hepatitis C treatment	0.63 (0.16, 2.51)	0.512
Substance Use Disorders		
Nicotine use disorder	0.82 (0.55, 1.22)	0.323
Alcohol use disorder	2.09 (1.38, 3.18)	**0.001**
Other substance use disorders	0.52 (0.30, 0.90)	**0.020**
Other Comorbidities		
Pain related diagnoses	0.99 (0.59, 1.66)	0.970

Covariate	AOR (95% CI)	p-value
Opioid prescription	0.65 (0.41, 1.01)	0.054
Mood disorders	0.98 (0.66, 1.47)	0.926
Anxiety disorders	0.81 (0.44, 1.52)	0.521
Schizophrenia	1.16 (0.48, 2.83)	0.742
Post-traumatic stress disorder	0.72 (0.43, 1.19)	0.202
Charlson Comorbidity Index (per point)	0.75 (0.61, 0.91)	**0.005**

*MOUD=Medication treatment for opioid use disorder; BMI=body mass index; MELD=model for end-stage liver disease; AOR=adjusted odds ratio; CI=confidence interval

Table 4.

Independent association between MOUD* and all-cause mortality in patients with cirrhosis and active opioid use disorder; overall and stratified by baseline decompensation status

	Overall		Compensated		Decompensated	
Covariate	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
MOUD	1.21 (0.96, 1.52)	0.099	1.20 (0.92, 1.57)	0.172	1.31 (0.81, 2.11)	0.267
Demographics						
Age (per year)	1.03 (1.01, 1.04)	**<0.001**	1.03 (1.01, 1.04)	**<0.001**	1.02 (0.99, 1.05)	0.249
BMI	0.99 (0.98, 1.01)	0.274	1.00 (0.98, 1.01)	0.619	0.97 (0.94, 1.01)	0.120
Race/Ethnicity (vs. Non-Hispanic White)						
Non-Hispanic Black	0.72 (0.61, 0.86)	**<0.001**	0.70 (0.57, 0.87)	**0.001**	0.86 (0.56, 1.34)	0.508
Hispanic	1.05 (0.87, 1.28)	0.606	0.99 (0.76, 1.27)	0.922	1.57 (0.95, 2.60)	0.079
Other race/ethnicity	0.84 (0.57, 1.24)	0.385	0.93 (0.61, 1.42)	0.739	0.73 (0.29, 1.84)	0.508
Female	0.66 (0.33, 1.32)	0.243	0.62 (0.26, 1.47)	0.275	0.64 (0.14, 2.93)	0.570
Marital status (vs. married)						
Single	0.97 (0.76, 1.23)	0.782	0.97 (0.74, 1.27)	0.825	1.05 (0.59, 1.86)	0.880
Divorced/widowed	1.09 (0.89, 1.35)	0.403	1.08 (0.87, 1.35)	0.484	1.32 (0.80, 2.16)	0.279
Homeless	0.93 (0.71, 1.20)	0.564	0.91 (0.68, 1.23)	0.544	0.85 (0.56, 1.28)	0.429
Liver Disease Factors						
Hepatitis C virus	1.26 (1.02, 1.55)	**0.033**	1.16 (0.93, 1.46)	0.196	1.83 (1.04, 3.21)	**0.035**
Prior hepatic decompensation	1.82 (1.49, 2.22)	**<0.001**	n/a		n/a	
Hepatocellular carcinoma	2.26 (1.54, 3.32)	**<0.001**	2.74 (1.89, 3.98)	**<0.001**	1.53 (0.74, 3.18)	0.253
MELD (per point)	1.05 (1.03, 1.07)	**<0.001**	1.05 (1.03, 1.07)	**<0.001**	1.03 (1.00, 1.06)	**0.034**
Prior hepatitis C treatment	1.03 (0.72, 1.47)	0.875	1.00 (0.67, 1.50)	0.993	1.25 (0.59, 2.65)	0.565
Substance Use Disorders						
Nicotine use disorder	1.00 (0.86, 1.16)	0.969	0.95 (0.79, 1.15)	0.607	1.11 (0.74, 1.65)	0.614
Alcohol use disorder	1.26 (1.08, 1.47)	**0.003**	1.39 (1.15, 1.66)	**<0.001**	0.90 (0.63, 1.30)	0.586
Other substance use disorders	1.08 (0.91, 1.28)	0.392	1.04 (0.86, 1.26)	0.675	1.38 (0.95, 1.99)	0.089

	Overall		Compensated		Decompensated	
Covariate	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Other Comorbidities						
Pain related diagnoses	0.91 (0.76, 1.08)	0.260	0.92 (0.75, 1.12)	0.390	0.94 (0.68, 1.31)	0.709
Opioid prescription	1.04 (0.87, 1.25)	0.650	1.03 (0.83, 1.29)	0.757	1.14 (0.77, 1.68)	0.513
Mood disorders	0.91 (0.77, 1.06)	0.223	0.86 (0.72, 1.01)	0.073	1.15 (0.82, 1.62)	0.412
Anxiety disorders	0.79 (0.63, 1.00)	**0.048**	0.77 (0.61, 0.99)	**0.042**	0.89 (0.53, 1.52)	0.679
Schizophrenia	0.95 (0.71, 1.27)	0.744	1.01 (0.72, 1.42)	0.955	0.68 (0.34, 1.33)	0.255
Post-traumatic stress disorder	0.91 (0.76, 1.09)	0.314	0.85 (0.68, 1.07)	0.164	1.07 (0.74, 1.56)	0.716
Charlson Comorbidity Index (per point)	1.13 (1.06, 1.21)	**<0.001**	1.13 (1.05, 1.20)	**0.001**	1.16 (1.00, 1.34)	**0.049**

*MOUD=Medication treatment for opioid use disorder; BMI=body mass index; MELD=Model for end-stage liver disease; HR=hazard ratio; CI=confidence interval