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Authors
Rogal, Shari
Youk, Ada
Zhang, Hongwei
et al.

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Impact of Alcohol Use Disorder Treatment on Clinical Outcomes among Patients with Cirrhosis

Shari Rogal[1,2,3], **Ada Youk**[1,4], **Hongwei Zhang**[1], **Walid F. Gellad**[1,5], **Michael J. Fine**[1,5], **Chester B. Good**[1,5,6], **Maggie Chartier**[7], **Andrea DiMartini**[2,8], **Timothy Morgan**[9,10], **Ramon Bataller**[3], **Kevin L. Kraemer**[1,5]

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

[2]Department of Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

[3]Division of Gastroenterology, Hepatology, and Nutrition, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

[4]Department of Biostatistics, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

[5]Division of General Internal Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

[6]Center for High Value Pharmacy Initiatives, University of Pittsburgh Medical Center Health Plan, Pittsburgh, PA

[7]HIV, Hepatitis and Related Conditions Programs, Office of Specialty Care Services, Veterans Health Administration, Washington, DC, USA

[8]Department of Psychiatry, University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinic, Pittsburgh, PA 15213, USA

[9]Gastroenterology Section, VA Long Beach Healthcare System, Long Beach, CA, USA

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

Abstract

Despite significant medical and economic consequences of coexisting alcohol use disorder (AUD) in patients with cirrhosis, little is known about AUD treatment patterns and their impact on clinical outcomes in this population. We aimed to characterize the use of and outcomes associated with AUD treatment in patients with cirrhosis. This retrospective cohort study included Veterans with cirrhosis who received Veterans Health Administration (VA) care and had an index diagnosis of AUD between 2011 and 2015. We assessed the baseline factors associated with AUD treatment (pharmacotherapy or behavioral therapy) and clinical outcomes for 180 days following the first AUD diagnosis code within the study time frame. Among 93,612 Veterans with cirrhosis, we

Corresponding Author: Shari S. Rogal, Center for Health Equity Research and Promotion, VA Pittsburgh Healthcare System, Building 30, Room 2A113, University Drive C (151C), Pittsburgh, PA 15240-1001, USA, Tel: 412-360-2149, Shari.Rogal@va.gov.

identified 35,682 with AUD, after excluding 2,671 who had prior diagnoses of AUD and recent treatment. Over 180 days following the index diagnosis of AUD, 5,088 (14%) received AUD treatment, including 4,461 (12%) who received behavioral therapy alone, 159 (0.4%) who received pharmacotherapy alone, and 468 (1%) who received both behavioral and pharmacotherapy. In adjusted analyses, behavioral and/or pharmacotherapy-based AUD treatment was associated with a significant reduction in incident hepatic decompensation (6.5% vs. 11.6%, adjusted odds ratio [AOR]=0.63, 95% confidence interval [CI]=0.52–0.76) and a non-significant decrease in short-term all-cause mortality (2.6% vs. 3.9%, AOR=0.79, 95% CI=0.57–1.08), and a significant decrease in long-term all-cause mortality (51% vs. 58%, AOR=0.87, 95% CI=0.80, 0.96).

Conclusion: Most patients with cirrhosis and coexisting AUD did not receive behavioral or pharmacotherapy treatment for AUD over a 6-month follow-up. The reductions in hepatic decompensation and mortality suggest that future studies should focus on delivering evidence-based AUD treatments to patients with coexisting AUD and cirrhosis.

Keywords

Addiction; alcoholism; decompensation; ascites; encephalopathy

Alcohol is a leading cause of morbidity and mortality globally.[1] Although alcohol use has been recognized as a leading cause of cirrhosis worldwide and a major contributor to ongoing liver injury among patients with cirrhosis,[2] advances in the field of alcohol-related liver disease lag behind those for other causes of chronic liver disease, such as viral hepatitis. In fact, the only effective treatment for alcohol-related cirrhosis is alcohol cessation.[3] Despite the importance of treating alcohol use disorder (AUD) in the context of cirrhosis, relatively little work has assessed the uptake of evidence-based AUD treatments in patients with this common disorder.

Evidence-based treatments for AUD include behavioral and pharmacological therapies. Behavioral therapies are considered to be the cornerstone of AUD treatment in patients with alcohol-related liver disease[2,4] and several forms of such therapy can be successful in patients with coexisting AUD and cirrhosis.[5] Pharmacotherapy combined with behavioral therapy is considered to be the best treatment for AUD in general populations.[6] However, the three FDA-approved pharmacotherapies for AUD, including disulfiram, naltrexone, and acamprosate, have not been tested in patients with cirrhosis in randomized trials.

Treating AUD in the context of alcohol-related liver disease is recognized as an important benchmark of high quality care.[7,8] However, it remains unclear how often patients with cirrhosis and AUD receive evidence-based behavioral and/or pharmacologically based therapies. We aimed to characterize the use of and outcomes associated with AUD treatment in patients with cirrhosis.

PATIENTS AND METHODS

Design and Data Sources

We conducted a retrospective cohort study that included all Veterans with clinical encounters in the national Veterans Health Administration (VA) Corporate Data Warehouse who were

diagnosed with cirrhosis, defined as 2 outpatient and/or 1 inpatient International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) codes for this medical condition or its complications, between 2011 and 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).[9] For further inclusion in the cohort, these Veterans were also required to have a diagnosis of AUD, defined as 2 outpatient or 1 inpatient ICD-9-CM codes (291.xx, 303.00–303.02, 303.90–303.92, 305.00–305.02; 535.3; 571.1) for alcohol dependence or abuse.[7,10] These codes for AUD have a specificity of 92–93% within VA.[11] We used the date of the first detected AUD diagnostic code within the study time frame to define the date of the AUD index diagnosis and excluded patients with prior AUD diagnoses and AUD treatment (defined below) in the 60 days prior to the AUD index diagnosis, to ensure that patients were not already receiving treatment, and thus had a new opportunity to receive treatment, consistent with prior literature.[7,12]

Baseline Data Collection

Baseline data were assessed using a one-year look back period prior to the index diagnosis of AUD. We extracted demographic information (age at index diagnosis, race, ethnicity, sex, marital status, period of military service, and homelessness, defined as ICD-9-CM codes V60.0 and V60.1). We assessed the etiology of cirrhosis, categorized as alcohol-related, hepatitis C virus (HCV)-related, or other, using previously-validated codes[9] and calculated baseline Model for End-Stage Liver Disease (MELD) scores using the laboratory values closest to the index diagnosis date.[13] We extracted comorbidities in the year prior to the index AUD diagnosis, including other mental health and substance use disorders and the Charlson Comorbidity Index (excluding liver disease).[14] All code-based comorbidities required 2 outpatient codes or 1 inpatient code to meet criteria for the condition. Hepatic decompensation was defined to include ICD-9-CM codes for bleeding varices, hepatic encephalopathy, hepatopulmonary syndrome, ascites, spontaneous bacterial peritonitis, or hepatorenal syndrome. Alcohol Use Disorders Identification Test-Consumption screening tool (AUDIT-C) scores were also extracted from the chart to further assess the pattern of alcohol use.[15] The AUDIT-C is a three-item alcohol screen scored from 0–12 that identifies at-risk drinkers in the general population.

Assessment of AUD Treatments

We obtained data from patients for 180 days after the AUD index diagnosis to assess new forms of behavioral and pharmacotherapy-based AUD treatments. We defined behavioral treatment using previously-validated Healthcare Effectiveness Data and Information Set measures based on ICD-9 and Common Procedural Terminology codes.[7,12] This definition requires that patients have a qualifying diagnosis of AUD and a mental health procedure code (either inpatient or outpatient), as validated for use in VA.[7] We used pharmacy data to identify pharmacotherapy based treatment, consisting of three FDA-approved agents for AUD (i.e., disulfiram, acamprosate, and naltrexone.).[16] Using all forms of therapy, w categorized patients as having any vs. no AUD treatment in the 180 days following the AUD

index diagnosis. We further categorized treatment as behavioral only, pharmacotherapy only, and both behavioral and pharmacotherapy-based treatment.

Assessment of Clinical Outcomes

All patients were followed for a total of 180 days from their AUD index diagnosis for clinical outcomes, including all-cause mortality and new hepatic decompensation (among the subgroup without baseline decompensation). Hepatic decompensation was defined to include ICD-9-CM codes for bleeding varices, hepatic encephalopathy, hepatopulmonary syndrome, ascites, spontaneous bacterial peritonitis, or hepatorenal syndrome. All-cause mortality and dates of death were extracted from the Corporate Data Warehouse. We excluded patients with a history of hepatic decompensation at baseline from the assessment of new onset decompensation. To do this, we removed patients with ICD-9 codes for hepatic decompensation in the baseline year from our models assessing decompensation as a clinical outcome. As a secondary analysis, we extended follow-up to the end of the study period. This allowed us to assess the impact of 180-day treatment on long-term mortality.

Statistical Analyses

We compared the baseline characteristics of the study cohort by treatment type (behavioral only, pharmacotherapy only, and both), using chi-square statistics (or Fisher's Exact) for the categorical variables, where appropriate, t-tests or ANOVA for normally distributed continuous variables, and Wilcoxon rank sum or Kruskal-Wallis tests for continuous, non-normally distributed variables. To assess the associations between the baseline factors and AUD treatment within 180 days of the AUD index diagnosis, we fit univariate logistic models for any treatment and multinomial models for treatment type (pharmacotherapy, behavioral therapy or both vs. none). Variables that were statistically significant ($p<0.05$) in the univariate models were included in the final multivariable logistic regression model for any treatment and multinomial model of treatment type. In addition, we fit logistic regression models to assess the factors associated with 180-day mortality and new hepatic decompensation (in the subgroup without baseline decompensation), using treatment as the primary independent variable of interest. We first fit univariate models and used those variables that were statistically significant ($p<0.05$) as adjustment variables in a multivariable logistic regression model. To be included as "treated" at the time of a clinical outcome, treatment had to have been initiated prior to the date of the outcome (either death or new hepatic decompensation) in these models; otherwise these patients were counted as "untreated" for the purposes of the clinical outcome modeling. We only assessed "any" AUD treatment, rather than type of treatment because relatively few patients received pharmacotherapy. Collinearity was assessed with variance inflation factors (using a prespecified cutoff of 5), and no collinearity was found in the models. Stata v15 was used for all analyses.

Secondary Analyses

To assess how our associations varied between subgroups we repeated the analyses for the following: 1) patients without HCV and 2) patients without hepatic decompensation prior to their index AUD diagnosis, and 3) patients with acute alcoholic hepatitis (AAH), defined as ICD-9 code 571.1. While baclofen is not an FDA-approved pharmacotherapy for AUD, there

is increasing interest in its efficacy and use for this indication.[17] We therefore assessed the prevalence of baclofen use and the factors associated with baclofen prescribing in a multivariable logistic regression model and then entered baclofen into the multivariable regression model for death.

RESULTS

Baseline characteristics of the study cohort

Of 93,612 Veterans with a diagnosis of cirrhosis in VA from 2011–2015, 38,353 (41%) met criteria for AUD, and 35,682 (38% of all Veterans with cirrhosis) had not received AUD treatment in the prior 60 days. These 35,682 patients were included in the final cohort (Figure 1). The mean age (standard deviation) of patients in the cohort was 59±8 years; the majority were white (71%), male (98%), and served in Vietnam (66%). Half of the cohort also had HCV as a cause of cirrhosis, and half had alcohol alone. Only 8% had hepatic decompensation in the preceding year. Nicotine and substance use disorders were found in 22% and 7% of the cohort respectively. Mental health disorders were relatively common in this cohort, with 22% having mood disorders, 12% post-traumatic stress disorder (PTSD), 6% with anxiety disorders and 3% with schizophrenia (Table 1).

AUD treatment over follow-up

In the 180 days following the AUD index diagnosis, 5,388 (14%) patients were initiated on AUD therapy (Figure 1). Of the 35,682 patients with concomitant cirrhosis and AUD, 4,461 (12%) received behavioral therapy only, 159 (0.4%) pharmacotherapy-based therapy only, and 468 (1%) received both forms of therapy within 180 days of their AUD index diagnosis (Figure 1). Of those receiving any pharmacotherapy, 94 (15%) received disulfiram, 163 (26%) received acamprosate, and 370 (59%) received naltrexone. Among the patients receiving naltrexone, 5 (1%) had a comorbid opioid use disorder diagnosis.

In univariate analyses, we found that patients with cirrhosis and AUD who received AUD treatment were significantly more likely to be younger, non-white, female, single, homeless, and non-Vietnam era of service (Table 1). They were more likely to have HCV and less likely to have prior hepatic decompensation or hepatocellular carcinoma. Patients receiving any treatment had significantly lower MELD and Charlson Comorbidity Index scores at baseline and were more likely to have other mental health and substance use disorders as well as higher AUDIT-C scores.

Multivariate models of the factors associated with receiving any AUD treatment at follow-up resulted in adjusted odds ratios (AOR) ranging from 0.87 (95% confidence interval [CI] .83–.91) for the Charlson Comorbidity Index to 1.77 (95% CI 1.46–2.16) for a history of cocaine use (Table 2). Patients with older age and higher Charlson Comorbidity Index scores had significantly lower adjusted odds of receiving any form of AUD treatment. In contrast, those with black race, homelessness, higher AUDIT-C scores, comorbid substance use disorders (opioid, cocaine, cannabis, and other substance use disorders), and co-existing psychological conditions (mood disorders, PTSD) had significantly higher adjusted odds of receiving treatment.

We then assessed the relationships between baseline factors and each treatment category (behavioral therapy alone, pharmacotherapy alone, both behavioral and pharmacotherapy). Per Table 1, the relationships between the baseline factors and any treatment remained consistent across the treatment categories, with the exception of race and HCV. Patients who were white and non-Hispanic were less likely to receive AUD behavioral therapy but more likely to receive pharmacotherapies than patients of other race/ethnic categories. Patients with HCV were more likely to receive behavioral therapies but less likely to receive pharmacotherapies than those without HCV.

In adjusted multivariable models of specific AUD treatments (Table 2), we consistently found independent significant associations between each treatment types and younger age, AUDIT-C scores, and mood disorders. Additionally, patients who were black, homeless, had other substance use disorders, PTSD, or less comorbidities were significantly more likely to receive behavioral therapy. Patients with HCV had significantly higher adjusted relative risk ratios of receiving behavioral therapy and significantly lower estimates of receiving pharmacotherapy.

Association between AUD treatment and clinical outcomes

Over follow-up, 1,336 (3.7 %) patients died and 3,554 (10.9 %) experienced new hepatic decompensation (Table 3). Treatment of any type was significantly associated with decreased death and decompensation in univariate testing ($p<0.01$, Figure 2). Controlling for factors that were statistically significant in the univariable models, Veterans receiving any AUD treatment had significantly decreased odds of decompensation (AOR=0.63, 95%CI=.52-.76) and a non-significantly decreased mortality (AOR=0.79, 95%CI=.57–1.08), controlling for other covariates. Notably, in these final models, AUDIT-C was significantly and independently associated with death (AOR=1.06/point, 95% CI=1.04,1.09) and decompensation (AOR/point=1.04, 95% CI= 1.02, 1.05), controlling for demographic and liver-related variables as well as comorbidities.

Long-term mortality.

When we extended the assessment of mortality beyond 180 days to any time over follow-up we found a significant association with mortality for any AUD treatment (AOR=0.87, 95% CI=0.80, 0.96), controlling for age, race, gender, marital status, era of service, baseline decompensation, MELD and comorbidities.

Subgroups without HCV and without baseline decompensation.

We found that the factors associated with treatment differed in minor ways for the subgroup of patients without HCV (Supplemental Table 1) and without baseline decompensation (Supplemental Table 2). Among patients without HCV, AUD treatment was NOT associated with SUDs or schizophrenia and that pharmacotherapy was no longer significantly associated with a lower Charlson comorbidity score. When we assessed the factors associated with treatment among the subgroup of patients without baseline decompensation, the point estimates and confidence intervals were minimally changed from those found for the overall cohort. We found that, within this subgroup, the association between HCV and pharmacotherapy became non-significant and that PTSD became non-significantly

associated with treatment. The associations between treatment and clinical outcomes remained unchanged when we excluded (vs. controlled for) these factors.

Acute Alcoholic Hepatitis.

Among the 687 patients (1.9%) with a diagnostic code for alcoholic hepatitis, 135 patients (20%) received AUD treatment and 58 patients (8.4%) died over 180 days of follow-up. There was a significant association between AUD treatment and decreased mortality (p=0.027) in this subgroup, where 4% of the treated group and 10% of the untreated group died over 180-day follow-up. Of the 426 patients with AAH who without baseline decompensation, 71 (17%) had new decompensation over follow-up. Over follow-up, 79 (19%) received AUD treatment and receipt of treatment was associated with a non-significant reduction in new decompensation (11% vs. 18%, p=0.16).

Baclofen.

We found that 703 patients (2%) received baclofen over follow-up. Within this group, 559 (79.5%) received no other AUD treatment, 126 (17.9%) received behavioral therapy for AUD, and 18 (2.5%) received an FDA-approved pharmacotherapy for AUD. Compared to other Veterans, those who received baclofen were significantly younger (AOR 0.98, 95% CI=0.97–0.998) had lower MELD scores (AOR=0.97, 95% CI=0.94–0.996), and were more likely to have mood disorders (AOR=1.64, 95% CI=1.29, 2.09) and HCV (AOR=1.29, 95% CI=1.04,1.60). The baclofen group had significantly *lower* AUDIT-C scores than the rest of the cohort (AOR=0.97, 95% CI=0.94,0.99). While we were unable to fully assess of the indications for baclofen, we found that 59% had a diagnostic code for a chronic painful condition. Baclofen was not associated with short-term mortality when controlling for other factors.

DISCUSSION

In this national retrospective cohort study of Veterans with coexisting cirrhosis and AUD, only 14% received behavioral or pharmacotherapy for AUD over a 180-day follow-up after the index diagnosis of AUD. Specifically, FDA-approved pharmacotherapy for AUD was rarely used in this population. We also found that AUD treatment was associated with a significantly decreased risk of new hepatic decompensation in this population and that AUD treatment was significantly associated with long-term but not short-term mortality. In the subgroup of patients with AAH, AUD treatment was also associated with reduced short-term mortality. These findings support a need to improve the provision of AUD care for a high-risk population of patients.

In recognition of the importance of this topic, the American Association for the Study for Liver Disease (AASLD) recently published guidelines for treating AUD in patients with liver disease. These guidelines recommend referral to an AUD professional, multidisciplinary management of AUD, and the use of pharmacotherapies, specifically acamprosate or baclofen, for the treatment of AUD in patients with chronic liver disease.[17] Our results support the efficacy of AUD treatment in patients with cirrhosis. The salutatory health effects of AUD treatment are likely mediated by decreased alcohol use. Abstinence

from alcohol is a key component in improving outcomes for patients with AAH, where abstinence is particularly important in predicting long-term outcomes.[18,19] Future work would benefit from prospective measurement of drinking behaviors over time, which could not be reliably obtained from our administrative dataset.

This lack of evidence-based treatment for AUD is not unique to the VA population or to patients with cirrhosis.[20] Overall, AUD is under-treated in all populations, and pharmacotherapy is particularly underutilized. The APA reported that less than 10% of all patients receive any treatment after an AUD diagnosis.[21,22] Even fewer receive evidence-based AUD treatments. For example, one study of 11 million individuals with AUD found that only 674,000 received psychopharmacological treatment.[23] While our findings are consistent with rates of specialty behavioral AUD care (13%) and pharmacotherapy (6%) among Veterans with chronic HCV,[24] patients with cirrhosis have not been previously investigated, despite the risk for greater consequences of alcohol use in this population.

Several studies investigated barriers to AUD treatment and potential ways to mitigate these barriers. However, these studies did not focus on patients with chronic liver disease. One study of 25 primary care providers in VA found that providers lacked knowledge and experience with AUD treatment and believed that specialty care for AUD was superior to primary care treatments.[25] Investigators identified alcohol-related stigma as a barrier.[25] A study assessing patient-level barriers found that patients with AUD lacked confidence in treatment and feared alcohol-related stigma.[26] In order to overcome these barriers, several systems attempted to improve the uptake of AUD treatment using care delivery interventions. For example, VA successfully implemented a multifaceted academic detailing program to increase AUD pharmacotherapy in general populations.[27] While this program increased AUD pharmacotherapy from 5 to 8% in intervention sites, more work is needed to develop implementation strategies to address this evidence to practice gap.[27,28] Moreover, given the unique medical complexities of patients with cirrhosis, it is likely unique approaches to AUD care may be required, such as colocation of care for AUD and cirrhosis.[29]

Behavioral therapies for AUD are extremely heterogeneous in nature. They range from individual cognitive behavioral therapy approaches to group therapy and 12-step-based programs. Therapies can be inpatient- or outpatient-based. However not all behavioral therapies that are used are equally efficacious or evidence-based. Cognitive behavioral therapy approaches are generally the most widely studied and evidence-based.[30] One strength of this study was our use of a rigorous approach to identifying evidence-based behavioral therapies for AUD.

We found that, while patients who were black were *more* likely to receive any treatment than white patients, this difference was driven by behavioral therapy alone. National VA studies of all Veterans have identified racial disparities in receipt of AUD pharmacotherapy but not overall AUD treatment.[31,32] Research outside of VA demonstrates racial disparities in AUD treatment. For example, black patients spend more time on waiting lists to be admitted to AUD treatment programs[26] and are less likely to be satisfied with their AUD treatment than white patients.[33] These racial disparities in treatment outside of VA are concerning,

particularly because black patients are more likely than white patients to report social consequences of drinking.[34]

While homelessness may be a barrier to treatment in some populations, many Veterans with codes for homelessness are participating in residential/transition programs that offer housing and AUD treatment. Thus, our finding that homelessness was positively associated with treatment initiation for AUD is likely not generalizable. Several studies are testing whether integrating AUD treatment in primary care can overcome barriers to AUD treatment.[35,36] Integrated care has been successfully trialed for patients with mental health and substance use disorders attending HCV clinics and shown to increase rates of HCV treatment.[37] Patients with cirrhosis, particularly those with hepatic encephalopathy, are often too sick or debilitated to reliably participate in behavioral therapies. This challenge may necessitate new approaches to behavioral therapy and makes pharmacotherapy a potentially attractive, albeit under-studied, option.[38,39]

Relatively little work has assessed the potential adverse impacts of the FDA-approved pharmacotherapies for AUD in patients with cirrhosis, and no randomized controlled trials have been conducted using these three agents in this population.[40] As such, it is not surprising that we found that pharmacotherapies were more commonly prescribed to healthier patients with cirrhosis (those without comorbid conditions and lower MELD scores). In fact, there are theoretical concerns with each of the three studied pharmacotherapies.

Acamprosate blocks withdrawal symptoms and has efficacy in maintaining alcohol abstinence.[21] Given this mechanism, there are theoretical concerns about encephalopathy related to acamprosate but few data to guide its use.[41] For patients with cirrhosis, the safety profile of acamprosate is considered to be the most favorable among the three FDA-approved agents.[39] However, acamprosate is a glutamate receptor antagonist which could theoretically lead to encephalopathy.[2141] Despite this theoretical concern, one study of 12 patients with cirrhosis found that a low dose of acamprosate was associated with no increase in subclinical encephalopathy, though there was a small decrease in diastolic but not systolic blood pressures.[42] However, acamprosate cannot be used in patients with renal failure, thus precluding its use in many patients with decompensated cirrhosis.

Naltrexone is an opioid receptor antagonist which works by reducing craving for alcohol and has been shown to be equivalent to acamprosate in efficacy. However, the American Psychiatric Association recommends caution when using naltrexone in patients with liver failure.[21] This is because naltrexone has been associated with hepatotoxicity, particularly in patients with decompensated disease. However, many providers still use this medication because the adverse consequences of ongoing alcohol use are considered to be greater than the medication-associated toxicities. Accordingly, we found that naltrexone was the most commonly prescribed AUD pharmacotherapy in this cohort.

Disulfiram inhibits acetaldehyde dehydrogenase, causing gastrointestinal symptoms, headache, and hypotension, when consumed with alcohol.[43] The potential for severe liver toxicity, hypotension, and psychiatric side effects may limit the use of disulfiram in patients

with cirrhosis.[2] It is generally accepted that disulfiram is not to be used as a first line medication in patients with cirrhosis, since it has been associated with fatal hepatotoxicity.[39,44]

We designed this study to focus on the three FDA-approved pharmacotherapies with demonstrated efficacy for AUD, following the example of other published studies. We did not include baclofen as an AUD pharmacotherapy in our primary analysis because it is not FDA approved for this indication, due to the lack of strong efficacy data. A well-designed 2018 meta-analysis of 12 studies of baclofen use for AUD concluded that the use of baclofen for AUD treatment was “premature” given its lack of impact on abstinent days, heavy drinking, craving, anxiety or depression.[45] Among patients with underlying liver disease, there have been mixed results in several small studies. For example, while two small trials found significantly increased abstinence with baclofen,[46,47] a more recent randomized control trial among Veterans with HCV and AUD found no significant difference between baclofen and placebo in alcohol-related outcomes.[48] The AASLD guidelines recommending baclofen as an AUD treatment were published after the study time period. Accordingly, we found that few patients were prescribed baclofen and that it was likely for other indications (e.g., they had lower AUDIT-C scores than the rest of the patients in the cohort and they had high rates of chronic pain). More data are needed to assess the comparative effectiveness and comparative risks of baclofen and acamprosate in this population. Ongoing trials assessing the efficacy of baclofen for treating AUD in general populations can help inform these efforts.

Despite the theoretical risks of AUD pharmacotherapy, we found that such treatments were not associated with worsened short-term outcomes in this large retrospective study. In fact, we found that any treatment was associated with decreased decompensation, even controlling for degree of alcohol use. However, given the low numbers of patients receiving pharmacotherapy, we may have been underpowered to detect less common adverse outcomes. Further studies of the efficacy and safety of these agents are urgently needed.[2]

While this study characterized the treatment of AUD in a large cohort of patients with cirrhosis, there are several limitations of this approach. First, though the diagnostic codes that were used have been validated and found to have a high specificity for AUD, the use of such codes is always imperfect. The lack of ICD-9-CM codes for non-alcoholic steatohepatitis (NASH) precluded an examination of the role of NASH as a comorbidity in this cohort. Second, while we used AUDIT-C to try to further assess the severity of AUD in this population, 27% of patients were missing baseline AUDIT-C scores, limiting our ability to control for severity of alcohol use. This limitation is somewhat mitigated by the fact that any alcohol use is unsafe for patients with cirrhosis. Third, while we followed highly validated measures of behavioral therapy, these measures do not account for brief, primary-care-based interventions, which may also be effective in treating AUD. The study was also not designed to assess continued engagement in care, though this may be an important factor to assess in future studies. Furthermore, we are unable to assess patient refusal or noncompliance with referral for AUD treatment. While the assessment of treatment intensity and duration were beyond the scope of these analyses, they will be assessed in future studies. Finally, the small numbers of patients receiving pharmacotherapy limited our ability

to assess the associations between specific pharmacotherapies and clinical outcomes. Future work evaluating the comparative effectiveness and relative harms of pharmacotherapies, particularly acamprosate vs. baclofen, would significantly add to our understanding of how to best manage AUD in patients with cirrhosis.

In conclusion, although AUD treatment, particularly pharmacotherapy, was uncommon among patients with cirrhosis and AUD, patients who received AUD treatment had improved clinical outcomes. The patient characteristics we have identified as being associated with AUD treatment initiation and use of pharmacotherapy provide targets for future interventions to address patient subpopulations at high risk of undertreatment. There is an urgent need to conduct randomized-controlled trials of treatments for AUD in cirrhosis and to develop targeted/tailored AUD treatments that account for the specific needs of patients with cirrhosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

AUD	alcohol use disorder
VA	Veterans Health Administration
ICD	International Classification of Diseases
HCV	hepatitis C virus
MELD	Model for End-Stage Liver Disease
AUDIT-C	Alcohol Use Disorders Identification Test-Consumption
PTSD	post-traumatic stress disorder
AOR	adjusted odds ratio
CI	confidence interval
FDA	Food and Drug Administration
NASH	non-alcoholic steatohepatitis

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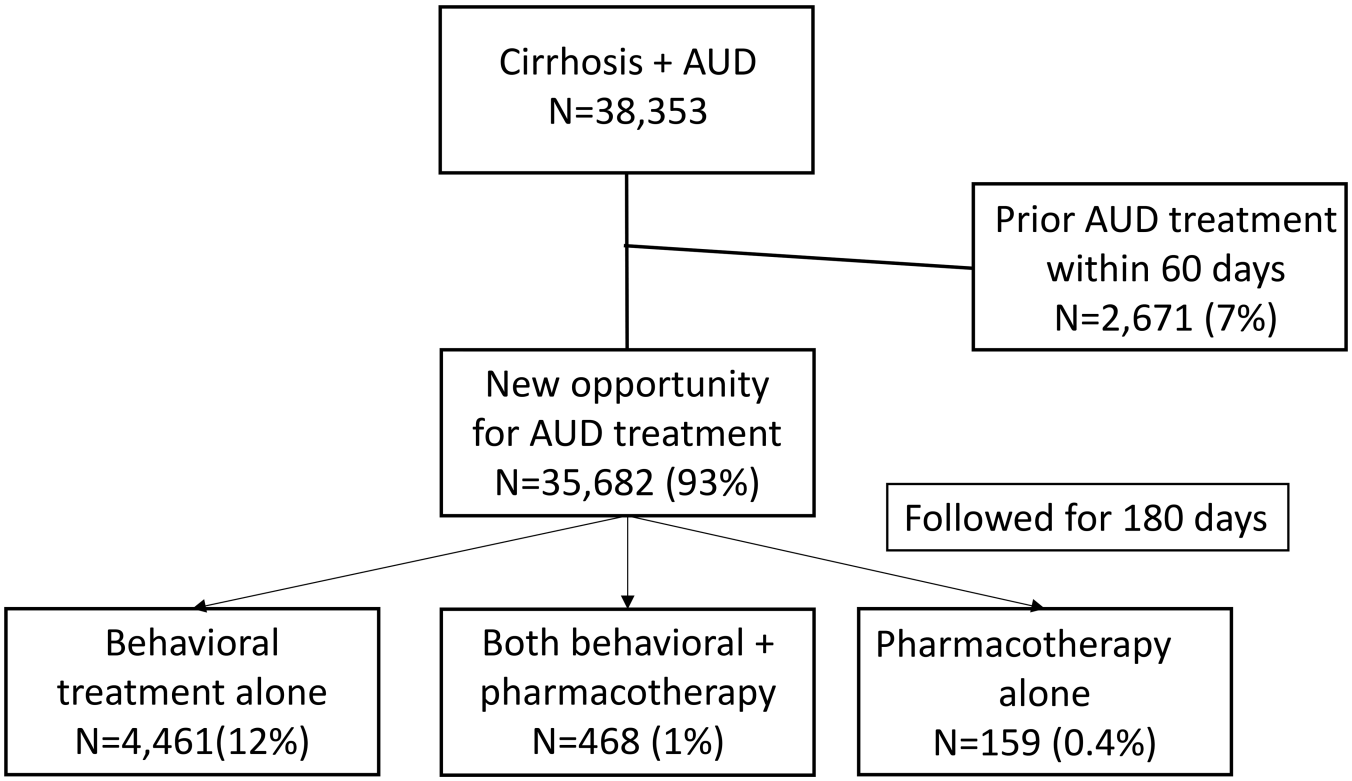

Figure 1. Cohort of Veterans with cirrhosis and alcohol use disorder (AUD).

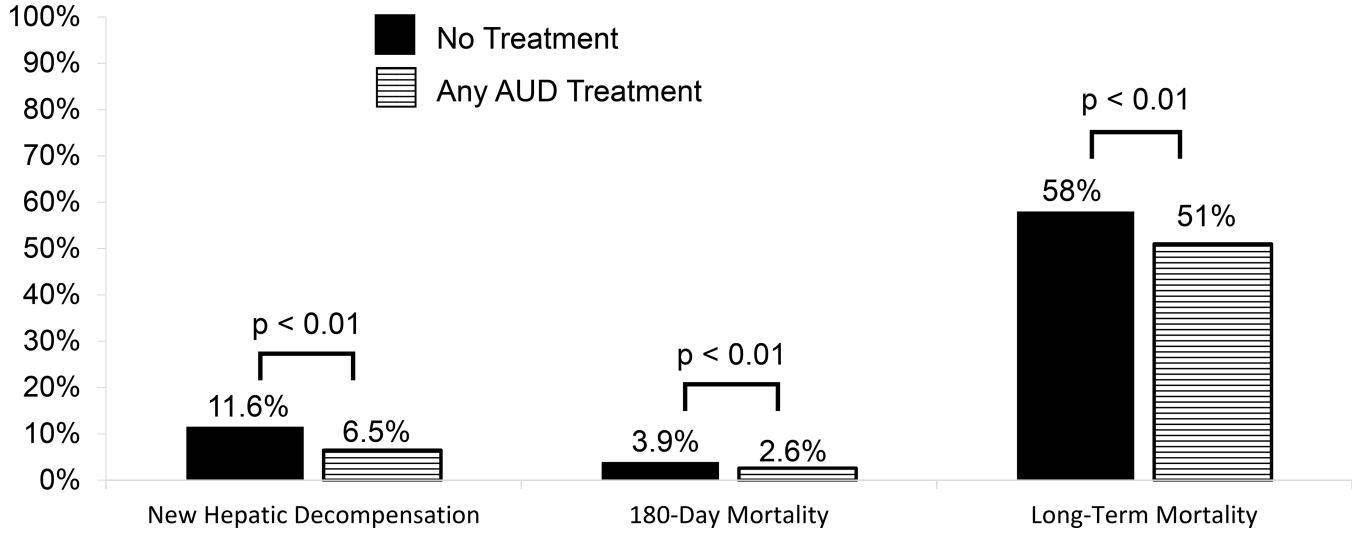

Figure 2. Univariate associations between AUD treatment and clinical outcomes

Table 1.

Baseline Demographic and Clinical Characteristics by AUD Treatment Status

	ANY TREATMENT				TYPE OF TREATMENT			
Patient Factors — Demographics	**Total cohort (n=35,682)**	**No treatment (n=30,594)**	**Any treatment (n=5,088)**	**p-value**	**Behavioral only (n=4461)**	**Pharmacotherapy only (n=159)**	**Both treatments (n=468)**	**p-value**
Age (mean sd)	58.7 (7.7)	59.3 (7.5)	55.7 (7.6)	<0.0001	55.9 (7.4)	54.8 (9.9)	53.9 (8.5)	<0.0001
Race/Ethnicity				<0.0001				<0.0001
Non-Hispanic White	25452 (71.3)	21898 (71.6)	3554 (69.9)		3053 (68.4)	127 (79.9)	374 (79.9)	
Hispanic	6723 (18.8)	5605 (18.3)	1118 (22.0)		1048 (23.5)	17 (10.7)	53 (11.3)	
Non-Hispanic Black	2045 (5.7)	1775 (5.8)	270 (5.3)		232 (5.2)	9 (5.7)	29 (6.2)	
Non-Hispanic Other	1462 (4.1)	1316 (4.3)	149 (2.9)		128 (2.9)	6 (3.8)	12 (2.6)	
N=33,390								
Sex (female)	712 (2.0)	569 (1.9)	143 (2.8)	<0.0001	124 (2.8)	4 (2.5)	15 (3.2)	<0.0001
Marital status				<0.0001				<0.0001
Married	9834 (27.6)	8691 (28.4)	1143 (22.5)		972 (21.8)	49 (30.8)	122 (26.1)	
Single	5709 (16.0)	4736 (15.5)	973 (19.1)		862 (19.3)	24 (15.1)	87 (18.6)	
Div/widowed/etc	17497 (49.0)	14993 (49.0)	2504 (49.2)		2213 (49.6)	72 (45.3)	219 (46.8)	
N=33,040								
Lack/inadequate housing	1955 (5.5)	1332 (4.4)	623 (12.2)	<0.0001	567 (12.7)	12 (7.6)	44 (9.4)	<0.0001
Period of service (Vietnam era)	23585 (66.1)	20802 (68.0)	2783 (54.7)	<0.0001	2499 (56.0)	82 (51.6)	202 (43.2)	<0.0001
Liver Disease Factors								
HCV (yes)	17699 (49.6)	14862 (48.6)	2837 (55.8)	<0.0001	2591 (58.1)	53 (33.3)	193 (41.2)	<0.0001
Prior decompensation	2989 (8.4)	2623 (8.6)	366 (7.2)	0.001	340 (7.6)	7 (4.4)	19 (4.1)	<0.0001
HCC (yes)	473 (1.3)	423 (1.4)	50 (1.0)	0.021	48 (1.1)	0 (0.0)	2 (0.4)	0.051
MELD (mean, sd)	10.6 (4.8)	10.7 (4.9)	10.3 (4.5)	<0.0001	10.4 (4.5)	9.8 (3.8)	9.7 (4.3)	0.0001
SUD Factors								

Patient Factors — Demographics	ANY TREATMENT				TYPE OF TREATMENT			
	Total cohort (n=35,682)	No treatment (n=30,594)	Any treatment (n=5,088)	p-value	Behavioral only (n=4461)	Pharmacotherapy only (n=159)	Both treatments (n=468)	p-value
Nicotine Use Disorder	7948 (22.3)	6742 (22.0)	1206 (23.7)	0.008	1069 (24.0)	41 (25.8)	96 (20.5)	0.016
Opioid Use Disorder	893 (2.5)	604 (2.0)	289 (5.7)	<0.0001	278 (6.2)	4 (2.5)	7 (1.5)	<0.0001
Cocaine Diagnosis	1464 (4.1)	934 (3.1)	530 (10.4)	<0.0001	498 (11.2)	7 (4.4)	25 (5.3)	<0.0001
Cannabis Diagnoses	1084 (3.0)	752 (2.5)	332 (6.5)	<0.0001	309 (6.9)	6 (3.8)	17 (3.6)	<0.0001
Other Drug-Related Diagnoses	2424 (6.8)	1641 (5.4)	783 (15.4)	<0.0001	700 (15.7)	18 (11.3)	65 (13.9)	<0.0001
AUDIT-C (mean, sd)	3.78 (3.8)	3.61 (3.7)	4.96 (4.4)	<0.0001	4.77 (4.4)	5.99 (4.71)	6.62 (4.46)	<0.0001
Other Comorbidities								
Mood Disorders	8006 (22.4)	6398 (20.9)	1608 (31.6)	<0.0001	1402 (31.4)	65 (40.9)	141 (30.1)	<0.0001
Anxiety disorders	2081 (5.8)	1682 (5.5)	399 (7.8)	<0.0001	341 (7.6)	22 (13.8)	36 (7.7)	<0.0001
Schizophrenia	960 (2.7)	792 (2.6)	168 (3.3)	0.004	157 (3.5)	5 (3.1)	6 (1.3)	0.001
PTSD	4143 (11.6)	3441 (11.3)	702 (13.8)	<0.0001	611 (13.7)	32 (20.1)	59 (12.6)	<0.0001
Charlson Comorbidity Index (mean, sd)	0.8 (1.0)	0.8 (1.0)	0.6 (0.9)	<0.0001	0.6 (0.9)	0.6 (1.0)	0.4 (0.7)	<0.0001

HCV=hepatitis C virus, ETOH=alcohol, HCC=hepatocellular carcinoma, MELD=model for end-stage liver disease, SUD=substance use disorders, AUDIT-C=AUD Identification Test Consumption screening tool, PTSD=posttraumatic stress disorder

Data cell values are N(%), unless otherwise labeled as mean (sd)

MELD was available for N=32,728 and AUDIT-C for N=26,148

Table 2.

Multivariable models of baseline factors associated with AUD treatment*

	Any Treatment	Behavioral only	Pharmacotherapy only	Both treatments
	AOR (95% CI)	ARRR (95% CI)		
Patient Factors—Demographics				
Age	**0.96 (.95,.96)**	**0.96 (.95,.96)**	**0.95 (.92,.99)**	**0.96 (.94,.98)**
Race/Ethnicity (vs. Non-Hispanic White)				
Hispanic	1.01 (.84,1.21)	0.99 (.83,1.18)	0.88 (.35,2.25)	1.28 (.82,1.99)
Non-Hispanic Black	**1.23 (1.07,1.41)**	**1.26 (1.09,1.46)**	1.06 (.61,1.87)	0.84 (.57,1.25)
Non-Hispanic Other	0.90 (.70,1.14)	.93 (.72,1.20)	0.56 (.15,2.07)	0.79 (.37,1.68)
Sex (vs. female)	0.86 (.67,1.10)	0.85 (.65,1.10)	0.92 (.27,3.16)	0.90 (.47,1.74)
Marital status (vs. married)				
Single	1.07 (.94,1.22)	1.10 (.96,1.26)	0.79 (.42,1.50)	0.91 (.62,1.33)
Divorced/widowed	1.04 (.95,1.13)	1.08 (.98,1.18)	0.89 (.57, 1.40)	0.75 (.56,.99)
Homeless	**1.73 (1.49,2.02)**	**1.76 (1.49,2.08)**	1.39 (.59,3.24)	1.51 (.98,2.33)
Period of service (Vietnam era)	0.96 (.84,1.09)	0.98 (.86,1.11)	0.87 (.49,1.56)	0.74 (.53,1.04)
Liver Disease Factors				
HCV	**1.20 (1.08,1.34)**	**1.27 (1.15,1.41)**	**0.64 (.40,.99)**	0.85 (.62,1.15)
Hepatic decompensation	1.02 (.86,1.21)	1.06 (.89,1.26)	0.85 (.40,1.84)	0.64 (.35,1.19)
MELD**	1.00 (0.99,1.00)	1.00 (.99,1.01)	0.97 (.94,1.01)	0.98 (.95,1.02)
SUD Factors				
Nicotine Use Disorder	0.95 (.85,1.06)	0.93 (0.82,1.05)	1.22 (.75,1.98)	1.10 (.84,1.43)
Opioid Use Disorder	**1.60 (1.28,2.00)**	**1.70 (1.36,2.12)**	0.91 (.29,2.83)	0.57 (.24,1.38)
Cocaine	**1.77 (1.46,2.16)**	**1.85 (1.53, 2.25)**	1.06 (.37,2.99)	0.92 (.46,1.84)
Cannabis	**1.25 (1.04,1.50)**	**1.32 (1.10,1.60)**	0.73 (.20,2.65)	0.70 (.32,1.54)
Other Drug-Related Diagnoses	**1.66 (1.43,1.93)**	**1.63 (1.41,1.89)**	1.13 (.58,2.18)	**2.43 (1.55,3.81)**
AUDIT-C	**1.09 (1.07,1.10)**	**1.08 (1.07,1.09)**	**1.14 (1.09,1.19)**	**1.17 (1.13,1.21)**
Other Comorbidities				
Mood Disorders	**1.56 (1.40,1.74)**	**1.47 (1.31,1.65)**	**2.86 (1.78,4.59)**	**2.29 (1.71,3.06)**
Anxiety disorders	1.10 (.95,1.28)	1.10 (0.94,1.29)	1.45 (.80,2.64)	0.99 (.61,1.60)
Schizophrenia	0.95 (.77,1.15)	0.97 (0.79,1.19)	1.16 (.35,3.84)	0.44 (.14,1.33)
PTSD	**1.14 (1.02,1.29)**	**1.14 (1.01,1.27)**	1.53 (.83,2.83)	1.04 (.70,1.53)
Charlson Comorbidity Index	**0.87 (.83,.91)**	**0.88 (.58,1.65)**	0.83 (.61,1.13)	**0.74 (.61,.89)**

*vs. no treatment; bold indicates statistically significant associations in multivariate models

**MELD measured at the date closest to but before the index diagnosis date baseline; complete labs available for N=32,728

HCV=hepatitis C virus, ETOH=alcohol, HCC=hepatocellular carcinoma, MELD=model for end-stage liver disease, AUDIT-C=AUD Identification Test Consumption screening tool, PTSD=posttraumatic stress disorder; CI=confidence interval

Table 3:

Death and hepatic decompensation over 180-day follow-up*

Clinical Outcomes	No AUD treatment n/N (%)	Any AUD treatment n/N (%)	Behavioral only n/N (%)	Pharmacotherapy only n/N (%)	Both treatments n/N (%)
Death	1,203/30,594 (3.9)	133/5,088 (2.6)	124 /4,461 (2.8)	1/159 (0.6)	8/468 (1.7)
New hepatic decompensation	3,267/28,282 (11.6)	287/4,411 (6.5)	251/3,835 (6.5)	8/146 (5.5)	28/430 (6.5)

* Denominators differ for death and decompensation analyses, because patients with prior decompensation were removed from the new decompensation analysis.