Received: 25 April 2022 | Accepted: 10 August 2022

DOI: 10.1002/hep4.2080

ORIGINAL ARTICLE

Naltrexone for alcohol use disorder: Hepatic safety in patients with and without liver disease

Divya Ayyala[1] | **Thomas Bottyan**[2] | **Christine Tien**[3] | **Michael Pimienta**[3] | **Jennie Yoo**[4] | **Kelli Stager**[5] | **Jose Luis Gonzalez**[3] | **Andrew Stolz**[1] | **Jennifer L. Dodge**[1,6] | **Norah A. Terrault**[1] | **Hyosun Han**[1]

[1]Division of Gastrointestinal and Liver Disease, Keck School of Medicine, University of Southern California, Los Angeles, California, USA

[2]Department of Psychiatry, Stanford University, Palo Alto, California, USA

[3]Department of Medicine, University of Southern California, Los Angeles, California, USA

[4]Keck School of Medicine, University of Southern California, Los Angeles, California, USA

[5]Department of Psychiatry, University of Southern California, Los Angeles, California, USA

[6]Department of Population and Public Health Sciences, University of Southern California, Los Angeles, California, USA

Correspondence
Hyosun Han, Division of Gastrointestinal and Liver Disease, HC1, 2 floor, USC Keck School of Medicine, 1510 San Pablo Street, Los Angeles, CA 90033, USA.
Email: hyosun.han@med.usc.edu

Abstract

Naltrexone is an approved drug for management of alcohol use disorder (AUD), but data in patients with liver disease (LD) are limited. We aimed to evaluate the safety of naltrexone in those with LD. This is a retrospective cohort of adults with and without LD who were prescribed naltrexone for AUD from 2015 to 2019 in a safety-net setting. Naltrexone hepatic safety was determined by liver enzyme changes during and after compared to before naltrexone prescription as well as rates of subsequent hospitalization and death by Kaplan-Meier methods. Factors associated with hospitalization were examined by Cox regression. Of 160 patients prescribed naltrexone for AUD, 100 (63%) had LD and 47 (47%) of those with LD had cirrhosis (47% decompensated). The total cohort, LD, and cirrhosis groups had lower adjusted mean aspartate aminotransferase and alanine aminotransferase levels after versus before naltrexone prescription ($p < 0.001$). Two-year survival was 97.7% (95% confidence interval [CI], 84.6–99.7), 95.4% (95% CI, 82.8–98.8), 90.8% (95% CI, 73.5–97.0), and 81.3% (95% CI, 41.2–93.8) in those without LD, LD without cirrhosis, cirrhosis, and decompensated cirrhosis groups ($p = 0.46$), respectively. Alcohol-related 2-year hospitalization rates were 8.2% (95% CI, 2.7–24), 27.7% (95% CI, 16.6–44.0), 40.5% (95% CI, 24.8–61.6), and 41.7% (95% CI, 23.3–66.6) for the groups without LD, LD without cirrhosis, cirrhosis, and decompensated cirrhosis ($p = 0.007$), respectively. Independent predictors of subsequent hospitalization were LD, (hazard ratio [HR], 3.70; 95% CI, 1.19–11.51; $p = 0.02$), cirrhosis (HR, 5.16; 95% CI, 1.69–15.75), and shorter duration (≤30 days) of naltrexone prescription (HR, 2.50; 95% CI, 1.l2–5.20; $p = 0.01$). *Conclusion*: Naltrexone is safe to use in patients with underlying LD, including those with compensated cirrhosis. Although encouraging, more safety data are needed for those with decompensated cirrhosis.

INTRODUCTION

Alcohol-associated liver disease (ALD) poses a significant burden to the US health care system, with 5.4 per 100,000 deaths attributed to ALD in 2012[1] and ALD-related mortality increasing in younger demographics.[1,2] ALD is the leading indication for liver transplantation,[3] accounting for substantial medical expenditures annually.[4] More urgently, during the corona virus disease 2019 (Covid-19) pandemic, alcohol use disorder (AUD) has increased, creating a larger population at risk for ALD.[5]

Treatment of underlying AUD prevents and can reverse complications of ALD.[3,6] The US Food and Drug Administration-approved treatments for AUD include disulfuram, naltrexone, and acamprosate, but a blackbox warning for hepatotoxicity (naltrexone) or an absence of safety data in patients with cirrhosis pose barriers for use in patients with ALD.[6] Guidelines endorse combination therapy (pharmaceuticals and psychosocial support) for treatment of AUD,[7] yet there is a paucity of data addressing safety and efficacy of AUD pharmaceuticals in patients with ALD.[6]

There is underutilization of AUD therapies among gastroenterology/hepatology specialists. In a study among veterans with ALD between 2011 and 2015, only 1% of patients received combination therapy for AUD.[8] Among a survey of 408 gastroenterologists and hepatologists, more than 50% reported discomfort with prescribing medications for AUD,[9] and of those that prescribed, baclofen was the preferred agent, possibly reflecting safety concerns as this was the only drug evaluated in patients with cirrhosis.[9,10] While the need for additional education and training in AUD care is highlighted by these studies, a lack of data supporting the safety and efficacy of these medications is an additional barrier.

Naltrexone, a μ-opioid antagonist, moderates dopamine surges from alcohol and opioids[11] and can decrease alcohol consumption, preventing relapse with superior efficacy compared to baclofen and acamprosate.[12,13] Naltrexone is well tolerated with mild side effects.[14] However, a blackbox warning exists for hepatotoxicity demonstrated in safety trials at higher doses (100 mg) for obesity.[15] Several small studies have shown no relative increase in serum aminotransferase levels with naltrexone,[11,16,17] but data in patients with underlying liver disease (LD), especially cirrhosis, are limited. We aimed to evaluate the hepatic safety of naltrexone in those with and without LD.

METHODS

Data source and study population

This study was exempt from institutional review board review after institutional review. The data source for this retrospective cohort of adults (≥18 years of age) at a large safety-net hospital was created by Cerner Powerinsight Clinical Reporting. Records were queried for all prescriptions of "naltrexone," "ReVia," or "Vivitrol" between May 24, 2015, and November 10, 2019, that were run on November 11, 2019, and provided prescription order start and stop dates and may have included noncontinuous naltrexone prescriptions. The study was restricted to patients with prescriptions of naltrexone for AUD (per Diagnostic and Statistical Manual of Mental Disorders-5 diagnostic criteria) in both inpatient and outpatient settings (n = 160). Those with naltrexone prescriptions for indications other than AUD (n = 49) or those with other known chronic liver diseases (chronic hepatitis B or C infection) were excluded (n = 20) as the purpose of the study was to examine the safety of naltrexone for those with AUD specifically.

Patients were categorized into two primary groups: (i) without LD (n = 60) and (ii) LD (n = 100) based on radiographic evidence of hepatic steatosis, the presence of nodular liver surface, or evidence of portal hypertension on liver imaging (splenomegaly or intra-abdominal collaterals) in combination with elevations in either liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST]), total bilirubin (Tbili), or International Normalized Ratio (INR) and/or thrombocytopenia. Among patients with LD, the presence of cirrhosis was defined as fibrosis-4 score ≥3.25,[18] International Classification of Diseases (Tenth Revision) codes for cirrhosis, or liver imaging demonstrating nodular liver surface or portal hypertension in combination with an elevation in INR or thrombocytopenia (n = 47). Patients with a history of ascites, variceal bleeding, spontaneous bacterial peritonitis, Child B/C cirrhosis, or hepatic encephalopathy were classified as decompensated cirrhosis (n = 22).

Data collection

Demographic variables captured at the time of naltrexone prescription included age, sex, race/ethnicity, health insurance, living situation, body mass index (BMI), psychiatric history, and metabolic risk factors (diabetes, hypertension, and hyperlipidemia). Laboratory data, including platelet count, INR, creatinine, albumin, alkaline phosphatase (ALP), ALT, AST, and Tbili, were collected at multiple time points and divided into the following three categories: before, within 1 year before the first naltrexone prescription; during, during naltrexone prescription; and after, 1–12 months after naltrexone discontinuation. Naltrexone variables included formulation, dose, and length of prescription (defined as the time from first to last naltrexone prescription) analyzed by longer (prescribed for >30 days) versus shorter (≤30 days) prescription.

Study endpoints

Assessment of liver safety with naltrexone use

Differences in mean AST, ALT, ALP, and Tbili at three time points (before, during, and after naltrexone) were assessed overall and by group (without LD, LD without cirrhosis, and cirrhosis). Liver enzyme elevations were defined as (i) ≥3× the upper limit of normal (ULN) if patients' prenaltrexone laboratory results were within the normal limits (ALT ≤ 19 U/L for women, ≤30 U/L for men; AST ≤ 50 U/L; Tbili ≤ 1 mg/dl)[19] or (ii) ≥3× the prenaltrexone laboratory value if patients' prenaltrexone laboratory results were more than the ULN. Severe liver enzyme elevations for ALT and AST were defined as >10× ULN (ALT > 190 U/L for women, >300 U/L men; or AST > 1500 U/L; or Tbili > 10 mg/dl).

Mortality and alcohol-related hospitalizations

Mortality (including deaths from all causes) and alcohol-related hospitalizations were ascertained from the electronic medical record. Alcohol-related hospitalizations included hospitalizations for alcohol withdrawal, alcohol-associated hepatitis, alcohol-induced gastrointestinal bleed or pancreatitis, and decompensated cirrhosis.

Statistical analysis

Demographic and clinical characteristics were described using medians with interquartile ranges (IQRs) and frequencies with percentages for numeric and categorical variables, respectively. Characteristics were compared by the presence of LD, using Wilcoxon rank sum, chi-square, and exact tests, as appropriate.

Multilevel mixed-effects linear regression estimated mean liver enzyme levels for ALT, AST, ALP, and Tbili and compared levels before to those during and after prescription. Random intercepts were used to address within-subject correlation as each patient could contribute multiple observations. ALT, AST, and ALP were evaluated using log base-2 transformations to achieve normality. To account for differences by sex and duration of naltrexone prescription, mean enzyme levels were adjusted for both factors. Models were estimated for the overall cohort, without LD, and LD without cirrhosis and with cirrhosis. The main analysis used all available laboratory observations, and a sensitivity analysis included only patients with enzyme levels available at all three time points (before prescription, during, and after prescription). Among patients with before and during prescription enzyme levels, liver enzyme elevations and severe liver enzyme elevations while on naltrexone were estimated as the proportion of patients with a qualifying elevation for ALT, AST, and Tbili separately. Clopper-Pearson exact 95% confidence intervals (CIs) were calculated for binomial proportions. As we were most interested in identifying clinically significant hepatotoxicity, we also individually examined and reported cases of liver enzyme elevations and severe liver enzyme elevations (ascertained from the above analysis).

The Kaplan-Meier method was used to estimate rates of survival and alcohol-related hospitalization. Follow-up time was measured from the date of naltrexone prescription until an event (death or first alcohol-related hospitalization) for the two respective analyses; those without events were censored on the date of last contact with the hospital system. The log-rank test was used to compare alcohol-related hospitalization rates by LD status and duration of naltrexone prescription, using Sidak p values to adjust for multiple comparisons. Cox proportional hazards regression estimated hazard ratios (HRs) and 95% CIs for characteristics associated with hospitalization for alcohol. Factors with $p < 0.1$ in the univariable analysis were assessed in the multivariable model selected by backward elimination ($p > 0.05$ for removal).

Differences with $p < 0.05$ were considered statistically significant. Analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC) and Stata MP 16.1 (StataCorp LLC, College Station, TX).

RESULTS

Baseline characteristics of cohort

Of 160 patients prescribed naltrexone for AUD during the study period, the majority were men, were self-identified as Hispanic/Latinx, were insured by Medicaid, had a median age of 49 years (IQR, 39–57), and were prescribed in outpatient clinics (Table 1). A total of 100 (63%) patients had evidence of LD, and among those with LD, 47 (47%) had cirrhosis. Patients with versus without LD were more often men of older age, self-identified Hispanic/Latinx, prescribed naltrexone in an outpatient clinic, and had a referral to a hepatologist. Of patients with cirrhosis, 47% (n = 22) qualified as decompensated. Of those with available data to determine Child class and Model for End-Stage Liver Disease (MELD) (n = 24 and 41, respectively), 42%, 37%, and 21% were Child class A, B, and C, respectively, with a median initial MELD of 10 (IQR, 8–16), MELD 9 (IQR, 8–11), and MELD 15 (IQR, 10–18) for those with cirrhosis (overall), compensated cirrhosis, and decompensated cirrhosis, respectively (Table S1).

The majority (94%) of patients had more than one contact with the health care system during a median follow-up duration of 10 months (IQR, 4–18) from first naltrexone prescription, with comparable follow-up among patients with and without LD (Table 1). The median duration of naltrexone prescription was 57 days (IQR, 28–115).

TABLE 1 Selected demographics and clinical features for the total cohort

Characteristics	Total cohort n = 160	Without liver disease n = 60	With liver disease n = 100	*p* value*
Age, years; median (IQR)	49 (39–57)	46 (34–56)	51(41–58)	0.05
Male (%)	80	70	86	0.01
Ethnicity (%)				
Black	12	10	13	0.03
Caucasian	4	8	2	
Asian	2	3	1	
Unknown	18	73	13	
Hispanic	64	52	71	
Unhoused (%)[a]	26	25	26	1.00
Psychiatric history (%)	54	80	39	<0.001
HIV positive (%)[b]	7	13	4	0.12
History of diabetes (%)	16	7	21	0.02
History of systemic arterial hypertension (%)	29	25	31	0.47
History of hyperlipidemia (%)	15	12	17	0.36
BMI (median, IQR)[c]	28 (24–30)	27 (24–29)	28 (23–31)	0.61
Psychosocial intervention offered (%)	66	93	74	0.36
Referral to hepatologist (%)	13	0	20	<0.001
Insurance (%)				
Medi-Cal	89	92	88	1.00
Medicare	8	7	8	
Uninsured	2	2	3	
Private	1	0	1	
Naltrexone prescription details				
Oral naltrexone formulation (%)	92, n = 160	88, n = 60	95, n = 100	0.40
Naltrexone dose (% prescribed)				
25 mg/day	4	3	5	0.27
50 mg/day	88	85	90	
380 mg/month	8	12	5	
Naltrexone prescription location (%)				
Clinic	63	58	65	0.02
Hospital	19	13	23	
Inpatient psychiatry	12	22	6	
Emergency room	6	7	6	
Duration naltrexone Prescription, days; median (IQR)	57 (28–118)	57 (30–97)	56 (2–127)	0.99
Duration of naltrexone prescription >30 days (%)	66	70	63	0.40
Follow-up time from naltrexone prescription to last medical encounter, months; median (IQR)	10 (4–18)	11 (3–18)	10 (4–18)	0.99
Alcohol-related hospitalization after naltrexone (%)	19	7	26	0.003
Death (%)[d]	5	2	7	0.26

Abbreviations: BMI, body mass index; HIV, human immunodeficiency virus; IQR, interquartile range.

[a]Missing data: total cohort, n = 11; without LD, n = 3; with LD, n = 8.

[b]Missing data: total cohort, n = 43; without LD, n = 21; with LD, n = 22.

[c]Missing data: total cohort, n = 6; without LD, n = 4; with LD, n = 3.

[d]Missing data: total cohort, n = 9; without LD, n = 3; with LD, n = 6.

*Significant at values ≤ 0.05.

Liver enzyme changes before, during, and after naltrexone prescription

A total of 441 ALT, 433 AST, 429 ALP, and 439 Tbili values were available for evaluation either before (median days from naltrexone start to laboratory results was 7 days [IQR, 1–50]), during, or after prescription. Among all patients, the adjusted mean ALT decreased from 33 U/L before to 29 during (p = 0.11) and 27 after (p = 0.001) prescription, and the adjusted mean AST decreased from 45 U/L before to 38 during (p = 0.01) and 34 after ($p < 0.001$) prescription (Table 2). Similar patterns were observed among those with LD (ALT, 39 versus 32 [p = 0.01] and 28 [$p < 0.001$]; AST, 59 versus 46 [p = 0.001] and 39 [$p < 0.001$]) (Table 2) and cirrhosis (ALT, 39 versus 27 [$p < 0.001$] and 26 [$p < 0.001$]; AST, 80 versus 49 [$p < 0.001$] and 47 [$p < 0.001$]) (Table 2). The mean Tbili also declined from before to during and after prescription (LD, 0.86 versus 0.82 [p = 0.54] and 0.58 [p = 0.003]; cirrhosis, 1.25 versus 1.01 [p = 0.18] and 0.87 [p = 0.01]). In contrast, in patients without LD, no significant differences in mean ALT or AST were observed during the study. In a sensitivity analysis that included only individuals with laboratory values available at all three time points (n = 182 for ALT, ALP, and Tbili; AST, n = 164; including 86.5% of patients with LD versus 44.7% of patients without LD, p = 0.001), results were similar although decreases in mean Tbili for the LD and cirrhosis groups did not achieve statistical significance (Table S2). Of those with normal liver tests before naltrexone (ALT, n = 19; AST, n = 25; ALP, n = 44; Tbili, n = 38), 31.58% (ALT), 20.00% (AST), 13.64% (ALP), and 15.79% (Tbili) were noted to be abnormal during treatment with naltrexone. Of the patients who developed abnormal tests while on naltrexone, 16.67% (ALT), 20.00% (AST), 50.00% (ALP), and 50.00% (Tbili) normalized while on treatment.

Cases of liver enzyme elevations during naltrexone therapy

Of 160 patients exposed to naltrexone, three cases of liver enzyme elevations occurred: one case of ALT liver enzyme elevation (1.2 events [95% CI, 0.3–4.7] per 1000 persons per year) and two cases of Tbili severe

TABLE 2 Mixed model analysis of adjusted means for total cohort, those with and without LD, and those with cirrhosis before, during, and after naltrexone

		Before	During		After	
Value	n	Mean	Mean	p value*	Mean	p value*
A	Liver enzymes for total cohort					
ALT (IU/L)	441	33	29	0.11	27	0.001
AST (IU/L)	433	45	38	0.01	34	<0.001
ALP (IU/L)	439	88	84	0.19	90	0.32
Tbili (mg/dl)	439	0.68	0.71	0.60	0.60	0.10
B	Liver enzymes LD group					
ALT (IU/L)	325	39	32	0.01	28	<0.001
AST (IU/L)	318	59	46	0.001	39	<0.001
ALP (IU/L)	325	98	94	0.26	100	0.43
Tbili (mg/dl)	324	0.86	0.82	0.54	0.58	0.003
C	Liver enzymes cirrhosis group					
ALT (IU/L)	169	39	27	<0.001	26	<0.001
AST (IU/L)	168	80	49	<0.001	47	<0.001
ALP (IU/L)	169	108	100	0.12	101	0.52
Tbili (mg/dl)	168	1.25	1.01	0.18	0.87	0.01
D	Liver enzymes without LD group					
ALT (IU/L)	116	22	25	0.21	25	0.11
AST (IU/L)	115	25	27	0.29	27	0.20
ALP (IU/L)	114	70	65	0.34	97	0.45
Tbili (mg/dl)	115	0.4	0.52	0.02	0.19	0.03

Note: n = number of laboratory observations as patients can have multiple laboratory values; means are adjusted for sex and length of naltrexone prescription; all p values are for comparison to values before naltrexone (within 1 year before first naltrexone prescription), during (during naltrexone prescription), and after (1–12 months after naltrexone discontinuation).

Abbreviations: ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; LD, liver disease; Tbili, total bilirubin.

*p significant at values ≤ 0.05.

liver enzyme elevations (1.6 events [95% CI, 0.5–4.9] per 1000 persons per year). Two of these three cases (one each ALT and Tbili) temporally coincided with naltrexone prescription.

The first patient with a severe liver enzyme elevation of Tbili had a Tbili of 36.2 mg/dl (baseline) that decreased to 23.3 mg/dl (28 days after naltrexone prescription) with similar elevations in ALP, AST, and ALT that did not qualify as a liver enzyme elevation and decreased after naltrexone prescription. The patient had Child C cirrhosis complicated by hepatic encephalopathy and ascites and had been abstinent for 2 months before naltrexone initiation. The patient had no history of metabolic syndrome, had a baseline BMI of 29.2 kg/m^2, and primarily used the outpatient clinic. The patient was admitted 29 days after naltrexone prescription with pneumonia provoking status epilepticus and ultimately died.

The second patient with a severe Tbili liver enzyme elevation had a Tbili of 1.4 mg/dl (baseline) that increased to 9.8 mg/dl following admission (7 days after naltrexone initiation) for an esophageal variceal bleed and alcohol withdrawal; the patient's Tbili peaked at 12.2 mg/dl (4 days after naltrexone discontinuation) with concomitant increases in ALP, AST, and ALT that did not qualify as liver enzyme elevations. The patient had metabolic syndrome, Child A cirrhosis with ascites, was unhoused, had a baseline BMI of 30.4 kg/m^2, continued alcohol use, and used both the emergency room and outpatient clinics.

The patient with an ALT liver enzyme elevation had an ALT level that increased from 25 IU/L (baseline) to 124 IU/L (18 months after naltrexone initiation); naltrexone was then discontinued. The last recorded ALT was 76 IU/L (135 days after naltrexone discontinuation) with no concomitant elevation in AST, ALP, or Tbili. The patient was unhoused, had no history of liver disease, had a baseline BMI of 29.2 kg/m^2, and continued heavy alcohol use. The patient's primary point of contact was the emergency department, and there were no recorded liver-related decompensations or alcohol-related admissions.

Mortality

During a median follow-up of 10 months (IQR, 4–18), eight patients died. Cumulative 2-year survival in patients without LD was 97.7% (95% CI, 84.6–99.7) compared to 95.4% (95% CI, 82.8–98.8; p = 0.93) for those with LD alone, 90.8% (95% CI, 73.5–97.0; p = 0.52) for those with cirrhosis, and 81.3% (95% CI, 51.2–93.8; p = 0.25) for those with decompensated cirrhosis (Figure 1). Deaths occurred a median of 5 months (IQR, 2–17) after initial naltrexone prescription. Of the deceased patients, 25% were women, the majority self-identified as Hispanic/Latinx (62%), had a mean age of 55 years, and had shorter naltrexone prescriptions (75%). No deaths were attributed to hepatic decompensation or naltrexone-related hepatotoxicity, and only one death was attributed to complications of alcohol (alcohol-induced anoxic brain injury).

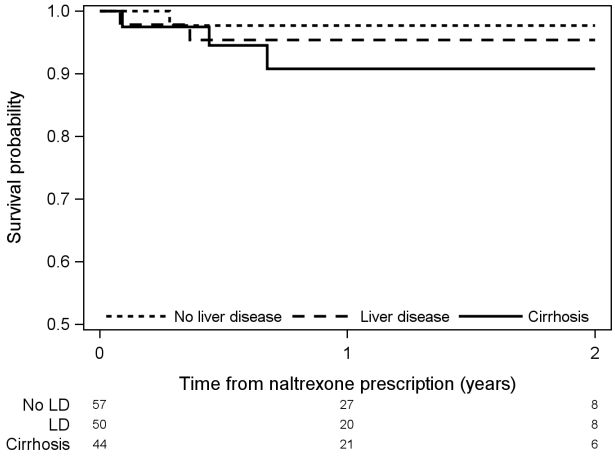

FIGURE 1 Cumulative 2-year survival by group. Survival rate at 2 years was 94.9% (95% CI, 89.0–97.7) overall, 97.7% (95% CI, 84.6–99.7) in those without LD, 95.4% (95% CI, 82.8–98.8) in those with LD without cirrhosis, and 90.8% (95% CI, 73.5–97.0) for those with cirrhosis (p = 0.46). CI, confidence interval; LD, liver disease.

Alcohol-related hospitalizations

After receiving a naltrexone prescription, 30 patients (19%) had at least one subsequent alcohol-related hospitalization and no hospitalizations related to naltrexone hepatoxicity. Cumulative incidence of 2-year alcohol-related hospitalizations after naltrexone prescriptions was 8.2% (95% CI, 2.7–24.0) for those without LD compared to 27.7% for LD alone (95% CI, 16.6–44.0; p = 0.09), 40.5% for LD with cirrhosis (95% CI, 24.8–61.6; p = 0.006), and 41.7% (95% CI, 23.3–66.6; p = 0.005) for decompensated cirrhosis (Figure 2). Alcohol-related hospitalization rates were highest among those with LD and shorter naltrexone prescriptions (45.3%; 95% CI, 28.6–66.0) and lowest in those without LD and shorter naltrexone prescriptions (0%) (p < 0.001) (Figure 3). While the cumulative incidence of 2-year alcohol-related hospitalizations after naltrexone prescriptions was higher (42.9%; 95% CI, 11.4–92.4) for those with 25 mg daily naltrexone prescriptions versus 50 mg daily naltrexone prescriptions (25.5%; 95% CI, 17.4–36.4), only seven subjects received the 25-mg dose, and statistical significance was not achieved (p = 0.42).

Patient characteristics at the time of naltrexone prescription were assessed for association with risk of alcohol-related hospitalization (Table 3). In multivariable analysis, LD (hazard ratio [HR], 3.70; 95% CI,

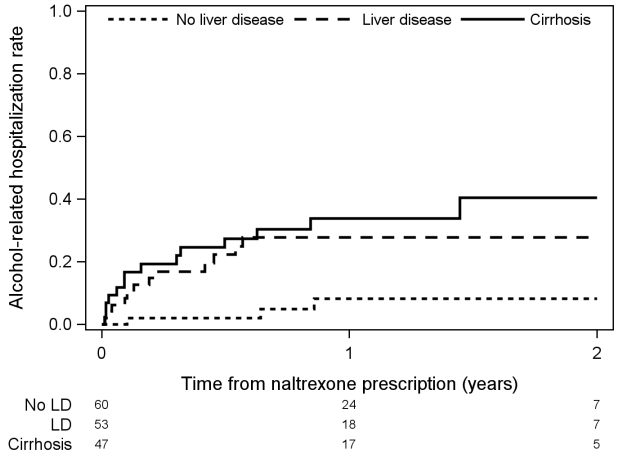

FIGURE 2 Cumulative 2-year alcohol-related hospitalizations by LD group. Two-year alcohol-related hospitalization of patients with naltrexone prescriptions was 8.2% (95% CI, 2.7%–24.0%) for those without LD compared to 27.7% for LD without cirrhosis (95% CI, 16.6%–44.0%) and 40.5% for cirrhosis (95% CI, 24.8%–61.6%) ($p = 0.007$). CI, confidence interval; LD, liver disease.

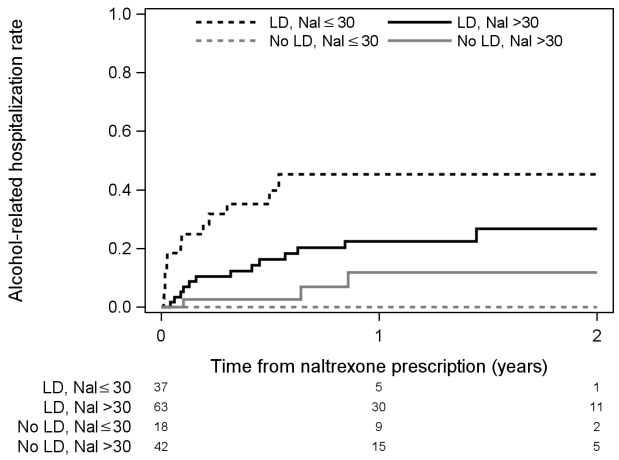

FIGURE 3 Cumulative probability of alcohol-related hospitalizations by LD and naltrexone duration. Two-year alcohol-related hospitalization rates were highest among those with LD and naltrexone prescriptions shorter than 30 days (45.3%; 95% CI, 28.6%–66.0%) and lowest in those without LD and naltrexone prescriptions less than 30 days (0%) ($p < 0.001$). CI, confidence interval; LD, liver disease; Nal, naltrexone.

1.19–11.51), cirrhosis (HR, 5.16; 95% CI, 1.69–15.75), and shorter naltrexone duration (HR, 2.50; 95% CI, 1.20–5.20) were independently associated with the risk of alcohol-related hospitalization.

DISCUSSION

Naltrexone has been shown to decrease heavy alcohol consumption and prevent alcohol relapse.[20–25] Despite this, concerns for impaired drug metabolism and hepatotoxicity in patients with underlying LD are a likely barrier for use of this drug despite recent evidence demonstrating its safety among various patient populations without LD.[11,16,26–28] We demonstrated that naltrexone is safe in patients with AUD and LD.

Only one case of ALT elevation was observed among 55 patients treated with naltrexone, representing an annual event rate of 1.2 events per 1000 persons, which is relatively low. This ALT elevation was modest (<10 ULN) and without bilirubin elevation. Given the lack of normalization of ALT after naltrexone discontinuation, other factors (e.g., ongoing alcohol use) may have been responsible for the observed increase. Two cases of jaundice (severe Tbili liver enzyme elevation) were observed among 60 patients with LD, with only one occurring during treatment with naltrexone. The first patient was jaundiced at baseline, and the Tbili declined after naltrexone prescription likely secondary to alcohol abstinence. The second patient was noted to be jaundiced before initiation of naltrexone and experienced an increase in Tbili approximately 1 week after initiation of naltrexone in the setting of a gastrointestinal bleed and continued alcohol use. Both cases are unlikely to be naltrexone-related drug-induced liver injury, which is usually hepatocellular without any known cases of severe jaundice.[29]

Overall reductions in AST and ALT were seen in all three groups (without LD, LD without cirrhosis, and cirrhosis) over the course of naltrexone treatment and follow-up. The declines in adjusted means of AST and ALT in patients with LD have been similarly reported in patients without LD.[11,16,23] We hypothesize that this potential benefit reflects reduced alcohol intake, with naltrexone use causing less liver-related injury, although the absence of information on alcohol use precludes any definitive conclusions on this relationship. Notably, no increase in adjusted means of AST and ALT supports a growing body of evidence supporting the safety of naltrexone in patients with LD prescribed naltrexone at dosages used for treating AUD.[11,16,27,28,30]

Overall, our cohort exhibited a high 2-year survival rate as expected for those without cirrhosis. Survival rates were comparable among those with cirrhosis, decompensated cirrhosis, LD, and without LD. The high survival rate within our decompensated cirrhosis group is somewhat unexpected given the natural history of decompensated ALD with an estimated 2-year survival of 54%.[31] Superior survival seen in our cohort, even for decompensated cirrhosis, could be associated with naltrexone usage, but given the lack of a comparator group, definitive conclusions cannot be made. Most reassuring, though, is the lack of naltrexone-related deaths, especially in those with decompensated cirrhosis, although continued vigilance is warranted as our sample size was small.

Not surprisingly, the 2-year alcohol-related hospitalization rates were highest among those with LD and cirrhosis. Published literature has cited reductions

TABLE 3 Factors associated with alcohol-related hospitalizations

	Univariate analysis		Multivariate analysis	
Clinical variable	**HR (95% CI)**	***p* value***	**HR (95% CI)**	***p* value***
Age (per year)	0.99 (0.96–1.02)	0.68		
Male (vs. female)	1.00 (0.43–2.33)	>0.99		
Hispanic ethnicity	1.19 (0.56–2.54)	0.66		
BMI (per kg/m^2)	0.95 (0.89–1.02)	0.20		
Naltrexone duration ≤ 30 days (vs. >30 days)	2.46 (1.19–5.07)	0.02	2.50 (1.20–5.20)	0.01
Liver disease status				
Without liver disease	1.00			
Liver disease without cirrhosis[a]	3.59 (1.16–11.14)	0.03	3.70 (1.19–11.51)	0.02
Liver disease with cirrhosis[a]	5.14 (1.69–15.65)	0.004	5.16 (1.69–15.75)	0.004

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio.

[a]Compared to without liver disease group.

**p* significant at values ≤ 0.05.

in alcohol drinking and relapse with approximately 12 weeks of therapy, which is longer than our median naltrexone prescription of 57 days.[12,26,30,32] However, the findings of our study may suggest that patients with shorter prescriptions are more prone to relapse and subsequent hospitalizations due to undertreatment or may just reflect a lack of outpatient care resulting in hospitalizations in those with liver disease.

The low rates of hospitalization in those without LD and shorter prescriptions are difficult to interpret and may possibly reflect a selection bias of patients with a lower risk of relapse who may not benefit from naltrexone. Future studies examining the efficacy of at least 12 weeks of naltrexone treatment for AUD in those with LD and cirrhosis are needed.

As a retrospective study, there are limitations. Liver enzyme elevations and severe liver enzyme elevations were detected only if laboratory values were checked, although severe liver enzyme elevations with jaundice would likely have triggered a health care encounter. Additionally, transient elevations caused by naltrexone may have been missed for the same reason, although these are usually self-limiting[29] and clinically meaningful hepatoxicity would have likely triggered a health care encounter. Although we did not include patients with LD not on naltrexone for comparison, those with cirrhosis had comparable MELD scores compared to previous studies describing those with LD and AUD and likely show a representative population.[8] Furthermore, as hepatologists were not involved in prescribing naltrexone for those with LD, it is less likely that selection was based on liver disease severity. The length of prescription duration was a proxy for naltrexone use, and adherence or gaps in prescriptions were not measured. Naltrexone prescriptions outside of our hospital system were not detected. Drinking history was not abstracted given limitations of retrospective quantification of alcohol intake from health records. Information regarding patient visits outside of our network hospital was lacking; however, as the majority of patients have insurance limitations, it is likely their follow-up would only be in our safety-net hospital. Our cohort was composed mainly of Hispanic/Latinx subjects, an understudied population, but this may limit the generalizability to the entire US population. The cohort of decompensated individuals with cirrhosis was small, limiting the power of this analysis. The potential confounding effect of psychotherapy was not captured in this study, although access to this resource is extremely limited in a safety-net setting and thus less likely to play a major confounding role. Finally, no conclusions could be drawn on the impact of naltrexone use on mortality and alcohol-related hospitalizations as no comparator group was included. Despite these limitations, the results of this study provide real-world safety data regarding naltrexone use in the setting of ALD, which is of clinical importance.

In conclusion, we have shown naltrexone to be safe in patients with underlying LD with a very low incidence of liver enzyme elevations and no evidence of hepatotoxicity. Moreover, prescribed naltrexone was associated with improved liver enzymes, suggesting clinical benefit. Naltrexone is likely a viable treatment option for AUD in those with LD, with continued close monitoring in decompensated cirrhosis. These results should encourage prospective studies in patients with AUD and cirrhosis, with the goal of expanding the data on safety and examining the contribution of AUD medications to stabilization of LD and patient survival.

ACKNOWLEDGMENTS

Divya Ayyala, Thomas Bottyan, Jennifer Dodge, Norah Terrault, and Hyosun Han were responsible for study concept, design, and interpretation of data. Divya

Ayyala, Thomas Bottyan, Jennie Yoo, Christine Tien, Michael Pimienta, and KelliStager were responsible for acquisition of data. Jennifer dodge was responsible for analysis and interpretation of data. Divya Ayyala, Thomas Bottyan, Christine Tien, Kelli Stager, Jennie Yoo, and Micheal Pimienta were responsible for drafting the manuscript. Critical revisions of the manuscript for important intellectual content were performed by Divya Ayyala, Hyosun Han, Jennifer Dodge, and Norah Terrault. Jose Gonzalez and Andrew Stolz were involved in study concept and design.

FUNDING INFORMATION

University of Southern California Research Center for Liver Disease; Grant Number: P30DK48522

CONFLICT OF INTEREST

Norah Terrault has received institutional grant support from Gilead Sciences, GSK, and Roche-Genentech and consulting fees from Saol Therapeutics, Moderna, and Exigo. The other authors have nothing to report.

TRANSPARENCY STATEMENT

Data, analytic methods, and study materials are available by request.

ORCID

Norah A. Terrault https://orcid.org/0000-0003-4143-1950

REFERENCES

1. Guirguis J, Chhatwal J, Dasarathy J, Rivas J, McMichael D, Nagy LE, et al. Clinical impact of alcohol-related cirrhosis in the next decade: estimates based on current epidemiological trends in the United States. Alcohol Clin Exp Res. 2015;39:2085–94.
2. Tapper EB, Parikh ND. Mortality due to cirrhosis and liver cancer in the United States, 1999–2016: observational study. BMJ. 2018;362:k2817.
3. Cholankeril G, Ahmed A. Alcoholic liver disease replaces hepatitis c virus infection as the leading indication for liver transplantation in the United States. Clin Gastroenterol Hepatol. 2018;16:1356–8.
4. Rehm J, Samokhvalov AV, Shield KD. Global burden of alcoholic liver diseases. J Hepatol. 2013;59:160–8.
5. Da BL, Im GY, Schiano TD. Coronavirus disease 2019 hangover: a rising tide of alcohol use disorder and alcohol-associated liver disease. Hepatology. 2020;72:1102–8.
6. Yoo ER, Cholankeril G, Ahmed A. Treating alcohol use disorder in chronic liver disease. Clin Liver Dis (Hoboken). 2020;15:77–80.
7. Crabb DW, Im GY, Szabo G, Mellinger JL, Lucey MR. Diagnosis and treatment of alcohol-associated liver diseases: 2019 practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2020;71:306–33.
8. Rogal S, Youk A, Zhang H, Gellad WF, Fine MJ, Good CB, et al. Impact of alcohol use disorder treatment on clinical outcomes among patients with cirrhosis. Hepatology. 2020;71:2080–92.
9. Im GY, Mellinger JL, Winters A, Aby ES, Lominadze Z, Rice J, et al. Provider attitudes and practices for alcohol screening, treatment, and education in patients with liver disease: a survey from the American Association for the Study of Liver Diseases alcohol-associated liver disease special interest group. Clin Gastroenterol Hepatol. 2021;19:2407–16.e8.
10. Addolorato G, Leggio L, Ferrulli A, Cardone S, Vonghia L, Mirijello A, et al. Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. Lancet. 2007;370:1915–22.
11. Tetrault JM, Tate JP, McGinnis KA, Goulet JL, Sullivan LE, Bryant K, et al. Hepatic safety and antiretroviral effectiveness in HIV-infected patients receiving naltrexone. Alcohol Clin Exp Res. 2012;36:318–24.
12. Srisurapanont M, Jarusuraisin N. Naltrexone for the treatment of alcoholism: a meta-analysis of randomized controlled trials. Int J Neuropsychopharmacol. 2005;8:267–80.
13. Kumar A, Sharma A, Bansal PD, Bahetra M, Gill HK, Kumar R. A comparative study on the safety and efficacy of naltrexone versus baclofen versus acamprosate in the management of alcohol dependence. Indian J Psychiatry. 2020;62:650–8.
14. Anton RF. Naltrexone for the management of alcohol dependence. N Engl J Med. 2008;359:715–21.
15. Atkinson RL, Berke LK, Drake CR, Bibbs ML, Williams FL, Kaiser DL. Effects of long-term therapy with naltrexone on body weight in obesity. Clin Pharmacol Ther. 1985;38:419–22.
16. Yen MH, Ko HC, Tang FI, Lu RB, Hong JS. Study of hepatotoxicity of naltrexone in the treatment of alcoholism. Alcohol. 2006;38:117–20.
17. Lucey MR, Silverman BL, Illeperuma A, O'Brien CP. Hepatic safety of once-monthly injectable extended-release naltrexone administered to actively drinking alcoholics. Alcohol Clin Exp Res. 2008;32:498–504.
18. Vallet-Pichard A, Mallet V, Nalpas B, Verkarre V, Nalpas A, Dhalluin-Venier V, et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. Comparison with liver biopsy and fibrotest. Hepatology. 2007;46:32–6.
19. Kasarala G, Tillmann HL. Standard liver tests. Clin Liver Dis (Hoboken). 2016;8:13–8.
20. Anton RF, O'Malley SS, Ciraulo DA, Cisler RA, Couper D, Donovan DM, et al. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. JAMA. 2006;295:2003–17.
21. Garbutt JC, Kranzler HR, O'Malley SS, Gastfriend DR, Pettinati HM, Silverman BL, et al.; Vivitrex Study Group. Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. JAMA. 2005;293:1617–25. Erratum in: JAMA. 2005;293:1978, 2864.
22. Hernandez-Avila CA, Song C, Kuo L, Tennen H, Armeli S, Kranzler HR. Targeted versus daily naltrexone: secondary analysis of effects on average daily drinking. Alcohol Clin Exp Res. 2006;30:860–5.
23. Kranzler HR, Tennen H, Armeli S, Chan G, Covault J, Arias A, et al. Targeted naltrexone for problem drinkers. J Clin Psychopharmacol. 2009;29:350–7.
24. Streeton C, Whelan G. Naltrexone, a relapse prevention maintenance treatment of alcohol dependence: a meta-analysis of randomized controlled trials. Alcohol Alcohol. 2001;36:544–52.
25. Srisurapanont M, Jarusuraisin N. Opioid antagonists for alcohol dependence. Cochrane Database Syst Rev. 2005;1:CD001867.
26. Berg BJ, Pettinati HM, Volpicelli JR. A risk-benefit assessment of naltrexone in the treatment of alcohol dependence. Drug Saf. 1996;15:274–82.
27. Brewer C, Wong VS. Naltrexone: report of lack of hepatotoxicity in acute viral hepatitis, with a review of the literature. Addict Biol. 2004;9:81–7.
28. Croop RS, Faulkner EB, Labriola DF. The safety profile of naltrexone in the treatment of alcoholism. Results from a

multicenter usage study. The Naltrexone Usage Study Group. Arch Gen Psychiatry. 1997;54:1130–5.
29. National Institute of Diabetes and Digestive and Kidney Diseases. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. 2012, updated July 15, 2022 [cited]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK547852/
30. Kranzler HR, Van Kirk J. Efficacy of naltrexone and acamprosate for alcoholism treatment: a meta-analysis. Alcohol Clin Exp Res. 2001;25:1335–41.
31. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol. 2006;44:217–31.
32. Bouza C, Angeles M, Muñoz A, Amate JM. Efficacy and safety of naltrexone and acamprosate in the treatment of alcohol dependence: a systematic review. Addiction. 2004;99:811–28. Erratum in: Addiction. 2005;100:573.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Ayyala D, Bottyan T, Tien C, Pimienta M, Yoo J, Stager K, et al. Naltrexone for alcohol use disorder: Hepatic safety in patients with and without liver disease. Hepatol Commun. 2022;6:3433–3442. https://doi.org/10.1002/hep4.2080