JHEP|Reports

Safety of naltrexone in patients with cirrhosis

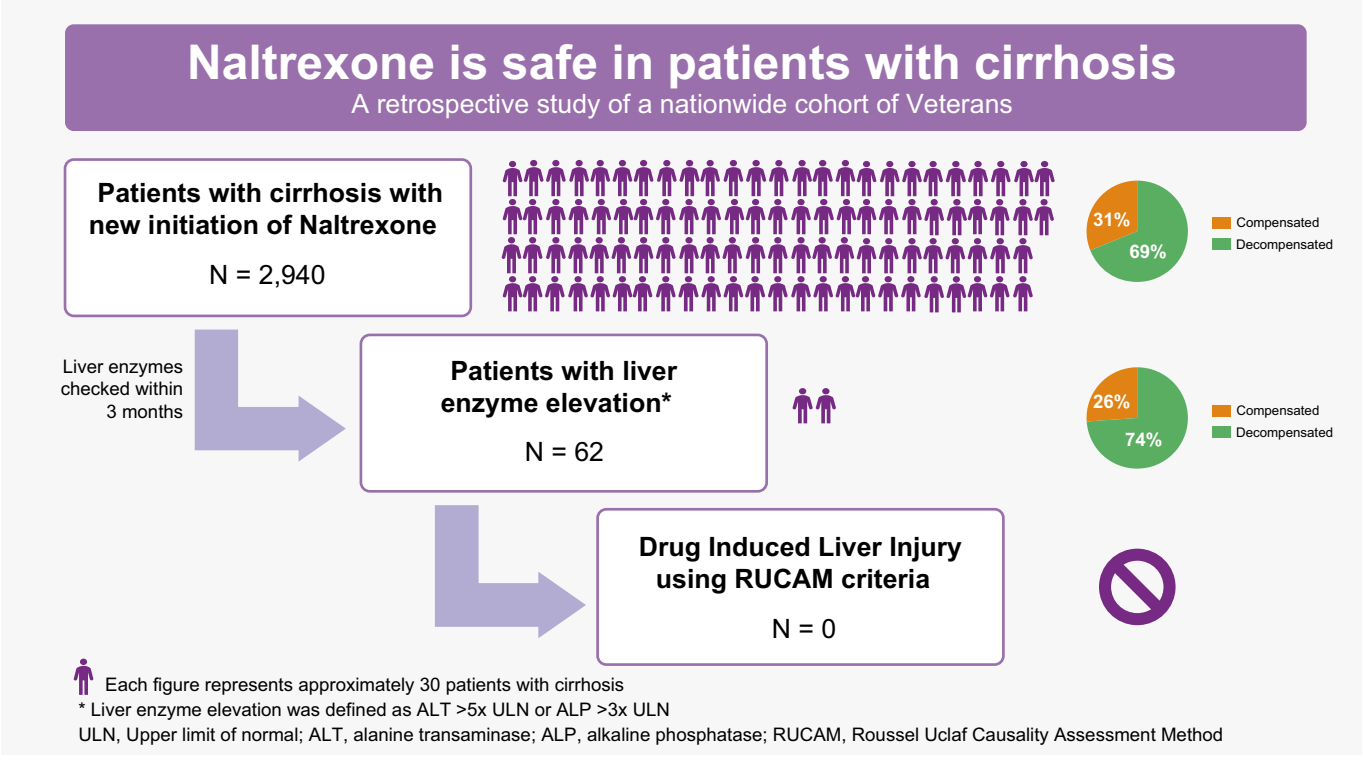
Authors

Rachel Thompson, Tamar Taddei, David Kaplan, Anahita Rabiee

Correspondence

anahita.rabiee@yale.edu (A. Rabiee).

Graphical abstract



Highlights:

- Naltrexone is an effective medication for alcohol use disorder but is underutilized owing to fears of hepatotoxicity.
- Naltrexone in patients with cirrhosis was not associated with development of DILI using RUCAM scoring.
- Naltrexone appears to be safe in patients with compensated and decompensated cirrhosis.
- This study may encourage use of naltrexone in patients with existing liver disease and ongoing alcohol use disorder.

Impact and Implications:

Naltrexone is an effective medication for treating alcohol use disorder but is underutilized in patients with underlying liver disease due to historical concerns regarding hepatotoxicity. This retrospective study shows no drug-induced liver injury in a large cohort of patients with cirrhosis with new initiation of naltrexone. This study may encourage providers to prescribe naltrexone to patients with existing liver disease with ongoing alcohol use disorder.

https://doi.org/10.1016/j.jhepr.2024.101095

Published by Elsevier B.V. on behalf of European Association for the Study of the Liver (EASL). This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/). JHEP Reports, 2024, 6, 1–5

JHEP|Reports

Safety of naltrexone in patients with cirrhosis

Rachel Thompson[1], Tamar Taddei[2,3], David Kaplan[4,5], Anahita Rabiee[2,3,*]

JHEP Reports **2024**. vol. 6 | 1–5

Check for updates

Background & Aims: Treatment of alcohol use disorder (AUD) improves survival in patients with alcohol-related cirrhosis. However, medications for alcohol use disorder (MAUD) are underutilized in this population, partially due to concerns regarding drug-induced liver injury (DILI). Our aim was to evaluate the safety of naltrexone in patients with cirrhosis.

Methods: This was a retrospective study of patients with cirrhosis who were prescribed naltrexone using the VOCAL (Veterans Outcomes and Costs Associated with Liver Disease) database. Patients with new initiation of naltrexone after diagnosis of cirrhosis who had liver enzymes checked within a 3-month time frame were included. A chart review was performed on patients who developed alanine aminotransferase or alkaline phosphatase elevations to more than 2× or 5× the upper limit of normal, respectively. The RUCAM (Roussel Uclaf causality assessment method) was used to determine if DILI occurred.

Results: A total of 3,285 patients with cirrhosis were initiated on naltrexone, of whom 2,940 had laboratory testing during the high-risk DILI period. Only 2% of patients had liver enzyme elevations, and among those, 30 (48%) were classified as "DILI excluded" and 32 (52%) were classified as "DILI unlikely". No patients were classified as possible, probable, or highly probable DILI. No deaths or new decompensations were attributed to naltrexone.

Conclusions: Naltrexone in patients with cirrhosis was not associated with development of DILI using RUCAM scoring. Naltrexone appears to be safe in patients with compensated and decompensated cirrhosis.

Published by Elsevier B.V. on behalf of European Association for the Study of the Liver (EASL). This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Ongoing alcohol consumption in patients with alcohol-related liver disease and cirrhosis increases risk of decompensation, alcohol-related hepatitis, hepatocellular carcinoma, and mortality.[1–3]

Medications for alcohol use disorder (MAUD) are effective for treating alcohol use disorder (AUD) by helping patients to achieve and maintain abstinence from alcohol.[4] In a nationwide retrospective cohort study of Veterans with alcohol-related cirrhosis and AUD performed by these authors, FDA-approved MAUD including naltrexone and acamprosate improved survival.[5]

Despite these benefits, MAUD are underutilized in patients with cirrhosis.[6,7] This underutilization is partially due to concerns regarding MAUD safety in patients with liver disease. A recent systematic review addressed this concern by demonstrating a 3% rate of adverse events related to MAUD in patients with cirrhosis; however, naltrexone, which is one of the three main US FDA-approved MAUD, was not evaluated in this review.[8]

Naltrexone-induced hepatotoxicity has been a historical concern due to studies in the 1980s that found asymptomatic liver enzyme elevations in patients receiving high-dose naltrexone.[9] This led to an FDA black-box warning for naltrexone-induced hepatotoxicity, which was later removed in 2013 given the lack of evidence of liver disease exacerbation.[10,11] A multicenter, non-randomized, open-label study of patients without liver disease receiving naltrexone *vs*. placebo for AUD demonstrated the overall safety of naltrexone with no significant differences in liver enzymes between groups.[12] In a review of existing randomized control trials of naltrexone in patients without liver disease, the most common adverse events included nausea, vomiting and dizziness and the main severe adverse event was precipitation of withdrawal from opioids.[4] Despite removal of the black-box warning, a precautionary note of possible hepatotoxicity persists in the naltrexone prescribing information, which fosters the perception that naltrexone should be avoided in liver disease.[13]

The survival benefit of treating AUD in patients with cirrhosis demands an objective assessment of the concern regarding naltrexone-induced hepatotoxicity. Therefore, we aimed to evaluate the safety of naltrexone in patients with compensated and decompensated cirrhosis based on risk of drug-induced liver injury (DILI).

Materials and methods

The VOCAL (Veterans Outcomes and Costs Associated with Liver Disease) cohort is an established time-updating dataset derived from the Veterans Affairs (VA) Corporate Data Warehouse. Approval for this study was obtained from the Institutional Review Boards at all participating VA sites. Veterans enrolled from 2008 to 2021 with a diagnosis of cirrhosis were

* Corresponding author. Address: 20 York St, New Haven, CT 06510, United States.
E-mail address: anahita.rabiee@yale.edu (A. Rabiee).
https://doi.org/10.1016/j.jhepr.2024.101095

included. Cirrhosis was diagnosed based on a previously validated methodology using ICD versions 9 or 10 diagnosis codes and required one inpatient ICD code or two outpatient ICD codes.[14,15] This methodology is predictive of cirrhosis diagnosis with a 90% positive predictive value and 87% negative predictive value in the VA database.[14]

Exposure was defined as new initiation of naltrexone after diagnosis of cirrhosis with no naltrexone in the preceding 12 months. Even a single dose of naltrexone was considered exposure. Only the first exposure after diagnosis of cirrhosis was considered for analysis. The high-risk DILI period was defined as day of drug initiation to 3 months based on Roussel Uclaf Causality Assessment Method (RUCAM) criteria.[16]

Patients with no labs in the high-risk DILI period were excluded. For baseline values, the closest alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin prior to starting naltrexone were obtained. Maximum ALT and ALP in the high-risk DILI period were identified. Liver enzyme elevation was defined as greater than 5x the upper limit of normal (ULN) for ALT, or greater than 2x the ULN for ALP.[16] In patients with abnormal baseline values, liver enzyme elevations were defined as ALT or ALP 5x or 2x the patient's baseline, respectively.

RUCAM criteria are used to predict if changes in liver enzymes are indicative of DILI. RUCAM divides liver enzyme elevations into either hepatocellular, cholestatic, or mixed injury based on "R value" (ratio of ALT to ALP as multiples of the ULNs). RUCAM assigns points based on time course of liver enzyme elevation, patient risk factors (age, alcohol use), concomitant drugs, alternative causes, and drug re-exposure to predict DILI likelihood for a specific drug.[16] In patients meeting liver enzyme elevation criteria, chart review was done by a trained internal medicine resident (RT) and RUCAM was scored. All inpatient, outpatient and consult notes in that time frame were reviewed to determine alternative diagnoses. All imaging, prescription medications, supplements, over the counter medications, blood work, imaging, and pathology were reviewed. In addition, charts for patients who died or newly decompensated within 3 months of starting naltrexone were reviewed to identify the cause of death or decompensation.

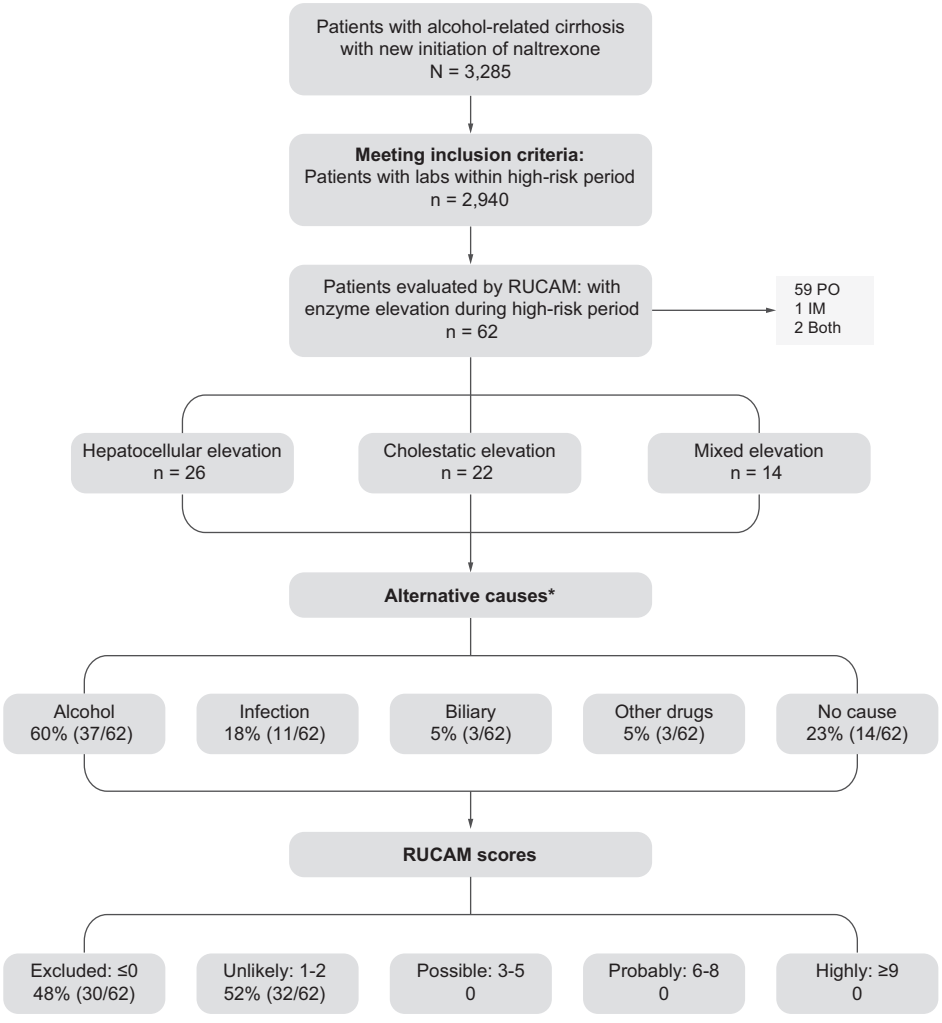


Fig. 1. Flow diagram of patients with liver enzyme elevation. High-risk period defined as day of drug initiation through 3 months. Liver enzyme elevation defined as 5x the ULN for ALT and/or 2x the ULN for ALP. Enzyme elevation groups determined by R value (ALT/ULN divided by ALP/ULN, with R >5 hepatocellular, R <2 cholestatic). *Multiple alternative causes were identified in 12 (19%) patients. RUCAM scores for drug induced liver injury assessment. ALT, alanine aminotransferase; ALP, alkaline phosphatase; PO, per os; IM, intramuscular; RUCAM; Roussel Uclaf causality assessment method; ULN, upper limit of normal.

Results

A total of 3,285 patients with cirrhosis were new initiators of naltrexone. Among these patients, only 2,940 had follow-up laboratory testing within the high-risk DILI period (Fig. 1). Average age was 58, 96% were male, 63% were White and 20% were Black. The etiology of cirrhosis was alcohol in 61%, and alcohol and hepatitis C in 32% (Table 1). Median time from diagnosis of cirrhosis to initiation of naltrexone was 22 months (IQR: 7–46). History of decompensation prior to initiation of naltrexone was present in 915 (31%) (ascites 13%, variceal bleeding 18%, hepatic encephalopathy 10%). A total of 433 (15%) had Child-Pugh class B or C cirrhosis at the time of initiation of naltrexone, and 6% had jaundice (bilirubin ≥3) (Table 1). Among the 2,940, 42 (1.4%) patients received intramuscular (IM) naltrexone.

In the cohort of 2,940, there were 37 deaths and 11 new decompensations within the first 3 months of naltrexone initiation. Most common etiologies of death included end-stage liver disease on hospice (8), septic shock (6), gastrointestinal bleeding (3), hepatocellular carcinoma on hospice (2), suicide (2), unknown (4). New decompensations included hepatic encephalopathy (5), ascites (2), variceal bleed (3) and hepatic encephalopathy with ascites (1). None of the decompensation episodes were attributed to naltrexone initiation.

Among the patients with baseline labs, we observed a median (IQR) reduction in AST of −5 (−30, 10) and in ALT of −2 (−17, 9). Total bilirubin nominally decreased in 53% of patients with median (IQR) change of −0.07 (−0.4, 0.2) (Table 1).

Among 2,940 patients, only 62 (2%) had significant enzyme elevation, consisting of 37 (1.3%) with a rise in only ALT, 21 (0.7%) with a rise in only ALP and 4 (0.1%) meeting both criteria (Fig. 1). From the 62 patients with liver enzyme elevation, 59 were prescribed oral (PO) naltrexone alone, one was prescribed IM naltrexone alone and two were prescribed IM and PO naltrexone. Twenty six of 62 patients (42%) had hepatocellular, 22 patients (35%) cholestatic and 14 patients (23%) mixed elevations (Fig. 1). Using the RUCAM scoring system, 48% were scored as "DILI excluded", and 52% scored "DILI unlikely." No patients scored "possible", probable" or "highly probable".

Among the 62 patients with liver enzyme elevation, 28 (45%) had additional lab work, 30 (48%) had abdominal imaging (ultrasound, cross-sectional imaging), and one (2%) had a biopsy. The biopsy did not show evidence of DILI. On review of clinic notes and lab values, 46/62 (74%) patients were found to have ongoing alcohol use.

Among the 62 patients with liver enzyme elevation, alternative causes were identified in 48 (77%) patients. This included 37 (60%) who were acutely intoxicated at the time of the elevation. Systemic infection was identified in 11 (18%), including a new diagnosis of hepatitis B (1), hepatitis C (2 new diagnoses, 5 previously diagnosed but newly commencing antiviral treatment), a new diagnosis of HIV (1), shock secondary to cellulitis (1), and COVID-19 infection (1). Other etiologies included biliary (3, 5%), pancreatic disease (4, 6%), cardiopulmonary shock (3, 5%), and alcohol-related hepatitis (1, 2%). Other high-risk DILI drugs were identified in 3 (5%) including new statin use (1), acetaminophen toxicity (1), and immunotherapy (1). In 12 (19%) patients, multiple alternative causes were identified. There were also 14 (23%) patients for whom no specific cause for liver enzyme elevation could be identified via chart review.

Table 1. Baseline characteristics of patients with cirrhosis who were prescribed naltrexone.

Baseline characteristics	N = 2,940
Gender (female %)	126 (4%)
Age, mean (SD)	58 (9%)
Race, n (%)	
White	1,862 (63%)
Black	579 (20%)
Other	599 (17%)
Etiology (%)	
Alcohol	1785 (61%)
Alcohol and hepatitis C	942 (32%)
Other	213 (7%)
Baseline laboratory values*, mean (SD)	
Bilirubin	1.3 (1.5)
AST	70.2 (77.1)
ALT	50.6 (53.1)
ALP	112.6 (64.5)
MELD-Na	11 (7)
Child Pugh class (%)	
A	2,506 (85%)
B	411 (14%)
C	22 (0.7%)
Decompensation** (%)	915 (31%)
Jaundice (%)	177 (6%)
History of ascites (%)	381 (13%)
History of hepatic encephalopathy (%)	282 (10%)
Spontaneous bacterial peritonitis (%)	43 (2%)
History of variceal bleeding (%)	520 (18%)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MELD-Na, model for end-stage liver disease-sodium.
*Baseline liver enzymes were missing in 32% of patients.
**Patients could have more than one decompensation.

Discussion

Our study is the largest study of safety of naltrexone among patients with cirrhosis, including 2,940 patients who were prescribed naltrexone and had lab work within 3 months of initiation. There was not a single case of DILI based on RUCAM scoring. Significant liver enzyme elevation was only seen in 2% of patients, and a clear alternative cause was identified in 77% of these cases. None of the deaths or new decompensations within the first 3 months after initiation of naltrexone were attributed to this medication. Among the patients with baseline labs, the median AST and ALT at follow-up decreased compared to baseline.

Medical treatment of AUD is associated with reduced incidence and progression of alcohol-related liver disease, including decreased progression to decompensated cirrhosis, and improved survival in patients with cirrhosis.[5,17] Despite these benefits, MAUD are vastly underutilized in patients with alcohol-related cirrhosis. Barriers to treatment for AUD in patients with cirrhosis include perceived stigma, cost of pharmacotherapy, challenges participating in counseling and lack of provider confidence in prescribing MAUD in liver disease.[18–20] Our study showing no cases of DILI in a large nationwide sample of patients with compensated and decompensated cirrhosis provides evidence of the safety of naltrexone in this population. Our findings are consistent with previous studies on the safety of naltrexone in patients with alcohol-related cirrhosis, however, these studies have been limited by small sample sizes.[21] We are hoping this safety data helps providers

feel more confident in prescribing naltrexone to patients with liver disease. The only current contraindication to naltrexone is active opioid use disorder, use of opiate agonists (methadone) or use of partial agonists (buprenorphine), so patients should be assessed for these prior to naltrexone initiation.[10] A minimum of 3 months of naltrexone has been recommended, and many recommend continuing it for at least a full year, as the risk of recurrence is highest during this time frame.[22]

Our study has several limitations. First, diagnosing DILI is very challenging in clinical practice and via retrospective chart review. RUCAM was chosen as our assessment tool as it has been previously validated and has good inter-observer agreement.[16,23] However, RUCAM, like any other instrument, has limitations given subjectivity of use.[24] We also reviewed notes for alternative causes that are not specifically listed in RUCAM, so as not to miss alternative diagnoses. Second, there is no uniform protocol in terms of checking liver enzymes after starting naltrexone, therefore potential cases of DILI could have been missed if patients developed DILI outside the high-risk window or were excluded if labs were not drawn after naltrexone initiation. This could have potentially resulted in selection bias, with exclusion of patients with less engagement in care. Third, we used ICD-9/10 codes to identify patients with cirrhosis, so we may not have detected all patients with cirrhosis. To minimize this limitation, we used a previously validated methodology with two outpatient or one inpatient code for cirrhosis.[14] Additionally, the patients in our study primarily received PO naltrexone. Therefore, our sample size is not large enough to comment on the safety of IM naltrexone in this population, and future studies focusing on IM naltrexone are needed. Lastly, the cohort included only 4% women, which could limit generalizability.

There was no significant association of DILI with naltrexone use in patients with cirrhosis using RUCAM scoring. Naltrexone appears to be safe in patients with compensated and decompensated cirrhosis.

Affiliations

[1]*Department of Internal Medicine, Yale School of Medicine, New Haven, CT, United States;* [2]*Section of Digestive Diseases, Yale School of Medicine, New Haven, CT, United States;* [3]*VA Connecticut Healthcare System, New Haven, CT, United States;* [4]*Corporal Michael J. Crescenz VA Medical Center, Philadelphia, Pennsylvania, United States;* [5]*Division of Gastroenterology and Hepatology, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, United States*

Abbreviations

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUD, alcohol use disorder; DILI, drug-induced liver injury; MAUD, medications for alcohol use disorder; PO, per os (oral); RUCAM, Roussel Uclaf causality assessment method; ULN, upper limit of normal; VA, Veterans Affairs.

Financial support

No funding source was provided for this research.

Conflict of interest

DK reports grants from AstraZeneca, Exact Sciences, Roche Genentech, and Bausch, and consulting fees from Sirtex, AstraZeneca, and Roche Genentech. All other authors report no conflict of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Rachel Thompson: data curation, investigation, formal analysis, visualization, writing – original draft. Tamar Taddei: methodology, supervision, writing – reviewing & editing. David Kaplan: writing – reviewing & editing. Anahita Rabiee: conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, validation, writing – reviewing & editing.

Data availability statement

All relevant data that support the findings are presented in the manuscript.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2024.101095.

References

Author names in bold designate shared co-first authorship

[1] **Lackner C**, **Spindelboeck W**, Haybaeck J, et al. Histological parameters and alcohol abstinence determine long-term prognosis in patients with alcoholic liver disease. J Hepatol 2017;66(3):610–618.

[2] Morgan TR, Mandayam S, Jamal MM. Alcohol and hepatocellular carcinoma. Gastroenterology 2004;127(5 Suppl 1):S87–S96.

[3] **Altamirano J**, **Lopez-Pelayo H**, Michelena J, et al. Alcohol abstinence in patients surviving an episode of alcoholic hepatitis: prediction and impact on long-term survival. Hepatology 2017;66(6):1842–1853.

[4] McPheeters M, O'Connor EA, Riley S, et al. Pharmacotherapy for alcohol use disorder: a systematic review and meta-analysis. JAMA 2023;330(17):1653–1665.

[5] Rabiee A, Mahmud N, Falker C, et al. Medications for alcohol use disorder improve survival in patients with hazardous drinking and alcohol-associated cirrhosis. Hepatol Commun 2023;7(4).

[6] Harris AH, Kivlahan DR, Bowe T, et al. Pharmacotherapy of alcohol use disorders in the Veterans health administration. Psychiatr Serv 2010;61(4):392–398.

[7] Rogal S, Youk A, Zhang H, et al. Impact of alcohol use disorder treatment on clinical outcomes among patients with cirrhosis. Hepatology 2020;71(6):2080–2092.

[8] Gratacos-Gines J, Bruguera P, Perez-Guasch M, et al. Medications for alcohol use disorder promote abstinence in alcohol-related cirrhosis: results from a systematic review and meta-analysis. Hepatology 2023;79(2):368–379.

[9] Bolton M, Hodkinson A, Boda S, et al. Serious adverse events reported in placebo randomised controlled trials of oral naltrexone: a systematic review and meta-analysis. BMC Med 2019;17(1):10.

[10] Administration USFDA. Safety information - revia (naltrexone HCl) tablets: safety labeling changes approved by FDA Centre for Drug Evaluation and Research (CDER). MedWatch safety information US. Department of Health and Human Services; 2013.

[11] Brewer C, Wong VS. Naltrexone: report of lack of hepatotoxicity in acute viral hepatitis, with a review of the literature. Addict Biol 2004;9(1):81–87.

[12] 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(12):1130–1135.

[13] Stoddard J, Zummo J. Oral and long-acting injectable naltrexone: removal of boxed warning for hepatotoxicity. J Clin Psychiatry 2015;76(12):1695.

[14] Kramer JR, Davila JA, Miller ED, et al. The validity of viral hepatitis and chronic liver disease diagnoses in Veterans Affairs administrative databases. Aliment Pharmacol Ther 2008;27(3):274–282.

[15] Kaplan DE, Dai F, Aytaman A, et al. Development and performance of an algorithm to estimate the child-turcotte-pugh score from a national electronic healthcare database. Clin Gastroenterol Hepatol 2015;13(13):2333–2341.e1-6.

[16] Danan G, Teschke R. RUCAM in drug and herb induced liver injury: the update. Int J Mol Sci 2015;17(1).

[17] Vannier AGL, Shay JES, Fomin V, et al. Incidence and progression of alcohol-associated liver disease after medical therapy for alcohol use disorder. JAMA Netw Open 2022;5(5):e2213014.

[18] Avancena ALV, Miller N, Uttal SE, et al. Cost-effectiveness of alcohol use treatments in patients with alcohol-related cirrhosis. J Hepatol 2021;74(6):1286–1294.

[19] Harris AHS, Ellerbe L, Reeder RN, et al. Pharmacotherapy for alcohol dependence: perceived treatment barriers and action strategies among Veterans Health Administration service providers. Psychol Serv 2013;10(4):410–419.
[20] Oliva EM, Maisel NC, Gordon AJ, et al. Barriers to use of pharmacotherapy for addiction disorders and how to overcome them. Curr Psychiatry Rep 2011;13(5):374–381.
[21] Ayyala D, Bottyan T, Tien C, et al. Naltrexone for alcohol use disorder: hepatic safety in patients with and without liver disease. Hepatol Commun 2022;6(12):3433–3442.
[22] Anton RF. Naltrexone for the management of alcohol dependence. N Engl J Med 2008;359(7):715–721.
[23] Tillmann HL, Suzuki A, Barnhart HX, et al. Tools for causality assessment in drug-induced liver disease. Curr Opin Gastroenterol 2019;35(3):183–190.
[24] Hayashi PH, Lucena MI, Fontana RJ, et al. A revised electronic version of RUCAM for the diagnosis of DILI. Hepatology 2022;76(1):18–31.

Keywords: cirrhosis; naltrexone; alcohol use disorder; drug induced liver injury.
Received 12 December 2023; received in revised form 1 April 2024; accepted 4 April 2024; Available online 10 April 2024