



Published in final edited form as:

J Addict Med. 2025 ; 19(3): 314–321. doi:10.1097/ADM.0000000000001421.

Drug-Induced Liver Injury due to Medications for Alcohol Use Disorder: Results from the DILIN Prospective Study

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Abstract

Objectives: Concerns about drug-induced liver injury (DILI) may deter physicians from prescribing medications for alcohol use disorder (MAUD). We aim to explore DILI due to MAUD in Drug Induced Liver Injury Network (DILIN) prospective study.

Methods: High confidence DILI cases (i.e., definite, highly likely, or probable) due to MAUD in DILIN prospective study (2004-2024) were included. Demographic, clinical, laboratory data and 6-month outcomes were analyzed. HLA allele frequency (AF) of disulfiram cases was compared to matched controls with DILI due to non-MAUD (DILI controls).

Results: Among 1975 high confidence cases, 13 were attributed to MAUD (11 disulfiram; 1 naltrexone and 1 baclofen; and none from acamprosate). Median age was 45 years, with 77% female and 85% White. All had hepatocellular injury. In disulfiram group, median time for DILI occurrence was 34 days. Eight patients developed jaundice, with 3 fatal or near-fatal cases (2 liver transplantation and 1 liver-related death). Five (71%) patients with severe or fatal disulfiram DILI had underlying liver disease. AF for HLA-C*01:02 (OR: 6.29, p=0.02) and DRB1*09:01 (OR: 10.16, p=0.02) were significantly higher in disulfiram cases than in DILI controls. DILI from baclofen and naltrexone was mild and self-limited with no chronic DILI.

Conclusion: Disulfiram is the leading cause of DILI among MAUD and is most common in women. Disulfiram can cause severe DILI and is associated with HLA-C*01:02 and DRB1*09:01.

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Author contributions: Study concept and design: HG, MG, JG, DEK, CK, NC; Acquisition of data: HG, MG, JG, CK, NC, RJF; Analysis and interpretation of data: HG, MG, JG, DEK, CK; Drafting of the manuscript HG, MG, JG, DEK, CK, NC, RJF; Critical revision of the manuscript for important intellectual content: All authors; Statistical analysis: HG, MG, JG, DEK, CK; Obtained funding: NC.

Baclofen and naltrexone can cause mild to moderate self-limited DILI. There were no cases of acamprosate. These findings suggest DILI due to MAUD are less frequent.

Keywords

alcohol-related disorders; hepatotoxicity; alcohol deterrents; naltrexone; baclofen

Introduction

Over 2.3 billion individuals, equating to 43% of the global population, engage in alcohol consumption, and approximately 40% of them are categorized as heavy drinkers.^{1,2} Globally, alcohol use is linked to nearly 3 million deaths annually, with the United States alone reporting nearly 140,000 alcohol-related deaths per year.³ The prevalence of alcohol use disorder (AUD) and alcohol-associated liver disease (ALD) presents a significant public health challenge, with 1 in 5 deaths among adults aged 20 to 49 attributable to alcohol misuse.³ Furthermore, excessive alcohol intake is a leading cause of cirrhosis and its complications, representing approximately 60% of cirrhosis cases in Europe, North America, and Latin America.⁴ The recent COVID-19 pandemic has witnessed a 25% surge in alcohol-related deaths among adults, underscoring the urgent need for effective intervention and prevention strategies.⁵

Continued alcohol consumption among individuals with underlying liver disease poses a significant risk for disease progression and complications. Conversely, treating AUD, even in patients with advanced liver disease, can yield survival benefits.^{6,7} A multidisciplinary approach to AUD treatment encompasses behavioral therapies and medications.⁸ Notably, medications for alcohol use disorder (MAUD), including acamprosate, naltrexone, and disulfiram, are Food and Drug Administration (FDA)-approved for AUD treatment, while baclofen is widely used off-label especially in those with liver disease.⁸ Despite the availability of these medications, their utilization remains low due to concerns regarding safety and efficacy.⁹ Although hepatotoxicity is less frequent with MAUD, it poses significant safety concern. Prior reports implicating disulfiram as a potential cause of drug-induced liver injury (DILI) largely from European centers.^{10,11} Limited information is available regarding the hepatotoxicity of other MAUD. Addressing these concerns is crucial to optimize the utilization of MAUD.

In this study, we explore the clinical characteristics, liver injury phenotypes, histology and outcomes of DILI attributed to MAUD who were enrolled into the prospective US Drug Induced Liver Injury Network (DILIN) over the past 20 years. Recent studies have shown that human leukocyte antigen (HLA) alleles can be associated and may play a role in pathogenesis of DILI.¹² Hence, we characterized the (HLA) alleles associated with disulfiram DILI cases compared to matched non-disulfiram DILI controls from DILIN.

Methods

Study Design

The DILIN is a multi-institutional network initiated in 2004 by the National Institutes of Health to conduct a prospective study on clinically apparent liver injury.^{13,14} This ongoing study, known as the DILIN Prospective Study, enrolls participants suspected of experiencing DILI within six months of onset. The DILIN prospective study protocol received approval from the Institutional Review Board at all participating sites. Written informed consent was obtained from all participants prior to their inclusion in the study. The DILIN prospective study is registered with [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00345930) (NCT # 00345930).

Eligibility criteria

Patients were included if i) aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level > 5 times the upper limit of normal (ULN) or > 5 times baseline levels if pre-treatment values were abnormal on at least 2 consecutive occasions, or (ii) alkaline phosphatase (ALP) level 2 times the ULN (or baseline if pre-treatment values were abnormal) on 2 consecutive occasions, or (iii) total bilirubin level ≥ 2.5 mg/dL accompanied by any elevation in AST, ALT or ALP level, or (iv) international normalized ratio (INR) > 1.5 accompanied by any elevations in AST, ALT or ALP level. Patients with pre-existing chronic hepatitis C (HCV), hepatitis B virus (HBV), ALD or metabolic dysfunction associated steatotic liver disease were eligible. However, patients with acetaminophen toxicity, history of autoimmune hepatitis, primary biliary cholangitis or primary sclerosing cholangitis were excluded. All patients were scheduled to be seen at 6 months after onset. Chronic DILI was defined as persistent elevation of serum AST, ALT or ALP level, histopathologic evidence of liver injury or evidence of portal hypertension at 6 months after DILI onset.¹³

Causality and severity scoring

Clinical and laboratory data were extracted and utilized for a comprehensive, independent evaluation of causality and severity grading of liver injury. Each suspected case of DILI was independently adjudicated by DILIN investigators on a five-category scale, ranging from 1—definite (>95%), 2—highly likely (75%-95%), 3—probable (50%-74%), 4—possible (25%-49%), to 5—unlikely (<25%), following established protocols.¹³ Only high confidence cases (i.e., probable, highly likely, or definite) were included in this study. The type of liver injury was categorized based on the *R* ratio, calculated using initial values of serum ALT divided by ALP: $R = \text{ALT/ULN} \div \text{ALP/ULN}$. An *R* ratio of <2 indicated a cholestatic pattern, >5 indicated a hepatocellular pattern, and 2–5 indicated a mixed injury pattern. A 5-point scale is used to define severity, ranging from 1 (mild), 2 (moderate), 3 (moderate and hospitalized), 4 (severe), and 5 (fatal, death or liver transplantation due to DILI within 6 months of onset). High confidence cases due to disulfiram, naltrexone, acamprosate and baclofen irrespective of indication for use was included. Since DILI due to topiramate and gabapentin were reported previously, it is not included here.¹⁵

Liver histopathology

Available liver biopsies were reviewed by a single expert liver histopathologist (DEK) and scored for multiple histological features as well as an overall pattern of liver injury. Histopathologist was not blinded of the medication exposure.

HLA data

A case-control study design was used to identify HLA alleles potentially associated with risk of developing of DILI due to disulfiram. The control group included high confidence DILI patients from DILIN who were not exposed to disulfiram and herbal and dietary supplements (HDS), referred to as, DILI controls. HLA sequencing for all DILIN patients was performed on DNA extracted from whole blood using the Illumina MiSeq platform at the Vanderbilt University Medical Center Immunogenomics, Microbial Genetics, and Single Cell Technologies core.^{15,16} Of the 11 disulfiram DILI cases, 9 have HLA data. Non-disulfiram DILI controls (n=456) were matched based on age, sex, and race. The sample counts per group based on race are listed in Supplementary Table 1.

Statistical analysis

Descriptive statistics were used to summarize the demographic and clinical data. The data analyses were performed by the Duke Clinical Research Institute, the data coordinating center of the DILIN. Continuous variables were summarized with median and range (minimum to maximum) and frequencies with percentage were used for categorical variables.

For HLA analysis, disulfiram DILI cases and non-disulfiram DILI controls were matched for race, sex, and age range within 5 years using MatchIt R package. The only exception is one South Asian disulfiram DILI case, for which no matched control was available within a 5-year age range. Therefore, we selected a non-disulfiram DILI control with an age match within an 11-year range. HLA allelic frequency (AF) was compared between disulfiram DILI cases and DILI controls by Fisher exact test. HLA alleles meeting p-value < 0.05 and having higher AF were considered potentially associated with the risk of developing disulfiram-DILI.

Results

Baseline characteristics – Overall cohort

Between 2004 and 2024, a total of 2622 participants with suspected DILI were enrolled in the DILIN prospective study. (Figure 1) Among the 2495 adjudicated cases, 1975 (79%) was classified as high confidence cases. Of the 13 high confidence MAUD cases, 11 were due to disulfiram and 1 case each to naltrexone and baclofen. Notably, no case associated with acamprosate was identified.

The demographic and clinical features of the DILI cases are summarized in Table 1. The median age was 45 years (range: 31 to 61 years), with 10 (77%) being female, 11 (85%) were White. As expected, 12 (92%) of patients had pre-existing alcohol use. The duration of drug exposure to onset of documented liver injury (latency) ranged from 8 days to 112

days (median 34 days). The pattern of liver injury at DILI onset was hepatocellular ($R = 5$) in all cases. Viral serologies were negative for all except one patient who had stable chronic hepatitis C. No participants were HIV positive or had history of HBV.

DILI due to Disulfiram

Eleven patients developed DILI due to disulfiram with 6 arising prior to 2015. As shown in Table 2, affected patients were mostly White (82%), females (73%), with median age of 44 years (range: 31 to 61 years). Five (46%) patients had prior drug allergies, and all had preexisting alcohol use. Five patients (46%) had alcohol associated liver disease and one had HCV (HCV RNA positive). (Table 1) Median duration of disulfiram exposure was 32 days (range: 11 to 74 days). Nine patients received a daily dose of 250 milligram (mg) of disulfiram, while 2 patients (case 5 and 7) received a higher dose of 500 mg per day. Median latency to symptom onset was 25 days (range 1 to 65 days) and drug was stopped after earliest sign or symptom in 8 days (range: 0 to 41 days). All patients were symptomatic at time of presentation and the most common symptoms were jaundice and abdominal pain (73%), followed by nausea (64%) and itching (36%), and only 1 had a rash. (Table 2)

The median peak ALT 2516 U/L (range: 1060-6698 U/L), AST 2009 U/L (range: 412 – 6403 U/L), ALP 244 U/L (range: 87-444 U/L), total bilirubin 16 mg/dL (range: 0.3-34 mg/dL) and INR was 1.6 (range: 1 to 9.4). All participants had 5-fold elevation in ALT, 3 had 2-fold elevation in ALP and 9 had total bilirubin 2.5 mg/dL. During follow-up, median time from peak total bilirubin to < 2.5 mg/dL was 51 days.

The majority (90%) of patients were either hospitalized or required prolonged hospitalization. The severity of DILI was scored mild 2 cases, 2 were moderate-hospitalized, 4 had severe and 3 experienced fatal DILI. Two patients with severe DILI were empirically treated with steroids. Among 3 patients with fatal DILI, 2 underwent liver transplant and 1 died due to liver-related causes. The patient who died had underlying cirrhosis with signs of portal hypertension secondary to ALD and developed jaundice within 11 days of exposure to the drug. Cause of death was deemed to be acute on chronic liver failure. In retrospect, all but one who had severe or fatal DILI developed jaundice and had total bilirubin level > 15 mg/dL.

DILI due to Naltrexone

A 59-year-old white female with history of alpha 1 antitrypsin deficiency with lung involvement on alpha-1 proteinase inhibitor replacement therapy for several years. She had known steatotic liver disease by imaging but no prior history of elevated liver enzymes. She developed DILI just 8 days into the treatment with 4.5 mg of daily naltrexone. She was asymptomatic at the time of presentation with an ALT of 730 U/L, AST of 216 U/L, and total bilirubin was 0.6 mg/dL. Abdominal imaging revealed hepatic steatosis. Even though blood acetaminophen level was negative, she received empiric treatment with N-acetylcysteine. Causality was determined to be probable, and severity was assessed as mild with fully recovery in less than a week of drug discontinuation.

DILI due to Baclofen

A 61-year-old white female with history of hyperlipidemia but no prior history of liver disease was treated with baclofen 5 mg thrice daily for AUD. She presented with nausea, and abdominal pain about 111 days after drug initiation. Notable concomitant medications included atorvastatin which she was taking for almost 10 years and ezetimibe for 18 months. Liver enzymes prior to baclofen initiation was normal. At onset of DILI, ALT was 1317 U/L, AST was 2078 U/L, and total bilirubin was 1.65 mg/dL. At peak, AST remained higher than ALT, total bilirubin was 2.6 mg/dL and INR was 1.1. She tested positive for ANA, but ASMA, and anti-double stranded DNA were negative and serum IgG level was 659 mg/dL. Abdominal imaging revealed normal appearing liver and spleen with no portal vein or hepatic artery thrombosis. Causality was determined to be probable, and severity was assessed to be moderate-hospitalized. Patient was sick with liver injury for a week and recovered completely without any chronic liver injury. (Supplementary Figure 1)

Liver Histology

Four liver biopsies were available for central review from disulfiram-associated DILI: 2 were biopsies (cases 6 and 7) obtained 18 and 5 days after DILI onset, respectively, and 2 were explants (cases 4 and 8) obtained 17 and 47 days after DILI onset, respectively. Both biopsies showed a cholestatic hepatitis with mild inflammation, bile duct injury and prominent canalicular cholestasis. The explants showed extensive panacinar necrosis with ductular reaction and regenerative nodules (Supplementary Figure 2A–D). Cholestasis was also seen, but the ducts were intact. Only rare eosinophils and plasma cells were seen in any of the cases. Case 6 showed advanced fibrosis (at least bridging fibrosis) and infiltration of neutrophils, which may have been due to underlying alcoholic liver disease. The other three cases showed no evidence of prior alcohol-related injury and no significant fibrosis or steatosis.

Biopsies from the baclofen- and naltrexone-induced DILI cases were not available for central review. By report, the liver biopsy in case 13 (baclofen) performed 4 days after DILI onset showed mild portal chronic inflammation with scattered plasma cells and a few eosinophils. There was no necrosis or fibrosis, and no features of alcohol-related injury were seen. In case 12 (naltrexone), the biopsy was performed 3 days after DILI onset and showed only mild steatohepatitis.

HLA association with disulfiram DILI

Among 9 disulfiram-DILI cases, 3 carried *C*01:02* (CF=0.33), and 2 had *DRB1*09:01* (CF=0.22). Interestingly, one carried both *C*01:02* and *DRB1*09:01*. (Supplementary Table 2) The AF for *HLA-C*01:02* (AF: 0.167 vs 0.031, OR: 6.29, 95% CI: 1.10-24.1) and *DRB1*09:01* (AF: 0.111 vs 0.012, OR: 10.16, 95% CI: 1/01, 52.7) were significantly higher in disulfiram DILI cases compared to matched DILI controls. The AF of these two HLA alleles in disulfiram-DILI cases were also notably higher than the population AF obtained from Allele Frequency Net Database (AFND).¹⁷

Discussion

DILI due to MAUD is rare but is a significant complication that can occur with treating AUD. Limited evidence regarding its hepatotoxicity can heighten apprehension among clinicians. However, our analysis of two decades of data from the DILIN prospective study provides some reassuring insights. Among the 1975 high-confidence DILI cases studied, only one case was attributed to baclofen and 1 to naltrexone. Importantly there were no cases of DILI due to acamprosate. These findings carry significant clinical implications. Firstly, they suggest that, aside from disulfiram, MAUD are generally not associated with a notable risk of DILI. We also identified 2 novel HLA alleles, *HLA-C*01:02*, and *HLA-DRB1*9:01* association with liver injury due to disulfiram.

Disulfiram was the first FDA-approved MAUD in 1951. Since disulfiram is primarily metabolized by the liver, mild increases in transaminases are common.¹⁸ However, several case reports and series have documented hepatotoxicity associated with disulfiram.^{10,11,19–22} A Swedish registry study spanning from 1966-2002 identified 82 disulfiram induced DILI cases, with 9.8% required liver transplant or died.¹⁰ Similarly, a single center Danish study from 2007 to 2012 found that 13 (30%) cases of DILI attributed to disulfiram, out of which 54% requiring transplant or died.¹¹ Our study, the largest series from US, reveals an interesting trend: females were commonly affected, contrary to prior reports. This is interesting considering that women are less likely to receive MAUD.²³ However, these results should be interpreted cautiously due to our small sample size. Jaundice was noted in 73% of our cohort compared to 60% in the Swedish study. In the Danish study, 54% of participants required transplant or died due to DILI, while the rate was 9.8% in the Swedish study.^{10,11} Our series demonstrates an intermediate level of 27% of participants having a poor outcome, either liver transplant or death. Of note, the high mortality rate seen in the Danish study is likely because of high prevalence (6 out of 13) of cirrhosis. In our series 2 out of 11 patients had underlying cirrhosis and in the Swedish study only 1 out of 17 patients with liver biopsy had cirrhosis. All but one case of disulfiram induced DILI was enrolled before 2020 which may reflect the decreasing trend in disulfiram prescription for AUD treatment.²⁴

Genetic susceptibility to DILI is well-established, with multiple studies demonstrating HLA associations with DILI due to different agents.¹² However, there are no prior reports of HLA association with DILI due to disulfiram. We found 2 novel HLA alleles *C*01:02*, and *DRB1*9:01* to be significantly associated with liver injury due to disulfiram compared to DILI controls. The AF for *HLA-C*01:02*, and *HLA-DRB1*9:01* was also found to be much higher than what is generally observed in population allele frequency. These findings, though not practice-changing, offers insights into the possible immunopathogenesis of disulfiram induced DILI. This can aid in risk stratification and identification of patients at risk for DILI but needs validation in larger cohorts.

Initially developed for opioid use disorder, naltrexone gained FDA approval as MAUD in 1994. It is primarily metabolized by the liver and excreted by the kidneys. Concerns about hepatotoxicity arose, particularly with higher doses (300 mg), leading to a “black-box warning” by the FDA. However, lower doses (200 mg daily) showed no liver-related

adverse events, resulting in removal of the warning in 2013.²⁵ A recent retrospective study of 160 patients receiving naltrexone in the US, including compensated and decompensated cirrhosis cases, reported very few cases of liver enzyme elevations. Among the two instances of persistent liver injury post-naltrexone cessation, alcohol use was a probable cause.²⁶ In the DILIN prospective study, only one case of self-limited, mild naltrexone-induced DILI was identified. In a randomized controlled trial evaluating naltrexone's efficacy in AUD, 2% of participants receiving naltrexone 100 mg daily experienced more than 5-fold rise in AST or ALT, which improved upon drug discontinuation. However, it remains unclear if naltrexone was the sole cause.²⁷ Overall, evidence suggests that naltrexone-associated hepatotoxicity is rare and self-limiting, emphasizing its generally favorable safety profile for AUD treatment.

Acamprosate was approved by the FDA for AUD in 2004. Since then, there were no reports of DILI due to acamprosate in our DILIN prospective study. This is in line with recent study which showed acamprosate was safer even in cirrhotic patients.²⁸ This could be because drug is not metabolized in liver and is excreted unchanged in urine.

Baclofen was developed as a muscle relaxant and approved by FDA for treatment of spasticity in 1977. Since the early 2000s, it has gained recognition for off-label use in treatment of AUD by promoting abstinence and preventing relapse.^{29,30} Notably, in a study with alcohol-dependent individuals with cirrhosis, baclofen exhibited superiority in promoting abstinence over placebo, all without any reported liver-related adverse events.²⁹ A recent meta-analysis which included all patients with AUD and co-morbid liver diseases treated with baclofen found no instances of liver function abnormality in patients treated with baclofen.³⁰ This favorable hepatic safety profile is thought to be because of its minimal hepatic metabolism.^{30,31} However, in addition to the case reported here, there was one prior case report of baclofen induced liver injury in a 46-year-old female who was treated for AUD after a recent episode of acute alcoholic hepatitis. Four days after starting the baclofen, she developed acute transient elevation in AST and ALT which normalized in 13 days after drug discontinuation.³² Similar to our case, the patient had hepatocellular pattern of liver injury, and liver enzymes improved with drug discontinuation. Our patient had longer latency period of 111 days from drug initiation to DILI onset. However, a small-scale retrospective study provides reassurance regarding baclofen's safety and efficacy in patients following an episode of alcoholic hepatitis.³³

Our findings suggest that DILI due to MAUD is less frequent. Another key finding is that disulfiram induced DILI, though uncommon, can be severe than DILI caused by other MAUD. Previous studies have shown that patients treated with medications have a reduced risk of developing and progressing to ALD.⁶ Furthermore, MAUD has been linked to improved survival, even among patients with alcohol-related cirrhosis without hepatic safety concern.³⁴ It is worth noting that the limited number of DILI cases attributed to MAUD in the DILIN prospective study may stem from its underutilization.³⁵ Nevertheless, it is important to note that the prescriptions for baclofen and naltrexone have been steadily increasing. In 2021, approximately 1.6 million and half a million individuals in the United States received baclofen and naltrexone prescriptions for various indications, respectively.^{36,37}

Strengths of this study includes its prospective multi-institutional data collection over a prolonged period of time. In addition, a standardized approach was employed for data collection, analysis, causality, and severity adjudication, focusing solely on high-confidence cases. However, a notable limitation of our study is its non-population-based design, potentially introducing selection bias and also limits the incidence and relative risk estimates of DILI. Another limitation is that the histopathologist was not blinded to the medication exposure during review of the biopsy. It is worth mentioning that not all side effects of medications are captured by DILIN.

Conclusions

In summary, the most frequent cause of DILI among MAUD is disulfiram and was common in female patients. In contrast, naltrexone and baclofen are less frequent causes of DILI and may induce a mild to moderate hepatocellular pattern of DILI that is self-limited. These findings, coupled with recent research, offer reassurance to physicians regarding the safety of MAUD. Disulfiram can cause severe DILI, so its risks and benefits must be carefully assessed before prescribing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

Authors thank participants and their families and research personnel for their contributions to the DILIN studies.

Grant support:

Research reported in this publication was supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health under award numbers U01DK065211 (Indiana University), U01DK065184 (University of Michigan), U01DK065201 (University of North Carolina-Chapel Hill), U01DK083020 (University of Southern California), U01DK083027 (Thomas Jefferson University/Albert Einstein Medical Center), U01DK100928 (Icahn School of Medicine at Mount Sinai), and U24DK065176 (Duke University). Additional support is provided by the intramural programs of the NIDDK and National Cancer Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Conflicts of Interest:

Dr. Chalasani has ongoing paid consulting activities (or had in preceding 12 months) with Madrigal, Zydus, Altimmune, Ipsen, GSK, Pfizer, and Merck. He has grant support from Exact Sciences. He has equity in Avant Sante, a contract research organization. These activities are not directly or significantly related to this paper. Dr Fontana conducts research supported by Kezar Pharmaceuticals and Takeda pharmaceuticals, but these activities are not related to this paper. Drs. Gopalakrishna, Ghabril, Gu, Li, Kleiner and Koh have no conflicts of interests to disclose.

Abbreviations:

AUD	Alcohol use disorder
ALD	Alcohol-associated liver disease
ANA	anti-nuclear antibody

ASMA	smooth muscle antibody
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ALP	Alkaline Phosphatase
MAUD	medications for alcohol use disorder
FDA	Food and Drug administration
HCV	hepatitis C virus
HBV	hepatitis B virus
DILI	Drug induced liver injury
DILIN	Drug-Induced Liver Injury Network
T Bili	Total bilirubin
ULN	upper limit of normal

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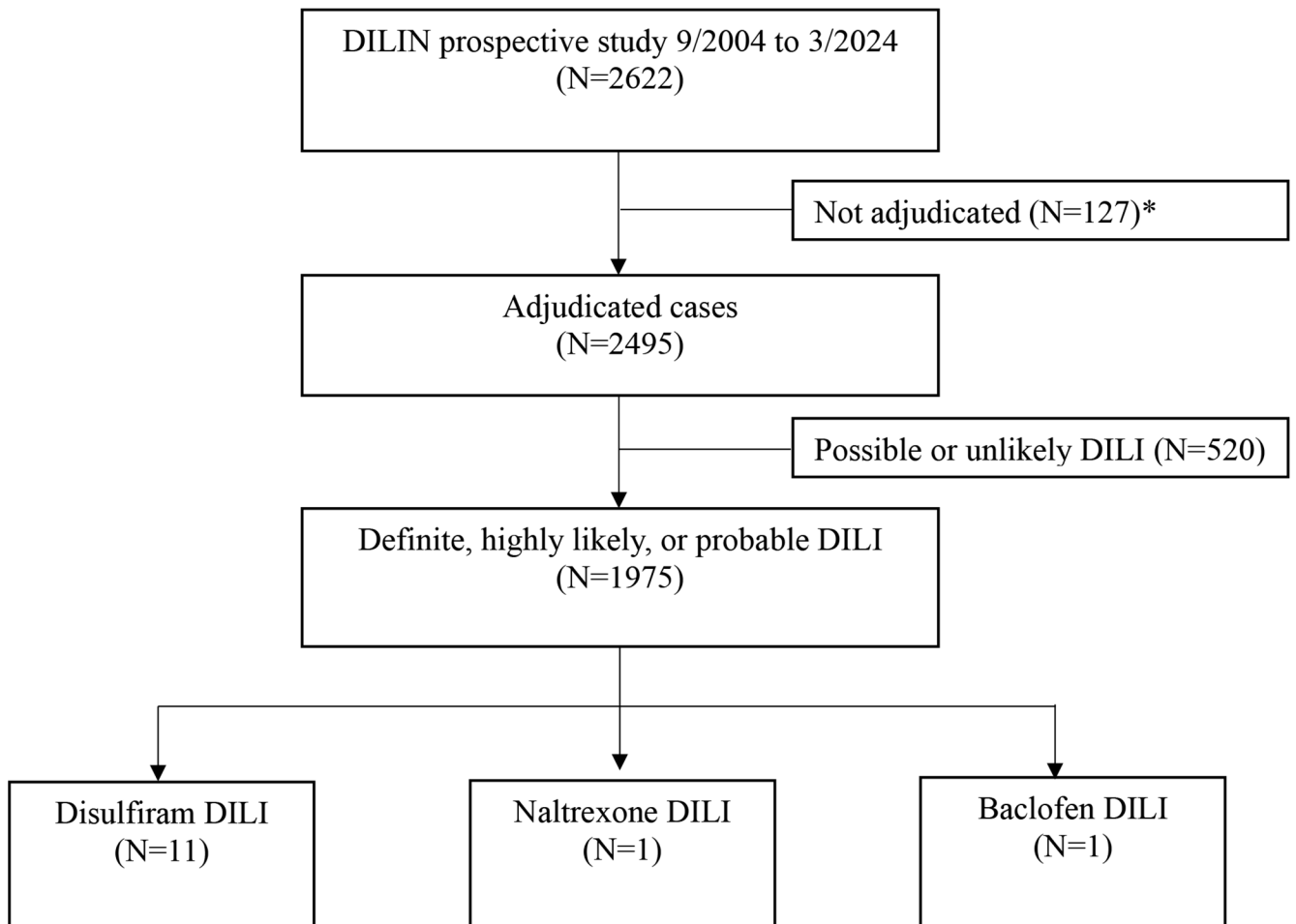


Figure 1.

Consort diagram showing selection of patients with DILI due to MAUD in the DILIN prospective study.

* Cases are adjudicated 6 months after enrollment on a monthly basis by the DILIN causality committee. A proportion of enrolled cases remain in queue for adjudication due to this process structure.

Table 1

Baseline characteristics of participants with DILI due to Medications for Alcohol Use Disorder

Characteristic	Disulfiram N=11	Baclofen N=1	Naltrexone N=1
Age, (years)	43.8 (31.5, 61.3)	61	59.7
Gender, Female	8 (72.7%)	1 (100.0%)	1 (100.0%)
Self-reported race			
White or Caucasian	9 (81.8%)	1 (100.0%)	1 (100.0%)
Asian	2 (18.2%)	-	-
Hispanic ethnicity	1 (9.1%)	-	-
Body mass index (kg/m ²)	24.3 (19.5, 33.8)	27.8	22.3
Prior drug allergies	5 (45.5%)	-	-
Alcohol use	11 (100.0%)	1 (100.0%)	-
Diabetes mellitus	1 (9.1%)	-	-
Underlying cirrhosis	2 (18.2%)	-	-
Duration of Therapy (days) median, range	32 (11, 74)	117	6
Days from drug start to earliest sign or symptom			
N	10	1	0
Median (range)	24.5 (1.0, 65.0)	111.0	-
Days from earliest sign or symptom to drug stop			
N	9	1	0
Median (range)	8 (0.0, 41.0)	5.0	-
Categorized days from drug start to DILI onset			
2 to 4 weeks	5 (45.5%)	-	1 (100.0%)
5 to 12 weeks	6 (54.5%)	-	-
13 to 24 weeks	-	1 (100.0%)	-
Treated with Prednisone or Corticosteroids	2 (18.2%)	-	-
Diagnostic serologies at initial study visit			
ANA or SMA positive	4 (36.4%)	1 (100.0%)	-
Eosinophilia (> 500/uL)	3 (30%)	-	-
Pattern of liver injury at DILI onset			
Hepatocellular/Mixed/Cholestatic	11/0/0	1/0/0	1/0/0
R-value at onset	27.9 (7.6, 72.5)	19.3	13.3
AST/ALT > 1	2 (18%)	1 (100%)	-
Improvement in liver tests-median days			
Peak ALT to below ULN	31 (12, 103)	13	1
Peak total bilirubin to <2.5 mg/dL	51.0	1.0	-
Hospitalization or non-DILI hospitalization was prolonged	10 (90.9%)	1 (100.0%)	1 (100.0%)
Liver-related death	1 (9.1%)	-	-
Liver transplantation	2 (18.2%)	-	-

Characteristic	Disulfiram N=11	Baclofen N=1	Naltrexone N=1
DILI persistent at 6 months, n/N	0/9	0/1	0/1

Continuous variables are presented as median (range) and categorical variables are presented as n (%). Latency is time from drug initiation to DILI recognition.

Abbreviations: ANA: Anti-nuclear antibody; SMA: Smooth muscle antibody; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; HCV: hepatitis C virus; ULN: Upper limit of normal; DILI: Drug induced liver injury; Kg/m²: kilograms-meters squared; µL: microliter; mg/dL: milligrams per deciliter.

Table 2. Selected characteristics of all DILIN cases due to medication for alcohol use disorder

Case	Drug	Age (years)/Sex	Prior liver disease	Indication for use	Latency (days)	At onset			Peak			Causality score	DILIN severity score	Known Outcomes
						ALT (U/L)	ALP (U/L)	T Bili (mg/d L)	ALT (U/L)	ALP (U/L)	T Bili (mg/d L)			
1	Disulfiram	34/M		AUD	24	1775	114	1.2	2467	176	1.7	1.47	Mild	Recovery
2	Disulfiram	44/F		AUD	20	6698	249	5.7	6698	444	13.6	1.2	Moderate-hospitalized	Recovery
3	Disulfiram	44/F	ALD	AUD	35	1141	286	5.5	1365	286	20	1.6	Severe	Treated with steroid resulting in improvement
4	Disulfiram	46/F		AUD	63	2670	381	11.7	2670	381	28.4	1.6	Fatal	Underwent liver transplant
5	Disulfiram	42/M	HCV	AUD	34	1715	95	5.9	1715	137	5.9	1.2	Moderate-hospitalized	Recovery
6	Disulfiram	57/F	Cirrhosis due to ALD	AUD	67	4691	220	16.2	4691	251	34	1.88	Severe	Treated with steroid. Had recovery
7	Disulfiram	45/M		AUD	46	1286	240	23.5	1286	244	30.6	2.3	Severe	Recovery
8	Disulfiram	31/F	ALD	AUD	52	893	117	0.6	2516	357	18.6	9.4	Fatal	Underwent liver transplant
9	Disulfiram	44/F		AUD	21	393	62	0.3	1060	87	0.3	1	Mild	Recovery
10	Disulfiram	50/F	ALD	AUD	28	5320	223	3.2	5320	232	4.9	1.57	Severe	Recovery
11	Disulfiram	61/F	Cirrhosis due to ALD	AUD	12	1257	170	12.5	3220	226	16	3.5	Fatal	Liver related death
12	Naltrexone	59/F		IgG deficiency	8	730	126	0.6	730	126	0.7	0.9	Mild	Recovery
13	Baclofen	61/F		AUD	112	1317	116	1.65	1446	129	2.6	1.1	Moderate-hospitalized	Recovery

Latency is time from drug initiation to DILI recognition; Definite - Greater than 95%; Very likely - 75–95%; Probable 50–75%.

Abbreviations: ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; ALD: alcohol associated liver disease; HCV: hepatitis C virus; DILIN: Drug induced liver injury network; AUD: Alcohol use disorder; IgG: Immunoglobulin G deficiency