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Heavy Consumption of Alcohol is Not Associated With Worse Outcomes in Patients With Idiosyncratic Drug-induced Liver Injury Compared to Non-Drinkers

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Abstract

Background & Aims—The relationship between alcohol consumption and idiosyncratic drug induced liver injury (DILI) is not well understood. We investigated the relationship between heavy consumption of alcohol and characteristics and outcomes of patients with DILI enrolled in the Drug-induced Liver Injury Network (DILIN) prospective study.

Methods—We collected data from 1198 individuals with definite, highly likely, or probable DILI enrolled in the DILIN study from September 2004 through April 2016. At enrollment, all participants were asked about alcohol consumption; those with any alcohol consumption during previous 12 months were asked to complete the Skinner questionnaire to assess drinking history. Heavy consumption of alcohol was defined as more than 3 drinks, on average, per day by men or more than 2 drinks, on average, per day by women.

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Conceptualized the study: LD, NC, VN, MG, JS
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Conflicts of Interests: Dr. Chalasani has ongoing consulting activities (or had in preceding 12 months) with NuSirt, Abbvie, Eli Lilly, Afimmune (DS Biopharma), Tobira (Allergan), Madrigal, Shire, Cempra, Ardelyx, Gen Fit and Amarin. These consulting activities are generally in the areas of nonalcoholic fatty liver disease and drug hepatotoxicity. Dr. Chalasani receives research grant support from Intercept, Lilly, Gilead, Galectin Therapeutics and Cumberland where his institution receives the funding. Over the last decade, Dr. Chalasani has served as a paid consultant to more than 30 pharmaceutical companies and these outside activities have regularly been disclosed to his institutional authorities. Drs. Gu, Navarro, Dakhoul, Ghabril, and Serrano have no conflicts of interest to disclose.

Results—Of the 601 persons who reported consuming at least 1 alcoholic drink in the preceding 12 months, 348 completed the Skinner questionnaire and 80 reported heavy consumption of alcohol. Heavy drinkers were younger (average age, 42 years) than non-drinkers (average age, 49 years) and a higher proportion were men (63% of heavy drinkers vs 35% of nondrinkers) ($P<.01$ for each comparison). Anabolic steroids were the most common cause of DILI among heavy drinkers (in 13% vs 2% in non-drinkers) ($P<.001$). Heavy drinkers had significantly higher peak serum levels of alanine aminotransferase (1323 U/L) than non-drinkers (754 U/L) ($P=.02$) and higher levels of bilirubin (16.1 mg/dL vs 12.7 mg/dL in non-drinkers) ($P=.03$) but there was no significant difference in liver-related death or liver transplantation between heavy drinkers (occurred in 10%) vs non-drinkers (occurred in 6%) ($P=.18$).

Conclusion—In an analysis of data from the DILIN, we found anabolic steroids to be the most common cause of DILI in individuals who are heavy consumers of alcohol. Compared to non-drinkers, DILI was not associated with a greater proportion of liver-related deaths or liver transplantation in heavy drinkers.

Keywords

Drug Induced Liver Injury; Drug Induced Liver Injury Network; Significant alcohol consumption; RUCAM; Chronic DILI; ALT

Introduction

The relationship between alcohol consumption and acetaminophen hepatotoxicity is well recognized, but the relationship between alcohol consumption and other causes of drug induced liver injury (DILI) is less well defined (1,2). Alcohol consumption is one of the criteria in the RUCAM causality instrument for assessing liver injury (3,4), although there is no evidence that alcohol consumption increases the risk from medications other than methotrexate, isoniazid, antiretroviral agents, or halothane (5). Heavy alcohol consumption is believed to increase the risk of liver damage in individuals taking methotrexate long term (6,7). Chronic alcohol abuse may increase the risk of liver injury from anti-tuberculosis (anti-TB) agents (8,9), but not all studies have shown significant relationship between alcohol consumption and liver injury from anti-TB medications (10,11,12). The labeling for duloxetine, a frequently prescribed anti-depressant, recommends that individuals with substantial alcohol consumption should not take this medication (13), although there is no published evidence to support this recommendation. In an earlier study from the Drug Induced Liver Injury Network (DILIN), alcohol consumption, defined as any alcohol intake in the preceding 12 months, was unexpectedly associated with less severe injury in individuals with DILI (14).

To better understand the relationship between alcohol consumption and DILI, we investigated the relationship between heavy alcohol consumption and the causative agents, characteristics and outcomes of patients with DILI enrolled in the DILIN Prospective Study.

Methods

Initiated in 2004, the DILIN Prospective Study (NCT00345930) enrolled individuals ≥ 2 years old with suspected DILI at several clinical centers across the United States. The inclusion and exclusion criteria, evaluation for competing etiologies, follow-up, and causality and severity assessment have been described in previous publications (14–16). Several publications have resulted from the DILIN Prospective Study over the last decade, so that many participants included in this analysis were included in previous publications (17–21). The DILIN Prospective Study was approved by the Institutional Review Boards of the enrolling clinical centers and all participants provided written informed consent. In addition, the protocol and consent form were approved and the study monitored by an independent data and safety monitoring board appointed by the National Institutes of Health.

This analysis consisted of individuals enrolled between September 2004 and April 2016 who were judged to have definite, highly likely, or probable DILI. At the time of enrollment, participants were questioned about their alcohol consumption, and a trained interviewer administered a shortened version of the Skinner Alcohol Dependence Scale to individuals with any reported alcohol use within the preceding 12 months (22–24). This questionnaire obtained the following details of participants' alcohol consumption history during five years before the DILI event: time and age range of alcohol consumption, drinks per day, drinking days per month, type of alcohol consumed, pattern of alcohol consumption (occasional, daily, weekend, binge), any life events influencing alcohol consumption, and perception of effect of alcohol consumption on their lives. For this analysis, heavy alcohol consumption was defined as regular average consumption of more than 2 drinks per for women and more than 3 drinks per day for men.

Statistics

Demographic and clinical data for subjects enrolled into the DILIN Prospective Study between September 2004 and April 2016 were extracted on September 9, 2016. Descriptive statistics, such as means with standard deviations, median with interquartile ranges and frequency distributions, were used to characterize the cohort. Differences between groups were tested using the χ^2 test for categorical variables and Wilcoxon/Kruskal-Wallis test for the continuous variables. The primary outcomes of interest were (a) DILIN severity score, (b) liver transplantation or liver-related death, and (c) chronic DILI. Other outcomes of interest were severity of liver injury and causality assessment categories. Primary comparison was between individuals with heavy alcohol consumption and those without any alcohol consumption. Other comparisons were between (a) individuals with heavy drinking and those with non-heavy drinking and (b) individuals with and without any reported alcohol consumption. Statistical analyses were performed using SAS software, version 9.2 (SAS Institute, Cary, NC) and P values <0.05 were considered statistically significant, and P values between 0.05–0.10 were considered to show trends towards significance.

Results

The DILIN Prospective Study enrolled 1723 participants between September 2004 and April 2016 and 1512 had undergone six-month follow-up and causality adjudication before September 9, 2016. Of this total, 1198 participants were judged to have definite, highly likely, or probable DILI, and constituted the study cohort (Figure 1). At least some alcohol consumption was reported by 601 individuals while 597 reported no alcohol consumption in the preceding 12 months. The 601 participants were invited to complete the alcohol consumption questionnaire and 348 (58%) agreed. There were no significant differences in the demographics and clinical characteristics of individuals with reported consumption who did (n=348) and did not (n=253) complete the alcohol consumption questionnaire (Supplementary Table 1). Of 348 individuals who filled the alcohol consumption questionnaire, 80 individuals reported heavy consumption. The frequency of pre-existing liver disease was 11% in non-drinkers, 9% in non-heavy drinkers, and 11% in heavy drinkers (p=ns). The frequency of heavy drinking among individuals with DILI who had known pre-existing liver disease was 10.6%.

Comparison between individuals with heavy alcohol consumption and without any alcohol consumption

Compared to individuals with no alcohol consumption, participants with heavy consumption were younger (mean age 42 vs 49 years) and more likely men (52% vs 35%) but their self-reported race and their body mass indices were not different (Table 1). Individuals with heavy alcohol consumption had lower frequency of diabetes mellitus (13% vs 28%, p=0.003), but the prevalence of preexisting liver disease was not different (11% in both groups). The latency to onset and the pattern of liver injury at presentation were similar between two groups. Individuals with heavy alcohol consumption had significantly higher peak serum ALT and total bilirubin levels but mean alkaline phosphatase or international normalized ratio (INR) values were similar as were the times to improvements in biochemical abnormalities.

The most commonly implicated therapeutic classes and specific agents are shown in Table 2. Interestingly, anabolic steroids were the most common cause of DILI in individuals with heavy alcohol consumption (13%) whereas they accounted few cases (2%) in those without alcohol consumption (p<0.001). Nevertheless, the overall characteristics (e.g., latency, pattern of liver injury, peak enzymes, pattern of recovery), severity and outcomes of liver injury due to anabolic steroids were not significantly different between individuals with heavy alcohol consumption (n=10) and those without alcohol consumption (n=12) (data not shown). The frequency of liver injury due to isoniazid was not different between two groups (6.3% in the heavy alcohol group vs. 5% in those without alcohol consumption, p=0.8).

Causality assessment and the proportion of cases judged to be definite vs highly likely vs possible were similar in the two groups (p=0.40, Table 3). While the overall distribution of severity scores were not different in the two groups, cases that were scored as severe or fatal were more frequent among those with heavy alcohol consumption compared to non-drinkers (36% vs 28%) as were numbers of death or liver transplantation (10% vs 6%, p=0.18), but these differences were not statistically significant (p=0.53). Finally, chronicity as defined as

continued evidence of liver injury at 6 months after onset was similar in frequency between the two groups (18% vs 15%, p=0.53).

Comparison between individuals with heavy drinking and those with non-heavy drinking

Comparison of patients with mild or moderate alcohol intake to those with heavy consumption demonstrated similar differences to those comparing non-drinkers to heavy drinkers (Table 1 or 2) although the statistical significance of the differences were less, perhaps due to the fewer number of non-heavy drinkers. Thus, latency, pattern of liver injury and time to recovery among the 80 individuals with heavy alcohol consumption compared to the 268 individuals with non-heavy alcohol consumption were similar, but mean peak ALT, total bilirubin and INR values were higher in patients with heavy alcohol consumption (Tables 1 and 3). Subjects with heavy alcohol consumption had trends toward more severe liver injury with higher average DILIN severity scores (2.9 vs 2.6, p=0.06) but did not have higher likelihood of fatalities or liver transplantation (10% vs. 6.3%, p=0.27). Anabolic steroids were more frequently implicated in cases among those with heavy alcohol intake than those with less than heavy intake (13% vs 5%) (Table 2).

Comparison between individuals with and without any reported alcohol consumption

There were 601 individuals who reported any alcohol consumption whereas 597 consumed no alcohol in preceding 12 months (Supplemental Table 2). Their age and BMI were similar, but there were fewer women in individuals with alcohol consumption. Individuals with alcohol consumption had lower prevalence of diabetes mellitus but the prevalence of preexisting liver disease was similar between two groups. The frequency of liver injury due to herbal and dietary supplements was significantly higher in individuals with alcohol consumption than those without alcohol consumption (21.5% vs 14.4%, p<0.001). The latency between initiating the suspected agent and DILI recognition and the pattern of liver injury at presentation were similar between two groups. Compared to those without alcohol consumption, individuals with alcohol consumption had significant higher peak serum ALT values but lower INR. Interestingly, individuals with alcohol consumption had lower DILIN severity score compared to those without alcohol consumption (2.6 ± 1.2 vs.2.7 ± 1.2, p=0.032) but liver related death or need for liver transplantation (7% vs 6.2%, p=0.6) and chronic DILI (15.3% vs. 18.3%, p=0.2) were similar between two groups (Supplemental Table 2).

Alcohol Consumption and liver injury due to isoniazid

As it has been suggested that alcohol consumption is a possible risk factor for isoniazid hepatotoxicity, we examined if there was an association between alcohol consumption and isoniazid hepatotoxicity in our cohort. The proportion of liver injury attributed to isoniazid among heavy drinkers was 6.3% and it was not significantly different from non-drinkers (5%, p=0.6) or non-heavy drinkers (2.2%, p=0.13).

Death or Liver Transplantation among heavy drinkers with DILI

Two individuals with a history of heavy alcohol consumption died due to their liver injury and 6 others underwent liver transplantation for the acute liver injury (Table 4). The two

fatal cases consisted on a 44 year old Caucasian male with underlying alcoholic cirrhosis and steatohepatitis who developed acute on chronic liver failure 11 days after initiating niacin, and a 76 year old Caucasian male with chronic obstructive pulmonary disease who received azithromycin for a bronchitis flare and developed severe liver injury and skin rash 6 days after initiating azithromycin, rapidly developing acute liver failure and dying 3 weeks later with multiorgan failure. Anti-HCV and HCV RNA were negative in all eight patients who died or received transplantation. Anti-HEV Ig G was negative in 6 patients and was positive in patients but without detectable anti-HEV Ig M. It appeared that 3 patients had underlying alcoholic liver disease and developed superimposed acute-on-chronic liver failure whereas five others developed acute liver failure to DILI without clinical evidence of preexisting alcoholic liver disease.

Analyses without individuals with probable DILI

When probable DILI cases were excluded, there were 445 non-drinkers, 205 non-heavy drinkers, and 63 heavy drinkers and their DILIN severity scores were 2.7 ± 1.2, 2.5 ± 1.1, and 2.9 ± 1.2 respectively. While there was no difference in the DILIN severity score between non-drinkers and heavy drinkers (p=0.33), it was significantly higher in heavy drinkers compared to non-heavy drinkers (p=0.03). There was no difference in liver-related deaths or liver transplantation (non-drinkers 4%, non-heavy drinkers 5.3%, and heavy drinkers 6.3% [p=0.33 vs. non-drinkers; p=0.75 vs non-heavy drinkers]), or chronic DILI (non-drinkers 15.9%, non-heavy drinkers 16.7%, and heavy drinkers 12.7% [p=0.55 vs. non-drinkers; p=0.48 vs non-heavy drinkers].

Discussion

Although there is large body of literature investigating the role of alcohol consumption and acetaminophen hepatotoxicity, there is scant literature examining the relationship between alcohol consumption and idiosyncratic DILI. In this report we comprehensively examined the relationship between heavy and non-heavy alcohol consumption and causative agents, characteristics and outcomes of liver injury in a large cohort of prospectively enrolled patients with well characterized DILI. Our main observations are (a) DILI in individuals with heavy alcohol consumption did not necessarily result in significantly higher frequency of liver related deaths or required liver transplantation, compared to those without any alcohol consumption; (b) there was significant enrichment of anabolic steroid related liver injury in subjects with heavy alcohol consumption; and (c) individuals who reported *any* alcohol consumption tended to have lower DILIN severity score but their outcomes were not different from those who reported no alcohol consumption.

The higher frequency of liver injury due to anabolic steroids in patients with heavy alcohol consumption may simply represent a behavioral association rather than any pathophysiologic link between the two. These behaviors are more frequent in younger men. In a recent comprehensive literature review, Dodge and Hoagland observed a strong bivariate relationship between anabolic androgenic steroid abuse and alcohol use (25). The lifetime use of anabolic androgenic steroid use was positively associated with recent as well as lifetime alcohol use, problem/harmful drinking, and binge drinking (25). Nevertheless, our

study cannot exclude the possibility that heavy alcohol consumption increases the risk of developing liver injury caused by anabolic steroids.

The relationship between isoniazid hepatotoxicity and chronic alcohol consumption in the published literature has not been consistent. Some studies found significant association between chronic alcohol consumption and liver injury due to isoniazid or anti-tuberculosis drugs (8,9,26) whereas this relationship could not be demonstrated in other studies (10–12). In our study, liver injury due to isoniazid among individuals with heavy alcohol consumption was not more common than those with no alcohol consumption or mild to moderate alcohol consumption, but our study was not designed to specifically investigate alcohol consumption as a risk factor for isoniazid hepatotoxicity.

One of the instruments frequently used to adjudicate the causality in patients with suspected DILI is Roussel Uclaf Causality Assessment Method (RUCAM) and it is based on 7 domains including age, alcohol, or pregnancy as risk factors (27). There is emerging consensus among the experts that alcohol consumption is not necessarily a risk factor for idiosyncratic DILI and arguably it should not be a criterion in assigning causality in suspected DILI (28). Although our study represents a detailed description of the relationship between DILI and alcohol consumption, because of it included only patients with suspected DILI it is not able to assess if alcohol consumption is a risk factor for DILI or its inclusion as one of the criteria in the RUCAM instrument.

Some aspects of our study design deserve further discussion. Our study consists of patients presenting to select clinical centers with well characterized DILI and thus it cannot address the causal relationship between alcohol consumption and all-cause DILI or liver injury caused by specific agents. Also, our study is based on self-reported alcohol use, which may underestimate the frequency and extent of alcohol consumption, but unfortunately there are no other practical methods to capture the details of alcohol consumption in studies of this nature. We also focus our discussion on the differences between non-drinkers and heavy drinkers where misclassification bias is probably lower. We had a significant number of patients that did not complete a Skinner questionnaire, but they did not differ significantly in terms of other clinical and demographic features. Counterbalancing these issues, are the DILIN’s unique strengths such as prospective study design, larger sample size, well characterized DILI phenotype and careful, structured adjudication of causality and severity.

In summary, anabolic steroids are the most common cause of DILI in individuals with heavy alcohol consumption. We did not find heavy alcohol consumption to be associated with worse outcomes in patients with DILI. Further, there was no evidence for heavy alcohol consumption as a risk factor for liver injury due to isoniazid in this experience.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ALK P	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
DILI	Drug induced liver injury
DILIN	Drug induced liver injury network
INR	International normalized ratio
ULN	Upper limit of normal

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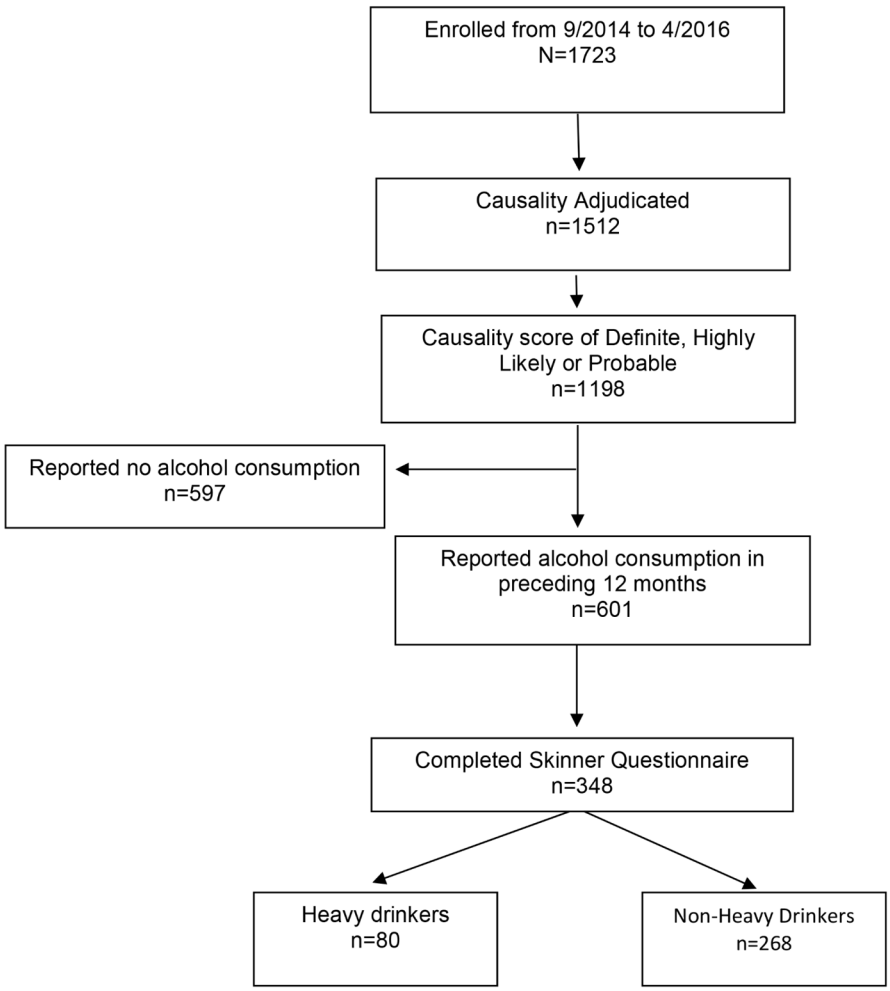

Figure 1.
Study Population: Flow Diagram

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Table 1

Demographics and selected clinical features of DILI individuals with no, non-heavy and heavy alcohol consumption

	No alcohol (Group A, n=597)	Non-heavy alcohol (Group B, n=268)	Heavy alcohol (Group C, n=80)	P-value	
				Groups A vs C	Groups B vs C
Age (years, mean [SD])	49 (18.4)	52 (15.3)	42 (14.2)	<0.001	<0.001
Females (%)	65	49	48	0.002	0.82
Self-reported race (%)				0.67	
White	72	85	85		0.90
Black or African-American	17	8	8		
Other/Multiracial	6	5	5		
BMI (kg/m^2, mean [SD])	28.0 (7.9)	27.0 (5.6)	26.4 (4.9)	0.27	0.60
Prior drug allergies (%)	45	44	40	0.38	0.56
Preexisting Liver Disease (%)	11	8.6	11	0.90	0.70
Concomitant medicines (%)				0.47	
0–2	22	23	28		0.67
3–5	28	30	27		
>5	50	47	45		
Diabetes mellitus (%)	28	21	12.5	0.003	0.08
Latency (days in median, IQR)	43 (21–118)	45 (24–104)	47 (29–90)	0.99	0.90
Jaundice (%)	67	70.5	69	0.75	0.76
Pattern of liver injury (%)				0.31	0.38
HC	54	53	62		
Chol	25	23	118		
Mixed (%)	21	24	19.5		
Liver Biochemistries –DILI recognition					

	No alcohol (Group A, n=597)	Non-heavy alcohol (Group B, n=268)	Heavy alcohol (Group C, n=80)	P-value	
				Groups A vs C	Groups B vs C
ALT (U/L, mean [SD])	754 (982)	788 (893)	1323.3 (1965)	0.02	0.12
Alk P (U/L, mean [SD])	301 (283)	280 (225)	242.0 (195)	0.08	0.19
Total bilirubin (mg/dL, mean [SD])	6.9 (7.0)	6.5 (6.1)	8.7 (8.1)	0.07	0.07
INR	1.5 (1.1)	1.4 (0.8)	1.5 (0.9)	0.88	0.79
Liver Biochemistries – Peak values					
ALT (U/L, mean [SD])	924 (1100)	966 (1002)	1452 (1957)	0.04	0.23
AST (U/L, mean [SD])	870 (1408)	797 (1119)	1322 (1890)	0.16	0.30
Alk P (U/L, mean [SD])	411 (403)	401 (363)	338.3 (253)	0.37	0.23
Total bilirubin (mg/dL, mean [SD])	12.7 (11.5)	12.5 (11.6)	16.1 (13.1)	0.04	0.05
INR	1.7 (1.4)	1.6 (1.5)	2.0 (2.1)	0.54	0.09
Eosinophilia (>500/μL) (%)	10	13	15	0.23	0.58
Improvement in biochemistries – [median days]					
- Peak ALT to below ULN	63	62	76	0.76	0.63
- Peak AST to below ULN	59	51	81	0.41	0.52
- Peak Alk P to below ULN	109	67	53	0.002	0.46
- Peak bilirubin to ≤ 2.5 mg/dL	28	28	36	0.50	0.48

Abbreviations used: ALT, serum alanine aminotransferase; AP, serum alkaline phosphatase; BMI, body mass index; Chol, cholestatic; DILI, drug-induced liver injury; HC, hepatocellular; INR, international normalized ratio; IQR, interquartile range (25–75%); SD, standard deviation; ULN, upper limit of normal.

Table 2

Top Implicated Classes of Agents and Agents among DILI individuals with no, non-heavy and heavy alcohol consumption

	No alcohol consumption (Group A, n=597)	Non-heavy alcohol consumption (Group B, n=268)	Heavy alcohol consumption (Group C, n=80)
Top 5 Implicated Classes of Agents (%)	Antimicrobials (45.6%)	Antimicrobials (44.6%)	Antimicrobials (33.8%)
	HDS (14.4%)	HDS (19.5%)	HDS (33.8%)
	CV Agents (10.2%)	Antineoplastics (9%)	Substance Abuse Agents (7.5%)
	CNS Agents (8.0%)	CV Agents (8.6%)	CNS Agents (6.3%)
	Antineoplastics (4.5%)	CNS Agents (7.5%)	Immunomodulatory (5.0%)
Top 10 Implicated Agents (%)	Amox-Clav (9.4%)	Amox-Clav (13.9%)	Anabolic Steroids (12.5%)
	Isoniazid (5%)	Nitrofurantoin (5.2%)	Amox-Clav (6.3%)
	Nitrofurantoin (5%)	Anabolic steroids (5.2%)	Isoniazid (6.3%)
	TMP-SMZ (4.5%)	TMP-SMZ (3.7%)	Nitrofurantoin (5.0%)
	Minocycline (3.2%)	Cefazolin (2.6%)	Minocycline (5.0%)
	Ciprofloxacin (2.5%)	Isoniazid (2.2%)	Azathioprine (2.5%)
	Azithromycin (2%)	Azithromycin (1.9%)	TMP-SMZ (2.5%)
	Anabolic steroids (2%)	Minocycline (1.5%)	Azithromycin (1.3%)
	Levofloxacin (1.8%)	Ciprofloxacin (1.5%)	Cefazolin (1.3%)
	Infliximab (1.7%)	Atorvastatin (1.1%)	Atorvastatin (1.1%)

Abbreviations used: HDS, herbal and dietary supplements; CNS, central nervous system; CV, cardiovascular; Amox-Clav, Amoxicillin-clavulanate, TMP-SMZ, trimethoprim-sulfamethoxazole

Table 3

Causality and Severity Scores and Outcomes of DILI in individuals without and with non-heavy and heavy alcohol consumption

	Patients with DILI & no alcohol consumption (Group A, n=597)	Patients with DILI & non-heavy alcohol consumption (Group B, n=268)	Patients with DILI & heavy alcohol consumption (Group C, n=80)	P-value	
				Group A vs Group C	Group B vs Group C
Causality Assessment (%)					
Definite	20	26	26	0.40	0.94
Highly likely	54	51	53		
Probable	26	23	21		
Severity of Liver Injury (%)					
Mild	22	22	23	0.53	0.06
Moderate	18	26	15		
Moderate-hospitalized	32.5	30	26		
Severe	21	15	26		
Fatal	7	6	10		
DILIN Severity Score	2.7 ± 1.2	2.6 ± 1.2	2.9 ± 1.3	0.35	0.06
Liver related deaths or liver transplantation (%)	6	6	10	0.18	0.27
Chronic DILI (%)	18.3	18.5	15.2	0.53	0.53

Abbreviations used: DILI, drug-induced liver injury; DILIN, drug-induced liver injury

Table 4

Selected Characteristics of 8 patients with heavy alcohol consumption who died or received liver transplantation[¶]

Implicated agent	Age (yrs)	Sex	Latency	Alcohol Consumption			Peak Bilirubin (mg/dL)	DILIN Causality score	Outcome	Comments
				Drinks/day	Days /Month	During Rx				
Performance Spectravite	44	F	Several months	4	30	Yes	27.7	Probable	Rapidly developed fulminant hepatic failure and underwent liver transplantation 2 weeks after presentation.	Explant showed extensive multi- and panacinar collapse. The collapsed areas were replaced by proliferating bile ductules and severe lymphoplasmacytic infiltrate. Surviving hepatocytes showed multinucleated giant cell change, cholestasis, and focal macrovesicular steatosis.
Ephedrine	34	M	42 days	6	30	Yes	9.7	Probable	Rapidly developed fulminant hepatic failure and underwent liver transplantation one week after presentation.	Liver histology showed massive coagulative necrosis involving 90% of hepatocytes
Valproate	28	F	30 days	3	24	Yes	19.0	Definite	Rapidly developed fulminant hepatic failure and underwent liver transplantation one week after presentation.	Explant showed panacinar confluent necrosis with complete lysis of the parenchyma in large areas (massive hepatic necrosis). Duct-like structures were associated with inflammatory cells including lymphocytes, eosinophils and occasional plasma cells

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Implicated agent	Age (yrs)	Sex	Latency	Alcohol Consumption			Peak Bilirubin (mg/dL)	DILIN Causality score	Outcome	Comments
				Drinks/day	Days /Month	During Rx				
Isoniazid	45	F	93 days	4	30	No	37.0	Highly likely	Rapidly developed fulminant hepatic failure and underwent liver transplantation 2 weeks after presentation.	Received isoniazid for latent tuberculosis infection
Niacin	44	M	11 days	6	10	No	22.7	Probable	Acute on chronic liver failure in a patient with known alcoholic cirrhosis and death within a week of presentation	Patient had underlying alcoholic cirrhosis with steatohepatitis
Azithromycin	76	M	6 days	14	30	Yes	14.0	Probable	Acute liver failure in a patient with suspected alcoholic liver disease and death 2 weeks after presentation	Was associated with skin rash. Skin biopsy showed vacuolar interface dermatitis with eosinophils compatible with drug reaction. This patient was previously reported as case 18 in the report by Martinez M, et al (29).
Telithromycin	51	F	5 days	3	28	Yes	29.0	Definite	Acute liver failure in a patient with suspected alcoholic cirrhosis and transplantation 7 weeks after presentation	Suspected to have undiagnosed underlying alcoholic cirrhosis
Oxyelite Pro	46	F	~ 3 months	6	20	No	27.9	Highly likely	Underwent liver transplantation for acute liver failure three weeks after presentation	Explant showed submassive necrosis and no evidence of underlying cirrhosis. This case was reported previously as case

Implicated agent	Age (yrs)	Sex	Latency	Alcohol Consumption			Peak Bilirubin (mg/dL)	DILIN Causality score	Outcome	Comments
				Drinks/day	Days /Month	During Rx				
										2 in the report by Heidemann LA, et al (30).

Abbreviations used: M, male; F, female;

¶All patients were Caucasian except for the 45 year old female with isoniazid induced liver injury whose race and ethnicity are not available.