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Clinical characteristics of antiepileptic-induced liver injury in patients from the DILIN prospective study

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Abstract

Background & Aims: Antiepileptic drugs (AEDs) are a common cause of drug induced liver injury (DILI). Over the last few decades, several newer AEDs were approved for marketing in the United States, and they are increasingly prescribed for indications other than seizures. Contemporaneous data related to trends and characteristics of liver injury due to AEDs are sparse.

Methods: We report the trends, characteristics, and outcomes of patients with AED DILI enrolled into DILIN Prospective Study between 2004 and 2020.

Results: Among 1,711 participants with definite, highly likely, or probable DILI, sixty-six (3.9%) had AED DILI [lamotrigine (n=18), phenytoin (n=16), carbamazepine (n=11), valproate (n=10), gabapentin (n=4), and others (n=7)]. The frequency of AED liver injury significantly decreased during the study period (from 8.5% of cases during 2004–2007 to 2.6% during

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Research Data for this article
Research data for this article where pertinent are included in the supplemental material.

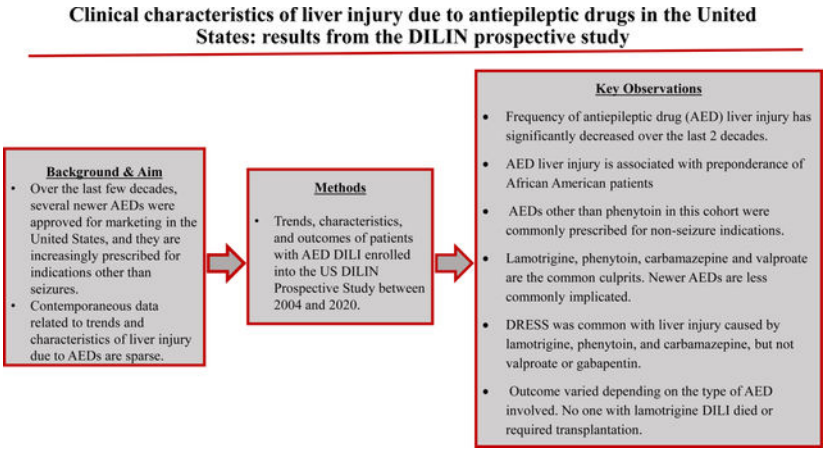
2015 −2020, P= 0.01). AEDs other than phenytoin were commonly prescribed for non-seizure indications. Compared to non-AEDs, patients with AED liver injury were younger (mean age 38.5 vs 50.1 y, p <0.001) and more likely African American (27% vs 12%, p=0.008). DRESS was common with liver injury caused by lamotrigine, phenytoin, and carbamazepine, but not valproate or gabapentin. Liver injury severity was moderate to severe in the majority: five died, and three underwent liver transplantation (OLT). None with lamotrigine DILI including 13 with hepatocellular jaundice died or needed OLT, compared to 3 of 16 (19%) with phenytoin DILI either died or required OLT.

Conclusion: The frequency of AED liver injury significantly decreased over the last two decades in our experience. AED liver injury has several distinctive features, including preponderance in African American patients and immunoallergic skin reactions with outcomes depending on the type of AED involved.

Lay Summary

Medications used to treat epilepsy may sometimes cause severe liver injury. However, several new medications have been approved over the last two decades and they may not be as toxic to liver as older anti epilepsy medications (AEDs). This study shows that overall liver injury due to AEDs is decreasing, likely due to decreasing use of older AEDs. Liver injury due to AEDs appears to be more common in African Americans and is commonly associated with allergic skin reactions.

Graphical Abstract



Keywords

African American; DRESS; Hepatotoxicity; Seizures; DILI risk score; DILI likelihood categories; LiverTox

Introduction

Antiepileptic drugs (AED) are among the most widely prescribed medications worldwide and, in addition to their use in treating seizure disorders, they are often used for other indications such as mood disorder, movement disorder, and chronic pain (1). As a therapeutic class, AED's are consistently ranked among the top causes of clinically apparent

liver injury and are a common cause for drug-induced acute liver failure (2–5). Currently, 30 AEDs are approved for use in the United States. Six AEDs (carbamazepine, fosphenytoin, lamotrigine, phenobarbital, phenytoin, and valproate) are well established causes of liver injury and are assigned a category "A" likelihood score, as defined by the LiverTox website (1). In contrast, 13 currently available AEDs (brivaracetam, cannabidiol, clobazam, clorazepate, diazepam, ethosuximide, ezogabine, methsuximide, perampanel, primidone, rufinamide, stiripenton, and tiagabine) appear to have no convincing reports in the published literature and are assigned a category "E" likelihood score in LiverTox (1). It is noteworthy that all AEDs with DILI likelihood scores A were approved for marketing prior to 1995, whereas the AEDs approved in the last quarter century are generally less or non-hepatotoxic. It is not entirely clear why the newer AEDs carry lower risk for hepatotoxicity. Although molecular aromaticity is thought to be a risk factor for hypersensitivity as attributed to phenytoin, phenobarbital, and carbamazepine (1), non-aromatic AEDs such as valproate and lamotrigine can also cause DILI. Recent studies have highlighted the potential role for compound-specific characteristics such as daily dose, lipophilicity, and potential to generate reactive metabolites in the pathogenesis of idiosyncratic DILI (6). However, it is not clear if such compound-specific characteristics are correlated with the hepatotoxic potential of the available AEDs. In addition, a recent paper showed that there has been a dramatic reduction in the number of patients with acute liver failure due to AEDs placed on the liver transplant waiting list for unclear reasons [7].

In this paper, we describe the demographic, clinical characteristics, and outcomes in individuals with liver injury due to AEDs who were enrolled into the DILIN Prospective Study. Although liver injury due to certain AEDs is well-recognized, contemporaneous studies focusing on racial representation, hypersensitivity features, and outcomes are lacking. Two additional objectives of the current study are to investigate the temporal trends in the frequency of DILI due to AEDS in the DILIN Prospective Study and to investigate whether compound-specific characteristics explain why some anticonvulsants are more hepatotoxic than others.

Methods

The Drug Induced Liver Injury Network (DILIN) is a cooperative agreement between the National Institutes of Health and multiple academic centers in the United States. It was established in 2003 to investigate the implicated agents, characteristics, risk factors, natural history, and outcomes of idiosyncratic DILI in the US. The DILIN Prospective Study (ClinicalTrials.gov Identifier: NCT00345930) is an ongoing multicenter observational study conducted at multiple centers throughout the United States. Its design and inclusion and exclusion criteria have been described previously in detail [8]. In brief, adults and children older than 2 years of age with suspected DILI are enrolled and undergo structured evaluation and assessment for competing etiology, disease severity, and causality. A scoring system for DRESS (drug reaction with eosinophilia and systemic symptoms) was developed by modifying the Regiscar score. Based on the presence and severity of skin rash and eosinophilia and the presence of liver involvement, fever, lymphadenopathy, other organ involvement, facial edema, atypical lymphocytes, and other hematological features, patients were assessed to have possible, probable, or definite DRESS. This study was approved by

the institutional review boards of the participating institutions, and all participants have provided an informed consent prior to enrollment. Some of the patients described in this paper have been included in other DILIN publications (2, 9,10)

The annual prescription volumes for selected AEDs were obtained from the Medical Expenditure Panel Survey (MEPS), a nationally representative survey of the civilian noninstitutionalized population of all ages in the US. Conducted by the Agency for Healthcare Research and Quality, the MEPS collects comprehensive data on health care utilization and expenditures. Data are collected over five rounds of in-person Household interviews that cover consecutive two-year periods. Each MEPS panel is a subsample of the prior year National Health Interview Survey respondents. The MEPS provides national estimates of prescribed medicine utilization for each calendar year. Only prescriptions purchased or obtained in an outpatient setting are included in these estimates. Sample design variables and weights were used to produce nationally representative estimates that accounted for the MEPS complex survey design, including its stratified multistage cluster sampling. A more detailed information can be found elsewhere (11). We used Stata MP Version 16.1 (StataCorp, College Station, TX) to display the estimates.

To determine compound-specific characteristics and the risk for DILI, a list of 31 AEDs currently marketed in the United States and their DILI likelihood categories were extracted from Liver Tox (https://www.ncbi.nlm.nih.gov/books/NBK547852/). Lipophilicity (logP), reactive metabolite generation, and daily dose for each AED were collected from the published literature. Dose-based DILI score was calculated using the equation 0.608*log(daily dose/mg) + 0.227*logP + 2.833*(RM formation) (https://nctr-crs.fda.gov/nctrcrs/ltkb/dili_score.html).

Data Management and Analyses

Demographic and clinical data for subjects enrolled into the DILIN Prospective Study between September 2004 and March 2020 were extracted on March 10, 2021. Descriptive statistics, such as means with standard deviations, medians with ranges and frequency distributions were used to describe the cohort. Between group difference were tested using the χ^2 test for categorical variables, Wilcoxon/Kruskal-Wallis test for the continuous variables, and log-rank test for time from enzyme peak to normalization. Two sided Cochran-Armitage test was used to test the temporal trend in the frequency of DILI due to antiepileptic drugs. The relationship between DILI risk score and DILI likelihood categories using multinomial and exact logistic regression analysis. Statistical analyses were performed using SAS software, version 9.2 (SAS Institute, Inc, Cary, NC) and P value <0.05 was considered statistically significant.

Results

Between September 2004 and March 2020, a total of 2,286 participants were enrolled into the DILIN Prospective Study, by which time 2,175 had gone through causality assessment and 1,711 cases adjudicated to have a causality score of definite, highly likely, or probable (high confidence DILI). Of those participants with high confidence DILI, 66 had liver injury due to AEDs (Supplemental Figure 1). The most frequent were lamotrigine (n=18),

phenytoin (n=16), carbamazepine (n=11) and valproate (n=10). For these 4 agents, causality scores were usually “definite” or “highly likely” (70% to 93%) rather than “probable”. Patients with liver injury due to 4 agents were commonly but variedly taking other AEDs, either currently or recently. Six patients with DILI due to carbamazepine received other AEDs and they include gabapentin (n=1), levetiracetam (n=2), topiramate (n=2) and lamotrigine (n=1). Six patients with liver injury due to lamotrigine received other AEDs and they include gabapentin (n=1), carbamazepine (n=1), oxcarbamazepine (n=1), topiramate (n=1) and levetiracetam (n=1). Nine patients with liver injury due to phenytoin received other AEDs and they include levetiracetam (n=5), levetiracetam plus gabapentin (n=1), levetiracetam and lamotrigine (n=1), and topiramate (n=1), zonisamide (n=1). Two patients with valproate liver injury had other AED use and they include lamotrigine (n=1) and zonisamide (n=1).

Miscellaneous AEDs with few cases included more recently approved agents such as gabapentin (n=4), topiramate (n=2), zonisamide (n=1), and pregabalin (n=1), and rarely used older agents – ethosuximide (n=1), fosphenytoin (n=1) and phenobarbital (n=1). Among these 11 cases, only 3 (27%) were considered definite or highly likely. Children accounted for 9 cases, 4 due to lamotrigine, and one each for phenytoin, phenobarbital, carbamazepine, fosphenytoin, and ethosuximide. The causality scores were mostly “definite” or “highly likely” for the four most implicated agents (lamotrigine 72%, phenytoin 93%, carbamazepine 72%, and valproate 70%) but were mostly “probable” for the newer and less commonly used AES (22% overall). Current or recent use of other

Temporal Trend

AEDs were among the most common classes of prescription agents to cause DILI in the DILIN prospective study, but the frequency decreased during the study period (Supplemental Table 1). Among all high-confidence DILI cases enrolled during the study period, the frequency of AED liver injury was 7.8% of participants enrolled between 2004–2007, 2.4% during 2008–2011, 4.1% during 2012–2015, and 2.6% during 2016 −2020 (Cochran-Armitage two-sided P-value 0.01). During this same time, the average annual prescription rates for the AEDs most commonly implicated in DILI varied (Supplemental Table 2), decreasing by 62% for phenytoin (6.8 to 2.5 million yearly) and by 90% for valproate (6.2 to 0.5 million), while remaining constant for carbamazepine and more than doubling for lamotrigine (4.7 to 11.9 million). In like manner, numbers of cases attributed to phenytoin and valproate decreased while those for lamotrigine increased. Other AEDs with rising and currently highest prescription rates were associated with few or no cases of liver injury including gabapentin (45.3 million), clonazepam (18.8 million), pregabalin (10.6 million), topiramate (9.3 million), and levetiracetam (7.7 million) and many of cases were judged as only “probable”.

Comparison with liver injury due to non-AEDs

Liver injury due to AEDs as a class had several distinctive features, compared to liver injury due to other agents (Table 1). Patients with liver injury due to AEDs were younger, more likely African American, and more likely to have systemic manifestations such as fever, rash, and eosinophilia, and Stevens-Johnson Syndrome or toxic epidermal necrolysis. Liver

injury appeared to be more severe and more likely to require hospitalization and to have been treated with corticosteroid therapy, but outcomes such as death, liver transplantation or chronic DILI were similar between AEDs and non-AEDs.

Lamotrigine

Liver injury was attributed to lamotrigine in 18 instances (Table 2 and Supplemental Table 3). Four were children, 15 women, 15 Caucasian, and mean BMI was 28.9 ± 9.4 kg/m^2. The indication for lamotrigine was bipolar disorder in 14 individuals, seizure disorder in 3, and both in 1. Median latency to onset was 37.5 (range 9 to 437) days. In 10 individuals, the onset of liver injury was preceded by an escalation of the daily dose of lamotrigine. DRESS was present in 13 individuals: definite in 5 (including two with full blown Stevens Johnson Syndrome), probable in 7, and possible in 1. The pattern of liver injury was hepatocellular in 15 individuals, whereas it was mixed in 2 and cholestatic in 1 individual. The peak total serum bilirubin was greater than 2.5 mg/dL in all but 2 individuals. The severity of liver injury was assessed as mild in 1, moderate in 11, and severe in 6 individuals. Interestingly, there were no deaths or liver transplantation among these 18 patients, and only 2 patients had evidence for chronic injury at 6 months. Liver biopsies on six patients (Supplementary Table 4), showed a mix of acute hepatitis and cholestatic hepatitis, all with eosinophilic infiltrates. A 47-year-old Caucasian woman (Supplemental Table 3, **patient # 16**) who received 50 mg lamotrigine for 437 days presented with hepatocellular liver injury (Peak ALT 798 U/L, Alk P 664 U/L, and total bilirubin 9.8 mg/dL) had a liver biopsy during the acute liver injury episode which showed cholestatic liver injury, with severe duct injury, focal bile duct loss, cholangitis and portal edema, raising the possibility of vanishing bile duct syndrome. Eight weeks later her ALT, Alk P, and total bilirubin were 305 U/L, 477 U/L, and 0.7 mg/dL, respectively. Unfortunately, this individual was lost to follow-up.

Phenytoin

Liver injury was attributed to phenytoin in 16 individuals. The mean age was 40.9 ± 18.5 years, eight were women, eight African American and eight Caucasian, and mean BMI was 25 ± 6.3 kg/m2 (Table 2 and Supplemental Table 4). Median latency to onset was 28.5 (range 2–47) days. DRESS was present in 10 patients (63%): which was scored as definite in 5, probable in 3, and possible in 2 patients. Biochemical pattern of liver injury at presentation was hepatocellular in 8, mixed in 6, and cholestatic in 2 individuals. Liver injury was assessed as mild in 7, moderate in 1, and severe in 8 patients. Two patients died following their liver injury; one patient died 10 months later due to brain cancer (Supplemental Table 4, **patient # 3**) and another died 2 months later due to cerebral bleed, pulmonary embolism, and sepsis (Supplemental Table 4, **patient # 13**). Liver injury improved in both and was not the cause for their deaths. A 44-year-old male with history of polysubstance abuse and phenytoin allergy received intravenous phenytoin loading for active seizures and developed acute liver injury after two days without rash, fever, or eosinophilia (Supplemental Table 4, **patient # 12**). He rapidly developed acute liver failure with coagulopathy and acute kidney injury. Liver biopsy showed mild lymphocytic inflammation and extensive zone 3 hepatic necrosis along with moderate steatosis, and hepatocellular rosettes in zones 1 and 2. He successfully underwent liver transplantation 8 days after developing liver injury.

Carbamazepine

Eleven patients had liver injury attributed to carbamazepine (Table 2 and Supplemental Table 5). They included 10 adults and 1 child and had been prescribed carbamazepine for seizure disorder in 5, mood disorder in 3, and neuropathic pain in 2 individuals. Median latency was 33 (range 25 – 244) days. Eight were Caucasian and 3 were African Americans. There were two distinct patterns of liver injury associated with carbamazepine. The first pattern arose in 7 individuals who presented with a cholestatic or mixed pattern liver injury after a median latency of 31 days, all of whom but one had systemic manifestations such as rash, fever, and eosinophilia. Five were deemed to have DRESS (45%) which was scored as definite in 4 including one with full blown SJS and probable in another individual. The second pattern arose in 4 individuals who presented with hepatocellular injury after a median latency of 153 days, none of whom had systemic manifestations. Liver injury was scored as mild in 2, moderate 5, severe 3, and fatal in 1 patient. Two individuals died following their presentation with liver injury, but liver injury was not the cause of death in either. A 43-year-old woman (Supplemental Table 5, **patient # 6**) developed severe cutaneous adverse reaction along with liver injury 33 days after starting carbamazepine for seizures. Liver biopsy showed mild portal inflammation with eosinophils, plasma cells and extramedullary hematopoiesis. Her liver injury gradually improved, to ALT 23 U/L, Alk Phos 53 U/L, and total bilirubin 2.4 mg/dL, but she inadvertently was rechallenged with carbamazepine which led to worsening of her skin reaction to 100% exfoliation and skin breakdown, and she succumbed to sepsis and organ failure nearly 2 months after the initial presentation. Another individual (Supplemental Table 5, **patient # 9**) who developed cholestatic liver injury 27 days after starting therapy with carbamazepine died from worsening of his underlying advanced cortical thymoma within a month. His biopsy showed only mild portal lymphocytic inflammation and minimal zone 3 necrosis. There was no evidence for chronic DILI at 6 months after presentation in other patients.

Valproic acid

Ten patients experienced liver injury attributed to valproic acid with causality scores of definite in 2, highly likely in 5, and probable in 3 (Table 2 and Supplemental Table 6). Eight were women and eight were Caucasian. All were adults. Indications for valproic acid use were bipolar disorder in 6, seizures in 3, and migraine in 1 individual. Median latency was 43 (range 31 to 315) days. The pattern of liver injury was hepatocellular in 9 and mixed in 1. No patients reported systemic hypersensitivity manifestations. Liver injury was mild in 3, moderate in 3 and severe in 4 individuals. No one died but one severely affected patient required liver transplantation. This patient (Supplemental Table 6, **patient 4**) was a 28-year-old woman who developed acute liver injury with massive hepatic necrosis 5 weeks after starting therapy with valproic acid for bipolar disorder. Another patient (**Patient 8 in** Supplemental Table 6) with mixed pattern liver injury at presentation had persistently elevated ALT (131 U/L), Alk P (419 U/L), and total bilirubin 0.4 mg/dL six months later. Interestingly, this individual had serum LDL-cholesterol exceeding 500 mg/dL during the DILI episode which spontaneously improved to 172 mg/dL subsequently.

Gabapentin and other AEDs

Four patients experienced liver injury attributed to gabapentin (Table 2 and Supplemental Table 7). All were Caucasian adults with ages, ranging from 46.5 years to 75.6 years and BMI ranging from 21.3 to 39.6 kg/m2. The latency ranged from 15 days to 58 days. The pattern of liver injury was hepatocellular in 2, cholestatic in 1, and mixed in 1. Three of four had jaundice, with peak serum total bilirubin ranging from 3.1 mg/dL to 25.3 mg/dL. No one had DRESS. One patient showed chronic cholestasis with ductopenia on biopsy. Their causality scores were probable in 2 and highly likely in another 2 individuals. The severity of liver injury was graded as moderate in 3 and severe in 1 individual. A 46-year female patient who presented with cholestatic DILI due to gabapentin (causality score 3, probable) died approximately 4 months following DILI recognition due to metastatic breast cancer. Supplemental Table 7 summarizes selected demographic and clinical characteristics and outcomes of liver injury due to topiramate, zonisamide, phenobarbital, pregabalin, fosphenytoin, and ethosuximide. A 63-year-old African American woman (**Patient 10,** Supplemental Table 7) who had taken topiramate for migraine for 154 days developed fulminant liver failure and underwent liver transplantation. Her explanted liver showed massive necrosis with eosinophilic and plasma cellular infiltrates. A 61-year-old Caucasian male (**Patient 11,** Supplemental Table 7) presented with cholestatic liver injury after taking zonisamide for 35 days for weight loss. Although his liver biochemistries gradually improved, he had evidence for liver injury at 6 months after initial presentation. His liver biopsy at presentation showed non-suppurative cholangitis with mild lobular hepatitis, and a repeat liver biopsy 8 months later showed periportal fibrosis, portal tract expansion with neutrophilic infiltration, marked bile ductular proliferation and focal ductopenia.

Liver Histology

Liver histology was reviewed centrally in 17 cases and their findings are described in Table 3. Figure 2 depicts histological findings from less common forms of AED DILI.

Relationship between the AED compound characteristics and DILI likelihood score

The AED characteristics (lipophilicity, reactive metabolite generation, and daily dose), DILI risk scores, and Liver Tox DILI likelihood categories for the currently marked antiepileptic drugs are described in Supplemental Table 8. The distribution of DILI risk scores for categories A, B, C, D, and E were 7.2 ± 0.45, 4.1 ± 2.5, 3.8 ± 0.48, 3.6 ± 0.9, and 4.29 ± 1.75, respectively. When the association between DILI risk score was assessed across levels of the likelihood score categories simultaneously (A, B, C, D vs E) there was no apparent significant overall relationship (P=0.21). When the association between DILI risk score and likelihood category A was examined specifically, the odds of category A versus category E increased 3.6 times per unit increase in DILI risk score (OR 3.6, 95% CI: 1.11–11.62, P=0.03). We also collapsed the likelihood categories to reflect a composite comparison between category A versus all others (B, C, D, E) using exact logistic regression and found that DILI score significantly predicted the odds for an AED to be in category A versus all others (OR 3.6, 95% CI: 1.49–12.24, P=0006).

Annual prescription volumes of AEDs in the United States

The estimated annual prescription volumes for selected AEDs between 2004 to 2018 are shown in Supplemental Table 2. Of 5 LiverTox DILI likelihood Category A AEDs (phenytoin, carbamazepine, valproate, lamotrigine, and fosphenytoin), the number of annual prescriptions for phenytoin, carbamazepine, and valproate have drastically reduced between 2004 and 2018 (Figure 1). For example, the number of prescriptions for phenytoin went from 8,445,359 in 2004 to 1,633498 in 2018 (− 81%), and for valproate from 5,787,654 in 2004 to 495,093 in 2018 (− 91%). However, there has been a dramatic increase in the number of prescriptions for lamotrigine from 3,423,811 in 2004 to 11,582, 775 in 2018 (+ 238%). Gabapentin is by far the most widely prescribed AED currently, with 45,586,654 estimated prescriptions written in 2018. Reliable annual prescription data were not available for lacosamide, rufinamide, vigabatrin, clobazam, ezogabine, perampanel, eslicarbamazepine, brivacetam, cannabidol, stiripentol, ethosuximide, methsuximide, felbamate, and fosphenytoin.

Discussion

In this analysis, the frequency of liver injury ascribed to AEDs in the DILIN prospective study has decreased over the last 15 years. This observation is consistent with a recent report showing a significant reduction in the number of individuals with acute liver failure due to AEDs necessitating liver transplant wait listing in the United States (5). There were 36 individuals with ALF due to AEDs on the liver transplant wait list during 1995 – 2003, but, despite population growth and increased numbers of patients listed for liver transplantation, this number decreased to 19 individuals during 2004–2012 and 8 individuals between 2013 and 2020. We believe this decreasing frequency of severe liver injury due to AEDs is likely the result of growing use of newer AEDs that are less hepatotoxic than the older AEDs such as carbamazepine, phenytoin, and valproate. However, one cannot entirely exclude the possibility of reporting bias contributing at least to some degree to this phenomenon. There have been 16 newer AEDs approved for marketing in the United States since 1997 and all have Liver Tox DILI likelihood scores E, D or C, implying a lower risk for liver injury. In this study, the newer anticonvulsants accounted for only 8 cases of DILI including 4 from gabapentin, 2 from topiramate, and 1 each from pregabalin and zonisamide. Interestingly, none of the 8 patients were receiving these AEDs for epilepsy. Furthermore, there were no cases attributed to clonazepam or levetiracetam, two of the most frequently used anticonvulsants in current use. A recent epidemiological study, based on the FDA Adverse Event Reporting System, observed that majority of the newer generation AEDs are not significantly associated with DILI (13) Newer AEDs are less likely to have unfavorable compound characteristics such as aromaticity, lipophilicity, and reactive metabolite formation (Supplemental Table 8).

An interesting observation was that individuals who developed liver injury due to lamotrigine, carbamazepine, valproate, and gabapentin, were often taking these medications for indications other than seizure disorder (e.g., mood disorder, neuropathy). For example, of 18 individuals who had liver injury due to lamotrigine, only 6 were prescribed this medication for seizures, whereas bipolar disorder was the reason in the other 12 patients.

In contrast, phenytoin was prescribed primarily to treat seizures in all those who had liver injury attributed to it. In addition, the majority of lamotrigine cases occurred following dose escalation although the maximum recommended dose was not exceeded in any. This suggests that the likelihood of DILI may be partially dose dependent. Practitioners using lamotrigine should be aware of this and may want to consider more careful laboratory and clinical assessment after increasing the dose of lamotrigine.

A striking observation was the over representation of self-reported African American race among those who developed liver injury due to phenytoin, lamotrigine, and carbamazepine. Thus, 8 of 16 patients who had liver injury due to phenytoin and both patients who had liver injury due to topiramate were of self-reported African American race. This propensity for African Americans to develop liver injury due to AEDs such as phenytoin and lamotrigine may be due to their HLA and non-HLA genetic risk factors, although one cannot exclude the possibility of higher prescription rates of certain AEDs to African American individuals. Genetic factors are likely the underpinnings for high prevalence of immunoallergic features such as severe cutaneous reactions, fever, and eosinophilia among patients with liver injury due to some AEDs. There was high frequency of DRESS like features among individuals with liver injury due to lamotrigine (11 out 18), phenytoin (10 out 16), and carbamazepine (5 out of 11), and 11 of 13 biopsies in this group showed eosinophilic infiltrate. In contrast, systemic features were absent in individuals who had liver injury due to valproate and gabapentin.

In this prospective study of DILI, lamotrigine emerged as the most commonly implicated AED. This change does not necessarily imply that lamotrigine is more hepatotoxic than older AEDs, but is likely a reflection of its heightened use, especially for managing mood disorders. As observed previously (1), the onset of liver injury was preceded by an escalation in the daily dose, implying that a critical dose may be necessary for initiating the onset of liver injury, in an otherwise susceptible individual. The biochemical pattern of liver injury from lamotrigine was hepatocellular in most patients, but also included one individual who presented with hepatocellular injury at onset, after very long latency, but with liver biopsy showing cholestatic hepatitis with features suggestive of vanishing bile duct syndrome [VBDS]. This scenario is similar to a case report by Bhayana et al (14). who reported VBDS in a 10-year male child who too presented with hepatocellular liver injury 4 weeks after initiating therapy with lamotrigine. It is intriguing that no one with liver injury due to lamotrigine in the current case series died or required liver transplantation, although 14 out of 16 patients had hepatocellular jaundice [R>5] and the injury was considered severe in 6 patients. This could in part be due to the lower average age of patients with lamotrigine DILI, compared to individuals with phenytoin, carbamazepine, or valproate DILI. However, it could also be due to relatively small number of patients with lamotrigine DILI in this series.

Consistent with previous descriptions (1), patients with liver injury due to carbamazepine presented in two distinct patterns: mixed or cholestatic liver injury with accompanying DRESS or hepatocellular liver injury without any systemic features of hypersensitivity. Age, gender, and race were not different between these two subgroups, but the latency was longer in those who presented with hepatocellular liver injury due to carbamazepine. Two of 11

individuals with liver injury due to carbamazepine died, both dying due to non-liver related reasons. Four individuals with hepatocellular jaundice with peak total bilirubin ranging between 4 – 27.6 mg/dL fully recovered with no evidence for chronic or residual liver injury.

Age less than 2 years and concomitant use of other antiepileptic medications are generally considered to be risk factors for valproate hepatotoxicity (1). Because the current study limited enrollment to individuals 2 years of age or older, there were no infants in this series. Only 3 of the 10 patients who developed liver injury attributed to valproate were prescribed the drug because of seizures, the other 7 having mood disorders. Perhaps for this reason, none of the cases due to valproate were taking concomitant AEDs. Valproate hepatotoxicity may present in multiple clinical patterns - either as hyperammonemia without other evidence of liver injury; as isolated, usually asymptomatic and transient serum aminotransferase elevations, as acute and often severe hepatocellular injury, or as a Reye's-like syndrome with hyperammonemia, elevated aminotransferases and microvesicular steatosis on liver biopsy. In this series, liver injury due to valproate was mostly hepatocellular in nature without any systemic, immunoallergic features, and none exhibited Reye's like picture. One of six individuals with hepatocellular jaundice ascribed to valproate (peak total bilirubin ranging from 11.2 to 20.3 mg/dL) required liver transplantation. The only biopsy available for review showed cholestatic hepatitis without evidence of microvesicular steatosis.

This analysis is based on our ongoing, long term prospective study that carefully characterizes DILI events and liver histology centrally reviewed by a single expert pathologist. Competing etiologies are comprehensively excluded and hepatologists with expertise in DILI systematically adjudicated the causality for all enrolled participants. The long-term nature of our study allowed us to describe the temporal trends of liver injury associated with AEDs, but one needs to interpret our data cautiously because this is not a population-based study and may have significant selection bias, with more severe reactions, perhaps, more likely to be referred for inclusion. Due to the nature of the study design, we are unable to able to assess the absolute risk of and risk-factors for DILI associated with AEDs. Further, steroid use was common in this cohort and yet the details related to the nature of steroid therapy (i.e., type, dose and duration) and response to therapy were not systematically collected.

In summary, liver injury due to AEDs decreased in frequency over the last two decades in the DILIN Prospective Study, likely due to growing use of newer and safer non-aromatic AEDs. There was an interesting relationship between DILI risk score and the LiverTox DILI likelihood category A, which indicates higher DILI potential. Lamotrigine was the most common AED to cause liver injury in this experience, and 60% of cases occurred after a rapid dose increase. The severity of liver injury was moderate or severe in the majority, with 3 individuals requiring liver transplantation. Compared to other drugs, there was enrichment of African American patients among individuals developing AED liver injury and there is greater frequency of DRESS syndrome and severe outcomes. It seems likely that such susceptibility is related to genetic factors. We suggest that aromatic AEDs be avoided in treating African American patients for epilepsy or mood disorders, or if used, that they be followed closely and advised to stop the drug promptly at the first signs of skin or liver damage.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

DILI	Drug induced liver injury
DILIN	Drug induced liver injury network
AED	Antiepileptic drugs
DRESS	Drug reaction with eosinophilia, systemic symptoms
SJS	Steven-Johnson Syndrome
TEN	Toxic epidermal necrolysis
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
Alk P	Alkaline Phosphatase
T Bili	Total bilirubin
AA	African-American
Cauc	Caucasian

OLT	Orthotopic liver transplantation
VBDS	Vanishing bile duct syndrome

References

1. Anticonvulsants: Liver Tox: Clinical and research information on drug-induced liver injury. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases. https://www.ncbi.nlm.nih.gov/books/NBK548365/ (Accessed on 6/5/2021)
2. Chalasani N, Bonkovsky HL, Fontana RJ, Lee W, Stolz A, Talwalkar J, et al. Features and Outcomes of 899 Patients With Drug-Induced Liver Injury: The DILIN Prospective Study. Gastroenterology 2015 Jun; 148(7):1340–1352. [PubMed: 25754159]
3. Reuben A, Koch DG, Lee WM, the Acute Liver Failure Study Group. Drug induced acute liver failure: results of a U.S. multicenter prospective study. Hepatology 2010; 52: 3065–2076
4. Andrade RJ, Lucena MI, Carmen Fernandez M, Pelaez G, Pachkoria K, et al. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. Gastroenterology 2005; 129: 512–521 [PubMed: 16083708]
5. Bjornsson E Hepatotoxicity by drugs: the most common implicated agents. Int J Mol Sci 2016; 17: 224–231 [PubMed: 26861310]
6. Chen M, Borlak J, Tong W. A model to predict severity of drug-induced liver injury in humans. Hepatology 2016; 64: 931–940 [PubMed: 27302180]
7. Ghabril M, Ma J, Patidar KR, Nephew L, Desai AP, Orman E, et al. Trends in liver transplant waitlisting and outcomes for drug-induced liver injury in the United States. Liver Transplantation (In revision)
8. Fontana RJ, Watkins PB, Bonkovsky HL, Chalasani N, Davern T, Serrano J, et al. Drug induced liver injury network (DILIN) prospective study: rationale, design and conduct. Drug Saf 2009;32:55–68 [PubMed: 19132805]
9. Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, et al. Idiosyncratic drug-induced liver injury in the United States: analysis of the first 300 patients prospectively enrolled by the DILIN. Gastroenterology 2008;136:1924–1934
10. Chalasani N, Reddy KR, Fontana RJ, Barnhart H, Gu J, Hayashi PH, et al. Idiosyncratic drug induced liver injury in African-Americans is associated with greater morbidity and mortality compared to Caucasians. Am J Gastroenterology 2017 Sep;112(9):1382–1388
11. Chowdhury SR, Machlin SR, Gwet KL Sample Designs of the Medical Expenditure Panel Survey Household Component, 1996–2006 and 2007–2016.Methodology Report #33. January 2019. Agency for Healthcare Research and Quality, Rockville, MD. https://meps.ahrq.gov/data_files/publications/mr33/mr33.pd
12. Kamitaki BK, Minacapelli CD, Zhang P, Wachuku C, Gupta K, Catalano C, et al. Drug-induced liver injury associated with antiseizure medications from the FDA Adverse Event Reporting System (FAERS). Epilepsy & Behavior 2021; 117. 107832 [PubMed: 33626490]
13. Bhayana H, Appasani S, Thapa BR, Das A, Singh K. Lamotrigine-induced vanishing bile duct syndrome in a child. JPGN 2012; 55: e1457–e148.

Highlights

- Frequency of antiepileptic drug (AED) liver injury significantly decreased over the last 2 decades.
- Lamotrigine, phenytoin, carbamazepine and valproate are the common culprits. Newer AEDs are less commonly implicated.
- AEDs other than phenytoin in this cohort were commonly prescribed for non-seizure indications.
- AED liver injury is associated with preponderance of African American patients and immunoallergic skin reactions
- Outcome varied depending on the type of AED involved.

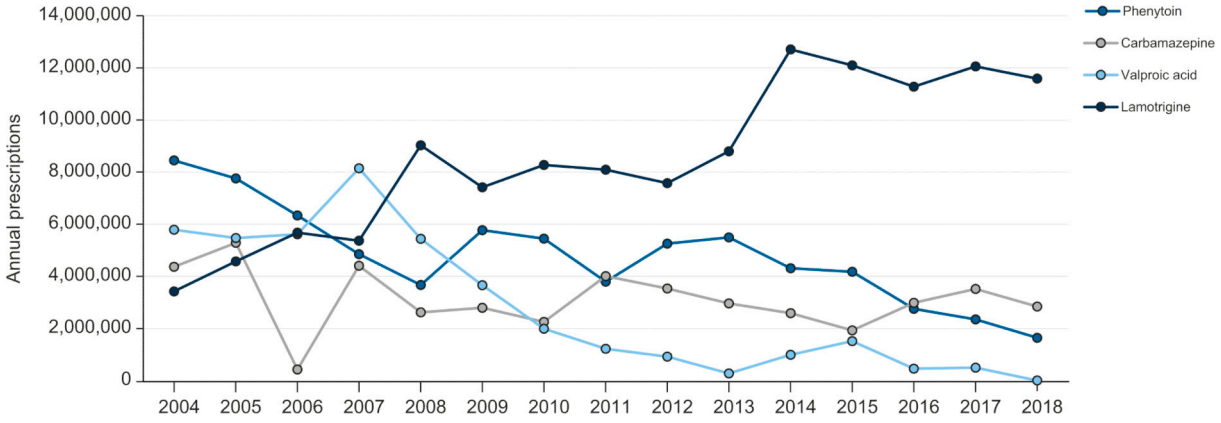

Figure 1.

Annual prescription volumes for lamotrigine, phenytoin, carbamazepine, and valproate in the United States from 2004 to 2018

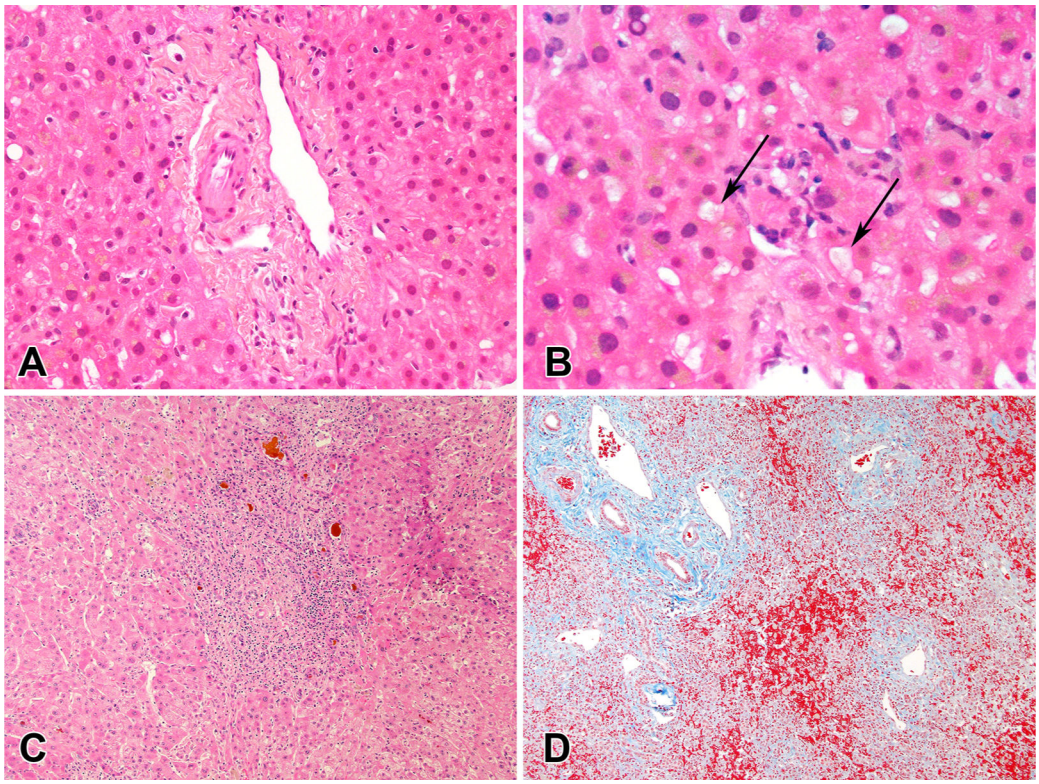

Figure 2.

Histological changes in less common forms of AED DILI. A,B. Vanishing bile duct syndrome due to Gabapentin. A. No bile ducts were seen in any portal area. (H&E, 400x). B. Canalicular (arrows) and hepatocellular cholestasis with mild inflammation. (H&E, 600x). C,D. Fulminant hepatic failure due to topiramate. C. Residual parenchyma with moderate portal inflammation and cholestasis. (H&E, 100x). D. Collapsed, necrotic parenchyma with approximation of portal areas. (Masson trichrome, 100x).

Table 1:

Selected clinical characteristics and outcomes of individuals with definite, highly likely, or probable DILI due to anti-epileptic drugs (AED) and all other implicated agents (N=1711)*

	AED (N=66)	Non-AED (N-1645)	P-value
Age	38.5 ± 18.3	50.1 ± 17.1	<0.001
Female (%)	70	58	0.06
Self-reported race (%)			0.008
- Caucasian	66 7	78.7	
- African American	27.3	12	
- Asian	1.5	3.5	
BMI (kg/m2)	27 ± 8.0	27.5 ± 6.4	0.4
Prior drug allergies (%)	48.5	43	0.36
Alcohol use (%)	41	49	0.24
Latency (days)	67 ± 96	134 ± 342	0.154
Fever (%)	45.5	21	<0.001
Rash (%)	48.5	19%	<0.001
Eosinophilia (%)	33.3	14.4	<0.001
SJS or TEN (%)	4.5	0.7	0.015
Liver tests at presentation			
ALT (U/L)	943 ± 947	807 ± 1051	0.08
Alk P (U/L)	265 ± 177	283 ± 254	0.7
Total bilirubin (mg/dL)	4.5 ± 4.8	6.7 ± 6.8	0.004
INR	1.4 ± 0.42	1.4 ± 1.2	0.1
Pattern of liver injury (%) HC/CS/mixed	65/14/21	54/23/23	0.16
Peak laboratory values			
ALT (U/L)	1365.5 ± 1339	977 ± 1137	<0.001
Alk P (U/L)	395 ± 253	396 ± 381	0.14
Total bilirubin (mg/dL)	9.3 ± 7.9	12.7 ± 11.8	0.06
INR	1.9 ± 1.69	1.6 ± 1.55	<0.001
Days from onset to peak values			
ALT	6.7 ± 19	11 ± 57	0.5
Alk P	14.9 ± 40	29.4 ± 80.5	0.3
Total bilirubin	8.9 ± 14	18.3 ± 45.6	0.004

	AED (N=66)	Non-AED (N-1645)	P-value
Days from peak to normalization (median)			
ALT	38	62	0.05
Alk P	36	67	0.10
Total bilirubin	16	33	0.05
Severity score (%) Mild/moderat[¶]/severe/fatal[δ]	21/38/35/6	25/51/17/7	0.004
Hospitalized (%)	86	62	<0.001
Causality (%) Definite/highly likely/probable	24/53/23	21/52/23	0.6
Steroid therapy (%)	42	21	<0.001
All deaths (%)	7.6	6.7	0.26
Liver-related deaths (%)	0	2.9	0.25
Liver transplant (%)	4.5	3.6	0.73
Chronic DILI (%)	9.8	16.6	0.20

*Values are in mean (standard deviation) unless shown otherwise.

**Moderate & Moderate-hospitalized combined

***Fatal includes liver transplantation.

Abbreviations: BMI: Body mass index; HC: Hepatocellular; CS: Cholestatic; ALT: Alanine aminotransferase; Bili: Bilirubin; OLT: Orthotopic liver transplantation; INR: International normalized ratio; DILI: Drug induced liver injury; HC: Hepatocellular; CS: Cholestatic

Table 2:

Selected clinical characteristics and outcomes of individuals with definite, highly likely, or probable DILI due to lamotrigine, phenytoin, carbamazepine, and valproate

	Lamotrigine N=18	Phenytoin N=16	Carbamazepine N=11	Valproate N=10
Age (years)	31.7 ± 14.3	41 ± 18.5	40.9 ± 16.3	41 ± .1 17
Female (%)	83	50	64	80
Self-reported race (%)				
- Caucasian	72	50	73	80
- African American	22	50	27	-
- Asian	6	-	-	-
BMI (kg/m2)	28.9 ± 9.4	25 ± 6.4	26.4 ± 6.6	27.7 ± 6.4
Prior drug allergies (%)	61	37.5	45.5	60
Latency (days)	78 ± 103	26.6 ± 12.3	73 ± 75	71 ± 86
Concomitant medicines in preceding 2 months (%)				
0–2	17	0	54.5	50
3–5	33	12.5	0	37.5
>5	50	87.5	45.5	12.5
Fever (%)	67	37.5	45.5	30
Rash (%)	72	75	36	0
Eosinophilia (%)	29	47	45.5	10
DRESS (%)	72	62.5	45	0
SJS or TEN (%)	11	-	9	0
Liver tests at presentation				
ALT (U/L)	964 ± 755	820 ± 897	554 ± 495	1676 ± 1295
Alk P (U/L)	235 ± 162	302 ± 156	338.5 ± 239	211 ± 111
Total bilirubin (mg/dL)	4.4 ± 5	1.9 ± 1.8	4.6 ± 5.8	6.8 ± 4.5
INR	1.1 ± 0.15	1.3 ± 0.22	1.2 ± 0.19	1.5 ± 0.47
Pattern of liver injury (%) HC/CS/mixed	83/11/6	50/37.5/12.5	36/36/27	89/0/11
Peak laboratory values				
ALT (U/L)	1699 ± 1771	1244 ± 1342	919 ± 542	1835 ± 1160
Alk P (U/L)	357 ± 221	454 ± 199	555 ± 322	235 ± 121
Total bilirubin (mg/dL)	10 ± 7.45	6.6 ± 7.5	9.1 ± 8.9	11.6 ± 7.65
INR	1.3 ± 0.28	2.4 ± 2.57	1.5 ± 0.66	2.0 ± 1.85

	Lamotrigine N=18	Phenytoin N=16	Carbamazepine N=11	Valproate N=10
Days from onset to peak values (median [IQR])	1.5 [0–9.5]		4 [0–11]	
ALT	6.0 [2–9]		9 [1–10]	
Alk P	3.0 [0 – 9.5]	2 [0–5]	3.5 [1–12]	0 [0–5]
Total bilirubin		4 [1–10]		2 [0–12]
		7 [3–9]		7 [4–12]
Days from peak to normalization (median)[¶]				
ALT	63	38	27	70
Alk P	73.5	48.5	27	38
Total bilirubin	16	8.6 6.5	5.0	29
Severity score (%) Mild/moderat[¶]/severe/fatal[δ]	6/61/33/0	44/6/44/6	18/45.5/27/9	30/30/30/10
Causality (%) Definite/highly likely/probable	39/44/17	19/75/6	27/64/9	20/50/30
Steroid therapy (%)	56	44	54.5	10
MELD score	14±4.7	18.6 ± 12.5	14.2 ± 8.4	16.7 ± 6
Hy's law (%)	22	19	18	22
nRHy's law (%)	33	25	27	50
All deaths (%)	0	12.5	18	0
Liver-related deaths (%)	0	0	0	0
Liver transplant (%)	0	6	0	10
DILI persistent at 6 months (%)	13	0	0	12.5

*Values are in mean (standard deviation) unless shown otherwise.

¶Interquartile ranges (25th – 75th) were not calculated for "days from peak to normalization" because 75% of the patients may not have normalized at the assessment.

**Moderate & Moderate-hospitalized combined

***Fatal includes liver transplantation.

Abbreviations: BMI: Body mass index; HC: Hepatocellular; CS: Cholestatic; ALT: Alanine aminotransferase; Bili: Bilirubin; OLT: Orthotopic liver transplantation; INR: International normalized ratio; DILI: Drug induced liver injury; HC: Hepatocellular; CS: Cholestatic

Table 3:

Histologic findings on liver biopsies and explant specimens reviewed centrally

Pt.	Days after onset	Inflammatory Activity	Granulomas	Plasma Cells	Eosinophils	Necrosis	Cholestasis	Duct Injury	Pattern of Injury
Carbamazepine									
1	12	mild	large	Absent	Present	none	none	Present	Granulomatous hepatitis
4	7	mild	small	Absent	Present	none	moderate	Present	Cholestatic hepatitis
5	10	moderate	none	Absent	Present	mild	none	Absent	Acute hepatitis
6	24	mild	small	Present	Present	none	none	Present	Chronic hepatitis
9	2	mild	small	Absent	Absent	minimal	none	Present	Chronic hepatitis
Gabapentin									
4	20	minimal	small	Absent	Absent	none	severe	Absent	Chronic cholestasis with vanishing bile duct syndrome
Lamotrigine									
5	4	moderate	small	Absent	Present	none	none	Present	Acute hepatitis
8	14	moderate	small	Present	Present	none	mild	Absent	Acute cholestatic hepatitis
9	11	moderate	none	Absent	Present	none	none		Chronic hepatitis
16	4	mild	small	Absent	Present	none	moderate	Present	Cholestatic hepatitis with severe duct injury, suspicious for vanishing bile duct syndrome
12	0	mild	small	Absent	Present	none	none	Present	Acute hepatitis
17	11	severe	none	Present	Present	mild	mild	Present	Acute hepatitis
Phenytoin									
9	13	moderate	small	Absent	Present	minimal	none	Present	Chronic hepatitis
12	3	mild	none	Absent	Absent	moderate	none	Absent	Zonal necrosis
12	8*	severe	none	Present	Absent	severe	moderate	Present	Zonal necrosis
Topiramate									
10	41*	severe	small	Present	Present	severe	severe	Absent	Massive necrosis
Valproic acid									
10	6	moderate	small	Present	Absent	none	mild	Present	Cholestatic hepatitis

*These specimens were liver explants.