Characteristics of Liver Injury due to Antiepileptic Drugs in the United States: Results from the DILIN Prospective Study

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INTRODUCTION

Antiepileptic drugs (AEDs) are one of the most common classes of agents to cause drug induced liver injury (DILI), but several newer AEDs with lower DILI potential are available in the United States.

AIM

To describe key clinical characteristics and outcomes of patients with liver injury due to AEDs enrolled into the DILIN Prospective Study over the last two decades.

METHODS & RESULTS

- The DILIN Prospective Study enrolls children and adults with suspected DILI meeting predefined eligibility criteria, and they undergo structured evaluation at baseline and at 6 months or longer.

- The DILIN causality and DILIN severity are adjudicated in a systematic fashion. Between 9/2004 and 3/2020, a total of 2,286 participants were enrolled, among whom 1,711 participants had high confidence DILI (causality scores: definite, highly likely, or probable).

- Among the 1,711 66 [3.86%] had liver injury due to AEDs [phenytoin (n=16), lamotrigine (n=18), carbamazepine (n=11), valproate (n=10), gabapentin (n=4), and others (n=7).

RESULTS

Table 1. Features of DILI due to AEDs vs Other Agents

	AED N=66	Non-AED N=1645	P-value
Age	38.5	50.1	<0.001
Female	70	58	0.06
Latency (days)	67	134	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
Pattern of liver injury HC/CS/mixed	65/14/21	54/23/23	0.16
Liver tests at entry			
ALT (U/L)	1365	977	<0.001
Alk P (U/L)	395	396	0.14
TRB (mg/dL)	9.3	12.7	0.06
INR	1.9	1.6	<0.001
Severity score Mild/moderate¶/ severe/fatal§	21/38/35/6	25/51/17/7	0.004
Steroid therapy	42	21	<0.001
Chronic DILI	9.8	16.6	0.20

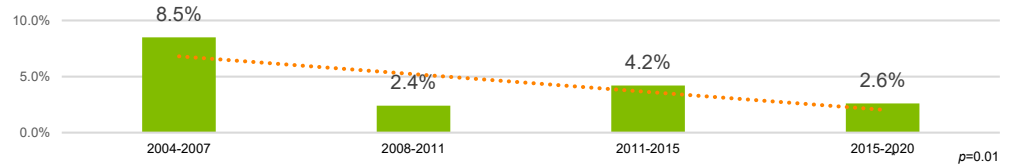
* Values are in percentages unless shown otherwise

Table 2. Salient Features of Subjects with DILI due to 4 common AEDs

	Lamotrigine N=18	Phenytoin N=16	Carbamazepine N=11	Valproate N=10
Age	31.7	41	40.9	41
Female	83	50	64	80
Latency (days)	78	26.6	73	71
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 entry				
ALT (U/L)	964	820	554	1676
Alk P (U/L)	235	302	339	211
TRB (mg/dL)	4.4	1.9	4.6	6.8
INR	1.1	1.3	1.2	1.5
Pattern of liver injury HC/CS/mixed	83/11/6	50/37.5/12.5	36/36/27	89/0/11
Liver transplant	0	6	0	10
Chronic DILI	13	0	0	12.5

* Values are in percentages unless shown otherwise

Figure 1. Decrease in the frequency of AED liver injury from 2004 to 2020 [% of all cases in US DILIN]



SUMMARY & CONCLUSIONS

- The frequency of AED liver injury decreased over the last two decades.
- Lamotrigine was the most common AED to cause liver injury; 60% of cases occurred after a rapid dose increase.
- 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.
- AED Liver injury as a class had several distinctive features compared to liver injury caused by other agents. AED liver injury was more severe, and corticosteroids were used more often. Still, the outcomes, such as death, liver transplant or chronic DILI were similar between AEDs and non-AEDs DILI.

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