

Pharmacokinetic Simulation Study: Exploring Lamotrigine's Impact Across Diverse Patient Populations

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Introduction

The Food and Drug Administration (FDA) and European Medicines Agency (EMA) have approved lamotrigine for treating various central nervous system symptoms [1,2], but recent warnings highlight its potential for serious reactions, including hepatotoxicity and cardiac effects [3]. Although rare, hepatotoxicity is a concern, particularly in populations like those with Type 2 Diabetes (T2D) and Non-Alcoholic Fatty Liver Disease (NAFLD) [4,5]. In this study, we investigate the effects of doses outside the therapeutic window to provide insights into the mechanisms underlying drug-induced liver injury (DILI) [6]. Overdosing amplifies the drug’s pharmacological effects, elucidating pathways involved in liver injury [7]. An incomplete understanding of lamotrigine's mechanisms poses challenges in interpreting secondary effects like DILI or cardiac issues, complicating adverse reaction assessments (figure 1). Dosing protocols vary by illness, necessitating vigilant healthcare professional monitoring [8,9]. **Objectives:** Investigate the influence of clinical parameters on lamotrigine pharmacokinetics across various patient populations to enhance therapeutic drug monitoring (TDM) and liver function assessment.

Methods

A retrospective exploratory analysis of 41 lamotrigine-treated patients at Hospital Santo António was conducted to identify changes in blood parameters and correlations among them. Subsequently, a Physiologically Based Pharmacokinetic (PBPK) model for lamotrigine was constructed in GastroPlus, incorporating ADMET predictions and literature data [10]. The model simulated lamotrigine's pharmacokinetics at increasing doses (200 mg, 400 mg, 600 mg, 1200 mg). DILIsym was employed, utilizing SimPops to introduce population variability, crucial for predicting low-frequency events like drug-induced liver injury (DILI), especially in patients with T2D and NAFLD.

Results

The retrospective analysis identified variations in blood parameters, including creatinine, albumin, gamma-glutamyl transferase, total bilirubin, and Vitamin B12 levels, with significant correlations observed. Notably, a **strong negative correlation was found between vitamin B12 and creatinine, suggesting potential interactions between lamotrigine, renal function, and nutrient metabolism**, which may impact immune system regulation and responsiveness to infection.

The PBPK model accurately predicted the distribution and elimination of lamotrigine. The calculated steady-state volume of distribution (Vss) was 1.84 L/kg, which agreed with the values reported in the literature [11,12]. The systemic clearance was estimated at 3.248 L/h, calculated as the product of the fraction of drug unbound in the plasma (fup) and the glomerular filtration rate (GFR). The elimination half-life (t1/2) was estimated to be 27.58 h. Normal ranges include 24 to 35 h and are dose-independent from 30 to 400 mg [12,13]. Peak plasma concentration (Cmax) increased with higher doses, potentially affecting drug efficacy and side effects, while time to reach peak concentration (Tmax) showed variability with dose increments (table 1 and figure 2).

Table 1. Results of the average PK parameters simulated: F%, Cmax, Tmax, AUC0–inf, AUC0–t, and 90% confidence interval for the different concentrations of lamotrigine. Each dose is presented with the values for the single simulation and a DILIsym population simulation. For 200 mg, a known therapeutic dose, we examined values from the literature for comparison [40]. The simulation length was 24 h for 176 selected subjects. Only the values for 200 mg doses were included, as all the other concentrations represent an overdose

Dose		F (%)	Cmax (µg/mL)	Tmax (h)	AUC0–inf (µg h/mL)	AUC0–24 (µg h/mL)
200 mg	Observed (mean or geo. mean ± SD)	98	2.46 ± 0.41 - 2.91 ± 0.26	1.11	-	94.6 ± 21.6 - 123 ± 14
	Single simulation	99.268	1.7306	1.68	61.218	27.137
	DILIsym simulation output (90% CI)	98.267 (97.92 - 98.62)	1.62 (1.576 - 1.664)	1.7188 (1.537 - 1.900)	60.218 (58.24 - 62.20)	25.161 (24.64 - 25.68)
400 mg	Single simulation	98.636	3.097	2.4	121.68	53.315
	DILIsym simulation output (90% CI)	95.459 (94.68 - 96.38)	3.0257 (2.918 - 3.133)	1.7108 (1.539 - 1.882)	124.65 (120.6 - 128.7)	48.889 (47.73 - 50.05)
	Single simulation	97.192	4.3525	0.48	180.05	77.604
600 mg	DILIsym simulation output (90% CI)	90.359	3.9353	1.8835	186.48	67.06
	Single simulation	84.868	8.0976	0.48	362.2	130.8
	DILIsym simulation output (90% CI)	77.406 (75.39 - 79.57)	7.089 (6.778 - 7.400)	1.2443 (0.959 - 1.530)	353.29 (337.1 - 369.5)	113.49 (109.5 - 117.5)

Conclusion

By integrating clinical parameters and physiological pathways, clinicians can identify individuals at high risk of adverse reactions to lamotrigine. Understanding its pharmacokinetics in diverse patients is crucial for improving outcomes and minimizing hepatotoxicity. Timely monitoring and liver assessments are vital, especially in patients with T2D and NAFLD, to ensure safe lamotrigine therapy.

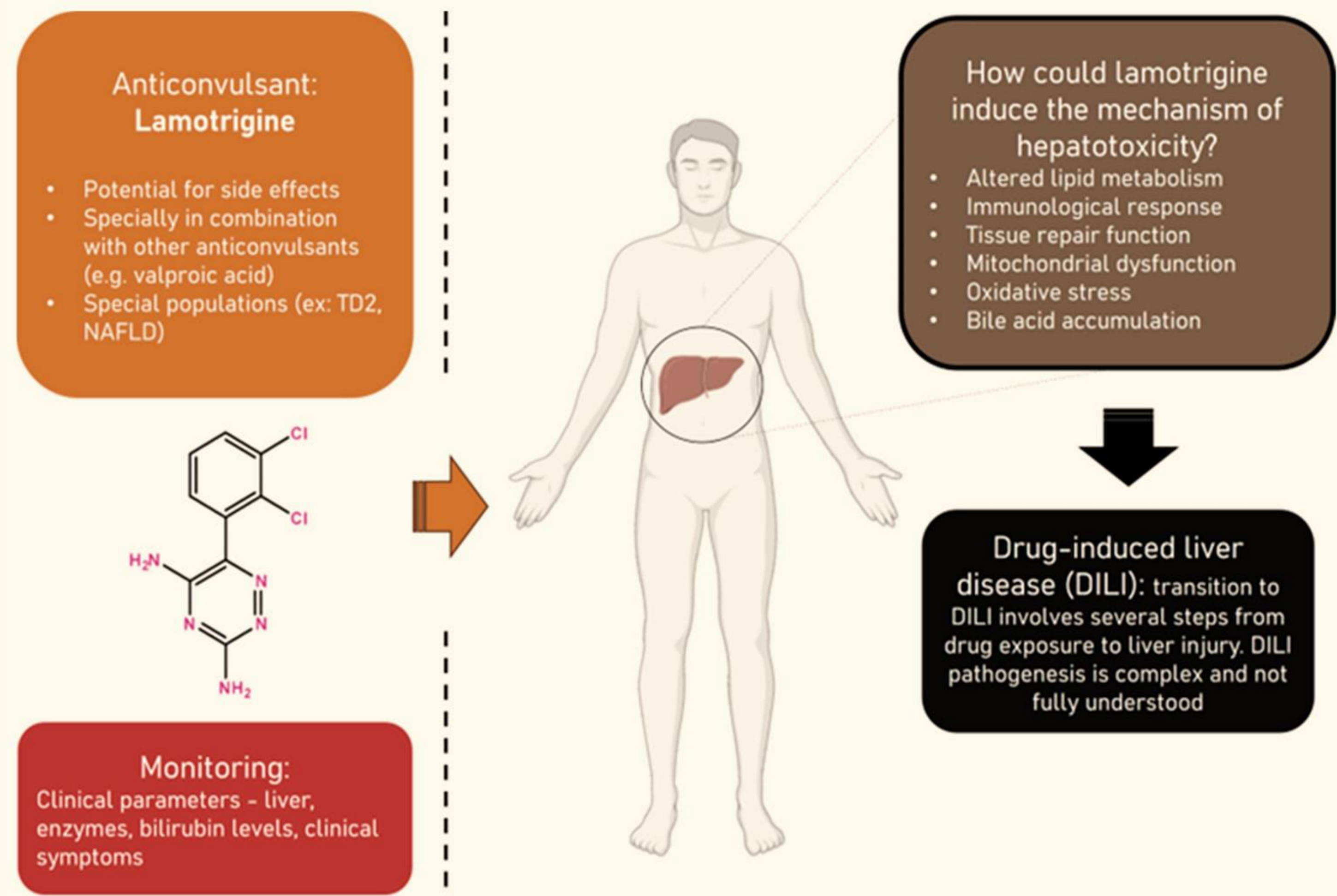


Figure 1. Overview of anticonvulsant lamotrigine, hepatotoxicity, and monitoring. Representation of the interplay between anticonvulsant lamotrigine, the potential risk of hepatotoxicity, and the crucial aspect of monitoring. The diagram encapsulates the dynamic relationship among these key concepts, offering a visual guide to enhance understanding and underscore the significance of vigilance in monitoring for optimal patient safety and therapeutic outcomes.

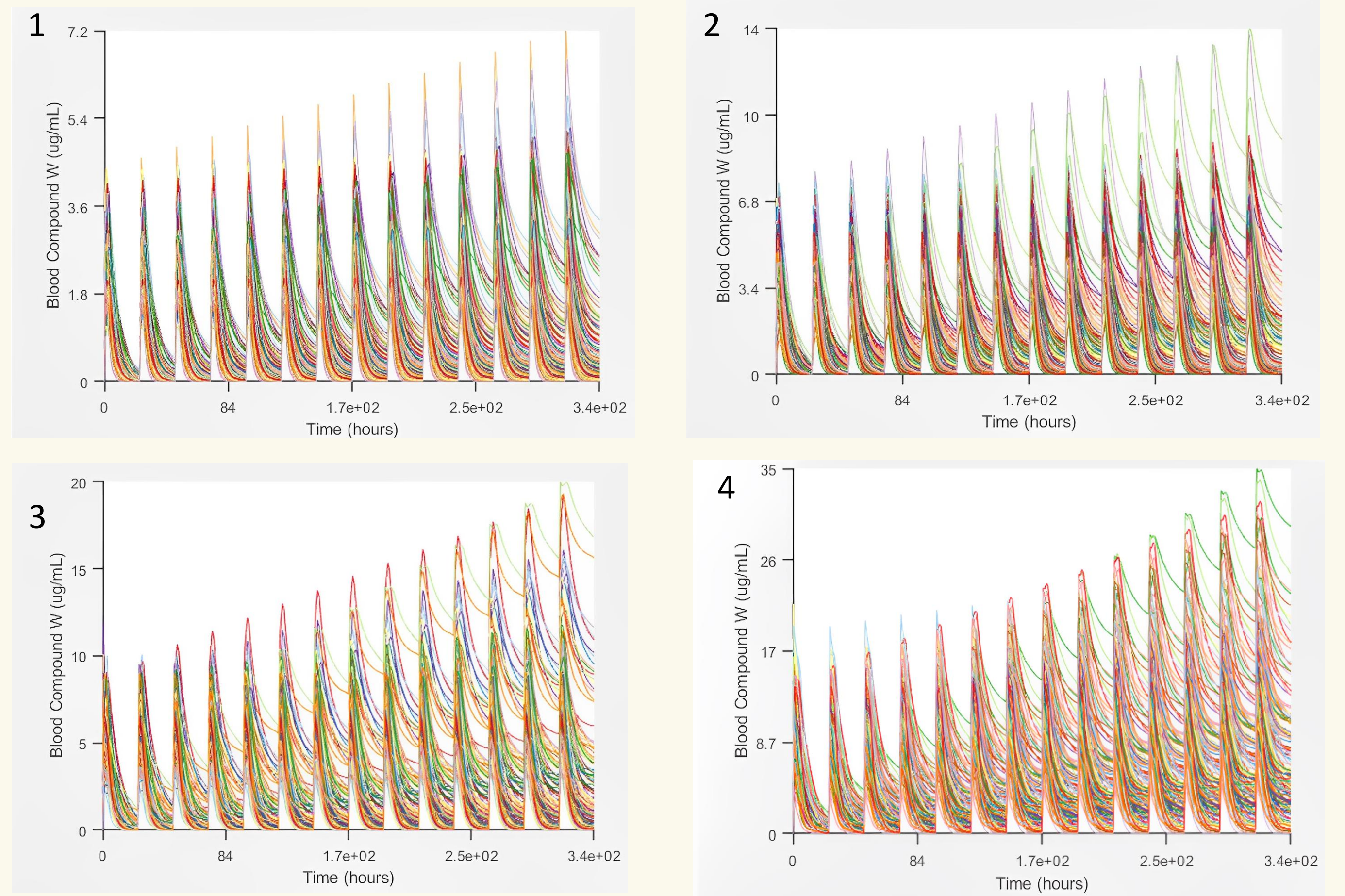


Figure 2. Plasma concentration profile of Lamotrigine in a 2-week regimen for different doses: (1)—200, (2)—400, (3)—600, and (4)—1200 mg.

DILIsym simulations demonstrated dose-dependent changes in plasma concentration profiles and highlighted the potential for drug-induced liver injury (DILI), particularly in specific populations like individuals with TD2 and NAFLD, emphasizing the importance of liver function monitoring (figure 3).

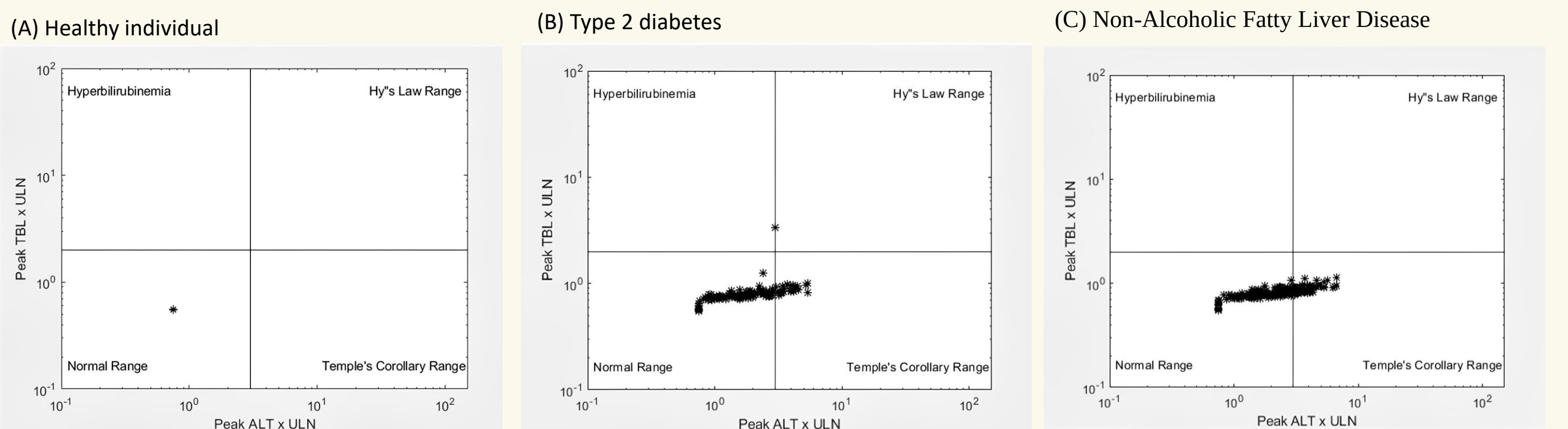


Figure 3. Graphical representation of the in silico results, to assess a drug’s liver safety profile (eDISH plot) for healthy individuals (A) and individuals with TD2 (B) and NAFLD (C)

However, none of the simulated individuals met the criteria for severe liver injury (Hy’s law), confirming the overall safety profile of lamotrigine [14]. The study's limitations include its retrospective nature, small sample size, and reliance on in silico simulations without real-world patient data validation for PBPK and DILIsym simulations. The results of this study have been published, for reference [15].

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