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Review | Обзор

Multi-Omics in Predicting Lamotrigine Neurotoxicity: Current Opportunities (Review)

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ABSTRACT

INTRODUCTION. Lamotrigine (LTG) is among the most commonly prescribed second-generation antiepileptic drugs due to its low teratogenic risk. However, LTG has pronounced neurotoxic, hepatotoxic, dermatotoxic potential (for genetic and metabolic causes) and in some cases can even cause multiple organ dysfunction syndrome. Understanding LTG mechanism can help personalise therapy and increase its safety, considering pharmacodynamics and pharmacometabolomics that determine its metabolism, transport, and elimination in a particular patient.

AIM. This study aimed to develop an approach to LTG therapy of epilepsy and other neurological and psychiatric diseases reducing neurotoxicity, with due regard to pharmacogenomics and pharmacometabolomics.

RESULTS. LTG is metabolised in the liver in two pathways: glucuronidation (major pathway) and P-oxidation (minor pathway). As a result, neutral and toxic (reactive) LTG metabolites are produced that can circulate in blood serum for a long time, penetrate the damaged blood-brain barrier in patients with therapy-resistant seizures and have a neurotoxic effect, triggering or maintaining neurotransmission disorders, impaired synaptic plasticity, neuronal apoptosis and other neurodegeneration mechanisms. An important role in LTG neurotoxicity belongs to transport proteins involved in the efflux (excretion) of reactive (toxic) metabolites from the brain into the systemic circulation, as well as from hepatocytes into the gastrointestinal tract by bile and through the kidneys with urine. Genetically determined delayed efflux through the blood-brain barrier (pharmacogenomics) increases LTG neurotoxic potential.

CONCLUSION. To assess the risk of LTG-induced adverse reactions, together with clinically assessing patient's condition, it is recommended to: 1) monitor drug distribution (blood, hair, saliva, breast milk); 2) analyse potentially toxic metabolites (blood, saliva, hair); 3) perform pharmacogenetic tests for non-functional polymorphisms of genes encoding key transport proteins and enzymes involved in LTG metabolism. Results of pharmacogenetic and pharmacometabolic tests applied in the clinical practice of an epileptologist will allow managing LTG neurotoxicity.

Keywords: lamotrigine; antiepileptic drug; lamotrigine metabolism; glucuronidation; P-oxidation; lamotrigine metabolites; pharmacogenetics; pharmacometabolomics; adverse drug reaction; neurotoxicity

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Мультиомические технологии в прогнозировании нейротоксичности ламотриджина: современные возможности (обзор)

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РЕЗЮМЕ

ВВЕДЕНИЕ. Ламотриджин (ЛТД) – один из наиболее часто назначаемых противоэпилептических препаратов второго поколения. Препарат имеет низкий тератогенный потенциал, однако обладает генетически и метаболически детерминированными нейротоксическим, гепатотоксическим, дерматотоксическим эффектами и в некоторых случаях может вызвать полиорганную недостаточность. Понимание механизмов действия ЛТД с учетом фармакогеномики и фармакометаболомики, определяющих особенности его метаболизма, транспорта и элиминации у конкретного пациента позволит обеспечить индивидуализацию терапии и повысить ее безопасность.
ЦЕЛЬ. Разработка подхода к терапии ламотриджином эпилепсии и других неврологических и психических заболеваний с учетом фармакогеномики и фармакометаболомики для снижения риска нейротоксичности препарата.
ОБСУЖДЕНИЕ. Метаболизм ЛТД осуществляется в печени глюкуронидацией (основной путь) и Р-окислением (второстепенный путь). В результате образуются как нейтральные, так и токсические (реактивные) метаболиты ЛТД, которые могут длительно циркулировать в крови, проникать через поврежденный гематоэнцефалический барьер у пациентов с терапевтически резистентными эпилептическими приступами и оказывать нейротоксический эффект, запуская или поддерживая механизмы нейродегенерации: нарушение нейротрансмиссии, синаптической пластичности, апоптоз нейронов. Большое значение в нейротоксичности ЛТД играют транспортные

белки, участвующие в эффлюксе (выведении) токсических метаболитов из головного мозга в системный кровоток, а также из гепатоцитов в желудочно-кишечный тракт с желчью и через почки с мочой. Генетически детерминированное замедление эффлюкса препарата через гематоэнцефалический барьер (фармакогеномика) повышает нейротоксический потенциал ЛТД.

ВЫВОДЫ. Для оценки риска ЛТД-индуцированных нежелательных реакций наряду с клинической оценкой состояния пациента целесообразно проводить: 1) терапевтический лекарственный мониторинг (кровь, волосы, слюна, грудное молоко); 2) анализ потенциально токсичных метаболитов (кровь, слюна, волосы); 3) фармакогенетическое тестирование носительства нефункциональных полиморфизмов генов, кодирующих ключевые белки-транспортеры и ферменты, участвующие в метаболизме ЛТД. Внедрение результатов фармакогенетического и фармакометаболического тестирования в клиническую практику эпилептолога позволит снизить риск нейротоксичности ЛТД.

Ключевые слова: ламотриджин; противоэпилептический препарат; метаболизм; глюкуронидация; Р-окисление; метаболиты ламотриджина; ламотриджин-N-оксид; ламотриджин-N-метил; фармакогенетика; фармакометаболомика; нежелательная реакция; нейротоксичность

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INTRODUCTION

Lamotrigine (LTG) is a second-generation antiepileptic drug (AED) and mood stabiliser. It is a derivative of phenyltriazine (3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine) used in adults and children over 12 years as a mono- and/or polytherapy for focal and generalised epileptic seizures, as well as in children over two years of age as a concomitant therapy for refractory focal epilepsy and Lennox-Gastaut syndrome [1–3]. LTG was the first drug after lithium to receive approval by the U.S. Food and Drug Administration (FDA) for maintenance treatment of type I bipolar disorder [3, 4]. Evidence suggests that LTG may be clinically effective in neuropathic pain and headaches[1] [5].

LTG is rapidly and almost completely absorbed after oral administration, with minimal first-pass metabolism in the liver and absolute bioavailability up to 98%. The LTG maximum plasma concentration occurs within 1.4 to 4.8 hours after oral intake and is directly proportional to the dose ranging from 50 to 400 mg (therapeutic plasma concentration varies from 4 to 10 μg/mL) [6]. Specificity of LTG pharmacokinetics and its low teratogenic potential results in its increased application and widespread prescription by neurologists and psychiatrists, including female patients of reproductive age [7, 8]. However, during pregnancy, LTG plasma concentration decreases on average by 68% [9], while the clearance increases by 300% compared to pre-pregnancy levels [10]. In pregnant women taking standard LTG doses, therapeutic efficiency in epilepsy or bipolar disorder decreases, creating life-threatening conditions for both the mother and the foetus [11].

Insufficient data on LTG pharmacokinetics during pregnancy impair the dose adjustment [12]. It was shown that in LTG, area under the curve (AUC) significantly decreases during pregnancy, thus the dose recommended in the first, second, and third trimester is 3-, 3-, and 5-fold higher, respectively, than the baseline dose taken before pregnancy. However, considering foetal safety, the maximum recommended single daily dose in the first, second, and third trimester should not exceed 400, 500, and 700 mg, respectively, while the total dose for twice-daily administration should be 300, 400, and 600 mg, respectively [13].

Recent studies have demonstrated that higher LTG doses entering the foetal bloodstream through the placenta or the newborn's bloodstream through the breast milk can lead to serious adverse drug reactions (ADRs) [14, 15]; some ADRs include foetal death, severe hyperbilirubinaemia with bilirubin-induced neurologic dysfunction, and even severe birth asphyxia (at LTG blood levels ≥4.87 mg/L in infants) [16].

An average LTG level in umbilical cord blood is approximately 60% of the maternal serum level at delivery [17]. The risk for both the mother taking

[1] Lamotrigine. https://go.drugbank.com/drugs/DB00555

LTG and the newborn significantly increases in the postpartum period, since the rate of LTG clearance returns to pre-pregnancy values within the first few weeks after delivery [7, 18]. According to Clark et al., LTG blood levels increase most dramatically in the first 1.5 weeks postpartum and then vary between 30% and 640% compared to the second and third trimester. The average LTG plasma concentration during the first 4 weeks postpartum is 154% to 402% higher than in the third trimester.

Pharmacokinetic studies of LTG levels in the blood of pregnant women, foetuses, newborns, and infants [19], as well as in breast milk [20] are essential for toxicity assessment and timely dose adjustment, while being difficult to implement in clinical practice. This review presents promising multi-omics (pharmacogenomic and pharmacometabolomic) methods for precise and safe LTG prescription [21].

The aim of the study is to develop an approach to lamotrigine therapy of epilepsy and other neurological and psychiatric diseases reducing neurotoxicity, with due regard to pharmacogenomics and pharmacometabolomics.

The bibliographic research was performed between March 2010 and March 2025 *(Figure 1)* according to PRISMA 2020[2] guidelines in bibliographic databases using inclusion/exclusion criteria, keywords, and their combinations in the Russian and English language *(Table 1)*. Following the exclusion of duplicate publications and negative studies, 35 out of 134 publications meeting the stated objectives and search criteria were included in this review.

MAIN PART

Transport proteins

The role of ATP-binding cassette (ABC) transporter superfamily in the LTG efflux (transport from the brain into the bloodstream) involves contradictory data, particularly for P-glycoprotein (P-gp) encoded by *ABCB1* gene (*MDR1*) [6] and breast cancer resistance protein encoded by gene member 2 of the ATP-binding cassette sub-family G (ATP-binding cassette sub-family G member 2, *ABCG2*; breast cancer resistance protein). Polymorphisms in genes encoding this transporter protein may significantly affect LTG pharmacokinetics and bioavailability [22].

LTG has been identified as a substrate for two main efflux transport proteins through the blood-brain barrier (BBB) – P-glycoprotein (P-gp) and ABCG2 – that play a synergistic or cooperative role in the efflux of dual substrates [23]. These transporter proteins may strongly influence the variable CNS response to LTG, particularly in epileptic patients who overexpress both transporters. Moreover, polymorphisms in *ABCC2* (*MRP2*) gene encoding canalicular multispecific organic anion transporter (multidrug resistance-associated protein 2, MRP2) are associated with drug resistance in different populations; this indicates the transporter involvement in LTG efflux [24]. ABCC3 (MRP3) protein is located on the hepatic sinusoid wall separating the cytosol from the bloodstream and transports LTG glucuronides from the liver cells into the circulation for further renal elimination [25].

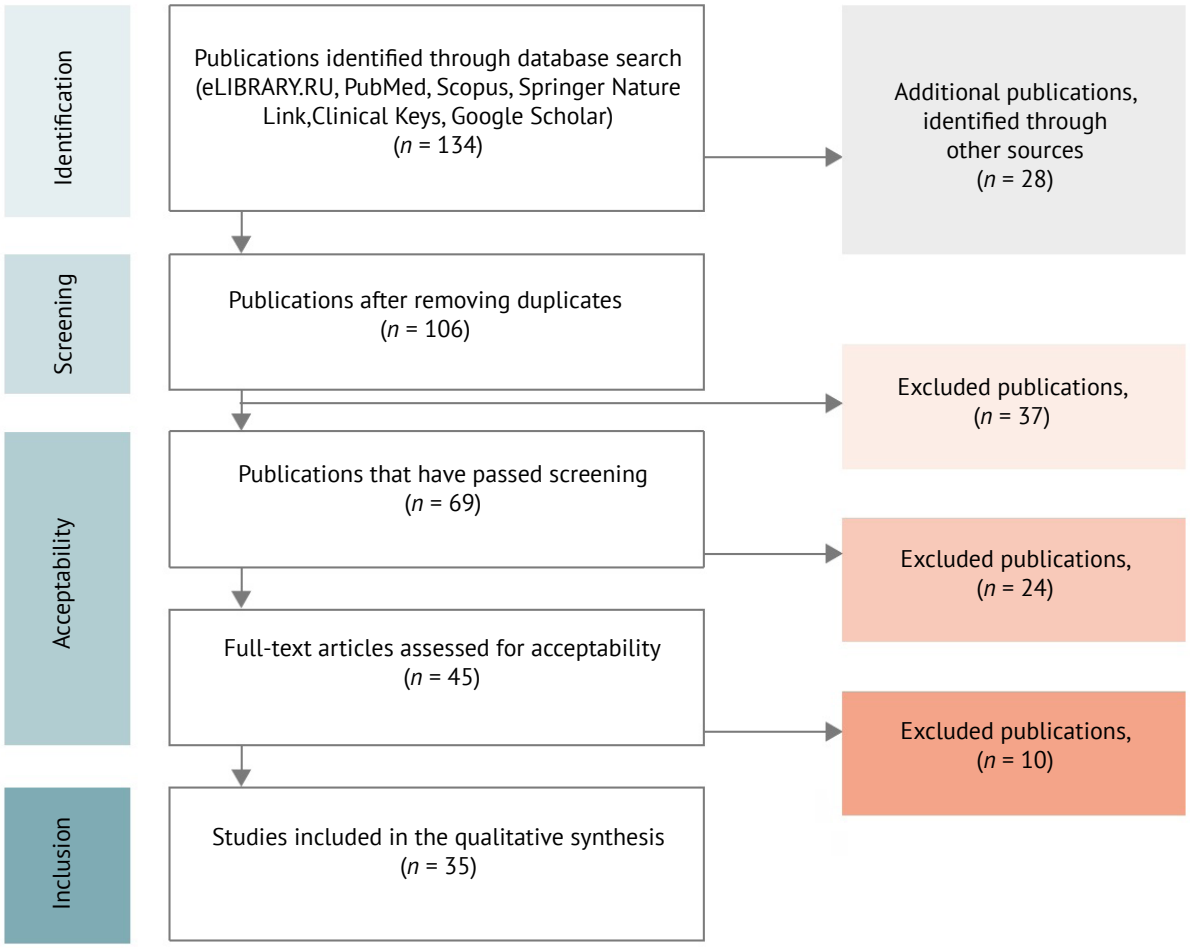
The mechanism allowing LTG to cross the BBB is not entirely clear; however, the role of organic cation transporters (OCT) in LTG transport has been identified. Specifically, LTG is a substrate for the transporter protein SLC22A1, also known as OCT1 [27].

Receptors

LTG shows affinity to several types of receptors expressed in the brain. It produces weak inhibition of serotonin receptors (5-HT2 and 5-HT3), weak binding to adenosine A1/A2 receptors, adrenergic receptors (α1/α2/β), dopamine 1 and 2 receptors (D1/D2), gamma-aminobutyric acid (GABA) A/B receptors, histamine H1 receptors, κ-opioid receptors (KOR), and muscarinic acetylcholine receptors (mACh). LTG also exerts a weak inhibitory effect on sigma-opioid receptors[3]. However, the leading hypothesis for the LTG anticonvulsant effect is its binding to voltage-gated sodium channels [28], heteromeric complexes regulating sodium exchange in the intra- and extracellular space between neurons.

LTG is believed to selectively inhibit voltage-gated sodium channels type 2 (VGSC) [29] by stabilising the neuronal membrane and thereby inhibiting presynaptic release of excitatory neurotransmitters (glutamate and aspartate). Sodium channel alpha subunits in the human brain have four major isoforms: SCN1A, SCN2A, SCN3A, and SCN8A [29, 30]. At rest, a sodium channel pore is closed. When neuronal membranes containing VGSC are sufficiently depolarised during an action potential, the protein changes its structure, causing the pore to open. Within milliseconds after opening, inac-

[2] https://www.prisma-statement.org/prisma-2020
[3] Lamotrigine. https://go.drugbank.com/drugs/DB00555



The figure was prepared by the authors using their own data

Fig. 1. PRISMA flowchart showing the number of publications selected for a review

tivation begins that blocks ion flow through the channel. At this point, the channel is considered deactivated. LTG binds to inactivated VGSC, thus acting as an antagonist [28].

LTG may also interact with N-, P-, and Q-type voltage-gated calcium channels (VGCC) encoded by the *CACN* gene, which makes LTG a broad-spectrum medicinal product. VGCCs are structurally similar to VGSCs but lack the intracellular inactivation loop typical for VGSCs. LTG inhibits Cav2.3 (R-type) calcium currents, which may represent one of its antiepileptic mechanisms [31].

Although LTG is not considered to directly target GABAergic receptors, they are the primary CNS inhibitory receptors; heterogeneity of GABA ionotropic receptors is linked to epileptogenesis [32]. Glutamate is an excitatory neurotransmitter playing an important role in epileptogenesis. Increased glutamate levels are associated with seizure initiation [33]. LTG reduces glutamate levels in the brain by inhibiting its overexcitation, which also explains LTG antiepileptic and mood-stabilising effects [33, 34].

Pharmacometabolomics and pharmacogenomics

The primary LTG metabolic pathway is glucuronidation catalysed predominantly by enzymes of the uridine 5'-diphospho-glucuronosyltransferase (UGT) system, specifically UGT1A4 and UGT2B7 [35, 36]; other involved UGT enzymes are UGT1A3, UGT2B15, UGT1A42, and UGT2B72 [36–38]. These UGT enzymes play a significant role in the interindividual variability of LTG metabolism.

LTG undergoes glucuronidation to form the following metabolites: LTG-2-N-glucuronide (main metabolite, pharmacologically inactive), LTG-5-N-glucuronide, LTG-2-N-methyl, and other minor compounds[4] [28, 39]. LTG-2-N-glucuronide

[4] Lamotrigine. https://go.drugbank.com/drugs/DB00555

Table 1. Inclusion and exclusion criteria of publications in the review

Parameters	Inclusion criteria	Exclusion criteria
Publication type	Full-text versions: original articles, clinical cases, systematic reviews, meta-analyses, and Cochrane reviews	Abstracts, conference materials, posters, and dissertations
Access to publication	Access to the full version	No access to the full version
Publication language	English, Russian	Other languages
Databases	eLIBRARY.RU, PubMed, Scopus, Springer Nature Link, Clinical Keys, Google Scholar	Other languages
Internet resource	State Register of Medicinal Products, U.S. Food and Drug Administration, DrugBank, PharmGKB, Online Mendelian Inheritance in Man, Human Metabolome Database, PubChem	Other online resources
Search depth	2010–2025 (15 years)	Until March 2010
Keywords	Lamotrigine; antiepileptic drug; lamotrigine metabolism; glucuronidation; P-oxidation; metabolites; pharmacogenetics; pharmacometabolomics; adverse drug reaction; neurotoxicity	Not applicable

The table was prepared by the authors using their own data

is a primary metabolite of UGT1A4 enzyme [12]. Valproic acid is known to inhibit LTG metabolism in the liver by increasing its half-life linearly (24 to about 72 hours) alongside with the dose [28]. The increased plasma concentration-to-dose ratio (C/D ratio) results from competitive inhibition of UGT1A4 or UGT2B7 enzymes by valproates [38] (valproic acid has a higher affinity for UGT2B7 and is also a substrate for UGT1A4 [39]), an important consideration in polytherapy.

Two promoter polymorphisms (rs3732218 –163G>A and rs373221 –219C>T) in the *UGT1A4* gene are associated with a 40–50% reduction in UGT1A4 enzyme activity and an increased risk of toxic LTG blood concentrations at average therapeutic doses [40]. The 142T>G polymorphism (rs2011425) in the coding region of the *UGT1A4* gene is linked to increased LTG blood concentrations and decreased clearance in patients with homozygous TT genotype compared to GT and GG genotypes [38, 41]. The rs2011425 polymorphism (UGT1A4*3) of the *UGT1A4* gene was associated with reduced concentration-to-dose (C/D) ratios during pregnancy [42]. Patients with the homozygous rs2011425 GG genotype (extensive or normal metabolisers) exhibit higher glucuronidation activity compared to those with the TT genotype (slow metabolisers) [43]. The rs6755571 polymorphism in the *UGT1A4* gene (70C>A) is associated with higher LTG blood concentrations and lower clearance, even during pregnancy [41, 42]. The rare rs34946978 polymorphism (more common in East Asians than Caucasians or Africans) is linked to a marked reduction in LTG glucuronidation activity. The impact of various haplotypes on LTG pharmacokinetics remains insufficiently studied.

The minor (rare) homozygous TT genotype of the rs7668258 polymorphism (–161C>T) in the *UGT2B7* gene is associated with an increased LTG C/D ratio compared to patients with the major (common) CC genotype [45]. Patients with the TT and CT genotypes have an average LTG clearance about 18% lower than those with the CC genotype [46]. A study of the –372A>G polymorphism in the *UGT2B7* gene showed that LTG clearance was 247% higher in the major homozygous GG genotype compared to the minor AA genotype [47]. A clinical case has been reported linking the –372A>G polymorphism of *UGT2B7* with dermatotoxicity and multiple organ dysfunction syndrome [48]. The rs7439366 polymorphism (802C>T) of *UGT2B7* is also associated with a decreased LTG C/D ratio in pregnant women [41].

Patients with the major homozygous CC genotype of the rs6755571 polymorphism (70 C>T) in the *UGT1A4* gene (normal metabolisers) showed a 22% decrease in LTG concentration compared to the heterozygous CT genotype (intermediate

metabolisers) [36]. Serum LTG level in patients with the minor homozygous TT rs7668258 (–161 C>T) genotype of the *UGT2B7* gene (slow metabolisers) was 1.2 times higher than in patients homozygous for the C allele (normal metabolisers) [36, 37].

The *UGT2B15*2* polymorphism that causes a G>T substitution in the *UGT2B15* gene and results in an amino acid change from aspartic acid (D) to tyrosine (Y) at position 85 of UGT2B15 enzyme is present in about 50% of the Caucasian population and to a lesser extent in Hispanic, African American, Chinese, Japanese, and Korean populations (allele frequencies range from 36% to 49%). This polymorphism is associated with significantly reduced LTG glucuronidation and may be a clinically important predictor of interindividual variability in LTG clearance. Patients with the homozygous TT genotype had LTG serum levels 18% higher than those with GG homozygous genotype [36]. Moreover, concomitant use of other products that inhibit UGT2B15, particularly valproate, may further affect LTG plasma level and clearance and potentially cause LTG toxicity, especially in pregnant women (second and third trimester), neonates, and infants [7]. The role of polymorphisms in the *UGT1A3* gene that can potentially influence LTG glucuronidation still remains unclear [37, 38], partly due to conflicting data on the role of the isoenzyme encoded by this gene in the formation of the main active LTG-2-N-glucuronide metabolite [49].

To a lesser extent LTG metabolism involves the liver cytochrome P450 system. According to L. Liu et al. [50], isoenzymes CYP2A6 and CYP2D6 are responsible for accumulating LTG oxidation products. CYP2A6 appears to be the main enzyme activating LTG in human liver microsomes [51]. Further formation of active LTG metabolites occurs in keratinocytes [28]. However, these results are inconclusive, since no additional studies have demonstrated LTG metabolism through the liver cytochrome P450 system.

Although PubChem database covers LTG metabolites, their biogenesis and physiological significance are insufficiently studied. This warrants an additional research aimed at understanding their metabolism and the potential roles in cellular and molecular processes.

Transport and excretion

ABCB1 and ABCG2 transporter proteins play a key role in LTG transport across the BBB [52]. This suggests that polymorphisms in the genes encoding these transporter proteins are associated with functional variations in LTG efflux through the BBB and may contribute to interindividual differences in therapeutic resistance and LTG neurotoxicity [28].

Polymorphisms rs1128503 (1236C>T), rs2032582 (2677G>T/A), and rs1045642 (3435C>T) in the *ABCB1* gene impact LTG transport and blood concentration: carriers of the haplotype 1236C-2677G-3435C have higher LTG serum concentrations compared to carriers of the haplotype 1236T-2677G-3435T, followed by haplotype 1236T-2677T-3435C [21].

Polymorphisms rs2231142 and rs3114020 of the *ABCG2* gene are associated with serum LTG concentration normalised to body weight [21, 23]. A study on the rs2231142 (421C>A) polymorphism of *ABCG2* showed that homozygous carriers of the minor AA genotype receiving LTG monotherapy had lower minimum LTG blood concentrations than homozygous carriers of the major CC genotype [53]. Moreover, this polymorphism accounted for 4.8% of the variability in LTG serum fluctuations among Chinese epileptic patients [54].

The rs717620 (–24C>T) polymorphism in the *ABCC2* gene is associated with LTG resistance and the risk of neurotoxicity in Caucasians and Asians, likely due to compensatory activation of the ABCB1 transporter [55]. In Chinese epileptic patients carrying the *ABCC2* –24C>T / 1249G>A / 3972C>T haplotype, there is a high risk of LTG resistance [55]. However, the –24C>T polymorphism in the *ABCC2* gene was not linked to LTG resistance in epileptic patients of other races and ethnic groups, including Han Chinese, Croats, and Austrians [28].

LTG plasma concentration and the rs628031 (1A>G) polymorphism in the *SLC22A1* gene that encodes efflux transporter SLC22A1 were shown to be linked. Patients with the minor homozygous GG genotype had significantly lower LTG plasma concentrations compared to the major homozygous AA genotype, indicating association of this polymorphism with slowed efflux of the product from the brain into the blood [54].

ABCC3 and ABCC4 (also known as MRP4) proteins are responsible for transporting LTG metabolites from the liver into the bloodstream[5]. About 80% of LTG glucuronides are excreted in the urine (primary elimination route), including LTG [-2-N-glucuronide] (main metabolite, 80–90%), LTG [-5-N-glucuronide], LTG [-N-oxide], and LTG [-N-methyl] *(Table 2)*.

[5] Lamotrigine. https://go.drugbank.com/drugs/DB00555

Table 2. Major lamotrigine metabolites

Metabolite	HMDB[6]	PubChem CID[7]	Detected in	Metabolite toxicity
Glucuronidation				
LTG-2-N-glucuronide	0061103	164342	Blood, urine, bile	Inactive (non-toxic/neutral)
LTG-5-N-glucuronide	–	71236569	Blood	Inactive (non-toxic/neutral)
N-glucuronide	–	–	Blood, urine, bile	Inactive (non-toxic/neutral)
P-oxidation				
LTG arene oxide	–	PA166170365[8]	Bile	Active (potentially toxic)
LTG-N-oxide	–	15089895	Urine, bile	Active (potentially toxic)
Methylation				
LTG-N-methyl	–	91810661	Urine, bile	Active (potentially toxic)

The table was prepared by the authors

Note. –, data not available.

Non-functional polymorphisms in *ABCC3* are very rare (maximum 4.7%), and their prevalence shows interethnic differences. However, the minor A allele of the −1767G>A polymorphism in the *ABCC3* gene is associated with a significantly decreased expression of the ABCC3 transporter protein in the human liver [56]; this may slow down the transport of LTG metabolites from hepatocytes into the blood.

ABCC4 (MRP4) transporter encoded by the *ABCC4* gene is expressed in multiple organs and can modify the effect of LTG or its metabolites on cells with various outcomes. ABCC4 is located on the basolateral membrane of the choroid plexus epithelium and on the luminal side of brain capillaries [57], which prevents many xenobiotics, including LTG, from rapidly entering the brain by effluxing them from blood capillaries into plasma. ABCC4 is also found on the basolateral membrane of human hepatocytes [58]. Only a few comprehensive studies (mainly *in vitro*) have been conducted regarding the influence of ABCC4 liver expression on drug pharmacokinetics, including LTG; thus its role warrants further investigation [59].

According to dbSNP[9], 30,185 polymorphisms have been registered for ABCC4; of them, two-thirds are located in intronic sequences. Some of these have direct or indirect clinical significance. ABCC4 is also localised on the apical membrane of renal proximal tubules. Polymorphisms rs1751034 and rs3742106 in the *ABCC4* gene play an important role in LTG elimination in the urine, being associated with an increased risk of kidney disease [60]; this can cause higher LTG plasma concentrations and an increased ADR risk including neurotoxicity and hepatotoxicity.

An additional elimination pathway for LTG glucuronides is their excretion from hepatocytes into bile by ABCC2 transporter (also known as MRP2)[10]. Data on genes encoding key enzymes involved in LTG metabolism and transport are summarised in *Table 3*, *Table 4*, and *Figure 2*.

Toxicity

The main LTG metabolites resulting from glucuronidation *(Table 2)* are inactive (neutral) and excreted by the kidneys [61]. However, some studies demonstrate that increased LTG glucuronides in the urine correlate with a higher level of its active metabolites in blood plasma. Examination of LTG glucuronides in urine samples is a non-invasive and promising strategy for safety assessment of LTG therapy that can be implemented using gas chromatography-mass spectrometry or micellar electrokinetic capillary chromatography [61].

Increased blood levels of active LTG metabolites resulting from P-oxidation *(Table 2)* are associated with neurotoxic, dermatotoxic, hepatotoxic, and cardiotoxic ADRs [28]. However, the exact production mechanism and the toxicity of these

[6] Human Metabolome Database. https://hmdb.ca/
[7] https://pubchem.ncbi.nlm.nih.gov/
[8] https://www.pharmgkb.org/chemical/PA166170365
[9] https://www.ncbi.nlm.nih.gov/snp/
[10] Lamotrigine. https://go.drugbank.com/drugs/DB00555

Table 3. Genes encoding key enzymes of lamotrigine metabolism

Gene	Chromosome location	Online Mendelian Inheritance in Men[11]	Enzyme	Organs with the highest expression
UGT1A4	2q37.1	606429	UGT1A4	Liver
UGT2B7	4q13.2	600068	UGT2B7	Liver
UGT1A3	2q37.1	606428	UGT1A3	Liver, intestine
CYP2A6	19q13.2	122720	CYP2A6	Liver
CYP2D6	22q13.2	608902	CYP2D6	Liver

The table was adapted by the authors from [12]

Table 4. Key transporter proteins of lamotrigine and its metabolites

Gene	Chromosome location	Online Mendelian Inheritance in Men[12]	Protein	Organs with the highest expression	Pathway
ABCC3	17q21.33	604323	ABCC3	Liver, intestines, kidneys	To the blood
ABCC4	13q32.1	605250	ABCC4 (MRP4)	Liver, kidneys, intestines, brain	To the blood
ABCC2	10q24.2	601107	ABCC2 (MRP2)	Liver	To the bile
ABCB1	7q21.12	171050	ABCB1 (P-gp)	Intestines, kidneys, blood-brain barrier, and placenta	Undifferentiated pathway
SLC22A1	6q25.3	602607	SLC22A1	Liver	

The table was prepared by the authors

metabolites based on their levels in the blood, brain (LTG target organ), and other tissues warrant a further study.

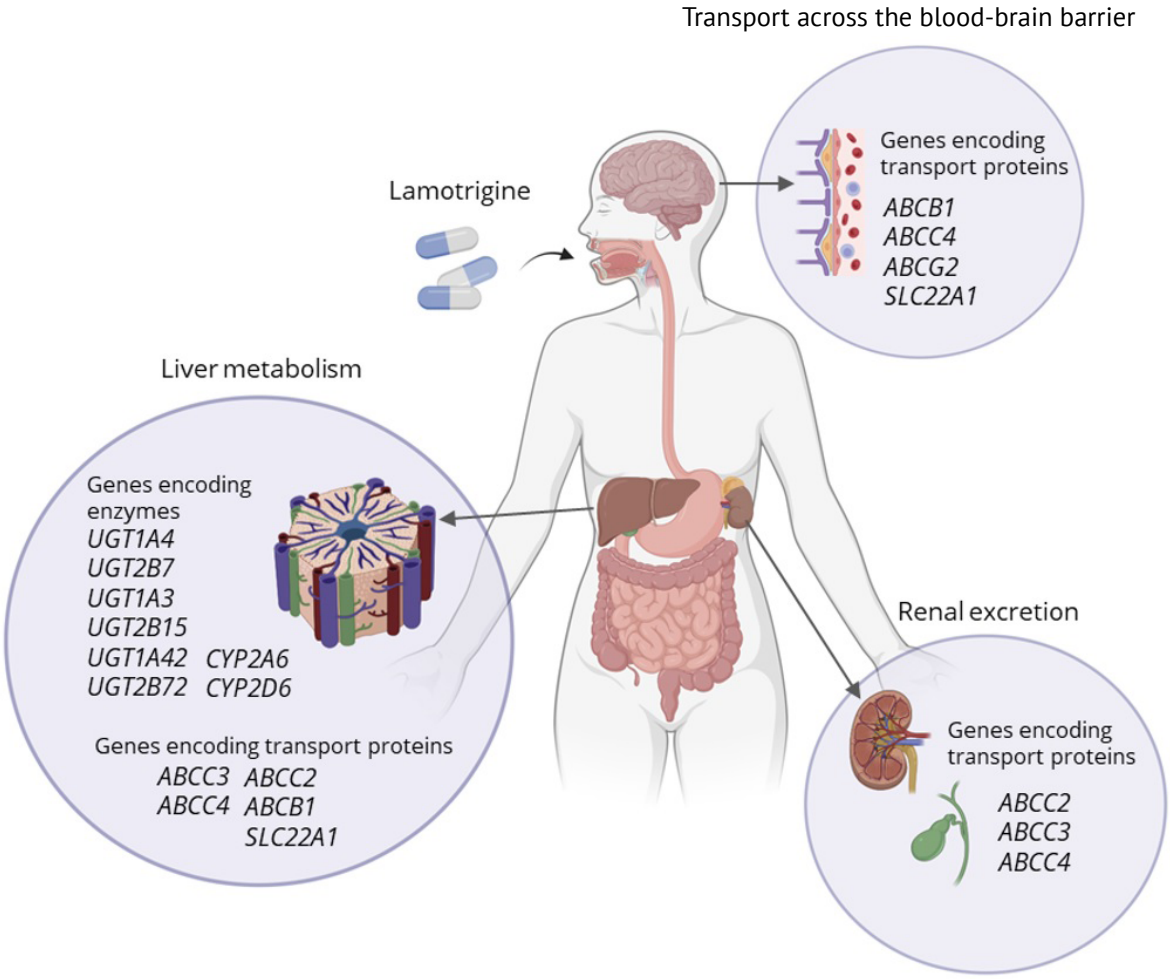
LTG neurotoxicity is rare and manifests itself as ataxia [62], dizziness, and diplopia, especially in newborns, infants [63], women of reproductive age [7], and older patients [64]. However, this ADR can lead to more severe problems including epileptic seizures (even in individuals without a history of seizures) [65–68]; optic neuritis with a sudden loss of vision; altered state of consciousness (Glasgow coma scale ⩽8); severe arterial hypotension; torsade de pointes ventricular tachycardia; and cardiac arrest (fatal cases reported for LTG 4 g and 7.5 g) [68]. LTG neurotoxicity also depends on an individual genotype, including polymorphisms in genes encoding key metabolic enzymes and transporter proteins involved in LTG efflux from the brain into blood (phenotypes: slow and intermediate metabolisers and/or slow and intermediate transporters) [66]. These genetically determined interindividual differences in LTG serum and brain levels may be critical for neurotoxic ADRs, since delayed BBB clearance may cause accumulation of toxic LTG metabolites in the brain during long-term high-dose therapy, as well as in postpartum women with breastfed infants [7].

Overall, a personalised multi-omics approach (pharmacogenomics + pharmacometabolomics) to LTG therapy reflects current clinical and laboratory diagnostic trends in neurology and psychiatry [66, 69]. The risk of neurotoxicity is higher in patients who are slow metabolisers and/or slow transporters (homozygous carriers of non-functional polymorphisms in the genes of LTG glucuronidation and/or P-oxidation isoenzymes (*Table 3*) and/or genes encoding key LTG transporter proteins (*Table 4*), respectively) compared to normal metabolisers and normal transporters (homozygous carriers of fully functional polymorphisms in genes encoding key LTG isoenzymes and transporter proteins, respectively). However, the prevalence of these phenotypes among patients taking LTG is unknown, since studies using the multi-omics approach are not yet available.

Evaluation of LTG metabolism and efflux in clinical practice

To assess the risk of LTG-induced ADRs, a clinical evaluation of the patient's condition [70] is recommended, alongside with 1) therapeutic drug

[11] Online Mendelian Inheritance in Man®. https://www.omim.org/
[12] Ibid.



The figure was prepared by the authors

Fig. 2. Genes responsible for lamotrigine metabolism and transport in the human body

monitoring (TDM) of LTG (blood, hair, saliva, breast milk) [70]; 2) assay of active (potentially toxic) LTG metabolites in biological samples (blood, saliva, hair) using gas-liquid chromatography; 3) pharmacogenetic testing (PGx) of carriers of non-functional polymorphisms in genes encoding key transporter proteins and enzymes involved in LTG metabolism [66, 71].

TDM ensures optimal LTG dose adjustment. Minimally invasive sample collection strategies for TDM (dried blood spot [70] or plasma [72], saliva, or hair [73, 74]) are promising for wide clinical adoption, allowing self-sampling, room temperature storage and transport. In certain clinical conditions (pregnancy, neonatal period, ageing, resistance, and toxicity), measuring LTG and active metabolites in plasma is reliable and sufficient. However, liquid chromatography-tandem mass spectrometry of blood, saliva, and hair is promising for safety monitoring and early toxicity diagnosis. LTG hair analysis can also be used to assess medication history and long-term adherence of a patient. LTG saliva and plasma concentrations correlate strongly (r=0.82, p<0.001); LTG hair concentration correlates with plasma concentrations (r=0.53, p<0.001) and daily dose (r=0.23, p=0.024) [74].

Predictive (pre-reactive) PGx will help assess the risk of LTG and its active metabolites increasing to toxic levels in order to exclude homozygous (primarily) or heterozygous non-functional polymorphisms in genes responsible for its metabolism and transport [66, 71, 75, 76]. For slow and intermediate metabolisers and/or transporters, it is recommended to avoid LTG prescription or reduce the average daily dose by 50% and 25%, respectively; to conduct TDM once every 3 and 6 months, respectively. If technically feasible, measurement of active LTG metabolites in biological fluids (plasma or serum, saliva, urine) is important. In case of potentially life-threatening toxicity symptoms, extra-

corporeal LTG elimination (haemodialysis, plasmapheresis) may be considered [77, 78].

CONCLUSIONS

The analysed pharmacogenomic and pharmacometabolic data on LTG metabolism, transport, and elimination show that the main active (potentially toxic) metabolites are LTG-N-oxide and LTG-N-methyl; their high blood and brain (target organ) concentrations can cause neurotoxicity. The high-risk group includes newborns and infants, pregnant women, older population, and patients with unfavourable pharmacogenetic profiles (intermediate and poor metabolisers) who are heterozygous and homozygous carriers of non-functional polymorphisms in genes encoding key glucuronidation enzymes (UGT1A4, UGT2B7, UGT1A3) and, to a lesser extent, P-oxidation (CYP2D6, CYP2A6) of LTG.

Reduced LTG efflux transport from brain to blood in patients with unfavourable pharmacogenetic transporter profiles (intermediate transporters and poor transporters - heterozygous and homozygous carriers of non-functional polymorphisms in genes encoding key LTG transporter proteins ABCC3, ABCC4, ABCC2, ABCB1, and SLC22A1) also significantly contributes to increased risk of severe LTG-induced neurotoxic ADRs.

The above approach using pharmacogenomic and pharmacometabolic data will enable a more accurate prediction of individual responses to LTG and reduce the risk of toxic ADRs. Advanced multi-omics technologies and artificial intelligence may facilitate the implementation of multi-omics phenotyping in real clinical practice, considering such factors as pharmacogenomics, pharmaco-metabolomics, environmental factors, comorbidities, and patient lifestyle for personalising psychopharmacotherapy.

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