Monitoring of Second-generation Antiseizure Medications in Epilepsy: Appendices

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Appendix I: Epidemiology and economic impact

Epidemiology

Approximately 1% of the U.S. population is estimated to have some form of epilepsy, including ~456,000 children and ~2.9 million adults.[1] Up to 70% of affected individuals could live seizure-free with proper diagnosis and treatment. However, the fact that nearly 80% of all those affected live in low or middle-income countries poses a significant impediment to diagnosis and care.[2,3]

Global incidence indicates that ~5 million new cases of epilepsy are diagnosed annually. However, rates differ significantly between high- and low-to-middle income countries. Whereas the incidence rate is ~49/100,000 diagnosed per year, in low- and middle-income countries this rate may be as high as 139/100,000 due to underlying factors resulting in brain injury underpinning epilepsy, including increased incidence of infectious diseases such as malaria or cysticercosis, birth-related injuries, increased risk of traumatic brain injuries, and poorer access to medical care in general.

Incidence also varies dependent on etiology. Per data from the Global Burden of Disease Study and analyzed by Zhang et al., the age-standardized incidence rate (ASIR) of idiopathic epilepsy (i.e., epilepsy of uncertain or genetic origin) was 38.82 cases/100,000 population in 2019, representing an overall increase of 55.86% from 1990 when the ASIR was 33.22/100,000. Incidence tends to be bimodal, with the majority of new cases emerging in the young (ages 15–19 in this study) and the elderly. Incidence for 15–19 year olds increased from ~33.5/100,000 in 1990 to ~39.5/100,000 in 2020 and is anticipated to rise to ~45/100,000 by 2035.

By far the largest increase in ASIR is anticipated for those over 90 years of age, increasing from ~49.5/100,000 in 2020 to 52/100,000 by 2035, while the second-greatest increase will be observed in those between the ages of 85 and 90, increasing from ~42.5/100,000 in 2020 to 47.5/100,000 by 2035.[4]

Economic impact

Epilepsy accounts for more than 0.5% of the global burden of disease.[2] In 2019, the total (global) number of disability life years (DALYs) attributed to idiopathic epilepsy was 13,077,624 with the greatest impact in terms of DALYs observed in the lowest sociodemographic index (SDI) countries (246.92/100,000 population) and low-middle SDI regions (213.08/100,000). There is also some disparity in DALYs between high-income nations with high-income countries of Asia Pacific recording 79.58 DALYs/100,000, while 95.22/100,000 DALYs were documented in North America.[4]

According to the cost analysis derived by Begley et al. using prevalence data included in the 2019 GBD collaboration study, the average annual cost per person with epilepsy was $4,467, ranging from an average of $204 for low and lower-middle income countries to $11,432 for upper-middle- and high-income countries (in 2019 US dollars, as classified by the World Bank income category). This equates to a global annual cost of $119.27 billion using a prevalence estimate of 52.51 million afflicted individuals and adjusting for SDI and country-associated treatment gaps. These estimates primarily capture the annual costs associated with direct healthcare/person (mean = $1,687), as well as annual indirect costs/person (mean = $2,780), including lost wages, excess unemployment, reduced work productivity and premature mortality for both patients and caregivers.

The majority of costs (83%) are borne by high-income countries where access to treatment is greatest and wages and incomes are generally higher than in low- and lower-middle SDI countries. This illustrates that the majority of costs are incurred by and benefit only ~15% of the total epilepsy population. The highest annual per person and total direct healthcare costs are incurred across eight countries in Australasia, South Asia, and North America (mean/person = $4,666; total = $28 billion), while the lowest mean direct per person costs are incurred by five South Asian countries ($146/person, $909 million, total) and 46 Sub-Saharan African countries ($446/person, $4 billion).[5]

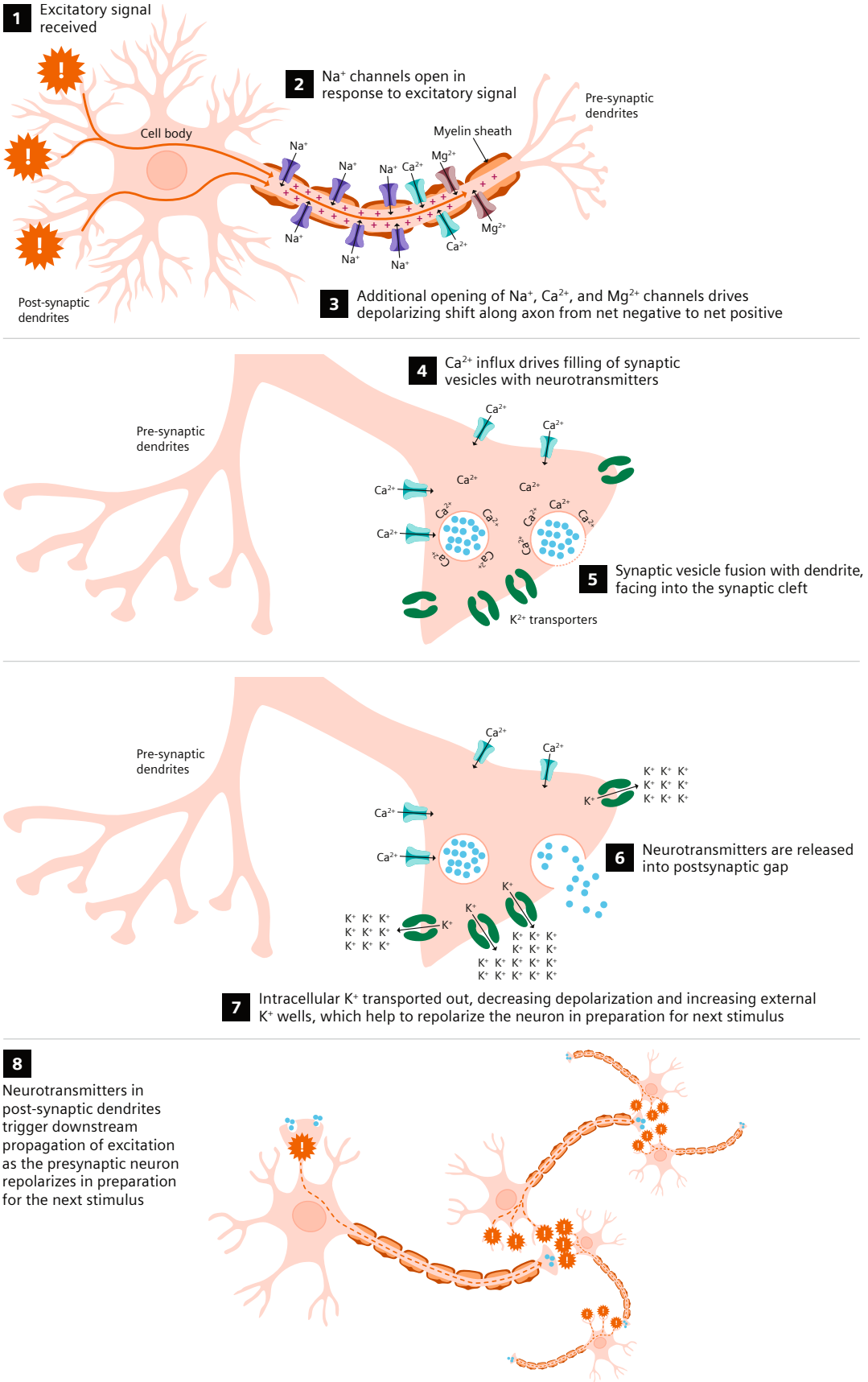
Appendix II: Normal/abnormal nerve function and triggering events

Normal nerve function[6]

The brain is composed of highly organized neurons. These are specialized cells comprised of a primary cell body with a variable number of extensions on one end (the dendrites) needed to receive signals from other cells and a single elongated axon on the other end that delivers signals to other cells. Neurons function by regulating the flow of cationic and anionic electrolytes—sodium (Na^+), potassium (K^+), magnesium (Mg^{2+}) and chloride (Cl^-)—through their respective transmembrane channels in response to stimulatory signals received via the neuron's dendrites, resulting in the following chain of events (Figure 1):

1. Excitatory signaling triggers the opening of Na^+ gated channels, allowing influx of Na^+ and causing a shift toward a more positively charged environment (depolarization).
2. Depolarization propagates down the axon length to its terminus through the opening of calcium (Ca^{2+}) and Mg^{2+} voltage-gated channels, triggering the membrane fusion and release of vesicles containing cell-specific neurotransmitters. K^+ channels also open and pump K^+ out of the neuron, further increasing the intracellular positive charges and creating a well of K^+ at the synaptic cleft.
3. Neurotransmitters released at the presynaptic cleft of a neuron can be excitatory (i.e., glutamate: an amino acid produced, released, and recycled by adjacent astrocytes) or inhibitory (e.g., γ-aminobutyric acid [GABA]: one of the major inhibitory neurotransmitters in the brain known to be associated with epilepsy).[7]
4. Glutamate crosses the synaptic cleft where it triggers ongoing propagation to downstream neurons by binding to a variety of receptors on the postsynaptic dendrites, principally the N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and Kainate receptors.
5. Meanwhile, the presynaptic axon hyperpolarizes, generating a short refractory period as the normal resting membrane potential is restored in preparation of the next triggering event through K^+ voltage-gated channels, while GABA-controlled receptors enable the influx of Cl^-, closing the Na^+, Mg^{2+}, and Ca^{2+} channels. Excess K^+ in the extracellular milieu diffuses back into cells in response to Cl^- migration.

Figure 1. Signal transmission along neural pathways.



Seizure initiation and propagation[6]

Seizures are the result of uncontrolled, hypersynchronus excitatory firing of a cluster of neurons concurrent with reduced control by inhibitory neurons or neurotransmitters. This process occurs in three steps:

1. Increased excitatory activity arises due to excess availability of glutamate by one or more types of the postsynaptic glutamate receptors, driving multiple, rapid depolarizations of a neuron. This is known as the paroxysmal depolarization shift (PDS). The PDS occurs when a "short circuit" arises due to dysfunction of adjacent astrocytes, both because they fail to take up and recycle glutamate released across the synaptic cleft, and because they also synthesize and release glutamate directly into the synaptic cleft in place of the release of glutamate via the normal action potential and vesicle binding sequence.
2. Multiple recurrent PDSs to a neuron drives more and more K^+ out of it and into the synaptic cleft, increasing the extracellular K^+ concentration. The increased concentration "pre-primes" adjacent neurons to a partially depolarized state, such that they are always ready to fire. This step is critical to recruiting additional neurons and propagating seizure activity to a larger locus or across the brain.
3. Finally, failure loss of inhibitory feedback—potentially due to GABA receptor dysfunction and reduced Cl^- cellular influx—results in loss of recovery hyperpolarization, excess glutamate stimulation, and increased intracellular Ca^{2+}. Ultimately, this increase in intracellular Ca^{2+} turns on the cell death pathway that destroys surrounding inhibitory neurons and creating a cellular locus that drives seizures.

Any brain can be provoked to suffer a seizure, and a number of different types of diseases or events can trigger a first or recurrent event (Table 1).[6]

Table 1. Common underlying events evoking seizure and examples.

Etiology	Examples
Vascular events	• Stroke (either ischemic or hemorrhagic) • Encephalopathy • Anoxic brain injury
Infectious agents (Fungal, viral, bacterial, parasitic pathogens)	• Meningitis • Encephalitis • Brain abscess
Trauma	• Hematoma (either epidermal or subdural)
Autoimmune disorders	• Systemic lupus erythematosus • Paraneoplastic syndromes (e.g., breast, lung cancer)
Metabolic disorders/ disregulation	• Electrolyte imbalance or deficiency – Hyper- or hypoglycemia – Hyper- or hyponatremia – Hypo- calcemia, magnesemia, or phosphatemia • Uremia • Liver failure • Thiamine deficiency • Hyperthyroidism
Idiopathic conditions	• Epilepsy (chronic seizures) • Antiepileptic medication under- or overdose
Neoplasms	• Glioblastoma • Meningioma • Metastatic brain cancer
Drugs (lower seizure threshold)	• Opioids • Tricyclic antidepressants • Isoniazid • Salicylate (aspirin) toxicity • Cocaine • Amphetamines • Metronidazole • Penicillins • Cefepime • Bupropion • Drug withdrawal (e.g., benzodiazepine, ethanol) • Lithium – Degenerative disorders (e.g., Alzheimer's) – Demyelinating diseases (e.g., multiple sclerosis)
Eclampsia and other	• Pregnancy + hypertension • Extreme fever (usually pediatric) • Genetics: – Phenylketonuria – Lysosomal storage disorders – Peroxisomal storage disorders – Angelman syndrome

Appendix III: Epilepsy types and seizure categorization

Focal seizures[6]

Focal seizures originate in one particular region of the brain, and their effects manifest according to the region's function. Focal seizures originating in the motor cortex of the frontal lobe (Figure 2) evoke the abnormal muscle activity most commonly associated with epilepsy. These can be **tonic**, generating increase muscle tone (stiffness, rigidity); **atonic** (loss of muscle tone, i.e., limpness); **clonic** (spasmodic activity generating rhythmic twitching); or **myoclonic** (spasmodic activity generating fast, jerky contractions). For example, a focal clonic seizure originating in the motor region of the left frontal cortex may cause muscle twitching or spasming in the right calf, whereas an atonic seizure originating in the right frontal cortex may result in sudden limpness in the left hand, causing the individual to suddenly drop whatever they are holding.

Focal seizures can also evoke responses that are not overt. For example, focal seizures of the olfactory region of the frontal lobe can cause the affected individual to experience unusual or intense smells, while those in other areas might cause transitory changes in personality, generate unexpected or inappropriate emotional responses, inability to concentrate, inability to understand the meaning of words, or inability to speak. Seizures originating in the parietal, temporal, or occipital lobes can cause sensory symptoms, such as paresthesia (e.g., tingling, numbness), phantom abnormal or intense tastes, or visual or auditory impairment or hallucinations. Seizures affecting the central autonomic network, including areas of the insula, anterior cingulate cortex, amygdala, hypothalamus, and brainstem, can disrupt autonomic functions, resulting in hypertension, tachycardia, urinary incontinency, sweating, and salivating.

Focal seizures may also cause loss of unawareness of their surroundings or consciousness. In some types of epilepsy, focal seizures may propagate throughout the originating hemisphere as well as across the corpus callosum to the opposite hemisphere and become generalized (see below). In other types of epilepsy, an individual may experience both focal and generalized activity, although generalized seizures may only be recognized due to the presence of certain types of electroencephalographic wave patterns.

Generalized seizures[6]

Generalized seizures originate from both brain hemispheres (Figure 2). They affect the entire brain and have systemic effects. As with focal seizures, generalized motor seizures may be atonic, tonic, clonic, or myoclonic, and are typically accompanied by loss of consciousness. In fact, when asked to describe a seizure, most people will likely think of the highly recognizable "grand mal" seizure often portrayed in popular media. Grand mal seizures are generalized tonic-clonic seizures and are characterized by sudden stiffening (increased tone) of the muscles accompanied by rhythmic jerking (clonus). As multiple motor pathways are affected, these events also cause uprolling of the eyes, pooling of oral secretions (often described as frothing), tongue biting, and loss of urinary and/or fecal control.

Generalized non-motor seizures are not analogous to focal non-motor seizures, however. A pediatric form of generalized non-motor seizure is the absence seizure. These seizures result in a brief loss of awareness, but no loss of muscle tone, although they may be accompanied by semi-coordinated repeated oral or manual actions (automatisms), such as rapid eye blinking, lip licking or smacking, chewing, fidgeting, hand rubbing, or picking or scratching at skin or clothing.[8] Because the child looks like they have merely "spaced out," absence seizures are often misdiagnosed as attention deficit disorder, especially since as many as 100 absence events can occur per day.

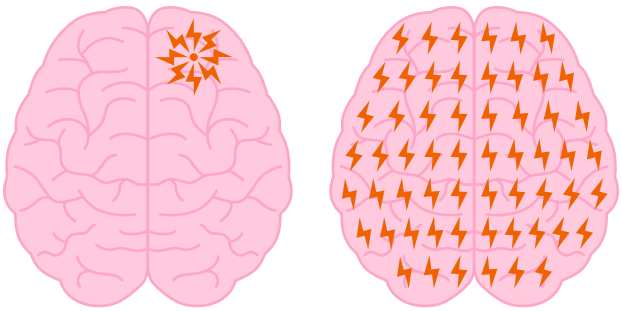


Figure 2. Focal vs. generalized seizure. In focal seizures, a hyperstimulatable region initiates and then propagates repeated hyperstimulated, hypersynchronus firing of adjacent, recruited neurons in a limited area of the brain. In generalized seizures, hyperstimulated or hypersynchronus neuronal firing occurs simultaneously across both hemispheres.

Appendix IV: Additional tables

Pharmaceutical treatment: antiseizure medication (ASM)

Table 2. Commonly used ASMs (adapted from the National Institute for Health and Care Excellence [NICE] 2022 guideline, Hananya et al., Reimers et al., Prescribers' Digital Reference®)[9-12]

Generation	ASM	Year[a]	Drug class	Action site(s)
First	Phenobarbital	1912	Barbiturate Anticonvulsant	GABAergic transmission
	Phenytoin	1939	Hydantoin	Na^+ Channel, GABAergic transmission
	Acetazolamide	1952	Carbonic Anhydrase Inhibitor	Carbonic anhydrase inhibition
	Ethosuximide	1960	Succininmide Anticonvulsant	Ca^{2+} Channel
	Primidone	1960	Barbituate Anticonvulsant	GABAergic transmission
	Carbamazepine	1965	Carboxamide Anticonvulsant	Na^+ Channel
	Valproate (Valproic acid)	1970	Anticonvulsant	Na^+ Channel Ca^{2+} Channel GABAergic transmission
	Clobazam	1975	Benzodiazepine Anticonvulsant	GABAergic transmission
	Clonazepam	1975	Benzodiazepine Anticonvulsant	GABAergic transmission
Second	Vigabatrin	1989	GABA-T Inhibitors Anticonvulsant	GABAergic transmission
	Oxcarbazepine	1990	Carboxamide Anticonvulsant	Na^+ Channel
	Lamotragine	1991	Anticonvulsant	Na^+ Channel Ca^{2+} Channel GABAergic transmission
	Gabapentin	1994	Gabapentinoids, Anticonvulsant	Ca^{2+} Channel
	Felbamate	1994	Carbamates, Anticonvulsant	NDMA[b] receptor (?[c])
	Topiramate	1995	Anticonvulsant	Na^+ Channel GABAergic transmission AMPA-R[d]
	Tiagabine	1996	GABA-T Inhibitors, Anticonvulsant	GABA reuptake inhibition
	Levetiracetam	2000	Anticonvulsant SV2A[e] inhibitor	Ca^{2+} Channel, SV2Ae receptor Intracellular Ca^{2+} release
	Pregabaline	2005	Gabapentinoids, Anticonvulsant	Increased neuronal GABA Increased Glu Decarboxylase activity Ca^{2+} Channel
	Zonisamide	2007	Anticonvulsant	Na^+ Channel
	Rufinamide	2007	Anticonvulsant	Na^+ Channel
Third	Eslicarbazepine	2010	Carboxamide Anticonvulsant	Na^+ Channel
	Lacosamide	2010	Anticonvulsant	Na^+ Channel CMRP2[f]
	Ezogabine	2011	Anticonvulsant	Transmembrane K^+ current enhancer (?[c])
	Perampanel	2016	Anticonvulsant	AMPA-R[d]

a. Year of introduction
b. N-methyl-D-aspartate
c. Uncertain mechanism of action
d. α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
e. Synaptic vesicle glycoprotein 2A
f. Collapsin response mediator protein-2R, receptor

Table 3. ASMs recommended for first-line therapy initiation in adults.[13]

Seizure type	ASM
Focal	LTG, LEV, OXC, CAR, LAC
Genetically based GTCS	LTG, LEV, VAL, TOP, ZON
Secondary GTCS	LTG, LEV, OXC, CAR, LAC
Absence	ETH, PAL
Myoclonic	LEV, VAL, ZON, CLO
Tonic/atonic	VAL, LTG, COB, ZON, LEV
Focal motor/epilepsia partialis continua	PHY, CAR, OXC

LTG: lamotrigine
LEV: levetiracetam
OXC: oxcarbazepine
CAR: carbamazepine
LAC: lacosamide
VAL: valproate
TOP: topiramate
ZON: zonisamide
ETH: ethosuximide
PAL: palproate
CLO: clonazepam
COB: cobazam
PHY: phenytoin

Appendix V: Factors related to therapeutic drug monitoring

Personalized medicine: genetic polymorphisms affecting ASM metabolism, clearance, and blood concentration

TDM can play an important role in precision medicine, particularly as more is learned about genetic polymorphisms affecting interindividual variability of drug metabolism. LTG metabolism is carried out in the liver by the UDP-glucuronsyl transferase isoenzymes, UGT2B7 and UGT1A4, which convert lipophilic molecules into water-soluble metabolites that can be excreted. Several studies have demonstrated that polymorphisms at these loci affect enzyme functionality and clearance of LTG. Du et al. demonstrated that a single nucleotide polymorphism (SNP) in UGT1A4 could either increase or decrease the serum levels of LTG in Chinese children (mean age = 12.33 years). The examined SNP replaced thymine (T) at DNA position 142 with guanine (G), resulting in a single amino acid (aa) change at protein position 48 from leucine (L) to valine (V). All children were administered a daily dose equivalent to an adjusted plasma LTG concentration of 2.58±0.87 µg/mL per mg/kg (dose/body mass), children with the TT (wild-type [WT]) genotype had a higher adjusted plasma LTG concentration, while those who were either heterozygous (TG) or homozygous (GG) for the G allele had a lower plasma concentration. Furthermore, LTG efficacy was good in the majority of the children with the TT genotype (56% vs 18% with poor efficacy), while the efficacy was poor in the majority of children with either one or two copies of the G allele (9% good, 17% poor [Table 4]).[14]

In a more recent study, Petrenaite et al. examined the impact on LTG metabolism of several genetic polymorphisms associated with UGT enzymes (UGT1A4, 70C>A, UGT2B7, UGT2B15, UGT2B17), as well as the P-glycoprotein (P-gp) transport protein ABCB1 (this protein transports water-soluble molecules out of the cell across the lipid bilayer). This study was conducted in 337 adults (mean age = 35 years), the majority of whom had either focal (61.4%) or generalized epilepsy (37.4%), and who were receiving either monotherapy (53.4%) or polytherapy (36.8%). Among the participants, 21.7% were smokers and 10.1% were taking contraceptives. In this study, they found that adjusted serum levels of LTG were higher in males carrying a heterozygous cytosine to adenine (C>A) SNP for the UGT1A4*2 allele, but this was not statistically significant. The difference was statistically significant, however, among females ($p < 0.05$), although the authors point out that the absence of statistical significance in males could be an artifact of smaller sample size. In the case of UGT2B7*2 (C>T), there was a significant elevation ($p < 0.05$) between the heterozygous and homozygous SNPs for both males and females, but only females demonstrated a significant difference between the WT allele and the homozygous SNP ($p < 0.05$). While no significant differences were observed among males between WT and homozygous or heterozygous SNPS for UGTB15*2 (G>T), LTG serum concentration was statistically *lower* among women ($p < 0.05$ for both WT vs TT, and between GT and TT). Copy number variations were investigated for UGT2B17. No significant difference was observed between a gene insertion or gene deletion among males, however LTG serum concentration was significantly greater in females when the gene was deleted (Figure 4). This indicates polymorphisms can be associated with either increased or decreased blood levels, and that sex can intensify genetic variation.[15]

Table 4. Association of genotype differences at the L48V (142T>G) locus of UGT1A4. (Adapted from Du et al.[14])

					Efficacy (%)		
Position 48 aa	Genotype	N	Adjusted serum LTG concentration µg/mL per mg/kg	Statistical significance vs TT (P)	Good	Poor	Statistical significance vs TT (P)
L	TT	74	2.77±0.87	–	56	18	–
V	TG	26	2.18±0.74	0.006	9	17	0.001
V	GG	2	1.95±0.49	0.006	1	1	0.001

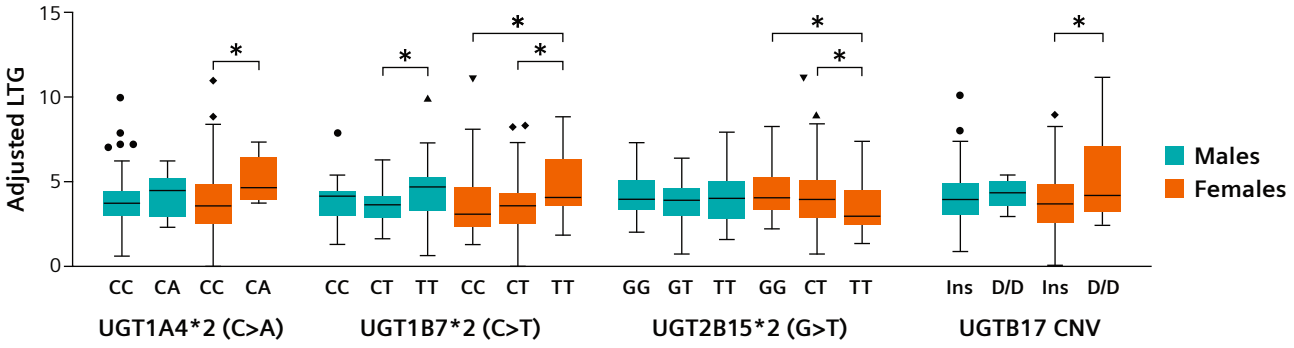


Figure 4. Variability of adjusted LTG serum concentration (mean of individual LTG concentration/(LTG dose/weight) by allele and sex: * indicates $p < 0.05$. (Adapted from Petrenaite et al.[15])

LEV is not extensively metabolized, however it is eliminated through P-gp transport, similar to LTG.[16] These transporters are also present in the brain, and have been found to be overexpressed in individuals with epilepsy. Noting that both renal elimination and efflux ability of these transporters at the blood-brain barrier could be affected by polymorphisms of the ABCB1 transport protein, Zhao et al. examined the impact of three well-characterized ABCB1 SNPs (C1236T, G2577T/A, C3435T) in 245 Uygur children with epilepsy, 117 who were nonresponsive to LEV and 128 who were responsive to LEV. They found no difference in the LEV overall serum concentration and the serum concentration/body mass dose in children with the C1236T genotype, however the GT, TT, GA, and AT genotypes of the G2677T/A allele was associated with significantly higher serum levels and concentration/body mass dose when compared to the WT (GG) in both responders and non-responders. The C3435T SNP also significantly increased LEV concentrations and concentration/ body mass dose levels. Despite this, they concluded that differences in these alleles could affect LEV efficacy in Uygur children and aid in establishing a better personalized approach to treatment for better outcomes.[17] Zhao et al. note, however, that others' studies have not demonstrated results similar to theirs and speculate that there could be important population differences in gene frequency distribution affecting observable results.

The above studies and others indicate that genetic polymorphisms can play a significant role in the clearance of LTG, affecting overall blood levels. In their comprehensive review on the necessity of monitoring ASMs and other neuropsychoactive medications based on pharmacodynamics, Hiemke et al. points out that these differences would be missed if LTG were only titrated or monitored based on clinical algorithms and observation, and standard adjustments could subsequently affect patient response and tolerability.[16] Furthermore, different drug formulations can affect the patient's response. For example, absorbance rate and body concentration can differ amongst the common formulations of LTG (conventional tablets, chewable tablets, orally disintegrating tablets). Additionally, peak concentration achieved by a drug (Cmax) across generic versions can vary by as much as 45%, since it is allowable for Cmax of generics to be as much as 20% lower or 25% higher than the original brand medication. (There are currently 13 generic formulations of LTG, as well as the original brand, Lamictal.) Switching from use of the brand formulation to a generic one or between generics can result in a substantial increase or decrease of total available drug/body mass. Hiemke et al. emphasize that it is better to use TDM to monitor such a switch instead of watching and waiting to see if problems such as loss of efficacy or tolerability arise.[16]

Age considerations

Age can play a significant role especially when evaluating the efficacy of a drug as a child progresses through different stages of development—especially during adolescence when hormonal changes can affect both efficacy and tolerance—and in the elderly, who are more likely to be hypersensitive to medications or medically frail.[13] For example, Wang et al. observed that young children are less likely to respond to LTG at low concentrations and found that the optimal blood concentration cut-off likely required for a therapeutic response was 3.29 µg/mL for children between the ages of 2 and <12 years, 2.06 µg/mL for adolescence between the ages of 12 and ≤18 years, and 1.61 for adults >18 years of age. They further noted that dose requirements for young children were less predictable than they were for adults.[18] While upper ranges for all groups fell within the upper range recommended by the AGNP, it should be observed the lowest optimal dose for adolescents and adults is *below* the recommended range, supporting the establishment of a patient-specific steady-state trough to provide the lowest possible dose at which the drug is effective.

Pregnancy

Hormonal fluctuations and complications (such as hyperemesis gravidarum) accompanying pregnancy and parturition can affect blood concentrations of ASMs administered at standard doses, apparently due to increased clearance. Fallik et al. evaluated 263 samples from 38 pregnant patients taking LEV. Samples were collected monthly. They found that blood concentration/dose decreased as pregnancy progressed. The most dramatic decrease in concentration/dose occurred over the course of the first trimester necessitating a 50% increase in dose, and a later dose increase of 25% in the third trimester (75% increase in blood concentration/dose over the course of pregnancy). Following parturition, the concentration/dose rebounded sharply, requiring readjustment to lower the dose and stabilize a new baseline.[19]

Similar findings have also been noted for LTG by Pennell et al. In the Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) study, the concentration/dose of LTG across 162 patients was found to decrease up to 56% by the end of the third trimester, then sharply increase postpartum. LEV (n = 151) was also found to decrease in this study, although only by 36% over the course of gestation, as compared to the 75% decreased observed by Fallik et al. noted above (Figure 5). It is possible this difference could be attributed to the much smaller population size used in the Fallik et al. study.[20] As a result of this study, Pennel et al. recommend close monitoring of both LTG and LEV throughout pregnancy to ensure good clinical response, and postpartum to reduce the risk of adverse events, including toxicity.

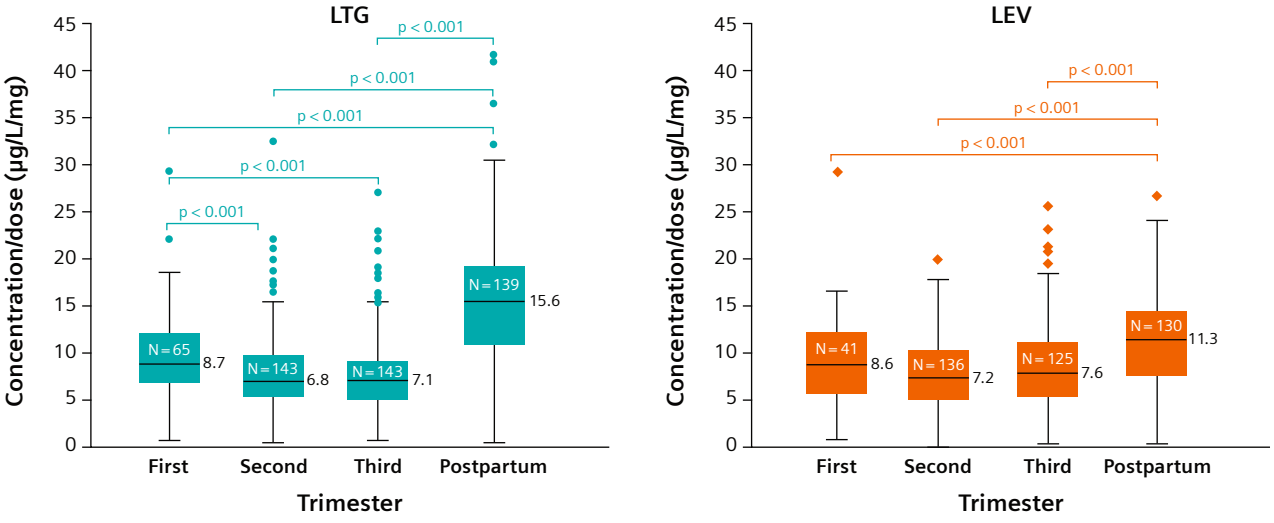


Figure 5. Mean and interquartile ranges for LTG and LEV during pregnancy and following parturition.

Renal clearance in chronic kidney disease (CKD)

Similar to the impact of renal clearance and ASM levels in pregnancy, it is important to adjust dosing in patients with CKD as renal function degrades.[21] Kaceski et al. recommend using only half of the normal dose of LEV in patients with a glomerular filtration rate (GFR) ≤60 mL/minute/1.73m^2 to compensate for reduced renal clearance, including in patients with end-stage disease.[13] They offer no recommended dosing level or schedule for LTG. However, they do recommend dosing for both LTG and LEV based on monitoring and individualized medication adjustment—especially during hemodialysis—to insure appropriate blood concentrations.[13]

References:

1. Centers for Disease Control. Epilepsy basics. CEDC. Updated May 15, 2024. https://www.cdc.gov/epilepsy/about/index.html#:~:text=Epilepsy%20is%20a%20brain%20disorder%20that%20causes%20repeated,contagious%20and%20cannot%20spread%20from%20person%20to%20person [accessed Jan. 12, 2025].
2. World Health Organization. Epilepsy. Available from https://www.who.int/news-room/fact-sheets/detail/epilepsy [accessed Jan. 1, 2025].
3. World Health Organization. Epilepsy: a public health imperative. Summary. Available from https://iris.who.int/bitstream/handle/10665/325440/WHO-MSD-MER-19.2-eng.pdf?sequence=1 [accessed Feb. 28, 2025].
4. Zhang YJ, Kong XM, Lv JJ, et al. Analysis of the global burden of disease study highlights the global, regional, and national trends of idiopathic epilepsy epidemiology from 1990 to 2019. Prev Med Rep. Dec 2023;36:102522.
5. Begley C, Wagner RG, Abraham A, et al. The global cost of epilepsy: A systematic review and extrapolation. Epilepsia. 2022;63(4):892-903.
6. Lowenstein D. Seizures and epilepsy. In: Kasper D, Fauci A, Longo D, Braunwald E, Hauser S, Jamison J, eds. Harrison's Principals of Internal Medicine. 16 ed. McGraw Hill; 2005:2357-72.
7. Sheffler Z, Reddy V, Pillarisetty L. Physiology, neurotransmitters. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK539894/ [accessed Jan. 12, 2025].
8. Sadleir LG, Scheffer IE, Smith S, et al. Automatisms in absence seizures in children with idiopathic generalized epilepsy. Arch Neurol. 2009;66(6):729-34.
9. Hanaya R, Arita K. The new antiepileptic drugs: Their neuropharmacology and clinical indications. Neurol Med Chir (Tokyo). 2016;56(5):205-20.
10. NICE Guideline: Epilepsies in children, young people and adults. Available from https://www.nice.org.uk/guidance/ng217 [accessed Jan. 23, 2025].
11. Prescribers' digital reference. Digital drug database. Available from https://www.pdr.net/ [accessed: Jan. 23, 2025].
12. Reimers A, Brodtkorb E. Second-generation antiepileptic drugs and pregnancy: a guide for clinicians. Expert Rev Neurother. 2012;12(6):707-17.
13. Karceski S, Shih T. Initial treatment of epilepsy in adults. Wolters Kluwer. Updated October 22, 2024. https://www.uptodate.com/contents/initial-treatment-of-epilepsy-in-adults?search=epilepsy%20treatment&topicRef=2220&source=see_link [accessed Jan. 24, 2025].
14. Du Z, Jiao Y, Shi L. Association of UGT2B7 and UGT1A4 polymorphisms with serum concentration of antiepileptic drugs in children. Med Sci Monit. 2016;22:4107-13.
15. Petrenaite V, Ohman I, Jantzen FPT, et al. Effect of UGT1A4, UGT2B7, UGT2B15, UGT2B17 and ABC1B polymorphisms on lamotrigine metabolism in Danish patients. Epilepsy Res. 2022;182:106897.
16. Hiemke C, Bergemann N, Clement HW, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: Update 2017. Pharmacopsychiatry. 2018;51(1-02):9-62.
17. Zhao T, Yu J, Wang TT, et al. Impact of ABCB1 polymorphism on levetiracetam serum concentrations in epileptic Uygur children in China. Ther Drug Monit. 2020;42(6):886-92.
18. Wang ML, Wang HX, Zhao MM, et al. Redefining the age-specific therapeutic ranges of lamotrigine for patients with epilepsy: A step towards optimizing treatment and increasing cost-effectiveness. Epilepsy Res. 2021;176:106728.
19. Fallik N, Trakhtenbroit I, Fahoum F, et al. Therapeutic drug monitoring in pregnancy: Levetiracetam. Epilepsia. 2024;65(5):1285-93.
20. Pennell PB, Karanam A, Meador KJ, et al. Antiseizure medication concentrations during pregnancy: Results from the maternal outcomes and neurodevelopmental effects of antiepileptic drugs (MONEAD) study. JAMA Neurol. 2022;79(4):370-379.
21. Couderc S, Chouchane M, Saint-Marcoux F. What is the therapeutic reference range for levetiracetam? Grand round/a case study. Ther Drug Monit. 2022;44(3):363-365. doi:10.1097/FTD.0000000000000972.

Notes

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We are a team of more than 72,000 Healthineers in over 70 countries passionately pushing the boundaries of what is possible in healthcare to help improve the lives of people around the world.

**Personalization of diagnosis, therapy selection and monitoring, aftercare, and managing health.*

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