Monitoring of Second-generation Antiseizure Medications in Epilepsy

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Key takeaways

- Antiseizure medications (ASMs) provide vital therapy to millions of individuals with epilepsy.
- Second-generation medications provide equivalent seizure control with fewer, and generally less severe, side effects.
- Laboratory evaluation plays a key role in patient care:
  - All ASMs should be monitored using blood testing at initiation and throughout therapy.
  - Therapeutic drug monitoring (TDM) provides vital information needed for control of breakthrough seizures and to appropriately titer dosage during medication changes.

Introduction and epidemiology

Epilepsy is a neurological disease characterized by paroxysmal hyperstimulative and hypersynchronous electrical brain activity causing seizures or unusual behavior.[1] It is the fourth most common neurological condition worldwide. Epilepsy can be comorbid to other conditions, and it can contribute to progressive brain injury resulting in motor, cognitive, and psychological dysfunctions such as learning disabilities, autism, anxiety, and depression.[1] Depending on the age at onset, seizures can alter neurological development and promulgate seizure susceptibility to additional areas of the brain.[1] Those with epilepsy are also subject to a higher prevalence of cardiovascular disease, respiratory disorders, diabetes, generalized inflammation, obesity, and disorders such as headache, migraine, and arthritis.[2] Consequently, epilepsy can shorten life expectancy.

In addition to mortality risk from associated underlying or acquired comorbidities, those with the disorder are at higher risk of sudden unexplained death in epilepsy (SUDEP), which occurs at a rate of 1 in 1,000 epileptics and is the leading cause of death in individuals with uncontrolled seizures.[3]

According to the World Health Organization (WHO) 2024 fact sheet and the 2019 joint WHO, International League Against Epilepsy (ILAE), and International Bureau for Epilepsy (IBE) public health summary on epilepsy, approximately 50 million individuals are affected worldwide, representing somewhere between 4 and 10 per 1,000 people.[4,5] (See Appendix 1 for a deeper discussion of the epidemiology and economic impact associated with epilepsy.)

Epilepsy definition and pathophysiology

The hallmark of epilepsy is marked by unprovoked and chronic seizures. A seizure is "a transient occurrence of symptoms and/or signs due to abnormal excessive or synchronous neuronal activity in the brain." (See appendix II for additional background on normal and abnormal neuronal function.)

Epilepsy types and seizure categorization

Not all seizures are an indication of epilepsy. In most cases, a seizure of new onset is provoked by one of the events listed in Appendix II, Table 1. In many cases, risk of a recurrent seizure can be minimized or eliminated once the underlying cause has been addressed and resolved.[1] According to the 2014 ILAE Commission's position paper updating the 2005 clinical definition, epilepsy may be diagnosed if an individual meets at least one of three criteria:

- Has experienced at least two unprovoked seizures occurring >24 hours apart
- Has experienced one unprovoked seizure and has at least a 60% probability of experiencing further seizures within the next 10 years
- Has been diagnosed with an epilepsy syndrome.[7]

Each of these conditions presupposes that the individual has a "pathologic and enduring tendency" to experience seizures because they have a lower threshold for seizure provocation. Many different types of seizures are associated with epilepsy, and levels of diagnostic criteria are used to determine diagnosis. (See Appendix III for additional information on types of epilepsy and seizure categories.)

Pharmaceutical treatment: antiseizure medication (ASM)

Treatment of epilepsy is crucial for seizure control and risk reduction of poor outcomes. According to WHO, Epilepsy Foundation, and other sources, therapy can successfully treat up to 70% of those with epilepsy.[1,3-5] In most cases, medication is the first line of treatment once a diagnosis of epilepsy has been established, with the goal being to reduce the risk of unprovoked seizures by rebalancing neurostimulative and neuroinhibitory activity, improve quality of life (QoL), and reduce negative outcomes.

There are currently more than 20 ASMs available for treating epilepsy.[8] Medications can be classified in several ways, including but not limited to their generation (first, second, or third), their pharmaceutical class, or whether they target specific receptors or electrolyte channels controlling excitatory or inhibitory actions. (See Appendix IV for a table of commonly used ASMs and their generations.)

An evidence-based guideline on management of an unprovoked first seizure in adults, published in 2015 by the American Academy of Neurology in conjunction with the American Epilepsy Society, evaluated the benefits of early treatment for reducing risk of seizure recurrence, reducing or altering short-term seizure recurrence, long-term prognosis for seizure freedom or remission, and risk of adverse events.[9] The study group noted that early treatment seems to reduce the risk of seizure recurrence within the first two years, when the risk is greatest (21–45% risk). However, it has no demonstrable effect on standard QoL measures and is unlikely to improve the chance of attaining sustained seizure remission over three or more years. They also noted that between 7% and 31% of adults treated with one of the variety of medications available experience an adverse event. Most of these were mild in the studies they evaluated, were reversible after switching to another ASM, and most were dose related. They further noted that newer ASMs, such as lamotrigine (LTG) and levetiracetam (LEV), may evoke fewer, more tolerable, or different adverse events than older drugs, such as phenytoin or valproate, which can result in nervous system reactions including nystagmus, ataxia, slurred speech, decreased coordination, and mental confusion.[9,10] In comparison, most of the adverse events provoked by LTG and LEV are mild to moderate. For example, the manufacturer's package inserts for LEV notes adverse events occurring in ≥5% of users, and include somnolence, asthenia, infection, and dizziness in adults, and fatigue, aggression, nasal congestion, decreased appetite, and irritability in children.[11] Adverse events for LTG experienced by ≥10% of users include somnolence (drowsiness), dizziness, headache, nausea, ataxia, diplopia, blurred vision, rhinitis, pharyngitis, and rash in adults. Additional adverse effects in children include vomiting, infection, fever, diarrhea, abdominal pain, tremor, and risk of accidental injury.[11,12] This is not to say that severe reactions do not occur with these medications as all ASMs have the potential of eliciting a severe adverse advent by the nature of their mechanism or individual bio-variability in tolerance and response.[9]

Once the determination has been made to initiate use of an ASM, selection is typically dictated by its efficacy for controlling specific types of seizures, whether it is considered a first-, second-, or third-line drug, whether it is sufficient as monotherapy, can be used in combination with other ASMs, has specific known interactions with other ASMs or is likely to interact with other medications the individual is taking (especially for patients with polypharmacy). Other considerations include cost, its suitability based on age (infant, pediatric, adult, and elderly), sex, and tolerability. Common side effects range from mild to moderate, such as increased somnolence, stomach upset, dizziness, or blurred vision, while others can be more severe, such as suicidal ideation, liver or pancreatic dysfunction or liver failure, leukopenia [low white-cell count], thrombocytopenia [low platelets], aplastic anemia, and rash.[13,17] Racial background can also dictate ASM selection. In its 2024 Guideline on Epilepsies in Children, Young People, and Adults, NICE calls out increased risk of serious skin reactions in people of Han Chinese or Thai background with phenytoin use, and that carbamazepine and medications with similar chemical structure carry an increased risk for severe skin reactions in those of Han Chinese, Thai, European, or Japanese backgrounds. Additionally, carbamazepine, phenytoin, primidone, and valproate are associated with decreased bone mineral density and increased risk of osteomalecea in all populations.[13] Although each of these drugs are considered for first-line monotherapy, both LEV and LTG may be used in their place as first- or second-line therapy for focal, myoclonic, and generalized tonic-clonic seizures (GTCS).[8]

One very important consideration that must be addressed when choosing the right drug for an individual is their biological sex. Several ASMs are teratogenic and not recommended for use in women or girls of childbearing age or potential. In particular, NICE incorporated the 2021 Medicines and Healthcare Products Regulatory Agency (MHRA) Drug Safety Update on valproate (a first-generation ASM) and the pending MHRA topiramate (second generation ASM) Drug Safety Update addressing avoidance of these drugs in anticipation of or during pregnancy, noting that these and other ASMs can results in congenital malformations, neurodevelopmental impairments, and fetal growth

restriction (some of these medications can also reduce the efficacy of hormonal birth control methods).[13,18] NICE recommends use of either LTG or LEV as either first- or second-line therapy for most types of seizures in women and girls (GTCS, focal, absence, myoclonic, tonic, and atonic seizures, as well as idiopathic generalized epilepsies, Dravet syndrome, Lennox-Gastaut syndrome, infantile spasms syndrome, self-limited epilepsy with centrotemporal spikes, and Doose syndrome).[13] It should be noted that risk of fetal adverse events is not eliminated using these two second-generation drugs—however it is reduced. Reimers et al. noted that LEV (2% at <300mg/day) and LTG accounted for the lowest frequence of fetal malformations (2.9% irrespective of dose) among pregnancies enrolled in the European and International Registry of Antiepileptic drugs in Pregnancy (EURAP), as compared to carbamazepine (5.6%), phenobarbital (7.4%) and valproate (9.7%).[19]

Use of second-generation drugs in neurology clinical practice: focus on levetiracetam and lamotrigine

The second-generation drugs LEV and LTG have become well accepted as first-line therapy. As noted in the College of American Pathologists (CAP) 2018 proficiency study, LTG ranked 63rd and LEV ranked 110th among the top 400 outpatient medications prescribed in 2017, outranking the three most commonly prescribed first-generation ASMs (valproic acid, 126th; carbamazepine, 176th; and phenytoin, 221st). LTG prescription outranked all second and third-generation drugs except gabapentin (11th), which is prescribed for many applications in addition to epilepsy.[20] The 2018 Practice Guideline published jointly by the American Academy of Neurology and the American Epilepsy Society recommend consideration of either LTG or LEV for new-onset focal seizures in adults, noting that efficacy in general was similar to or better than other first-line drugs for one or both of these medications, but with less discontinuation among patients due to their greater tolerability.[17] Kim et al. note that LEV and LTG are among the first choices of drugs recommended for focal seizures and GTCS in the 2019 Expert Opinion Survey in Korea. Additionally, they comment that these two drugs are the most commonly selected second-line medications chosen for focal seizures and GTCS if first-line therapy fails or is not well tolerated. However, they add the proviso that care must be taken with LTG as it can aggravate myoclonus, and recommend use of LEV instead in the case of tonic-clonic seizures.[8]

A study authored by Fox et al. examined patterns of ASM utilization for monotherapy as part of the human epilepsy project, based on inclusion of 433 patients between the ages of 12 and 60 years (median age 32) with a median follow-up of 3.2 years.[14] Although this was an international study, 86.5% of participants received their care in the U.S. This study found that the most common medication prescribed at treatment initiation was LEV (57.3%), followed by LTG (17.4%), and the first-generation drugs oxycarbazine (8.6%) and carbamezapine (5.4%), however the mean amount of time patients remained on LTG was 2.8 years, which was significantly longer than patients continued use of LEV (2 years) or other drugs in the study. In contrast to the U.S. patients, only 36.7% of those outside the U.S. were started on LEV, while 18.3% were started on LTG and 23.3% were started on carbamazepine. Overall, 47.5% of patients discontinued their first-line drug by the end of the study: 51.2% of those taking LEV discontinued its use, while only 26.7% of those taking LTG discontinued its use (Table 1).[14]

Table 1. Use pattern of LEV and LTG over three years.[14]

		By study's end					
Initial therapy	**n**	**Continued initial n (%)**	**Switched monotherapy n (%)**	**Initial + polytherapy n (%)**	**Switched + polytherapy n (%)**	**Total continuing initial n (%)**	**Total discontinuing initial n (%)**
Levetiracetam	254	79 (31.1%)	108 (42.5%)	44 (17.3%)	23 (9.1%)	93 (48.4%)	131 (51.6%)
Lamotrigine	77	43 (55.8%)	19 (24.7%)	10 (13.0%)	5 (6.5%)	53 (68.8%)	24 (31.2%)

As discussed previously, initial ASM selection is based on a number of factors, including seizure type, tolerance to potential adverse effects and sex. Additional considerations should also be made for patients with liver disease since several first-generation drugs (carbamazepine, felbamate, phenytoin, and valproate) are known to be hepatotoxic. ASMs generally considered to be safe include the second-generation drugs LEV, gabapentin, and pregabalin. Select second- and third-generation drugs (LEV, LTG, lacosamide) are good candidates for use with patients undergoing cancer chemotherapy as they do not inhibit or induce enzymes of transporters that can impact chemotherapeutic efficacy.

This is also true for patients receiving antiretroviral therapy (ART) for HIV and immunosuppressant therapy following solid organ transplant.[21] Karceski et al. note that LTG dosage may need to be increased when used with some ARTs, which raises several questions: what methods are currently used, or should be used, to monitor patients receiving ASMs? Which patients should be monitored, and when? How can testing for serum levels be used as a monitoring aid and as a tool for considering a dose or medication change?[21]

A list of recommended first-line medications for children and adults, based on the critical literature review of Karceski et al. and their personal clinical experiences can be found in Appendix IV.

Therapeutic range setting for LTG and LEV

The goal of ASM therapeutic range setting is to determine the range in which the probability of response (i.e., seizure prevention) is greatest.[22,23] Manufacturers and laboratories typically develop a reference range that is set between two values: the lower limit is typically the lowest value at which the dose is likely to be effective, while the upper level expresses the blood concentration at which toxicity is likely to occur.[24] The currently best available ranges were recommended by the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (Working Group for Neuropsychopharmacology and Pharmacopsychiatry, AGNP), and presented in a 2017 updated guideline document.[23] Despite the recommended ranges for LTG (3–15 µg/mL, alert level = 20 µg/mL) and LEV (10–40 µg/mL, alert level = 50 µg/mL), individual studies have noted therapeutic benefit outside of their recommended ranges due to individual variability. In an earlier position paper, Patsalos et al. noted that Perucca et al. made the argument that these variations alone warranted determination of individualized therapeutic dose determination, which could be extended to individualized ranges over time if/as dosage required adjustment.[24,25]

Individualized dosage or range is established by determining the blood concentration once the patient has reached a steady-state level after use of the drug for several dosing cycles (typically four to six drug half-lives at a constant dose).[23] Steady state is defined as the drug level at trough—that is, the time at which the drug concentration is expected to be at its nadir. Trough is standardly measured just before administration of the next drug dose (Figure 1).[23] If the dose requires adjusting, testing must be repeated after four to six cycles to establish the new trough blood concentration. Ideally, testing for trough at steady state should be conducted at least twice, initially and again after each change. This established trough is then used as the baseline whenever a new evaluation is needed.[23,24]

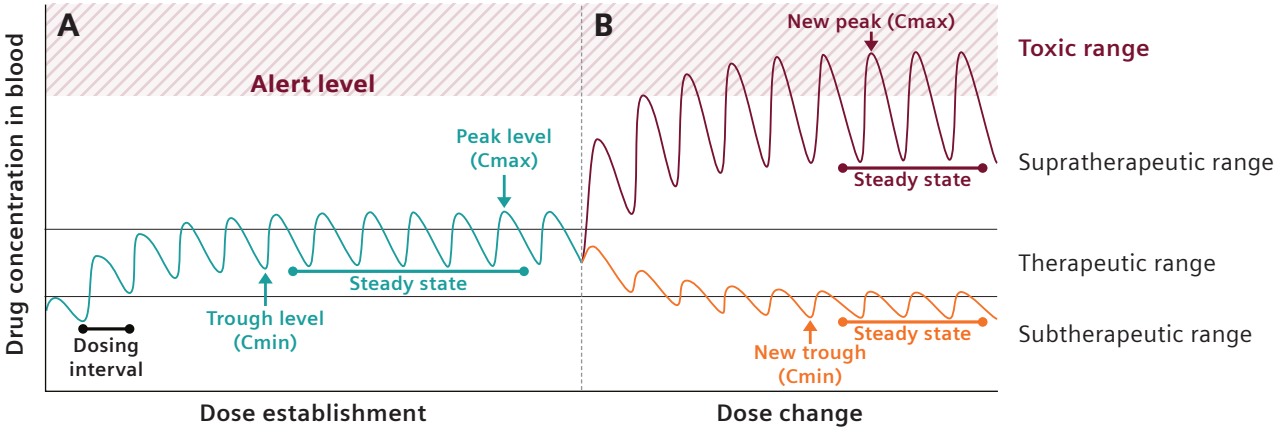


Figure 1. Concentration time curve for oral medication: A. Establishment of steady state in the therapeutic range based on empirical evidence of seizure control for at least six months. B. Effect of increased (red) or decreased (orange) dose change on development of toxicity or loss of therapeutic range, respectively. (Adapted from Hiemke et al.[23])

Therapeutic drug monitoring (TDM) for LTG and LEV

In clinical practice, initial ASM selection is made as discussed above. In general, decisions on medication use and dosage adjustment are made empirically. Medications are introduced at a low dose and gradually increased (titrated) to reach the lowest dose that is effective for eliminating seizures with the least degree of side effects, especially severe skin reactions that can occur with some ASMs, such as LTG. If seizures return or are not controlled, increasing levels of drug are attempted.[26] Empirical or scheduled upward titration of dosage is not optimal for all patients, however. There are many factors that can affect interpatient variability, necessitating establishment and monitoring of a patient-specific therapeutic range. Kwan et al. indicate several reasons for monitoring blood levels of ASMs.[26] (Details on many of these reasons are discussed in Appendix V.)

- To establish a personalized concentration level for later evaluation of changes in drug response (e.g., genetics affecting drug metabolism and clearance)
- To aid in the diagnosis of clinical toxicity
- To determine the degree of patient adherence, especially in patients with breakthrough seizures or uncontrolled seizures (i.e., is the patient correctly dosing, indicating a need to adjust dosage, switching to a different monotherapy, or adding additional medication to the patient's regimen, or are they deliberately underdosing for any number of reasons, such as drug affordability, reduction of undesirable or adverse effects, etc.)
- To guide dose adjustment in patients with changing needs (e.g., metabolic changes related to age, growth, and development; changes in drug formulation affecting pharmacokinetics; considerations associated with comorbid conditions, such as diminishing renal function in chronic kidney disease)
- To increase surveillance when a potentially important change affecting pharmacokinetics is anticipated (e.g., changes occurring throughout pregnancy as renal clearance and hepatic metabolism change in response to increasing maternal blood volume; addition or removal of potentially interacting medications, both ASMs and polypharmacy associated with comorbidities).

Monitoring adherence

One of the primary reasons for monitoring ASMs is nonadherence.[23] Although ASMs play a vital role in achieving good seizure control or freedom, not all patients are adherent. Donahue et al. note that nonadherence rates range between 29% and 60%, and that nonadherence increases the rate of hospital visits and healthcare costs.[27] Nonadherence and subsequent seizure breakthrough also contributes to greater risk of death: approximately 34% of individuals with SUDEP were found to be nonadherent, either because they intentionally undertreated to reduce unwanted side effects, or skipped or stopped taking ASMs altogether. Among those nonadherent SUDEPs, records revealed at autopsy that 39% were prescribed LEV and 26% were prescribed LTG.[28] There are several reasons why patients do not adhere to either the dose or the dosing schedule of prescribed ASMs. The predominant reasons for nonadherence recorded in studies include trying to avoid or reduce side effects, forgetting or missing doses, lack of pharmacy accessibility, and stopping medication without medical consultation after not experiencing seizures for a year or longer.[23,28,29]

When to monitor ASMs

The AGNP recommends measuring ASMs in blood (concentration/dose) when titrating the initial dose of an ASM—whether or not it is the drug of first choice—when switching between drugs or when introducing polytherapy—including over-the-counter medications. This can be especially important when introducing a second or third medication that can inhibit or induce the P-glycoprotein (P-gp) transport protein functionality required for clearance of LTG and LEV as this could result in either increased or decreased blood levels.[23] (See discussion on genotype differences in Appendix V for more information on P-gp transport proteins.) The level at which good seizure control is achieved can then be used as the base level for later comparison.[23] Subsequent testing should be conducted when there is a diagnostic reason to do so, such as occurrence of breakthrough seizures, hospitalization for seizures, or suspicion of

toxicity. Development of breakthrough seizures can indicate poor adherence or nonadherence, development of resistance to a currently used ASM, or another physiological factor mentioned previously, such as changing hormonal or comorbidity status, or an underlying genetic modifier. (See Appendix V for additional discussion of genetic and physiological factors affecting ASM dosage adjustment.)

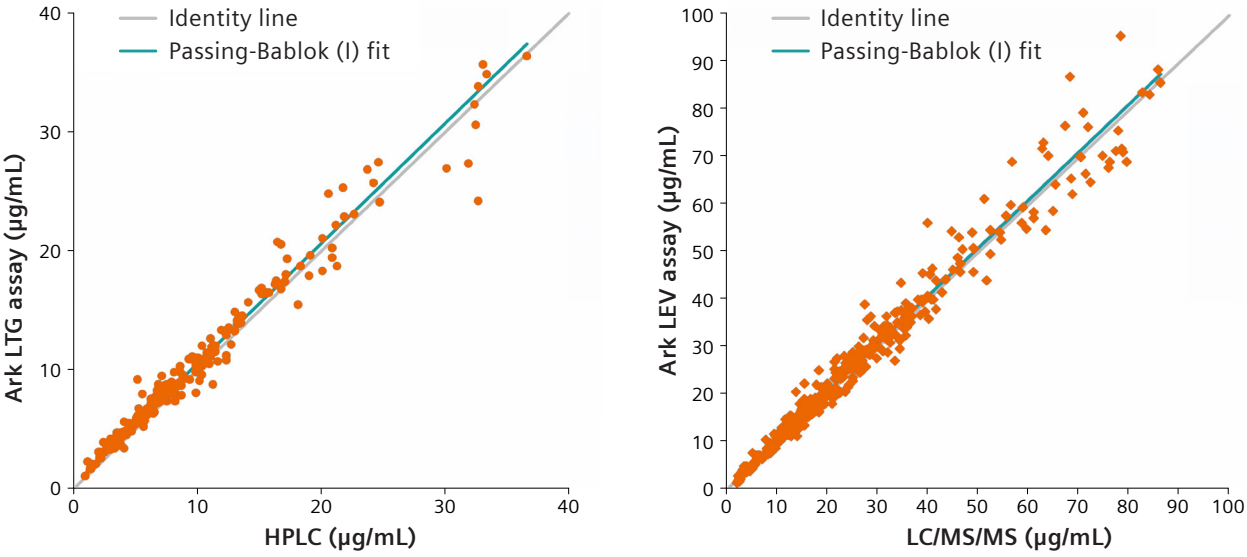
Regardless of the reason, blood testing can indicate if ASMs are at a subtherapeutic level relative to either accepted reference ranges or to a previously established baseline and serve as a valuable aid in diagnosis and adjustment.[23] Additionally, Hiemke et al. recommend regular blood monitoring during maintenance therapy to detect changes in the concentration/dose before seizures breakthrough or hospitalization is required and suggest using a more frequent schedule for monitoring if the treating physician suspects or anticipates poor adherence.[23] Monitoring is especially important during and after pregnancy for the mother's benefit, but also to minimize risks of drug toxicity to her nursing infant, since both LTG and LEV can be transmitted through milk. Because LTG has been associated with apnea, rash, poor suckling, and impaired liver function, monitoring of the infant is recommended if there is reason for concern. LEV is associated with fewer adverse events in the infant, but there is suspicion that it can reduce maternal milk supply in some women, and monitoring can help detect if the postpartum dose can be safely reduced.[30,31]

Testing methods

There are a variety of methods for conducting TDM of LTG and LEV. Most of these employ separation of blood components using high performance or ultra-high performance liquid chromatography (HPLC/U-HPLC), gas chromatography (GC) or solid phase extraction followed by analyte detection and measurement using mass spectrophotometry (MS) or tandem mass spectrophotometry (MS/MS), ultraviolet spectrophotometry (UV), or fluorescence directly within the chromatography column. Regardless of the technology, accurate measurement depends on sensitivity, specificity, analytical precision, and clinical accuracy. Additionally, testing methods should be reproducible, use stable reagents, and be well validated.[23,32-34]

Although, in its 2017 guideline, the AGNP states a preference for HPLC-MS/MS methods for TDM of neuropsychiatric drugs in general due to their precision, accuracy, and overall robustness, immunoassays for both LTG and LEV have been validated for close to two decades.[20,23,33,35-40] The 2021 CAP proficiency survey indicates increasing use of immunoassays between the years analyzed in the report (2013–2018), increasing by 82% for LTG and by 173% for LEV.[20] ARK Diagnostics, an independent developer of in vitro diagnostic TDM immunoassays (whose assays are used by Siemens Healthineers), has developed assays for both LTG and LEV that can be adapted for use across immunoassay methods and platforms.[36,37] Unlike HPLC-MS or similar assays, ARK's LTG and LEV assays are homogeneous and thus require no initial separation step. These assays use enzyme labeled glucose 6-phosphate dehydrogenase (G6PDH) in a competitive format to detect the target analyte in either serum or plasma (i.e., the higher the signal, the lower the blood concentration of the drug).[36,37]

Performance of these two assays have been evaluated by ARK. Both assays have demonstrated tight correlation when compared head-to-head against HPLC-MS assays in regression analyses. The correlation coefficient determined by Passing-Bablok regression analysis for the LTG assay is 0.97 with a slope of 1.0 at a y-intercept of 0.37, indicating results determined using the ARK assay are highly likely to be nearly identical to those derived using HPLC. Similar results were determined in a comparison of HPLC with the ARK LEV assay (Figures 2A and B).[36,37] Equally high correlations have been reported in independent studies as well (Table 2).[33,38-41] Furthermore, results from the CAP proficiency study demonstrated very low percent difference in means across the range of 0–25mg/L for LTG when comparing all enzyme immunoassays to LC-MS/MS determinations. This is also true for LEV, although there is a trend toward a small positive bias at higher LEV concentrations. However, since the CAP data do not report based on individual assay type, it is impossible to determine if this bias can be applied to LEV (Figures 3A and B).[20]



Parameter	Value (95% confidence interval)
Slope	1.01 (0.99 to 1.03)
y-intercept	0.37 (0.22 to 0.55)
Correlation (r^2)	0.97 (0.96 to 0.98)
Samples (n)	193
Assay range	0.85–40µg/mL

Parameter	Value (95% confidence interval)
Slope	1.01 (0.99 to 1.03)
y-intercept	0.25 (-0.24 to 0.63)
Correlation (r^2)	0.97 (0.96 to 0.97)
Samples (n)	305
Assay range	2.0–100.0µg/mL

Figure 2. Method comparisons of the ARK LTG (A) and LEV (B) immunoassays to HPLC. (adapted from ARK Diagnostics Product Data Sheets).[37,42]

Table 2. Method comparison results from independent studies.[33,38-41]

Assay	Study	Year	N	Regression type	Correlation	y-intercept	Slope
LEV	Mendoza et al.[33]	2020	50	Passing-Bablok	R^2 = 0.8796	-0.2971	1.0116
	Reineks et al.[40a]	2011	59	Deming	R^2 = 0.9962	0.61[b]	0.98[b]
	Juenke et al.[39] Lot 1	2011	121	Deming	r = 0.993	0.96[b]	1.70[b]
	Lot 2				r = 0.996	1.84[b]	0.92[b]
LTG	Juenke et al.[38]	2012	44	Deming	r = 0.999	0.44[b]	0.93[b]
	LeGatt et al.[41c]	2011	100	Deming	R^2 = 0.996	1.0513[b]	0.0631[b]

[a] *Performed on the Siemens ADVIA 1200 automated chemistry analyzer*
[b] *Confidence intervals not reported*
[c] *Conference abstract*

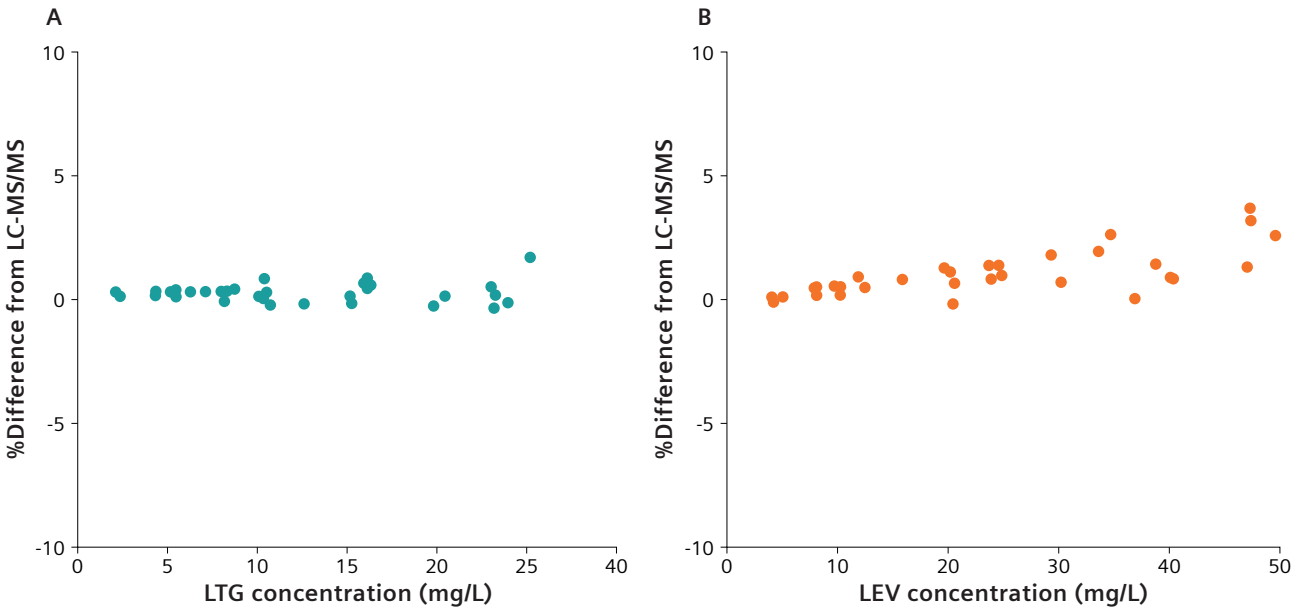


Figure 3. Differences between mean concentration of all LTG (A) and LEV (B) immunoassays and LC-MS/MS values reported in the 2021 CAP proficiency survey.[20]

ARK Diagnostics and independent studies also indicate acceptable performance with respect to standard parameters. Assay range, recovery (range), linearity, sensitivity, specificity, and precision for the LTG and LEV immunoassays indicate good precision and overall performance in evaluations using serum from patients (Table 3).[35-38,41]

Table 3. Assay performance characteristics from ARK data and independent studies reporting results using patient samples.[35-38,41]

					Precision (low–high concentration in human serum)		
Assay	**Source**	**Range (µg/mL)**	**%Recovery**	**Linearity (%Difference)**	**Within run SD (%CV)**	**Between day SD (%CV)**	**Total SD (%CV)**
LTG	ARK IFU[36]	0.85 – 40.00[a]	95.2 – 105.1	-0.1 – 7.1	0.8 – 1.33 (3.5 – 5.2)	0.09 – 1.12 (3.7– 4.3)	0.12 – 1.88 (5.2 – 7.3)
	Juenke[38]	1.0 – 30.5[b]	92 – 105	NR[c]	0.06 – 1.33 (2.75 – 5.77)	0.09 – 1.11 (0.79 – 4.81)	0.12 – 1.73 (5.9 – 7.51)
	LaGatt[41]	2.0 – 160[a]	NR	NR	NR	NR	NR (3.5 – 6.6)
LEV	ARK IFU[37]	2.0 – 100[a]	94.6 – 105.3	-0.1 – 13.2	0.26 – 2.19 (2.9 – 3.8)	0.22 –2.35 (3.1 –3.7)	0.33 – 3.31 (4.1 – 4.8)
	Ali[35]	0 – 95.4[b]	NR	0 – 0.08	0.209 – 0.59[d] (1.7 – 3.6)	0.420 – 1.36[d] (3.7 – 6.6)	NR

[a] *Analytical measurable range*
[b] *Range of measured samples*
[c] *Not reported*
[d] *Values reported for mean low- and high concentrations*

Conclusion

ASMs provide vital therapy to millions of individuals with epilepsy of different types and origins. Second-generation ASMs such as LEV and LTG can provide safe and effective therapy while avoiding or minimizing negative side effects and adverse events associated with first-generation medications. Despite their improved safety profiles, however, there is still a need to monitor blood concentrations in patients receiving these drugs. Consideration must be given to individual variability with respect to age, sex, comorbidities, and genetic polymorphisms to ensure continued optimal efficacy and prevent toxicity. Of equal importance is early detection of nonadherence—especially in patients at risk of underdosing—so as to prevent the occurrence of breakthrough seizures necessitating emergency care or hospitalization, and to prevent additional morbidity or potentially mortality. In the event of breakthrough seizures, it is essential to have a previously determined baseline based on the patient's serum concentration at the most recently prescribed dosage to ascertain if breakthrough indicates a change in drug efficacy, the need to increase dosage or initiate additional therapy, and to avoid increases that could result in adverse events or toxicity.

Although chromatography and spectrographic methods serve as the accepted standard for TDM across a wide range of drugs and medications, use of currently available immunoassay methods have proven to be of equal quality and performance, enabling laboratories to rapidly provide information needed by physicians to provide essential care in outpatient, emergent, and inpatient scenarios.

References:

1. Stafstrom CE, Carmant L. Seizures and epilepsy: an overview for neuroscientists. Cold Spring Harb Perspect Med. 2015;5(6). doi:10.1101/cshperspect.a022426
2. Strine TW, Kobau R, Chapman DP, et al. Psychological distress, comorbidities, and health behaviors among U.S. adults with seizures: results from the 2002 National Health Interview Survey. Epilepsia. 2005;46(7):1133-9.
3. Epilepsy Foundation. SUDEP. 2025. Available from https://www.epilepsy.com/complications-risks/early-death-sudep [accessed Jan. 22, 2025].
4. World Health Organization. Epilepsy. Updated February, 2024. Available from https://www.who.int/news-room/fact-sheets/detail/epilepsy [accessed Jan. 12, 2025].
5. World Health Organization. Epilepsy: a public health imperative. Summary. 2019 Available from https://iris.who.int/bitstream/handle/10665/325440/WHO-MSD-MER-19.2-eng.pdf?sequence=1 [accessed Feb. 28, 2025].
6. International League Against Epilepsy. Seizure Classification. Updated June, 2024. [accessed December 5, 2024].
7. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014;55(4):475-82.
8. Kim H, Kim DW, Lee ST, et al. Antiepileptic drug selection according to seizure type in adult patients with epilepsy. J Clin Neurol. 2020;16(4):547-555.
9. Krumholz A, Wiebe S, Gronseth GS, et al. Evidence-based guideline: Management of an unprovoked first seizure in adults: Report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 2015;84(16):1705-13.
10. Parke-Davis. Dilantin (extended phenytoin sodium capsules) for oral use. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/084349s088lbl.pdf [accessed Feb. 20, 2025].
11. Lamactil (lamotrigine) package insert. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/020241s064,020764s057,022251s028lbl.pdf [accessed Feb. 27, 2025]
12. KEPPRA (levetiracetam) package insert, reference ID: 5344664. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/021035s115,021505s053lbl.pdf [accessed Feb. 27, 2025].
13. NICE Guideline: Epilepsies in children, young people and adults. Available from https://www.nice.org.uk/guidance/ng217 [accessed: Jan. 23, 2025].
14. Fox J, Barnard S, Agashe SH, et al. Patterns of antiseizure medication utilization in the Human Epilepsy Project. Epilepsia. 2023;64(12):3196-3204.
15. Epilepsy Foundation. Side effects of seizure medicine. Available from https://www.epilepsy.com/treatment/medicines/side-effects [accessed Jan. 23, 2025].
16. Ha H, Bellanger R. Epilepsy: Treatment and Management. US Pharmacist. 2013;38(1):35-39.
17. Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new-onset epilepsy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 2018;91(2):74-81.
18. Medicines and Healthcare Products Regulatory Agency (MHRA). Topiramate (Topamax): introduction of new safety measures, including a Pregnancy Prevention Programme. Available from https://www.gov.uk/drug-safety-update/topiramate-topamax-introduction-of-new-safety-measures-including-a-pregnancy-prevention-programme [accessed Jan. 20, 2025].
19. Reimers A, Brodtkorb E. Second-generation antiepileptic drugs and pregnancy: a guide for clinicians. Expert Rev Neurother. 2012;12(6):707-17.
20. Krasowski MD, Long TA, Snozek CLH, et al. Therapeutic Drug Monitoring of Second- and Third-Generation Antiepileptic Drugs. Arch Pathol Lab Med. 2021;145(12):1485-1491.
21. Karceski S, Shih T. Initial treatment of epilepsy in adults. UptoDate. 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].
22. 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.
23. Hiemke C, Bergemann N, Clement HW, et al. Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Updated 2017. Pharmacopsychiatry. 2018;51(1-02):9-62.
24. Patsalos PN, Berry DJ, Bourgeois BF, et al. Antiepileptic drugs--best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia. 2008;49(7):1239-76.
25. Perucca E. Is there a role for therapeutic drug monitoring of new anticonvulsants? Clin Pharmacokinet. 2000;38(3):191-204.

26. Kwan P, Nicolo J-P. Antiseizure medication maintenance therapy and drug monitoring. UptoDate Wolters Kluwer. Updated March 5, 2024. https://www.uptodate.com/contents/antiseizure-medication-maintenance-therapy-and-drug-monitoring?search=epilepsy%20treatment&topicRef=2212&source=see_link [accessed Jan. 24, 2025]
27. Donahue MA, Akram H, Brooks JD, et al. Barriers to medication adherence in people living with epilepsy. Neurol Clin Pract. 2025;15(1):e200403.
28. Verducci C, Hussain F, Donner E, et al. SUDEP in the North American SUDEP Registry: The full spectrum of epilepsies. Neurology. 16 2019;93(3):e227-e236.
29. Teh KX, Henien NPB, Wong LS, et al. A cross-sectional study on the rate of non-adherence to anti-seizure medications and factors associated with non-adherence among patients with epilepsy. PLoS One. 2020;15(7):e0235674.
30. Drugs and Lactation Database (LactMed). Lamotrigine. NIH. Updated January 15, 2025. https://www.ncbi.nlm.nih.gov/books/NBK501268/ [accessed Jan. 31, 2025]
31. Drugs and Lactation Database (LactMed). Levetiracetam. NIH. Updated January 15, 2025. https://www.ncbi.nlm.nih.gov/books/NBK501229/ [accessed Jan. 31, 2025]
32. Palte MJ, Basu SS, Dahlin JL, et al. Development and Validation of an ultra-performance liquid chromatography-tandem mass spectrometry method for the concurrent measurement of gabapentin, lamotrigine, levetiracetam, monohydroxy deriative of oxcarbazepine, and zonisamide concentrations in serum in a clinical setting. Ther Drug Monit. Aug 2018;40(4):469-476.
33. Mendoza Aguilera M, Belles Medall MD, Alvarez Martin T, et al. Therapeutic drug monitoring of levetiracetam in daily clinical practice: high-performance liquid chromatography versus immunoassay. Eur J Hosp Pharm. 2020;27(e1):e2-e6.
34. Soufi G, Badillo-Ramirez I, Serioli L, et al. Solid-phase extraction coupled to automated centrifugal microfluidics SERS: Improving quantification of therapeutic drugs in human serum. Biosens Bioelectron. 2024;266:116725.
35. Ali M, Tam E, Roper SM, et al. Validation of an automated assay for levetiracetam (Keppra) on Vitros 5600. J Appl Lab Med. 2017;1(5):494-501.
36. ARK Diagnostics Inc. ARK™ Lamotrigine Assay Instructions for Use1600-0179-00 Rev 06 Updated November, 2023. https://www.ark-tdm.com/products/epilepsy/lamotrigine/pdfs/1600-0179-00_ARK_Lamotrigine_Assay_Web_Rev6.pdf [accessed Feb. 1, 2025]
37. ARK Diagnostics Inc. ARK™ Levetiracetam Assay Product Data Sheet, MKT12-009 Rev 05. Updated May 2017. https://www.ark-tdm.com/products/epilepsy/levetiracetam/pdfs/1600-0169-00_ARK_Levetiracetam_Assay_Web.pdf [accessed Feb. 20, 2025]
38. Juenke JM, McGraw JP, McMillin GA, Johnson-Davis KL. et al. Performance characteristics and patient comparison of the ARK Diagnostics levetiracetam immunoassay with an ultra-high performance liquid chromatography with tandem mass spectrometry detection method. Clin Chim Acta. 2012;413(3-4):529-31.
39. Juenke JM, Miller KA, Ford MA, et al. A comparison of two FDA approved lamotrigine immunoassays with ultra-high performance liquid chromatography tandem mass spectrometry. Clin Chim Acta. 2011;412(19-20):1879-82.
40. Reineks EZ, Lawson SE, Lembright KE, et al. Performance characteristics of a new levetiracetam immunoassay and method comparison with a high-performance liquid chromatography method. Ther Drug Monit. 2011;33(1):124-7.
41. LeGatt DF, Shalapay CE, Langman LJ, et al. The ARK diagnostics lamotrigine assay: development of a novel application on the Roche cobas c501 analyzer. Conference Abstract. Therapeutic Drug Monitoring. 2011;33(4):521.
42. ARK Diagnostics Inc. ARK™ Lamotrigine Assay Data Sheet, MKT 12-008 Rev 05 Updated May 2017 https://www.ark-tdm.com/products/epilepsy/lamotrigine/pdfs/LamotrigineDataRev5May2017.pdf [accessed Feb. 20, 2025]

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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]

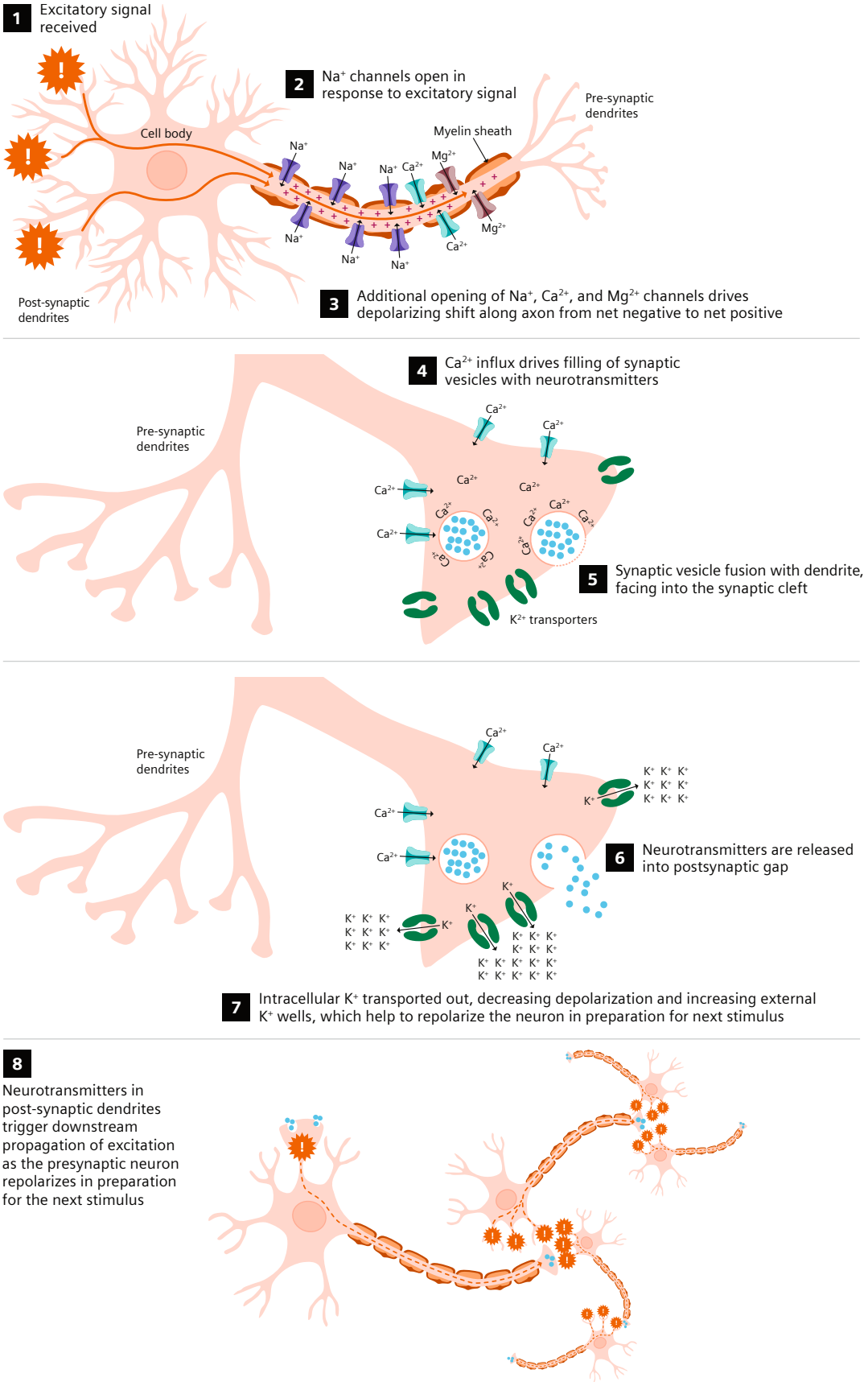
Appendix II: Normal/abnormal nerve function and triggering events

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.

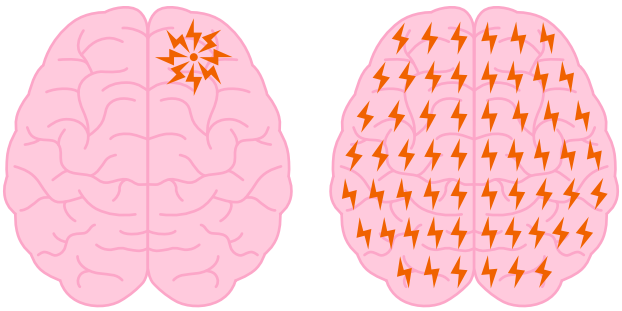


Figure 2. Focal vs. generalized seizure. In focal seizures, a hyperstimulatable region initiates and then propagates repeated hyperstimulated, hypersynchronus firing of adjacent, recruited neurons in a limited area of the brain. In generalized seizures, hyperstimulated or hypersynchronus neuronal firing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

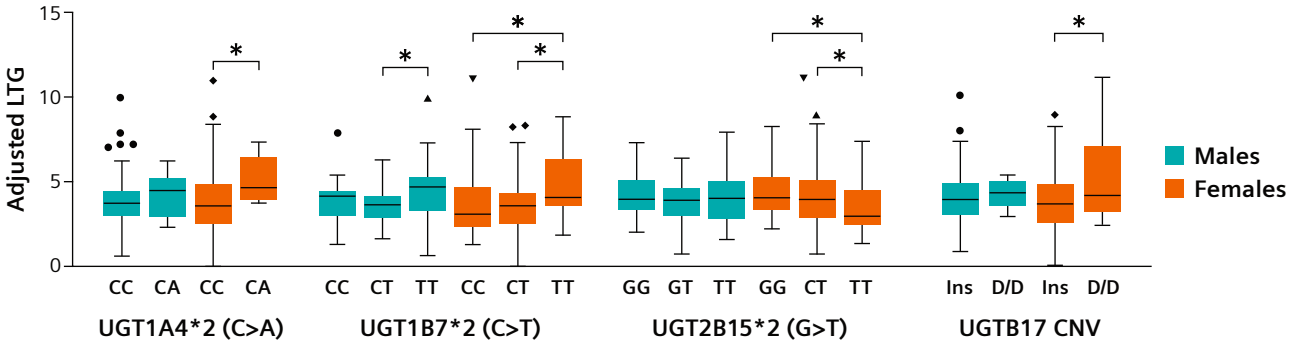


Figure 4. Variability of adjusted LTG serum concentration (mean of individual LTG concentration/(LTG dose/weight) by allele and sex: * indicates $p < 0.05$. (Adapted from Petrenaite et al.[15])

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.

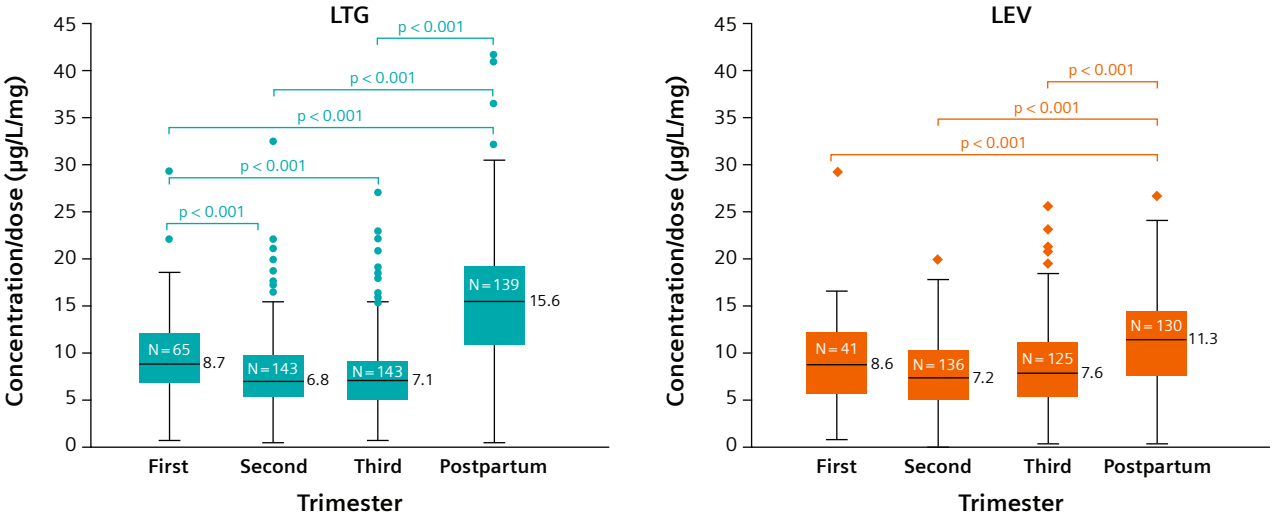


Figure 5. Mean and interquartile ranges for LTG and LEV during pregnancy and following parturition.

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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