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]

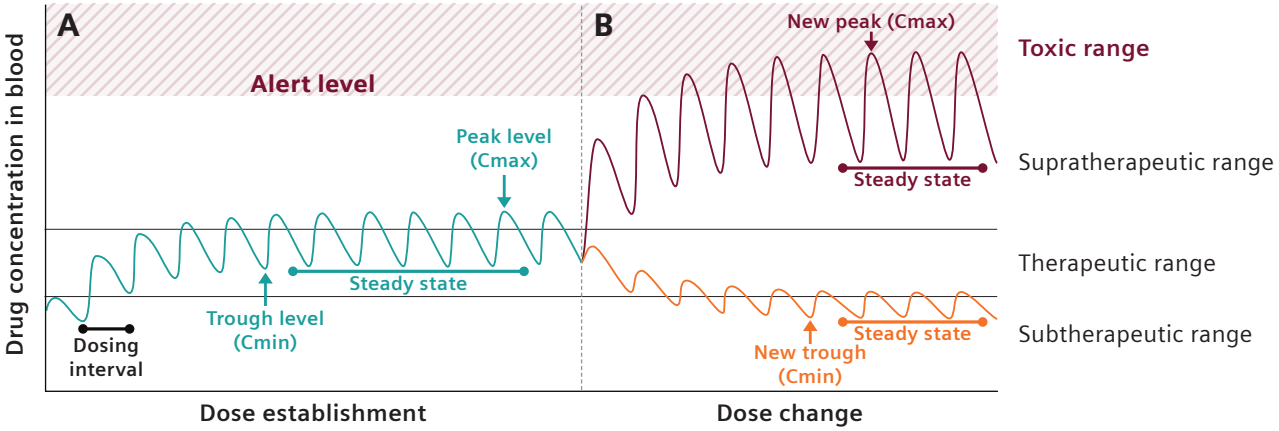


Figure 1. Concentration time curve for oral medication: A. Establishment of steady state in the therapeutic range based on empirical evidence of seizure control for at least six months. B. Effect of increased (red) or decreased (orange) dose change on development of toxicity or loss of therapeutic range,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

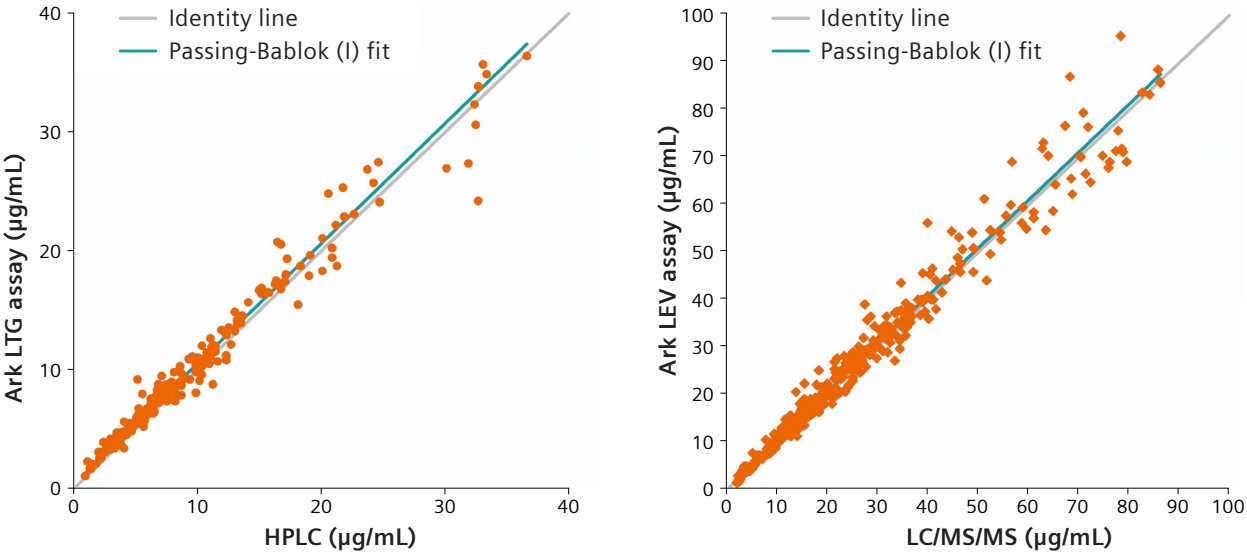
Regardless of the reason, blood testing can indicate if ASMs are at a subtherapeutic level relative to either accepted reference ranges or to a previously established baseline and serve as a valuable aid in diagnosis and adjustment.[23] Additionally, Hiemke et al. recommend regular blood monitoring during 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*

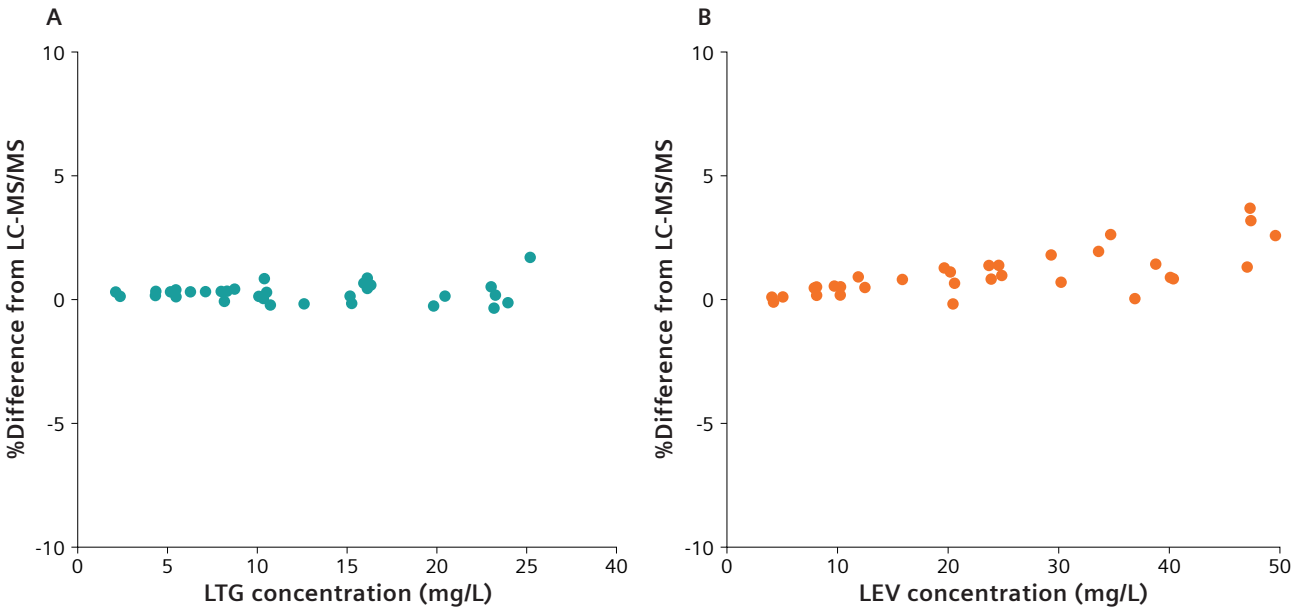


Figure 3. Differences between mean concentration of all LTG (A) and LEV (B) immunoassays and LC-MS/MS values reported in the 2021 CAP proficiency survey.[20]

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.

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