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Epileptic Disorders

SEMINAR IN EPILEPTOLOGY

Pharmacological aspects of antiseizure medications: From basic mechanisms to clinical considerations of drug interactions and use of therapeutic drug monitoring

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Abstract

Antiseizure medications (ASMs) are the cornerstone of treatment for patients with epilepsy. Several new ASMs have recently been introduced to the market, making it possible to better tailor the treatment of epilepsy, as well as other indications (psychiatry and pain disorders). For this group of drugs there are numerous pharmacological challenges, and updated knowledge on their pharmacodynamic and pharmacokinetic properties is, therefore, crucial for an optimal treatment outcome. This review focuses on educational approaches to the following learning outcomes as described by the International League Against Epilepsy (ILAE): To demonstrate knowledge of pharmacokinetics and pharmacodynamics, drug interactions with ASMs and with concomitant medications, and appropriate monitoring of ASM serum levels (therapeutic drug monitoring, TDM). Basic principles in pharmacology, pharmacokinetic variability, and clinically relevant approaches to manage drug interactions are discussed. Furthermore, recent improvements in analytical technology and sampling are described. Future directions point to the combined implementation of TDM with genetic panels for proper diagnosis, pharmacogenetic tests where relevant, and the use of biochemical markers that will all contribute to personalized treatment. These approaches are clinically relevant for an optimal treatment outcome with ASMs in various patient groups.

KEYWORDS

analytical methods, antiepileptic drugs, epilepsy, interations, pharmacokinetic variability

1 | INTRODUCTION

The pharmacology of antiseizure medications (ASMs) has been in focus for the past century. ASMs are the cornerstone of treatment for patients with epilepsy. In recent years several new ASMs have been introduced to the market, and around 30 different drugs are available internationally.[1–3] The armamentarium of drugs to choose from helps to tailor the treatment for groups and individuals with epilepsy and also in other disorders, that is, psychiatry and pain management.[3–7] Pharmacological challenges with all these drugs are numerous and therefore warrant detailed knowledge of the pharmacodynamic and pharmacokinetic properties of the drugs. Their

mechanisms of action often include several molecular targets, the pharmacokinetic variability is extensive, and few other drug classes involve such a large number of drug interactions as ASMs.[3,8,9] Often there is an unpredictable relationship between the dosage given and the exposure in the body in the individual patient. Factors such as environmental, physiological, and genetic factors contribute to extensive variability in the obtained serum concentrations of any given ASM.[8–10] Therapeutic drug monitoring (TDM) can be used to determine and adjust for pharmacokinetic variability and—interactions, and thereby facilitate optimal dosing in the individual patient.[10–12] TDM is used in many countries as part of the follow-up in patients with e.g. refractory epilepsy, even if there is a lack of evidence to support the routine use of TDM. There is level A evidence that TDM does not provide benefits in the management of patients with epilepsy on a general basis, and a Cochrane review found no clear evidence to support the routine use of ASMs.[13,14] Thus, it is important to know how to use TDM correctly in clinically relevant situations.

To cover pharmacological aspects of ASMs, we aimed at elucidating lines "from basic mechanisms to clinical considerations of drug interactions and use of therapeutic drug monitoring." The purpose of the present review is to develop a seminar educational paper addressing three learning objectives of the International League Against Epilepsy (ILAE) curriculum,[15] based on the literature as well as clinical experience:

- 3.1.2 Demonstrate knowledge of pharmacokinetics and pharmacodynamics
- 3.1.4 Demonstrate knowledge of appropriate monitoring of AED (=ASM) serum levels
- 3.1.5 Demonstrate knowledge about drug interactions (e.g. enzyme induction, etc.) for AED/AED and AED/concomitant medication (e.g. oral contraceptives, treatment of tuberculosis (TB), HIV, etc.)

2 | METHODS

2.1 | Literature search and selection criteria

This review was based on published articles and search in relevant databases, Google Scholar and PubMed, up to December 2022, with a focus on recent advances during the last decade. Peer-reviewed articles in international journals and scientific books written in English were included, and primary sources were preferred. Included search terms were one or more of the following, alone or in combination: antiseizure medications or antiepileptic drugs; individual ASMs: brivaracetam, cannabidiol, carbamazepine, cenobamate, clobazam, clonazepam, diazepam, eslicarbazepine acetate, ethosuximide,

Learning objectives of the International League Against Epilepsy (ILAE) curriculum and details on how these are achieved through this article

- *3.1.2 Demonstrate knowledge of pharmacokinetics and pharmacodynamics*
  - Pharmacokinetic processes: Absorption, Distribution, Metabolism, Excretion.
  - Pharmacokinetic variability in various patient groups.
  - Pharmacodynamics = Mechanisms of action of antiseizure medications (ASMs).
- *3.1.4 Demonstrate knowledge of appropriate monitoring of AED (=ASM) serum levels*
  - Principles for therapeutic drug monitoring.
  - Recent advances in analytical procedures and sample collection.
  - Implementation of TDM in a clinical setting.
- *3.1.5 Demonstrate knowledge about drug interactions (e.g., enzyme induction, etc.) for AED/AED and AED/concomitant medication (e.g., oral contraceptives, treatment of tuberculosis (TB), HIV, etc.)*
  - Principles for pharmacokinetic and pharmacodynamic interactions.
  - Examples of clinically relevant interactions between ASMs and with other drug classes.
  - Clinical handling of interactions and use of TDM.

Key points

- Pharmacokinetic processes: Absorption, Distribution, Metabolism, Excretion.
- Pharmacokinetic variability in various patient groups.
- Pharmacodynamics = Mechanisms of action of antiseizure medications (ASMs).
- Principles for therapeutic drug monitoring (TDM).
- Recent advances in analytical procedures and sample collection.
- Implementation of TDM in a clinical setting.
- Principles for pharmacokinetic and pharmacodynamic interactions.
- Clinically relevant interactions between ASMs and with other drug classes.
- Clinical handling of interactions and use of TDM.

everolimus, felbamate, fenfluramine, gabapentin, ganaxolone, lacosamide, lamotrigine, levetiracetam, midazolam, oxcarbazepine, perampanel, phenobarbital, phenytoin, pregabalin, primidone, rufinamide, stiripentol, sulthiame, tiagabine, topiramate, valproic acid, vigabatrin, and zonisamide. Other terms: cytochrome P450 (CYP)-enzymes, uridine glucuronyl transferase (UGT), drug interactions, epilepsy, mechanism of action, pharmacology, pharmacodynamics, pharmacokinetics, pharmacokinetic variability, pharmacogenetics, precision medicine, serum, or plasma, therapeutic drug monitoring.

3 | MAIN BODY

3.1 | Basic pharmacology—pharmacodynamics and pharmacokinetics

In this section, the following learning outcome should be fulfilled: *3.1.2 Demonstrate knowledge of pharmacokinetics and pharmacodynamics.*[15]

3.1.1 | Spectrum of activity

In Table 1 all ASMs are listed according to their classification of 1st, 2nd, or 3rd generation drugs. In general, the spectrum of activity varies, where the majority of drugs first have approved indication as add-on drug in focal seizures, and following clinical experience, the indications may be expanded, such as for lamotrigine and levetiracetam. Benzodiazepines and valproic acid are generally indicated in generalized epilepsies.[3] Drugs with specific and narrow indications are noted in Table 1.

3.2 | Pharmacodynamics: Mechanisms of action of ASMs

Most drugs currently used in the treatment of epilepsy prevent its symptom (seizures), and not the underlying disease. Hence, the use of the term 'antiseizure medications' (ASMs) for describing them.[16] Primary mechanisms of action of ASMs are depicted in Figure 1 and pharmacokinetic processes with examples of interactions in Figure 2.

3.2.1 | Inhibition of voltage-gated ion channels

The primary mechanism of action of phenytoin, carbamazepine, oxcarbazepine, eslicarbazepine acetate, lamotrigine, and lacosamide is the blockade of voltage-gated sodium channels, which prevents repetitive neuronal firing. Sodium channel blockade also contributes to the activity of felbamate, rufinamide, topiramate, zonisamide, and cenobamate.[3,17,18] Ethosuximide reduces the flow of calcium ions through T-type calcium channels. This inhibits the thalamic rhythm in the spikes-and-wave discharges of absence seizures. Gabapentin and pregabalin also exert their effects by binding to voltage-activated calcium channels.[18]

TABLE 1 Antiseizure medications.

Older drugs/first generation	Newer drugs/second generation	Newest drugs/third generation
Bromide (BRM)	Felbamate (FBM)	Brivaracetam (BRV)
Carbamazepine (CBZ)	Gabapentin (GBP)[g]	Cannabidiol[a] (CBD)
Clonazepam (CNP)	Lamotrigine (LTG)	Cenobamate (CNB)
Clobazam (CLB)	Levetiracetam (LEV)	Eslicarbazepine (ESL)
Ethosuximide[e] (ESM)	Oxcarbazepine (OXC)	Everolimus[b] (EVR)
Phenobarbital (PB)	Pregabalin (PGB)[g]	Fenfluramine[a] (FNF)
Phenytoin (PHT)	Tiagabine (TGB)	Ganaxolone[a] (GNX)
Primidone (PRM)	Topiramate (TPM)	Lacosamide (LCM)
Sulthiame[f] (SLT)	Vigabatrin[d] (VGB)	Perampanel (PMP)
Valproic acid (VPA)	Zonisamide (ZNS)	(Retigabine)[c] (RTG)
		Rufinamide[a] (RFM)
		Stiripentol[a] (STM)

Note: Classification of the ASMs used for prophylactic treatment, according to the time of approval, from the 1850s for bromide, to fenfluramine in 2021 was based on previous reviews, see.[3,10,11] Abbreviations in parentheses.

[a]Orphan drugs, specific indications in one or more of the following; Dravet syndrome, Lennox Gastaut syndrome or epilepsy associated with tuberous sclerosis complex (TSC), CDKL5-related epilepsy (*cyclin-dependent kinase-like 5) deficiency disorder*.

[b]Indication in tuberous sclerosis complex only.

[c]Withdrawn from the marked due to adverse effects.

[d]Limited use in infantile spasms due to visual field restriction.

[e]Used in absence epilepsies, primarily in children/adolescents.

[f]Used in benign childhood epilepsies in some countries. In addition to these drugs, steroids were also mentioned, as treatment in specific immune-related epilepsies.

[g]Gabapentin and pregabalin are now considered as N02A, Other analgesics, from 2023, according to the whocc.no/atc_ddd_index.

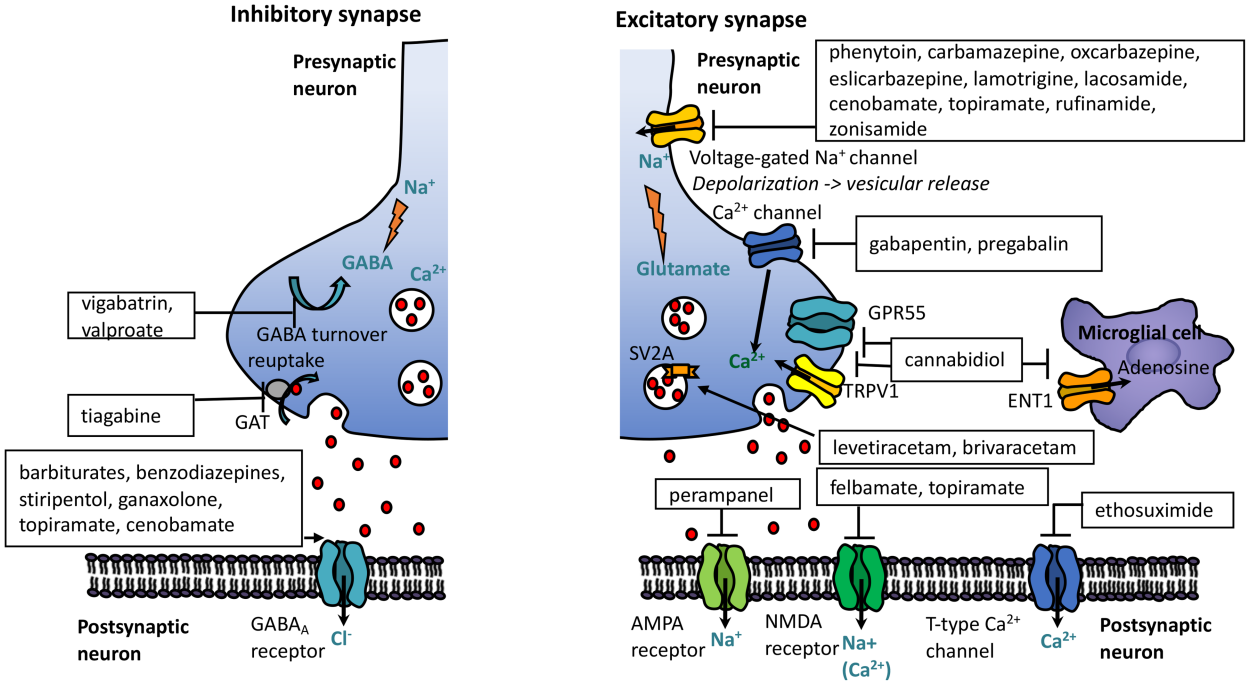

FIGURE 1 Pharmacodynamic features of antiseizure medications with their main proposed mechanisms of action. Left, inhibitory synapse; right, excitatory synapse. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ENT, equilibrative nucleoside transporter; GABA, gamma amino-butyric acid; GAT, GABA transporter; NMDA, N-methyl-D-aspartate; GPR55, G protein-coupled receptor-55; TRPV, transient receptor potential vanilloid. The mechanisms of action of fenfluramine and everolimus are not shown. The figure is based on.[3,20]

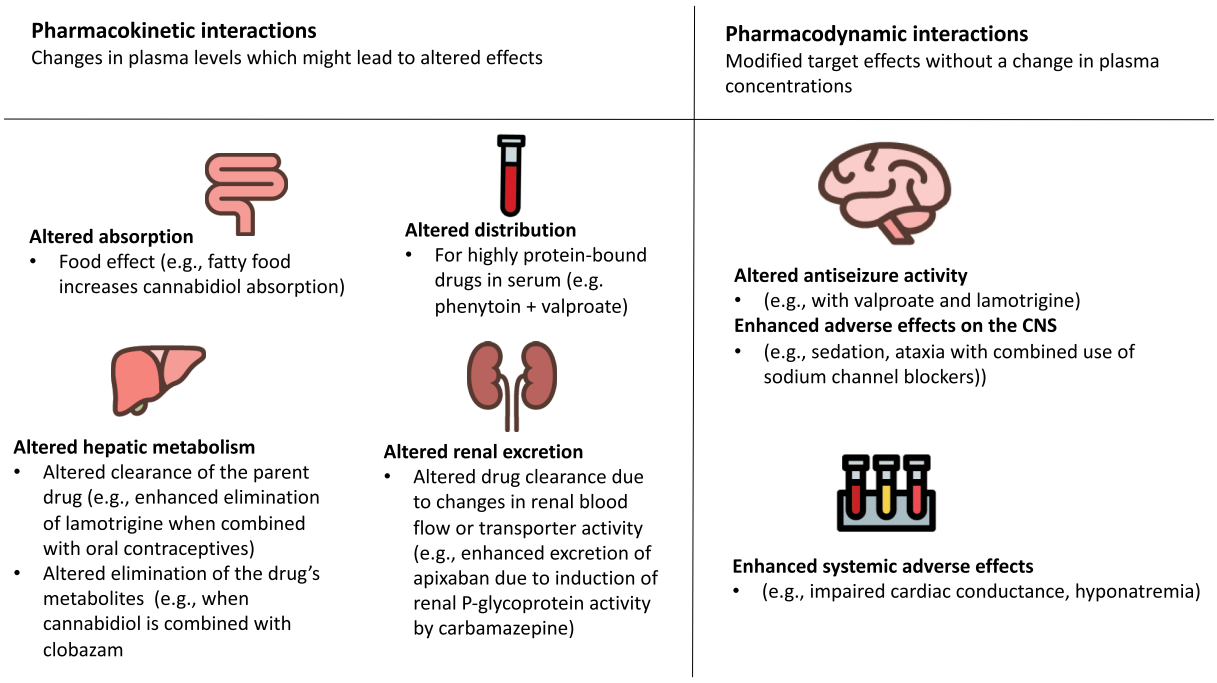

FIGURE 2 Pharmacokinetic and pharmacodynamic interactions with examples of drugs involved.

3.2.2 | Effects on GABAergic targets

Benzodiazepines (e.g., clobazam, clonazepam, diazepam and midazolam) and barbiturates (phenobarbital and its prodrug primidone) are allosteric modulators of $GABA_A$ receptors. Binding of these ASMs to the receptor enhances chloride influx in response to GABA and membrane polarization.[3,17,18] Phenobarbital and its prodrug primidone

at high dosages may also act as agonists of $GABA_A$ receptors, limiting the use (because of the risk of overdose/death). Allosteric modulation of $GABA_A$ receptors is also a mechanism of action of stiripentol, felbamate, topiramate, ganaxolone, and cenobamate.[18] Vigabatrin and tiagabine increase the accumulation of GABA in the brain by irreversible inhibition of its degradation by GABA transaminase or blockade of its reuptake into presynaptic neurons and glia, respectively.[3,17,18]

3.2.3 | Effects on glutamatergic targets

Among the glutamate receptors, two types that play a role in the generation and propagation of seizures are targeted by ASMs: (1) the alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors are selectively and non-competitively inhibited by perampanel; (2) blockade of the type *N*-methyl-D-aspartate (NMDA) receptors contribute to the pharmacological activity of felbamate and topiramate[3,17,18] Levetiracetam and brivaracetam bind to the synaptic vesicle protein 2A (SV2A) located presynaptically. The effect of binding is assumed to modulate vesicle fusion to the plasma membrane of nerve terminals and subsequent release of neurotransmitters to the synapse.[18]

3.2.4 | Other mechanisms

The recently approved drug cenobamate is considered to have a dual mechanism of action, acting as both an inhibitor of voltage-dependent sodium channels and a weak allosteric modulator of $GABA_A$ receptors.[1,18] Topiramate and zonisamide, in addition to their aforementioned mechanisms of action, are weak inhibitors of carbonic anhydrase in the central nervous system.[18] Valproic acid has various mechanisms of action which are still not fully understood, but include stimulation of GABAergic activity, blockade of voltage-dependent sodium channels, and weak inhibitory effect on T-type calcium currents.[3,17,18] The recently approved fenfluramine (repurposed as an orphan drug) in Dravet and Lennox Gastaut syndrome indirectly stimulates serotonergic 5-HT_{2C} and 5-HT_{1D} receptors and interacts with sigma-1 receptors.[1,19] Cannabidiol has yet other proposed mechanisms, as it may exert its therapeutic activity by antagonism of G protein-coupled receptor-55 (GPR55), desensitization of transient receptor potential vanilloid (TRPV1) channels, decreasing Ca-mediated excitation, and enhancement of adenosine-mediated signaling.[18,20] For example, by inhibiting its uptake into microglia.[18,20]

Everolimus differs from other ASMs by targeting the underlying disease pathology. Everolimus inhibits mammalian target of rapamycin (mTOR), a protein kinase that is a central cell growth regulator. The rationale for using everolimus in the treatment of tuberous sclerosis complex is the hyperactivity of the mTOR signaling cascade underlying abnormal cerebral cortical development that leads to seizures.[18]

3.3 | Principles of pharmacokinetics

Pharmacokinetics implies the processes of what the body does to handle the drug, that is, absorption, distribution, metabolism, and excretion (Figure 2). In general, absorption is extensive and bioavailability is high for most ASMs.[21] Exceptions are gabapentin which displays dose-related absorption and cannabidiol with extensive first-pass metabolism and limited absorption (around 6%), which increases 4–5-fold with fat-rich food.[22,23] For both these drugs there is, therefore, an unpredictable variability in bioavailability.[24] Most ASMs are lipid-soluble and can readily cross the blood–brain barrier, and are generally widely distributed in the body.[21] However, valproic acid, gabapentin, and pregabalin are ionized in serum and their cerebral distribution is largely mediated by uptake transport across the blood–brain barrier.[25] The degree of protein binding varies between drugs.[26] ASMs that are >90% protein bound, include phenytoin, and valproic acid, in addition to cannabidiol, clobazam, clonazepam, perampanel, stiripentol, and tiagabine.[26] Alterations in protein binding, and a change in the proportion of free, unbound pharmacologically active drug, can occur in cases of hypoalbuminemia, chronic liver or renal disease, pregnancy, and displacement from binding sites by other highly protein-bound drugs or endogenous substances (e.g., in uremia).[11,27] Under such circumstances, these changes may be of clinical significance and call for close follow-up and monitoring.

The majority of ASMs undergo extensive metabolism, mainly through oxidation by cytochrome P450 (CYP) enzymes (phase I reactions) or glucuronidation by UGTs (phase II reactions).[21,28] Exceptions include levetiracetam and rufinamide which undergo hydrolysis, and gabapentin, pregabalin, and vigabatrin which are excreted unchanged through the kidneys.[21] Polymorphisms in CYP2C9/19 genes may affect serum concentrations of phenytoin, cannabidiol, and *N*-desmethylclobazam (the active metabolite of clobazam).[23,29] Altered renal function is an important determinant of the clearance of drugs that are predominantly eliminated through renal excretion, including levetiracetam, gabapentin, and pregabalin.[21]

3.4 | Pharmacokinetic variability

Most ASMs are subject to pronounced pharmacokinetic variability both between and within patients. Pharmacokinetic variability is much larger between patients than within patients, and for most drugs (with few exceptions including phenytoin), there is a linear and predictable correlation between drug dose and serum concentration in the individual patient.[30,31] Pharmacokinetic variability is an important determinant of differences in response to ASMs.[32] It may be a result of differences in absorption, distribution, metabolism, and excretion and is determined by genetic factors, age, physiological states, pathological conditions, environmental factors, and interactions with other drugs.[8] As numerous factors contribute to this variability, the net effect in the individual patient can be hard to predict, and it is therefore difficult to anticipate exposure based on dose alone. Based on the assumption that clinical effect correlates better with drug concentrations than dose, TDM can be used to tailor treatment to the patient.[21,27,33,34] In TDM, quantification of drug levels in blood or serum is combined with information on pharmaceutical properties, patient characteristics, and a clinical evaluation of effects and adverse effects to individualize treatment.[12,21]

3.5 | Drug interactions involving ASMs

In this section, the following learning outcome is emphasized: *3.1.5 Demonstrate knowledge about drug interactions (e.g., enzyme induction, etc.) for AED/AED and AED/concomitant medication (e.g., oral contraceptives, treatment of TB, HIV, etc.)*, according to the roadmap presented by Blumcke et al.[15]

Approximately 20%–25% of patients with epilepsy and >75% of patients with drug-resistant epilepsy are treated with two or more ASMs.[6,35,36] Polypharmacy in which ASMs are co-prescribed with other drugs is also common, and the number of concomitant drugs is higher among the elderly, due to co-morbidities.[4,37] Patients may additionally use over-the-counter medications and dietary supplements that are not always reported to caregivers.[35] With a larger number of concomitant drugs, the risk of adverse reactions due to drug–drug interactions (DDIs) increases, and DDIs have long been recognized as a preventable cause of morbidity and mortality.[38]

Many clinically important DDIs involving ASMs are pharmacokinetic (when one drug alters the concentrations of the other), resulting from induction or inhibition of drug metabolism (Figure 2). This is because many ASMs are substrates, inducers, and/or inhibitors of drug-metabolizing enzymes. The magnitude of interaction, which is one determinant of its clinical relevance, depends on the fraction of the dose that is eliminated by the affected pathway. The elimination of many ASMs (e.g., carbamazepine, everolimus, lamotrigine, and midazolam) depends largely on one predominant drug-metabolizing enzyme. Therefore, they are prone to DDIs as the interaction "victims" (Figure 2, Table 2). Displacement-interactions at the site of protein binding are relevant in a few combinations such as stiripentol + valproic acid, leading to an altered balance between the bound and free (pharmacologically active) fraction of the drug. Although drug interactions may result in lower protein binding, this seldomly results in significant symptoms of overdose because the free fraction of a drug is also the part eliminated, resulting in lower total (free + bound) concentrations and thus not necessarily an increase in the free concentration of the drug.

3.5.1 | Drug interactions between ASMs

Carbamazepine, phenytoin, phenobarbital, and primidone are strong inducers of CYP isoenzymes, UGTs, and several drug transporters.[39,40] Accordingly, they can reduce the efficacy of co-administered ASMs such as lamotrigine (a UGT substrate), perampanel, and everolimus (CYP3A4/5 substrates). The newer ASMs topiramate (at doses ≥200 mg/day), oxcarbazepine, eslicarbazepine acetate, cenobamate, felbamate, and rufinamide also reduce the serum concentrations of some concomitantly administered ASMs. However, they are generally weak-to-moderate and not strong inducers.[41–43] Valproic acid, cannabidiol, cenobamate, clobazam, felbamate, and stiripentol inhibit drug-metabolizing enzymes. For instance, valproic acid can reduce the clearance of lamotrigine by one-half, leading to an increased risk of lamotrigine intoxication and life-threatening hypersensitivity reactions.[44] Combination of cannabidiol and clobazam increases exposure to major metabolites of both compounds, particularly *N*-desmethylclobazam.[45]

Enzyme inhibition-based interactions have relatively rapid timelines, with new steady-state concentrations achieved within hours or days. In contrast, the maximal effect of enzyme induction may be observed only days to weeks after the onset of co-medication due to the time required to synthesize more metabolizing enzymes. Caution is also required when the inducer is discontinued, because serum concentrations of the affected drug(s) may return to baseline even weeks after the change.[40,42] It is worth mentioning that the induction/de-induction of UGT is much more rapid than the induction/de-induction of CYP.[46]

Pharmacodynamic DDIs between ASMs involve additive effects, synergism, or antagonism of the drug

TABLE 2 Classification of drugs that may cause pharmacokinetic interactions with ASMs, and other drug classes (clinically relevant examples).

Enzyme inducers	Mixed inducer/inhibitor	Neutral ASMs	Enzyme inhibitors
ASMs			
Carbamazepine	Cenobamate	Clonazepam	(Brivaracetam)
Phenobarbital	(Clobazam)	Ethosuximide	Cannabidiol
Phenytoin	Eslicarbazepine	Everolimus	Stiripentol
Primidone	Felbamate	Gabapentin	Sulthiame
Rufinamide	Oxcarbazepine	Lacosamide	Valproic acid (certain enzymes)
Topiramate (<200 mg/day)		Lamotrigine	
		Levetiracetam	
		Perampanel	
		Pregabalin	
		Tiagabine	
		Vigabatrin	
		Zonisamide	
Other drug classes			
Ethinyl-estradiol			Erythromycin
Carbapenem antibiotics (e.g. imipenem, meropenem)			Isoniazid
Cisplatin			Proton pump inhibitors (e.g. omeprazole)
			Ritonavir (used for Covid-19)
			Azole antifungals

Note: The table is based on main categories, even if some drugs may exhibit some properties of induction/inhibition as shown in vitro or specific combinations. The table is not exhaustive but points to a clinically relevant approach of categorization. Based on the following references: [8, 10, 11, 42, 43, 90] and Prescribing Information of the various drugs.

action without alterations in their serum concentrations. Such DDIs may be beneficial or hazardous. One example is the potentiation of the lamotrigine effect by valproic acid. Although this combination can improve the therapeutic outcomes, adverse effects may be exacerbated as well.[43] Combinations of sodium channel blockers are often associated with increased incidence of CNS side effects in the absence of significant additive efficacy.[43,47,48]

3.5.2 | Interactions between ASMs and other drug classes

Valproic acid, felbamate, and, to a lesser extent, cenobamate, can decrease the clearance of drugs other than ASMs, including psychotropic drugs, calcium channel blockers, and anticoagulants, and lead to toxicity.[41,43] Cannabidiol is emerging as an inhibitor of multiple drug-metabolizing enzymes, which can inhibit the clearance of many drugs.[23,49] Drugs that require adjustments when prescribed with enzyme-inducing ASMs include old and new anticoagulants, calcium channel blockers and statins, immunosuppressants, and chemotherapeutic agents, antibiotics and anti-HIV drugs, psychotropic drugs, antidiabetic drugs, and oral contraceptives.[43,44,50] Proton pump inhibitors may increase the concentration of CYP2C19-substrates such as *N*-desmethyl-clobazam, carbapenem antibiotics (e.g., imipenem, meropenem) can reduce the serum concentration of valproic acid, and the chemotherapeutic agent cisplatin can decrease phenytoin concentrations.[42,43]

The preferred contraception methods in women treated with enzyme-inducing ASMs is the use of copper-containing intrauterine devices, medroxyprogesterone acetate-depot, or levonorgestrel-releasing intrauterine devices.[43] Vice versa, the use of combined contraceptive pills may decrease serum lamotrigine concentrations by approximately 50% or more,[51] resulting in seizures in some women. The underlying mechanism is the induction of lamotrigine glucuronidation by ethinylestradiol.[52]

As a group, DOACs are particularly prone to pharmacokinetics interactions with ASMs as "victims" of enzyme and transporter induction or inhibition.[53] All DOACs are substrates of P-glycoprotein (P-gp) whose induction would reduce their concentrations in plasma. However, DOACs differ in their metabolic pathways. CYP3A4 is responsible for the metabolism of rivaroxaban (50%) and to a lesser extent apixaban (20%). Edoxaban and dabigatran are minimally dependent on CYP450-mediated metabolism.[54,55] Co-administration of DOACs and enzyme-inducing ASMs can lower the serum concentrations of DOACs and may predispose the patient to therapeutic failure. In addition, DOAC-ASM pharmacodynamic interactions may result from the effects of ASMs on the coagulation system, e.g. by valproic acid-induced thrombocytopenia or bleeding with concomitant use of phenytoin, valproic acid, or levetiracetam[55] In a nested case–control study involving 89 284 patients with atrial fibrillation and venous thromboembolism, the use of DOACs combined with phenytoin, carbamazepine, valproic acid, and levetiracetam was associated with 2.18 higher risk of stroke and systemic embolism.[56] Levetiracetam has however been associated with a lower risk of cardiovascular death associated with levetiracetam compared with carbamazepine treatment in patients with poststroke epilepsy in a population-based setting.[57] To date, the clinical significance of DOAC interactions with mild-to-moderate CYP3A4/P-gp-inducing ASMs such as oxcarbazepine and cenobamate or enzyme-inhibiting ASMs (e.g., cannabidiol, felbamate) is unknown. According to the relevant European Heart Rhythm Association Guide,[55] when an ASM therapy should be started in a patient treated with a DOAC (or vice versa), interdisciplinary review with the treating cardiologist, neurologist, primary care physician, and clinical pharmacist is crucial, and measurement of DOAC serum concentrations and close follow-up is advised.[55] Notably, some adverse effects of ASMs and other medications used in cardiovascular disorders may be additive due to a pharmacodynamic interaction. For instance, the combination of carbamazepine or oxcarbazepine with diuretics is associated with an increased risk of hyponatremia.[58]

Concerns of DDIs peaked with the emergency authorization of the anti-Covid-19 nirmatrelvir/ritonavir combination. Both compounds are CYP3A4 substrates and ritonavir is a strong and irreversible inhibitor of CYP3A4, a weak-to-moderate inhibitor of several other CYP isoenzymes, and an UGT inducer. Accordingly, it has been recommended that everolimus should not be combined with this preparation. Patients treated with ASMs that are CYP3A4 substrates or lamotrigine should be monitored for drug efficacy and adverse reactions. In addition, benzodiazepines other than buccal midazolam were suggested as rescue therapy.[40]

3.5.3 | Other interactions (food, environmental factors)

The most striking example of a food-ASM interaction currently documented is the 4-5-fold increase in cannabidiol exposure when taken with a high-fat meal.[59] Use of the antidepressant St. John's wort (an inducer of drug-metabolizing enzymes) can result in subtherapeutic levels of several ASMs, particularly those which are CYP3A4 substrates, but the effect is mostly observed with high-dose preparations of the plant.[60]

Alcohol consumption is generally not recommended for patients with epilepsy, particularly those who use barbiturates or benzodiazepines and perampanel, due to additive CNS suppression or mood changes.

3.5.4 | Practical advice

Given the abundance of potential DDIs involving ASMs, drug interaction compendia may be used by prescribers for optimizing comedication. However, databases vary in the information provided, especially when the interaction is theoretical, relying on class effects.[61] In such cases, it is recommended to access the primary source of information, if available, or consult a pharmacist or a clinical pharmacologist. Also, serum concentration measurements of drugs in question, if available, can reveal and determine the magnitude of pharmacokinetic interactions.

In this section, the following learning outcome is highlighted: *3.1.4 Demonstrate knowledge of appropriate monitoring of AED serum concentrations*.[15]

Theoretical aspects are accompanied by practical advice on the appropriate use of TDM in a clinical setting in appropriate situations, as listed in Table 3, and the concepts are illustrated in Figure 3.

3.6 | Principles and clinical use of TDM

3.6.1 | Concepts and use of TDM

A key concept to the appropriate implementation of TDM includes a proper clinical evaluation and rationale for measuring the serum concentration. There are several reasons why TDM has become a commonly used tool to optimize treatment in epilepsy: Unpredictable pharmacokinetic variability and drug interactions as described

TABLE 3 Examples of situations where therapeutic drug monitoring is considered useful.

Situation	Rationale
After initiation of therapy	Detect unexpected pharmacokinetics
Treatment outcome is satisfactory	Establish individual therapeutic range
Seizure control is not achieved despite apparently adequate dosage	Determine actual exposure to drug
Unexpected change in seizure control	Aid in diagnosis and management
Change in dose	Especially if ASM displays non-linear pharmacokinetics
Change in other treatment (ASMs or other drugs)	Potential (change in) pharmacokinetic interactions Establish new therapeutic range in case of pharmacodynamic interactions Measurement of free concentration when combining highly bound ASMs
Suspected adverse events, toxicity, or overdose	Aid in diagnosis and management
In infants, children, or elderly	Change in pharmacokinetic parameters over time Particularly large pharmacokinetic variability at extremes of age Difficulties in communicating adverse effects Presence of comorbidities in many elderly patients Measurement of free concentration for highly bound ASMs in infants/elderly given the possible deviation in protein binding
During and after pregnancy	Ensuring adequate therapy in mother, while minimizing exposure to the fetus Changes in pharmacokinetics expected for many ASMs but large individual differences Measurement of free concentrations, highly bound ASMs Avoid overexposure of mother or the breastfed infant due to change in dosage during pregnancy
Comorbidities	Altered organ function (liver/kidney) that can affect the pharmacokinetics of drugs Measurement of free concentrations of highly bound ASMs Use of concomitant drugs, identify (or exclude) drug–drug interactions Difficulty/inability to communicate adverse effects
Change in drug formulations	Potential change in serum concentrations
Examine adherence	Patients often take medications differently from how they are prescribed Non-adherence has been shown to be an important cause of hospitalizations in patients with epilepsy
Emergency situations, status epilepticus	Aid in clarifying the reasons for loss of seizure control Aid in dose titration

Note: Based on the following references: [10–12, 21, 42, 62, 66].

above, as well as adherence and other treatment challenges, where TDM contributes to provide a quality assurance of the treatment (Figure 3). Treatment of epileptic seizures is prophylactic, with seizures occurring at unpredictable intervals, there are no reliable clinical surrogate markers of effect, and therapeutic failure can have drastic consequences.[10,12] Furthermore, signs and symptoms of toxicity can be subtle and difficult to distinguish from the illness itself.[12] TDM should be used on clear indications[8,11,12,62] and Table 3 provides some examples of situations where TDM is usually considered useful.

3.6.2 | Definitions

The ILAE issued guidelines for TDM in 1993 and these were updated in 2008.[12] Further updates on recommendations and use have been published in 2018 and 2020.[10,12,62] The following terms should be used: The "reference range" is defined as "a range of drug concentrations, which is quoted by a laboratory and specifies a lower limit below which a therapeutic response is relatively unlikely to occur, and an upper limit above which toxicity is relatively likely to occur".[12] Patients may achieve therapeutic benefit at concentrations outside these ranges, and hence one should use "individual therapeutic concentrations," defined as "the range of drug concentrations which is associated with the best achievable response in a given person".[12,34] Thus, based on the correct interpretation of these concepts, the clinical use of TDM relies on subsequent measurements over time in the individual patient, and the individual therapeutic concentration may then be established and followed when various patient- and drug-related factors vary over time.

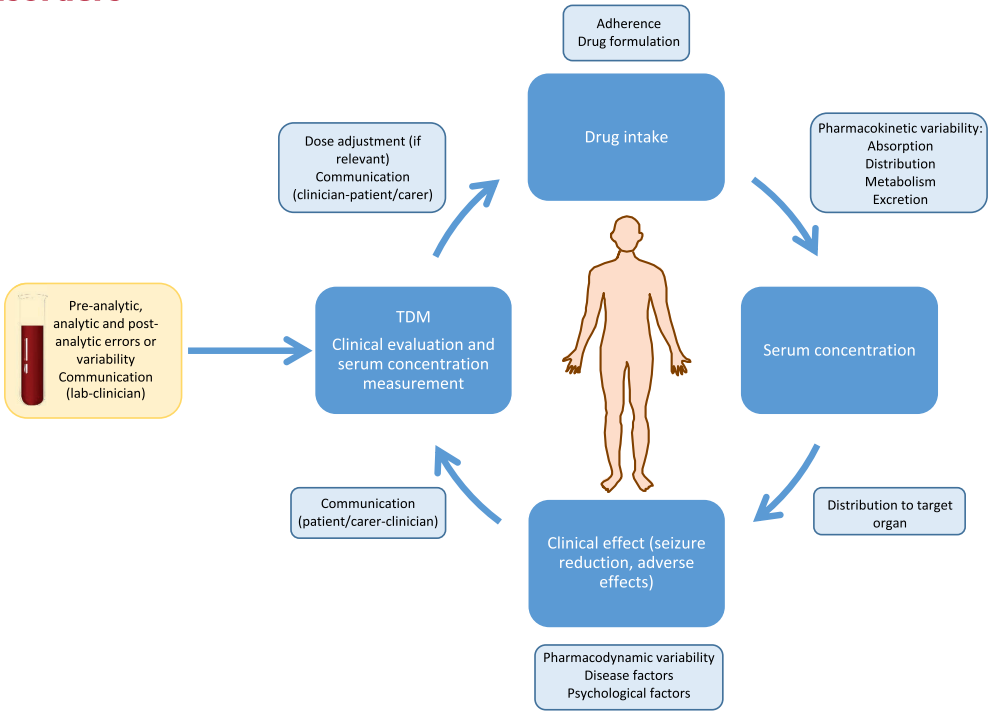

FIGURE 3 Pharmacokinetic processes and implementation of therapeutic drug monitoring. The light blue squares indicate factors affecting the various processes or actions, and the yellow square highlights factors that affect the results or interpretation of the results of serum concentration measurements.

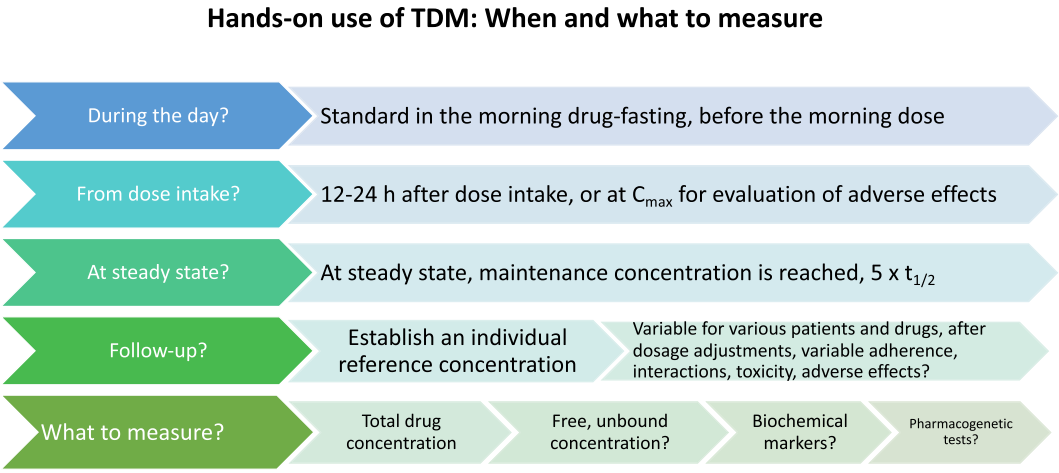

FIGURE 4 Practical and hands-on advice on the use of TDM: When and what to measure. The figure summarizes important considerations for the use of TDM in clinical practice.

3.6.3 | What and when to measure

Practical advice and hands-on use of TDM are summarized in Figure 4. Total drug concentrations are usually measured. However, the pharmacologically active part of a drug is the "free unbound" proportion. It has been demonstrated that, for example, the concentration of topiramate in cerebrospinal fluid (CSF) is equal to the unbound proportion of topiramate in plasma. Thus, serum/plasma is a relevant matrix for TDM.[63] The same applies to carbamazepine in serum and CSF, based on an older study.[64] If altered protein-binding of highly bound ASMs is suspected, measurements of free, unbound concentrations can be performed where available, and carefully considered when interpreting the results in the clinical context. This is illustrated in, for example, vulnerable young patients with Dravet syndrome.[31] This is most often done for valproic acid and phenytoin, ASMs with protein binding >90%, in acute as well as maintenance situations. If protein binding is significantly altered, the total

drug level is no longer representative for the exposure to pharmacologically active drug. The result of serum concentration measurements in such situations needs to be interpreted in light of this.[10,12,62,65]

Therapeutic drug monitoring should be used with serum concentration measurements at a standard time point, drug-fasting before intake of the morning dose at steady-state conditions. For subsequent measurement and to establish the individual reference concentration for a patient, the first measurements could then be used as a basis for comparison within that patient and related to the reference range for the drug(s) in use, as illustrated in Figure 3.[10–12] If concentration-related adverse effects are suspected, a serum sample may be drawn after a few hours around C_{max} to evaluate whether for instance a switch to a sustained-release formulation or division of the daily dose could be advised (Figure 4).

3.6.4 | Special patient groups across the ages

During the transition from childhood to adolescence, adulthood, and further to older age, significant changes in physiology (such as hepatic and renal function) occur and pathology may develop, affecting the pharmacokinetics of various ASMs.[8,11,66] Children are in rapid development, and careful consideration should be given to physiology and organ function and maturation, pharmacokinetic features, and overall capacity for drug elimination.[10,11,67] Recent studies with young and vulnerable children include cannabidiol and fenfluramine.[68,69]

Pregnancy is a time of particularly rapid and pronounced pharmacokinetic changes. Absorption may be affected by physiological changes or vomiting, volume of distribution can change due to an increase in body water and fat stores, and free, unbound concentrations of highly protein-bound drugs may increase.[10,12,62,65,70] Furthermore, the activity of drug-metabolizing enzymes is altered during pregnancy. The activity of e.g. UGT1A4 and many of the CYPs increase whereas a few CYPs display decreased activity.[66,70,71] In addition, renal blood flow and glomerular filtration rate increase, affecting renal clearance.[8,11,66] Pharmacokinetics changes documented for ASMs include a decrease in serum concentrations of lamotrigine, levetiracetam, phenytoin, phenobarbital, licarbazepine (measured when oxcarbazepine or eslicarbazepine is used), topiramate and total carbamazepine and VPA, but data are limited or lacking for a number of other ASMs.[70,71] Such changes vary considerably between individuals and are also influenced by other patient-related and environmental factors. Regular monitoring on a monthly basis is therefore recommended to avoid breakthrough seizures and to ensure a consistent exposure of ASMs that may also reduce the risks for the offspring.[10,71]

In the elderly clearance is generally lower than in younger adults, either as a result of decreased renal function and/or less efficient drug-metabolizing activity, but factors such as frailty, nutritional status, and comorbidities common to old age also play important roles.[8,11,66]

To better follow up vulnerable patients, long-term TDM in patients with multiple measurements has been introduced as a tool to investigate intra- and interpatient pharmacokinetic variability of drugs over a long time as recently demonstrated with carbamazepine over 20 years,[72] or TDM used in specific epilepsy syndromes such as juvenile myoclonus epilepsy and Dravet syndrome.[10,30]

3.6.5 | Analytical methodologies and recent development of TDM

Antiseizure medication measurements are performed using laboratory-developed methods or commercial kits, for research purposes and/or clinical analyses. Most laboratories presently use chromatographic methods or immunoassays in serum/plasma or alternative biological fluids such as saliva.[12] Immunoassays are usually easy to use, specific, rapid to perform, and are available for most of the old-generation ASMs and for some of the newer ASMs. These assays are limited to the determination of a single drug.[73] Chromatographic separation techniques permit the simultaneous quantification of several ASMs and related metabolites in a single analysis. Liquid chromatography combined with tandem mass spectrometry (LC–MS/MS) represents the most used methodology due to its high sensitivity and specificity.[74,75]

Serum or plasma represents the matrixes normally used for TDM and they can be used interchangeably. Saliva is an alternative matrix to serum/plasma of increasing utility for some ASMs as sample collection is non-invasive.[68] In addition, for many ASMs the measured levels in saliva correlate with the unbound, pharmacologically active component in blood.[12] Other biological matrices are rarely used in a clinical setting.[76]

Due to recent advances in LC–MS techniques with a major improvement in sensitivity, alternative microsampling techniques, include dried blood spots and volumetric absorptive microsampling have become feasible. Dried blood spot analysis is useful when venipuncture is undesirable, and it is based on the collection of a blood spot onto a piece of filter paper. After drying, the sample can be mailed to the laboratory where the dried blood spot sample will be processed. This approach has been implemented for many ASMs, but there are still technical issues needing

improvement.[77–80] Volumetric absorptive microsampling is another technique successfully applied to monitor ASMs.[81,82] These devices are porous hydrophilic tips that allow the collection of a small, fixed blood volume (10 or 30 μL) avoiding hematocrit bias.[82–84] Further advances in the clinical validation of these methods are needed, as analytical errors can result in inappropriate clinical decisions, and patient correlation studies are scarce.

As a general rule, any laboratory providing TDM services should be involved in internal and external quality assessment programs to ensure interlaboratory consistent results.[85]

3.6.6 | Proper implementation of TDM

TDM should be used based on a clinical indication and thus indiscriminate or routine use of TDM without an indication in unselected groups of patients is not advised. The impact in refractory patients with various treatment challenges or in situations such as during pregnancy is far more useful. There is not a clear correlation between clinical effects and serum concentrations for all ASMs, and therefore "therapeutic range" is not used as a term to define within what range the patient should stay for maintenance therapy. The term "individual therapeutic range" is therefore more suitable, as it elucidates where the individual patient has the best treatment outcome. Such outcomes are not easily investigated through randomized controlled trials (RCTs). Serum concentrations are difficult to blind, and vulnerable patients are not ethical to randomize to omit necessary measurements. Appropriate studies on the value of the use of TDM have therefore been difficult to implement. There is a lack of high-level evidence for the use of TDM. There are only a few RCTs trying to determine the impact of TDM in patients with epilepsy without conclusive evidence in favor of the use of TDM. Limitations of these studies include properly defined clinical outcomes and difficulties in design, blinding, and randomization.[13,14,86] This poses challenges when it comes to pre-selection of patients where the probability of TDM being clinically useful is high and ethical considerations of the value for individual patients. Before conducting such studies, it must be considered whether true equipoise exists for the clinical indication for TDM that is to be studied. It must also be emphasized that the need for TDM is much more prominent in patients with refractory epilepsy than in those with new-onset seizures. Real-life studies examining the clinical efficacy and tolerability of ASMs in relation to serum concentrations have in our experience been valuable in improving TDM services for the recently approved ASMs.[47,48,69,87,88] There is a need for studies in selected populations and for homogeneous indications for TDM to increase the level of evidence and benefits of use in terms of improved patient treatment and care, patient safety, and economical outcomes.

3.7 | Future perspectives

In the transition from medicine to personalized medicine also in the treatment of epilepsy, the use of TDM together with supplementary testing may facilitate proper treatment decisions. This constitutes an important part of future directions. Genetic panels are increasingly used to assess genetic epileptic etiologies and enable proper treatment choices such as certain precision treatment with everolimus in seizures associated with tuberous sclerosis. Furthermore, pharmacogenetic testing may be indicated to adjust the dosage to the individual better from the initiation of therapy in those patients who have deviating drug metabolizing capacities or to avoid exposure of drugs such as carbamazepine in patients with HLA-B*1502 polymorphism increasing the risk of serious adverse effects. Biochemical markers may also be used to monitor ASM therapy,[89] adverse effects, and avoid hepatotoxicity seen with valproic acid or cannabidiol.

4 | CONCLUSIONS

Insight into and understanding of basic and clinical pharmacology forms the basis for rational and safe treatment with ASMs in various patient groups. Pharmacological challenges include pronounced pharmacokinetic variability and numerous interactions both between ASMs and between ASMs and other drug classes. These are clinical indications for the individualized treatment approach in epilepsy by using TDM. To provide the best possible monitoring and follow-up and safe treatment of patients with epilepsy, it is essential that research and routine go hand in hand to facilitate safer and more efficacious treatment with ASMs in vulnerable patient groups. Future directions point to the combined implementation of TDM with complementary tests, such as genetic panels for proper diagnosis, pharmacogenetic tests where relevant, and the use of biochemical markers that will all contribute to personalized treatment.

CONFLICT OF INTEREST STATEMENT

CJL has received advisory board/speaker's honoraria from Angelini, Eisai, Jazz, and UCB Pharma. SE is a consultant for BioPass, Israel. SIJ, MLB, and VF have no disclosures.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX

TWO CASES

Case, interactions with food and drugs

A young boy, three years old with Dravet syndrome and difficult seizure situation uses valproate and clobazam. In addition, cannabidiol was recently added. The parents report increasing drowsiness, unsteady gait, sleepiness, reduced appetite and weight loss during the past weeks. The patient was admitted to hospital, and clinical and laboratory investigations were performed. The serum concentration of the active metabolite *N*-desmethyl-clobazam had doubled since the last analyses. A dosage reduction by 50% of clobazam led to improvement in the symptoms. Furthermore, when the appetite increased, diet adjustment was done with fat-rich food in the morning and evening.

What kind of interactions happened here?

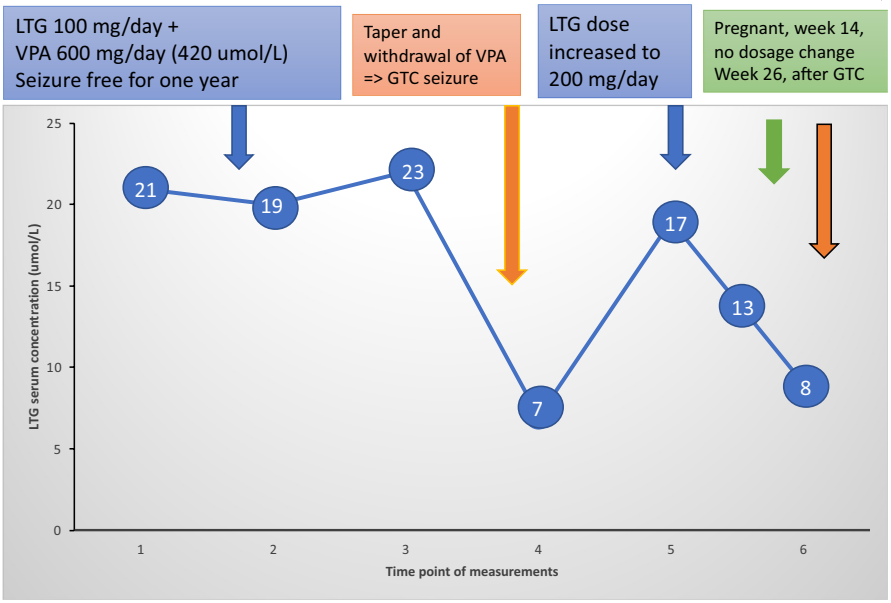
Comments:

Cannabidiol inhibits the metabolism of clobazam, leading to the increase in N-desmethyl-clobazam, which gave rise to excessive adverse effects. Cannabidiol has limited and variable absorption (about 5%), but this increases 4-5-fold if it is taken with fat-rich food. Thus, upon increased apetite, the absorption of cannabidiol will possibly increase. Close follow-up to monitor the efficacy and tolerability will be necessary.

Case, pregnancy: PK changes and use of TDM

A woman, 28 years, with JME has been seizure free for one year. She uses valproate, 600 mg/day + lamotrigine, 100 mg/day with stable serum concentrations for some time (se illustration). Adherence has been a challenge but is now better. Now valproate was tapered due to restrictions in use in women of childbearing age. She experienced a generalized tonic clonic (GTC) seizure for the first time in several years, and the serum concentration of lamotrigine was low and below the reference range. The dose was doubled and she continued on monotherapy. After some months she became pregnant, and at a control in week 14, showed that the serum concentration of lamotrigine was lower than at the last visit, but no dosage adjustment was done. In week 26 she experienced another GTC, and the serum concentration of lamotrigine was again very low.

What is next? What would you do? How often should she be followed? Possible pharmacokinetic interactions, use of TDM and changes during pregnancy?



Comments:

Initially, when valproate is tapered, a de-inhibition will occur, which led to a decrease in the serum concentration of lamotrigine from around 20 to 10 μmol/L. The dose of lamotrigine was therefore increased from 100 to 200 mg/day, and the next measurement showed 17 μmol.

Treatment with lamotrigine during pregnancy is a strong clinical indication for the use of TDM in a pro-active manner. This includes to monitor baseline values and regular serum concentrations (every 1–3 months) during pregnancy, aiming at increasing the dose when the serum concentration tends to decrease to avoid breakthrough seizures. By using the baseline value as her reference as an optimal therapeutic concentration, dosage adjustments should aim at keeping the same level. Valproate should be avoided according to international restrictions in women, but it is possible that this drug kept her seizure free before. Valproate inhibits the metabolism of lamotrigine through UGT1A4, and therefore the serum concentration of lamotrigine dropped when the inhibitor was discontinued. During pregnancy the increased endogenous estrogen will induce the metabolism of lamotrigine through the same metabolic pathway, leading to a decrease in the serum concentration. Thus, the dosage of lamotrigine should be increased, here perhaps 2.5-fold to reach pre-pregnancy values. TDM of lamotrigine should also be performed at the time of birth and afterwards, as this de-induction rapidly normalizes to pre-pregnancy state within few days. Then the dosage of lamotrigine should be adjusted to baseline, at 200 mg/day.

Test yourself

1. Antiseizure medications commonly act through the following mechanisms:
   A. Inhibition of chloride channels.
   B. As ligands of receptors for GABA or glutamate.
   C. Activation of voltage-gated sodium channels.
   D. Inhibition of voltage-gated sodium channels.
2. Pharmacological variability may include:
   A. Pharmacodynamic factors.
   B. Pharmacokinetic factors.
   C. Pharmacogenetic factors.
   D. All of the above.
3. Factors that contribute to pharmacokinetic variability between or within patients include:
   A. Age.
   B. Pregnancy.
   C. Comedication.
   D. Pharmacodynamic differences.

4. During pregnancy, the following ASMs often need a dosage increase due to increased metabolism and a decrease in serum concentration in the order of 30% or more:
   A. Carbamazepine.
   B. Lamotrigine.
   C. Levetiracetam.
   D. Oxcarbazepine.

5. Which statement(s) is/are correct regarding pharmacological variability in children:
   A. Age-dependent changes do not require dosage adjustments of ASMs.
   B. Physiological changes affect pharmacokinetic processes (absorption, distribution, metabolism, and excretion).
   C. Pharmacodynamic sensitivity is not regarded as a factor of variability.
   D. Children aged about 2–6 years have a high capacity of eliminating drugs.

6. Common pharmacological challenges in the elderly may include:
   A. Increased clearance of drugs that are metabolized in the liver.
   B. Decreased clearance of drugs that are excreted renally.
   C. Increased blood flow to eliminating organs, liver, and kidneys.
   D. Decreased blood flow to the brain.

7. If an enzyme inhibitor is added to a treatment, is it most possible that:
   A. It will inhibit the formation of active metabolites.
   B. It will induce metabolizing enzymes and decrease the serum concentration of concomitantly used drugs.
   C. It will inhibit metabolizing enzymes and increase the serum concentration of concomitantly used drugs.
   D. It will induce metabolizing enzymes and increase the serum concentration of concomitantly used drugs.

8. Pharmacokinetic interactions often involve enzyme induction or inhibition. Which statement(s) is/are correct:
   A. Enzyme induction usually occurs within 2–4 weeks for CYP-enzymes.
   B. The process of enzyme inhibition is dependent on the half-life of the inhibited drug only and not the one causing the interaction.
   C. Enzyme inhibition by one drug may increase the serum concentration of other drugs several-fold.
   D. Pharmacogenetic variability in metabolizing enzymes will not affect drug–drug interactions caused by enzyme induction or inhibition.

9. Which of the following is a clinical indication for the use of therapeutic drug monitoring:
   A. The patient using lamotrigine is starting an oral contraceptive.
   B. Variable adherence is a challenge.
   C. Comedication with possible drug–drug interactions.
   D. Use of vigabatrin for infantile spasms.

10. How would you react during interpretation of a serum concentration measurement?
   A. Ask the patient how he/she is doing and do no changes in the dosages of ASMs.
   B. Increase the dose if the patient has a serum concentration below the reference range.
   C. Evaluate how the patient is doing (seizures and adverse effects) and compare with the patient‘s concentration of antiseizure medication before possible dosage adjustments.
   D. Evaluate the result in relation to the reference range and do dosage adjustments accordingly.

Answers may be found in the supporting information.