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MODERN APPROACHES TO THE PHARMACOKINETICS AND PHARMACODYNAMICS OF ANTISEIZURE MEDICATIONS IN PATIENTS WITH EPILEPSY

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Abstract

Epilepsy is a chronic neurological disorder characterized by a persistent predisposition to epileptic seizures. Antiseizure medications (ASMs) are the principal pharmacological treatment, but their clinical performance is determined by a complex relationship between drug exposure, molecular targets, seizure biology, comorbidities, adherence and patient-specific pharmacokinetic variability. This narrative review examines contemporary pharmacokinetic and pharmacodynamic principles relevant to commonly used ASMs and emphasizes how these principles can be translated into individualized treatment. Particular attention is given to absorption, distribution, protein binding, hepatic and renal elimination, nonlinear kinetics, enzyme induction and inhibition, therapeutic drug monitoring, pharmacogenetics, pregnancy-associated changes, and model-informed precision dosing. Traditional ASMs such as carbamazepine, phenytoin, phenobarbital and valproate remain clinically useful but present substantial interaction and exposure–response challenges. Newer agents such as levetiracetam, brivaracetam and lacosamide generally offer more predictable pharmacokinetics and fewer interactions, although clinically relevant limitations remain. Therapeutic drug monitoring is most useful when there is a defined clinical question rather than as an isolated numerical target. Pharmacogenetic testing has its strongest current clinical role in predicting severe cutaneous reactions associated with selected aromatic ASMs and in supporting phenytoin dose optimization in genetically susceptible patients. Pregnancy illustrates the importance of dynamic monitoring because clearance and concentration-to-dose relationships may change substantially for several ASMs. Population pharmacokinetic models, Bayesian forecasting, microsampling, pharmacogenomics and digital adherence tools are emerging components of precision epilepsy care. Overall, modern ASM management should integrate seizure classification, pharmacodynamic mechanism, pharmacokinetic behavior, interaction burden, organ function, reproductive considerations and patient-specific therapeutic response.

Keywords: epilepsy; antiseizure medications; pharmacokinetics; pharmacodynamics; therapeutic drug monitoring; pharmacogenetics; drug interactions; precision medicine; population pharmacokinetics; individualized therapy.

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1. INTRODUCTION

Epilepsy is a common neurological disorder with major consequences for health, education, employment, social participation and quality of life (1). The International League Against Epilepsy (ILAE) defines epilepsy through a clinical framework that includes recurrent unprovoked seizures, a sufficiently high probability of further seizures after a first unprovoked seizure, or the diagnosis of an epilepsy syndrome (2). Pharmacological treatment remains the foundation of seizure prevention for most patients. The principal therapeutic objective is sustained seizure freedom with the lowest feasible burden of adverse effects and treatment complexity.

The terminology used for pharmacological agents has also changed. The ILAE has recommended the collective term “antiseizure medications” because these drugs primarily suppress seizure activity and should not automatically be interpreted as eliminating the underlying disease process (3). This distinction is clinically important when discussing treatment expectations, adherence and decisions about long-term therapy.

The pharmacology of ASMs is unusually diverse. Some agents have narrow therapeutic windows, nonlinear kinetics, extensive protein binding or strong effects on drug-metabolizing enzymes. Others have predominantly renal elimination and limited hepatic metabolism. Consequently, two patients receiving the same nominal dose may have very different systemic exposure. Age, body size, renal function, hepatic function, pregnancy, nutritional status, interacting medications, genetic variation and adherence can all modify the relationship between prescribed dose and achieved concentration.

Pharmacodynamics is equally important. ASMs reduce neuronal excitability through several mechanisms, including modulation of voltage-gated sodium or calcium channels, enhancement of inhibitory GABAergic signaling, attenuation of glutamatergic transmission and regulation of synaptic vesicle release. Pharmacodynamic response is not necessarily proportional to plasma concentration; an apparent treatment failure may reflect incorrect seizure classification, inadequate adherence, an inappropriate drug choice or drug resistance rather than inadequate exposure.

The objective of this review is to synthesize current evidence on the pharmacokinetic and pharmacodynamic principles of commonly used ASMs and to describe contemporary strategies for individualized treatment, including therapeutic drug monitoring, pharmacogenetics and population pharmacokinetic approaches.

2. METHODS

A narrative literature review was prepared using PubMed-indexed biomedical literature, international professional guidance and regulatory pharmacogenetic resources. The search concepts included epilepsy, antiseizure medication, anticonvulsant, pharmacokinetics, pharmacodynamics, therapeutic drug monitoring, drug interactions, pharmacogenetics, HLA, CYP2C9, pregnancy and population pharmacokinetics. Priority was given to systematic reviews, consensus statements, practice guidelines, pharmacokinetic studies and clinically relevant original investigations. Particular attention

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was given to recent literature while retaining landmark studies when they established principles that remain clinically applicable.

The synthesis was organized around clinically relevant questions: how ASM exposure is determined; which mechanisms create clinically important variability; when plasma concentration measurement is useful; how drug interactions alter exposure or response; which pharmacogenetic associations have sufficient evidence for clinical translation; and how individualized dosing can be improved in special populations. Because this is a narrative review and not a systematic review with quantitative meta-analysis, no pooled effect estimate was generated and the conclusions should be interpreted as an evidence-based clinical synthesis rather than a formal systematic-review result.

Eligibility and synthesis approach. Studies and guidance were considered relevant when they addressed clinically applicable pharmacokinetic or pharmacodynamic characteristics of ASMs, therapeutic drug monitoring, drug interactions, pharmacogenetic testing, pregnancy, organ dysfunction, or individualized dosing. Evidence was synthesized narratively according to pharmacological domain and clinical application. No quantitative meta-analysis was undertaken because the objective was to integrate heterogeneous pharmacological and clinical evidence rather than calculate a pooled effect estimate.

3. RESULTS

The literature synthesis identified several clinically important determinants of ASM exposure and response. These findings are organized below into pharmacodynamic mechanisms, pharmacokinetic determinants, interaction pathways, therapeutic drug monitoring, precision dosing, pharmacogenetics, special populations, and adherence-related factors.

3.1 Pharmacodynamic foundations of antiseizure therapy

The neuronal network underlying epilepsy is characterized by excessive synchronization and abnormal excitability. Pharmacodynamic interventions therefore aim to reduce repetitive neuronal firing, strengthen inhibitory signaling or reduce excitatory neurotransmission. The clinical effect of an ASM depends on the molecular target, the distribution of that target in relevant neural circuits, the functional state of neurons and the relationship between target engagement and seizure generation.

Voltage-gated sodium-channel modulation is a major mechanism for carbamazepine, phenytoin and lamotrigine. These agents preferentially limit repetitive high-frequency firing by stabilizing sodium channels in inactive states. Lacosamide has a mechanistically distinct effect on slow inactivation of voltage-gated sodium channels. The distinction matters because apparently similar target classes can produce different clinical and tolerability profiles.

Valproate has a broad pharmacodynamic profile. Its actions include effects on voltage-gated sodium channels and enhancement of inhibitory neurotransmission, among other mechanisms. The broad activity contributes to its usefulness across several seizure

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phenotypes, but its adverse-effect and reproductive-safety profile substantially influences contemporary treatment selection.

Levetiracetam and brivaracetam act principally through synaptic vesicle protein 2A (SV2A). Their pharmacological profiles illustrate a modern strategy in which relatively selective synaptic mechanisms are combined with comparatively simple pharmacokinetics. Brivaracetam has a high affinity for SV2A, although receptor affinity alone cannot be used as a surrogate for clinical superiority across all patient populations.

Pharmacodynamic adverse effects may become dose limiting before seizure suppression reaches a maximum. Somnolence, dizziness, diplopia, ataxia, cognitive impairment, behavioral symptoms, rash, hepatic injury and hematological abnormalities are examples of clinically important toxicity domains. Consequently, the therapeutic goal is an optimal exposure–response balance rather than maximal exposure.

3.2 Absorption and bioavailability

Most commonly used oral ASMs are sufficiently absorbed to support routine oral therapy, but the extent and predictability of absorption differ among agents and formulations. Modified-release formulations may change peak concentration and fluctuation without necessarily changing the total exposure. Food can influence the absorption of selected medicines, while gastrointestinal disorders or enteral feeding can complicate administration in hospitalized patients.

An important example of nonlinear absorption is gabapentin. Its intestinal uptake is mediated by a saturable transporter, so bioavailability decreases as the dose increases. This differs from a simple linear dose–exposure model and illustrates why doubling a dose does not necessarily double systemic exposure for every ASM.

Cannabidiol is another example in which formulation and food conditions can meaningfully affect exposure. High-fat meals can increase cannabidiol exposure, making consistency of administration particularly important when clinical response is being interpreted. These examples reinforce the principle that dose, formulation, meal timing and adherence should be considered together when evaluating unexpected changes in response.

3.3 Distribution, protein binding and the free-drug concept

After absorption, ASMs distribute between plasma and tissues according to physicochemical properties, blood flow and protein binding. Phenytoin and valproate are highly protein bound. Changes in albumin concentration, endogenous substances and competing drugs can alter the free fraction of these agents. Because the pharmacologically active fraction is the unbound drug, total concentration may not always accurately represent pharmacological exposure.

This issue is especially relevant in hypoalbuminemia, pregnancy, critical illness and advanced organ dysfunction. A total phenytoin concentration within a conventional reference interval can coexist with an unexpectedly high free concentration. In such

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situations, measurement of the free concentration may be more informative than relying on total concentration alone. Correction equations can be used when free measurement is unavailable, but direct measurement is preferable when the clinical situation is complex.

The concept is clinically important beyond laboratory interpretation. If an increase in the free fraction is mistaken for a fall in efficacy because only total concentration is considered, unnecessary dose escalation can produce toxicity. Modern TDM therefore emphasizes clinical context and, where appropriate, free rather than total concentrations.

3.4 Metabolism and enzyme induction

Hepatic metabolism is a major determinant of exposure for many traditional ASMs. Carbamazepine, phenytoin and phenobarbital are important enzyme-inducing agents. Enzyme induction can accelerate the clearance of concomitant medicines and may reduce their concentrations to clinically relevant degrees. The consequences can involve hormonal contraceptives, anticoagulants, immunosuppressants, antineoplastic agents and numerous cardiovascular or psychotropic medicines (4,5).

Carbamazepine also undergoes autoinduction. During the early phase of treatment, hepatic enzyme activity increases, accelerating carbamazepine clearance and changing the concentration-to-dose relationship. As a result, a dose that initially produces a particular concentration may produce a lower concentration after enzyme induction has developed. This phenomenon demonstrates why timing matters when interpreting ASM concentrations.

Enzyme induction is not simply a laboratory phenomenon. It can produce clinically important treatment failure in co-medications and can persist during chronic therapy. Conversely, withdrawal of an inducer may increase the exposure of previously induced drugs, creating a delayed toxicity risk if doses are not reconsidered. For this reason, medication reconciliation should be repeated when an inducing ASM is initiated, discontinued or substantially changed.

3.5 Enzyme inhibition and interaction networks

Valproate has clinically relevant inhibitory effects on several metabolic pathways and can alter the exposure of other ASMs. The combination of valproate with lamotrigine is particularly important because valproate reduces lamotrigine clearance and can substantially increase lamotrigine exposure. This is one reason why lamotrigine must be titrated cautiously when valproate is present.

Drug interactions can also occur through competition for plasma protein binding and through effects on transport proteins. Phenytoin and valproate provide a classic example in which protein-binding displacement changes the free fraction. In a patient receiving both drugs, the total phenytoin concentration may not predict the pharmacological effect as accurately as the free concentration.

Modern interaction management should therefore move beyond a simple list of “interacting drugs.” The clinician should ask which pharmacokinetic process is being

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modified, whether the change affects exposure or effect, whether the therapeutic index is narrow, and whether clinical or laboratory monitoring can detect the consequence early. Contemporary reviews continue to emphasize that interaction risk is particularly relevant in polypharmacy and that newer ASMs generally offer a lower interaction burden than many enzyme-inducing traditional agents (6,7).

3.6 Nonlinear pharmacokinetics: phenytoin as a model

Phenytoin is the classic clinical example of capacity-limited elimination. At therapeutic concentrations, metabolic pathways can approach saturation, so an apparently small dose increase may cause a disproportionate increase in plasma concentration. This creates a narrow margin for empirical dose escalation and increases the value of careful concentration monitoring when toxicity or loss of seizure control is suspected.

The clinical consequences of phenytoin kinetics are amplified by protein binding and pharmacogenetic variation. CYP2C9 genotype can affect metabolic capacity, and HLA-B*15:02 is associated with severe cutaneous reactions. The 2024 Dutch Pharmacogenetics Working Group guideline considers CYP2C9 genotyping important for preventing phenytoin toxicity in appropriate clinical contexts (8).

The phenytoin example illustrates a broader principle: when pharmacokinetics are nonlinear, dose changes should be conservative and supported by clinical observation and, when indicated, serum concentration measurement. A population reference interval is not a substitute for understanding the patient's individual exposure–response relationship.

3.7 Therapeutic drug monitoring

Therapeutic drug monitoring is most valuable when the measured concentration can answer a defined clinical question. The ILAE position paper identifies several situations in which monitoring can be useful: establishing an individual reference concentration after a desired response has been achieved, investigating suspected toxicity, evaluating adherence, managing patients with unusually variable pharmacokinetics, responding to pregnancy-related changes, and guiding therapy with dose-dependent pharmacokinetics such as phenytoin (9).

The later TDM update emphasizes that monitoring should be interpreted in the context of clinical response rather than as a rigid laboratory target (10). A patient who is seizure-free and tolerating treatment may not benefit from dose adjustment simply because the concentration lies outside a population “therapeutic range.” Conversely, a concentration inside the range does not prove that a particular dose is effective or safe for a specific patient.

Sampling time is essential. Trough concentrations are often preferred when standardized interpretation is required, but the appropriate timing depends on the medicine, formulation, dosing interval and clinical question. The laboratory result should therefore be accompanied by the exact dose, formulation, time of the last dose, time of sampling and relevant clinical circumstances.

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Emerging sampling technologies, including dried-blood-spot and microsampling methods, may make TDM more accessible and reduce the burden of conventional venous sampling. These approaches are promising but require analytical validation and appropriate interpretation before they can replace established laboratory methods.

3.8 Population pharmacokinetics and Bayesian dosing

Population pharmacokinetics describes typical pharmacokinetic parameters and the variability around them across a patient population. Covariates such as age, body weight, creatinine clearance, albumin concentration and concomitant medications can be incorporated into models. The resulting framework can estimate how patient characteristics modify clearance, volume of distribution and exposure.

Bayesian forecasting adds an individual patient's measured concentration to a population model. Instead of starting from the population average alone, the model updates the estimate of the patient's individual pharmacokinetic parameters. This is particularly attractive for medicines with narrow therapeutic windows or high interindividual variability.

Levetiracetam provides an illustrative example in pregnancy. Population pharmacokinetic studies have demonstrated clinically relevant changes in clearance and have explored dosing optimization during pregnancy (11). Such models can support a more dynamic approach in which dose is adjusted according to changing exposure rather than pregnancy trimester alone.

Model-informed precision dosing should not be presented as a replacement for clinical judgment. The quality of the model, assay, sampling strategy and patient data determines the reliability of the recommendation. The greatest value is achieved when pharmacometric estimates are integrated with seizure frequency, adverse effects, adherence and organ-function assessment.

3.9 Pharmacogenetics and pharmacogenomics

Pharmacogenetics is one of the clearest examples of precision medicine in epilepsy. HLA-B*15:02 is strongly associated with carbamazepine-induced Stevens–Johnson syndrome and toxic epidermal necrolysis in susceptible populations. HLA-A*31:01 is associated with several carbamazepine hypersensitivity phenotypes. CPIC and other expert groups have developed genotype-informed recommendations, and the FDA maintains a pharmacogenetic association table that includes carbamazepine and HLA-B*15:02 (17,13).

More recent DPWG guidance extends the pharmacogenetic discussion to HLA-B and CYP2C9 associations involving carbamazepine, oxcarbazepine, lamotrigine and phenytoin. The guideline emphasizes that HLA-B*15:02-positive patients have increased risk of severe cutaneous adverse reactions and recommends alternative therapy when appropriate; CYP2C9 genotype can also inform phenytoin dosing (8).

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The clinical utility of pharmacogenomics is not uniform across all candidate genes. Associations involving HLA alleles and severe cutaneous reactions have stronger and more reproducible clinical evidence than many proposed pharmacogenetic predictors of seizure response. A 2026 systematic review concluded that only a limited number of genetic associations currently have sufficient consistency for broad clinical translation, while many response-related findings remain heterogeneous across populations (14).

Therefore, pharmacogenetic testing should be used selectively and interpreted with population context. Genotype does not replace clinical vigilance: an individual without a recognized risk allele can still develop a severe reaction, and a positive genotype does not by itself determine every aspect of treatment selection.

3.10 Pregnancy as a pharmacokinetic stress test

Pregnancy produces coordinated physiological changes that can alter drug disposition. Plasma volume expands, renal filtration changes, plasma protein concentrations may fall and hepatic metabolic activity can change. These effects can modify both total and free concentrations of ASMs.

Lamotrigine and levetiracetam are particularly important examples. A 2024 systematic review and meta-analysis of 674 pregnancies found substantial pharmacokinetic changes for lamotrigine, levetiracetam and oxcarbazepine-related therapy, with lower concentration-to-dose relationships reported particularly in later pregnancy (15). This supports individualized monitoring when seizure control depends on maintaining a relatively stable exposure.

The objective is not simply to normalize a laboratory concentration. The clinically meaningful target is the patient's effective exposure associated with seizure control and acceptable tolerability. Establishing a pre-pregnancy or early-pregnancy individual reference concentration can therefore be useful when later concentrations are interpreted.

Reproductive safety must be integrated with pharmacokinetics. Valproate has well-established fetal risks, and current evidence continues to support avoiding it when effective and safer alternatives are available. A 2025 meta-analysis reported higher risks of several major congenital malformation categories with valproate compared with other ASMs (16). Treatment decisions in women and girls of childbearing potential therefore require both seizure-control and reproductive-risk assessment.

3.11 Renal and hepatic impairment

Renal function is a major determinant of exposure for ASMs that are substantially eliminated unchanged by the kidneys. Levetiracetam, gabapentin and pregabalin are prominent examples. Dose adjustment is therefore required when renal function is reduced. Creatinine concentration alone may underestimate the clinical relevance of renal impairment in older or low-muscle-mass patients; an appropriate estimate of renal function should be used in dosing decisions.

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Hepatic dysfunction creates a different problem. Drugs with extensive hepatic metabolism may have reduced clearance, while hypoalbuminemia may alter free concentrations of highly protein-bound medicines. The clinical response may therefore change even when the prescribed dose has not changed.

When organ function changes, clinicians should review the entire ASM regimen rather than adjust a single dose in isolation. Polytherapy can produce additional interaction effects, and a dose reduction of one medicine can alter the exposure of another if an inducing or inhibiting relationship is present.

3.12 Older adults and polypharmacy

Older adults frequently have multiple chronic conditions and therefore receive several medicines simultaneously. This increases the probability of pharmacokinetic and pharmacodynamic interactions. Reduced renal function can increase exposure to renally eliminated ASMs, while age-related sensitivity can amplify sedation, dizziness and gait impairment even when plasma concentrations are not markedly elevated.

A practical approach is to prioritize ASMs with appropriate seizure-spectrum coverage, relatively low interaction potential and manageable dosing schedules. Simplification of therapy may improve adherence, while careful titration can reduce falls and cognitive adverse effects. Medication review should include over-the-counter drugs and supplements because interaction databases do not always capture every combination equally well.

3.13 Newer ASMs and the shift toward predictable pharmacokinetics

The development of newer ASMs has not eliminated pharmacokinetic variability, but it has reduced several classic interaction problems. Levetiracetam is primarily renally eliminated and has limited CYP-mediated interactions. Brivaracetam also has a relatively low interaction burden, although CYP2C19 contributes to its metabolism. Lacosamide has mixed renal and hepatic elimination and generally fewer clinically important interactions than enzyme-inducing traditional ASMs.

This shift has practical value in patients with cancer, cardiovascular disease, psychiatric comorbidity, transplant therapy or extensive polypharmacy. Nevertheless, “few interactions” does not mean “no interactions.” Renal impairment, dose-related adverse effects, additive central nervous system effects and specific metabolic pathways can still be clinically relevant.

The choice of a newer ASM should therefore be individualized rather than based solely on the assumption that newer is better. Efficacy for the relevant seizure type, adverse-effect profile, reproductive safety, cost, availability, adherence and comorbidity remain important determinants of treatment selection.

3.14 Pharmacodynamic interactions in polytherapy

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When two ASMs are combined, pharmacodynamic effects can be additive or synergistic, but adverse effects can also accumulate. Combining agents that independently cause dizziness, sedation or ataxia may produce clinically significant impairment even when their pharmacokinetic interaction is minimal.

The same principle applies to psychotropic and analgesic medicines. An absence of a major CYP interaction does not exclude additive central nervous system depression, behavioral effects or cognitive impairment. Conversely, some pharmacodynamic combinations may provide complementary seizure control without a major increase in toxicity, but this must be demonstrated clinically rather than assumed from mechanisms alone.

For patients receiving polytherapy, the goal should be rational combinations with complementary mechanisms and minimal overlapping toxicity. If seizure control is inadequate despite appropriate trials of two tolerated and appropriately selected ASM regimens, the patient meets the conventional ILAE framework for drug-resistant epilepsy and should be considered for specialist evaluation rather than indefinite medication escalation (18).

3.15 Adherence, digital monitoring and exposure–response interpretation

Poor adherence is a major confounder in the assessment of apparent treatment failure. A low concentration may reflect missed doses rather than rapid clearance. Increasing the prescribed dose without identifying non-adherence can increase toxicity when adherence later improves.

Digital medication reminders, electronic dispensing records, patient-reported seizure diaries and selected wearable technologies may help characterize adherence and seizure patterns. Their role is complementary: they should generate clinically useful information rather than replace direct communication with the patient.

A useful modern framework is to distinguish three scenarios: inadequate exposure, adequate exposure with inadequate pharmacodynamic response, and adequate prescribed therapy with inadequate actual exposure because of adherence or interactions. This classification can prevent inappropriate dose escalation and guide the next clinical decision.

3.16 Limitations of current precision pharmacotherapy

Precision medicine in epilepsy is promising but remains limited by incomplete biomarkers, heterogeneous seizure biology, variable assay availability and unequal access to pharmacogenetic testing. Many pharmacogenomic associations reported in research have not been replicated consistently across populations. Population pharmacokinetic models may also perform less accurately when applied to patients who differ substantially from the population used for model development.

Therapeutic concentration ranges are population-based constructs and should not be interpreted as universal biological thresholds. The clinical outcome of interest remains

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seizure control with acceptable safety. Consequently, individualized treatment must remain clinically anchored even when sophisticated laboratory and computational tools are available.

Another limitation is that epilepsy is not a single disease. Seizure type, epilepsy syndrome, etiology and comorbidity influence treatment response. A pharmacokinetic model can estimate exposure accurately while the underlying pharmacodynamic drug choice remains inappropriate. Precision dosing therefore cannot compensate for an incorrect diagnosis or inappropriate seizure classification.

3.17 Future directions

The next generation of ASM pharmacotherapy is likely to combine pharmacometrics, pharmacogenomics, digital health and longitudinal clinical phenotyping. Bayesian dosing systems could use sparse concentration measurements to individualize therapy. Microsampling could facilitate home-based or outpatient monitoring. Pharmacogenetic panels may become more integrated into electronic prescribing systems, allowing actionable variants to be considered before high-risk medicines are started.

Machine-learning methods may eventually combine seizure diaries, EEG characteristics, medication exposure, laboratory results and genomic information to predict treatment response. However, predictive performance must be validated prospectively, externally and across diverse populations before such systems can safely influence treatment decisions.

The most realistic near-term model is therefore an integrated clinical decision-support framework rather than fully automated prescribing. The clinician remains responsible for interpreting the patient's seizure phenotype, treatment goals, adverse effects, laboratory results and preferences.

3.18 Summary of contemporary individualized ASM management

Key pharmacological domain	Main clinical implication	Modern individualized approach
Pharmacodynamics	Drug efficacy depends on seizure type, molecular target, and patient response; higher exposure does not necessarily mean better control.	Select the ASM according to seizure phenotype and balance seizure control against adverse effects.
Absorption and bioavailability	Food, formulation, gastrointestinal factors, and saturable absorption can alter exposure.	Consider formulation, administration conditions, adherence, and clinically relevant changes in exposure.
Protein binding	Changes in albumin and	Interpret total

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	competing drugs may increase the free fraction of highly protein-bound ASMs such as phenytoin and valproate.	concentrations cautiously and consider free-drug measurement when clinically appropriate.
Metabolism and interactions	Enzyme induction/inhibition can substantially change exposure to ASMs and concomitant medicines.	Review the complete medication regimen whenever an inducer/inhibitor is started, stopped, or changed.
Nonlinear pharmacokinetics	Small dose increases of phenytoin may produce disproportionate concentration increases.	Use conservative titration and targeted therapeutic drug monitoring when toxicity or loss of seizure control is suspected.
Therapeutic drug monitoring	A concentration is most useful when it answers a defined clinical question; population ranges are not universal targets.	Interpret TDM together with seizure control, adverse effects, adherence, sampling time, and individual reference concentrations.
Pharmacogenetics	Selected HLA and CYP2C9 variants can predict important adverse reactions or influence phenytoin dosing.	Use genotype-guided treatment selectively where evidence supports clinical action.
Pregnancy	Physiological changes can increase clearance and alter concentration-to-dose relationships for several ASMs.	Use longitudinal clinical and, when indicated, concentration monitoring; anticipate pregnancy and postpartum changes.
Renal/hepatic function	Organ dysfunction can markedly alter clearance and/or free-drug exposure.	Adjust therapy according to appropriate renal/hepatic assessment and reassess the entire regimen.
Newer ASMs	Levetiracetam, brivaracetam, and lacosamide generally have fewer clinically important interactions and more predictable kinetics.	Prefer simpler pharmacokinetic profiles when clinically appropriate, while still matching efficacy and safety to the patient.
Polytherapy and adherence	Pharmacodynamic toxicity may accumulate, while missed doses can mimic inadequate drug exposure.	Use rational combinations, adherence assessment, seizure diaries, and digital tools when useful.
Precision dosing	Population PK and Bayesian	Integrate pharmacometric

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	methods can incorporate patient-specific covariates and measured concentrations.	estimates with clinical judgment rather than replacing clinician decision-making.

4. DISCUSSION

The pharmacokinetic and pharmacodynamic management of epilepsy has moved beyond the traditional concept of selecting a drug and escalating the dose until seizures stop. Contemporary practice recognizes that exposure varies among individuals and that the same concentration can produce different outcomes. This makes the clinical interpretation of pharmacology more important than the memorization of isolated reference ranges.

Traditional ASMs remain important because of their efficacy, long clinical experience and availability, but enzyme induction, nonlinear kinetics and protein-binding effects create additional management demands. Newer ASMs frequently provide a simpler interaction profile and more predictable exposure, which can be particularly valuable in polypharmacy. The choice, however, must still be matched to seizure type and patient characteristics.

Therapeutic drug monitoring should be targeted. The most defensible indication is a clinical question that the concentration can help answer: Is toxicity due to excessive exposure? Has adherence changed? Has pregnancy altered clearance? Has renal function changed? Has an interacting drug been introduced or withdrawn? Establishing an individual's effective concentration during stable seizure control can be particularly useful for future comparison.

Pharmacogenetics provides a second dimension of individualized treatment. HLA testing for selected aromatic ASMs and CYP2C9 information for phenytoin represent the clearest examples of clinically actionable genetic information. Broader pharmacogenomic prediction of efficacy remains promising but insufficiently standardized for routine universal implementation.

Pregnancy demonstrates why precision treatment must be longitudinal. A dose that was effective before conception may become inadequate later because clearance changes. Conversely, postpartum pharmacokinetics can change again. Treatment planning should therefore anticipate transitions rather than react only after breakthrough seizures occur.

Overall, the most useful contemporary strategy is a layered approach: establish the correct epilepsy diagnosis; choose an appropriate ASM; identify interaction and organ-function risks; titrate carefully; monitor clinical response; use TDM when a specific indication exists; apply pharmacogenetic information when evidence supports it; and consider population pharmacokinetic or Bayesian tools when variability is high. This framework connects pharmacological theory with practical patient care.

Summary of Contemporary Individualized ASM Management

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The principal implication of these findings is that ASM selection and dose adjustment should be treated as an integrated exposure–response problem. Pharmacokinetic variability can be reduced or recognized through interaction review, organ-function assessment, selective TDM, pharmacogenetic testing and model-informed dosing, while pharmacodynamic appropriateness must remain anchored to seizure classification and individual tolerability.

5. CONCLUSION

Modern antiseizure therapy is increasingly based on individualized interpretation of pharmacokinetic exposure and pharmacodynamic response. Differences in absorption, protein binding, metabolism, renal elimination, enzyme induction, enzyme inhibition and genetic background can materially alter treatment outcomes. At the same time, seizure classification and the intrinsic pharmacodynamic suitability of a medicine remain fundamental.

The most clinically relevant advances include selective therapeutic drug monitoring, model-informed dosing, pharmacogenetic risk assessment, improved interaction management and closer attention to special populations such as pregnant patients and individuals with renal or hepatic impairment. Newer ASMs can simplify pharmacokinetic management but do not eliminate the need for individualized assessment.

Future precision epilepsy care will likely integrate clinical phenotyping, longitudinal exposure data, pharmacogenomics, pharmacometric modeling and digital adherence information. The central objective should remain unchanged: durable seizure control with the lowest reasonable risk of adverse effects and treatment burden.

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