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NEW-GENERATION ANTICONVULSANTS IN EPILEPSY: PRACTICAL SELECTION AND SAFETY MONITORING

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Abstract: Epilepsy is a chronic neurological disorder characterized by recurrent seizures. The main goals of treatment are to control seizures, minimize adverse effects, and improve patients' quality of life. In recent years, new-generation antiseizure medicines (ASMs) - brivaracetam, lacosamide, perampanel, cenobamate, cannabidiol, and fenfluramine - have stood out due to diversification of mechanisms and additional clinical options in some pharmacoresistant cases. This article, using an evidence-informed review approach, summarizes indications, efficacy signals, drug-drug interactions, and principles of safety monitoring for these agents. The findings suggest that new-generation ASMs are most often used as add-on therapy; optimal outcomes depend on patient-centered selection tailored to seizure type/syndrome, age and comorbidities, potential drug-drug interactions, and titration rate. In practice, targeted monitoring of treatment retention (persistence), cognitive and psychobehavioral effects, fall risk, and relevant laboratory indicators improves medication safety.

Keywords: epilepsy; antiseizure medicines (ASMs); new-generation anticonvulsants; brivaracetam; lacosamide; perampanel; cenobamate; monitoring.

INTRODUCTION

Epilepsy is clinically heterogeneous and may present with focal, generalized, or unknown-onset seizures. Therefore, treatment strategy should not follow a 'one drug fits all' principle but rely on selection aligned with seizure type and epileptic syndrome. Although seizure control is the most important outcome for patients, in real life cognitive function, sleep quality, mood, social adaptation, and the ability to work safely are integral parts of care. In pupils, adolescents, and university students, adverse effects involving attention and memory can reduce learning performance, while in older adults dizziness and ataxia can increase the risk of falls. From an epidemiological perspective, epilepsy creates a substantial burden for health systems: emergency calls, trauma and occupational hazards, driving restrictions, family stress, and stigmatization all require a multidisciplinary approach beyond medication alone. Consequently, when choosing antiseizure therapy, the aim is not only 'stopping seizures' but also preserving everyday functioning and organizing a safe lifestyle (sleep hygiene, regular medication intake, reducing provoking factors). In practice, patients often take multiple drugs, which increases the likelihood of interactions and unexpected adverse effects such as sedation or dizziness.

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In clinical practice, antiseizure drug selection usually begins with first-line monotherapy. If seizures persist despite two appropriately chosen ASMs used for an adequate duration, the probability of pharmacoresistance increases. In such cases, the medication strategy should be reconsidered, including switching to an agent with a different mechanism of action or planning rational polytherapy (add-on). New-generation ASMs show their clinical value particularly at this stage: they target different receptors and ion channels; some have fewer metabolic interactions, and dose titration may be more convenient. It is useful to frame the evolution of therapy in clinical logic: although classic agents (e.g., strong enzyme inducers) can be very effective in some situations, in patients taking many medications they may substantially alter drug metabolism. New-generation agents modulate seizure-generating networks through relatively selective targets and often provide a 'simpler' pharmacokinetic profile. This simplicity can improve outcomes by facilitating dose adjustment, enabling better risk calculation when adding other drugs, and increasing adherence through more convenient dosing schedules.

However, 'new' does not automatically mean 'best'. New-generation agents may still require surveillance for psychobehavioral changes, sedation, dizziness, issues related to cardiac conduction, or laboratory indicators (e.g., liver enzymes). Therefore, a modern approach is to select therapy based on a risk-benefit assessment, a full review of the patient's medication list (polypharmacy), and monitoring that is targeted to available resources. The purpose of this article is to systematize new-generation ASMs from the perspective of practical decision-making: (1) mechanisms and areas of use, (2) interpretation of efficacy and retention as practical indicators, (3) management of safety signals through screening and monitoring, and (4) precautions for special populations (children, pregnant women, older adults).

METHODOLOGY

This work was prepared as a narrative review. Sources were selected from open scientific databases, including review articles, clinical trials, practice recommendations, and educational-methodological materials. The search used keywords such as 'epilepsy', 'antiseizure medications', 'brivaracetam', 'lacosamide', 'perampanel', 'cenobamate', 'cannabidiol', and 'fenfluramine'. Priority was given to publications from 2010-2026 reporting clinical outcomes (seizure reduction, responder rate, retention, adverse effects).

Inclusion criteria were: (a) availability of clinical outcome measures in epilepsy; (b) clearly defined indication for the medication; and (c) reporting of safety signals and monitoring recommendations. Exclusion criteria included preclinical-only studies, reports without clinical endpoints, and duplicate materials. Results were synthesized by grouping evidence according to mechanism and practical scope of use, and overarching recommendations were stated cautiously in a way that supports (rather than replaces) clinicians' decisions. During synthesis, the lack of uniform endpoints (differences in seizure counting, follow-up duration, or populations across studies) was considered; therefore, results are presented as practical interpretation rather than a meta-analysis. Safety signals and precautions were evaluated together with study design (randomized controlled trials vs real-world). While this approach can help standardize clinical decisions, final selection should rely on specialist judgment and the individual patient context. For each medication, the following 'practical extraction blocks' were used: (1) indication and target population; (2) titration logic and dosing convenience; (3) most common adverse effects and their management; (4) interactions (enzyme induction/inhibition,

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cumulative sedation); and (5) clinical monitoring points. The synthesized information was aimed at creating a rapid decision matrix for the clinician.

Limitations: Compared with a meta-analysis, a narrative review yields less 'numerical' conclusions because study designs, populations, and endpoints vary. In addition, long-term real-world data for some newer agents may be limited, making time an important factor in detecting rare adverse effects. Differences in drug availability and diagnostic resources in local settings may also limit transferability to other regions. Therefore, the recommendations in this article are presented as decision-support guidance and should be integrated with individual clinical assessment and current national protocols.

RESULTS

The analysis shows that new-generation ASMs are mainly used as add-on therapy for focal epilepsy, and as adjunct treatment in certain syndrome-specific cases. In practice, medication choice tends to revolve around three criteria: seizure type/syndrome, the patient's individual profile (age, comorbidities, lifestyle), and pharmacologic constraints (interactions, titration, monitoring).

Brivaracetam modulates synaptic transmission via the SV2A target and is used primarily for focal seizures. In clinical practice it is chosen in some patients because of dosing convenience and relatively fewer metabolic interactions. Nevertheless, screening for adverse effects such as mood changes, irritability, or somnolence is recommended.

Lacosamide enhances slow inactivation of sodium channels. It is used for focal seizures as mono-therapy or add-on therapy. During titration, dizziness, diplopia, or worsening ataxia may occur; in patients with risk factors related to cardiac conduction, the need for ECG assessment should be considered.

Perampanel is an AMPA receptor antagonist that reduces glutamatergic excitation. Once-daily dosing is convenient; however, because psychobehavioral adverse effects (aggressiveness, impulsivity) may occur, close monitoring is required, especially in adolescents and in patients with pre-existing behavioral problems. When used together with enzyme inducers, exposure may decrease, potentially requiring dose adjustment.

Cenobamate is one of the agents considered for drug-resistant focal epilepsy, and some reports note a high responder rate. From a safety perspective, slow titration, assessment of drug-drug interactions, and careful follow-up for individual risk signals are essential.

Cannabidiol and fenfluramine are more often considered as add-on therapy in syndrome-specific epilepsies (especially in children). In this group, liver enzymes, somnolence, gastrointestinal adverse effects, and combination safety issues should be monitored.

Beyond efficacy, the adverse-effect profile remains a key determinant of outcomes. With SV2A ligands, irritability or mood changes can be clinically relevant; with AMPA antagonism, dizziness and psychobehavioral symptoms; and with sodium-channel modulators, vestibular complaints such as diplopia/ataxia. Therefore, discussing a 'potential adverse effects list' with the patient in advance, explaining when to seek care if warning signs occur, and individualizing titration tends to improve treatment retention.

Dosing and titration emerged as one of the most practical determinants. Too rapid titration can exacerbate sedation and dizziness and increase discontinuation risk; too slow titration may delay clinical response. Thus, many sources recommend stepwise progression toward the minimal effective dose, with temporary pauses or dose reduction followed by re-titration if adverse effects occur.

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Organizing medication intake using reminders, blister calendars, smartphone apps, or family support significantly improves adherence.

Drug-drug interactions play a distinct role. Enzyme inducers (e.g., some classic ASMs) may reduce exposure of certain new agents; conversely, some combinations may increase sedation or dizziness. Therefore, before selecting therapy, it is recommended to review the patient's entire medication list, including over-the-counter products. Overall, the results suggest that new-generation ASMs do not fully replace 'classic' drugs; rather, they serve to fine-tune therapy and strengthen control through mechanism diversification in selected individuals.

Table 1. Practical notes on new-generation ASMs

Drug	Mechanism	Use	Advantage	Caution/monitoring
Brivaracetam	SV2A ligand	Focal (mono/add-on)	Fewer interactions	Mood/behavior; sedation
Lacosamide	Slow inactivation of Na+ channels	Focal (mono/add-on)	Convenient titration	Dizziness; ECG in at-risk patients
Perampanel	AMPA antagonist	Focal/GTCS (add-on)	Once daily	Psychobehavioral; caution with inducers
Cenobamate	Multimodal	Refractory focal	May have high responder rate	Slow titration; interactions
Cannabidiol	Pleiotropic	Syndrome-specific	Adjunct option in refractory cases	Monitor liver enzymes in at-risk patients
Fenfluramine	Serotonergic	Syndrome-specific	Benefit in difficult syndromes	Specialist supervision

Figure 1. Selection and follow-up algorithm (simplified).

DISCUSSION

The main takeaway is that the selection of new-generation ASMs should be viewed not as a 'list of drugs' but as an algorithm. First, the seizure type and epileptic syndrome are identified; then monotherapy is titrated up to the optimal dose within the patient's tolerability; if control is insufficient, switching to an agent with a different mechanism or considering add-on therapy follows. In these steps, retention (persistence) is a useful practical indicator: when patients continue a medication, they have usually reached a satisfactory balance between efficacy and adverse effects.

In rational polytherapy, diversifying mechanisms makes sense, but the potential 'accumulation effect' of adverse events (sedation, ataxia, dizziness) must be assessed in advance. Therefore, clinicians focus on dose optimization, simplifying the dosing schedule, and educating patients and families about early warning signs. Psychobehavioral screening for perampanel and SV2A ligands, caution with cardiac risk factors for lacosamide, and targeted laboratory monitoring for cannabidiol (when risk factors exist) improve practical safety.

Decision-making can be simplified using clinical scenarios. For example, when first-line therapy is insufficient in focal seizures, adding an agent with a different mechanism (e.g., SV2A + a sodium-

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channel modulator) or diversifying with an AMPA antagonist can be considered. If a patient has anxiety or depressive symptoms, monitoring is intensified because the risk of psychobehavioral adverse effects may be higher. In older adults, titration is carried out more slowly and the regimen is simplified due to higher dizziness and fall risk. Such a profile-matched approach tends to yield more stable outcomes in practice.

Practical monitoring is effective when organized as a checklist. At Visit 1 (initiation), the seizure phenotype, full medication list, sleep and mood screening, and history of hazardous work/driving are assessed. At 2-4 weeks, titration follow-up focuses on sedation, dizziness, irritability, and gastrointestinal complaints, with dose adjustment as needed. At 8-12 weeks, clinical response and retention are evaluated and compared with the seizure diary. In risk populations (cardiac history, liver disease, extensive polypharmacy), targeted tests (ECG or laboratory markers) are added. This sequence improves patient safety and brings medication selection closer to evidence-informed practice.

When seizure control remains inadequate, reducing triggers is also important: sleep deprivation, missed doses, fever/infection, alcohol use (in adults), or severe stress can lower the seizure threshold. Patient education (maintaining a seizure diary, managing medication intake with reminders) is not merely an extra recommendation but part of the clinical outcome. In pharmacoresistant cases, the correct approach is not only to change drugs but also to consider re-evaluation at an epilepsy center, etiologic diagnostics, and discussion of non-pharmacologic options.

In special populations, selection is more complex: in children, dose calculations, formulation, and neurodevelopmental outcomes; in pregnancy, maintaining seizure control with the safest possible regimen; in older adults, fall risk, polypharmacy, and reduced renal/hepatic clearance. In resource-limited settings, a 'minimal monitoring package' is useful: at each visit, review the seizure diary, assess sedation/dizziness, and conduct brief screening for mood and sleep; add ECG or laboratory tests when risk factors exist. This approach reduces unnecessary testing while maintaining safety.

In local practice, medication availability and cost influence selection. Nevertheless, the clinical logic remains unchanged: accurate phenotyping, checking interactions, individualized titration, and early detection of adverse effects through monitoring. Where available, new-generation ASMs should be introduced stepwise for pharmacoresistant cases based on multidisciplinary consultation.

CONCLUSION

In conclusion, new-generation anticonvulsants provide important additional options for epilepsy management. Brivaracetam, lacosamide, perampanel, and cenobamate may have clinical value as adjunct therapy in focal epilepsy, whereas cannabidiol and fenfluramine may be valuable in certain syndrome-specific cases. However, optimal outcomes depend on patient-centered selection, slow and controlled titration, and targeted monitoring.

Practical recommendations: (1) clearly define the seizure type/syndrome; (2) evaluate monotherapy up to the maximally tolerated dose; (3) if control is insufficient, switch to an agent with a different mechanism or plan add-on therapy; (4) regularly screen for psychobehavioral, cognitive, and vestibular adverse effects; (5) when risk factors exist, perform ECG and laboratory checks in a targeted manner. This approach can improve seizure control while sustainably enhancing the patient's quality of life.

In the future, establishing local real-world registries (retention, adverse effects, and pharmacoeconomic indicators), continuously updating clinical protocols, and systematizing patient

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education will help maximize the benefits of new-generation ASMs. For clinicians, the core principle is to understand mechanisms, accurately assess the patient profile, and organize monitoring in a 'minimal but targeted' manner.

To keep the treatment plan stable in practice, re-evaluation every 3-6 months is recommended: seizure frequency, adverse effects, adherence, sleep, and mood are reassessed. The goal is not only dose escalation but maintaining seizure control with the simplest and safest regimen. When necessary, multidisciplinary consultation and re-diagnosis help optimize the treatment strategy.

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