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Review paper

Anticonvulsant drugs: Mechanisms of action and Therapeutic limitations

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ABSTRACT

Convulsions remain a major therapeutic challenge despite the availability of multiple antiseizure medications (ASMs), with nearly one-third of patients exhibiting pharmacoresistance. Current anticonvulsant drugs primarily exert their effects by modulating voltage-gated sodium and calcium channels, enhancing γ-aminobutyric acid (GABA)–mediated inhibition, suppressing glutamatergic excitation, or regulating synaptic vesicle release through targets such as synaptic vesicle protein 2A (SV2A). While these mechanisms effectively suppress neuronal hyperexcitability, they largely provide symptomatic control rather than disease modification. Persistent excitation–inhibition imbalance, network remodeling, genetic variability, and adaptive changes in receptor and ion channel function limit long-term efficacy. In addition, pharmacokinetic barriers such as blood–brain barrier efflux transporters, enzyme induction or inhibition, narrow therapeutic indices, and significant central nervous system adverse effects further compromise treatment outcomes. Teratogenicity, tolerance, dependence, and drug–drug interactions pose additional challenges to sustained therapy. This review critically examines the neurobiological basis of convulsions, mechanism-based classification of anticonvulsant drugs, and key pharmacokinetic and pharmacodynamic factors influencing their clinical performance. Emphasis is placed on therapeutic limitations that underlie drug resistance and treatment failure. Emerging strategies, including multi-target agents, novel molecular targets, and advanced drug delivery approaches, are also discussed as potential avenues to overcome existing barriers. A comprehensive understanding of these limitations is essential for guiding the development of next-generation anticonvulsant therapies with improved efficacy and safety.

INTRODUCTION

Convulsions, often linked to epilepsy, remain pharmacologically challenging because about one-

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third of cases are drug-resistant despite over 20 available antiseizure medications (ASMs)[1]. Heterogeneity in seizure types and epilepsy causes complicates treatment, as ASMs target specific mechanisms like sodium channels or GABA receptors but fail against diverse pathologies. Drug efflux transporters, such as P-glycoprotein overexpressed at the blood-brain barrier, actively pump medications out of brain tissue, reducing their effectiveness. Genetic factors, receptor downregulation from chronic use (e.g., benzodiazepines), and network remodeling further contribute to resistance[2]. Newer ASMs have not significantly improved seizure freedom rates since early drugs like phenytoin, due to multifactorial resistance mechanisms that vary by patient. Combination therapies show limited benefits and risk interactions, while non-drug options like surgery address only select cases. Ongoing research targets efflux inhibitors and novel pathways, but full resolution remains elusive[3].

Neurobiological Basis of Convulsions

Excitation-inhibition (E/I) imbalance refers to disruptions in the brain's precise balance between excitatory neural signals (mainly glutamate-driven) and inhibitory ones (primarily GABA-mediated), which underlies normal brain function and is central to epilepsy and convulsions[4]. This imbalance favors hyperexcitability when excitation exceeds inhibition or inhibition weakens, leading to hypersynchronous neuronal firing that manifests as seizures. In epilepsy, factors like ion channel mutations, synaptic dysfunction, or network remodeling shift the E/I ratio dynamically, often regionally in areas like the hippocampus or amygdala[5]. Pharmacological interventions target either enhancing inhibition (e.g., benzodiazepines boosting GABA) or dampening excitation (e.g., sodium channel blockers), but chronic epilepsy involves adaptive changes like depolarizing GABA shifts or compensatory inhibition that limits efficacy. Pre-seizure phases show paradoxical inhibition surges as failed protection, highlighting why restoring true E/I balance pharmacologically remains unsolved despite multiple mechanisms. Apart from these alterations, accumulating evidence suggests that increased depolarizing GABAergic signaling during development can be a contributor to epileptogen-esis in both NDDs and epilepsy, and that this relationship is bidirectional[6]

Mechanism-Based Classification of Anticonvulsant Drugs

- Sodium channel blockers - Sodium channel blockers are a cornerstone of antiseizure medications (ASMs) used to treat epilepsy and convulsions by targeting voltage-gated sodium channels (VGSCs) in neurons. These drugs stabilize the inactive state of the channels, reducing high-frequency repetitive firing that drives hyperexcitable states[7].

Mechanism of Action - Voltage-gated sodium channel blockers, such as phenytoin, carbamazepine, lamotrigine, and lacosamide, exert their antiseizure effects primarily through use-dependent inhibition of neuronal excitability. These drugs preferentially bind to voltage-gated sodium channels (VGSCs) in their open or fast-inactivated states during periods of high-frequency repetitive firing, which is characteristic of epileptic activity, thereby stabilizing the inactivated conformation and slowing recovery to the resting state. This mechanism limits sodium influx required for action potential propagation, reduces post-tetanic potentiation, and prevents the spread of hypersynchronous discharges without significantly affecting normal low-frequency neuronal signaling, thus selectively targeting hyperexcitable networks while preserving baseline brain function[9].

Role in Epilepsy Treatment - These blockers effectively control focal and generalized tonic-clonic seizures by restoring excitation-inhibition balance through dampened neuronal excitability, yet resistance arises from channel mutations, overexpression, or adaptive changes like incomplete inactivation in chronic epilepsy[8].

Limitations - Despite their efficacy in many patients, they fail in drug-resistant cases due to factors like blood-brain barrier efflux and network remodeling, mirroring broader pharmacological challenges in fully resolving convulsions[10].

- **Calcium Channel Modulators** - Calcium channel modulators, including T-type blockers like ethosuximide and high-voltage-activated (HVA) ligands such as gabapentinoids (gabapentin, pregabalin), primarily reduce neuronal excitability by inhibiting calcium influx through voltage-gated calcium channels (VGCCs), thereby limiting presynaptic neurotransmitter release—especially glutamate—that drives excitation-inhibition imbalance in epilepsy[11].

Mechanism of Action - Ethosuximide targets T-type VGCCs (CaV3 family) in thalamic relay neurons, suppressing low-threshold bursts and thalamocortical oscillations critical for absence seizures, while gabapentinoids bind α2δ subunits of HVA channels (N-, P/Q-, L-type), reducing calcium currents and synaptic vesicle fusion without directly gating channels[12].

Roles in Epilepsy Treatment - These modulators excel against absence seizures (ethosuximide as first-line) and adjunctively manage focal or neuropathic pain-related epilepsies by dampening hyperexcitability; novel T-type antagonists like Z944 show disease-modifying potential in preclinical epileptogenesis models by restoring E/I balance regionally[13].

Limitations - Calcium channel modulators in epilepsy, such as ethosuximide for T-type channels and gabapentinoids (gabapentin, pregabalin) for high-voltage-activated channels, face key limitations including poor selectivity due to structural homology with cardiac and vascular VGCCs, leading to off-target effects like bradycardia, AV block, and hypotension that restrict dosing[14].

- **GABA enhancers** - GABA enhancers boost inhibitory neurotransmission in the brain by targeting gamma-aminobutyric acid (GABA), the primary inhibitory neurotransmitter, to counteract excitation-inhibition imbalance in epilepsy and convulsions. Key classes include benzodiazepines (e.g., diazepam, clonazepam), barbiturates (e.g., phenobarbital), vigabatrin (GABA-T inhibitor), tiagabine (GABA uptake blocker), and newer agents like ganaxolone (neurosteroid allosteric modulator)[15].

Mechanism of Action - Benzodiazepines like diazepam bind allosteric sites on GABAA receptors to increase channel opening frequency, enhancing chloride influx for phasic inhibition; barbiturates prolong channel open time at higher doses; vigabatrin irreversibly inhibits GABA-transaminase to boost GABA synthesis, while tiagabine blocks GAT-1 reuptake transporters[18].

Roles in Epilepsy Treatment - These agents effectively terminate status epilepticus (IV benzodiazepines), manage generalized tonic-clonic and focal seizures (phenobarbital), and treat infantile spasms or refractory cases (vigabatrin), restoring E/I balance by amplifying inhibition, with ganaxolone approved for CDKL5 deficiency disorder[16].

Limitations - GABA enhancers in epilepsy treatment encounter substantial limitations that hinder their long-term efficacy and broad

applicability. Chronic administration of benzodiazepines leads to rapid tolerance through GABAA receptor desensitization, internalization, and uncoupling from chloride channels, reducing inhibitory postsynaptic currents (IPSCs) by up to 50% within days, while barbiturates induce profound sedation, respiratory depression, cognitive impairment, and dependence due to their non-selective prolongation of channel open times at both synaptic and extrasynaptic receptors[17].

- **Glutamate antagonists** - Glutamate antagonists reduce excessive excitatory neurotransmission by blocking ionotropic glutamate receptors (iGluRs) like NMDA, AMPA, and kainate receptors, which mediate the bulk of fast synaptic excitation driving seizures and excitation-inhibition imbalance in epilepsy[19].

Mechanism of Action - These agents competitively or non-competitively inhibit glutamate binding or channel pore function: NMDA antagonists (e.g., felbamate, ketamine) block glycine co-agonist sites or Mg2+-sensitive pores to prevent Ca2+ influx and burst firing; AMPA/kainate blockers like perampanel reduce Na+/Ca2+ entry underlying rapid depolarization and epileptiform synchronization[20].

Roles in Epilepsy Treatment - They effectively control pharmacoresistant focal seizures (perampanel as adjunctive therapy) and refractory status epilepticus (ketamine infusion), with preclinical data showing prevention of epileptogenesis by normalizing glutamate homeostasis and astrocytic uptake via GLT-1/GLAST transporters[21].

Limitations - Glutamate antagonists in epilepsy face critical limitations including severe neurotoxicity, psychotomimetic effects, sedation, ataxia, high dropout rates from adverse events, and limited efficacy against generalized seizures due to compensatory mechanisms like astrocytic glutamate overflow and receptor adaptations[21].

- **SV2A modulators (levetiracetam)** - SV2A modulators like levetiracetam (LEV) target synaptic vesicle protein 2A (SV2A), a glycoprotein integral to synaptic vesicles that regulates neurotransmitter release and vesicle trafficking, helping restore excitation-inhibition balance in epilepsy[22].

Mechanism of Action - LEV binds SV2A with high affinity, inducing conformational changes that reduce the readily releasable pool of synaptic vesicles, selectively inhibiting excessive presynaptic release (especially glutamate) during high-frequency firing while sparing normal synaptic transmission; this contrasts with broad ion channel blockade[23].

Roles in Epilepsy Treatment - LEV effectively treats focal-onset seizures, myoclonic, and primary generalized tonic-clonic seizures as monotherapy or adjunctive therapy, with rapid onset, minimal drug interactions, and evidence of antiepileptogenic effects in kindling models by preventing seizure progression[24].

Limitations - Psychiatric side effects (irritability, aggression, psychosis in 5-15%), somnolence, and growth suppression in children limit tolerability; efficacy plateaus in drug-resistant epilepsy (~30% refractory) due to SV2A-independent network remodeling and heterogeneous pathologies[25].

Pharmacokinetic and Pharmacodynamic Considerations

BBB Penetration - In drug-resistant epilepsy, P-glycoprotein (P-gp/ABCB1) overexpression at the blood-brain barrier actively effluxes lipophilic antiseizure medications like phenytoin,

carbamazepine, and lamotrigine, reducing epileptogenic zone concentrations by 2-5 fold despite therapeutic serum levels, as demonstrated by PET imaging with P-gp substrates and verapamil reversal studies showing restored cortical drug levels. Polar agents like levetiracetam achieve excellent CSF penetration via organic cation transporters (OCT1), explaining refractory focal seizure efficacy, while BBB damage from seizures paradoxically reduces free phenytoin brain delivery due to serum protein extravasation[26].

CYP Enzyme Issues - Enzyme-inducing ASMs (phenytoin, carbamazepine, phenobarbital) strongly activate CYP3A4, CYP2C9, and UGT1A4, accelerating co-administered drug clearance by 50-70% (e.g., lamotrigine AUC reduced 40-60%), oral contraceptives inactivated, and autoinduction complicating carbamazepine dosing over 2-4 weeks; valproate inhibits CYP2C9/UGT enzymes, doubling lamotrigine levels and precipitating toxicity. Phenytoin's saturable CYP2C9 metabolism creates zero-order kinetics where small dose increases cause disproportionate toxicity (nystagmus, ataxia at 20-30 μg/mL)[27].

Therapeutic Window - Narrow therapeutic indices characterize phenytoin (10-20 μg/mL), carbamazepine (4-12 μg/mL), and valproate (50-100 μg/mL), where >10% dose changes precipitate subtherapeutic failure or toxicity due to saturable protein binding (>90%), nonlinear elimination, and polytherapy interactions affecting 60-80% patients; therapeutic drug monitoring is mandatory during pregnancy (30-50% level drops), hepatic impairment, or enzyme interactions[28].

Therapeutic Limitations of Current Anticonvulsants

Approximately 30% of epilepsy patients exhibit drug-resistant seizures despite optimal dosing of multiple antiseizure medications (ASMs), driven by P-glycoprotein (P-gp) efflux transporter overexpression at the blood-brain barrier reducing brain drug levels 2-5 fold, genetic polymorphisms in target genes (SCN1A, KCNQ2), network remodeling with hyperexcitable circuits, and neuroinflammation activating ABC transporters[29].

CNS Adverse Effects: Dose-dependent cognitive impairment (phenytoin/valproate slowing processing speed 20-30%), psychiatric effects (perampanel aggression 10-15%, levetiracetam psychosis 5%), cerebellar ataxia (phenytoin 15% at >20μg/mL), and sedation limit long-term compliance, with 20-30% trial dropout rates from dizziness/agitation[30].

Teratogenicity: Valproate carries 10-11% major malformation risk (neural tube defects 1-2%), spina bifida (0.5-1%), cognitive impairment (30-40% IQ loss), far exceeding lamotrigine (2-3%) or levetiracetam (2.5%); enzyme inducers reduce contraceptive efficacy in 50-70% women[28].

Tolerance & Dependence: Benzodiazepines lose 50-70% efficacy within 3-6 months via GABAA receptor α1 subunit downregulation/internalization; vigabatrin tolerance emerges from GABAergic interneuron exhaustion and depolarizing GABA shifts in chronic epilepsy[31].

Narrow Therapeutic Index: Phenytoin (10-20μg/mL), carbamazepine (4-12μg/mL), valproate (50-100μg/mL) exhibit zero-order kinetics and >90% protein binding where 10% dose increases cause toxicity (nystagmus, gingival hyperplasia); therapeutic drug monitoring essential in 60-80% polytherapy cases[32].

Emerging Strategies and Future Directions

New Targets: Cenobamate targeting CRMP2-cytoskeletal regulation achieves 20-50% seizure freedom in refractory focal epilepsy via persistent Na+ channel inactivation and glutamate homeostasis restoration. Fenfluramine modulates 5-HT/σ1 receptors for Dravet syndrome (40% responder rate). AAV-delivered GABA/galanin gene therapies (NV-5138 Phase 2) show 40% seizure reduction[33].

Hybrid Molecules: Multi-mechanism compounds combine sodium channel blockade with SV2A binding (brivaracetam derivatives) or GABA enhancement with glutamate uptake (novel vigabatrin hybrids), achieving 60-70% seizure reduction in polytherapy models vs. 30-40% monotherapy. AMPA/NMDA dual antagonists with P-gp inhibitors overcome BBB resistance[34].

Nanocarriers: Liposomal levetiracetam-PLGA nanoparticles bypass P-gp efflux (3-5x brain levels), intranasal nanogels terminate status epilepticus in 2-5 min vs. 10-15 min IV lorazepam. Magnetic iron oxide nanoparticles enable epileptogenic zone targeting[35].

CONCLUSION

Despite the availability of more than two dozen antiseizure medications, convulsions remain pharmacologically unresolved for a substantial proportion of patients. Current anticonvulsant drugs act primarily by modulating voltage-gated ion channels, enhancing GABAergic inhibition, suppressing glutamatergic excitation, or regulating synaptic vesicle release; however, these mechanisms provide symptomatic seizure suppression rather than disease modification. The persistent reliance on similar molecular targets explains why seizure-freedom rates have plateaued and why approximately one-third of patients develop drug-resistant epilepsy.

Therapeutic limitations — including pharmacoresistance driven by blood–brain barrier efflux transporters, genetic and target-site alterations, narrow therapeutic indices, CNS toxicity, teratogenic risk, tolerance, and complex pharmacokinetic interactions—significantly restrict long-term efficacy and patient adherence. Even newer agents with improved selectivity and pharmacokinetics have failed to overcome network-level remodeling and neuroinflammatory processes that sustain epileptogenic circuits.Emerging strategies such as multi-target hybrid molecules, SV2A-based modulation, nanocarrier-mediated brain delivery, and therapies targeting non-canonical pathways offer promising directions but remain largely adjunctive rather than curative. Future anticonvulsant development must move beyond single-target ion channel modulation toward mechanism-integrated approaches that address drug resistance, improve CNS selectivity, and potentially modify disease progression. Until such advances are realized, the pharmacological management of convulsions will continue to be constrained by efficacy ceilings and clinically significant adverse effects.

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