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NEUROLOGY

EPILEPSY: PATHOPHYSIOLOGY, CLINICAL CLASSIFICATION, AND CONTEMPORARY MANAGEMENT APPROACHES

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ABSTRACT

Background: Epilepsy is a frequent disabling neurological disorder and it affects more than 50 million of people worldwide. In the past few decades a remarkable progress has been achieved in the treatment and efficiency of the anti-epileptic drugs (ASMs), however around 30% of the patients with epilepsy do not respond to treatment. **Objectives:** This review seeks to integrate and disseminate all current knowledge regarding etiology, classification, epidemiology and therapy of epilepsy focusing especially on drug-resistant epilepsy (DRE) and new therapeutic approaches. **Methods:** An extensive literature review was conducted searching for contemporary reports, system reviews, updated clinical guidelines with a focus on ILAE 2025 classification guidelines. **Results:** The pathogenesis of epilepsy is varied and includes imbalances in excitatory-inhibitory neurotransmission, inflammatory cascades utilizing pro-inflammatory cytokines such as IL-1, IL-6, IL-8, IL-17, and IL-18, ion channel mutations, especially nAChR subunit genes, and alterations in the organization of hubs in brain networks. The updated 2025 ILAE classification breaks down seizure types into 4 categories, 21 different types of seizures and gives enhanced, syndrome based diagnostic guidelines according to age of onset and etiology. The DALY burden globally for epilepsy is high with a bimodal pattern of age-related prevalence. For DRE there appears to be a relationship between augmented neuroinflammation (including the astrocyte mediated SerpinA3N/NF-B pathways) and number of seizures as well as lack of responsiveness to treatment. While rational polypharmacy and optimal monotherapy remain important, vagal nerve stimulation, IVIG, pFUS, and modulating the microbiota-gut-brain axis may offer some hope. Considerable disparities still exist in the management of epilepsy in terms of race and diagnostic workup and the need for better counseling in women with epilepsy. **Conclusions:** The management of epilepsy is evolving rapidly due to developments in the area of molecular neurobiology, increasingly precise classification systems, and new neuromodulatory and immunomodulatory treatments. However, to translate such advances into equal, patient-centred treatment access, there must be sustained integrated multidisciplinary frameworks, continued funding for translational science and concerted efforts to overcome health disparities between a multitude of patient groups.

KEYWORDS : epilepsy; drug-resistant epilepsy; seizure classification; neuroinflammation; antiseizure medications; neuromodulation; ILAE; pathophysiology; precision medicine; healthcare disparities

1. INTRODUCTION

Approximately 50 million people worldwide have epilepsy, which is classified as a disorder of the brain that causes a patient to have repeated unprovoked seizures at random times.[1] Brain disorders are one of the most widespread categories of diseases in the world, and epilepsy has major medical, social, and economic ramifications. The International League Against Epilepsy defines "epilepsy" as a disorder of the brain characterized by a propensity to develop epilepsy and the repercussions (biological, psychological, and social) of that tendency.[2][3] The Global Burden of Disease [GBD] study estimated there were 45.9 million people living with epilepsy in 2016, with an overall prevalence of 621.5 cases per 100,000 people.[4].

Despite the emergence of novel antiepileptic agents, about 30% of epilepsy patients still remain pharmacologically refractory (drug resistant epilepsy or DRE) [5]. Patients with DRE carry higher morbidities, potential mortality risks and a significantly reduced life quality. Additionally, the important co-morbid conditions are cognitive dysfunction, psychiatric illness and SUDEP in epilepsy.[1] The knowledge on the various and heterogeneity mechanisms responsible for epilepsy will aid in the application of precision-based therapy and a better clinical outcome.

2. PATHOPHYSIOLOGY OF EPILEPSY

2.1 EXCITATORY-INHIBITORY IMBALANCE

Seizures result from an imbalance of the inhibitory and excitatory neurotransmission. Excitatory transmission is conveyed via ionotropic receptors for the glutamatergic pathway and, to a lesser extent, metabotropic receptors, and inhibitory control is exerted by the GABAergic system via GABA-A and GABA-B receptors.[6] The deviation of excitatory-inhibitory balance is common to all epilepsy syndromes.

Recent transcriptomic analyses in human temporal cortex tissues taken from patients with temporal lobe epilepsy found marked differences in both the excitatory and inhibitory neural populations of these brains. Most notably, glutamate signaling is grossly disrupted in the disease state with very significant increased levels of AMPA receptor accessory subunits, and other glutamate receptor associated gene sets present in all neuronal classes including layer 5–6 pyramidal neurons, as well as parvalbumin-positive interneurons.[7] The alterations in gene expression identified would indicate that glutamate

excitotoxicity plays a role in hippocampal disease and susceptibility to seizures in this prevalent form of focal epilepsy.

An often overlooked epileptogenic mechanism is depolarizing GABAergic signaling. The early immature brain relies on depolarizing GABAergic signaling, as intracellular chloride levels are higher as a result of differences in the levels of chloride import (NKCC1) and export (KCC2). The developmental transition from depolarizing to hyperpolarizing GABAergic signaling is important for normal neuronal development, and alterations in this process due to imbalances in NKCC1/KCC2 have been proposed in some developmental disorders and in epilepsy.[8] This emphasizes the role of developmental processes in seizures, and especially with regard to pediatric epilepsy.Neuroinflammation and Immunopathogenesis

Increasing evidence supports a role for neuroinflammation in the development of both seizures and epilepsy. Acute seizures trigger potent neuroinflammatory responses, characterized by increased pro-inflammatory cytokine levels, activation of innate immunity and compromised BBB Integrity.[9,10] The inflammasome- a multimodular protein that facilitates inflammatory responses through the production of IL-1 and IL-18-is proving to be a pivotal player in this inflammation.

There is evidence for significantly elevated levels of serum IL-1, IL-6, IL-8, IL-17 and IL-18 in epilepsy patients relative to healthy controls, with elevated levels being yet greater still in drug-resistant populations.[11]

These pro-inflammatory cytokines show a significant relationship with frequency of seizures and response to treatment, which may be useful biomarkers to stratify the disease. IL-6 and IL-8 showed good diagnostic accuracy in differentiating between healthy controls and epilepsy patients (AUC=1.00) and the good accuracy was observed in IL-6 as well between DR and DR patients (AUC=0.99). [11]. Peripheral immune cell trafficking to the central nervous system is another crucial component in epileptogenesis. This infiltrate of monocytes and T cell to the brain, triggered by disruption of BBB and subsequent recruitment by chemokines, is a key player in the perpetuation of neuroinflammation and propagation of seizures. [12]. Investigating these peripheral responses temporally and functionally would be useful to design immunomodulatory therapies in epilepsy.

2.2 ION CHANNELS AND GENETIC MECHANISMS

Major genetic factors of inherited epilepsy susceptibility include gene mutations affecting ion channels and receptors activated by neurotransmitters. The nicotinc acetylcholine receptor (nAChRs) is densely expressed in both hippocampal and cortical neurons and has crucial roles in modulating forebrain excitability via ascending cholinergic system. Mutations of nAChR subunit genes (CHRNA4, CHRNB2, CHRNA2) induce ADNFLE, also named ADSHE.[13,14] The mechanisms of ADSHE-related nAChR mutations indicated that potentiation of receptor function generating prolonged hyper excitability of cortical and thalamic network underlie the epileptogenic mechanism. These effects emerge through alterations in GABAergic interneuron function during mature network operation as well as disrupted synaptogenesis during developmental periods.[14] The complexity of nAChR-dependent epileptogenesis underscores the necessity of understanding how genetic mutations produce age-dependent phenotypes and how targeting specific molecular.

2.3 NETWORK NEUROSCIENCE AND BRAIN CONNECTIVITY

Beyond cellular mechanisms, epilepsy is increasingly recognized as a disorder of brain networks characterized by atypical functional and structural connectivity patterns. Brain hubs—highly connected regions situated along major communication pathways—play crucial roles in supporting large-scale neural communication and higher-order cognitive functions.[15] Aberrant hub organization has been identified in multiple common epilepsy syndromes on both structural neuroimaging and functional electrophysiological recordings.

Principal hubs including the thalamus, hippocampus, and default mode network nodes show altered connectivity patterns in focal and generalized epilepsies. These network-level abnormalities are implicated in seizure spread, seizure propagation across distributed brain regions, and epilepsy-related phenotypes including cognitive dysfunction.[15] Network neuroscience approaches offer novel perspectives for understanding epilepsy heterogeneity and for identifying candidate biomarkers of treatment responsiveness and postsurgical outcome prediction.

3. INTERNATIONAL CLASSIFICATION OF SEIZURES AND EPILEPSIES

The International League Against Epilepsy (ILAE) has established comprehensive classification frameworks designed to standardize epilepsy diagnosis, facilitate international communication, and guide clinical management and prognosis. The current classification system, updated in 2025, reflects evolving understanding of seizure semiology and syndrome-specific features.[16,17,18]

3.1 SEIZURE CLASSIFICATION

The updated 2025 ILAE seizure classification maintains four principal seizure classes: Focal, Generalized, Unknown (whether focal or generalized), and Unclassified.[16] This revision introduced important refinements including operational classification of seizures by state of consciousness for focal seizures and seizures of unknown origin, defined through clinical assessment of patient awareness and responsiveness. The distinction between preserved and impaired consciousness during focal seizures carries significant therapeutic implications, as consciousness impairment often necessitates earlier pharmaceutical intervention and consideration of rescue therapies.

Focal seizures, originating from specific brain regions, encompass both motor and non-motor manifestations with or without awareness. Generalized seizures, arising from distributed brain networks, are categorized into absence seizures, generalized tonic-clonic seizures, and other generalized seizure types including newly recognized negative myoclonus.[16] This updated classification comprises twenty- one distinct seizure types, designed to be accessible across varied clinical settings from resource-limited environments to highly specialized epilepsy centers.

Epileptic syndromes are well-defined groups of symptoms and signs, clinical (clinical events), electroencephalographic (EEGs), and often etiology, having prognostic and therapeutic value. The ILAE Task Force on Nosology and Definitions has defined syndromic diagnostic criteria divided by age at onset of the first seizure, seizure type, and etiology (structural, genetic, infectious, metabolic, immune or unknown etiology).[2,19,20]

3.2 EPILEPSY SYNDROME CLASSIFICATION

The neonatal and infant period (0-2 years of age) can be subdivided into syndromes with presumed favorable outcome (self-limited epilepsies with expected remission) and developmental and epileptic encephalopathies (developmental deficit due to an underlying etiology and to epileptic dysfunction).[20] A population based Norwegian cohort study identified some ILAE syndrome groups within 1053 children with epilepsy. The cumulative incidence of self-limited epilepsies was 2.25 per 1,000; that of idiopathic generalized epilepsies was 1.75 per 1,000; that of developmental and/or epileptic encephalopathies was 2.62 per 1,000 children.[21]

Childhood-onset syndromes comprise self-limited focal epilepsies, generalized epilepsies including childhood absence epilepsy and epilepsy with myoclonic absence, and developmental and/or epileptic encephalopathies including Lennox-Gastaut syndrome and hemiconvulsion-hemiplegia-epilepsy syndrome.[19] Idiopathic generalized epilepsies, comprising childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with generalized tonic-clonic seizures alone, represent an important syndrome grouping among genetic generalized epilepsies with distinct prognostic and therapeutic significance.[22]

4. EPIDEMIOLOGY AND GLOBAL DISEASE BURDEN

Data on the epidemiology of epilepsy from 195 countries and territories are available for 2016 in the Global Burden of Disease Study.4 Epidemiological estimates of the global prevalence of active epilepsy (including secondary) are currently 45.9 million, with an age-standardized prevalence of 621.5 per 100,000 population. The active idiopathic epilepsy cohort represents an estimated 24 million people (prevalence 326.7 per 100,000) of the overall cohort. Prevalence of active epilepsy displays a bimodal age distribution, with increased rates at 5–9 years of age (374.8 per 100,000) and in people >80 years of age (545.1 per 100,000).4

Age-standardized mortality rates attributed to idiopathic epilepsy reached 1.74 per 100,000 population globally, with higher rates in males (2.09 per 100,000) compared to females (1.40 per 100,000).[4] Disability-adjusted life-years (DALYs) associated with epilepsy totaled 182.6 per 100,000 population (163.6 in women, 201.2 in men), with substantial geographic variation related to socioeconomic development index. Importantly, between 1990 and 2016, age-standardized mortality rates decreased significantly by 24.5%, and DALY rates declined by 19.4%, reflecting improvements in epilepsy management and treatment access in higher-income regions.[4]

For older people (aged 60+), the epidemiology of epilepsy varies significantly with that of younger groups. In more affluent countries, an abrupt rise in the incidence of epilepsy is reported in people aged over 60-65 years and is largely due to stroke, head trauma, dementia and brain tumours.[23] This trend has not been consistently reported in less developed countries, hinting at differences in etiology based on level of economic development. This upward trend in epilepsy incidence in an aging population will bring its own challenges for healthcare systems and requires an age-specific diagnostic and treatment approach.

5. DRUG-RESISTANT EPILEPSY: MECHANISMS AND MANAGEMENT

Approximately 30% of patients with epilepsy fail to achieve seizure control despite optimal trials of multiple antiseizure medications (ASMs)—a condition defined as drug-resistant epilepsy (DRE).[5] Multiple mechanisms have been proposed to explain treatment refractoriness, including altered drug metabolism, ion channel dysfunction, neuroinflammation, and network-level abnormalities.

5.1 NEUROINFLAMMATORY MECHANISMS IN TREATMENT RESISTANCE

Increasing evidence also indicate an exaggerated neuroinflammatory response differentiates drug-resistant versus drug-responsive epilepsy. Significantly increased serum pro-inflammatory cytokine (IL-1, IL-6, IL-8, IL-17, IL-18) levels are found in DRE patients and positively correlate with the frequency of seizures as well as with treatment refractoriness.[11] these studies indicate that the neuroinflammatory signaling is a reasonable target to treat epilepsy patients with ASMs refractoriness.

It is not clear which molecular mechanisms contribute to linking neuroinflammation and treatment refractoriness. A recent study has revealed that astrocyte released SerpinA3N stimulates seizure severity via NF-B signaling.[24] Loss and gain of function experiments revealed that elevated and decreased SerpinA3N expression levels enhance and decrease seizures accordingly, respectively. Astrocyte-mediated inflammatory signaling thus seems a valid strategy to mitigate seizure induced brain damage and potentially treat patients unresponsive to therapy.

5.2 THERAPEUTIC APPROACHES FOR DRUG-RESISTANT EPILEPSY

The modern management of DRE involves a variety of therapeutic options beyond maximizing antiepileptic drug therapy, such as surgery (temporal lobectomy, focal cortical resections, corpus callosum sectioning), neuromodulation (vagal nerve stimulation, deep brain stimulation, responsive neurostimulation), and experimental options such as immunotherapy and novel stimulation techniques.

Vagal nerve stimulation is an FDA-approved neuromodulatory device that has shown promise in the management of SRSE and NORSE. A recent retrospective review on 15 patients (14 F, 16-77 yrs) who received a vagal nerve stimulator for SRSE, the therapy was effective in weaning anesthetic infusions without recurrence in 14 of 15 patients and resulted in no procedure-related complications.[25] NORSE patients trends toward better outcomes

long-term functional outcomes (Glasgow Outcome Scale-Extended score of 7 versus 1, p = 0.31) despite longer hospitalization and similar antiseizure medication burden, suggesting potential advantages of early VNS implantation in this catastrophic seizure condition.[25]

An emerging approach in adjunctive immunotherapy of pediatric DRE has been the use of intravenous immunoglobulin (IVIG). In a retrospective study evaluating 60 patients (ages 2-18) treated with IVIG for 1 year for intractable epilepsy, a decrease of at least 50% in seizure frequency was found at 1 year in 36.7% and seizure freedom in 36.4% of patients who were considered to be responders.[26] Only patients with generalized seizure types showed statistically significant reductions in seizure frequency (p = 0.019), indicating that seizure type may influence response to this immunomodulatory agent.[26] This information may guide further research in immunomodulation, particularly in patient groups with significant neuroinflammatory components to their disorder.

Pulsed focused ultrasound (pFUS) represents an emerging non-invasive neuromodulation approach for DRE that achieves seizure control through non-thermal mechanical mechanisms.[27] Preclinical studies demonstrate seizure suppression through modulation of mechanosensitive ion channels and restoration of excitation-inhibition balance, particularly in thalamus-hippocampus circuits. Early human trials confirm excellent safety profile with reversible effects, while providing preliminary evidence of seizure frequency reduction in patients with refractory focal epilepsy.[27]

6. ANTISEIZURE MEDICATIONS AND RATIONAL POLYTHERAPY

Contemporary management of ASMs involves selecting drugs according to seizure type, epilepsy syndrome, comorbidities, drug interactions etc. Advances continue and there have been novel third- and fourth generation ASMs, which show efficacy and favorable tolerability profiles in selected groups.

Highly selective sodium channel modulator CEN (CNB; [Onfi]; [Yondelis]) was approved for the adjunctive treatment of DRE in focal onset seizures. Clinical real-life practice shows a significant effectiveness profile in DRE. A retrospective single center analysis has evaluated the effect of adjunctive low-

dose clobazam (CLB) therapy in 85 adults with DRE who were not fully controlled with CNB monotherapy. Median reduction in seizure frequency increased from 80.0% at three months after initiation of CLB therapy to 95.8% at 12 months ($p < 0.001$), responder rates (50% reduction) varied from 72.9% to 82.1%, and approximately one third of patients were seizure-free. [28] These data provide evidence for pharmacokinetic-pharmacodynamic interactions between CNB and CLB and further strengthen the hypothesis for mechanism driven rational polytherapy in refractory epilepsy.

6.1 CONTRACEPTION, PREGNANCY, AND WOMEN'S HEALTH

Women with epilepsy (WWE) face unique management challenges related to reproductive health, contraception interactions with ASMs, and pregnancy-related considerations. A retrospective analysis at a specialized women's epilepsy clinic identified substantial counseling gaps: 22% of patients on ASMs had never received contraception counseling, 48% were unaware of fetal malformation risks from ASMs and folic acid supplementation benefits, and 71% had not received bone health counseling.[29] These findings highlight the critical importance of age-specific, targeted patient education to optimize clinical outcomes and improve medication adherence in WWE populations.

7. COMORBIDITIES AND HEALTHCARE DISPARITIES

Many medical comorbidities such as cognitive dysfunction, depression, anxiety and cardiovascular diseases have also been shown to be common in patients with epilepsy. An important question for future research is the mechanism behind cognitive impairment associated with epilepsy and markers predictive of cognitive course. Psychiatric conditions including depression, anxiety disorders and behavioral disorders are also highly prevalent in the epilepsy population and the combination of psychiatric and neurological care has become essential.[30]

Healthcare disparities in epilepsy management have significant clinical implications. One study was a 2-year retrospective analysis at a tertiary epilepsy center which showed striking racial disparities in provider decision-making regarding the necessity of diagnostic evaluation

Black patients who recently had a seizure were more likely to be admitted to the EMU for workup than White patients (OR 1.34; 95% CI, 1.11-1.62). Black patients with recent seizures were disproportionately more likely to be admitted to the EMU for differential diagnosis, while White patients were disproportionately more likely to be admitted for presurgical evaluation ($p<0.004$).These results remained statistically significant even after accounting for seizure severity and socio-economic factors, suggesting that racial biases by the provider are a contributing factor to diagnostic disparities and delays in epilepsy management. [30]

8. EMERGING THERAPEUTIC AND ADJUNCTIVE APPROACHES

8.1 GUT MICROBIOTA AND THE MICROBIOTA-GUT-BRAIN AXIS

In recent years, the gut microbiota and microbiota-gut-brain axis have been increasingly linked to the susceptibility to and development of epilepsy.A dysbiosis of the intestinal microbial population has been found in both animal and human epilepsy models. The use of probiotics can serve as an additional treatment strategy with several mechanistic pathways: decrease in seizure intensity, seizure latency prolongation, reduction of neuroinflammation, and enhancement of cognition and emotion.[31]

An exhaustive review including 79 (19 preclinical, 3 clinical) papers investigating probiotics and their role in epilepsy concluded that preclinical data largely support seizure-suppressing effects mediated by modulating neuroinflammation, reducing oxidative stress, and maintaining intestinal barrier integrity. However, clinical data is insufficient and is still preliminary, based on small heterogeneous patient populations with almost exclusively uncontrolled designs. Initial findings suggest that probiotics can have an effect in reducing seizure frequency and improving the quality of life for a subset of patients, and stronger conclusions regarding therapeutic benefits must be made on the basis of further well-designed randomized controlled studies.[31]

9. FRAMEWORK FOR EVIDENCE-BASED EPILEPSY MANAGEMENT

Optimal current epilepsy management involves an organized, multidisciplinary strategy that utilizes precise seizure and epilepsy syndrome classification, determines etiologies of epilepsy, rational selection of ASMs and vigilance for co morbidities and side effects. Initial workup should comprise complete clinical history and physical, if possible, video Electroencephalography (vEEG) and structural neuroimaging (when possible with Magnetic Resonance imaging [MRI], or with Computed Tomography if MRI is not an option).[2].

ASM selection should be tailored to seize and epilepsy type, presence of comorbities, possibility of drug interactions, and to characteristics of the patient that include their status of reproduction (in pre-menopausal females), their renal and hepatic functions, and their metabolism and metabolic functions. Subsequent treatment with a single ASM, when ineffective after optimal trial doses are attempted, would require a switch to polytherapy.

Refractory cases of patients should be quickly evaluated for referral to a specialized epilepsy center and for further evaluation regarding nonpharmacologic treatment options. Referral to an epilepsy program for thorough evaluation is recommended and should address potential etiologies, psychogenic non-epileptic seizures, other seizure mimics, and associated comorbid medical and psychiatric conditions. Seizure related disability, drug adverse effects, and quality of life should be monitored regularly during the course of the disease.

10. SUMMARY TABLES

Table 1: ILAE Classification of Seizure Types (2025 Updated Classification)

Seizure Class	Seizure Type Examples	Key Clinical Features
Focal Seizures	Motor seizures (tonic, clonic, myoclonic) Non-motor seizures (autonomic, behavioral, sensory)	Consciousness preserved or impaired Localized neuronal activity May secondarily generalize
Generalized Seizures	Absence seizures Tonic-clonic seizures Myoclonic seizures	Bilateral onset Impaired consciousness typical Generalized EEG abnormalities
Unknown Origin	Seizures of uncertain focal vs. generalized origin	Insufficient clinical or EEG data May later be reclassified

Table 2: Key Molecular Mechanisms in Epileptogenesis and Targeted Therapeutic Approaches

Mechanism	Pathophysiological	Therapeutic Targets
Excitatory-Inhibitory Imbalance	Increased glutamate signaling, altered GABA function	Sodium channel blockers, calcium channel blockers, GABA enhancers
Neuroinflammation	IL-1β, IL-6, IL-8 elevation; inflammasome activation; BBB disruption	IL-1β inhibitors, TNF-α antagonists, immunomodulatory therapies

Ion Channel Dysfunction	Mutations in sodium, potassium, calcium channels	Channel-specific modulators, precision gene therapies
Network Abnormalities	Altered hub organization, hypersynchrony in circuits	Deep brain stimulation, responsive neurostimulation

11. CONCLUSION AND FUTURE DIRECTIONS

Epilepsy is a heterogeneous and complex neurological disorder, which is associated with a multifactorial pathophysiology including altered neurotransmitter system, neuroinflammatory mechanisms, network dysfunctions and gene predisposition factors. The newer classification system proposed by the ILAE are of great help to correctly classify the seizure types and syndrome entities, leading to a unified nomenclature and guiding well-designed clinical studies and management strategies based on evidence. The recent management options, which include newer ASMs, neuromodulation and immunomodulatory therapies have led to an excellent outcome in a large majority of patients, but a subgroup of approximately 30% of patients still remains refractory to therapy.

Future advances in epilepsy management will likely derive from several key developments: (1) deeper understanding of molecular mechanisms underlying drug resistance; (2) utilization of artificial intelligence for seizure prediction and patient stratification; (3) expansion of precision medicine approaches incorporating genomic and imaging biomarkers; (4) development of non-invasive neuromodulation technologies; and (5) implementation of integrated multidisciplinary care models. Resolution of healthcare disparities through systemic interventions and equity-focused research initiatives is essential for ensuring equitable access to advanced therapies across diverse populations.

The goal of contemporary epilepsy research and clinical practice is to achieve complete seizure freedom and optimize quality of life for all patients with epilepsy. This objective requires continued investment in translational research bridging basic neurobiology to clinical applications, rigorous clinical trials, and health systems approaches addressing accessibility and cost in epilepsy care globally.

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