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Modern Approaches to Epilepsy Treatment: A Comprehensive Review of Pharmacological, Surgical, and Alternative Therapies

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Abstract*—This review performs an exhaustive evaluation of present epilepsy treatment alternatives which include drug medications together with surgery and additional supportive methods. Before focusing on modern therapeutic approaches, the manuscript first addresses epilepsy types and prevalence as well as how medical treatment has evolved for this condition. The article describes antiseizure medications with detailed assessments based on both generational groups and operational principles. The review analyzes drugs which influence voltage-gated ion channels as well as GABAergic pharmaceuticals and medication that manage synaptic release processes and glutamate receptors. The essay explores both the outcome success of temporal lobe resection and investigates the brain's cognitive modifications after the procedure. The evaluation examines vagus nerve stimulation along with the ketogenic diet as alternative options in conjunction with planned research on herbal medicine treatments. Additionally, the paper explores recent uses of artificial intelligence in the diagnosis and clinical management of epilepsy. New medical findings from different epilepsy treatments merge into an extensive compilation of modern epilepsy therapy methods that outlines possible future research directions.*

***Keywords*—** *Alternative therapies; Antiseizure medications; Artificial intelligence in epilepsy; Herbal medicines; Pharmacological approaches; Surgical interventions.*

I. INTRODUCTION

The neurological disease epilepsy shows itself through abnormal brain electrical signals between its neurons. Epilepsy has multiple triggers that include head injuries, cerebrovascular accidents, infections between meningitis and encephalitis and genetic elements as well as birth injury.[1] Nevertheless worldwide over 50 million people suffer from epilepsy according to the World Health Organization.[2] The epilepsy classification follows parameters such as seizure type and age of onset and genetic factors and EEG results combined with MRI findings and additional diagnostic and clinical information. The International League Against Epilepsy (ILAE) created a new classification approach for seizure types and epilepsy syndromes when they released it in 2017. This modified classification system allows better understanding and classification of epilepsy through solving previous ambiguities in seizure type definitions. Since its 2010 updated version it has become essential for medical practice to accurately identify and assign seizure types to patients. The 2010 version replaced the previous 1981, 1989 editions. The introduction of phenobarbital in 1912 established current epilepsy treatment standards. The animal-based seizure test models used for antiepileptic effectiveness evaluations allowed scientists to develop phenytoin in the late 1930s. The treatment options comprise two main categories of herbal medicine and surgical interventions as well as neurostimulation equipment and dietary control strategies and artificial intelligence systems. [3-10]

II. METHODS

We searched multiple databases including PubMed and Scopus starting from 15 years ago up to current available publications. Our research focused on these specific terms: epilepsy studies, traditional Chinese medicine research, herbal drugs for epilepsy, GABA system, ion channels and oxidative stress effects. Research teams included both experimental and medical studies as long as they analysed TCM-derived herbs for preventing seizures. The research included only papers offering clear mechanisms and consistent protocols on a particular topic. We reviewed findings related to therapeutic aims, experimental models of seizures, and drug effectiveness to determine drug testing significance.

Anti Seizure Drugs

Antiseizure drugs (ASDs) are divided into three generations: older first generation and more recent second- and third-generation medications. The initial group of ASDs introduced more than 40 years ago included phenobarbital, phenytoin, primidone, ethosuximide, valproate, carbamazepine, clonazepam, and clobazam. Beginning in the late 1980s, a new wave of ASDs was approved for epilepsy treatment. These second-generation drugs include, in order of introduction, vigabatrin, oxcarbazepine, lamotrigine, gabapentin, felbamate, topiramate, tiagabine, levetiracetam, and zonisamide. The most recent third-generation ASDs category comprises pregabalin, rufinamide, eslicarbazepine, retigabine (also called ezogabine), perampanel, brivaracetam, cannabidiol, stiripentol, cenobamate, and fenfluramine.[11-14] The categorization of the ASDs currently in use is shown in

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Fig. 1. Up-to-date details regarding other medications under development can be accessed from the epilepsy foundation website.[15]

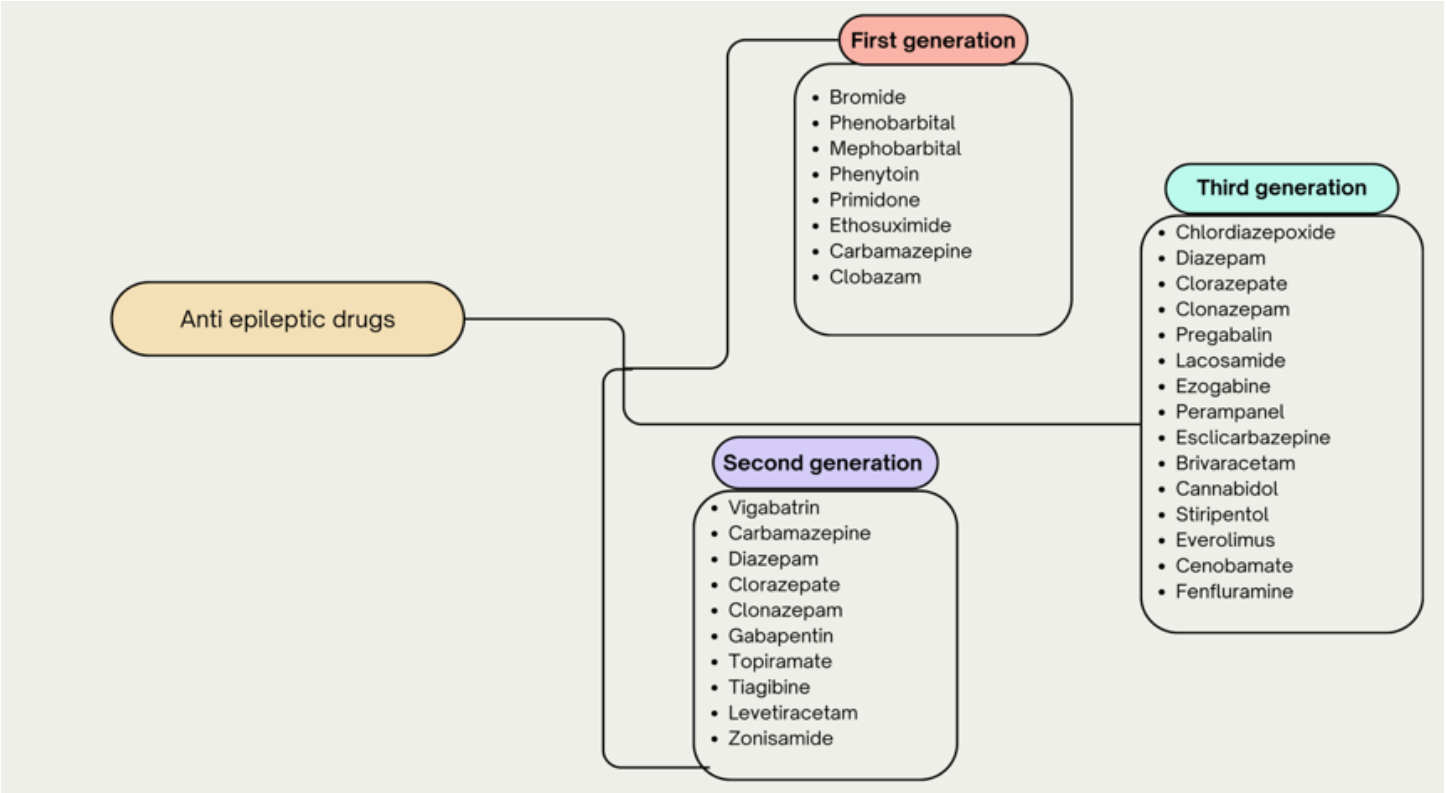

Fig. 1. Antiseizure drugs (ASDs) classification.

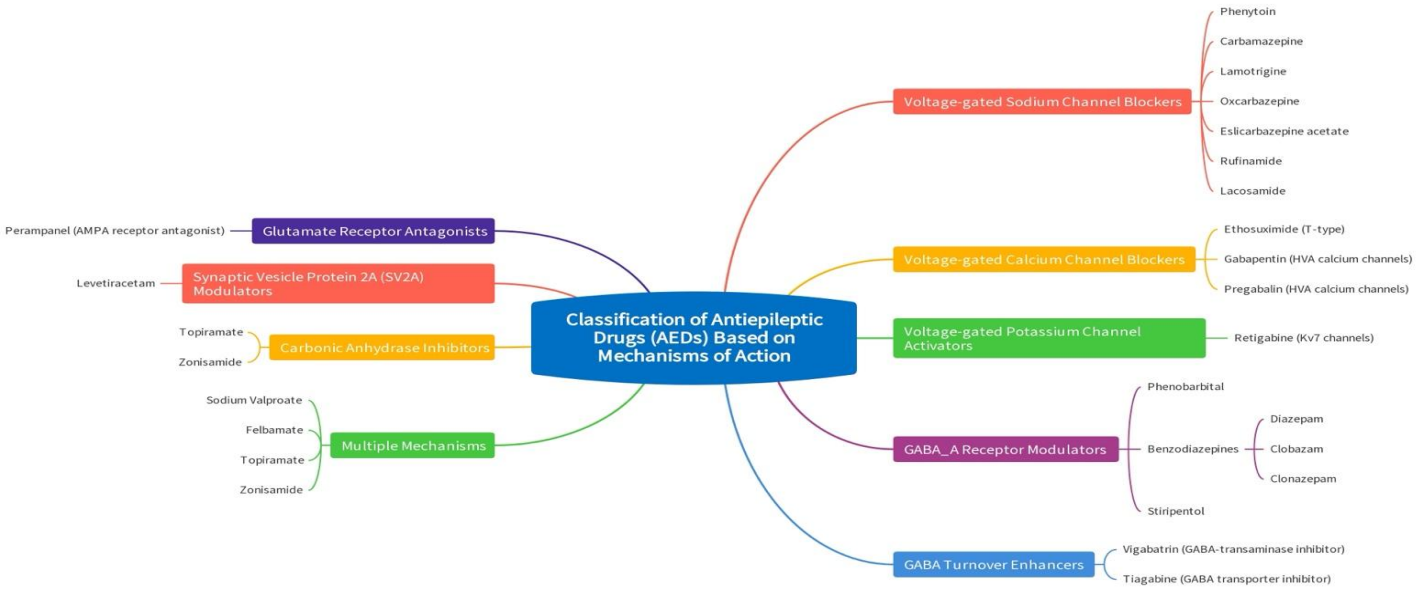

Fig. 2. Classification of antiepileptic drugs based on mechanism of action.

The antiepileptic medications that are widely used are described in the scientific literature to be mediated primarily by four mechanisms of actions. The first relates to the regulation of voltage dependent ion channels including sodium, calcium and potassium channels that are necessary to the initiation and conduction of neuronal signals. The second category comprises drugs that boost inhibitory neurotransmission, mainly by targeting the gamma-aminobutyric acid (GABA) system, either by increasing GABA production, decreasing GABA reuptake, or directly

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stimulating GABA receptors. The third category of antiepileptic agents work by reducing excitatory neurotransmission, typically by modulating ionotropic glutamate receptors. The fourth category includes medications that influence neurotransmitter release at the presynaptic level, thus altering the overall equilibrium between excitatory and inhibitory signals within neural networks.[16,17]Classification of antiepileptic drugs based on their mechanism of action is shown in Fig. 2.

Mechanism of Action of Anti-Epileptic Drugs

Voltage-Gated Ion Channel

Voltage-gated sodium channel

Voltage-gated sodium channels are essential for initiation and propagation of neuronal action potentials.**[18]** Minor depolarization, often triggered by glutamate receptor activation (AMPA and NMDA), opens sodium channels, allowing sodium influx along the electrochemical gradient. These channels are inactivated within milliseconds, generating a depolarization phase of the action potential. However, ~1% of the current persists (INaP). This lowers the action potential threshold and allows sustained firing and so promotes epileptic burst firing). Some antiseizure drugs (ASDs), such as phenytoin, inhibit INaP and contribute to its therapeutic effects.[19]

Sodium channels are composed of a large α-subunit (forming four homologous domains) and β-subunits**,** which modulate kinetics and trafficking.[20,21] Among the ten known α-subunits, Nav1.1, Nav1.2, Nav1.3, and NaV1.6, are predominant in the brain.[22,23] Mutations in these channels have been linked to genetic epilepsy**.**[24]

Sodium Channel-Blocking ASDs

ASDs that target sodium channels, such as phenytoin, carbamazepine, lamotrigine, oxcarbazepine, rufinamide, and lacosamide, are used to treat focal and generalised tonic-clonic seizures. These drugs exhibit use-dependent and voltage-dependent blocking, inhibiting high-frequency action potential trains, while sparing normal activity. They also reduce glutamate release by preventing the action potential invasion of nerve terminals**,** although their therapeutic role remains unclear.[25]

The sodium-binding site of ASDs coincides with the local anaesthetic binding site within the channel pore, stabilizing the inactivated state.[18,26] This inactivation is prolonged during rapid firing, allowing drug accumulation, which explains their seizure-preventing effects.

Lacosamide, unlike classical ASDs, does not inhibit rapid spike firing but rather affects longer spike trains (1-2 sec)**.** It is thought to enhance slow inactivation or to bind more gradually to inactivated sodium channels.[27] This slower action may enable selective targeting of pathological seizure-like firing, while sparing normal neural activity**.**

T-type voltage-gated calcium channels

T-type calcium channels, activated at low voltages, are essential for thalamocortical oscillations that underlie spike-wave discharges in generalized absence seizures.[28-30] These channels are encoded by three genes: Cav3.1 (α1G) in thalamic relay neurons is crucial for absence seizures; Cav3.2 (α1H) is located in thalamic reticular neurons and cortical layer V; Cav3.3 (α1I) exists in the thalamus and cortex but in lower amounts.[31] During non-REM sleep, thalamocortical circuits switch from tonic to oscillatory firing, producing δ waves, spindles, and K complexes. During wakeful episodes epilepsy causes abnormal neurological oscillations because thalamic reticular nucleus GABAergic neurons trigger a shift which suppresses relay neuron activity then activates burst firing.[32-34]Medical research demonstrates that ethosuximide effectively hinders all three T-type calcium channel variants and shows stronger efficacy during high-frequency neuronal activity which makes it an effective anti-seizure treatment. Early intake of ethosuximide as a treatment option may reduce long-term seizure risk by potential epigenetic effects but its primary mechanism involves blocking INaP, calcium-activated potassium and inward rectifier potassium currents.[35-39] Continual administration leads to better remission results than valproate. Additional antiseizure drugs possibly affect T-type calcium channels.[40-42] The main activity of Zonisamide occurs through sodium channels though T-type channel blockage also contributes to its effectiveness in controlling absence epilepsy.[43,44]Additional actions of valproate treatment involve T-type channels suppression.[36]

HVA Calcium Channels

Gabapentin and pregabalin, although originally created to mimic GABA, do not exhibit GABAergic activity. Instead, they attach to the α2δ-1 subunits of voltage-gated calcium channels, which is likely the basis for their therapeutic effects. Recent structural research indicates that this binding induces conformational changes in α2δ-1, influencing its interactions with proteins other than calcium channels. While α2δ-1 facilitates the insertion of α1-subunits into membranes, the absence of α2δ-1 does not alter calcium currents in neurons, and gabapentinoids do not consistently affect calcium channels. Although they might decrease the release of excitatory neurotransmitters by modulating presynaptic calcium channels, there is limited experimental evidence to support this. Some studies suggest that α2δ-1 might interact with NMDA receptors, but this interaction alone does not fully account for their antiseizure effects, implying the existence of other unidentified targets. In contrast, other antiepileptic drugs (ASDs) such as lamotrigine, levetiracetam, phenobarbital, and topiramate inhibit high-voltage-activated calcium channels (e.g., N-, P/Q-, and L-type), which contributes to a reduction in glutamate release. Although the significance of these effects varies, they indicate a broader and more conventional mechanism of calcium channel inhibition among ASDs.[45,46,47]

K_v7 Voltage-Gated Potassium Channels

Voltage-gated potassium (Kv) channels are activated upon membrane depolarization, facilitating the efflux of K+ ions to induce hyperpolarization, thereby reducing excitability. In 1998, the first genes associated with epilepsy, KCNQ2 and KCNQ3, were identified. These genes encode the Kv7.2 and Kv7.3 subunits, which are analogous to the cardiac Kv7.1 channel (KCNQ1/LQT1).[48] In the brain, these Kv7 channels generate the M current, which increases as the membrane

approaches the action potential threshold, thus limiting excitability.[49]

Kv7 channels are involved in regulating after-hyperpolarization (AHP), counterbalancing after-depolarization caused by persistent sodium currents (INaP), and preventing bursting.[50] The Kv7 family comprises five members: Kv7.1, present in the heart, and Kv7.2–Kv7.5, located in the nervous system, particularly in the hippocampus and neocortex (Brown & Passmore, 2009).[51] Kv7.2/Kv7.3 heterotetrametric channels, which are prevalent in axons, nodes of Ranvier, and initial segments, are crucial for controlling neuronal excitability.[52] Kv7.5 also contributes to the M current and AHP in the hippocampus.[53]

Ezogabine (Retigabine) & Its Mechanism

Ezogabine, an activator of Kv7 potassium channels, is effective in treating focal seizures by modulating Kv7.2–Kv7.5 channels without affecting Kv7.1 (; Gunthorpe et al., 2012).[54,55] Ezogabine shifts Kv7 activation to more hyperpolarized potentials, enhancing the M current near the resting potential.[56] It promotes channel opening without altering single-channel conductance. Kv7.2/Kv7.3 channels are particularly sensitive to ezogabine (EC50 = 1.6 μM).[55] Therapeutic plasma concentrations range from 1.2 to 2.4 μM, likely providing moderate enhancement of Kv7 activity.[57] The binding site is located between the S5 and S6 segments of adjacent subunits, stabilizing the open-state conformation.[58,59]

Kv7 Channels & Antiseizure Activity

Mice genetically modified to have Kv7 channel defects exhibit reduced sensitivity to ezogabine. The Kv7 inhibitor XE-991 partially reverses the effects of ezogabine (Gunthorpe et al., 2012).[55] Ezogabine inhibits the release of neurotransmitters, including GABA and possibly glutamate.[60] However, its impact on excitatory versus inhibitory neurons is still debated: Some studies suggest a reduction in glutamate release, which aligns with seizure protection, while others report increased glutamatergic transmission through sodium channel modulation, potentially explaining proconvulsant effects at high doses (≥61.9 mg/kg).[61]

Ezogabine & GABAergic Mechanisms

In addition to modulating Kv7 channels, ezogabine also affects GABAergic transmission: At high concentrations (>10 μM), The substance fulfills a positive allosteric potential on GABAA receptors.[62] The compound enhances only extra synaptic GABAA receptors which contain δ-subunits, which may contribute to seizure protection.[63] Ezogabine may increase GABA synthesis, though the exact mechanism remains unclear.[64] Kv7-independent GABAergic effects could be crucial to its antiseizure activity.[63] While ezogabine's primary antiseizure action is through Kv7 activation, its influence on GABAergic transmission may also play a role. Its paradoxical proconvulsant activity at high doses suggests a complex interaction between Kv7 activation, neurotransmitter modulation, and sodium channel effects.

GABA Inhibition

The neurotransmitter GABA, generated by local inhibitory interneurons, functions through GABA A and GABA B receptors. The following discussion emphasizes GABA A receptors since they represent Cys loop-type ligand-gated chloride channels and serve as critical targets for ASDs. In contrast, GABA B receptors, structurally and functionally distinct heterodimeric G-protein-coupled receptors that activate potassium channels and inhibit calcium channels, are not targeted by ASDs. Despite GABAergic neurons comprising only about 20% of cortical neurons, they play a crucial role in regulating the firing rate and timing of principal (excitatory) neurons. Furthermore, these neurons synchronize local neuronal groups and inhibit the development of abnormal epileptic activity. As a result, enhancing GABAergic inhibition is a fundamental mechanism of ASD action.[65]

$GABA_A$ Receptors

GABA_A receptors are pentameric proteins found on the postsynaptic membrane of inhibitory synapses, playing a role in both rapid and tonic neuronal inhibition. These receptors consist of 19 subunits (α1–6, β1–3, γ1–3, δ, ε, θ, π, and ρ1–3), with the α1β2γ2 configuration being the most prevalent in synaptic settings. Meanwhile, α4βxδ and α5-containing receptors are associated with tonic signalling in brain regions linked to epilepsy. Benzodiazepines, such as diazepam and lorazepam, and barbiturates, like phenobarbital, function as positive allosteric modulators of GABA_A receptors. Benzodiazepines specifically target receptors with γ2 subunits, enhancing synaptic inhibition by increasing the frequency of channel opening. In cases of absence epilepsy, they influence α3-containing receptors in the thalamic reticular nucleus, thereby disrupting pathological oscillations. Barbiturates, although less selective, prolong channel open time and also affect other ion channels, such as calcium and sodium, but their non-specific action can exacerbate absence seizures.[66,67]

GAT1 GABA Transporter

The neurotransmitter GABA leaves the extra cellular space after its removal by transport mechanisms located on neurons and glial cell membranes. There are four different GABA transporter families which comprise GAT1 and BGT1 together with GAT2 and GAT3. The expression of GAT1 results from the SLC6A1 gene while this transporter exists primarily in the forebrain structures such as the neocortex and hippocampus. GAT1 operates from GABAergic terminal parts together with glial processes that sit near GABA synapses. Tiagabine functions as a precise blocking agent of GAT1 in glial cells and neurons.[68] By blocking GAT1, tiagabine prevents the movement of extracellular GABA into cells, resulting in increased extracellular GABA concentrations. This leads to extended GABA-mediated inhibitory synaptic responses. The significant increase in extracellular GABA caused by tiagabine may also trigger the activation of extra synaptic GABA receptors.[69]

GABA Transaminase

GABA transaminase (The enzyme 4-aminobutyrate aminotransferase catalyzes GABA breakdown through a reaction which converts it with 2-oxoglutarate into succinic semialdehyde and glutamate. By blocking GABA transaminase with Vigabatrin (γ-vinyl GABA) brain GABA concentrations rise.[70] Since enzyme inhibition relates to seizure reduction the compound does not boost GABA A receptor-mediated synapse transmission like tiagabine.[71-72]

Instead it decreases inhibitory postsynaptic currents of both miniature and evoked scale. This occurs when synaptic vesicle GABA content decreases. The antiseizure mechanism of vigabatrin primarily depends on its effect of increasing tonic GABA A receptor currents by reversing GABA transporters to elevate extracellular GABA. The drug reduces seizure threshold first before its late protective effects become evident because it suppresses synaptic GABA activity while spilling GABA into the space surrounding synapses.[73-74] Genetic deficiency of GABA transaminase leads to refractory seizures which supports the theory of increased proconvulsant activity through GABA transaminase inhibition.[75]

Synaptic Release Machinery

SV2A

SV2A, a membrane glycoprotein located in the secretory vesicles of neurons and other cells, serves as the main target for levetiracetam (LEV). There is a significant correlation between LEV's binding affinity for SV2A and its success in seizure prevention, as demonstrated by the reduced effectiveness of LEV in SV2A+/– mice. Although the precise role of SV2A is not fully understood, it is thought to be involved in vesicle priming, neurotransmitter loading, and exocytosis. LEV attaches to SV2A without significantly changing its shape but may subtly influence its function. The absence of SV2A leads to fatal seizures, highlighting its importance in controlling seizures. LEV reduces the release of excitatory (glutamate) and inhibitory (GABA) neurotransmitters during high-frequency activity, selectively suppressing epileptic discharges. This supports the "supply-rate depression" concept—a form of short-term synaptic plasticity during intense activity—that LEV enhances, relying on SV2A. LEV's effect necessitates prolonged high-frequency neuronal activation, indicating a use-dependent mechanism. Besides binding to SV2A, LEV also inhibits high-voltage-gated calcium channels, modifies calcium release from internal stores, influences GABA turnover, affects neuronal activity in critical brain regions, and counteracts zinc-induced inhibition of GABA_A receptors. The precise significance of these additional actions in relation to LEV's antiseizure effects is still being explored.[76,77]

Ampa Receptors

Approximately 80–90% of brain synapses are excitatory, predominantly involving the release of glutamate at synapses between presynaptic terminals and postsynaptic dendritic spines. Ionotropic glutamate receptors, particularly AMPA receptors, facilitate rapid excitatory postsynaptic potentials (EPSPs), which are essential for fast synaptic transmission and epileptic synchronization, especially within the hippocampal CA3 region. Epilepsy frequently results from inadequate GABAergic inhibition, with chronic inhibitory alterations implicated in its pathogenesis. AMPA receptors play a pivotal role in epileptic activity, as their inhibition suppresses synchronization. In contrast, kainate receptors are less critical, and NMDA receptor blockade alone does not eliminate seizures and may exacerbate them clinically. AMPA receptor antagonists demonstrate broad antiseizure effects in models, and increased AMPA receptor expression in epileptic brain tissue suggests a role in the hyperexcitability associated with focal epilepsy. Perampanel, the sole clinically approved AMPA receptor antagonist, is a selective, noncompetitive inhibitor that exhibits antiseizure efficacy without affecting NMDA receptors or other ion channels at therapeutic levels. Even minimal AMPA blockade is sufficient for seizure control, although side effects such as dizziness and somnolence are common at higher doses. Despite their potent antiseizure activity, AMPA antagonists lack antiepileptogenic effects. In generalized seizures, extensive cortical and subcortical involvement, including the thalamus and basal ganglia, is facilitated by glutamatergic transmission. AMPA receptors mediate rapid excitation in these circuits, accounting for the efficacy of AMPA antagonists in treating secondarily and primarily generalized tonic-clonic seizures. These drugs also suppress EEG abnormalities in photosensitive epilepsy.[78,79,80]

Mixed Targets

Valproate

Despite being one of the most commonly prescribed antiseizure drugs (ASDs), valproate's mechanism of action in preventing seizures remains unclear. The drug exhibits multiple pharmacological effects, and it has been suggested that its broad spectrum of clinical efficacy may result from a combination of these actions on various targets. While valproate's impact on GABA systems is complex, its effects on GABA-related mechanisms are considered among the most likely to contribute to its antiseizure properties. For example, valproate specifically boosts GABA turnover in certain areas of the brain,[81] which may enhance synaptic or extrasynaptic inhibition. Although high concentrations of valproate affect voltage-gated sodium channels, recent brain slice recording studies have not supported sodium-channel blockade as a significant mechanism for its clinical effectiveness. Similarly, despite its efficacy in treating absence epilepsy, there is limited evidence for valproate's effects on T-type calcium channels. It is evident that some of valproate's The pharmacological mechanisms that contribute to its antiseizure effects have yet to be identified..[82]

Felbamate

The substance behaves as a GABA A receptor enhancer while simultaneously disabling NMDA receptors. The compound binds to a GABA A receptor site unique from benzodiazepine recognition sites and this allows effective treatment of patients in clinical settings. The effectiveness of felbamate blocking NMDA receptors remains unknown for both focal and generalized seizures since evidence demonstrates these receptors are not proven targets for seizure treatment. [83]

Topiramate

Topiramate works through several recognized drug actions yet doctors still must discover how all these effects block seizures. Topiramate blocks sodium channels in addition to acting on GABA A receptor subtypes and several other receptor types like AMPA/kainate and carbonic anhydrases II and IV. Instead of directly controlling ion channels topiramate

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makes its impact by altering how protein molecules become activated.[84]

Topiramate works similarly to other antiseizure drugs by blocking sodium channels while also inhibiting I_NaP just like phenytoin. At therapeutic levels. Although it does not work in PTZ models that respond to GABA A regulation it shows activity in absence epilepsy models and increases resistance to PTZ effects which demonstrates a role for GABA A receptors.[85-88]

In experiments with neurons topiramate showed it blocks kainate and blocks AMPA/kainate receptor activity at relevant dosages.[89]but recent research points away from targeting kainate receptors as antiseizure therapy.[80] Despite initial scepticism of its carbonic anhydrase inhibition role in epilepsy it now seems to explain some of its effect in animal models because of lack of cross-tolerance with acetazolamide in mice.[90]

Headache and reduced attention memory skills emerge when oral carbamazepine reaches certain blood levels. Science has not found the exact reason for this yet.[91]

TABLE 1. Anti-epileptic drugs and their side effects

Drug	psychotropic effect
Carbamazepine (CBZ)	No effect on mental state or mood.[97]
	increased anxiety, irritability, sleep disturbance, compared with PTH and VPA.[98]
	Sleepiness, depression.[99]
	agitation, depression, insomnia, somnolence.[100]
Diazapam (DZP)	euphoria, nervousness, somnolence.[101]
	nervousness, somnolence.[102]
Felbamate (FBM)	increased anxiety.[103]
	Depression.[104]
Gabapentin (GBP)	Drowsiness.[105]
	somnolence, emotional liability.[105]
	improving mental health, especially emotional well-being.[106]
	decreased depression.[107]
Lacosamide (LCS)	Somnolence.[108]
	doesn't alter mental state or cognition.[109]
Lamotrigine (LTG)	sleepiness, depression.[99]
	doesn't affect mental state or cognition.[110]
	Insomnia.[111]
	anxiety, somnolence.[112]
	emotional liability, somnolence, insomnia.[113]
	irritability, anxiety, depression, pyschosis.[104]
Levetiracetam (LEV)	depression, aggression, insomnia, somnolence.[114]
	affective disorder, aggression, psychosis.[115]
	sleep disturbances.[116]
Oxcarbazepine	emotional liability.[97]
	Sedation.[117]
	Somnolence.[118]
	depression, anxiety, behaviour change.[104]
Perampanel	behaviour change, dizziness, slurred speech, confusion.[119]
	ataxia, irritability, cognitive slowing.[120]
Phenobarbitone	hyperactivity, aggression.[121]
Phenytoin (PHT)	anxiety, depression.[122]
	Sedation.[121]
Pregabalin	somnolence, depression, anxiety, insomnia.[123]
Retigabine	somnolence, headache, dizziness, vertigo.[124]
Tiagabine (TGB)	Psychosis, somnolence.[125]
	irritability, anxiety, depression.[104]
Topiramate	somnolence, mood disturbance, aggression, nervousness.[126]
	Psychosis.[127]
	aggression, anxiety, sleep disturbance.[128]
	irritability, behavioural change.[104]
Valproate (VPA)	Drowsiness.[129]
	Hyperactivity.[121]
	Somnolence.[110]
	insomnia, irritability.[130]
Vigabatrin (VGA)	aggression, anxiety, depression, psychosis.[131]
	agitation, somnolence.[100]
zonisamide (ZNS)	Somnolence, abnormal thinking, nervousness.[132]
	Psychosis.[133]
	irritability, anxiety, depression, abnormal behaviour.[104]

Fate of synthetic drugs

Antiepileptic drugs (AEDs) are widely used for treating epilepsy, but they come with various side effects that can significantly impact patients' quality of life. Common adverse effects of AEDs include dose-related issues, idiosyncratic reactions, behavioural and psychiatric comorbidities, and

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chronic problems.[92] Antiepileptic drugs (AEDs) are associated with various adverse effects that can significantly impact patient outcomes and quality of life. A cross-sectional study of 354 adult epileptic patients found that about one-sixth of patients reported adverse drug effects, with fatigue (5.08%), gastrointestinal disturbance (4.24%), and sedation/depression (4.24%) being the most common.[93] These adverse effects were more prevalent in patients with low educational status, increased number of AEDs, and certain seizure patterns. Interestingly, a randomized controlled trial comparing AED treatment with and without therapeutic drug monitoring found no clear evidence that routine serum concentration measurement improved outcomes or reduced adverse effects.[94] This suggests that individualizing drug dosages based on serum levels may not necessarily lead to better tolerability. While AEDs are essential for seizure control, their adverse effects remain a significant concern. Newer AEDs have been `developed with the aim of improving the benefit-risk balance, but evidence suggests they may only be somewhat better tolerated than older molecules.[95] Clinicians should carefully consider patient characteristics, comorbidities, and specific medication toxicities when prescribing AEDs to minimize adverse effects and optimize treatment outcomes.[96] Few of the anti-epileptic drugs and their side effects are given in the Table 1.

Current treatment approach

Brivaracetam- Brivaracetam (BRV) is a high-affinity ligand for synaptic vesicle protein 2A, demonstrating a binding capacity that is 10 to 30 times greater than that of levetiracetam (LEV).[134,135] In early randomized controlled trials (RCTs), BRV demonstrated significant efficacy in reducing focal-onset seizures and was associated with a well-tolerated safety profile.[136,137] BRV has been shown to effectively reduce seizure frequency in individuals with epilepsy, achieving a ≥50% responder rate of 35.1%, with 8.8% of patients attaining complete seizure freedom.[138] Experiments with SV2A knockout mice confirmed that BRV specifically targets SV2A, as no binding was observed in the brains of these mice. Additionally, BRV does not significantly interact with other receptors, channels, or enzymes, even at concentrations much higher than those needed to bind SV2A. This suggests that BRV's primary mechanism of action is through its interaction with SV2A.

Ganaxolone GNX stands out as a medication well known for its effective seizure suppression performance in human patients. The Food and Drug Administration recognizes neurosteroid as the sole compound for epilepsy treatment. Ganaxolone contains a 3β-methyl group in its chemical structure so that back-conversion cannot occur thus minimizing unwanted side effects while minimizing breakdown and tolerance development. Results from Phase 2 clinical testing demonstrated that ganaxolone possesses potential to be used independently in treating patients with refractory status epilepticus. Medical staff conducted a trial to test intravenous administration of ganaxolone for patients who did not respond to benzodiazepines or at least one intravenous antiseizure medication. Treatment started with an initial bolus dose and included a continuous infusion with dropping concentration rates spanning 48 to 96 hours before an 18-hour ending fase. The research divided participants into three dosage groups consisting of 500 mg each day for the low dose and 650 mg each day for the medium dose as well as 713 mg each day for the high dose. The onset of seizure cessation from ganaxolone infusion therapy lasted approximately five minutes on average. The treatment with ganaxolone did not lead any patient to require a third-line anesthetic medication within 24 hours after treatment application thus demonstrating potential value in refractory status epilepticus treatment. [139-142]

Cenobamate (YKP3089)-

Cenobamate, an antiepileptic medication approved by the FDA on November 21, 2019, shows promising neuroprotective effects.[143] Its action mechanism includes decreasing neuronal excitability by enhancing both fast and slow sodium channel inactivation and inhibiting the persistent sodium current component.[144] In an extensive eight-year study with 49 patients suffering from drug-resistant focal-onset seizures, cenobamate proved highly effective: 16% of participants were seizure-free for more than six months, 29% saw a reduction in seizure frequency by 90% or more, and 45% experienced a reduction of at least 75% in seizure frequency.[145] Furthermore, a real-world study assessing one-year treatment outcomes in adults with highly drug-resistant epilepsy found seizure freedom rates of 8% at three months, 5% at six months, and 19% at twelve months, with a median dose of 250 mg/day. Remarkably, effectiveness was also noted at a lower median dose of 100 mg/day.[146]These results underscore cenobamate's potential as a viable treatment for drug-resistant focal epilepsy, with long-term benefits evident in both clinical and real-world contexts.

Herbal Medicine: Traditional Knowledge, Therapeutic Potential and Contemporary Applications

Despite the availability of 30 antiepileptic drugs (AEDs), their administration is frequently linked to adverse side effects. These side effects can greatly affect a patient's quality of life, sometimes even more than the seizures they aim to control. This creates a therapeutic dilemma for healthcare providers, as the most potent AEDs are often associated with notable side effects. Additionally, some AEDs might trigger severe adverse reactions without offering significant therapeutic advantages.[147] Herbal medicines, which rank among the most commonly used forms of complementary and alternative medicine (CAM), are acknowledged for their safety and efficacy. Their role in managing neurological diseases and disorders is gaining prominence. Herbal formulations provide polypharmacological effects by engaging multiple biological pathways due to their multi-component nature.[148]

Herbal pharmacological agents frequently interact with GABA receptors and ion channels, with some also affecting AMPA and NMDA receptors. GABA receptors, especially GABAA receptors, are pentameric ligand-gated chloride-ion channels that are essential for inhibitory neurotransmission.[149] These receptors are targeted by various pharmacologically active compounds, including certain herbal

drugs, which can modulate their function by enhancing GABA-mediated inhibition. Interestingly, while many herbal drugs primarily target GABA receptors, some also interact with voltage-sensitive ion channels, such as sodium channels. This mechanism is similar to that of certain antiepileptic drugs, like lamotrigine, which prolongs the inactivation of voltage-dependent sodium channels.[150] Additionally, some herbal compounds may influence glutamate receptors, including AMPA and NMDA receptors, which play a critical role in excitatory neurotransmission and have been associated with various neurological disorders.[151] Few herbal anti-epileptic drugs are given in the table no.2.

TABLE 2. Herbal anti-epileptic drug models and their mechanism of action

Drug	Animals / Humans	seizure model	target action	mechanism of action
Acorus calamus	In vivo animal model (cerebral cortex from rats)	Ferric chloride	antioxidant enzyme (SOD, CAT, LPO)	Modulating oxidative stress to prevent epileptogenesis.[152]
Albizzia lebbeck	In vivo animal model	Maximal Electric shock (MES), Pentylenetetrazole (PTZ), Lithium-pilocarpine	GABA-A	Increased GABA and serotonin levels in the brain.[153]
Aloe vera	In vivo animal model	Maximal Electric shock (MES), Pentylenetetrazole (PTZ), Increased current electroshock seizure (ICES) test,	NMDA, COX	By modulating NMDA receptors, inhibiting COX enzymes, and utilizing antioxidant properties, an anticonvulsant effect is achieved.[154]
Asparagus recemosus	Invivo animal model (cortex and hippocampus from mice)	Pentylenetetrazole (PTZ)	Monoaminergic system, cholinergic system	a multifaceted approach involving monoaminergic and cholinergic systems, decreasing nitrosative stress, and inhibiting the development of epilepsy.[155]
Bacopa monnieri	In vivo animal model (hippocampus from rat)	Pilocarpine	GABA A, GAD	Increases the density of GABA receptors and upregulates the GAD (Glutamate decarboxylase) gene expression required for the GABA synthesis.[156]
Boerhaavia diffusa	In vivo animal model (hippocampus and cortex from rat)	Pentylenetetrazole (PTZ), BAY k-8644	Voltage gated calcium channel, GABAergic system	Blocks voltage gated calcium channels and modulates GABAergic neurotransmission contributing to it anti-epileptic activity.[157]
Butea monosperma	In vivo animal model (hippocampus and cortex from rat and mice)	Maximal electric shock (MES), Pentylenetetrazole(PTZ), Lithium-pilocarpine	Voltage gated ion channels	Inhibits voltage gated sodium and calcium channels, enhances inhibitory neurotransmission.[158]
Calotropis gigantea	Invivo animal model (hippocampus and cortex from rat)	Pentylenetetrazole (PTZ)	GABAergic system, voltage gated ion channels	enhancement of GABAergic neurotransmission.[159]
Calotropis procera	In vivo animal model (hippocampus and cortex from mice)	Pentylenetetrazole (PTZ), Pilocarpine, strychnine	GABA-A, NMDA	Enhancement of GABA-A receptor activity, potential NMDA inhibition.[160]
Carum copticum	In vivo animal model (hippocampus, amygdala and cortex from rat)	Pentylenetetrazole (PTZ)	GABA-A, Calcium channel, H3 receptors	Enhances GABAergic activity, calcium channel blockage.[161]
Cedrus deodara	In vivo animal model (hippocampus and cortex from mice and rat)	Pentylenetetrazole (PTZ), Maximal electric shock (MES), Pilocarpine	GABA-A, NMDA	BDNF increases brain GABA levels, less effective towards NMDA inhibition.[162]
Curcuma longa	In vivo animal model (hippocampus and cortex from rat)	Pilocarpine	GABA-A, Glutamate, Calcium channels	Increases GABAergic activity while reducing glutamatergic excitability, thereby restoring exitatory-inhibitoy balance. Prevents neuronal damage by reducing oxidative stress and calcium mediated excitotoxicity.[163]
Ferula assa-foetida	In vivo animal model (hippocampus and cortex from mice)	Pentylenetetrazole (PTZ)	GABAergic system, voltage gated calcium channels	GABAergic and calcium channel modulation leading to reduced excitability and neuroprotection.[164]
Moringa oleifera	In vivo animal model (ventral tegmental area, nucleus accumbens, ventral pallidum)	Pentylenetetrazole (PTZ), picrotoxin, strychnine	GABAergic sytem, Dopaminergic system, Serotonergic system, cholinergic and adrenergic system	Enhances GABAergic and inhibits glycinergic pathways, also inhibits noradrenaline and acetylcholine.[165]
Nardostachys jatamansi	In vivo animal model (hippocampus and cortex from rat)	Maximal Electric shock (MES), Pentylenetetrazole (PTZ)	GABA-A, Voltage gated sodium channel	enhancing GABAergic nerve transmission, modulating voltage-gated sodium channels and increasing the seizure threshold, while exiting minimal neurotoxicity.[166]
Ocimum gratissimum	In vivo animal model (cortex and hippocampus from mice)	Maximal Electric shock (MES), Pentylenetetrazole (PTZ)	GABA-A, voltage gated ion channels	Essential oil obtained in spring season showed strongest anticonvulsant activity, due to higher percentage of sesquiterpenes.[167]
Passiflora incarnata	In vivo and Invitro animal model (hippocampus and cortex from rats)	Pentylenetetrazole (PTZ)	GABA-A, serotonergic system	Direct GABA-A agonist, modulate benzodiazepine sites on GABA-A receptors.[168]

Punica granatum	In vivo animal model (hippocampus and cortex from mice)	Pentylenetetrazole (PTZ), Strychnine(STR)	GABA-A, Glycenergic system	Enhances GABAergic neurotransmission, reduces oxidative stress, delays seizure onset.[169]
Rubia cordifolia	In vivo animal model (hippocampus and cortex from rat and mice)	Pentylenetetrazole (PTZ), Maximal electric shock (MES), Lithium-Pilocarpine, Electric kindling	GABA-A, serotonergic system	Increases brain GABA and serotonin levels, increases inhibitory neurotransmission.[170]
Sesbania grandiflora	In vivo animal model (hippocampus and cortex from rat and mice)	Pentylenetetrazole (PTZ), Maximal electric shock (MES), Lithium-Pilocarpine, Electric kindling	GABA-A, serotonergic system	Enhances GABAergic and serotonergic activity, reduces seizure severity, CNS depressant effects.[171]
Trichosanthes tricuspidata	In vivo animal model (hippocampus from mice)	Pilocarpine	GABAergic system	Reduces oxidative stress, increases antioxidant enzyme activity, and preventing hippocampal neurodegeneration.[172]
Vitex negundo	In vivo animal model (hippocampus and cortex from rat)	Maximal Electric shock (MES), Pentylenetetrazole (PTZ)	GABAergic system, voltage gated ion channels	Increases GABA activity, modulates voltage-gated ion channels.[173]
Withania somnifera	In vivo animal model (hippocampus and cortex from rat)	Pilocarpine	GABAergic system, AMPA receptors, GLAST	Modulates AMPA receptor function, increases GABA activity and decreases glutamate excitotoxicity by improving motor coordination.[174]
Zingiber officinale	In vivo animal model (hippocampus and cortex from mice)	Pentylenetetrazole (PTZ)	GABAergic system, voltage gated calcium channels	Modulates excitatory and inhibitory neurotransmission, reduces oxidative stress, inhibits calcium channels.[175]
Piper longum	In vivo animal model (hippocampus, striatum and cortex from mice)	Pilocarpine	GABA-A, Neuroinflammatory pathways (TNF-Alpha)	Increases GABAergic neurotransmission, reduces neuroinflammation (TNF-ALPHA expression) in the hippocampus, and mitigating oxidative stress, thereby increasing seizure latency and survival rates.[176]
Caesalpinia bonducella	In vivo animal model (hippocampus and cortex from mice)	Maximal Electric shock (MES), Pentylenetetrazole (PTZ), Strychnine, picrotoxin	GABA-A, Glycinergic system	Increase in the GABA levels and modulates glycine receptors.[177]
Ficus platyphylla	In vivo animal model (cortex and hippocampus from mice)	Maximal Electric shock (MES), Pentylenetetrazole (PTZ), Picrotoxin, isoniazid, strychnine, aminophylline	GABA-A	Increases the GABA neurotransmission likely through GABA-A receptor modulation, reduces locomotory activity, prolongs sleep duration and delays seizure onset.[178]

Herbal drug under use and clinical trail

Several herbal drugs despite of their good effect towards management of epilepsy only few drugs are under clinical trial and currently used for treatment of epilepsy.

Cannabinoids: Cannabinoids, particularly cannabidiol (CBD), show promise in treating refractory epilepsy in humans. CBD has demonstrated efficacy in reducing seizure frequency in patients with Dravet syndrome, as evidenced by a randomized clinical trial. In preclinical studies, CBD exhibited anticonvulsant effects in several animal models, including the Pentylenetetrazole (PTZ) and maximal electroshock (MES) tests.[179] Additionally, cannabidivarin (CBDV) showed anticonvulsant properties in mouse and rat models of seizures.[180] Cannabidiol (CBD) has shown promising results in treating refractory epilepsy in human patients, particularly in children with Dravet syndrome. In a randomized clinical trial, CBD demonstrated significant efficacy in reducing seizure frequency. Specifically, 43% of patients taking CBD experienced at least a 50% reduction in seizure frequency, compared to 27% in the placebo group. Moreover, 5% of patients became seizure-free during the treatment period. CBD has also shown potential in treating other forms of epilepsy. In an open-label interventional study involving patients with various types of treatment-resistant epilepsy, including Dravet and Lennox-Gastaut syndromes, CBD administration resulted in a 36.5% reduction in motor seizures, with 4% of patients becoming seizure-free over a 12-week follow-up period.[181]

Bacopa monnieri This improves memory performance but experts claim it helps manage conditions related to heart health and respiratory system problems and neuropharmacological disorders which include insomnia and insanity as well as depression and psychosis and epilepsy alongside stress indications..[182] Individuals with epilepsy often face cognitive impairments. These can result from multiple factors, including the cause of seizures, pre-existing brain lesions, seizure type, age of onset, frequency, duration, and severity of seizures. Cognitive function is also affected by interictal and ictal brain dysfunction, recurrent or prolonged seizures, genetic predisposition, psychosocial factors, and treatments like antiepileptic drugs or surgery.[183-185] In a triple blinded randomized control trail Bacopa monnieri had shown significant improvement cognitive performance score whereas it has no significant improvement in sleep quality.[186]

Surgical Approach:

Vagus Nerve Stimulation:

About two-thirds of epilepsy patients achieve seizure control with anti-seizure medications. Drug resistance in the remaining cases may stem from non-adherence, misdiagnosis, incorrect medication choice or dosage, or lifestyle factors. According to the International League Against Epilepsy, drug-resistant epilepsy is defined as the failure of two appropriate and well-tolerated medications to sustain seizure freedom. Temporal lobe resection has shown promising outcomes, with many patients achieving remission and improved quality of

life (HRQOL), even if minor memory decline occurs. Seizure freedom, even partial, was linked to better HRQOL. Studies showed that 62% of patients reached cure or near-cure status without significant cognitive decline, and some improved in intelligence scores. In patients with low-grade temporal lobe tumours, 81% were completely seizure-free post-lobectomy, and 10% had minimal seizures. Memory issues were mild and seen in 32%. A longitudinal study comparing surgical and medical treatments found 63% of surgical patients became seizure-free versus 12% of medically treated ones. However, memory decline occurred in 60% of surgical and 50% of medical cases. Surgery enhanced cognition in seizure-free individuals but could worsen it if seizures persisted. Seizure freedom is crucial for better cognitive, psychosocial, and quality of life outcomes. Despite its benefits, surgery can lead to complications like depression, psychosis, visual impairments, hemiparesis, and meningitis, highlighting the need for careful patient selection and follow-up.[187-203]

Ketogenic Diet

Around 400 BC, Hippocrates noted that some believed certain sea and farm animals could influence seizures. Traditional epilepsy treatments include medication, surgery, and vagus nerve stimulation. However, one-third of patients do not respond to drugs, prompting neurologists to consider dietary changes like the ketogenic diet. This diet is typically introduced after two antiepileptic drugs fail. It's a widely recognized non-pharmacological option, especially for children with drug-resistant epilepsy, and has been in use since 1921 with minor adaptations. The ketogenic diet affects GABA transaminase enzyme levels and boosts energy production, helping counteract temporary GABAergic inhibition. Its seizure control is largely attributed to changes in the GABAergic system. A 1998 study found that after six months on the diet, 55% of patients saw seizures reduced by over 50%; at one year, 40% reported similar benefits. Despite its effectiveness, side effects like fatigue, dehydration, behavioural changes, and gastrointestinal issues were noted, particularly in the first three months. Recent research links gut microbiome changes to drug-resistant epilepsy. People with uncontrolled seizures often exhibit abnormal gut bacteria. The ketogenic diet appears to influence these microbes, contributing to its anti-seizure effects. While studies in animals show promise, human trials remain limited. [204-209]

Future studies ought to concentrate on extensive, regulated clinical trials. Nevertheless, securing funding poses a difficulty since the diet does not generate commercial returns. More studies are needed to identify ideal candidates and potentially shift from strict ketogenic diets to microbiome-focused dietary therapies using probiotics and prebiotics.

Artificial Intelligence In Epilepsy

Artificial Intelligence (AI) is playing a crucial role in modern healthcare, significantly altering the ways in which diseases are diagnosed, treated, and managed. AI encompasses a range of computational techniques, including machine learning, deep learning, and natural language processing.[210] Despite extensive research efforts in epilepsy treatment across various fields, one of the most significant hurdles remains the variability in treatment outcomes among different individuals. Treatment results can differ greatly from one patient to another, influenced by intrinsic factors such as the specific types and characteristics of seizures, brain lesions, or accompanying neuropsychological disorders, as well as extrinsic factors like the stage at which treatment is initiated and the conditions under which it is administered. Consequently, it is essential to adopt personalized strategies that accurately assess each patient's condition and select the most suitable treatment approach for them.[211-213]

Machine learning helps programs make automated improvements by analysing statistics and science rules over raw data sets (Efficient Learning Machines: Theories, Concepts, and Applications for Engineers and System Designers). Study methods mainly exist as supervised or unsupervised types. Supervised learning algorithms work with labelled datasets through k-NN, regression models, naïve Bayes, random forest and SVM. With unused data input the system finds patterns by implementing k-means, k-medoids, fuzzy C-means, Gaussian mixtures, and hidden Markov models.

ANNs imitate brain processes by changing network connections when processing supervised or unsupervised learning data. ANN technology becomes deep neural networks (DNNs) when there are more than two hidden layers that enable them to detect features automatically for deep learning applications. Deep learning utilizes CNNs for image analysis and RNNs for handling time-dependent datasets (Efficient Learning Machines: Theories, Concepts, and Applications for Engineers and System Designers).[214-216]

Several significant applications of artificial intelligence were discovered to provide useful benefits

- Automatic seizure detection
- Diagnosis and classification of epilepsies
- Understanding the epileptogenesis
- Wearable electronic devices for PWE.

Automatic seizure detection

The key components of a seizure prediction system are data acquisition followed by EEG signal preprocessing and feature extraction next to classification then evaluation of results. The initial preprocessing step removes noise and increases signal-to-noise ratio by finding faulty channels and applying referencing methods.[217] Engineers create surrogate channels by implementing common spatial pattern filters and averaging EEG signals. The detection of seizures in EEG data relies on three kinds of noise elimination techniques: Butterworth bandpass filtering, notch filtering, wavelet transforms, and empirical mode decomposition. Supervised learning methods including k-NN, SVM, and deep learning approaches complete the detection process.[218-223]

EEG monitoring through scalp and invasive recordings enables researchers to identify when patients experience seizures along with determining non-seizure states. A neural network operated by Daoud and Bayoumi analyzed [224] EEG recordings of eight pediatric patients by using five-second non-overlapping segments which allowed CNN to handle spatial features and RNN to handle temporal data. Both groups received 80% of training content and 20% for validation.

During one-hour forecasting the model demonstrated a 99.6% accuracy level and a false alarm occurrence rate of 0.004/hour. Modern studies focus on personalized seizure prediction because patients demonstrate different patterns that demand several seizure recordings. The monitoring technology now extends beyond EEG by incorporating video and EMG in addition to mobile systems. Neural networks evaluating newborn limb motions in video recordings produced detection outcomes with 90% accuracy and precision when combined with electroencephalogram analysis.[225-226] The addition of SVM processing limb accelerometer data led to a detection accuracy reaching 90% alongside rare daily erroneous results and 10–30 second reaction speeds. The use of detection models based on CNN achieved more than 70% accuracy for seizure identification.[227-228]

Diagnosis and classification of epilepsies

Correct identification and categorization of seizures together with epilepsy and epilepsy syndromes stands as the core element for successful epilepsy treatment. Epileptologists who have experience with such analysis must handle the extensive examination of clinical history, imaging, EEG and genetic information but it proves time-consuming as a traditional method. The process of diagnosis might become faster through implementation of machine learning techniques. Researchers now investigate deep learning algorithms including CNN together with hybrid models that unite CNN and RNN to address this task apart from older machine learning methods such as SVM and kNN. The CNN/RNN hybrid model analysed time Fourier transform features from ictal EEG data to achieve 97.4% and 97.2% F1 scores in separate datasets.[229,230]

When fMRI data of resting-state was submitted to the SVM algorithm researchers obtained a brain network differentiation success rate of 85% sensitivity together with 82.5% specificity between epileptic patients and control subjects. The combination of diffusion tensor imaging with SVM led to effective patient classification between active epileptic and remission and control groups.[231,232] The scientists combined resting-state MEG data with an ANN to detect focal from generalized seizures in one study which reached a 88% sensitivity and 86% specificity level.[233]

Understanding epileptogenesis

Modern medical research identifies epilepsy as a neurological condition which materializes because brain network functions fail to operate properly. Network behavior exploration with evolutionary aspects remains an essential scientific pursuit because it strengthens knowledge about epilepsy emergence. Researchers have employed three main strategies for their work: animal models and lesional models in addition to cell-based models. The models present fundamental restrictions because they show incomplete aspects of an epileptic brain. The implementation of machine learning technology enables us to merge different brain measurement data collected from neuroimaging and EEG and MEG and functional imaging sessions. The combined data allows researchers to build virtual laboratory simulation platforms for brain epilepsy interventions. [234-238]

Wearable devices for PWE

People with epilepsy show high acceptance for wearable devices as seizure-monitoring tools. [239-240] However, acceptance depends on device accuracy and masks necessity of discreet design and comfort development since this phase is generally ignored. Rudimentary form of sleep discomfort stands as the prime factor driving PWEs to quit their monitoring devices. [241-245] By contrast stable device operations throughout daily activities remain necessary for seizure recording.[246] Wristbands and EEG headsets together with ECG monitors received endorsement from eight adult PWEs in interviews. The medical function of wearables goes beyond healthcare support since they intensify safety mechanisms and reinforce trust bonds between patients and providers. These devices simultaneously affect social dynamics and personal self-consciousness. [247,248] A seizure detection algorithm benefited from bigger data sets which particularly recognized daily seizure patterns better while demonstrating maximum accuracy for tonic-clonic shakes.[249]

III. Conclusion

This review studied all current treatment ways for epilepsy including medications, surgery, and other treatment options. The main discovery shows antiseizure drugs keep serving as main therapy while newer drugs work better and cause less side effects. These drugs affect ion channels while supporting calming GABA signals and decreasing excitatory glutamate activity.

The removal of seizure areas from the brain helps control epilepsy when other medications fail yet doctors must weigh how the treatment affects thinking skills.

Clinicians use vagus nerve stimulation along with the ketogenic diet and several herbal treatments as supplementary therapeutic approaches for epilepsy treatment.

Using artificial intelligence to identify and forecast seizures will better assist in epilepsy treatment. Research still faces hurdles in giving every patient complete seizure control with less medicine side effects. Researchers must work on creating specific medical treatments and identifying how patients respond to care while also checking if treatments can change the progress of epilepsy. When patients receive medical interventions that include pharmaceuticals with distinctive surgeries alongside alternative methods which doctors customize for each person they get their best possible medical benefits.

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] N. Taspinar, A. Hacimuftuoglu, S. Butuner, B. Togar, G. Arslan, A. Taghizadehghalehjoughi, U. Okkay, E. Agar, R. Stephens, H. Turkez, and M. A. Hassibelnaby, "Differential effects of inhibitors of PTZ-induced kindling on glutamate transporters and enzyme expression," *Clinical and Experimental Pharmacology and Physiology*,

vol. 48, no. 12, pp. 1662–1673, Aug. 2021, doi: 10.1111/1440-1681.13575.

[2] O. P. Musekwa, L. Makhado, and A. Maphula, "Exploration of health care providers' knowledge-based care and support given to family members and caregivers of people living with epilepsy," *Frontiers in Psychology*, vol. 15, Jul. 2024, doi: 10.3389/fpsyg.2024.1396874.

[3] K. M. Aaberg, P. Surén, C. L. Søraas, I. J. Bakken, M. I. Lossius, C. Stoltenberg, and R. Chin, "Seizures, syndromes, and etiologies in childhood epilepsy: The International League Against Epilepsy 1981, 1989, and 2017 classifications used in a population-based cohort," *Epilepsia*, vol. 58, no. 11, pp. 1880–1891, Sep. 2017, doi: 10.1111/epi.13913.

[4] E. Perucca, "Antiepileptic drugs: evolution of our knowledge and changes in drug trials," *Epileptic Disorders*, vol. 21, no. 4, pp. 319–329, Aug. 2019, doi: 10.1684/epd.2019.1083.

[5] E. Rutebemberwa, C. Ssemugabo, R. Tweheyo, J. Turyagaruka, and G. W. Pariyo, "Biomedical drugs and traditional treatment in care seeking pathways for adults with epilepsy in Masindi district, Western Uganda: a household survey," *BMC Health Services Research*, vol. 20, no. 1, Jan. 2020, doi: 10.1186/s12913-019-4879-2.

[6] E. Auditeau, L. M. Moyano, G. Bourdy, M. Nizard, J. Jost, V. Ratsimbazafy, P.-M. Preux, and F. Boumediene, "Herbal medicine uses to treat people with epilepsy: A survey in rural communities of northem Peru," *Journal of Ethnopharmacology*, vol. 215, pp. 184–190, Jan. 2018, doi: 10.1016/j.jep.2018.01.003.

[7] L. Jehi, N. Jette, C.-S. Kwon, C. B. Josephson, J. G. Burneo, F. Cendes, M. R. Sperling, S. Baxendale, R. M. Busch, C. C. Triki, J. H. Cross, D. Ekstein, D. J. Englot, G. Luan, A. Palmini, L. Rios, X. Wang, K. Roessler, B. Rydenhag, G. Ramantani, S. Schuele, J. M. Wilmshurst, S. Wilson, and S. Wiebe, "Timing of referral to evaluate for epilepsy surgery: Expert Consensus Recommendations from the Surgical Therapies Commission of the International League Against Epilepsy," *Epilepsia*, vol. 63, no. 10, pp. 2491–2506, Jul. 2022, doi: 10.1111/epi.17350.

[8] M. Dümpelmann, "Early seizure detection for closed loop direct neurostimulation devices in epilepsy," *Journal of Neural Engineering*, vol. 16, no. 4, p. 041001, Feb. 2019, doi: 10.1088/1741-2552/ab094a.

[9] E. H. Kossoff , B. A. Zupec-Kania, S. Auvin, K. R. Ballaban-Gil, A. G. C. Bergqvist, R. Blackford, J. R. Buchhalter, R. H. Caraballo, J. H. Cross, M. G. Dahlin, E. J. Donner, O. Guzel, R. S. Jehle, J. Klepper, H.-C. Kang, D. A. Lambrechts, Y. M. C. Liu, J. K. Nathan, D. R. Nordli Jr., H. H. Pfeifer, J. M. Rho, I. E. Scheffer, S. Sharma, C. E. Stafstrom, E. A. Thiele, Z. Turner, M. M. Vaccarezza, E. J. T. M. van der Louw, P. Veggiotti, J. W. Wheless, and E. C. Wirrell, "Optimal clinical management of children receiving dietary therapies for epilepsy: Updated recommendations of the International Ketogenic Diet Study Group," *Epilepsia Open*, vol. 3, no. 2, pp. 175–192, Apr. 2018, doi: 10.1002/epi4.12225.

[10] F. Xiao *et al.*, "Identification of different MRI atrophy progression trajectories in epilepsy by subtype and stage inference," *Brain*, vol. 146, no. 11, pp. 4702–4716, Oct. 2023, doi: 10.1093/brain/awad284.

[11] L. J. Stephen and M. J. Brodie, "Pharmacotherapy of epilepsy," *CNS Drugs*, vol. 25, no. 2, pp. 89–107, Nov. 2010, doi: 10.2165/11584860-000000000-00000.

[12] J. A. French, A. M. Kanner, J. Bautista, B. Abou-Khalil, T. Browne, C. L. Harden, W. H. Theodore, C. Bazil, J. Stern, S. C. Schachter, D. Bergen, D. Hirtz, G. D. Montouris, M. Nespeca, B. Gidal, W. J. Marks Jr, W. R. Turk, J. H. Fischer, B. Bourgeois, A. Wilner, R. E Faught Jr, R. C. Sachdeo, A. Beydoun, T. A. Glauser, "Efficacy and tolerability of the new antiepileptic drugs, I: Treatment of New-Onset Epilepsy: Report of the TTA and QSS Subcommittees of the American Academy of Neurology and the American Epilepsy Society," *Epilepsia*, vol. 45, no. 5, pp. 401–409, May 2004, doi: 10.1111/j.0013-9580.2004.06204.x.

[13] A. G. Marson, Z. A. Kadir, J. L. Hutton, and D. W. Chadwick, "The new Antiepileptic Drugs: A Systematic Review of their efficacy and tolerability," *Epilepsia*, vol. 38, no. 8, pp. 859–880, Aug. 1997, doi: 10.1111/j.1528-1157.1997.tb01251.x.

[14] F. J. E. Vajda, "Pharmacotherapy of epilepsy: New armamentarium, new issues," *Journal of Clinical Neuroscience*, vol. 14, no. 9, pp. 813–823, Jul. 2007, doi: 10.1016/j.jocn.2007.02.008.

[15] International League Against Epilepsy Syndromes, https://www.epilepsydiagnosis.org/syndrome/epilepsy-syndrome-groupoverview.html (accessed on March 2, 2025)

[16] P. Kwan, G. J. Sills, and M. J. Brodie, "The mechanisms of action of commonly used antiepileptic drugs," *Pharmacology & Therapeutics*, vol. 90, no. 1, pp. 21–34, Apr. 2001, doi: 10.1016/s0163-7258(01)00122-x.

[17] R. J. Porter, Ashish. Dhir, R. L. Macdonald, and M. A. Rogawski, "Mechanisms of action of antiseizure drugs," *Handbook of Clinical Neurology*, pp. 663–681, Jan. 2012, doi: 10.1016/b978-0-444-52899-5.00021-6.

[18] M. Mantegazza, G. Curia, G. Biagini, D. S. Ragsdale, and M. Avoli, "Voltage-gated sodium channels as therapeutic targets in epilepsy and other neurological disorders," *The Lancet Neurology*, vol. 9, no. 4, pp. 413–424, Mar. 2010, doi: 10.1016/s1474-4422(10)70059-4.

[19] C. E. Stafstrom, "Persistent sodium current and its role in epilepsy," *Epiliepsy Currents/Epilepsy Currents*, vol. 7, no. 1, pp. 15–22, Jan. 2007, doi: 10.1111/j.1535-7511.2007.00156.x.

[20] B. S. Meldrum and M. A. Rogawski, "Molecular targets for antiepileptic drug development," *Neurotherapeutics*, vol. 4, no. 1, pp. 18–61, Jan. 2007, doi: 10.1016/j.nurt.2006.11.010.

[21] G. A. Patino and L. L. Isom, "Electrophysiology and beyond: Multiple roles of Na+ channel β subunits in development and disease," *Neuroscience Letters*, vol. 486, no. 2, pp. 53–59, Jun. 2010, doi: 10.1016/j.neulet.2010.06.050.

[22] F. H. Yu and W. A. Catterall, "Overview of the voltage-gated sodium channel family.," *Genome Biology*, vol. 4, no. 3, p. 207, Jan. 2003, doi: 10.1186/gb-2003-4-3-207.

[23] H. Vacher, D. P. Mohapatra, and J. S. Trimmer, "Localization and targeting of Voltage-Dependent ion channels in mammalian central neurons," *Physiological Reviews*, vol. 88, no. 4, pp. 1407–1447, Oct. 2008, doi: 10.1152/physrev.00002.2008.

[24] M. Oliva, S. F. Berkovic, and S. Petrou, "Sodium channels and the neurobiology of epilepsy," *Epilepsia*, vol. 53, no. 11, pp. 1849–1859, Aug. 2012, doi: 10.1111/j.1528-1167.2012.03631.x.

[25] P. C. Waldmeier, P. A. Baumann, P. Wicki, J. -j. Feldtrauer, C. Stierlin, and M. Schmutz, "Similar potency of carbamazepine, oxcarbazepine, and lamotrigine in inhibiting the release of glutamate and other neurotransmitters," *Neurology*, vol. 45, no. 10, pp. 1907–1913, Oct. 1995, doi: 10.1212/wnl.45.10.1907.

[26] N. Taspinar, A. Hacimuftuoglu, S. Butuner, B. Togar, G. Arslan, A. Taghizadehghalehjoughi, U. Okkay, E. Agar, R. Stephens Jr., H. Turkez, and A. M. Abd El-Aty, "Differential effects of inhibitors of PTZ-induced kindling on glutamate transporters and enzyme expression," *Clinical and Experimental Pharmacology and Physiology*, vol. 48, no. 12, pp. 1662–1673, Aug. 2021, doi: 10.1111/1440-1681.13575.

[27] M. A. Rogawski, A. Tofighy, H. S. White, A. Matagne, and C. Wolff, "Current understanding of the mechanism of action of the antiepileptic drug lacosamide," *Epilepsy Research*, vol. 110, pp. 189–205, Dec. 2014, doi: 10.1016/j.eplepsyres.2014.11.021.

[28] M. Avoli, J. Louvel, R. Pumain, and R. Köhling, "Cellular and molecular mechanisms of epilepsy in the human brain," *Progress in Neurobiology*, vol. 77, no. 3, pp. 166–200, Oct. 2005, doi: 10.1016/j.pneurobio.2005.09.006.

[29] J. R. Huguenard, "Block of T-Type Ca2+ Channels Is an Important Action of Succinimide Antiabsence Drugs," *Sage Journals*, vol. 2, no. 2, pp. 49–52, Mar. 2002, doi: 10.1111/j.1535-7597.2002.00019.x.

[30] R. J. Lamberts *et al.*, "Sudden cardiac arrest in people with epilepsy in the community," *Neurology*, vol. 85, no. 3, pp. 212–218, Jun. 2015, doi: 10.1212/wnl.0000000000001755.

[31] W. A. Catterall, "Structure and function of Voltage-Sensitive ion channels," *Science*, vol. 242, no. 4875, pp. 50–61, Oct. 1988, doi: 10.1126/science.2459775.

[32] A. Novak, K. Vizjak, and M. Rakusa, "Cognitive Impairment in People with Epilepsy," *Journal of Clinical Medicine*, vol. 11, no. 1, p. 267, Jan. 2022, doi: 10.3390/jcm11010267.

[33] M. Wong, "Cortical interneurons join the mix in absence seizures," *Epiliepsy Currents/Epilepsy Currents*, vol. 14, no. 4, pp. 215–217, Jul. 2014, doi: 10.5698/1535-7597-14.4.215.

[34] L. Danober, C. Deransart, A. Depaulis, M. Vergnes, and C. Marescaux, "Pathophysiological mechanisms of genetic absence epilepsy in the

rat," *Progress in Neurobiology*, vol. 55, no. 1, pp. 27–57, May 1998, doi: 10.1016/s0301-0082(97)00091-9.

[35] D. A. Coulter, J. R. Huguenard, and D. A. Prince, "Characterization of ethosuximide reduction of low-threshold calcium current in thalamic neurons," *Annals of Neurology*, vol. 25, no. 6, pp. 582–593, Jun. 1989, doi: 10.1002/ana.410250610.

[36] T. Broicher, T. Seidenbecher, P. Meuth, T. Munsch, S. G. Meuth, T. Kanyshkova, H.-C. Pape, and T. Budde "T-current related effects of antiepileptic drugs and a Ca2+ channel antagonist on thalamic relay and local circuit interneurons in a rat model of absence epilepsy," *Neuropharmacology*, vol. 53, no. 3, pp. 431–446, Jun. 2007, doi: 10.1016/j.neuropharm.2007.05.030.

[37] M. Z. Gören and F. Onat, "Ethosuximide: From bench to bedside," *CNS Drug Reviews*, vol. 13, no. 2, pp. 224–239, Jun. 2007, doi: 10.1111/j.1527-3458.2007.00009.x.

[38] J. C. Gomora, A. N. Daud, M. Weiergräber, and E. Perez-Reyes, "Block of cloned human T-Type calcium channels by succinimide antiepileptic drugs," *Molecular Pharmacology*, vol. 60, no. 5, pp. 1121–1132, Nov. 2001, doi: 10.1016/s0026-895x(24)12522-9.

[39] C.-W. Huang and C.-C. Kuo, "Flow- and voltage-dependent blocking effect of ethosuximide on the inward rectifier K+ (Kir2.1) channel," *Pflügers Archiv - European Journal of Physiology*, vol. 467, no. 8, pp. 1733–1746, Sep. 2014, doi: 10.1007/s00424-014-1611-2.

[40] H. Blumenfeld, J. P. Klein, U. Schridde, M. Vestal, T. Rice, D. S. Khera, C. Bashyal, K. Giblin, C. Paul-Laughinghouse, F. Wang, A. Phadke, J. Mission, R. K. Agarwal, D. J. Englot, J. Motelow, H. Nersesyan, S. G. Waxman, and A. R. Levin, "Early treatment suppresses the development of spike-wave epilepsy in a rat model," *Epilepsia*, vol. 49, no. 3, pp. 400–409, Dec. 2007, doi: 10.1111/j.1528-1167.2007.01458.x.

[41] G. Dezsi, E. Ozturk, D. Stanic, K. L. Powell, H. Blumenfeld, T. J. O'Brien, and N. C. Jones, "Ethosuximide reduces epileptogenesis and behavioral comorbidity in the GAERS model of genetic generalized epilepsy," *Epilepsia*, vol. 54, no. 4, pp. 635–643, Mar. 2013, doi: 10.1111/epi.12118.

[42] A. T. Berg, K. Rychlik, S. R. Levy, and F. M. Testa, "Complete remission of childhood-onset epilepsy: stability and prediction over two decades," *Brain*, vol. 137, no. 12, pp. 3213–3222, Oct. 2014, doi: 10.1093/brain/awu294.

[43] K. L. Powell, K. Lukasiuk, T. J. O'Brien, and A. Pitkänen, "Are alterations in transmitter receptor and ion channel expression responsible for epilepsies?," *Advances in Experimental Medicine and Biology*, pp. 211–229, Jan. 2014, doi: 10.1007/978-94-017-8914-1_17.

[44] S. Suzuki, K. Kawakami, S. Nishimura, Y. Watanabe, K. Yagi, M. Scino, and K. Miyamoto "Zonisamide blocks T-type calcium channel in cultured neurons of rat cerebral cortex," *Epilepsy Research*, vol. 12, no. 1, pp. 21–27, Jun. 1992, doi: 10.1016/0920-1211(92)90087-a.

[45] R. H. Dworkin *et al.*, "Pregabalin for the treatment of postherpetic neuralgia," *Neurology*, vol. 60, no. 8, pp. 1274–1283, Apr. 2003, doi: 10.1212/01.wnl.0000055433.55136.55.

[46] H. Lesser, U. Sharma, L. LaMoreaux, and R. M. Poole, "Pregabalin relieves symptoms of painful diabetic neuropathy," *Neurology*, vol. 63, no. 11, pp. 2104–2110, Dec. 2004, doi: 10.1212/01.wnl.0000145767.36287.a1.

[47] C. J. Landmark, G. Beiske, A. Baftiu, M. L. Burns, and S. I. Johannessen, "Experience from therapeutic drug monitoring and gender aspects of gabapentin and pregabalin in clinical practice," *Seizure*, vol. 28, pp. 88–91, Feb. 2015, doi: 10.1016/j.seizure.2015.02.017.

[48] C. Charlier, N. A. Singh, S. G. Ryan, T. B. Lewis, B. E. Reus, R. J. Leach, and M. Leppert "A pore mutation in a novel KQT-like potassium channel gene in an idiopathic epilepsy family," *Nature Genetics*, vol. 18, no. 1, pp. 53–55, Jan. 1998, doi: 10.1038/ng0198-53.

[49] N. Gu, K. Vervaeke, H. Hu, and J. F. Storm, "Kv7/KCNQ/M and HCN/h, but not KCa2/SK channels, contribute to the somatic medium after-hyperpolarization and excitability control in CA1 hippocampal pyramidal cells," *The Journal of Physiology*, vol. 566, no. 3, pp. 689–715, May 2005, doi: 10.1113/jphysiol.2005.086835.

[50] C. Yue and Y. Yaari, "Axo-Somatic and apical dendritic KV7/M channels differentially regulate the intrinsic excitability of adult rat CA1 pyramidal cells," *Journal of Neurophysiology*, vol. 95, no. 6, pp. 3480–3495, Feb. 2006, doi: 10.1152/jn.01333.2005.

[51] T. J. Jentsch, "Neuronal KCNQ potassium channels:physislogy and role in disease," *Nature Reviews. Neuroscience*, vol. 1, no. 1, pp. 21–30, Oct. 2000, doi: 10.1038/35036198.

[52] H. Vacher, D. P. Mohapatra, and J. S. Trimmer, "Localization and targeting of Voltage-Dependent ion channels in mammalian central neurons," *Physiological Reviews*, vol. 88, no. 4, pp. 1407–1447, Oct. 2008, doi: 10.1152/physrev.00002.2008.

[53] A. V. Tzingounis *et al.*, "The KCNQ5 potassium channel mediates a component of the afterhyperpolarization current in mouse hippocampus," *Proceedings of the National Academy of Sciences*, vol. 107, no. 22, pp. 10232–10237, May 2010, doi: 10.1073/pnas.1004644107.

[54] C. Tober, A. Rostock, C. Rundfeldt, and R. Bartsch, "D-23129: a potent anticonvulsant in the amygdala kindling model of complex partial seizures," *European Journal of Pharmacology*, vol. 303, no. 3, pp. 163–169, May 1996, doi: 10.1016/0014-2999(96)00073-8.

[55] M. J. Gunthorpe, C. H. Large, and R. Sankar, "The mechanism of action of retigabine (ezogabine), a first-in-class K+ channel opener for the treatment of epilepsy," *Epilepsia*, vol. 53, no. 3, pp. 412–424, Jan. 2012, doi: 10.1111/j.1528-1167.2011.03365.x.

[56] L. Tatulian and D. A. Brown, "Effect of the KCNQ potassium channel opener retigabine on single KCNQ2/3 channels expressed in CHO cells," *The Journal of Physiology*, vol. 549, no. 1, pp. 57–63, May 2003, doi: 10.1113/jphysiol.2003.039842.

[57] R. Hermann, G. M. Ferron, K. Erb, N. Knebel, P. Ruus, J. Paul, L. Richards, H.-P. Cnota, and S. Troy "Effects of age and sex on the disposition of retigabine," *Clinical Pharmacology & Therapeutics*, vol. 73, no. 1, pp. 61–70, Jan. 2003, doi: 10.1067/mcp.2003.12.

[58] T. V. Wuttke and H. Lerche, "Novel anticonvulsant drugs targeting voltage-dependent ion channels," *Expert Opinion on Investigational Drugs*, vol. 15, no. 10, pp. 1167–1177, Sep. 2006, doi: 10.1517/13543784.15.10.1167.

[59] W. Lange, J. Geissendörfer, A. Schenzer, J. Grötzinger, G. Seebohm, T. Friedrich, and M. Schwake "Refinement of the binding site and mode of action of the anticonvulsant retigabine on KCNQ K+ channels," *Molecular Pharmacology*, vol. 75, no. 2, pp. 272–280, Nov. 2008, doi: 10.1124/mol.108.052282.

[60] M. Martire, P. Castaldo, M. D'Amico, P. Preziosi, L. Annunziato, and M. Taglialatela, "M Channels Containing KCNQ2 Subunits Modulate Norepinephrine, Aspartate, and GABA Release from Hippocampal Nerve Terminals," *Journal of Neuroscience*, vol. 24, no. 3, pp. 592–597, Jan. 2004, doi: 10.1523/jneurosci.3143-03.2004.

[61] K. Vervaeke, N. Gu, C. Agdestein, H. Hu, and J. F. Storm, "Kv7/KCNQ/M-channels in rat glutamatergic hippocampal axons and their role in regulation of excitability and transmitter release," *The Journal of Physiology*, vol. 576, no. 1, pp. 235–256, Jul. 2006, doi: 10.1113/jphysiol.2006.111336.

[62] C. Rundfeldt and R. Netzer, "Investigations into the Mechanism of Action of the New Anticonvulsant Retigabine - Interaction with GABAergic and glutamatergic neurotransmission and with voltage gated ion channels," *Arzneimittelforschung*, vol. 50, no. 12, pp. 1063–1070, Dec. 2011, doi: 10.1055/s-0031-1300346.

[63] M. Treven, X. Koenig, E. Assadpour, E. Gantumur, C. Meyer, K. Hilber, S. Boehm, and H. Kubista "The anticonvulsant retigabine is a subtype selective modulator of GABAA receptors," *Epilepsia*, vol. 56, no. 4, pp. 647–657, Mar. 2015, doi: 10.1111/epi.12950.

[64] I. M. Kapetanovic, W. D. Yonekawa, and H. J. Kupferberg, "The effects of D-23129, a new experimental anticonvulsant drug, on neurotransmitter amino acids in the rat hippocampus in vitro," *Epilepsy Research*, vol. 22, no. 3, pp. 167–173, Nov. 1995, doi: 10.1016/0920-1211(95)00050-x.

[65] S. Sahara, Y. Yanagawa, D. D. M. O'Leary, and C. F. Stevens, "The Fraction of Cortical GABAergic Neurons Is Constant from Near the Start of Cortical Neurogenesis to Adulthood," *Journal of Neuroscience*, vol. 32, no. 14, pp. 4755–4761, Apr. 2012, doi: 10.1523/jneurosci.6412-11.2012.

[66] J. Simon, H. Wakimoto, N. Fujita, M. Lalande, and E. A. Barnard, "Analysis of the set of GABAA receptor genes in the human genome," *Journal of Biological Chemistry*, vol. 279, no. 40, pp. 41422–41435, Jul. 2004, doi: 10.1074/jbc.m401354200.

[67] W. Sieghart and G. Sperk, "Subunit Composition, distribution and function of GABA-A receptor subtypes," *Current Topics in Medicinal*

Chemistry, vol. 2, no. 8, pp. 795–816, Aug. 2002, doi: 10.2174/1568026023393507.

[68] A. Schousboe, K. K. Madsen, M. L. Barker-Haliski, and H. S. White, "The GABA synapse as a target for antiepileptic drugs: A historical overview focused on GABA transporters," *Neurochemical Research*, vol. 39, no. 10, pp. 1980–1987, Mar. 2014, doi: 10.1007/s11064-014-1263-9.

[69] S. M. Thompson and B. H. Gahwiler, "Effects of the GABA uptake inhibitor tiagabine on inhibitory synaptic potentials in rat hippocampal slice cultures," *Journal of Neurophysiology*, vol. 67, no. 6, pp. 1698–1701, Jun. 1992, doi: 10.1152/jn.1992.67.6.1698.

[70] O. a. C. Petroff, D. L. Rothman, K. L. Behar, D. Lamoureux, and R. H. Mattson, "The effect of gabapentin on brain gamma-aminobutyric acid in patients with epilepsy," *Annals of Neurology*, vol. 39, no. 1, pp. 95–99, Jan. 1996, doi: 10.1002/ana.410390114.

[71] L. S. Overstreet and G. L. Westbrook, "Paradoxical reduction of synaptic inhibition by vigabatrin," *Journal of Neurophysiology*, vol. 86, no. 2, pp. 596–603, Aug. 2001, doi: 10.1152/jn.2001.86.2.596.

[72] Y. Wu, W. Wang, and G. B. Richerson, "Vigabatrin induces tonic inhibition via GABA transporter reversal without increasing vesicular GABA release," *Journal of Neurophysiology*, vol. 89, no. 4, pp. 2021–2034, Apr. 2003, doi: 10.1152/jn.00856.2002.

[73] W. Löscher, R. Jäckel, and F. Müller, "Anticonvulsant and proconvulsant effects of inhibitors of GABA degradation in the amygdala-kindling model," *European Journal of Pharmacology*, vol. 163, no. 1, pp. 1–14, Apr. 1989, doi: 10.1016/0014-2999(89)90389-0.

[74] A. StuchlíK, H. Kubová, and P. Mareš, "Single systemic dose of vigabatrin induces early proconvulsant and later anticonvulsant effect in rats," *Neuroscience Letters*, vol. 312, no. 1, pp. 37–40, Oct. 2001, doi: 10.1016/s0304-3940(01)02195-4.

[75] L. K. Medina-Kauwe *et al.*, "4-Aminobutyrate aminotransferase (GABA-transaminase) deficiency," *Journal of Inherited Metabolic Disease*, vol. 22, no. 4, pp. 414–427, Jun. 1999, doi: 10.1023/a:1005500122231.

[76] A. L. Meehan, X. Yang, B. D. McAdams, L. Yuan, and S. M. Rothman, "A new mechanism for antiepileptic drug action: vesicular entry may mediate the effects of levetiracetam," *Journal of Neurophysiology*, vol. 106, no. 3, pp. 1227–1239, Jun. 2011, doi: 10.1152/jn.00279.2011.

[77] A. L. Meehan, X. Yang, L. Yuan, and S. M. Rothman, "Levetiracetam has an activity-dependent effect on inhibitory transmission," *Epilepsia*, vol. 53, no. 3, pp. 469–476, Jan. 2012, doi: 10.1111/j.1528-1167.2011.03392.x.

[78] M. A. Rogawski, "AMPA receptors as a molecular target in epilepsy therapy," *Acta Neurologica Scandinavica*, vol. 127, pp. 9–18, Mar. 2013, doi: 10.1111/ane.12099.

[79] C. R. Houser, "Do structural changes in GABA neurons give rise to the epileptic state?," *Advances in Experimental Medicine and Biology*, pp. 151–160, Jan. 2014, doi: 10.1007/978-94-017-8914-1_12.

[80] B. Fritsch, J. Reis, M. Gasior, R. M. Kaminski, and M. A. Rogawski, "Role of GLUK1 kainate receptors in seizures, epileptic discharges, and epileptogenesis," *Journal of Neuroscience*, vol. 34, no. 17, pp. 5765–5775, Apr. 2014, doi: 10.1523/jneurosci.5307-13.2014.

[81] W. Löscher, "Valproate enhances GABA turnover in the substantia nigra," *Brain Research*, vol. 501, no. 1, pp. 198–203, Oct. 1989, doi: 10.1016/0006-8993(89)91044-5.

[82] M. Englund, L. Hyllienmark, and T. Brismar, "Effect of valproate, lamotrigine and levetiracetam on excitability and firing properties of CA1 neurons in rat brain slices," *Cellular and Molecular Neurobiology*, vol. 31, no. 4, pp. 645–652, Feb. 2011, doi: 10.1007/s10571-011-9660-y.

[83] J. M. Rho, S. D. Donevan, and M. A. Rogawski, "Direct activation of GABAA receptors by barbiturates in cultured rat hippocampal neurons.," *The Journal of Physiology*, vol. 497, no. 2, pp. 509–522, Dec. 1996, doi: 10.1113/jphysiol.1996.sp021784.

[84] R. Guerrini and L. Parmeggiani, "Topiramate and its clinical applications in epilepsy," *Expert Opinion on Pharmacotherapy*, vol. 7, no. 6, pp. 811–823, Mar. 2006, doi: 10.1517/14656566.7.6.811.

[85] K. A. Lyseng-Williamson and L. P. H. Yang, "Topiramate," *Drugs*, vol. 67, no. 15, pp. 2231–2256, Jan. 2007, doi: 10.2165/00003495-200767150-00008.

[86] G. Sun, T. R. Werkman, A. Battefeld, J. J. Clare, and W. J. Wadman, "Carbamazepine and topiramate modulation of transient and persistent sodium currents studied in HEK293 cells expressing the NAV1.3 A–Subunit," *Epilepsia*, vol. 48, no. 4, pp. 774–782, Mar. 2007, doi: 10.1111/j.1528-1167.2007.01001.x.

[87] M. Rigoulot, A. Boehrer, and A. Nehlig, "Effects of topiramate in two models of genetically determined generalized epilepsy, the GAERS and the audiogenic Wistar AS," *Epilepsia*, vol. 44, no. 1, pp. 14–19, Jan. 2003, doi: 10.1046/j.1528-1157.2003.32902.x.

[88] T. A. Simeone, K. S. Wilcox, and H. S. White, "Topiramate modulation of β1- and β3-homomeric GABAA receptors," *Pharmacological Research*, vol. 64, no. 1, pp. 44–52, Mar. 2011, doi: 10.1016/j.phrs.2011.03.004.

[89] J. W. Gibbs, S. Sombati, R. J. DeLorenzo, and D. A. Coulter, "Cellular actions of topiramate: blockade of Kainate-Evoked inward currents in cultured hippocampal neurons," *Epilepsia*, vol. 41, no. s1, pp. 10–16, Jan. 2000, doi: 10.1111/j.1528-1157.2000.tb02164.x.

[90] R. P. Shank and B. E. Maryanoff, "Molecular Pharmacodynamics, clinical therapeutics, and Pharmacokinetics of topiramate," *CNS Neuroscience & Therapeutics*, vol. 14, no. 2, pp. 120–142, May 2008, doi: 10.1111/j.1527-3458.2008.00041.x

[91] G. F. Ahmed, X. Koenig, E. Assadpour, E. Gantumur, C. Meyer, K. Hilber, S. Boehm, and H. Kubista "Pharmacokinetic–pharmacodynamic modelling of intravenous and oral topiramate and its effect on phonemic fluency in adult healthy volunteers," *British Journal of Clinical Pharmacology*, vol. 79, no. 5, pp. 820–830, Nov. 2014, doi: 10.1111/bcp.12556.

[92] R. J. A. De Kinderen, S. M. A. A. Evers, R. Rinkens, D. Postulart, C. I. Vader, M. H. J. M. Majoie, and A. P. Aldenkamp,"Side-effects of antiepileptic drugs: The economic burden," *Seizure*, vol. 23, no. 3, pp. 184–190, Nov. 2013, doi: 10.1016/j.seizure.2013.11.009.

[93] M. B. Ayalew and E. A. Muche, "Patient reported adverse events among epileptic patients taking antiepileptic drugs," *SAGE Open Medicine*, vol. 6, p. 205031211877247, Jan. 2018, doi: 10.1177/2050312118772471.

[94] T. Tomson, M.-L. Dahl, and E. Kimland, "Therapeutic monitoring of antiepileptic drugs for epilepsy," *Cochrane Library*, vol. 2010, no. 5, Feb. 2007, doi: 10.1002/14651858.cd002216.pub2.

[95] R. Guerrini, G. Zaccara, G. La Marca, and A. Rosati, "Safety and Tolerability of Antiepileptic Drug Treatment in Children with Epilepsy," *Drug Safety*, vol. 35, no. 7, pp. 519–533, Jun. 2012, doi: 10.2165/11630700-000000000-00000.

[96] S. M. LaRoche and S. L. Helmers, "The new antiepileptic drugs," *JAMA*, vol. 291, no. 5, p. 615, Feb. 2004, doi: 10.1001/jama.291.5.615.

[97] M. Dam, R. Ekberg, Y. Løyning, O. Waltimo, and K. Jakobsen, "A double-blind study comparing oxcarbazepine and carbamazepine in patients with newly diagnosed, previously untreated epilepsy," *Epilepsy Research*, vol. 3, no. 1, pp. 70–76, Jan. 1989, doi: 10.1016/0920-1211(89)90070-3.

[98] I. Berg, A. Butler, M. Ellis, and J. Foster, "PSYCHIATRIC ASPECTS OF EPILEPSY IN CHILDHOOD TREATED WITH CARBAMAZEPINE, PHENYTOIN OR SODIUM VALPROATE: a RANDOM TRIAL," *Developmental Medicine & Child Neurology*, vol. 35, no. 2, pp. 149–157, Feb. 1993, doi: 10.1111/j.1469-8749.1993.tb11616.x.

[99] M. J. Brodie, A. Richens, and A. Yuen, "Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy," *The Lancet*, vol. 345, no. 8948, pp. 476–479, Feb. 1995, doi: 10.1016/s0140-6736(95)90581-2.

[100] D. Chadwick, "Safety and efficacy of vigabatrin and carbamazepine in ne wly diagnosed epilepsy: a multicentre randomised double-blind study," *The Lancet*, vol. 354, no. 9172, pp. 13–19, Jul. 1999, doi: 10.1016/s0140-6736(98)10531-7.

[101] F. E. Dreifuss, "A comparison of rectal diazepam gel and placebo for acute repetitive seizures," *New England Journal of Medicine*, vol. 338, no. 26, pp. 1869–1875, Jun. 1998, doi: 10.1056/nejm199806253382602.

[102] R. L. Kriel, J. C. Cloyd, J. M. Pellock, W. G. Mitchell, J. J. Cereghino, and N. P. Rosman, "Rectal diazepam gel for treatment of acute repetitive seizures," *Pediatric Neurology*, vol. 20, no. 4, pp. 282–288, Apr. 1999, doi: 10.1016/s0887-8994(98)00156-8.

[103] T. A. Ketter, B. A. Malow, R. Flamini, D. Ko, S. R. White, R. M. Post, and W. H. Theodore, "Felbamate monotherapy has stimulant-like effects in patients with epilepsy," *Epilepsy Research*, vol. 23, no. 2, pp. 129–137, Mar. 1996, doi: 10.1016/0920-1211(95)00089-5.

[104] D. Weintraub, R. Buchsbaum, S. R. Resor, and L. J. Hirsch, "Psychiatric and behavioral side effects of the newer antiepileptic drugs in adults with epilepsy," *Epilepsy & Behavior*, vol. 10, no. 1, pp. 105–110, Nov. 2006, doi: 10.1016/j.yebeh.2006.08.008.

[105] D. Chadwick, D. B. Leiderman, W. Sauermann, J. Alexander, and E. Garofalo, "Gabapentin in generalized seizures," *Epilepsy Research*, vol. 25, no. 3, pp. 191–197, Nov. 1996, doi: 10.1016/s0920-1211(96)00020-4.

[106] K. R. Dimond, A. C. Pande, L. Lamoreaux, and M. W. Pierce, "Effect of gabapentin (neurotonin®) on mood and well-being in patients with epilepsy," *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, vol. 20, no. 3, pp. 407–417, Apr. 1996, doi: 10.1016/0278-5846(96)00005-x.

[107] C. L. Harden, L. M. Lazar, L. H. Pick, B. Nikolov, M. A. Goldstein, D. Carson, L. D. Ravdin, J. H. Kocsis, and D. R. Labar, "A Beneficial Effect on Mood in Partial Epilepsy Patients Treated with Gabapentin," *Epilepsia*, vol. 40, no. 8, pp. 1129–1134, Aug. 1999, doi: 10.1111/j.1528-1157.1999.tb00830.x.

[108] E. Ben-Menachem, V. Biton, D. Jatuzis, B. Abou-Khalil, P. Doty, and G. D. Rudd, "Efficacy and Safety of Oral Lacosamide as Adjunctive Therapy in Adults with Partial-Onset Seizures," *Epilepsia*, vol. 48, no. 7, pp. 1308–1317, Jul. 2007, doi: 10.1111/j.1528-1167.2007.01188.x.

[109] P. Halász, R. Kälviäinen, M. Mazurkiewicz-Beldzińska, F. Rosenow, P. Doty, D. Hebert, and T. Sullivan, "Adjunctive lacosamide for partial-onset seizures: Efficacy and safety results from a randomized controlled trial," *Epilepsia*, vol. 50, no. 3, pp. 443–453, Jan. 2009, doi: 10.1111/j.1528-1167.2008.01951.x.

[110] F. Gilliam, B. Vazquez, J. C. Sackellares, G. Y. Chang, J. Messenheimer, J. Nyberg, M. E. Risner, and G. D. Rudd, "An active-control trial of lamotrigine monotherapy for partial seizures," *Neurology*, vol. 51, no. 4, pp. 1018–1025, Oct. 1998, doi: 10.1212/wnl.51.4.1018.

[111] M. Sadler, "Lamotrigine Associated with Insomnia," *Epilepsia*, vol. 40, no. 3, pp. 322–325, Mar. 1999, doi: 10.1111/j.1528-1157.1999.tb00712.x.

[112] L. Parmeggiani, A. Belmonte, A. R. Ferrari, E. Perucca, and R. Guerrini, "Add-On Lamotrigine treatment in children and young adults with severe partial epilepsy: An Open, Prospective, Long-Term Study," *Journal of Child Neurology*, vol. 15, no. 10, pp. 671–674, Oct. 2000, doi: 10.1177/088307380001501006.

[113] V. Biton, P. Levisohn, S. Hoyler, A. Vuong, and A. E. Hammer, "Lamotrigine versus Valproate Monotherapy—Associated Weight change in adolescents with epilepsy: results from a post hoc analysis of a randomized, Double-Blind clinical trial," *Journal of Child Neurology*, vol. 18, no. 2, pp. 133–139, Feb. 2003, doi: 10.1177/08830738030180021701.

[114] T. Betts, H. Yarrow, L. Greenhill, and M. Barrett, "Clinical experience of marketed Levetiracetam in an epilepsy clinic—a one year follow up study," *Seizure*, vol. 12, no. 3, pp. 136–140, Mar. 2003, doi: 10.1016/s1059-1311(02)00258-3.

[115] M. Mula, M. R. Trimble, A. Yuen, R. S. N. Liu, and J. W. A. S. Sander, "Psychiatric adverse events during levetiracetam therapy," *Neurology*, vol. 61, no. 5, pp. 704–706, Sep. 2003, doi: 10.1212/01.wnl.0000078031.32904.0d.

[116] J. Opp, I. Tuxhorn, T. May, G. Kluger, A. Wiemer-Kruel, G. Kurlemann, G. Gross-Selbeck, D. Rating, U. Brandl, U. Bettendorf, C. Härtel, and E. Korn-Merker, "Levetiracetam in children with refractory epilepsy: A multicenter open label study in Germany," *Seizure*, vol. 14, no. 7, pp. 476–484, Sep. 2005, doi: 10.1016/j.seizure.2005.08.002.

[117] P. McKee, J. Blacklaw, G. Forrest, R. A. Gillham, S. M. Walker, D. Connelly, and M. J. Brodie, "A double-blind, placebo-controlled interaction study between oxcarbazepine and carbamazepine, sodium valproate and phenytoin in epileptic patients.," *British Journal of Clinical Pharmacology*, vol. 37, no. 1, pp. 27–32, Jan. 1994, doi: 10.1111/j.1365-2125.1994.tb04234.x.

[118] S. C. Schachter, B. Vazquez, R. S. Fisher, K. D. Laxer, G. D. Montouris, D. T. Combs-Cantrell, E. Faught, L. J. Willmore, G. L. Morris, L. Ojemann, D. Bennett, P. Mesenbrink, J. D'Souza, and L. Kramer, "Oxcarbazepine," *Neurology*, vol. 52, no. 4, p. 732, Mar. 1999, doi: 10.1212/wnl.52.4.732.

[119] H. Coyle, P. Clough, P. Cooper, and R. Mohanraj, "Clinical experience with perampanel: Focus on psychiatric adverse effects," *Epilepsy & Behavior*, vol. 41, pp. 193–196, Oct. 2014, doi: 10.1016/j.yebeh.2014.09.072.

[120] B. J. Steinhoff, M. Bacher, T. Bast, R. Kornmeier, C. Kurth, J. Scholly, A. M. Staack, and I. Wisniewski, "First clinical experiences with perampanel—The Kork experience in 74 patients," *Epilepsia*, vol. 55, no. s1, pp. 16–18, Jan. 2014, doi: 10.1111/epi.12492.

[121] N. Thilothammal, K. Banu, and R. S. Ratnam, "Comparison of phenobarbitone, phenytoin with sodium valproate: Randomized, double-blind study," *Indian Pediatrics*, vol. 33, no. 7, pp. 549-555, Jul. 1996.

[122] V. Pulliainen and M. Jokelainen, "Comparing the Cognitive Effects of Phenytoin and Carbamazepine in Long-Term Monotherapy: A Two-Year Follow-Up," *Epilepsia*, vol. 36, no. 12, pp. 1195–1202, Dec. 1995, doi: 10.1111/j.1528-1157.1995.tb01062.x.

[123] P. Kwan, M. J. Brodie, R. Kälviäinen, L. Yurkewicz, J. Weaver, and L. E. Knapp, "Efficacy and safety of pregabalin versus lamotrigine in patients with newly diagnosed partial seizures: a phase 3, double-blind, randomised, parallel-group trial," *The Lancet Neurology*, vol. 10, no. 10, pp. 881–890, Sep. 2011, doi: 10.1016/s1474-4422(11)70154-5.

[124] S. Rheims and P. Ryvlin, "Retigabine for partial onset seizures," *Expert Review of Neurotherapeutics*, vol. 12, no. 5, pp. 509–517, May 2012, doi: 10.1586/ern.12.33.

[125] J. C. Sackellares, G. Krauss, K. W. Sommerville, and R. Deaton, "Occurrence of Psychosis in Patients with Epilepsy Randomized to Tiagabine or Placebo Treatment," *Epilepsia*, vol. 43, no. 4, pp. 394–398, Apr. 2002, doi: 10.1046/j.1528-1157.2002.16000.x.

[126] R. D. Elterman, T. A. Glauser, E. Wyllie, R. Reife, S. -c. Wu, and G. Pledger, "A double-blind, randomized trial of topiramate as adjunctive therapy for partial-onset seizures in children," *Neurology*, vol. 52, no. 7, p. 1338, Apr. 1999, doi: 10.1212/wnl.52.7.1338.

[127] A. Khan, E. Faught, F. Gilliam, and R. Kuzniecky, "Acute psychotic symptoms induced by topiramate," *Seizure*, vol. 8, no. 4, pp. 235–237, Jun. 1999, doi: 10.1053/seiz.1999.0287.

[128] J. Christensen, F. Andreasen, J. H. Poulsen, and M. Dam, "Randomized, concentration-controlled trial of topiramate in refractory focal epilepsy," *Neurology*, vol. 61, no. 9, pp. 1210–1218, Nov. 2003, doi: 10.1212/01.wnl.0000091867.09720.6b.

[129] A. Richens and S. Ahmad, "Controlled trial of sodium valproate in severe epilepsy.," *BMJ*, vol. 4, no. 5991, pp. 255–256, Nov. 1975, doi: 10.1136/bmj.4.5991.255.

[130] A. P. Aldenkamp, G. Baker, O. G. Mulder, D. Chadwick, P. Cooper, J. Doelman, R. Duncan, C. Gassmann-Mayer, G. J. de Haan, C. Hughson, J. Hulsman, J. Overweg, G. Pledger, T. W. Rentmeester, H. Riaz, and S. Wroe, "A Multicenter, Randomized Clinical Study to Evaluate the Effect on Cognitive Function of Topiramate Compared with Valproate as Add-On Therapy to Carbamazepine in Patients with Partial-Onset Seizures," *Epilepsia*, vol. 41, no. 9, pp. 1167–1178, Sep. 2000, doi: 10.1111/j.1528-1157.2000.tb00322.x.

[131] I. C. K. Wong, "Retrospective study of vigabatrin and psychiatric behavioural disturbances," *Epilepsy Research*, vol. 21, no. 3, pp. 227–230, Jul. 1995, doi: 10.1016/0920-1211(95)00022-3.

[132] D. Schmidt, R. Jacob, P. Loiseau, E. Deisenhammer, D. Klinger, A. Despland, M. Egli, G. Bauer, E. Stenzel, and V. Blankenhorn, "Zonisamide for add-on treatment of refractory partial epilepsy: a European double-blind trial," *Epilepsy Research*, vol. 15, no. 1, pp. 67–73, May 1993, doi: 10.1016/0920-1211(93)90011-u.

[133] E. Faught, R. Ayala, G. G. Montouris, and I. E. Leppik, "Randomized controlled trial of zonisamide for the treatment of refractory partial-onset seizures," *Neurology*, vol. 57, no. 10, pp. 1774–1779, Nov. 2001, doi: 10.1212/wnl.57.10.1774.

[134] P. Kwan, E. Trinka, W. Van Paesschen, I. Rektor, M. E. Johnson, and S. Lu, "Adjunctive brivaracetam for uncontrolled focal and generalized epilepsies: Results of a phase III, double-blind, randomized, placebo-controlled, flexible-dose trial," *Epilepsia*, vol. 55, no. 1, pp. 38–46, Oct. 2013, doi: 10.1111/epi.12391.

[135] M. D. Wood and M. Gillard, "Evidence for a differential interaction of brivaracetam and levetiracetam with the synaptic vesicle 2A protein,"

Epilepsia, vol. 58, no. 2, pp. 255–262, Dec. 2016, doi: 10.1111/epi.13638.

[136] V. Biton, S. F. Berkovic, B. Abou-Khalil, M. R. Sperling, M. E. Johnson, and S. Lu, "Brivaracetam as adjunctive treatment for uncontrolled partial epilepsy in adults: A phase III randomized, double-blind, placebo-controlled trial," *Epilepsia*, vol. 55, no. 1, pp. 57–66, Nov. 2013, doi: 10.1111/epi.12433.

[137] P. Klein, J. Schiemann, M. R. Sperling, J. Whitesides, W. Liang, T. Stalvey, C. Brandt, and P. Kwan, "A randomized, double-blind, placebo-controlled, multicenter, parallel-group study to evaluate the efficacy and safety of adjunctive brivaracetam in adult patients with uncontrolled partial-onset seizures," *Epilepsia*, vol. 56, no. 12, pp. 1890–1898, Oct. 2015, doi: 10.1111/epi.13212.

[138] F. Zahnert, K. Krause, I. Immisch, L. Habermehl, I. Gorny, I. Chmielewska, L. Möller, A. M. Weyand, P. M. Mross, J. Wagner, K. Menzler, and S. Knake, "Brivaracetam in the Treatment of Patients with Epilepsy—First Clinical Experiences," *Frontiers in Neurology*, vol. 9, Feb. 2018, doi: 10.3389/fneur.2018.00038.

[139] J. F. Kerrigan, W. D. Shields, T. Y. Nelson, D. L. Bluestone, W. E. Dodson, B. F. Bourgeois, J. M. Pellock, L. D. Morton, and E. P. Monaghan, "Ganaxolone for treating intractable infantile spasms: a multicenter, open-label, add-on trial," *Epilepsy Research*, vol. 42, no. 2–3, pp. 133–139, Dec. 2000, doi: 10.1016/s0920-1211(00)00170-4.

[140] V. Nohria and E. Giller, "Ganaxolone," *Neurotherapeutics*, vol. 4, no. 1, pp. 102–105, Jan. 2007, doi: 10.1016/j.nurt.2006.11.003.

[141] Ş. Türkmen, M. Löfgren, V. Birzniece, T. Bäckström, and I. -m. Johansson, "Tolerance development to Morris water maze test impairments induced by acute allopregnanolone," *Neuroscience*, vol. 139, no. 2, pp. 651–659, Jan. 2006, doi: 10.1016/j.neuroscience.2005.12.031.

[142] H. Vaitkevicius, R. E. Ramsay, C. B. Swisher, A. M. Husain, A. Aimetti, and M. Gasior, "Intravenous ganaxolone for the treatment of refractory status epilepticus: Results from an open-label, dose-finding, phase 2 trial," *Epilepsia*, vol. 63, no. 9, pp. 2381–2391, Jun. 2022, doi: 10.1111/epi.17343.

[143] S. J. Keam, "Cenobamate: First approval," *Drugs*, vol. 80, no. 1, pp. 73–78, Jan. 2020, doi: 10.1007/s40265-019-01250-6.

[144] M. Nakamura, J.-H. Cho, H. Shin, and I.-S. Jang, "Effects of cenobamate (YKP3089), a newly developed anti-epileptic drug, on voltage-gated sodium channels in rat hippocampal CA3 neurons," *European Journal of Pharmacology*, vol. 855, pp. 175–182, May 2019, doi: 10.1016/j.ejphar.2019.05.007.

[145] R. Elizebath, E. Zhang, P. Coe, E. G. Gutierrez, J. Yang, and G. L. Krauss, "Cenobamate treatment of focal-onset seizures: Quality of life and outcome during up to eight years of treatment," *Epilepsy & Behavior*, vol. 116, p. 107796, Feb. 2021, doi: 10.1016/j.yebeh.2021.107796.

[146] Y. Novitskaya, E. Schütz, B. Metternich, A. Schulze-Bonhage, and M. Hirsch, "Add-on treatment with cenobamate is already effective at low doses in refractory focal epilepsy: A prospective observational study," *Epilepsia*, vol. 65, no. 3, pp. 630–640, Dec. 2023, doi: 10.1111/epi.17874.

[147] B. Á. Rogvi-Hansen and L. Gram, "Adverse effects of established and new antiepileptic drugs: An attempted comparison," *Pharmacology & Therapeutics*, vol. 68, no. 3, pp. 425–434, Jan. 1995, doi: 10.1016/0163-7258(95)02014-4.

[148] L. Wu, Y. Wang, J. Nie, X. Fan, and Y. Cheng, "A Network Pharmacology approach to evaluating the efficacy of Chinese medicine using Genome-Wide transcriptional Expression data," *Evidence-based Complementary and Alternative Medicine*, vol. 2013, pp. 1–8, Jan. 2013, doi: 10.1155/2013/915343.

[149] S. Enna, "GABAB receptor agonists and antagonists: pharmacological properties and therapeutic possibilities," *Expert Opinion on Investigational Drugs*, vol. 6, no. 10, pp. 1319–1325, Oct. 1997, doi: 10.1517/13543784.6.10.1319.

[150] B. S. Meldrum, "Update on the mechanism of action of antiepileptic drugs," *Epilepsia*, vol. 37, no. s6, Dec. 1996, doi: 10.1111/j.1528-1157.1996.tb06038.x.

[151] M. A. Rogawski, "Revisiting AMPA receptors as an antiepileptic drug target," *Epiliepsy Currents/Epilepsy Currents*, vol. 11, no. 2, pp. 56–63, Mar. 2011, doi: 10.5698/1535-7511-11.2.56.

[152] R. Hazra, K. Ray, and D. Guha, "Inhibitory role of Acorus calamus in ferric chloride–induced epileptogenesis in rat," *Human & Experimental Toxicology*, vol. 26, no. 12, pp. 947–953, Dec. 2007, doi: 10.1177/0960327107087791.

[153] V. S. Kasture, C. T. Chopde, and V. K. Deshmukh, "Anticonvulsive activity of Albizzia lebbeck, Hibiscus rosa sinesis and Butea monosperma in experimental animals," *Journal of Ethnopharmacology*, vol. 71, no. 1–2, pp. 65–75, Jul. 2000, doi: 10.1016/s0378-8741(99)00192-0.

[154] N. Rathor, T. Arora, S. Manocha, A. N. Patil, P. K. Mediratta, and K. K. Sharma, "Anticonvulsant activity of Aloe vera leaf extract in acute and chronic models of epilepsy in mice," *Journal of Pharmacy and Pharmacology*, vol. 66, no. 3, pp. 477–485, Nov. 2013, doi: 10.1111/jphp.12181.

[155] P. Pahwa and R. K. Goel, "Ameliorative effect of Asparagus racemosus root extract against pentylenetetrazol-induced kindling and associated depression and memory deficit," *Epilepsy & Behavior*, vol. 57, pp. 196–201, Mar. 2016, doi: 10.1016/j.yebeh.2016.01.025.

[156] J. Mathew, G. Gangadharan, K. P. Kuruvilla, and C. S. Paulose, "Behavioral Deficit and Decreased GABA Receptor Functional Regulation in the Hippocampus of Epileptic Rats: Effect of Bacopa monnieri," *Neurochemical Research*, vol. 36, no. 1, pp. 7–16, Sep. 2010, doi: 10.1007/s11064-010-0253-9.

[157] M. Kaur and R. K. Goel, "Anti-Convulsant Activity of Boerhaavia diffusa: Plausible Role of Calcium Channel Antagonism," *Evidence-based Complementary and Alternative Medicine*, vol. 2011, no. 1, Dec. 2009, doi: 10.1093/ecam/nep192.

[158] V. S. Kasture, S. B. Kasture, and C. T. Chopde, "Anticonvulsive activity of Butea monosperma flowers in laboratory animals," *Pharmacology Biochemistry and Behavior*, vol. 72, no. 4, pp. 965–972, Jul. 2002, doi: 10.1016/s0091-3057(02)00815-8.

[159] A. Argal and A. K. Pathak, "CNS activity of Calotropis gigantea roots," *Journal of Ethnopharmacology*, vol. 106, no. 1, pp. 142–145, Jan. 2006, doi: 10.1016/j.jep.2005.12.024.

[160] R. C. De Sousa Lima, M. C. C. Silva, C. C. T. Aguiar, E. M. C. Chaves, K. C. F. Dias, D. S. Macêdo, F. C. F. de Sousa, K. de M. Carvalho, M. V. Ramos, and S. M. M. Vasconcelos, "Anticonvulsant action of Calotropis procera latex proteins," *Epilepsy & Behavior*, vol. 23, no. 2, pp. 123–126, Jan. 2012, doi: 10.1016/j.yebeh.2011.11.008.

[161] M. E. Rezvani, A. Roohbakhsh, M. H. Mosaddegh, M. Esmailidehaj, F. Khaloobagheri, and H. Esmaeili, "Anticonvulsant and depressant effects of aqueous extracts of Carum copticum seeds in male rats," *Epilepsy & Behavior*, vol. 22, no. 2, pp. 220–225, Aug. 2011, doi: 10.1016/j.yebeh.2011.07.017.

[162] D. Dhayabaran, E. J. Florance, K. Nandakumar, A. Shanmugarathinam, and A. Puratchikody, "Anticonvulsant activity of fraction isolated from ethanolic extract of heartwood of Cedrus deodara," *Journal of Natural Medicines*, vol. 68, no. 2, pp. 310–315, Aug. 2013, doi: 10.1007/s11418-013-0798-4.

[163] N. A. Noor, H. S. A. Ezz, A. R. Faraag, and Y. A. Khadrawy, "Evaluation of the antiepileptic effect of curcumin and Nigella sativa oil in the pilocarpine model of epilepsy in comparison with valproate," *Epilepsy & Behavior*, vol. 24, no. 2, pp. 199–206, May 2012, doi: 10.1016/j.yebeh.2012.03.026.

[164] Z. Kiasalari, M. Khalili, M. Roghani, H. Heidari, and Y. Azizi, "Antiepileptic and Antioxidant Effect of Hydroalcoholic Extract of Ferula Assa Foetida Gum on Pentylentetrazole- induced Kindling in Male Mice.," *PubMed*, vol. 4, no. 4, pp. 299–306, Jan. 2013, [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/25337361

[165] A. G. Bakre, A. O. Aderibigbe, and O. G. Ademowo, "Studies on neuropharmacological profile of ethanol extract of Moringa oleifera leaves in mice," *Journal of Ethnopharmacology*, vol. 149, no. 3, pp. 783–789, Aug. 2013, doi: 10.1016/j.jep.2013.08.006.

[166] V. S. Rao, A. Rao, and K. S. Karanth, "Anticonvulsant and neurotoxicity profile of Nardostachys jatamansi in rats," *Journal of Ethnopharmacology*, vol. 102, no. 3, pp. 351–356, Aug. 2005, doi: 10.1016/j.jep.2005.06.031.

[167] C. M. M. Freire, M. O. M. Marques, and M. Costa, "Effects of seasonal variation on the central nervous system activity of Ocimum gratissimum L. essential oil," *Journal of Ethnopharmacology*, vol. 105, no. 1–2, pp. 161–166, Nov. 2005, doi: 10.1016/j.jep.2005.10.013.

[168] S. -m. Elsas, D. J. Rossi, J. Raber, C.-A. Seeley, W. L. Gregory, C. Mohr, T. Pfankuch, "Passiflora incarnata L. (Passionflower) extracts elicit GABA currents in hippocampal neurons in vitro, and show anxiogenic and anticonvulsant effects in vivo, varying with extraction method," *Phytomedicine*, vol. 17, no. 12, pp. 940–949, Apr. 2010, doi: 10.1016/j.phymed.2010.03.002.

[169] S. Mehrzadi, S. Sadr, A. Hosseinzadeh, B. Gholamine, A. Shahbazi, H. FallahHuseini, and H. Ghaznavi, "Anticonvulsant activity of the ethanolic extract ofPunica granatumL. seed," *Neurological Research*, vol. 37, no. 6, pp. 470–475, Nov. 2014, doi: 10.1179/1743132814y.0000000460.

[170] V. S. Kasture, V. K. Deshmukh, and C. T. Chopde, "Anticonvulsant and behavioral actions of triterpene isolated from Rubia cordifolia Linn.," *PubMed*, vol. 38, no. 7, pp. 675–80, Jul. 2000, [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/11215310

[171] V. S. Kasture, V. K. Deshmukh, and C. T. Chopde, "Anxiolytic and anticonvulsive activity of Sesbania grandiflora leaves in experimental animals," *Phytotherapy Research*, vol. 16, no. 5, pp. 455–460, Aug. 2002, doi: 10.1002/ptr.971.

[172] G. S. B. Aseervatham, T. Sivasudha, M. Suganya, A. Rameshkumar, and R. Jeyadevi, "Trichosanthes tricuspidata Modulates Oxidative Toxicity in Brain Hippocampus Against Pilocarpine Induced Status Epilepticus in Mice," *Neurochemical Research*, vol. 38, no. 8, pp. 1715–1725, May 2013, doi: 10.1007/s11064-013-1075-3.

[173] V. R. Tandon and R. K. Gupta, "An experimental evaluation of anticonvulsant activity of Vitex-negundo.," *PubMed*, vol. 49, no. 2, pp. 199–205, Apr. 2005, [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/16170989

[174] S. Soman, T. R. Anju, S. Jayanarayanan, S. Antony, and C. S. Paulose, "Impaired motor learning attributed to altered AMPA receptor function in the cerebellum of rats with temporal lobe epilepsy: Ameliorating effects of Withania somnifera and withanolide A," *Epilepsy & Behavior*, vol. 27, no. 3, pp. 484–491, Apr. 2013, doi: 10.1016/j.yebeh.2013.01.007.

[175] A. Hosseini and N. Mirazi, "Acute administration of ginger (Zingiber officinale rhizomes) extract on timed intravenous pentylenetetrazol infusion seizure model in mice," *Epilepsy Research*, vol. 108, no. 3, pp. 411–419, Jan. 2014, doi: 10.1016/j.eplepsyres.2014.01.008.

[176] G. M. P. Da Cruz, C. F. B. Felipe, F. A. Scorza, M. A. C. da Costa, A. F. Tavares, M. L. F. Menezes, G. M. de Andrade, L. K. A. M. Leal, G. A. C. Brito, M. da G. Naffah-Mazzacoratti, E. A. Cavalheiro, and G. S. de B. Viana "Piperine decreases pilocarpine-induced convulsions by GABAergic mechanisms," *Pharmacology Biochemistry and Behavior*, vol. 104, pp. 144–153, Jan. 2013, doi: 10.1016/j.pbb.2013.01.002.

[177] A. Ali, Shalam, Ashfaq, N. V. Rao, S. H. Gouda, and S. M. Shantakumar, "Anticonvulsive Effect of Seed Extract of Caesalpinia bonducella (Roxb.)," *Iranian Journal of Pharmacology & Therapeutics*, vol. 8, no. 2, pp. 51–55, May 2009. Available: http://ijpt.iums.ac.ir/article-1-188-en.html

[178] B. A. Chindo, J. Ya'U, N. M. Danjuma, S. E. Okhale, K. S. Gamaniel, and A. Becker, "Behavioral and anticonvulsant effects of the standardized extract of Ficus platyphylla stem bark," *Journal of Ethnopharmacology*, vol. 154, no. 2, pp. 351–360, Apr. 2014, doi: 10.1016/j.jep.2014.03.061.

[179] O. Devinsky, E. Marsh, D. Friedman, E. Thiele, L. Laux, J. Sullivan, I. Miller, R. Flamini, A. Wilfong, F. Filloux, M. Wong, N. Tilton, P. Burno, J. Bluvstein, J. Headlund, R. Kamens, J. Maclean, S. Nangia, N. S. Singhal, C. A. Wilson, A. Patel, and M. R. Cilio, "Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial," *The Lancet Neurology*, vol. 15, no. 3, pp. 270–278, Dec. 2015, doi: 10.1016/s1474-4422(15)00379-8.

[180] N. A. Jones, A. J. Hill, I. Smith, S. A. Bevan, C. M. Williams, B. J. Whalley, and G. J. Stephens "Cannabidiol displays antiepileptiform and antiseizure properties in vitro and in vivo," *Journal of Pharmacology and Experimental Therapeutics*, vol. 332, no. 2, pp. 569–577, Nov. 2009, doi: 10.1124/jpet.109.159145.

[181] O. Devinsky, E. Marsh, D. Friedman, E. Thiele, L. Laux, J. Sullivan, I. Miller, R. Flamini, A. Wilfong, F. Filloux, M. Wong, N. Tilton, P. Bruno, J. Bluvstein, J. Hedlund, R. Kamens, J. Maclean, S. Nangia, N. S. Singhal, C. A. Wilson, A. Patel, and M. R. Cilio, "Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial," *The Lancet Neurology*, vol. 15, no. 3, pp. 270–278, Dec. 2015, doi: 10.1016/s1474-4422(15)00379-8.

[182] A. Russo and F. Borrelli, "Bacopa monniera, a reputed nootropic plant: an overview," *Phytomedicine*, vol. 12, no. 4, pp. 305–317, Apr. 2005, doi: 10.1016/j.phymed.2003.12.008.

[183] C. E. Elger, C. Helmstaedter, and M. Kurthen, "Chronic epilepsy and cognition," *The Lancet Neurology*, vol. 3, no. 11, pp. 663–672, Oct. 2004, doi: 10.1016/s1474-4422(04)00906-8.

[184] M. M. Saling, S. F. Berkovic, M. F. O'shea, R. M. Kalnins, D. G. Darby, and P. F. Bladin, "Lateralization of verbal memory and unilateral hippocampal sclerosis: Evidence of task-specific effects," *Journal of Clinical and Experimental Neuropsychology*, vol. 15, no. 4, pp. 608–618, Jul. 1993, doi: 10.1080/01688639308402582.

[185] A. Aldenkamp and J. Arends, "The relative influence of epileptic EEG discharges, short nonconvulsive seizures, and type of epilepsy on cognitive function," *Epilepsia*, vol. 45, no. 1, pp. 54–63, Dec. 2003, doi: 10.1111/j.0013-9580.2004.33403.x.

[186] M. Delfan, P. Kordestani-Moghaddam, M. Gholami, K. Kazemi, and R. Mohammadi, "Evaluating the effects of Bacopa monnieri on cognitive performance and sleep quality of patients with mild cognitive impairment: A triple-blinded, randomized, placebo-controlled trial," *EXPLORE*, vol. 20, no. 5, p. 102990, Mar. 2024, doi: 10.1016/j.explore.2024.02.008.

[187] P. Kwan, A. Arzimanoglou, A. T. Berg, M. J. Brodie, W. A. Hauser, G. Mathern, S. L. Moshé, E. Perucca, S. Wiebe, and J. French "Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies," *Epilepsia*, vol. 51, no. 6, pp. 1069–1077, Nov. 2009, doi: 10.1111/j.1528-1167.2009.02397.x.

[188] J. T. Langfitt, M. Westerveld, M. J. Hamberger, T. S. Walczak, D. V. Cicchetti, A. T. Berg, B. G. Vickrey, W. B. Barr, M. R. Sperling, D. Masur, and S. S. Spencer, "Worsening of quality of life after epilepsy surgery," *Neurology*, vol. 68, no. 23, pp. 1988–1994, Jun. 2007, doi: 10.1212/01.wnl.0000264000.11511.30.

[189] M. Keogan, D. McMackin, S. Peng, J. Phillips, T. Burke, S. Murphy, M. Farrell, and H. Staunton, "Temporal Neocorticectomy in Management of Intractable Epilepsy: Long-Term Outcome and Predictive Factors," Epilepsia. 1992;33(5):852–861. Available from: https://doi.org/10.1111/j.1528-1157.1992.tb02193.x

[190] P. J. Kirkpatrick, M. Honavar, I. Janota, and C. E. Polkey, "Control of temporal lobe epilepsy following en bloc resection of low-grade tumors," Journal of Neurosurgery. 1993;78(1):19–25. Available from: https://doi.org/10.3171/jns.1993.78.1.0019

[191] C. Helmstaedter, M. Kurthen, S. Lux, M. Reuber, and C. E. Elger, "Chronic epilepsy and cognition: A longitudinal study in temporal lobe epilepsy," Annals of Neurology. 2003;54(4):425–32. Available from: https://doi.org/10.1002/ana.10692

[192] G. Erba, K. R. Winston, J. R. Adler, K. Welch, R. Ziegler, and G. W. Hornig, "Temporal lobectomy for complex partial seizures that began in childhood," Surgical Neurology. 1992;38(6):424–432. Available from: https://doi.org/10.1016/0090-3019(92)90110-9

[193] S.-K. Kim, K.-C. Wang, Y.-S. Hwang, K. J. Kim, J. H. Chae, I.-O. Kim, and B.-K. Cho, ". Epilepsy surgery in children: outcomes and complications," Journal of Neurosurgery Pediatrics. 2008;1(4):277–283. Available from: https://doi.org/10.3171/ped/2008/1/4/277

[194] P. Bailey and F. Bremer, "A Sensory Cortical Representation Of The Vagus Nerve: With A Note On The Effects Of Low Blood Pressure On The Cortical Electrogram," Journal of Neurophysiology. 1938;1(5):405–12. Available from: https://doi.org/10.1152/jn.1938.1.5.405

[195] A. Zanchetti, S. C. Wang, and G. Moruzzi, "The effect of vagal afferent stimulation on the EEG pattern of the cat," *Electroencephalography and Clinical Neurophysiology*, vol. 4, no. 3, pp. 357–361, Aug. 1952, doi: 10.1016/0013-4694(52)90064-3.

[196] J. Zabara, "Inhibition of experimental seizures in canines by repetitive vagal stimulation," *Epilepsia*, vol. 33, no. 6, pp. 1005–1012, Nov. 1992, doi: 10.1111/j.1528-1157.1992.tb01751.x.

[197] J. S. Lockard, W. C. Congdon, and L. L. DuCharme, "Feasibility and safety of vagal stimulation in Monkey model," *Epilepsia*, vol. 31, no. s2, Jun. 1990, doi: 10.1111/j.1528-1157.1990.tb05844.x.

[198] J. W. Woodbury and D. M. Woodbury, "Vagal stimulation reduces the severity of maximal electroshock seizures in intact rats: use of a cuff

electrode for stimulating and recording," *Pacing and Clinical Electrophysiology*, vol. 14, no. 1, pp. 94–107, Jan. 1991, doi: 10.1111/j.1540-8159.1991.tb04053.x.

[199] R. S. McLachlan, "Suppression of interictal spikes and seizures by stimulation of the vagus nerve," *Epilepsia*, vol. 34, no. 5, pp. 918–923, Sep. 1993, doi: 10.1111/j.1528-1157.1993.tb02112.x.

[200] A. Fernández-Guardiola, A. Martínez, A. Valdés-Cruz, V. M. Magdaleno-Madrigal, D. Martínez, and R. Fernández-Mas, "Vagus nerve prolonged stimulation in Cats: Effects on epileptogenesis (Amygdala Electrical kindling): Behavioral and electrographic changes," *Epilepsia*, vol. 40, no. 7, pp. 822–829, Jul. 1999, doi: 10.1111/j.1528-1157.1999.tb00787.x.

[201] J. K. Penry and J. C. Dean, "Prevention of intractable partial seizures by intermittent vagal stimulation in humans: preliminary results," *Epilepsia*, vol. 31, no. s2, Jun. 1990, doi: 10.1111/j.1528-1157.1990.tb05848.x.

[202] M. Brázdil, I. Doležalová, E. Koritáková, J. Chládek, R. Roman, M. Pail, P. Jurák, D. J. Shaw, J. Chrastina, "EEG reactivity predicts individual efficacy of vagal nerve stimulation in intractable epileptics," *Frontiers in Neurology*, vol. 10, May 2019, doi: 10.3389/fneur.2019.00392.

[203] L. De Taeye, K. Vonck, M. Van Bochove, P. Boon, D. Van Roost, L. Mollet, A. Meurs, V. De Herdt, E. Carrette, I. Dauwe, S. Gadeyne, P. van Mierlo, T. Verguts, R. Raedt. "The P3 Event-Related Potential is a Biomarker for the Efficacy of Vagus Nerve Stimulation in Patients with Epilepsy," *Neurotherapeutics*, vol. 11, no. 3, pp. 612–622, Apr. 2014, doi: 10.1007/s13311-014-0272-3.

[204] R. Pluta and M. Jabłoński, "The ketogenic diet for epilepsy therapy in children: Quo vadis?," *Nutrition*, vol. 27, no. 5, pp. 615–616, Apr. 2011, doi: 10.1016/j.nut.2010.12.015.

[205] N. Calderón, L. Betancourt, L. Hernández, and P. Rada, "A ketogenic diet modifies glutamate, gamma-aminobutyric acid and agmatine levels in the hippocampus of rats: A microdialysis study," *Neuroscience Letters*, vol. 642, pp. 158–162, Feb. 2017, doi: 10.1016/j.neulet.2017.02.014.

[206] E. P. G. Vining *et al*., "A multicenter study of the efficacy of the ketogenic diet," *Archives of Neurology*, vol. 55, no. 11, p. 1433, Nov. 1998, doi: 10.1001/archneur.55.11.1433.

[207] Y. Fan, H. Wang, X. Liu, J. Zhang, and G. Liu, "Crosstalk between the Ketogenic Diet and Epilepsy: From the Perspective of Gut Microbiota," *Mediators of Inflammation*, vol. 2019, pp. 1–9, Jun. 2019, doi: 10.1155/2019/8373060.

[208] A. Peng, X. Qiu, W. Lai, W. Li, L. Zhang, X. Zhu, S. He, J. Duan, L. Chen, "Altered composition of the gut microbiome in patients with drug-resistant epilepsy," *Epilepsy Research*, vol. 147, pp. 102–107, Sep. 2018, doi: 10.1016/j.eplepsyres.2018.09.013.

[209] Y. Zhang, S. Zhou, Y. Zhou, L. Yu, L. Zhang, and Y. Wang, "Altered gut microbiome composition in children with refractory epilepsy after ketogenic diet," *Epilepsy Research*, vol. 145, pp. 163–168, Jun. 2018, doi: 10.1016/j.eplepsyres.2018.06.015.

[210] S. Russell and P. Norvig, "Artificial intelligence," *Pearson eLibrary*, 2016. https://elibrary.pearson.de/book/99.150005/9781292153971

[211] Y. L. Niriayo, A. Mamo, T. D. Kassa, S. W. A. Asgedom, T. M. Atey, K. Gidey, G. T. Gomez, and S. Ibrahm, "Treatment outcome and associated factors among patients with epilepsy," *Scientific Reports*, vol. 8, no. 1, Nov. 2018, doi: 10.1038/s41598-018-35906-2.

[212] S. Wiebe, W. T. Blume, J. P. Girvin, and M. Eliasziw, "A randomized, controlled trial of surgery for Temporal-Lobe epilepsy," *New England Journal of Medicine*, vol. 345, no. 5, pp. 311–318, Aug. 2001, doi: 10.1056/nejm200108023450501.

[213] J. Engel, "Early surgical therapy for Drug-Resistant temporal lobe epilepsy," *JAMA*, vol. 307, no. 9, p. 922, Mar. 2012, doi: 10.1001/jama.2012.220.

[214] B. Abbasi and D. M. Goldenholz, "Machine learning applications in epilepsy," *Epilepsia*, vol. 60, no. 10, pp. 2037–2047, Sep. 2019, doi: 10.1111/epi.16333.

[215] B. A. Richards, T. P. Lillicrap, P. Beaudoin, Y. Bengio, R. Bogacz, A. Christensen, C. Clopath, R. Ponte Costa, A. de Berker, S. Ganguli, C. J. Gillon, D. Hafner, A. Kepecs, N. Kriegeskorte, P. Latham, G. W. Lindsay, K. D. Miller, R. Naud, C. C. Pack, P. Poirazi, P. Roelfsema, J. Sacramento, A. Saxe, B. Scellier, A. C. Schapiro, W. Senn, G. Wayne, D. Yamins, F. Zenke, J. Zylberberg, D. Therien, K. P. Kording, "A deep learning framework for neuroscience," *Nature Neuroscience*, vol. 22, no. 11, pp. 1761–1770, Oct. 2019, doi: 10.1038/s41593-019-0520-2.

[216] A. Esteva, A. Robicquet, B. Ramsundar, V. Kuleshov, M. DePristo, K. Chou, C. Cui, G. Corrado, S. Thrun, J. Dean, "A guide to deep learning in healthcare," *Nature Medicine*, vol. 25, no. 1, pp. 24–29, Dec. 2018, doi: 10.1038/s41591-018-0316-z.

[217] N. Bigdely-Shamlo, T. Mullen, C. Kothe, K.-M. Su, and K. A. Robbins, "The PREP pipeline: standardized preprocessing for large-scale EEG analysis," *Frontiers in Neuroinformatics*, vol. 9, Jun. 2015, doi: 10.3389/fninf.2015.00016.

[218] J. Rasekhi, M. R. K. Mollaei, M. Bandarabadi, C. A. Teixeira, and A. Dourado, "Preprocessing effects of 22 linear univariate features on the performance of seizure prediction methods," *Journal of Neuroscience Methods*, vol. 217, no. 1–2, pp. 9–16, Apr. 2013, doi: 10.1016/j.jneumeth.2013.03.019.

[219] H. Adeli, S. Ghosh-Dastidar, and N. Dadmehr, "A Wavelet-Chaos methodology for analysis of EEGs and EEG subbands to detect seizure and epilepsy," *IEEE Transactions on Biomedical Engineering*, vol. 54, no. 2, pp. 205–211, Jan. 2007, doi: 10.1109/tbme.2006.886855.

[220] S. M. Usman, M. Usman, and S. Fong, "Epileptic seizures prediction using machine learning methods," *Computational and Mathematical Methods in Medicine*, vol. 2017, pp. 1–10, Jan. 2017, doi: 10.1155/2017/9074759.

[221] N. Z. Zhang and K. K. Parhi, "Seizure detection using wavelet decomposition of the prediction error signal from a single channel of intra-cranial EEG," *2014 36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, vol. 96, pp. 4443–4446, Aug. 2014, doi: 10.1109/embc.2014.6944610.

[222] S. Siuly and Y. Li, "Designing a robust feature extraction method based on optimum allocation and principal component analysis for epileptic EEG signal classification," *Computer Methods and Programs in Biomedicine*, vol. 119, no. 1, pp. 29–42, Jan. 2015, doi: 10.1016/j.cmpb.2015.01.002.

[223] J.-H. Kang, Y. G. Chung, and S.-P. Kim, "An efficient detection of epileptic seizure by differentiation and spectral analysis of electroencephalograms," *Computers in Biology and Medicine*, vol. 66, pp. 352–356, May 2015, doi: 10.1016/j.compbiomed.2015.04.034.

[224] H. Daoud and M. Bayoumi, "Deep Learning approach for Epileptic Focus localization," *IEEE Transactions on Biomedical Circuits and Systems*, vol. 14, no. 2, pp. 209–220, Dec. 2019, doi: 10.1109/tbcas.2019.2957087.

[225] N. B. Karayiannis, G. Tao, J. D. Frost, M. S. Wise, R. A. Hrachovy, and E. M. Mizrahi, "Automated detection of videotaped neonatal seizures based on motion segmentation methods," *Clinical Neurophysiology*, vol. 117, no. 7, pp. 1585–1594, May 2006, doi: 10.1016/j.clinph.2005.12.030.

[226] Y. Ogura, H. Hayashi, S. Nakashima, Z. Soh, T. Shibanoki, K. Shimatani, A. Takeuchi, M. Nakamura, A. Okumura, Y. Kurita, and T. Tsuji, "A neural network based infant monitoring system to facilitate diagnosis of epileptic seizures," *2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, pp. 5614–5617, Aug. 2015, doi: 10.1109/embc.2015.7319665.

[227] M. Milosevic, A. Van de Vel, B. Bonroy, B. Ceulemans, L. Lagae, B. Vanrumste, and S. Van Huffel. "Automated detection of Tonic–Clonic seizures using 3-D accelerometry and surface electromyography in pediatric patients," *IEEE Journal of Biomedical and Health Informatics*, vol. 20, no. 5, pp. 1333–1341, Jul. 2015, doi: 10.1109/jbhi.2015.2462079.

[228] A. Emami, N. Kunii, T. Matsuo, T. Shinozaki, K. Kawai, and H. Takahashi, "Seizure detection by convolutional neural network-based analysis of scalp electroencephalography plot images," *NeuroImage Clinical*, vol. 22, p. 101684, Jan. 2019, doi: 10.1016/j.nicl.2019.101684.

[229] S. Raghu, N. Sriraam, Y. Temel, S. V. Rao, A. S. Hegde, and P. L. Kubben, "Performance evaluation of DWT based sigmoid entropy in time and frequency domains for automated detection of epileptic seizures using SVM classifier," *Computers in Biology and Medicine*, vol. 110, pp. 127–143, May 2019, doi: 10.1016/j.compbiomed.2019.05.016.

[230] T. Rüber, B. David, G. Lüchters, R. D. Nass, A. Friedman, R. Surges, T. Stöcker, B. Weber, R. Deichmann, G. Schlaug, E. Hattingen, and C. E. Elger, "Evidence for peri-ictal blood–brain barrier dysfunction in patients with epilepsy," *Brain*, vol. 141, no. 10, pp. 2952–2965, Aug. 2018, doi: 10.1093/brain/awy242.

[231] I. Amarreh, M. E. Meyerand, C. Stafstrom, B. P. Hermann, and R. M. Birn, "Individual classification of children with epilepsy using support vector machine with multiple indices of diffusion tensor imaging," *NeuroImage Clinical*, vol. 4, pp. 757–764, Jan. 2014, doi: 10.1016/j.nicl.2014.02.006.

[232] J. Zhang, B. David, G. Lüchters, R. D. Nass, A. Friedman, R. Surges, T. Stöcker, B. Weber, R. Deichmann, G. Schlaug, E. Hattingen, and C. E. Elger, "Pattern Classification of Large-Scale Functional Brain Networks: Identification of informative neuroimaging markers for epilepsy," *PLoS ONE*, vol. 7, no. 5, p. e36733, May 2012, doi: 10.1371/journal.pone.0036733.

[233] M. C. Soriano, G. Niso, J. Clements, S. Ortín, S. Carrasco, M. Gudín, C. R. Mirasso, and E. Pereda, "Automated Detection of Epileptic Biomarkers in Resting-State Interictal MEG data," *Frontiers in Neuroinformatics*, vol. 11, Jun. 2017, doi: 10.3389/fninf.2017.00043.

[234] B. Elahian, M. Yeasin, B. Mudigoudar, J. W. Wheless, and A. Babajani-Feremi, "Identifying seizure onset zone from electrocorticographic recordings: A machine learning approach based on phase locking value," *Seizure*, vol. 51, pp. 35–42, Jul. 2017, doi: 10.1016/j.seizure.2017.07.010.

[235] O. Grinenko, J. Li, J. C. Mosher, I. Z. Wang, J. C. Bulacio, J. Gonzalez-Martinez, D. Nair, I. Najm, R. M. Leahy, P. Chauvel, "A fingerprint of the epileptogenic zone in human epilepsies," *Brain*, vol. 141, no. 1, pp. 117–131, Oct. 2017, doi: 10.1093/brain/awx306.

[236] P. Fergus, A. Hussain, D. Hignett, D. Al-Jumeily, K. Abdel-Aziz, and H. Hamdan, "A machine learning system for automated whole-brain seizure detection," *Applied Computing and Informatics*, vol. 12, no. 1, pp. 70–89, Feb. 2015, doi: 10.1016/j.aci.2015.01.001.

[237] S. Ahn, S. B. Jun, H. W. Lee, and S. Lee, "Computational modeling of epileptiform activities in medial temporal lobe epilepsy combined with in vitro experiments," *Journal of Computational Neuroscience*, vol. 41, no. 2, pp. 207–223, Jul. 2016, doi: 10.1007/s10827-016-0614-8.

[238] W. Woldman, H. Schmidt, E. Abela, F. A. Chowdhury, A. D. Pawley, S. Jewell, M. P. Richardson, J. R. Terry, "Dynamic network properties of the interictal brain determine whether seizures appear focal or generalised," *Scientific Reports*, vol. 10, no. 1, Apr. 2020, doi: 10.1038/s41598-020-63430-9.

[239] S. K. Simblett, E. Bruno, S. Siddi, F. Matcham, L. Giuliano, J. Hortas López, A. Biondi, H. Curtis, J. Ferrão, A. Polhemus, M. Zappia, A. Callen, P. Gamble, T. Wykes, "Patient perspectives on the acceptability of mHealth technology for remote measurement and management of epilepsy: A qualitative analysis," *Epilepsy & Behavior*, vol. 97, pp. 123–129, Jun. 2019, doi: 10.1016/j.yebeh.2019.05.035.

[240] P. Meritam, P. Ryvlin, and S. Beniczky, "User-based evaluation of applicability and usability of a wearable accelerometer device for detecting bilateral tonic-clonic seizures: A field study," *Epilepsia*, vol. 59, no. S1, pp. 48–52, Jun. 2018, doi: 10.1111/epi.14051.

[241] E. Bruno, S. Simblett, A. Lang, A. Biondi, C. Odoi, A. Schulze-Bonhage, T. Wykes, M. P. Richardson, "Wearable technology in epilepsy: The views of patients, caregivers, and healthcare professionals," *Epilepsy & Behavior*, vol. 85, pp. 141–149, Jun. 2018, doi: 10.1016/j.yebeh.2018.05.044.

[242] C. Hoppe, M. Feldmann, B. Blachut, R. Surges, C. E. Elger, and C. Helmstaedter, "Novel techniques for automated seizure registration: Patients' wants and needs," *Epilepsy & Behavior*, vol. 52, pp. 1–7, Sep. 2015, doi: 10.1016/j.yebeh.2015.08.006.

[243] D. F. T. Quiroga, J. W. Britton, and E. C. Wirrell, "Patient and caregiver view on seizure detection devices: A survey study," *Seizure*, vol. 41, pp. 179–181, Aug. 2016, doi: 10.1016/j.seizure.2016.08.004.

[244] A. D. Patel, R. Moss, S. W. Rust, J. Patterson, R. Strouse, S. Gedela, J. Haines, S. M. Lin, "Patient-centered design criteria for wearable seizure detection devices," *Epilepsy & Behavior*, vol. 64, pp. 116–121, Oct. 2016, doi: 10.1016/j.yebeh.2016.09.012.

[245] A. Ozanne, D. Johansson, U. H. Graneheim, K. Malmgren, F. Bergquist, and M. A. Murphy, "Wearables in epilepsy and Parkinson's disease—A focus group study," *Acta Neurologica Scandinavica*, vol. 137, no. 2, pp. 188–194, Jul. 2017, doi: 10.1111/ane.12798.

[246] S. Hamine, E. Gerth-Guyette, D. Faulx, B. B. Green, and A. S. Ginsburg, "Impact of MHealth Chronic Disease Management on treatment adherence and Patient Outcomes: A Systematic review," *Journal of Medical Internet Research*, vol. 17, no. 2, p. e52, Feb. 2015, doi: 10.2196/jmir.3951.

[247] M. Beck, C. Simony, I. Zibrandtsen, and T. W. Kjaer, "Readiness among people with epilepsy to carry body-worn monitor devices in everyday life: A qualitative study," *Epilepsy & Behavior*, vol. 112, p. 107390, Aug. 2020, doi: 10.1016/j.yebeh.2020.107390.

[248] L. S. Olsen, J. M. Nielsen, C. Simonÿ, T. W. Kjær, and M. Beck, "Wearables in real life: A qualitative study of experiences of people with epilepsy who use home seizure monitoring devices," *Epilepsy & Behavior*, vol. 125, p. 108398, Nov. 2021, doi: 10.1016/j.yebeh.2021.108398.

[249] M. Halimeh, M. Jackson, T. Loddenkemper, and C. Meisel, "Training size predictably improves machine learning-based epileptic seizure forecasting from wearables," *Neuroscience Informatics*, vol. 5, no. 1, p. 100184, Dec. 2024, doi: 10.1016/j.neuri.2024.100184.

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