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Review Article

A Review on Epilepsy: Recent Advancements in Modern Therapy

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ABSTRACT

Epilepsy is one of the most prevalent chronic neurological disorders, affecting approximately 50 million people worldwide, with nearly 90% of cases residing in developing nations. It is characterized by recurrent unprovoked seizures resulting from an imbalance between neuronal excitation and inhibition. Despite the availability of over twenty-five different pharmacological agents, a persistent "thirty percent rule" remains, where nearly one-third of patients suffer from drug-resistant or refractory epilepsy. This review evaluates the evolution of therapeutic strategies, examining various etiologies including genetic mutations, CNS infections, and structural brain injuries. Significant emphasis is placed on recent advancements in modern therapy, including novel anti-seizure medications (ASMs) such as Cannabidiol, Fenfluramine, and Cenobamate. Furthermore, it highlights the emergence of non-pharmacological interventions like Vagus Nerve Stimulation (VNS), Responsive Neurostimulation (RNS), and Deep Brain Stimulation (DBS). This abstract concludes that while traditional medicine focused primarily on symptom suppression, the 21st-century approach is shifting toward disease modification and precision medicine to improve the quality of life for patients globally.

INTRODUCTION

Up to 1% of people have epilepsy, making it the second most frequent major neurologic illness after stroke [1]. Approximately 50 million people worldwide suffer from epilepsy, with 90% coming from underdeveloped nations [2]. It is a prevalent long-term neurological condition where the balance is characterised by repeated unprovoked seizures and tilted toward uncontrolled excitability between brain excitability and inhibition [3-5]. A person might lose awareness briefly during one, making accidents more likely while disrupting school or work routines. Found everywhere, they ignore differences in age, gender, location, income level, or ethnic background [6]. Epilepsy is not a single condition but a group of disorders characterized by a wide range of symptoms, all involving recurring episodes of abnormal electrical activity in the brain. Not all forms of epilepsy last a lifetime, some occur only during specific periods of childhood. The standard

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approach to treatment mainly involves the use of anticonvulsant drugs. Nevertheless, more than 30% of individuals with epilepsy continue to experience seizures despite using the most effective medications currently available [7-8]. Epilepsy is a long-term neurological disorder marked by repeated seizures and can affect individuals regardless of age, gender, or location. In Western countries, about 1% of the population lives with some form of epilepsy, while as many as 10% may experience at least one seizure at some point in their lives [9]. In contemporary medical research, a critical distinction is made between the concepts of ictogenesis and epileptogenesis. Ictogenesis refers to the immediate physiological triggers that result in an acute seizure event, whereas epileptogenesis is the long-term, progressive process by which a healthy brain becomes chronically prone to spontaneous electrical discharges. While the pharmaceutical industry has been highly successful in developing anti-seizure medications (ASMs) that manage ictogenesis, the ability to prevent or reverse the process of epileptogenesis remains a major hurdle. This distinction is vital for modern therapy because most current treatments are symptomatic rather than curative. Despite the availability of more than twenty-five different pharmacological agents, approximately thirty percent of the patient population continues to suffer from drug-resistant or refractory epilepsy. This persistent "thirty percent rule" highlights the limitations of traditional medicine and underscores the urgent necessity for advancements in therapeutic strategies [9].

1.1 DEFINITION

According to the International League Against Epilepsy (ILAE), Epidemiology Commission advises that epilepsy be defined as 2 or more unprovoked seizures occurring at least 24 h apart or a single unprovoked seizure with a recurrence risk of at least 60% over the next 10 years [10].

Current research is shifting its focus from merely suppressing symptoms (anti-ictogenesis) to modifying the actual disease process (anti-epileptogenesis). This review article aims to provide a comprehensive overview of epilepsy, moving from its basic pathophysiology and classifications to the most recent advancements in modern therapy. It further explores the emerging pharmacological interventions and technological breakthroughs that are redefining the standards of care for refractory epilepsy in the 21st century.

2. EPIDEMIOLOGY

At least 8% of those without epilepsy will experience at least one seizure. An unprovoked initial crisis in 5 years had a recurrence probability ranging from 23% to 80%. The annual age-adjusted incidence of epilepsy is 44 per 100,000 individuals. Approximately 125,000 new instances of epilepsy are diagnosed each year, with 30% of those cases occurring in individuals under the age of 18. It is now known that epilepsy is comparatively common in older people. About 10% or more of patients in long-term care facilities are on at least one antiepileptic medication [11]. In a comprehensive review and meta-analysis of studies on incidence, the combined incidence rate of epilepsy was found to be 61.4 per 100,000 person-years (95% CI 50.7–74.4) [12]. The incidence was 139.0 (95% CI 69.4–278.2) in low/middle-income countries (LMIC) compared to 48.9 (95% CI 39.0–61.1) in high-income countries (HIC) [13]. Over 10 million people in India are thought to have epilepsy (PWE). In our population, its prevalence is roughly 1% [14]. A prevalence rate of 8.8/1000 was noted in the Bangalore Urban-Rural Neuro-Epidemiological Survey, which included 102,557 participants. The estimated prevalence rate in rural populations was

11.9, about twice as high as the rate seen in urban areas (5.7) [15]. There is little information on the prevalence of epilepsy in India. According to a Kolkata study, the annual age-standardized incidence rate is 27.3/100,000 [16]. The youngest and oldest age groups have a greater incidence of epilepsy with estimates of 86 per 100,000 annually in a well-defined population in the first year of age, a decline to roughly 23–31 per 100,000 in individuals between the ages of 30 and 59, and a subsequent rise to 180 per 100,000 in those over 85 [12,17].

3. ETIOLOGIES OF EPILEPSY

Certain epileptic symptoms, such as reading, intermittent seizures, and triggering seizures, are referred to as epileptic reflexes. Patients with epilepsy have identified a number of triggering factors, including emotional stress, sleep deprivation, heat stress, alcohol, and fever sickness. Specifically, with epilepsy syndrome, different inciting causes have different effects [18].

3.1 GENETIC

Seizures are a common manifestation of an epilepsy that is thought to have a genetic origin if there is a known or suspected particular disease-causing mutation in a gene or copy number variant [19]. Genes encoding ion channels, such as KCNQ2 in benign familial neonatal seizures [20], SCN2A in benign familial infantile epilepsy [21], and SCN1A in Dravet syndrome [22], are mutated by genetic processes. Increased neuronal hyperexcitability brought on by a loss of function in these channels may result in spontaneous seizures. In particular, SCN1A mutations cause GABAergic neurones to become less excitable, which causes hyperexcitability in the brain [23].

3.2 CNS INFECTION

According to population-based cohorts of CNS infection survivors from wealthy nations, the probability of spontaneous seizures is between 6.8 and 8.3%, and it is higher in LMICs. In this case, neurotropic infectious agents that attack the central nervous system (CNS) such as cysticercus, human immunodeficiency virus, cytomegalovirus, toxoplasma gondii, mycobacterium tuberculosis, and Plasmodium falciparum, among many others, cause brain changes that result in seizures [24].

3.3 NEUROCYSTICERCOSIS

In India, one of the most frequent causes of epilepsy is NCC. It is caused by the larval stage of Taenia solium, a cestode tapeworm. The feco-oral route of transmission happens when there is inadequate cleanliness and sanitation [25].

3.4 BRAIN TUMOR

Brain tumours, whether benign or malignant, are a prevalent cause of epilepsy, accounting for approximately 30% of cases [26]. However, brain tumours affect about 4% of people with epilepsy. Adults are more likely than children to acquire epilepsy [27].

3.5 STROKE

A significant risk factor for epilepsies is stroke, which accounts for one-third of cases in the elderly [28,29]. Epilepsy affects 2-4% of stroke cases in prospective studies and up to 39% in retrospective studies [30].

These pathological mechanism of major epilepsy etiologies are shown in figure 1 [31].

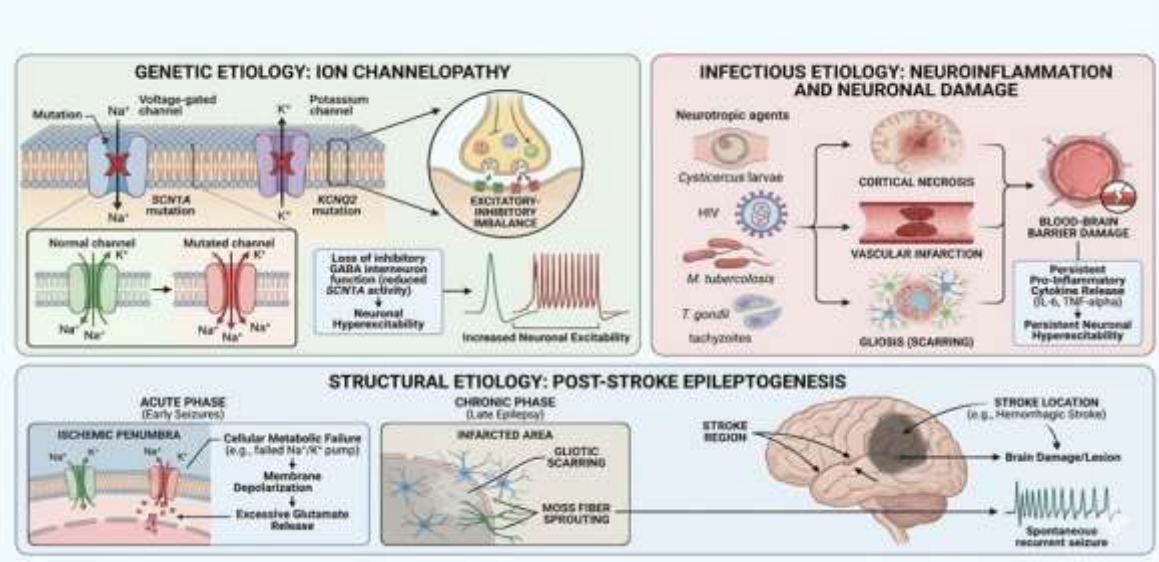

Figure 1: Pathological mechanism of major epilepsy etiologies.

4. CLASSIFICATION

Table 1: International classification of epileptics seizures [32,33].

TYPES	SUB-TYPES
Partial (focal) seizures (seizures begin locally)	A. Simple (without impairment of consciousness) 1. With motor symptoms. 2. With special sensory or soma to sensory symptoms. 3. With psychic symptoms. B. Complex (with impairment of consciousness) 1. Simple partial onset followed by impairment of consciousness with or without automatisms. 2. Impaired consciousness at onset-with or without automatisms. C. Secondarily Generalized (partial onset evolving to generalized tonic clonic seizures)
generalized seizure (bilaterally symmetrical and without local onset)	A. Absence seizure B. Tonic seizure C. Atonic seizure D. Clonic seizure E. Tonic-clonic seizure F. Myoclonic seizure
Unclassified seizures	
Status epilepticus	

4.1 PARTIAL (FOCAL) SEIZURE

Simple partial seizures (focal cortical epilepsy) are characterised by a seizure focus in the context of a specific muscle group. Without losing consciousness, patients lose their ability to control the afflicted bodily parts voluntarily. The discharge starts locally and frequently stays localised in complex partial seizures. Often referred to as psychomotor epilepsy, symptoms include involuntary muscle contractions, aberrant sensory experiences or autonomic secretion, or behavioural and emotional changes [34].

4.2 GENERALIZED SEIZURE

Because the entire brain, including the reticular system, is involved in generalised seizures, abnormal electrical activity is produced in both hemispheres. instantaneous loss of recognition is a feature of epileptic convulsions that are generalised [35]. Children frequently experience absence seizures (petitmal), which are characterised by a brief loss of consciousness but lack muscular components or modest bilateral

shaking. (from the eyelid flashing to the clonic body moving more widely) [36]. Often defined by a period of unconsciousness or diminished awareness lasting 3 to 30 seconds [37]. Myoclonus is the motor expression of epileptic seizures that are myoclonic. Loss of awareness, autonomic symptoms, and clonic rhythmic characteristics of all muscles are the hallmarks of clonics. Loss of awareness and autonomic symptoms followed by tonic limb contractions are linked to tonic convulsions[38].

4.3 UNCLASSIFIED SEIZURES

Unclassified indeterminate epilepsy and epileptic disorders fall into a third group. Conditions like febrile convulsions, when seizures are linked to certain circumstances, are examples of special syndromes. Two to four percent of children suffer from conditions linked to tissue diseases. In recent years, just two to three percent of these kids develop epilepsy. Compared to the overall population, this represents a six-fold increase in risk. Pre-existing neurological disorders, developmental delays, a family history of febrile convulsions, or complex epilepsy are all linked to an elevated risk [39].

4.4 STATUS EPILEPTICUS

A protracted seizure or a period of repeated seizures lasting longer than five to ten minutes is considered epileptic state. Needs immediate medical attention. Epileptic status can result from any kind of seizure, but the most prevalent and hazardous kind is generalised clonic tonic epileptic status

These include:

1. Staring intently.
2. Children under 2 years old typically experience benign tremors when they are tired or excited.
3. Self-gratifying actions include nodding, swaying, and head banging.
4. Conversion disorder (head trembling and shaking) [40].

5. PATHOPHYSIOLOGY

Seizures are paroxysmal cerebral cortical presentations. When there is an abrupt imbalance between the excitatory and inhibitory strengths of the cortical neurons, a seizure occurs. An unsteady cell film or surrounding back or neighboring cells can reveal the basic physiology of a convulsive scenario. Gray matter in either cortical or subcortical zone is the source of seizures. A little percentage of neurons concentrate inappropriately at first. At the local level, normal membrane conductance, the breakdown of inhibitory synaptic current, and excessive diffusion excitability might result in a localized or, more broadly, a widespread assault. Through physiological routes, this house spreads to nearby rural locations. A malfunction in voltage-dependent ion channels, an aberrant conductance of potassium, or a lack of membrane ATPases linked to ion transport can all result in an unstable neuronal membrane and an attack. While butyric acid-amino (GABA) and dopamine inhibit neuronal activity and propagation, certain neurotransmitters (such as glutamate, aspartate, acetylcholine, norepinephrine, histamine, corticotropin releasing factor, purines, peptides, cytokines, and steroid hormones) increase excitability and neuronal activity.Increased blood flow to the brain during a seizure is necessary to supply CO2 and substrate for neuronal metabolic activity. As the seizure lasts longer, the brain experiences greater ischemia, which can lead to brain damage and neuronal death [11]. Certain

kinds of epilepsy may be linked to mutations in several genes. Genes that code for ion channel protein subunits that are sensitive to activated voltage ligands have been linked to infantile seizure disorders and generalized epilepsy [41]. Electrolyte imbalance, acid-base disorders, phospholipid bilayer disruption, oxidative damage from the release of free fatty acids, and increased release of the excitatory neurotransmitter glutamate are all part of the present pathological process of early PSE, as shown in (Figure 2) [42]. The pathophysiologic distinctions between early and late seizures should be the basis for differentiation. Stroke itself causes subsequent tissue injury, which leads to early seizures.(Figure 3). On the other hand, gliotic scarring in the cortex, an imbalance of neurovascular units, and disruption of neural networks are the causes of late seizures [43].

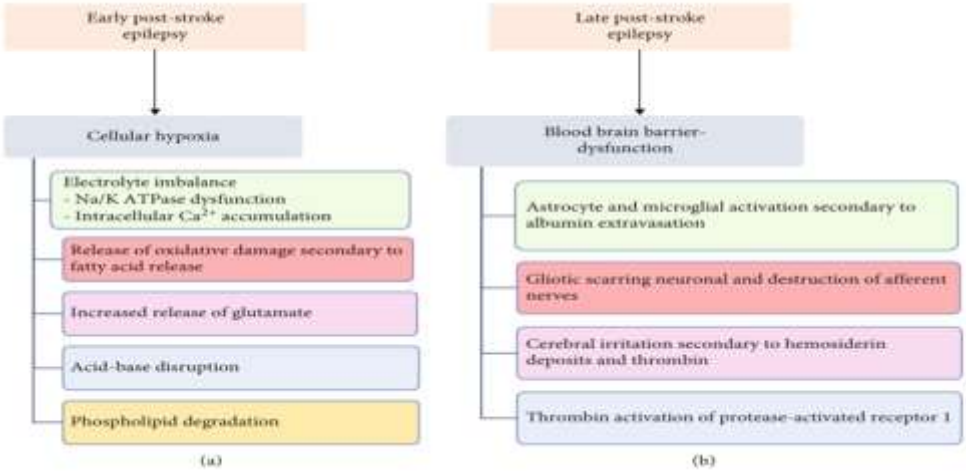

Figure 2: (a) General pathophysiology of early poststroke epilepsy (PSE). (b) General pathophysiology of late PSE.

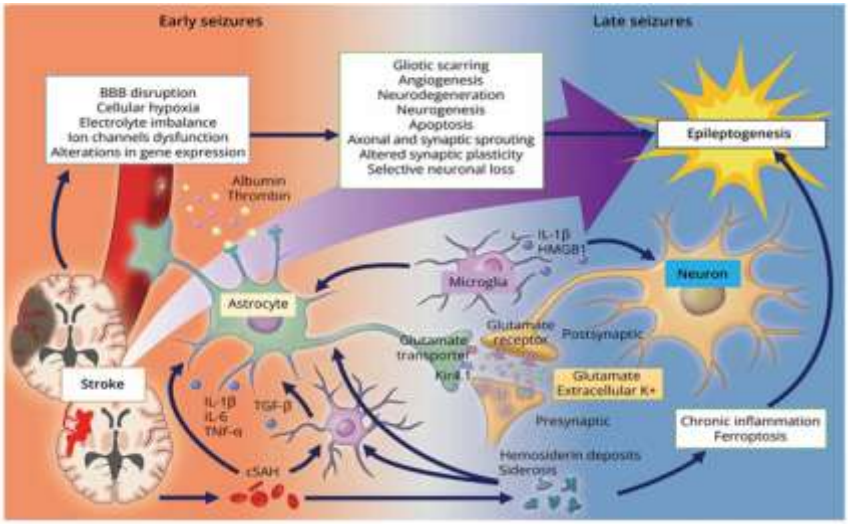

Figure 3: An illustration of epileptogenesis following stroke.

6. CONVENTIONAL TREATMENTS FOR EPILEPSY

The phrases "anticonvulsant" and "antiepileptic" are synonymous. An anticonvulsant is a medication that prevents laboratory animals from experiencing artificially induced seizures and a medication used in medicine to treat epilepsies is called an antiepileptic [44].

The antiepileptic drugs have been classified as follows in Table 2 and their mechanism of action in table 3 [45].

Table 2: Classification of drugs (conventional) used in the therapy of epilepsies.

Seizure type	Conventional anti-epileptic drug
Partial seizures (i) Simple partial	▪ Carbamazepine ▪ Phenytoin ▪ Phenobarbital ▪ Primidone ▪ Valproate
(ii) Complex partial	▪ Carbamazepine ▪ oxcarbazepine ▪ Phenytoin ▪ Primidone ▪ Valproate
(iii) Partial with secondly generalized tonic clonic seizure	▪ Carbamazepine ▪ Phenobarbital ▪ Phenytoin ▪ Primidone ▪ Valproate
Generalized seizure 1) Absence Seizures	• Clonazepam • Ethosuximide • Valproate
2) Myoclonic Seizure	• Valproate
3) Tonic-clonic Seizure	• Carbamazepine • Phenobarbital • Phenytoin • Primidone • Valproate
4) Atonic Seizure	• Valproate • Clonazepam • Nitrazepam • Phenobarbital
5) Tonic Seizure	• Valproate • Phenytoin • Carbamazepine • Phenobarbital
6) Clonic Seizure	• Valproate • Phenytoin • Phenobarbital • primidone
Status Epilepticus	• Lorazepam(IV) • Diazepam(IV) • Phenytoin(IV)

Table 3: Mechanism of action of anti-epileptic agents.

Anti-epileptic agent	Mechanism(s) of action
Benzodiazepines	Enhances GABA action Reduces sustained repetitive firing
Carbamazepine	Blocks voltage-dependent Na+ channels Limitation of sustained repetitive firing
Ethosuximide	Reducing T-type Ca++ currents Blocking synchronized thalamic firing
Felbamate	Inhibition of glutamatergic neurotransmission (reduces NMDA action, blocks glycine-site on NMDA receptor) GABA potentiation Blocks voltage-dependent Na+ channels Blocks L-type Ca++ channels
Oxcarbazepine	Inhibition of voltage-dependent Na+ channels Inhibition of voltage-activated Ca++ currents
Phenobarbital	Enhances GABA action Reduces sustained repetitive firing Reduces voltage-dependent Ca++ currents
Phenytoin	Blocks voltage-gated Na+ channels Reduces Ca++ currents
Primidone	Reduces sustained repetitive firing - blocks voltage-dependent Na+ currents
Valproate	Increases CNS GABA levels by increased synthesis and reduced catabolism Blocks T-type Ca++ currents Enhances Na+ channel inactivation
Nitrazepam	Enhance GABA action by binding to benzodiazepine receptors increase chloride channel opening frequency
clonazepam	Enhance GABA action

7. MODERN THERAPY FOR EPILEPSY

The causes of epilepsy, which affects more than 50 million people globally, are still somewhat unknown, giving doctors and patients a lack of clarity on the disease's genesis and the most effective treatment strategy [46]. The International League Against Epilepsy (ILAE) refers to patients who do not respond to the combination of two carefully selected and administered anti-seizure medications (ASMs) as "drug-resistant," since over 30% of people do not respond to common traditional ASMs(like phenytoin, phenobarbital) [47,48]. In order to improve patients' symptoms and their quality of life (QoL), as well as those of their caregivers, a great deal of responsibility is placed on the research and development of novel pharmacological and non-pharmacological therapies provided a targeted approach. Although there are still difficulties, the treatment of epilepsy has advanced significantly since it was first described in ancient literature [49].

7.1 Challenges in Achieving Seizure Control with Traditional Therapies

- First, not every patient reacts well to conventional ASMs, which can result in drug-resistant epilepsy. Despite adequate trials of two or more ASMs, up estimated one-third of individuals with epilepsy still have seizures [50].

- Another element causing treatment resistance is pharmacokinetic variability [51]. Individual differences in ASM distribution and metabolism can impact medication levels and therapeutic efficacy [52,53].

- Traditional ASMs such sodium valproate, phenytoin, and phenobarbital may also have serious side effects that affect tolerance and treatment compliance. Adverse symptoms like severe sleepiness (sedation), lightheadedness, mood swings, cognitive impairment, and major systemic issues such hepatotoxicity (liver toxicity) may occur in some patients [54].

7.2 The Need for Novel Treatment Approaches to Address Drug-Resistant Epilepsy

- The persistence of drug-resistant epilepsy emphasizes how urgently new and creative treatment strategies are needed [55,56,57].

- Researchers can create more potent treatments to improve seizure control and improve the quality of life for people with epilepsy by comprehending the complexity of treatment resistance and discovering new targets, such as certain genes or neuronal circuits [58].

- For individuals who do not respond to conventional ASMs, neurostimulation devices such RNS, VNS, and DBS may be viable options [55].

- Furthermore, developments in tailored methods and precision medicine provide the potential to customize treatments for each patient [57].

The figure 4 shows the recent technologies and therapy used in the management of epilepsy [57].

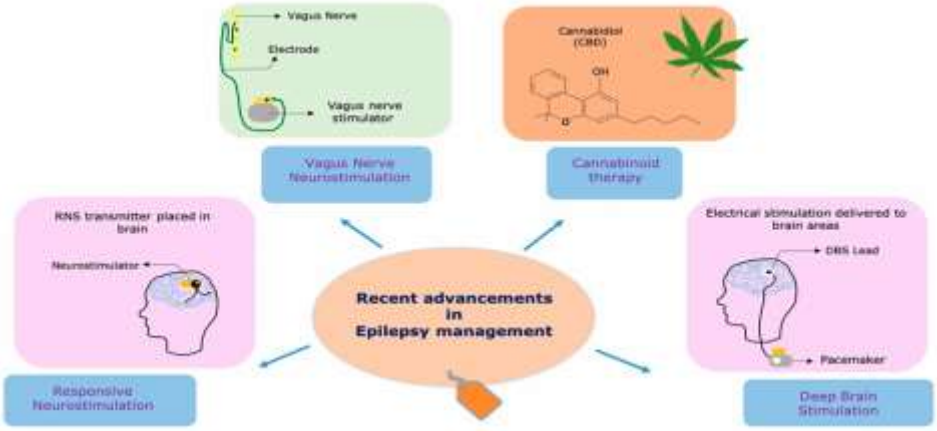

Figure 4: Recent technologies and therapies used in the management of epilepsy.

7.3 NOVEL ANTI-SEIZURE MEDICATION (ASMs)

The pharmacological management of epilepsy has evolved significantly over the last century. From the early use of traditional agents like Phenobarbital to the development of cutting-edge molecules, each era has introduced medications with improved efficacy and better safety profiles. The following (table 4) summarizes the timeline of various anti-seizure medications (ASMs) introduced into the market, highlighting the rapid progress made in recent decades toward modern therapy. Because of the differences in these medications' pharmacokinetics, effectiveness, and adverse effect profiles, there are previously unheard-of chances to customize therapy options to meet the needs of each patient [59].

Table 4: Years of introduction in the market of currently available antiseizure medications.[59]

1900–1950	1951–1985	1986–2000	2001–2015	2015–2021
Phenobarbital Phenytoin	Carbamazepine Clobazam Clonazepam Diazepam Ethosuximide Midazolam Primidone Valproic acid	Felbamate Fosphenytoin Gabapentin Lamotrigine Levetiracetam Lorazepam Oxcarbazepine Tiagabine Topiramate Vigabatrin Zonisamide	Eslicarbazepine -acetate Lacosamide Perampanel Pregabalin Rufinamide Stiripentol	Brivaracetam Cannabidiol Cenobamate Everolimus Fenfluramine

CANNABIDIOL

The first-in-class medication made from the cannabis plant, CBD, was approved by the FDA in 2018. Epidiolex® (cannabidiol) oral solution, mostly recommended for the treatment of seizures in children two years of age or older who have Lennox-Gastaut Syndrome (LGS) or Dravet Syndrome (DS) [60]. The median frequency of convulsive seizures in patients treated with CBD dropped from 12.4 to 5.9 per month, as compared with a decrease from 14.9 to 14.1 per month with the placebo, according to important findings from clinical trials [61]. Five percent of patients under CBD became seizure-free, while none in the placebo group did.

Additionally, studies show that combining CBD with Clobazam (CLB) produces better efficacy results; however, if patients experience somnolence, a dose reduction of CLB may be required [62]. Over 48 weeks of treatment, CBD consistently reduces seizure frequency (between 42.9% and 44.3%), according to long-term follow-

up studies [63]. Additionally, at 12 weeks of treatment, 5 out of 104 patients (4.8%) had no convulsive seizures, and more than 40% had a decrease in convulsive seizure frequency of at least 50% at each scheduled follow-up appointment [64]. RCTs conclude that CBD is a well-tolerated medication, with the main side effects reported by patients being decreased appetite, diarrhea, and somnolence [62,65].

MECHANISM OF ACTION

The mechanism of action of Cannabidiol (CBD) is multimodal. As shown in Figure 5(a,b), CBD exerts an inhibitory role on FAAT/FAAH, leading to increased levels of the endogenous cannabinoid Anandamide (AEA). Additionally, it modulates TRPV1 receptors and ion channels to reduce neuronal hyperexcitability. Unlike THC, CBD interacts indirectly with CB1 and CB2 receptors, making it a potent and non-psychoactive therapeutic agent for seizure management [66].

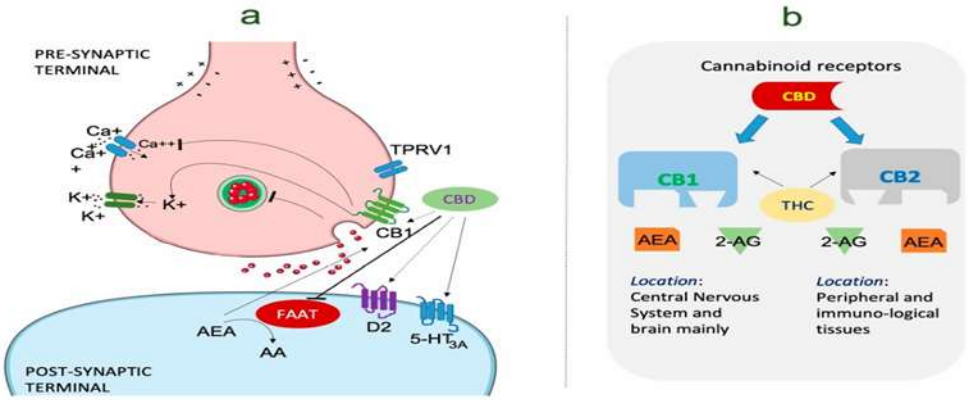

Figure 5: The mechanism of action of cannabidiol in the management of epilepsy.

FENFLURAMINE

The FDA authorized fenfluramine (FFA) in June 2020 for its anti-seizure properties. FFA was previously used as a weight-loss medication at 10 times larger dosages (up to 120 mg/day) [62]. It acts as a positive modulator of sigma-1 receptors and releases serotonin, which stimulates several 5-HT receptor subtypes [62,67-69]. The European Medicines Agency (EMA) is now testing it for a number of epileptic conditions.

Phase-3 trials on people with Dravet Syndrome (DS) have shown clinical evidence that FFA is highly beneficial. Seizures were reduced by an average of 64% in the group treated with 0.8 mg/kg/day, with >75% reduction in 45% of patients [69]. Additionally, over a median of 445 days, FFA has continued to produce a clinically significant decrease in the frequency of convulsive seizures; some trials have reported a median percent reduction in monthly seizure frequency of 83.3% [62]. Overall, 62% of patients showed a 50% reduction in convulsive seizure frequency [62].

Regarding safety and pharmacological interactions, FFA has comparatively little interactions with other medications, including CBD, Clobazam, and Valproate [65]. However, when combined with Stiripentol (STP), the dosage must be reduced to 0.5 mg/kg/day. Reduced appetite, weight loss, diarrhea, fatique, and pyrexia are the most frequently reported adverse effects (AEs) [61].

CENOBAMATE

Cenobamate, also referred to as Xcopri or YKP3089, is a new ASM that was just approved

by the FDA to treat adult focal-onset seizures. It is a carbamate chemical generated from tetrazole that has a distinct dual mode of action: it operates as a positive allosteric modulator of the GABA-A receptors by binding at a non-benzodiazepine location and increases the inactivated state of voltage-gated sodium channels [70].

According to clinical research, cenobamate administered as an adjuvant at doses of 100, 200, and 400 mg/day consistently reduces the incidence of focal seizures. The 200 and 400 mg/day dosing groups showed the highest decrease and responder rates (≥50% seizure reduction) [71]. Further evidence that seizure frequencies dropped early in the titration period was provided by post-hoc analysis, which also showed that a considerably higher number of patients achieved seizure independence than those on placebo.

Cenobamate is generally well-tolerated in terms of safety and interactions. Common adverse effects (AEs) include somnolence, dizziness, and abnormalities in gait and coordination. However, severe hypersensitivity reactions like DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) require caution from medical professionals. To lessen these hazards, it is advised to start with a lower dose and titrate more slowly [70,71].

BRIVARACETAM

Brivaracetam is another medication in the class of SV2A protein vesicle inhibitors. The drug's pharmacokinetics were assessed in two investigations, NCT04882540 and NCT03405714. Participants with epilepsy who were older than one month but younger than sixteen were particularly included in the latter. The mean age of the 46 participants in the third study, NCT03021018, was 42.12 ± 13.06 years.

Within 6, 8, and 12 hours, the medication controlled seizures without causing the patients to have any significant side effects. Participants in the trial group NCT01954121 were split into two groups: 218 individuals received LVT treatment, while 215 individuals received CBZ treatment. During this time, 47.3% of the 186 participants in the LVT group did not experience any seizures. Of the 171 individuals in the CBZ group, 68.4% did not experience any seizures.

Nasopharyngitis, a non-serious adverse reaction, was the most frequently reported adverse effect during the research, occurring in 42.20% of the LVT group and 43.26% of the CBZ group [72].

GANAXOLON

Patients with cyclin-dependent kinase-like 5 (CDKL5) deficient disease can be treated for seizures with ganaxolone, an FDA-approved first-in-class drug [73,74]. It is believed to modulate both synaptic and extrasynaptic GABAA receptors via attaching to their allosteric regions. This lowers the likelihood of a successful potential depolarization by hyperpolarizing the cell and inhibiting neurotransmission [75,76]. With a focus on drug-resistant partial onset seizures, CDKL5 deficient disease, and tuberous sclerosis, ganaxolone has been used in six clinical trials with 605 individuals. status epilepticus, convulsive status epilepticus, non-convulsive status epilepticus, sclerosis, and epilepsy associated with PCDH19.

The intravenous application concentration of ganaxolone ranged from 500 to 1800 mg·day−1, and the dosage used in clinical trials varied according to the administration mode. The largest ganaxolone experiment was NCT01963208, which included 405 primarily white male and female subjects with a mean age of 39.7 ± 11.7 years.

From baseline to week 14 of the study, the clinical trial NCT01963208 showed a 21.28% drop in seizure frequency; within the same period, 28.1% of the ganaxolone-treated patients reported at least a 50% reduction in 28-day seizure frequency. Fatigue, nasopharyngitis, somnolence, headaches, and dizziness are the most frequent side effects of ganaxolone treatment. Due to its high lipophilicity (logP = 4.0) and low water solubility (0.71 mg/L), ganaxolone is categorized as a BCS Class 2 medication in terms of pharmacokinetics [77,78]. Co-administration with a high-fat meal can boost its bioavailability (AUC) by five to fifteen times, demonstrating a notable "food effect" [79].

7.4 NOVEL NON-PHARMACOLOGICAL TREATMENTS

Neurostimulation is a collection of methods that have already been used in clinical practice. These methods involve delivering electrical or magnetic currents to the brain in a non-invasive or invasive manner, which modifies neuronal activity to reduce seizures.

VAGUS NERVE STIMULATION (VNS)

The implantation of a device that stimulates the vagus nerve, a main nerve that runs from the brainstem to several organs, is known as vagus nerve stimulation (VNS), a neuromodulation therapy [80-82]. Patients with refractory or intractable epilepsies who are not candidates for surgery and have not responded to one or more antiseizure medications may use it as an additional treatment. It is specifically authorized for use in adults and adolescents with partial-onset seizures who are older than 12 [80,82]. while it is also often used and well tolerated in younger children [83]. In addition to partial seizures, VNS is recommended for infantile spasms, atonic and tonic seizures, and Lennox-Gastaut Syndrome [84,85]. The VNS system is made up of a lead wire that is wrapped around the left vagus nerve in the neck and a tiny generator that is usually implanted beneath the skin in the chest [86]. Because the right vagus nerve innervates the sinoatrial (SA) node, which increases the risk of cardiac side effects such arrhythmias and bradycardia, the left vagus nerve is carefully selected [87]. The afferent nerve endings of VNS are the main source of its antiepileptic action. These fibers enter the medulla at the nucleus tractus solitarius (NTS), which innervates the locus coeruleus (LC), the brain's primary noradrenaline supply source. Therefore, by sending its projections to LC, NTS regulates the release of noradrenaline, which significantly lowers seizures [88,89].

Additionally, VNS raises the amount of the inhibitory neurotransmitter GABA in the cerebrospinal fluid and boosts cerebral blood flow to brain regions including the cortex and thalamus. The immunomodulatory effect of VNS through the cholinergic anti-inflammatory route has also been identified in recent years [90]. The creation of closed-loop or on-demand VNS systems (responsive VNS) [91,92]. and transcutaneous VNS (tVNS) as a non-invasive substitute are noteworthy recent developments [93]. Hoarseness, dyspnea, coughing, and paresthesia are common side effects of VNS, although the treatment is nonetheless effectively used in a variety of populations, including children and pregnant women [83,94].

TRANSCUTANEOUS VNS

Similar to VNS, tVNS is a non-invasive method of stimulating the vagus nerve. It is administered to the vagus nerve of the auricular branch, which is made up of the vagus, glossopharyngeal, and face nerves [95,96].

A programmable stimulation apparatus and an ear electrode make up the device [97]. By using ramps

of increasing and decreasing intensity, the stimulation setup can be adjusted to a level that is clearly below the pain threshold but somewhat over the individual detection threshold. tVNS is typically applied by patients for one hour, three times a day [98].

Local skin irritation, headaches, weariness, and nausea are the most common mild or severe adverse effects, yet trials consistently show a 55% decrease in seizure frequency [99,100].

RESPONSIVE NEUROSTIMULATION

The RNS system consists of one or two intracranial electrodes positioned in or close to the epileptogenic brain region that initiates seizures, as well as a tiny neurostimulator device that is surgically implanted in the skull [101-103]. Based on the basic idea of closed-loop neurostimulation, the device continuously analyzes brain activity and applies electrical stimulation when it detects abnormal patterns [104].

The mechanism of action of RNS includes the following:(1) Brain activity monitoring: The implanted electrodes continuously capture electrical impulses from the brain, identifying minute alterations that occur before a seizure.The RNS system's sophisticated algorithms evaluate the captured brain activity in real time.(2) Seizure onset detection: The RNS system is trained to identify particular electrical activity patterns linked to the beginning of a seizure. Each person's specific seizure characteristics are taken into account when designing this customized detection system.(3) Responsive stimulation: The technology sends short electrical pulses to the epileptic brain region after detecting the predetermined seizure activity. The goal of the stimulation is to stop the seizure from fully developing by interfering with the aberrant neuronal firing patterns.(4) Learning and adaptation: Over time, the RNS system is intended to learn and adapt. It can improve treatment success by fine-tuning its algorithms to optimize seizure detection and stimulation parameters for each patient while it continuously monitors brain activity and stimulation effectiveness [102,104].

The RNS system showed notable advantages for individuals with medically resistant focal epilepsy in a critical clinical trial [105,106]. Despite receiving therapy with various ASMs, individuals in the trial had eight or more incapacitating partial-onset seizures on average each month. The frequency of seizures was significantly reduced in RNS-treated patients, with a median reduction of 44% at one year and 53% at two years after implantation, according to the results [105].

FDA has approved this adjunctive therapy for patients aged ≥ 18 years and these patients must follow the following criteria [107,108];

- Resistant to more than two ASDs
- Frequent seizures (three or more per month during the previous three months) and incapacitating seizures, such as motor, complicated partial, and/or two generalized seizures
- Not more than two epileptogenic locations

DEEP BRAIN STIMULATION

Deep brain stimulation (DBS) is a minimally invasive neurosurgery procedure that uses implanted electrodes to stimulate deep brain areas. Individuals who are not candidates for surgery and have refractory focal epilepsies are typically suitable candidates [109]. DBS is intended to modify abnormal neural activity linked to seizure genesis by delivering electrical impulses to particular brain regions in a controlled and targeted manner [110,111]. DBS for epilepsy usually targets particular brain regions that are

known to play a role in the start and spread of seizures. The anterior nucleus of the thalamus (ANT), a region important in transmitting motor and sensory information to the cerebral cortex, is the most often targeted area for DBS in epilepsy [112].

The SANTE (Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy) trial, a seminal multinational randomized controlled trial (NCT00101933), showed that DBS was successful in lowering seizures [113]. The active stimulation group experienced a significant decrease in seizure frequency, with >41% of patients at the 1-year follow-up and >68% of patients at the 5-year follow-up reporting a 50% or higher reduction. Moreover, long-term follow-up studies of the SANTE trial participants have indicated maintained advantages of DBS over time, with ongoing decreases in seizure frequency and increases in quality of life observed years after the original implantation.(171)Aside from the immediate side effect of implantation, the most pertinent reported adverse effects were depressed mood and memory impairment [114,115].

CONCLUSION

In conclusion, epilepsy is a very common brain disorder that affects millions of people globally. Through this review, we have seen that it is not just one disease, but a group of brain problems that can happen due to many reasons like genetics, head injuries, infections, or stroke. Even though we have understood the brain much better now than in ancient times, epilepsy still causes a lot of social and mental stress for the patients. One of the biggest challenges in pharmacy today is that nearly 30% of patients do not respond to traditional medicines like Phenytoin or Carbamazepine. These patients have "drug-resistant" epilepsy, and for them, older drugs are not enough. Also, traditional drugs often cause bad side effects like liver problems and dizziness, which makes it hard for patients to continue their treatment. However, modern therapy has brought a lot of hope. New medicines like Cannabidiol (CBD), Fenfluramine, and Cenobamate are now available to help those patients who do not get relief from old drugs. Apart from medicines, we now have amazing technologies like VNS, RNS, and Deep Brain Stimulation. These devices work like a "brain pacemaker" to control electrical activity and stop seizures. In the future, the focus should be on finding the right treatment for each patient based on their specific condition. By combining these new drugs and technologies, we can help patients live a normal, seizure-free life.

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