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Review Article

Evolving Pharmaceutical Approaches in Epilepsy: From Mechanisms to Medication

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ABSTRACT

In today's fast-paced society, people are under a variety of stressors, and many suffer from neurological problems. Epilepsy is one of the most common neurological diseases, affecting over 50 million individuals worldwide, with 90% of instances happening in poor nations. Genetic factors, brain infections, strokes, tumors, and high fevers can all produce the condition. Epilepsy puts a huge economic load on healthcare systems and is frequently associated with stigma and discrimination, affecting not just patients but also their families in a variety of settings such as the community, employment, school, and home. Many individuals with epilepsy endure severe emotional distress, behavioral issues, and significant social isolation. Seizures can occur due to a variety of causes and mechanisms, the most common of which are neuronal hyperexcitability and neural circuit hypersynchrony. Several mechanisms alter the balance of excitation and inhibition, resulting in increased neuronal excitability and hypersynchrony in specific or extensive areas of the brain. This review will look at the history, epidemiology, pathophysiology, categorization, symptoms, diagnosis, and treatment of epilepsy.

INTRODUCTION

Epilepsy impacts approximately 1% of the global population, positioning it as the second most prevalent serious neurological disorder after stroke. Roughly 50 million individuals worldwide are afflicted with epilepsy, with a significant majority—90%—residing in developing nations. Over recent years, there have been notable advancements in our comprehension of epilepsy across various aspects. this condition is a frequently occurring, long-term neurological issue where there's an imbalance favouring excessive brain activity over control, resulting in repeated, spontaneous seizures typically ranging from 3 to 5 without an apparent trigger (Ghosh *et al.,* 2021). Current evidence strongly suggests that there are notable variations in both the development stage of the brain and its response to seizures. This disorder encompasses a diverse array of seizure types, varying greatly in their intensity, presentation, underlying causes, outcomes, and treatment approaches. These seizures are linked with distinct indicators or manifestations of abnormal levels of neuronal activity in the brain *(*Schmidt & Sillanpää, 2012*).* Seizures associated with epilepsy frequently result

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in temporary loss of consciousness, posing a risk of physical injury and frequently disrupting educational and occupational pursuits. This condition affects individuals universally, without regard to age, gender, location, socioeconomic status, or race. Epilepsy tends to be more prevalent in young children or individuals over 65 years old, although it can manifest at any age. It's not a singular disorder but rather a syndrome encompassing a wide range of symptoms, characterized by intermittent abnormal electrical activity in the brain. While some forms of epilepsy persist throughout life, others are limited to specific stages of childhood. Traditional treatment approaches for epilepsy are diverse. Epidemiologically, epilepsy affects approximately 1% of the global population, ranking second only to stroke among serious neurological conditions. Roughly 50 million people worldwide are affected by epilepsy, with 90% of cases concentrated in developing nations (Berg *et al*., 2010).

Epilepsy comprises a range of diverse seizure types, differing significantly in their severity, appearance, causes, outcomes, and treatment methods. These seizures manifest with distinct signs or symptoms indicative of abnormal, excessive, or synchronized neuronal activity in the brain. They frequently lead to temporary loss of consciousness, putting individuals in jeopardy of physical harm and frequently disrupting their educational and occupational pursuits. Epilepsy affects individuals universally, without discrimination based on age, gender, geographical location, social status, or race. While it tends to be more prevalent in young children or those over 65 years old, it can manifest at any stage of life. Epilepsy isn't a singular disorder but rather a syndrome encompassing a wide range of symptoms, characterized by intermittent abnormal electrical activity in the brain (Fisher *et al*., 2005).

Not all epilepsy syndromes persist throughout life; certain forms are limited to specific childhood stages. The standard treatment for epilepsy primarily involves anticonvulsant medications. However, even with the most effective medications available, over 30% of individuals with epilepsy experience inadequate seizure control. While these drugs often succeed in managing or decreasing seizure frequency, some patients see minimal to no improvement, prompting consideration of surgery in challenging cases. Treatment for epilepsy is primarily focused on managing symptoms, as currently available medications aim to suppress seizures but do not offer prevention or cure. Ensuring patient adherence to medication is challenging due to the prolonged duration of therapy and the potential side effects associated with many drugs. This overview aims to offer general guidance and strategies for the management of epilepsy (Brodie & Kwan, 2002).

Over recent years, our comprehension of epilepsy has expanded on various fronts. This prevalent chronic neurological condition involves an imbalance favouring excessive cerebral excitability over inhibition, leading to recurrent, unprovoked seizures typically numbering between 3 and 5. Clear evidence now indicates notable variances in both the development stage and the subsequent effects of seizures on the brain between immature and mature individuals.

Not all epilepsy syndromes persist throughout life; certain forms are limited to specific childhood stages. The standard treatment for epilepsy primarily involves anticonvulsant medications. However, even with the most effective medications available, over 30% of individuals with epilepsy experience inadequate seizure control. While these drugs often succeed in managing or decreasing seizure frequency, some patients see minimal to no improvement, prompting consideration of surgery in challenging cases. Treatment for epilepsy is primarily focused on managing symptoms, as currently available medications aim to suppress seizures but do not offer prevention or cure. Ensuring patient adherence to medication is challenging due to the prolonged duration of therapy and the potential side effects associated with many drugs. This overview aims to offer general guidance and strategies for the management of epilepsy (Perucca, 2021).

Pathophysiology of Epilepsy

Seizures are sudden occurrences arising from the cerebral cortex. They occur due to an abrupt disruption in the balance between excitatory and inhibitory forces within the network of cortical neurons as shown in figure 1. The fundamental physiology underlying a seizure is rooted in the instability of a cell membrane or its surrounding supportive cells. The seizure begins in the gray matter of either cortical or subcortical regions. Initially, a small group of neurons exhibit abnormal firing patterns. This abnormal firing disrupts normal membrane conductance and inhibitory synaptic currents, leading to heightened excitability. This increased excitability can spread locally, resulting in a focal seizure, or more extensively, causing a

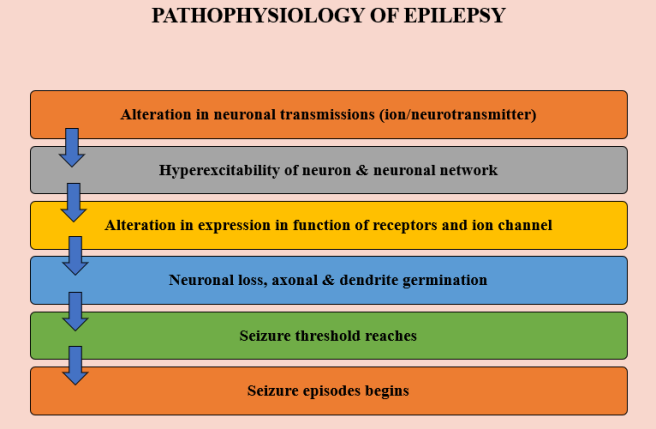

Figure 1: Pathophysiology of epilepsy

generalized seizure. This initiation then spreads through physiological pathways to involve nearby and distant areas (Meador, 2020).

Disturbances in potassium conductance, faults in voltage-activated ion channels, or insufficiencies in membrane ATPases associated with ion transport can induce instability in neuronal membranes, potentially precipitating seizures. Specific neurotransmitters like glutamate, aspartate, acetylcholine, norepinephrine, histamine, corticotropin-releasing factor, purines, peptides, cytokines, and steroid hormones heighten neuronal excitability and the spread of neural activity. Conversely, γ-amino butyric acid (GABA) and dopamine serve to suppress neuronal activity and its spread During a seizure, there's an increased need for blood flow to the brain to remove carbon dioxide and provide substrates for the metabolic activity of neurons (Dalic & Cook, 2016). Prolonged seizures can lead to ischemia, causing potential neuronal destruction and brain damage. Certain types of epilepsy may be associated with mutations in various genes. Genes encoding protein subunits of voltage-sensitive and ligand-activated ion channels have been linked to generalized epilepsy and infantile seizure syndromes (Thom & Bertram, 2012).

One proposed mechanism for certain types of hereditary epilepsy involves mutations in genes responsible for encoding sodium channel proteins. These faulty sodium channels remain open for extended periods, leading to hyperexcitability of neurons. Consequently, glutamate, an excitatory neurotransmitter, may be released in large quantities from these neurons. This excessive glutamate binding with nearby glutamatergic neurons can trigger an over-release of calcium ions (Ca^2+) in the postsynaptic cells, potentially acting as neurotoxins to the affected cells.

Traditional Approach as Antiepileptic Drugs (AEDs)

The traditional approach to treating epilepsy with antiepileptic drugs (AEDs) primarily involves the use of medications that target the stabilization of neuronal activity in the brain. Traditional AEDs work by altering the balance of neurotransmitters or ion channels to prevent the abnormal electrical discharges that lead to seizures (Domingo Sánchez et al. 2024). These drugs are typically divided into several classes based on their mechanisms of action:

Sodium Channel Blockers

Drugs like phenytoin, carbamazepine, and valproate inhibit the repetitive firing of neurons by blocking sodium channels. This stabilizes hyperexcitable membranes and reduces the likelihood of seizures (Brodie, 2017).

GABA Modulators

AEDs such as benzodiazepines and barbiturates enhance the activity of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter. By increasing GABA's inhibitory effects, these drugs help in suppressing abnormal neuronal firing (Valentina, Marco, & Mirko, 2012).

Calcium Channel Modulators

Drugs like ethosuximide block T-type calcium channels, which are involved in the generation of certain types of seizures (e.g., absence seizures).

Glutamate Inhibitors

Some traditional AEDs work by reducing the activity of glutamate, an excitatory neurotransmitter. By inhibiting glutamate release, these drugs lower the chances of seizure onset.

While traditional AEDs are effective for many patients, they often come with side effects such as dizziness, fatigue, cognitive impairment, and potential drug interactions. Moreover, not all patients respond adequately to these drugs, leading to the development of newer-generation AEDs. Nonetheless, traditional AEDs remain essential in epilepsy management due to their long-established efficacy (Solomon et al 2019).

It's imperative to delve into the pharmacodynamics of conventional antiepileptic drugs (AEDs) to better understand their efficacy, mechanisms, and limitations as shown in figure 2. Epilepsy, a neurological disorder characterized by unprovoked seizures, affects around 50 million people worldwide. The primary goal of AEDs is to control seizure activity by targeting the aberrant neuronal signalling pathways. The traditional AEDs, such as phenytoin, carbamazepine, and valproate, have played a critical role in managing epilepsy, particularly in the 20th century, but their use is still prominent due to cost-effectiveness and familiarity (Petroff, 2002).

Phenytoin

Phenytoin is a first-generation antiepileptic drug (AED) widely used to treat tonic-clonic seizures and focal seizures. It works by inhibiting voltage-gated sodium channels, stabilizing the inactive state of these channels, and preventing the rapid firing of neurons during seizures. This reduces abnormal electrical discharges in the brain, making it effective in seizure control. Phenytoin is a voltage-gated sodium channel blocker. It stabilizes the inactivated state of sodium channels in neurons, thus preventing the repetitive firing of action potentials during a seizure. By inhibiting sodium channels, phenytoin reduces the spread of abnormal electrical discharges from the epileptic focus (Coghlan et al., 2012).

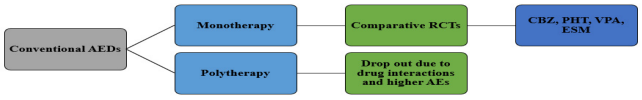

Figure 2: Illustration of conventional AEDs

Phenytoin is particularly effective in treating tonic-clonic seizures and focal seizures. A notable case study involves a patient with generalized tonic-clonic seizures who achieved seizure control with phenytoin but experienced mild ataxia as a side effect (Valentina, Marco, & Mirko, 2012).

Despite its effectiveness, phenytoin's use is limited by significant side effects, such as gingival hyperplasia, hirsutism, and osteomalacia. Gingival hyperplasia, which occurs in up to 40% of patients, often limits its long-term use. Furthermore, phenytoin has a narrow therapeutic index and requires therapeutic drug monitoring to prevent toxicity, such as nystagmus, ataxia, and cognitive impairment (Abhinav Prasoon, Ankit, & Awani Kumar, 2019).

Carbamazepine

Carbamazepine is a widely used antiepileptic drug (AED) that primarily works by inhibiting voltage-gated sodium channels, thereby stabilizing hyperexcited neuronal membranes and reducing repetitive firing. It is particularly effective in managing focal (partial) seizures and generalized tonic-clonic seizures, as well as trigeminal neuralgia and bipolar disorder. Like phenytoin, carbamazepine primarily blocks voltage-gated sodium channels, inhibiting the repetitive firing of neurons. This reduction in neuronal excitability helps control seizure propagation. Additionally, carbamazepine influences potassium and calcium channels, contributing to its antiepileptic effects.

Carbamazepine is particularly effective for focal seizures and trigeminal neuralgia. In a study involving patients with focal epilepsy, carbamazepine significantly reduced seizure frequency, although some patients experienced adverse effects like dizziness and nausea (Ambrosio et al. 2002).

Carbamazepine is a first-line agent for focal (partial) seizures, but its use is complicated by autoinduction of liver enzymes (CYP3A4), which accelerates its own metabolism and necessitates dose adjustments. Hyponatremia, a relatively common side effect, poses risks, particularly in the elderly. Moreover, carbamazepine's association with Stevens-Johnson syndrome (SJS) in patients with the HLA-B*1502 allele, especially those of Asian descent, underscores the importance of genetic screening before initiating therapy (Sheets, Heers, Stoehr, & Cummins, 2008).

Valproate (Valproic Acid)

Valproate, also known as valproic acid, is a broad-spectrum antiepileptic drug widely used in the treatment of various seizure types, including generalized tonic-clonic, absence, and myoclonic seizures, as well as bipolar disorder and migraine prophylaxis. Valproate has a broader mechanism of action compared to phenytoin and carbamazepine. It enhances gamma-aminobutyric acid (GABA)-mediated inhibitory neurotransmission, reduces abnormal neuronal firing, and also blocks voltage-gated sodium channels. Additionally, valproate inhibits T-type calcium channels, which is particularly useful in controlling absence seizures (Ravinder et al., 2013).

In patients with generalized epilepsy, valproate is highly effective. For instance, a 10-year-old girl with absence epilepsy exhibited complete seizure control with valproate treatment. However, she developed mild weight gain and required liver function monitoring.

Valproate is a first-line agent for generalized seizures, including absence, myoclonic, and tonic-clonic seizures. Its broad efficacy, however, is overshadowed by significant side effects, including weight gain, tremor, and hepatotoxicity, particularly in children under two years of age. Most importantly, valproate carries a high teratogenic risk, and its use during pregnancy is associated with neural tube defects and cognitive impairment in the fetus. This has led to the contraindication of valproate in women of childbearing age unless no alternative is available.

Ethosuximide

Ethosuximide is a well-established antiepileptic drug (AED) primarily used for treating absence seizures. It functions by inhibiting T-type calcium channels in the thalamic neurons, which are responsible for the abnormal oscillatory activity seen in absence epilepsy. By reducing this abnormal neuronal activity, ethosuximide effectively prevents the onset of seizures. Ethosuximide selectively inhibits T-type calcium channels in thalamic neurons, preventing the oscillatory activity that generates absence seizures. Unlike sodium channel blockers, ethosuximide targets thalamocortical circuits that are involved in the generalized seizure activity characteristic of absence epilepsy (Lamb, 2022).

Ethosuximide is highly effective in children with absence seizures. In a pediatric cohort, ethosuximide resulted in a 75% reduction in absence seizure frequency, with minimal side effects.

Ethosuximide is the drug of choice for absence seizures. It is generally well-tolerated, but common side effects include gastrointestinal distress, headache, and lethargy. Rare but severe side effects, such as blood dyscrasias (e.g., agranulocytosis), necessitate regular blood monitoring during treatment (Dolphin, 2018).

Phenobarbital

Phenobarbital is one of the oldest and most widely used antiepileptic drugs (AEDs), classified as a barbiturate. It is primarily used to treat generalized tonic-clonic seizures, focal seizures, and status epilepticus, particularly in resource-limited settings. Its mechanism of action involves enhancing the activity of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) at the GABA-A receptors, thereby increasing the duration of chloride channel opening. This hyperpolarizes the neuronal

membrane, reducing excitability and preventing seizure propagation. Phenobarbital is a GABA-A receptor agonist that enhances the inhibitory action of GABA by increasing the duration of chloride channel opening, leading to hyperpolarization of neurons. This reduces the likelihood of seizure activity (Brodie, Zuberi, Scheffer, & Fisher, 2018). Although its use has diminished with the advent of newer AEDs, phenobarbital remains effective for generalized tonic-clonic seizures and status epilepticus in resource-limited settings. A case in point involves its use in a patient with refractory status epilepticus, where phenobarbital, in combination with other agents, controlled the seizures. Phenobarbital's main limitation is its sedative effects, which can impair cognition and motor skills. Its long half-life, coupled with potential for tolerance and dependence, has reduced its use in favour of newer AEDs. However, its cost-effectiveness and availability make it a valuable option in certain healthcare settings (Domingo Sánchez et al., 2024).

Challenges with Conventional AEDs

While conventional AEDs like phenytoin, carbamazepine, valproate, ethosuximide, and phenobarbital have been invaluable in managing epilepsy, they are not without challenges: Most conventional AEDs carry significant side effect burdens, ranging from sedation (phenobarbital) and gastrointestinal disturbances (ethosuximide) to severe teratogenic effects (valproate). Approximately 30% of epilepsy patients become drug-resistant, meaning conventional AEDs fail to control their seizures (Wahab, 2010). Drug resistance can arise due to genetic polymorphisms affecting drug metabolism or alterations in drug targets (e.g., sodium channels). Conventional AEDs like phenytoin and carbamazepine are potent inducers of liver enzymes, leading to significant interactions with other medications. This complicates therapy, especially in patients on polypharmacy for comorbid conditions. Drugs like phenytoin and valproate have a narrow therapeutic index, necessitating regular monitoring of blood levels to avoid toxicity and ensure efficacy (Stefan et al., 2001).
Conventional AEDs, including phenytoin, carbamazepine, valproate, and phenobarbital, have been the backbone of epilepsy management for decades. Their mechanisms of action—ranging from sodium and calcium channel blockade to GABAergic modulation—have proven effective across various seizure types. However, their use is often limited by significant side effects, drug interactions, and the risk of resistance. As a result, newer AEDs with improved safety profiles and fewer drug interactions are increasingly favoured, but the traditional agents remain critical in certain patient populations and settings (Asconape, 2002).

Emerging Therapies of New Generation AEDs

New generation antiepileptic drugs (AEDs), such as levetiracetam, lacosamide, and perampanel, have emerged as effective alternatives to traditional AEDs, offering novel mechanisms of action and improved safety profiles. These drugs target specific neuronal pathways, making them effective in managing a variety of seizure types (Hanaya & Arita, 2016).
Levetiracetam is widely used due to its unique mechanism of binding to the synaptic vesicle protein SV2A, which modulates neurotransmitter release and reduces neuronal hyperexcitability. Levetiracetam has shown efficacy in treating focal and generalized seizures, with fewer side effects compared to traditional AEDs like phenytoin or carbamazepine. In clinical practice, levetiracetam's favourable safety profile, with minimal drug interactions and a low risk of cognitive impairment, makes it a popular choice, especially for patients on polypharmacy (North et al.,1983).
Lacosamide offers a novel mechanism by selectively enhancing the slow inactivation of voltage-gated sodium channels. This action stabilizes hyperexcitable neuronal membranes without affecting normal neuronal activity, making it effective for focal seizures. Lacosamide has a lower incidence of side effects such as sedation and dizziness compared to older sodium channel blockers like phenytoin. Its use is particularly beneficial in patients who do not respond to first-line AEDs, as it shows excellent tolerability (Naidech et al., 2009).
Perampanel, a selective AMPA receptor antagonist, works by inhibiting glutamate-mediated excitatory transmission in the brain. This unique mechanism helps reduce seizure frequency in focal and generalized tonic-clonic seizures. Although perampanel is associated with behavioural side effects like irritability and aggression, its efficacy in refractory epilepsy cases makes it a valuable option for treatment-resistant patients (Yang et al., 2015).

Future Prospects of AEDs

The future of pharmaceutical approaches in epilepsy management is poised for transformative advancements, driven by ongoing research and technological innovations. As our understanding of the complex mechanisms underlying epilepsy deepens, several promising directions are emerging. Advances in genomics and pharmacogenomics are paving the way for personalized treatment strategies. By identifying genetic markers associated with drug response and seizure types, clinicians can tailor AEDs to individual patient profiles, optimizing efficacy and minimizing adverse effects. This approach not only promises improved seizure control but also enhances patient adherence and quality of life. Emerging research is focusing on new drug targets beyond traditional sodium and calcium channels. Innovations include modulating neuroinflammatory pathways, targeting synaptic plasticity, and harnessing the potential of neuropeptides and ion channel modulators. These novel mechanisms aim to address the limitations of current therapies, such as drug resistance and side effects. Innovations in drug delivery

systems, including controlled-release formulations and nanotechnology-based delivery methods, are expected to enhance the therapeutic efficacy of AEDs. For example, developing sustained-release formulations can improve medication adherence and reduce the frequency of dosing, while targeted delivery systems can optimize drug concentration at the epileptic focus, minimizing systemic side effects. Advances in neuromodulation techniques, such as responsive neurostimulation and deep brain stimulation, offer adjunctive options for patients with drug-resistant epilepsy. These approaches, combined with emerging non-pharmacological therapies like ketogenic diets and biofeedback, provide additional avenues for seizure control and management. The integration of artificial intelligence and big data analytics in epilepsy research is enhancing the ability to predict seizure patterns, personalize treatment, and discover new therapeutic targets. AI-driven tools can analyze vast amounts of patient data to identify trends and optimize therapeutic strategies, contributing to more effective and individualized care. The future of epilepsy treatment is increasingly characterized by personalized medicine, novel drug targets, advanced delivery systems, and integrative therapies. These evolving approaches promise to address current limitations, enhance therapeutic outcomes, and improve the overall management of epilepsy.

Conclusion

Epilepsy, a complex neurological disorder characterized by recurrent seizures, affects approximately 1% of the global population, equating to about 50 million people worldwide. This condition, which can result from genetic predispositions or acquired brain injuries such as trauma or stroke, remains a significant public health issue, particularly in developing countries where 90% of affected individuals reside. The term "epilepsy" originates from the Greek word "Epilepsia," meaning "to take hold of," reflecting the sudden and uncontrollable nature of seizures. Historically, the understanding of epilepsy dates back over 4,000 years, as evidenced by ancient Akkadian tablets describing symptoms akin to modern-day seizures. Epilepsy encompasses several types of seizures: partial seizures, generalized seizures, unclassified seizures, and status epilepticus. These classifications help in diagnosing and tailoring treatment to the specific needs of the individual. For instance, while seizures in children are managed similarly to adults, they may respond differently to treatments. Despite extensive research, the exact causes of epilepsy remain elusive. The condition can be triggered by various factors, including genetic mutations, brain injuries, strokes, infections, high fever, or tumors. The clinical presentation of seizures varies based on the location of epileptic discharges in the brain, leading to a wide range of symptoms and severities. The global prevalence of epilepsy underscores its importance as a major neurological disorder. In India, approximately 5.5 million people are affected, with 2 million in the United States and 300,000 in the United Kingdom. Each year, around 120 per 100,000 individuals in the U.S. seek medical attention for newly recognized seizures, highlighting the ongoing need for effective treatment and management strategies. Epilepsy's impact on millions worldwide necessitates continued research and advancements in understanding, diagnosis, and treatment. Addressing this disorder with a comprehensive approach that includes early intervention and personalized care is crucial for improving the quality of life for those affected.

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