Review 0f Anticonvulsant Drug: Mechanism, Uses and Clinical Considerations

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Abstract—**Epilepsy is a neurological disorder affecting a large scale of the population, which accounts for about 1% of the world's burden of diseases. A large number of agents called antiepileptic drugs are available to treat various types of seizures with the objective to reduce seizure frequency and severity within a framework of an acceptable level of side effects. There are number of drugs available for treatment of epilepsy in modern therapy. But the major disadvantage being faced is their chronic side effects. Treatment of epilepsy with herbal drugs as adjuvant seems to be more beneficial and is gaining more popularity due to their fewer side effects. Herbal drugs are acting at target site having same mechanism of action as that of synthetic drugs. There is still a need for new antiepileptic drugs (AEDs), may be derived from natural sources, as the clinical efficacy tolerability, toxicity properties of existing synthetic AEDs may not be satisfactory.**

Index Terms— **Neurological, Epilepsy, Transmitter, Seizure, Neurosyphills, AEDs**

I. INTRODUCTION

Epilepsy is a major public health concern, directly affecting an estimated 50 million people worldwide and involving an additional 500 million people as family members and caregivers of patients. In 2006, the International League against Epilepsy (ILAE) published a review aimed at providing an evidence-based answer to the following question: "For patients with newly diagnosed or untreated epilepsy, which AEDs have the best evidence for long-term efficacy or effectiveness as initial monotherapy". This restricted analysis resulted from the inability to address all the other variables that affect initial antiepileptic drug (AED) selection in an evidence-based fashion. In 1983, a systematic assessment of the frequency and severity of adverse effects showed differences between the standard AEDs (phenobarbital, primidone, phenytoin, carbamazepine, and valproate). the beginning, doctors mainly used older drugs like phenobarbital, phenytoin, carbamazepine, and valproic acid. These drugs helped control seizures, but long-term use often caused side effects and drug interactions (Brodie & Dichter, 1996).[1]

New drugs such as gabapentin, lamotrigine, and topiramate were introduced. These gave better options for patients who did not respond to older medicines (Dichter & Brodie,1996).[2]

Scientists found that most anticonvulsants work by either blocking overactive nerve signals, increasing calming signals in the brain, or reducing excitatory signals (Macdonald & Kelly, 1995; Kwan et al., 2001).[3]

However, about 30% of epilepsy patients still do not get full seizure control with available drugs (Löscher & Schmidt, 2011). Because of this, researchers are now working on new medicines that target different parts of the brain (Rogawski & Löscher, 2004). [4]

Modern drugs like cenobamate are more effective and have fewer side effects (Abou-Khalil, 2025). In the future, treatment may become more personalized, based on a patient's genes (Brodie et al., 2021).[5]

II. EPILEPSY

Epilepsy is a neurological malfunctioning that affects people in every country throughout the world. About 7.2 million people will experience at least one seizure during their lifetime. Epilepsy can develop at any age. New cases of epilepsy are most common among the children, especially during the first year of life. The rate of new cases gradually declines until about age 10, and then becomes stable. After the age 55 or 60, the rate increases, as people develop strokes, brain tumors or AD. The term epilepsy includes a variety of complex disorders with distinct etiologies and pathological manifestations. To standardize and

categorize the disease, the International League Against Epilepsy (ILAE) introduced a descriptive model in 2017 to improve the diagnosis and subsequent treatment of epilepsy patients. This model presents three levels: the first level corresponds to seizures that can be focal, generalized or of unknown origin; the second level represents focal epilepsy, generalized epilepsy or combination of both, and also an unknown type of epilepsy and the third level correspond to the epilepsy syndrome. [6]

III. ANTICONVULSANTS

Conventional antiepileptic drugs have diverse mechanisms of action but many block sodium channels or enhance γ-aminobutyric acid (GABA) function. Several antiepileptic drugs have multiple or uncertain mechanisms of action. Next to voltage-gated sodium channels and components of the GABA system, their targets include GABAA receptors, the GABA transporter type 1, and GABA transaminase. Additional targets include voltage-gated calcium channels, SV2. By blocking Anticonvulsants (also known as antiepileptic drugs, antiseizure drugs, or anti-seizure medications (ASM)) are a diverse group of pharmacological agents used in the treatment of epileptic seizures. Anticonvulsants are also used in the treatment of bipolar disorder and borderline personality disorder,since many seem to act as mood stabilizers, and for the treatment of neuropathic pain. Anticonvulsants suppress the uncontrolled and excessive firing of neurons during seizures and in doing so can also prevent the spread of the seizure within the brain.[7]

sodium or calcium channels, antiepileptic drugs reduce the release of the excitatory neurotransmitter glutamate, whose release is considered to be elevated in epilepsy, but also that of GABA. This is probably a side effect or even the actual mechanism of action for some antiepileptic drugs, since GABA can itself, directly or indirectly, act pro-convulsively. Another potential target of antiepileptic drugs is the peroxisome proliferator-activated receptor alpha.[8]

IV. CURRENT ANTICONVULSANTS DRUG TARGETS

Voltage-Gated Sodium Channels

Voltage-gated sodium channels are responsible for depolarization of the nerve cell membrane and conduction of action potentials across the surface of neuronal cells (White HS, 20030). They are expressed throughout the neuronal membrane, on dendrites, soma, axons, and nerve terminals. Density of expression is highest in the axon initial segment (AIS) where action potentials are generated. Sodium channels belong to the super-family of voltage-gated channels that areformed of multiple protein subunits and which form ion-selective pores in the membrane. The native sodium channel consists of the single alpha-subunit protein, which contains the poreforming region and voltage sensor, associated with one or more accessory beta-subunit proteins which can modify the function of the alpha-subunit but are not essential for basic channel activity. There are four predominant sodium channel alpha-subunit genes expressed in mammalian brain, denoted SCN1A, SCN2A, SCN3A. [9]

Voltage-Gated Calcium Channels

Voltage-gated calcium channels contribute to the overall electrical excitability of neurons, are closely involved in neuronal burst firing, and are responsible for the control of neurotransmitter release at pre-synaptic nerve terminals [13]. Likewise,the sodium channels, voltage-gated calcium channels consist of a single alpha-subunit, of which at least seven are known to be expressed in mammalian brain. There are also accessory proteins, including beta- and alpha2-delta-subunits, that modulate the function and cell-surface expression of the alpha-subunit but which are not necessarily essential for basic channel functionality. Voltage-gated calcium channels are usually distinguished upon the basis of their biophysical properties and patterns of cellular expression. [10]

Voltage-Gated Potassium Channels

Voltage-gated potassium channels are primarily responsible for repolarization of the cell membrane in the aftermath of action potential firing and also regulate the balance between input and output in individual neurons. As a group, they are highly

heterogeneous. More than 40 voltage-gated potassium channel alpha-subunits have been identified thus so far, each of which is structurally similar to the alpha-subunits of voltage-gated sodium and calcium channels. These are classified into 12 sub-families (Kv1 to Kv12), with individual channels comprising four alpha-subunits from the same sub-family arranged around a central K+ sensitive pore, typically in a 'two plus two' conformation. Two functional classes of voltage-gated potassium channel are well described in the literature. Kv1 to Kv4 channels are expressed in dendrites, axons and nerve terminals and carry the delayed rectifier current (IK) that repolarizes the neuronal membrane after action potential firing. [11]

V. COMMONLY USED ANTICONVULSANTS

1.Phenytoin: Phenytoin (also known as diphenylhydantoin or Dilantin) effectively treats partial and tonic-clonic seizures but is not effective against absence seizures. Its action occurs in the motor cortex, where it stabilizes neuronal membranes, preventing seizure spread. Current evidence indicates that it limits high-frequency repetitive firing by blocking sodium channels in a frequency-dependent manner. Additionally, it enhances calcium binding to neuronal membrane phospholipids, collectively resulting in a more stable membrane configuration. Phenytoin demonstrates antiseizure effects without inducing widespread CNS depression. However, in excessive doses, it can manifest excitatory symptoms, and at lethal levels, it may lead to a form of decerebrate rigidity.[12]

2.Benzodiazepines: - Diazepam (DZP) and midazolam (MDZ) are frequently employed in treating early (stage I) Status epilepticus. Midazolam, a water-soluble benzodiazepine, offers various administration routes: intravenous, intramuscular, buccal, and intranasal. In contrast, DZP can be given intravenously or rectally. Rectal DZP is commonly used for prehospital management of early SE in Spain and potentially elsewhere, although its administration is often socially unacceptable. Additionally, its use entails removing clothing and positioning the patient properly, which may cause significant treatment delays. Similar challenges exist with intravenous administration of DZP or other drugs like lorazepam, necessitating intravenous access placement.[12]

3.Zonisamide: - Zonisamide, a sulfonamide compound with chemical similarities to an indole, was identified for further development as an antiepileptic drug due to its effectiveness in maximal electroshock experiments. It is approved for use as both monotherapy and adjunctive therapy for partial onset and generalized epilepsies in Japan and South Korea, and for partial onset epilepsy in Europe. Zonisamide exhibits broad-spectrum antiepileptic properties with various mechanisms of action, including reducing sustained high-frequency repetitive firing of sodium-dependent action potentials, inhibiting low threshold T-type calcium currents, modulating GABA-mediated neuronal inhibition, inhibiting glutamate release, and weakly inhibiting carbonic anhydrase. [13]

4.Cenobamate: - Cenobamate, an antiseizure medication prescribed for partial-onset (focal) seizures, is characterized by a single chiral center. It operates through a distinctive dual mechanism: enhancing both fast and slow inactivation of sodium channels, with a preference for inhibiting persistent current, and positively modulating GABAA receptor-mediated ion channels. [14]

5.Vigabatrin: - Vigabatrin (VGB) is a drug closely resembling gamma-aminobutyric acid (GABA), a neurotransmitter. By inhibiting the breakdown of GABA, VGB elevates its levels in the brain, thereby curbing neuronal hyperactivity, which underlies its antiepileptic effect. As a first-line treatment, VGB is particularly effective in managing infantile spasms, especially in patients with tuberous sclerosis complex. Its efficacy in addressing focal seizures is comparable to that of primary antiepileptic drugs such as carbamazepine, with similar side effects. However, the main drawback of VGB usage lies in the significant risk of irreversible visual field loss, a concern exacerbated by high doses, prolonged exposure, and increasing patient age.[15]

6.Valproic Acid: - Valproic acid (VPA), also referred to as valproate, is one Kaur et al. Journal of Drug Discovery and Therapeutics (JDDT)12 |Page of the most frequently prescribed medications for epilepsy treatment. It is estimated that around one million

individuals worldwide use VPA on a daily basis. The mechanism of action of VPA involves enhancing the effects of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) through several means: inhibiting GABA degradation, suppressing GABA transamination activity, and stimulating GABA synthesis. Moreover, VPA prolongs N-methyl-D-aspartate-mediated stimulation while also inhibiting calcium and sodium channels.Valproic acid (VPA) suppresses histone deacetylases (HDACs), promoting histone acetylation and loosening chromatin structure. This process facilitates gene expression and offers favorable effects for conditions such as cardiac arrhythmia, cardiac fibrosis, cardiac hypertrophy, hypertension, and myocardial infarction. [16]

7.Felbamate: - Felbamate, known as FBM, is highly effective in treating focal seizures and Lennox-Gastaut syndrome. FDA approved it in 1993 specifically for partial epilepsy treatment, often used alone or alongside CBZ and PHT for uncontrolled focal epilepsy. Chemically, FBM is 2-phenyl-1,3-propanediol dicarbamate. Initially synthesized in the late 1950s to study the structure-activity relationship of the widely used anxiolytic drug meprobamate. [17]

Summary Table of Commonly Used Anticonvulsant Drugs

Drug Name	Clinical Indications / Uses	Mechanism(s) of Action
Phenytoin (Diphenylhydantoin / Dilantin)	Effectively treats partial and tonic-clonic seizures. Note: Not effective against absence seizures.	Stabilizes neuronal membranes in the motor cortex to prevent seizure spread. Blocks sodium channels in a frequency-dependent manner to limit high-frequency repetitive firing. Enhances calcium binding to neuronal membrane phospholipids.
Diazepam (DZP) (Benzodiazepine)	Frequently used in treating early (stage I) Status epilepticus.	Specific molecular mechanism not detailed in text, but categorized broadly under conventional agents that enhance aminobutyric acid (GABA) function.
Midazolam (MDZ) (Benzodiazepine)	Frequently used in treating early (stage I) Status epilepticus.	Specific molecular mechanism not detailed in text, but categorized broadly under conventional agents that enhance aminobutyric acid (GABA) function.
Zonisamide	Approved as monotherapy and adjunctive therapy for partial onset and generalized epilepsies (in Japan/South Korea) and partial onset epilepsy (in Europe).	Reduces sustained high-frequency repetitive firing of sodium-dependent action potential. Inhibits low-threshold T-type calcium currents. Modulates GABA-mediated neurona inhibition. inhibits glutamate release .
Cenobamate	Prescribed for partial-onset (focal) seizures.	Enhances both fast and slow inactivation of sodium channels, with a preference for inhibiting persistent current. Positively modulates GABA receptor-mediated ion channels.
Vigabatrin (VGB)	First-line treatment for managing infantile spasms, especially in patients with tuberous sclerosis complex	Inhibits the breakdown (degradation) of GABA, which elevates GABA levels in the brain and curbs underlying neuronal hyperactivity.
Valproic Acid (VPA) (Valproate)	One of the most frequently prescribed medications for epilepsy treatment. Also offers favorable effects for cardiac arrhythmia, cardiac fibrosis, cardiac hypertrophy, hypertension, and myocardial infarction.	Enhances inhibitory GABA effects by inhibiting GABA degradation, suppressing GABA transamination activity, and stimulating GABA synthesis. Prolongs N-methyl-D-aspartate (NMDA)-mediated stimulation.Inhibits calcium and sodium channels. Suppresses histone deacetylases (HDACs).
Felbamate (FBM)	Highly effective in treating focal seizures and Lennox-Gastaut syndrome. Used alone or alongside CBZ (carbamazepine) and PHT (phenytoin) for uncontrolled focal epilepsy.	Specific molecular targets not heavily detailed in text, though noted as a 2-phenyl-1, 3-propanediol dicarbamate structurally studied against meprobamate.

VI. ADVERSE EFFECTS OF ANTICONVULSANTS

1.Certain antiseizure drugs (ASDs) have thepotential to induce central nervous system deterioration, neuronal demise, aplasticanemia, liver failure, and in severe cases, fatalities such as sudden unexpected death inepilepsy (SUDEP). [18]
2.Carbamazepine has the potential to induceneural tube defects and craniofacial abnormalities. [18]
3.The utilization of phenytoin is linked tofetal hydantoin syndrome. [19]
4.Topiramate administration in the initial trimester of pregnancy is correlated with a tenfold rise in the risk of oral clefts.Phenobarbital usage can lead to congenital malformations, primarily cardiacdefects. [20]
5.Phenobarbital induces a spectrum of adverse effects, spanning from renal failure, myocardial dysfunction, and sedation, torespiratory depression, contingent on the dosage. These effects may encompass diminished consciousness levels, hypotension, paralysis, and coma, particularly at high doses or due to drugaccumulation attributed to its extended half-life of 3-7 days. [21]
6.Carbamazepine and phenytoin were identified as the medications most closely linked to reductions in T4 and T3 hormone levels, whereas topiramate notably increased TSH levels. Oxcarbazepine has been associated with decreased levels of serum FT4 and FT3, indicating potential central hypothyroidism. Phenobarbital demonstrated a significant reduction in FT3 levels.Levetiracetam and valproic acid use may lead to subclinical hypothyroidism. Lamotrigine was observed to have the least impact on thyroid hormone levels among the antiseizure drugs studied. Recently, there has been increased attention on additional side effects including: [22]

1 Weight alterations.
2 Blocking carbonic anhydrase, potentially resulting in metabolic acidosis, kidney stone formation, reduced sweating, and intolerance to heat.[23]
3 Stimulating enzyme activity
4 Adverse effects on vision.
5 Negative reactions on the skin. [24]
6 Other adverse effects such as liver toxicity, kidney damage, colitis, and the onset of systemic lupus erythematosus (SLE). [25]

VII. CONCLUSION

Anticonvulsant drugs are still the main treatment for epilepsy. They have changed the lives of millions of people by helping control seizures. These medicines work in different ways: some calm down overactive brain cells, some boost the brain's natural "stop" signals, and others block the "go" signals that cause seizures. Old drugs like phenytoin and valproic acid, as well as newer ones like zonisamide, vigabatrin, and cenobamate, all help manage different types of epilepsy.
But there are still problems. Taking these drugs for a long time can cause side effects like memory problems, liver damage, hormone issues, birth defects, weight changes, and bad reactions with other medicines. On top of that, about 1 in 3 patients still have seizures even when they take the right drugs. This is called drug-resistant epilepsy.
Because of these challenges, scientists keep searching for better options. New research in genetics and brain science is helping us understand why seizures happen. This has led to newer drugs that work better and have fewer side effects. Some researchers are also looking at natural and herbal medicines that could be used along with standard drugs.

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