A Review on Pharmacological Treatment for Epileptic Seizures

By

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Declaration

It is hereby declared that

1. The project submitted is my own original work while completing degree at BRAC University.
2. The project does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The project does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The project titled “A Review on Pharmacological Treatment for Epileptic Seizures” submitted by Umme Fathima Tuz Zohora (20146053) of Spring, 2020 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics Statement

This review article does not involve any kind of trials on either animal or human models.

Abstract

Epilepsy is a chronic neurological disorder that leads to uncontrollable recurrent seizures. This might occur either due to genetic or different environmental factors. Controlling epileptic seizures is of great challenge and so different antiepileptic drugs of generations first, second, third and so on were discovered throughout past few decades and are still under constant research. Drugs such as phenytoin, carbamazepine, ganaxolone, cannabidiol, lamotrigine, vigabatrin and many more were introduced under different generations. These drugs have different mechanisms of action such as enhancement of GABA action, inhibition of sodium channel and inhibition of calcium channel etc. Some of the newer AEDs are more emphasized and are under continuous research due to having fewer adverse effects that effectively control seizures accompanied by epilepsy.

Keywords: Epilepsy, Chronic, Cannabidiol, Ganaxolone, GABA action, AEDs, Seizures.

Dedication

This work is entirely dedicated to my parents, family and faculties who showed their continuous support throughout my entire journey.

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List of Acronyms

AEDs	Antiepileptic Drugs
EEG	Electroencephalography
CNS	Central Nervous System
SUDEP	Sudden Unexpected Death in Epilepsy
SE	Status Epilepticus
GABA	Gamma aminobutyric Acid
$GABA_A$	Gamma aminobutyric Acid-A
FDA	Food and Drug Administration
EMA	European Medicines Agency
CYP	Cytochrome P450
CBD	Cannabidiol
CLB	Clobazam
CDKL5	Cyclin-Dependent-Kinase-Like 5
PTZ	Pentylenetetrazole
LTG	Lamotrigine
CSF	Cerebrospinal Fluid
OXC	Oxcarbazepine
CBZ	Carbamazepine

VGB	Vigabatrin
TSC	Tuberous Sclerosis Complex
PCOS	Polycystic Ovary Syndrome
ASMs	Anti-Seizure Medications
ACTH	Adrenocorticotropic Hormone
MRI	Magnetic Resonance Imaging
SJS	Steven-Johnson Syndrome
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms

Chapter 1

Introduction

1.1 Overview on Epilepsy:

Epilepsy is the third most chronic, non-transmissible neurological conditions characterized by occasional, uncontrollable seizures. It has been reported that, at present, 70 million people worldwide are affected by epilepsy (Lattanzi, Riva, et al., 2021). The brain experiences aberrant electrical activity during these seizure events. Epileptogenesis is the process of epileptic arousal in a brain that is otherwise normal. Epilepsy might occur due to several reasons such as occasional changes in blood sugar or sodium levels, brain infections like encephalitis or meningitis, strokes, and brain tumors (Ghosh et al., 2021). Epilepsy prevalence is variable with age, onset of action in the elderly and pediatric populations. It is believed that 25% of epileptic individuals experience seizures that are uncontrollably severe despite the use of current antiepileptic drugs (AEDs) (Monaghan et al., 1999). Synaptic recombination, glial formation, and neurotransmitter dysregulation are all strongly linked to the epileptic seizure process. Additionally, oxidative stress, sugar degradation disorders, and mitochondrial damage might result from epileptic convulsions (He et al., 2021). This demonstrates the pressing necessity to create suitable treatment plans to address the intricate epilepsy scenario. Developing more effective strategies through pharmacological and therapeutic approaches would require its deeper understanding for prevention and control of epileptic seizures (Ghosh et al., 2021).

1.2 Significance of Pharmacological Treatment:

Majority of epileptic patients experience long-term remission from seizures with symptomatic therapy. Over the past few decades, the burden of refractory epilepsy has remained essentially constant, despite the availability of novel therapeutic alternatives. However, in one-third of cases, seizures remain uncontrollable regardless of effective treatment (Lattanzi, Riva, et al.,

2021). Comprehending the molecular and cellular processes associated with ictogenesis and epileptogenesis is essential for precise diagnosis and the creation of targeted treatments (Sharifi-Rad et al., 2021). The impact of treatment-resistant epilepsies on quality of life, behavioral and cognitive abilities is significant (Lattanzi, Trinka, et al., 2021). Selecting AEDs for adjunctive therapy, initial therapy, or subsequent replacement monotherapy requires a great deal of direction. The range of effectiveness of the antiepileptic drug, its safety and tolerability profile, its pharmacokinetic features, and its effectiveness in combating comorbidities, as applicable to the patient's particular circumstances, must all be considered when selecting an antiepileptic drug (Abou-Khalil, 2019). As a result, researchers are always looking for better ways to manage seizures, especially in those who have refractory epilepsies (Lattanzi, Riva, et al., 2021).

1.3 Aim:

The sole purpose of this systematic review article is to get a brief concept about epilepsy and discuss different pharmacological treatments available to treat seizures accompanied by epilepsy.

1.4 Objective:

A comprehensive examination of antiepileptic drugs (AEDs) assesses their availability and successful application in treating epileptic seizures. The evaluation involves comparing these drugs to identify those with superior efficacy and minimal to no adverse effects.

Chapter 2

Understanding Epilepsy

2.1 Types of Epilepsy:

By far, 30 different forms of epilepsy syndromes and 15 different types of epileptic seizures may be used to diagnose epilepsy which is associated with anxiety, sadness, significant comorbidity, and a higher death rate are also present (Ghosh et al., 2021). The two main types of epilepsy are primary and partial generalized epilepsy. Complex partial seizures, which affect only a portion of the brain yet impair cognitive abilities, are the most typical kind of seizures that affect adults and are the most challenging to treat. Infantile spasms, also known as West syndrome, is a type of generalized epilepsy that primarily manifests in the early stage of life, and peaks between the ages of four and eight months (Monaghan et al., 1999). Precisely, there are three classifications for epilepsy: focal, generalized, and unknown onset (Chávez-González et al., 2021). Of these, focal and generalized were based on symptoms. Additionally, the etiology was used to classify the conditions into two groups: symptomatic epilepsies and idiopathic epilepsies. There were no brain lesions and a normal baseline electroencephalography (EEG) in idiopathic epilepsies, which were caused by genetics. Unlike idiopathic epilepsies, symptomatic epilepsies were defined by brain lesions (Sharifi-Rad et al., 2021). Here, in the focal onset, the awareness may or may not be impaired and a focal seizure may become focal to bilateral tonic-clonic seizures by spreading to both sides of the brain. The generalized and the unknown onset exhibit tonic-clonic as well as absence seizures although the generalized onset has impaired awareness (Falco-Walter et al., 2018). Focal seizures are more common than generalized seizures in both adults and children. Individuals with nocturnal seizures, drug-resistant epilepsy, and generalized tonic-clonic seizures are most likely to have sudden unexpected death. The hallmarks of epileptic seizures are repetitive paroxysmal episodes with stereotyped behavioral changes that represent the fundamental neurological

mechanisms of the syndrome. Many clinical disorders that are marked by transient changes in awareness and behavior are included in the multiple diagnoses of epilepsy (Beghi, 2020).

ILAE (2017) proposed the classification of epileptic seizures (See Table 1).

Table 1: Classification of epileptic seizures proposed by ILAE (2017) (Chávez-González et al., 2021).

Focal onset	Generalized onset	Unknown onset
• Aware/ impaired awareness • Motor onset • Non-motor onset • Focal to bilateral tonic-clonic	• Motor onset • Non-motor onset	• Motor onset • Non-motor onset • Unclassified onset

2.2 Impact on Individuals and Society:

In a study, it was observed that, in comparison to higher-income countries, the incidence of epilepsy was greater in low-income and middle-income countries. This might be because of the varying composition of vulnerable populations, increased exposure to prenatal health risks, and higher incidence of traumatic brain injury and CNS infections in lower-middle-income countries. Men have a somewhat greater frequency and severity of epilepsy than do women. This might be due to keeping it from the people in fear of their socio-cultural condition in that specific area. The incidence is highest in the infants and the older patients. However, in the last few decades, this incidence has significantly reduced in children and has increased in the older patients with an increased risk of cancer, stroke, and neurological diseases in this age group (Beghi, 2020). Epileptic patients and their families face discrimination due to the stereotypes that have been set for many years everywhere in the world. Many individuals with epilepsy are unable to work, drive, or get married, and many children with the condition do not attend

school. The human rights violations that people with epilepsy encounter globally are intolerable (Braga et al., 2020). Death caused by idiopathic epilepsy reduced to a greater extent over the past few decades which eventually reflects the improvement in the overall life expectancy including better health facilities. Epileptic patients are at greater risk of death compared to the normal people. These risks include Sudden Unexpected Death in Epilepsy (SUDEP), suicide, and Status Epilepticus (SE) (Beghi, 2020). Moreover, a study showed that families with epileptic children experienced higher levels of stress, communication difficulties, a lack of social support from family members, and worse financial standing. Four prevalent areas of concern among family members that impacted the family's quality of life were identified as- poor communication, inadequacy in normalizing, possessive parents, and limitation in activity (Ostendorf & Gedela, 2017).

Chapter 3

Pharmacological Treatment Options

3.1 Antiepileptic Drugs (AEDs):

Some of the antiepileptic drugs include ganaxolone, phenobarbital and benzodiazepines which work by the enhancement of GABA action; carbamazepine, phenytoin, lamotrigine, oxcarbazepine, lacosamide, rufinamide and eslicarbazepine acetate that work by the inhibition of sodium channel (Brodie, 2017); and ethosuximide by the inhibition of calcium channel. Whereas, sodium valproate work by multiple mechanisms of action that include inhibition of sodium channel, inhibition of calcium channel and by enhancement of GABA action. Besides, newer AEDs include vigabatrin, tiagabine, plant derived cannabidiol, brivaracetam, stiripentol, and so on (Abou-Khalil, 2019).

3.2Classification and Mechanisms of Action:

The management of epilepsy are classified into three different mechanisms of action which are:

- **Enhancement of GABA action:**

The activity of GABA can be increased by either increasing the GABA receptor activation or reducing the breakdown of GABA or by decreasing the reuptake of GABA transporter. The reduction of both the breakdown of GABA and the reuptake of its transporter leads to increasing the GABA levels in the synaptic cleft of the neuron. Antiepileptic drugs such as phenobarbital and benzodiazepines increase the GABA receptor activation which leads to the opening of the chloride channel allowing enhanced chloride influx (Abou-Khalil, 2019). This in turn results in increased hyperpolarization which eventually lead to decrease in neuronal activation and signaling. Thus, it helps in controlling the occurrence of seizures. Besides, there are also plant derived natural ingredients such as flavonoids, terpenoids, alkaloids etc. that exhibit antiepileptic properties. There are few plant-derived flavonoids that show same efficacy

as benzodiazepines. Cannabidiol, a plant-derived compound of terpenoid class is one of the newer antiepileptic drugs introduced for its antiseizure activities (Sharifi-Rad et al., 2021). The mechanism of action showing the enhancement of GABA action has been shown in the following Figure 1.

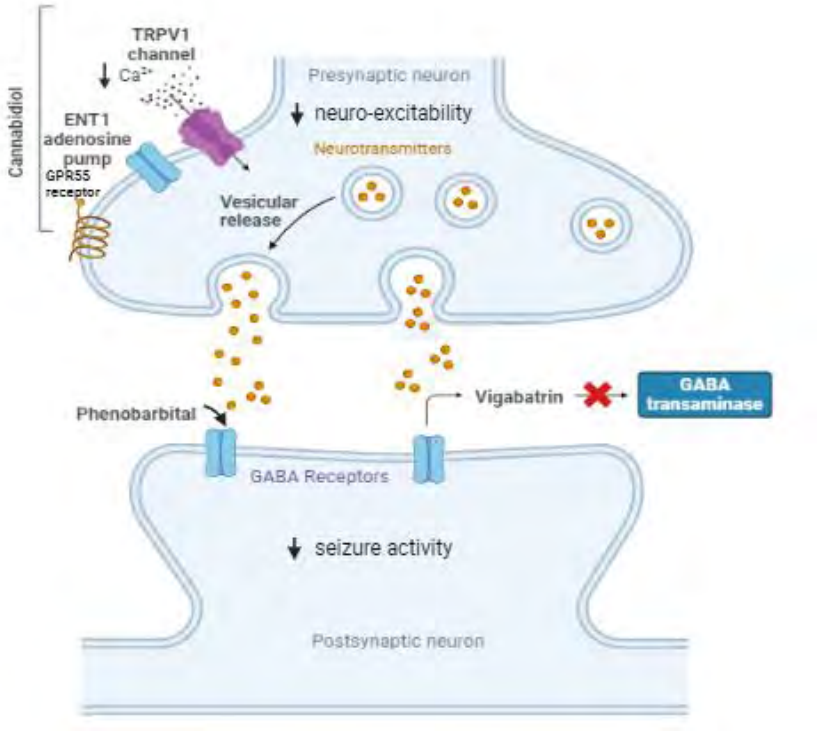

Figure 1: Enhancement of GABA action by introducing AEDs (Sharifi-Rad et al., 2021).

- **Inhibition of sodium channel:**

AEDs such as phenytoin, carbamazepine, oxcarbazepine etc. inhibits the sodium channel opening which decreases the depolarization of the neurons resulting in the decreased generation of the action potential. Thus, the neuronal excitation is gradually decreased which aid in controlling the seizure induced by epilepsy. Although drugs such as rufinamide, lacosamide and lamotrigine are slightly teratogenic besides being the inducers of enzyme (Brodie, 2017). The mechanism of action showing the inhibition of sodium channel has been shown in the following Figure 2.

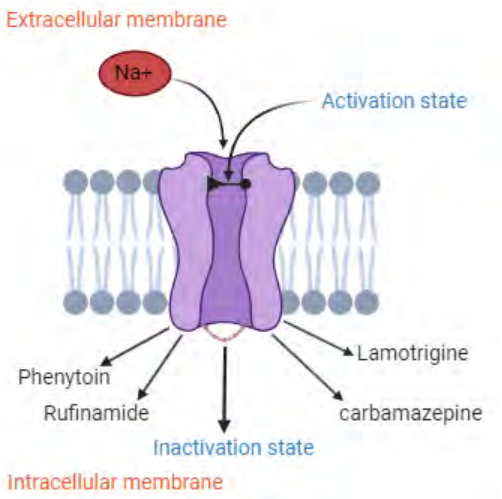

Figure 2: Inactivation of sodium channel by AEDs (Ochoa, 2022).

- **Inhibition of calcium channel:**

Antiseizure medications such as gabapentin, valproate, ethosuximide etc. are often used to treat absence seizures. These drugs inactivate the T-type channels which prevents the firing of action potentials and excitation in the thalamic neurons resulting it to inhibit the formation of absence epilepsy. Excitation of the nervous system by massive Ca2+ influx not only results in neuronal injury but also raises the concentration of Ca2+ within the cells (He et al., 2021).

The mechanism of action showing the inhibition of calcium channel has been shown in the following Figure 3.

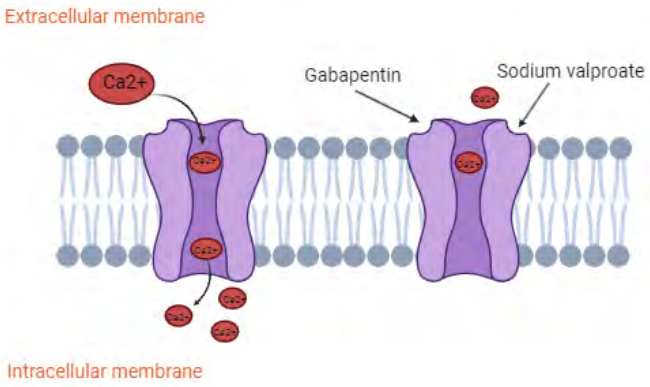

Figure 3: Decreased current through T-type calcium channel by AEDs (Ochoa, 2022).

3.3 Commonly Used AEDs:

Phenobarbital:

One of the commonly used and conventional form of drugs as first line treatment is phenobarbital (Balagura et al., 2019), which although primarily used as a sedative, later it came into use widely as an antiseizure medication. It shows its efficacy against focal seizures and generalized tonic-clonic seizures. Whereas, it is ineffective against absence seizures. The main side effects of phenobarbital include drowsiness, impaired focus, and mood swings, especially depression. It may result in hyperactivity in children. There is a link between prolonged use and reduction of bone density, frozen shoulder, plantar fibromatosis, Dupuytren contractures, and plantar fibromatosis. However, due to teratogenicity and the elevated risk of heart abnormalities in the exposed fetus, phenobarbital is contraindicated in pregnancy. Although it is widely available as well as cost effective, it is, nowadays, not the first line treatment due to its various adverse effects (Abou-Khalil, 2019). An increase in dose might also lead to adverse effects. Methylphenobarbital and primidone are the structurally modified version of already existing phenobarbital in order to increase its pharmacological efficacy (Perucca, 2021).

Ganaxolone:

Ganaxolone is an antiepileptic drug which falls under the class neuroactive steroids known as epalons (Lattanzi, Riva, et al., 2021). It is a broad-spectrum AED and is used to treat clonic seizures (Monaghan et al., 1999) and infantile spasms and mainly it's effective in partial-onset of seizures (Chávez-González et al., 2021). These neurosteroids interacts with the $GABA_A$ receptors and exert its antiseizure activity. GNX had more antiepileptogenic action, a more favorable therapeutic index, and was more successful in suppressing tonic-clonic seizures in mice that were induced with pentylenetetrazol. There is currently no evidence of end-organ toxicity from preclinical safety pharmacology at dosages appropriate for long-term human

administration or human clinical trials, nor have investigations indicated that GNX induces carcinogenicity or cellular modifications. Increased Ganaxolone clearance has been seen by CYP inducers like phenytoin, and phenobarbital, carbamazepine; however, there was no discernible difference in the reaction of individuals taking these medicines against those who were not (Lattanzi, Riva, et al., 2021). The adverse effects even if exists maybe related to the CNS which is somnolence probably due to increased doses or it might be due to organ toxicity associated with single or multiple-dose therapy with GNX (Monaghan et al., 1999). Other side effects include fatigue and dizziness (Chávez-González et al., 2021). Physicians stated that many patients showed remarkably better behavior in every pediatric study, including enhanced interactions with others and consciousness. Patients with both West Syndromes or infantile spasms and complex partial seizures have shown that ganaxolone has an antiseizure effect and is well-tolerated and safe in both children and adults (Monaghan et al., 1999).

Cannabidiol:

Cannabidiol is one of the newly recognized plant-derived antiepileptic drugs by the Food and Drug Administration (FDA) and also approved by European Medicines Agency (EMA) (Sharifi-Rad et al., 2021). It has been in use for treating focal seizures with tuberous sclerosis complex (Perucca, 2021) and has undergone class I trial for Dravet syndrome and Lennox-Gastaut syndrome in children greater than or equal 2 years of age. It has the evidence of increasing the enzyme activity when used as an adjunct therapy with valproate or its association with clobazam (Abou-Khalil, 2019). Cannabidiol (CBD) has several mechanisms of action besides exerting its GABAergic effects (Perucca, 2021) for inhibiting neuronal excitability(He et al., 2021). It also has adverse effects such as sedation, diarrhea, anorexia, sleep and behavioral disturbances, and fatigue. It shows drug-drug interaction by inhibiting the metabolism of the active metabolites of clobazam (CLB), norclobazam (Perucca, 2021). Pharmaceutical-grade pure CBD showed positive effects in several children with extremely

refractory seizures as well as refractory status epilepticus (Lattanzi, Trinka, et al., 2021). Research has also been carried out on the efficacy of cannabidiol therapy for individuals suffering from different genetic epileptic encephalopathies and CDKL5 gene mutations and results showed that it significantly reduced the seizure recurrence (Encephalopathy et al., 2020). Cannabidiol, which is regarded as the only natural antiseizure medication, substantially reduced the rate of the rare and chronic seizure state and its fatality when it came to the effect of CBD on PTZ-induced seizures (Sharifi-Rad et al., 2021).

Phenytoin:

Phenytoin is the first line treatment of choice for tonic-clonic seizures and second line treatment of choice for focal seizures (Balagura et al., 2019). Its main mode of action is to prevent the fast inactivation state of voltage-gated sodium channels in the membranes of neuronal cells by selectively suppressing aberrant epileptic seizures. It's an enzyme inducer and minor teratogen (Brodie, 2017). This AED maybe potentially worsening for absence seizures, myoclonic seizures and tonic-clonic seizures (Balagura et al., 2019). Although phenytoin sodium has a remarkable therapeutic efficacy, side effects including anemia after birth and transient cerebellar paralysis may result after therapy. Prolonged use of phenytoin sodium can result in hyperplasia of the gingival area, malfunction in the nervous system, and abnormalities with the hematological system in addition to gastrointestinal distress when used as individual therapy (He et al., 2021). In addition to extreme idiosyncratic reactions to skin including Steven-Johnson syndrome and harmful epidermal necrolysis, phenytoin can cause morbilliform skin rashes. Genetic indicators are becoming more and more linked to these potentially fatal issues. Discontinuation of Phenytoin may result in neurotoxicity. Lamotrigine and oxcarbazepine can be associated with phenytoin as an adjunct therapy where the dose of the rapid sodium channel inhibitor need to be minimized for better tolerability (Brodie, 2017). Phenytoin in combination

with Naringin provides a better antiepileptic effect (He et al., 2021). It is to be mentioned that phenytoin is less sedative compared to phenobarbital (Abou-Khalil, 2019).

Carbamazepine:

Carbamazepine, a voltage gated sodium channel blocker (Balagura et al., 2019) that inhibits its fast inactivation state (Brodie, 2017) is effective against generalized tonic-clonic seizures as first line treatment and focal seizures as second line treatment (Balagura et al., 2019). It might exacerbate myoclonic seizures, atonic seizures, and absence seizures and so, contraindicated for idiopathic generalized epileptic seizures (Abou-Khalil, 2019). Carbamazepine is a minor teratogen and a broad-spectrum enzyme inducer. Because carbamazepine causes metabolism in the liver on its own (Brodie, 2017), also known as autoinduction causing reduction of the efficacy of the CYP450 enzyme metabolized drugs (Abou-Khalil, 2019), different people will have significantly varied circulating concentrations of the same dosage. Therefore, in certain circumstances, therapeutic drug monitoring of carbamazepine may be beneficial (Brodie, 2017). Carbamazepine should be discouraged in cases of Dravet syndrome linked to SCN1A mutations (Balagura et al., 2019). The tendency to cause dose-dependent hyponatremia is shared by carbamazepine, oxcarbazepine, and eslicarbazepine acetate. This can be especially problematic for older individuals and those using diuretics. Aggression, confusion, and agitation are the probable side effects associated with carbamazepine (Chávez-González et al., 2021). Besides, treatment with carbamazepine may also result in adverse effects such as diplopia, rashes, neurotoxicity, dermatomyositis, impairments related to the blood and respiratory systems, and so on. When carbamazepine is used alone, side effects include nausea, vomiting, dizziness, and ataxia, along with granulocytopenia and aplastic anemia may take place. When coupled with carbamazepine, gastrodin can enhance the overall therapeutic benefits and the improvement of abnormalities in electroencephalogram in patients with epilepsy who are receiving considerable clinical efficacious therapy (He et al., 2021). The use

of carbamazepine during polytherapy has been linked to a higher incidence of spina bifida in children exposed during pregnancy (Abou-Khalil, 2019).

Lamotrigine:

Lamotrigine (LTG) is a first-line treatment of choice for generalized seizures and focal seizures (Ghosh et al., 2021) and second-line treatment of choice for absence seizures and focal seizures. Based on individual study reports, co-administration of LTG is associated with an increased incidence of Steven-Johson syndrome in pediatric patients, particularly during the initial eight weeks of LTG treatment (Balagura et al., 2019). It's a minor teratogen and an enzyme inducer. Lamotrigine is also effective for infantile spasms (Monaghan et al., 1999), Lennox-Gastaut syndrome and juvenile myoclonic seizures in young female patients although it might sometimes worsen the seizure. Additionally, lamotrigine increases K+ repolarizing currents and blocks P-type and N-type high-voltage generated calcium currents. Lamotrigine and sodium valproate together can treat generalized and partial-onset seizures and is the only available AEDs giving its synergistic effect (Brodie, 2017). Besides, combining lamotrigine and topiramate can manage a variety of seizures (Ghosh et al., 2021). In a randomized study, lamotrigine monotherapy was shown to be less effective than ethosuximide plus sodium valproate for children with recently confirmed absence seizures. It's one of the newer antiepileptic drugs having a broader range of efficacy since it has multiple mechanisms of action. Furthermore, it is approved to treat bipolar illness, which may make it an especially good option for individuals with mental concurrent conditions. Its adverse effects include insomnia which is observed particularly with lamotrigine (Brodie, 2017), allergic reactions and might induce myoclonic seizures (Chávez-González et al., 2021). Besides, adverse effects associated with dosage include vertigo, blurred vision, instability, diplopia, headache, convulsion, nausea, and vomiting. Compared to conventional AEDs, lamotrigine is less sedative and has fewer detrimental effects on cognition (Abou-Khalil, 2019). Lamotrigine has

a disadvantage in that it must be gradually titrated to reduce the possibility of severe skin rashes. As a result, individuals with severe recurrent seizures who need an immediate start of antiseizure action may not be the best candidates for lamotrigine. An increase in dose might also increase the risk of adverse effects (Brodie, 2017). Valproate reduces lamotrigine clearance, but pregnancy, estrogen, and enzyme inducers enhance it (Abou-Khalil, 2019).

Lacosamide and Eslicarbazepine Acetate:

Lacosamide and eslicarbazepine acetate are newer AEDs that has proved its tolerability and efficacy in the clinical trials more than that of the conventional AEDs (Abou-Khalil, 2019). Lacosamide is a functionalizing amino acid which enhances the depolarization of sodium channels. It exhibits CNS related side effects besides nausea and diplopia and is hypothetically believed to provide neuroprotection (Chávez-González et al., 2021). It seems that lacosamide is a narrow-spectrum antiepileptic drug that prevents focal seizures (Abou-Khalil, 2019) and tonic-clonic seizures (Brodie, 2017). However, it does not affect myoclonic or absence seizures. At larger dosages, the most frequent side effects are drowsiness, exhaustion, headaches, nausea, vomiting, diplopia, and dizziness. Additionally, there is a higher chance of these side effects when lacosamide is associated with different sodium channel inhibitors. When combined with a drug that is of the non-sodium channel, lacosamide administered as adjunct therapy may be more effective and more tolerable. On the other hand, eslicarbazepine acetate is a third-generation AED belonging to the family of carbamazepine and oxcarbazepine that prevents focal seizures having the potential to be used as a first-line monotherapy. The lack of a CSF spike after eslicarbazepine acetate is thought to be the cause of acute side effects related to dosage that include somnolence, ataxia and other effects similar to lacosamide (Abou-Khalil, 2019). Discontinuation of the drug within a few weeks might result in elevated concentration of all the drugs that are induced (Brodie, 2017). The history of teratogenicity is unknown with Lacosamide and eslicarbazepine acetate. Although they are pharmacologically

effective in slowly inactivating the sodium channel. Lacosamide and eslicarbazepine acetate is clinically approved for both adjunctive and monotherapy (Abou-Khalil, 2019). Lacosamide is not an enzyme inducer whereas, eslicarbazepine acetate is an enzyme inducer. When used in daily clinical settings, lacosamide has minimal possible side effects and can be tolerable at large dosages. Lacosamide and eslicarbazepine acetate are less likely to cause fatal idiosyncratic reactions than the conventional AEDs (Brodie, 2017).

Oxcarbazepine:

A well-researched and efficacious first-line AED for children with untreated or recently diagnosed focal seizures is oxcarbazepine (OXC). On the other hand, it's the second-line treatment of choice for tonic-clonic seizures and may exacerbate in case of absence seizures. But since there isn't often an OXC pediatric formulation available, carbamazepine (CBZ) is still the most commonly used AED for this kind of seizure in clinical practice including valproic acid and phenobarbital (Balagura et al., 2019). Oxcarbazepine was developed through in-patient presurgical studies with failure in treatment as the major end point (Monaghan et al., 1999). This sodium channel blocker is a narrow spectrum enzyme inducer and a minor teratogen and have a tendency to cause idiosyncratic skin responses such as Steven-Johnson syndrome (SJS) and toxic epidermal necrolysis besides morbilliform rashes in skin. Both oxcarbazepine and monohydroxy carbamazepine, its active metabolite, inhibit the sodium channel's rapid inactivation state. It may worsen the myoclonic and absence seizures. Patients using diuretics and the elderly are more susceptible to dose-dependent hyponatremia, which is a common side effect of oxcarbazepine. Discontinuation of the drug within a few weeks might result in elevated concentration of all the drugs that are induced. Compared to immediate-release carbamazepine (Abou-Khalil, 2019), oxcarbazepine has a more anticipated dose-response relationship and is typically well tolerated as an AED. It has greater efficacy in the reduction of sodium levels in serum even at higher doses (Brodie, 2017). Oxcarbazepine may

cause to feel fatigued, drowsy, or have a headache. Increased dosages may result in ataxia, nausea, vomiting, diplopia, dizziness, and impaired vision (Abou-Khalil, 2019).

Gabapentin:

Gabapentin is a narrow-spectrum AED used as an adjunct for the treatment of focal seizures (Abou-Khalil, 2019) and generalized seizures (Ghosh et al., 2021). It is an FDA approved drug used to treat postherpetic neuralgia. Fatigue, ataxia, somnolence, dizziness, and weight gain are among the side effects. It can result in myoclonus. It may lead to children's emotional instability and cognitive slowdown in the elderly. The likelihood of peripheral edema increases with age. Despite being authorized for primary monotherapy in Europe, an extensive randomized comparison study revealed that it was not as effective as lamotrigine (Abou-Khalil, 2019). Gabapentin was developed through in-patient presurgical studies with failure in treatment as the major end point (Monaghan et al., 1999). The risk of psychoses related to gabapentin is very scarce (Górska et al., 2019) although it exacerbates myoclonic seizures (Balagura et al., 2019).

Sodium Valproate:

Sodium valproate is a first-line drug of choice for absence, myoclonic and tonic-lonic seizures and second-line for focal seizures (Balagura et al., 2019). There is mounting evidence that valproic acid use during pregnancy carries a high risk of dose-dependent teratogenic consequences and poor cognitive development in the infant after birth (Balagura et al., 2019) and so, it’s contraindicated for pregnancy and also those with childbearing potential (Perucca, 2021). Due to its broad-spectrum mechanism of action (Balagura et al., 2019) which include inhibition of voltage-gated sodium channels, reducing the impact of excitatory amino acids, increasing the transmission of gamma-aminobutyric acid (GABA), and controlling serotoninergic and dopaminergic transmission, it’s not an ideal treatment of choice nowadays. A frequent and typically temporary side effect of treatment is hair changes at least three months

into the therapy, which can range from minor shedding or permanent baldness to a change in hair color to grey and curling. Hepatotoxicity, tremor, nausea, vomiting, and tiredness can all result with valproate alone (He et al., 2021). Anorexia, stomach irritation, diarrhea, confusion, weight gain, and peripheral edema are some more side effects (Abou-Khalil, 2019). Increase in dose might result in increased risk of toxicity (Perucca, 2021) such as thrombocytopenia (Abou-Khalil, 2019). Besides, women might show side effects related to endocrine glands such as PCOS, insulin resistance, hyperinsulinemia and so on. Moreover, chronic adverse effects such as gait disorder, dementia, brain atrophy and reversible Parkinson disease might take place in elderly. In case of polytherapy with topiramate, hyperammonemia and encephalopathy may occur (Abou-Khalil, 2019). Evidence that lamotrigine and sodium valproate together can treat generalized and partial-onset seizures (Ghosh et al., 2021) by inhibition of its glucuronidation (Brodie, 2017) has been validated by several animal models. Valproate and ethosuximide are two recommended drugs as an adjunct therapy for managing absence seizures (Ghosh et al., 2021) and is more effective than lamotrigine monotherapy (Brodie, 2017). Stiripentol with valproate are used to treat tonic-clonic seizures (Chávez-González et al., 2021). Valproic acid has little efficacy to treat infantile-spasms (Monaghan et al., 1999). Sodium valproate, however, decreases frequency of seizures (Brodie, 2017). Valproate might increase the levels of carbamazepine epoxide when used concomitantly. It is a potent inhibitor that reduces the removal of carbamazepine epoxide, rufinamide, lamotrigine, and phenobarbital and so should begin with low dose for better tolerance (Abou-Khalil, 2019).

Rufinamide:

Rufinamide is one of the inhibitors of sodium channel by inhibiting its fast inactivation state, (Chávez-González et al., 2021) although it has several modes of action making it a wide-spectrum antiepileptic drug. It went through class I trials (Abou-Khalil, 2019) for Lennox-Gastaut Syndrome for children of age 4 years and above (Brodie, 2017) and approved as

adjunct therapy by the FDA. The clearance of rufinamide is decreased by valproate resulting in the increase of its level by 70%. Its side effects include headache, exhaustion, somnolence, dizziness, and vomiting may take place in children. The QT interval may get shorter if rufinamide is used (Abou-Khalil, 2019). Rufinamide is ineffective for focal seizures in patients receiving carbamazepine or lamotrigine already but is slightly effective as adjunct therapy for focal seizures. There are no reports of teratogenicity associated with rufinamide so far. In addition to having similar adverse effects to other sodium channel blockers, rufinamide has also been linked to infrequent hypersensitivity events such Stevens-Johnson syndrome (SJS) and DRESS. All sodium channel blockers are equally effective in treating focal and generalized tonic-clonic seizures except rufinamide (Brodie, 2017).

Vigabatrin:

Vigabatrin is a second-generation AED whose mechanism of action is the selective inhibition of GABA transaminase irreversibly, which ultimately raises the level of GABA in the CNS (Golec et al., 2021) as the inhibition prevents the breakdown of GABA in astrocytes and GABA neurons. It effectively treats focal seizures and infantile spasms, a chronic epileptic encephalopathy that further leads to different types of epilepsy such as Lennox-Gastaut Syndrome, and specifically in patients with tuberous sclerosis complex (TSC), a type of genetic disorder (Golec et al., 2021) and hypsarrhythmia on EEG (Biswas et al., 2020). The European Medicines Agency (EMA) restricted the utilization of vigabatrin (VGB) to monotherapy for infantile spasms (IS) and adjunctive treatment for children and adults with refractory focal epilepsy. In TSC, VGB may possess antiseizure, antiepileptogenic, or disease-modifying properties due to having multiple mechanisms of action by partial blocking of the mTOR pathway. For children with IS, adjunct therapy of VGB and ACTH is far more efficient and rapid in producing clinical improvements. The dose dependent adverse effects are irritation, restlessness, somnolence (Golec et al., 2021), insomnia and weight gain (Chávez-González et

al., 2021). Besides, there are major side effects including retinopathy (Golec et al., 2021), which is basically a VGB- associated visual abnormalities and includes visual field defect and retinal toxicity; and VGB- associated MRI abnormalities (Biswas et al., 2020). At present, vigabatrin is the only available antiepileptic drug to effectively prevent epileptic seizures (Golec et al., 2021).

There are different types of AEDs for the treatment of epileptic seizures which are shown in Table 2.

Table 2: Different types of AEDs to treat epileptic seizures

AEDs	**Mechanism of action**	**Targets**	**Adverse effects**
Phenobarbital	Enhancement of GABA action	Focal and generalized tonic-clonic seizures	Drowsiness, impaired focus, mood swings, depression
Ganaxolone	Binds to $GABA_A$ receptors	Generalized tonic-clonic seizures and infantile spasms	CNS related side effect such as, somnolence, fatigue and dizziness
Cannabidiol	Enhancement of GABA action	Focal seizure, Dravet syndrome and Lennox-Gastaut syndrome	Sedation, diarrhea, anorexia, fatigue, sleep and behavioral disturbances
Vigabatrin	Inhibition of GABA transaminase	Focal seizures, infantile spasms, and tuberous sclerosis complex	Irritation, restlessness and somnolence, insomnia, weight gain, VGB-associated MRI abnormalities and visual field defects
Phenytoin	Inhibition of sodium channel	Focal and generalized tonic-clonic seizures	Anemia, gingival hyperplasia, cerebellar paralysis

Carbamazepine	Inhibition of sodium channel	Focal and generalized tonic-clonic seizures	Aggression, confusion, agitation, diplopia, rashes, neurotoxicity, dermatomyositis
Lamotrigine	Inhibition of sodium channel	Focal, generalized tonic-clonic, and absence seizures	Vertigo, blurred vision, instability, diplopia, headache, convulsion, nausea, and vomiting, insomnia, skin rashes
Oxcarbazepine	Inhibition of sodium channel	Focal and tonic-clonic seizures	Fatigue, drowsy, headache, ataxia, nausea, vomiting, diplopia, dizziness, impaired vision, skin rash, Steven-Johnson syndrome
Rufinamide	Prolongs inhibition of sodium channel	Less effective for treating focal seizures	Headache, exhaustion, dizziness, somnolence, vomiting, DRESS and Steven-Johnson syndrome
Lacosamide & Eslicarbazepine Acetate	Inhibition of sodium channel	Focal seizures	Drowsiness, exhaustion, headaches, nausea, vomiting, diplopia, and dizziness, somnolence, ataxia
Sodium Valproate	Inhibition of calcium channel	Absence, myoclonic, tonic-clonic and focal seizures	Hair greying, permanent baldness, hepatotoxicity, tremor, nausea, vomiting, anorexia, tiredness, stomach irritation, diarrhea, confusion, weight gain and peripheral edema
Gabapentin	Inhibition of calcium channel	Focal and generalized seizures	Fatigue, ataxia, somnolence, dizziness, weight gain and myoclonus

Chapter 4

Conclusion

To conclude, there are several AEDs with unique benefits and drawbacks that can be used to treat epilepsy. Certain AEDs are also effective in treating comorbid conditions including bipolar disorder and migraines. The therapeutic efficacy of the AED and patient-specific parameters are considered while choosing an antiepileptic drug. There are few drugs that work great as monotherapy and few drugs require adjunct therapy for utmost efficacy (Abou-Khalil, 2019). Second-generation ASMs have not significantly decreased the strains of pharmacoresistance, although improvements in epilepsy therapy persist. Advances in ASMs can be attributed to better knowledge of their safety and efficacy profile, as well as the introduction to new AEDs (Perucca, 2021).The FDA approved new antiepileptic drugs to control seizure effectively. Some of them are lacosamide, lamotrigine, eslicarbazepine, vigabatrin and so on. (Abou-Khalil, 2019). Besides, there have also been natural plant derived AEDs such as cannabidiol, which belongs to the terpenoid family. CBD's clearance marks a significant milestone in the medicinal application of cannabis for seizure disorders. The oral solution of pharmaceutical-grade cannabidiol is the first product derived from the cannabis plant to be approved by regulatory bodies. It is also the first in a new category of antiseizure drugs (Lattanzi, Trinka, et al., 2021). Moreover, the sodium channel blockers are equally efficacious to treat generalized tonic-clonic seizures, focal seizures and refractory epilepsy. In clinical practice, there is a probability that the lacosamide and eslicarbazepine acetate may be more well-tolerated than phenytoin, carbamazepine, and oxcarbazepine at large dosages (Brodie, 2017). Considering the discoveries of AEDs over the years through first, second, third generations and so on, cannabidiol might be a great choice of naturally derived drug. Besides, the newer antiepileptic drugs such as ganaxolone, vigabatrin and lamotrigine may also be ideal as it has no major adverse effects. These AEDs are undergoing extensive research as it has a

great potential in controlling epileptic seizures to some extent and thus reducing the risk of seizure induced death in children and in adults in the near future.

References

Abou-Khalil, B. W. (2019). Update on Antiepileptic Drugs 2019. *CONTINUUM Lifelong Learning in Neurology*, *25*(2), 508–536. https://doi.org/10.1212/CON.0000000000000715

Balagura, G., Iapadre, G., Verrotti, A., & Striano, P. (2019). Moving beyond sodium valproate: choosing the right anti-epileptic drug in children. *Expert Opinion on Pharmacotherapy*, *20*(12), 1449–1456. https://doi.org/10.1080/14656566.2019.1617850

Beghi, E. (2020). The Epidemiology of Epilepsy. *Neuroepidemiology*, *54*(2), 185–191. https://doi.org/10.1159/000503831

Biswas, A., Yossofzai, O., Vincent, A., Go, C., & Widjaja, E. (2020). Vigabatrin-related adverse events for the treatment of epileptic spasms: systematic review and meta-analysis. *Expert Review of Neurotherapeutics*, *20*(12), 1315–1324. https://doi.org/10.1080/14737175.2020.1840356

Braga, P., Hosny, H., Kakooza-mwesige, A., Rider, F., Tripathi, M., & Guekht, A. (2020). *Seminar in Epileptology How to understand and address the cultural aspects and consequences of diagnosis of epilepsy, including stigma*. *22*(5), 531–547.

Brodie, M. J. (2017). Sodium Channel Blockers in the Treatment of Epilepsy. *CNS Drugs*, *31*(7), 527–534. https://doi.org/10.1007/s40263-017-0441-0

Chávez-González, E., Nodarse-Concepción, A., Donoiu, I., Rodríguez-González, F., Puerta, R., & Elizundia, J. (2021). Increased QRS duration and dispersion are associated with mechanical dyssynchrony in patients with permanent right ventricular apical pacing. *Discoveries*, *9*(2), e128. https://doi.org/10.15190/d.2020.7

Encephalopathy, E., Jakimiec, M., & Paprocka, J. (2020). *brain sciences CDKL5 Deficiency Disorder — A Complex*. 1–9.

Falco-Walter, J. J., Scheffer, I. E., & Fisher, R. S. (2018). The new definition and classification of seizures and epilepsy. *Epilepsy Research*, *139*, 73–79. https://doi.org/10.1016/j.eplepsyres.2017.11.015

Ghosh, S., Sinha, J. K., Khan, T., Devaraju, K. S., Singh, P., Vaibhav, K., & Gaur, P. (2021). Pharmacological and therapeutic approaches in the treatment of epilepsy. *Biomedicines*, *9*(5), 1–14. https://doi.org/10.3390/biomedicines9050470

Golec, W., Sołowiej, E., Strzelecka, J., Jurkiewicz, E., & Jóźwiak, S. (2021). Vigabatrin — new data on indications and safety in paediatric epilepsy. *Neurologia i Neurochirurgia Polska*, *55*(5), 429–439. https://doi.org/10.5603/PJNNS.a2021.0063

Górska, N., Słupski, J., & Cubała, W. J. (2019). Antipsychotic drugs in epilepsy. *Neurologia i Neurochirurgia Polska*, *53*(6), 408–412. https://doi.org/10.5603/PJNNS.A2019.0052

He, L. Y., Hu, M. B., Li, R. L., Zhao, R., Fan, L. H., He, L., Lu, F., Ye, X., Huang, Y. L., & Wu, C. J. (2021). Natural Medicines for the Treatment of Epilepsy: Bioactive Components, Pharmacology and Mechanism. *Frontiers in Pharmacology*, *12*(March), 1–28. https://doi.org/10.3389/fphar.2021.604040

Lattanzi, S., Riva, A., & Striano, P. (2021). Ganaxolone treatment for epilepsy patients: from pharmacology to place in therapy. *Expert Review of Neurotherapeutics*, *21*(11), 1317–1332. https://doi.org/10.1080/14737175.2021.1904895

Lattanzi, S., Trinka, E., Striano, P., Rocchi, C., Salvemini, S., Silvestrini, M., & Brigo, F. (2021). Highly Purified Cannabidiol for Epilepsy Treatment: A Systematic Review of

Epileptic Conditions Beyond Dravet Syndrome and Lennox–Gastaut Syndrome. *CNS Drugs*, *35*(3), 265–281. https://doi.org/10.1007/s40263-021-00807-y

Monaghan, E. P., McAuley, J. W., & Data, J. L. (1999). Ganaxolone: A novel positive allosteric modulator of the GABA(A) receptor complex for the treatment of epilepsy. *Expert Opinion on Investigational Drugs*, *8*(10), 1663–1671. https://doi.org/10.1517/13543784.8.10.1663

Ostendorf, A. P., & Gedela, S. (2017). Effect of Epilepsy on Families, Communities, and Society. *Seminars in Pediatric Neurology*, *24*(4), 340–347. https://doi.org/10.1016/j.spen.2017.10.007

Perucca, E. (2021). The pharmacological treatment of epilepsy: recent advances and future perspectives. *Acta Epileptologica*, *3*(1). https://doi.org/10.1186/s42494-021-00055-z

Sharifi-Rad, J., Quispe, C., Herrera-Bravo, J., Martorell, M., Sharopov, F., Tumer, T. B., Kurt, B., Lankatillake, C., Docea, A. O., Moreira, A. C., Dias, D. A., Mahomoodally, M. F., Lobine, D., Cruz-Martins, N., Kumar, M., & Calina, D. (2021). A Pharmacological Perspective on Plant-derived Bioactive Molecules for Epilepsy. *Neurochemical Research*, *46*(9), 2205–2225. https://doi.org/10.1007/s11064-021-03376-0

Ochoa, J. G. (2022, February 18). *Antiepileptic Drugs*. Medscape. https://emedicine.medscape.com/article/1187334-overview#a2