Project on

Review on Clinical development of drugs for epilepsy

[In the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy]

Submitted To

The Department of Pharmacy,

Faculty of Allied Health Sciences,

Daffodil International University

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APPROVAL

This project paper, **"Review on Clinical development of drugs for epilepsy",** submitted to the Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, has been accepted as satisfactory for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy and approved as to its style and contents.

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DECLARATION

I hereby declare that this project report, **"Review on Clinical development of drugs for epilepsy".** I am declaring that this Project is my original work. I also declare that neither this project nor any part thereof has been submitted elsewhere for the award of Bachelor or any degree.

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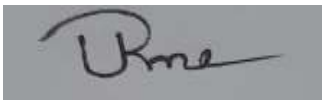

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I might want to communicate my profound applause to the All-powerful Allah who has given me the capacity to finish my undertaking work and the chance to concentrate in this subject.

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Dedication……

My Parents

The persons who always encourage me in every sphere of my life.

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Abstract

Epilepsy is still unmanageable in about a third of patients despite the licensed antiepileptic medications (AEDs) having increased exponentially over the previous 25 years. Antiepileptic medications that are now on the market have a limited efficacy, which restricts their use and makes patient treatment challenging. Antiepileptic medications can only treat symptoms since they reduce seizures but cannot reverse epileptogenesis. Antiepileptic medications shouldn't be taken for an extended period of time because to their negative side effects, withdrawal effects, harmful drug combinations, and financial load, especially in developing nations. Additionally, some antiepileptic medications may even intensify some types of seizures. The most recent significant relatively wide AEDs that are helpful for people who experience both various types of seizures and mostly widespread seizures include **lamotrigine, topiramate, and zonisamide**. In 2008, the FDA granted **rufinamide** approval for the adjunctive treatment of Lennox Gastaut syndrome-related seizures in patients 4 years of age and older. In 2009, the European Union certified **eslicarbazepine** acetate as an adjuvant treatment for partial seizures in adults. It has a similar potency to **carbamazepine and oxcarbazepine** in inhibiting the release of neurotransmitters that are dependent on sodium channels. **Ezogabine** is the first AED to targeted and activate the voltage-gated potassium channel (also known as **retigabine** in Europe) (Kv7). The first glutamate receptor blocker to receive approval was **Perampanel**, which was first made available in Europe in July 2012. The FDA granted vigabatrin approval in 2009 for the treatment of juvenile contractions in children. In Australia, **clobazam** was initially authorized in 1970; it had been used for many years in Europe. Lennox Gastaut syndrome supplemental therapies in patients 2 years of age and older was given FDA approval in 2011.

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Introduction

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1. Introduction

The mechanism by which a neural network where random seizures occur forms is known as epileptogenesis. A brain condition known as epilepsy is defined by a persistent propensity to induce epileptic seizures. Epilepsy affects people of all ages, from infants to the old. It has a broad variety of causes and manifestations, as well as many distinct seizure types, many distinguishable illnesses, and a lot of poorly classified epilepsies. [1] Several of the comorbidities that make assessment and patient management challenging include learning disabilities, permanent cerebral deficits, progressive disorders, psychological and mental issues, and combined health problems, particularly in the older age group. Seizures from epilepsy and the classification of disorders are continuously evolving. The recently suggested categorization is based on five axes that consider various seizure types, the beginning of focal or generalized seizures, the illness, the reason, and any associated deficits. In this setting, people who are 16 years of age or higher are considered adults. [2] The National Institute for Health and Clinical Excellence (NICE) of the UK published extensive, scientific recommendations for managing the medical results for epilepsy patients in October 2004. (panel). [3] Further recommendations come from the American Academy of Neurology and the Scottish Multidisciplinary Guidelines Network. Because of stigma and prejudice, epilepsy is different from other neurological conditions. Over the past ten years, epilepsy research has made major strides, as has public awareness. There therefore exists much work to be done, especially for those who do not respond to medicine. The fact that the majority of epileptics live in underdeveloped countries with insufficient epilepsy therapies is a serious problem that needs to be addressed right away. [4] There is a sizable diagnostic gap in many parts of the world due to a lack of healthcare facilities and trained employees. The WHO-led Global Campaign for Epilepsy, which seeks to address these issues, is strongly supported by the International League opposing Epilepsy and the International Bureau for Epilepsy, the two primary international non-governmental organizations in the discipline of epilepsy. [5]

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1.1 Epidemiology

Epilepsy occurs in wealthy countries at a rate of about 50 cases per 100,000 people, with infants and the elderly being more vulnerable. A higher incidence is observed in those who are less wealthy for unknown reasons. Poor sanitation, inadequate health care delivery systems, an increased likelihood of parasites and brain diseases, and the fact that the majority of epilepsy sufferers in commodity nations usually do not receive therapy could all add to a higher frequency. [6] Usually, more than 100 per 100,000 people annually. In industrialized nations, the incidence of childhood has decreased over the past three decades, which may be linked to expectant mothers pursuing healthier lifestyles, receiving improved prenatal care, and participating in immunization programs. The concomitant increase in incidence in the elderly may be due to higher survival rates for people with cerebrovascular disease and brain degeneration. Every year, 4 to 10 individuals out of every 1000 suffer from epilepsy. Few (usually small) studies from isolated geographic areas with unique genetic or environmental factors have found higher rates. [7] Lifetime rates of epilepsy are considerably higher than present incidence rates of epilepsy, even in resource-poor countries where the vast majority of the population has limited access to antiepileptic drugs. The majority of those who develop the disease eventually stop having seizures, but higher epilepsy mortality rates also play a role in this imbalance. Risk factors vary based on age and location. Epilepsy can be brought on by tumors, CNS infections, and head trauma in people of any age. Cerebral vascular dysfunction is the much more common risk category in people over 60. In terms of preventable causes of epilepsy, neurocysticercosis and other endemic parasitic diseases like falciparum malaria are among the most frequently met. Recently, onchocerciasis and toxocariasis have been cited as important risk factors. [8] The risk of developing epilepsy may be partially affected by genetics. Because of the complex interactions between genetic and environmental variables, we may not fully understand the dynamics of the disease's population. Additionally, some epilepsy conditions evolve over time. Lennox and infantile spasms are two instances of this development. Infants with Gastaut illness, an especially severe type of epilepsy, are said to have intermittent convulsions and later develop medial temporal lobe epilepsy. While the processes for growth have not yet been completely understood from an epidemiological or biological viewpoint, genetic factors are likely to play a role. In wealthy countries, more

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than 60% of patients achieve long-term remission within five years of diagnosis; the probability of recovery decreases the longer epilepsy is operative. A successful outcome is demonstrated by early onset, fewer early seizures, and an early reaction to medication therapy. [9] The widespread use of antiepileptic drugs in wealthy countries is occasionally cited as the cause of the usually beneficial result. Additionally, many patients in wealthy countries without recourse to these treatments achieve long-term remission, lending credence to the idea that the underlying cause of the epilepsy, rather than the therapeutic regimen, determines the result. A third of people who have convulsions develop chronic epilepsy. 26 Though many more could benefit from the best care, it's conceivable that up to 20% of people with intractable epilepsy who are referred to clinics had their diagnoses incorrect. Additionally, people with persistent seizures are more likely to have concurrent diseases like cardiovascular and cerebrovascular disorders, gastro intestinal issues, injuries, pneumonia, chronic lung problems, and diabetes. [10]

1.2 Pathophysiology

An epileptic seizure, which is a brief occurrence of signs, sensations, or both, is caused by unusually intense or synchronized neuronal activity in the brain. The interracial spike, which is distinct from a seizure and lasts for less than 70 MS, is brought about by a short burst of synchronized activity among a number of neurons. In fact, where interracial spiking occurs can vary from where seizures start. An early hypothesis that stated seizures were brought on by a disruption of the brain's normal balance of exhilaration and repression is now thought to be overly simplistic. [11] The brain requires coordination between different networks, which is probably controlled by fluctuations within specific networks. Inhibitory neurons, synaptic transmission, and intrinsic neuronal properties, such as a neuron's capacity for burst firing, all play a role in the oscillations that cortical networks generate. Epileptic activity may manifest in such rhythmic networks as an emergent property. The shift from normal to epileptiform behavior is likely brought on by enhanced diffusion and neuronal affinity as a consequence of a combination of bigger connection, increased excitatory propagation, a breakdown of regulatory systems, and changes in intrinsic neuronal properties. Studies on human’s reveal that the electroencephalogram (EEG) in important cortical regions becomes less erratic during a seizure, referring to wide synchronization. [12] centered pathological changes, such as tumors, or occasionally a

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genetic condition, such as autosomal dominant frontal lobe epilepsy, can result in focused operational disruption in focal epilepsies, which causes seizures to begin locally and then propagated by attracting more brain regions. [13] The focus site, the spread's speed, and the spread's magnitude all affect how the seizure manifests clinically. Widespread lowering of the seizure threshold results in generalized seizures in widespread epilepsies, which are usually genetically determined. Exclusion seizures are a particular kind of generalized seizure brought on by thalamocortical circuits. It was once believed that thalamic neurons prompting neocortical neuron migration created suspensions subcortically. [14] In absence of seizures in rats, the somatosensory cortex, not the thalamus, suggests to be the cause of paroxysmal oscillations within thalamocortical loops, with synchronization being made easier by quick intracortical propagation of seizure activity. [15] Due to observations of minor cortical pathological changes in some absent seizure patients and the potential for focal pathological alterations in the medial frontal lobe to produce abrogation seizures, the distinction between focal and widespread epilepsies has become more blurred. [15]

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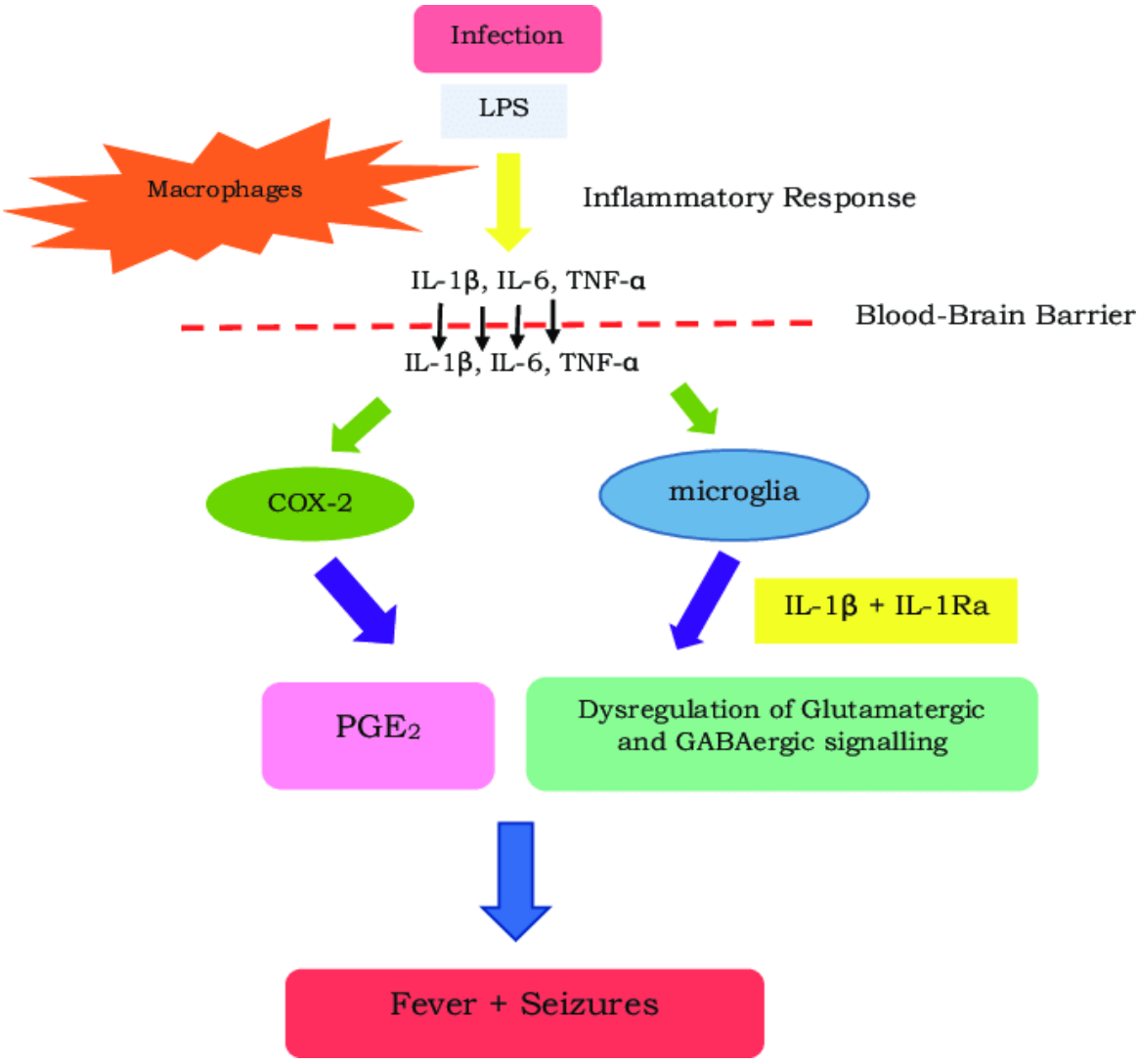

Figure 1: Pathogenesis of epilepsy [16]

1.3 Diagnosis of epilepsy

The first seizures that bring a patient to a doctor's attention are commonly tonic-clonic ones. Early epilepsy is likely present if there is no evidence that the seizure was provoked or that there is a real cause, such as drug abuse, insufficient sleep, or a medical condition. particularly in people who seem to have had a lot of unexpected tonic-clonic seizures. More seizures are frequently discovered after a comprehensive history. including blank, myoclonic, and—more frequently—complex partial seizures, all of which not only permit but frequently facilitate the epilepsy diagnostic. A seizure can typically be diagnosed with

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certainty. [17] situations by gathering all relevant information and performing a real clinical evaluation with an emphasis on neurological and mental health state. It is important to record the lengthiest and shortest times for each form of seizure, as well as the age and surrounding circumstances at the beginning. A seizure diary is useful for assessing how well a therapy is working. Any prenatal or perinatal events, induced abortions, febrile seizures, any unusual seizures, and any family history of epilepsies must all be mentioned in the narrative. Confirming the aura's presence is important, and the patient should write down any details they think may have contributed to the seizure. It is necessary to look for and assess any prior histories of toxic incidents, infections, or head trauma. It's important if seizures or neurological conditions run in the family. [18]

1.4 Classification of seizers

Practical implications

Furthermore, for practical reasons, being able to differentiate amongst widespread absence, notably myoclonic seizures and partial seizures, is adequate. [19]

Partial (focal) seizures

Simple and complex partial seizures, also referred to as focal seizures or subsequent GTC seizures, are caused by a problem with normal brain activity. Depending on where the malfunction occurs, status epilepticus will appear differently clinically. There are numerous examples, such as complex automatic actions (temporal lobe, anteromedial temporal lobe), graphic hallucinations with formed images (posterior temporal lobe), bilateral antinociceptive posture (supplementary motor cortex, frontal lobe), localized muscle spasms during a Jacksonian seizure (motor cortex, frontal lobe), and localized numbness or tingling (sensory cortex, parietal lobe). [20]

Generalized seizures

The consciousness of an epileptic seizure may be impacted, and bilateral motor symptoms may appear immediately. These attacks commonly have a metabolic or genetic cause. Main or secondary extension is indicated by bilateral cerebral cortex involvement at the start.

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(local cortical onset with subsequent bilateral spread). The most common types of generalized seizures are absent, tonic-clonic, and myoclonic. [21]

Unclassifiable seizures

Un-categorized seizures are seizures that cannot be classified as either focal or widespread depending on their clinical or EEG signs. (for example, atonic, tonic, and tonic-clonic seizures lacking obvious focal onset). When epilepsy has these characteristics based on focal and generalized EEG results, this term is also used to characterize incomplete and widespread seizures in affected individuals. Atonic seizures, which occasionally but not always impact children, are brief, broad seizures. They are recognized by a complete breakdown of muscular tone and consciousness. [22] When the child falls or pitches to the ground while having convulsions, the risk of critical trauma, particularly a head injury, rises. Even to a trained spectator, they might, however, mimic a tonic seizure with a very speedy focal onset. [23]

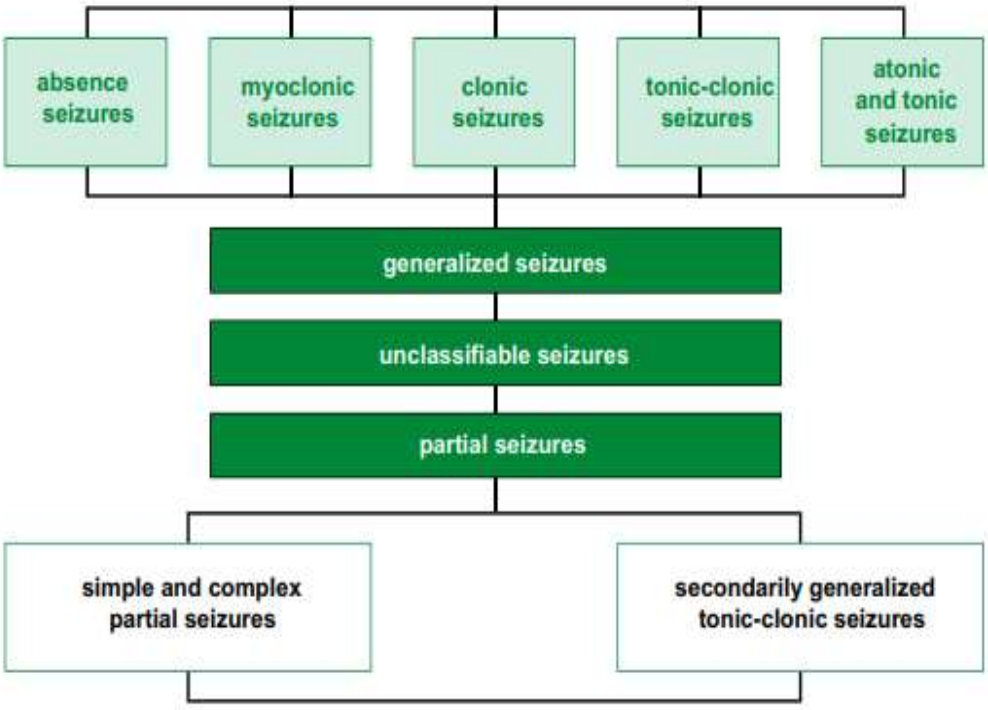

Figure 2: Classification of seizers [24]

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1.5 Risk factors of epilepsy

Your risk of epilepsy may be impacted by the following factors:

Age.

Although epilepsy can develop at any age, it most frequently does so in children and older individuals.

Family background.

You may be more likely to experience a seizure problem if you have a family background of epilepsy.

head trauma.

Some cases of epilepsy are produced by head injuries. Hitting on a helmet while biking, skiing, riding a motorbike, or contributing in other sports where there is a high danger of head injury can help your reduction your risk.

stroke and many vascular conditions.

Damage to the brain from a stroke or other vascular (blood vessel) condition may result in epilepsy. Several actions can be taken to lower your chance of developing these illnesses, such as restricting your alcohol intake, leaving smoking, keeping a healthy diet, and appealing in regular exercise. [26]

Dementia.

In elderly persons, dementia can raise the risk of epilepsy.

infection of the brain.

infection of the brain Your risk can be raised by illnesses like meningitis, which could also result in inflammation of the brain or spinal cord. [27]

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seizures in young children.

Seizures with high fevers in children can sporadically coexist. Maximum kids who experience seizures since of high fevers won't go on to have epilepsy. If a youngster suffers an extended fever-related seizure, their risk of developing epilepsy rises. [28]

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Chapter 2
Purpose of the study

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2.1 Purpose of the study

A prevalent illness that impairs the brain and frequently results in seizures is epilepsy. Bursts of electrical activity that briefly impair the functioning of the brain are seizures. They can result in a variety of symptoms. Although epilepsy can begin at any age, it typically does so in children or adults over 60. The aim of this review following points:

• The goals of this project are to get a thorough understanding of the medical problem being researched.

• To learn more about the variables that contribute to the development of epilepsy.

• To have a better grasp of the many diagnostic procedures used to diagnose this ailment.

• To gain a thorough understanding of the disease, including its cause, signs and symptoms, consequences, and medical and nursing treatment choices.

• The purpose of this investigation was to understand more about epilepsy in the world.

• Designate the epidemiology of epilepsy.

• Review the exhibition of a patient infected with epilepsy.

• Recognize common complications of epilepsy.

• Recapitulate the role of the interprofessional healthcare team in epilepsy sickness preclusion and moderation measures.

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Chapter 3
Methodology

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3.1 Methodology

A framework of research methodologies, as well as methods for gathering and analyzing data, is provided by a methodological review. This chapter discusses the techniques used in the investigation. Key phrases including **"epilepsy " "epilepsy pathogenesis," "epilepsy management," and "diagnostic"** were searched for utilizing web-based search engines, academic bibliographic databases, **PubMed, Research Gate, Google scholar and Medline**. It gives an account of the learning environment. There are many variables to take into account, including the study sample, the study population, the research tools, the methodology, and the data analysis. This is a summary of earlier examination on the demonstration of epilepsy. All research on the causes, diagnoses, and therapies of the epilepsy sickness. A piece of the information was collected by directly reading previous research articles, while the other part came from scouring the internet for pertinent data. The activities of many treatments were recorded. All of the information gathered from prior study publications was numerically coded and imported.

3.2 Data analysis strategy

Data analysis is the methodical application of statistical and/or logical tools for describing and illustrating, condensing and summarizing, and evaluating data. Microsoft Excel was used to analyses the data.

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Chapter 4
Literature Review

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4.1 Clinical Drug Development in Epilepsy Revisited: A Proposal for a New Paradigm Streamlined Using Extrapolation [29]

If data from adult clinical experiments are applied to predict benefits in pediatric patients, then fewer or smaller investigations may be needed to obtain a novel medicine authorization for pediatrics. The part that such extrapolation plays in the development of drugs to treat pediatric epilepsies is discussed in this paper. A novel approach for the clinical formulation of drugs for focal epilepsies is put forth based on professional consensus. Phase I data for adults should still be collected, and phase II and phase III trials should involve both adults and toddlers over the age of 2. Following the collection of phase IV neurodevelopmental safety data in this age range, medications would be granted a temporary permission for use in children. For the drug to be authorized for use as either a monotherapy or adjunctive therapy, only one set of trials would be required. This new system would benefit patients, clinicians, and marketers evenly by means of cost savings and early entry to novel medicines. More investigation is required, as well as opinions from governing authorities, businesses like the National Institute for Health and Care Quality, as well as patients' parents and guardians as needed. (UK).

4.2 Drug development for refractory epilepsy: The past 25 years and beyond [30]

Regardless of the approved antiepileptic drug (AED) market expanding exponentially over the preceding 25 years, it is expected that one-third of patients still have untreated seizures. This paper reviews the therapeutic trials and properties of the AEDs created at this time, as well as the pre-clinical and clinical models, methods, and AEDs that are used today. We discuss possible reasons for the apparent loss to develop more efficient chemicals. We also look at forthcoming changes as well as the US and European regulatory frameworks in place for medication registration. Positively, recent study has increased our knowledge of the pathophysiological processes underlying pharmaco resistance and epilepsies, allowing us to revise our approach and develop more potent therapies. A new phase of the pharmaceutical age of therapy modality is regarding to begin. Future pharmacotherapy research for drug epilepsy will advance thanks to cooperation between scientists, doctors, and the business.

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4.3 Difficulties in Treatment and Management of Epilepsy and Challenges in New Drug Development [31]

Epilepsy is a serious neurological disease that affects more than 50 million people worldwide. Drug resistance, which is connected to psychological issues, social exclusion, reliant behavior, low marriage rates, unemployment, and a poorer quality of life, affects nearly 30% of epileptic patients. The effectiveness of antiepileptic drugs currently available on the market is restricted, which limits their use and complicates patient care. because antiepileptic drugs lessen seizures but cannot stop epileptogenesis, they can only address symptoms. Antiepileptic drugs shouldn't be taken for a long time due to their undesirable side effects, withdrawal symptoms, dangerous drug combinations, and financial burden, particularly in developing countries. Additionally, some antiepileptic medications may even intensify some types of seizures. Some antiepileptic drugs may even make certain kinds of seizures worse. Numerous new antiepileptic drugs have recently hit the market, and numerous in vivo and in vitro animal models have been proposed; yet, many patients continue to exhibit pharmaco resistance. This research will highlight the difficulties in treating and managing epilepsy, as well as the drawbacks of available treatment options and animal seizure models.

4.4 Innovations in Epilepsy Management – An Overview [32]

In the past twenty years, thirteen novel antiepileptic drugs (AEDs) have been created, each with distinct efficacy ranges, way of conduct, pharmacokinetics, safety, and adaptation characteristics. These newer AEDs offer a hopeful future in the treatment of epilepsy because they can cause a noticeable decrease in symptom severity in up to 40% to 50% of patients who had been unresponsive to older generation drugs. Even though these new drugs are now available, only a tiny percentage of patients with highly susceptible seizures can be said to be seizure-free. Even though they are not more effective than traditional medicines, some contemporary drugs have been shown to be non-inferior in this respect. Greater tolerance, simplicity, and a reduced contact profile are additional advantages. Older generation therapies are still considered the best option in most situations, despite recent research suggesting that new generation medications may be fully justified for first management in many ailments. This emphasizes the requirement for the creation of brand-

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new, improved antiepileptic drugs for the management of unpredictable seizures. More direct assessments of newer drugs against newer drugs and newer drugs against older drugs are needed in clinical trials, both for adjunctive therapy and monotherapy. There have been discovered and are currently being studied pharmacologically more than 20 elements. These compounds have potential as neuroprotective and antiepileptic medications.

4.5 Drug treatment of epilepsy in adults [33]

Most people can successfully manage the symptoms of epilepsy, a severe and occasionally fatal brain condition, by taking one or more antiepileptic drugs. About two thirds of people with newly identified epilepsy may experience a lifelong seizure remission while taking or not taking these medicines, however about half will experience mild to moderately serious adverse reactions. Epilepsy patients, especially the 20–30% of patients whose seizures are not fully controlled with existing drugs, have a significantly greater chance of dying, as well as psychiatric and somatic complications, as well as negative side effects from antiepileptic medications. (drug resistant epilepsy). Newer medications, some of which, including levetiracetam, generate fewer drug interactions and less hypersensitivity than earlier ones, have made more therapeutic options accessible. They do not, however, prevent the onset of epilepsy in people at high risk, such as those who have experienced a severe brain injury, or reduce the prevalence of drug-resistant epilepsy. In order to find more effective antiseizure drugs for handling cases of medication-resistant epilepsy, especially catastrophic forms, antiepileptic research on drugs must be revived. Additionally, antiepileptogenic drugs must be created in order to prevent epilepsy in at-risk patients earlier than the first seizure happens, and illness drugs must be created in order to halt persistent severe epilepsy driven on by a deteriorating baseline situation.

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Chapter 5
Results & Discussion

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5.1 Results

5.1.1 History of Antiepileptic Drug Development

For thousands of years, different plants and botanicals have been used to cure epileptic disorders. The medication was the first to be created to treat epilepsy after Sir Charles Locock's surprising discovery of potassium bromide's activity in this location in 1857. since bromide salts were the only treatment for epilepsy accessible at the time. Phenobarbital was the second compound unintentionally discovered for the therapy of epilepsy. Alfred Hauptmann made this finding in 1912 while using phenobarbital as a sedative for his epileptic patients. He then unintentionally discovered that it also has anticonvulsant properties. Since its introduction, phenobarbital has been widely utilized as an antiepileptic drug. [34] The ketogenic diet was first made available as an epileptic treatment in the 1920s. This specific diet was developed to mimic some of the characteristics of fasting, a condition thought to lessen seizures in some individuals. It has a high fat content, little protein, and very few carbs. One of the first-choice medicines for generalized tonic-clonic and occasional seizures, the first antiepileptic drug was discovered employing an animal seizure model. Merritt and Putnam's pioneering studies using a cat electroshock-induced seizure model helped establish phenytoin as the first non-sedating antiepileptic drug when it was first synthesized in 1908. because then, new drugs for the management of epilepsy have been developed using the electroshock-induced seizure model. It has been found that drugs that are effective at stopping tonic hind limb extension in animals caused by electroshock are usually effective at managing generalized tonic-clonic seizures in humans. [35] **Trimethadione,** the first medication specifically for partial seizures, was authorized in the 1940s following a clinical examination by Lennox in 1945 and a scientific evaluation by Richards and Everett in 1944 using the **pentylenetetrazole** animal seizure model. **Primidone** became a widely accessible antiepileptic drug in the 1950s. **Primidone** is not commonly used in clinical settings due to its higher incidence of adverse reactions, despite the fact that it transforms into the active substances phenobarbital and **phenylethylmalonamide. Ethosuximide** has been the drug of choice for children with absence seizures ever since it was first used in clinical situations in 1960. [36] Initially made accessible in the late 1960s, benzodiazepines are now commonly used to treat

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condition epilepticus. Carbamazepine was developed by Schindler in 1953, and it was first made available as a drug to treat trigeminal neuralgia in the 1960s. After discovering that it had antiepileptic properties, it was marketed as an antiepileptic drug in the 1970s. [37] **Valproic acid** was accidentally discovered in 1963 while being used as a solvent, but it wasn't until the late 1970s that it was first commercially available. Over the past 20 years, a number of novel drugs have been authorized to treat cases of epilepsy, including **felbamate, gabapentin, lamotrigine, topiramate, tiagabine, levetiracetam, oxcarbazepine, zonisamide, pregabalin, rufinamide, stiripentol, clobazam, vigabatrin, and lacosamide.** Both an extended variant of the drug carbamazepine and a pro-drug of phenytoin known as fosphenytoin have been introduced. A combination of anti-seizure medications and vagus nerve stimulation has also been authorized for the management of partial epilepsy in adults. Chemical substances, the primary subjects of growth, and injectable antiepileptic devices are presently the subjects of investigation. [38]

5.1.2 New AEDs for recent-onset idiopathic generalized epilepsy

Lamotrigine (LTG) and topiramate (TPM) have been compared to VPA for its efficacy in managing idiopathic extensive epilepsy in a section of Arm B of the SANAD trial. The purpose of SANAD was to decide whether TPM or LTG should replace VPA as the preferred first-line treatment. Therefore, for all patients as well as the subset with idiopathic generalized epilepsy, VPA was found to be superior to LTG and similar to TPM. [39] Although the study showed that TPM and VPA were equally advantageous, it should be emphasized that TPM was considerably less advantageous. LTG was equally shown to be less efficacious than VPA for the previously untreated juvenile myoclonic epilepsy. More recently, 453 children with freshly identified juvenile absent epilepsy received therapy with ESM, LTG, or VPA in a multidisciplinary double-blind prospective study. After 16 weeks of therapy, the independence rates for ESM and VPA were similar (53% and 58%, correspondingly), despite the fact that for the two, rates of independence were higher than for LTG (29%; p 0.001 for both analyses). [40]

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5.1.3 New AEDs for recent-onset focal epilepsy

The Arm A of the SANAD study was designed as a pragmatic trial to ascertain whether **LTG, gabapentin (GBP), oxcarbazepine (OXC), or TPM** should replace CBZ as the first-line drug in light of the novel AEDs. The only criterion taken into consideration here is effectiveness, and none of the new AEDs fared better than CBZ in this regard. On the other hand, it was believed that CBZ was more successful than GBP, while LTG and OXC were considered to be non-inferior in terms of effectiveness. The finding that GBP was less successful indicates that the SANAD trial has an adequate selectivity to differentiate among productive and less-effective treatment. [41] Levetiracetam (LEV), which was subsequently made available, could not be investigated in SANAD. Additionally, an under control noninferiority study has shown that, at per-protocol evaluation, 72.8% of patients getting monitored CBZ and 73.0% of patients getting LEV were seizure-free at the last evaluated dose (with modifications absolute distinction 0.2%, 95% CI 7.8% to 8.2%). This shows that the rates of epilepsy remission with LEV and slow release CBZ are comparable. One current trial could not demonstrate TPM (100 mg/day) was better to oral PHT for new-onset focal seizures. Research on monotherapy in elderly patients with newly diagnosed epilepsy are discussed on their own and are not addressed in this section. Furthermore, it should be noted that the absence of research comparisons and thorough clinical records renders the empirical evidence for comparing newer to older AEDs unreliable. According to investigations, the board of the International League Against Epilepsy (ILAE) expert connecting expressed concerns. [42] It's interesting to note that the benchmark investigations comparing older and newer AEDs for new-onset epilepsy are less comprehensive than the current data collection. In summary, none of the novel AEDs performed any better than older AEDs like CBZ and VPA in large, carefully designed trials of epilepsy with recent onset. Additionally, studies have shown that a few novel AEDs, such as LEV, LTG, and OXC, are noninferior to CBZ in terms of managing seizures by a small percentage. Additionally, it was shown that LTG was more successful than VPA and that GBP was more effective than CBZ in focal epilepsy that was largely neglected. LTG was also shown to be less successful than VPA and ETS in treating untreated childhood absence epilepsy. This persuasively demonstrates that current post marketing trial designs

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for new-onset epilepsy—even though they are not designs used mostly for regulatory purposes—are capable of identifying less appropriate treatment, if it occurs. [43]

Seizure type	First line agents	Alternatives
Partial	Carbamazepine, Phenytoin	Valproate, Phenobarbital, Topiramate, Lamotrigine, Vigabatrin, Gabapentin
Generalized tonic-clonic	Carbamazepine, phenytoin, valproate	Phenobarbital, topiramate, lamotrigine
Generalized myoclonic	Valproate, clonazepam	Phenobarbital, topiramate, lamotrigine
Generalized absence	Ethosuximide, valproate	Clonazepam, topiramate, lamotrigine
Generalized atonic/ clonic	Valproate	Clonazepam, nitrazepam, topiramate, lamotrigine
Infantile spasms	Vigabatrin	Valproate, Topiramate, lamotrigine
Dravet Syndrome	Valproate	Clobazam, Topiramate
Atonic, tonic, atypical absence in Lennox Gastaut Syndrome	Lamotrigine	Valproate, Topiramate, Felbamate

Table 1: AEDs used in different seizure types and epilepsy syndromes [44]

The most recent significant somewhat wide AEDs that are helpful for people who encounter both various kinds of convulsions and widely prevalent seizures are **lamotrigine, topiramate and and zonisamide.** Several of these new substances have usually a higher tolerance than second-line broad-spectrum drugs including barbiturates and benzodiazepines, which is primarily the cause of this. Due to the broad range of action and the variety of seizure types that can occur in Dravet Syndrome, valproate is thought to be the first medication of choice. **Lamotrigine, topiramate, and felbamate** have been given official authorization for the management of Lennox Gastaut Disease after randomly allocated, double-blind, controlled studies showed they were much more effective than placebo**.** Vigabatrin is viewed as a potential first-line treatment against juvenile spasms, especially those associated with tuberous sclerosis, regardless its tendency to result in permanent visual field irregularities. **Felibamate** is only prescribed to patients after all other treatments have been unable to help them because of its severe toxicity problems.

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Other more recent AEDs have a more constrained range of efficacy and are typically used to treat partial seizures. Several common seizure types may even be made worse by newer drugs including **carbamazepine and phenytoin (vigabatrin, tiagabine, gabapentin, and oxcarbazepine).** [45]

5.1.4 Recent FDA Approved AEDS (Anti-Epileptic drugs)

as 2007, six novel AEDs have received approval from the European Medicine Agency and the US Food and Drug Administration. (EMEA). **Ezogabine, rufinamide Perampanel, an eslicarbazepine acetate, stiripentol, lacosamide, and (retigabine).** These drugs' clinical effects, such as tolerance, efficiency, and tolerance, have been found to be completely explained by a number of mechanisms and patterns of behavior.

- The EMEA approved **stiripentol for Clobazam and valproic acid** as an adjunctive therapy to treat juvenile patients with Dravet syndrome who experience frequent tonic-clonic seizures that resist medication. No It is found that a different AED has antiepileptic properties. comparable to stiripentol in Dravet syndrome patients. It intensifies the stimulation of transgenic GABAA receptors and boosts gamma-aminobutyric acid neurotransmission. (GABA). It has nonlinear pharmacokinetics. Similar to stiripentol treatment, neurobehavioural and digestive issues are common. Negative side effects like drowsiness, tremor, ataxia, nausea, and weight loss were most commonly reported. Also reported are leucopenia and transitory aplastic anemia. **Stiripentol** is available in pills (250 mg and 500 mg) and powder for oral suspension. (250 mg, 500 mg). [46]
- The FDA approved **samide** in 2008 as an adjuvant medication for individuals with partial-onset seizures who are 17 years of age or older. It was the first AED to enhance the delayed inactivation component of voltage-gated sodium channels. [47] It is unknown if **lacosamide's** interactions with the protein identified as the contractile responding facilitator add to their antiepileptic properties. Ataxia, exhaustion, nausea, and dizziness are among the most commonly reported side effects. **Lacosamide** and carbamazepine gradually released as monotherapy in newly or eventually identified patients with epilepsy, age 16 and older, is presently the subject of phase III studies evaluating both its safety and effectiveness. Both

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the treatment of clinical symptoms and the administration of status epilepticus have been investigated. [49]

- In 2008, the FDA approved **rufinamide** for use in patients 4 years of age and older who were experiencing seizures linked to Lennox Gastaut syndrome as an adjunctive therapy. It extends the inactive condition of voltage-gated sodium channels. Drowsiness, nausea, exhaustion, headaches, diplopia, and gastrointestinal issues are the most commonly mentioned adverse effects. For generalized anxiety disorder, refractory status epilepticus, and its efficacy in comparison to the ketogenic diet in people with drug-resistant epilepsy, the FDA is currently reviewing it. It is offered in 200 mg and 400 mg tablet doses. [35]
- **Eslicarbazepine acetate** was approved as an adjuvant therapy for partial seizures in adults by the European Union in 2009. It is equally effective as carbamazepine and oxcarbazepine at preventing the release of hormones that are sodium channel-dependent. Headaches, diplopia, nausea, abnormal cooperation, disorientation, and somnolence have all been connected to it. People with methods for therapy seizures are presently the subject of phase III trials, and bipolar patients are the subject of phase II trials. 800 mg tablets are the most common variety. [42]
- **Ezogabine, also known as retigabine** in Europe, is the first AED to target and stimulate the voltage-gated potassium channel. (Kv7). It was approved in 2011 as an additional treatment for people over the age of 18 with status epilepticus and refractory incomplete epilepsy. Urinary retention is a significant adverse effect of retigabine therapy since it affects the voltage-gated potassium channel subunits Kv7.2-Kv7.5 found in the bladder urothelium. Adverse reactions like fatigue, dizziness, and confusion are frequently dose-related. The available pill strengths are 50 mg, 100 mg, 200 mg, 300 mg, and 400 mg. [47]
- **Perampanel**, which became obtainable in Europe for the first time in July 2012, was the first glutamate receptor blocker to obtain clearance. For people 12 years of age and older who were having incomplete onset seizures, either with or without secondary generalized seizures, it was granted FDA approval in October 2012. It can now be used as a further treatment. Some of the most common adverse effects include dizziness, gait interruption, somnolence, fatigue, injuries, and suicidal

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behavior. For this drug, there is a dearth of therapeutic information. Tablets with the following concentrations are available: 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg. [41]

- In 2009, the FDA approved **vigabatrin** as a remedy of juvenile contractions in children among the ages of one month and two years old, as well as as an adjunctive treatment for people with complex partial seizures that are refractory. However, it was first offered in Europe in the late 1980s, and in 1993 and 1994, accordingly, Australia and Canada approved it. Although vigabatrin is accessible in many countries, until lately it wasn't in the US due to the medication's well-known link to patients developing irreversible peripheral vision loss. Because it is a permanent GABA transaminase antagonist, it raises GABA levels in the brain. There are both 500 mg tablets and 500 mg sublingual powder solutions available. [48]
- **Clobazam** was first approved in Australia in 1970 after being used for a while in Europe. In 2011, the FDA approved supplemental treatments for patients with Lennox Gastaut syndrome who were 2 years of age or later. **Clobazam** treatment has reduced drop seizures in these individuals by up to 70%. subsequently improves GABAnergic neurotransmission by binding to the GABAA receptor's benzodiazepine region. **Lamotrigine, felbamate, topiramate, or valproic acid** are commonly present in regimens that also involve it. It is being researched for use as an adjuvant treatment for status epilepticus and febrile seizures in both adults and children, as well as a monotherapy for focal or generalized seizures in adults. [41]

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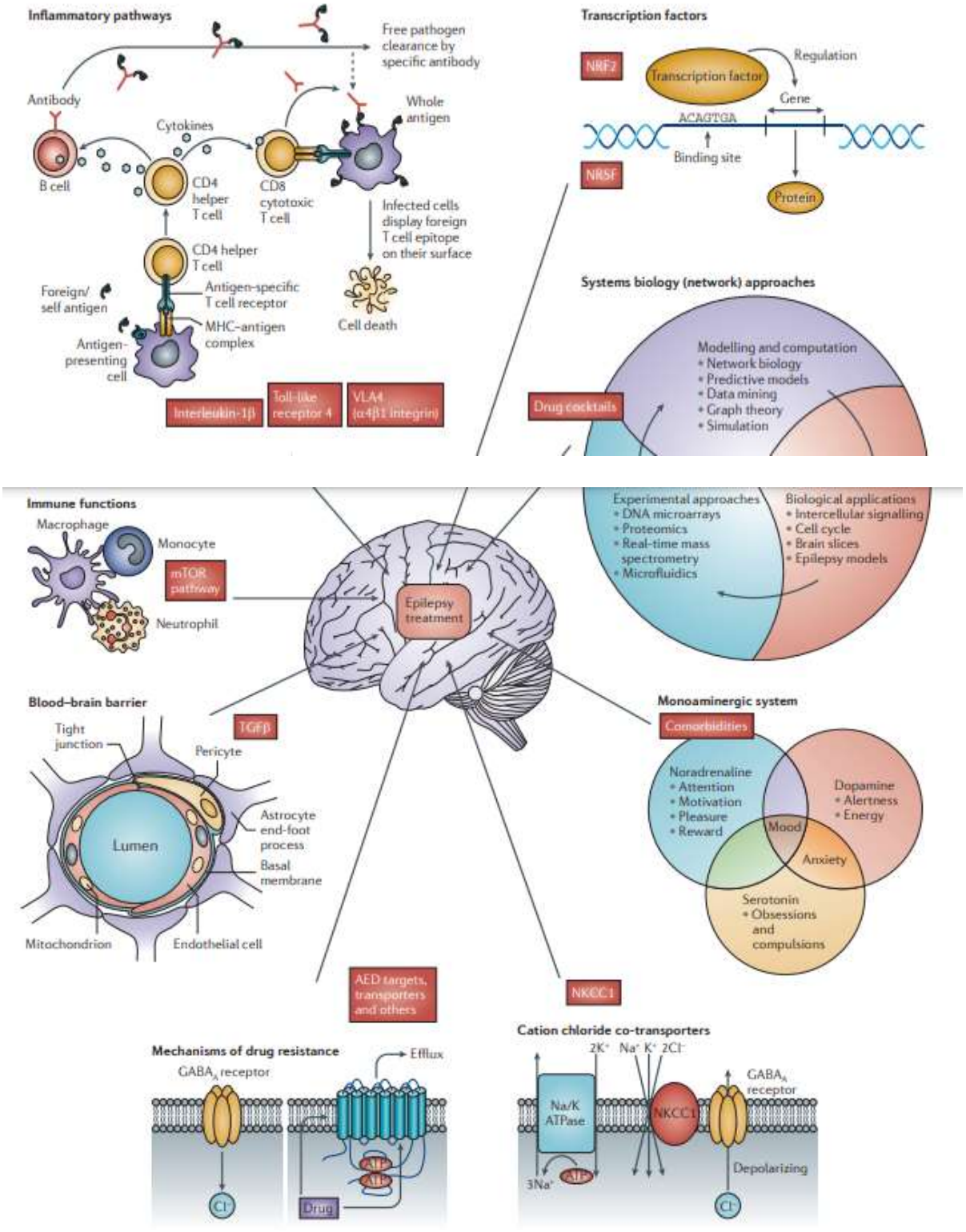

Figure 3: Anti-Epileptic drugs working pathways [49]

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5.1.5 New clinical trial design

Throughout the early stages of clinical research, potential clinical trial designs for epilepsy medications should demonstrate the drug's efficacy (ideally by objective seizure counts), supremacy over the generally recognized standard of care at the optimal dose, and the ability to assess the ability of potential new drugs to treat epilepsy before the individuals who are at risk for seizures encounter their first or second risk of epilepsy happening. Clinical research techniques are provided to determine whether possible novel medications can change the undiagnosed epilepsy after the onset of seizures. (that is, disease modification). Prospective preclinical findings should be incorporated into approaches to development using trustworthy and impartial biomarkers in early and decisive Phase-I challenges. [33]

Stage	Key activities
Target identification	Identification of novel targets and/or repurposing of compounds with novel mechanisms from other therapeutic areas
Target validation	Genetic validation by transgenic animals and/or pharmacological validation with relevant probe compounds
Hit identification, hit-to-lead, lead optimization	Drug discovery searching for hits and translation of these into leads with drug-like properties
Candidate selection	Selection of candidates with optimal drug-like properties, including confirmation of target validation by comparative preclinical proof-of-concept studies
Preclinical development	Conventional GLP-driven programme to permit onset of Phase I studies, including preclinical studies with relevant PET ligand and validation of biomarkers
Phase I and initial proof-of-concept 'light' studies	Conventional Phase I programme to determine safety, tolerability and DMPK properties, and initial proof-of-concept 'light' studies with PET ligands and biomarkers to assess target engagement and its biological consequences
Phase II proof-of-concept studies	Proof-of-concept study versus comparator and placebo assessing potential for differentiation
Phase III confirmatory studies	Confirmatory studies versus comparator and placebo (optional) to prove superior efficacy for drug approval and marketing authorization

Table 2: Discovery and development of medications for drug-resistant epilepsy and for epilepsy prevention or disease modification [48]

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To allow early de-risking and assessment of the growth and differentiation, Phase II trials should be compared with the standard of care (if any) before committing to confirmatory Phase III investigation. Future clinical trial designs using placebo drugs must manage the variability of the placebo response observed with the conventional commercial trial design. [31]

5.2 Discussion

The efficacy of antiepileptic drugs currently available on the market is restricted, which limits their use and complicates patient care. because antiepileptic drugs lessen seizures but cannot stop epileptogenesis, they can only address symptoms. According to available data, pharmacological epilepsy therapy's efficacy and tolerability haven't improved significantly because the early 1990s, despite the introduction of numerous new antiepileptic drugs (AEDs). What factors account for the current AED development's apparent inability to produce drugs with higher efficacy? All AEDs were discovered using the same conventional animal models, with only minor variations, including the maximal electroshock seizure test (MES) in rodents, which served as an essential gatekeeper. Although these investigations led to the development of useful novel AEDs, it is evident that they had little bearing on the development of AEDs that were more successful in managing patients who had not yet developed AED resistance. This problem is not brand-new, but it's fascinating that for a while it went largely unnoticed. A different one obviously speculative, argument is that until we develop drugs that specifically treat the root cause of the circumstance, we won't advance in the pharmacological treatment of drug-resistant epilepsy. Even though better preclinical methods won't be able to circumvent regulatory restrictions, more effective medications may enable us to abandon therapeutically dubious studies with intentionally less effective supervision and noninferiority designs and expect documentation for relative performance. The collapse of AED development will probably prevent any further developments in the management of epilepsy if we are unable to resolve this dilemma. Medical professionals, basic scientists, and business have all experienced this frustration. Consequently, in order to completely change and advance AED development and study, we necessitate novel ideas and innovative methods of thinking. In this respect, the authors of this in-depth analysis will look at a number of cutting-edge ideas that may, in the future, lead to more successful drug therapies for epilepsy.

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Chapter 6
Conclusion

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6.1 Conclusion

To discover effective therapies for people with epilepsy, improved methods of evaluating preclinical models, more dependable protocols, and a more uniform evaluation of results are required. The present discussion should not be seen as an exhaustive list of recommendations but as a starting point for the development of specific ideas. These rules could also be used to direct the grant approval process to ensure that the financial applications that have the best chance of generating findings that are clinically pertinent are backed. Future research can involve the definition of a hierarchical list of preclinical proof that is recommended to proceed to official clinical testing, as well as a second list of optional, supplementary material. As a result, based on data from preclinical research, it would be possible to contrast various AETs in terms of their revolutionary value, giving each one an alternate measure of probability for therapeutic advantage. Preclinical AET results that have been documented should be regularly evaluated. Such reviews ought to include information on the viability and best use of animal models, methods for behavioral or outcome tracking, methodological design, and an evaluation of the preclinical effectiveness findings for specific seizure types or disorders. This would make it possible to adapt suggestions to the shifting needs of the sector. A Cochrane-like partnership would be beneficial to achieving this objective. A platform for the publication of both good and negative studies would be helpful in order to impartially assess the potential of novel AETs.

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Chapter 7
Reference

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