Project on

Review on Clinical development of drugs for epilepsy

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

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Faculty of Allied Health Sciences,

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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", is done by me under the supervision of Md. Mominur Rahman, Lecturer, Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University. 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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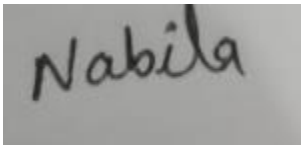

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I might want to communicate my profound applause to the All-powerful Allah who has given me the capacity to finish my undertaking work and the chance to concentrate in this subject.

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

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.

Contents

List of figures

List of tables

Chapter one
Introduction

1. Introduction

Epileptogenesis is the process by which a neural network where spontaneously seizures take place develops. Epilepsy is a brain illness characterized by a lasting propensity to cause epileptic seizures. From newborns to elderly individuals, epilepsy impacts the entire age spectrum. It has a wide range of causes and expressions, as well as numerous discrete seizure types, numerous recognizable disorders, and a great deal of poorly categorized epilepsy. [1] Learning difficulties, fixed cerebral deficiencies, progressive disorders, psychological and mental issues, and concurrent health problems, especially in the older age group, are just a few of the comorbidities that make evaluation and patient management difficult. Epileptic seizures and disorder categorization are constantly changing. The newly proposed classification is established on five axes that take into account different seizure types, the start of focal or widespread seizures, the condition, the cause, and any accompanying deficiencies. Adults in this context are those who are 16 years of age or older. [2] In October 2004, the UK's National Institute for Health and Clinical Excellence (NICE) released comprehensive, evidence-based recommendations for the treatment outcomes of people with epilepsy (panel). [3] The Scottish Multidisciplinary Guidelines Network and the American Academy of Neurology have additional recommendations. Epilepsy stands apart from other neurological disorders due to stigma and discrimination. Research on epilepsy has advanced significantly over the past ten years, as has public knowledge. Therefore, much work needs to be done, particularly for those for whom medications are unsuccessful. The reality that most epileptics reside in resource-poor nations with inadequate epilepsy treatments is a significant issue that requires immediate attention. [4] Since there are insufficient medical facilities and skilled workers, there is a significant diagnostic gap in many regions of the world. The International League Against Epilepsy and the International Bureau for Epilepsy, the two main international non-governmental organizations in the field of epilepsy, are actively supporting the WHO-led Global Campaign for Epilepsy, which aims to solve these problems. [5]

1.1 Epidemiology

In affluent nations, the incidence rate of epilepsy is roughly 50 per 100,000 persons, with newborns and the elderly being more susceptible. For unexplained causes, a higher prevalence is seen in those who are less rich. In commodity nations where the majority of epilepsy sufferers typically do not receive treatment, poor sanitation, deficient health delivery systems, and a higher risk of brain illnesses and parasites could all contribute to a higher incidence. [6] typically, above 100 per 100 000 persons per year. Incidence of childhood has decreased over the past three decades in industrialized countries, which may be related to expecting mothers adopting healthier lives, better prenatal care, and immunization programs. Improvements in survival rates for those suffering from brain deterioration and cerebrovascular illness may be responsible for a concurrent rise in occurrence in the elderly. Epilepsy affects 4 to 10 people out of every 1000 persons annually. Higher rates have been observed in a few (usually small) research from remote geographic locations with distinctive genetic or environmental variables. [7] Even in resource-poor nations where the majority of people limited access to antiepileptic's, lifetime prevalence rates are significantly greater than rates of current epilepsy. Usually people who get the illness stop having seizures, however greater mortality in epilepsy also contributes to this disparity. Risk variables affect depending on age and region. Any age can experience epilepsy brought on by head injuries, CNS infections, and tumors. The much more frequent relative risk in adults over 60 is cerebral vascular impairment. Internationally, neurocysticercosis and other endemic parasitic disorders like falciparum malaria are among the most frequently encountered avoidable factors for epilepsy. Onchocerciasis and toxocariasis have recently been mentioned as significant risk factors. [8] Epilepsy susceptibility may be inherited influenced to some extent. We may not fully comprehend the population dynamics of the illness due to the intricate interplay between genetic and environmental factors. Some epileptic disorders also change over time. Infantile spasms developing into Lennox are two examples of this progression. Infants who experience intermittent convulsions and go on to acquire medial temporal lobe epilepsy are said to have Gastaut disorder, a particularly severe form of epilepsy. Genetic variables are probably to play a part, although from an epidemiological or biological perspective, the

mechanisms of development have not yet been fully clarified. Within five years of diagnosis, more than 60% of individuals in affluent nations get long-term remission; the likelihood of recovery declines the further epilepsy is active. Early onset, fewer early seizures, and an early response to medication treatment are all indicators of a satisfactory result. [9] The extensive use of antiepileptic medications in affluent nations is sometimes cited as the reason for the generally favorable outcome. Furthermore, numerous patients in asset nations without access to such medications experience long-term recovery, supporting the idea that the outcome is determined by the underlying etiology of the epilepsy rather than by therapeutic therapy. One-third of those who experience seizures go on to have persistent epilepsy. 26 However, it's possible that up to 20% of individuals with intractable epilepsy who are referred to clinics were misdiagnosed, and many more could benefit from the best care. Additionally, concomitant illnesses such as cardiovascular and cerebrovascular disorders, gastro intestinal problems, injuries, pneumonia, chronic lung problems, and diabetes are more common in those with chronic epilepsy. [10]

1.2 Pathophysiology

A temporary incidence of signs, sensations, or both, known as an epileptic seizure, is brought on by abnormally intense or synchronized neuronal activity within the brain. The interracial spike, which has a length of less than 70 MS and is separate from a seizure, is caused by a brief bout of synchronized activity among a group of neurons. In fact, the location of interracial spiking can be different from the area where seizures begin. It is now believed that an early theory that claimed seizures are caused by interruption of the brain's normal balance of excitement and repression was oversimplified. [11] Coordination among various networks, which is likely regulated by oscillations within certain networks, is necessary for the brain to function. Cortical networks produce oscillations, which depend on inhibitory neurons, neuronal connectivity (such as synaptic transmission), and intrinsic neuronal characteristics (such as a neuron's capacity for burst firing). Such oscillatory networks may exhibit epileptic activity as an emergent characteristic. Greater dispersion and neuronal attraction as a result of a confluence of increased connection, increased excitatory propagation, a breakdown of regulatory systems, and changes in intrinsic neuronal characteristics is likely what triggers the transition from normal to epileptiform

behavior. Investigations on humans show that during a seizure, the electroencephalogram (EEG) in significant regions of cortex has become less erratic, pointing to broad synchronization. [12] In focal epilepsies, focused operational disruption, which is frequently caused by focal pathological alterations (such as tumors) or sporadically by a genetic disorder (such as autosomal dominant frontal lobe epilepsy), causes seizures to start locally and then spread by recruiting additional brain regions. [13] The clinical presentation of the seizure depends on the focus site, the spread's speed, and its size. Generalized epilepsies, which are typically genetically determined, cause seizures to occur throughout the cortex as a result of a generalized lowering of the seizure threshold. A specific type of generalized seizure caused by thalamocortical loops is called an exclusion seizure. Suspensions were once thought to be produced subcortically by thalamic neurons activating neocortical neuron migration. [14] The somatosensory cortex, as opposed to the thalamus, appears to be the source of paroxysmal oscillations within thalamocortical loops in absence seizures in rats, with synchronization being mediated by rapid intracortical transmission of seizure activity. [15] The line separating focal and generalized epilepsies has slipped as a result of reports of modest cortical pathological changes in some absence seizure patients45 and the possibility of focal pathological alteration in the medial frontal lobe to cause abrogation seizures. [15]

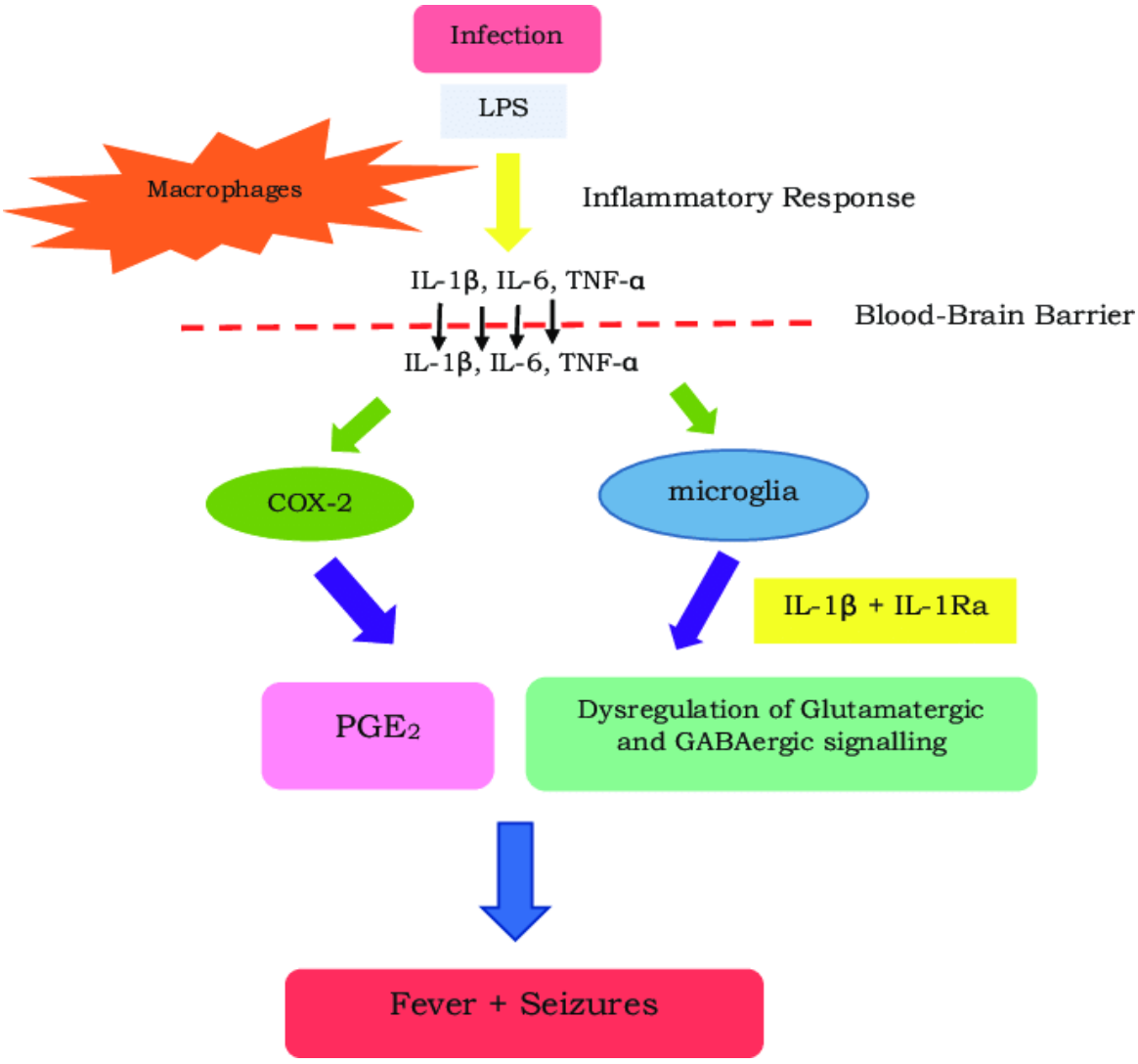

Figure 1: Pathogenesis of epilepsy [16]

1.3 Diagnosis of epilepsy

Tonic-clonic seizures are frequently the first ones that draw a patient's awareness to a doctor. If there is no indication that the seizure was induced or that there is an actual cause, such as substance misuse, lack of sleep, or a medical condition, Early epilepsy is probably present. especially in those who appear having experienced numerous spontaneous tonic-clonic seizure. A thorough history frequently reveals further seizures. such as blank, myoclonic, and—more frequently—complex partial seizures, which not only allow for the

epilepsy diagnosis but also frequently enable it. In most cases, a definitive diagnosis of a seizure can be made. [17] situations by collecting a complete history and doing an actual clinical exam with a focus on neurological and mental health status. The largest and narrowest durations amongst each type of seizure, as well as the age and environmental factors present at the time of commencement, should be noted. A seizure diary aids in evaluating the effectiveness of treatment. The history must include any prenatal and perinatal occurrences, induced abortion, febrile seizures, any unexplained seizures, and any family history of epilepsies. The presence of an aura should be confirmed, and the patient should record any circumstances they believe may have led 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 known as focal seizures or secondary GTC seizures, are brought on by an improve brain function abnormality. The clinical presentation of status epilepticus is dependent on the site of malfunction. For instance, intricate automatic conduct (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) are instances. [20]

Generalized seizures

Epileptic seizures have the potential to affect awareness and result in bilateral motor symptoms right away. These assaults frequently have a genetic or metabolic origin. Bilateral cerebral cortex involvement at onset indicates either primary or secondary

generalization (local cortical onset with subsequent bilateral spread). Absent, tonic-clonic, and myoclonic seizures are prevalent varieties of generalized seizures. [21]

Unclassifiable seizures

Seizures that are unable to categorize as either focal or generalized based on their clinical or EEG symptoms are known as uncategorizable seizures (for example, atonic, tonic, and tonic-clonic seizures lacking obvious focal onset). This phrase is also used to describe partial and widespread seizures in people whose epilepsy has these features based on focal and generalized EEG results. Atonic seizures are transient widespread seizures that sometimes but not always affect youngsters. Total breakdown of muscular tone and awareness is how they are identified. [22] The danger of major trauma, especially head injury, increases when the kid falls or pitches to the ground during convulsions. They might, however, resemble a tonic seizure with a very rapid focal onset, even to a skilled observer. [23]

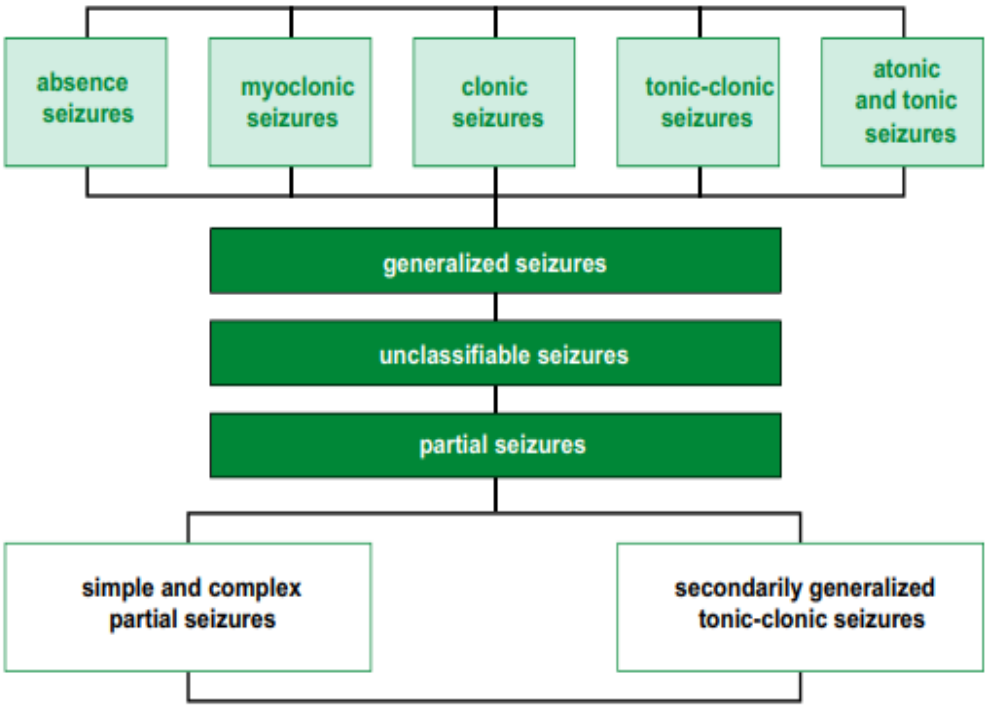

Figure 2: Classification of seizers [24]

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 caused by head injuries. Putting on a helmet while biking, skiing, riding a motorbike, or participating in other sports where there is a high danger of head injury can help you decrease your risk.

stroke and many vascular conditions.

Impairment 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, quitting smoking, maintaining a healthy diet, and engaging 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]

seizures in young children.

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

Chapter two
Purpose of the study

2.1 Purpose of the study

• 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.

Chapter three
Methodology

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, 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 research on the manifestation 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.

Chapter four
Literature Review

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

A new medication permit for pediatrics may require fewer or smaller studies if data from adult clinical trials are extrapolated to predict advantages in pediatric patients. This article describes the role that such generalization plays in the creation of medications for pediatric epilepsies. On the basis of professional consensus, a new paradigm for the clinical development of medications for focal epilepsies is proposed. Adult phase I data should still be obtained, and both adults and children over the age of 2 should be included in phase II and phase III trials. Drugs would be given a temporary authorization for use in children after phase IV neurodevelopmental safety data gathering in this age range. The medicine would only need one set of studies to be approved for usage as either a monotherapy or supplementary treatment. Through cost savings and earlier access to novel medicines, this new arrangement would improve patient, clinicians, and advertisers equally. More research is required to obtain the opinions of patients, their parents and guardians where necessary, governing bodies, and organizations like the National Institute for Health and Care Excellence (UK).

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

Estimated one-third of patients still have uncontrolled epilepsy despite the licensed antiepileptic drug (AED) market having grown exponentially over the previous 25 years. This article discusses the pre-clinical and clinical models and methods of contemporary AEDs and summarizes the clinical trials and properties of the AEDs developed during this time. We go over potential explanations for the seeming failure to create chemicals that are more effective. We also examine upcoming developments as well as the current medication registration regulatory regimes in the US and Europe. Positively, current research has improved the understanding of the pathophysiological mechanisms underlying pharmaco resistance and the epilepsies, enabling a modified strategy for the creation of more effective treatments. The pharmaceutical era of treatment modality is about to enter a new phase. A collaborative effort among researchers, physicians, and the industry will progress pharmacotherapy exploration for substance epilepsy in the future.

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

A dangerous neurological condition known as epilepsy impacts over 50 million people globally. Nearly 30% of epileptic patients experience pharmaco resistance, which is linked to psychological problems, social exclusion, dependent behavior, poor marriage rates, joblessness, and a lower quality of life. 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. Numerous in vivo and in vitro animal models have been suggested, and numerous novel antiepileptic medications have lately entered the market, however many patients continue to be pharmaco resistant. The challenges of treating and managing epilepsy will be highlighted in this study, along with the shortcomings of treatment modalities currently on the market and animal seizure models.

4.4 Innovations in Epilepsy Management – An Overview [32]

Thirteen new antiepileptic medicines (AEDs) have been developed in the previous twenty years, with each having unique efficacy ranges, mechanisms of action, pharmacokinetics, safety, and tolerance profiles. Since they are able to generate a notable decrease in symptom severity in up to 40% to 50% of patients who had been unresponsive to old generation medications, these newer AEDs provide a promising future in the care of epilepsy. Despite the fact that that these new medications are currently accessible, only a small number of patients with severely resistant seizures can be declared seizure-free. Some modern medications have been demonstrated to be non-inferior in regards to their efficacy, even while they are not superior to the older ones. They also have added benefits like improved tolerance, simplicity, and a lower interaction profile. While fresh research indicates that new generation medications may be completely justified for first therapy in many illnesses, older generation therapies are still the preferred option in the majority of circumstances.

This highlights the need for the development of novel, more effective antiepileptic medications for the treatment of uncontrollable seizures. In clinical studies, more direct comparisons of newer versus newer and newer compared older medications are required, both for adjunctive therapy and monotherapy. More than 20 substances have been found and are through various phases of pharmacological research. These substances show promise as antiepileptic and neuroprotective agents.

4.5 Drug treatment of epilepsy in adults [33]

The symptoms of epilepsy, a serious and sometimes fatal brain illness, can be effectively handled in the majority of individuals by taking one or more antiepileptic medications. On or off these medications, about two in three persons with newly diagnosed epilepsy may obtain a permanent seizure recovery, although about half will encounter mild to fairly severe side effects. Patients with epilepsy have a substantially higher risk of dying, as well as psychiatric and somatic comorbidities, as well as negative side effects from antiepileptic medications, particularly the 20–30% of patients whose seizures are not completely controlled with available medications (drug resistant epilepsy). More therapy choices are now available thanks to newer medicines, some of which, like levetiracetam, produce fewer drug interactions and less hypersensitivity than earlier ones. They don't, though, lessen the incidence of drug-resistant epilepsy or stop the onset of epilepsy in patients at high risk, like those who have suffered a severe brain injury. It is critically necessary to revive antiepileptic drug research in order to find more potent antiseizure medications for the management of drug-resistant epilepsy, particularly catastrophic forms. It is also necessary to develop antiepileptogenic drugs to stop epilepsy before the first seizure occurs in at-risk patients and illness drugs to stop persistent severe epilepsy brought on by a deteriorating underlying condition.

Chapter five
Results & Discussion

5.1 Results

5.1.1 History of Antiepileptic Drug Development

Various botanicals and plants have been used for thousands of years to treat epileptic diseases. Following Sir Charles Locock's unexpected result of potassium bromide's activity in this location in 1857, this substance was the first to be developed to treat epilepsy. since at that time, the only medication available for the care of epilepsy was bromide salts. The second substance to be accidentally found for the treatment of epilepsy was phenobarbital. Alfred Hauptmann, who had been using phenobarbital as a sedative for his epileptic patients when he unexpectedly realized that it also has anticonvulsant qualities, made this discovery in 1912. Phenobarbital has been used as an antiepileptic medication extensively since its. [34] The 1920s saw the introduction of the ketogenic diet as a method of treating epilepsy. This particular diet was created to imitate some of the features of fasting, a state believed to reduce seizures in certain people. It is heavy in fat, low in protein, and contains hardly any carbohydrates. The first antiepileptic medicine was found using an animal seizure model and is one of the first-choice medications for generalized tonic-clonic and intermittent seizures. When phenytoin was originally synthesized in 1908, Merritt and Putnam's groundbreaking experiments utilizing a cat electroshock-induced seizure model led to its recognition as the first non-sedating antiepileptic medication. Ever since, the electroshock-induced seizure model has been used to discover new medicines for the treatment of epilepsy, and it has been discovered that medications that are successful in preventing tonic hind limb extension in animals induced by electroshock are typically successful in treating generalized tonic-clonic seizures in humans. [35] Upon clinical examination by Lennox in 1945 and scientific assessment by Richards and Everett in 1944 using the pentylenetetrazole animal seizure model, trimethadione, the first medicine particularly for partial seizures, was approved in the 1940s. In the 1950s, primidone was made available as an antiepileptic medication. Although it is converted into the active substances phenobarbital and phenylethylmalonamide, other medications are chosen over primidone for clinical use due to its higher frequency of side effects. Since it was first used in clinical settings in 1960, ethosuximide has been the medication of choice for kids with absence seizures. [36] Diazepam was first made available in the late 1960s and is now

frequently used to manage status epilepticus. Schindler created carbamazepine in 1953, and in the 1960s it was first introduced as a medication to treat trigeminal neuralgia. Its antiepileptic action was later identified, and in the 1970s it was commercialized as an antiepileptic medicine. [37] Despite a coincidental discovery in 1963 when it was being employed as a solvent, valproic acid was first sold in the late 1970s. Numerous novel medications, notably felbamate, gabapentin, lamotrigine, topiramate, tiagabine, levetiracetam, oxcarbazepine, zonisamide, pregabalin, rufinamide, stiripentol, clobazam, vigabatrin, and lacosamide, have been approved for the treatment of of epilepsy over the past 20 years. A pro-drug of phenytoin called fosphenytoin as well as a prolonged derivative of the medication carbamazepine have both been launched. Additionally, vagus nerve activation combined with anti-seizure drugs has been approved for the treatment of partial epilepsy in adults. Currently, research is being conducted on injectable antiepileptic devices as well as chemical substances, which are the main subjects of development. [38]

5.1.2 New AEDs for recent-onset idiopathic generalized epilepsy

In a portion of Arm B of the SANAD study, **lamotrigine** (LTG) and **topiramate** (TPM) were compared to VPA for its effectiveness in treating idiopathic widespread epilepsy. The goal of SANAD was to determine whether LTG or TPM should take the role of VPA as the standard first-line medication. Consequently, VPA was found to be more effective than LTG and comparable to TPM for all patients as well as the subset of those with idiopathic widespread epilepsy. [39] Whereas the study demonstrated that TPM and VPA were equally beneficial, it should be noted that TPM was significantly less beneficial. For juvenile myoclonic epilepsy, which had not been previously treated, LTG was similarly demonstrated to be less effective than VPA. More recently, in a multicenter double-blind prospective study, 453 kids with newly diagnosed juvenile absence epilepsy were treated with ESM, LTG, or VPA. The independence rates for ESM and VPA were comparable after 16 weeks of treatment (53% and 58%, respectively), although for both, the rates were greater than for LTG (29%; p 0.001 for both analyses). [40]

5.1.3 New AEDs for recent-onset focal epilepsy

The SANAD study's Arm A was created as a pragmatic trial to determine whether because of the new AEDs, LTG, gabapentin (GBP), TPM, or oxcarbazepine (OXC), should take the role of CBZ as first-line medication. None of the new AEDs outperformed CBZ in terms of efficacy, which will be the only criteria considered here. LTG and OXC, on the other hand, were thought to be non - inferior in terms of efficacy, whereas CBZ was said to be more effective than GBP. The fact that GBP was discovered to be less effective suggests that the SANAD trial has the testing specificity to distinguish between effective and less-effective therapy. [41] The later-released levetiracetam (LEV) couldn't be tested in SANAD. Moreover, a well-controlled noninferiority trial has demonstrated that, at per-protocol analysis, 73.0% of patients randomized to LEV and 72.8% receiving managed CBZ were seizure free at the last assessed dose (modified absolute distinction 0.2%, 95% CI 7.8% to 8.2%) for at least 6 months. This indicates that LEV and slow release CBZ provide equivalent seizure remission rates. For new-onset focal seizures, one recent trial could not definitively prove that TPM (100 mg/day) was superior to oral PHT. The topic of monotherapy studies for people over 65 with recently-onset epilepsy is covered separately and is not covered in this section. Furthermore, it ought to be mentioned that the empirical support for evaluating newer to older AEDs cannot be deemed robust due to the lack of comparative studies or extensive clinical records. Research shows worries have been raised by an expert panel of the International League Against Epilepsy (ILAE) board. [42] Interestingly, the benchmark studies evaluating a number of older AEDs for new-onset epilepsy fall short of the present data base for assessing older against newer AEDs in this condition. In conclusion, in large, well-controlled trials of recent-onset epilepsy, none of the new AEDs were more effective than older AEDs like CBZ and VPA. Furthermore, research has demonstrated that a number of novel AEDs, including LEV, LTG, and OXC, are noninferior to CBZ in terms of controlling seizures by a certain margin. Furthermore, in focal epilepsy that was primarily ignored, GBP was demonstrated to be less effective than CBZ, while LTG was less effective than VPA. LTG was also proven to be less effective than VPA and ETS for childhood missing epilepsy that had not already been treated. This persuasively demonstrates that current postmarketing trial designs 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]

Lamotrigine, topiramate, and zonisamide are the latest important somewhat wide AEDs that are beneficial for individuals who experience both different types of seizures and largely widespread seizures. This is mostly due to the fact that some of these novel compounds have generally greater tolerability than second-line broad-spectrum medications like barbiturates and benzodiazepines. Valproate is regarded as the first medicine of choice due to the variety of seizure types that can occur in Dravet Syndrome and its wide range of activity. Lamotrigine, topiramate, and felbamate have received formal licensure for the treatment of Lennox Gastaut Disorder after proving to be significantly more effective than placebo in randomized, double-blind, controlled trials. Despite its propensity to cause irreversible visual field abnormalities, vigabatrin is seen as a potential first-line treatment versus juvenile spasms, particularly those linked with tuberous sclerosis. Due to its considerable toxicity issues, felbamate is only used in patients who have failed to respond to other medications. Other recent AEDs are usually used to treat

partial seizures and have a more restricted range of effectiveness. Newer medications (vigabatrin, tiagabine, gabapentin, and oxcarbazepine), like carbamazepine and phenytoin, may even make some widespread seizure kinds worse. [45]

5.1.4 Recent FDA Approved AEDS (Anti-Epileptic drugs)

The US Food and Drug Administration and the European Medicine Agency have authorized six new AEDs since 2007. (EMEA). Stiripentol, lacosamide, an eslicarbazepine acetate, ezogabine, and rufinamide Perampanel and (retigabine). These medications have discovered to have numerous mechanisms and places of behavior that fully explains their perceived. clinical consequences, such as tolerance, tolerance, and effectiveness.

- The EMEA gave **stiripentol** permission for Clobazam and valproic acid as an add-on treatment to combat widespread tonic-clonic seizures that refuse treatment in young Dravet syndrome patients. No It is discovered that another AED has antiepileptic capability. similar to stiripentol in cases of Dravet syndrome. It exacerbates the activation of transgenic GABAA receptors and enhances the neurotransmission of gamma-aminobutyric acid (GABA). Its pharmacokinetics are not linear. As during stiripentol therapy, neurobehavioural and gastrointestinal problems are frequent. Being most frequently reported negative side effects were sleepiness, tremor, ataxia, nausea, and weight loss. Leucopenia and transient aplastic anemia have also been documented. There are capsules (250 mg, 500 mg) and powder for oral suspension of stiripentol accessible (250 mg, 500 mg). [46]
- **Samide** was given FDA approval in 2008 as an adjuvant treatment for people 17 years of age and older experiencing partial onset seizures. It was the first AED to improve the voltage-gated sodium channels' slow deactivation element. [47] **Lacosamide** also interacts with the protein known as the contracting responsive facilitator, however it is unclear if this contributes to its antiepileptic effects. The most frequently reported side effects include ataxia, tiredness, nausea, and dizziness. Phase III studies evaluating the safety and effectiveness of lacosamide and carbamazepine controlled release as monotherapy in newly or finally diagnosed patients with epilepsy, age 16 and older, are currently being conducted. It has been

studied for the management of status epilepticus as well as the treating of clinical symptoms in both adults and children with epilepsy. [49]

- 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. It prolongs the voltage-gated sodium channels' inactive state. The most frequently reported negative impacts are drowsiness, nausea, exhaustion, headaches, diplopia, and gastrointestinal disorders. The FDA is evaluating it for generalized anxiety disorder, refractory status epilepticus, and its effectiveness in compared to the ketogenic diet in individuals with drug-resistant epilepsy. It is sold in tablets in dosages of 200 mg and 400 mg. [35]
- 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. It has been linked to headaches, diplopia, nausea, aberrant coordination, dizziness, and somnolence. Phase III trials are currently being conducted on people with approach to treatment seizures, and phase II trials are being conducted on bipolar illness. Tablet 800 mg is the prevalent formulation. [42]
- **Ezogabine** is the first AED to targeted and activate the voltage-gated potassium channel (also known as retigabine in Europe) (Kv7). For patients over 18 with status epilepticus and refractory partial epilepsy, it was licensed in 2011 as an additional therapy. Because the bladder urothelium contains voltage-gated potassium channel subunits Kv7.2–Kv7.5, urine retention is a major side effect of retigabine treatment. Adverse effects like sleepiness, lightheadedness, and disorientation are usually dose-related. 50 mg, 100 mg, 200 mg, 300 mg, and 400 mg tablets are offered. [47]
- The first glutamate receptor blocker to receive approval was **Perampanel,** which was first made available in Europe in July 2012. It was given FDA approval in October 2012 to be used as an additional therapy for individuals 12 years of age and older who were experiencing partial onset seizures either with or without secondary generalized seizures. Dizziness, gait disruption, somnolence, weariness, injuries, and suicidal conduct are some of the prevalent side effects seen. Only a

small amount of clinical data is available for this medication. It is sold as tablets in strengths of 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg. [41]

- The FDA granted **vigabatrin** approval in 2009 for the treatment of juvenile contractions in children between the ages of one month and two years old as well as supplementary therapy for adults with refractory complex partial seizures. But it was initially marketed in Europe in the late 1980s, and it received approval in Australia and Canada in 1993 and 1994, respectively. Vigabatrin is available in many nations, but until recently, it wasn't in the US due to the drug's widespread association with irreversible peripheral vision loss in patients. It increases GABA levels in the brain because it is an irreversible GABA transaminase antagonist. Both a 500 mg tablet and a 500 mg powder for oral solution are accessible. [48]
- 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. In these patients, clobazam medication has reduced drop seizures by up to 70%. By attaching to the benzodiazepine site of the GABAA receptor, it enhances GABAnergic neurotransmission. It is frequently included in regiments that also contain topiramate, felbamate, lamotrigine, or valproic acid. It is being studied for usage as a monotherapy for focal or generalized seizures in adults and as an adjuvant therapy for status epilepticus and febrile seizures in both adults and children. [41]

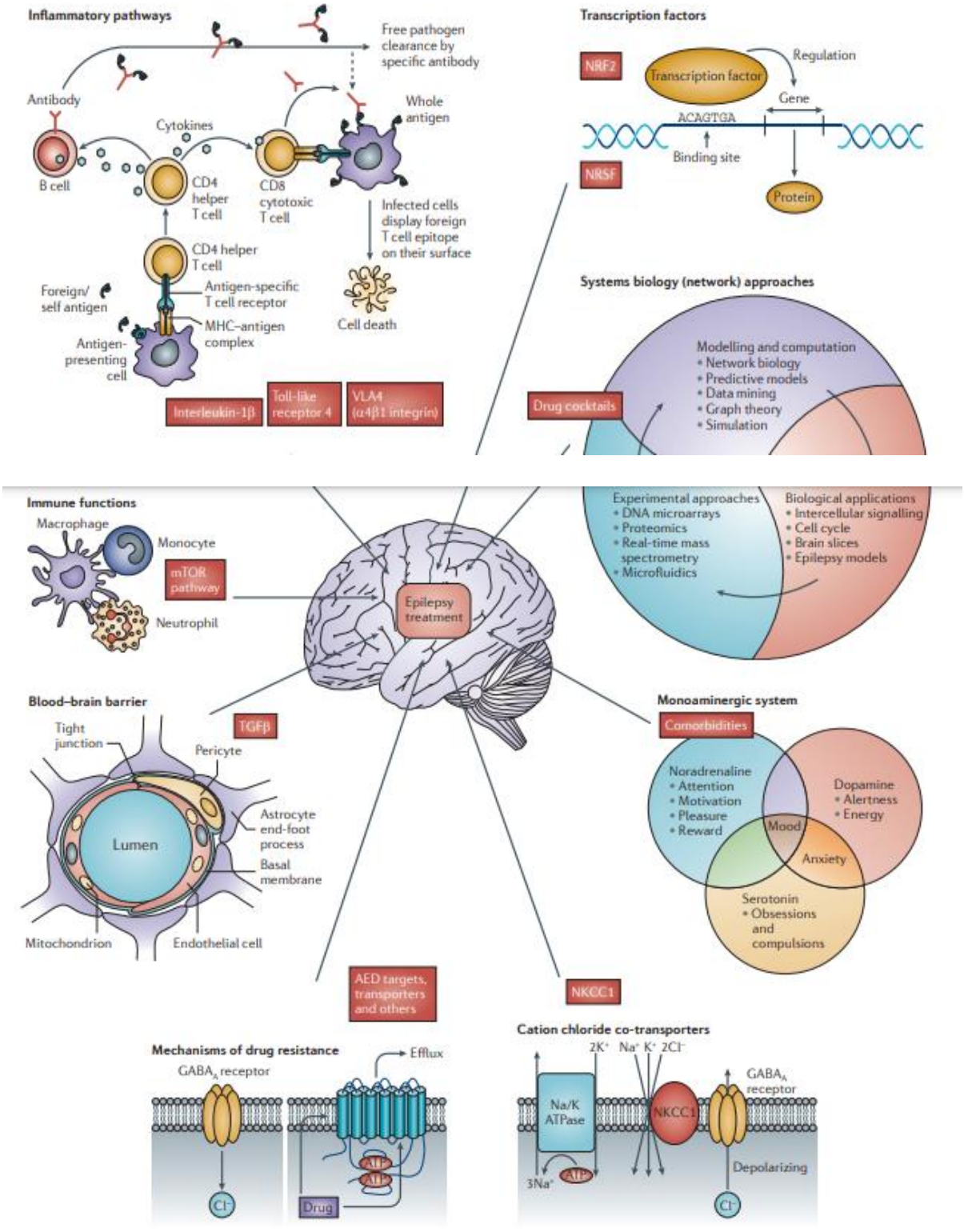

Figure 3: Anti-Epileptic drugs working pathways [49]

5.1.5 New clinical trial design

Prospective clinical trial designs for epilepsy medications should establish the effectiveness of the drug (ideally by objective seizure counts) during the initial phases of clinical research, and show superiority over the accepted standard of care at the optimum dose and be able to judge the capacity of potential new drugs to treat epilepsy before the people who are at risk for seizures experience their first or second risk of epilepsy occurring. Following the start of seizures, Clinical study approaches are offered to determine regardless of whether potential new medications can alter the unrecognized epilepsy (that is, disease modification). Future Preclinical discoveries should be translated into development plans employing reliable and objective biomarkers in Phase-I challenges, early and decisive (but "light"; that is, less intense) clinical proof-of-concept investigations, which are pricey. [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]

Prior investing in confirmatory Phase III research, comparing Phase II trials with the standard of care (if any) should be done to enable early de-risking and evaluation of the proliferation and differentiation. The variability of the placebo reaction seen with the conventional clinical trial design needs to be controlled in future clinical trial designs incorporating placebo medications. [31]

5.2 Discussion

Antiepileptic medications that are now on the market have a limited effectiveness, which restricts their use and makes patient treatment challenging. Antiepileptic medications can only treat symptoms since they reduce seizures but cannot reverse epileptogenesis. The current information suggests that, despite the launch of numerous new antiepileptic medications (AEDs) since about the early 1990s, the effectiveness and tolerability of pharmacological epilepsy therapy has not much enhanced. What are the causes of the present AED development's seeming failure to find medications with greater efficacy? In particular, the maximal electroshock seizure test (MES) in rodents, which functioned as a crucial gatekeeper, all AEDs were identified using the same standard animal models, with very few variations. These studies produced helpful new AEDs, but it is clear that they had little impact on the creation of AEDs that were more effective in treating patients who were not yet AED-resistant. This issue is not new, but interestingly, it has gone mostly unnoticed for a number of years. Another, admittedly speculative, rationale is that we won't make headway in the pharmacological therapy of drug-resistant epilepsy until we create medications that directly combat the underlying condition. More effective medications may allow us to ditch clinically dubious studies with purposefully less effective supervision and noninferiority designs, and demand evidence for relative effectiveness, even while improved preclinical methodologies won't be able to get around regulatory restrictions. If we can't find a solution to this conundrum, the collapse of AED research will likely block any further advancements in the treatment of epilepsy. This frustration has been felt by physicians, fundamental scientists, and industry. Therefore, we require novel ideas and innovative ways of thinking about how to fundamentally alter and enhance AED advancement and research. In this regard, the authors of this comprehensive examination will examine a number of novel concepts that could, in the future, result in more effective medication treatments for epilepsy.

Chapter six
Conclusion

6.1 Conclusion

Enhanced ways of assessing preclinical models, more reliable protocols, and a more uniform assessment of results are needed to find effective treatments for individuals with epilepsy. The current discussion should not be viewed as a comprehensive list of suggestions but rather as a foundation for the creation of particular proposals. To guarantee that the funding submissions that have the best chance of producing results that are clinically relevant are supported, such guidelines could also be used to guide the grant approval process. The definition of a hierarchical list of preclinical evidence that is suggested to advance to formal clinical testing, as well as a second list of optional, complimentary material, may be included in future study. As a result, it would be possible to compare various AETs in terms of their transformative value, assigning each a different scale of likelihood of clinical benefit based on information from preclinical research. Regular assessments of preclinical AET results that have been reported would be beneficial. The feasibility and optimal application of animal models, techniques for behavioral or consequence monitoring, methodological design, and a critical, comparison was made of the preclinical efficacy evidence for certain seizure types or syndromes should all be covered in such reviews. This would enable recommendations to be adjusted to the changing demands of the industry. To achieve this goal, a Cochrane-like partnership would be helpful. A platform for the publication of both good and negative studies would be helpful in order to impartially assess the potential of novel AETs.

Chapter seven
Reference

Reference

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