"EVALUATION OF ANTIEPILEPTIC ACTIVITIES OF RAMIPRIL AND TELMISARTAN AND POTENTIATION OF THE ANTIEPILEPTIC EFFECT OF PHENYTOIN SODIUM AND VALPROIC ACID IN RAT MODELS"

By

DR. SNEHA

Dissertation Submitted to the

BLDE University Vijayapura, Karnataka

In partial fulfilment

of the requirements for the degree of

DOCTOR OF MEDICINE

IN

PHARMACOLOGY

Under the guidance of

DR. AKRAM A. NAIKAWDI

Professor and H.O.D

DEPARTMENT OF PHARMACOLOGY

B.L.D.E. U's SHRI B.M. PATIL MEDICAL COLLEGE

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Sneha

Place: VIJAYAPURA

Signature of the Candidate

Date: 20-05-2024

DR. SNEHA

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This is to certify that the dissertation entitled **"EVALUATION OF ANTIEPILEPTIC ACTIVITIES OF RAMIPRIL AND TELMISARTAN AND POTENTIATION OF THE ANTIEPILEPTIC EFFECT OF PHENYTOIN SODIUM AND VALPROIC ACID IN RAT MODELS"** is a bonafide research work done by **DR. SNEHA** under my supervision and guidance, in partial fulfilment of the requirement for the degree of M.D. (Pharmacology)

.

Signature of Guide

DR. AKRAM A. NAIKAWDI
Professor and HOD,
Department of Pharmacology,
B.L.D.E. U's Shri B.M.Patil Medical College,
Vijayapura.

Place: VIJAYAPURA

Date: 20-05-2024

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Signature and Seal of the HOD

DR. AKRAM A. NAIKAWDI
M.D. (Pharmacology)
Professor and Head
Department of Pharmacology
B.L.D.E. U's Shri B.M. Patil
Medical College, Vijayapura

Signature and Seal of the Principal

DR. ARAVIND V. PATIL
M.S. (GENERAL SURGERY)
Principal
B.L.D.E. U's Shri B.M. Patil
Medical College, Vijayapura

Place: VIJAYAPURA

Date: 20-05-2024

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Signature of the Candidate

Date: 20-05-2024

DR. SNEHA

B.L.D.E. U's SHRI B.M. PATIL MEDICAL COLLEGE, VIJAYAPUR

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Chairman
Institutional Animal EthicsCommittee
B.L.D.E. U's Shri B.M. Patil Medical College,
Vijayapura

Date: 20-05-2024
Place: VIJAYAPURA

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Date: 20-05-2024

Place: Vijayapura **DR. SNEHA**

LIST OF ABBREVIATIONS

AEDs	Antiepileptic drugs
AMPA	alpha amino-2,3-dihydroisoxazolepropanoic-5-methyl-3-oxo-4 acid
ANOVA	One way analysis of variance
GABA	γ-aminobutyric acid
GTCS	Generalized-tonic-clonic seizure
HLE	Hind limb tonic extension
i.p.	Intraperitoneal
ILAE	International League Against Epilepsy
MES	Maximal Electroshock
NMDA	N-methyl-D-aspartate receptor
PDS	Paroxysmal depolarization shift
PTZ	Pentylenetetrazole
SEM	Standard error of mean
SV2A	Synaptic vesicle glycoprotein 2A
TLE	Temporal lobe epilepsy

ABSTRACT

Background: Epilepsy is a chronic disorder with heterogeneous symptoms characterized by recurrent seizures resulting from abnormal discharge of cerebral neurons. Several different drugs are available and act through diverse mechanisms. However, most of them have a low safety margin and provide seizure control in 60 - 70% of patients. Attempts are being made to explore the anti-epileptic potentials of several different groups of drugs. Drugs interfering with Renin- Angiotensin- Aldosterone system (RAAS) have shown potential as an add-on therapy with existing anti-epileptic drugs.

Objectives: To evaluate the anti-epileptic potential of Ramipril and Telmisartan using the Maximum Electroshock (MES) model and PTZ model in rats and also to evaluate its effect as an add-on with Phenytoin and Sodium Valproate

Methods: The study was conducted on Male Wistar rats to investigate the effects of Ramipril (2mg/kg) and Telmisartan (30 mg/kg) individually, as well as in combination with Phenytoin and Sodium Valproate, in models of epilepsy. In the maximal electroshock (MES) model, the rats were administered Ramipril (2mg/kg) and Telmisartan (30 mg/kg) alone and in combination with Phenytoin (Ramipril 1mg/kg + Phenytoin Sodium 50 mg/kg) and (Telmisartan 15 mg/kg + Phenytoin Sodium 50 mg/kg). Phenytoin Sodium (100mg/kg) was used as the standard reference. The effects were assessed based on the abolition of Hind Limb Tonic Extension (HLTE), serving as an index of anti-epileptic activity. Similarly, in the pentylenetetrazole (PTZ) model, the rats received Ramipril (2mg/kg) and Telmisartan (30 mg/kg) alone and in combination with Sodium Valproate (Ramipril 1mg/kg + Sodium Valproate 125 mg/kg) and (Telmisartan 15 mg/kg + Sodium Valproate 125 mg/kg). Sodium Valproate (250mg/kg) was the standard reference. The effects were evaluated based on the delay in the onset of convulsions, another index of anti-epileptic activity.

Results: Both Ramipril and Telmisartan exhibited significant anti-epileptic effects when used alone. Both drugs potentiated the anti-epileptic effect of Phenytoin and Sodium Valproate.

Conclusion: Drugs interfering with RAS, like Ramipril (ACEI) and Telmisartan (ARB), can be used alone for generalized tonic-clonic convulsions (GTC). In patients receiving ACEIs or ARBs for other clinical conditions, a dose of Phenytoin and Sodium Valproate can be reduced if these patients also have epilepsy.

Keywords: Ramipril, Telmisartan, Phenytoin, Sodium Valproate, GTC, MES and PTZ Induced Convulsions.

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INTRODUCTION

Epilepsy is a chronic neurological disorder characterized by periodic and unpredictable episodes of seizures resulting from abnormal synchronous and rhythmic firing of brain neurons. Seizures often result in transient impairment of consciousness, exposing an individual to the risk of bodily injury. It often interferes with an individual's quality of life, including educational and employment opportunities. [1]

Although many underlying disease mechanisms can lead to epilepsy, the exact cause is unknown in 50% of cases globally.[2] Several different causes have been identified, which include brain damage from prenatal or perinatal causes, congenital malformations or genetic conditions with associated brain malformations, severe head injury, and infections of the brain such as meningitis, encephalitis or neurocysticercosis, specific genetic syndrome, and brain neoplasm. If properly diagnosed and treated, up to 70% of people with epilepsy could live a seizure-free life. The main objective of the treatment of epilepsy is to achieve complete seizure control with maximally accepted unwanted effects of the drugs. Unfortunately, neither curative nor effective prophylactic therapy is available for epilepsy. [3]

Several different drugs with varied mechanisms are available for effective control of seizures.[4] Patients' compliance with the prescribed course of treatment is a significant problem because long-term therapy is often associated with the undesired effects of many drugs.[5] Many studies have evidenced the role of the inflammatory process and immune-mediated events causing neuronal damage. Animal experiments have shown that neuroinflammation can increase the permeability of the blood-brain barrier and enhance neuronal excitability. [6]

Various animal studies support the role of oxidative stress in the pathogenesis of epilepsy. In the Lithium-Pilocarpine model of temporal epilepsy in animals, mitochondrial-related oxidative stress plays a vital role in the pathogenesis of epilepsy. [7] Antioxidants can be important in reducing oxidative stress, neuronal injury, and, therefore, precipitation of seizures. [8] [9] Evidence supports that a tissue-based Angiotensin II-producing system regulates blood pressure, thirst, water balance, memory, inflammatory process, remodeling, and apoptosis. The brain contains all components of RAS.[10] Drugs that interfere with RAS have overall pharmacological advantages over existing antiepileptic drugs, such as no effect on the hepatic microsomal enzyme system, devoid of sedation, non-interference with quality of life, and wide therapeutic range. They are suitable for all age groups. [3]

Considering the limitation of existing antiepileptic drugs, the favorable pharmacological profile of drugs interfering with RAS, and the significant role of RAS in the brain, the present study is undertaken to evaluate the antiepileptic effect of clinically used drugs interfering with RAS and also to evaluate their ability to potentiate the antiepileptic effect of existing drugs.

OBJECTIVES

AIMS AND OBJECTIVES OF THE STUDY

1. To evaluate the anti-epileptic activity of Ramipril and Telmisartan in the rat model.

2. To evaluate the ability of Ramipril and Telmisartan to potentiate the anti-epileptic effect of Phenytoin sodium and Sodium Valproate.

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REVIEW OF LITERATURE

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REVIEW OF LITERATURE

A. EPILEPSY

Origin

Epilepsy traces back to ancient Mesopotamia, where seizures were recorded on a 4000-year-old tablet. The Babylonians attributed seizures to divine causes, treating them spiritually. Hippocrates suggested a brain-based origin in ancient Greece. Medical understanding evolved with contributions from Maisonneuve, Todd, and Jackson, recognizing epilepsy as a neurological disorder due to abnormal brain activity. [11]

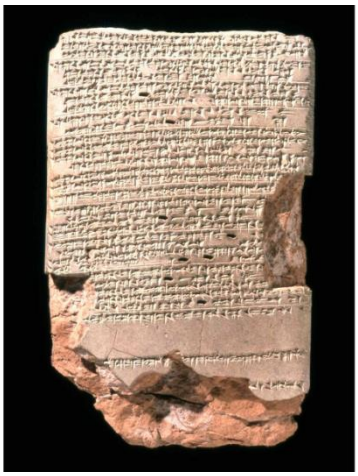


FIGURE 1 [11]

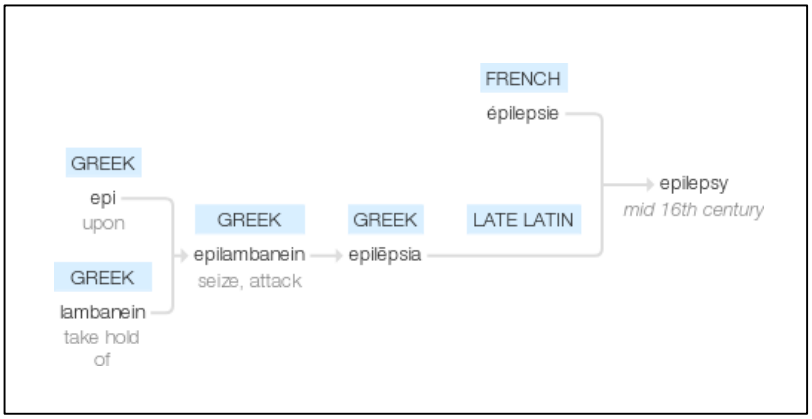


FIGURE 2

The word “epilepsy” originates from the ancient Greek word “epilambanein,” meaning “to seize upon” or “to attack suddenly.” This term reflects the sudden and unpredictable nature of seizures characteristic of the condition. [12]

Definition

Epilepsy is a complex neurological condition characterized by a predisposition to recurrent epileptic seizures, affecting approximately 10% of the population. **[13]**

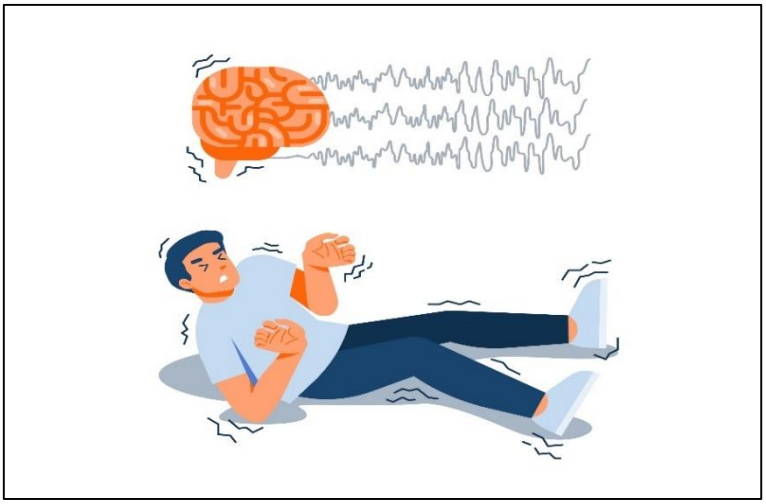


FIGURE 3: Epilepsy

Traditionally, *epilepsy* was defined as the occurrence of two unprovoked seizures more than 24 hours apart. However, in 2005, the International League Against Epilepsy (ILAE) broadened this definition to include various scenarios, such as one unprovoked seizure with a high likelihood of recurrence over the next ten years or the diagnosis of an epilepsy syndrome.

In 2014, ILAE updated the meaning of epilepsy as a person has epilepsy if they:

1. Have at least two seizures that are not provoked, happening more than 24 hours apart.

2. Have one seizure and a high chance of more seizures, like a 60% rise in the next 10 years.

3. Get a diagnosis of an epilepsy syndrome.

So, a person can be diagnosed with epilepsy after just one seizure, based on why it happened and the kind of syndrome. [14]

Aetiology

Epilepsy, a chronic brain disorder, is characterized by a persistent predisposition to generate seizures, which are unprovoked by immediate central nervous system insults. It affects individuals of all sexes and ages worldwide, with slightly higher prevalence and incidence rates in men and the elderly. Notably, focal seizures are more common than generalized seizures in both children and adults. [15]

The etiology of epilepsy varies based on sociodemographic characteristics and the extent of diagnostic workup, with approximately 50% of cases in high-income countries lacking a documented cause. Reports from low/middle-income countries (LMIC) indicate overlapping prevalence and remission rates with high-income countries, possibly due to misdiagnosis, acute symptomatic seizures, and premature mortality. [15] The prognosis of epilepsy varies, with about half of the cases achieving prolonged seizure remission. However, recent reports highlight differing prognostic patterns, including early and late remission, a relapsing-remitting course, and a worsening course. While epilepsy per se carries a low mortality risk, significant differences in mortality rates exist among different demographic groups. [15]

The identification of epilepsy's etiology is crucial for diagnosis, prognostic counseling, and management. The etiologies can be categorized into structural, genetic, infectious, metabolic, immune, and neurodegenerative factors. Genetic predisposition plays a significant role in epilepsy, with varying degrees of influence across different populations. [16]

Genetics has emerged as a critical aspect of epilepsy research, with advances in gene sequencing technologies revealing a more significant genetic contribution to epilepsy than previously recognized. Progress in epilepsy genetics has led to the identification of molecular

discoveries in various epilepsy groups, shedding light on genetic and non-genetic causes. [17] Early childhood epilepsies often resist therapy and are associated with cognitive and behavioral comorbidities. Etiology-focused precision medicine, including gene-based therapies, holds promise for preventing seizures and comorbidities. [18]

Despite the significance of etiology in epilepsy management, official classifications of epilepsy have historically focused more on seizure semiology and electroencephalographic features rather than etiology. However, there is a growing recognition of the importance of considering etiology in classification schemes to guide treatment and prognosis. [19]

Recent advancements, such as the new classification of epileptic seizures and epilepsies by the International League Against Epilepsy (ILAE), emphasize the importance of etiology in optimizing management strategies. Precision therapies targeting the molecular underpinnings of epilepsy are emerging, offering hope for improved treatment outcomes. [20]

The prevalence and incidence of epilepsy vary globally, with higher rates observed in low- and middle-income countries. However, estimating the burden of epilepsy requires considering factors such as age, sex, country income level, epilepsy syndrome, seizure type, and etiology, among others. [21, 22] Meta-analytic techniques can help quantify the burden of epilepsy and explore sources of heterogeneity between estimates. [23]

These categories are not mutually exclusive, and many etiologies can overlap between different groups. Genetic factors play a significant role in the risk of seizures in individuals with epilepsy. Advances in diagnostic tools, such as neuroimaging and genetic testing, have improved our ability to identify underlying causes of epilepsy. Understanding the etiology of epilepsy is crucial for personalized treatment approaches and prognostic counseling. [16]

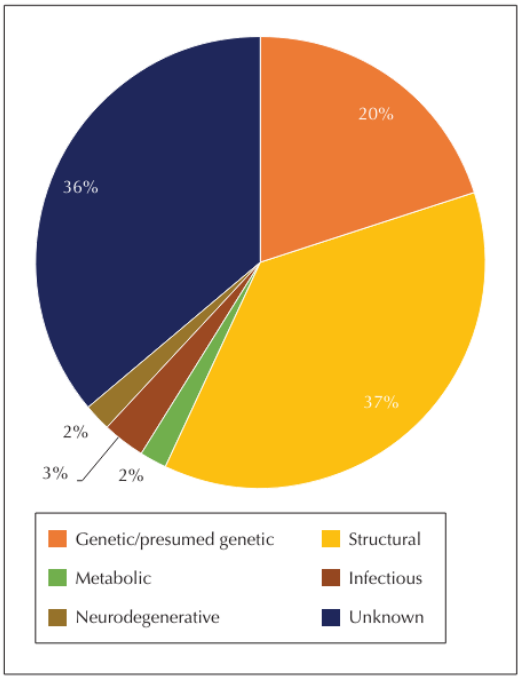


FIGURE 4 [16]

Here is a detailed overview of the various Aetiologies of epilepsy:

Structural Aetiologies: Structural abnormalities in the brain, such as tumors, malformations, vascular lesions, hippocampal sclerosis, or traumatic brain injury, can lead to epilepsy. These abnormalities can disrupt normal brain function and trigger seizures. Structural imaging techniques like MRI are essential for identifying these causes. [16]

Genetic Aetiologies: Genetic factors play a significant role in epilepsy. Some forms of epilepsy have a vital genetic component, with specific gene mutations or variations increasing the risk of developing the condition. Genetic epilepsy can be inherited in a monogenic or polygenic manner, and the identification of genetic causes can inform prognosis, treatment decisions, and genetic counseling for family members. [16]

Infectious Aetiologies: Infections of the central nervous system, such as bacterial, viral, fungal, or parasitic infections, can lead to epilepsy. In some regions, infectious causes are more prevalent, with conditions like neurocysticercosis contributing significantly to the burden of epilepsy. Infections can cause inflammation and structural damage in the brain, leading to seizure activity. [16]

Metabolic Aetiologies: Metabolic disorders, both acquired and genetic, can result in epilepsy. Inborn errors of metabolism, glucose transport defects, pyridoxine-dependent seizures, and mitochondrial pathologies are examples of metabolic causes of epilepsy. These conditions often present with specific clinical manifestations and biochemical abnormalities, and early diagnosis is crucial to prevent brain damage. [16]

Immune Aetiologies: Autoimmune conditions affecting the central nervous system, such as Rasmussen encephalitis or autoimmune encephalitis with antibodies against neuronal proteins like LGI1 or NMDA receptors, can lead to epilepsy. Immune-mediated inflammation in the brain can disrupt neuronal function and trigger seizures. Immunomodulatory therapies are often used to manage epilepsy of immune origin. [16]

Neurodegenerative Aetiologies: Neurodegenerative diseases, such as Alzheimer's disease, Down syndrome, or progressive myoclonic epilepsies, are increasingly recognized as causes of epilepsy. These conditions involve progressive degeneration of brain structures and functions, leading to seizure activity. Understanding the neurodegenerative causes of epilepsy is essential for tailored management approaches. [16]

Understanding the diverse etiological factors contributing to epilepsy is essential for effective diagnosis, prognosis, and treatment. Advances in genetics, precision medicine, and epidemiological research offer new insights into the complex nature of epilepsy and hold promise for improved management strategies in the future.

Pathophysiology

The pathophysiology of epilepsy is a multifaceted phenomenon influenced by various factors, encompassing genetic predisposition, brain injury, infections, and structural abnormalities in the brain. [24] These factors disrupt the delicate balance between excitatory and inhibitory neurotransmission, culminating in hyperexcitability and hyper synchronization of neuronal networks, hallmark features of epilepsy.

A crucial aspect of epilepsy research revolves around the paroxysmal depolarization shift (PDS), which mirrors the cellular events underlying interictal spikes observed in electroencephalogram (EEG) recordings.[24] PDS entails transient depolarization of neuronal membranes, often accompanied by bursts of action potentials, driven by glutamate receptor-mediated currents and L-type voltage-gated calcium channels. While PDS is implicated in both pro-epileptic and anti-ictal roles, its long-term effects may contribute to epileptogenesis by influencing gene transcription and inducing morphological changes in neuronal networks.

Conversely, in the short term, PDS might exhibit anti-ictal properties by inducing transient electrical refractoriness in neuronal circuits, potentially impeding the spread of seizure activity. [24] Understanding the intricate interplay of these mechanisms is pivotal for developing targeted therapeutic interventions aimed at modulating neuronal excitability and enhancing seizure control in epilepsy patients.

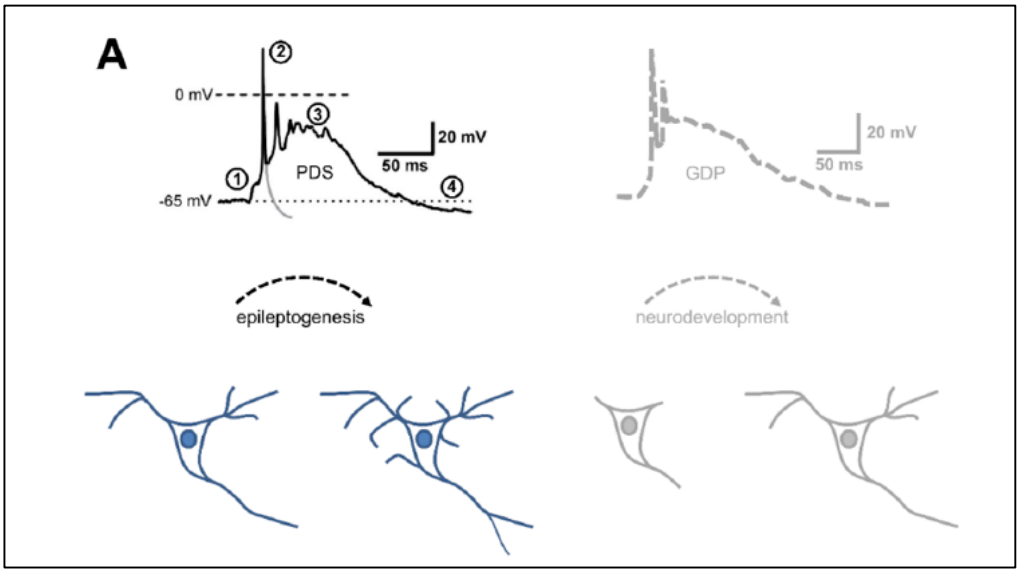


FIGURE 5 [25] **(A):** Depicts a typical Paroxysmal Depolarization Shift (PDS), highlighting its synaptic triggering, action potentials of decreasing amplitude, a depolarized plateau, and termination by repolarization, resembling giant depolarizing potentials (GDPs) observed in neonatal rats. The figure suggests potential pathogenic neuronal changes initiated by PDS.

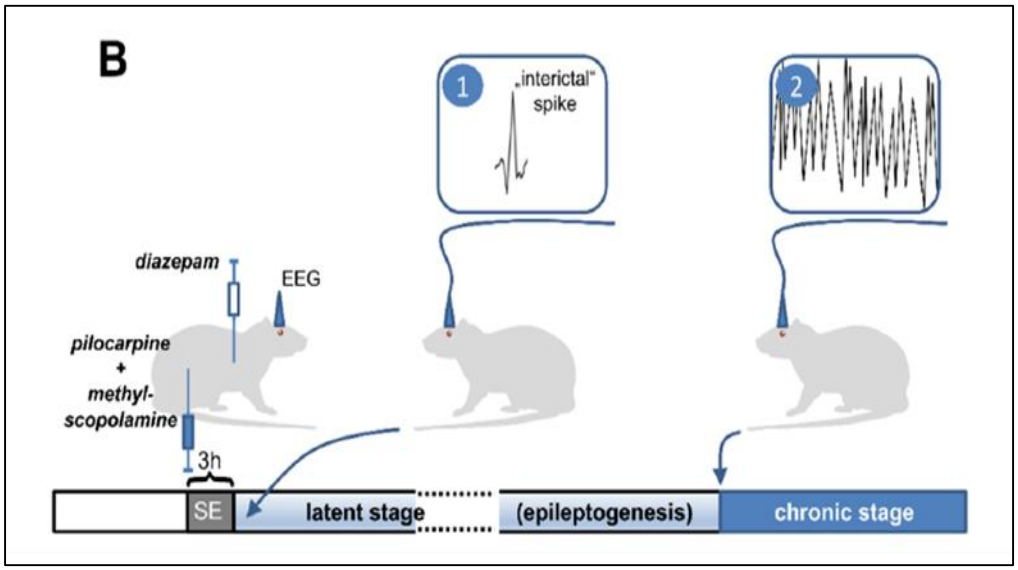


FIGURE 5 [25] **(B):** Illustrates the early appearance of electrographic spikes, the multi-unit correlate of PDS, in post-status epilepticus animal models of acquired epilepsy. It demonstrates the timing of electrographic spikes following the insult, indicating their association with the initiation of epileptogenesis.

Moreover, genetic channelopathies play a pivotal role in shaping the pathophysiology of epilepsy. [25] Recent studies have shed light on the involvement of PDS in epilepsy, challenging prior assumptions regarding its significance in the disorder. Interictal spikes associated with PDS, originally linked solely to epilepsy, have been observed in various neurological conditions, broadening the spectrum of PDS implications in neuro-pathologies [25]. Additionally, genetic channelopathies, particularly mutations in ion channels such as sodium and calcium channels, contribute significantly to epilepsy's etiology. [25]

Up-regulation of specific ion channels like Ca v 1.3 has been implicated in both acquired and genetically predisposed forms of epilepsy, underscoring the importance of genetic factors in epilepsy development. Understanding the intricate relationship between PDS and genetic channelopathies provides valuable insights into the underlying mechanisms of epilepsy pathophysiology, offering avenues for targeted therapeutic interventions and personalized treatment approaches. [25]

Thalamocortical circuits play a crucial role in generalized epilepsies, affecting millions of individuals worldwide. The intrinsic properties of thalamic neurons and their connections with cortical regions contribute to different firing patterns that influence brain states. Transitions from tonic to burst firing in thalamic neurons can lead to seizures that rapidly generalize, causing altered awareness. Understanding the regulation of thalamic activity in generalized epilepsy syndromes is crucial in identifying new therapeutic targets for treating pharmaco-resistant epilepsy through thalamic modulation and dietary therapy. Further research is needed to unravel the complexities of thalamocortical circuits in epilepsy and improve treatment outcomes for affected individuals. [26]

The pathophysiology of Mesial Temporal Lobe Epilepsy (TLE) involves various mechanisms contributing to seizure development, often linked to hippocampal sclerosis with neuronal and interneuronal loss. Network rearrangement, axonal sprouting, and changes in receptor functioning are key factors in TLE. Disruption of the blood-brain barrier in regions like the hippocampus is significant, with potential preventive therapies like ghrelin analogs. Challenges in anti-epileptogenic therapy highlight the need for deeper understanding and exploration of preventive strategies due to TLE's drug resistance. Research emphasizes investigating pathophysiological phenomena in specific brain regions and extrahippocampal areas to guide treatment strategies. Understanding TLE's multifaceted pathophysiology is crucial for developing effective therapies, necessitating further research for innovative management approaches. [27]

Classification

Epilepsy, a multifaceted neurological disorder characterized by recurrent seizures, necessitates a meticulous classification system to facilitate accurate diagnosis, treatment planning, and research endeavors. [30] The International League Against Epilepsy (ILAE) has spearheaded the development of classification frameworks, with the 2017 model representing a significant advancement in this domain. [30] By refining terminologies and incorporating previously unaddressed seizure types, the 2017 ILAE model aims to enhance comprehension among clinicians, patients, and caregivers. [28] This revision underscores the imperative of employing clear and inclusive language to categorize seizures based on their origin, awareness level, and motor manifestations. [28]

The evolution of these classifications highlights the importance of the new operational classification introduced in 2017. [30]

Historical Perspective:

The first modern classification of epileptic seizures was proposed in 1964 by Gastaut et al. This classification was further refined and popularized in 1970 by Gastaut. Prior to these classifications, there was a lack of clear distinction between seizure types and epilepsy types. The need for separate classifications became evident as a significant percentage of patients with seizures were unclassifiable according to the 1989 criteria. [30]

Importance of Classification:

- Classifications of seizures and epilepsy are essential for patients, clinicians, and researchers.
- For patients, having a specific diagnosis/etiology improves understanding and facilitates communication with healthcare providers.
- Clinicians and care teams benefit from classifications as they enhance communication, aid in treatment decisions, and help predict clinical outcomes.

Researchers rely on classifications to investigate treatment responses, clinical courses, and genetic correlations for different types of seizures and epilepsy. [30]

New Operational Classification (2017):

The 2017 operational classification introduced by the ILAE represents a significant advancement over previous classifications. This new classification system utilizes alternative terms and includes significant additions that enhance the classification's intuitiveness, transparency, and versatility. It allows for the inclusion and classification of previously unclassifiable seizure and epilepsy types, addressing a longstanding challenge in epilepsy diagnosis. [30]

Expanded Seizure Type Classification:

The new classification system provides flexibility by incorporating additional terms to categorize seizures with similar semiology. These additional terms enable clinicians and researchers to communicate more effectively about specific groups of patients with epilepsy, facilitating targeted drug therapy and genetic correlations. [30]

Clinical Application:

Clinicians can now provide patients with more specific descriptions of their epilepsy, improving diagnosis and patient understanding. The new classifications help distinguish different seizure types, essential for tailoring treatment approaches and predicting outcomes. [30]

The classification system consists of three main levels: seizure type, epilepsy type, and epilepsy syndrome, focusing on incorporating etiology at each stage of diagnosis. [29]

- Seizure Type: The classification begins with identifying the type of seizure the patient is experiencing. It is assumed that the patient is having epileptic seizures as defined by the 2017 ILAE Seizure Classification. This step is crucial as it lays the foundation for further classification and treatment decisions. [29]

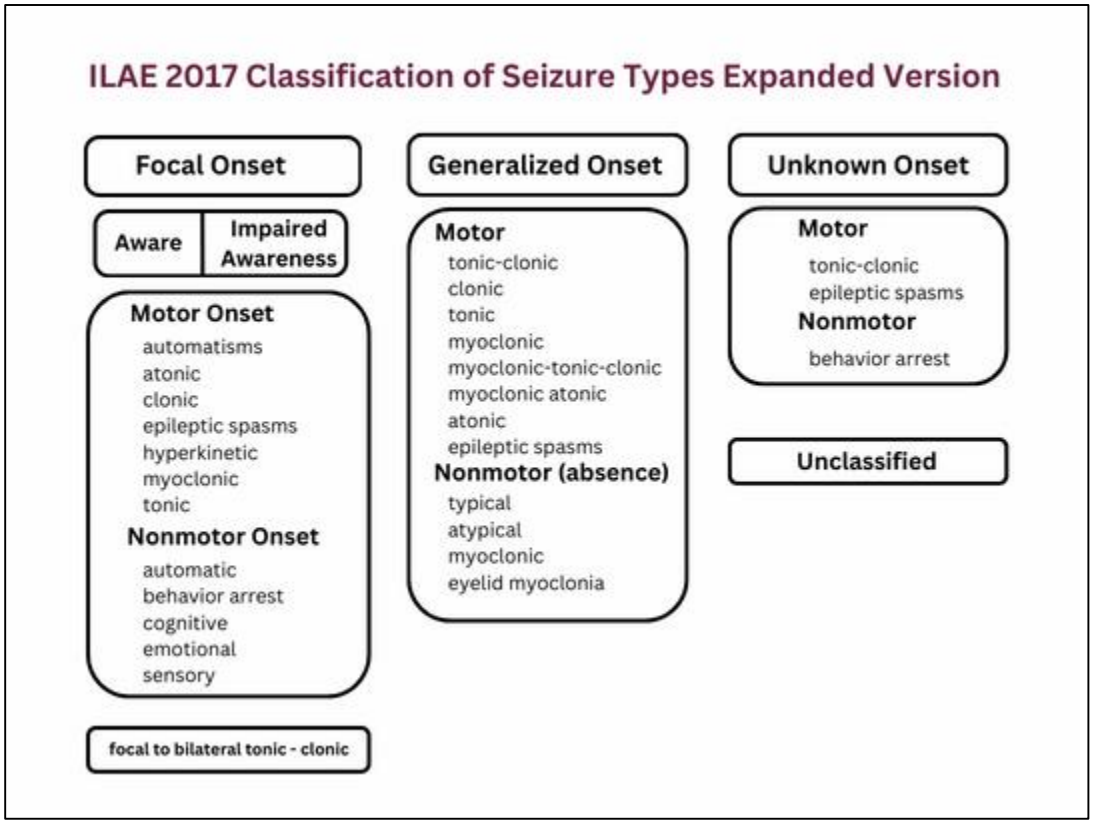


FIGURE 6

- Epilepsy Type: Once the seizure type is determined, the next step is to classify the epilepsy type. This includes categorizing the epilepsy as focal epilepsy, generalized epilepsy, combined generalized and focal epilepsy, or an unknown epilepsy group. This classification helps understand the underlying mechanisms of epilepsy and guides treatment strategies. [29]

- Epilepsy Syndrome: The third classification level involves identifying a specific epileptic syndrome if possible. This allows for a more precise diagnosis and can provide valuable information on prognosis and treatment options tailored to the specific syndrome. [29]

- Etiology: Throughout the classification process, emphasis is placed on considering the etiology of the epilepsy. Etiology is divided into six subgroups, each with potential therapeutic implications. Understanding the underlying cause of epilepsy is essential for selecting appropriate treatment approaches. [29]

At the crux of epilepsy classification lies a hierarchical structure encompassing seizure type, epilepsy type, and epilepsy syndrome, each serving as a pivotal determinant in treatment stratification and prognostication. [29] The journey begins with identifying the specific seizure type experienced by the patient, laying the groundwork for subsequent classification and therapeutic decisions. [29] Subsequently, attention shifts to characterizing the epilepsy type, delineating between focal, generalized, or combined generalized and focal epilepsies, or identifying cases falling within an unknown epilepsy group. [29] This categorization facilitates a deeper understanding of the underlying pathophysiological mechanisms, guiding tailored therapeutic interventions. [29]

The multidimensional classification model introduced in the 2017 ILAE framework represents a paradigm shift in epilepsy classification, integrating various dimensions such as clinical semiology, disease etiology, anatomical localization, and associated comorbidities [30]. This holistic approach fosters improved communication among healthcare participants and enhances diagnostic precision and treatment efficacy. [30].

Moreover, the revision introduces novel seizure types and replaces outdated terminologies with more precise descriptors, refining the lexicon utilized in epilepsy classification. [28] By acquainting themselves with the intricacies of the classification system, healthcare professionals can boost their proficiency in diagnosing and managing epilepsy cases. [28]

In summary, epilepsy classification based on the 2017 ILAE model represents a pivotal stride toward standardizing diagnostic practices and enhancing patient care. [30] This evolution in classification systems mirrors the relentless progress fueled by insights gleaned from global clinical and research endeavors. [29] A robust classification framework empowers clinicians to deliver personalized care and fosters collaboration and innovation within the epilepsy community, ultimately driving improvements in patient outcomes and quality of life. [30]

Clinical Diagnosis

History Taking and Physical Examination:

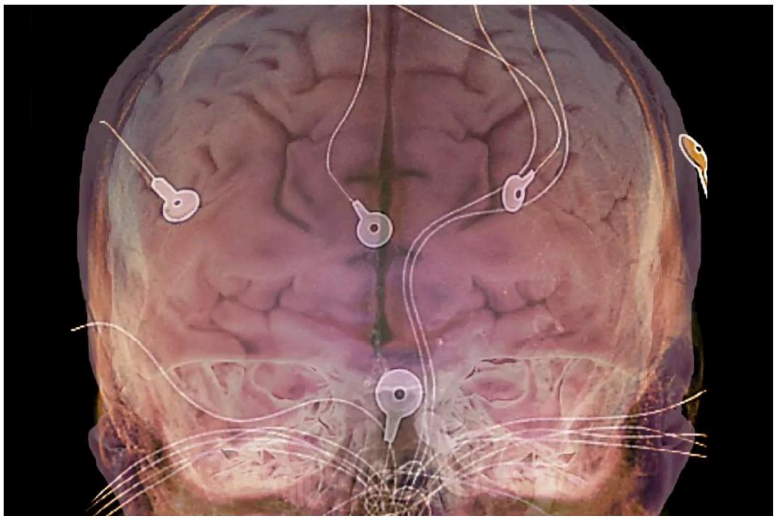
The literature emphasizes the pivotal role of history-taking and physical examination in epilepsy diagnosis. Detailed inquiry into the nature of events, including onset, duration, and associated symptoms, is imperative. [31] Differential diagnoses, such as syncope and psychogenic non-epileptic events, underscore the necessity of a thorough evaluation to distinguish between epileptic and non-epileptic seizures. [31]

Diagnostic Tests:

Electroencephalography (EEG) emerges as a cornerstone in epilepsy evaluation, aiding in the classification of seizures and guiding treatment decisions.[31] The presence of specific EEG patterns, like bursts of spike waves in the absence of seizures, offers valuable diagnostic insights. Additionally, neuroimaging techniques such as MRI or CT scans complement EEG findings by identifying structural brain abnormalities associated with epilepsy. [31]

Differential Diagnosis:

The literature highlights the challenges posed by differential diagnoses, particularly in distinguishing psychogenic non-epileptic seizures (PNES) from epileptic seizures. [32] PNES, often misdiagnosed as epilepsy, necessitates a nuanced approach involving detailed history, EEG monitoring, and psychological consultations. Differential diagnoses also encompass syncope, migraine aura, and organic causes in young children, underlining the need for comprehensive evaluation. [32]



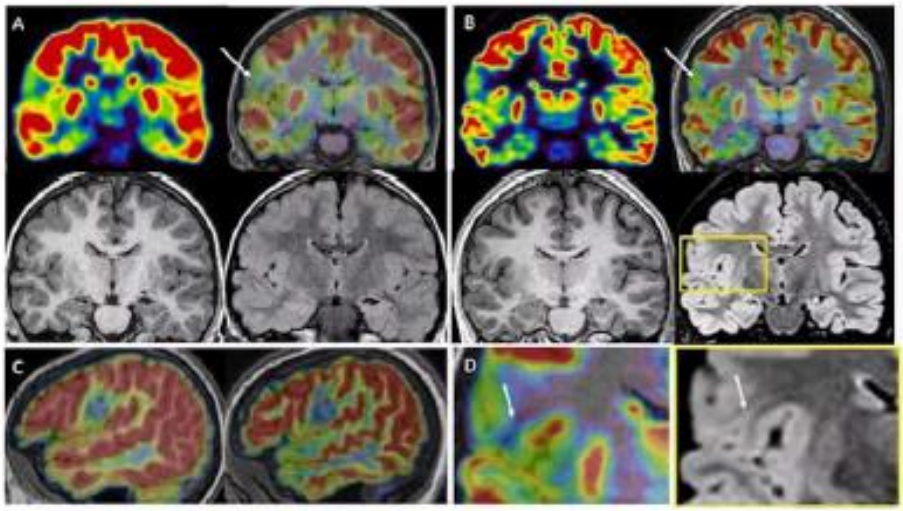
Electrodes on an epileptic patient's head monitoring the brain's electrical activity and producing an electroencephalogram

FIGURE 7 [32]

Advanced Imaging Techniques:

Recent literature underscores the emerging role of advanced imaging techniques, such as PET/MRI, in challenging epilepsy case. [33] PET/MRI facilitates the identification of epileptogenic brain lesions, especially in drug-resistant epilepsy cases where standard approaches may falter. The integration of PET and MRI offers superior lesion detection compared to standalone scans, potentially enhancing surgical outcomes. [33]

The literature underscores the multidimensional nature of epilepsy diagnosis, encompassing history-taking, physical examination, and diagnostic tests. Differential diagnosis remains pivotal in distinguishing between epileptic and non-epileptic events, with a focus on conditions like PNES. Advanced imaging techniques, particularly PET/MRI, offer promise in enhancing lesion detection and optimizing surgical outcomes in challenging epilepsy cases. Collaborative efforts between healthcare professionals are essential for ensuring accurate diagnosis and tailored management strategies for patients with epilepsy.



Comparison between PET+MRI (A) and PET/MRI (B); axial and coronal plane, PET alone and co-registered on MRI. The subject is a 17-year-old female with drug-resistant epilepsy since the age of 2 years; nocturnal frontal seizures (3 times per night), left frontotemporal ictal onset, negative MRI (3 tesla). Her first PET examination co-registered on MRI at 11 years considered negative; PET/MRI six years later, showing a focal hypometabolism involving the posterior part of the left orbitofrontal cortex, relative involvement of the adjacent cortex (gyrus rectus, anterior part of the left inferior frontal gyrus) and the temporal pole. This hypometabolism was retrospectively found on the previous PET but remained inconclusive. Note that the co-registration was imperfect on this examination, whereas it was almost perfect on the PET/MRI, allowing a better confidence for the visual analysis. The patient was operated on without invasive monitoring despite a negative MRI scan. Surgery was based on a PET/MR guided cortical resection, including the hypometabolic orbitofrontal cortex and the adjacent inferior frontal gyrus, in front of Broca area. FCD type 2 A was found in the cortical specimen. The patient has been seizure-free for two years and the use of antiepileptic drugs greatly reduced. Image courtesy of Epilepsy Research.

FIGURE 8[33]

B. ANTIEPILEPTIC DRUGS (AEDs)

First, Second and Third generation AEDs

Epilepsy is a chronic neurological disorder characterized by recurrent seizures, affecting millions of individuals worldwide. Antiepileptic drugs (AEDs) play an essential role in the management of epilepsy, aiming to control seizures and improve the quality of life for patients. Over the years, the development of AEDs has progressed through distinct generations, each with advancements in efficacy, safety, and mechanisms of action. This essay thoroughly examines first, second, and third-generation AEDs, highlighting their evolution and clinical significance.

The first-generation AEDs, also known as traditional or classic AEDs, include phenobarbital, Phenytoin, carbamazepine, valproate, and ethosuximide.[34] These drugs were introduced in the mid-20th century and have been fundamental in the treatment of epilepsy for decades. They exert their antiepileptic effects through various mechanisms, including modulation of voltage-gated ion channels, enhancement of inhibitory neurotransmission, and inhibition of excitatory neurotransmission. Phenytoin, for instance, primarily acts by blocking voltage-gated sodium channels, stabilizing neuronal membranes and preventing the generation of abnormal electrical discharges. However, despite their efficacy, first-generation AEDs are associated with significant adverse effects, such as sedation, cognitive impairment, teratogenicity, and hepatic enzyme induction, limiting their use in specific patient populations.

The advent of second-generation AEDs, also referred to as newer or modern AEDs, marked a significant milestone in epilepsy treatment. This generation includes drugs such as lamotrigine, Levetiracetam, gabapentin, and topiramate, among others.[35] Second-generation AEDs were developed to improve efficacy and tolerability while minimizing adverse effects compared to their predecessors. Lamotrigine, for instance, exhibits a broad spectrum of antiepileptic activity by inhibiting voltage-gated sodium channels and modulating glutamate release. Conversely, Levetiracetam acts by binding to synaptic vesicle protein 2A (SV2A), thereby reducing neurotransmitter release and neuronal excitability. Second-generation AEDs offer advantages such as once or twice-daily dosing, fewer drug interactions, and a better side effect profile, making them valuable options for patients with epilepsy.

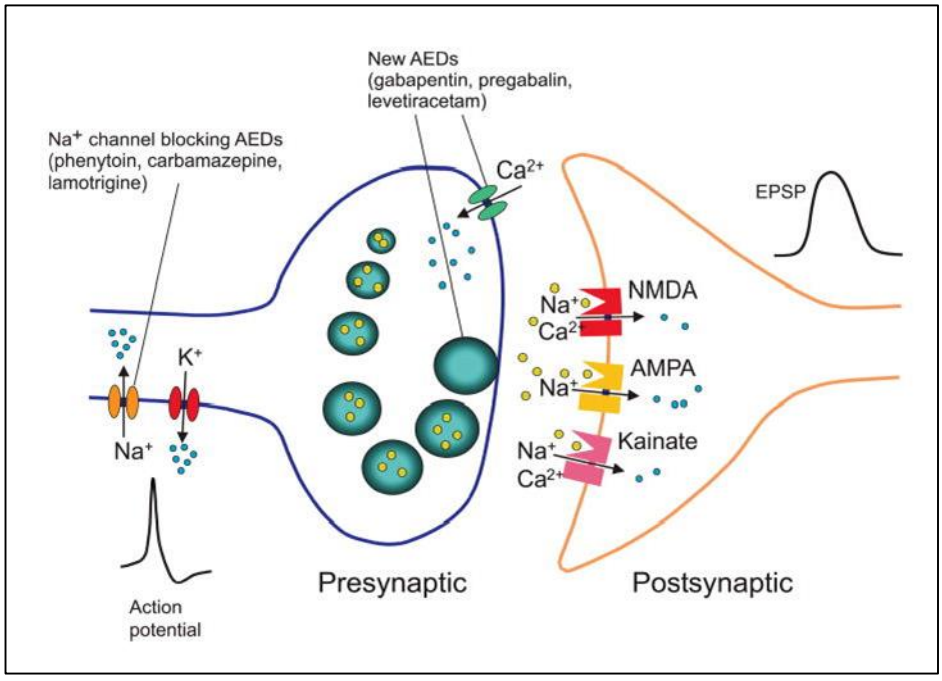


FIGURE 9[38]

In recent years, developing third-generation AEDs has further expanded the therapeutic armamentarium for epilepsy management. Third-generation AEDs, also known as novel or advanced AEDs, include drugs such as Lacosamide, Perampanel, and Brivaracetam. **[36]** These drugs were designed to address specific unmet needs in epilepsy treatment, such as refractory seizures and focal-onset seizures. Lacosamide, a third-generation AED, selectively enhances the slow inactivation of voltage-gated sodium channels, stabilizing neuronal membranes and reducing hyperexcitability. Perampanel, another third-generation AED, is a selective antagonist of AMPA receptors, which play a crucial role in excitatory neurotransmission. These drugs offer the potential for improved seizure control, reduced frequency of adverse effects, and novel mechanisms of action, enhancing treatment options for patients with epilepsy.

The evolution of antiepileptic drugs from first to third generation reflects ongoing efforts to optimize epilepsy management through advancements in efficacy, safety, and tolerability. While first-generation AEDs laid the foundation for epilepsy treatment, second and third-generation drugs have introduced innovative mechanisms of action and improved therapeutic profiles. However, despite these advancements, challenges such as drug resistance, adverse effects, and individual variability persist, underscoring the need for continued research and development in the field of epilepsy pharmacotherapy. By understanding the evolution of AEDs and their mechanisms of action, healthcare professionals can make informed decisions to provide personalized and effective treatment for patients with epilepsy.

Mechanism of Action

Understanding the mechanisms of action of antiepileptic drugs (AEDs) is crucial for optimizing treatment strategies and improving outcomes for patients with epilepsy. AEDs exert their effects through various pathways, targeting neuronal excitability, ion channels, neurotransmitter systems, and synaptic transmission. This essay provides an in-depth exploration of the mechanisms of action of AEDs, shedding light on their diverse pharmacological properties and clinical implications.

Modulation of Ion Channels:

One of the primary mechanisms through which AEDs exert their antiepileptic effects is the modulation of ion channels, particularly voltage-gated sodium and calcium channels. [37] Drugs such as Phenytoin, carbamazepine, and lamotrigine block voltage-gated sodium channels, inhibiting the generation and propagation of abnormal neuronal impulses. By stabilizing neuronal membranes, these AEDs reduce hyperexcitability and suppress seizure activity. Similarly, drugs like ethosuximide and valproate modulate calcium channels, impacting neurotransmitter release and neuronal excitability.

Enhancement of GABAergic Transmission:

Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the central nervous system, playing a crucial role in regulating neuronal excitability. Several AEDs enhance GABAergic transmission by various mechanisms, such as increasing GABA synthesis, inhibiting GABA degradation, or potentiating GABA receptor activity. [38] Benzodiazepines, such as diazepam and clonazepam, enhance GABA receptor-mediated

inhibition, leading to neuronal hyperpolarization and reduced seizure susceptibility. Similarly, barbiturates like phenobarbital enhance GABAergic transmission by increasing the GABA receptor channel opening duration, further contributing to seizure control.

Modulation of Glutamatergic Pathways:

Glutamate is the primary excitatory neurotransmitter in the central nervous system, playing a pivotal role in synaptic transmission and neuronal excitability. AEDs such as topiramate and felbamate modulate glutamatergic pathways by inhibiting glutamate receptors or reducing glutamate release. [39] Topiramate, for example, blocks AMPA/kainate receptors and enhances GABAergic transmission, resulting in decreased neuronal excitability and seizure propagation. By targeting glutamatergic neurotransmission, these AEDs provide an additional mechanism for controlling seizures, particularly in cases of refractory epilepsy.

The mechanisms of action of AEDs are diverse and multifaceted, reflecting the complex nature of epilepsy and neuronal excitability. By targeting ion channels, neurotransmitter systems, and synaptic transmission, AEDs exert their antiepileptic effects through various pharmacological pathways. Understanding these mechanisms is essential for tailoring treatment strategies, optimizing drug selection, and improving outcomes for patients with epilepsy. Moreover, ongoing research into novel therapeutic targets and mechanisms holds promise for developing more effective and well-tolerated AEDs in the future.

Antiepileptic drugs (AEDs) act at the synapse through various mechanisms to control seizures. They enhance GABAergic inhibition, reducing neuronal excitability, and inhibit sodium channels, preventing abnormal firing. AEDs also modulate calcium channels to regulate excitability and stabilize membrane potential through potassium channel modulation.

Additionally, they target glutamate receptors to reduce excitatory neurotransmission and inhibit carbonic anhydrase, impacting brain pH levels for anticonvulsant effects. These combined actions help maintain the balance between excitation and inhibition in the brain, ultimately preventing seizures. [40]

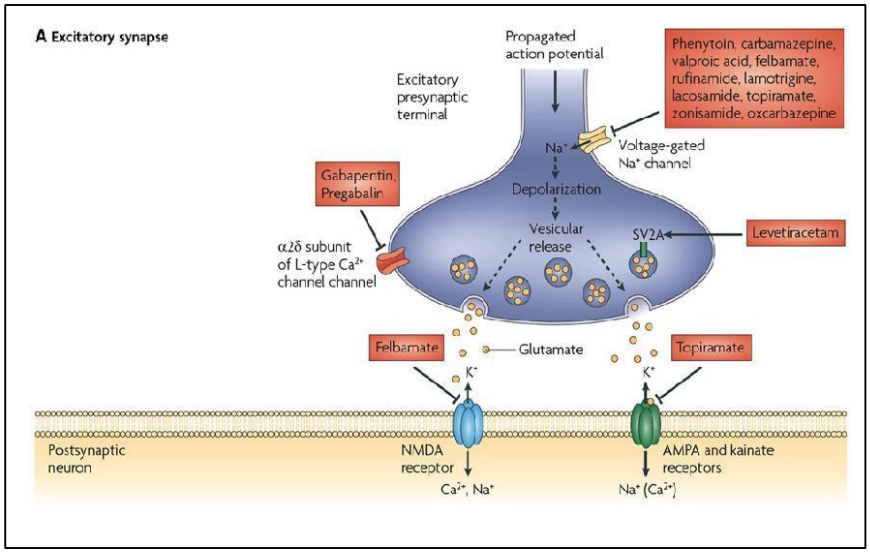


FIGURE 10 (A)

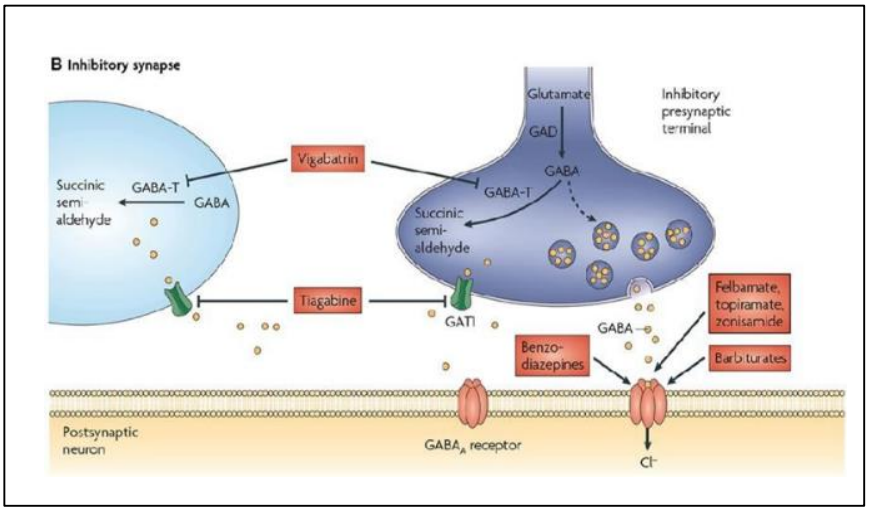


FIGURE 10 (B)

FIGURE 10[39]: Excitatory (A) and inhibitory (B) synapse in the central nervous system and the sites of action of various anticonvulsants

Pharmacokinetics

Pharmacokinetics, the study of how drugs move through the body, is crucial for understanding the effectiveness and safety of antiepileptic drugs (AEDs). It revolves around four fundamental principles: absorption, distribution, metabolism, and excretion. [42,44] These principles outline the journey of AEDs from absorption into the bloodstream, distribution across tissues and metabolism within the body to eventual elimination. By grasping these dynamics, clinicians can optimize AED therapy, balancing therapeutic benefits with potential adverse effects. This exploration of pharmacokinetics sheds light on the intricate relationship between AEDs and the human body, offering insights into their pharmacological mechanisms and clinical implications.

Absorption is a critical aspect of understanding the pharmacokinetics of antiepileptic drugs (AEDs), marked by several key considerations. [41] The process of absorption dictates how AEDs move from their administration site into the bloodstream, influenced by factors such as the drug's physicochemical properties, formulation, and route of administration. [42] This step is pivotal in determining the onset, intensity, and duration of the therapeutic effect of AEDs, with factors like solubility, lipophilicity, and gastrointestinal conditions playing crucial roles. [43] Particularly for AEDs, absorption dynamics are crucial as they directly impact the drug's effectiveness in managing epileptic seizures. [44] Understanding the intricacies of absorption in the context of AEDs involves considering factors such as membrane permeability, first-pass metabolism in the liver, and the overall pharmacological profile of the drug, contributing to the kinetics of its action in seizure control.

Drug transporters are integral proteins facilitating the movement of drugs across cell membranes, thereby influencing drug absorption and bioavailability.[41] Notable examples include P-glycoprotein, which actively transports drugs out of cells, potentially reducing drug absorption, and Organic Anion Transporting Polypeptides (OATPs), which facilitate the uptake of various drugs. [42] P-glycoprotein, for instance, can pump certain drugs back into the gastrointestinal lumen, impacting their absorption and subsequent bioavailability. [43] Another example is OATPs, which are responsible for the uptake of drugs like statins into hepatocytes, affecting their distribution and metabolism. [44]

Changes in gut function have profound implications for drug absorption, primarily by affecting the time drugs spend in the intestine, altering the pH of the stomach or intestine, and potentially reducing the absorptive surface area due to surgical procedures like gastric bypass. [41] Rapid transit time in the gastrointestinal tract, as seen in conditions such as rapid transit time, can lead to decreased absorption of drugs, requiring more extended dissolution and absorption times. [42] Additionally, gastric surgeries like gastric bypass can significantly impact the absorption surface area, thereby affecting the bioavailability of drugs (Marvanová, 2016). These changes in gut function, including rapid transit time and surgical alterations to the GI tract, may result in decreased absorption time and potentially reduce drug efficacy.[43] Moreover, surgical interventions might bypass areas where specific drugs are optimally absorbed. Consequently, alterations in gut function, whether due to disease or surgery, can lead to significant variations in drug absorption, with rapid gastrointestinal transit time potentially decreasing absorption rates, while surgical procedures like bariatric surgery may impact the available surface area for absorption, ultimately influencing overall medication effectiveness. [44]

Drug distribution is a complex process influenced by multiple factors such as tissue permeability, blood flow to tissues, binding of drugs to plasma proteins and tissues, and the drug's lipophilicity. [41] Once a drug enters the bloodstream, it is distributed to various body tissues, with the volume of distribution determined by factors including tissue perfusion, plasma protein binding, and tissue binding. [42] Factors impacting the volume of distribution encompass a drug's lipophilicity, molecular size, binding to plasma proteins, and tissue penetration. Distribution entails the spread of the drug to different body compartments post-absorption. [43] The distribution of drugs within the bloodstream is influenced by factors such as blood flow, tissue permeability, and plasma protein binding. Different tissues may uptake the drug at varying rates, with lipid solubility and molecular size further influencing the volume of distribution.[44] This complex interplay of factors ultimately determines the spatial dispersion of drugs throughout bodily fluids and tissues, shaping their pharmacological effects and distribution kinetics.

Phase I and Phase II drug metabolism reactions are crucial processes in drug metabolism. [41] Phase I reactions involve functionalization reactions, typically oxidation, reduction, or hydrolysis, while Phase II reactions entail conjugation reactions, where polar groups are added to make drugs more water-soluble. [42] Calculating loading doses based on the volume of distribution is essential for promptly achieving therapeutic drug levels. [43] This calculation relies on the volume of distribution (Vd) and the desired plasma concentration of the drug. The formula for calculating loading doses is straightforward: Loading dose = Vd x target concentration. [44]

The loading dose of a medication is determined to attain a target concentration in the bloodstream rapidly. [41] This calculation involves multiplying the volume of distribution by the desired plasma concentration, utilizing the formula: Loading dose = Vd x Target Concentration. Changes in kidney function can significantly impact drug elimination, especially for drugs primarily excreted through the kidneys. Equations such as the Cockcroft-Gault and the Modification of Diet in Renal Disease formula are commonly employed to estimate the glomerular filtration rate, providing insights into renal function. [43] Reduced kidney function can diminish the elimination of drugs, potentially resulting in drug accumulation and heightened effects or toxicity. Utilizing equations like the Cockcroft-Gault formula or the Modification of Diet in Renal Disease study equation becomes imperative in assessing renal function and adjusting medication dosages to mitigate adverse outcomes.

Different responses to drugs can be expected among individuals such as children, the elderly, and those with renal or hepatic dysfunction. Such populations often require specific pharmacologic studies after initial drug approval to tailor AED therapy. Each AED has a unique pharmacokinetic profile, which should be considered alongside efficacy and safety to choose the best therapeutic option for individual patients, considering age, sex, ethnicity, other concurrent illnesses, and medications.

Drug-drug and drug-disease interactions

Antiepileptic drugs (AEDs) constitute the cornerstone of epilepsy management. However, drug interactions can profoundly influence their efficacy and safety. **[45-48]** Understanding these interactions is paramount for optimizing treatment outcomes and ensuring patient safety, which explores the complex landscape of AED interactions, encompassing pharmacokinetic and pharmacodynamic considerations. **[47,48]**

A major subset of AED interactions stems from alterations in drug metabolism, primarily mediated by cytochrome P450 enzymes and uridine glucuronyl transferases.**[45-47]** Notable examples include enzyme induction by older AEDs like carbamazepine, Phenytoin, phenobarbital, and primidone, leading to accelerated metabolism of concomitant medications. **[45][47]** Conversely, enzyme inhibition, such as that caused by Valproic acid, can elevate plasma concentrations of certain AEDs, predisposing patients to toxicity. **[46][47]** The clinical significance of AED interactions varies, ranging from minor changes in serum concentrations to severe adverse effects. **[45][46]** Enzyme-inducing AEDs pose a substantial risk, potentially compromising the efficacy of co-administered medications. **[46][48]** Vigilant monitoring and individualized management strategies are imperative, especially in patients with polytherapy or with comorbid conditions. **[45][46]**

While second and third-generation AEDs generally exhibit lower interaction potentials, they are not devoid of interactions. **[46]** Awareness of the metabolism and interaction profiles of newer agents like Eslicarbazepine Acetate, Lacosamide, Rufinamide, and Stiripentol is crucial for safe prescribing.**[45]** Effective management of AED interactions necessitates a multifaceted approach. **[46][48]** Strategies include regular monitoring of drug levels,

judicious selection of AED combinations, and patient education on medication adherence. **[46][48]** Additionally, individualized dosing and consideration of alternative therapies play pivotal roles in mitigating adverse interactions. **[47]**

The COVID-19 pandemic introduces new challenges, with potential interactions between AEDs and antiviral drugs warranting careful evaluation. **[48]** First-generation AEDs like carbamazepine and Phenytoin may interact with COVID-19 medications, emphasizing the need for heightened vigilance. **[48]** By comprehensively understanding the mechanisms, clinical implications, and management strategies associated with drug interactions, healthcare providers can tailor treatment regimens to individual patient needs and enhance therapeutic outcomes. **[45-48]** Continued research and education in this field are imperative to ensure safe and effective pharmacotherapy for individuals living with epilepsy. **[46][48]**

Angiotensin Converting Enzyme Inhibitor and Epilepsy

The intersection of epilepsy management and pharmacotherapy presents a fascinating realm of investigation, with recent studies spotlighting the potential synergies between antiepileptic drugs (AEDs) and Angiotensin Converting Enzyme Inhibitors (ACEi). **[49]** These inhibitors, typically utilized in the management of hypertension, have unveiled intriguing prospects in the realm of seizure control. Animal models have elucidated interactions between ACEi and AEDs, showcasing augmented anticonvulsant activity against seizures.**[49]** Notably, ACEi such as Fosinopril and Zofenopril have demonstrated the capacity to potentiate the anticonvulsant effects of AEDs against audiogenic seizures in mice, underscoring their potential adjunctive role in seizure management. **[49]** Moreover, studies have unveiled ACEi's ability to modulate the renin-angiotensin system (RAS), implicating pathways crucial

in epileptogenesis. **[49]** For instance, Captopril, an ACEi, exhibited a reduction in seizures in murine models, suggesting a plausible link between ACEi and epilepsy pathophysiology. **[49]** These findings illuminate a promising avenue for targeted therapies in epilepsy, necessitating further exploration to unravel the precise mechanisms underpinning ACEi's beneficial effects and optimize their integration as adjunctive treatments for seizure control.

Epilepsy, characterized by recurrent seizures, presents clinicians with formidable challenges in its management and treatment. Recent inquiries into novel therapeutic avenues have spotlighted the potential utility of Angiotensin-Converting Enzyme Inhibitors (ACEIs) in epilepsy management. **[50]** Captopril has emerged as a compelling candidate among these inhibitors, demonstrating efficacy in reducing seizure severity and shielding against neuronal damage in experimental models **[50]**.

Studies have showcased Captopril's capacity to diminish seizure scores, delay the onset of generalized tonic-clonic seizures (GTCS), and mitigate neuronal injury, particularly in critical brain regions like the hippocampus. **[50]** Furthermore, Captopril's ability to mitigate oxidative stress levels and enhance gamma-aminobutyric acid (GABA) flux into neurons underscores its antiepileptic properties. **[50]** Given the presence of the renin-angiotensin system (RAS) in the central nervous system, ACEIs wield the potential to modulate neurological functions profoundly. **[50]**

By inhibiting ACE and curbing angiotensin II activity in the brain, ACEIs may confer neuroprotective benefits and ameliorate seizure outcomes.**[50]** Moreover, the cognitive enhancement and mood-stabilizing effects exhibited by ACEIs accentuate their potential in epilepsy management. **[50]** While the precise mechanisms underlying ACEIs' antiepileptic

effects necessitate further elucidation, their promise as adjunctive therapy in epilepsy, particularly in individuals with concomitant hypertension, beckons further exploration to harness their full therapeutic potential and refine their clinical application.

Angiotensin Receptor Blockers and Epilepsy

The convergence of research findings from recent studies has shed light on the intriguing relationship between Angiotensin Receptor Blockers (ARBs) and epilepsy [1]. Initially prescribed primarily for hypertension management, ARBs have now emerged as potential therapeutic agents for epilepsy, marking a significant shift in the understanding of their pharmacological actions. One notable study investigated the association between ARB therapy and epilepsy incidence, revealing compelling evidence supporting the use of ARBs in epilepsy prevention [51]. Analysing data from a large cohort of hypertensive patients demonstrated a significantly decreased incidence of epilepsy among those treated with ARBs compared to other antihypertensive drug classes. This finding expands the therapeutic horizon for ARBs and highlights the need to explore alternative mechanisms of action for existing medications.

Furthermore, animal studies have provided invaluable insights into the neuroprotective effects of ARBs in epilepsy [52]. Losartan, a prominent ARB, has been particularly noteworthy for its ability to modulate the renin-angiotensin system (RAS) pathways implicated in epileptogenesis. By mitigating microglia-mediated inflammation and cognitive impairment, ARBs offer a promising avenue for ameliorating the neurological manifestations of epilepsy [52]. The potential synergistic interaction between ARBs and antiepileptic drugs (AEDs) presents an exciting opportunity for optimizing seizure control and refining epilepsy

management strategies [51]. Although further research is warranted to elucidate the specific mechanisms underlying ARB's beneficial effects and their integration as adjunctive treatments for epilepsy, the prospect of personalized therapeutic interventions holds tremendous promise for improving patient outcomes. In conclusion, the recent evidence highlighting the therapeutic potential of ARBs in epilepsy management signifies a significant advancement in neurology. By expanding their role beyond hypertension management and uncovering their neuroprotective properties, ARBs offer new avenues for enhancing seizure control and preserving neurological function in patients with epilepsy.

C. IN VIVO EXPERIMENTAL MODELS OF EPILEPSY

Introduction to Research on Experimental Models of Epilepsy

Epilepsy, a multifaceted neurological disorder characterized by recurrent seizures, poses significant challenges in understanding its underlying mechanisms and developing effective treatments [55, 56]. The condition encompasses a spectrum of manifestations, including alterations in consciousness, motor disturbances, and structural changes in key brain regions such as the hippocampus [53, 54]. At the core of epilepsy's pathophysiology lies the intricate interplay between inhibitory GABAergic and excitatory glutamatergic neurotransmission [53, 54]. Disruptions in this delicate balance can precipitate neuronal hyperexcitability and the onset of seizures, highlighting the importance of experimental models in unravelling the complex neurochemical and neurophysiological pathways involved. [55, 56]

Experimental models of epilepsy serve as indispensable tools in replicating epileptic phenomena and elucidating the diverse manifestations of the disorder. [53, 54] These models, which range from chemically induced to genetically modified, have enabled researchers to simulate epileptic activity in controlled laboratory settings and investigate the role of key neurotransmitter systems and ion channels in seizure generation and propagation [53, 54]. For instance, ionotropic glutamate receptors (AMPA, kainite, NMDA) and GABA receptors (GABAA, GABAB) have been identified as pivotal players in modulating neuronal excitability and seizure genesis within these models [53, 54]. Activation of glutamate receptors triggers ion influx, culminating in membrane depolarization and subsequent action potential firing. In contrast, GABA receptors orchestrate inhibitory responses by facilitating

Cl- ion permeability, hyperpolarizing the membrane, and quelling seizure activity [53, 54].

Despite advancements in epilepsy research, a significant proportion of patients remain refractory to conventional treatments, underscoring the need for innovative approaches [53, 54]. Experimental models offer platforms for testing novel interventions and bridging the gap between preclinical investigations and clinical applications [55, 56]. Through a translational lens, researchers aim to pave the way for improved treatments and enhanced quality of life for individuals affected by epilepsy and its related comorbidities [53-56]. By delving into the diverse experimental models of epilepsy, each offering unique insights into the multifaceted nature of the disorder, researchers strive to uncover new avenues for personalized treatment approaches and novel therapeutic interventions in the field of epilepsy research.

Animal Models of ILAE against Epilepsy

1. Models of Simple Partial Seizures
    - Cortically Implanted Metals: Aluminium, Cobalt, Zinc
2. Complex Partial Seizure Model
    - Kainic Acid Administration (KA)
    - Repetitive Electrical Stimulation ("Kindling")
    - Administration of Tetanus Toxin
3. Generalized Tonic Clonic Seizure Models
    - Maximum electroshock (MES)
    - Pentylenetetrazol (PTZ)

4. Generalized Partial Seizure Models
    - Penicillin
    - GABA
    - Bicuculine
5. Generalized Absence Seizure Models
    - Audiogenic seizures in mice.
    - Genetic: Photosensitive Papio papio
6. Status Epilepticus
    - Pilocarpine

In recent years, significant advancements in understanding epilepsy and developing therapeutic interventions have predominantly originated from laboratory research involving animal models, particularly rats or mice. These experimental models serve as the foundation for studying antiepileptic and pharmacological treatments. Various animal models have been devised to mimic human epilepsy, including commonly utilized and in vivo exclusive models. Notably, these models vary in methodologies: the electroshock model employs electrical stimulation, while the kindling model similarly applies electric stimuli but differs in administration location. The kindling model is a critical advantage in studying partial and generalized seizures.

Among models utilizing metals, the alumina cream model was the earliest developed to induce chronic epileptogenic foci, yet its applicability is limited due to several factors. Consequently, the alumina model has seen reduced favourability compared to more contemporary techniques like kindling. Other models induce epilepsy through receptor

affinity, such as the KA model, Bicuculine, and GABA withdrawal. However, they pose limitations, including the generation of lesions beyond the injection site. Moreover, the KA model's excessive susceptibility in temporal lobe structures restricts its utility. Despite limited investigation, the baboon model faces extensive limitations. Conversely, the penicillin-induced seizure model in the cerebral cortex of experimental animals has received extensive study and is among the models most elucidating various epilepsy mechanisms.

In our present study, we selected two epileptic rat models to assess the antiepileptic effects of clinically used drugs, including Phenytoin and Sodium Valproate, along with the effects of Ramipril (ACEI) and Telmisartan (ARB) in enhancing the efficacy of existing treatments.

Electroshock Seizure (MES) Model

The Maximal Electroshock Seizure (MES) model stands as a cornerstone in the preclinical evaluation of potential antiepileptic drugs (AEDs) [57]. This model, involving the induction of maximal seizures through electrical stimulation, is a robust platform for assessing the efficacy of investigational anticonvulsant compounds. [57] Widely regarded as a gold standard in early-stage testing, the MES test can predict drugs effective against generalized tonic-clonic seizures, offering valuable insights into seizure propagation through neural tissue. [57]

Conducting the MES test is relatively straightforward and requires minimal investment in equipment and technical expertise, rendering it an attractive option for routine laboratory screening. [57] The methodology entails applying an electrical stimulus of adequate intensity

to provoke maximal hind limb seizures in rodents, with tonic extension serving as the endpoint. [57] Parameters such as current intensity, pulse frequency, pulse width, and stimulus duration are meticulously standardized, ensuring experiment consistency. [57]

Despite its utility, the MES model has limitations. Animals can only be utilized once, and several factors may influence the experimental outcomes, underscoring the importance of careful experimental design. [57] Crucially, the choice of appropriate animal models for initial in vivo testing of potential anticonvulsant compounds plays a pivotal role in the reliability and relevance of the results. [57] Moreover, while the MES model provides valuable insights into the central nervous system bioavailability of investigational AEDs and offers clear seizure endpoints, its predictive value regarding clinical efficacy remains partial. [57] Ultimately, the definitive assessment of anticonvulsant activity necessitates clinical validation through studies involving patients. [57]

In a recent study exploring the anticonvulsant activity of an Isatin derivative in albino Wistar mice, the MES-induced seizure method served as a crucial experimental paradigm.[58] Comparative analysis with the standard drug Valproic acid revealed significant anticonvulsant effects, highlighting the potential of novel agents in addressing the unmet needs in epilepsy treatment. [58]

The discussion on electrical stimulation-induced models of seizures further elucidates the diverse methodologies employed in seizure induction. [60] Electroshock seizures, including minimal clonic seizures and maximal tonic-clonic seizures, are induced through varying frequencies and intensities of stimulation, with mice predominantly utilized in experimental settings. [58] These models are vital in advancing our understanding of epilepsy pathophysiology and facilitating the development of novel anticonvulsant therapies. [60]

Pentylenetetrazole (PTZ) Model

The Pentylenetetrazole (PTZ) model stands as a cornerstone in epilepsy research, offering a versatile approach to investigating seizure disorders. [61-64] Administered through intraperitoneal injection, PTZ induces seizures across a dosage spectrum of 20 to 300 mg/kg, primarily involving the hippocampus. [61, 63, 64] Notably, PTZ-induced epilepsy is characterized by heightened axonal growth within the CA3 layer of the hippocampus, accompanied by alterations in voltage-gated potassium channels, which contribute to seizure generation and propagation. [61-64] The dysregulation of inhibitory and excitatory neurotransmission systems, coupled with a loss of inhibition mediated by GABA, further exacerbates the epileptic phenotype. [61-64] PTZ acts as a GABA-selective antagonist by blocking the GABAA receptor, disrupting inhibitory signaling in the brain. [61-64] Moreover, alterations in the expression of NMDA receptors underscore the complexity of PTZ-induced seizures, with region-specific changes observed in kindled seizures of rats. [61-64] The PTZ model offers a controlled means of inducing seizures, facilitating the study of epilepsy pathology and the screening of potential antiepileptic drugs. [61, 62, 63] Through repetitive administration of sub-convulsive PTZ doses, the PTZ kindling model mimics primary tonic-clonic generalized epilepsy in humans. [62, 64] This chronic administration induces epileptic seizures primarily within the hippocampus and is accompanied by pronounced axonal growth and alterations in voltage-gated potassium channels. [62, 64] The intricate interplay between inhibitory and excitatory neurotransmission systems underscores the complexity of PTZ-induced seizures, highlighting the model's utility in elucidating the neurobiological mechanisms underlying epileptogenesis [62, 64].

Various antiepileptic drugs, including Carbamazepine, Phenytoin, and Pentobarbital, have demonstrated efficacy in suppressing PTZ-induced seizures, underscoring their potential as therapeutic options for epilepsy [61, 63]. The PTZ kindling model provides a valuable platform for studying epilepsy and testing antiepileptic compounds in mice, offering insights into the neurobiological mechanisms underlying seizure development and propagation [61, 63, 64]. By recapitulating key aspects of human epilepsy, including hippocampal involvement and alterations in neurotransmitter systems, this model facilitates the evaluation of potential treatments for epilepsy [61, 63, 64].

The PTZ model is a crucial experimental paradigm for studying epilepsy and exploring novel treatment strategies [61, 62, 63, 64]. By elucidating the underlying molecular mechanisms and evaluating potential therapeutic interventions, this model offers valuable insights into seizure generation and propagation, thereby contributing to the development of targeted therapies for epilepsy.

D. REVIEW OF CHEMICALS/DRUGS USED

Pentylenetetrazole (PTZ)

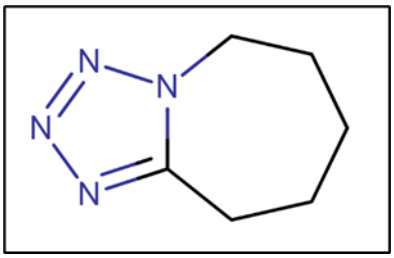


FIGURE 11

Chemical Properties:

- Formula: C6H10N4
- Molecular Weight: 138.2
- Trade Names: Corozol, Leptazol, Pentamethazol, Pentazol, Cardiazol, Metrazol
- Chemical Nature: Slightly pungent, bitter crystals
- Melting Point: 57-60 degrees Celsius
- Solubility: Freely soluble in water and most organic solvents
- Stability: Very stable, not easily attacked by other substances
- Toxicity: LD50 in Rats: 82 ± 1 mg/kg subcutaneously, 62 mg/kg intraperitoneally

Pharmacological Properties:

- Central and respiratory stimulant similar to Doxapram hydrochloride
- Used in cases of respiratory depression, but other agents are generally preferred for respiratory stimulation

Pentylenetetrazole (PTZ) is a chemical compound with various trade names and specific chemical properties. It acts as a central and respiratory stimulant similar to Doxapram hydrochloride but is not commonly used for respiratory depression due to the preference for other agents. PTZ exhibits a stable nature and is moderately toxic, with specific LD50 values in rats.

Carboxymethyl Cellulose (CMC)

Chemical Properties:

- Chemical Structure: Sodium Carboxymethyl cellulose (NaCMC) or cellulose gum
- Chemical Formula: [C6H7O2(OH)3-x(OCH2COONa) x] n
- Molecular Weight: Varies based on degree of substitution
- Appearance: White to off-white powder or fibrous material
- Solubility: Soluble in water, forming viscous solutions or gels
- Stability: Stable under normal storage conditions

Applications:

- Food Industry: Used as a thickener, stabilizer, and emulsifier in various food products, including ice cream, sauces, and baked goods
- Pharmaceuticals: Commonly employed as a binder, disintegrant, and viscosity modifier in pharmaceutical formulations, including tablets, suspensions, and ointments
- Cosmetics: Utilized in personal care products such as toothpaste, shampoo, and lotion as a thickening agent and moisture-retaining additive
- Industrial Applications: Employed in oil drilling fluids, detergents, and textile processing for its thickening and water-retention properties

- Paper Industry: Added to paper coatings and adhesives to improve strength, printability, and water resistance

Pharmacological Properties:

- Biocompatibility: Generally considered safe for oral and topical use, with low toxicity and minimal systemic absorption
- Mucoadhesive Properties: Forms a protective film on mucosal surfaces, prolonging contact time and enhancing drug delivery in topical formulations
- Wound Healing: Used in wound dressings to promote moist wound healing and create a barrier against pathogens
- Ophthalmic Applications: Formulated into eye drops and ointments to improve ocular lubrication and provide relief from dry eye symptoms

Carboxymethyl cellulose (CMC) is a versatile polymer with widespread applications across various industries, including food, pharmaceuticals, cosmetics, and textiles. Its unique properties, including solubility in water, biocompatibility, and viscosity-modifying capabilities, make it a valuable additive in numerous products. Understanding the diverse uses and properties of CMC facilitates its effective incorporation into formulations to achieve desired performance characteristics.

Phenytoin

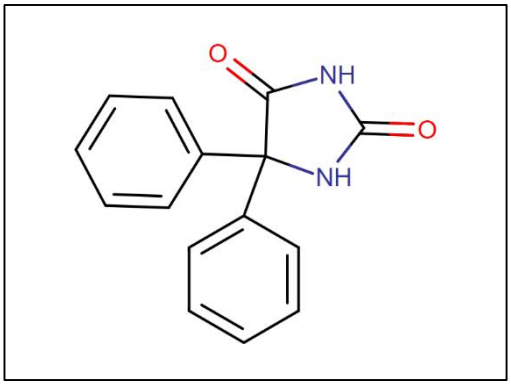


FIGURE 12

Chemical Properties:

- Chemical Name: 5,5-Diphenylhydantoin
- Formula: C15H12N2O2
- Molecular Weight: 252.27 g/mol
- Trade Names: Dilantin, Phenytek, Epanutin, Epamin
- Physical Form: Crystalline powder
- Solubility: Slightly soluble in water, soluble in organic solvents
- Stability: Stable under normal conditions

Pharmacological Properties:

- Mechanism of Action: Blocks voltage-gated sodium channels, stabilizing neuronal membranes
- Indications: Treatment of seizures, including generalized tonic-clonic seizures, complex partial seizures, and status epilepticus
- Metabolism: Primarily metabolized by hepatic enzymes, predominantly cytochrome P450 enzymes

- Half-Life: Variable, approximately 22 hours in adults but may vary based on individual factors
- Therapeutic Drug Monitoring: Due to its narrow therapeutic index, monitoring of serum levels is essential to ensure optimal dosing and prevent toxicity

Drug Interactions:

- Phenytoin interacts with numerous drugs, including those affecting hepatic enzyme activity, protein binding, and folate metabolism
- Adverse Effects: Common adverse effects include gingival hyperplasia, hirsutism, and neurological symptoms such as ataxia and nystagmus
- Toxicity: LD50 in Rats: Approximately 750 mg/kg orally

Phenytoin is a widely used antiepileptic drug with complex pharmacological properties. It acts by blocking voltage-gated sodium channels, making it effective in the treatment of various seizure types. Phenytoin metabolism is primarily hepatic, and its narrow therapeutic index necessitates careful monitoring of serum levels. Despite its efficacy, Phenytoin is associated with numerous drug interactions and potential adverse effects. Understanding its pharmacokinetic and pharmacodynamic properties is essential for safe and effective clinical use.

Sodium Valproate

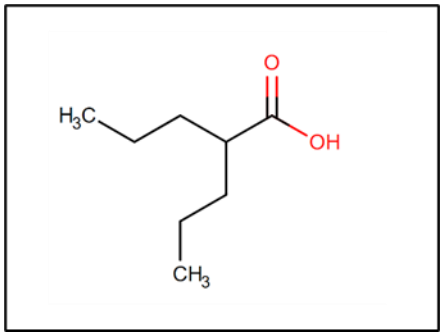


FIGURE 13

Chemical Properties:

- Chemical Structure: Sodium salt of Valproic acid
- Chemical Formula: C8H15NaO2
- Molecular Weight: 166.19 g/mol
- Appearance: White crystalline powder
- Solubility: Soluble in water
- Stability: Stable under normal storage conditions

Pharmacological Properties:

- Mechanism of Action: Enhances gamma-aminobutyric acid (GABA) activity, inhibits voltage-gated sodium channels, and modulates calcium channels, leading to neuronal membrane stabilization
- Indications: Used as an antiepileptic drug for the treatment of various seizure types, including generalized tonic-clonic seizures, absence seizures, and myoclonic seizures

- Other Indications: Also prescribed for bipolar disorder, migraine prophylaxis, and neuropathic pain
- Metabolism: Metabolized in the liver via glucuronidation and mitochondrial beta-oxidation pathways
- Therapeutic Drug Monitoring: Monitoring of serum levels is recommended due to its narrow therapeutic index and variable pharmacokinetics
- Dosage Forms: Available in various formulations, including tablets, capsules, oral solutions, and intravenous injections

Adverse Effects:

- Common Side Effects: Nausea, vomiting, dizziness, sedation, and tremor Serious Adverse Effects: Hepatotoxicity, pancreatitis, thrombocytopenia, and teratogenicity (Sodium Valproate should be avoided during pregnancy, particularly in the first trimester) Long-Term Effects: Potential for weight gain, hair loss, and cognitive impairment with prolonged use

Drug Interactions:

- Enzyme Inhibition: Can inhibit hepatic enzymes, leading to interactions with other drugs metabolized via the cytochrome P450 system
- Protein Binding: May displace protein-bound drugs, altering their pharmacokinetics and increasing the risk of toxicity
- Folate Metabolism: Interferes with folate metabolism, potentially increasing the risk of neural tube defects in pregnant women

Sodium Valproate is a widely used antiepileptic medication with additional indications for psychiatric and neurological disorders. Its mechanism of action involves multiple pathways, contributing to its efficacy in controlling seizures and mood stabilization. However, Sodium Valproate is associated with a range of adverse effects and drug interactions, necessitating careful monitoring and individualized therapy. Understanding its pharmacological properties and potential risks is essential for safe and effective clinical use.

Ramipril

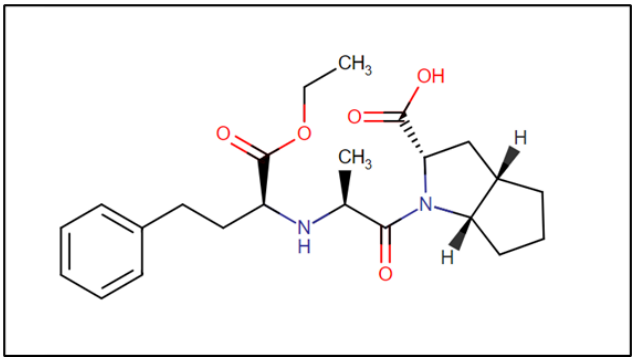


FIGURE 14

Chemical Properties:

- Chemical Structure: Carboxylic acid group (COOH) attached to a cyclic dipeptide moiety
- Chemical Formula: C23H32N2O5
- Molecular Weight: 416.51 g/mol
- Appearance: White to off-white crystalline powder
- Solubility: Soluble in water
- Stability: Stable under normal storage conditions

Pharmacological Properties:

- Mechanism of Action: Inhibits ACE, reducing the conversion of angiotensin I to angiotensin II, thereby decreasing vasoconstriction and aldosterone secretion
- Indications: Used for the treatment of hypertension, heart failure, and prevention of cardiovascular events in high-risk patients
- Metabolism: Primarily metabolized in the liver to the active metabolite ramiprilat
- Dosage Forms: Available as oral capsules or tablets

Adverse Effects:

- Common Side Effects: Cough, dizziness, hypotension, hyperkalemia, and renal impairment
- Serious Adverse Effects: Angioedema, renal failure, and neutropenia
- Drug Interactions: Potential interactions with potassium-sparing diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), and lithium

Special Considerations:

- Renal Impairment: Dose adjustments may be necessary in patients with renal impairment due to the risk of hyperkalemia and renal dysfunction
- Pregnancy: Contraindicated during pregnancy due to potential harm to the fetus

Ramipril is an ACE inhibitor commonly used for the management of hypertension and heart failure. Its mechanism of action involves inhibition of ACE, leading to vasodilation and reduced aldosterone secretion. While generally well-tolerated, Ramipril can cause adverse effects such as cough, hypotension, and hyperkaliemia. Careful monitoring is required, especially in patients with renal impairment or those taking concomitant medications.

Telmisartan

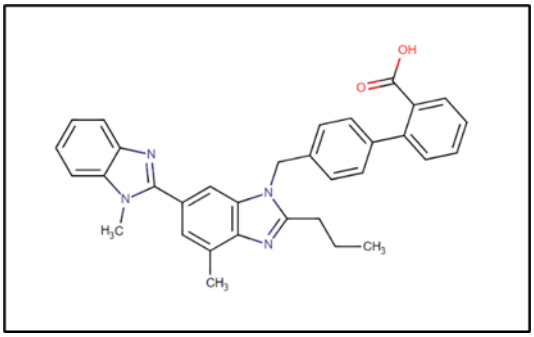


FIGURE 15

Chemical Properties:

- Chemical Structure: Biphenyl-tetrazole group linked to an imidazole moiety
- Chemical Formula: C33H30N4O2
- Molecular Weight: 514.63 g/mol
- Appearance: White to off-white crystalline powder
- Solubility: Sparingly soluble in water
- Stability: Stable under normal storage conditions

Pharmacological Properties:

- Mechanism of Action: Blocks the angiotensin II type 1 (AT1) receptor, inhibiting the vasoconstrictor and aldosterone-secreting effects of angiotensin II
- Indications: Used for the treatment of hypertension, either alone or in combination with other antihypertensive agents
- Metabolism: Metabolized in the liver via glucuronidation and oxidation pathways
- Dosage Forms: Available as oral tablets

Adverse Effects:

- Common Side Effects: Headache, dizziness, hypotension, and hyperkalemia
- Serious Adverse Effects: Angioedema, renal failure, and hepatotoxicity (rare)
- Drug Interactions: Potential interactions with potassium-sparing diuretics, NSAIDs, and lithium

Special Considerations:

- Renal Impairment: Dose adjustments may be necessary in patients with renal impairment due to the risk of hyperkalemia and renal dysfunction
- Pregnancy: Contraindicated during pregnancy due to potential harm to the fetus

Telmisartan is an ARB widely used for the treatment of hypertension. Its mechanism of action involves blocking the AT1 receptor, leading to vasodilation and reduced aldosterone secretion. Although generally well-tolerated, Telmisartan can cause adverse effects such as headache, hypotension, and hyperkalemia. Careful monitoring is required, especially in patients with renal impairment or those taking concomitant medications that may interact with Telmisartan.

METHODOLOGY

MATERIALS AND METHODS

STUDY DESIGN : Experimental study was conducted on 72 inbred male Wistar rats.

LOCUS OF STUDY : Animal house attached to Department of Pharmacology. BLDE (DU)'s Shri B.M. Patil Medical College Hospital & Research Centre, Vijayapura.

SEX : Male

DRUGS : 1) Phenytoin Sodium
2) Sodium Valproate
3) Ramipril
4) Telmisartan

Animals were divided into two sets of 36 animals each for Model I & Model II: All drugs were administered by oral route per kg BW.

Model I : Maximal electro shock seizure (MES Model) 150mA for 0.2sec [66]

GROUPING OF ANIMALS:

Thirty-six rats were divided into six groups of 6 rats each (n=6).

Group 1: Vehicle control (Carboxy methyl cellulose) [66]

Group 2: Standard positive control (Phenytoin Sodium 100 mg/kg) [66]

Group 3: Ramipril 2mg/kg [68]

Group 4: Telmisartan 30mg/kg [66]

Group 5: Ramipril 1mg/kg+ Phenytoin Sodium 50mg/kg

Group 6: Telmisartan 15mg/kg + Phenytoin Sodium 50mg/kg

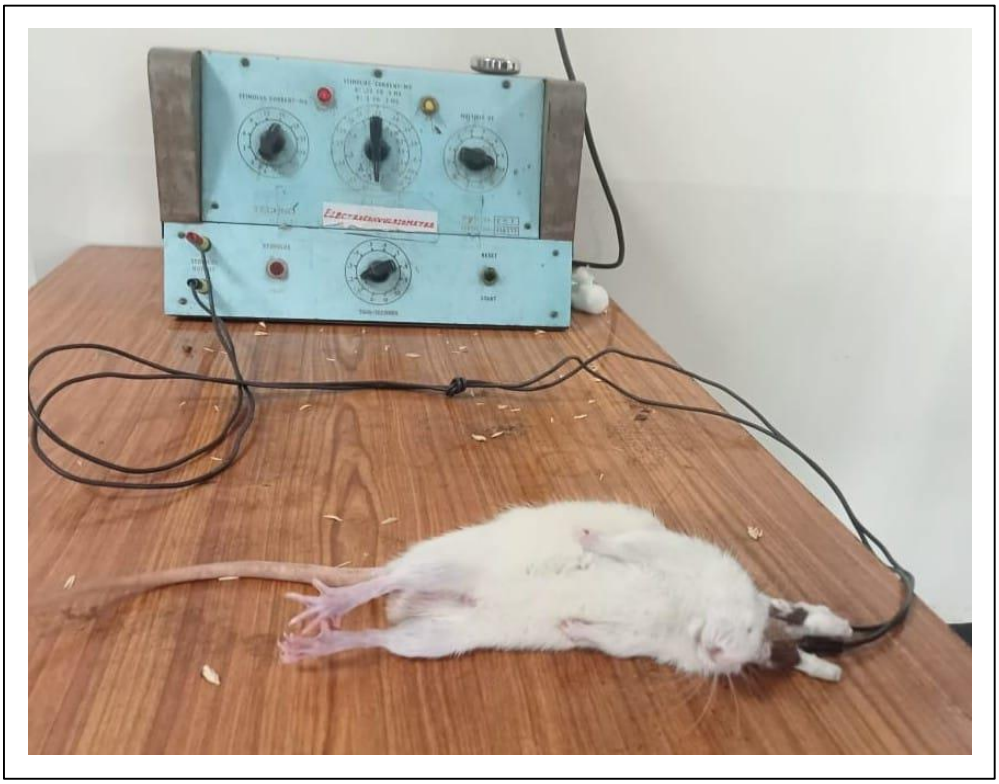


FIGURE 16: Rat showing tonic extension of Hind Limbs onMES Stimulation (150mA for 0.2sec)

Model II : Pentylenetetrazole Model 70mg/kg i.p. [65]

GROUPING OF ANIMALS:

Thirty-six rats were divided into six groups of 6 rats each (n=6).

All the drugs were administered by oral route per kg BW.

Group 1: Vehicle control (Carboxy methyl cellulose) [66]

Group 2: Standard positive control (Sodium Valproate 250mg/kg) [67]

Group 3: Ramipril 2mg/kg [68]

Group 4: Telmisartan 30mg/kg [66]

Group 5: Ramipril 1mg/kg + Sodium Valproate 125mg/kg

Group 6: Telmisartan 15mg/kg + Sodium Valproate 125mg/kg

All animals had access to food and water *ad libitum*.

FIGURE 17: Rat showing clonic convulsion on treatment with Pentylenetetrazole stimulation (70mg/kg i.p,)

Parameters to be studied:

For MES model

Animals were observed for: Abolition of hind limb extensor tone (HLE) and Righting reflex.

For the PTZ model:

Animals were observed for: Abolition of clonic convulsions.

No animal was sacrificed during the study.

Statistical Analysis:

- All the values were expressed as the mean ± SEM and analyzed by one-way analysis of variance (ANOVA) in order to test differences between groups
- The level of statistical significance was set at $p<0.05$

RESULTS

RESULTS

OBSERVATIONS & RESULTS

Table – 1: Intergroup Comparison of HLTE (sec)

Group	HLTE (sec)	
	Mean	SD
Group 1	21.67	1.366
Group 2	6.50	1.517
Group 3	9.00	.894
Group 4	13.17	.753
Group 5	6.67	1.751
Group 6	9.83	3.601
ANOVA	F=54.33, **p<0.001**	

The mean and standard deviation (SD) values for Hind Limb Tonic Extension (HLTE) in seconds were assessed across six groups. In Group 1, the mean HLTE was 21.67 seconds with a standard deviation of 1.366. Group 2 exhibited a mean HLTE of 6.50 seconds with an SD of 1.517. For Group 3, the mean HLTE was 9.00 seconds with an SD of 0.894. In Group 4, the mean HLTE was 13.17 seconds, and the SD was 0.753. Group 5 had a mean HLTE of 6.67 seconds, with a standard deviation of 1.751. Finally, Group 6 showed a mean HLTE of 9.83 seconds and an SD of 3.601. An analysis of variance (ANOVA) was conducted, revealing a statistically significant difference among the groups ($F=54.33$, $p<0.001$).

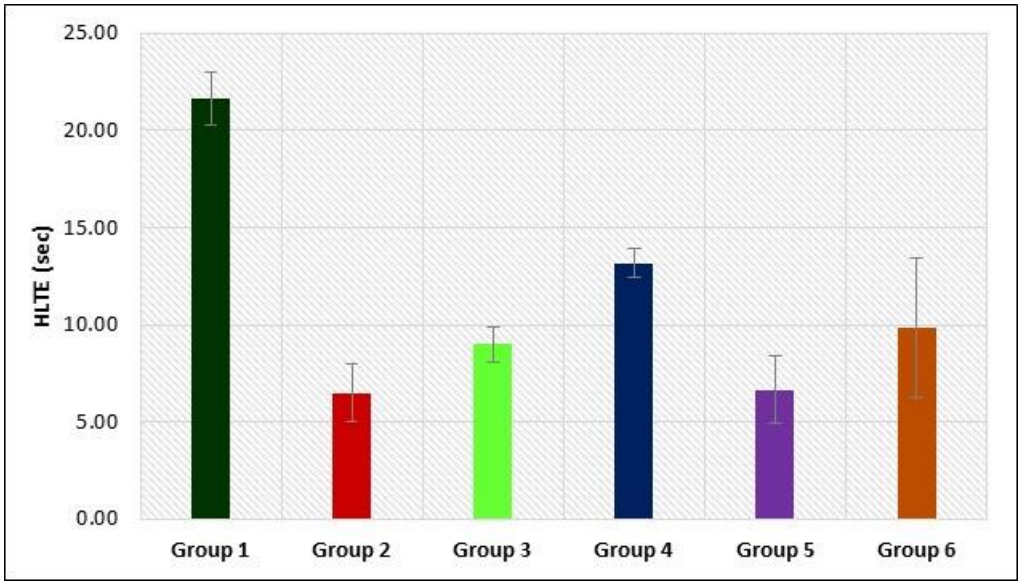


FIGURE 18

Table – 2: Paired Comparisons of HLTE (sec) between Group Pairs

Group Pair	HLTE (sec)		
	Mean Diff.	SE	p-value
Group 1 vs Group 2	15.17	1.09	**<0.001**
Group 1 vs Group 3	12.67	1.09	**<0.001**
Group 1 vs Group 4	8.50	1.09	**<0.001**
Group 1 vs Group 5	15.00	1.09	**<0.001**
Group 1 vs Group 6	11.83	1.09	**<0.001**
Group 2 vs Group 3	2.50	1.09	0.232
Group 2 vs Group 4	6.67	1.09	**<0.001**
Group 2 vs Group 5	0.17	1.09	1.000
Group 2 vs Group 6	3.33	1.09	0.050
Group 3 vs Group 4	4.17	1.09	**0.008**
Group 3 vs Group 5	2.33	1.09	0.299
Group 3 vs Group 6	0.83	1.09	0.972
Group 4 vs Group 5	6.50	1.09	**<0.001**
Group 4 vs Group 6	3.33	1.09	0.050
Group 5 vs Group 6	3.17	1.09	0.070

The mean difference, standard error (SE), and p-values for pairwise comparisons of Hind Limb Tonic Extension (HLTE) in seconds between different groups were analyzed. Comparing Group 1 with other groups, significant differences were observed: Group 1 versus Group 2 (mean difference = 15.17, SE = 1.09, $p < 0.001$), Group 1 versus Group 3 (mean difference = 12.67, SE = 1.09, $p < 0.001$), Group 1 versus Group 4 (mean difference = 8.50, SE = 1.09, $p < 0.001$), Group 1 versus Group 5 (mean difference = 15.00, SE = 1.09, $p < 0.001$), and Group 1 versus Group 6 (mean difference = 11.83, SE = 1.09, $p < 0.001$). Comparisons between other groups revealed both significant and non-significant differences. For instance, Group 2 versus Group 3 showed a non-significant difference (mean difference 2.50, SE = 1.09, $p = 0.232$), while Group 2 versus Group 4 (mean difference = 6.67, SE = 1.09, $p < 0.001$) and Group 4 versus Group 5 (mean difference = 6.50, SE = 1.09, $p < 0.001$) displayed significant differences. Additionally, several comparisons yielded marginal significance, such as Group 2 versus Group 6 (mean difference = 3.33, SE = 1.09, $p = 0.050$) and Group 5 versus Group 6 (mean difference = 3.17, SE = 1.09, $p = 0.070$).

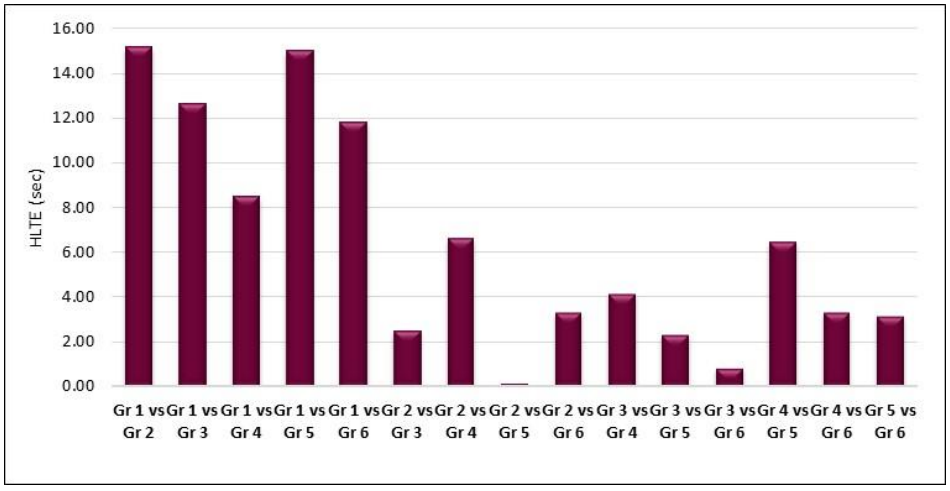


FIGURE 19

Table – 3: Intergroup Comparison of RIGHTING REFLEX (sec)

Group	**RIGHTING REFLEX (sec)**	
	Mean	SD
Group 1	140.00	34.756
Group 2	180.50	19.736
Group 3	144.50	12.661
Group 4	136.17	2.563
Group 5	126.50	10.578
Group 6	138.17	7.387
ANOVA	F=6.52, **p<0.001**	

The mean and standard deviation (SD) of the righting reflex time in seconds were examined across different groups. Group 1 exhibited a mean righting reflex time of 140.00 seconds with an SD of 34.756, while Group 2 showed a mean time of 180.50 seconds with an SD of 19.736. In Group 3, the mean time was 144.50 seconds with an SD of 12.661, whereas Group 4 had a mean time of 136.17 seconds with an SD of 2.563. Group 5 displayed a mean time of 126.50 seconds with an SD of 10.578, and Group 6 had a mean time of 138.17 seconds with an SD of 7.387. The analysis of variance (ANOVA) indicated a significant difference among the groups ($F = 6.52$, $p < 0.001$), suggesting variations in the righting reflex time across different experimental conditions.

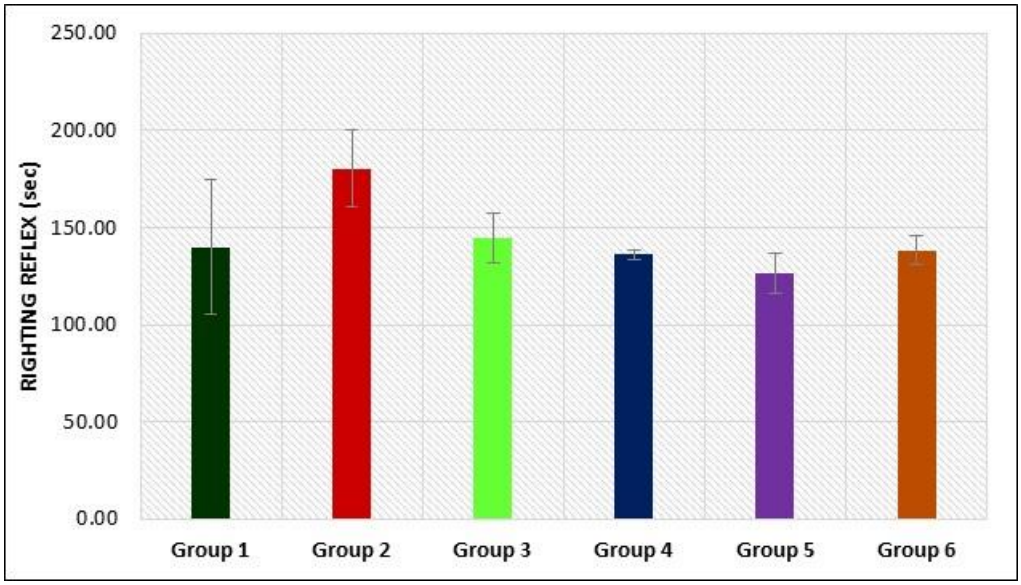


FIGURE 20

Table – 4: Paired Comparisons of RIGHTING REFLEX (sec) between Group Pairs

Group Pair	RIGHTING REFLEX (sec)		
	Mean Diff.	SE	p-value
Group 1 vs Group 2	40.50	10.36	**0.006**
Group 1 vs Group 3	4.50	10.36	0.998
Group 1 vs Group 4	3.83	10.36	0.999
Group 1 vs Group 5	13.50	10.36	0.781
Group 1 vs Group 6	1.83	10.36	1.000
Group 2 vs Group 3	36.00	10.36	**0.018**
Group 2 vs Group 4	44.33	10.36	**0.002**
Group 2 vs Group 5	54.00	10.36	**<0.001**
Group 2 vs Group 6	42.33	10.36	**0.004**
Group 3 vs Group 4	8.33	10.36	0.964
Group 3 vs Group 5	18.00	10.36	0.519
Group 3 vs Group 6	6.33	10.36	0.989
Group 4 vs Group 5	9.67	10.36	0.935
Group 4 vs Group 6	2.00	10.36	1.000
Group 5 vs Group 6	11.66	10.36	0.867

Differences in mean righting reflex times (in seconds) between various group pairs were analyzed. When comparing Group 1 to Group 2, the mean difference was 40.50 seconds (SE = 10.36, p = 0.006). However, there were no significant differences between Group 1 and Group 3 (mean difference = 4.50, SE = 10.36, p = 0.998), Group 1 and Group 4 (mean difference = 3.83, SE = 10.36, p = 0.999), Group 1 and Group 5 (mean difference = 13.50, SE = 10.36, p = 0.781), or Group 1 and Group 6 (mean difference = 1.83, SE = 10.36, p = 1.000). Significant differences were observed between Group 2 and Group 3 (mean difference = 36.00, SE = 10.36, p = 0.018), Group 2 and Group 4 (mean difference = 44.33, SE = 10.36, p = 0.002), Group 2 and Group 5 (mean difference = 54.00, SE = 10.36, p < 0.001), and Group 2 and Group 6 (mean difference = 42.33, SE = 10.36, p = 0.004). No significant differences were found between Group 3 and Group 4, Group 3 and Group 5, Group 3 and Group 6, Group 4 and Group 5, Group 4 and Group 6, or Group 5 and Group 6.

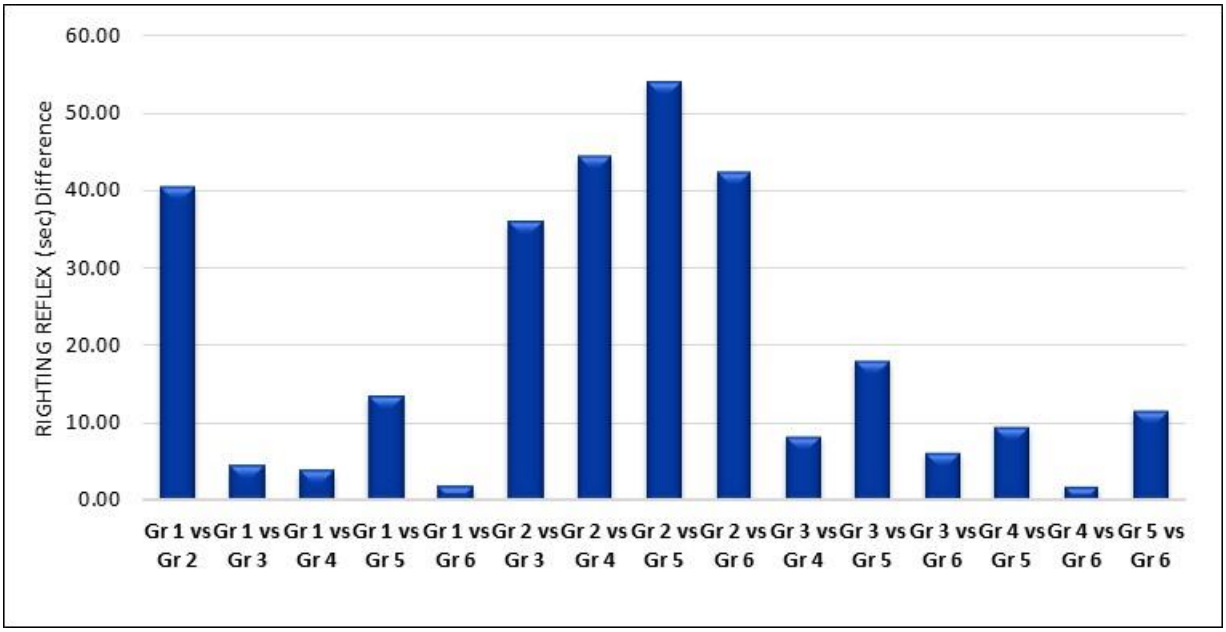


FIGURE 21

Table – 5: Intergroup Comparison of ONSET OF CLONIC CONVULSIONS (sec)

Group	**ONSET OF CLONIC CONVULSIONS (sec)**	
	Mean	SD
Group 1	51.33	3.445
Group 2	147.00	29.584
Group 3	49.50	7.287
Group 4	63.67	14.841
Group 5	131.33	11.219
Group 6	185.17	35.701
ANOVA	F=46.5, **p<0.001**	

The onset of clonic convulsions was measured in seconds across different groups, revealing significant variations. Group 1 exhibited a mean onset time of 51.33 seconds, with a standard deviation (SD) of 3.445 seconds. In contrast, Group 2 had a markedly longer onset time, with a mean of 147.00 seconds and a SD of 29.584 seconds. Group 3 showed a mean onset time of 49.50 seconds (SD = 7.287), Group 4 had a mean onset time of 63.67 seconds (SD = 14.841), Group 5 had a mean onset time of 131.33 seconds (SD = 11.219), and Group 6 had the longest mean onset time of 185.17 seconds (SD = 35.701). Analysis of variance (ANOVA) revealed a significant overall difference in onset times across the groups ($F = 46.5$, $p < 0.001$), indicating variability in the onset of clonic convulsions among the different experimental groups.

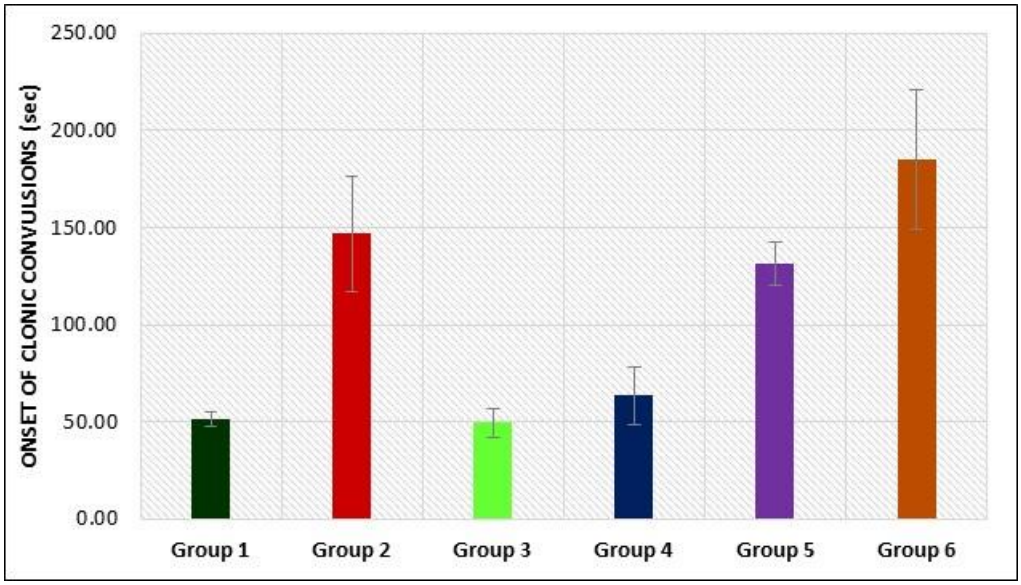


FIGURE 22

Table – 6: Paired Comparisons of ONSET OF CLONIC CONVULSIONS (sec) between Group Pairs

Group Pair	ONSET OF CLONIC CONVULSIONS (sec)		
	Mean Diff.	SE	p-value
Group 1 vs Group 2	95.66	11.93	**<0.001**
Group 1 vs Group 3	1.83	11.93	1.000
Group 1 vs Group 4	12.33	11.93	0.903
Group 1 vs Group 5	80.00	11.93	**<0.001**
Group 1 vs Group 6	133.80	11.93	**<0.001**
Group 2 vs Group 3	97.50	11.93	**<0.001**
Group 2 vs Group 4	83.33	11.93	**<0.001**
Group 2 vs Group 5	15.67	11.93	0.775
Group 2 vs Group 6	38.16	11.93	**0.035**
Group 3 vs Group 4	14.16	11.93	0.839
Group 3 vs Group 5	81.83	11.93	**<0.001**
Group 3 vs Group 6	135.60	11.93	**<0.001**
Group 4 vs Group 5	67.66	11.93	**<0.001**
Group 4 vs Group 6	121.50	11.93	**<0.001**
Group 5 vs Group 6	53.83	11.93	**0.001**

The comparison of the onset of clonic convulsions between different group pairs revealed significant differences in mean onset times, as indicated by the p-values. Group 1 versus Group 2 exhibited the most substantial difference, with a mean difference of 95.66 seconds (SE = 11.93, $p < 0.001$). Similarly, significant differences were observed between Group 1 and Group 5 (mean difference = 80.00 seconds, SE = 11.93, $p < 0.001$), Group 1 and Group 6 (mean difference = 133.80 seconds, SE = 11.93, $p < 0.001$), Group 2 and Group 3 (mean difference = 97.50 seconds, SE = 11.93, $p < 0.001$), Group 2 and Group 4 (mean difference = 83.33 seconds, SE = 11.93, $p < 0.001$), Group 3 and Group 5 (mean difference = 81.83 seconds, SE = 11.93, $p < 0.001$), Group 3 and Group 6 (mean difference = 135.60 seconds, SE = 11.93, $p < 0.001$), Group 4 and Group 5 (mean difference = 67.66 seconds, SE = 11.93, $p < 0.001$), Group 4 and Group 6 (mean difference = 121.50 seconds, SE = 11.93, $p < 0.001$), and Group 5 and Group 6 (mean difference = 53.83 seconds, SE = 11.93, $p = 0.001$). Additionally, Group 2 versus Group 6 exhibited a significant difference with a mean difference of 38.16 seconds (SE = 11.93, $p = 0.035$). Conversely, several comparisons did not show statistically significant differences, including Group 1 versus Group 3, Group 1 versus Group 4, Group 2 versus Group 5, Group 3 versus Group 4, and Group 3 versus Group 5.

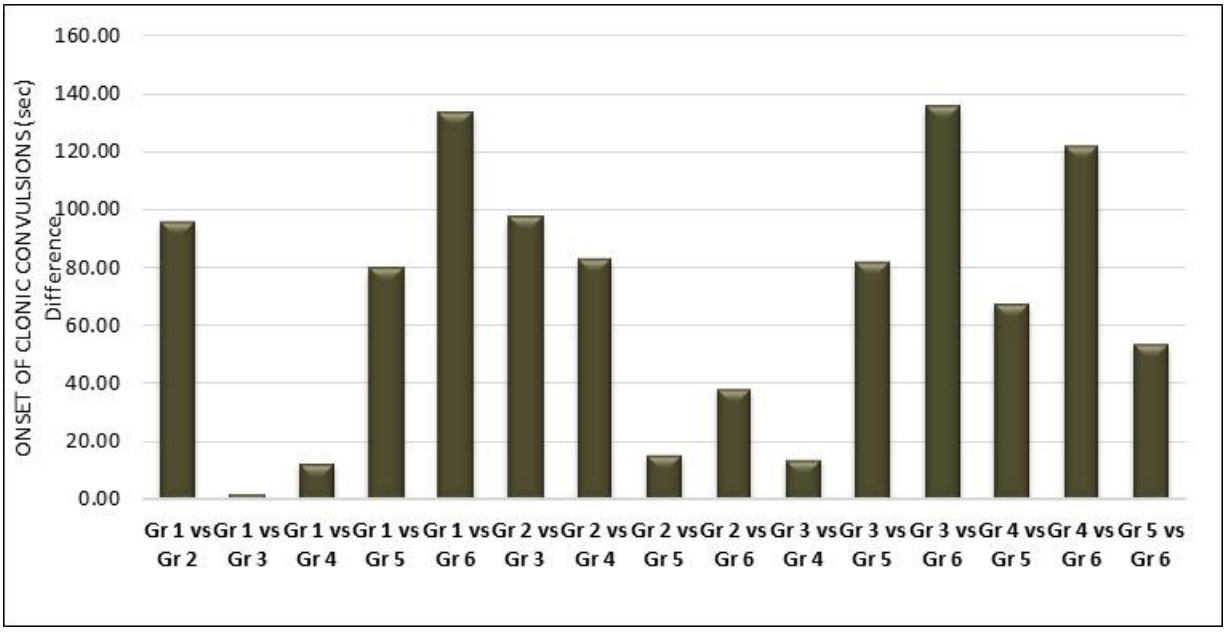


FIGURE 23

Table – 7: Multivariate Regression Analysis to Establish Relationship of HLTE with Group Treatments

Influencers	Dependent: HLTE (sec)				
	B	p-value	95% CI Lower	95% CI Upper	effect size
Intercept	10.83	0.000	5.84	15.82	0.396
Group 1	-0.33	0.924	-7.39	6.72	0.000
Group 2	-0.17	0.962	-7.22	6.89	0.000
Group 3	0.67	0.848	-6.39	7.72	0.001
Group 4	1.17	0.738	-5.89	8.22	0.004
Group 5	0.50	0.886	-6.56	7.56	0.001
Group 6	Ref				
Model Fit	$R^2 = 0.009$				

The influencers on the dependent variable, HLTE (seconds), were assessed using a linear regression model. The intercept was found to be 10.83 seconds ($p < 0.001$), with a 95% confidence interval ranging from 5.84 to 15.82 seconds and an effect size of 0.396. When considering the influence of different groups, Group 1 exhibited a coefficient of -0.33 (p =

0.924) with a negligible effect size (0.000), indicating no significant impact on HLTE. Similarly, Group 2 showed a coefficient of -0.17 (p = 0.962) with an effect size of 0.000, suggesting no substantial influence on HLTE. Group 3 displayed a coefficient of 0.67 (p = 0.848) with a small effect size of 0.001, implying a minimal effect on HLTE. Group 4 had a coefficient of 1.17 (p = 0.738) with a modest effect size of 0.004, indicating a slightly greater impact on HLTE compared to the other groups. Group 5 demonstrated a coefficient of 0.50 (p = 0.886) with an effect size of 0.001, indicating a minor effect on HLTE. Group 6 was used as the reference category. The overall model fit was evaluated, resulting in an R-squared value of 0.009, suggesting that only a small proportion of the variance in HLTE was explained by the predictors in the model.

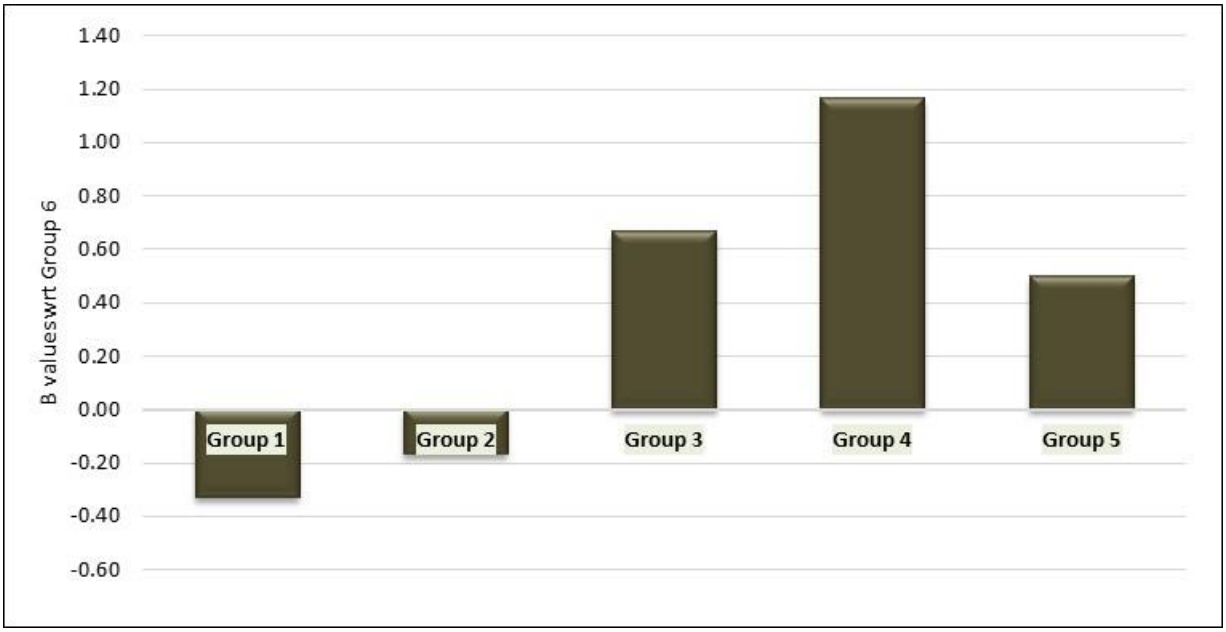


FIGURE 24

Table – 8: Multivariate Regression Analysis to Establish Relationship of RIGHTING REFLEX with Group Treatments

Influencers	Dependent: RIGHTING REFLEX (sec)				
	B	p-value	95% CI Lower	95% CI Upper	effect size
Intercept	144.00	0.000	124.07	163.93	0.879
Group 1	16.50	0.241	-11.68	44.68	0.045
Group 2	-1.67	0.905	-29.85	26.51	0.000
Group 3	-14.50	0.302	-42.68	13.68	0.036
Group 4	-2.17	0.876	-30.35	26.01	0.001
Group 5	3.67	0.792	-24.51	31.85	0.002
Group 6	Ref				
Model Fit	$R^2 = 0.150$				

The influencers on the dependent variable, RIGHTING REFLEX (seconds), were examined using a linear regression model. The intercept was determined to be 144.00 seconds ($p < 0.001$), with a 95% confidence interval ranging from 124.07 to 163.93 seconds and an effect size of 0.879. When analyzing the influence of different groups, Group 1 exhibited a coefficient of 16.50 seconds ($p = 0.241$) with a small effect size of 0.045, indicating a slight impact on RIGHTING REFLEX, although not statistically significant. Group 2 displayed a coefficient of -1.67 seconds ($p = 0.905$) with an effect size of 0.000, suggesting no significant influence on RIGHTING REFLEX. Similarly, Group 3 showed a coefficient of -14.50 seconds ($p = 0.302$) with a modest effect size of 0.036, implying a minor effect on RIGHTING REFLEX, although not statistically significant. Group 4 had a coefficient of -2.17 seconds ($p = 0.876$) with a small effect size of 0.001, indicating a negligible impact on RIGHTING REFLEX. Group 5 demonstrated a coefficient of 3.67 seconds ($p = 0.792$) with an effect size of 0.002, suggesting a minimal effect on RIGHTING REFLEX. Group 6 was used as the reference category. The overall model fit was evaluated, resulting in an R-squared

value of 0.150, indicating that a moderate proportion of the variance in RIGHTING REFLEX was explained by the predictors in the model.

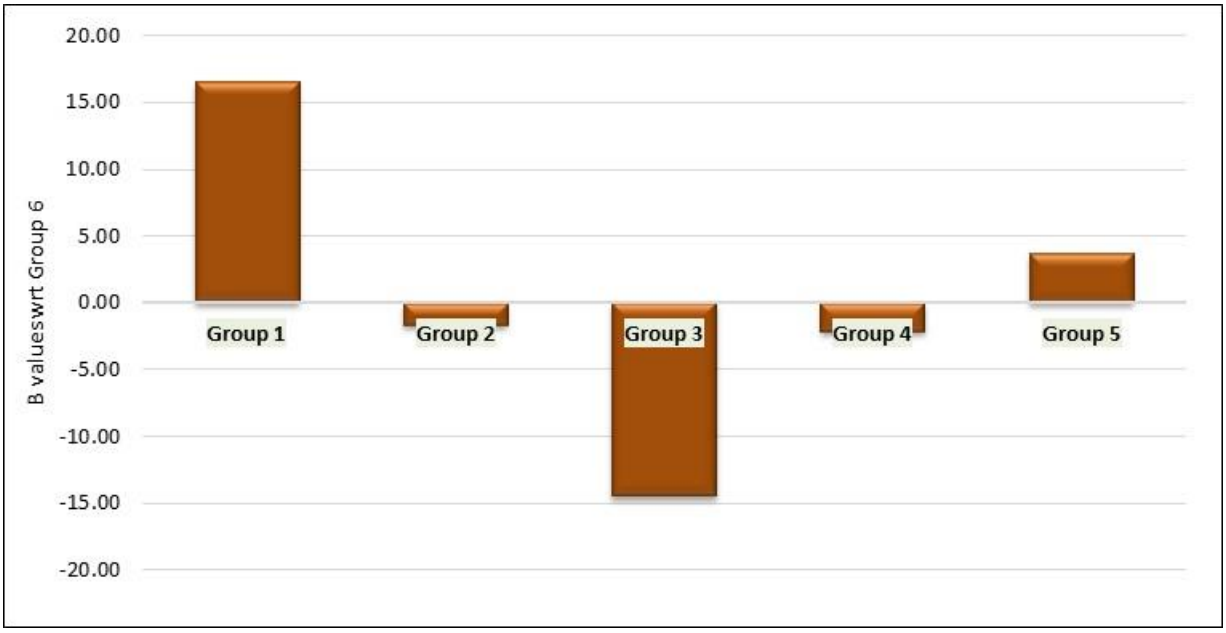


FIGURE 25

Table – 9: Multivariate Regression Analysis to Establish Relationship of ONSET OF CLONIC CONVULSIONS with Group Treatments

Influencers	Dependent: ONSET OF CLONIC CONVULSIONS (sec)				
	B	p-value	95% CI Lower	95% CI Upper	effect size
Intercept	107.83	0.000	57.13	158.53	0.386
Group 1	-1.67	0.962	-73.37	70.03	0.000
Group 2	6.17	0.862	-65.53	77.87	0.001
Group 3	-7.17	0.840	-78.87	64.53	0.001
Group 4	-12.17	0.731	-83.87	59.53	0.004
Group 5	-4.17	0.906	-75.87	67.53	0.000
Group 6	Ref				
Model Fit	$R^2 = 0.011$				

The influencers on the dependent variable, ONSET OF CLONIC CONVULSIONS (seconds), were analyzed using a linear regression model. The intercept was estimated to be 107.83 seconds ($p < 0.001$), with a 95% confidence interval ranging from 57.13 to 158.53 seconds and an effect size of 0.386. Regarding the influence of different groups, Group 1 exhibited a coefficient of -1.67 seconds ($p = 0.962$) with an effect size of 0.000, indicating no significant impact on the onset of clonic convulsions. Group 2 showed a coefficient of 6.17 seconds ($p = 0.862$) with a small effect size of 0.001, suggesting a negligible effect on the onset of clonic convulsions. Similarly, Group 3 displayed a coefficient of -7.17 seconds ($p = 0.840$) with an effect size of 0.001, indicating no significant influence on the onset of clonic convulsions. Group 4 had a coefficient of -12.17 seconds ($p = 0.731$) with a small effect size of 0.004, implying a minor impact on the onset of clonic convulsions, although not statistically significant. Group 5 demonstrated a coefficient of -4.17 seconds ($p = 0.906$) with an effect size of 0.000, suggesting no significant effect on the onset of clonic convulsions. Group 6 was utilized as the reference category. The overall model fit was evaluated, resulting in an R-squared value of 0.011, indicating that a small proportion of the variance in the onset of clonic convulsions was explained by the predictors in the model.

DISCUSSION

DISCUSSION

Despite advancements in understanding the pathophysiology of epilepsy and improvements in its pharmacotherapy, drug treatment remains unsatisfactory. In India, individuals with epilepsy experience social stigma and encounter challenges such as lack of education and limited resources, including access to neuro specialists, medications, and diagnostic investigations, leading to inadequate medical treatment. In developing countries, the cause of epilepsy is known in less than 40% of cases, compared to 60-70% in industrialized nations. Antiepileptic drugs are the mainstay of treatment for epilepsy patients. However, non-compliance with drug treatment is a major issue, often due to the high incidence of side effects from these medications and a lack of awareness. [69]

Angiotensin-converting enzyme (ACE) inhibitors and Angiotensin Receptor Blockers both have significant effects on the heart, primarily through their actions on the renin-angiotensin-aldosterone system (RAAS). Angiotensin-converting enzyme (ACE) inhibitors namely Ramipril and Angiotensin Receptor Blockers namely Telmisartan are screened for anticonvulsant activity by two most widely used models of epilepsy, viz. Pentylenetetrazole model for absence seizures and the Maximal Electroshock Model for generalized tonic-clonic seizures (GTCS). The test compounds showed anticonvulsant activity in both methods.

In MES induced seizure, our study finding showed, in combination treated groups Ramipril + Phenytoin (Group 5) and Telmisartan + Phenytoin (Group 6) have shown statistically significant decrease ($p < 0.05$) in duration of hind limb tonic extension when

compared to control group (Group 1) and there was no significant change in the duration of Righting Reflex in combination treated groups as compared to control groups.

In PTZ induced seizure, our study finding showed, in combination treated groups Sodium Valproate + Ramipril (Group 5) and Sodium Valproate + Telmisartan (Group 6) have shown statistically significant increase ($p < 0.05$) in onset of clonic convulsions when compared to control group (Group 1).

Various experimental studies have reported anticonvulsant potential of Ramipril and Telmisartan in combination with existing antiepileptic drugs or alone. Pushpa V H et al. (2022), evaluated the anticonvulsant activity of ARBs Telmisartan and Olmesartan in mice using Maximal Electroshock induced seizures, and Pentylenetetrazole (PTZ) induced convulsion methods. This study confirmed the dose-dependent anticonvulsant activities of these drugs. [65]

The result of HOPE and SECURE trials has suggested that ACE inhibitors decrease vasoconstriction, increase the bioactivity of NO, and can inhibit vascular superoxide production at its source. Therefore, drugs that interfere with RAS may be considered good therapeutic agents against vascular oxidative stress and, therefore, a good addition to existing therapy in patients with epilepsy. [70]

The study carried out by Asha D.J. et al (2020), to evaluate the anti-Convulsant activity of ARBs, Losartan, Telmisartan and Candesartan in Swiss Albino mice. Maximal Electroshock (MES) method and Pentylenetetrazole (PTZ) methods were used. Inverted screen tests and assessment of spontaneous motor activity were used for testing neurological deficits. ARBs

exhibited an anticonvulsant effect, with the Losartan group exhibiting a highly significant ($p<0.01$) increase in latency to convulsion as compared to the control group. [66]

In a study carried out by Yasar (2020), ACE Inhibitor Captopril exhibited a positive effect on Pentylenetetrazole-induced epileptic seizures in mice. In this study, total antioxidant status (TAS) and total oxidant status (TOS) were measured, and total oxidative stress index (OSI) was calculated. This study indicated that ACE inhibitor Captopril has anti-epileptic and neuroprotective properties by reducing oxidative stress levels and increasing GABA influx into neurons. This provides consideration of ACEIs or ARBs as good therapeutic agents in the management of epileptic patients with hypertension. [71]

The role of the Angiotensin pathway and its target therapy in epilepsy management has been reviewed by Shaip Kransigi and Armond Daci. Recently, advanced RAS research has clarified its role and involvement in brain physiology. Angiotensin peptides have been implicated in the control of seizures, during which they also act as neurotransmitters and neuromodulators in neuronal pathways, including the hypothalamus and forebrain. The positive effect of Renin inhibition has been confirmed in the PTZ – induced seizure model that was treated with anti-epileptic drugs, and this combination contributed to an increase in the PTZ threshold, which enhanced the protective actions of Clonazepam, Phenobarbital, and Valproic acid in PTZ test, offering additional benefits in memory impairment. **[72]** These data, also replicated in a maximum Electroshock Seizure (MES) model in mice, supporting synergistic beneficial effects in anticonvulsive action, suggesting its potential for prevention or management of epilepsy. [73]

The study carried out by A. Mandy (2014), showed the potential of anticonvulsant activity of Valproate in mouse Pilocarpine-induced seizure models. It suggested that these interactions were pharmacodynamic in nature. The combination of drugs interfering with RAS (ACEIs / ARBs) with Valproic acid decreased the brain insult caused by seizures and prolonged the latency of seizure appearance. Thus, RAS inhibition may positively interact with anti-epileptic drugs in epileptic patients. [67]

Our research aligns with the discoveries of the previously referenced authors. Nonetheless, there is a scarcity of information regarding this topic, necessitating additional experimental investigations, particularly since the initial reports are limited to rodents. It is imperative to conduct further studies involving higher animals such as canines and subhuman primates.

SUMMARY AND CONCLUSION

SUMMARY AND CONCLUSION

Epilepsy is a neurological disorder characterized by recurrent seizures, affecting millions of people worldwide. Despite the availability of several antiepileptic drugs (AEDs), a significant proportion of patients continue to experience seizures. This has led to ongoing research to identify new therapeutic agents with antiepileptic properties. One area of interest is the potential antiepileptic effects of drugs typically used to treat other conditions, such as Ramipril and Telmisartan, which are known for their role in managing hypertension and cardiovascular diseases. Ramipril and Telmisartan are members of the angiotensin system-modifying class of drugs, with Ramipril being an angiotensin-converting enzyme (ACE) inhibitor and Telmisartan being an angiotensin II receptor blocker (ARB). While their primary indications are for hypertension and heart-related conditions, emerging evidence suggests that these drugs may also have antiepileptic properties. The exact mechanisms by which Ramipril and Telmisartan exert their antiepileptic effects are not fully understood but are believed to involve modulation of the renin-angiotensin system (RAS) and other pathways implicated in epilepsy. As an ACE inhibitor, Ramipril blocks the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor. Angiotensin II also plays a role in inflammation and oxidative stress, which are involved in the pathogenesis of epilepsy. By inhibiting ACE, Ramipril reduces angiotensin II levels, potentially mitigating these processes and exerting antiepileptic effects. Telmisartan, an ARB, blocks the effects of angiotensin II by selectively antagonizing the angiotensin II type 1 (AT1) receptor. In addition to its effects on RAS, Telmisartan has been shown to activate peroxisome proliferator-activated receptor-gamma (PPAR-γ), which has anti-inflammatory and neuroprotective properties. This dual mechanism may contribute to its potential antiepileptic effects. On this background we have evaluated the

modulatory effects of ACEIs and ARBs on the anticonvulsant effects of standard antiepileptic drugs like Phenytoin and Sodium Valproate in Pentylenetetrazole (PTZ) and Maximal Electroshock (MES) in Wistar rats. Ramipril showed anticonvulsant activity in both Pentylenetetrazole induced and Maximal Electroshock induced seizures by increasing the latency for convulsion and reducing mean duration of convulsions. Telmisartan also showed anticonvulsant activity in both Pentylenetetrazole induced and Maximal Electroshock induced seizures by increasing the latency for convulsion and reducing mean duration of convulsions. Ramipril and Telmisartan, primarily used for hypertension and cardiovascular diseases, show promise as potential antiepileptic agents.

Their mechanisms of action, including modulation of the RAS and other pathways, suggest a multifaceted approach to epilepsy treatment. Further research, particularly large-scale clinical trials, is warranted to establish their efficacy and safety in the management of epilepsy.

Conclusions drawn from this study are as follows:

1. Alone Ramipril and Telmisartan have shown moderate antiepileptic effect against Pentylenetetrazole and Maximal Electroshock induced seizures.
2. Combination of Ramipril and Telmisartan with existing antiepileptic drugs (Phenytoin and Sodium Valproate) has shown potential antiepileptic effect to potentiate the anticonvulsant activity against Pentylenetetrazole and maximal electroshock induced seizures.
3. Therapeutically, this enhancing profile for ACEIs and ARBs fosters a safer and more effective drug-combination regimen than existing antiepileptic drugs.

BIBLIOGRAPHY

BIBLIOGRAPHY

1. https:/www.who.int/news-room/fact-sheets/detail/epilepsy; 9feb:2022
2. Beghi E. The epidemiology of epilepsy. Neuroepidemiology. 2020;54(2):185-91.
3. Laurence L. Bruton, Randa Hilal-Dandan, Bjorn C. Knollmann. The pharmacological basis of therapeutics. Goodman Gilman's; 13th edition
4. Porter RJ, Dhir A, Macdonald RL, Rogawski MA. Mechanisms of action of antiseizure drugs. Handbook of clinical neurology. 2012 Jan 1;108:663-81.
5. Löscher W, Klein P. The pharmacology and clinical efficacy of Antiseizure medications: from bromide salts to cenobamate and beyond. CNS drugs. 2021 Sep;35(9):935-63.
6. Vera-González A. Pathophysiological Mechanisms Underlying the Etiologies of Seizures and Epilepsy. Exon Publications. 2022 Apr 2:1-3.
7. Kumar S, Singh G. Pathophysiology of epilepsy: an updated review. International Journal of Medical and Health Research. 2016;2(10):32-6.
8. Rana A, Musto AE. The role of inflammation in the development of epilepsy. Journal of neuroinflammation. 2018 Dec;15(1):1-2.
9. Lee KH, Cha M, Lee BH. Neuroprotective effect of antioxidants in the brain. International journal of molecular sciences. 2020 Sep 28;21(19):7152.
10. Wright JW, Harding JW. Brain renin-angiotensin—a new look at an old system. Progress in neurobiology. 2011 Sep 15;95(1):49-67.
11. Kaculini, Christian M et al. “The History of Epilepsy: From Ancient Mystery to Modern Misconception.” *Cureus* vol. 13,3 e13953. 17 Mar. 2021, doi:10.7759/cureus.13953
12. Patel, Puja, and Solomon L Moshé. “The evolution of the concepts of seizures and epilepsy: What's in a name?.” Epilepsia open vol. 5,1 22-35. 10 Jan. 2020, doi:10.1002/epi4.12375

13. Linka, Louise et al. “Effect of the revised definition of epilepsy on treatment decisions and seizure recurrence after a first epileptic seizure.” *European journal of neurology* vol. 30,6 (2023): 1557-1564. doi:10.1111/ene.15769
14. Fisher, Robert S et al. “ILAE official report: a practical clinical definition of epilepsy.” *Epilepsia* vol. 55,4 (2014): 475-82. doi:10.1111/epi.12550
15. Beghi, Ettore. “The Epidemiology of Epilepsy.” *Neuroepidemiology* vol. 54,2 (2020): 185-191. doi:10.1159/000503831
16. Balestrini, S., Arzimanoglou, A., Blümcke, I., Scheffer, I.E., Wiebe, S., Zelano, J. and Walker, M.C. (2021), The aetiologies of epilepsy. Epileptic Disorders, 23: 1-16. https://doi.org/10.1684/epd.2021.1255
17. Perucca, Piero et al. “The Genetics of Epilepsy.” *Annual review of genomics and human genetics* vol. 21 (2020): 205-230. doi:10.1146/annurev-genom-120219-074937
18. Symonds, Joseph D et al. “Early childhood epilepsies: epidemiology, classification, aetiology, and socio-economic determinants.” *Brain: a journal of neurology* vol. 144,9 (2021): 2879-2891. doi:10.1093/brain/awab162
19. Shorvon, Simon D. “The etiologic classification of epilepsy.” *Epilepsia* vol. 52,6 (2011): 1052-7. doi:10.1111/j.1528-1167.2011. 03041.x
20. Perucca, Piero et al. “The management of epilepsy in children and adults.” *The Medical journal of Australia* vol. 208,5 (2018): 226-233. doi:10.5694/mja17.00951
21. Ngugi, Anthony K et al. “Incidence of epilepsy: a systematic review and meta-analysis.” *Neurology* vol. 77,10 (2011): 1005-12. doi:10.1212/WNL.0b013e31822cfc90
22. Keezer, Mark R et al. “Comorbidities of epilepsy: current concepts and future perspectives.” The Lancet. Neurology vol. 15,1 (2016): 106-15. doi:10.1016/S1474-4422(15)00225-2

23. Fiest KM, Sauro KM, Wiebe S, et al. Prevalence and incidence of epilepsy: A systematic review and meta-analysis of international studies. Neurology. 2017 Jan;88(3):296-303. DOI: 10.1212/wnl.0000000000003509. PMID: 27986877; PMCID: PMC5272794.
24. Hotka, Matej, and Helmut Kubista. “The paroxysmal depolarization shift in epilepsy research.” *The international journal of biochemistry & cell biology* vol. 107 (2019): 77-81. doi:10.1016/j.biocel.2018.12.006
25. Kubista, Helmut et al. “The Paroxysmal Depolarization Shift: Reconsidering Its Role in Epilepsy, Epileptogenesis and Beyond.” *International journal of molecular sciences* vol. 20,3 577. 29 Jan. 2019, doi:10.3390/ijms20030577
26. Lindquist, Britta E et al. “Thalamocortical circuits in generalized epilepsy: Pathophysiologic mechanisms and therapeutic targets.” *Neurobiology of disease* vol. 181 (2023): 106094. doi:10.1016/j.nbd.2023.106094
27. Curia, G et al. “Pathophysiogenesis of mesial temporal lobe epilepsy: is prevention of damage antiepileptogenic?.” *Current medicinal chemistry* vol. 21,6 (2014): 663-88. doi:10.2174/09298673206613119152201
28. Sarmast, Shah T et al. “Current Classification of Seizures and Epilepsies: Scope, Limitations and Recommendations for Future Action.” *Cureus* vol. 12,9 e10549. 20 Sep. 2020, doi:10.7759/cureus.10549
29. Scheffer, Ingrid E et al. “ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology.” *Epilepsia* vol. 58,4 (2017): 512-521. doi:10.1111/epi.13709
30. Falco-Walter, Jessica J et al. “The new definition and classification of seizures and epilepsy.” *Epilepsy research* vol. 139 (2018): 73-79. doi:10.1016/j.eplepsyres.2017.11.015

31. Blume, Warren T. "Diagnosis and management of epilepsy." *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne* vol. 168,4 (2003): 441-8.
32. *The Pharmaceutical Journal*, PJ, April 2022, Vol 308, No 7960;308(7960)::DOI:10.1211/PJ.2022.1.139730
33. Will Morton : PET/MRI proves valuable in difficult epilepsy cases; Nov 23, 2021
34. Löscher W, Schmidt D. Modern antiepileptic drug development has failed to deliver: ways out of the current dilemma. Epilepsia. 2011 Apr;52(4):657-78. doi: 10.1111/j.1528-1167.2011.03024.x. Epub 2011 Mar 22. PMID: 21426333.
35. French, J.A. and Faught, E. (2009), Rational polytherapy. Epilepsia, 50: 63-68. https://doi.org/10.1111/j.1528-1167.2009.02238.x
36. Perucca E. Current trends in antiepileptic drug therapy. Epilepsia. 2003;44 Suppl 4:41-7. doi: 10.1046/j.1528-1157.44.s4.1.x. PMID: 12823568.
37. Schmidt D, Löscher W. Drug resistance in epilepsy: putative neurobiologic and clinical mechanisms. Epilepsia. 2005 Jun;46(6):858-77. doi: 10.1111/j.1528-1167.2005.54904.x. PMID: 15946327.
38. Löscher W, Schmidt D. New Horizons in the development of antiepileptic drugs: Innovative strategies. Epilepsy Res. 2006 Jun;69(3):183-272. doi: 10.1016/j.eplepsyres.2006.03.014. PMID: 16835945; PMCID: PMC1574365.
39. Löscher W. Basic pharmacology of valproate: a review after 35 years of clinical use for the treatment of epilepsy. CNS Drugs. 2002;16(10):669-94. doi: 10.2165/00023210-200216100-00003. PMID: 12269861.

40. Magheru, Calin et al. “Antiepileptic Drugs and Their Dual Mechanism of Action on Carbonic Anhydrase.” *Journal of clinical medicine* vol. 11,9 2614. 6 May. 2022, doi:10.3390/jcm11092614

41. Alavijeh, Mohammad S et al. “Drug metabolism and pharmacokinetics, the blood-brain barrier, and central nervous system drug discovery.” *NeuroRx : the journal of the American Society for Experimental NeuroTherapeutics* vol. 2,4 (2005): 554-71. doi:10.1602/neurorx.2.4.554

42. Marvanova, Marketa. “Pharmacokinetic characteristics of antiepileptic drugs (AEDs).” *The mental health clinician* vol. 6,1 8-20. 8 Mar. 2016, doi:10.9740/mhc.2015.01.008

43. Faught, E. (2001), Pharmacokinetic Considerations in Prescribing Antiepileptic Drugs. Epilepsia, 42: 19-23. https://doi.org/10.1111/j.1528-1167.2001.00004.x

44. Goldenberg, Marvin M. “Overview of drugs used for epilepsy and seizures: etiology, diagnosis, and treatment.” *P & T : a peer-reviewed journal for formulary management* vol. 35,7 (2010): 392-415.

45. Johannessen, Svein I, and Cecilie Johannessen Landmark. “Antiepileptic drug interactions - principles and clinical implications.” *Current neuropharmacology* vol. 8,3 (2010): 254-67. doi:10.2174/157015910792246254

46. Perucca, Emilio. “Clinically relevant drug interactions with antiepileptic drugs.” *British journal of clinical pharmacology* vol. 61,3 (2006): 246-55. doi:10.1111/j.1365-2125.2005.02529.x

47. Philip N Patsalos, Emilio Perucca, Clinically important drug interactions in epilepsy: general features and interactions between antiepileptic drugs, The Lancet Neurology, Volume 2, Issue 6, 2003, Pages 347-356, ISSN 1474-4422, https://doi.org/10.1016/S1474-4422(03)00409-5.

48. Karaźniewicz-Łada, Marta et al. “Pharmacokinetic Drug-Drug Interactions among Antiepileptic Drugs, Including CBD, Drugs Used to Treat COVID-19 and Nutrients.” *International journal of molecular sciences* vol. 22,17 9582. 3 Sep. 2021, doi:10.3390/ijms22179582

49. Krasniqi, Shaip, and Armond Daci. “Role of the Angiotensin Pathway and its Target Therapy in Epilepsy Management.” *International journal of molecular sciences* vol. 20,3 726. 8 Feb. 2019, doi:10.3390/ijms20030726

50. Taştemur, Yaşar, et al. “Positive Effects of Angiotensin-converting Enzyme (ACE) Inhibitor, Captopril, on Pentylenetetrazole-induced Epileptic Seizures in Mice.” *Tropical Journal of Pharmaceutical Research*, vol. 19, no. 3, Apr. 2020, pp. 637–43. https://doi.org/10.4314/tjpr.v19i3.26.

51. Doege, Corinna et al. “Association Between Angiotensin Receptor Blocker Therapy and Incidence of Epilepsy in Patients With Hypertension.” *JAMA neurology* vol. 79,12 (2022): 1296-1302. doi:10.1001/jamaneurol.2022.3413

52. Krasniqi, Shaip, and Armond Daci. 2019. "Role of the Angiotensin Pathway and its Target Therapy in Epilepsy Management" *International Journal of Molecular Sciences* 20, no. 3: 726. https://doi.org/10.3390/ijms20030726

53. Chakraborti, Ayanabha et al. “Editorial: Experimental Models of Epilepsy and Related Comorbidities.” *Frontiers in pharmacology* vol. 10 179. 4 Mar. 2019, doi:10.3389/fphar.2019.00179

54. Garcia Garcia, M E et al. “Modelos experimentales en epilepsia” [Experimental models in epilepsy]. *Neurologia (Barcelona, Spain)* vol. 25,3 (2010): 181-8.

55. Wang, Yilin et al. “Animal Models of Epilepsy: A Phenotype-oriented Review.” *Aging and disease* vol. 13,1 215-231. 1 Feb. 2022, doi:10.14336/AD.2021.0723

56. Reddy, Doodipala Samba, and Ramkumar Kuruba. “Experimental models of status epilepticus and neuronal injury for evaluation of therapeutic interventions.” *International journal of molecular sciences* vol. 14,9 18284-318. 5 Sep. 2013, doi:10.3390/ijms140918284
57. Castel-Branco, M M et al. “The Maximal Electroshock Seizure (MES) model in the preclinical assessment of potential new antiepileptic drugs.” *Methods and findings in experimental and clinical pharmacology* vol. 31,2 (2009): 101-6. doi:10.1358/mf.2009.31.2.1338414
58. Nirmala M, Suhasini G.E, Venkata Lakshmi K, Archana Giri, and Solomon Sunder Raj B. "Maximal Electroshock (MES) Induced Convulsions Model for Evaluating Antiepileptic Activity of New Isatin Derivative -N’-(7-Chloro-2-Oxo-2, 3-Dihydro-1H-Indol-3-yl) Benzohydrazide." International Journal of Research in Pharmaceutical Sciences (IJRPS), 5 (1), 2014, 329-334.
59. Xiang, Cheng et al. “Threshold for Maximal Electroshock Seizures (MEST) at three developmental stages in young mice.” *Zoological research* vol. 40,3 (2019): 231-235. doi:10.24272/j.issn.2095-8137.2019.038
60. Asla Pitkänen, Philip A. Schwartzkroin, Solomon L. Moshé : Models of Seizures and Epilepsy Chapter 12 , Electrical stimulation induced models of seizure Page Number 153
61. Shimada, Tadayuki, and Kanato Yamagata. “Pentylenetetrazole-Induced Kindling Mouse Model.” *Journal of visualized experiments : JoVE* ,136 56573. 12 Jun. 2018, doi:10.3791/56573
62. Ergul Erkec, O. (2015) ‘Pentylenetetrazole Kindling Epilepsy Model’, Journal of the Turkish Epilepsi Society [Preprint]. doi:10.5505/epilepsi.2015.08108.

63. Aleshin, Vasily A et al. “Pentylenetetrazole-Induced Seizures Are Increased after Kindling, Exhibiting Vitamin-Responsive Correlations to the Post-Seizures Behavior, Amino Acids Metabolism and Key Metabolic Regulators in the Rat Brain.” *International journal of molecular sciences* vol. 24,15 12405. 3 Aug. 2023, doi:10.3390/ijms241512405

64. Dhir, A. (2012), Pentylenetetrazole (PTZ) Kindling Model of Epilepsy. Current Protocols in Neuroscience, 58: 9.37.1-9.37.12. https://doi.org/10.1002/0471142301.ns0937s58

65. Pushpa VH, Shetty P, Suresha RN, Jayanthi MK, Ashwini V, Vaibhavi PS. Evaluation and comparison of the anticonvulsant activity of Telmisartan and olmesartan in experimentally induced animal models of epilepsy. Journal of clinical and diagnostic research: JCDR. 2014 Oct;8(10):HC08.

66. Jadhav AD, Jadhav R, Padwal S, Kale A, Jadhav S, Gade P. Determining the Evaluation of Anti-convulsant Activity of Angiotensin Receptor Antagonists in an Animal Model. Highlights on Medicine and Medical Science Vol. 14. 2021 Jul 20:74-82.

67. Mahdy A, Hegazy R, S Ali R. Renin-angiotensin system inhibitors potentiate the anticonvulsant activity of Valproate in the mouse pilocarpine-induced seizure model. Standard research Journal of pharmacy and pharmacology vol 1 (2): 025-033, August 2014.

68. Saager M, Hahn EW, Peschke P, Brons S, Huber PE, Debus J, Karger CP. Ramipril reduces incidence and prolongates latency time of radiation-induced rat myelopathy after photon and carbon ion irradiation. Journal of radiation research. 2020 Sep;61(5):791-8.

69. Das K, Banerjee M, Mondal GP, Devi LG, Singh OP, Mukherjee BB. Evaluation of socio-economic factors causing discontinuation of epilepsy treatment resulting in seizure recurrence: a study in an urban epilepsy clinic in India. Seizure 2007;16(7):601-7.

70. Münzel T, Keaney Jr JF. Are ACE inhibitors a "magic bullet" against oxidative stress? Circulation. 2001 Sep 25;104(13):1571-4.

71. Tastemur Y, Gumus E, Ergul M, Ulu M, Akkaya R, Ozturk A, Taskiran AS. Positive effects of angiotensin-converting enzyme (ACE) inhibitor, captopril, on Pentylenetetrazole-induced epileptic seizures in mice. Tropical Journal of Pharmaceutical Research. 2020 Apr 9;19(3):637-43.
72. Krasniqi S, Daci A. Role of the angiotensin pathway and its target therapy in epilepsy management. International journal of molecular sciences. 2019 Feb 8;20(3):726.
73. Kalra J, Prakash A, Kumar P, Majeed AB. Cerebroprotective effects of RAS inhibitors: Beyond their cardio-renal actions. Journal of the Renin-Angiotensin-Aldosterone System. 2015 Sep;16(3):459-68.

ANNEXURES

ANOVA for comparing mean study parameter among study groupsin MES method

Groups	**Mean study parameter**	*P-value*
Group I		
Group II		
Group III		
Group IV		
Group V		
Group VI		

Multiple comparison (ANOVA) followed by post hoc Tukey's test of mean study parameter among study groups

Multiple comparison		**Mean difference of study parameter**	**p value**
Group I	Group II		
	Group III		
	Group IV		
	Group V		
	Group VI		
Group II	Group III		
	Group IV		
	Group V		
	Group VI		
Group III	Group IV		
	Group V		
	Group VI		
Group IV	Group V		
	Group VI		
Group V	Group VI		

ANOVA for comparing mean study parameter among study groupsin PTZ method

Groups	**Mean study parameter**	*P-value*
Group I		
Group II		
Group III		
Group IV		
Group V		
Group VI		

Multiple comparison (ANOVA) followed by post hoc Tukey's test of mean study parameter among study groups

Multiple comparison		**Mean difference of study parameter**	**p value**
Group I	Group II		
	Group III		
	Group IV		
	Group V		
	Group VI		
Group II	Group III		
	Group IV		
	Group V		
	Group VI		
Group III	Group IV		
	Group V		
	Group VI		
Group IV	Group V		
	Group VI		
Group V	Group VI		

The "*p*" value of <0.05 was considered as statistically significant

EVALUATION OF ANTIEPILEPTIC ACTIVITIES OF RAMIPRIL AND TELMISARTAN AND POTENTIATION OF THE ANTIEPILEPTIC EFFECT OF PHENYTOIN SODIUM AND VALPROIC ACID IN RAT MODELS

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