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Recent Advances And Emerging Trends In The Diagnosis And Management Of Epilepsy

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Abstract: Epilepsy is a widespread neurological condition characterized by repeated, unprovoked seizures, affecting millions of people worldwide. Despite available treatments, a significant number of patients do not respond to conventional medications, highlighting the need for improved diagnostic and therapeutic approaches. This review summarizes recent progress in diagnostic strategies, including advanced neuroimaging, high-resolution EEG and MEG, biomarkers, and artificial intelligence-based seizure prediction. It also discusses therapeutic advances, covering new-generation antiepileptic drugs, innovative mechanisms of action, drug combinations, and precision medicine tailored to individual patients. Non-drug interventions, such as minimally invasive surgeries, neurostimulation devices, gene and stem cell therapies, dietary strategies, and nanotechnology -driven targeted drug delivery, are explored as complementary options. Emerging research on microRNAs, epigenetics, gut microbiota, 3D brains organoids, and CRISPR-based gene editing provides insights for future personalized treatments. Challenges such as drug resistance, treatment costs, accessibility, and ethical concerns are addressed, emphasizing the need for a multidisciplinary approach. Integration of omics technologies, digital health, and precision neurology offers hope for more effective therapies and improved quality of life for people living with epilepsy.

Index Terms **-** Epilepsy, Seizure disorders, Neuroimaging, EEG, Drug-resistant epilepsy, Nanotechnology, Epigenetics, Neurostimulation, Artificial Intelligence.

I. INTRODUCTION

Epilepsy is a long-term brain disorder that causes repeated seizures without any specific trigger. These seizures happen because of sudden and abnormal electrical activity in the brain. The condition can affect people of any age, gender, or background and i s considered one of the most common neurological disorders across the world. As reported by the World Health Organization (WHO), more than 50 million people suffer from epilepsy globally, and nearly 80% of them live in low- and middle-income countries. Although epilepsy can often be treated successfully, it still creates serious social, emotional, and financial problems for patients and their families. [1] [2]

Detecting epilepsy early and providing proper treatment are very important to prevent frequent seizures, avoid complications, and improve the patient's overall quality of life. Knowing the exact type of seizure and its cause helps doctors decide the most suitable treatment for each person. However, there are still some major challenges in current therapy. Traditional antiepileptic drugs (AEDs) are the main treatment option, but they fail to fully control seizures in almost one-third of patients, resulting in a condition known as drug-resistant epilepsy. In

addition, long-term use of these medicines can lead to side effects, drug interactions, and poor treatment adherence. [3] [4] [6]

Because of these limitations, researchers are continuously exploring new ways to diagnose and manage epilepsy more effectively. Recent studies are focused on advanced diagnostic tools, improved medications, and modern treatment technologies. This review aims to discuss the recent progress made in diagnostic methods and new therapeutic strategies that are improving the overall management of epilepsy. [6]

II. PATHOPHYSIOLOGY OVERVIEW

Epilepsy develops due to abnormal, excessive, or synchronous electrical activity in the brain's neurons. Under normal conditions, brain cells (neurons) communicate through balanced electrical and chemical signals. When this balance is disturbed, it leads to sudden bursts of abnormal neuronal firing, resulting in a seizure.

The pathophysiology of epilepsy involves neurochemical, genetic, structural, and metabolic factors that affect how brain cells generate and transmit signals. [7]

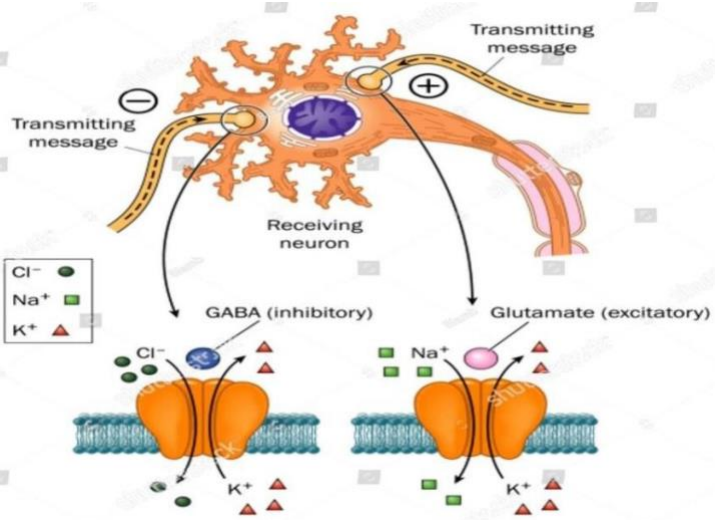

Fig. 1 Neurotransmitter Imbalance in Epilepsy

1. Abnormal Electrical Activity in Neurons

In a healthy brain, there is a balance between excitatory and inhibitory signals. This balance ensures controlled communication between neurons. [8]
In epilepsy, this balance is disrupted due to:

- Increased excitatory activity (overactivation of glutamate receptors)
- Reduced inhibitory control (defective GABAergic inhibition)

When groups of neurons become hyperexcitable, they start firing excessively and synchronously. This uncontrolled electrical discharge spreads to nearby brain regions, leading to seizures. [9]

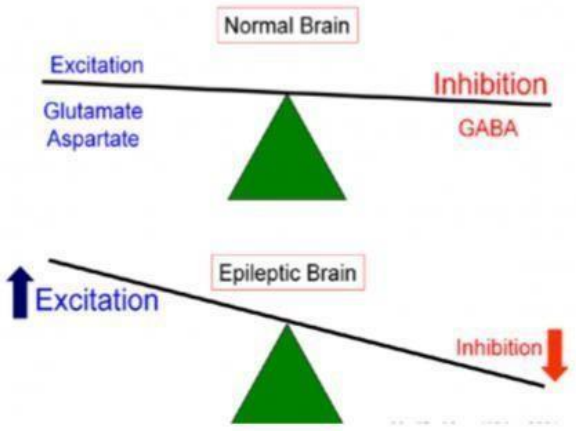

Fig. 2: Neuronal Excitation–Inhibition Imbalance

2. Role of Neurotransmitters (GABA and Glutamate)

Two major neurotransmitters regulate brain excitability:
Glutamate is the main excitatory neurotransmitter that promotes neuronal firing.
Gamma-Aminobutyric Acid (GABA)—the main inhibitory neurotransmitter that prevents overactivation. In epilepsy, glutamate activity increases, while GABAergic inhibition decreases.
This imbalance causes abnormal electrical discharges and recurrent seizures.
Some genetic mutations affect the function of GABA or glutamate receptors, further contributing to neuronal hyperexcitability.
[10] [11]

3. Genetic and Molecular Mechanisms

Genetic factors play a vital role in epilepsy. Several gene mutations alter ion channels, neurotransmitter receptors, and synaptic proteins responsible for neuronal signaling.
These mutations may:
Change the function of sodium, potassium, or calcium channels (ion channelopathies). Disrupt GABA or glutamate receptor function.
Affect synaptic vesicle proteins and neuronal connectivity
Some common genetic epilepsies include Dravet syndrome, Lennox–Gastaut syndrome, and juvenile myoclonic epilepsy. Epigenetic modifications such as DNA methylation and microRNA expression also influence neuronal excitability and drug response. [9]

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5. Structural and Metabolic Changes in the Brain

In many patients, epilepsy arises due to structural abnormalities in the brain, such as

- Cortical dysplasia
- Brain tumors
- Stroke or trauma
- Hippocampal sclerosis

These structural lesions can become the focus of abnormal neuronal firing, known as an epileptogenic focus.
Metabolic changes such as oxidative stress, mitochondrial dysfunction, and altered glucose metabolism can also make neurons more vulnerable to excitation. For example, energy deficiency in brain cells can impair ion channel activity, promoting spontaneous depolarization and seizure activity. [8] [9]

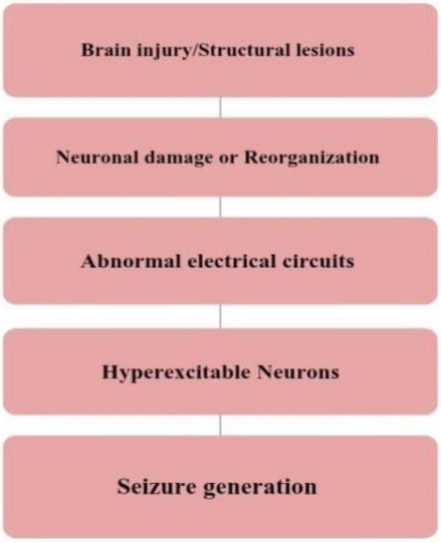

Fig. 3: Structural and Metabolic Contribution

6. Integrated Concept of Epileptogenesis

Epileptogenesis is the process through which a normal brain gradually becomes epileptic after an injury, infection, or genetic change. It mainly occurs in three stages:

1. Initiation Phase – The first trigger, such as trauma or mutation, increases neuronal excitability.
2. Latent Phase—Silent stage where brain networks reorganize, and inhibitory control weakens.
3. Chronic Phase – The brain develops recurrent spontaneous seizures due to permanent network changes. [8]

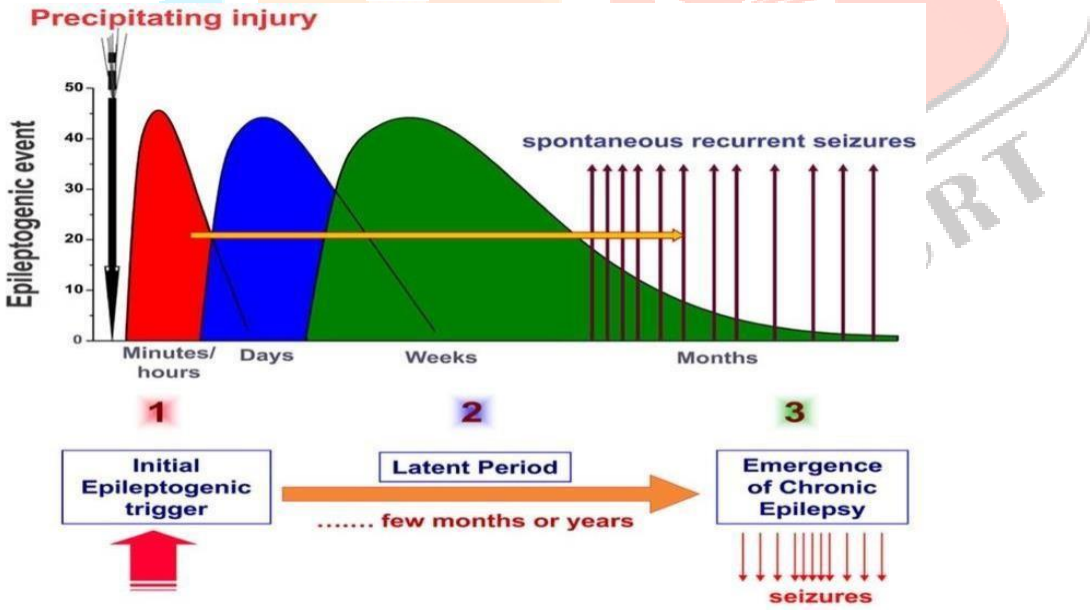

Fig. 4: Stages of Epileptogenesis

III. ADVANCES IN DIAGNOSIS OF EPILEPSY

In recent years, major technological progress has improved the accuracy and speed of epilepsy diagnosis. These innovations help clinicians identify the type, cause, and location of seizures more precisely, which is essential for selecting the right treatment. The major trends in diagnostic advances are described below:

1. Neuroimaging Techniques

Modern imaging technologies such as functional MRI (fMRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), and high-resolution MRI have revolutionized the understanding of brain function in epilepsy. fMRI detects brain activity by measuring changes in blood flow,

helping identify seizure foci and functional brain regions before surgery.
PET and SPECT are useful for detecting metabolic or blood flow abnormalities during or between seizures.
High-resolution MRI provides detailed brain images, allowing the detection of small structural lesions, cortical dysplasias, or hippocampal sclerosis that may not be visible on standard MRI. The diagnosis and treatment of epilepsies have greatly benefited from the development of contemporary structural and functional brain imaging techniques. More understanding of the pathophysiology behind symptomatic epilepsies has been made possible by the combination of suitable new imaging techniques. In order to provide patients and their families with an accurate prognosis, neuroimaging is used in clinical practice to detect pathologies like granulomas, malformations, vascular or traumatic lesions, tumors, etc., that call for particular treatments. It also aids in the development of syndromic and etiological diagnoses. [11]

2. Electrophysiological Techniques

The electroencephalogram (EEG) is still the most reliable method for detecting epilepsy, but new versions like high-density EEG, ambulatory EEG, and magnetoencephalography (MEG) have made diagnosis more accurate.
High-density EEG improves spatial detail, helping locate the exact brain area causing seizures. Ambulatory EEG allows continuous monitoring of brain activity in daily life settings.
MEG records magnetic signals from neurons and gives additional information to EEG, especially useful before epilepsy surgery. Epileptic seizures themselves serve as specific biomarkers of both epileptogenesis and epileptogenicity—that is, the development and severity of an epileptic condition. However, because seizures occur unpredictably and at irregular intervals, obtaining ictal EEG recordings is not ideal in terms of time, cost, or patient risk when assessing the effectiveness of current or new anti-seizure drugs, evaluating potential anti-epileptogenic therapies, or performing presurgical assessments.

In individuals with epilepsy, EEG recordings also show other transient electrical abnormalities that appear more frequently than seizures. These include interictal EEG spikes and sharp waves (IIS), pathological high-frequency oscillations (HFOs) ranging from 80 to 600 Hz, and more recently identified events such as electrographic seizure-like activities and focal periodic epileptiform discharges occurring at sub-millimeter spatial scales, known as “microseizures” and “micro-periodic epileptiform discharges,” respectively.

HFOs and microseizures were identified through wide-bandwidth recordings obtained using small-diameter electrodes or microelectrodes. Such intracerebral recording techniques have driven advancements in clinical technology—improved electrodes, amplifiers, and data digitization systems—which are now being used more commonly in diagnostic presurgical evaluations. These innovations have broadened the spatial and temporal resolution available for studying abnormal brain electrical activity.
[11] [14]

3. Biomarker Discovery

Epilepsy represents a long-lasting tendency to experience seizures. Its diagnosis is primarily clinical and usually relies on the patient’s own description of symptoms or accounts from witnesses. However, even when one or more seizures occur, it can still be challenging to distinguish whether they indicate a true persistent seizure tendency or are the result of temporary factors such as an acute brain condition or substance use. As a result, misdiagnosis is frequent. A false epilepsy diagnosis brings significant human and economic consequences, including stigma, lifestyle restrictions, adverse effects from antiseizure medications (ASMs), and the premature discontinuation of efforts to search for other possible causes of the symptoms.

The absence of dependable biomarkers also creates difficulties for patients who definitely have epilepsy. At present, the burden of the disease is assessed mainly through the patient’s or caregiver’s memory of seizure events, sometimes noted in seizure diaries— an approach that is highly unreliable. Despite its limitations, seizure recording through diaries is still used in clinical trials designed to evaluate new ASMs. Naturally, this method only accounts for seizures recognized by the patient and excludes many individuals with epilepsy who are unable to report their seizure activity.
Emerging research focuses on genetic, proteomic, and metabolic biomarkers to support early diagnosis and

personalized therapy. Genetic biomarkers help identify inherited epilepsy syndromes and predict drug response. Proteomic and metabolic markers can indicate neuronal injury or inflammation associated with epilepsy. These biomarkers may allow for faster diagnosis and help monitor treatment response in the future. [13] [12]

4. Artificial Intelligence (AI) and Machine Learning (ML)

AI and ML are transforming epilepsy diagnosis by analyzing complex EEG and imaging data. These systems can predict seizures, detect subtle abnormalities, and recognize patterns that may be missed by humans. AI-based models also assist in automated EEG interpretation, improving accuracy and saving time. Such tools hold promises for early intervention and better management of epilepsy. Artificial intelligence (AI) refers to the use of computer algorithms that mimic aspects of human intelligence, enabling machines to solve problems in a more natural and human-like manner. AI is often described as the fusion of scientific and engineering principles aimed at creating intelligent systems that benefit humanity. It can include functions such as learning, perception, problem-solving, language understanding, logic, and reasoning. Consequently, AI draws contributions from multiple disciplines, including philosophy, mathematics and logic, psychology, cognitive science, computer science, and neuroscience.

Machine learning (ML), a subfield of AI, focuses on developing computer systems that learn from experience without being explicitly programmed, using various programming languages to construct and guide algorithms.

Detecting epileptic abnormalities in an electroencephalogram (EEG) can be time-consuming and requires careful analysis by trained neurologists and epileptologists. Additionally, differences in experts' clinical experience may lead to variability in their diagnostic judgments. Hence, developing an automated, computer-based system for epilepsy diagnosis has become highly important. Using entropy-based features extracted from EEG signals, several ML methods have been designed for epilepsy detection, including the fuzzy Sugeno classifier, support vector machine (SVM), k-nearest neighbor classifier (KNN), probabilistic neural networks, decision trees (DT), Gaussian mixture models, naïve Bayes classifiers, and pre-trained deep two-dimensional convolutional neural networks (CNNs).[15]

5. Wearable Devices

The development of wearable technologies has made continuous seizure monitoring possible. Devices like smartwatches, headbands, and biosensors can track physiological changes such as heart rate, body movement, and electrical signals.

They provide real-time alerts during seizures and allow remote monitoring.

This helps improve patient safety, especially for those with frequent or nocturnal seizures. [16]

Wearable digital health technologies have become valuable tools in the management of epilepsy. These devices—worn directly on the body or embedded in clothing and accessories—enable continuous monitoring and real-time data collection, giving both patients and healthcare professionals deeper insight into seizure trends and patterns. By supporting early detection, prediction, and ongoing tracking of seizures, wearable devices allow individuals with epilepsy to take more proactive steps in managing their condition. Additionally, these technologies help strengthen communication between patients and clinicians, ultimately contributing to more personalized and effective treatment plans.

Wearable sensing technologies are becoming increasingly popular, both among the general public and within clinical settings such as seizure detection. Despite this rise in use, there is still limited evidence about their clinical reliability and overall usefulness. Concerns also remain regarding data privacy, security, and ownership, as well as determining the most suitable software, hardware, and data-transfer methods. Several factors must be considered when using wearables: how the data is collected, which systems are best for this purpose, and how the recorded information can be used to offer more advanced feedback to patients and caregivers. These devices could also support accurate seizure-likelihood forecasting, enabling individuals with epilepsy to adjust activities or take fast-acting medication in anticipation of a seizure.

While chronically implanted intracranial EEG systems have provided significant insight into the rhythms and mechanisms of epileptic activity, their high cost, procedural risks, and limited spatial coverage make them unsuitable for widespread use. Although these devices capture many electrographic seizure events that show no obvious behavioral signs, this information is important for both epilepsy management and seizure prediction. Chronic EEG data remain essential for developing and validating independent wearable systems. Recent research indicates that seizure forecasting could be achieved by analyzing patterns and trends in multimodal data from individuals and larger populations, then applying advanced machine-learning techniques to integrate these signals and estimate seizure risk. Ultimately, such forecasting tools may help patients better manage daily life and assist clinicians in evaluating treatment effectiveness. [45]

IV. PHARMACOLOGICAL ADVANCES IN EPILEPSY

In recent years, treatment options for epilepsy have improved significantly with the development of new antiepileptic drugs (AEDs). These advances provide better seizure control, especially for patients who do not respond to older medications.

1. New-generation AEDs:

New drugs such as Brivaracetam, Cenobamate, Perampanel, and Lacosamide have been introduced. They are more effective, better tolerated, and generally cause fewer side effects than traditional AEDs. Epilepsy is one of the most prevalent neurological disorders, and antiepileptic drugs (AEDs) remain the primary treatment option. AEDs are generally categorized into first-, second-, and third- generation agents. Commonly used first-generation drugs include phenytoin (PHT), phenobarbital (PB), carbamazepine (CBZ), valproic acid (VPA), zonisamide (ZNS), and clobazam (CLB). In North America and Europe, ZNS is classified as a second-generation drug. Third-generation AEDs consist of lacosamide (LCM) and eslicarbazepine acetate, while other recently introduced agents are grouped as second-generation or "new AEDs."

In Japan, newer AEDs were approved as add-on therapies starting in 2006. Drugs such as gabapentin (GBP), topiramate (TPM), lamotrigine (LTG), levetiracetam (LEV), and rufinamide (RFN) are available as oral formulations. Vigabatrin (VGB), oxcarbazepine (OXC), perampanel (PER), and lacosamide (LCM) are currently under review by the Ministry of Health, Labour and Welfare. Traditionally, guidelines recommended carbamazepine (CBZ) and valproic acid (VPA) as first-line choices for focal and generalized seizures; however, recent expert opinions and updated guidelines now support several newer AEDs as first - or second-line options. In Japan, LTG and LEV are also approved for monotherapy use. [17] [18] [19]

2. Novel Mechanisms of Action:

Many of these newer drugs work in unique ways, like modifying sodium channels or blocking AMPA receptors, which helps manage seizures in patients who do not respond to conventional therapies.

Perampanel (PER, Fycompa®) is the first epilepsy medicine approved from the group of selective, non-competitive AMPA receptor blockers. AMPA receptors are the main type of ionotropic glutamate receptors in the brain. PER mainly reduces brain cell overactivity by blocking these AMPA receptors. It is taken once a day and is used worldwide as an add-on treatment for partial seizures and primary generalized tonic-clonic seizures. Still, the complete way in which PER works to control different types of seizures is not fully understood.

Studies also show that PER can reduce different kinds of pain, including spontaneous pain. It may also help improve recovery and memory problems after a stroke by acting through various pathways. Research further suggests that PER can be useful in conditions like Parkinson's disease, motor neuron diseases, and epilepsy caused by glioma tumors. However, some reports say that not all of PER's effects are linked only to its action on AMPA receptors.

3. Drug Repositioning and Combination Therapies:

Scientists are also exploring the use of existing medications for new purposes (drug repositioning) and combining drugs with different mechanisms. This can improve seizure control while reducing side effects.

A growing strategy in modern drug development is drug repositioning. Drug repositioning—also called repurposing, recycling, redirecting, re-tasking, or reprofiling—refers to finding new therapeutic uses for existing drugs beyond their original purpose. This method is becoming popular, especially for older, well-known drugs,

as researchers look for new diseases these medicines can treat. Its appeal lies in the ability to meet medical needs, especially for conditions with limited or costly treatment options, while also offering financial benefits. As Nobel Prize–winning pharmacologist James Black famously said, "The most fruitful basis for the discovery of a new drug is to start with an old drug". The rising interest in this field is evident from the more than 1,000 PubMed articles on "drug repositioning" published by 2020. A classic example is Sildenafil (Viagra), originally developed for heart disease but later repurposed to treat erectile dysfunction. Another example is Duloxetine, initially created as an antidepressant and now widely used for stress urinary incontinence (SUI).

Drug repositioning has become extremely important in pharmaceutical research because it significantly reduces development costs—by roughly $300 million—and lowers the risks associated with new drug discovery. This is because the safety profile of these drugs has already been established in humans and preclinical studies. It also shortens the development timeline since many safety and formulation studies do not need to be repeated. Moreover, repositioning gives a second chance to older drugs that were previously abandoned, often due to long-term safety concerns. A notable case is Thalidomide, a drug banned in 1962 after causing severe birth defects (phocomelia) in over 10,000 infants across Europe, Australia, and Japan. With improved safety measures, Celgene later repurposed Thalidomide into a successful treatment for multiple myeloma, earning $271 million in revenue in 2003 alone. [20]

4. Personalized Medicine:

There is increasing emphasis on precision medicine, where treatment is tailored to each patient's genetic makeup, metabolism, and clinical profile. This helps doctors choose the right drug, adjust the dose, and improve outcomes while minimizing adverse effects. Patients with epilepsy who do not respond to medications may choose surgical removal of the seizure-producing area or neuromodulation, which targets key brain regions involved in seizure spread. Compared to traditional surgery, neuromodulation is a non-destructive and effective alternative. Because individuals with epilepsy often show distinct but consistent brain activity patterns at the start of a seizure, neuromodulation allows doctors to provide personalized treatment by using these specific neurophysiological signals. [21] [22]

V. RECENT RESEARCH TRENDS

In the evolving field of epilepsy research, several exciting trends are emerging that promise to transform diagnosis and treatment.

1. AI-Based Seizure Prediction Models

Researchers are now using artificial intelligence and machine learning to anticipate seizures before they occur. By studying large sets of EEG and imaging data, these systems can spot subtle changes in brain activity that are often too complex for humans to detect. This technology has the potential to provide early alerts, helping patients and doctors manage seizures more effectively and improve overall safety. Recent progress in epileptic seizure detection has incorporated advanced Machine Learning (ML) and Deep Learning (DL) methods, greatly improving the precision and speed of seizure identification and prediction. For early detection, various feature-extraction and classification approaches have been introduced, including discrete wavelet transform (DWT), t-distributed stochastic neighbor embedding (t-SNE), K-means clustering, and K-Nearest Neighbors (K-NN). These tools help achieve more reliable and timely seizure recognition.

Furthermore, several practical ML algorithms have been applied to classify EEG signals in different healthcare contexts—such as analyzing electrical brain activity, detecting emotional responses to music, cardio-oncology applications, tracking eye movements, speech interpretation, diagnosing mental disorders, and wearable biofeedback systems. Numerous studies have also proposed diverse feature-based and classifier-based approaches, offering detailed explanations of seizure prediction techniques and highlighting potential directions for future research. [30]

2. MicroRNA and Epigenetic Studies

Scientists are investigating the roles of microRNAs (miRNAs) and epigenetic mechanisms (changes in gene expression without altering the DNA sequence) in epilepsy. These small molecules and regulatory systems influence neuronal development, inflammation, and excitability. Findings suggest they could serve as biomarkers for epilepsy risk, progression, or response t o treatment, and might become therapeutic targets in the future. [32]

3. Role of Gut Microbiota in Epilepsy

Research into the gut-brain axis has revealed links between changes in the gut microbiome (the community of microorganisms in the intestine) and epilepsy. Altered bacterial populations may influence neural excitability, inflammation, and overall brain health. Modulating the gut microbiota—for example, via diet, probiotics, or other interventions—may offer new adjunctive strategies for managing epilepsy. [34] [35]

4. 3D Brain Organoid Models for Drug Testing

Lab-grown 3D human brain organoids (mini-brain models derived from stem cells) are being used to simulate human brain structure and function in the lab. These models allow researchers to study epileptic mechanisms, test new drugs, and observe how neurons respond in a human-like environment. They bridge the gap between animal studies and clinical trials. [35] [36] [37]

5. CRISPR-based Gene Editing

Gene editing toolkits such as CRISPR/Cas systems are being explored for their potential in epilepsy. By precisely modifying genes that are known to contribute to seizure disorders, researchers aim to correct underlying defects, reduce neuronal hyperexcitability, and bring about lasting benefits. While still largely experimental, this approach could redefine how we treat genetically-driven epilepsies. [39]

VI. CHALLENGES AND FUTURE DIRECTIONS

Despite many advances in epilepsy care, several important challenges remain—and the future path offers exciting possibilities.

A major hurdle is drug resistance, with about one-third of patients not achieving seizure control despite appropriate treatment. The cost and availability of advanced diagnostics and therapies (such as genetic tests, neurostimulation devices, and personalized treatments) limit access, especially in resource-poor regions. [40]

The use of gene therapies, AI-driven tools, and other new approaches brings up ethical concerns, including data privacy, long-term
safety, equity of access, and informed consent. [41]

Looking ahead, the integration of omics technologies (genomics, proteomics), digital health tools (wearables, remote monitoring), and precision neurology (tailored treatments based on individual patient profiles) promises to reshape epilepsy care. [43] [44]

VII. CONCLUSION

In conclusion, epilepsy remains a complex neurological disorder, but recent advances in diagnosis, pharmacological treatments, non-drug therapies, and cutting-edge research are improving outcomes. Innovations such as AI-based seizure prediction, novel antiepileptic drugs, gene and stem cell therapies, dietary interventions, and precision medicine offer new hope, especially f or patients with drug-resistant epilepsy. Effective epilepsy care requires a multidisciplinary approach, combining clinical expertise, technology, and personalized strategies tailored to each patient. With ongoing research and integration of digital health, omics, and targeted therapies, the future promises more accurate diagnosis, safer treatments, and improved quality of life for individuals living with epilepsy.

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