RESEARCH PAPER

"Epilepsy: Current Insights into Etiology, Pathophysiology, Classification, Diagnosis, and Therapeutic Advances."

Amim Aktar[1], Dr. Arijit Chaudhuri[2*]

[1]M Pharm Research scholar, Department of Pharmacology, School of Pharmaceutical Sciences, Bahra University, Solan
Email id : samimaktar0204@gmail.com

[2*]Associate professor, Department of Pharmacology, School of Pharmaceutical Sciences, Bahra University, Solan
Author for correspondence: Email id : armanchaudhuri92@gmall.com

ABSTRACT

Epilepsy is the commonest neurological disorder where the normal excitability of the neurons is altered, resulting in unpredictable and recurrent seizures. It occurs in all continents and is a medical and social issue, as about 50 million people have it. Stigma, misinformation, and access to care continue to be barriers to patients' health. Despite over 20 antiepileptic drugs, 30-40% of patients are drug-resistant, and many patients who are taking antiepileptic drugs have side effects that affect their mood, quality of life, and cognitive functioning. In this paper, we briefly summarize the current understanding of the biology, diagnosis, and therapeutic advances in epilepsy. It includes the history of the disease, how we have come to understand the properties of neuronal excitability and network synchronization, and how changes to genetic, structural, viral, and neurodegenerative processes contribute to the pathogenesis of the disease. The epidemiological information highlights inequalities between high-income and low-income countries and suggests there are inequalities in treatment. New research in pharmacology, neuroimaging, and surgical techniques has failed to provide a solution to the issue of medication resistance, and innovation is needed. Future directions include identifying predictors of seizure control that affect quality of life; establishing a new strategy based on artificial intelligence and network pharmacology for individualized seizure prediction and optimizing therapeutic interventions; and investigating the potential for neuroprotective and disease-modifying therapy based on epileptogenesis itself as the therapeutic target. The overall results underscore the need for early diagnosis and tailored therapeutic approaches to provide effective and compassionate treatments. Treatment of epilepsy is more than managing symptoms; using patient-centered care and the progress of science, it can be more than managing symptoms and towards claiming autonomy, dignity, and hope.

KEY WORDS

Epilepsy, seizure classification, drug-resistant epilepsy, antiepileptic drugs, genetic etiology, structural brain lesions, neurodegeneration, epilepsy surgery, artificial intelligence, network pharmacology, quality of life, epidemiology.

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1. INTRODUCTION

1.1. Definition and Global health impact of epilepsy

Epilepsy is the disorder of neuronal excitability, whereas a seizure, a transient change of behavioral pattern, results from synchronous firing of neuronal populations of the central nervous system. In simple terms, epilepsy can be denoted as a neurological disorder marked by unpredictable, intermittent seizures. The term "epileptic seizure" draws a distinction between seizures brought on by aberrant neuronal firing and non-epileptic events, like psychogenic seizures. Recurrent, spontaneous seizures are the hallmark of the condition known as "epilepsy." Many of the causes of epilepsy correspond to underlying brain dysfunction. Seizures caused by reversible insults, such as fever or hypoglycemia, do not meet the criteria for epilepsy, as they are temporary secondary syndromes rather than chronic conditions.[1] According to the **International League Against Epilepsy (ILAE)**, epilepsy can be confirmed by any of the following circumstances: "(i) at least two unprovoked (or reflex) seizures occurring more than 24 hours apart; (ii) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; or (iii) a diagnosis of an epilepsy syndrome. Additionally, epilepsy is considered to be resolved for individuals who either had an age-dependent epilepsy syndrome but are now past the applicable age or have remained seizure-free for the last 10 years, with no anti-seizure medication for the last 5 years." This approach preserves the distinction between unprovoked and provoked non-reflex (or acute symptomatic) seizures. Provoked seizures are not diagnosed as epilepsy since they are produced by conditions that temporarily decrease the seizure threshold and are not associated with a long-term propensity. This category includes seizures that occur within seven days after a stroke or brain injury, as well as those that coexist with a metabolic disorder.[2] Epilepsy is one of the most frequent neurologic conditions, with an incidence of about 50 new cases per year per 100,000 population, and the world's third most common neurological cause of years lived with disability. About 75% of epilepsy cases begin in childhood, indicating the vulnerability the developing brain is to seizures. The **World Health Organizatio**n estimates that approximately 50 million individuals worldwide suffer from epilepsy, despite it being one of the most challenging neurological conditions to treat (WHO, 2024). Prejudice, misinformation, social stigma, and the stress of having a chronic, unpredictable illness can cause people with epilepsy to lose their independence in daily tasks. Although most cases of epilepsy may be successfully treated, there is a significant treatment gap, particularly in low- and middle-income countries where antiepileptic drugs are either unavailable or too expensive. However, there is mounting evidence that surgery and other therapies (such as diet and neurostimulation) can be beneficial, even if not all patients respond to existing medical treatments. Even after the significant advancements in standard anti-epileptic medications, between 30 and 40 percent of people still have resistance to these drugs, and many more experience debilitating adverse drug reactions, such as cognitive impairment or

metabolic abnormalities.[3] In addition to affecting people of all ages worldwide, epilepsy is one of the most prevalent serious brain diseases with a growing burden. It can increase a person's risk of dying young by up to three times compared to the general population and places a significant financial, psychological, physical, and mental burden on societies, health systems, affected individuals, and their families. In 2022, the World Health Organization designated epilepsy as one of the top priorities in the management and prevention of non-communicable diseases, and a specific intersectoral global action plan on epilepsy and other neurological disorders for 2022–31 was developed during the 75th World Health Assembly. Accurate and frequently updated data on epilepsy incidence, prevalence, death, and disability by age, sex, and location are also necessary to support evidence-based actions and
awareness campaigns, as well as public and private efforts to enhance quality and access to care and reduce the impact of the disease.[4]

1.2. Historical perspective

Epilepsy has been recognized from early medical publications. Since antiquity, the disease has been associated with both genuine and imagined behavioral abnormalities. The first medical texts on epilepsy were written on Egyptian papyri and Babylonian cuneiform tablets. The Babylonians (about 1050 bc) thought epilepsy was caused by demons and ghosts who controlled some individuals. The frightening aspect of tonic-clonic seizures, as well as the behavioral abnormalities associated with epilepsy and other neurologic illnesses, undoubtedly led to early beliefs in supernatural causation. Although the myth that epilepsy is divine retribution has been largely disproven in Western countries, many sufferers continue to feel stigmatized by the disease. Furthermore, throughout documented history and medicine, seizures were mostly tonic-clonic and conversion events, with complex partial and other "minor" seizures being infrequently identified or clearly categorized. This complicates the history of epilepsy and the behavioral changes that go with it. Around 400 BC, the Greek physician Hippocrates wrote On the Sacred Disease, the first book on epilepsy. He rejected the notions that people with epilepsy could predict the future and that seizures were a curse from the gods, recognizing that epilepsy was a brain disorder. Early in the 19th century, the first asylums were established to shelter people with mental illnesses and epilepsy. The generation of non-epileptic psychogenic seizures in the psychiatric population likely "confirmed" the idea that epilepsy was communicable. These two groups were divided as a result of the clever observation but false theory. For instance, Etienne Esquirol, one of the pioneers of psychiatry, was concerned about epilepsy spreading to those with just mental illnesses. However, the first chance to thoroughly examine and methodically observe epilepsy in a community came from asylums. In the late 1800s, institutions for the crippled and epileptic were established as a result of the two groups' segregation; they included Blackwell's Island in New York (1867) and Queen Square in London (1860). Historically, there has been a vast range of epilepsy therapies limited only by the capacity of the human mouth and imagination, rather than pain tolerance or effectiveness. "There is hardly a substance in the world capable of passing through the gullet of man that has not at one time or another enjoyed the reputation of being an anti-epileptic," Edward Sieveking, the famous English neurologist, observed. Cups of recently deceased people's blood, powdered human skull, mistletoe, digitalis, silver nitrate, zinc oxide, and vulture liver were among the medications consumed. Trephining (opening) the skull to release malevolent spirits, pressing a hot metal button or iron on the head to drain a poisonous humor, bloodletting, vomiting, diuresis, sweating, and advice on greater coital activity or abstinence. Onanism was long regarded to be a cause of epilepsy and insanity.[5]
Interictal personality changes have been recognized in patients with persistent epilepsy since
antiquity. The abnormalities were considered to be produced by wounds acquired during paroxysms or by the sickness itself. A behavioral change associated with a localization-related epilepsy suggests that certain structures play a role in the pathogenesis, but how? Although they may not be related to the frequency or severity of behavioral disorders, anatomical lesions such as mesial temporal sclerosis or dysplasia may play a role. Sir Charles Symonds introduced the groundbreaking hypothesis of "the epileptogenic disorder of function" about sixty-five years ago. When discussing the pathophysiology of TLE patients' interictal psychosis. Gastaut was the first to identify that certain personality features in individuals with temporal lobe epilepsy are the opposite of KBS symptoms. According to Geschwind, KBS is a reflection of sensory-limbic disconnection. In contrast to KBS, Bear proposed that a sensory-limbic hyperconnection is the cause of behavioral abnormalities in temporolimbic epilepsy. The mechanisms causing behavioral change in epilepsy
remain unclear due to the ongoing challenges in characterizing the characteristics, frequency, and specificity of behavioral alterations in various epileptic syndromes.[5]

1.3. Importance of understanding neurobiological mechanisms and modern treatment approaches

Current hypotheses try to explain the process or mechanisms that cause the brain's unusually high tendency to generate excessive cerebral neuron discharges. It's probable that the initial theory, which held that seizures are triggered by an imbalance between excitement and inhibition in the brain, was oversimplified. Cortical networks that create oscillations are thought to be key components in seizure generation, relying on inhibitory neurons, neuronal communication (such as synaptic transmission), and intrinsic neuronal properties (such as a neuron's ability to sustain burst firing). Epileptic activity could be an emergent property of such oscillatory networks. A range of causes, including increased spread and neuronal recruitment as a result of expanded connection, increased excitatory transmission, failure of inhibitory mechanisms, and changes in intrinsic neuronal properties, can cause a behavior to shift from normal to seizure-like.[6] In recent years, there has been a significant surge in new

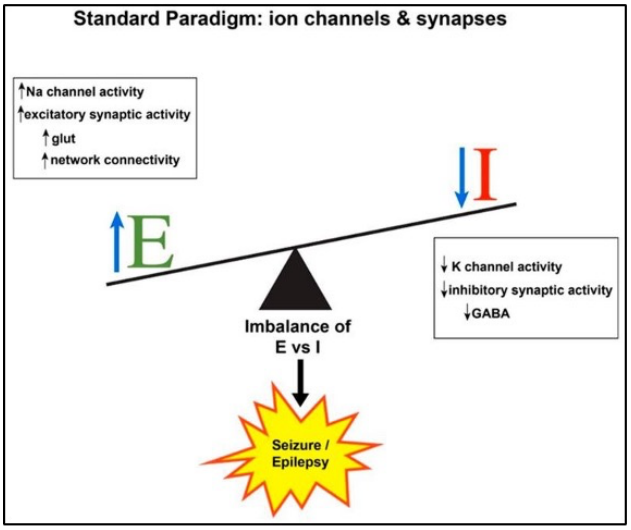


Figure 1.
Imbalance between the inhibitory and excitatory neurotransmitters, paradigm shift of ion channels and synapses in epilepsy. E, Excitatory neurotransmitter (Glutamate); I, Inhibitory neurotransmitter (GABA).

information about the genetic etiology of epileptic disorders. Both monogenic and polygenic mutations can cause epilepsy. The fundamental cause of many epilepsies, which have a complex genetic history with numerous gene abnormalities, is a state of enhanced cellular excitability. Copy number variants, for example, are deletions or duplications that are inherited or created >1 kb, are increasingly recognized as a cause of genetic disorders in people with epilepsy.[1]

The distinction between seizure and epilepsy is often misunderstood, but clearly there is a difference between them. If an individual experiences a seizure for once, that doesn't mean that they have epilepsy, as the seizure might have been provoked, and they might never have a seizure again. We can comprehend the mechanisms underlying seizures, epileptogenesis, and epilepsy by using basic concepts from neurobiology. Some of the most basic features of nerve cell activity, such as the electrical basis of the transmembrane potential and action potential, are helpful to review in order to comprehend how seizures might be triggered. Understanding can also be gained from mechanisms controlling synaptic transmission. Lastly, the mechanisms underpinning epileptogenesis represent one of the most amazing features of the nervous system: its adaptability.

Glutamatergic and γ-aminobutyric acid (GABA)-ergic transmission have been extensively researched as the main excitatory and inhibitory transmitters in the nervous system. It is crucial to keep in mind that there might not be a clear connection between glutamate and GABA and seizures. Depending on the duration of exposure, desensitization of glutamate and GABA receptors may

lessen effects. In addition, instead of producing hyperpolarization, GABA-ergic transmission may cause depolarization if the gradients that regulate ion flow across GABA receptors are modified.

Chloride, for example, is the main ion that conducts current through GABAA receptors and frequently causes neurons to become hyperpolarized as it enters the cell from the external environment. However, the essential K^+Cl^- co-transporters (KCCs) for the gradient of chloride are not always present. Seizures are not always brought on by excessive discharge alone. It involves the synchronization of a network of neurons. As a result, it becomes crucial to take synchronization into account. Neurons can synchronize in a variety of ways. Matsumoto and Ajmone-Marsan discovered in 1964 that synchronous paroxysmal depolarization shifts (PDS) of cortical pyramidal cells correlated with electrographic events recorded at the cortical surface during seizures.[7]

Almost 70% of epileptic patients can be successfully treated with an armamentarium of >20 drugs. Epilepsy medications reduce brain electrical activity by either blocking sodium or calcium channels to prevent neural depolarization, improving potassium channel function, preventing excitation mediated by the neurotransmitter glutamate, or promoting inhibition mediated by GABA. The effectiveness of these drugs varies depending on the cause. Patients who have no known etiology are most likely under control, especially if their developmental history and neurological examination are normal. A neurologist's choice about which seizure medication to begin depends on the type of seizure, age, other medical conditions, and possible side-effect profile. Because witness accounts of seizures may be insufficient, wide-spectrum drugs are often used. In recent years, levetiracetam has gained popularity as a first-line treatment due to its efficacy, ease of titration, and well-known side-effect profile. In the past, carbamazepine was the preferred choice for focal seizures, whereas valproic acid was the primary treatment for generalized seizures.[1]

Removing the brain region responsible for epilepsy has been the most successful method of preventing seizures in DRE patients for more than a century. Its safety and effectiveness have been enhanced by major developments in neurosurgery techniques and epilepsy localization technologies, and it remains the most successful treatment option.[8]

2. EPIDEMIOLOGY And RISK FACTORS

2.1. Global and regional prevalence

Epilepsy affects people of all ages, races, social classes, and geographical locations. Every year, there are 29–39 acute symptomatic seizures for every 100,000 people. The youngest age group (less than one year old) and the elderly are most likely to experience acute symptomatic seizures. The most frequent causes include fever, traumatic brain injury (TBI), cerebrovascular disease, drug withdrawal, infection, and metabolic insults. The pooled incidence rate of epilepsy in a systematic review and meta-analysis of incidence studies was 61.4 per 100,000 person-years (95% CI 50.7–74.4).[9] The incidence was 139.0 (95% CI 69.4–278.2) in low/middle-income countries (LMIC) compared to 48.9 (95% CI 39.0–61.1) in high-income countries (HIC). The unique makeup of at-risk groups, greater exposure to perinatal risk factors, and higher rates of TBI and CNS infections in LMICs may all contribute to this. Additionally, individuals from the lowest socioeconomic strata in HIC and those from different ethnic backgrounds residing in the same neighborhood had higher rates of epilepsy.

Depending on the number of seizures at diagnosis, the geographic distribution of risk and etiologic factors, and whether to include cases in remission (lifetime prevalence) or only active epilepsy (active prevalence), the prevalence of epilepsy varies greatly between nations. With a lifetime prevalence of 7.60 per 1,000 individuals (95% CI 6.17-9.38), epilepsy was more common in LMIC (8.75 per 1,000; 95% CI 7.23-10.59) than in HIC (5.18 per 1,000; 95% CI 3.75-7.15). The point prevalence of active epilepsy was 6.38 per 1,000 (95% CI 5.57–7.30). The median point prevalence of active epilepsy was 5.49 (4.16–7.26) in HIC and 6.68 (95% CI 5.45–8.10) in LMIC.

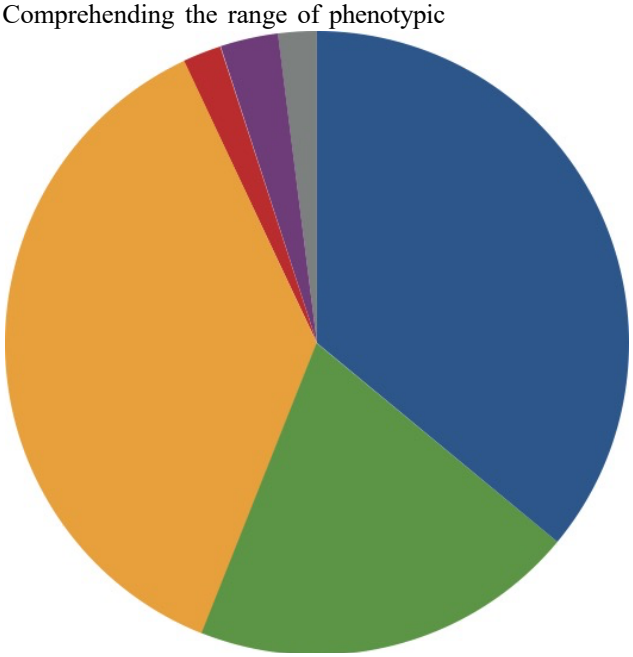
Furthermore, prevalence estimates differ by population and are typically higher for people with poor health, members of particular ethnic groups, and those from socially disadvantaged backgrounds. The study population's demographics, the frequency of environmental risk factors, and the standard of medical care could all be contributing factors to problems with the study design. Men are slightly more prone to have epilepsy than women, that might be because of the most prevalent risk factors and how sociocultural factors can sometimes mask the condition in women. The incidence of epilepsy in younger age groups has decreased over the last few decades, likely due to improved prenatal care, enhanced sanitation, and greater management of infectious diseases. But the number of cases has gone up in older people, probably because doctors are better at finding diseases in this age group and people are living longer (along with a rise in diseases that cause epilepsy, like stroke, cancer, and neurodegenerative disorders).[10]

2.2. Etiological classification

When one or more brain regions are more excitable than a particular threshold, seizures can occur in any part of the brain. The group of neurological conditions known as epilepsies lowers the intrinsic seizure threshold because of underlying brain dysfunction, increasing the risk of spontaneous recurrent seizures. One of the most important parts of diagnosing and treating epilepsies is figuring out the underlying aetiology. The diagnosis of epilepsy, for which a seizure recurrence risk of 60% is a recognized requirement, may be affected by aetiology since it affects the chance of recurrence after a single seizure. Seizure type, epilepsy type, and epilepsy syndrome are the three categories of the most recent classification of epilepsies, which offers a new framework and emphasizes the significance of taking aetiology into account at every level. The International League Against Epilepsy (ILAE) classifies epilepsy into structural, genetic, infectious, metabolic, immunological, and unknown etiological groups. The ILAE program also includes

a category for neurodegeneration. The unknown group, which is still among the largest, reflects our ignorance or even a lack of appropriate diagnostic tools. Low-resource nations are more likely to have infectious causes, especially parasite diseases. In some endemic areas, neurocysticercosis accounts for about one-third of all cases of active epilepsy.[11] Despite the fact that numerous epidemiological studies look at the incidence of each of the etiological categories (Figure 2), they are frequently carried out in nations with abundant resources and do not accurately reflect the range and prevalence of epileptic aetiologies worldwide. Notably, some etiologies can increase the risk of dying young and cause a variety of other neurological and systemic diseases.

Comprehending the range of phenotypic



manifestations highlights the necessity of all-encompassing treatment approaches.[12] Figure 2. Etiologies of epilepsy in a resource-rich European region (after Syvertsen et al. 2015).

- **Common structural etiologies**

Seizures and epilepsy can be caused by any anatomical abnormality affecting the brain. However, the location of the lesion—rather than its type—will determine the seizure semiology. A definitive diagnosis necessitates histological analysis, either from excised brain tissue (as part of epilepsy surgery for drug-resistant focal epilepsy) or post-mortem, even though neuroimaging can help us understand the type of structural lesion. The ILAE Commission on Diagnostic Methods has established protocols for the neuropathological workup of brain tissue from epilepsy surgery, and each resected six main disease categories that comprise the structural lesions that are frequently resected for the treatment of focal epilepsy (Table 1).[14] The loss of neurons in anatomically defined hippocampal formation sectors is a hallmark of hippocampal sclerosis.[15] On MRI T1-weighted sequences, the atrophic hippocampus appears as volume loss; on T2/fluid-attenuated inversion recovery (FLAIR)-weighted sequences, it appears as a hyper-intense signal.[16]

Table 1. Major categories of structural brain lesions associated with human focal epilepsies

Category	Number (%)	Age at onset	**Disease duration**	Age at surgery
HS	2,144 (36.3)	11.4	22.7	34.1
Tumour	1,680 (28.4)	15.4	11.5	26.8
Malformation	1,238 (20.9)	6.0	12.1	18.3
Vascular	369 (6.2)	23.1	12.7	35.9
Scar	344 (5.8)	9.7	14.9	25.3
Encephalitis	138 (2.3)	13.2	7.7	20.7
Total	**5,913**	**11.7**	**15.9**	**27.8**

HS: hippocampal sclerosis; abnormalities in cortical development; vascular abnormalities, such as cavernoma and meningoangiomatosis in Sturge-Weber syndrome, but not ischemic strokes or hypertensive hemorrhages; glial or glio-mesodermal scars, such as traumatic brain injury and pre-, peri-, or postnatal stroke, excluding postsurgical scarring; encephalitis, including limbic, Rasmussen's, or other focal infection; age at onset, duration, and age at surgery in years. Information from University Hospital Erlangen, Germany's German Neuropathology Reference Center for Epilepsy Surgery.

Brain tumors, which account for 10% to 15% of all epilepsies in adults and 0.2% to 6% of all epilepsies in children, are often the cause of focal-onset seizures. Glioneuronal brain tumors are particularly interesting in relation to epilepsy because they are typically located in the temporal lobe, have a low malignancy rate, and frequently cause seizures in children. Drug-resistant seizures are the most common symptom of abnormalities in early childhood cortical development. Focal cortical dysplasia (FCD), which mainly affects the frontal lobe, is the most common brain abnormality associated with epilepsy. Arteriovenous malformations and cortically located cavernous hemangiomas (cavernomas) are vascular anomalies linked to seizures. Seizures are also linked to Sturge-Weber illness; meningeal angiomatosis can cause both short-term and long-term hypoxic shocks to the underlying neocortex.[11]

- **Genetic causes of epilepsy**

The development of next-generation sequencing (NGS) has led to the identification of numerous genes linked to the genesis of epilepsy. Genetic variants that contribute to the etiology of epilepsy can be classified as common or rare depending on whether they affect ≥1% or <1% of the population. The impact of a genetic risk factor on the development of disease is inversely correlated with its prevalence in the population.[17] When pathogenic mutations in the protein-coding sequence caused amino acid changes (such as a missense variant) or protein truncation (such as nonsense, frameshift, deletion, or splicing variants), the earliest genetic etiologies were discovered in family monogenic diseases. The pathogenic variant's effect on the function of the encoded protein, which may directly affect brain activity or development,

brain tissue should undergo comprehens

supports its causal role. While autosomal recessive or X-linked inheritance is less common, many genes associated with monogenic epilepsies follow autosomal dominant inheritance. Monogenic causative pathogenic alterations have been found in many epileptic genes; these are typically rare or unique variants (i.e., rare or nonexistent in healthy populations). The relationship between phenotype and genotype may be difficult in monogenic epilepsies. Understanding the interrelationship is still difficult, even in situations where there is a well-established genotype-phenotype correlation, such as the connection between SCN1A mutations and Dravet syndrome.[18] However, a variety of epilepsies, including benign conditions like hereditary epilepsy with febrile seizures additionally and developmental and epileptic encephalopathies (DEEs), which are more severe than Dravet syndrome, are linked to SCN1A mutations. Epilepsies with a monogenic etiology are frequently extremely uncommon. Common epilepsies with complicated inheritance include genetic generalized epilepsies and localized epilepsies. This implies that they have a polygenic foundation, meaning that the illness is caused by several gene variants, either alone or in conjunction with environmental factors. Even though each alteration might only have a small impact, when they come together, they cause epilepsy. How these variations interact to lower the seizure threshold and contribute to the pathophysiology of epilepsy is unknown. The most extensive genome-wide association mega-analysis of epilepsies found 16 genome-wide significant loci by comparing over 15,000 patients with 29,000 controls in an effort to find common variants causing common epilepsies.[19] However, these loci only identify genomic regions linked to disease; they do not offer a mechanistic explanation. The American College of Medical Genetics (ACMG) classifies genetic variants into five categories: benign, likely benign, variant of unknown significance (VUS), likely pathogenic, and pathogenic. Variation type (i.e., whether it has been previously reported in disease-affected individuals), segregation in families, de novo occurrence, prevalence in controls, functional study results, expected impact on the protein, location in functional domains, and conservation across species are some of the factors that go into this classification.[20] Somatic mosaicism plays an increasingly significant role in the genetics of epilepsy. Every cell in the body has genetic variations, most of which are germline. A germline pathogenic variation may be inherited by an individual's offspring. A person with two cell populations—one pathogenic and one wild-type (or normal)—is said to exhibit mosaicism. Unless the patient has gonadal mosaicism, in which case it is unlikely to be passed on to the patient's offspring, the pathogenic variant may be limited to a single tissue (somatic mutation). 8% of people in the DEEs had a parent with mosaicism, despite the fact that the majority of patients had de novo mutations.[21] The parent is usually unaffected if the degree of mosaicism in the parental salivary or blood-derived DNA is low (<13%). However, if the percentage of mosaicism is higher, the parent may experience milder symptoms like febrile convulsions. Mosaicism is a major concern because it greatly raises the chance that the family will have a second child with a DEE.[22]

- **Common neurodegenerative causes of epilepsy**

People with neurological disorders frequently have epilepsy. It's not always evident, though, whether this correlation is merely the consequence of network disruption brought on by neuronal death, the outcome of the underlying neurodegenerative pathophysiological process, or a coincidence. Parkinson's and Alzheimer's diseases have been linked to an increased incidence of epilepsy in epidemiological studies.[23,24] However, the ILAE classification of epilepsy favors categorizing the disorder under multiple etiological categories rather than neurodegeneration as a distinct etiological category. Dementias, of which Alzheimer's disease is the most prevalent, are the most prevalent neurological conditions. Impaired episodic memory is usually the first sign of Alzheimer's disease, followed by cognitive problems in other areas. Although certain gene abnormalities have been linked to rare early-onset familial Alzheimer's disease, the cause of sporadic Alzheimer's disease, which accounts for 98% of all cases of the disease, is unknown. Regardless of age or co-occurring conditions like stroke or trauma, a comprehensive epidemiological study has shown that dementia in general and Alzheimer's disease in particular increase the prevalence of epilepsy by about four times.[25] Certain dementia-related epilepsies have symptoms that are similar to those of structurally based epilepsies. Seizures may be semiologically associated with regions of regional atrophy in these patients, and there is a temporal correlation between the onset of dementia and subsequent epilepsy. However, neuroimaging typically reveals no obvious structural abnormalities linked to epilepsy.[26] Alzheimer's disease-related seizures may be caused by both increased network excitability and cell loss; this hyper-excitability may result in compensatory increases in inhibition that affect cognition. Certain types of Alzheimer's disease, such as a specific family variant caused by a mutation in presenilin 2, are more likely to cause epilepsy. Compared to late-onset Alzheimer's disease, early-onset Alzheimer's disease, which is more likely to be genetic, often has a much higher risk of epilepsy. According to recent research, drug-resistant temporal lobe epilepsy may result in cognitive impairment due to disruption of the amyloid and tau signaling pathways, which are similar to those seen in Alzheimer's disease. This suggests a reciprocal relationship between epilepsy and Alzheimer's.[27]

- **Infectious causes of seizure and epilepsy**

Even if severe systemic infections do not directly affect the brain, they can raise the risk of seizures because they can cause pyrexia, cytokine release, metabolic issues, and autoimmune diseases.[28] Among the most frequent causes of seizures and epilepsy worldwide are cerebral infections brought on by bacteria, viruses, fungi, and parasites; these infections are especially common in developing nations. Numerous mechanisms, including the organism's production of toxins, the direct effects of infection and brain tissue death, and the induction of inflammation, can result in seizures. Crucially, in individuals with brain infections, seizures are a unique risk factor for death.[29] Up to 26% of people in Sub-Saharan Africa suffer from epilepsy as a result of infections.[30] Malaria or fever (OR = 2.28), Toxocara Canis (OR = 1.74), Toxoplasma Gondii

(OR = 1.39), Onchocerca volvulus (OR = 2.23), and Taenia Solium (OR = 7.03) are the most frequent causes of convulsive seizures in adults. [31]The most prevalent parasite brain infection linked to epilepsy worldwide, neurocysticercosis, affects up to 30% of community seizure patients in endemic areas.[32] All types of viral encephalitis frequently result in acute seizures, and the type of virus and the frequency of early convulsions determine the likelihood of developing epilepsy. Herpes simplex virus (HSV) type 1 is the most frequent cause of sporadic viral encephalitis; other significant causes include enteroviruses, varicella zoster, cytomegalovirus, and HSV type 2. Examples of arthropod-borne viruses that commonly cause encephalitis and have varied regional distributions are Japanese B encephalitis, West Nile virus, and Nipah virus.[33] Each year, around one million individuals globally experience bacterial meningitis, which is often brought on by Meningococcus, Haemophilus influenzae, and Streptococcus pneumoniae. In developing nations, bacterial meningitis is far more prevalent and carries a high risk of neurological complications. One of the main causes of epilepsy and seizures in developing nations is tuberculous meningitis, which frequently corresponds with HIV.[30]

Table 2. Risk of epilepsy associated with central nervous system infections.

Clinical feature	Risk ratio	20-year risk of epilepsy
Encephalitis with acute seizures	22.5	22%
Bacterial meningitis with acute seizures	11.5	13%
Encephalitis without acute seizures	9.5	10%

The risk is higher with encephalitis and in the with presence of acute seizures.

- **Metabolic causes of epilepsy**

Metabolic causes of seizures/epilepsy can be acquired (organ failure, nutritional deficiencies, autoimmune disease, toxins like alcohol) or genetic (inborn errors of metabolism). Acquired causes usually lead to acute seizures, sometimes progressing to epilepsy if brain damage occurs (e.g., hypoglycemia, hyperammonemia). Alcohol is a common acquired cause, withdrawal triggers seizures, and chronic use increases epilepsy risk. Inborn errors of metabolism are rare but important: seizures often resist antiseizure drugs but improve with metabolic correction. Mostly the mechanisms are failure of brain metabolism, vitamin or cofactor deficiency, toxin accumulation, neurotransmitter disruption, or cortical malformations. Neonatal seizures, developmental delay, regression, seizures linked to fasting or food intake, vomiting, dysmorphic features, family history, consanguinity are the clinical clues. Although metabolic epilepsies are uncommon, it is important to identify them because they frequently react poorly to conventional antiepileptic medications but well to specific metabolic therapies (dietary modifications, vitamin/cofactor supplementation).[11]

2.3. Socioeconomic Determinants Influencing Disease Burden

Both people with epilepsy and those who care for them may experience significant psychological, financial, and physical difficulties. The UK and other WHO member states backed the Intersectoral Global Action Plan on epilepsy and other neurological disorders (IGAP) report in 2022 as a response to this burden. A public health response to epilepsy and epilepsy prevention were among its strategic objectives. Socioeconomic health disparities include variations in epilepsy rates based on individual, local, or national socioeconomic factors (e.g., education, occupation, and socioeconomic status or position, Townsend score, or Index of Multiple Deprivation [IMD]). Although little is known about the factors underlying these socioeconomic disparities, the broader determinants of poor brain health, such as potentially modifiable behavioral factors (such as physical inactivity, tobacco use, and harmful alcohol consumption), infectious diseases (such as meningitis and encephalitis), non-communicable diseases (such as diabetes, obesity, and hypertension), head trauma, and exposure to environmental pollutants, are likely involved. Beyond these variables, epilepsy disparities are likely to result from complex intersections between genetic risk, coexisting intellectual disability, environmental exposures, individual behaviors, comorbid diseases, access to care (including disparities, discrimination, and the rural-urban divide), and the effects of broader social and commercial determinants of brain health. Higher illness burdens or worse outcomes may have different causes, even though the set of factors influencing this association is anticipated to be similar across nations. Adverse outcomes for individuals with epilepsy have been linked to socioeconomic disparities; in the UK, the poorest groups have higher rates of comorbidities, epilepsy-related deaths, and emergency hospital admissions.[34]

3. PATHOPHYSIOLOGY

It is essential to comprehend the pathobiology of epilepsy for a number of reasons. First, it makes clear the fundamental mechanisms that cause and worsen the illness, which aids in guiding the creation of more precise diagnostic instruments and focused treatment approaches. Second, by clarifying the intricate interactions between genetic, molecular, and cellular elements that cause epilepsy, researchers can find possible biomarkers and create tailored treatment plans. Furthermore, a better comprehension of the pathobiology of epilepsy may clarify the disease's heterogeneity, allowing doctors to more precisely forecast how the condition will progress and customize treatment plans to meet the needs of individual patients. In the end, increasing our understanding of the pathobiology of epilepsy may enhance the lives of people who suffer from this crippling neurological condition. To advance the field and enhance patient outcomes, it is crucial to comprehend the pathobiology of epilepsy. To find new therapeutic targets, create individualized treatment plans, and eventually enhance care for people with this complicated condition, a

review of the current knowledge of the molecular, cellular, and genetic pathways causing epilepsy is required.[35]

3.1. Neuronal Hyperexcitability

One of the main characteristics of epilepsy is neuronal hyperexcitability, or the increased propensity of individual neurons or groups of neurons to produce and disseminate abnormal electrical activity. Ion channel dysfunction, imbalances between excitatory and inhibitory inputs, and modifications to neurotransmitter receptor expression and signaling could all contribute to this. Large neuronal groups may fire simultaneously as a result of hyperexcitable neurons, producing the distinctive seizure behavior linked to epilepsy.[35] Seizures are not just about “too much excitation or too little inhibition.” They reflect complex, evolving interactions among neurons, circuits, genetics, and brain states.[36]

3.2. Imbalance Between Excitation and Inhibition

The disturbance of the delicate equilibrium between the brain's excitatory and inhibitory neurotransmitter systems is a crucial component of the pathobiology of epilepsy. Either increased excitatory neurotransmission, mediated by glutamate and its receptors, or decreased inhibitory neurotransmission, mediated by GABA and its receptors, are frequently linked to epilepsy. Increased neuronal excitability and seizures could result from this imbalance.[35] Early in development, increased intracellular chloride (via the NKCC1 transporter) causes GABA to become excitatory. KCC2 then inhibits GABA by lowering chloride. Because of this developmental shift, GABA-enhancing medications like phenobarbital and benzodiazepines can either prevent or exacerbate newborn seizures. During adult seizures, GABA may occasionally return to an excitatory state (epileptogenesis, trauma). Through shunting mechanisms, GABA can modify inhibition even during excitatory stages.[36]

3.3. Channelopathies

"Channelopathies" are disorders that can be inherited or acquired and are brought on by abnormalities in ion channels. Channelopathies are common in a variety of nervous system
disorders because ion channels are essential for neuronal signaling.[37] Ion channels are essential for controlling the movement of ions, such as calcium, potassium, and sodium, across neuronal membranes and preserving the resting membrane potential. Ion homeostasis issues and the hyperexcitability seen in epilepsy may result from modifications in the expression, function, or trafficking of these ion channels. For instance, various types of hereditary epilepsy have been connected to mutations in voltage-gated sodium or potassium channels.[35] Membrane-spanning proteins called “ion channels" create holes only for Na^+, K^+, Cl^-, or Ca^{2+} ions. Membrane voltage mediates precise control of ion channel gating during action potentials, whereas some neurotransmitters, such as acetylcholine (ACh), bind during synaptic transmission. Voltage-gated and ligand-gated channels, two different and structurally conserved types of ion channels, evolved as a result of these fundamental ideas. Only these two channel types have been demonstrated to be impacted by epilepsy-causing mutations thus far.[38]

3.4. Neuroinflammation, Oxidative Stress and Glial Cell Dysfunction

There is growing evidence that the pathobiology of epilepsy is significantly influenced by neuroinflammation and immune system involvement. Cytokines, chemokines, and prostaglandins are examples of inflammatory mediators that can alter synapse function, neuronal excitability, and blood-brain barrier integrity. All of these alterations may play a role in the onset and development of seizures. Furthermore, different forms of epilepsy have been linked to autoimmune processes, in which the immune system targets particular glial or neuronal components.[35]

Even though it is still unclear whether oxidative stress causes epileptic events or epileptic seizures cause oxidative stress, it is clear that prolonged neuronal excitement brought on by epileptic seizures increases ROS concentrations, which subsequently leads to brain damage. Furthermore, problems with intracellular calcium homeostasis caused by an overabundance of free oxygen radicals affect neuronal excitability and synaptic transmission, raising the possibility of energy crashes and neuronal death. Additionally, it is well known that the buildup of free radicals brought on by frequent epileptic seizures damages the brain over time, increasing the risk of developing other neurological disorders.[39]

Gliosis (growth of glial cells) and neuronal loss are two morphological and functional changes that epilepsy can cause in the brain. Actually, gliosis is likely present in all types of epilepsy, and a noticeable gliotic scar has been associated with chronic focal epilepsy. The term "gliosis" describes a range of physiological and physicochemical alterations in glial cells, especially astrocytes and microglia, that are frequently brought on by various CNS traumas and disorders. The type and severity of the damage determine how much and what kind of changes occur. Gliosis can either positively or negatively impact neighboring cells, depending on the specific circumstances. By reducing inflammation, eliminating debris, and promoting synaptic plasticity and tissue remodeling, reactive glia produce cytokines, chemokines, growth factors, and other compounds to lessen or prevent trauma-induced brain damage. Unchecked reactive gliosis can result in tissue damage, excessive inflammation, and neuronal death.[40]

3.5. Epigenetic Modulation and Network Reorganization

Dysregulation of gene expression and the onset of epilepsy are associated with epigenetic modifications, including DNA methylation, histone modifications, and the control of non-coding RNAs. Aberrant expression of genes associated with ion homeostasis, neurotransmitter signaling, and neuronal function can be caused by changes in transcriptional regulation, post-transcriptional mechanisms, and epigenetic modifications. For example, epilepsy models and patient samples have shown alterations in DNA methylation patterns, histone modifications, and the control of non-coding RNAs (such as microRNAs). The long-term changes in gene expression and brain network
remodeling that are typical of epileptic disease may be influenced by these epigenetic modifications.

Epilepsy is frequently linked to changes in synaptic plasticity and reorganization of neural networks. Dendritic structural modification, the development of new synaptic connections, and the strengthening or weakening of preexisting synapses are some of these alterations. The formation of epileptogenic foci and the spread of seizure activity may be facilitated by such synaptic and network remodeling. For instance, increased excitatory synaptic transmission brought on by glutamate receptor overexpression or the development of new excitatory connections may encourage neuronal hyperexcitability and seizure production.

The intricate pathobiology of epilepsy is produced by a variety of molecular and cellular processes, including genetic mutations, epigenetic changes, and synaptic plasticity. To create more focused and successful treatment plans for this neurological condition, it is essential to comprehend these complex pathways.[35]

4. CLASSIFICATION AND CLINICAL MANIFESTATIONS

Seizure type classification is helpful for a number of reasons. Classification enables grouping for the application or testing of treatments for various seizure types. It offers a basis for epidemiological investigations as well as scientific and clinical research.Classification gives medical professionals a shared vocabulary to work together on patient care. People with epilepsy and their family can use a categorization system to identify the many types of seizures they experience. The commission of the International League Against Epilepsy (ILAE) created the categorization in 1981 that is used by the majority of epileptologists. But this classification has limitations. Other than a general partial motor category, the categorization does not accommodate various focal motor seizure types, such as tonic, clonic, atonic, or myoclonic. Even though it may be clear that a seizure is tonic-clonic, it is not diagnosed if the commencement is overlooked.[41]

The ILAE began classifying seizures and epilepsy in 1964. For more than ten years, research and clinical practice have been significantly impacted by the ILAE-1981 classification of seizures and the ILAE-1989 classification of epilepsy and epileptic syndrome.

ILAE-1989 classified epilepsies into three categories: generalized, indeterminate, and localization-related (focal, local, or partial).

ILAE-2017 classified epilepsies into four categories: focal, generalized, combination generalized and focal, and unknown.[42]

4.1. Focal Onset Seizures

Focal seizures are episodes of highly disruptive brain activity that are believed to originate from localized areas of pathological abnormalities in the brain. Focal seizures may have distinct onset processes, according to clinical research. Clinical results clearly contradict this:

Medication or surgical excision of the likely epileptic foci only works for a small percentage of patients. One of two typical onset types is often followed by the morphology and appearance of focal seizure activity: The two types of activity are high amplitude slow (HAS) activity, which is typically defined as a slower oscillation below the alpha range with a high amplitude at onset, and low amplitude fast (LAF) activity, which is characterized by oscillations in the beta to gamma range of initially low amplitude that gradually increases as the seizure progresses. The majority of research indicates that the LAF pattern is the most prevalent pattern and that its removal is associated with a satisfactory surgical outcome. The LAF pattern is associated with a larger seizure start zone in both temporal and extratemporal lobe seizures, which is based on the number of contacts that initially show epileptic activity. Moreover, cortico-cortical evoked potentials (CCEPs)

show that the seizure initiation zone of the LAF pattern has lower cortical excitability than the HAS pattern. This implies that distinct processes are responsible for the different onset patterns.[43]

Focal onset aware seizures and focal onset impaired awareness seizures are the two primary types of focal seizures. Numerous clinical signs can accompany focal seizures. This categorization system provides a crucial foundation for understanding the many ways that these seizures appear and impact individuals.

- **Focal onset aware seizures;** sometimes called focal onset conscious seizures, were once known as simple partial seizures. They are characterized by limited aberrant neuronal activity in a particular area of the brain. Consciousness is unaffected during these seizures, despite the presence of certain neurological symptoms. Mild or severe motor abnormalities may accompany motor symptoms in focal-onset conscious seizures. They may be as simple as single jerks or twitches of particular muscle segments, or they could be as complex as repeats or automatisms.

- **Focal onset impaired awareness seizures;** formerly known as complex partial seizures, are characterized by a more complicated relationship between aberrant brain activity and altered consciousness. Unlike focal-onset conscious seizures, people with these seizures frequently show less awareness of their environment and may make random or partly deliberate motions. The shift in consciousness is one feature that sets apart focal onset seizures with reduced attention. A blank look, a shift in their response to external stimuli, or even complete unconsciousness are possible. Aberrant electrical activity that spreads to other brain regions causes these alterations while maintaining focus and cognitive engagement.[44]

4.2. Generalized Onset Seizures

The 2017 classification of generalized onset seizures is like the 1981 classification, but with a few more types added. There are two types of seizures: motor seizures with a wide onset and non-motor (absence) seizures.

- **Motor Onset**

Most of the time, tonic-clonic seizures that start all over the body last less than two minutes. During the tonic phase, the person's arms and legs stiffen, and they suddenly pass out. The clonic phase is when the arms and legs shake in a regular way. Some signs are biting the tongue, losing control of urination, falling backwards, and screaming at first.

A generalized onset clonic seizure is different from a tonic phase because it makes the head and/or leg move back and forth in a rhythmic way on both sides. These seizures usually happen to kids who are still very young.

During generalized onset tonic seizures, all limbs become rigid, although there is no clonic phase. One symptom of

generalized onset myoclonic seizures is that the arms, legs, face, eyes, or eyelids jerk uncontrollably and in an erratic way.[45]

- **Non-Motor (Absence) Onset**

The symptoms of absence seizures, which can last anywhere from five to thirty seconds, include fleeting moments of staring, diminished awareness and alertness, and sometimes myoclonus or flapping of the eyelids. In "simple" typical absences, the altered consciousness may be solitary; in "complex" typical absences, it may be associated with clonic, tonic, or automatic motor components. Widespread spike and wave EEG discharges with a consistent frequency of 3/second are associated with simple or complex absence. Absent seizures are caused by abnormal network oscillations involving the thalamus and cortex, according to research on both people and animals.[46]

4.3. Combined Onset

Combined epilepsies have just recently been recognized by the ILAE classification of epilepsies, and their genetic composition is yet unclear. Different but related genetic variables cause both localized and widespread epilepsy. Despite the odd discordant twin, monozygotic twins are frequently concordant for the kind of epilepsy, indicating that each variant has distinct genetic roots. These cases fall into two groups: older children or adults with both extensive and localized onset seizures and neonates or babies with epileptic encephalopathies (such as Dravet and Lennox-Gastaut syndromes).

One of the fundamental subtypes of epilepsy that mixed epilepsies may fall under is idiopathic photosensitive occipital epilepsy (IPOE), a kind of generalized epilepsy with underlying genetic origins different from those of focal epilepsy.

According to a second theory, mixed epilepsy happens when different risk genes for focal and generalized epilepsy coexist in one individual.

A third theory holds that mixed epilepsy differs from focal or generalized epilepsy in that it has different genetic roots.[47]

4.4. Unknown Onset

Tonic-clonic seizures with an unexplained onset are often reported to doctors. Either the patient was asleep by themselves, or onlookers were too preoccupied with seizure symptoms to notice the focused features. Even if the cause of the seizure is unknown, it should be easy to quickly describe it. Therefore, when significant features like tonic-clonic activity or behavior arrest were seen throughout the event, the Task Force permitted more thorough descriptions of seizures with unclear starts. With a high degree of confidence (e.g., ≥80%) in the accuracy of the evaluation, the Task Force recommends classifying seizures as either focal or generalized. Otherwise, until more information is gathered, the seizure should remain unclassified.

Unclassified seizures are ones that cannot be identified due to a lack of information or the unique features of the seizure. Rarely, if the physician is certain that the occurrence is a seizure but is unable to offer further information, it might be labeled as unclassified.[48]

5. DIAGNOSTIC APPROACHES

Although epilepsy has existed for 3,000 years, it was just recently identified. There is now a lot of research being done on the diagnosis, prevention, and treatment of epilepsy due to the wealth of medical facilities.[49] The principles of neurological diagnosis to be followed in order to achieve a precise and complete examination and the classification of signs and symptoms? (clinical diagnosis) where (topological diagnosis) and why. (diagnóstico etiológico). A detailed history, a complete general clinical and neurologic examination, a diagnostic hypothesis, and a careful selection of subsequent tests are all important elements in the diagnosis of epilepsy.[50] New structural and morphological data obtained with modern diagnostic technologies such as magnetic resonance imaging (MRI) and voxel-based morphometry have shown different susceptibilities of the cerebral hemispheres to epileptogenesis in recent years. Thus, it has been shown that patients with left temporal epileptic foci present white and gray matter abnormalities together with a reduction in the size of the amygdala.[51]

For the purpose of prediction and diagnosis of brain disorders, a variety of signal and image processing techniques are employed, such as EEG (electroencephalogram), video EEG telemetry, MEG (magnetoencephalography), CT (computed tomography), MRI (magnetic resonance imaging), fMRI (functional MRI), MRA (MRI angiography), MRS (magnetic resonance spectroscopy), PET (positron emission tomography), and SPECT (single photon emission computed tomography).[49]

5.1. Clinical Evaluation and Seizure Semiology

The main sign of epilepsy is seizures. We analyze in detail their symptomatology, allowing us to classify patients with different kinds of seizures. This is the basis of our diagnosis. When combined with data from several sources and analyzed with a multidimensional system of categorization, they result in epileptic syndromes. Semiology is marked by observation as well as by meticulous recording of historical facts. The difference between epileptic seizures and non-epileptic events is based on the description of the event and the confirmed completeness of data from all other sources. Classification of seizure types as focal, generalized, or undetermined may be of use also.[52] Electrocardiography, skin temperature, auditory classification, and respiration rate change techniques can be used to evaluate physiological signals, while semiology can be evaluated by accelerometers, surface electromyography, video detection systems, mattress sensors, and seizure-alert dogs. However, each of these approaches is limited to a specific set of epileptic symptoms (e.g., speech or motor symptoms).[53] In patients with chronic epilepsy being investigated for surgical therapy, a detailed semiologic history is fundamental not only for diagnosis but also for localizing the seizure focus. The role of electroencephalography (EEG), video monitoring, and magnetic resonance imaging (MRI) in identifying seizure foci cannot be overemphasized. However, the difference in the investigative armamentarium between clinical semiology localization and other tests raises questions about the accuracy of the localization.[54] Seizure semiology is a very useful approach but needs

standardization by the assessors. Many experienced observers must agree that only unambiguous signs should be used. During a single seizure, conflicting lateralizing or localizing impulses are often seen. Here, the meaning of each symptom is interpreted by its specificity and the order in which it appears during the seizure.[55]

5.2. Neurophysiological Monitoring

Neurophysiological knowledge, neuroanatomical information, and clinical judgment all work together to accurately diagnose neurological illnesses, determine long-term prognoses, and choose the best course of therapy.[56]

- **EEG**

The EEG, the diagnostic test for epilepsy, can be used to verify the diagnosis of epilepsy and epileptic syndrome. Hans Berger recorded the first human EEG in 1924 and found an alpha wave pattern dominated by occipital activity associated with eye closure. The EEG has excellent temporal resolution of brain activity. Understanding the physiological basis of interictal and ictal EEG patterns can help us better understand the pathogenesis and therapeutic approaches for various epilepsies. The two main EEG markers of epilepsy are interictal spikes or sharp waves in focal epilepsy and frontocentral spike-wave discharges in generalized epilepsy.[57] The EEG findings in juvenile myoclonic epilepsy are predominantly fragmented irregular polyspike waves, widespread 3–6 Hz SWs with frontal dominance, and normal background activity. These results are often seen at the onset of sleep or upon waking up. Ictal data of myoclonus showed wide, rhythmic, rapid polyspikes at about 20 Hz. The EEG images of patients diagnosed with JME are quite different.[58] The most accurate "laboratory" test for epilepsy is the electroencephalogram (EEG), which detects interictal and ictal epileptic discharges (ED), the two most significant functional indicators. Numerous classification techniques have been used, and clinical EEG, imaging, genetic, and molecular biology research have all contributed to our understanding of epilepsy. The latest ILAE position paper on improved terminology and concepts for seizures and epilepsy is the result of these efforts.[59]

- **Video-EEG**

A video-EEG is a current record of both the EEG and the patient's clinical semiology, allowing you to match the final EEG changes to the patient's clinical history, signs, and symptoms. It enables
linking the final EEG alterations to the patient's prior clinical history, signs, and symptoms. There are several applications for VEM. Identification, differentiation, classification, characterization of ictal events, recording of seizures, clinical and electrical characterization of episodes, differentiation of non-epileptic paroxysmal episodes, precise diagnosis and treatment selection, detection of underdiagnosed epileptic seizures, measurement of seizures and correlation with sleep-wake cycle, detection and analysis of interictal EEG abnormalities and ictal patterns, and seizure monitoring. Both video and EEG data are digitalized by contemporary video-EEG systems, enabling interpretation through a variety of montages. CCTV cameras are used to capture footage.[56]

5.3. Advanced Neuroimaging

In order to identify the location of epilepsy and seizure foci before a possible surgical treatment, neuroimaging becomes essential. The site and lateralization of the seizure focal are the main purposes of structural imaging. Functional radionuclide imaging or advanced magnetic resonance imaging can provide additional information when no epileptogenic substrate is discovered or when clinical and anatomical data are ambiguous.[60] Functional imaging techniques like positron emission tomography (PET), s ingle- photon emission computed tomography (SPECT), magnetoencephalography (MEG), and advanced MRI techniques like arterial spin labeling (ASL), diffusion tensor imaging (DTI), functional MRI (fMRI), and magnetic resonance spectroscopy (MRS) complement structural imaging by offering metabolic and perfusion information that is crucial for preoperative assessment.[61]

- **MRI**

In both common and uncommon forms of epilepsy, clear structural brain abnormalities that may be the cause of seizures may be seen using conventional MRI scans. Even in cases when there is a strong suspicion of an epileptogenic structural lesion, such as in patients referred for epilepsy surgery, a standard brain MRI may not reveal any abnormalities. Advanced neuroimaging technologies include MRI fingerprinting, brain morphometry, functional MRI, and ultra-high field MRI, all of which can offer further diagnostic information and aid in the detection of mild or cryptic lesions that would not be seen on a regular brain scan. This can help with more accurate clinical assessments of patients with epilepsy or whose etiology is uncertain.[62]

- **fMRI**

Functional MRI techniques (eg, blood-oxygenation-level-dependent [BOLD] contrast imaging) can be used to monitor changes in oxygenated blood flow over time. Simultaneous EEG-fMRI is of great importance in epilepsy. EEG is recorded during fMRI acquisition, and timing of EEG events is used to map BOLD changes in response to electrographic discharges. Another fMRI technique with great promise for imaging networks in lesion-free epilepsy is resting state fMRI. Resting state fMRI scans patients at rest using conventional BOLD fMRI and interprets brain regions with connected BOLD fluctuations as networks. Resting-state fMRI showed changes in functional connectivity in patients with infantile absence epilepsy.[63]

- **PET**

Because the vast majority of clinical PET applications are in cancer therapy, clinical PET neuroimaging is often performed with PET-CT scanners. However, most of the PET-CT scanners can generate good PET brain images if the acquisition and reconstruction parameters are appropriately selected. However, most PET-CT scanners are able to generate good PET brain images if acquisition and reconstruction parameters are appropriately set. Seizure foci are accompanied by focal interictal hypometabolism as shown on 2-deoxy-2[18F]fluoro-D-glucose positron emission tomography (FDG-PET), but the hypometabolic regions found by PET may occasionally extend well beyond the true epileptic zone.

Indeed, PET data reveal neuronal activity in regions of ictal onset, postictal depression, and ictal spread. Whether hypometabolism derives from the underlying pathogenic process, the effects of several seizures on the brain, or an initial
shock, such as early status epilepticus, is unknown. In nonlesional neocortical epilepsy, PET can be used to facilitate intracranial electrode implantation and overall localization, but not to refine surgical restrictions.[64]

5.4. Precision Diagnostics

Among the levels at which "precision" in epilepsy may be investigated are the aetiologies, underlying pathophysiology leading to epileptogenesis, or clinical and EEG features of epileptic syndromes, including comorbidities. The outlook is more favorable when the cause is known and an aetiological treatment is selected. In some patients with structural problems, surgery could be a treatment option for epilepsy. The specific approach is designed to enhance the understanding of molecular pathways and network disruption through a dynamic multilevel evaluation, focusing on unique neurobiological mechanisms of illness.[65]

- **Genetic Testing**

Genetic abnormalities are responsible for more than 70% of epileptic syndromes. Consequently, genetic testing has become an essential part of the evaluation procedure for juvenile epilepsy. Individuals with intellectual impairments, developmental delays/cognitive regression, refractory epilepsy, or concurrent dysmorphism are the most likely candidates for genetic testing.[66] Our knowledge of the genetic causes, contributions, and regulators of epilepsy has increased as a result of recent discoveries in molecular genetics. Next-generation sequencing has made it possible to accurately identify up to 50% of monogenic epilepsies, which has resulted in an explosion of gene discoveries in human diseases. New technologies that allow the study of epigenetic regulation, longer read lengths, functional evaluation of changes of unknown importance, even in known genes, and systematic match-making exchange are needed to help with genetic diagnosis.[67] The first year of life is when epilepsy is most frequent, and as children become older, it becomes less common.[68] Early-onset monogenic epilepsy syndromes have a wide spectrum of clinical presentations and outcomes, from benign and self-limiting (familial) epilepsies to severe developmental and epileptic encephalopathies. A genetic diagnosis allows for more directed genetic counseling and provides important information on the natural history and prognosis of a disease. It also allows the individual and his family to join gene-specific networks of similar affected families.[67]

Numerous genetic tests are currently available to investigate the genesis of epileptic disorders. In fact, the rapid evolution of narrowly applicable tools (like FISH and single-gene testing) to multigene panels, clinical exome sequencing, clinical genome sequencing, and chromosomal microarrays for testing infants and children with epilepsy has been made possible by advances in diagnostic techniques to massively parallel sequencing.[66] When determining an epileptic diagnosis and clinical profile, it is essential to consider the limits and potential benefits of each test. For instance, cytogenetic investigations are very helpful for people with both epilepsy and intellectual disability, especially when dysmorphic characteristics overlap and a firm epileptic diagnosis is not attainable.[69,70,71]

6. THERAPEUTIC STRATEGIES

Treatment decisions for epilepsy are based on a number of factors. Some of these variables include patient characteristics, cost and reimbursement issues, efficacy of different drugs in various seizure types and syndromic forms, their relative tolerability profile, potential for interactions, and ease of administration. The type of health system, the social setting, the availability of pharmaceuticals, and above all, commercial pressure, exert a great influence on the therapeutic methods. Recovery from problems with prefrontal lobe development may be impacted by the length of an active seizure. In a variety of epileptic illnesses, children with shorter active seizure durations recover from anomalies in prefrontal lobe development more rapidly.[72] More than 15 third-generation anti-epileptic
medications (AEDs) have been developed during the past 30 years, significantly improving the management of a variety of seizure types.[73] The cure rate for newly diagnosed epilepsy patients using current AEDs is 70-80%. In 20–30% of patients, these drugs do not control the seizures. There is also drug-resistant epilepsy, which is treated with AEDs but does not respond to AEDs. A deeper comprehension of the various clinical and experimental strategies for developing and discovering more effective treatment methods that can help prevent and control the disease is necessary to develop better epilepsy treatment paradigms based on various pharmaceutical and therapeutic approaches.[74]

6.1. Pharmacological Treatment

Since the introduction of bromide in the nineteenth century, pharmacological therapy has been a mainstay of the treatment of epilepsy.[75] There are currently about two dozen AEDs available for treating epilepsy. Pharmaceutical therapies enable between 65% and 80% of people with epilepsy to become seizure-free. For myoclonic seizures, standard antiepileptic medications (AEDs) such as valproic acid, levetiracetam, and benzodiazepines are frequently used as first-line therapy.[76] AEDs are frequently used as monotherapy to avoid toxicity; however, they can also be used in combination.[77] Although most ASMs now on the market reduce neuronal excitability and seizure frequency, they might not be able to treat the underlying cause of epilepsy. By blocking excitatory neurotransmission via ion channels, a number of ASMs exhibit anticonvulsant properties.[76]

- **AED Mechanism**

AEDs are neither preventive nor curative; they are only used to treat symptoms like seizure suppression. In essence, these drugs restore the balance between neuronal inhibition and stimulation.[78] Antiepileptic drugs generally block GABA receptors, GABA-metabolizing enzymes, GABA transporters, and voltage-dependent sodium, potassium, and calcium channels. Antiepileptic drugs may function by focusing on excitatory amino acid receptors and synaptic proteins.[79] Most antiepileptic

drugs work in a variety of ways.[80] *Deckers et al.*[81] classified antiepileptic drugs by these criteria. The first group comprises antiepileptics (carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, topiramate, and valproate). These drugs prevent repetitive firing of some neurons by blocking voltage-dependent sodium or calcium channels. These drugs are effective in treating both partial and generalized tonic-clonic seizures. The second family of medications that increase the inhibitory effects of γ-aminobutyric acid (GABA) includes benzodiazepines, gabapentin, phenobarbital, tiagabine, topiramate, vigabatrin, and valproate. Certain medications can be used to treat any kind of seizure, including absence, partial, and generalized tonic-clonic seizures. The third category includes ethosuximide, a medication that reduces absences by inhibiting T-type calcium channels. Zonisamide may act as a T-type calcium channel inhibitor, according to recent research.[82] Antiepileptic medications that lessen the effects of excitatory amino acids (like glutamate) may represent a new class of drugs. As of right now, felbamate, phenobarbital, and topiramate are the three antiepileptics included by this definition.[81]

- **Drug Resistance**

Some 20–40% of newly treated epileptic patients do not achieve long-term remission for several years while taking several anti-epileptic drugs. Many of these patients continue to have drug-resistant epilepsy with frequent disabling seizures despite the best available medical care and modern AEDs. Drug-resistant epilepsy, one of the most frequent chronic neurological diseases, is a serious public health problem.[83] Drug-resistant seizures are four to seven times more common in those with drug-resistant epilepsy, which can have disastrous consequences.[84] Drug-resistant epilepsy is defined by the International League Against Epilepsy as "failure of adequate trials of two tolerated, appropriately chosen, and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom." Approximately one quarter of people with epilepsy are diagnosed with drug-resistant epilepsy.[85] Numerous variables, such as genetics, drug-

related processes, and disease-related mechanisms, have been connected to pharmacoresistance. According to the transporter theory, which is connected to pharmacokinetic issues, overexpressed efflux transporters at the blood-brain barrier restrict AED brain entry.[86] The MDR1 and MDR1a genes in rodents and humans, respectively, encode a family of closely related intrinsic membrane proteins implicated in multidrug resistance that make up P-glycoprotein (P-gp), one of the glycoprotein active efflux systems.[87] Preclinical studies show that the absence of its counterpart (mdr1a or mdr1b genes) increases the brain's absorption of lipophilic medications.[88] ATP-dependent multidrug transporters such as P-gp or MRP2 are located on the apical cell membrane of endothelial cells and act as an active efflux pump, preventing many lipophilic drugs from reaching the brain parenchyma and pumping part of the drug back into the circulation. In addition, multidrug transporter proteins lower the drug concentrations in endothelial cells such that the passage of drugs from the brain extracellular space into endothelial cells is promoted. Barrier function may be supported by these transporters' strong expression. Therefore, AED concentrations would be inadequate to provide antiepileptic effects.[86]

- **Adverse Effects**

Every drug has side effects, which can be short-term, long-term, severe, or mild. Antiepileptic drugs (AEDs) differ in the kind and intensity of adverse effects, particularly during the initial phases of treatment. Pharmacodynamic tolerance is typically impacted by dosage and start time; however, idiosyncratic pharmacological effects are uncommon and unexpected.[89] Adverse events (AEs), some of which are lethal, are a common side effect of antiepileptic drugs (AEDs).[90] Up to 61% of patients on conventional AEDs like phenobarbital, carbamazepine, valproate, or phenytoin experience adverse reactions[91]; they are considered to be responsible for up to 40% of all first therapy failures in patients.[92] The side effect profiles of many medications vary greatly. When selecting an AED, side effect profiles are typically the most important factor to take into account because success rates do not seem to vary significantly across AEDs that are effective against a certain type of seizure. Which AED has the best side effect profile isn't always obvious. The incidence of side effects of the same medicine may differ significantly between studies due to the fact that AE data may be obtained in a number of methods, including well-planned clinical trials.[93] For instance, when checklists were used to analyze adverse effects (AEs) in two distinct prospective trials comparing carbamazepine and valproate, the AE rates for both medications were much higher.[94] compared to when the evaluation was predicated on spontaneous reports.[95] AED side effects include memory problems, tiredness, tremors, gastrointestinal problems, osteoporosis, depression, lethargy, dizziness, weight fluctuations, nausea, and more. These might include simple counseling, expensive medical care, and hospital stays.[96]

6.2. Non-Pharmacological Interventions

Epilepsy is commonly treated with antiepileptic drugs (AEDs), but drug-resistant seizures may require brain surgery. A very small percentage of people seek medical advice even though they are opposed to pharmaceutical and surgical treatments. They should have access to alternatives based on logical ideas. even if it is difficult to find unbiased, controlled data that quantifies or records the effectiveness of such methods.[97] Nutritional treatment may still be beneficial in reducing the frequency of seizures in children, adolescents, and adults with refractory (or intractable) epilepsy.[98]

- **Ketogenic Diet**

The ketogenic diet (KD), a high-fat, low-carb, high-protein diet, is a proven non-pharmacological treatment for children with intractable epilepsy, which is defined as epilepsy that has not responded to three or more AEDs. This type of therapy may be a good alternative for those with chronic epilepsy who are not candidates for surgery. Patients are usually referred to the KD after failing 5 or more AEDs.[99] The traditional KD is carefully regulated, customized for each patient, and produced using various methods in various nations, often with notable differences in its administration. The interdisciplinary execution of the diet should be overseen by a physician and dietitian.[100] It is believed that KDT reduces seizures in several ways. The main antiseizure mechanisms involve the inhibition of the generation of reactive oxygen species (ROS) and the mitochondrial permeability transition pore, which can stop excessive Ca^{2+} release and protect the cell from oxidative damage by ketone bodies (KB).[101] KB may also inhibit vesicular glutamate transporters (VGLUTs), reducing the amount of glutamate transported into vesicles and the size of glutamate quanta released during synaptic transmission.[102]

Figure 3. **Likely effect of a ketogenic diet on seizure activity. ↑- increase, ↓- decrease.**

- **Vagus Nerve Stimulation (VNS)**

Vagal nerve stimulation (VNS) is a relatively new therapy for medically intractable epilepsy, first introduced in 1988. It was safe and effective, as clinical trials in the mid-1990s showed, and its popularity grew. It periodically stimulates the left vagus nerve in the neck with implanted electrodes attached to a subcutaneous generator behind the collarbone.[103] The VNS system is a battery-operated device that looks like a cardiac pacemaker.[104] The VNS treatment equipment comprises a pulse generator, a bipolar VNS lead, a programming wand with portable computer software, a tunneling instrument, and portable magnets. The lead transmits electrical signals from the generator to the vagus nerve. This software allows the programming wand to be placed over the generator to read and change the stimulation settings. There are many possible parameters, but there are recommendations for doctors on where to start with the most popular and effective settings for each type of generator. Each phase of stimulation is preceded by a 2 s ramp-up and followed by a 2 s ramp-down.[105] VNS treatment may be helpful in lowering seizure frequency and enhancing quality of life (QOL), even if total seizure

independence is uncommon.[106]

- **Surgical Options**

Surgical treatment of epilepsy is one of the most underutilized medical procedures known to be effective. Surgical referral is often considered a last resort for those who suffer from epileptic seizures that are resistant to AEDs.[107] For both patients and physicians, fear of surgery is often a reason to continue with medication after recurrent failure of AEDS.[108] However, it is well recognized that the morbidity and mortality associated with persistent, incapacitating seizures far outweigh the risks of surgery.[109] Reconstructive surgery may be helpful for patients with drug-resistant, uncontrolled, disabling focal epilepsy if seizures occur in a location that can be excised with minimal risk of neurologic or cognitive deficits. While they are more likely to become seizure independent following surgery, patients with lesional epilepsy react less effectively to AEDs than those with cryptogenic/idiopathic epilepsy. Consequently, mesial temporal sclerosis (MTS), low-grade neoplasms, vascular malformations, encephalomalacia following stroke or trauma, and isolated cortical dysplasias are among the abnormalities that typically produce persistent, intractable epilepsy in surgical candidates.[110] Reconstructive surgery has been a major intervention in the
treatment of epileptic patients since the late 19th century, when likely epileptogenic foci were removed. Different epileptic groups have very different advantages from epilepsy surgery. Over the next several decades, the practice of epilepsy surgery changed, and an increasing number of case series and observational studies (>100) documented its efficacy.[111] Most epilepsy patients considered for surgery will need to be admitted to an epilepsy monitoring unit (EMU) for continuous EEG and video monitoring. Depth electrodes are usually implanted bilaterally, targeting the amygdalo-hippocampal area. This may suggest lateralization in situations where it would be difficult to distinguish mesial from lateral temporal lobe epilepsy. Mesial temporal sclerosis (MTS) is a common cause of localization-related epilepsy and has been shown to be quite responsive to surgery in carefully selected patients. Radiosurgery is also being explored for the treatment of epilepsy associated with mesial temporal lobe sclerosis.[112]

6.3 Emerging and Personalized Therapies

Next-generation sequencing (NGS), whole exome sequencing (WES), and whole genome sequencing (WGS) are among the new techniques that have revolutionized our understanding of the pathophysiology and etiology of many types of epilepsy. We now know that most epilepsies are genetic, especially those that start in infancy, and that hundreds of monogenic forms of epilepsy have been identified. The most common gene family associated with epilepsy is ion channel genes, which encode for sodium, potassium, and calcium components.[113] Recent advances in our knowledge of the genetic basis of epilepsy have facilitated the development of a new therapeutic strategy that targets the fundamental pathophysiology of seizures and associated disorders.[114] This has enabled a more individualized treatment of different diseases, with the development of new and repurposed drugs intended to restore poor brain function and/or stop or resolve the pathogenic process. These specific therapeutic techniques are found in three categories of therapy: treatments involving modification of cell signaling pathways, substitutive therapies, and function-based therapies.[113]

Genetic mutation can alter both the pharmacokinetic (e.g., polymorphism in a drug metabolism gene) and pharmacodynamic (e.g., polymorphism in brain AED targets such as ion channels) responses to AEDs. Other potential factors include mutations in the genes causing epilepsy and altered expression of enzymes and other molecules implicated in the pathophysiology of pharmacoresistance or adverse medication responses. The activity of the cytochrome P450 (CYP) enzymes is now known to be the main cause of most AED clearance. Genetic variants in CYP enzymes can cause drug toxicity and inter-individual variations in serum AED levels. For example, phenytoin is a first-generation AED that is mainly metabolized by CYP2C9 and CYP2C1. Some individuals have polymorphisms in CYP2C9 that decrease the activity of the enzyme, resulting in increased serum phenytoin concentrations, reduced phenytoin clearance, and an associated increased risk of central nervous system injury.[115] Genome-wide screening of patients has revealed an increasing number of genes, single nucleotide gene variations (SNVs), and genomic hotspots associated with epilepsy.

One or more genetic factors may be responsible for about 70% of epilepsy cases. Disease modeling studies of SCN1A mutations, which cause the vast majority of Dravet syndrome cases, have revealed a decrease in the sodium ion channel activity of inhibitory interneurons as the epileptic etiology. The choice of treatment for Dravet syndrome has been reevaluated as a result of this finding; drugs that block sodium ion channels should be avoided since they may exacerbate seizures and interneuron activity.[116] Clinical practice is actively investigating a wide range of drugs, from those having processes comparable to well-known ASMs, like GABA-A receptor agonists, to those with unique mechanisms, like melatonin receptor activation. Moreover, many drugs have no clear mechanism of action, while some are still recognized drugs that were once utilized for different
purposes.[117] Exogenous nucleic acids are injected into target cells to change gene expression in gene-based treatment, which is now undergoing preclinical testing. These big, negatively charged macromolecules are usually transported by carriers, often referred to as vectors. The transgene, promoter, and viral vector are some of the factors that need to be taken into account while using gene therapy in clinical settings.[118]

The majority of epileptic treatments are still grounded on empirical science, and individuals with epilepsy cannot be prescribed medications based on their mechanisms of action. The effectiveness of tailored treatment is hampered by the wide variety of clinical phenotypes and underlying aetiologies. A new age in epilepsy therapy, where patients will benefit from medications depending on the underlying etiology of the disease, is being ushered in by recent scientific discoveries regarding genetic

pathways, neuroimaging research, and epileptic neurobiology.[119]

7. DISCUSSION AND FUTURE PERSPECTIVE

7.1 Seizure control predictors and quality of life (QoL) outcomes

The control of seizures is a clinical goal and is the most important determinant of life for persons with epilepsy. In the face of more general psychological factors like stress, sleep quality, and social support, physicians can rely on predictors like age of onset, seizure type, etiology, and adherence to therapy. Epilepsy is one of the most difficult brain illnesses to control and is found in approximately 50 million people worldwide. A lot of people experience negative reactions such as metabolic issues or mental fog, and 30-40% of sufferers are resistant to existing medications.

Improved seizure control is highly correlated with improved quality of life and is associated with decreased stigma, anxiety, and cognitive decline and increased independence. However, inequalities in access to care are still a major obstacle, especially in low- and middle-income countries where antiepileptic drugs are not available or are too costly. Moving forward, predictive analytics needs to be combined with patient-reported outcomes to ensure epilepsy care not only aims to reduce seizures but also restores dignity, autonomy, and everyday function.

7.2 Integration of AI and network pharmacology in seizure prediction

The merging of network pharmacology and artificial intelligence (AI) is changing epilepsy research. AI models, particularly those based on deep learning, can be used to analyze EEG data and clinical histories to detect subtle pre-ictal changes that can be used for real-time seizure prediction. Meanwhile, network pharmacology provides insight into the overall system of drug-target interactions and proposes the antagonistic or synergistic effects of antiepileptic drugs. This is especially important given the article's focus on the shortcomings of existing treatments, where more than 20 medications are available, but a large percentage of patients continue to be drug-resistant.

AI and pharmacology are forces to fine-tune treatment regimens for each patient's biology, unlocking the potential for a future of personalized medicine. However, there are challenges to be overcome before this technology becomes ubiquitous, such as data heterogeneity, algorithm transparency, and ethical privacy concerns. This shift from a reactive to a proactive therapeutic approach for epilepsy could shift the paradigm of the patient experience once these barriers are overcome.

7.3 On the horizon: Neuroprotective and disease-modifying therapies

The main goal of the current therapies is to control seizures, and medicine that helps protect the brain and alter the course of the disease is the next frontier. One important target is the process that makes a healthy brain go bad and develop epilepsy, known as epileptogenesis. Seizures are not only

caused by excessive discharge of neurons but rather by synchronization of neural networks, and that increased excitability is due to genetic and anatomical defects. These insights make interventions possible that could stop or reverse epileptogenesis.

Anti-inflammatory drugs, antioxidants, stem cell therapies, and gene-editing techniques like CRISPR-Cas9 are promising treatments. Preclinical studies have indicated that drugs that reduce oxidative stress and mitochondrial dysfunction have promise; modifying neuroinflammation pathways may help lessen seizure and cognitive dysfunction. Translational research that connects the molecules with the therapeutic uses will be important. The ultimate target is ambitious: to alter the disease itself and not just to suppress symptoms for life and, as such, to ensure neurons' resilience and better cognitive outcomes in epilepsy treatment.

- **Closing Perspective**

The convergence of these paths points towards the future of accuracy, creativity, and change. Predictive models will help doctors predict outcomes and tailor treatments. Neuroprotective therapies will attempt to modify the disease itself, and AI and pharmacology will help to allow for personalized, proactive care. Epilepsy is one of the most common severe brain disorders, and the impact of this condition is increasing globally. However, there is a clear path forward beyond the androgyny of epilepsy as a lifelong burden and back to freedom, normalcy, and hope for millions of people around the world.

8. CONCLUSION

Epilepsy is more than just a neurological condition; it has an impact on many features about the life of a person. Around 50 million people in the world experience such disorders. Epilepsy is a huge physical, social, and emotional burden for those who have it. Although there has been progress over the last decades, there remain a considerable number of patients who suffer from a range of long-term health issues. Continue to experience resistance to the available treatments, and many patients continue to suffer from stigma and poor access to care. These data are to remind us to treat epilepsy, which requires a more comprehensive focus on the health of patients than only preventing seizures.

The learnings from this review highlight three key directions. First, from seizure onset to genetic and plasma drug levels, a variety of factors are known to influence seizure control. Structural factors must be identified early, as structural factors have a direct impact on long-term outcomes and quality of life. Second, the incorporation of artificial intelligence and network pharmacology has great potential to predict seizure and medication personalization, moving from a reactive to proactive approach to care. Last but not least, the opportunity for neuroprotective and disease-modifying treatments suggests a potential for modifying the process of epileptogenesis at some point instead of suppressing the symptoms. As far as clinical viewpoints, the message is very clear: early diagnosis and personal care, such as individualized care, are essential. Early intervention results in better seizure control, increases thinking ability and being self-sufficient. To provide high-quality, compassionate care, treatment needs to be individualized to the patient's biology, environment, and life experience. Precision medicine and patient-centered approaches are

the backbone of the future of treating epilepsy. Rather than seeing epilepsy as a lifelong condition, we can help the people who suffer with it to restore their dignity, resilience, and optimism.

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