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# Review of the Epilepsy, Including Its Causes, Symptoms, Biomarkers, and Management

**Yash Srivastav [a++*], Akhandnath Prajapati [a], Prachi Agrahari [b] and Madhaw Kumar [a]**

*[a] Department of Pharmacy, Goel Institute of Pharmacy & Sciences (GIPS), Lucknow, Uttar Pradesh, India.*
*[b] Department of Pharmacy, Rameshwaram Institute of Technology and Management (RITM), Lucknow, Uttar Pradesh, India.*

***Authors' contributions***

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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## ABSTRACT

Epilepsy is a long-term medical disorder that frequently causes unpredictable, unprovoked repeated seizures that have an impact on both physical and mental abilities. It is among the most prevalent neurological conditions. Greek term epilambanein, which is the root of the English word epilepsy, means "to be seized." Both the sickness and the one-time attack were meant by this. The word refers to the magical beliefs of the time, which led to the stigma associated with epilepsy because people with epilepsy were seen to be dirty or bad. A recent study found that nearly 90% of the 70 million epileptics worldwide live in developing countries. Genetic testing has expanded the possibility of figuring out the aetiology of different types of epilepsies. It needs some prior clinical application knowledge to complete this challenging endeavour. Genetic testing techniques include

*[++] Master of Pharmacy in Pharmaceutics;*
**Corresponding author: E-mail: neelashsrv76@gmail.com;*

chromosome microarray analysis, karyotyping, single-gene testing, gene panel testing, whole exome sequencing, and whole genome sequencing. The allegedly first documented account of epilepsy, as it was then perceived and understood, may be found in one of the earliest Babylonian medical manuals, Sakikku (English translation: "All Diseases"), which dates from around 1050 BC. The pathogenesis, aetiology, treatment, biomarkers, and risk factors for epilepsy are reviewed in this review article.

*Keywords: Epilepsy; history; causes; symptoms and signs; risk factors; pathophysiology; biomarkers and treatments.*

## 1. INTRODUCTION

Epilepsy is the second-most prevalent and frequently occurring neurological illness, and it places a significant strain on patients, their families, and healthcare systems. According to a recent study, there are almost 90% of the world's 70 million epileptics in poor nations [1]. Epilepsy is a neurological illness that affects people of all genders, social classes, locations, and races. This is a collection of symptoms rather than a single illness that points to underlying brain disorders. Recurrent spontaneous seizures with a multi-factored aetiology are brought on by an aberrant dynamism of neuronal networks that generate abnormally synchronically discharged neurons [2,3]. The Greek term epilambanein, which is the root of the English word epilepsy, means "to be seized." Both the sickness and the one-time attack were meant by this. The word refers to the magical beliefs of the time, which led to the stigma associated with epilepsy because people with epilepsy were seen to be dirty or bad [4]. The term "epilepsy" refers to a brain condition that is primarily characterized by unpredictable, repetitive disruptions of regular brain function known as epileptic seizures. Epilepsy is a group of disorders that reflect underlying brain malfunction and can have several origins. It is not a single disease entity. There is little widespread consensus over the definitions of seizures and epilepsy. Such definitions are crucial for medical professionals to communicate with one another as well as with others involved in lawmaking, disability pensions, driving regulations, workplace safety, education, and a variety of other purposes. Common symptoms include significant neuropathological alterations in the hippocampus, fluctuations in awareness, issues with motor coordination, stigma, and other brain processes. In addition to the absence of vitally important powerful medications, the development and optimization of effective treatment have been significantly hampered by inadequate drug delivery systems and early detection of this condition. More than 50% of remitted instances, medical medication resistance, and ongoing understanding of the aetiology and classification of epilepsy all contribute to prognosis and therapeutic problems [5-8]. Because of physical injury caused by seizures, long-term seizure disorders, inability to work or go to school, adverse treatment effects, coexisting diseases, psychosocial impairment, the emergence of drug-resistant seizures, and early mortality, epilepsy may hurt a person's quality of life. At least two unprovoked seizures that are separated by at least 24 hours constitute epilepsy or a seizure disease. People who experience one seizure but are more likely to experience subsequent ones, such as those who experience seizures associated with primary brain tumours, may be diagnosed with epilepsy and treated as such. Epilepsy is typically defined as the state of experiencing recurrent, repeated occurrences. Studies addressing the epidemiology of seizures or epilepsy can be prone to error because the diagnosis of epilepsy is clinical and there is no set test or biomarker that formally identifies a person as having epilepsy [9,10]. Nearly 70 million people worldwide are thought to have epilepsy, and the prevalence of the condition is thought to be 5 to 9 cases per 1,000 people. Epilepsy accounted for 0.7% of the worldwide burden of more than 17 million DALYs in 2010, according to the GBD analysis, and over 90% of these cases were reported from low- and middle-income countries (LMICs). Southeast Asia contributed 3.2 million DALYs, up from 0.3 to 0.5% between 1990 and 2010, with DALYs ranging from 6.2 million in Africa to as low as 1.6 million in the European region. In the Southeast Asian region, the prevalence of epilepsy ranged from 2 to 10 per 1,000 people, and India accounted for more than half of all DALYs associated with epilepsy (as reported by GBD 2010). A vast population, poor income, inadequate resources, sociocultural prejudices, competing infectious and noncommunicable diseases, and the low priority given to public health elements of epilepsy are likely to be the causes of this enormous burden coming from India [6,11,12]. The International League against Epilepsy (ILAE) most recently

changed its conceptual definition of epilepsy to an operational definition to align the term with everyday usage. As a result, epilepsy is described as a brain illness that includes any of the following symptoms: At least two unprovoked (or reflex) seizures occurring more than 24 hours apart, two unprovoked (or reflex) seizures, one unprovoked (or reflex) seizure, and a likelihood of additional seizures equal to the general recurrence risk (at least 60%) after two unprovoked seizures occurring over the next 10 years, in addition to the epilepsy syndrome diagnosis [13]. To ease surgical intervention for refractory focal epilepsies, functional imaging tests like positron emission tomography (PET) and single photon emission CT (SPECT) can aid in detecting and confirming the ictal focus. The likelihood of discovering the causes of various types of epilepsies has increased as a result of genetic testing. This is a difficult Endeavor that calls for some clinical application experience. Chromosome microarray analysis, karyotyping, single-gene testing, gene panel testing, whole exome sequencing, and whole genome sequencing are examples of genetic testing methodologies. When utilised wisely, it can aid in clinical diagnosis and management using effective approaches [13,14]. With low-cost medication, such as the standard antiepileptic drugs: carbamazepine, phenobarbital, phenytoin, valproic acid, and benzodiazepines, epilepsy can be treated effectively and affordably. The majority of new medications improve these individuals' medical care more through tolerance than through efficacy. Due to better compliance, these can occasionally have a significant impact on the outcome and result in a seizure-free condition. About one-third of newly diagnosed epilepsy patients experience refractory seizures [13,15].

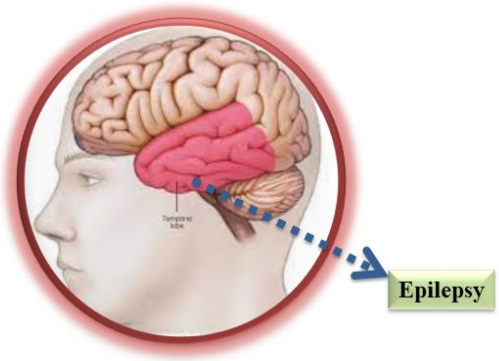


**Fig.1. Epilepsy's effects on the brain**

## 2. CLASSIFICATION

Seizures and epilepsies have been organized and classified in numerous ways. The ILAE Commission on Classification and Terminology proposed changes to nomenclature and methodology (panel 1) in 2010 in light of recent scientific advancements. These changes involve a flexible multidimensional framework, the specifics of which are still being developed based on feedback from the epilepsy community [16-19]. The term "focal" has taken the role of "partial" in the proposal for seizures coming from neuronal networks that are exclusive to one brain hemisphere. A diagnosis of focal seizure should be made whenever there are focused symptoms and signs, even if a person has bilateral motor manifestations. Focal seizures are no longer dichotomized into simple versus complicated on the basis of supposed changes in the degree of consciousness. Generalized seizures can affect cortical and subcortical regions, although not always the entire cortex. They are assumed to start in bilaterally dispersed cortical or cortical-subcortical networks that quickly engage without a specific focality. While both focal and generalized seizure types can occur in many disorders, every effort should be taken to determine whether epilepsy is caused by focal pathology because it may have an impact on available surgical alternatives. The following categories are used in place of the prior classifications of idiopathic, symptomatic, or cryptogenic causes of epilepsy in the 2010 ILAE proposal: genetic, used only for epilepsies in which genetic factors play a significant role in the disorder's cause and the causative or susceptibility genes are inherited (with Mendelian, mitochondrial, or complex patterns of inheritance), or result from novel mutations that may or may not be passed down through the family; structural or metabolic, in which the aetiology is clearly structural or metabolic and is either genetically or non-genetically determined (for example, stroke, trauma, brain tumours, cortical abnormalities, aminoacidopathies); and unknown [18-20].

## 3. HISTORY OF EPILEPSY

The word epilepsy is derived from the Greek verb epilambanein, which means to take, and the verb epilepsia, which means to grasp hold of. Epilepsy was once associated with outdated faiths or being possessed by a demon. Epilepsy was once thought to as a sacred sickness, and many

people held this opinion because they thought it only affected those who had been partially possessed by demons or because the visions experienced by those with epilepsy were sent by the Gods. Even among the animist Hmong generations, for example, epilepsy was regarded as a demonic spirit's attack, albeit the sick individual could become a shaman via their own experiences [21]. In the Salpetriere, the birthplace of modern neurology, Jean-Martin Charcot observed that the epileptic people were all nothing but mentally retarded, as they were affected by chronic syphilis or criminally insane. It may be mentioned that people with epilepsy have historically been stigmatised and even kept in prison. Tanzanians, like those in other countries in Africa, still hold the belief that epilepsy is brought on by poisoning, evil spirits, witchcraft, or other forms of witchcraft. Romans thought that epilepsy was a curse delivered by God and referred to it as Morbus comitialis, or "disease of the assembly hall." Although stigma still exists today, individuals are aware that it is gradually fading, at least in industrialized nations. Hippocrates stated that since epilepsy is not a divine disease, it will be eliminated quickly [22,23]. They also suggest that epilepsy was considered to be a spiritual disorder throughout ancient history. The oldest known description of an epileptic seizure comes from a document written approximately 2000 BC in the extinct language Akkadian, which was once widely spoken in ancient Mesopotamia (modern-day Iraq). The person who the book describes as having epilepsy was determined by Magiorkinis, Kalliopi, and Diamantis to be under the spell of a Moon God and required an exorcism. According to Jacobs and Louis, exorcism is a religious or spiritual practise that involves driving out demons or other spiritual beings from a person or place that they are thought to have possessed. The Babylonian medical document from 1067–1046 BC has the earliest known thorough description of epilepsy, according to Saraceno, Avanzini, and Lee. The ancient cultural region of Babylonia is located in central-southern Iraq. Magiorkinis, Kalliopi, and Diamantis also noted that this record provides signs and symptoms in addition to information on the treatment and expected results. In other words, this record lists numerous characteristics of various seizure kinds. However, Saraceno, Avanzini, Lee, Magiorkinis, Kalliopi, and Diamantis note that Babylonians did not have a biomedical understanding of the nature of this disease and as a result believed that these seizures were caused by the possession of evil spirits. As a result, spiritual remedies were used as a form of treatment [24-26]. Epilepsy was characterized as a loss of consciousness by one Punarvasu Atreya around 900 BC. On this term, the ancient Greeks had divergent opinions, though. They insisted that epilepsy was a type of possession by spirits and connected it to genius and the divine. The Greeks thought notable individuals with the condition included Hercules and Julius Caesar. Due to their belief that some epileptics were brilliant, the Greeks did not harbour any animosity against all epileptics [27,28].

## 4. CAUSES

Epilepsy's root cause is absolutely unknown. The term "epilepsy" means nothing about the origin or intensity of a person's seizures; while some cases are brought on by genetics, epilepsy can also be brought on by head trauma, stroke, infections, high temperature, or tumours. Although it can affect persons of any age, it has been shown that inheritance (genetics) plays a significant part in many causes of epilepsy in very young children. For instance, not everyone who suffers from a severe head injury, which is a known trigger for seizures, will acquire epilepsy [8,29]. According to patients with epilepsy, certain epilepsy syndromes known as reflex epilepsy require particular precipitants or triggers for seizures to occur, such as reading or flashing lights. Other precipitants cited by epilepsy patients include emotional stress, sleep deprivation, heat stress, alcohol, and febrile illness. Notably, how different precipitants affect an epilepsy state varies. When a woman has epilepsy, her menstrual cycle can affect her seizure recurrence patterns and catamenial epilepsy, which is a seizure that is associated with the menstrual cycle [30,31]. The most frequent causes of hypoxic-ischemic encephalopathy in the neonatal period and early infancy are CNS infections, trauma, congenital CNS abnormalities, and metabolic disorders. The most frequent febrile seizures in late infancy and early childhood may be brought on by CNS illnesses and trauma. Well-defined epilepsy syndromes are typically seen in children. The causes are more likely to be secondary to any CNS damage in adolescence and adulthood. The most frequent cause of dementia in older people is cerebrovascular illness; other causes include CNS tumours, head trauma, and 22 other degenerative diseases [32].

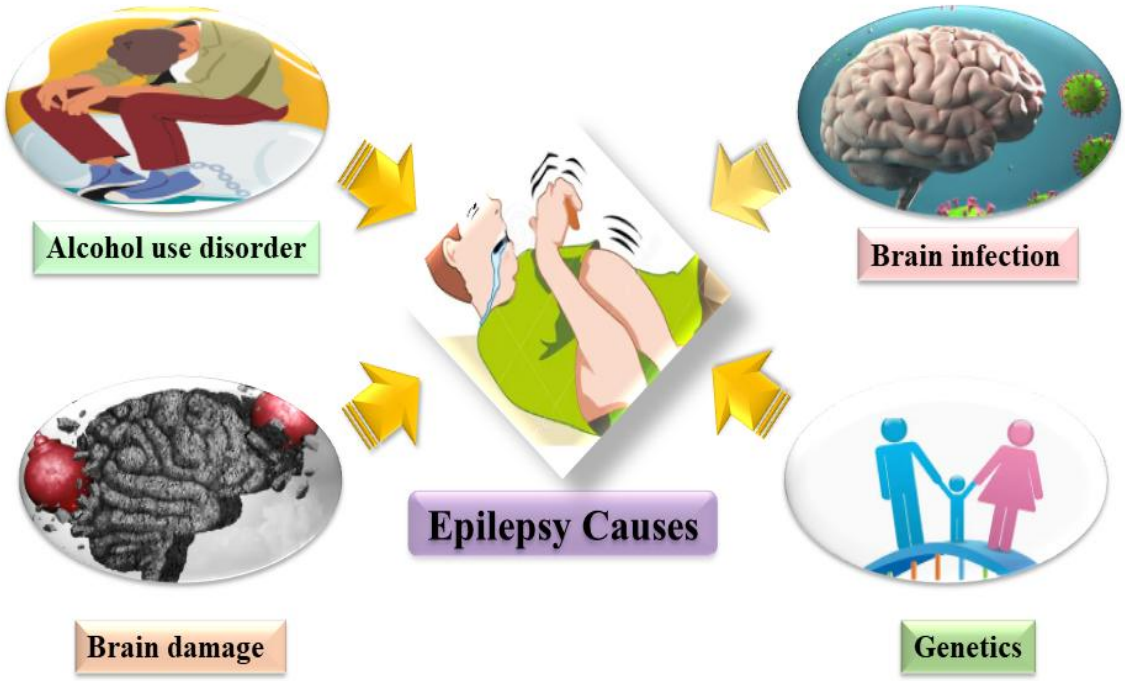


**Fig. 2. Most Common causes of epilepsy**

## 5. SYMPTOMS AND SIGNS

Neurologically speaking, epilepsy is characterized by aberrant brain activity that causes seizures, which frequently cause total loss of consciousness as well as odd behaviour and emotional emotions. A diagnosis of epilepsy is normally made when a person has at least 2 seizures that are unrelated to another recognized medical condition, including opiate withdrawal or extremely low blood sugar. Functions of the affected section are disturbed by that region of the brain where early seizures commonly start. The left half of the brain controls the right side of the body, while the right half of the brain controls the left side. Doctors typically categorize seizures as generalized or focal depending on where and how aberrant brain activity begins [33-35]. While generalized seizures appear to encompass the entire brain, focal seizures are brought on by abnormal brain activity in a particular area of the brain. Partial and generalized seizures have been categorized into two primary categories by neuro-experts. It can be used to identify symptoms of partial seizures, which are caused by injury to the cerebral hemisphere. Additionally, simple partial and complex-partial partial seizures fall into two major groups. Simple-partial patients are usually able to speak and act normally, whereas individuals with complex-partial behave erratically, become disoriented, and frequently mumble or chew. Generalized seizures consist of two basic parts. Non-conclusive seizures can be distinguished by their obvious motor symptoms, whereas definitive seizures can be difficult to detect since they lack motor indications. individual is unable to speak or move, and is only able to look [36-40]. Some individuals simply stare aimlessly for a predetermined amount of time during a seizure, while others repeatedly shake their limbs or legs. Epilepsy may not always be present after a single episode. At least two unprovoked seizures (seizures brought on by unknown causes) must take place during a 24-hour period in order to be classified as epileptic. Seizures can interfere with any brain-coordinated process because epilepsy is caused by abnormal brain activity. Epilepsy type is determined by a few distinct symptoms. The sensations listed below will vary in frequency, while others will become recurring. An individual with epilepsy typically has the same kind of seizure every other time. Symbols and seizure signs may include: Brief confusion, Spell of Steady Eye, Motion of a Rigid Body, Spasmodic movement that is uncontrollable, Incognizance and ignorance, Indicators of the spirit and such as anxiety or terror [41-43].

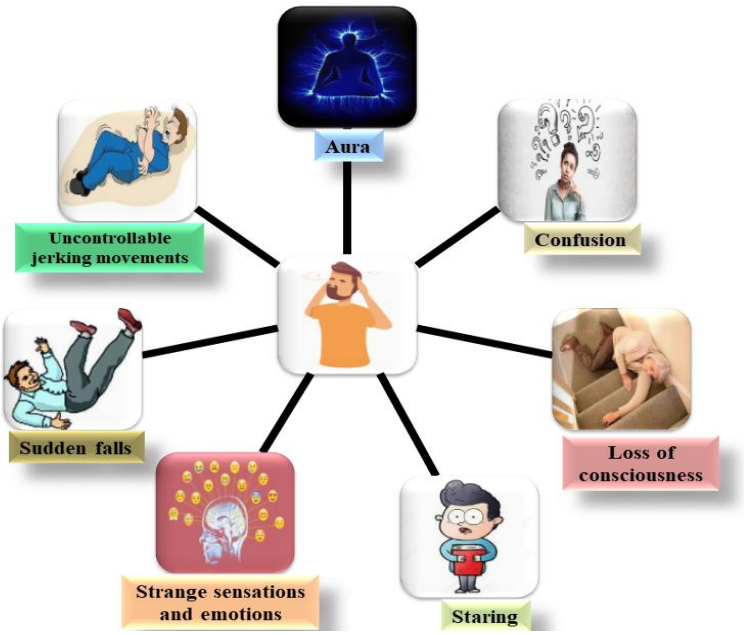


**Fig. 3. Epilepsy symptoms and signs [44]**

## 6. RISK FACTORS

It has been demonstrated beyond doubt in experimental research that frequent seizures in animals cause cumulative alterations in brain networks. There is a dearth of information regarding progressive seizure-induced changes in human epilepsy that are related to seizure type, length, or frequency. We should underline that seizures that have progressed past the class III stage are secondary generalized seizures, which are uncommon in the majority of people with drug-resistant temporal lobe epilepsy [45]. Epidemiological research has shown that seizures in people usually stop on their own. According to Tinuper and colleagues, secondarily generalized seizures cease to occur in 84% of individuals with partial-onset seizures at about the age of 50. According to certain accounts, a subset of patients may experience new-onset seizures that develop over time. Hauser and Lee recently demonstrated for the first time a gradual rise in seizure risk with increasing seizure frequency. Individuals with a low risk of seizure recurrence-patients with unexplained seizures of unclear aetiology, without risk factors, family history, or abnormal electroencephalograms-were shown to be at risk [46-48]. This epidemiological finding is a little unexpected because the elevated risk was seen in people who would otherwise have a strong chance of experiencing remission. The unexpected finding has an intriguing corollary in experimental models; subsequent seizures had less of an impact on cumulative neuronal death in animals who had experienced their first SE episode than in normal animals who had undergone kindling. The progressive effects of seizures may thus differ depending on the previous activity in neural circuitry, as suggested by experimental and clinical studies on human epilepsy. This possibility is also supported by the different effects of pre-existing lesions on the onset of kindling and the protection of previously kindled rats from the harmful effects of SE [49-53]. Cognitive deterioration brought on by poorly managed seizures is another functional indication of progression. It is crucial for people with epilepsy to consider whether seizures could be causing progressive cognitive decline. Recent cross-sectional and longitudinal investigations have provided information on the consequences of recurrent seizures on cognitive performance. A finding of interest given evidence of a causal relationship in experimental models between the number of secondarily generalized seizures and memory dysfunction and a relation between neuronal loss/dysfunction measured by magnetic resonance spectroscopy and generalized tonic-clonic seizures is that the longitudinal studies revealed a mild but consistent relationship between seizures and mental decline that was apparent in patients with seizures that were tonic-clonic in nature [54-56]. Cognitive decline is yet another functional indicator of development. Altering the seizure type from partial to

secondarily generalized may eventually lower the chance of long-term harm. The danger of activity-dependent induction of molecular, cellular, and network alterations may be reduced overall by shortening seizure duration. Use of neuroprotectants (when they become available) could lessen the cognitive deterioration associated with increasing neuronal death brought on by recurrent seizures if antiepileptic medication is not totally effective. Candidates for experimental neuroprotective treatments include neurotropins, calcium-channel blockers, glutamate receptor blockers, vaccines, stem cells, and gene treatments [57].

## 7. PATHOPHYSIOLOGY

The cerebral cortex manifests itself in paroxysmal seizures. When the equilibrium between the excitatory and inhibitory forces within the network of cortical neurons suddenly shifts, seizures take place. An unstable cell membrane or its neighboring or adjacent supporting cells are where the basic physiology of a seizure episode is found. Any cortical or subcortical location in the grey matter is the seizure's primary site of origin. A small portion of neurons first activate improperly. Excess excitability spreads either locally to cause a focal seizure or more broadly to cause a generalized seizure due to normal membrane conductance, inhibitory synaptic current breakdown, and excess excitability. Through physiologic pathways, this onset spreads to affect nearby and far-off locations. The membrane of the neuron can become unstable and induce seizures due to abnormalities in potassium conductance, voltage-activated ion channel dysfunction, or a lack of membrane ATPases involved in ion transport. Glutamate, aspartate, acetyl choline, norepinephrine, histamine, corticotropin releasing factor, purines, peptides, cytokines, and steroid hormones are a few neurotransmitters that increase the excitability and propagation of neuronal activity, while GABA and dopamine inhibit this process. The demand for blood flow to the brain increases during a seizure to remove CO2 and provide substrate for the neurons' metabolic activity. As the seizure lasts longer, the brain experiences greater ischemia, which may cause neuronal death and brain damage [58]. Some kinds of epilepsy may be caused by mutations in various genes. There are 23 generalized epilepsy and infantile seizure syndromes, and voltage-sensitive and ligand-activated ion channel protein subunit genes have been linked to these disorders. One proposed mechanism for some types of inherited epilepsy is mutation of the genes encoding for sodium channel proteins; these defective sodium channels remain open for long periods of time and cause the neurons to become overly excitable as a result. This excitatory neurotransmitter, glutamate, may then be released in large amounts from the neurons, which, upon binding with nearby glutamanergic neurons, causes an excessive release of calcium (Ca2 +) in the post synaptic cells, which may be neuro [17,59].

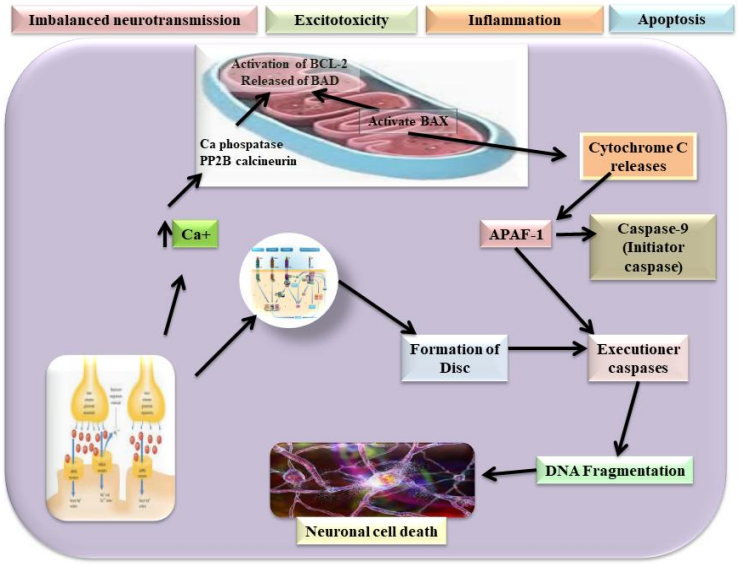


**Fig.4. Epilepsy's pathophysiology [60]**

## 8. EPILEPSY BIOMARKERS

Other factors that contribute to ineffective therapeutic approaches for epilepsy include methodological issues, inclusion criteria, diagnostic uncertainty, and varied character (age group, gender, and ethnicity) of distribution. Another barrier to a better theragnostic treatment for epilepsy is the disorder's ambiguous and shifting classification. It has been discovered that the most effective therapeutics are based on the etiological classes of the disease, which include genetics, infectious, metabolic, immune, and other factors. As a result, the updated categorization of epilepsy noted by the International League Against Epilepsy (ILAE) in 2017 can be helpful in identifying the various treatment modalities and a better understanding of epilepsy. But many other kinds of seizures are still retained in the unclassified division for further study [61]. According to the epilepsy incident's prompt diagnosis, professional competence, and seriousness, it is deemed curable. Seizure predictability, epileptic focal coordinates, and careful monitoring could reduce morbidity in patients' lives and minimise suffering and fatalities. Sensing technology developments can get over these challenges and quickly locate the epilepsy focus. The most important tools for accurate illness sensing, detection, and diagnosis are highly selective and precise biomarkers. There is a summary of several biomarkers for epilepsy. These suggested factors, either individually or collectively, can be connected to epilepsy by systematic analysis [62-64]. Electrophysiological signals, neuroimaging, and molecular biomarkers can all be used to classify epilepsy biomarkers. Ophysiology is the study of electrical activity, which includes high-frequency oscillations, interictal spikes, and aberrant alterations in neuronal status. Electrocorticography (ECoG), Electrocardiography (ECG), Electromyography (EMG), and Electroencephalography (EEG) are performed on the brain, the heart, and the muscles, respectively. Imaging technologies such as magnetic resonance imaging (MRI), computerised axial tomography (CAT) scan, positron emission tomography (PET), and others can diagnose lesions, injuries, or epileptiform abnormalities using imaging biomarkers. The molecular biomarkers for epilepsy include measures of changes in ribonucleic acid (RNA) or gene expression, metabolite levels such as enzymes, neuropeptides, proteins, etc., in blood or tissues, in such a way that the expression and levels correspond to distinct aspects of illness. The epilepsy type may be determined via a closed loop sensor system that generates profiles of various biomarkers, as only a small number of these biomarkers are associated to all types of epilepsy and others may be syndrome specific. A smart approach to managing epilepsy can be achieved by combining these biomarkers with an understanding of the impact of nanotechnology, the miniaturization of devices, and the accompanying synergism. In addition to addressing hazy epidemiology, hybrid theragnostic units can aid in the discovery of hitherto unappreciated disease causes at the molecular and cellular levels [65-67].

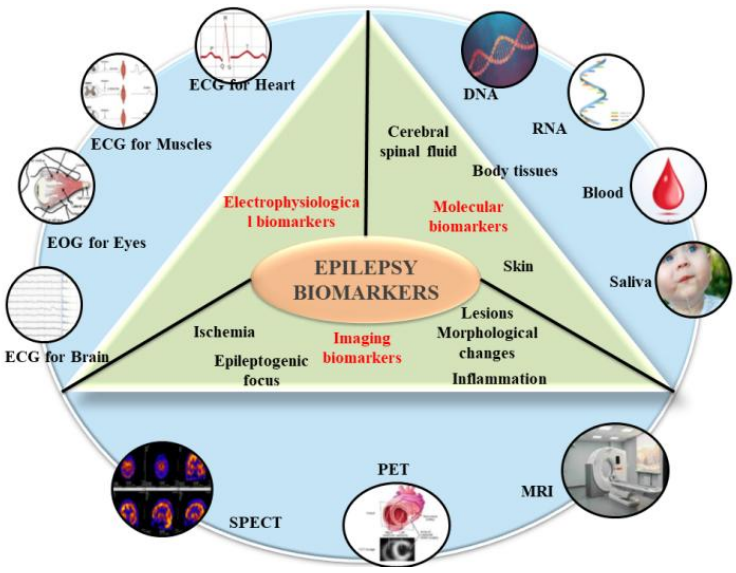


**Fig. 5. Epilepsy-related biomarkers [67]**

## 9. MANAGEMENT OF EPILEPSY

Antiepileptic and anticonvulsant are interchangeable terms. An anticonvulsant is a substance that prevents seizures in lab animals during experiments, while an antiepileptic medicine is one that is prescribed to treat the 32 epilepsies [68]. management principles Any epilepsy triggers, such as cerebral tumours, must be treated. Patients need to be informed about the disease, the length of the course of treatment, and the need of adherence. Alcohol, lack of sleep, and emotional stress are precipitating variables that should be avoided. Natural variation should be expected, for example, fits may occur more frequently or solely in women during their periods. Only if the form and frequency of the seizure, such as more than one fit per 6–12 months, call for the administration of an antiepileptic medicine [69]. One of three main processes may underlie the action of antiepileptic medications: (i) lowering the electrical excitability of cell membranes, particularly (by blocking) the voltage-dependent sodium channels that are in charge of the inward current that generates an action potential; (ii) enhancing GABA-mediated synaptic inhibition, by inhibiting GABA transaminase or by medications with direct GABA agonist properties; the result is increased membrane permeability to chloride ion, which lowers cell excitability; and (iii) inhibiting T-type such as glutamate [69,70].

## 10. MEDICAL TREATMENT

The most common form of treatment for most patients, antiepileptic drug (AED) therapy, has four main objectives: to prevent seizures or to reduce their frequency as much as possible, to avoid the side effects of long-term treatment, to help patients maintain or resume their regular psychosocial and occupational activities, and to help patients maintain a normal lifestyle. The choice to begin AED medication should be based on a thorough evaluation of the risk of seizure recurrence, the patient consequences of ongoing seizures, and the advantages and disadvantages of the selected pharmacological agent [71,72]. It is debatable whether to start therapy with a patient who has only had one seizure. If there is clear evidence that a single seizure was brought on by a lesion that has been identified—such as a CNS tumour, an infection, or trauma—and that lesion is epileptogenic, treatment should be administered. The primary objective of AED therapy is to entirely eliminate seizures. Depending on the type or spectrum of seizures, the relative risk of epilepsy recurrence can change. Patients who have congenital neurological abnormalities or epileptiform discharges on an EEG are at a significant probability of recurrence (almost 90%). When starting AED therapy, the patient's and their family's perspectives should also be taken into account. It could be better to start using AEDs early in order to stop additional seizures. Having seizures in the future could be upsetting for those who need to drive, go to work, or look after other family members. Depending on the type of epilepsy and any related neurological and medical issues, the likelihood of seizure recurrence differs among patients. However, pharmacotherapy has a risk of side effects that increases after initial treatment by a rate of around 30%.4 When a drug is used repeatedly, treating children offers extra issues, particularly with regard to brain development, learning, and behaviour [32,71,73-75]. The perfect AED should prevent all seizures without resulting in any unfavourable side effects. Unfortunately, some patients who are treated with currently available AEDs not only experience uncontrollable seizure activity, but they also regularly experience side effects that can range in severity from mild CNS impairment to fatal aplastic anaemia or liver failure. The AED or drug combination that best controls seizures with a tolerable level of adverse effects must be selected by the treating doctor or practitioner. It is generally acknowledged that up to 50% of patients can obtain total seizure control, and another 25% experience significant improvement. The success rate of treatment varies depending on the type of seizure, family history, and severity of the underlying neurological abnormalities, and it is higher in people with newly diagnosed epilepsy [76,77]. The possibility of a seizure recurrence, the repercussions of ongoing seizures, and the positive and negative effects of the drug in avoiding a recurrence can all be taken into consideration when deciding whether to start AED treatment. Depending on the seizure type or syndrome, there may be a range in the relative likelihood of recurrence. Patients who have congenital neurological abnormalities or epileptiform discharges on an EEG are at a significant risk (up to 90%) of recurrence. Additionally, patients with brain abnormalities, prior symptomatic seizures, and Todd's paralysis (a momentary, transitory paralysis following a seizure) have higher recurrence risks [78,79].

**Table. 1. Current status of clinical trials on Epilepsy**

| Drug | Mode of administration | Disease | Enrollment | Allocation/Intervention model/Masking | Official Title of the study | Status | Clinical trial | Year |
|---|---|---|---|---|---|---|---|---|
| ReACT/ Supportive Therapy | Interventional | Epilepsy | 94 | Randomized/ Parallel Assignment/ None (Open Label) | Treatment Outcomes of Retraining and Control Therapy (ReACT) for Psychogenic Non-epileptic Seizures (PNES) | NA | NCT02801136 | 2022 |
| Topiramate | Observational | Epilepsy | 80 | NA | An Open Observational Safety Study During Administration of Topamac, as Monotherapy in Epileptic Patients With no Prior Treatment or Unsuccessfully Treated With Other Antiepileptic Drug | NA | NCT00297323 | 2010 |
| NA | Observational [Patient Registry] | Epilepsy | 40 | Case-Control | Arak University of Medical Sciences , Ministry of Health and Education,I.R.Iran | NA | NCT01764516 | 2013 |
| Placebo/ 2400mg SPN-804/1200mg SPN-804 | Interventional | Epilepsy | 366 | Randomized/ Parallel Assignment/ Quadruple | Phase III Study to Evaluate the Efficacy and Safety of OXC XR as Adjunctive Therapy in Subjects With Refractory Partial Seizures | Phase-3 | NCT00772603 | 2014 |
| lacosamide | Interventional | Epilepsy | 308 | N/A/ Single Group Assignment/ None (Open Label) | An Open-label Extension Trial to Determine Safety and Efficacy of Long-term Oral SPM 927 in Patients With Partial Seizures | Phase-3 | NCT00522275 | 2018 |
| Placebo/ Pregabalin | Interventional | Epilepsy | 65 | Randomized/ Parallel Assignment/ Quadruple | A Placebo-Controlled, Escalating Dose, Multiple Dose Study To Evaluate The Safety, Tolerability And Pharmacokinetics Of Pregabalin In Pediatric Patients With Partial Onset Seizures | Phase-1 &2 | NCT00437281 | 2021 |
| gabapentin | Interventional | Epilepsy | 65 | Non-Randomized/ Single Group Assignment/None | A 52 Weeks, Open-Label, Multicenter Study Evaluating | Phase-3 | NCT00620555 | 2021 |

| Drug | Mode of administration | Disease | Enrollment | Allocation/Intervention model/Masking | Official Title of the study | Status | Clinical trial | Year |
|---|---|---|---|---|---|---|---|---|
| | | | | (Open Label) | The Efficacy And Safety Of Gabapentin As Adjunctive Therapy In Pediatric Patients Who Have Completed The 12 Weeks Treatment In Study A9451162 (NCT00603473) | | | |
| Pregabalin | Interventional | Epilepsy | 54 | Non-Randomized/ Single Group Assignment/ None (Open Label) | A 12-month Open-label Extension Study Evaluating The Safety And Tolerability Of Flexible Doses Of Pregabalin In Pediatric Patients With Partial Onset Seizures | Phase-3 | NCT00448916 | 2021 |
| Gabapentin | Observational | Epilepsy | 1273 | Case-Only | Drug Use Investigation Of Gabapen | NA | NCT00567268 | 2021 |
| Lyrica (pregabalin)/ placebo | Interventional | Epilepsy | 187 | Randomized/ Triple (ParticipantCare ProviderInvestigator) | PROSPECTIVE RANDOMIZED 12-WEEK CONTROLLED STUDY OF VISUAL FIELD CHANGE IN SUBJECTS WITH PARTIAL SEIZURES RECEIVING PREGABALIN OR PLACEBO | Phase-4 | NCT00351611 | 2021 |
| gabapentin | Interventional | Epilepsy | 92 | Non-Randomized/ Single Group Assignment/ None (Open Label) | An Open-Label, Multicenter Study Evaluating, The Efficacy, Safety And Pharmacokinetics Of Gabapentin As Adjunctive Therapy In Pediatric Patients With Partial Seizures When Other Antiepileptics Do Not Provide Satisfactory Effects | Phase-3 | NCT00603473 | 2021 |
| lacosamide | Interventional | Epilepsy | 370 | N/A/ Single Group Assignment/ None (Open Label) | An Open-label Extension Trial to Determine Tolerability and Efficacy of Long-term Oral SPM 927 as Adjunctive Therapy in Patients With Partial Seizures | Phase-2 | NCT00552305 | 2018 |
| SPM 927 | Interventional | Epilepsy | 160 | Non-Randomized/ Single | A Multicenter, Open-label Trial | Phase-2 | NCT00151 | 2014 |

| Drug | Mode of administration | Disease | Enrollment | Allocation/Intervention model/Masking | Official Title of the study | Status | Clinical trial | Year |
|---|---|---|---|---|---|---|---|---|
| | | | | Group Assignment/ None (Open Label) | to Investigate the Safety and Tolerability of Intravenous SPM 927 as Replacement for Oral SPM 927 in Subjects With Partial Seizures With or Without Secondary Generalization. | & 3 | 879 | |
| Functional magnetic resonance imaging exam | Interventional | Epilepsy | 30 | Non-Randomized/ Parallel Assignment/ None (Open Label) | Co-operative Behavior and Decision-making in Frontal Lobe Epilepsy | NA | NCT02441478 | 2015 |
| Sensor Dot | Interventional | Epilepsy | 496 | N/A/ Sequential Assignment/ None (Open Label) | A Multicenter Study to Examine Clinical Scenarios for Long-term Monitoringof Epileptic Seizures With a Wearable Biopotential Technology | NA | NCT04284072 | 2022 |
| RWJ 333369: | Interventional | Epilepsy | 47 | Non-Randomized/ Single Group Assignment/None (Open Label) | A Double-Blind, Placebo-Controlled, Dose-Titration Study to Determine Safety, Tolerability and Preliminary Efficacy of RWJ-333369 as Adjunctive Therapy in Subjects With Treatment-Resistant Partial Seizures (With or Without Secondary Generalization) or Primarily Generalized Tonic-Clonic Seizures | Phase-2 | NCT00210652 | 2013 |
| RWJ 333369 | Interventional | Epilepsy | 421 | Non-Randomized/ Single Group Assignment/ None (Open Label) | A Double-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Efficacy, Safety, and Tolerability of RWJ-333369 as Adjunctive Therapy in Subjects With Refractory Partial Seizures (Protocol 333369-EPY-2003 [Double-blind] and Protocol | Phase-2 | NCT00210522 | 2013 |

| Drug | Mode of administration | Disease | Enrollment | Allocation/Intervention model/Masking | Official Title of the study | Status | Clinical trial | Year |
|---|---|---|---|---|---|---|---|---|
| | | | | | 333369-EPY-2006 [Open-label Extension]) | | | |
| NA | Observational | Epilepsy | 117 | NA | Preliminary Testing of a Novel Device to Detect Epileptic Seizures | NA | NCT02286271 | 2017 |
| Pregabalin | Interventional | Epilepsy | 337 | Non-Randomized/ Single Group Assignment/ None (Open Label) | Pregabalin Open-Label Add-On Trial: An Open-Label, Multicenter Follow-On Study to Determine Long-Term Safety and Efficacy in Patients With Partial Seizures. | Phase-3 | NCT00150293 | 2015 |
| Pregabalin | Interventional | Epilepsy | 455 | Non-Randomized/ Single Group Assignment/ None (Open Label) | Pregabalin Open-Label Add-On Trial: An Open-Label, Multicenter Follow-On Study to Determine Long-Term Safety and Efficacy in Patients With Partial Seizures. | Phase-3 | NCT00141388 | 2009 |
| Pregabalin | Interventional | Epilepsy | 750 | Non-Randomized/ Single Group Assignment/ None (Open Label) | Pregabalin BID Open-Label Add-On Trial: An Open-Label, Multicenter Follow-On Study to Determine Long-Term Safety and Efficacy in Patients With Partial Seizures. | Phase-3 | NCT00141336 | 2007 |
| Pregabalin | Interventional | Epilepsy | 325 | Non-Randomized/ Single Group Assignment/ None (Open Label) | Pregabalin Open-Label, Multicenter Add-On Trial Following a 4-Day Double-Blind Transition Period to Determine Long-Term Safety and Efficacy in Patients With Partial Seizures. | Phase-3 | NCT00141245 | 2007 |
| motivational interviewing/ standard psychotherapy | Interventional | Epilepsy | 60 | Randomized/ Parallel Assignment/ None (Open Label) | Motivational Interviewing to Enhance Adherence of Patients With Psychogenic Non-epileptic Seizures: A Model of Patient Engagement in Functional Neurological Symptom Disorders | NA | NCT02598076 | 2019 |

| Drug | Mode of administration | Disease | Enrollment | Allocation/Intervention model/Masking | Official Title of the study | Status | Clinical trial | Year |
|---|---|---|---|---|---|---|---|---|
| gabapentin | Observational | Epilepsy | 82 | Case-Only | Special Investigation Of Gabapen For Pediatric (Regulatory Post Marketing Commitment Plan) | NA | NCT01441401 | 2021 |
| Levetiracetam | Interventional | Epilepsy | 398 | N/A/ Single Group Assignment/ None (Open Label) | A Multicenter, Open, Long-term Follow-up Study to Evaluate the Safety and Efficacy of L059 (Levetiracetam) at Individual Optimal Dose Ranging From 500 to 3000 mg/Day in Twice Daily Administration in Subjects From 16 to 65 Years With Epilepsy Suffering From Partial Onset Seizures Whether or Not Secondarily Generalized Who Completed in a Previous Study | Phase-3 | NCT00367432 | 2020 |
| NA | Observational | Epilepsy | 576 | Cohort | A Non-interventional Post-marketing Study, Evaluating Seizure Control and Tolerability of Vimpat® as Adjunctive Therapy to One Baseline Antiepileptic Drug in Epilepsy Patients With Partial-onset Seizures With or Without Secondary Generalization in Daily Clinical Practice in Germany | NA | NCT01098162 | 2014 |
| ganaxolone | Interventional | Epilepsy | 123 | N/A/ Single Group Assignment/ None (Open Label) | An Open-label Extension Study to Evaluate the Safety, Tolerability, and Efficacy of Ganaxolone as add-on Therapy in Adult Patients With Epilepsy Consisting of Uncontrolled Partial-onset Seizures. | Phase-2 | NCT00512317 | 2023 |

| Drug | Mode of administration | Disease | Enrollment | Allocation/Intervention model/Masking | Official Title of the study | Status | Clinical trial | Year |
|---|---|---|---|---|---|---|---|---|
| SPN-804O | Interventional | Epilepsy | 18 | Non-Randomized/ Parallel Assignment/ None (Open Label) | Multiple Dose, Open-Label, Multi-Center Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of OXC XR as Adjunctive Therapy in Pediatric Subjects With Refractory Partial Epilepsy | Phase-1 | NCT00918047 | 2017 |
| Lacosamide | Observational | Epilepsy | 1005 | Cohort | Post-Authorization Safety Study to Evaluate the Long-Term Safety and Tolerability of Vimpat® (Lacosamide) as Add-On Therapy in Epilepsy Patients With Partial-Onset Seizures Who Are Uncontrolled on Current Therapy | NA | NCT00771927 | 2014 |
| NA | Observational | Epilepsy | 72 | NA | MRI in Autosomal Dominant Partial Epilepsy With Auditory Features | NA | NCT00072813 | 2017 |
| Andrews/Reiter behavioral treatment for epilepsy | Interventional | Epilepsy | 8 | Non-Randomized/ Single Group Assignment/ None (Open Label) | Nonrandomized Pilot Trial of the Andrews/Reiter Behavioral Treatment for Epilepsy | Phase-1&2 | NCT00212745 | 2019 |
| Lacosamide | Interventional | Epilepsy | 100 | N/A./ Single Group Assignment/ None (Open Label) | A Multicenter, Open Label Study to Evaluate the Tolerability, Safety and Efficacy of Lacosamide (200mg - 400mg/Day) as add-on Therapy for Patients With Partial Onset Epilepsy Using a Flexible Dose-escalation Schedule and Individualized Maintenance Doses | Phase-4 | NCT01235403 | 2018 |
| NA | Observational | Epilepsy | 190 | NA | Neuropsychiatric Correlates of Psychogenic Movement Disorder and Non-Epileptic Seizure | NA | NCT00255411 | 2017 |

| Drug | Mode of administration | Disease | Enrollment | Allocation/Intervention model/Masking | Official Title of the study | Status | Clinical trial | Year |
|---|---|---|---|---|---|---|---|---|
| Levetiracetam 250 mg/ Levetiracetam 500 mg/ Placebo | Interventional | Epilepsy | 352 | Randomized/ Parallel Assignment/ Triple (ParticipantCare ProviderOutcomes Assessor) | A Double-blind, Randomized, Placebo-controlled 5 Parallel Groups, Confirmatory Trial on the Efficacy and Safety of Levetiracetam Used as add-on Therapy at Doses of 0.5 to 3 g/Day in Patients From 16 to 65 Years With Epilepsy With Partial Onset Seizures Under Treatment With 1 to 3 Anti-epileptic Drug(s) | Phase-3 | NCT00280696 | 2015 |
| Lacosamide | Interventional | Epilepsy | 461 | Non-Randomized/ Parallel Assignment/ None (Open Label) | An Open-Label, Multicenter, Multinational Study of Lacosamide as First Add-On Anti-epileptic Drug (AED) Treatment in Subjects With Partial-Onset Seizures | Phase-4 | NCT00955357 | 2018 |
| NA | Observational | Epilepsy | 175 | NA | Antiseizure Medication-Induced Elevation of Serum Estradiol and Reproductive Dysfunction in Men With Epilepsy | NA | NCT00179426 | 2017 |
| figure-of-eight active rTMS coil | Interventional | Epilepsy | 11 | Randomized/Crossover Assignment/Triple (Participant Care ProviderOutcomes Assessor | Multimodal Image-guided Repetitive Transcranial Magnetic Stimulation (rTMS) in the Treatment of Refractory Partial Epilepsy. | NA | NCT01745952 | 2023 |
| NA | Observational | Epilepsy | 38 | Cohort | Positron Emission Tomography Measurement of Neuroinflammation in Focal Epilepsy | NA | NCT01663545 | 2018 |
| Auricular acupuncture | Interventional | Epilepsy | 29 | N/A/ Single Group Assignment/ None (Open Label) | Auricular Acupuncture For The Treatment Of Non-Epileptic Seizures | NA | NCT01919307 | 2018 |
| Electroencephalogram (EEG) and visual evaluation | Observational | Epilepsy | 100 | Case-Control | Clinical Validation of Criteria for Identification of Epileptiform Electroencephalography | NA | NCT03533374 | 2020 |

| Drug | Mode of administration | Disease | Enrollment | Allocation/Intervention model/Masking | Official Title of the study | Status | Clinical trial | Year |
|---|---|---|---|---|---|---|---|---|
| | | | | | Discharges in Sensor Space and Source Space | | | |
| Project UPLIFT | Interventional | Epilepsy | 8 | Randomized/ Parallel Assignment/ None (Open Label) | The Feasibility of Project UPLIFT for the Treatment of Psychogenic Non-Epileptic Seizures | NA | NCT03329703 | 2021 |
| NA | Observational | Epilepsy | 97 | Case-Only | Epidemiologic Follow Up Study of Newly Diagnosed Epilepsy Among Seniors From Different Ethnic Groups | NA | NCT01351727 | 2017 |
| MRI | Interventional | Epilepsy | 78 | N/A/ Single Group Assignment/ None (Open Label) | Usefulness of Sodium MRI in the Presurgical Assessment of Drug-resistant Partial Epilepsy | NA | NCT02304029 | 2022 |
| Trigeminal Nerve Stimulation | Interventional | Epilepsy | 50 | Randomized/ Parallel Assignment/ Quadruple | Randomized Double Blind Study of External Trigeminal Nerve Stimulation for Intractable Epilepsy | Phase-2 | NCT01159431 | 2013 |
| FruitiVits | Interventional | Epilepsy | 11 | N/A/ Single Group Assignment/ None (Open Label) | A Taste and Acceptance Study of FruitiVits, for Use in the Dietary Management of Young Children Requiring Very Restrictive Diets Such as the Ketogenic Diet. | NA | NCT02229318 | 2019 |
| Collection of patient data | Observational | Epilepsy | 200 | Cohort | Epileptic Seizures in Intensive Care Units | NA | NCT03860467 | 2022 |
| Dexmedetomidine | Interventional | Epilepsy | 16 | N/A/ Single Group Assignment/ None (Open Label) | The Pharmacokinetics and Pharmacodynamics of Dexmedetomidine in Patients With Seizure Disorders | Phase-1 | NCT01116700 | 2013 |

## 11. SURGICAL TREATMENT OF EPILEPSY

When seizures are disruptive to quality of life and are not controlled with the best medical care, surgery should be considered. However, quantifying these issues has been challenging, which is presumably justified given that intractability involves more than just continuous seizures. While some people with refractory seizures are only mildly impaired, others find that their lives are significantly impacted by rare bouts. Some people have had surgery that has entirely cured them, yet they may still be crippled and unable to work. If seizures are still uncontrolled after two trials of high-dose monotherapy with two suitable AEDs and one trial of combination therapy, few people benefit from additional medical treatment. There are currently few absolute prohibitions to epilepsy surgery. Surgery might be a wise choice if a treatable brain issue underlies the seizure's origin [75,80].

## 12. CONCLUSION AND FUTURE DIRECTION

The beginning section of our review articles gives a complete introduction to epilepsy, covering its aetiology, pathophysiology, histology, biomarkers, therapy, symptoms, and classification. Although pharmaceutical remedies take some time to work and don't have any side effects, our research shows that they finish the body's restoration. Additional randomised controlled study has to be done to understand more about how to treat epilepsy. Epilepsy research is something we intend to keep doing. With the help of our colleagues, a second study integrating counselling will be conducted in our nation or state to evaluate the physical and mental well-being of patients and to provide a more in-depth understanding of epilepsy and its enhanced treatment.

## CONSENT AND ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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