Chapter 11

A General Overview of Epilepsy: its Classification, and Management

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Abstract

Epilepsy is one of the most common neurological disorders, with about 50 new cases per 100,000 people each year. It affects roughly 1% of the population and one-third of patients have refractory seizures. About 75% of patients present in childhood, reflecting the growing susceptibility of the developing brain to seizures. The classification of seizures is determined by their onset and can be divided into four types: focal, generalized, unknown or unclassifiable. The latest classification elaborates the basic categorization system previously described, extending the "motor" and "non-motor" groupings to include all three types of seizures (focal, generalized, and unknown).

Epilepsy is a difficult diagnosis with no simple, attainable gold standard. The key to diagnosis is a comprehensive history and reliable eyewitness account. Because no single symptom or sign is specific to epilepsy, determining whether a seizure has occurred is based on a combination of signs and symptoms. The primary treatment for diagnosed patients is administration of anti-seizure medications. The aim is to protect the individual from adverse effects that could potentially endanger the individual's standard of living and to terminate seizures immediately.

Epilepsy is a treatable condition; 80% of patients remain seizure-free and almost 50% remain seizure-free even after treatment is stopped. With more than 20 drugs used in treatment, it is possible to obtain effective treatment at rates close to 70% of diagnosed individuals. With this review we wrote, we aimed to summarize this very broad subject with recent articles.

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Background and definitions

A "seizure" is a paroxysmal change in neurologic function induced by the brain's excessive, hypersynchronous discharge of neurons[1]. The term "epileptic seizure" refers to a seizure induced by aberrant neuronal firing as opposed to a non-epileptic event, such as a photogenic seizure[2]. The disorder known as "epilepsy" is characterized by recurring, unprovoked seizures[3]. A seizure caused by reversibl insult (eg. Fever, hypoglycemia) does not qualify as epilepsy because it is a temporary secondary diseases rather than a chronic condition[4].

Epilepsy is one of the most prevalent neurologic disorders, with roughly 50 new cases per 100.000 people each year. Epilepsy affects roughly 1% of the population, and one-third of the patients have refractory epilepsy (seizures that are not controlled by two or more appropriately chose antiepileptic medications or other therapy).[5]

Approximately 75% of epilepsy originated in childhood, reflecting the developing brain's increased susceptibility to seiiuzres[6]. The term "epilepsy syndrome" refers to a combination of clinical characteristics that occur together on a continuous basis, such as comparable seizure types(s), age of onset, and response to antiepileptic drug (AEDs). The broad phase "seizure disorder" should be avoided[7].

Wirrell et al. outline in detail the methods used by the International League Against Epileptic (ILAE) Nosology and Definitions Taskforce (2017-2021) in defining epileptic syndromes and classifying them by age of onset[8]. An epilepsy syndrome is characterized by a distinct set of clinical and electroencephalographic (EEG) symptoms, which are frequently accompanied by particular etiological findings (structural, genetic, metabolic, immunological, and infections). A syndrome diagnosis in a person with epilepsy typically has prognostic and treatment consequences, syndromes frequently have age-dependent manifestations and a variety of unique comorbidities, a conditions has a "variable age" of onset if it can begin in both 18-year-old and 19-year-old (i.e., in both juvenile and adult patients)[9].

The ILAE defines epilepsy as any of the following conditions: (1) the occurrence of at least two unprovoked (or reflex) seizures that are more than 24 hours apart; (2) the occurrence of one unprovoked (or reflex) seizure with a possibility of subsequent seizures comparable to the general recurrence risk (at least 60%) after two unprovoked seizures that occur within the next ten yea4rs; and (3) the diagn0osi of an epilepsy syndorm[10].

The beginning of seizures might be focal (in one hemisphere of the brain). Generalized (in both hemisphere at the same time), or unknown. Active epilepsy is defined as the use of antiepileptic drugs on a regular basis or when the most recent seizure happened during the last 5 years. Status epilepticus (SE) is an epileptic episode that lasts long enough or is repeated at shout enough intervals to cause an epileptic condition. Depending on the kind and duration of the seizures, SE might have long-term repercussions such as neuronal injury or death, as well as changes in the neuronal networks. A new SE diagnostic categorization was recently developed and it will be seen in the last parts of this chapter[11].

Sudden Unexpected Death in Epilepsy (SUDEP) is a phenomenon characterized by sudden, unforeseen, and non-traumatic death in individuals with epilepsy, whether observed or not, and with or without evidence of a seizure. This definition excludes documented status epilepticus and requires that postmortem examination reveals no toxicological or anatomical cause of death[12].

Epidemiology and pathophysiology

The prevalence of epilepsy varies greatly across nations, based on the geographical distribution of risk and etiologic variables, the number of seizures upon diagnosis, and whether active epilepsy (active prevalence) or cases in remission (lifetime prevalence) is include. According to the Fiest et al. the total lifetime prevalence of epilepsy was 7.60 per 1,000 population (95%) confidence interval [CI] 6.17-9.38) and was greater in LMIC 98.75 per 1,000; the median point prevalence of active epilepsy was 6.68 (95% CI 5.45-8.10), while in HIC, it was 5.49 (4.16-7.26)[1314].

According to the sex, men have somewhat higher incidence and prevalence of epilepsy than women. The difference might be because the most common risk factors are more or less common in different places, or because women in some place hide the disease for social and cultural reasons[15].

Epilepsy is more common in the youngest and oldest age groups, with estimates of 86 per 100,000 per year in a well-defined population in the first year of life (figure 1), dropping to about 23-31 per 100,000 in people aged 30-59 years, and then going up to 180 per 100,000 in the over 85 age group. Epilepsy is most common in children in their first of life. By the end of age 10, the number of children with epilepsy drops to the same level as adults[16].

The most common type of seizure in both children and adults is a focal seizure. About 36% of all people who have seizures have a focal decreased

awareness seizure this is the most common type of focal seizure. In most LMIC, however, generalized tonic-colonic seizures are by far the most common type. The rate of SE has been found to range from 6.8 to 41 per 100,000 people per year, with peaks in children younger than 1 year and older people[17].

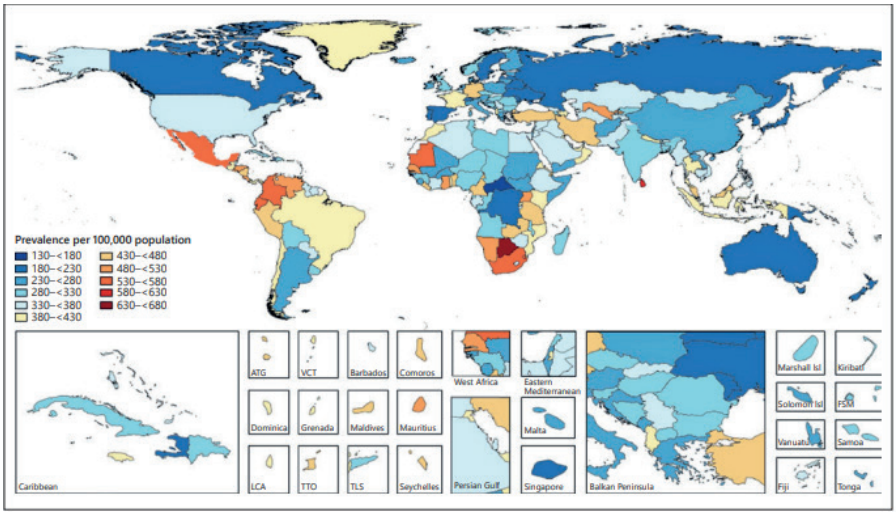


Figure 1: Age related prevalence per 100,000 of idiopathic epilepsy by country, 2016 form global burden of diseases 2016

Seizures happen when neurons in a part of the brain or the whole brain fire at the same time n a way that is not normal. This can happen when networks are not put together right or when there is a structural, infections, or metabolic problem. Most seizures in children are caused by genetics, injuries that happen before or during birth, or problems with how the brain develops. Common causes of seizures in people who do not have genetic predisposition of epilepsy include encephalitis/meningitis, traumatic brain injury, and brain tumors (figure 2). Epilepsy in older people is generally caused by neurodegenerative disorders, head injuries, or brain tumors. Because the causes of epilepsy are different for different age groups, the frequency of epilepsy is bimodal, with generic and developmental causes peaking in childhood and accumulated brain damage (such as from trauma or tumors) peaking in the elderly. It is important to know that the cause of about half of all seizures is unknown[18].

Etiologies of Epilepsy by Age

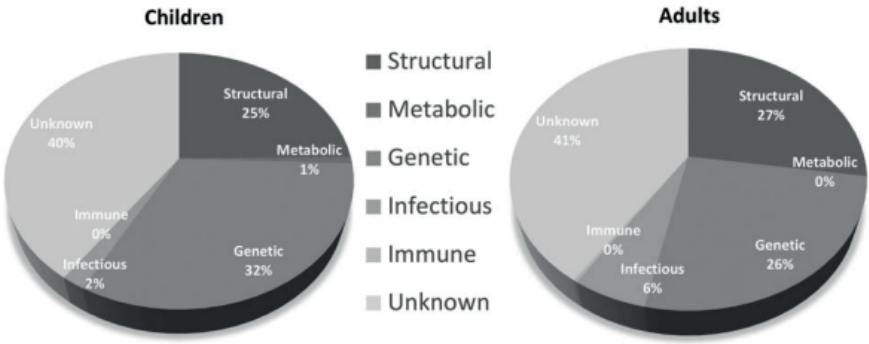


Figure 2: Etiologies of epilepsy according to the age by ILAE

The condition known as epilepsy is distinguished by an atypical synchronization of firing among clusters of neurons, which arises form an in-equilibrium in the neurotransmission on excitatory and inhibitory signals, historically, epilepsy research has been primarily focused on the neurological aspects of the conditon. In the past twenty years, there has been a significant increase in research regarding the function of glial cells in regulating and altering neuronal activity. This has resulted in compelling evidence supporting the involvement of glial cells in the development of epilepsy[19].

Classification of seizure and epilepsy

Basic classification

The categorization of seizures is determined by their initiation and can be classified into four types: focal, generalized, unknown, or unclassifiable, as presented in Table 1. The term "focal" can be considered as a synonym for the previously used term "partial." The term "generalized" has remained unaltered. A seizure of generalized onset is characterized by the simultaneous activation of both hemispheres, which may exhibit asymmetry, at the onset of the seizure, as determined by behavioral and electroencephalographic observations. The term "unknown onset" pertains to a scenario wherein the onset remains unidentified, while other indications are recognized. Further elaboration is provided below. The category of "Unclassified" persists, although its usage may diminish with the inclusion of novel seizure types and the "unknown onset" classification. There exist a limited number of occurrences that are unequivocally seizures, yet they cannot be categorized[20].

Table 1: International League Against Epilepsy 2017 basic classification of seizures.

Focal seizure	**Generalized onset**	**Unknown**
Aware Impaired awareness Motor onset Non-motor onst Focal to bilateral tonic-clonic	Motor • Tonic-clonic • Other motor Non-motor absence	Motor • Tonic-clonic • Other motor Non-motor absence Unclassified

Expanded classification

The extended categorization system elaborates on the fundamental categorization system delineated earlier, by extending the "motor" and "non-motor" groupings to encompass all three types of seizures (focal, generalized, and unknown), as presented in tables 2 and 3.

Table 2: ILAE 2017 expanded classification of seizures

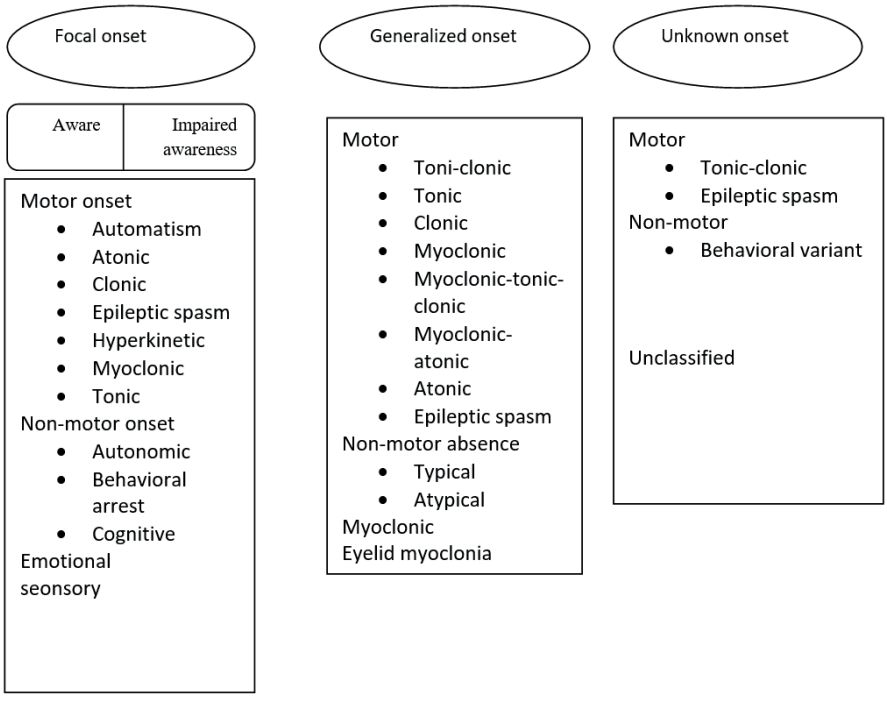
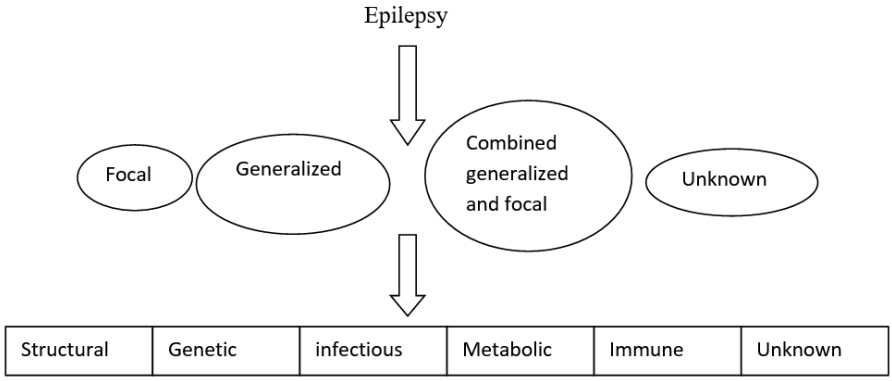


Table 3: The 2017 ILAE classifications of the Epilepsies



Epilepsy syndrome

Etiology

The revised categorization of epilepsy offers a tripartite diagnostic structure that underscores the significance of etiological factors throughout all phases. The initial step involves the delineation of the seizure classification. The second category pertains to epilepsy classification, encompassing focal, generalized, combined focal and generalized, and epilepsy of unknown etiology. The third aspect pertains to the diagnosis of the epilepsy syndrome. The classification of etiological categories, which holds significant implications for management, encompasses structural, genetic, infectious, metabolic, immune, and unknown factors[21].

Diagnostic evaluation

Epilepsy is a difficult diagnosis that lacks a simple, obtainable gold standard. The key to diagnosis is a thorough history and a credible eyewitness narrative, because no single symptom or sign is distinctive to epilepsy, the determination of whether a seizure has occurred or not is based on a combination of symptoms and signs. Epilepsy is polymorphic with numerous presentations and a wide range of mimics, which adds to its complexity. Always rule out non-epileptic paroxysmal occurrences because epilepsy misdiagnoses are frequent and can have negative effects. The most frequent syncope presentation is a brief loss of consciousness, and the most significant epileptic mimics are those caused by psychogenic or functions factors. All people who may be having seizure should be given electrocardiogram, especially if they also have a brief loss of consciousness. Epilepsy is not defined by an abnormal electroencephalogram (EEG), but

inter-ictal epileptiform discharges may support a clinical diagnosis. Finding the likely type of epilepsy (focal or generalized), diagnosing and epileptic syndrome, and determining the likelihood of recurrence are all made easier by an abnormal EEG. Long-term video-EEG monitoring may be able to provide a conclusive diagnosis in patients who still have diagnostic challenges following clinical evaluation and standard EEG, particularly if the episode frequency is high[22].

The history and neurological examination serve as the fundamental basis for the diagnosis of seizures and epilepsy, while laboratory testing is utilized as supplementary measures. The historical features that are significant include the clinical setting in which the seizure took place, which encompasses premonitory indications, as well as the seizure's specific characteristics, such as phenomenology, responsiveness, focal features, and the post-ictal state. Subsequent inquiry is directed towards ascertaining the presence of an epilepsy syndrome, which serves to delineate the nature and extent of the assessment, as well as to establish the appropriate course of treatment and prognosis.

The neurological exam evaluates localized indications that may implicate or locate cerebral disease. Increased tone on one side of the body, for example, could suggest pathology in the contralateral hemisphere, such us cortical dysplasia. A general physical examination is also necessary to assess whether or not the patient has an underlying ailment. Atypical skin marks, for example cough suggest a neurocutanous illness characterized by epilepsy, such as tuberous sclerosis or neurofibromatosis[23].

Electroencephalogram (EEG): an EEG is a recording of the electrical activity of the brain. It is capable of detecting aberrant electrical activity such as focal spikes or waves (which are compatible with focal epilepsy) or diffuse bilateral spike waves (which are consistent with generalized epilepsy). Because the prevalance of epileptiform abnormalities changes in the distinct states of consciousness, routine EEG should cover wakefulness, drowsiness, and sleep. Hyperventilation and photic stimulation are EEG activation procedures used to increase the yield of epileptic activity. The clinical information is used to make and epilepsy diagnosis and the EEG should be considered confirming rather than diagnostic. The conventional wisdom is to "treat the patient, not the EEG." Absence epilepsy is an exception to this rule, as brief generalized bursts of spike-wave activity, even if not linked with evident clinical alterations, indicate a significant likelihood of unreported absence seizure recurrences[24].

Metabolic evaluation: seizures are frequently associated with other anomalies in metabolic diseases, such as developmental delay, unexpected vomiting, or unconsciousness. A metabolic study is required in neonatal convulsions, including a screening of serum amino acids and urine organic acids, as well as blood lactate to rule out mitochondrial dysfunctions. Cerebrospinal fluid can examine for glucose transporter abnormalities (LUT1 deficient syndrome) in addition to its more usual usage to evaluate CNS illness.

Immunology: The identification of encephalopathies and epilepsies that were previously unknown has been made possible by the discovery of neuronal antibodies. The prevalence of autoimmune epilepsy is currently uncertain; however, it seems to affect a considerable proportion of patients with focal epilepsy. The most commonly observed etiologies of encephalitis are antibodies directed against glutamic acid decarboxylase (GAD)-65, LGI1, CASPR2, and NMDA receptors. This is particularly true when the initial assessment fails to reveal an underlying cause and the patient presents with symptoms or indications of limbic encephalitis. Diagnostic indicators include cognitive decline, personality changes, autonomic seizures, dyskinesia, comorbid autoimmune conditions, and mesial temporal MRI alterations that may potentially progress to mesial temporal sclerosis.

Imaging: The predominant modality for imaging is magnetic resonance imaging (MRI), which discloses epileptogenic lesions in nearly 20% of recently diagnosed epilepsy patients and over 50% of those with drug-resistant focal epilepsy. In contrast to individuals without an MRI lesion, those with an MRI lesion exhibit a greater likelihood of recurrence following a first seizure or persistent seizure activity after treatment. The MRI protocol necessitates the incorporation of volumetric T1-weighted imaging in three dimensions with a minimum slice thickness of 1mm. Additionally, the protocol must include axial and coronal T2-weighted and fluid attenuated inversion recovery sequences, which should encompass hippocampal angulation. Furthermore, the protocol should comprise axial hemosiderin or calcification-sensitive T2 sequences or susceptibility-weighted sequences.

Epileptic syndromes

The contemporary classification system has incorporated the epilepsy syndrome as a novel component. The term refers to a constellation of symptoms that typically co-occur, encompassing various types of seizures, electroencephalogram (EEG) readings, and imaging results. Epilepsy syndrome is influenced by various factors such as age of onset, remission,

triggers, diurnal variation, intellectual and psychiatric dysfunction, EEG findings, imaging studies, familial history, and genetic predisposition. The International League Against Epilepsy (ILAE) has not officially categorized a comprehensive list of epileptic syndromes. Nevertheless, recognized and established syndromes have been delineated and a selection of them is examined herein. For a comprehensive inventory of epilepsy syndromes, it is recommended to consult the website of the International League Against Epilepsy (ILAE). In the past, the term "benign" was utilized to classify certain epilepsy syndromes. However, this terminology is no longer favored as it suggests that the epilepsy has negligible effects on the patient. Presently, it is acknowledged that all types of epilepsy can have social implications and may be linked to comorbidities such as psychiatric and learning disorders. Presently, the phrase "self-limiting" is employed.

Idiopathic or Genetic Generalized Epilepsy Syndromes:

The category of idiopathic generalized epilepsies encompasses various types of seizures, including childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and generalized tonic-clonic seizures occurring in isolation (as presented in table 4). The utilization of the term idiopathic in the classification of epilepsy has been a subject of controversy, with some advocating for its removal. The term "idiopathic" was originally coined to connote a self-originating or genetically determined condition. There exists a concern regarding the use of the term "genetic" as it may connote inheritance, while a significant proportion of epilepsy patients exhibit de novo mutation or complex genetic syndromes that may manifest with or without environmental exposure. The ILAE task force has resolved to maintain the usage of the term "idiopathic generalized epilepsy" to denote the epilepsies mentioned earlier, owing to the preference of a significant number of stakeholders in the epilepsy domain to retain its usage. In cases where a clinician has identified a specific genetic cause, the term "genetic generalized epilepsy" may be employed to characterize the epilepsy syndrome. Patients diagnosed with idiopathic generalized epilepsies exhibit typical electrographic background and generalized spike-wave patterns in their EEGs.

Childhood absence epilepsy is a condition that is known to be self-limiting and has a higher incidence rate in neurologically normal females as compared to males. Onset of the condition is commonly observed to manifest between the ages of 4 and 10, while remission is typically observed to occur during the period of adolescence. Patients exhibit episodes of absence seizures and occasionally experience tonic-clonic generalized seizures. The premature

manifestation of generalized tonic-clonic seizures is linked to a poorer prognosis.[27].

Juvenile absence epilepsy manifests during the period of adolescence and early adulthood, with the most favorable age of onset ranging from 10 to 13 years. Both genders are equally affected by absence seizures, although these occur less frequently in childhood than absence epilepsy. At the outset of the presentation, there is a manifestation of generalized tonic-clonic seizures, and albeit infrequent, myoclonic seizures may also transpire. In contrast to infantile absence epilepsy, the aforementioned syndrome is not characterized by a self-limiting course.

One of the most prevalent epilepsy syndromes is juvenile myoclonic epilepsy, the onset period spans from before the age of 10 through the middle of the 20s, and occasionally later. Women are more likely than men to develop juvenile myoclonic epilepsy[28]. Every patient experiences myoclonic seizures, which are frequently followed by generalized tonic-cloni seizures. Rarely do absence seizures happen, most patients don't go into spontaneous remission and need to take antiepileptic drugs for the rest of their lives.

The hallmark of piously with generalized tonic-clonic seizures only is characterized by generalized tonic-clonic seizures that occur within an age range spanning from childhood to mid-adulthood, with a peak onset typically observed during the second decade of life. The term "generalized tonic-clonic seizures at awakening" was initially used, but was later revised upon the recognition that seizures could occur at any point during the day. Generalized tonic-clonic seizures in epilepsy, as well as juvenile absence epilepsy and juvenile myoclonic epilepsy, are not inherently self-limiting conditions. As a result, individuals with these forms of epilepsy often require lifelong treatment with antiepileptic medication.[29].

Tabel 4: Idiopathic or Genetic Epilepsy Syndromes

Epilepsy Syndrome	Seizure types	Age of onset	Self-limiting	EEG findings
Childhood Absence Epilepsy	Absence generalized tonic-clonic seizure (rare)	4 to 10 years	Yes	Normal background, occipital intermittent rhythmic delta activity, 3-3.5Hz generalized spike wave discharges
Juvenile Absence Epilepsy	Absence generalized tonic-clonic seizure, myoclonic (rare)	adolescence to early adulthood	No	Normal background, polyspikes may be present, -3.5Hz generalized spike wave discharges
juvenile Myoclonic Absence	myoclonic, generalized tonic-clonic, absence (rare	10 years to mid-20s	No	Normal background, -3.5Hz generalized spike wave discharges, > 4Hz generalized spike wave discharges, high amplitude polyspike wave discharges with myoclonic seizures, photoparoxysmal response in up to 40% of patients
Epilepsy with generalized tonic-clonic seizures alone	generalized tonic-clonic	childhood to mid-adulthood	No	Normal background, generalized, spike or polyspike wave discharges,

Focal Epilepsy Syndromes

Focal epilepsy disorders such as childhood epilepsy with centro-temporal spikes and Panayiotopoulos syndrome have been extensively documented. Formerly, the condition known as childhood epilepsy was referred to as benign epilepsy with centro-temporal spikes (as presented in Table 5). Childhood epilepsy with centro-temporal spikes is a type of epilepsy that is self-limited. It typically presents during the school years and is characterized by short focal motor hemifacial seizures and nocturnal focal motor seizures that eventually develop into bilateral tonic-clonic seizures. The occurrence of centro-temporal spikes during sleep is in accordance with the electroencephalogram (EEG) background. Panayiotopoulos syndrome is a type of self-limited epilepsy that is distinguished by focal autonomic seizures that are often prolonged, as well as focal occipital high-amplitude sleep-

activated spikes on the electroencephalogram (EEG). Possible autonomic symptoms include vomiting, pallor, mydriasis, as well as symptoms related to the digestive, respiratory, and thermoregulatory systems. Additionally, incontinence and hypersalivation may also be observed.

Reflex Epilepsy Syndromes:

Reflex epilepsy syndromes refer to a type of epilepsy in which the occurrence of seizures is triggered by a specific stimulus. Whilst generalized tonic-clonic seizures are the most commonly occurring type of seizure, it is important to note that other types of generalized seizures may also manifest. Focal seizures may occasionally present as reflex epilepsy. The most commonly occurring reflex epilepsy syndromes are those that are triggered by photosensitivity. Two additional types of epilepsy that fall under the category of reflex epilepsy are reading epilepsy and startle epilepsy[30].

Table 5: Examples of epilepsy syndromes according to age of onset:

Neonatal

- Benign familial neonatal epilepsy (BFNE)

Infancy

- West syndrome
- Dravet syndrome

Childhood

- Generalized epilepsy with febrile seizures plus (GEFS+)
- Childhood absence epilepsy
- Lennox-Gastaut syndrome
- Landau-Kleffner syndrome

Adolescence and adulthood

- Juvenile myoclonus epilepsy

Disorders that mimic epilepsy

According to their clinical presentation or medical history, many paroxysmal behaviors resemble epileptic seizures. Here, a few of the more typical illnesses are mentioned, it is critical to distinguish between epileptic and non-epileptic behaviors since some non-epileptic phenomenon can be treated with drugs other than EDs and others only need reassurance or avoidance of the situationsthattrigger the spell[31].

Non-epileptic Seizures (NES): NES are episodic changes in motor function or behavior that bear resemblance to epileptic seizures, but do not exhibit any corresponding electroencephalogram (EEG) activity. These events are commonly referred to as psychogenic seizures or pseudo-seizures, as they differ from epileptic seizures. The condition known as NES has the potential to cause significant impairment and is often associated with underlying psychopathological conditions. The manifestation of the medical condition, namely seizure, is a genuine occurrence. However, as abnormal neural discharges are not involved, the primary objective of therapy is to target the fundamental psychological issues. This statement provides reassurance to both the patient and their family.

Breath-Holding Spells (BHS): BHS are not voluntary responses but rather involuntary reflexes, despite their name. BHS are at their peak in preschoolers and are often gone by the time children reach the school age. There are two subtypes of BHS: cyanotic and pallid. Cyanotic BHS is also referred to as cyanotic infantile syncope, while pallid BHS is often referred to as reflex anoxic seizures. Anger and irritation are two of the most prominent triggers for cyanotic BHS, which is the more prevalent form. Thee kid will stop breathing (in expiration), get cyanotic, and lose consciousness while they are weeping, whichisthedefining characteristics of this conditon. A pallid BHS is more prone to become agitated in response to a frightening experience or an unpleasant stimulation (such as a minor form of trauma). After a gasp, the patient will experience loss of consciousness, as well as pallor, bradycardia, diaphoresis, and limpness. Neither a type of BHS is associated with and increased predisposition to epilepsy, although seizure activity can occur at the end of a BHS.

*Syncope: H*istory is generally enough to tell the difference between syncope (fainting) and an epileptic seizure. Lightheadedness, blurred vision, pallor, nausea, and diaphoresis are all possible pre-attack warning indicators (presyncopal symptoms). Loss of consciousness and a gradual descent to the ground follow these wringing sings, in contrast to the sudden collapse seen in myoclonic and atonic seizures. When compared to the extended postictal state that follows and epileptic seizure, consciousness returns relatively quickly. Syncope is caused by a temporary drop in blood flow to the brain. This can be caused by an irregular heartbeat (arrhythmia) a condition called orthostasis or Valsalva, or a vasovagal response (fear, pain, or mental upset).

Parasomnias: are problems with sleep that can look like seizures. Night terrors are a common parasomnia that happens to kids between the ages of 18 months and 8 years. In early (non-REM) sleep, the child wakes up

screaming, sweating, and moving his or her arms and legs out of sync. The children then goes back to sleep and doesn't remember what happened. Night terrors are often passed down from generation to generation. The case history is use to make the diagnosis; video-EEG is rarely needed. Nightmares which happen during REM sleep, and nighttime epileptic seizures that start in the frontal lobe are the main things that make a diagnosis difficulty.

General approach of epilepsy management

The primary mode of treatment for individuals diagnosed with epilepsy involves the administration of anti-seizure medications. The objective is to promptly terminate seizures while avoiding any adverse effects that may potentially compromise the individual's standard of living. By utilizing a pharmacological arsenal comprising over 20 medications, it is possible to achieve effective treatment in up to 70% of individuals who have received a recent diagnosis of epilepsy[32]. Pharmaceutical agents employed in the management of epilepsy function by impeding neuronal depolarization through the blockade of sodium or calcium channels, augmenting the activity of potassium channels, inhibiting glutamate-mediated neuronal excitation, or enhancing the inhibitory effects of gamma-aminobutyric acid (GABA) on neuronal activity. The efficacy of medications varies depending on the underlying etiology as they operate through distinct mechanisms. Patients with idiopathic conditions are more likely to experience improvement, particularly if their developmental and neurological assessments yield normal results[33]. The selection of a particular seizure medication by a neurologist is contingent upon various factors such as the nature of the seizure, the age of the patient, and the coexistence of other medical ailments. Furthermore, the potential adverse effects of the intervention should be taken into consideration. Oftentimes, a medication with a wide range of efficacy is employed due to the possibility of an insufficient description of a seizure provided by a witness. Levetiracetam has become increasingly favored as a primary treatment option in recent times owing to its effectiveness, convenient dosage adjustment, and established adverse effects profile. In the past, carbamazepine was the favored therapeutic option for focal seizures, whereas valproic acid was the preferred treatment for generalized seizures.

Typically, it is advisable to administer an initial modest dosage of medication in order to mitigate the likelihood of adverse effects. In the event of a need for escalation, incremental dosages may be administered at predetermined intervals. The aim is to effectively control seizures while utilizing the minimum feasible dosage. A trial that is deemed appropriate entails a duration of two months during which a therapeutic dosage is

administered and well-tolerated.[34]. The possibility of increased toxicity resulting from drug interactions is a potential concern in combination therapy. Nevertheless, specific combinations, such as lamotrigine and valproic acid, have demonstrated notable efficacy in treating generalized seizures (refer to table 6). The central nervous system (CNS) adverse effects are a common occurrence among anticonvulsant drugs, owing to their respective mechanisms of action. As an illustration, drowsiness is a prevalent unfavorable outcome of almost all antiepileptic drugs (refer to table 7). Certain medical practitioners may consider the possibility of discontinuing a particular medication in the event that seizures have not manifested for a minimum duration of two years. In cases where medication proves to be ineffective in managing seizures, alternative options such as dietary therapy (ketogenic diet), epilepsy surgery (lesionectomy, hemispherotomy), and palliative epilepsy surgery (stimulation therapy,callosotomy) may be considered[35]. Modifying one's lifestyle is an essential element of the management of epilepsy. Improving epilepsy outcome can be achieved through the optimization of sleep, enhancement of medication adherence, and minimization of stress. Ultimately, it is imperative that individuals in good health advocate for those who are experiencing digestive wellness. Individuals diagnosed with epilepsy encounter considerable obstacles to achieving a typical way of life as a result of the negative attitudes and prejudicial treatment they encounter.

Table 6: Range of efficacy and chose of Antiepileptic Drugs

Antiepileptic Drug	Focal seizures	Generalized tonic-clonic seizures	generalized absence seizures	generalized myoclonic seizures	Lennox-Gastaut syndrome/Infantile spasm/ Dravetsyndorme
Phenobarbital	Class 1 trial	Suggested, but not proven in Class 1 trails	Not effective	Class 1V evidence	
Phenytoin	Class 1 trial	Suggested, but not proven in Class 1 trails	Not effective	Not effective	
Carbamazepine	Class 1 trial	Suggested, but not proven in Class 1 trails	Not effective	Not effective	
Oxcarbazepine	Class 1 trial	Unknown	Not effective	Not effective	
Eslicarbazepine acetate	Class 1 trial	Unknown	Not effective	Not effective	
Valproate	Class 1 trial	Suggested, but not proven in Class 1 trails	Class 1 trial	Suggested, but not proven in Class 1 trails	Suggested, but not proven in Class 1 trails
Ethosuzimide	Not effective	Not effective	Class 1 trial	Not effective	Class 1 trial Lennox-Gastaut syndrome
Clobazam	Suggested, but not proven in Class 1 trails	Suggested, but not proven in Class 1 trails	Suggested, but not proven in Class 1 trails	Suggested, but not proven in Class 1 trails	Class 1 trial Lennox-Gastaut syndrome
Felbamate	Class 1 trial	Suggested, but not proven in Class 1 trails	Unknown	Unknown	
Gabapentin	Class 1 trial	Not effective	Not effective	Not effective	
Pregabalin	Class 1 trial	Not effective	Not effective	Not effective	
Lamotrigine	Class 1 trial	Class 1 trial	Suggested, but not proven in Class 1 trials	Variable	Class 1 trial Lennox-Gastaut syndrome
Topiramate	Class 1 trial	Class 1 trial	Not effective in Class 1 trial	Unknown	Class 1 trial Lennox-Gastaut syndrome
Tiagabine	Class 1 trial	Not effective	Not effective	Not effective	
Levetiracetam	Class 1 trial	Class 1 trial	Suggested, but not proven in Class 1 trials	Class 1 trial	
Brivaracetam	Class 1 trial	Unknown	Unknown	Unknown	

Zonisamide	Class 1 trial	Suggested, but not proven in Class 1 trails	Suggested, but not proven in Class 1 trials	Suggested, but not proven in Class 1 trials	
Lacosamide	Class 1 trial	Unknown	Not effective	Not effective	
Vigabatrin	Class 1 trial	Not effective	Not effective	Not effective	Class 1 trial Infantile Spasm
Rufinamide	Class 1 trial, but not FDA approved	Suggested, but not proven in Class 1 trails	Unknown	Unknown	Class 1 trial Lennox-Gastaut syndrome
Perampanel	Class 1 trial	Class 1 trial	Unknown	Class IV evidence	
Cannabidiol	Class IV evidence	Unknown	Unknown	Unknown	Class 1 trial Lennox-Gastaut syndrome/ Infantile Spasm

Table 7: Pharmacokinetic aspects of Antiepileptic Drugs

Antiepileptic drug	Oral bioavailability	Protein binding[a]	Metabolism	Half-life[b]	Drug interaction
Phenobarbital	Good	Low	>70%	Long	High
Phenytoin	Variable	High	Extensive not linear	Intermediate (long with toxicity)	High
Carbamazepine	Good	Intermediate	Extensive	Intermediate	High
Oxcarbazepine	Good	Low	Extensive	Short	Moderate
Eslicarbazepine acetate	Good	Low	~40%	Intermediate	Moderate
Valproate	Good	High	Extensive	Intermediate	High
Ethosuzimide	Good	Low	Extensive	Long	Moderate
Clobazam	Good	High	Extensive	Intermediate	High
Felbamate	Good	Low	~50%	Intermediate	High
Gabapentin	Low	Low	None	Short	No/minimal
Pregabalin	Good	Low	None	Short	No/minimal
Lamotrigine	Good	intermediate	Extensive	Intermediate	Moderate
Topiramate	Good	Low	~30%	Intermediate	No/minimal
Tiagabine	Good	High	Extensive	Short	High
Levetiracetam	Good	Low	~30% non-hepatic	Short	No/minimal
Brivaracetam	Good	Low	Extensive	Short	Moderate
Zonisamide	Good	Low	~65%	Short	Moderate
Lacosamide	Good	Low	~60%	Intermediate	No/minimal
Vigabatrin	Good	Low	None	Intermediate	No/minimal
Rufinamide	Good	intermediate	Extensive	Short	Moderate
Perampanel	Good	High	Extensive	Long	Moderate
Cannabidiol	Low	High	Extensive	Long	HIgh

[a] Low: <50%; intermediate: 50% to 85%; high: >85%.

[b] Short: <10 hours; intermediate: 10 to 30 hours; long: >30 hours.

Status Epilepticus

Status epilepticus (SE) is considered to be one of the most critical neurological emergencies. It is characterized by prolonged or recurrent seizures that do not allow the individual to fully return to their baseline state. Based on estimates, there exists a range of 10-40 cases and a corresponding mortality rate per 100,000 individuals, approximately 20% of whom experience a return to previous levels of functionality at a rate of only one-third.[36].

In 2015, the ILAE Task Force on Classification of Status Epilepticus emphasized the significance of timing in the assessment of seizures. The International League Against Epilepsy (ILAE) introduced two operational dimensions that pertain to the duration of a seizure. These dimensions are defined by the period of epileptic activity that may lead to permanent brain damage with long-term consequences, and the duration beyond which a seizure should be identified as unusually prolonged. According to findings from studies conducted on both animals and humans, it has been projected that the anticipated time intervals for convulsive tonic-clonic status epilepticus (SE) are 5 minutes and 30 minutes, correspondingly. The available data on non-convulsive status epilepticus (NCSE) is limited as most studies have primarily focused on convulsive forms. However, the International League Against Epilepsy (ILAE) has recommended time points of 10 minutes (t1) and 60 minutes (t2) for focal status epilepticus with impaired consciousness[37].

The extant guidelines and protocols for the management of status epilepticus (SE) prescribe specific timing recommendations for each line of therapy. These recommendations stipulate that first-line treatment should be administered within the initial 10 minutes of seizure activity, second-line treatment within the initial 20 minutes, and third-line treatment should be considered if SE persists despite the administration of at least two anti-seizure medications (ASM) with optimal dosing within the initial 60 minutes. Several studies and meta-analyses have concurred that there exist systematic delays in the treatment of SE when compared to the recommended guidelines (refer to Table 8).

Current guidelines recommend several pharmacological treatments for SE. initial administration of benzodiazepines recommend occurs in the earliest prehospital phases of seizures, in the early phase of an established SE, anticonvulsant medications are administered intravenously (IV) after hospital admission (table 9a and 9b). If IV ASM administration fails to control refractory seizures, general anesthesia is administered, such as by

IV infusion of midazolam, propofol, or ketamine. Continuous infusion of anesthetics is administered until the seizure subsidies and is continued for 12-24 hours after the last seizure. If SE persists or recurs despite the use of anesthetic for at least 24 hours, it is defined as super-refractory SE (SRSE)[38].

Table 8: General approach of Status epilepticus management

	General Measures	Medications
Immediate Management (0-5 minutes)	➢ Note the time, call for help ➢ Secure airway (semi-prone position, nasopharyngeal airway), give oxygen ➢ IV cannulation, finger glucose, blood gas, LFT, RFT, electrolytes, AED levels, CRP ➢ History: past medications, overdose and drug addiction	➢ Observe prehospital treatment ➢ Give thymine if suspected of Alcohol excess ➢ Dextrose infusion if hypoglycemic ➢ Benzodiazepines for IV preparations
Early Status Epilepticus (5-20 minutes)	➢ Monitoring vital signs ➢ Cardiac monitoring ➢ ICU possibility	give benzodiazepines if no response repeat after 5 minutes
Established Status Epilepticus (20-40 minutes)	➢ ICU review ➢ chest x ray ➢ CT head ➢ Consider intubation	Give 2nd line AEDs ➢ Phenytoin/ Fosphenytoin ➢ Sodium valproate ➢ Levetiracetam
Refractory Status Epilepticus (>30 mins)	➢ Intubate and admit ICU ➢ continuous EEG monitoring	Anesthetic agents like (Thiopental, propofol, midazolam)

Table 9: Doses of first-line and second-line ASM for SE

Table 9a: Benzodiazepines as first-line in SE

Intravenous	Non-intravenous
Lorazepam 0.1mg/kg (max 4mg)	Midazolam IM/IN/buccal 10mg 5mg in elderly or <40kg
Diazepam 0.15-2mg/kg (max 10mg)	Diazepam 10mg rectal 5mg in elderly or <40kg
Clonazepam 0.015mg/kg (max 1mg)	Lorazepam intranasal 0.1mg/kg or <40kg

Table 9b: Second line of ASMs in SE

Drug	Dose; Rate, Maximum	Suggestion	Caution
Phenytoin/ Fosphenytion	20mg/kg 50g/min (2000mg)	Already taking phenytoin. Suspected poor adherence	• significant hypotension • bradycardia, heart block • Porphyria • generalized Epilepsy • Overdose of recreation drugs or antidepressants
Valproate	30mg/kg 10mg/kg/min (3000mg)	Already taking Valproate. Suspected poor adherence generalized epilepsy	• women of childbearing age • pre-existing of liver disease or pancreatitis • known metabolic disorder • caution in acute stroke or brain injury
Levetiracetam	60mg/kg 6mg/kg/min (4500mg)	Already taking Levetiracetam, Suspected poor adherence	• acute or brain injury • known mood/behavioral disorder • renal impairment

Women and epilepsy

The occurrence of seizures and the administration of antiepileptic medications have the potential to interfere with hormone regulation, thereby posing a threat to the sexual and reproductive well-being of women diagnosed with epilepsy. Women diagnosed with epilepsy encounter social stigmatization in several developing nations. According to a study conducted by Komolafe et al. (2012), the economic status of WWE in Nigeria is comparatively lower than that of non-epileptic women.[39]. According to Santosh et al. (2007), a significant proportion of individuals with epilepsy in India concealed their condition from their prospective spouses due to apprehension of social ostracism and the possibility of disrupted marriage negotiations. Specifically, over 50% of individuals with epilepsy who participated in the study reported hiding their condition prior to marriage[40]. Women with epilepsy typically experience a higher frequency of seizures during periods of hormonal fluctuations such as puberty, menstruation, pregnancy, and menopause. Catamenial epilepsy exacerbates seizures during menstruation in females with epilepsy. The prevalence of catamenial epilepsy among women with epilepsy (WWE) ranges from 33% to 50%. The works cited are those of Foldvary-Schaefer and Falcone (2003) and Morrell (1999).[41]. The

prevalence of menstruation issues in WWE was found to be 2.5 times higher than that of the general population. The occurrence of epilepsy in relation to the menstrual cycle, known as catamenial epilepsy, has been found to have a correlation with the varying levels of hormones, particularly estrogen and progesterone. It has been observed that progesterone exhibits anticonvulsant properties while estrogen has proconvulsant effects. The condition known as catamenial epilepsy exhibits three discernible patterns of heightened seizure frequency, namely C1 (perimenstrual pattern), C2 (perovulatory pattern), and C3 (luteal pattern). C1 takes place in the follicular phase, which spans from day 4 to day 10 of the menstrual cycle. C2 occurs during the ovulatory phase, which takes place from day 10 to day 14 of the cycle. Finally, C3 occurs in the luteal phase, which spans from day 17 to day 3 of the menstrual cycle. According to research conducted by Harden and Pennell (2013) and Reddy, the levels of progesterone exhibit a decline during phases C1 and C3, whereas estrogen levels experience an increase during phase C2[42]. Antiepileptic drugs (AEDs) have the potential to impact or bear resemblance to the menstrual cycle. Seizures have the potential to induce disturbances in neuroendocrine activity, resulting in menstrual irregularities in women with epilepsy, as well as serving as an adverse reaction of antiepileptic drugs. An increasing body of evidence suggests that the utilization of valproate among females is associated with a higher likelihood of encountering menstrual irregularities, such as polycystic ovarian syndrome (PCOS). According to Johnston and Crawford (2014), there exist bidirectional pharmacokinetic interactions between oral contraceptives and AEDs. There exist a number of antiepileptic drugs (AEDs) that are recognized for their ability to induce cytochrome activity, specifically within the CYP3A4 group. Such drugs include carbamazepine, oxcarbazepine, topiramate, phenobarbitone, and phenytoin[43]. The cytochromes play a role in the metabolic process of the primary constituents of the combined oral contraceptive pill, namely estrogen and progesterone. Hence, the effectiveness and efficacy of oral contraceptive pills (OCPs) could be reduced when co-administered with cytochrome-inducing antiepileptic drugs (AEDs).

According to Harden et al. (2009a), a significant proportion of women with epilepsy (WWE) do not experience any alteration in seizure activity during gestation compared to their pre-pregnancy baseline. This finding is noteworthy as WWE often express apprehension regarding the efficacy of seizure management during pregnancy. Given that AEDs are excreted in breast milk in minimal quantities, it is commonly accepted that breastfeeding while taking AEDs is a safe practice. According to the National Institute for Health and Care Excellence (2012), it is recommended to administer vitamin

K intravenously to neonates born to mothers undergoing antiepileptic drug (AED) therapy for women with epilepsy (WWE).[44]

Prognosis

From a demographic perspective, the majority of individuals with epilepsy exhibit a positive prognosis. The likelihood of recurrence following an initial seizure is subject to significant variability contingent upon whether the seizure was characterized by acute and symptomatic features or occurred spontaneously. In contrast to single unprovoked seizures, acute symptomatic seizures exhibit a comparatively lower recurrence rate of approximately 19% over a decade According to Beghi's (2003) findings, the aggregate likelihood of recurrence subsequent to an initial unprovoked seizure varies between 23 and 71%. Two factors that have a high likelihood of predicting return are the presence of a known cause and an atypical EEG pattern, characterized by epileptiform and/or slow activity[45].

Epilepsy is a treatable conditon, with up to 80% of people having long times without seizures and up to 50% of people still not having seizure after treatment stops. Patients with unexplained or cryptogenic first seizures have shown that there is a link between having seizures again and having them in the past. Only in LMIC, where most people with epilepsy don't get treatment (the treatment gab is between 70 and 94%), can be the outcome of untreated epilepsy be determined. The cause of epilepsy is the best prediction of whether or not seizures will happen again, in a well-defined US community, people with symptomatic epilepsy had a much lower chance of remission after 5 years than those with idiopathic epilepsy (42 vs. 30% at 15 years), and people with neurological dysfunction at birth had the lowest change of remission. Type of seizure and EEG epileptiform changes were also used to predict the outcome. Europe also had lower remission rates for people with symptomatic epilepsy[46]. The chance of dying from epilepsy is low, but when incidence and prevalence studies area compared, mortality rates are likely to be different. When epilepsy or seizures cause death, some of the most important causes are SUDEP, SE, accidental injury, and suicide.

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