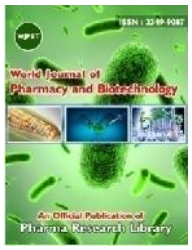
World Journal of Pharmacy and Biotechnology

Journal Home Page: www.pharmaresearchlibrary.com/wjpbt



Review Article Open Access

A Review on Epilepsy

B. Kumar*, G. Divya, M. Gobinath

Department of Pharmacy Practice, Ratnam Institute of Pharmacy, Pidthapolur, Nellore, A.P, India

A B S T R A C T

Epilepsy is intermingled with the history of human existence, defined as a brain disorder characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The brain is involved in nearly every bodily function, including the higher cortical functions. If the affected cortical network is in the visual cortex, the clinical manifestations are visual phenomena. The pathophysiology of focal-onset seizures differs from the mechanisms underlying generalized-onset seizures. Overall, cellular excitability is increased, but the mechanisms of synchronization appear to substantially differ between these 2 types of seizure, Alcohol may cause seizures either by direct intoxication or by withdrawal.

Keywords: epilepsy, Seizures, brain, Predisposition.

A R T I C L E I N F O

CONTENTS

Article History: Received 19 September 2015, **Accepted** 28 October 2015, **Available Online** 29 December 2015

***Corresponding Author**
B. Kumar
Department of Pharmacy Practice,
Ratnam Institute of Pharmacy, Nellore.
Manuscript ID: WJPBT2831

PAPER-QR CODE

Citation: B. Kumar, *et al.* A Review on Epilepsy. *W. J. Pharm. Biotech.*, 2015, 2(2): 62-71.

1. Introduction

The history of epilepsy is intermingled with the history of human existence; the first reports on epilepsy can be traced back to the Assyrian texts, almost 2,000 B.C. Most importantly in the ancient Greek medical texts of the Hippocratic collection. For example, Hippocrates in his book on Sacred Disease described the first neurosurgery procedure referring that craniotomy should be performed at the opposite side of the brain of the seizures, in order to spare patients from “phlegma” that caused the disease . However, it was not until the 18th and 19th century, when medicine made important advances and research on epilepsy was emancipated from religious superstitions such as the fact that epilepsy was a divine punishment or possession. At the beginning of the 18th century, the view

that epilepsy was an idiopathic disease deriving from brain and other inner organs prevailed. One should mention the important work in this field by William Culen (1710–1790) and Samuel A. Tissot whose work set the base of modern epileptology describing accurately various types of epilepsies.

Definition

Epilepsy is defined as a brain disorder characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition.

Classification

I. Focal seizures (Older term: partial seizures)

- **A. Simple partial seizures – consciousness is not impaired**
  1. With motor signs**.**
  2. With sensory symptoms.
  3. With autonomic symptoms or signs.
  4. With psychic symptoms**.**
- **B. Complex partial seizures – consciousness is impaired**
  1. Simple partial onset, followed by impairment of consciousness
  2. With impairment of consciousness at onset.
- **C. Partial seizures evolving to secondarily generalized seizures.**
  1. Simple partial seizures evolving to generalized seizures
  2. Complex partial seizures evolving to generalized seizures

3 Simple partial seizures evolving to complex partial seizures evolving to generalized seizures

II. Generalized seizures

- A. Absence seizures (Older term: petit mal)
  1. Typical absence seizures
  2. Atypical absence seizures
- B. Myoclonic seizures
- C. Clonic seizures
- D. Tonic Seizures.
- E. Tonic–clonic seizures (Older term: grand mal)
- F. Atonic seizures

Pathophysiology

Seizures are paroxysmal manifestations of the electrical properties of the cerebral cortex. A seizure results when a sudden imbalance occurs between the excitatory and inhibitory forces within the network of cortical neurons in favor of a sudden-onset net excitation. The brain is involved in nearly every bodily function, including the higher cortical functions. If the affected cortical network is in the visual cortex, the clinical manifestations are visual phenomena. Other affected areas of primary cortex give rise to sensory, gustatory, or motor manifestations. The psychic phenomenon of déjà-vu occurs when the temporal lobe is involved. The pathophysiology of focal-onset seizures differs from the mechanisms underlying generalized-onset seizures. Overall, cellular excitability is increased, but the mechanisms of synchronization appear to substantially differ between these 2 types of seizure.

Pathophysiology of focal seizures

The electroencephalographic (EEG) hallmark of focal-onset seizures is the focal interictal epileptic form spike or sharp wave. The cellular neurophysiologic correlate of an interictal focal epileptic form discharge in single cortical neurons is the paroxysmal depolarization shift (PDS). The PDS is characterized by a prolonged calcium-dependent depolarization that results in multiple sodium-mediated action potentials during the depolarization phase, and it is followed by a prominent after-hyperpolarization, which is a hyperpolarized membrane potential beyond the baseline resting potential. Calcium-dependent potassium channels mostly mediate the after-hyperpolarization phase. When multiple neurons fire PDSs in a synchronous manner, the extracellular field recording shows an interictal spike. If the number of discharging neurons is more than several million, they can usually be recorded with scalp EEG electrodes. Calculations show that the interictal spikes need to spread to about 6 cm^2 of cerebral cortex before they can be detected with scalp electrodes. Several factors may be associated with the transition from an interictal spike to an epileptic seizure. The spike has to recruit more neural tissue to become a seizure. When any of the mechanisms that underlie an acute seizure becomes a permanent alteration, the person presumably develops a propensity for recurrent seizures (ie, epilepsy).

The following mechanisms (discussed below) may coexist in different combinations to cause focal-onset seizures:

- Decreased inhibition
- Defective activation of gamma-aminobutyric acid (GABA) neurons

Increased activation: If the mechanisms leading to a net increased excitability become permanent alterations, patients may develop pharmacologically intractable focal-onset epilepsy. Currently available medications were screened using acute models of focal-onset or generalized-onset convulsions. In clinical use, these agents are most effective at blocking the propagation of a seizure (i.e. spread from the epileptic focus to secondary generalized tonic-clonic seizures). Further understanding of the mechanisms that permanently increase network excitability may lead to development of true antiepileptic drugs that alter the natural history of epilepsy.

Decreased inhibition:

The release of GABA from the interneuron terminal inhibits the postsynaptic neuron by means of 2 mechanisms: (1) direct induction of an inhibitory postsynaptic potential (IPSP), which a GABA-A chloride current typically mediates, and (2) indirect inhibition of the release of excitatory neurotransmitter in the pre-synaptic afferent projection, typically with GABA-B potassium current. Alterations or mutations in the different chloride or potassium channel subunits or in the molecules that regulate their function may affect the seizure threshold or the propensity for recurrent seizures.

Mechanisms leading to decreased inhibition include the following:

- Defective GABA-A inhibition
- Defective GABA-B inhibition
- Defective activation of GABA neurons

- Defective intracellular buffering of calcium
- Normal GABA-A inhibitory function

GABA is the main inhibitory neurotransmitter in the brain, and it binds primarily to 2 major classes of receptors: GABA-A and GABA-B. GABA-A receptors are coupled to chloride (negative anion) channels, and they are one of the main targets modulated by the anticonvulsant agents that are currently in clinical use. The reversal potential of chloride is about negative 70 mV. The contribution of chloride channels during resting potential in neurons is minimal, because the typical resting potential is near -70 mV, and thus there is no significant electromotive force for net chloride flux. However, chloride currents become more important at more depolarized membrane potentials. These channels make it difficult to achieve the threshold membrane potential necessary for an action potential.

The influence of chloride currents on the neuronal membrane potential increases as the neuron becomes more depolarized by the summation of the excitatory postsynaptic potentials (EPSPs). In this manner, the chloride currents become another force that must be overcome to fire an action potential, decreasing excitability. Properties of the chloride channels associated with the GABA-A receptor are often clinically modulated by using benzodiazepines (eg, diazepam, lorazepam, clonazepam), barbiturates (eg, phenobarbital, pentobarbital), or topiramate. Benzodiazepines increase the frequency of openings of chloride channels, whereas barbiturates increase the duration of openings of these channels. Topiramate also increases the frequency of channel openings, but it binds to a site different from the benzodiazepine-receptor site. Alterations in the normal state of the chloride channels may increase the membrane permeability and conductance of chloride ions. In the end, the behavior of all individual chloride channels sum up to form a large chloride-mediated hyperpolarizing current that counterbalances the depolarizing currents created by the summation of EPSPs induced by activation of the excitatory input. The EPSPs are the main form of communication between neurons, and the release of the excitatory amino acid glutamate from the pre-synaptic element mediates EPSPs. Three main receptors mediate the effect of glutamate in the postsynaptic neuron: N -methyl-D-aspartic acid (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)/kainate, and metabotropic. These are coupled by means of different mechanisms to several depolarizing channels. IPSPs temper the effects of EPSPs. IPSPs are mediated mainly by the release of GABA in the synaptic cleft with postsynaptic activation of GABA-A receptors.

All channels in the nervous system are subject to modulation by several mechanisms, such as phosphorylation and, possibly, a change in the tridimensional conformation of a protein in the channel. The chloride channel has several phosphorylation sites, one of which topiramate appears to modulate. Phosphorylation of this channel induces a change in normal electrophysiologic behavior, with an increased frequency of channel openings but for only certain chloride channels.

Defective GABA-A inhibition:

Some epilepsies may involve mutations or lack of expression of the different GABA-A receptor complex subunits, the molecules that govern their assembly, or the molecules that modulate their electrical properties. Changes in the distribution of subunits of the GABA-A receptor complex have been demonstrated in several animal models of focal-onset epilepsy, such as the electrical-kindling, chemical-kindling, and pilocarpine models. In the pilocarpine model, decreased concentrations of mRNA for the alpha 5 subunit of the surviving interneurons were observed in the CA1 region of the rat hippocampus.

Defective GABA-B inhibition:

The GABA-B receptor is coupled to potassium channels, forming a current that has a relatively long duration of action compared with the chloride current evoked by activation of the GABA-A receptor. Because of the long duration of action, alterations in the GABA-B receptor are thought to possibly play a major role in the transition between the interictal abnormality and an interictal event (ie, focal-onset seizure). The molecular structure of the GABA-B receptor complex consists of 2 subunits with 7 trans-membrane domains each. G proteins, a second messenger system, mediate coupling to the potassium channel, explaining the latency and long duration of the response. In many cases, GABA-B receptors are located in the pre-synaptic element of an excitatory projection.

Defective activation of GABA neurons

GABA neurons are activated by means of feed forward and feedback projections from excitatory neurons. These 2 types of inhibition in a neuronal network are defined on the basis of the time of activation of the GABAergic neuron relative to that of the principal neuronal output of the network, as seen with the hippocampal pyramidal CA1 cell.

In feed forward inhibition, GABAergic cells receive a collateral projection from the main afferent projection that activates the CA1 neurons, namely, the Schaffer collateral axons from the CA3 pyramidal neurons. This feedforward projection activates the soma of GABAergic neurons before or simultaneously with activation of the apical dendrites of the CA1 pyramidal neurons. Activation of the GABAergic neurons results in an IPSP that inhibits the soma or axon hillock of the CA1 pyramidal neurons almost simultaneously with the passive propagation of the excitatory potential (ie, EPSP) from the apical dendrites to the axon hillock. The feedforward projection thus primes the inhibitory system in a manner that allows it to inhibit, in a timely fashion, the pyramidal cell's depolarization and firing of an action potential.

Feedback inhibition is another system that allows GABAergic cells to control repetitive firing in principal neurons, such as pyramidal cells, and to inhibit the surrounding pyramidal cells. Recurrent collaterals from the pyramidal neurons activate the GABAergic neurons after the pyramidal neurons fire an action potential. Experimental evidence has indicated that some other kind of interneuron may be a gate between the principal neurons and the GABAergic neurons. In the dentate gyrus, the mossy cells of the hilar polymorphic region appear to gate inhibitory

tone and activate GABAergic neurons. The mossy cells receive both feedback and feed forward activation, which they convey to the GABAergic neurons.

In certain circumstances, the mossy cells appear highly vulnerable to seizure-related neuronal loss. After some of the mossy cells are lost, activation of GABAergic neurons is impaired. Synaptic reorganization is a form of brain plasticity induced by neuronal loss, perhaps triggered by the loss of the synaptic connections of the dying neuron, a process called differentiation. Formation of new sprouted circuits includes excitatory and inhibitory cells, and both forms of sprouting have been demonstrated in many animal models of focal-onset epilepsy and in humans with intractable temporal-lobe epilepsy. Most of the initial attempts of hippocampal sprouting are likely to be attempts to restore inhibition. As the epilepsy progresses, however, the overwhelming number of sprouted synaptic contacts occurs with excitatory targets, creating recurrent excitatory circuitries that permanently alter the balance between excitatory and inhibitory tone in the hippocampal network.

Defective intracellular buffering of calcium:

In rodents, recurrent seizures induced by a variety of methods result in a pattern of interneuron loss in the hilar polymorphic region, with striking loss of the neurons that lack the calcium-binding proteins parvalbumin and calbindin. In rat hippocampal sections, these interneurons demonstrate a progressive inability to maintain a hyperpolarized resting membrane potential; eventually, the interneurons die.

Increased activation Mechanisms leading to increased excitation include the following:

- Increased activation of NMDA receptors
- Increased synchrony between neurons due to ephaptic interactions
- Increased synchrony and/or activation due to recurrent excitatory collaterals

Increased activation of NMDA receptors:

Glutamate is the major excitatory neurotransmitter in the brain. The release of glutamate causes an EPSP in the postsynaptic neuron by activating the glutaminergic receptors AMPA/kainate and NMDA and the metabotropic receptor. Fast neurotransmission is achieved with the activation of the first 2 types of receptors. The metabotropic receptor alters cellular excitability by means of a second-messenger system with later onset but a prolonged duration. Calcium is a catalyst for many intracellular reactions that lead to changes in phosphorylation and gene expression. Thus, it is in itself a second-messenger system. NMDA receptors are generally assumed to be associated with learning and memory. The activation of NMDA receptors is increased in several animal models of epilepsy, such as kindling, kainic acid, pilocarpine, and other focal-onset epilepsy models. Some patients with epilepsy may have an inherited predisposition for fast or long-lasting activation of NMDA channels that alters their seizure threshold. Other possible alterations include the ability of intracellular proteins to buffer calcium, increasing the vulnerability of neurons to any kind of injury that otherwise would not result in neuronal death.

Increased synchrony between neurons caused by ephaptic interactions:

Electrical fields created by synchronous activation of pyramidal neurons in laminar structures, such as the hippocampus, may increase further the excitability of neighboring neurons by nonsynaptic (ie, ephaptic) interactions. Changes in extracellular ionic concentrations of potassium and calcium are another possible nonsynaptic interaction, as is increased coupling of neurons due to permanent increases in the functional availability of gap junctions. This last may be a mechanism that predisposes to seizures or status epilepticus.

Increased synchrony and/or activation from recurrent excitatory collaterals:

Neuropathologic studies of patients with intractable focal-onset epilepsy have revealed frequent abnormalities in the limbic system, particularly in the hippocampal formation. A common lesion is hippocampal sclerosis, which consists of a pattern of gliosis and neuronal loss primarily affecting the hilar polymorphic region and the CA1 pyramidal region. These changes are associated with relative sparing of the CA2 pyramidal region and an intermediate severity of the lesion in the CA3 pyramidal region and dentate granule neurons. Recurrent excitatory collaterals have been demonstrated in human temporal lobe epilepsy and in all animal models of intractable focal-onset epilepsy. The effect of mossy-fiber sprouting on the hippocampal circuitry has been confirmed in computerized models of the epileptic hippocampus. Other neural pathways in the hippocampus, such as the projection from CA1 to the subiculum, have been shown to also remodel in the epileptic brain.

Pathophysiology of generalized seizures:

The best-understood example of the pathophysiologic mechanisms of generalized seizures is the thalamocortical interaction that may underlie typical absence seizures. The thalamocortical circuit has normal oscillatory rhythms, with periods of relatively increased excitation and periods of relatively increased inhibition. It generates the oscillations observed in sleep spindles. The thalamocortical circuitry includes the pyramidal neurons of the neocortex, the thalamic relay neurons, and the neurons in the nucleus reticularis of the thalamus (NRT). Altered thalamocortical rhythms may result in primary generalized-onset seizures. The thalamic relay neurons receive ascending inputs from the spinal cord and project to the neocortical pyramidal neurons. Cholinergic pathways from the forebrain and the ascending serotonergic, noradrenergic, and cholinergic brainstem pathways prominently regulate this circuitry.

The thalamic relay neurons can have oscillations in the resting membrane potential, which increases the probability of synchronous activation of the neocortical pyramidal neuron during depolarization and which significantly lowers the probability of neocortical activation during relative hyperpolarization. The key to these oscillations is the transient low-threshold calcium channel, also known as T-calcium current. In animal studies, inhibitory inputs from the NRT control the activity of thalamic relay neurons. NRT neurons are inhibitory and contain GABA as their

main neurotransmitter. They regulate the activation of the T-calcium channels in thalamic relay neurons, because those channels must be de-inactivated to open transitorily.

T-calcium channels have 3 functional states: open, closed, and inactivated. Calcium enters the cells when the T-calcium channels are open. Immediately after closing, the channel cannot open again until it reaches a state of inactivation. The thalamic relay neurons have GABA-B receptors in the cell body and receive tonic activation by GABA released from the NRT projection to the thalamic relay neuron. The result is a hyperpolarization that switches the T-calcium channels away from the inactive state into the closed state, which is ready for activation when needed. The switch to closed state permits the synchronous opening of a large population of the T-calcium channels every 100 milliseconds or so, creating the oscillations observed in the EEG recordings from the cerebral cortex. Findings in several animal models of absence seizures, such as lethargic mice, have demonstrated that GABA-B receptor antagonists suppress absence seizures, whereas GABA-B agonists worsen these seizures. Anticonvulsants that prevent absence seizures, such as valproic acid and ethosuximide, suppress the T-calcium current, blocking its channels. A clinical problem is that some anticonvulsants that increase GABA levels (eg, tiagabine, vigabatrin) are associated with an exacerbation of absence seizures. An increased GABA level is thought to increase the degree of synchronization of the thalamocortical circuit and to enlarge the pool of T-calcium channels available for activation.

Etiology:

A substantial number of cases, the cause of epilepsy remains unknown. Identified causes tend to vary with patient age. Inherited syndromes, congenital brain malformations, infection, and head trauma are leading causes in children. Head trauma is the most common known cause in young adults. Strokes, tumors, and head trauma become more frequent in middle age, with stroke becoming the most common cause in the elderly, along with Alzheimer disease and other degenerative conditions. The genetic contribution to seizure disorders is not completely understood, but at the present time, hundreds of genes have been shown to cause or predispose individuals to seizure disorders of various types. Seizures are frequently seen in patients that are referred to a genetics clinic. In some cases, the seizures are isolated in an otherwise normal child. In many cases, seizures are part of a syndrome that may also include intellectual disability, specific brain malformations, or a host of multiple congenital anomalies. For the sake of brevity and clarity, genetic disorders that can cause seizures will be broken into the following categories:

Syndromes in which seizures are common Chromosomal deletion or duplication syndromes that causes seizures

Metabolic diseases mitochondrial diseases:

Genetic syndromes with seizure disorder:

A number of genetic syndromes are known to causes seizures; therefore, this list is not meant to be authoritative. However, a number of more common syndromes should be considered in the patient who presents with seizures and other findings.

Angelman syndrome: Angelman syndrome is an inherited disorder that is most frequently (68%) caused by a deletion in the maternally inherited region of chromosome 15q11.2-q13. Approximately 7% of cases are caused by paternal disomy of the same region. An additional 11% of cases of Angelman syndrome are due to sequence variants in the maternally inherited UBE3A gene. Patients with Angelman syndrome generally have a normal prenatal and birth history, with the first evidence of developmental delay occurring between 6 and 12 months of age. Seizures occur in over 80% of patients with Angelman syndrome, with onset before age 3 years. Patients generally have deceleration of head growth, resulting in microcephaly by early childhood. Dysmorphic facies are typical and include a protruding tongue, prognathia, and a wide mouth with widely-spaced teeth. Patients with a deletion also have hypopigmentation. Intellectual impairments are typically severe and speech impairment is quite severe, with most patients having few or no words. Patients also have ataxia and frequent laughter with a happy demeanor.

Rett syndrome:

Rett syndrome in its classical form is caused by mutations in the MECP2 gene, although other similar forms caused by different genes are described. Additionally, although Rett syndrome has generally been described only in female patients (with the supposition that this would be a lethal disease in males), rare cases have been described in males.

Seizures are reported in greater than 90% of females with Rett syndrome. Seizures may be of any type, but generalized tonic-clonic and complex partial seizures are the most common.

Pitt-Hopkins syndrome: Pitt-Hopkins syndrome is classically caused by mutations in the TCF4 gene, although several forms of Pitt-Hopkins–like syndrome have been described. Patients with Pitt-Hopkins syndrome have severe intellectual disability, microcephaly, and little or no speech. They also have an unusual breathing pattern characterized by intermittent hyperventilation followed by periods of apnea. Patients with Pitt-Hopkins also have distinctive facies, which may not be apparent in early childhood. These features include microcephaly with a coarse facial appearance, deeply set eyes, upslanting palpebral fissures, a broad and beaked nasal bridge with a downturned nasal tip, a wide mouth and fleshy lips, and widely spaced teeth. There is also a tendency toward prognathism. Seizures are seen in this syndrome, with one study reporting a frequency of 20%. Earlier studies suggested that around 50% of patients with Pitt-Hopkins have seizures.

Tuberous sclerosis: Tuberous sclerosis complex is caused by mutations in the TSC1 or TSC2 genes. Major features of this disease include the following:

Table 1: Major features of this disease include the following

Facial angiofibromata	Ungual or periungual fibromas
Hypopigmented macules	Connective tissue nevi
Retinal hamartomas	Cortical tubers
Subependymal nodules or	Cardiac rhabdomyomas

giant cell astrocytomas	
Lymphangiomyomatosis	Renal angiomyolipomas
Seizure disorders caused by single-gene mutations	

Epidemiology:

Hauser and collaborators demonstrated that the annual incidence of recurrent nonfebrile seizures in Olmsted County, Minnesota, was about 100 cases per 100,000 persons aged 0-1 year, 40 per 100,000 persons aged 39-40 years, and 140 per 100,000 persons aged 79-80 years. By the age of 75 years, the cumulative incidence of epilepsy is 3400 per 100,000 men (3.4%) and 2800 per 100,000 women (2.8%). Studies in several developed countries have shown incidences and prevalences of seizures similar to those in the United States. In some countries, parasitic infections account for an increased incidence of epilepsy and seizures

Diagnosis:

The diagnosis of epileptic seizures is made by analyzing the patient's detailed clinical history and by performing ancillary tests for confirmation. Physical examination helps in the diagnosis of specific epileptic syndromes that cause abnormal findings, such as dermatologic abnormalities (eg, patients with intractable generalized tonic-clonic seizures for years are likely to have injuries requiring stitches).

Testing:

Potentially useful laboratory tests for patients with suspected epileptic seizures include the following: Prolactin levels obtained shortly after a seizure to assess the etiology (epileptic vs non-epileptic) of a spell; levels are typically elevated 3- or 4-fold and more likely to occur with generalized tonic-clonic seizures than with other seizure types; however, the considerable variability of prolactin levels has precluded their routine clinical use Serum levels of anticonvulsant agents to determine baseline levels, potential toxicity, lack of efficacy, treatment noncompliance, and/or auto-induction or pharmacokinetic change CSF examination in patients with obtundation or in patients in whom meningitis or encephalitis is suspected .

Imaging studies The following 2 imaging studies must be performed after a seizure: Neuroimaging evaluation (eg, MRI, CT scanning)

EEG:

The clinical diagnosis can be confirmed by abnormalities on the interictal EEG, but these abnormalities could be present in otherwise healthy individuals, and their absence does not exclude the diagnosis of epilepsy. Video-EEG monitoring is the standard test for classifying the type of seizure or syndrome or to diagnose pseudoseizures (ie, to establish a definitive diagnosis of spells with impairment of consciousness). This technique is also used to characterize the type of seizure and epileptic syndrome to optimize pharmacologic treatment and for pre-surgical workup.

2. Treatment

The goal of treatment in patients with epileptic seizures is to achieve a seizure-free status without adverse effects. This goal is accomplished in more than 60% of patients who require treatment with anticonvulsants. Many patients experience adverse effects from these drugs, however, and some patients have seizures that are refractory to medical therapy. Monotherapy is desirable because it decreases the likelihood of adverse effects and avoids drug interactions. In addition, monotherapy may be less expensive than polytherapy, as many of the older anticonvulsant agents have hepatic enzyme–inducing properties that decrease the serum level of the concomitant drug, thereby increasing the required dose of the concomitant drug.

People with seizures experience psychosocial adjustments after their diagnosis; therefore, social and/or vocational rehabilitation may be needed. Many physicians underestimate the consequences that an epilepsy diagnosis may have on patients. For example, patients with epilepsy may live in fear of experiencing the next seizure, and they may be unable to drive or work at heights.

Class of Drugs Summary:

These agents prevent seizure recurrence and terminate clinical and electrical seizure activity. Anticonvulsants are normally reserved for patients who are at increased risk for recurrent seizures.

Carbamazepine (Tegretol, Tegretol XR, Carbatrol, Epitol, Equetro)

Carbamazepine is indicated for the management of partial seizures and generalized tonic-clonic seizures. It has an active metabolite, 10-11 epoxide, which has anticonvulsant activity and can be measured in the serum. This agent works by binding to voltage-dependent sodium channels and inhibiting the generation of action potentials. Serum carbamazepine levels should be measured frequently when initially starting this medication, with a goal of being seizure free. Like phenytoin, carbamazepine has been associated with osteopenia.

Clobazam (ONFI)

Clobazam is a 1,5-benzodiazepine that possesses potent anticonvulsant properties. Its mechanism of action is binding to the gamma-aminobutyric acid–A (GABA-A) receptor. This agent is thought to potentiate GABAergic neurotransmission. The active metabolite, N-demethylclobazam, is largely responsible for its long duration of action. Clobazam is indicated for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in patients older than 2 years.

Ethosuximide (Zarontin)

Ethosuximide is a succinimide antiepileptic drug (AED) that is effective only against absence seizures. It has no effect on generalized tonic-clonic, myoclonic, atonic, or partial seizures. The mechanism of action is based on reducing current in T-type calcium channels on thalamic neurons. The spike-and-wave pattern during petit mal seizures is thought to be initiated in thalamocortical relays by activation of these channels. Ethosuximide is available in large 250-mg capsules, which may be difficult for some children to swallow, and as a syrup (250 mg/5 mL). Blood levels should be measured 1-3 weeks after starting ethosuximide. The therapeutic concentration of ethosuximide is 40-100 mcg/mL. The major side effects of

the drug include nausea, vomiting, drowsiness, hyperactivity and sleep disturbance.

Ezogabine (Potiga): Ezogabine is a neuronal potassium channel opener that stabilizes neuronal KCNQ (Kv7) channels in the open position, increasing the stabilizing membrane current and preventing bursts of action potentials during the sustained depolarizations associated with seizures. It is indicated as adjunctive therapy in partial-onset seizures uncontrolled by current medications. Owing to the presence of potassium channels in the bladder, there is a small risk of urinary retention. In addition, in April 2013 the FDA issued a warning that ezogabine can cause skin discoloration and abnormalities of the eye characterized as changes in the pigment in the retina. Whether these changes are permanent and whether pigment changes in the retina have the potential to cause loss of vision are unknown.

The FDA recommends that all patients taking ezogabine undergo baseline and periodic eye examinations and discontinue the medication if changes are observed, unless there is no other treatment option. Skin discoloration most often appeared as blue around the lips and nail beds but was also reported to be widespread on the face and legs.In patients with skin discoloration, alternative treatments should be considered, but the FDA warns of serious and life-threatening reactions to the sudden discontinuance of the medication.

Felbamate (Felbatol):

Felbamate is approved by the FDA for medically refractory partial seizures and Lennox-Gastaut syndrome. This agent has multiple mechanisms of action, including (1) inhibition of N-methyl-D-aspartate (NMDA)–associated sodium channels, (2) potentiation of GABAergic activity, and (3) inhibition of voltage-sensitive sodium channels. Felbamate is used only as a drug of last resort in medically refractory cases because of the risk of aplastic anemia and hepatic toxicity, which necessitates regular blood tests.

Lamotrigine (Lamictal, Lamictal ODT, Lamictal XR): Lamotrigine, a triazine derivative, is an antiepileptic drug with a very broad spectrum of activity, like valproate. It is approved by the FDA for primary generalized and partial-onset epilepsy. Other indications include adjunctive therapy in the treatment of generalized seizures of Lennox-Gastaut syndrome, treatment of juvenile myoclonic epilepsy (JME) and maintenance treatment of bipolar I disorder. The mechanism of action is based on inhibiting the release of glutamate and voltage-sensitive sodium channels, leading to stabilization of the neuronal membrane. Lamotrigine is quickly absorbed when given orally, and 55% is bound to plasma proteins. The therapeutic serum levels have not been definitively established. Side effects of lamotrigine include rash and nausea. The dose has to be increased very slowly over several weeks to minimize the chance of rash, especially if the patient is on valproic acid. The risk of developing Stevens-Johnson syndrome, toxic epidermal necrolysis, and angioedema is 1 in 1000 adults and higher in children, but this risk is decreased with slower titration.

Levetiracetam (Keppra, Keppra XR):

Levetiracetam is indicated for adjunctive therapy in the treatment of primary generalized tonic-clonic seizures, JME, and partial-onset seizures in adults and children. The mechanism of action is thought to be through modulation of synaptic vesicle proteins. The metabolism of this drug is independent of the CYP450 system, which limits the potential for interaction with other antiepileptic drugs. Levetiracetam has a rapid onset of action and is well tolerated. Common side effects include fatigue, somnolence, dizziness, and irritability. This medication is available in oral (including extended-release) and intravenous formulations.

Phenytoin (Dilantin, Phenytek):

Phenytoin is used to treat patients with partial, generalized, or mixed seizures, such as the tonic-clonic (grand mal) type. This agent works by blocking voltage-dependent neuronal sodium channels. The therapeutic concentration range of phenytoin in serum is 10-20 mcg/mL for patients who have normal renal function and serum albumin levels.

The risk of osteopenia and cerebellar ataxia, both of which are long-term adverse effects associated with phenytoin, now temper the drug's use by neurologists. This agent is one of the most difficult AEDs to use because of its zero-order kinetics and narrow therapeutic index. In addition, it can have significant bidirectional drug interactions.

Primidone (Mysoline):

Primidone is indicated for the management of grand mal, psychomotor, and focal seizures. In addition, it is commonly used for benign familial tremors. When metabolized, primidone breaks down to phenobarbital, another active antiepileptic drug. Primidone decreases neuron excitability and increases the seizure threshold. Common side effects of this drug include sedation, drowsiness, fatigue, and depression.

Rufinamide (Banzel):

Rufinamide modulates sodium channel activity, particularly prolongation of the channel's inactive state. It significantly slows sodium channel recovery and limits sustained, repetitive firing of sodium-dependent action potentials. Rufinamide is indicated for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome. It is well tolerated, with the most common side effects being somnolence and vomiting.

Topiramate (Topamax):

Topiramate is an AED with a broad spectrum of antiepileptic activity. This agent is approved for generalized, primary generalized, tonic-clonic, and partial-onset seizures. Topiramate has multiple mechanisms of action, including state-dependent sodium channel–blocking action, enhancement of the inhibitory activity of the neurotransmitter GABA, and antagonism of the NMDA-glutamate receptor. It may block glutamate activity and is a weak carbonic anhydrase inhibitor. Weight loss, impaired cognition, and mood problems are common side effects of topiramate. The drug is also approved for migraine prevention.

Valproic acid (Depakote, Depakote ER, Depakene, Depacon, Stavzor): Valproate, a broad-spectrum AED, is effective against most seizure types, including myoclonic seizures. It can also be used alone or in combination for the

treatment of generalized or partial seizures. Valproate has multiple mechanisms of anticonvulsant action, including increasing GABA levels in the brain, as well as T-type calcium channel activity. The extended-release (ER) formulation allows for once-a-day administration. Valproate also has FDA approval for migraine prevention and prevention of mania in bipolar patients.

Zonisamide (Zonegran): Zonisamide has been studied extensively in Japan and Korea and seems to have broad-spectrum properties. It blocks T-type calcium channels, prolongs sodium channel inactivation, and is a carbonic anhydrase inhibitor. Dose adjustments may be required when zonisamide is given with other anticonvulsants, such as carbamazepine, phenytoin, and phenobarbital. The most common side effects of this drug include ataxia, anorexia, and fatigue.

Perampanel (Fycompa):

Perampanel is a noncompetitive antagonist of the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor. It is indicated as adjunct treatment for partial-onset seizures (with or without secondary generalized seizures) and for primary generalized tonic-clonic seizures in adults and children aged 12 years or older.

Lacosamide (Vimpat):

Lacosamide selectively enhances slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes and inhibition of repetitive neuronal firing. It is indicated as monotherapy or adjunctive therapy for partial-onset seizures.

Barbiturates:

Like benzodiazepines, barbiturates bind to the gamma-aminobutyric acid (GABA) receptor, enhancing the actions of GABA by extending GABA-mediated chloride channel openings and allowing neuronal hyper polarization. The principal barbiturate used for status epilepticus is phenobarbital; for refractory cases, pentobarbital is used.

Phenobarbital (Luminal):

Phenobarbital works at GABA receptors in the central nervous system (CNS) to potentiate CNS inhibition. This agent is the best-studied barbiturate for the treatment of status epilepticus. In status epilepticus, achieving therapeutic levels as quickly as possible is important. Intravenous dosing may require approximately 15 minutes to attain peak levels in the brain. To terminate generalized convulsive status epilepticus, administer up to 15-20 mg/kg. If the patient has received a benzodiazepine, the potential for respiratory suppression significantly increases. Ventilation and intubation may be necessary. Hypotension may require treatment. In status epilepticus, phenobarbital is generally used after phenytoin or fosphenytoin fails. However, it can be used in lieu of phenytoin in certain circumstances. A trend is to recommend agents other than phenobarbital (propofol, midazolam, other barbiturates) for refractory status epilepticus; however, for super-refractory status epilepticus, phenobarbital should be used.

Patient education:

To prevent injury, provide education about seizure precautions to patients who have lapses of consciousness during wakefulness and in whom seizures are suspected. Most accidents occur when patients have impaired consciousness. This is one of the reasons for restrictions on driving, swimming, taking unsupervised baths, working at significant heights, and the use of fire and power tools for people who have epileptic seizures and other spells of sudden-onset seizures. The restrictions differ for each patient because of the individual features of the seizures, the degree of seizure control, and, in the United States, state laws. Other countries have more permissive or more restrictive laws regarding driving. Check state driving laws before making recommendations.

Epilepsy Foundation of America has a large library of educational materials that are available to healthcare professionals and the general public. The American Epilepsy Society is a professional organization for people who take care of patients with epilepsy. Their Website provides a large amount of credible information.

Precipitating factors : Lack of sleep, sleep deprivation, especially it combine with alcohol is often trigger for primary generalized epilepsy

Alcohol may cause seizures either by direct intoxication or by withdrawal. Some patients with mild epilepsy will only have seizures after alcohol. Avoidance is the best treatment

Photosensitivity Some young people have seizures when exposed to either flashing light or repetitive visual pattern. This trigger is often suspected but is not particularly common seizures beginning discos, while playing computer games or watching television Watch television at minimum distance 2-3 metres, have a small screen, use remote control and have the contrast low.

In Pregnancy:

It is vital that you discuss your epilepsy before getting pregnant. Any change to drug treatment should be made before pregnancy. This may include train to stop the drugs altogether is possible. At the very least the lowest affective amount of medication should be used using long acting formulations and smaller frequent dose may reduce any risks. 90% of pregnancies in a epilepsy result in normal healthy babies but the risk of abnormalities is 2-3 times that in babies of mothers without epilepsy. Such abnormalities may be major or minor. Sodium valproate is associated with a 2% and carbanazepine 1% risk of spina bifida the older drugs are associated with risk of heart and palate malformation. The risk is greater if more than 1 drug is used

Folate: Folic acid 5 mg daily should be given to patients on phenytoin, phenobarbitone, valproate or carbamazepine or who have a family history of spina. All other patients should take folic acid 0.4 mg starting before pregnancy

During pregnancy:

In a quarter to a third of pregnancies seizures become more frequent. It is important to avoid generalized seizures that may harm the baby. Patients on valproate or carbamazepine need careful screening to detect spina bifida. Drug dosage should not be guided by drug levels but by clinical conditions

Breast feeding:

Most anti-epileptic drugs come out in the breast milk but only in the small amount that are not harmful counseling children and patients about epilepsy.

3. Conclusion

The social structure is changing in the developing countries. Industrial globalization, cultural mix and extensive migration, changing social norms, and economy-driven social attitudes have altered the differences between the developing and the developed world. Seizures are paroxysmal manifestations of the electrical properties of the cerebral cortex. The pathophysiology of focal-onset seizures differs from the mechanisms underlying generalized-onset seizures. The goal of treatment in patients with epileptic seizures is to achieve a seizure-free status without adverse effects. This goal is accomplished in more than 60% of patients who require treatment with anti epileptic drugs. Monotherapy is desirable because it decreases the likelihood of adverse effects and avoids drug interactions.

4. Reference

[1] Fisher RS, van Emde Boas W, Blume W, et al. Epileptic seizures and epilepsy: definitions proposed by the International League against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia. **2005** Apr. 46(4):470-2.

[2] Epilepsy surgery in childhood can protect memory. Medical News Today. November 14, **2014**.

[3] Skirrow C, Cross JH, Harrison S, Cormack F, Harkness W, Coleman R, et al. Temporal lobe surgery in childhood and neuroanatomical predictors of long-term declarative memory outcome. Brain. **2014** Nov 12.

[4] Goodkin HP. The founding of the American Epilepsy Society: 1936-1971. Epilepsia. **2007** Jan. 48(1):15-22.

[5] Rho JM, Sankar R, Cavazos JE. Epilepsy: Scientific Foundations of Clinical Practice. New York, NY: Marcel Dekker; **2004**.

[6] Kramer MA, Cash SS. Epilepsy as a disorder of cortical network organization. Neuroscientist. **2012** Aug. 18(4):360-72.

[7] Houser CR, Esclapez M. Vulnerability and plasticity of the GABA system in the pilocarpine model of spontaneous recurrent seizures. Epilepsy *Res*. **1996** Dec. 26(1):207-18.

[8] Sloviter RS. Status epilepticus-induced neuronal injury and network reorganization. Epilepsia. **1999**. 40(suppl 1):S34-9; discussion S40-1.

[9] Scharfman HE, Schwartzkroin PA. Protection of dentate hilar cells from prolonged stimulation by intracellular calcium chelation. Science. **1989** Oct 13. 246(4927):257-60.

[10] Cavazos JE, Das I, Sutula TP. Neuronal loss induced in limbic pathways by kindling: evidence for induction of hippocampal sclerosis by repeated brief seizures. J Neurosci. **1994** May. 14(5 pt 2): 3106-21.

[11] Sutula T, Cascino G, Cavazos J, et al. Mossy fiber synaptic reorganization in the epileptic human temporal lobe. Ann Neurol. 1989 Sep. 26(3):321-30.

[12] Mastrangelo M, Leuzzi V. Genes of early-onset epileptic encephalopathies: from genotype to phenotype. Pediatr Neurol. **2012** Jan. 46(1):24-31.

[13] McCormick DA. Cellular mechanisms underlying cholinergic and noradrenergic modulation of neuronal firing mode in the cat and guinea pig dorsal lateral geniculate nucleus. J Neurosci. **1992** Jan. 12(1):278-89.

[14] Hosford DA, Clark S, Cao Z, et al. The role of GABAB receptor activation in absence seizures of lethargic (lh/lh) mice. Science. **1992** Jul 17. 257(5068):398-401.

[15] Hagberg B, Hanefeld F, Percy A, Skjeldal O. An update on clinically applicable diagnostic criteria in Rett syndrome. Comments to Rett Syndrome Clinical Criteria Consensus Panel Satellite to European Paediatric Neurology Society Meeting, Baden Baden, Germany, 11 September 2001. Eur J Paediatr Neurol. **2002**. 6(5):293-7.

[16] Steffenburg U, Hagberg G, Hagberg B. Epilepsy in a representative series of Rett syndrome. *Acta* Paediatr. **2001** J an. 90(1):34-9.

[17] Whalen S, Héron D, Gaillon T, Moldovan O, Rossi M, Devillard F, et al. Novel comprehensive diagnostic strategy in Pitt-Hopkins syndrome: clinical score and further delineation of the TCF4 mutational spectrum. Hum Mutat. **2012** Jan. 33(1): 64-72.

[18] Roach ES, Sparagana SP. Diagnosis of tuberous sclerosis complex. J Child Neurol. **2004** Sep. 19(9): 643-9.

[19] Kao A, Mariani J, McDonald-McGinn DM, Maisenbacher MK, Brooks-Kayal AR, Zackai EH, et al. Increased prevalence of unprovoked seizures in patients with a 22q11.2 deletion. Am J Med Genet *A*. **2004** Aug 15. 129A (1):29-34.

[20] Battaglia A, Filippi T, South ST, Carey JC. Spectrum of epilepsy and electroencephalogram patterns in Wolf-Hirschhorn syndrome: experience with 87 patients. Dev Med Child Neurol. **2009** May. 51(5):373-80.

[21] Battaglia A, Hoyme HE, Dallapiccola B, Zackai E, Hudgins L, McDonald-McGinn D, et al. Further delineation of deletion 1p36 syndrome in 60 patients: a recognizable phenotype and common cause of developmental delay and mental retardation. Pediatrics. **2008** Feb. 121(2):404-10.

[22] Hauser WA, Annegers JF, Rocca WA. Descriptive epidemiology of epilepsy: contributions of population-based studies from Rochester, Minnesota. Mayo Clin Proc. **1996** Jun. 71(6):576-86.

[23] Hirsch LJ, Donner EJ, So EL, Jacobs M, Nashef L, Noebels JL, et al. Abbreviated report of the NIH/NINDS workshop on sudden unexpected death in epilepsy. Neurology. **2011** May 31. 76(22):1932-8.

[24] Luders H, Acharya J, Baumgartner C, et al. Semiological seizure classification. Epilepsia.

1998 Sep. 39(9):1006-13.

[25] Loddenkemper T, Kellinghaus C, Wyllie E, Najm IM, Gupta A, Rosenow F. A proposal for a five-dimensional patient-oriented epilepsy classification. Epileptic Disord. **2005** Dec. 7(4): 308-16.

[26] Engel J Jr. Report of the ILAE classification core group. Epilepsia. **2006** Sep. 47(9):1558-68. .

[27] Wolf P. Basic principles of the ILAE syndrome classification. Epilepsy Res. **2006** Aug. 70 suppl 1:S20-6.

[28] Berg AT, Berkovic SF, Brodie MJ, et al. revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia. **2010** Apr. 51(4):676-85.

[29] Engel J Jr. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE Task Force on Classification and Terminology. Epilepsia. **2001**, 42(6):796-803.