# Epilepsy – A Comprehensive Review

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**ABSTRACT**
Epilepsy is a disorder of the central nervous system characterized by periodic loss of consciousness with or without convulsions associated with abnormal electrical activity in the brain. In some cases it is due to brain damage, but in most cases the cause is unknown. Epilepsy is a common, sometimes chronic, neurological condition with physical risks and psychological and socioeconomic consequences which impair quality of life. It is estimated that there are more than 10 million in India and more than 50 million people with epilepsy worldwide. Epilepsy foundation has also estimated that every 1 in 26 people in United Sates of America will develop epilepsy at some point in their lifetime. The prime requirements for successful management of epilepsy are a complete diagnosis and selection of an optimal treatment to benefit the patient as it is most commonly observed in paediatrics and children, who needs extreme care and counselling by an experienced doctor. The present review article focuses on providing the basic understanding on all aspects of epilepsy as a neurological disorder, considering its classification, causes, diagnosis, and various types of treatments, thus focussing on model of care to be designed in order to prevent, manage or control its occurrence as it cannot be cured.

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## INTRODUCTION

An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiological, cognitive, psychological, and social consequences of this condition. An epileptic seizure is the clinical manifestation of an abnormal and excessive discharge of a set of neurons in the brain. The definition of epilepsy requires the occurrence of at least one epileptic seizure. Therefore, a seizure is the event and epilepsy is the disorder. By definition, one seizure does not make epilepsy, nor does a small series of seizures that have an immediate precipitating factor, for example, alcohol withdrawal seizures. The seizures must be spontaneous and recurrent to represent epilepsy. Seizures result from an electrochemical disorder in the brain. Brain cells use chemical reactions to produce electrical discharges. Each brain cell either excites or inhibits other brain cells with its discharges. When the balance of excitation and inhibition in a region of brain is moved too far in the direction of excitation, then a seizure can result [1-3].

The brain contains millions of nerve cells (neurons). Normally, the nerve cells are constantly sending tiny electrical messages down nerves to all parts of the body. Different parts of the brain control different parts and functions of the body. Therefore, the symptoms that occur during a seizure depend on where the abnormal burst of electrical activity occurs. Symptoms that may occur during a seizure can affect your muscles, sensations, behaviour, emotions, consciousness, or a combination of these.

The type of seizure depends upon several factors. One of the most important factors is where in the brain the abnormal electrical discharge occurs. Strength and sensation are laid out along the border of the frontal and parietal lobes, with strength more toward the front (frontal) and skin sensation more toward the back (parietal) of the strip. In simple terms, if an abnormal electrical discharge originates in motor cortex: the patient will experience a motor seizure; if in sensory cortex: a sensory perception; if in visual cortex: lights, flashes, or jagged lines. Seizures in deep temporal lobe structures present with arrest of activities, loss of memory or awareness, and automatic (robot-like) behaviour. If a seizure spreads to all regions of brain, then a tonic-clonic (grand mal) seizure results, with loss of consciousness, stiffening and jerking [1-7].

## CLASSIFICATION OF EPILEPTIC SEIZURES [1, 8-13]

Table 1 presents the International classification of epileptic seizures proposed by the Commission on Classification and Terminology of the International League against Epilepsy (ILAE) and approved in September 1981. This classification is based on the clinical expression of the seizure and the electroencephalographic picture during and between the seizures [1, 8, 9].

**Table 1: International classification of epileptic seizures** [1, 3, 9]

| I. PARTIAL SEIZURES (seizures beginning locally) | | |
|---|---|---|
| **A. Simple partial seizures (consciousness not impaired)** | **B. Complex partial seizures (with impairment of consciousness)** | **C. Partial seizures secondary generalized** |
| 1. With motor symptoms<br>2. With somato-sensory or special sensory symptoms<br>3. With autonomic symptoms<br>4. With psychic symptoms | 1. Beginning as simple partial seizures and progressing to impairment of consciousness<br>(a) With no other features<br>(b) With features as in A 1–4<br>(c) With automatisms<br>2. With impairment of consciousness at onset<br>(a) With no other features<br>(b) With features as in A 1–4<br>(c) With automatisms | |

**II. GENERALIZED SEIZURES (bilaterally symmetrical and without local onset)**
A. 1. Absence seizures (petit mal)
   2. Atypical absence seizures
B. Tonic-clonic seizures (grand mal)
C. Myoclonic seizures
D. Atonic seizures
E. Tonic seizures
F. Clonic seizures

**III. UNCLASSIFIED EPILEPTIC SEIZURES (inadequate or incomplete data)**

**Partial Seizures** [1, 8, 9]
Partial seizures have onset on one side of the brain, resulting in focal symptomatology such as twitching in an arm or face, a sensory change, or even the focal type of change in memory that occurs with temporal lobe seizures Partial seizures are further divided into simple partial seizures with no alteration of consciousness or memory, or complex partial seizures with alteration of consciousness or memory.
Simple Partial Seizures
Simple partial seizures can be motor seizures with twitching, abnormal

sensations, abnormal visions, sounds or smells, and distortions of perception. Seizure activity can spread to the autonomic nervous system, resulting in flushing, tingling, or nausea. All such simple partial seizures will be in clear consciousness and with full recall on the part of the patient. If the patient becomes confused or cannot remember what is happening during the seizure, then the seizure is classified as a complex partial seizure.

Complex Partial Seizures

Complex partial seizures previously were called "psychomotor seizures", "temporal lobe seizures" or "limbic seizures". Complex partial seizures may have an aura, which is a warning for the seizure, typically a familiar feeling (deja vu), nausea, heat or tingling, or distortion of sensory perceptions. About half of the patients do not have any remembered aura. During the complex partial seizure patients may fumble or perform automatic fragments of activity such as lip smacking, picking at their clothes, walking around aimlessly, or saying nonsense phrases over and over again. These purposeless activities are called automatisms. About 75% of people with complex partial seizures have automatisms. Those who do not simply stop, stare and blank out for a few seconds to minutes.

**Generalized Seizures** [1, 9]

Generalized seizures apparently start on both sides of the brain. In fact, epilepsy specialists believe that generalized seizures originate in deep structures of the brain and travel to the cortical surface where we can see the manifestations of the seizure emerge relatively simultaneously. "Generalized Seizures are further classified as:

Absence Seizures

Absence seizures previously were called petit mal seizures. Absence seizures usually have onset in childhood, but they can persist into adulthood. Absence seizures present with staring spells lasting several seconds, sometimes in conjunction with eyelid fluttering or head nodding. These seizures can be difficult to distinguish from complex partial seizures that also may result in staring. Absence seizures usually are briefer and permit quicker recovery.

The EEG also helps to distinguish an absence from a complex partial seizure

Tonic-Clonic Seizures

Generalized tonic-clonic seizures previously were called grand mal seizures. These seizures start with sudden loss of consciousness and tonic activity (stiffening) followed by clonic activity (rhythmic jerking) of the limbs. The patient‟s eyes will roll up at the beginning of the seizure and the patient will typically emit a cry, not because of pain, but because of contraction of the respiratory muscles against a closed throat. Generalized tonic-clonic seizures usually last from one to three minutes. The seizure itself is called an ictus. After the seizure, the patient is "post-ictal": sluggish, sleepy and confused, variably for hours.

Secondarily Generalized Seizures

Seizures that begin focally can spread to the entire brain, in which case a tonic-clonic seizure ensues. It is important, however, to distinguish those that are true grand mal, generalized from the start, from those that start focally and secondarily generalize. Secondarily generalized seizures arise from a part of the brain that is focally abnormal. Drugs used to treat primarily and secondarily generalized tonic-clonic seizures are different. Patients with secondarily generalized tonic-clonic seizures may be candidates for curative epilepsy surgery (see below); whereas, primarily generalized tonic-clonic seizures are not surgical candidates, because there is no seizure origin site (focus) to remove. Seizure surgery is discussed below.

Atonic Seizures

A Atonic seizures are epileptic drop attacks. Atonic seizures typically occur in children or adults with widespread brain injuries. People with atonic seizures suddenly become limp and may fall to the ground. Football helmets are sometimes required to protect against serious injuries.

Myoclonic Seizures

A Myoclonic seizure is a brief un-sustained jerk or series of jerks, less organized than the rhythmic jerks seen during a generalized tonic-clonic seizure. Other specialized seizure types occasionally are encountered.

Tonic Seizures

Tonic seizures involve stiffening of muscles as the primary seizure manifestation. Arms or legs may extend forward or up into the air. Consciousness may or may not be lost. By definition, the clonic (jerking) phase is absent. Classification can be difficult, because stiffening is a feature of many complex partial seizures. Tonic seizures, however, are much less common than are complex partial or tonic-clonic seizures.

**Mixed Seizure Types**

Patients can have more than one seizure type. One seizure type may progress into another as the electrical activity spreads throughout the brain. A typical progression is from a simple partial seizure, to a complex partial seizure (when the patient becomes confused), to a secondarily generalized tonic-clonic seizure (when the electrical activity has spread throughout the entire brain). The brain has control mechanisms to keep seizures localized. Anti- epileptic medications enhance the ability of the brain to limit spread of a seizure [9].

**Unclassified Epileptic Seizures**

This category includes all seizures which cannot be classified because of inadequate or incomplete data, or seizures that defy classification in the categories as presently defined [1].

**Status Epilepticus**

Status epilepticus (SE) is a life-threatening condition in which the brain is in a state of persistent seizure. Definitions vary, but traditionally it is defined as one continuous, unremitting seizure lasting longer than 5 minutes, or recurrent seizures without regaining consciousness between seizures for greater than 5 minutes. A status epilepticus occurs whenever a seizure persists for at least 30 minutes, without full recovery of consciousness or is repeated so frequently that recovery between attacks does not occur. It is always considered a medical emergency. It is a dangerous condition which may result in brain damage (cerebral necrosis) with severe morbidity or death. A status may be the patient's first epileptic event, or may be precipitated by suddenly discontinuing anticonvulsant therapy [12].

**CLASSIFICATION OF EPILEPSY SYNDROMES** [1, 10, 11, 14-17]

A seizure classification does not specify much about the clinical condition of the patients, for example, cause, severity, or prognosis. An additional classification system therefore has been developed to classify epileptic syndromes. This is a broader classification, since it includes, not just a description of the seizure type, but information about the clinical features of the whole patient

Syndrome names employ the terms "symptomatic," "idiopathic," and "cryptogenic". Symptomatic implies that the seizures have a known underlying cause, for example, a prior stroke. Idiopathic literally means without known cause. However, among epilepsy specialists, the term has taken on the meaning of epilepsy with genetic causes, and no known structural brain abnormality. Cryptogenic implies that a symptomatic cause is suspected, but not yet found.

**Localization-Related Epilepsy**

Localization-related epilepsy connotes partial (focal) seizures. The EEG pattern typically shows a focal electrical abnormality. Prognosis is highly variable, depending upon the cause and location of the focal brain abnormality.

**Infantile spasms / West's syndrome**

Infantile spasms are a type of symptomatic generalized epilepsy. Spasms appear in children, age 3 months to about 3 years, associated with sudden epileptic flexor spasms and a high risk for cognitive impairment. During flexor spasms, the child may suddenly extend his or her limbs, flex forward at the trunk and emit a cry. The episode is over within seconds, but can recur multiple times per hour.

**Lennox-Gastaut Syndrome**

The Lennox-Gastaut syndrome, symptomatic generalized epilepsy, is a relatively rare disorder with the following criteria:

1. Multiple seizure types, usually including atonic or tonic seizures;
2. Variable degrees of cognitive impairment (but not all are impaired);
3. Abnormal EEG with a slow spike-wave pattern, and other associated EEG changes.

Onset usually is in childhood, but adults also suffer from this syndrome. Lennox-Gastaut epilepsy is very difficult to treat, with only 10-20% of patients showing a satisfactory response. Since the epilepsy usually is widespread in the brain, a focal surgical procedure is not a good option. The split-brain operation, officially called corpus callosotomy, can reduce the sudden onset of seizures and prevent injuries.

**Febrile seizures**

A febrile seizure is a seizure that is provoked by fever. Febrile seizures tend to present as convulsions (tonic clonic) in children age 6 months to 6 years of age. The clinician must distinguish a febrile seizure from a seizure with fever caused by some underlying serious condition, such as meningitis. Although alarming to parents, febrile seizures usually are benign. Occurrence of a febrile seizure is a mild risk factor for later development of complex partial epilepsy, but there is no good evidence that trying to prevent febrile seizures reduces this risk. The large majority of children who have febrile seizures will not go on to have lifelong epilepsy. This is an important issue, since seizure medications can impair a child's learning and personality.

**Dravet Syndrome**

Dravet syndrome is a combination of various types of seizures like febrile seizures, clonic, hemiclonic or tonic-clonic seizures, erratic myoclonus, myoclonic absences, atypical absences, massive bilateral myoclonus, tonic seizures, myoclonic status, tonic-clonic status; non-epileptic segmental myoclonus. It is activated by sleep and drowsiness, fever, infection, and hot-water immersion trigger seizures; movement may elicit non-epileptic myoclonus. Febrile and clonic seizures appear first; myoclonic jerks and developmental delay appear later; myoclonus frequently disappears with age but can persist; EEG becomes more disorganized and spike-waves and polyspike-waves increase in prominence. EEG shows electrodecrement followed by slow spike-waves are associated with tonic-clonic seizures; tonic-clonic seizures as in idiopathic epilepsies except initial tonic phase is vibratory due to high frequency clonic activity; polyspike-waves occur with myoclonic jerks; slow spike-waves (2-3.5 Hz) appear during atypical absences; no EEG correlate for multifocal erratic myoclonus.

**Benign Rolandic Epilepsy**

Benign Rolandic epilepsy (BRE) is a seizure type usually appearing in children or adolescents, around age 6 to 16 years old. It represents idiopathic localization-related epilepsy. The Rolandic region is the area of the brain at the frontal-parietal, motor-sensory junction. Seizures at this region usually produce twitching or tingling of a face or hand. Seizures in BRE can secondarily generalize to tonic-clonic seizures. Seizures are more common upon falling asleep. EEGs usually show prominent spikes over the central and temporal areas. The term "benign" is used, not because individual seizures are minor, but because the long-term prognosis for outgrowing the seizures by age 21 (usually even earlier) is very good.

**Juvenile Myoclonic Epilepsy**

Juvenile myoclonic epilepsy (JME) is the most common generalized seizure syndrome in young adults. JME represents a type of idiopathic generalized epilepsy. The genetic abnormality has been localized (at least in some families) to chromosome number 6, and in others to chromosome 20. Patients typically have myoclonus (limb jerking), and occasional generalized tonic-clonic seizures. EEG shows a 3-6 per second generalized spike-wave pattern. Brain MRI is expected to be normal.

**Ohtahara Syndrome**

Ohtahara syndrome represents tonic spasms, focal clonic or hemiclonic seizures; less commonly myoclonus. Infant who is usually normal develops seizures within the first 10 days postpartum; seizures progressively increase in frequency as psychomotor retardation develops; OS often evolves to WS; burst-suppression may evolve to hypsarrhythmia or multifocal spikes. EEG shows burst episodes may be accompanied by tonic spasms also burst-suppression with loss of normal background features; silent periods last 10-20 sec.

**CAUSES (ETIOLOGIES) OF SEIZURES** [1, 2, 11-13, 17-20]

The medical word for "cause" is "etiology." Etiology of seizures varies with the type of seizure, whether it starts focally in one part of the brain or whether it is apparently generalized all over the brain at the start.

There is often no apparent reason why a seizure occurs at one time and not another. However, some people with epilepsy find that certain 'triggers' make a seizure more likely. These are not the cause of epilepsy, but may trigger a seizure on some occasions. Possible triggers include:

- Stress or anxiety
- Some medicines such as anti-depressants, anti-psychotic medication, anti-malarial (by lowering the seizure threshold in the brain)
- Lack of sleep or tiredness
- Irregular meals which may cause a low blood sugar level
- Heavy alcohol drinking
- Flickering lights such as from strobe lighting or video games
- Menstruation cycle in woman
- Illnesses which cause fever such as 'flu or other infections

**Causes for Focal Seizures**

Focal seizures, more commonly referred to as partial simple seizures, occur when there is an abnormal electrical discharge in one part of the brain. The symptoms are usually motor, but can be sensory or emotional. These seizures do not spread to the entire brain and there is no loss of consciousness. Focal seizures are caused by injury or malfunctioning of one or more parts of the brain. A brain injury may generate an immediate (defined loosely as being within one week of an injury) seizure, but these early seizures often do not lead to later seizures

Head Trauma

The bumps on the head and the falls from the swings that all children experience are usually too mild to produce epilepsy. But epilepsy can result from head trauma severe enough to produce many hours of loss of consciousness or amnesia, penetrating injury of the brain or bleeding in the brain.

Stroke

During a stroke, brain cells die or are injured by blockage of blood flow to a part of the brain. About 10% of strokes lead to subsequent epilepsy. Some of these strokes may be so small as to have gone unnoticed, and may be detected only by a CT or MRI brain scan. Related to strokes is brain hemorrhage, which also can be an etiology for epilepsy. A seizure after a stroke does not mean that there has been another stroke.

Tumours (Neoplasms)

The appearance of a seizure in an adult should always raise the suspicion of a brain tumour. Brain tumours can be primary, that is arising from the brain, or secondary, meaning they have metastasized from elsewhere in the body. The type of seizure is determined by the location of the tumour in the brain, not by the type of tumour. Tumours cause many different symptoms, but a seizure might be the first.

Infection

Worldwide, infection is probably the most common cause for focal seizures. Organisms that can cause seizures include bacteria, viruses, fungi or parasites (most importantly Cysticercoids, a microscopic worm from bad pork). If the bug infects the lining of the brain, the condition is meningitis. If the brain is infected, it is called encephalitis. Seizures may occur at the time of a brain infection or after a delay. Some of those viral "colds" or "flus" that we had in the past, with headache, fever and confusion, may have included brain infections, leading later to seizures.

Congenital Defect

Collections of abnormal tissue in the brain are often a cause of partial seizures in children. These are often part of syndromes that cause many other symptoms. If the underlying condition is not lethal, the epileptic foci will remain as the child ages and can continue to cause seizures. The first seizures associated with congenital defects usually appear in childhood.

**Causes for Generalized Seizures**

Metabolic

A wide variety of medical conditions can cause generalized seizures. As just a few examples, we can list low oxygen, low blood sugar, low blood sodium, low blood calcium, alcohol or sedative medication withdrawal, certain recreational or prescription drug overdoses, kidney or liver failure, hyperthyroid disease and toxemia in

pregnancy. Enzyme deficiencies, often on a genetic basis, are important causes of seizures in young children. Metabolic causes produce seizures, but not epilepsy, since the seizures result from an immediate provoking factor, namely the metabolic derangement.

Medication Reactions

There are certain over-the-counter or prescription drugs can provoke seizures in people who are susceptible. A partial list of such medications includes: antihistamines (but not Claritin or Allegra, which do not get into the brain), ciprofloxacin, metronidazole, tricyclic antidepressants, lithium, buproprion, haloperidol, high-dose meperidine, some cancer chemotherapy agents, digoxon, bromocriptine, verapamil, theophyline, tramadol. Your doctor should be aware that you have a seizure condition while prescribing any such drug. Avoid over-the-counter remedies containing phenylpropanolamine or ephedrine (Ephedra, Ma-Huang).

Idiopathic (cause unknown)

Idiopathic seizures are those whose cause is unknown. Unfortunately, about 60% of all seizures are idiopathic. In the case of focal seizures, we presume that there is an irritation to or scar on some part of the brain, but the scar is invisible to MRI. With generalized seizures, the genetic or metabolic abnormality is unidentified.

**Genetic Causes of Seizures**

Scientists and clinicians increasingly recognize the importance of genetic factors in the origin of epilepsy. Genetics are most relevant to generalized seizures, including absence, generalized tonic-clonic, and myoclonic seizures. Defects in genes do not lead directly to epilepsy, but they can alter the excitability of brain in a way to predispose to seizures. Development of epilepsy can require multiple gene abnormalities, or a gene abnormality in concert with an environmental trigger.

**Circumstances that Provoke Seizures**

Most seizures occur "out-of-the-blue", without rhyme or reason. However, some people with epilepsy list variety of factors that contribute to their seizures. These possible factors include: missing seizure medications, times of the menstrual cycle in women, pregnancy, flashing lights, TV or video games, missing sleep, general physical illness, migraine headaches, rarely certain sounds, foods, sensory inputs or changes in temperature. Many people list stress as a provoking factor for seizures, but this relationship is inexact. Stress is everywhere, and most of the time it does not provoke seizures. Why some stress does, and some does not, provoke seizures is unknown.

Alcohol and alcohol withdrawal are common triggers for seizures, as is withdrawal from barbiturates or benzodiazepines. Commonly used medications or drugs that can lead to seizures in susceptible people include: stimulants such as cocaine or diet pills, antihistamines, certain asthma medications, major tranquilizers, etc. No scientific evidence documents that caffeine, cigarettes, or Nutra-Sweet (aspartame) causes seizures, but a few people claim individual sensitivity. People report individual and highly unusual provoking factors, for example, a certain type of smells or specific kinds of music, or the thinking of certain thoughts. Most seizures do not have provoking factors, and some factors are falsely blamed due to coincidence.

**DIAGNOSIS OF EPILEPSY** [1, 2, 21]

Coming to terms with the diagnosis of epilepsy may be difficult. This may be because of wrong or old ideas about epilepsy. Some parents become over-protective towards children with epilepsy. This is understandable, but may need to be resisted for the child's best interests.

Like a lot of conditions, it is sometimes the attitude towards the condition that may be more disabling than the condition itself. If you find that you are over-anxious or become depressed because of epilepsy, it may be best to have counselling. Ask your doctor for advice about this.

History & Physical Examination

The most important diagnostic test in epilepsy is a careful history, taking detailed information on the nature of the patient's episodes. To an experienced clinician, the events should sound like seizures. The physician will then perform a physical and neurological examination looking for evidence of brain injury that might give a clue as to the cause and location of the seizure focus. In epilepsy, however, the

history is usually more important than the physical examination.

A thorough physical and neurologic examination should be performed. Vital signs, including temperature, heart rate, and blood pressure, should be obtained. Fever is the most common cause of seizures in children (as discussed later). The head should be examined for microcephaly, dysmorphic features, signs of trauma, and the presence of a VP shunt. In infants, a measurement of the head circumference may be helpful. A bulging fontanelle indicates increased intracranial pressure. The eyes should be examined for papilledema and retinal hemorrhages. Evaluate the neck for signs of meningeal irritation. The presence of hepatosplenomegaly may indicate a metabolic or glycogen storage disease. Assess the skin for lesions such as cafe´ au lait spots (neurofibromatosis), adenoma sebaceum or ashleaf spots (tuberous sclerosis), and port wine stains (Sturge-Weber syndrome).Unexplained bruising should raise the suspicion of a bleeding disorder or child abuse.

Laboratory Testing

Blood tests will be done to look for infectious or chemical causes of seizures, such as low blood sugar, low blood calcium, low oxygen, kidney failure or liver failure, or drugs or toxins in the blood. Blood tests are also important as a baseline if antiepileptic medications are to be used, since they indicate baseline normality of white blood counts, red blood counts, platelets, liver and kidney function.

Imaging

The physician may get an x-ray of the brain to see if there is an underlying structural cause of the seizures such as tumour, blood clot, or abnormal blood vessels, abscess, old stroke, or other structural causes. A magnetic resonance imaging (MRI) scan is more detailed and useful for seizure diagnosis than is the older CT scan, but individual doctors may choose one over the other. If there is any question of infectious meningitis causing the seizure, then a physician may perform a lumbar puncture (spinal tap) to rule out this condition.

Electroencephalography

The electroencephalogram (EEG) has special importance in the diagnosis of epilepsy. The EEG measures electrical activity of the brain. Normal brain electrical patterns can be recognized by experienced electroencephalographers. During a seizure the brain shows a high voltage rhythmical pattern of activity, which is a little different for each seizure type. The abnormal electricity appears in a certain region of the brain which can give a clue to what part of the brain has the seizure focus, or place of origin. The EEG can also help classify the type of seizures. EEGs would not be very useful if they required recording during a seizure. EEG never makes a diagnosis of epilepsy. It is only an adjunctive test to support a clinical history which is consistent with epileptic seizures. Some people may have abnormal spikes in their EEG but never have a seizure and should not be diagnosed as having epilepsy. Second, the EEG may be normal between seizures in people with epilepsy. If a patient has a good story for seizures, a negative EEG should not discourage the clinician from treating the patient for those seizures. Therefore, t the EEG is helpful as additional information to secure a diagnosis of epilepsy, and to classify and localize the type of seizures.

**TREATMENT OF EPILEPSY**

**DIETARY THEARAPIES** [22-33]

Conventional treatment of epilepsy consists primarily of anticonvulsant medications. Although these drugs often control or reduce the frequency of seizures, some patients show little or no improvement. A number of dietary modifications, nutritional supplements, and hormones have been found to be beneficial for some patients with epilepsy. Potentially useful dietary interventions include measures to stabilize blood glucose levels, identification and avoidance of allergenic foods, and avoidance of potential inciting agents (such as ethanol and aspartame).

Since 1921, dietary therapies have remained valuable options in the treatment of intractable childhood epilepsy. The traditional ketogenic diet and the more recent alternative diets such as the medium-chain triglyceride diet, modified Atkins diet, and low glycaemic index

treatment have expanded the use of this modality to more children as well as adults [22, 26].

## Ketogenic Diet

In the early part of the 1900's, a few people noticed that their children's seizures improved during times of fasting. The ketogenic diet is designed to imitate the chemistry of the fasting state, by depriving the brain of sugar. The diet is very low in carbohydrates (bread, sugar, fruits, vegetables, etc.), and is very high in fat and protein. The resulting body chemistry changes make the brain more resistant to seizures. Although there have been some well-publicized dramatic successes from the ketogenic diet, the majority of people will not benefit from the diet. It seems to work best for children under the age of 12 with drop (atonic or tonic) seizures. Some adults also can benefit, if they stay on the diet. Partial adherence to the diet is not useful - it is all the way or nothing. Even one piece of bread will destroy the needed chemical changes for at least two days. Long-term safety of this diet has not been established. The ketogenic diet can raise blood fats and cholesterol, inhibit growth and weaken bones. In some cases, the diet can be stopped after two years and seizures do not re-turn. The diet can be tried with anti-seizure medications, or on its own. The guidance of an experienced medical team is crucial.

The ketogenic diet provides nutrition with 1 g/kg protein and 5–10 g of carbohydrate per day, with the remainder of calories (usually 75% of the recommended daily allowance) as long-chain triglycerides. Meal plans are carefully tailored by a nutritionist for each individual patient. The ratio of fat to carbohydrate and protein ranges from 2:1 to 4:1, with higher ratios seen as more restrictive and possibly more effective. Meals can be quite palatable, including bacon, eggs, tuna, shrimp, vegetables, mayonnaise, and sausages. It is perhaps easiest to give the diet to formula-fed infants and patients fed through a gastrostomy tube, because it can be prepared as a liquid preparation—eg, Carbohydrate-Free, Mead Microlipid, and Polycose. The proportion of total energy derived from fat ranges from 82-92 percent.

Consuming a ketogenic diet produces a state of ketosis, which helps control seizures through an unknown mechanism. Fluid intake is restricted to maintain urine specific gravity at 1.020-1.025, since fluid intake dilutes blood ketones. The ketogenic diet has been successful for many patients, but because of its highly restrictive nature and potential to cause significant adverse effects, its use is restricted to severe cases that fail to respond to other treatments. Patients on the ketogenic diet must be monitored closely by a practitioner experienced in its use [21-27].

## Ketogenic Diet with Medium-chain Triglycerides

The use of the medium-chain triglyceride (MCT) rich diet is quite similar in efficacy. The MCT ketogenic diet, which provides 50-70 percent of total energy in the form of MCTs, has been used as an alternative to the classic ketogenic diet. This diet is theoretically more palatable; however, bloating is a common complaint. The triglycerides of octanoic and decanoic acids (medium-chain triglycerides (MCTs)) are more ketogenic than long-chain triglycerides present in dietary fats. Diets containing large proportions of MCTs (usually provided by supplementing with MCT oil) are also easier to prepare, more palatable, better tolerated, and require less carbohydrate and protein restriction than standard ketogenic diets. The diet can be provided in many different cultures, religions, and food practices worldwide with several different high-fat foods including 36% heavy whipping cream, butter, MCT oil, sesame or peanut oil, ghee, and Orley Whip [22, 26, 28, 29].

## Atkins Diet

The Atkins diet was created in the 1970s by the late Dr. Robert C Atkins as a means to combat obesity; like the ketogenic diet, it encourages fat intake, restricts carbohydrates, can induce weight loss, and has been avoided in medical research. The Atkins diet is a low-carbohydrate, high fat diet used by millions of people for weight reduction. Like the ketogenic diet, the Atkins diet can induce a state of ketosis, but it has fewer restrictions on calories and protein. Ketones are produced as a by-product of this increased "fat burning"

process (this is what is meant by ketosis) and the brain quickly adapts to using these as the main fuel source for energy production. In addition, the Atkins diet does not require fluid restriction and does not need to be started in the hospital. The Atkins diet can create ketosis if carbohydrates are reduced sufficiently, it does not restrict protein or calories, can be started without a fast or hospital admission, and may have fewer side-effects. In general, the ketogenic diet is 80% fat, 15% protein, and 5% carbohydrate; whereas the Atkins diet is 60% fat, 30% protein, and 10% carbohydrate. Unlike the ketogenic diet, ready-made Atkins products are now available in many groceries and restaurants, although the actual carbohydrate content may be too high for patients with epilepsy despite advertised "net carbs". However, it allows a child to choose items from a menu at a school cafeteria or restaurant, which is nearly impossible on the ketogenic diet. Families can buy the paperback, Dr Atkins' New Diet Revolution in almost any bookstore nowadays and begin the diet at home; although close dietary and neurological monitoring are required throughout for anyone attempting the diet [22, 26, 30-32].

## Low Glycaemic Index Diet

The Low Glycaemic Index Treatment regime produces a metabolic shift along similar lines but because a larger amount of carbohydrate is generally included, ketosis may be minimal or even absent. So essentially, these modified carbohydrate regimes alter the balance of fuel available to the brain; stabilising glucose levels and providing an alternative fuel source in the form of ketones. It is thought that stable blood glucose levels and/ or the shift towards the use of ketones brings about a greater stability of brain energy channels and produces many small chemical changes that can modify the chain reaction that leads up to a seizure. The degree of response to diet, varies between individuals. We still have much to learn about the exact mechanisms involved - research is ongoing. However diet treatments are used across the world for the management of seizure syndromes and drug resistant epilepsy in children. The use

of this therapy for adults is relatively new (and limited) and still only offered by a few centres across the world, often as an extension to an existing paediatric service with a skilled and enthusiastic neurology / dietetic team [22, 26, 33].

## NUTRITIONAL SUPPLEMENTS AS THERAPIES [34-52]

### Vitamin B6

Experimentally-induced vitamin B6 deficiency resulted in seizures in rats and swine. In the early 1950s, numerous infants in the United States developed convulsions traced to the use of a formula that was deficient in pyridoxine. Seizures also occurred in an infant fed exclusively on powdered goat's milk, which had undetectable levels of the vitamin. The seizures resolved after supplementation with vitamin B6. Vitamin B6 should be tried in all infants and young children with intractable epilepsy. For children and adults whose seizures are well controlled on medication, moderate doses of vitamin B6 (such as 10-50 mg/day) may be considered to prevent possible drug induced vitamin B6 deficiency. Although larger doses might be appropriate in selected cases, high-dose vitamin B6 appears to interfere with some anticonvulsant medications. Patients being treated with vitamin B6 should probably also receive a magnesium supplement, in view of evidence that these nutrients work together and anecdotal reports that vitamin B6 supplementation increases the requirement for magnesium [34-37].

### Magnesium

Severe magnesium depletion can cause seizures or increase susceptibility to seizure-inducing stimuli. Intravenously infused magnesium exerted an anticonvulsant effect against experimentally-induced epileptic foci in cats and dogs. In humans, parenterally administered magnesium is an effective treatment for the seizures of neonatal tetany and eclampsia and possibly for those associated with ethanol withdrawal and acute intermittent porphyria. Magnesium concentrations in serum and cerebrospinal fluid (CSF) were significantly lower in 40 patients with grand mal epilepsy than in controls. Serum and CSF magnesium levels fell with increasing duration and frequency

of seizures. Oral administration of magnesium has been associated in some case with an improvement in EEG findings and a reduction in seizure frequency [38-42].

Manganese

In rats, manganese deficiency increased susceptibility to electroshock-induced convulsions. In addition, hydralazine-induced seizures in rats were prevented by prior administration of manganese. In humans with epilepsy, whole-blood manganese levels were significantly lower by 20-41 percent than in controls. Manganese concentrations in epileptic patients did not correlate with seizure frequency or the type, dose, or plasma levels of anticonvulsant medication. Concentrations of other minerals, such as zinc and copper, were generally normal, suggesting that the association between manganese deficiency and epilepsy was not due to general malnutrition. Patients whose epilepsy was a result of trauma had significantly higher blood manganese concentrations than patients with no history of trauma, which suggests that manganese deficiency is a primary contributing factor, rather than a consequence, of epilepsy or its treatment [43-46].

Folic Acid

Seizures occur in some infants with cerebral folate deficiency, a syndrome that also includes slow head growth, psychomotor retardation, cerebellar ataxia, and other neurological abnormalities. This syndrome is caused by impaired transport of folate across the blood-brain barrier into the central nervous system. The transport defect can be overcome by administration of folinic acid (an active form of folic acid), which bypasses the blocked folate transport mechanism. There are several case reports in which administration of folinic acid (2.5-20 mg twice daily in one study, 0.5-1.0 mg/kg body weight per day in another) resulted in improvement or complete control of seizures in infants [44, 48].

Thiamine

Severe thiamine deficiency can cause seizures in both alcoholic and non-alcoholic patients; these seizures are reversible with thiamine supplementation. Low thiamine status was found in 25 percent of 620 epileptic patients attending an outpatient clinic in one study, and in 31 percent of 72 patients in another study. In a placebo-controlled trial, supplementation of epileptic patients with 50 mg thiamine daily for six months was associated with significant improvements in tests of both verbal and non-verbal IQ. Thus, suboptimal thiamine status may be a factor in the impaired cognitive function seen in some patients with epilepsy [49].

Essential Fatty acids

Five severely mentally handicapped patients (ages 12-26 years) with more than 3-4 grand mal seizures per month received a daily supplement providing 900 mg eicosapentaenoic acid (EPA), 2.3 g docosahexaenoic acid (DHA), and 50 mg alpha-linolenic acid. All five patients experienced a marked reduction in both frequency and severity of grand mal seizures. In a double-blind study that included 57 adults (mean age, 39 years), supplementation with fish oil (providing 1 g/day EPA and 0.7 g/day DHA) reduced seizure frequency during the first six weeks of treatment, but the beneficial effect was not sustained thereafter. In contrast to the possible beneficial effect of omega-3 fatty acids, the omega-6 fatty acids in evening primrose oil may have deleterious effects in some patients with epilepsy. There are several case reports in which administration of evening primrose oil appeared to exacerbate or unmask temporal lobe epilepsy [50-52].

**HORMONAL SUPPLEMENTS AS THERAPIES** [53-57]

Melatonin

In one study, 3 mg melatonin was given each night for three months to six children (ages 2-15 years) with severe, intractable seizures. The mean seizure frequency decreased from 3.6 per day at baseline to 1.5 per day during treatment (58% reduction; p<0.05). Melatonin has also been used in doses of 2-10 mg before bedtime to treat sleep disturbances in children with epilepsy. Melatonin treatment was associated with an increase in seizure frequency in some patients and a decrease in others. Because melatonin appears to have unpredictable effects on seizure

frequency, it should be used with caution in patients with epilepsy [53-56].

Progesterone

According to one study, progesterone may be beneficial for women who have seizure exacerbations at specific times during the menstrual cycle. Twenty-five women with cyclic exacerbation of complex partial or secondary generalized motor seizures of temporal origin received progesterone lozenges (200 mg 3 times per day). Women with premenstrual exacerbations received treatment on days 23 to 25 of each cycle; women who had exacerbations during the entire luteal phase were treated from days 15 to 25 of each menstrual cycle. In both groups of women, progesterone was tapered after day 25 and discontinued by day 28. Progesterone was well tolerated by 23 of the 25 women. Two women experienced asthenia and emotional depression, which resolved within one day of discontinuing treatment. Eighteen women (72%) experienced a decline in seizure frequency during the three-month treatment period, compared with the three months prior to therapy. Among the 23 women who continued treatment, the average frequency of complex partial seizures declined by 54% and the frequency of secondary generalized motor seizures declined by 58% [57].

## MEDICATIONS FOR EPILEPSY [1-4, 58-66]

Treatment can reduce or prevent seizures in most people who have epilepsy, which can improve the quality of your life. Controlling your epilepsy also lowers the risk of falling and other complications that can happen when you have a seizure. First your doctor will determine what type of epilepsy and what kinds of seizures you have. Use of anti-seizure medications is the standard of care in the treatment of individuals with a seizure disorder. There is no formula to choose which seizure medicine to use for a particular patient. No one medicine dominates for effectiveness, and all have various side effects. Doctors and patients choose Anti-epileptic drugs (AEDs) after considering which side effects should be avoided in particular cases, convenience of use, cost and physician experience. It may take time for you and your doctor to find the right combination,

schedule, and dosage of medicines to manage your epilepsy. The goal is to prevent seizures while causing as few unwanted side effects as possible. An important start is to know which AEDs work for which seizure types.

### Initial Treatment

Initial treatment for epilepsy depends on the severity, frequency, and type of seizures and whether a cause for your condition has been identified. Medicine is the first and most common approach. Antiepileptic medicines do not cure epilepsy, but they help prevent seizures in well over half of the people who take them.

### Ongoing Treatment

If epileptic seizures continue even though you are being treated, additional or other antiepileptic medicines may be tried. A thorough classification of drugs as per their mechanism of action can provide a better understanding for selection of treatment.

## CLASSIFICATION OF ANTI-EPILEPTIC DRUGS ACCORDING TO MECHANISMS OF ACTION [58-71]

### Sodium Channel Blockers

Sodium channel blockade is the most common and best-characterized mechanism of currently available antiepileptic drugs (AEDs). AEDs that target sodium channels prevent the return of the channels to the active state by stabilizing the inactive form. In doing so, repetitive firing of the axons is prevented.

Phenytoin

Phenytoin is the most common inexpensive AED used by general physicians. The primary site of action appears to be the motor cortex where spread of seizure activity is inhibited. Possibly by promoting sodium efflux from neurons, Phenytoin tends to stabilize the threshold against hyper-excitability caused by excessive stimulation or environmental changes capable of reducing membrane sodium gradient. Phenytoin reduces the maximal activity of brain stem centres responsible for the tonic phase of tonic clonic (grand mal) seizures. Typical adult recommended dose is around 300 mg/day. Common side effects are unsteadiness and moderate cognitive problems. There are long-term potential cosmetic (body/face hair growth, skin problems), and bone problems

(osteoporosis). Phenytoin causes a rash rate of a few percent, sometimes even the dangerous rash called Stevens-Johnson syndrome.

## Carbamazepine

Carbamazepine is a favourite partial seizure medicine in the developed world. Carbamazepine affects sodium channels, and inhibits rapid firing of brain cells. Long-acting forms such as Carbatrol or Tegretol-XR can be given once a day. Typical adult dose is 400 mg TID. Potential side effects include GI upset, weight gain, blurred vision, low blood counts, low blood sodium (hypo-natremia). Carbamazepine causes a rash rate of a few percent, sometimes even the dangerous rash called Stevens-Johnson syndrome. People of Asian descent with HLA-B*1502 antigen are more at risk.

## Oxcarbazepine

Slightly different from Carbamazepine, it is at least as effective, and may have fewer side effects, except for more risk for low blood sodium (hyponatremia). Oxcarbazepine does not produce the toxic 10,11epoxide metabolite, which is largely responsible for the adverse effects reported with Carbamazepine. It is more expensive than generic Carbamazepine. A typical adult dose is 600 mg twice a day. An immediate switch from Carbamazepine to full-dose Oxcarbazepine is possible in some cases.

## Lamotrigine

Lamotrigine is a broad-spectrum alternative to Valproic acid, with a better side effect profile. However, LTG may not be as effective for myoclonic seizures. Lamotrigine works by several mechanisms including s blocking voltage-dependent sodium-channel conductance, blocking release of glutamate, the brain's main excitatory neurotransmitter. It has the usual side effects of dizziness and fatigue, usually mild cognitive (thinking) impairment. Severe medical side effects are unusual. The practical side effect issue is rash, occurring in 5-10% of people who take it, especially if the dose is increased too fast. There-fore, it takes a couple of months to get up to the typical adult dose of 200 mg twice a day. This is slower than the package insert suggested starting dose, however, a slow starting dose is especially important if the patient also takes Valproic acid, to reduce risk for rash. Lamotrigine is also used for mood stabilization.

## Zonisamide

Zonisamide exerts its mechanism of action by reduction of neuronal repetitive firing by blocking sodium channels and preventing neurotransmitter release. It also exerts influence on T-type calcium channels and prevents influx of calcium. In addition, ZNS exhibits neuroprotective effects through free radical scavenging. It is rather similar in its coverage and side effects to Topiramate, except glaucoma is not usually listed. Some find less cognitive impairment than with Topiramate but this is individual and dose-dependent. Typical adult dose is 100-300 mg twice a day.

## Lacosamide

Lacosamide is a new (2009) antiepileptic drug, for partial and secondarily generalized seizures. It is chemically related to the amino acid, serine. They blocks sodium channels (but in a different way from other seizure medicines), and this block reduces brain excitability. Side effects include dizziness, headache, nausea or vomiting, double vision, fatigue, memory or mood problems. It may affect the internal organs, blood counts or heart rhythm, but these potentially serious side effects are infrequent. The recommended starting dose is 50 mg twice daily, increased each week by an extra 100 mg, to the recommended maintenance dosage of 100-200 mg twice a day.

## GABA Receptor Agonists

A seizure reflects an imbalance between excitatory and inhibitory activity in the brain, with an increment of excitation over inhibition. The most important inhibitory neurotransmitter in the brain is gamma-aminobutyric acid (GABA). There is a fascinating relationship between this most abundant and important inhibitory agent (GABA) and glutamate, the engine of excitation. GABA-A receptors have multiple binding sites for benzodiazepines, barbiturates, and other substances (e.g., neurosteroids). These drugs bind to different sites around the receptor to exert their action, but the clinical implications of each receptor site are not well understood. The benzodiazepines most commonly used for treatment of epilepsy are lorazepam,

diazepam, midazolam, clonazepam, chlorazepate and clobazam.

## Phenobarbital

Phenobarbital is a traditional, very inexpensive and effective in a single daily dose. Phenobarbital increases the effect of GABA, the main inhibitory neurotransmitter in the brain. Phenobarbital is used for tonic–clonic and partial seizures and may also be tried in atypical absence; atonic and tonic seizures. Phenobarbital is mildly addictive and requires slow withdrawal. During pregnancy, there is a significant rate of birth defects. Typical adult dose is around 100 mg per day. The target serum level is 10-40 mcg per ml. Watch for sedation, thinking/memory problems and depression and also can cause long-term bone problems.

## Clonazepam

Clonazepam is a member of the drug class known as benzodiazepines, to which diazepam, lorazepam, clorazepate, alprazolam also belongs. Benzodiazepines are used as anti-seizure drugs, sedatives, tranquilizers and muscle relaxants. Benzodiazepines increase the effectiveness of GABA, the brain's main inhibitory neurotransmitter. Clonazepam is more long-acting against seizures than are diazepam or lorazepam. Side effects of Clonazepam include sedation, thinking/memory impairment, mood changes, and addiction. More so than most, its effects wear off over time. A typical adult dose is 0.5-1.0 mg three times a day.

## GABA Reuptake Inhibitors

Reuptake of gamma-aminobutyric acid (GABA) is facilitated by at least 4 specific GABA-4transporting compounds; these carry GABA from the synaptic space into neurons and glial cells, where it is metabolized. Nipecotic acid and Tiagabine (TGB) are inhibitors of these transporters; this inhibition makes increased amounts of GABA available in the synaptic cleft. GABA prolongs inhibitory postsynaptic potentials (IPSPs).

## Tigabine

Tiagabine is a "designer drug", formulated to block inactivation (uptake) of the brain's main inhibitory neurotransmitter, GABA. When more GABA accumulates in the brain, seizures are harder to initiate and sustain. It is useful for partial and secondarily generalized seizures. It is not effective for absence or myoclonic seizures. The side effect profile is acceptable, with some sedation, abnormal thinking, and dizziness. Typical adult dose begin with 4 mg at bedtime for a week, then increase 4 mg each week to 16-56 mg/d in two divided doses.

## GABA Transaminase Inhibitors

Gamma-aminobutyric acid (GABA) is metabolized by transamination in the extracellular compartment by GABA-transaminase (GABA-T). Inhibition of this enzymatic process leads to an increase in the extracellular concentration of GABA. Vigabatrin (VGB) inhibits the enzyme GABA-T.

## Vigabatrin

Vigabatrin is a "designer drug," made to block metabolism of GABA, the brain's main inhibitory neurotransmitter. It is a close structural analogue of GABA, binding irreversibly to the active site of GABA-T. Vigabatrin has been used for over a decade in many countries, and it is effective for partial seizures, with or without secondary generalization. It also may be very effective for infantile spasms, a serious type of seizures in young children. Release in the US was delayed because the drug is toxic to the retina of the eye in up to 30% of people who take it long-term. This toxicity can result in permanent loss of peripheral vision. Regular vision testing is required for all people on this drug. A typical regimen begins with 500 mg twice a day, and can increase over a month or two to 1500 mg twice a day.

## AEDs with Potential GABA Mechanism of Action

The enzyme glutamic acid decarboxylase (GAD) converts glutamate into gamma-aminobutyric acid (GABA). Currently, Valproate (VPA) and Gabapentin (GBP) are known to have some effect on this enzyme and thereby enhance the synthesis of GABA, in addition to other potential mechanisms of action. VPA also blocks the neuronal sodium channel during rapid sustained repetitive firing. GBP has a weak competitive inhibition of the enzyme GABA-T.

## Gabapentin

Gabapentin has the reputation of being a safe but not particularly powerful AED. The effectiveness criticism probably is because it is often prescribed at too low a dose. The drug probably works by influencing transport of GABA and effects on calcium channels. , the exact mechanism by which GBP increases the intracellular concentration of GABA is unknown. It has no drug interactions, is not metabolized in the liver and it does not bind to blood proteins. Side effects are unsteadiness, weight gain, fatigue, dizziness. Typical adult dose is 300-600 mg three times a, but doses can be up to 1200 mg three times a day. Gabapentin often is used also for chronic pains of certain types.

Pregabalin

A relative of Gabapentin, it may be better, and can be given twice a day. Some believe that it is more effective against seizures than is Gabapentin. Pregabalin does not alter GABA concentration in brain tissues or inhibit GABA transport in vitro. Pregabalin binds with high affinity to both the alpha2 delta-1 and alpha2delta-2 subtypes. Pregabalin has no drug interactions, no liver metabolism, no protein binding, and similar side effects to Gabapentin. Typical adult dose is 150 - 600 mg bid. This is slower than the package insert suggested starting dose, but avoid sedation. Pregabalin often is used also for chronic pains of certain types.

Valproic Acid

This is the standard broad-spectrum AED (treats all types of seizures) and no other AED is more effective for generalized seizure types. Valproates has effects on GABA (at least in very high doses), and a neurotransmitter called NPY to block seizures, and maybe also on calcium channels. VPA has significant side effects: weight gain, tremor, hair loss, GI up-set, blood count decreases, hepatic or pancreatic injury, bone weakness over time (osteoporosis), birth defects in up to 10% (folic acid can help to prevent them). Typical adult dose is 250 mg - 500 mg three times a day, but dose can be higher. An extended release form can be taken once a day.

**Glutamate Blockers**

Glutamate and aspartate are the most two important excitatory neurotransmitters in the brain. The glutamate system is a complex system that contains macromolecular receptors with different binding sites (i.e., alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid [AMPA], kainate, N -methyl-D-aspartate [NMDA], glycine, and metabotropic sites). The AMPA and the kainate sites open a channel through the receptor, allowing sodium and small amounts of calcium to enter. The NMDA site opens a channel that allows large amounts of calcium to enter along with the sodium ions. This channel is blocked by magnesium in the resting state. The glycine site facilitates the opening of the NMDA receptor channel. The metabotropic site is regulated by complex reactions and its response is mediated by second messengers. NMDA antagonists have a limited use because they produce psychosis and hallucinations. In addition to these adverse effects, learning and memory may be impaired by blocking these receptors, because NMDA receptors are associated with learning processes and long-term potentiation.

Felbamate

Felbamate has been proposed to a unique dual mechanism of action as a positive modulator of GABAA receptors and as a blocker of NMDA receptors, particularly isoforms containing the NR2B subunit. Although it is clear that Felbamate does cause pharmacological inhibition of NMDA receptor of relevance of NMDA receptor blockade as a strategy for the treatment of human epilepsy has been questioned. Therefore, the importance of the effects of Felbamate on NMDA receptors to its therapeutic action in epilepsy is uncertain. Felbamate indications were broad spectrum for a variety of seizure types. It has efficacy against atonic seizures, as well as partial and secondarily generalized seizures. Felbamate has substantial drug interactions, which make it difficult to use in conjunction with other medications. A typical adult dose of Felbamate is 400-1200 mg orally three times per day (total of 1200 - 3600 mg per day).

Topiramate

Topiramate is a very potent anticonvulsant that is structurally different from other

AEDs. Topiramate has multiple mechanisms of action. It exerts an inhibitory effect on sodium conductance, decreasing the duration of spontaneous bursts and the frequency of generated action potentials, enhances GABA by unknown mechanisms, inhibits the AMPA subtype glutamate receptor, and is a weak inhibitor of carbonic anhydrase. Blocking the enzyme carbonic anhydrase affects the acidity of brain tissue. More acidity (to a point) suppresses seizures. Side effects include thinking and memory problems in about 1/3rd, renal stones in 1-2%, rare cases of glaucoma (increased eye pressure) and weight loss. Typical adult dose is 150-200 mg twice a day.

**AEDs with Other Mechanisms of Action**

Levetiracetam

Levetiracetam is one of the more used medicines in seizure clinics because it probably is effective for a broad-spectrum of seizures types, has a relatively low incidence of causing thinking/memory problems, and can be started at 500 mg twice a day, which is an effective dose. The mechanism of action is possibly related to a brain-specific stereo-selective binding site, synaptic vesicle protein 2A (SV2A). SV2A appears to be important for the availability of calcium-dependent neurotransmitter vesicles ready to release their content. The lack of SV2A results in decreased action potential-dependent neurotransmission, while action potential independent neurotransmission remains normal. In addition, it reduces Bicuculline-induced hyperexcitability in rat hippocampal CA3 neurons, suggesting a mechanism that does not involve release of gamma-aminobutyric acid (GABA). LEV inhibits Ca2+ release from the inositoltrisphosphate (IP3)-sensitive stores without reducing Ca2+ storage, which could explain some of its antiepileptic properties. It has no drug interactions, is not metabolized in the liver and it does not bind to blood proteins. The most common side effects are dizziness, fatigue, insomnia, but the more troublesome problem can be irritability and mood changes. This may occur to some degree in up to a third of those taking the medicine. A typical adult dose is 500 - 1500 mg twice a day.

Rufinamide

Rufinamide is approved for add-on treatment of children age 4 and older and adults with the Lennox Gastaut Syndrome This syndrome can include seizure types such as atonic (drop) seizures, tonic (stiffening) seizures, myoclonic (brief jerking) seizures, or staring (absence) seizures, as well as partial seizures. Banzel works on sodium channels in brain cells, in a way to make them less excitable. Common side effects include headache, dizziness, fatigue and sleepiness, double vision and tremor (trembling). People who have the "short QT syndrome," a rare heart rhythm irregularity, should not take Banzel. The drug comes as 200 and 400 mg tablets. Children will usually be started at doses of approximately 10 mg/kg/day administered in two equally divided doses. Dosing can increase by adding additional 10 mg/kg amounts every two days, until the child is taking 45 mg/kg/day or a maximum of 3200 mg/day, divided into two doses each day.

**Device – The Vagus Nerve Stimulator**

The vagus nerve stimulator was approved by the U.S. Food and Drug Administration (FDA) in 1997 for use in people with seizures that are not well-controlled by medication. The vagus nerve stimulator is a battery-powered device that is surgically implanted under the skin of the chest, much like a pacemaker, and is attached to the vagus nerve in the lower neck. This device delivers short bursts of electrical energy to the brain via the vagus nerve. On average, this stimulation reduces seizures by about 20 - 40 percent. Patients usually cannot stop taking epilepsy medication because of the stimulator, but they often experience fewer seizures and they may be able to reduce the dose of their medication. Side effects of the vagus nerve stimulator are generally mild but may include hoarseness, ear pain, a sore throat, or nausea. Adjusting the amount of stimulation can usually eliminate most side effects, although the hoarseness typically persists. The batteries in the vagus nerve stimulator need to be replaced about once every 5 years; this requires a minor operation that can usually be performed as an outpatient procedure [72-75].

Several new devices may become available for epilepsy in the future. Researchers are studying whether transcranial magnetic stimulation (TMS), a procedure which uses a strong magnet held outside the head to influence brain activity, may reduce seizures. They also hope to develop implantable devices that can deliver drugs to specific parts of the brain.

## Surgery

Medications can control seizures in most people with epilepsy, however it is ineffective and or intolerable in almost 30% of population, for them brain surgery may be an option. Surgery for epilepsy is performed either with a "curative" indication aiming to complete freedom of seizures or "palliative" aiming to decrease the frequency of occurrence of seizures. The type of surgery depends on the type of seizure and the area of the brain where the seizure start. The surgical options include lobe resection, lesionectomy, corpus callostomy, functional hemispherectomy, multiple subpial transaction, radiotherapy etc. This requires a better understanding of all the risks, benefits and consequences associated with surgery, neurological deficits and surgery failure before opting a surgical technique as a treatment option in patients. The effectiveness varies, depending on the type of surgery, with success rates varying between 50% and 80%. It is a very new and emerging area in the field of a treatment option and needs wider approach for further development [76-79].

## CONCLUSION

A tremendous amount of research is focused on the diagnosis, prevention, treatment, and cure of epilepsy. Prevention of injury is always better than treatment. Safety is primarily the most important think to be taken care of. Arrange your home and if possible, work or study space, to be safe should you have a seizure. Many people with epilepsy lead productive and outwardly normal lives. Medical and research advances in the past two decades have led to a better understanding of epilepsy and seizures than ever before. Advanced brain scans and other techniques allow greater accuracy in diagnosing epilepsy and determining when a patient

may be helped by surgery. More than 20 different medications and a variety of surgical techniques are now available and provide good control of seizures for most people with epilepsy. Other treatment options include the ketogenic diet, Atkins diet, hormonal supplements, natural supplements and the first implantable device, the vagus nerve stimulator, surgeries. Research on the underlying causes of epilepsy, including identification of genes for some forms of epilepsy and febrile seizures, has led to a greatly improved understanding of epilepsy that may lead to more effective treatments or even newer ways of preventing epilepsy in the future.

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