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EPILEPSY – A COMPREHENSIVE REVIEW

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ABSTRACT

Epilepsy is one of the most common neurological disorders that is associated with abnormal electrical activity in the brain. It is affecting about 50 million individuals worldwide and 80% of these people live in low and middle-income countries with limited resources. Epilepsy can start at any age, but more cases are observed in younger children and older adults. It occurs slightly more in men than in women. Genetic factors, head trauma, infections in brain, stroke, tumor can cause epilepsy. Many patients with epilepsy may suffer severe psychological and socio-economic conditions that may negatively impact their quality of life. Brain generates seizures through different mechanisms and seizures are classified into many types. Different types of diagnostic procedures are used to identify and classify the seizure type along with its site of origin. Drugs that are given for treatment of epilepsy are known as anti-epileptic drugs. The main objective of this review is to provide the updated epidemiology, etiology, risk factors, diagnostic procedures, newer classification and treatments for epilepsy.

KEYWORDS: Epilepsy, epidemiology, seizure, anti-epileptic drugs, classification.

INTRODUCTION[1,6]

A seizure occurs due to abnormal excessive or synchronous neuronal activity in the brain resulting in a temporary disturbance of motor, sensory or mental function. Epilepsy is a neurological disorder of the brain that is characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological and social consequences of this condition.[1] It is a condition in which a patient has recurrent seizures separated by greater than 24 hours. Thus, seizure is an event and epilepsy is a disorder. It is a common condition where about 0.5-1% of the population are being affected. In the U.S.

about 1 in 100 people had a single unprovoked seizure or has been diagnosed with epilepsy. 1 in 26 people will develop epilepsy in their lifetime. According to the 2017, "Morbidity and Mortality Weekly Report from the Centers for Disease Control and Prevention (CDC), atleast 3.4 million people in the U.S. live with seizures,which includes 470,000 children.[2] It is one of the most common and disabling neurological disorder effecting almost all the age groups and mostly seen in younger children and older adults. Brain cells use chemical reactions to produce electrical discharges or messages. Each brain cell excites or inhibits other brain cells by its electrical messages. When these brain cells undergo hyper-excitation, then a seizure may occur. The brain contains millions of nerve cells (neurons). These neurons send tiny electrical messages to all the parts of the body down the nerves. Different parts and functions of the body are controlled by various parts of the brain. Thus, the symptoms that occur during the seizure depend on the site where abnormal burst of electrical activity occurs. For example, if the abnormal electrical activity originates in the motor cortex – a motor seizure is experienced by the patient. Similarly, if in the sensory cortex – a sensory perception is seen. And if in the visual cortex– lights, flashes and jagged lines are experienced by the patient. When this seizure spreads to all the regions of the brain, a tonic – clonic seizure is seen with loss of consciousness, stiffening and jerking.[3] Comparing with a general population, people with epilepsy has an increased risk of mortality. Sudden unexpected death in epilepsy (SUDEP) is a well-known condition in an epilepsy patient of sudden unexpected, witnessed or unwitnessed death.[6] Substantial risk of epilepsy–related death including sudden, unexplained death is associated with the childhood – onset epilepsy.[4,5]

EPIDEMIOLOGY[7,8]

Epilepsy is the second most common chronic neurological condition seen by neurologists. Approximately 50 million people currently live with epilepsy worldwide. The estimated proportion of active epilepsy (i.e., continuing seizures or with the need of treatment) in general population is between 4-10 per thousand people. Some studies in low and middle-income countries submits that the proportion is much higher between 7-14 per thousand people. 80% of the people with epilepsy live in low-middle income countries.[7] Globally an estimated 2.4 million people are diagnosed with epilepsy each year. This is likely due to increased risk of endemic conditions such as malaria or neurocysticercosis, higher incidents of road traffic injuries, birth related injuries etc. It is estimated that there are 55, 00, 000 persons with epilepsy in India, 20, 00, 000 in USA and 3, 00, 000 in UK.[8]

CLASSIFICATION[9]

International League Against Epilepsy(ILAE) 2017 classification of seizure types – According to the latest version of classification (from ILAE 2017), seizures are divided into groups depending on the following -

(i) Where they start in the brain (onset)

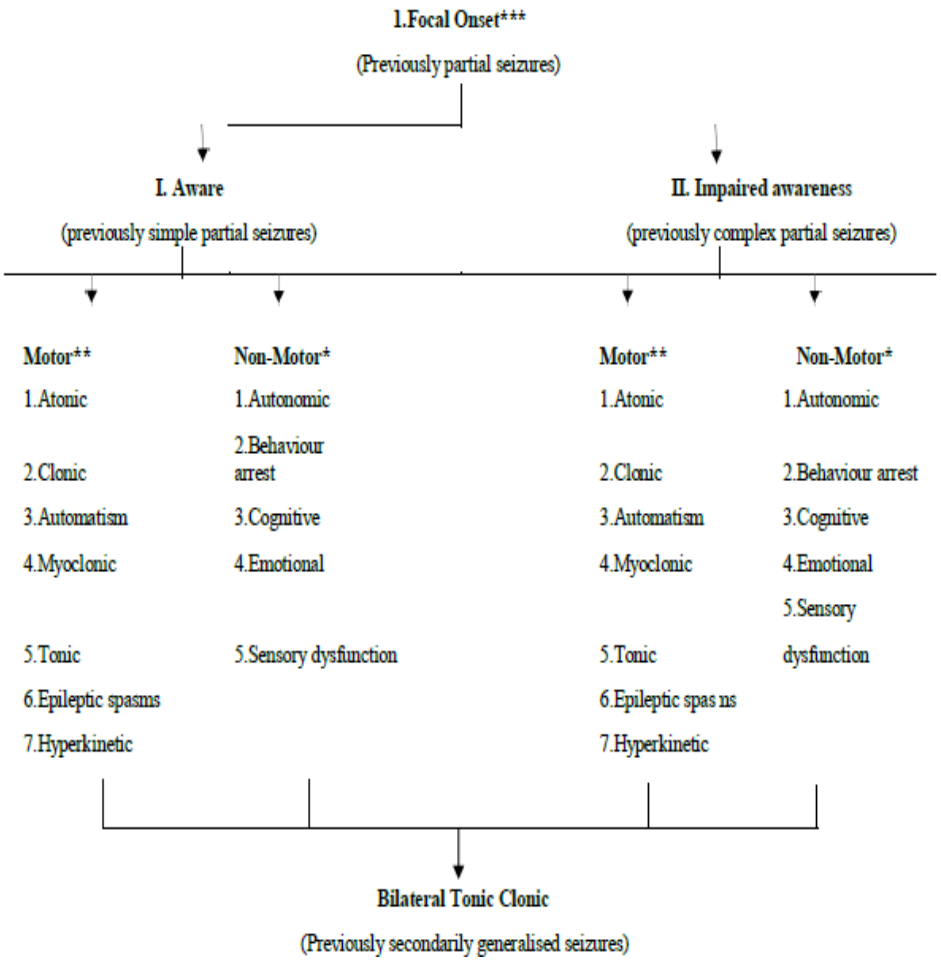
(ii) Whether the person is aware or not.

(iii) Depending on the site where they start, they are described as being focal onset, generalised onset or unknown onset.

(iv) This classification applies to the seizures in both children as well as adults.

1. Focal Onset***

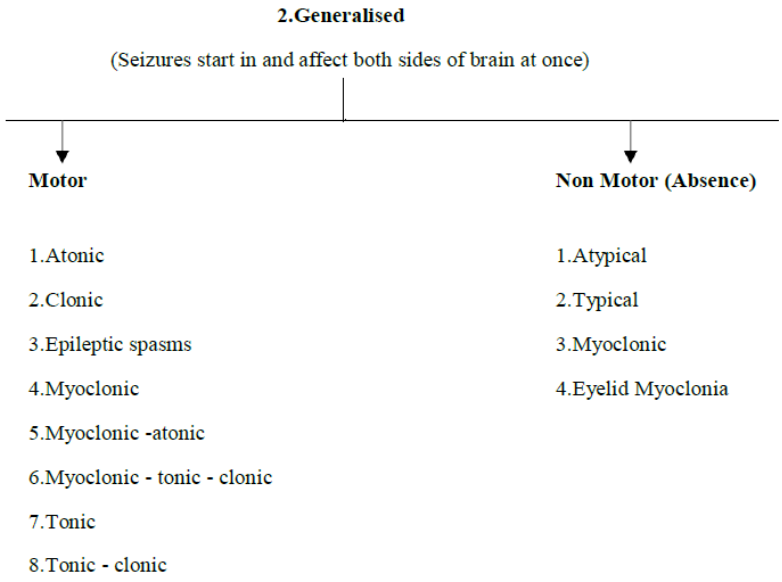
(Previously partial seizures)

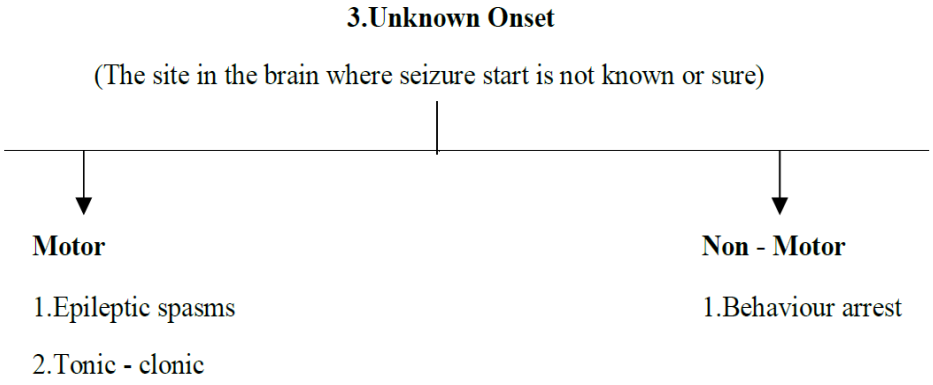


***Seizures start in and affect one side of the brain.

**Seizures with physical movement.

*Seizures without physical movement.





2. **Unclassified**
3. A seizure might be unclassified due to inadequate information or inability to place the seizure in other categories. The classification is reserved for only seizures. If an event is not clearly a seizure, then it should not be called as an unclassified seizure.

ETIOLOGY[10,14]

Epilepsy has no identifiable cause in about half of the people with the condition. In other half, the condition maybe traced to various factors including:

1. Genetic factors – The seizure type or part of brain that is affected, run in families. In such cases, there is a genetic influence. In others, certain genes may make a person more sensitive to environmental. conditions that trigger seizures.
2. Head trauma – Road accidents or other traumatic injuries can cause epilepsy.

3. Brain conditions – The conditions that cause damage to the brain and can lead to epilepsy are brain tumours, strokes and tuberculoma.
4. Infectious diseases - Meningitis, AIDS, cerebral malaria and viral encephalitis can cause epilepsy.
5. Prenatal injury – As babies are sensitive to brain damage before birth, several factors such as an Infection in mother, poor nutrition or oxygen deficiencies may result in epilepsy or cerebralpalsy.
6. Developmental disorders – Disorders like autism, and neurofibromatosis which are seen commonly in children and adults may sometimes cause epilepsy.
7. Degenerative diseases – Dementia and cerebral macular degeneration can cause epilepsy and are mostly seen in elderly patients.
8. Idiopathic seizures - About 6 out of 10 seizures are idiopathic. In such cases (focal seizures) we presume that there is an irritation or scar on some part of the brain that is invisible to MRI. With generalised seizures, the genetic or metabolic abnormalities are unidentified.
9. Toxic – Epilepsy might also occur in alcoholics and withdrawal from alcohol, organophosphorus insecticide poisoning, carbon monoxide poisoning, lead poisoning, drugs (high dose IV – penicillin, strychnine etc).
10. In some cases, certain "triggers" make a seizure more likely [13]. These are not the cause of epilepsy but may trigger a seizure occasionally. Possible triggers include –

(i) Stress or anxiety (in about 30% of people).
(ii) Some medicines such as antidepressants, anti-psychotic medication, anti-malarial (by lowering the seizure threshold in the brain).
(iii) Lack of sleep or tiredness (in about 18% of people).[12]
(iv) Irregular meals which may cause low blood sugar level.
(v) Heavy alcohol drinking.
(vi) Menstruation cycle in women.
(vii) Flickering lights such as strobe lighting or video games.[13]

RISK FACTORS[10,15]

The risk factors may include

1. Age – The onset is most common in children and elderly people, but may occur at any age. The children aged 1-3 years had elevated rate of febrile seizures re-admission with peak age of 2. Boys had 75 times higher rate of febrile seizures readmission than girls.

Children with very low-income levels are more likely to be readmitted compared to those with high income levels.[15]

2. Head Injuries
3. Dementia – It may increase the risk of epilepsy in adults.
4. Brain infections – Infections like meningitis that causes inflammation in brain or spinal cord can increase the risk. Family History – Any family history of epilepsy may increase risk of developing a seizure disorder.
5. Stroke and other vascular diseases – They can lead to brain damage that may trigger epilepsy.
6. Seizures in childhood – High fevers in childhood can sometimes cause seizures. These kind generally don't develop epilepsy but the risk may increase if a child has a long seizures.

SIGNS AND SYMPTOMS[16,17]

Characteristics of seizures vary & depend on where in the brain the disturbance first starts and how far it spreads.

1. Focal seizures

(i) In simple focal seizures, sometimes called as "Aura" – there is no loss of consciousness, but the patient may experience a vague feeling of sensory or visual hallucinations and twitching of fingers, arms and legs can also be observed sometimes.

(ii) focal seizures In complex which involves mainly loss of consciousness and staring blank. Sometimes smacking of lips, laugh, cry can be seen but only for a short time.

2. Generalized seizures

(i) Tonic-clonic seizures (previously grand mal) – Stiffening of body, jerks, shakes and loss of consciousness and sometimes loss of bladder control are seen in general.

(ii) Clonic which involves muscle spasms mainly the muscles of the face, neck and arm that jerk repeatedly.

(iii) Tonic seizures which involves muscles in the arms, legs or trunk tense up and the patient may lose their balance and fall if he is standing and often happens in the sleep.

(iv) Absence seizures (previously petit mal) involves staring straight ahead, repetitive swallowing and lapsing into complete immobility for few seconds may characterise absence seizures which may recur many times a day.

(v) In Atonic seizures there is a loss in the muscle control i.e., muscles go suddenly limp and the head may lean forward usually making the patient drop to the floor suddenly.

(vi) Myoclonic seizures may affect either some part or the whole body which involves sudden, short lasting jerks.

-Physical problems such as fractures and bruising from injuries those related to seizures are more commonly seen in patients with seizures. The premature death risk is up to 3 times higher in people with epilepsy than in the general population.

DIAGNOSIS[18]

Different types of diagnostic tests are performed to detect epilepsy. The aim in evaluation of epilepsy patients is to determine the type of seizures the patient is having and their cause. It may be difficult to diagnose the type of seizure or epilepsy syndrome as there are many other disorders that can cause changes in behaviour and is confused with epilepsy. Thus, the crucial first step is knowing what kind.

- History and physical examination – In epilepsy the most important diagnostic test is a careful history, taking detailed information on nature of patient's episodes. The physician will then perform a physical and neurological examination like checking for any evidence of brain injury that might be helpful for identifying the cause and location of the seizure focus, examining the vital signs like temperature, heartrate and blood pressure. The head should be examined for dysmorphic features, signs of trauma, microcephaly. The eyes should be examined for papilledema and retinal haemorrhages. The presence of hepatosplenomegaly may indicate metabolic or glycogen storage disease.
- Laboratory tests – Blood tests are done to identify any infectious or chemical causes of seizures like low blood sugar, low blood calcium, low oxygen, kidney failure or liver failure, drugs or toxins in the blood.
- Computerised tomography (CT scan) – Imaging is done to check for any underlying structural cause of seizures such as tumour, blood clot, or abnormal blood vessels, old stroke, abscess and other structural causes.
- Magnetic resonance imaging (MRI) – By using powerful magnets and radio waves it generates a detailed view of the brain. It helps in detecting lesions or abnormalities in the brain that may cause seizures.

- In case of infectious meningitis causing the seizure, a lumbar puncture (spinal tap) may be done.
- Electroencephalogram (EEG) – It measures electrical activity in the brain. During a seizure, the brain shows a high voltage rhythmical pattern of activity which is slight different for each seizure type. The EEG can also help classify the seizure type and thus has a special importance in the diagnosis.
- Functional MRI (fMRI) – It measures the blood flow changes that occur when specific parts of the brain are working. This is usually done before surgery (so as to identify the exact locations of critical functions like speech and movement, so that surgeons while operating can avoid injuring those places).
- Positron emission tomography (PET)–A small amount of low dose radioactive material is injected into a vein to help visualise active areas of the brain and detect abnormalities.
- Single Proton Emission Computerised Tomography (SPECT) –A small amount of low dose radioactive material that is injected into a vein to create a detailed 3D map of blood flow activity in brain during seizures.
- Neuropsychological tests – It is done to assist thinking, memory, and speech skills which helps in identifying the affected areas of the brain.

TREATMENT[19,26]

1. Dietary therapies – Conventional treatment of epilepsy consists primarily of anti-convulsant medications. Although these drugs control or reduce the frequency of the seizures, some patients show little or no improvement. A number of dietary modifications, nutritional supplements, hormones have been found beneficial for some patients with epilepsy. Dietary therapies like ketogenic diet and other diets such as medium chain triglycerides, modified Atkins diet and low glycaemic index diet have been used in both children and adults to control seizures.[19]

- Ketogenic diet – This diet is designed to mimic the biochemical changes of starvation, by depriving the brain sugar that is ketosis. The diet is very low in carbohydrates (bread, fruits, vegetables etc.) and is very rich in fat and protein. The result in body chemistry changes makes the brain more resistant to seizures. It seems to work best for children under the age of 12 with intractable seizures and also be beneficial as an adjunct to anti-epileptic drugs for management of chronic epilepsy and refractory status epilepticus in adults.[24] But experienced medical staff guidance is important. It is stricter than the modified Atkin's diet. Potential adverse effects are seen, most likely the gastrointestinal

side effects (constipation, diarrhoea, occasional vomiting), weight loss and transient increase in lipids in adults.[20,23,24] In type-2 diabetic people following this low carbohydrate ketogenic diet, improved glycaemic control is seen but only when the diabetic medications are discontinued or reduced in most of the people.[25]

- Atkins diet – Like the ketogenic diet, it encourages fat intake, restricts carbohydrates and can induce weight loss and has been avoided in medical research. The Atkins diet can also induce a state of ketosis like in ketogenic diet. Due to this increased "fat burning" process, the ketones are produced as a by-product and the brain quickly adapts to using these as the main fuel source for energy production. It may have less side effects. The diet is 60% fat, 30% protein and 10% carbohydrates. Thus, is an effective and well tolerated therapy for intractable paediatric epilepsy.[20,21]
- Low glycaemic index diet – In this diet, larger amount of carbohydrate is included. Ketosis maybe minimal or even absent. So essentially this modified carbohydrate regimens alter the balance of fuel available to the brain; stabilising the glucose levels and producing an alternative fuel source in the form of ketones. Thus, these stable blood glucose levels and the shift towards the use of ketones bring about a greater stability of brain energy channels and produces many small chemical changes that can modify the chain reaction that leads to a seizure. The exact mechanism is not known and the research on this is ongoing. Its tolerability is improved and implementation is simpler which is not the case in ketogenic diet.[22]

This low glycaemic index diet is advisable for the patients with diabetes for control of postprandial glucose levels.[26]

MEDICATIONS FOR EPILEPSY[27,32]

Treatment can reduce or prevent seizure in most people suffering from epilepsy which can improve the quality of life. Use of anti-epileptic drugs (AED) is the standard of care in treatment of individuals with epilepsy. The goals of therapy are to make the patients free from seizures. Monotherapy is preferred due to potential AED interactions and toxicity with other drugs. Addition of second AED improves the control of seizures in patients with intractable epilepsy in about 40% of patients and seizure freedom in only 9%.[28] The antiepileptic drugs offer many options in the treatment of epilepsy, each with unique mechanisms of action as well as adverse effect profiles. These are well tolerated with minimal drug interactions, and a broad spectrum of activity.[29] A brief classification of drugs

along with their mechanism of action is given below for better understanding in treatment selection. AED treatment is started in the patient following the single seizure and where the recurrence risk is high (abnormal neurological examination, structural lesions on MRI, EEG etc).

1. Sodium channel blockers – It is the most common and best characterised mechanism of currently available AED's. They target sodium channels, prevent the return of channels to active state by stabilizing inactive form. Thus, prevents the repetitive firing of axons.

- Phenytoin – Most common and inexpensive AED. The primary site of action is at motor cortex where spread of seizure activity is inhibited, possibly by promoting the sodium efflux from neurons. It tends to stabilize the threshold against hyper-excitability that is caused by excessive stimulation or environmental changes.
- Carbamazepine – It affects sodium channels and inhibits rapid firing of brain cells. It is a favourite focal seizure medicine in the developed world.
- Oxcarbazepine – Similar to carbamazepine efficacy but have fewer side effects except for more risk of low blood sodium (hyponatremia). It is effective for initial monotherapyfor children with focal-onset seizures.[31]
- Lamotrigine – It is a broad-spectrum alternative to valproic acid. It works by several mechanisms like blocking voltage dependent sodium channel conductance, blocking release of glutamate which is the brains main excitatory neurotransmitter. The adverse effects seen with this drug are allergic rashes and Steven Johnson syndrome. It may be considered as monotherapy in adolescent females with idiopathic generalized epilepsy.[31]
- Zonisamide – It acts by reduction of neuronal repetitive firing by blocking sodium channels and preventing neurotransmitter release. Weight loss, CNS and cognitive effects are commonly seen with this drug.
- Lacosamide – It is a new AED for focal and secondarily generalised seizure. It is chemically related to amino acid serine. They work by blocking sodium channels and this reduces brain excitability. Prolonged PR interval, dizziness, headache, diplopia are the side effects associated with this drug.

2. 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 Gama Amino Butyric Acid (GABA). GABA-A receptors have several binding sites for benzodiazepines, barbiturates and other

substances. The benzodiazepines commonly used are lorazepam, clonazepam, diazepam, midazolam, clobazam and clorazepate.

- Clonazepam – Benzodiazepines are used as anti-seizure drugs, sedatives, tranquilizers and muscle relaxants. They increase the effectiveness of GABA, the brains main inhibitory neurotransmitter.
- Phenobarbital – It is inexpensive and effective in a single daily dose. It acts by increasing the effect of GABA in the brain.

2. GABA reuptake inhibitors – Reuptake of GABA is facilitated by at least 4 specific GABA transporting compounds; these carry GABA from the synaptic space into neurons and glial cells where it is metabolised. Nipecotic acid and Tiagabine (TGB) are inhibitors of these transporters. This inhibition makes increased amounts of GABA available in the synaptic cleft. GABA thus prolongs inhibitory post synaptic potentials.

- Tiagabine – It works by blocking the uptake of brain's main inhibitoryneurotransmitter, GABA. More GABA thus accumulates in brain and seizures are hard to initiate and sustain. It is useful for focal seizures in adults and is not effective for absence or myoclonic seizures.

3. GABA Transaminase Inhibitors – GABA is metabolised by transamination in the extracellular compartment by enzyme GABA-Transaminase (GABA-T). Inhibition of this enzymatic process leads to an increase in extracellular concentration of GABA.

- Vigabatrin – It inhibits the enzyme GABA-T by irreversibly binding to its active site and thus blocks the metabolism of GABA, the brains main inhibitory neurotransmitter. The common side effects witnessed with this drug are hyperkinesia, weight gain, insomnia and visual field defects.[32] It is the drug of choice for infantile spasms associated with tuberous sclerosis.[31]

4. AED'S with potential GABA mechanism of action - The enzyme glutamic acid decarboxylase (GAD) converts glutamate to GABA. Knowing this fact, currently Valproate (VPA) and Gabapentin (GBP) are designed and are known to have some effect on the enzyme and thereby enhance the synthesis of GABA.

- Gabapentin (GBP) – 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.
- Valproic acid – This is the standard broad-spectrum AED for all types of seizures and no other AED is more effective for generalized type of seizures. Valproates has effects on

GABA (at very high doses) and a neurotransmitter called NPY to block seizures and maybe also on calcium channels.

5. Glutamate blockers – Glutamate and Aspartate are the two important excitatory neurotransmitters in the brain. The glutamate system contains macromolecular receptors with different binding sites [like Alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), N-Methyl-D-Aspartate (NMDA), Kainite, Glycine and metabotropic sites]. This NMDA receptor is involved in transfer of electrical signals between neurons by allowing Na+ and Ca+ ions enters through it. For these signals to pass, NMDA must be open. To remain open, glutamate and glycine must bind to NMDA receptor. Thus, blocking the glutamate, inhibit the excitatoryeffects.

- Felbamate – It has dual mechanism of actions– positive modulator of GABA receptors and secondly blocks NMDA receptors. It is used to treat variety of seizure types and is known effective against atonic seizures, focal and secondarily generalized seizures.
- Topiramate – It is a potent AED with multiple mechanism of actions like inhibitory effect on sodium conductance, decrease the duration of abnormal burst and frequency of action potentials, enhances GABA, inhibits AMPA receptor and weak inhibitor of enzyme carbonic anhydrase which in-turn increases the acidity of brain tissue and thus supresses seizures. The adverse events observed with topiramate are fatigue, impaired concentration, weight loss, dizziness, and paresthesias. It acts good by controlling symptoms in patients especially with resistant focal seizures(30) and also in patients with epileptic encephalopathies such as Lennox-Gastaut syndrome and myoclonic astatic epilepsy.[31]

7. Levetiracetam – It is widely used medicine as it is effective against many seizure types. It acts by binding to SV2A, a synaptic vesicle glycoprotein-2A and inhibits presynaptic calcium channels, thus reducing the neurotransmitter release. Behavioural disturbances is seen mainly as an adverse effect.[32]
8. Rufinamide – It's mechanism of action is unknown but there is some evidence that it can modulate the voltage-gated sodium channels in brain cells in a way to make them less excitable. Occasional CNS side effects are seen in the patients taking this drug.

OTHER NEW AED's[32,33]

1. Ezogabine – It is an investigational AED that is developed as an adjunctive treatment for focal epilepsy. It works by opening of voltage-gated KCNQ2/3 and KCNQ3/5 potassium channels leading to cellular membrane hyperpolarization. It is mainly used in the

treatment of benign familial neonatal convulsions that is caused by loss of function mutations involving the KCNQ2/3 genes.[32]

2. Brivaracetam – It is an analogue of levetiracetam[33] and similarly works on a protein SV2A in the brain and is known to bind to the site of action up to 30 times more than the levetiracetam. It is used as an add-on therapy in uncontrolled focal-onset epilepsy.[32]
3. Eslicarbazepine - It is structurally related to carbamazepine and oxcarbazepine and thus works by blocking the sodium channels in the brain which are responsible for generating the seizures. It has been used as adjunctive therapy for adults with focal seizures. The advantage of eslicarbazepine when compared with other drugs is its ease of administration with single daily dosing.[32]
4. Perampanel – It is a non-competitive antagonist of α-amino-3-hydroxy 5-methyl-4-isoxazolepropionic acid (AMPA) – a type glutamate receptors, thus reducing the effects of glutamate which is associated with seizures.[32] It is currently in clinical development as adjunctive therapy for the treatment of uncontrolled focal-onset seizures and for adult patients with generalized tonic-clonic seizures.

SURGERY[34-36]

- Epilepsy surgery may be an option for people whose seizures are not controlled by medication. It is a procedure that removes or alters an area in the brain where the seizures originate. It is performed either to decrease the frequency of occurrence of seizure or for complete freedom from seizures. Different methods of surgeries are done depending on the seizure type and the area in the brain where the seizure start. Surgical options include lobe resection, lesionectomy, corpus callosotomy, functional hemispherectomy, Laser Interstitial Thermal Therapy, multiple subpial transection etc.[35] Depending on the surgery type, the effectiveness varies with success rates between 50-80%. There is a high quality evidence that epilepsy surgery is effective at reducing seizure frequency and only 0.1% mortality rate is observed with surgery.[34] Higher rate of freedom from seizures after the epileptic surgery is seen especially in children and adolescents with drug-resistant epilepsy.[36]

VAGUS NERVE STIMULATOR[37,38]

- It is a device used in the people whose seizures are not controlled by the medications. It is a small device that is surgically implanted under the skin of the chest which is attached to the vagus nerve in the lower neck. It sends regular, mild impulses of electrical energy to

the brain via the vagus nerve and this stimulation reduces the seizures. It is sometimes referred to as "pacemaker for the brain". It is a viable palliative surgical strategy in children with refractory epilepsy. The treatment is generally well-tolerated and efficacious for many children.[38] It has been successful, due to patient acceptability, safety, and a low incidence of side effects.

CONCLUSION

Epilepsy is the most common neurological disease that is characterised by abnormal electrical activity in the brain and that may occur at any age. A new classification of seizures by ILAE helps in better understanding of seizure and epilepsy diagnoses. Different types of diagnostic tests can be done for identification of seizure type and the site of origin. Presently a large number of medications for management of seizure are available and a variety of surgical techniques for the patients whose seizures are not controlled by the medications are accessible for its good control. Other treatment options include the dietary therapies like ketogenic diet, Atkins diet and low glycaemic diet and a surgically implantable device, vagus nerve stimulator. Research has helped us for better understanding of epilepsy and its epidemiology, etiology, risk factors, diagnostic procedures, newer classification and treatment and even newer ways of preventing epilepsy in the future.

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