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REVIEW ARTICLE ON MANAGEMENT OF EPILEPSY

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ABSTRACT

Epilepsy is one of the most common, non contagious, serious brain disorder that can be treatedsuccessfully in most patients with one or more Ant seizure drugs. The management of patients with epilepsy demands long term commitment from both the general practitioner and specialist. This article provides an overview of classification, pathophysiology, aspects of differential diagnosis, newer treatment and treatment options, prognosis, including a consideration of conditions that accompany epilepsy.

KEYWORDS: Epilepsy, Classification, Diagnosis, Newer treatment, prognosis.

INTRODUCTION

SEIZURE – A seizure is a paroxysmal event characterized by abnormal, excessive,hypersynchronous discharge of cortical neuron activity.

EPILEPSY- It can be defined as a chronic seizure disorder or group of disorders characterized by seizures that usually recur unpredictably in the absence of a consistent provoking factor. Epilepsy has numerous causes, each reflecting underlying brain dysfunction.

Epilepsy is non contagious, not a mental illness or a cognitive disability. The neurological dysfunction seen in epilepsy can begin at birth, childhood, adolescence or even in adulthood.

EPIDEMIOLOGY

With an estimated incidence of 34 to 76 new cases per year per 100,000 people, epilepsy affects about 70 million people worldwide. Nowadays Epilepsy is an major burden for public health systems. The disease burden from epilepsy was higher than that for Alzheimer's disease and other dementias, multiple sclerosis and Parkinson's disease combined.

Epilepsy also imposes a large economic burden on patients and their families, particularly in rural and remote regions where access to skilled medical care is difficult.

ETIOLOGY

Epilepsy may result from primary or acquired disturbances of CNS function, metabolic derangements, or a variety of systemic disorders. common cause of seizures vary according to patient age. For example, fever is only a precipitant of seizures during infancy and early childhood.

In adulthood,acquired cause of seizures and epilepsy e.g., stroke, CNS tumor, CNS infection and drug and alcohol toxicity and more common, and are referred to as "**symptomatic"** epilepsy.

When no cause of seizures can be identified by history, physical examination, laboratory investigation, or neuroimaging studies, the seizure disorder is termed **"cryptogenic".**

CLASSIFICATION

CLASSIFICATION

I. *Partial seizures*

A. Simple seizures
(without impairment of consciousness)
1. With motor symptoms
2. With special sensory or somatosensory symptoms
3. With psychic symptoms

B. Complex seizures
(with impairment of consciousness)
1. Simple partial onset followed by impairment of consciousness
2. Impaired consciousness at onset

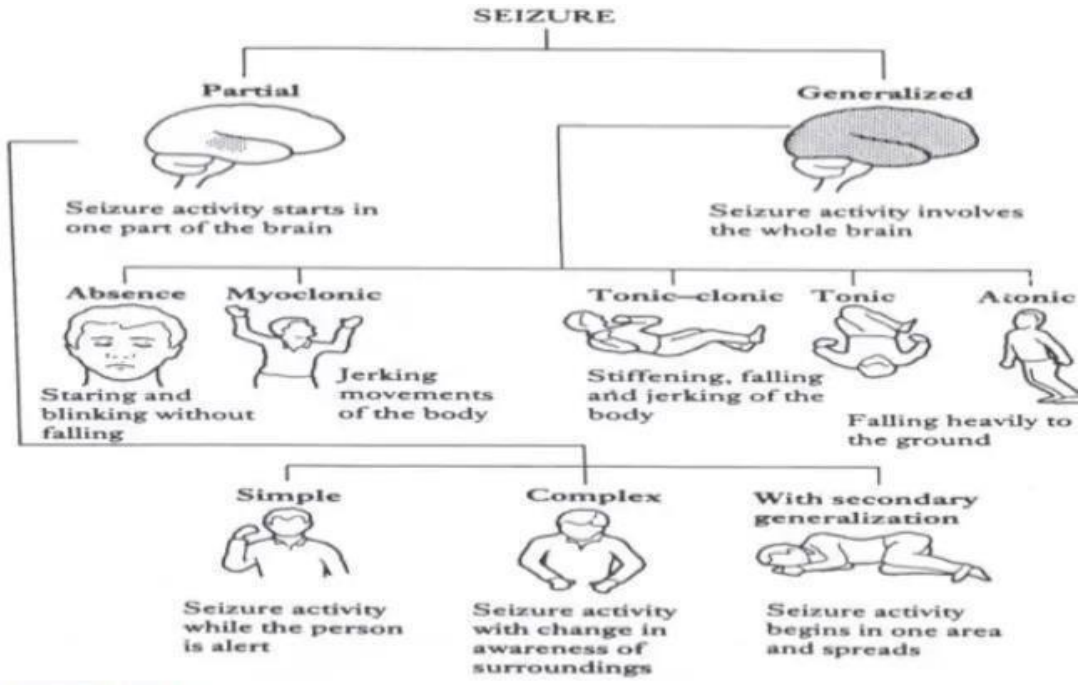
C. Secondarily generalized
(partial onset evolving to generalized tonic-clonic seizures)

II. Generalized seizures

A. Absence
B. Myoclonic
C. Clonic
D. Tonic
E. Tonic-clonic
F. Atonic
G. Infantile spasms

III. Unclassified seizures

IV. Status epilepticus



1. Partial seizure: It is common in 80% 0f people.
Simple partial seizures: It do not cause loss of consciousness. Itssigns and symptoms are.

Motor – convulsive jerking, chewing motions, lip smacking. Sensoryand somatosensory – Paresthesia's, auras

Automatic – sweating, flushing, pupil dilation.
Behavioral – hallucinations, dysphasia, impaired consciousness(rare).

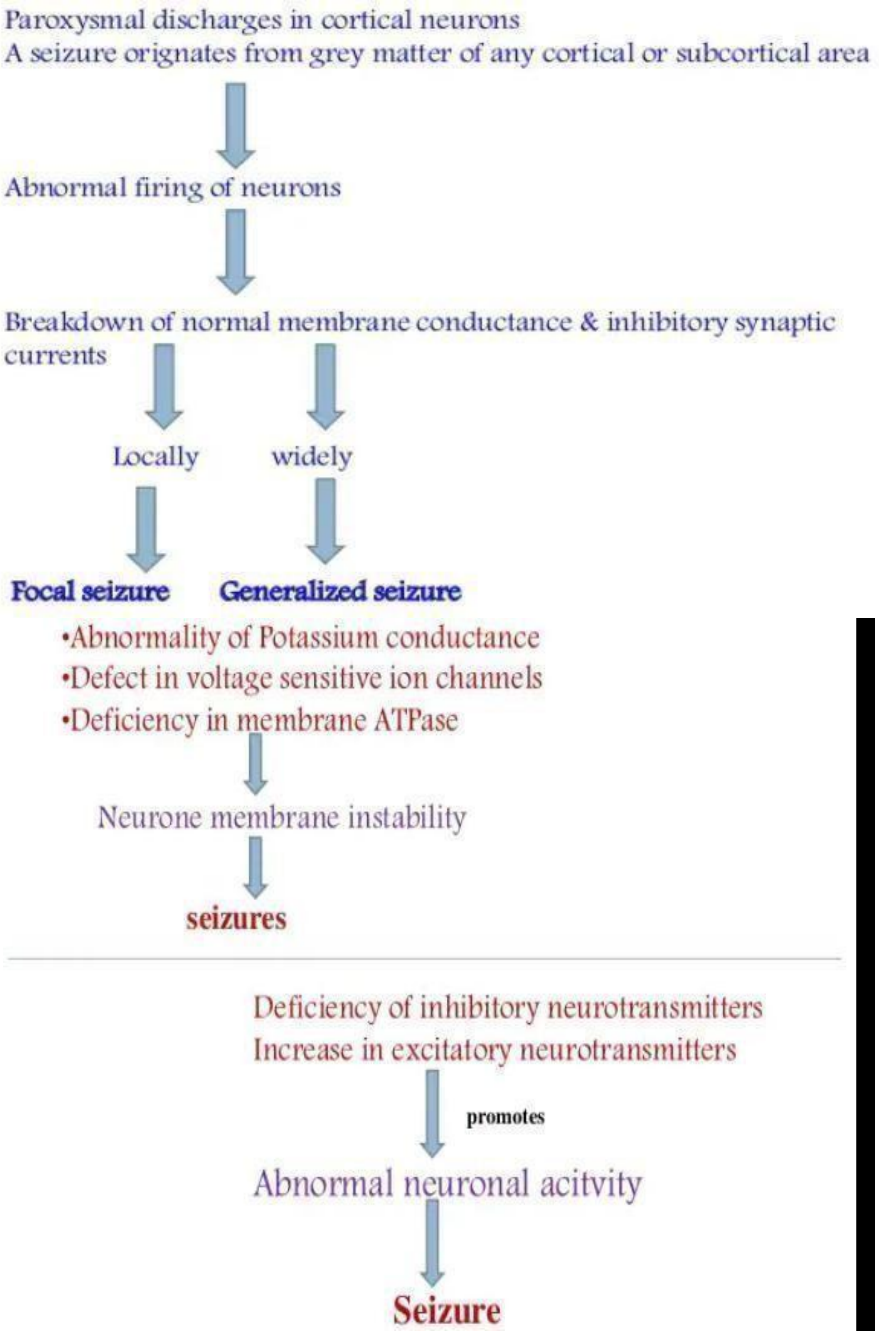
Complex partial seizures
Complex partial seizures may have impairment of consciousness, purposeless behavior is common. Affected person may wander about aimlessly, aggressive behaviour, automatism, visual, auditory, or olfactory hallucinations.

2. **Generalized seizures:** Affecting both hemispheres. These are of three types :
1) Idiopathic epilepsies
2) Symptomatic epilepsies
3) Cryptogenic epilepsies

A) Absence seizures : alteration of consciousness lasting 10 – 30sec, staring and loss in postural tone. Onset occurs from 3-16 years, disappear by 40yrs.
B) Myoclonic : sudden, involuntary jerking of facial, limb or trunk muscles, inrhythmic manner
C) Clonic : sustained muscle contractions alternating with relaxations.
D) Tonic : sustained muscle stiffening.
E) Tonic – clonic : sudden loss of consciousness
F) Atonic : sudden loss of postural tone, patient fails to the ground. Occur primarilyin children.

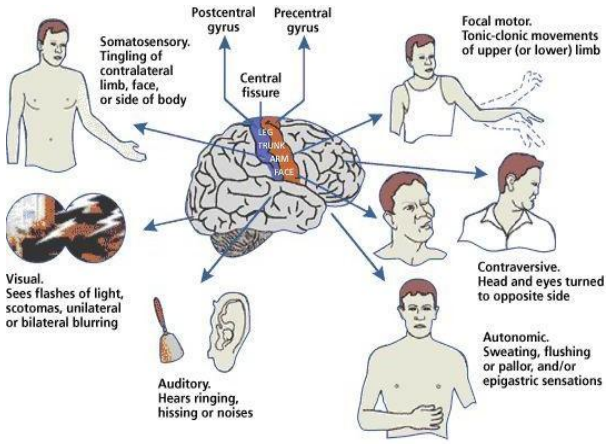
3. **Unclassified seizures :** Neonatal
4. **Status epilepticus:** Seizure occur repeatedly with no recovery of consciousness betweenattacks.

PATHOPHYSIOLOGY



SIGNS AND SYMPTOMS

Characteristics of seizures vary and depend on where in the brain the disturbance first starts, and symptoms occurs such as Loss of consciousness, disturbances of movement, sensation (including vision, hearing and taste), mood, or other cognitive functions.



RISK FACTORS

Some of the risk factors observed in epilepsies are sleep deprivation, Missed doses of anti-epileptic drugs in treated patients. Alcohol withdrawals, drug misuse. Physical and mental exhaustion. Flickering lights (includes TV, Computer screens; comes under generalized epilepsy Syndrome).

DIAGNOSIS

Patient History

- Perinatal and development history
- Historyof febrile seizures
- Historyof CNS infection, trauma
- Family history of epilepsy

Physical Examination

- Seizure Description
- Preictal phenomena (aura)
- Ictal manifestation (including level of consciousness)
- Postictal state
- Provocative factors

Laboratory assessment

- Blood urea nitrogen
- Cerebrospinal fluid profile (only if meningitis is suspected)
- Complete blood count
- Electrolytes and glucose
- Osmolality
- Toxicology screen (if indicated)

Neurological examination

- Electroencephalogram (EEG)
- Computed tomography
- Magnetic resonance imaging (MRI)

EEG

EEG is a medical device for analyzing the electrical activity of the brain. It can detect Epilepsy or Alzheimer's diseases. The general mechanism is picking up the charge of electrical potentials. The neurons are negative when they are at rest and become positive when they Synapse. The EEG can record this change by electrodes to the amplifiers because the power of brain signal is very small. It's a safe procedure. It can detect abnormal electrical activity, such as focal spikes or waves (consistent with focal epilepsy), or diffuse bilateral spike waves (consistent with generalized epilepsy). A routine EEG will, preferably, include wakefulness, drowsiness, and sleep because the prevalence of epileptiform abnormalities varies in these different states of consciousness.

Neuroimaging

Computed tomography (CT) and magnetic resonance imaging (MRI) scans are the important scans to the clinical examination and EEG in the evaluation of a person with seizures. Neuroimaging techniques are especially for central nervous system (CNS) structural lesions. Focal neurologic findings on examination (e.g., unilateral weakness, asymmetric reflexes) mandate neuroimaging.

MRI is more likely to show an abnormality in a patient with focal seizures, abnormal neurologic findings, or focal discharges on EEG. MRI is more sensitive than CT and is therefore preferred, especially for the detection of cortical malformation, dysgenesis, or hippocampal sclerosis.

Quantitative, computer-assisted volume analysis of the temporal lobes may detect asymmetries that are not readily apparent on visual analysis of the scan. CT scan usually detects hemorrhage, calcification, or tumors.

Several new imaging techniques are available to aid in the assessment of epilepsy. MRI abnormalities can be correlated directly with EEG activity. Functional MRI (FMRI) takes advantage of blood oxygen level dependence (BOLD) to image neuronal activation and map interictal or ictal epileptiform activity and localize language and memory. Magnetic resonance (MR)

spectroscopy measures the concentrations of a variety of neurochemicals in different brain regions and can sometimes assist in localizing a seizure focus. Positronemission tomography (PET) images the brain's regional use of glucose with asymmetries suggesting areas of interictal or ictal abnormality.

Epileptic Syndromes

- Infantile- onset epilepsies.
- Childhood – onset epilepsies.
- Adolescent – onset epilepsies.

INFANTILE – ONSET EPILEPSIES

- West syndrome.

The most common epileptic encephalopathy with an incidence of 3 to 4.5 per 10000 live births.

- Dravet syndrome.

Previously called severe myoclonic epilepsy of infancy.

CHILDHOOD – ONSET EPILEPSIES

- Panayiopoulos syndrome (Early- onset Benign occipital Epilepsy)
- Benign epilepsy with centrotemporal spikes (benign Rolandic epilepsy)
- Electrical status epilepticus in slow sleep
- Myoclonic- Atonic epilepsy (Doose Syndrome)
- Lennox – Gastaut Syndrome.

ADOLESCENT- ONSET EPILEPSIES

- Juvunile Absence Epilepsy
- Juvenile Myoclonic Epilepsy

Management of Epilepsy

The decision to start treatment should not be taken lightly. Sometimes it may leads to sudden orunexpected death.

The main goals of treatment are to control and reduce seizure frequency. To focus on minimum possible dosage of AEDs and to improve patient quality of life.

Non Pharmacological Treatment

- Ketogenic diet : ketogenic diet containing high content of fats, followed by proteins, carbohydrates were found to reduce seizures in some children Side effects – constipation, slow growth because of nutritional deficiencies, build up of uric acid in blood, kidney stones.
- Surgeries: medications can control seizures in most people with epilepsy, but they don't work for everyone. About 30% of people taking the drugs can't tolerate the side effects. In such cases, brain surgery may be an option.

1. Lobe resection: the lobe within which seizures focus is cutoff. Extemporal resection involves brain tissue from areas outside of the temporal lobe.
2. Lesionectomy: this surgery removes the brain lesions, areasof injury or defect like a tumor or malformed blood vessel that cause seizures. Seizures usually stop once the lesion is removed.
3. Corpus callostomy or split-brain surgery: corpus callosum is a band of nerve fibers connecting the two halves (called hemispheres) of the brain. In this operation, corpus callosum is cut off and the communication between hemispheres is prevented, no spread of seizures from one side to other side. It works best for people with extreme forms of uncontrollable epilepsy who have intense seizures that can lead to violent falls and serious injury.
4. Functional hemispherectomy: entire hemispheres or half of the brain is removed. It is mostly used for children younger than 13 who have one hemispheres that doesn't work like it should.
5. Multiple subpial transection: this procedure can help to control seizures that began in areas of the brain that can't be safely removed. The surgeon makes a series of shallow cuts in the brain tissue. These cuts interrupt the flow of seizure impulse but don't disturb normal brain activity.
6. Vagus nerve stimulation: a device implanted under the skin sends an electric jolt to the vagus nerve, which controls activity between brain and major internal organs. It lowers seizure activity in some people with partial seizures.

Prophylactic Treatment

Prophylactic treatment has sometimes been advocated, notably in patients with severe head injury. While immediate treatment may reduce the risk of early post-traumatic seizures (within one week of injury) it does not influence the risk of late post-traumatic epilepsy.3 Studies addressing this issue in other neurological conditions with a high prospective risk of epilepsy (febrile seizures, craniotomy, cerebral tumors) have failed to show anyevidence of benefits.

Single seizure

Patients presenting with a first seizure, where avoidable provocative factors have been excluded, represent a common clinical dilemma. Methodological differences explain the widely varying estimates of risk of recurrence. Treatment after a first tonic-clonic seizure halves the two-year risk of seizures from approximately 40% to 20%.

Recurrent seizures

The decision to start treatment is much more straightforward in a patient with recurrent seizures and a clear-cut diagnosis of epilepsy, especially if he or she has an identifiable syndrome with a predictable prognosis—for example, juvenile myoclonic epilepsy.

Medication are the most common treatment for people with epilepsy. Most epilepsy syndromes and the vast majority of genetic syndromes that cause seizures are adequately treated with existing medication. The good news is that if they get identified properly and are prescribed the right kind of medication, most people with

epilepsy will do well. But the bad news is that many doctors don't recognize specific epilepsy syndromes and don't use the right medication to treat them. If you're on the right drug, you're likely to have good control of your seizures. But if you're on the wrong drug, you may keep having seizures -- and you might not even know that there are better approaches out there. That's why getting expert care can be important.

Drugs Used to Treat Epilepsy

There are numerous drugs now used to treat epilepsy. They include.

Narrow-spectrum Antiepileptic drugs (for specific types of seizures): carbamazepine (Carbatrol, Epitol, Equetro, Tegretol), clobazam (Onfi), diazepam (Diastat, Valium), divalproex (Depakote). eslicarbazepine acetate (Aptiom), ethosuximide (Zarontin), felbamate (Felbatol), gabapentin (Gralise, Neurontin), lamotrigine (Lamictal), levetiracetam (Keppra), lacosamide (Vimpat), methsuximide (Celontin), phenytoin (Dilantin, Phenytek), pregabalin (Lyrica), rufinamide (Banzel), tiagabin hydrochloride (Gabitril), vigabatrin (Sabril).

Broad-spectrum AEDs (for seizures in one of more part of the brain): clonazepam (Klonopin), clorazepate (Tranxene-T), ezogabine (Potiga), felbamate (Felbatol), lamotrigine (Lamictal), levetiracetam (Keppra, Spritam), lorazepam (Ativan), primidone (Mysoline), topiramate (Topamax, Qudexy XR, Trokendi XR), valproic acid (Depacon, Depakene, Depakote, Stavzor),or zonisamide (Zonegran). The nice things about these newer drugs are they tend to have fewer side effects. They're easier to use and more predictable. That's helpful, since we know that drug interactions are the bane of many patients. The drug Epidiolex, which is made from cannabidiol (CBD) a form of medical marijuana has been found to be effective in treating very severe orhard- to-treat seizures.

Surgery can lead to long-term remission. It can be a true cure for epilepsy. When epilepsy isn't being controlled by medication and surgery isn't an option, we turn to devices.There are two on the market now.
Vagus nerve stimulator (VNS). NeuroPace - a reactive neurostimulator both are considered low-risk procedures.

Vagus Nerve Stimulator work

VNS therapy works by sending an electrical pulse to the vagus nerve in the neck. It's not clear how VNS therapy stops seizures, but it's believed that the device blocks certain brain impulses thatdirect the body to start a seizure. The VNS device is powered by a small battery implanted in the chest. In some cases, it can make someone almost seizure-free.

The Neuro Pace is a reactive neurostimulator that detects seizures and shocks the brain to stop them. The device is set to send out pulses of a certain duration at certain intervals and it goes around the clock. It uses the technology from cardiac defibrillator devices to respond to electrical activity in your brain. Electrodes are placed where seizures are suspected of coming from, either on the surface of the brain or deep within it. This is hooked up to a miniature recording device that samples brain activity, like a tiny EEG machine. When it senses that the pattern is abnormal, it fires an electrical pulse to disrupt the pattern.

Antiepileptic drugs and hormonal contraception.

Medication	Starting Dose	Common Side Effects	Pros	Cons
Phenobarbital	*Both dogs and cats:* 2-3 mg/kg q12 hours	Sedation, ataxia, polyphagia, PU/PD	- Know to be very effective in dogs for reducing seizure frequency and severity - Well tolerated in cats	- May cause increased sedation and ataxia in older dogs - Contraindicated in dogs with impaired liver function
Levetiracetam	*Dogs:* 20-30 mg/kg q8 hours OR 30-40 mg/kg q12 hours extended release formulation *Cats:* 20-30 mg/kg q8 hours OR 500 mg q24 hours extended release formulation (Barnard et al. 2017)	Sedation, ataxia, decreased appetite, vomiting, behavior change	- Very safe and well tolerated in most animals	- May be less effective as a monotherapy compared to other anticonvulsants - Every 8 hour dosing unless large enough to receive extended release formulation
Zonisamide	*Dogs:* 5-10 mg/kg q12 hours *Cats:* 5-10 mg/kg q24 hours	Sedation, ataxia, vomiting, inappetence	- Tends be less sedating than phenobarbital and KBr - Shown to be effective in reducing seizure frequency and severity	- May cause decreased appetite; especially in cats
Potassium bromide (KBr)	*Dogs:* 30-40 mg/kg q24 hours	Sedation, ataxia, PU/PD, polyphagia, nausea/vomiting, diarrhea	- Safe to give in dogs with impaired liver function - Once daily dosing	- May cause profound sedation and ataxia in older dogs - Long half-life makes dose adjustments difficult - Not safe to use in cats

Drugs that reduce the effectiveness of hormonal contraception

Phenobarbital.Phenytoin.
Primidone. Oxcarbazepine
Topiramate, carbamazepine.

Drugs that do not reduce the effectiveness of hormonal contraception

Gabapentin. Lamotrigine. Levetiracetam.Tiagabine.
Valproate. Vigabatrin. Zonisamide.

Newer Management of Epilepsy

Drug*	Presumed Main Mechanism of Action	Approved Use (FDA, EMA)	Main Uses	Main Limitations
Vigabatrin (1989, U.K.; 2009, U.S.)	GABA potentiation	Infantile spasms, complex partial seizures (currently for adjunctive use only)	No clinical hepatotoxicity; use for infantile spasms, focal and generalized seizures with focal onset	Not useful for absence or myoclonic seizures; causes a visual field defect and weight gain; not as efficacious as carbamazepine for focal seizures
Lamotrigine (1990, Ireland; 1994, U.S.)	Na^+ channel blocker	Partial and generalized convulsive seizures, Lennox-Gastaut syndrome, bipolar disorder	First-line drug for focal and generalized seizures	Enzyme inducer, skin hypersensitivity; not as effective as valproate for new-onset absence seizures
Oxcarbazepine (1990, Denmark; 2000, U.S.)	Na^+ channel blocker	Partial seizures	First-line drug for focal and generalized seizures with focal onset	Enzyme inducer, hyponatremia, skin hypersensitivity; not useful for absence or myoclonic seizures
Gabapentin (1993)	Ca^{2+} blocker (α28 subunit)	Partial and generalized convulsive seizures, postherpetic and diabetic neuralgia, restless legs syndrome	No clinical hepatotoxicity; use for focal and generalized seizures with focal onset	Currently adjunctive use only; not useful for absence or myoclonic seizures, and can cause weight gain; not as effective as carbamazepine for new-onset focal seizures
Topiramate (1995)	Multiple (GABA potentiation, glutamate [AMPA] inhibition, sodium and calcium channel blockade)	Partial and generalized convulsive seizures, Lennox-Gastaut syndrome, migraine prophylaxis	First-line drug for focal and generalized seizures; no clinical hepatotoxicity	Cognitive side effects, kidney stones, speech problems, weight loss; not as effective as carbamazepine for new-onset focal seizures
Tiagabine (1996 Europe, 1997 U.S.)[10]	GABA potentiation	Adjunctive therapy in adults and children 12 years of age and older in the treatment of partial seizures[16]	No clinical hepatotoxicity; adjunctive use for partial seizures[10]	Currently for adjunctive use only; narrow spectrum, may exacerbate generalized myoclonic and absence seizures[10,14]
Levetiracetam (2000)	SV2A modulation	Partial and generalized convulsive seizures, partial seizures, GTCS, juvenile myoclonic epilepsy	First-line drug (IV) for focal and generalized seizures with focal onset and myoclonic seizures; no clinical hepatotoxicity; as efficacious as carbamazepine for new-onset focal seizures	Not useful for absence or myoclonic seizures; psychiatric side effects
Zonisamide (2000)	Na^+ channel blocker	Partial seizures	First-line drug for focal and generalized seizures; no clinical hepatotoxicity; non-inferior to carbamazepine for new-onset focal seizures	Cognitive side effects, kidney stones, sedative, weight loss
Stiripentol (2002)	GABA potentiation, Na^+ channel blocker	Dravet syndrome	Use for seizures in Dravet syndrome; no clinical hepatotoxicity	Currently for adjunctive use only
Pregabalin (2004)	Ca^{2+} blocker (α28 subunit)	Partial seizures, neuropathic pain, generalized anxiety disorder, fibromyalgia	Use for focal and generalized seizures with focal onset; no clinical hepatotoxicity	Currently for adjunctive use only; not useful for absence or myoclonic seizures; weight gain
Rufinamide (2004)	Na^+ channel blocker	Lennox-Gastaut syndrome	Use for seizures in Lennox-Gastaut syndrome; no clinical hepatotoxicity	Currently for adjunctive use only
Lacosamide (2008)	Enhanced slow inactivation of voltage-gated Na^+ channels	Partial seizures	Use (IV) for focal and generalized seizures with focal onset; no clinical hepatotoxicity	Currently for adjunctive use only

CONCLUSION

This review introduced the concepts of classification, diagnosis, management of epilepsy. Antiepileptic drugs that prevent the development of epilepsy before the first seizure. patients with non-epileptic attacks should be handled sensitively; a multidisciplinary approach isessential. The optimal management of patients with epilepsy requires cooperation between specialist, general physician, and patient. when initiating treatment a start slow, go slow approach reduces risk of intolerance. Carbamazepine and valproate are standard drugs of first choice of partial and generalized onset seizures, respectively.

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