www.jmscr.igmpublication.org
Index Copernicus Value: 79.54
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v7i3.229

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

A Review on Epilepsy

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Abstract
Epilepsy is one of the most common neurologic disorders of the brain, affecting about 50 million individuals worldwide, among them 90% patients are from developing countries. It is a universal disorder which affects all age groups. Genetic factors as well as infection in brain, stroke, tumour and high fever are some of the causes of epilepsy. Each year about 125,000 new epilepsy cases occur; of these, 30 % are younger than age 18 at the time of diagnosis. Prevalence of 3-11/1000 and incidence of 0.2-0.6/1000are observed in India. The hallmarks of seizure generation are hyperexcitability of neurons and hypersynchrony of neural networks. Mechanisms underlying the epilepsy are imbalance between excitatory and inhibitory neurotransmitters. Depending on areas of the brain are involved, epileptic seizures may consist of loss of awareness with tremors, confusion, difficulty in responding; visual or other sensory symptoms are observed. Seizures are classified based on site of origin and symptoms. Benzodiazepines, barbiturates and ion channel modulators are used in the treatment of epilepsy. Treatment should usually be started with single antiepileptic drug. Phenytoin, phenobarbitone, carbamazepine, oxcarbazepine and valproate are usually called first-line drugs. This review discusses epidemiology, aetiology, pathophysiology, classification of epilepsy, symptoms, diagnosis and management of epilepsy.
Keywords: *Epilepsy, Seizures, hyperexcitability, anti-epileptic drugs.*

Introduction

Epilepsy is a disorder of the central nervous system and is characterized by periodic loss of consciousness with or without convulsions associated and with abnormal electrical activity in the brain. Epilepsy is seen as the clinical manifestation of an abnormal and excessive discharge of a set of neurons in the brain[1].

Seizure result from sudden excessive nerve-cell discharges in the brain resulting in abnormal function of the body, often causes loss of consciousness, excessive muscular activity, or an abnormal sensation[2].

Epidemiology

Epidemiology in world-wide: Epilepsy is one of the most common neurological disorders. Each

year 120 per 100,000 people in the USA come with newly recognized seizure. At least 8% of the general population will have one seizure. The rate of recurrence of the first unprovoked seizure within 5years ranges between 23% and 80%. Each year about 125,000 new epilepsy cases occurs; of these, 30 % are in people younger than 18 years of age at the time of diagnosis[3]. The economic burden of neurological diseases are about 800 billion dollars annually in the United States. Epilepsy itself contributes about 37 billion dollars annually in United States[4].

Epidemiology in India: Nearly 12 million people with epilepsy are expected to be found in India; which contributes to nearly one-sixth of the global burden. Data from recent studies in India reported prevalence of 3-11/1000 and incidence of0.2-0.6/1000. Prevalence of epilepsy was higher in rural areas compared to urban areas (in developing countries) [5].

Aetiology: Epilepsy and epileptic seizures are universal disorders affect in gall ages, race, social class and geographical regions around the world[6]. Genetic factors, environmental factors, infection in brain, stroke, tumour and high fever are few causes of epilepsy[4].

Phases of seizures

Four phases of a seizure can be distinguished. These components include:

a) Prodromal phase
b) Aura
c) Seizure(ictal phase)
d) Post-ictal phase

a) Prodromal phase: This phase starts few hours before or even days before the actual seizure and should not be confused with the aura. The symptoms of prodromal phase include: headache, irritability, insomnia, bad temper, depression or increased activity.

b) Aura: This phase precedes the seizure by seconds or a few minutes. It is the beginning of the seizure episode. The feelings of the aura include extreme fear, strange epigastric sensations, dreamlike experiences, unpleasant smells, etc. The patient remembers the aura phase very well.

c) Seizure (ictus phase): In almost many seizures there is a loss of consciousness, and the patient may not able to give any information about the actual ictus.

d) Post-ictal phase: This phase may not be present, or may last for several hours, and sometimes even for days. There symptoms include deep sleep and waking up with headache, tiredness, irritability, confusion, muscular aches or ataxia. Transient paralysis may occur for a few hours or even days[2].

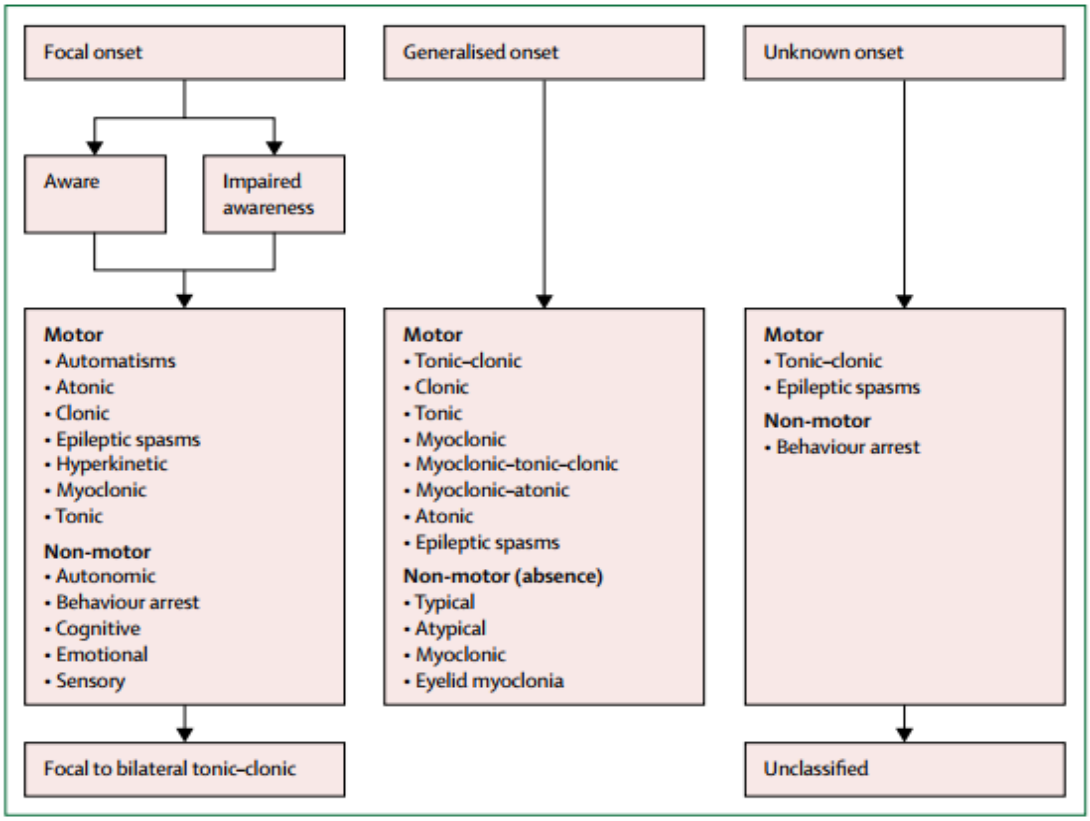
Triggering factors

Various types of external and internal stimuli trigger seizures. Typical seizure triggers are sleep deprivation, systemic infection, fever, critical phases of the menstrual cycle, intake or withdrawal of certain drugs and substances including alcohol, homeostatic imbalances such as hyponatraemia. Flickering light is a classic trigger, potential external sensory stimuli include: touch, hot water, specific visual patterns, reading, music[7].

Classification of epilepsy

Seizures are classified based on whether consciousness is retained or impaired and whether there is motor involvement. Focal seizures with preserved awareness are known as "simple partial" seizures and the focal seizures with impaired awareness are known as "complex partial" seizures. Seizures that lead to bilateral motor involvement have a stiffening (tonic) phase, followed by a muscle jerking (clonic) phase are known as tonic-clonic seizures[8].

Table-1 Classification of epilepsy (International League Against Epilepsy framework for the classification of epileptic seizures[10])



Diagnosis

Neuroimaging studies play an integral role in evaluation of seizures for the determination of the structural and functional aetiology of seizures. Various diagnostic tools are used to identify and classify the seizure type and aetiology, including Electroencephalogram (EEG), Magnetic Resonance Imaging (MRI), and Positron Emission Tomography (PET), single photon emission computed tomography (SPECT), Magneto Encephalogram (MEG), and neuropsychiatric testing[4]. The EEG often is critical for identifying specific seizure types. CT scan may help in assessing newly diagnosed patients, but MRI is preferred. MRI may locate brain lesions or anatomic defects that are missed by conventional radiographs or CT scans[10].

Serum prolactin level obtained within 10 to 20 minutes of a tonic-clonic seizure can be useful in differentiating seizure activity from pseudo seizure activity but not from syncope[11]. EEG is mostly useful in the diagnosis of various types of seizures.

Pathophysiology

Seizure results when a sudden imbalance occurs between excitatory and inhibitory neurotransmitters within the network of cortical neurons. The basic physiology of a seizure episode is an unstable cell membrane or its surrounding cells. The seizure originates from the grey matter of any cortical or subcortical area. Initially a small number of neurons fire abnormally. Normal membrane conductance and inhibitory synaptic current breakdown and increased excitability spread either locally to produce a focal seizure or more widely to produce a generalized seizure. This onset propagates by physiologic pathways towards adjacent areas[3]. Seizures occurs from transient abnormal synchronization of neurons in the brain which disrupts normal patterns of neuronal communication and results in electrical discharges in the EEG. This disruption can produce various symptoms and signs that depend on the site of origin of the seizure and its connections. Within the epileptic focus, seizures originate from

increased excitation or decreased inhibition, based on a model that involves communication between two neurons where the activity of the second neuron has a measurable outcome[13]. During a seizure, demand for blood flow to the brain increases to carry off CO_2 and to bring the substrate for metabolic activity of the neurons. As the seizures prolong, the brain suffers more from ischemia that resulting in neuronal destruction and brain damage[3].

Clinical manifestations: Signs and symptoms are due to abnormal, excessive or synchronous neuronal activity in the brain. Depending on which areas of the brain are involved, epileptic seizures may consist of loss of awareness with tremors, confusion and difficulty in responding; visual or other sensory symptoms; isolated posturing or jerking of a single limb; or brief loss of awareness. Seizure origin, pattern of spread, and brain networks determine the signs and symptoms of a seizure[8].

Table-2 Signs and symptoms of epilepsy[13]

Type	Area affected	Function affected	Clinical features of seizures
Generalised	All parts of brain affected		
Tonic clonic		Motor, consciousness	Tonic and clonic convulsions, loss of consciousness
Myoclonic		Motor	Jerking limbs
Absence		Attention, consciousness	Brief periods of reduced awareness.
Partial			
	Frontal lobe	Motor	Twitching, jerking
	Temporal lobe	Sensory	Smells, epigastric sensation & any other sensations.
		Behaviour	Psychiatric
	Parietal lobe	Sensory	Tingling etc;

Risk factors

- Onset of seizures after age of 12
- Family history of seizures
- Uncontrolled seizures for >2-6 years
- Increased number of seizures episodes (>30)
- History of absence seizures
- Moderate to severe mental retardation
- History of febrile seizures[10]

Complications

Epilepsy rarely stands alone, more than 50% of people with epilepsy have one or several additional medical problems. Psychiatric conditions (eg, depression, anxiety disorder, psychosis, and autism spectrum disorder) have long been associated with epilepsy, but more recently somatic conditions (eg, type 1 diabetes, arthritis, digestive tract ulcers, and chronic obstructive pulmonary disease) have also been associated to epilepsy[9].

Treatment

Treatment should be started with a single conventional Anti-Epileptic Drug (AED). The dose should be gradually increased until seizure control is achieved. If the initial treatment is ineffective then second AED can be tried. The dose of the second drug is increased slowly until maximum tolerated dose is achieved. The first drug is then gradually tapered of If the treatment is ineffective, then combination therapy can be considered. Phenytoin, phenobarbitone, carbamazepine, oxcarbazepine and valproate are usually called “conventional” or “first-line drugs”. The other AEDs such as vigabatrin, topiramate, zonisamide, are called “new” or “second-line drugs”. It is preferable to use a conventional AED as the initial drug as they are less expensive and with lesser side effects. Newer AEDs can also be used when there are contraindications to the first-line drugs[13].

Table-3 Treatment of epilepsy

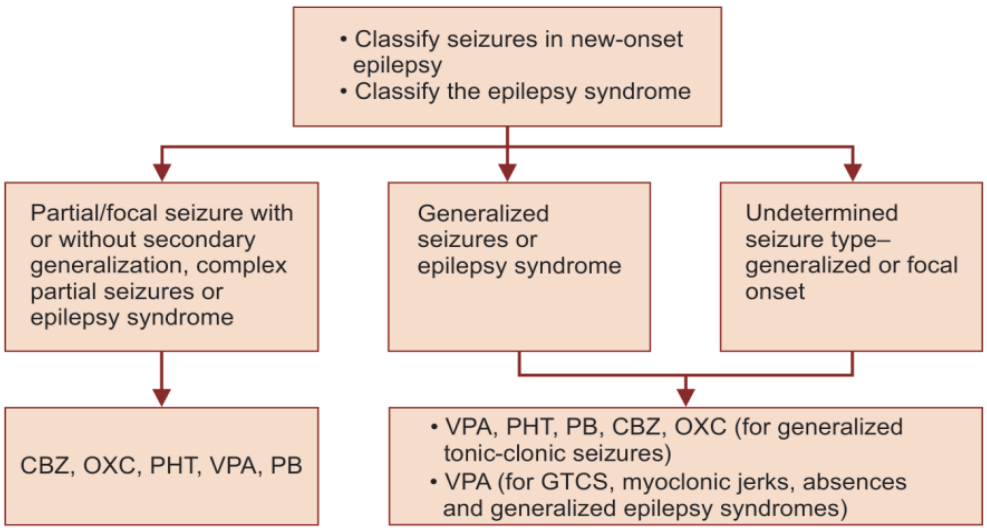


Table-4 Indication and dosing of Anti-epileptic drugs[15,16].

Drug	Indication	Starting dose	Standard dose	Dose titration
Carbamazepine	Partial seizures and GTCS	200mg	400-2000mg	Given 2-4 times daily increase dosage every 2-3 weeks until the response is reached.
Clobazam	Partial and generalised seizures	10mg	10-40mg	Patient weight >30kgs increase to 20mg on day 7 then to 40mg on day 14.
Clonazepam	Myoclonic and GTCS	1 mg	2-8mg	Given in 3 divided doses: increases by 0.5-1mg every 3days until the response is reached.
Ethosuximide	Absence seizures	500mg	500-2000mg	Given once daily. Titrate over 1-2 weeks to maintain dosage of 20mg/kg daily.
Gabapentin	Partial seizures	300-400mg	1800-3600mg	Given in 3 divided doses. Titrate to effective dosage over approximately 3 days.
Lamotrigine	Partial seizures and GTCS	25mg	200-400mg	Specific dosage recommendation depends on other AEDs.
Levetiracetam	partial seizures	500-1000 mg	1000-3000mg	Given in 2 divided doses, increases every 2 weeks.
Oxcarbazepine	Partial seizures	300-600mg	2400-300mg	Given in 2 divided doses. 300mg 3 days to maximum.
Phenobarbital	Partial seizures, GTCS, myoclonic, status epilepticus	60mg	60-240mg	Given in 2-3 divided doses.
Phenytoin	Partial seizures, GTCS, myoclonic, status epilepticus	200mg	100-700mg	Given in 4 equal doses 6 hours apart.
Primidone	Partial and GTCS	250mg	250-1500mg	Day1-3: 100-125mg HS Day4-6: 100-125mg BD Day 7-9: 100-125mg TID Day 10 onwards: 250mg TID
Topiramate	Partial and generalised seizures	50mg	100-400mg	Week 1: 25mg BD Week 2: 50mg BD Week 3: 75mg BD Week 4: 100mg BD Week 5: 150mg BD Week 6: 200mg BD
Valproic acid	All generalised seizures	500mg	500-3000mg	Given once or twice daily.
Vigabatrin	Partial seizures	500mg	1000-4000mg	Given twice daily and titrated up by 25-50mg/kg daily every 3 days.
Tiagabine	Partial seizures	5-10mg	30-45mg	Given once or twice daily.
Nonivamide	Partial seizures	100-200mg	400-600mg	Given once or twice daily and increased every 2 weeks.

Abbreviations: CBZ, Carbamazepine; OXC, Oxcarbazepine; PHT, Phenytoin; VPA, Valproate; PB, Phenobarbitone; GTCS, Generalized tonic-clonic seizure[14].

Treatment approaches: The following are few targets for anti-Epileptic drugs.

- Inhibition of excitatory neurotransmitter Glutamate
- Enhancement of inhibitory neurotransmitter Gamma Amino Butyric Acid (GABA).
- Blockage of voltage-gated positive current, Na^{+} and Ca^{+2}
- Increase outward positive current[13]

Table-5 Mechanism and adverse effects of Anti-epileptic drugs[11,17,18].

Drug	Mechanism of action	Adverse effects
Phenytoin	Enhances the release of inhibitory neurotransmitter.	Hirsutism, Megaloblastic anaemia, Hyperglycaemia, Hypocalcaemia, gingival hyperplasia.
Carbamazepine	Suppress seizure spread. Inhibit voltage gated sodium channel.	Diplopia, Dizziness, Headache, Nausea, Drowsiness, Neutropenia, Hyponatraemia, Hypocalcaemia.
Lamotrigine	Blocks sodium channels. Presynaptically, it inhibits the release of excitatory amino acids. Postsynoptically, it diminishes the excitability of neurons.	Drowsiness, Diplopia, Headache Ataxia, Insomnia.
Oxcarbazepine	Inhibits voltage-dependent fast sodium channels.	Hyponatremia, sedation, dizziness.
Ethosuximide	Inhibition of T-type calcium channels.	Nausea, Anorexia, Vomiting.
Zonisamide	Blockade of sodium channels, reduction of voltage dependent calcium currents and glutamate induced synaptic excitation.	Sedation, dizziness, cognitive impairment.
phenobarbital	Binds and activates $GABA_A$ receptor which increase the frequency of Cl^-channel opening.	Tiredness, Depression Insomnia, Hyperkinesia, Irritability Aggression, Poor memory, Folate deficiency.
Diazepam	Binds and activates $GABA_A$ receptor, which increase the frequency of Cl^-channel opening.	Drowsiness, fatigue, muscle weakness.
Clobazam	Binds and activates $GABA_A$ receptor which increase the frequency of Cl^-channel opening.	Fatigue, Drowsiness, Dizziness, Ataxia Irritability, Weight gain.
Vigabatrin	Inhibits GABA-transaminase and increase synaptic GABA concentration.	Drowsiness, Fatigue, Headache, Ataxia Nystagmus, Diplopia, Irritability Aggression, Weight gain, Tremor Impaired concentration.
Tiagabine	Inhibits GABA uptake.	Dizziness, Headache, Difficulty concentrating, Light-headedness.
Sodium valproate	Prolongation of Na^+ channel inactivation and augments release of GABA.	Weight gain,alopecia, Anorexia Dyspepsia, Alopecia ,Drowsiness, Hyperammonaemia, Amenorrhoea, Polycystic ovary–like syndrome.
Gabapentin	Enhances GABA release.	Weight gain, Somnolence, Dizziness Ataxia Fatigue, Diplopia.
Felbamate	Increases intracellular $Ca^{2+}$and blocks excitatory postsynaptic potentials.	Anorexia, nausea, vomiting, headache, insomnia.
Topiramate	Potentiation of $GABA_A$ receptor-mediated currents.	Anorexia, Weight loss, Impaired concentration, impaired memory.
Levetiracetam	Enhances the release of inhibitory neurotransmitter.	Sedation, behavioural disturbance.

Non pharmacological approaches

Neuroblation and neuro modulation are the two non-pharmacological surgical treatment approaches for epilepsy: The following are the techniques under neuroblation and neuro modulation**:**

Radiofrequency (RF) thermo coagulation: This procedure is done using a RF generator connected to the electrode contacts. This is well tolerated by the patient and does not require general anaesthesia. Lesions can be seen in multiple sites with real-time clinical and electrophysiological feedback.

MR-guided focused ultrasound: Magnetic resonance-guided focused ultrasound surgery is an accurate method of delivering high doses of transcranial ultrasound energy to a discrete intracranial focal point consists of 1024 ultrasound elements.

Laser ablation: This can also be achieved by MRI-guided laser interstitial thermal therapy. The commercially available Visualize Thermal Therapy System combines a 15W 980 nmdiode laser and cooled laser application system with an image processing workstation. The applicator is inserted to reach the target and laser treatment is applied in the MR scanner, with MR thermal imaging to visualize the thermal ablation.

Stereotactic radio-surgery is a well-established technique that uses focused ionizing radiation to target deep-seated lesions, sparing damage to surrounding tissue. The ionizing radiation breaks chemical bonds and results in the production of free radicals.

Neuro modulation: Functional neurosurgery refers to the surgical manipulation of brain behaviour by the stimulation or removal of the set of neurons. This includes:

Vagal nerve stimulation: This is a well-established treatment for epilepsy, in patients who cannot undergo surgery. Current evidence points towards the deactivation of the solitary tract nucleus, with widespread projections to the dorsal raphe nucleus, locus coeruleus, hypothalamus, thalamus, amygdala and hippocampus.

Deep brain stimulation: The deep brain stimulation for epilepsy control is being used from many years. The postulated mechanism of action is through interrupting the propagation of seizure activity, or by increasing the overall seizure threshold[19].

Diet therapy

Low-carbohydrate, high-fat diet is effective in the treatment of focal and generalized epilepsies, with 22-55% of patients experiencing at least50% reduction in seizures on the classical ketogenic diet. Other types of dietary therapy are available, including the medium-chain triglyceride diet and low glycaemic index diet. Many patients report improved cognition and mood in addition to seizure control while on dietary therapies. Initially, ketone bodies were thought to control seizures[8]. After 3 months of adequate diet therapy, around50% and 70% patients have >90% and >50% reduction in seizure frequency[20].

Withdrawal of drugs

AEDs should not be withdrawn abruptly. Rebound seizures is seen with barbiturates and benzodiazepines. Withdrawal of individual AEDs should be carried out in a slow stepwise fashion for 2-3 months to avoid the precipitation of withdrawal seizures. This risk is particularly high with barbiturates[21].

Conclusion

Epilepsy is common neurological disorder characterised by abnormal excessive synchronous neuronal activities in the brain. It is seen with or without loss of consciousness. The prevalence of epilepsy is 5–8 per 1000 population in high-income countries and 10 per 1000 population in low-income countries and even higher in rural areas. Epilepsy is a universal disorder affecting all ages and predisposed by sleep deprivation, systemic infection, potential external sensory stimuli. Epilepsy is characterised by excessive firing of excitatory neurotransmitters and decrease in function of inhibitory neurotransmitters. Benzodiazepines, barbiturates and ion channel modulators are preferred for the treatment of epilepsy. If seizures are not controlled with monotherapy, then polytherapy is recommended.

References

1. Suruchi Sharma, Vaishali Dixit, Epilepsy – A Comprehensive Review, International Journal of Pharma Research & Review, 2013, 2(12):61-80.
2. P.A. Dekker, Epilepsy: A manual for medical and clinical officers in Africa, 2002.
3. Hirak Kumar Mukhopadhyay, Chandi Charan Kandar, Sanjay Kumar Das, Lakshmikanta Ghosh, Bijan Kumar Gupta, Epilepsy and its Management: A Review, Journal of PharmaSci Tech 2012; 1(2):20-26.
4. Hae Won Shin*, Valerie Jewells, Eldad Hadar, Tiffany Fisher and Albert Hinn, Review of Epilepsy - Etiology, Diagnostic Evaluation and Treatment, Int J Neuro rehabilitation Eng 2014, 1:3.
5. Senthi Amudhan, Gopalkrishna Gururaj, Parthasarathy Satishchandra, Epilepsy in India, I: Epidemiology in public health. Ann Indian Acad Neurol 2015;18:263-277.
6. J Engel Jr, Epilepsy; Overview, Elsevier 2014.
7. Johannes D. Lang a, David C. Taylor b, Burkhard S. Kasper, Stress, seizures, and epilepsy: Patient narratives, Epilepsy &Behaviour 80 (2018) 163–172

8. Emily L. Johnson, Seizures and epilepsy, 0025-7125/18/Elsevier 2018.
9. Roland D Thijs, Rainer Surges, Terence J O'Brien, Josemir W Sande, Epilepsy inadults, January 24, 2019 ,S0140-6736(18)32596-0.
10. Mary Anne Koda-Kimble, Lloyd Yee Young, Brian K. Alldredge, Robin L. Corelli, B.Joseph Guglielmo, Wayne A. Kradjan, Bradely B.Williams, Apppied therapeutics a clinical use of drugs 9th edition.
11. Joseph T.Dipiro, Robert L.Talbert, Gary C. Yee, Gary R.Matzke, Barbara G,Wells, L.MichaelPosey, Pharmacotherapy A pathophysiologic approach, seventh edition.
12. Solomon L Moshe, Emilio Perucca, Philippe Ryvlin, Torbijorn Tomson, Epilepsy: new advances. Lancet 2015;385:884-98.
13. Russell J Greene Norman D Harris, Pathology and therapeutics for pharmacy, third edition.
14. Mrinal Kanti Roy, Dhiman Das, Indian Guidelines on Epilepsy, chapter 116.
15. F.J Rugg-gunn and H.B, stapely, Epilepsy 2017.
16. Gerald liu, Nicole slater, Allen perkins, Epilepsy: treatment options, American family physician july 15, 2017 Volume 96, Number 2.
17. Ravitas Deshmukh*, Alok S. Thakur and Dhansay Dewangan, Mechanism of action of anticonvulsant drugs: a review, international journal of pharmaceutical research 2017.
18. J.W. Sander, Overview of established antiepileptic drugs, chapter 28.
19. Sushil Tandel, Recent advances in epilepsy, chapter 84.
20. Sheffali Gulati, Biswaroop Chakrabarty, Dietary therapy in childhood epilepsy, an overview, international journal of epilepsy XXX (2014) 1-9.
21. Roger walker and C. Whittlesea, Clinical pharmacy and therapeutics 5th edition.