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AN OVERVIEW ON EPILEPSY

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Abstract:
Epilepsy as defined by the International League against Epilepsy (ILAE) is a disease of the brain that results in at least two unprovoked seizures at least 24 hours apart. A person may also be diagnosed with epilepsy if they have one unprovoked seizure and have a high chance (>60%) of having another seizure within the next 10 years or if they have an epilepsy syndrome. Epilepsy is a disease historically associated with evil spirits and mystery, and still to this day often carries social stigmas. Its long history, along with its social implications, makes epilepsy a unique disorder. This review will discuss epilepsy's extensive history as well as how societal perceptions of people with epilepsy have evolved over time.[1]

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HISTORY OF EPILEPSY:

Ancient civilizations often attributed seizures to supernatural causes. The Greeks, for instance, believed it was a sacred disease. Hippocrates, the ancient Greek physician, proposed a more naturalistic view, suggesting that epilepsy had a biological basis.

Over the centuries, misconceptions persisted, but advancements in understanding epilepsy's neurological basis emerged in the 19th and 20th centuries. Electroencephalography (EEG) in the 1920s allowed for the recording of brain activity during seizures, aiding in diagnosis.

Epilepsy's long history can be traced back to a 4000-year-old Akkadian tablet found in Mesopotamia; inscribed on it is a description of a person with "his neck turning left, hands and feet are tense, and his eyes wide open, and from his mouth froth is flowing without him having any consciousness". Nearly a millennium later, the Late Babylonians wrote a diagnostic manual entitled, Sakikku, which included texts describing epilepsy. In this guide, the Babylonians describe several seizure types and they based on their presentation. They also had some understanding categorized of prognostics, as the text detailed different outcomes depending on the type of seizure, including poor outcomes in status epilepticus, as well as post-ictal states in other seizure types. This tablet further described terms relating to epilepsy such as miqtu (fall), hayyatu (fit), and sibtu (seizure). This rudimentary nomenclature further underlines that the ancient world had some understanding of epilepsy. Due to the belief that these episodes of rapid contractions were caused by evil spirits invading the body, the treatment often involved spiritual intervention. Evidence of epilepsy has also been found in ancient Egypt, as indicated by the Edwin Smith Surgical Papyrus written circa 1700 BC. It describes several of epilepsy, one of which is of particular interest. The Egyptians documented an accounts case in which direct stimulation of the brain resulted in a physiologic response. The case described a man with "a gaping wound in his head" and when the wound was palpated, the man would "shudder exceedingly". Distinguishing themselves from the Mesopotamians, who believed spirits and gods the cause of seizures, the Egyptians proved that seizures can be caused by cortical were disruption. Documentation of epilepsy is also found in Chinese texts, dating to approximately 770-221 B.C. A group of physicians published The Yellow Emperor's Classic of Internal Medicine, Huang Di Nei Ching, which outlined generalized seizures. In 610 A.D, Cao Yuan Fang was thought to have classified and categorized epilepsy. Traditional principles of Yin Yang Wu Xing were employed to treat epilepsy, consisting of herbs, massage, and acupuncture.[1]

DEFINATION:

Epilepsy is a paroxysmal, uncontrolled electrical discharge of neurons in the brain that nterrupts normal function.

- Epilepsy is a neurological disorder that is characterised by an enduring predisposition to generate epileptic seizures and is associated cognitive, psychological and social consequences.
- No sex differences however it is after under reported among females.
- The neurological dysfuntion seen in epilepsy can
- ➢ Epilepsy affects all ages.Begin at birth
- ➢ Childhood
- ➢ Adolescence or even in adulthood
- Term epilepsy is derived from the Greek word ‘’Epilamvanein or epilepsia ‘’ which means to be seized to be taken hold of or to be attacked.[2]

SEIZURES

A seizures is a paroxysmal event characterised by abnormal excessive hypersychronous discharge of cortical neuron activity.[2]

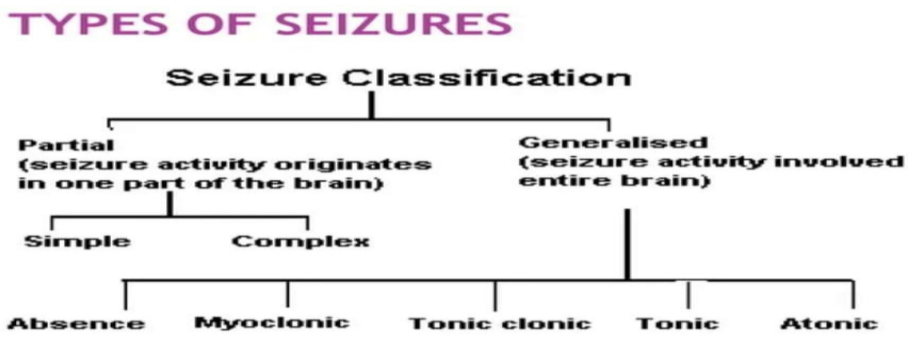


FIG-1 CLASSIFICATION OF SEIZURES[3]

PARTIAL SEIZURES

When seizures appears to result from abnormal activity in just one part of the brain.

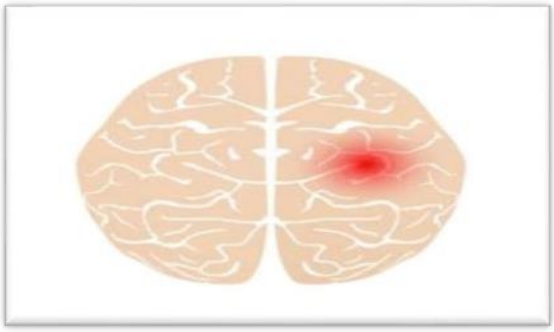


FIG.2

SIMPLE PARTIAL SEIZURE:

Manifest motor , somatosensory and psychomotor symptoms without impairment of consciousness.

- Last 1\2 minutes

COMPLEX PARTIAL SEIZURE:

Manifest impairment of consciousness with or without simple partial symptoms.

- Last 1-2 minutes
- A common seizure type in adulthood

GENERALISED SEIZURE

Generalised seizure involve both hemisphere of brain as well as deeper brain structures such as thalamus, basal ganglia, upper brain stem.

- Consciousness is always impaired.[3]

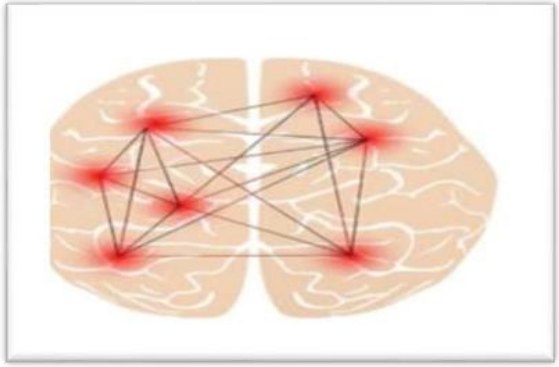


FIG-3

TYPES OF GENARAILESD SEIZURE

ABSENCE SEIZURE

Also known as petit mal seizure. Involves a brief sudden lapse of conscious activity occurring most often in children.

- Can be subtle with only a Cognitive dysfunction with a sudden onset
- Slight turn of the head or eye blinking.
- Lasting 1\2 minutes
- Minor epilepsy
- EEG shown characteristics 3 cycles per second spike and wave pattern.

MYOCOLONIC SEIZURE

- Sudden , quick , arrhythmic muscle contraction
- No loss of consciousness
- EEG generalised polyspike and wave activity
- Occur in genetic epilepsies

TONIC- CLONIC SEIZURE

Also known as grand mal.

- The most common seizure
- Last for 1-2 minutes
- Loss of consciousness
- Involve in muscle rigidly
- EEG: generalised polyspike

TONIC SEIZURE

Produce constant contractions of the muscles .A person after turn blue as breathing is stopped.

- Duration 2-20 seconds.

ATONIC SEIZURE

- A kinetic epilepsy
- Unconsciousness
- Relaxation of all muscles due to excessive inhibitory discharge
- Patient may fall

CLONIC SEIZURE

- Loss of consciousness
- Sudden loss of muscle tone
- Limb jerking
- After the shaking has stopped it

may take 10-30 minutes for the person to return to normal.

- This period is called the ‘’ postictal state or postictal phase ‘’.[5]

STATUS EPILEPTICUS

- When seizure activity occurs for > 30 min, two or more seizures occurs without recovery of consciousness , the condition is called status epilepticus
- That lasts longer than 5 minutes.

FIG.4

ETIOLOGY

FIRST 6 MONTH OF LIFE

- Birth injury
- Congenital defects involving the CNS
- Infection
- Trauma
- Genetic factor

2-20 YEARS OF AGE

- Birth injury
- Infection
- Trauma

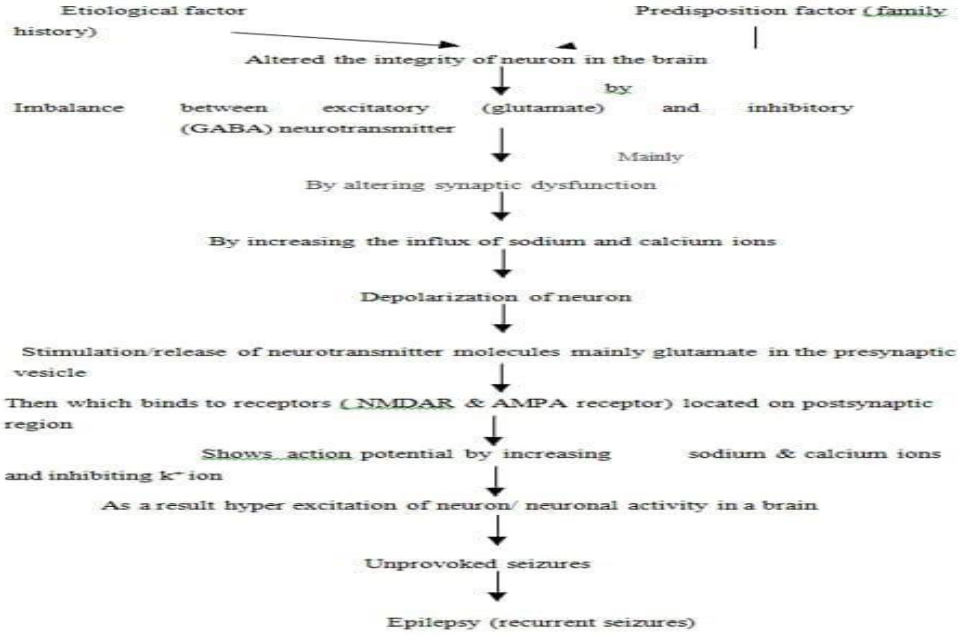
20-30 YEARS OF AGE

Structural lesion such as trauma, brain tumors, vascular disease AFTER 50 YEARS

- Cerebrovascular lesions
- Metastatic brain tumors .[6]

EPIDEMIOLOGY

Epilepsy accounts for a significant proportion of the world’s disease burden, affecting around 50 million people worldwide. The estimated proportion of the general population with active epilepsy (i.e. counting seizures or need for treatment) at a given time is betwee4 and 10 per 1000 people. Globally an estimated 5 million people are diagnosed with epilepsy each year. In high income countries, there are estimated each year to be 49 per 100 000 people diagnosed with epilepsy each year. In low-and middle – income counties, this figure can be as high as 139 per 100 000. This is likely due to the increased risk of endemic conditions such as malaria or neurocysticercosis; [7]



PATHOPHYSIOLOGY:

FIG-5 PATHOPHYSIOLOGY [6]

CLINICALPRESENTATION

Epilepsy may be classified according to age of onset, cause, area of origin, abnormalities on EEG, and clinical manifestations of seizures.

- According to the international classification of epileptic seizures, based on clinical seizure type and on EEG findings during seizures (the ictal period) and between seizures (the interictal period). There are two major categories.
- **PARTIAL SEIZURES**: the neurologic abnormality may be limited to a specific part or focus of brain.
- SIMPLE PARTIAL SEIZURE: they have elementary or simple symptoms & there is no loss of consciousness.
- COMPLEX PARTIAL SEIZURE: they have consciousness is altered during the event. Patient may have no movement or moves automatically but inappropriately for time.
- **GENERALISED SEIZURES:** these seizures involve both hemispheres of the brain.
- **TONIC SEIZURE**: simultaneous contraction of the diaphragm & chest muscles which produce characteristic epileptic cry.

❖ Face may become pale, head turned to one side.

❖ Loss of consciousness. Tongue is bitten.

❖ Frothy discharge from the mouth.

❖ Pulse become weak& irregular.

CLONIC SEIZURE:

❖ Jerky movement last for 1-2 minutes

❖ Incontinence of urine & stool

❖ The patient relaxes after jerky movements & goes into the deep sleep breathing is noisy.[10]

DIAGNOSIS

❖ Primary diagnosis of epilepsy includes eye-witness and family history.

❖ ELECTRO ENCEPHALO GRAPH (EEG) TEST: Is the cornerstone for diagnosis of epilepsy and measures the brain wave activity.

➢ Electrical activity recorded is produced by extracellular current flow associated with summated excitatory and inhibitory

➢ EEG does not record individual action potentials.

❖ **COMPUTED TOMOGRAPHY (CT) SCAN**: This imaging study normally takes about 10 to 15 minutes.

✓ It provides a detailed picture of the brain.

✓ A brain CT scan can help in diagnosing many different neurological conditions

✓ Sometimes a brain CT scan may show development changes that could lead to epilepsy.

❖ MAGNETIC RESONANCE IMAGING (MRI) SCAN: This imaging study requires you to lie still for around 20 minutes. A MRI of the brain provides a more detailed picture than a CT scan and often identify damage that could lead to epilepsy.

❖ POSTION–EMISSION TOMOGRAPHY (PET): Used to diagnose abnormalities in structure and function of different areas of the brain.

❖ Single – photon emission computerized tomography (SPECT)

❖ Physical examination

❖ Blood routines

❖ Urine analysis

❖ NEUROPSYCHOLOGICAL TESTS/ NEUROLOGICAL EXAMINATION: Usually neuropsychological tests are considered part of the physical examination.

✓ However, in some circumstances neuropsychological testing could be done along with FMRI, PETSACN, OR SPECT to see changes in brain activity during testing.

❖ GENETIC TESTING: In some people with epilepsy, genetic testing may give more information about the condition and how to treat it. Genetic testing is most often performed in children but also may be helpful in some adults with epilepsy.

❖ BLOOD TESTS: A blood sample can detect signs of infections genetic conditions or other conditions that may be associated with seizures.[11]

PHARMACOTHERAPY

GOALS OF THERAPY

❖ To control or reduce the frequency and severity of seizures

❖ Minimize side effects

❖ Ensure compliance (60% of patients with epilepsy are noncompliant)

❖ Allowing the patient to live as normal a life as possible

❖ In most patients the goal is complete seizure freedom. However in 20% to 35% of patients this may not be possible, and seizure control must be balanced with QOL goals.

❖ Main is monotherapy

❖ No interactions with other medication

❖ Eliminate seizures without causing side effects .

ALGORITHM OF EPILEPSY

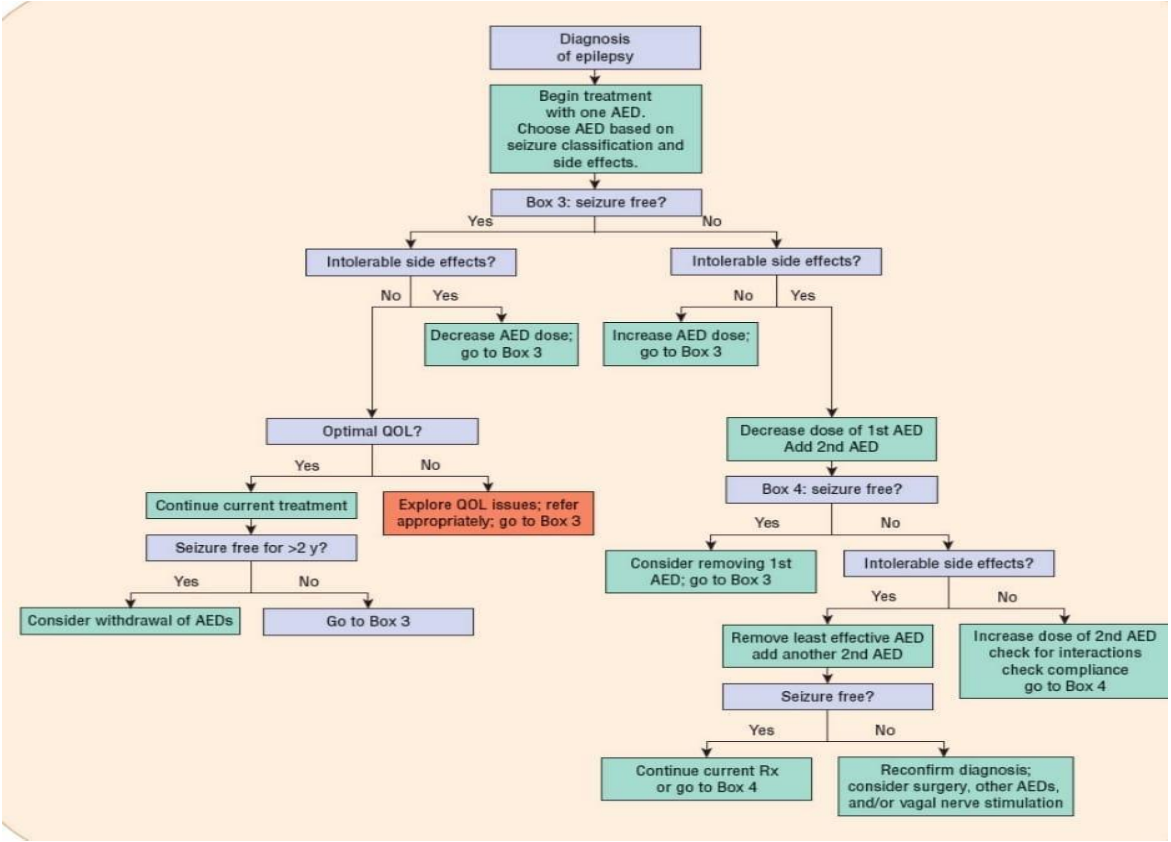


FIG-6 SCHEMATIC REPRASENTATION OF ALGORITHM OF EPILEPSY(12)

CLASSIFICATION

BARBITURATE: Phenobarbitone

HYDANTOIN: Phenytoin, Fosphenytoin SUCCINIMIDE: Ethosuximide

BENZODIAZEPINES: Clonazepam, Diazepam, Lorazepam, Clobazam

NEWER DRUGS: Topiramate, Levetiracetam, Zonisamide, Vigabatrin, Tiagabine, Lacosamide.

DEOXYBARBITURATE: Primidone

IMINOSTIBENE: Carbamazepine, Oxcarbazepine, Eslicarbazepine

ALIPHATIC CAEBOXYLIC ACID: Valproate (valproic acid), Divalproex

PHENYLTRIAZINE: Lamotrigine

CYCLIC GABA ANALOGUES: Gabapentin, Pregabalin (13)

DRUGS USED IN TREATMENT 1. PHENYTOIN

MECHANISAM OF ACTION:

✓ Prevents repetitive detonation of normal brain cells during depolarization shift Prolonging the inactivation of voltage sensitive Na+ channel.

✓ No high frequency discharges

✓ No interference with kinding only on high frequency firing.

PHARMACOKINETICS

✓ Slow oral absorption

✓ 80- 90% bound to plasma protein

✓ Metabolized in liver by hydroxylation and glucoronide conjugation

✓ Elimination varies with dose first order to zero order

✓ T ½ life is 12 to 24 hrs.

✓ Cannot metabolize by liver if plasma conc. Is above 10 mcg/ml

✓ Monitoring of plasma concentration

DOSAGE: 10 -15 mg/kg infused under 50 mg/kg

ADVERSE EFFECTS:

- Cognitive impairment
- Hyperglycaemia
- Gum hypertrophy and gingival hyperplasia
- Hirsutism, coarsening of facial features and ace
- Hypersensitivity-rashes , lymphadenopathy
- Exacerbates absence seizures
- Fetal Hydantoin syndrome
- Osteomalacia

2. PHENOBARBITONE:

MECHANISAM OF ACTION:

✓ Enhancing the activation of GABA receptors facilitating the GABA mediated opening of chloride ion channels.

✓ It is also an enzyme inducer

PHARMACOKINETICS

✓ Slowly absorbed and long t1/2 (80 – 120 hrs.')

✓ Metabolized in liver and excreted uncharged in kidney

✓ Single dose after 3 wks.' – steady state

DOSAGE:

✓ 60 mg 1-3 times a day Child: 3-6 mg/kg/d

ADVERSE EFFECTS

❖ Sedation

❖ Behavioural abnormalities

❖ Hyperactivity in children

❖ Rashes, megaloblastic anaemia

❖ osteomalacia

3. CARBAMAZEPINE

MECHANISAM OF ACTION:

✓ Stabilizes Na+ channel (voltage gated) in inactivated state less excitability

✓ Potentiation of GABA receptor.

PHARMACOKINETICS

✓ Poorly water soluble and oral absorption is low

✓ 75% bound to plasma protein

✓ Metabolised in liver: active 10-11 epoxy carbamazepine

✓ Substrate and inducer of CYP3A4

✓ Half-life- 20 to 40hrs.Decreases afterwards due to induction

DOSAGE:

✓ Adults and children older than age 12: initially, 200mg po BID (conventional or extended – release tablets) , or 100mg po QID of suspension with meals

✓ Available as tabs- 30/60mg, syr &inj.

ADVERSE EFFECTS

❖ Autoinduction of metabolism

❖ Nausea, vomiting, diarrhoea and visual disturbances

❖ Hypersensitivity- rash, photosensitivity, hepatitis, granulocyte suppression and aplastic anaemia

❖ ADH action enhancement- hyponatremia and water retention

❖ Teratogenicity

❖ Exacerbates absence seizures

4. ETHOSUXIMIDE

MECHANISAM OF ACTION:

✓ It has an important effect on CA 2+ currents,

reducing the low- threshold (t- type) current.

PHARMACOKINETICS

- ✓ Ethosuximide is rather slowly absorbed
- ✓ Largely metabolised in liver
- ✓ Excreted in urine
- ✓ Plasma t ½ averages 48 hours in adults and 32 hours in children

DOSAGE:

- ✓ 20 – 30 mg/kg/day
- ✓ Available as syr. /caps.

ADVERSE EFFECTS

GI intolerance, tiredness, and mood changes
Agitation, headache, drowsiness
Inability to concentrate

5. VOLPORIC ACID

MECHANISAM OF ACTION:

- ✓ Na + channel inactivation
- ✓ Increases the synthesis of GABA by increased activity of GABA synthase
- ✓ Decreases the metabolism of GABA transaminase enzyme.

PHARMACOKINETS

- ✓ Well absorbed orally
- ✓ 90% bound to plasma protein and completely metabolised in liver
- ✓ Excreted in urine t1/2 is 10-15hrs

DOSAGE:

Available as tabs. (200/300/500, Syr. & inj.)

ADVERSE EFFECTS

- ❖ GIT: Nausea , vomiting
- ❖ CNS: sedation , ataxia, tremors
- ❖ Hypersensitivity reactions
- ❖ Alopecia
- ❖ Fulminant hepatitis
- ❖ Neural tube defects
- ❖ Pancreatitis

6. GABAPENTIN

MECHANISAM OF ACTION:

- ✓ increases the activity of GABA in brain by
- ▪ increasing its synthesis
- ▪ decreasing its metabolism

PHARMACOKINETCS

- ✓ Absorbed orally
- ✓ Not metabolised in humans
- ✓ Not bound to plasma proteins and excreted unchanged in urine
- ✓ Half-life is 4 to 6 hrs.'
- ✓ No known drug interaction

ADVERSE EFFECTS

- ❖ Headache
- ❖ Sedation
- ❖ Ataxia
- ❖ Fatigue

DOSAGE:

- ✓ Adults and children 12 years of age and older- at first, 300mg 3 times per day. Children 3 to 11 years – dose is based on body weight

7. LAMOTRIGINE

MECHANISAM OF ACTION:

- ✓ Delays recovery from inactivation of Na+ channels prolong Na+ channel inactivation
- ✓ Glutamate and aspartate inhibition : by directly blocking Na+ channels stabilizes pre synaptic membrane and prevent release by excitatory neurons
- ✓ Inhibition of CA++ in neurons

PHARMACOKINETICS

- ✓ Completely absorbed from GIT and metabolised by glucoronidation
- ✓ Plasma half- life 15 to 30 hrs.
- ✓ Phenobarbitone , carbamazepine and phenytoin – reduces half life
- ✓ Valproate- increases plasma concentration but its concentration reduces
- ✓ Together with carbamazepine- increases in 10,11-epoxide and toxicity

DOSAGE:

The minimum dose is at 200 mg per day

ADVERSE EFFECTS

- ❖ Nausea , vomiting, headache
- ❖ Ataxia
- ❖ Sedation
- ❖ Skin rashes

8. TOPIRAMATE

MECHAISAM OF ACTION:

- ✓ Blocks sodium channels(membrane stabilization)
- ✓ Potentiates the inhibitory effect of GABA

PHARMACOKINETICS

- ✓ Rapidly absorbed orally, 10-20% bound to plasma protein
- ✓ Excreted unchanged in urine
- ✓ Metabolised by hydroxylation, giucoronidation and hydrolysis
- ✓ Reduction in estradiol level

DOSAGE:

Children usually start with a dose of 15 to 25 mg or less per day, based on a range of 1 to 3 mg per kilograms

ADVERSE EFFECTS

- ❖ Impairment of attention
- ❖ **S**edation
- ❖ Ataxia
- ❖ Word finding difficulties
- ❖ Poor memory
- ❖ Weight loss
- ❖ Paresthesias and renal stones

9. LACOSAMIDE

MECHANISAM OF ACTION

- ✓ Lacosamide facilitates slow inactivation of voltage gated channels
- ✓ Binds to a collapsing response mediator protein-2
- ✓ This protein performs important roles like cytoskeletal, vesicle, and synaptic functions in the developing brain

PHARMACOKINETICS

- ✓ Metabolism: CYP2C19 by demethylation
- ✓ No significant induction/ inhibition or interaction

DOSAGE

- ✓ Adult: 50 mg twice daily; may be increased at weekly intervals by 100 mg/day
- ✓ Maintenance dose: 200-400 mg/day

ADVERSE EFFECTS

- ❖ Dizziness , headache , nausea, diplopia, tremor, vomiting

10. DIAZEPAM

MECHANISAM OF ACTION

- ✓ Potentiate the effect of GABA and other inhibitory neurotransmitters by binding to specific benzodiazepines receptors in the limbic and cortical areas of the CNS. GABA inhibits excitory stimulation which helps to control emotional behaviour. Diazepam supress the spread of seizures activity caused by seizure producing foci in the cortex, thalamus and limbic system.

PHARMACOKINETICS

- ➢ Bioavailability: After oral administration more than 90% of diazepam is absorbed from GI tract
- ➢ Peak plasma concentration: 30-90 min
- ➢ Metabolism: it is completely metabolised in the liver
- ➢ Elimination: it takes place in the kidney as urine.

ADVERSE EFFECTS

- ➢ Sedation
- ➢ Fatigue
- ➢ Confusion
- ➢ Anterograde amnesia
- ➢ Depression
- ➢ Ataxia
- ➢ Irritability
- ➢ Disinhibition

DOSAGE

0.2- 0.3 mg/kg slow i.v. injection followed by small repeated small doses as required, maximum 100mg/kg[14]

ACCORDING TO THE SEIZURE TYPES

SEIZURE TYPE	FIRST LINE	SECOND LINE

Generalised tonic – clonic or simple partial seizure	Carbamazepine, phenytoin and valproic acid	Phenobarbitone
Absence seizure	Valproic acid	Ethosuximide
Complex partial seizure with or without generalised	Phenytoin, Carbamazepine and valproic acid	Gabapentin , Lamotrigine
Myoclonic	Valproic acid	Lamotrigine , Topiramate
Status epilepticus	Diazepam , Loarazepam	Phenytoin , Phosphenytoin

NON-PHARMAC OLOGICAL THERAPAY SURGERY:
Up to 90% of patients may improve or become seizure free. In epileptic syndromes such as Lenox gastaut syndrome may prevent or lessen neurologic deterioration & development delay.

KETOGENIC DIET (low- carbohydrate, high- fat):
For patients who cannot tolerate AEDs or seizures that are not completely responsive to AEDs: persistent ketosis, which is believed to play a major role in therapeutic effect. Most commonly used& seems to be most beneficial in children

VAGUS NERVE STIMULATOR
For treatment of intractable partial seizures

AVOIDING OF PRECIPTING FACTORS
Stress, sleep deprivation, ingestion of excessive amounts of caffeine or alcohol.

RESPONSIVE NEUROSTIMULATION (RNS)
This involves a neurostimulator implanted in the brain to detect and respond to abnormal electrical activity.

YOGA/ MEDITATION

- Yoga is known for its relaxation and stress reduction effect
- It can bring changes in metabolism blood flow and oxygen levels in the brain by improving circulation
- These is turn result in relaxation state and reduced levels of stress
- Now this day yoga has been found effective in reducing seizure attacks in people who used anticonvulsants.
- However , its efficacy is controlled seizure is not yet dertmined
- Also a meditation practice for20 minutes a day has been found effective in reducing seizure frequency.[15]

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