Epilepsy: Its chronic neurological disorder characterized by recurrent unprovoked seizure which is due to hypersynchronous neuronal discharge at one part or more at the brain.

* Epilepsy comes from Greek word "Epilepsis" (to take a firm grip on), it also called sacred disease because people thought that the epileptic seizure were a form of attack by demons, so called Morbus Comitalis.
* Seizure is specific for epilepsy but convulsion and fit may not due to epilepsy (May due to metabolic conditions).

**Types of epilepsy:-**

1. **Generalized:**
2. Absence seizure.
3. Tonic clonic seizure.
4. Myoclonic seizure.
5. Atonic seizure.
6. Febrile seizure.
7. **Localized:**
8. Simple partial seizure.
9. Complex partial seizure.
10. **Status epilepticus:-** recurrent attack of seizure without rest.

**Pathophsiology:**

* Mutations of the genes which code for sodium channel proteins; these defective sodium channels stay open for too long thus making the neuron hyper-excitable.
* Glutamate, an excitatory neurotransmitter, may thereby be released from these neurons in large amounts, which— by binding with nearby glumtamenergic neurons—triggers excessive Ca+2 release in these post-synaptic cells. Such excessive calcium release can be neurotoxic to the affected cell.
* Ineffective GABA action.
* Epilepsy-related mutations in some non-ion channel genes have also been identified.
* Decrease in seizure "threshold."

Other causes of epilepsy are brain lesions, where there is scar tissue or another abnormal mass of tissue in an area of the brain.so the final mechanism of seizure are: ↓ GABA (↓ the inhibitory), ↑ Glutamate and aspartate (↑ the excitatory), ↓ Seizure threshold and membrane depolarization by electrical or chemical stimuli.

**Drug of epilepsy treatment:-**

* General drug therapy:-
* Start with single non – toxic drug.
* The dosage adjusted.
* If first drug failed, substituted by another.
* Avoid abrupt withdrawal.
* Drug should be continuing for 2 -3 years from last seizure.

**Phenytoin**

**Mechanism:-**

* Block voltage – gated Na+ channel.
* Block voltage – dependent Ca+ channel.
* Interfere with monoaminergic neurotransmitter release.
* **Indications:**
* All types of epilepsy except absence attack (Petit mal).
* Digitalis induced tachycardia.
* Peripheral neuropathy.
* **S.E.:-**
* DNA (Dizziness, Nystagmus, Ataxia).
* Gingival hyperplasia.
* Enzyme inducer.
* Megaloblastic anemia.
* ↓ ADH.
* ↓ Insulin, so lead to hyperglycemia.
* Coarsening of face.
* Hirsutism and hallucination.
* Teratogenic.

**Fosphenytoin**

 Is a prodrug and is rapidly converted to phenytoin in the blood. Fosphenytoin may also be administered intramuscularly (IM).

**Carbamazepin**

**Mechanism:-**

* Block Na+ channels.
* Block repetitive action potential.
* Stabilize the inactive Na+ channel.
* **Indications:-**
* All types of epilepsy except absence attack.
* Trigeminal neurolagia.
* Manic depressive psychosis.
* Diabetes neuropathy.
* Nephrogenic Diabetes insipidus(NDI).

**S.E.:-**

* DNA.
* Enzyme inducer.
* Aplastic anemia due to epoxide metabolite.
* ↑ ADH and hyponatremia.
* Osteomalacia due to ↓ vit. D.

**Oxcarbamazepin** similar to **carbamazepin** but it different by:-

* Less potent.
* Less S.E.
* Don’t form epoxide.
* Less enzyme inducer.

**Ethosuximide**

**Mechanism:-**

* Block T – type Ca+ channel.
* ↓ Abnormal electrical propagation.

**Indications: -** only for absence attack.

**S.E.:-**

* Enzyme inhibitor.
* Steven – Johnson syndrome.
* Urticaria.
* Aplastic anemia.
* SLE (Systemic Lupus Erythromabsus).
* DNA.

**Phenobarbital**

**Mechanism:-**

* ↑ GABA effect.
* Membrane stabilization.

**Indications:-**

* All types of epilepsy except absence attack.
* Prophylaxis of febrile convulsion.
* Status epilepticus.
* Sedative, anxiolytic.
* Hemolytic jundace…Why

**S.E.:-**

* DNA.
* Enzyme inducer.
* Morbiliform rash.
* Hyperalgesia so not used as analgesic.

**Primidon** structurally related to **phenobarbiton**, but cause less S.E.

**Benzodiazepine:-** used for all types of epilepsy

* **Diazepam** → used for status epilepticus.
* **Lorazepam** → used for all types of epilepsy.
* **Clonazepan** → used for absence seizure.
* **Clorazepate** → used for partial seizure.

**Valproic acid**

**Mechanism:-**

* Block Na+ channels.
* ↑ GABA effect, ↑ K+ conductance.
* Block GABA transaminase (enzyme destroys GABA).
* ↑ GABA synthesis.

**Indications:-**

* All types of epilepsy.
* Manic depressive psychosis.
* Migraine prophylaxis.
* Hiccup.
* Lennox – Gastauts syndrome.
* Reduction of HIV infection, because valproic acid blocks viral histon deacetylase I enzyme needed for HIV infection.

**S.E.:-**

* DNA.
* Enzyme inhibitor.
* Hepatotoxicity.
* Alopecia.
* Thrombocytopenia and inhibit platelet aggregation.
* Bleeding tendency.

**Divalproex sodium** is a combination of sodium valproate and valproic acid that is converted to valproate when it reaches the gastrointestinal tract. It was developed to improve gastrointestinal tolerance of valproic acid

**Vigabatrin**

Acts as an irreversible inhibitor of γ-aminobutyric acid transaminase (GABA-T). GABA-T is the enzyme

responsible for metabolism of GABA.

Adverse effects: visual field loss

**Fellpamate**

**Mechanism:-**

* Block voltage dependant Na+ channel.
* Block NMDA glutamate receptor.
* Prevent glutamate receptor stimulation.
* Block Ca+ channel.

**Uses: -** refractory epilepsy.

**S.E.:-** **Aplastic anemia** due to toxic metabolite that bind bone marrow and liver DNA, so only used for refractory epilepsy.

**Gapapentin:** its GABA analogue.

**Mechanism:-**

* Block Ca+ channel.
* Open Cl- channel.

**Indications:-**

* All types of epilepsy.
* Mood stabilizer agent in maniac depressive psychosis.
* Neuropathic pain.
* Postherpetic pain.

**Pregabalin**

* Binds to the subunit of voltage-gated calcium channels in the CNS,
* Inhibiting excitatory neurotransmitter release.
* effective in partial onset seizures, neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, and fi bromyalgia.
* S.E Drowsiness, blurred vision, weight gain, and peripheral edema .

**Rufinamide**

* Block the sodium channels.
* treatment of seizures associated with Lennox-Gastaut syndrome
* weak inhibitor of CYP2E1 and a weak inducer of CYP3A4
* Food increases absorption of rufinamide
* affected by other antiseizure medications.
* It is induced by carbamazepine and phenytoin and inhibited when given with valproate.
* Adverse effects include the potential for shortened QT intervals.

**Tiagabine**

**Mechanism:-**Block GABA re – uptake.↑ GABA inhibitory effect.

Used for all types of epilepsy.

**Lomatrigen**

**Mechanism:-**

* Block Na+ channel (voltage dependent).
* Block Ca+ channel (voltage dependent).
* Block glutamate receptor.

Used for all types of epilepsy, ((not used in children < 6 years)) due to high serious S.E.

**Levetiracetam:-**

* Unknown mechanism.
* Used as adjunctive therapy for epilepsy

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**Topiramate**

**Mechanism:-**

* Block voltage dependant Na+ channel.
* ↑ Cl- channel opening.
* Block L – type Ca+ channel.
* ↑ GABA effect.

**Indications:-**

* All types of epilepsy.
* Refractory epilepsy.
* **S.E.:-**
* ↑ IOP.
* Enzyme inducer.
* DNA.
* Renal stone.

**Zonisamide**

* Sulfonamide derivative.
* Block Na+ and Ca+ T – type channel.
* ↑ GABA effect.

**S.E.:**

* Olighodrosis.
* Renal stone.

**Lacosamide:** inhibit voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes and inhibition of repetitive neuronal firing, binds to collapsin response mediator protein-2 (CRMP-2), a phosphoprotein

mainly expressed in the nervous system and involved in neuronal differentiation and control of axonal outgrowth. The role of CRMP-2 binding in seizure control is unknown, is approved for adjunctive treatment of partial seizures. In clinical trials, the drug caused euphoria similar to that produced by alprazolam and is labeled as a controlled

**Retiagabine**: is a novel AED in clinical trials that acts on a specific type of voltage-dependent K+ channel (M-channel).

**Perampanel** : is an antiepileptic drug  that acts as a selective non-competitive antagonist of AMPA receptors, the major subtype of ionotropic glutamate receptors. Perampanel has a prolonged terminal half-life in humans of approximately 105 hours. The drug is 95% bound to plasma protein. Its primary route of metabolism is by CYP3A4. It does not induce P450 enzymes. About 70% of the dose is excreted in the feces and 30% in the urine; less than 2% of the dose is excreted unchanged into the urine.

**Seletracetam** : anti-epileptic effects are due to its high affinity binding to synaptic vesicle glycoprotein 2A (SV2A) part of a calcium ion regulator. The SV2A protein assists with the coordination of synaptic vesicle exocytosis  which induces neurotransmitter release in the presence of an influx in Ca2+. It is thought that seletracetam binds to N-type Ca2+ channels and inhibits their ability to allow calcium ions to enter the cell,although the drug does not bind to T-type channels that mediate low-voltage activated Ca2+ currents. The dual effect of seletracetam is an overall decrease in the amount of Ca2+ influx in the cell during an action potential due to binding at N-type channels, which prevents over-excitation of the neuron, as well as a decrease in neurotransmitter release as a product of cellular excitation due to the interaction of the drug with SV2A, which reduces the spread of excitation to nearby cells. Compared to levetiracetam, which binds at the same site, seletracetam binds to SV2A with ten times higher affinity.

**Licarbazepine** is a voltage-gated sodium channel blocker with anticonvulsant and mood-stabilizing effects that is related tooxcarbazepine. It is an active metabolite of oxcarbazepine.

## Use in pregnancy

During pregnancy, the metabolism of several anticonvulsants is affected. There may be an increase in the clearance and resultant decrease in the blood concentration of lamotrigine, phenytoin, and to a lesser extent carbamazepine, and possibly decreases the level of levetiracetam and the active oxcarbazepine metabolite, the monohydroxy derivative. Therefore, these drugs should be monitored during use in pregnancy.

Valproic acid, and its derivatives such as sodium valproate and divalproex sodium, causes cognitive deficit in the child, with an increased dose causing decreased intelligence quotient. On the other hand, evidence is conflicting for carbamazepine regarding any increased risk of congenital physical anomalies or neurodevelopmental disorders by intrauterine. On the other hand, valproate, phenobarbital, phenytoin, and carbamazepine probably are not transferred into breast milk in clinically important amounts. In animal models, several anticonvulsant drugs have been demonstrated to induce neuronal apoptosis in the developing brain

* **Other treatments**
* [**Ketogenic diet**](http://en.wikipedia.org/wiki/Ketogenic_diet)- a high [fat](http://en.wikipedia.org/wiki/Fat), low [carbohydrate](http://en.wikipedia.org/wiki/Carbohydrate) diet developed in the 1920s, largely forgotten with the advent of effective [anticonvulsants](http://en.wikipedia.org/wiki/Anticonvulsants), and resurrected in the 1990s. The mechanism of action is unknown. It is used mainly in the treatment of children with severe, medically intractable epilepsies.
* **Electrical stimulation**
* [**Vagus nerve stimulation**](http://en.wikipedia.org/wiki/Vagus_nerve_stimulation)
* [**Deep brain stimulation**](http://en.wikipedia.org/wiki/Deep_brain_stimulation)
* **Noninvasive surgery**
* **Avoidance therapy**
* **Warning systems**-, a [seizure response dog](http://en.wikipedia.org/wiki/Seizure_response_dog) is a form of [service dog](http://en.wikipedia.org/wiki/Service_dog) that is trained to summon help or ensure personal safety when a seizure occurs.