Pharmacology II, 4th Stage

Lippincott's Illustrated Reviews, 6th ed.

Unit III: Drugs Affecting the Central Nervous System

12-Drugs of Epilepsy

م.د شيرين محمد مكي الحسيني
ماجستير في الأدوية و السموم/ كلية الطب/
جامعة بابل
دكتوراه في الأدوية/ كلية الطب /جامعة النهرين

Epilepsy

- Globally, epilepsy is the third most common neurologic disorder after cerebrovascular and Alzheimer's disease.
- Epilepsy is not a single entity but an assortment of different seizure types and syndromes originating from several mechanisms that have in common the sudden, excessive, and synchronous discharge of cerebral neurons.
- This abnormal electrical activity may result in a variety of events, including loss of consciousness, abnormal movements, atypical or odd behavior, and distorted perceptions that are of limited duration but recur if untreated.

- The site of origin of the abnormal neuronal fi ring determines the symptoms that are produced.
- For example, if the motor cortex is involved, the patient may experience abnormal movements or a generalized convulsion.
- Seizures originating in the parietal or occipital lobe may include visual, auditory, and olfactory hallucinations.
- Medications are the most widely used mode of treatment for patients with epilepsy.

Etiology

- **Genetic predisposition:** These seizures result from an inherited abnormality in the central nervous system (CNS).
- **Structural/metabolic epilepsy:** A number of causes, such as illicit drug use, tumor, head injury, hypoglycemia, meningeal infection, and the rapid withdrawal of alcohol from an alcoholic, can precipitate seizures.
- **Unknown cause:** When no specific anatomic cause for the seizure, such as trauma or neoplasm, is evident, a patient may be diagnosed with seizures where the underlying cause is unknown.

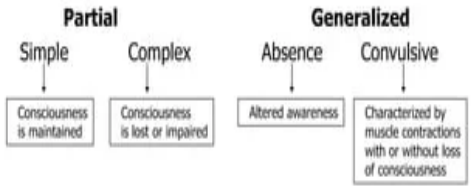
Classification of Seizures

Classifying Seizures

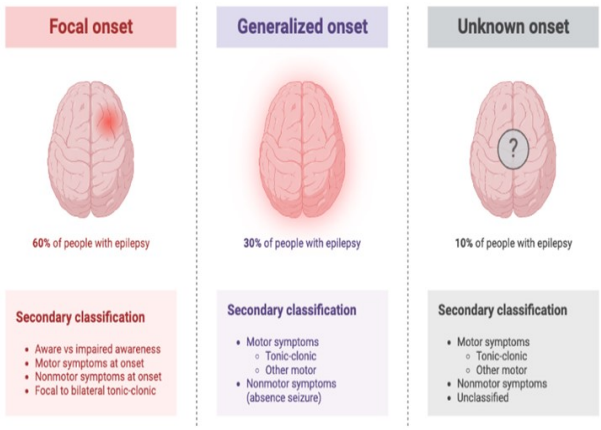
Focal (previously 'partial') seizure – initial activation of only part of one cerebral hemisphere occurs. (although may generalize*)

Generalized seizure – discharge from both cerebral hemispheres occurs. Loss of consciousness may occur.

- Seizure types:



Classification of seizure

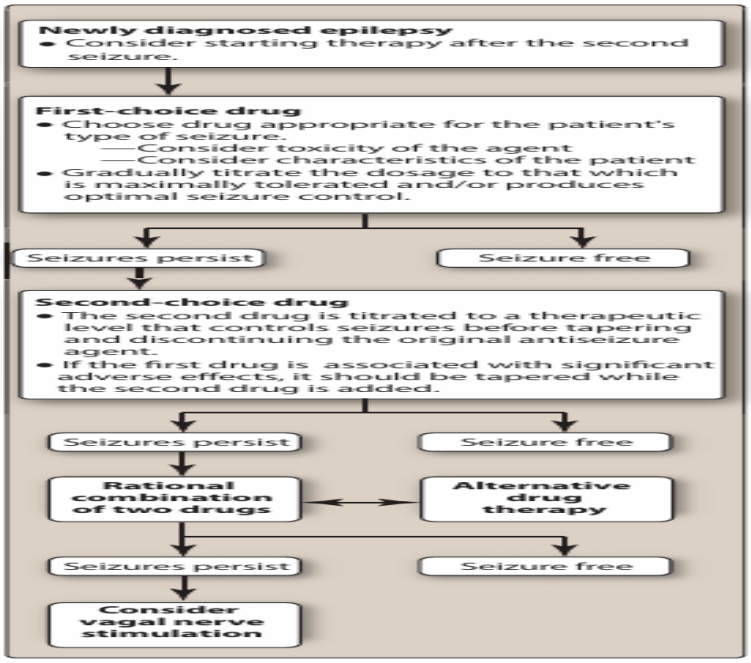


Mechanism of action of antiepilepsy medications

1. Drugs reduce seizures through such mechanisms as blocking voltage-gated channels (Na+ or Ca2+).
2. Enhancing inhibitory γ-aminobutyric acid (GABA)-ergic impulses and interfering with excitatory glutamate transmission.
3. Some antiepilepsy medications appear to have multiple targets within the CNS, whereas the mechanism of action for some agents is poorly defined.

1. Antiepilepsy medications suppress seizures but do not "cure" or "prevent" epilepsy.

Mechanism of Drug selection



ANTIEPILEPSY MEDICATIONS

- 1- Benzodiazepines.
- 2- Carbamezepine:
- blocks sodium channels.
- effective for treatment of focal seizures and, additionally generalized tonic–clonic seizures, trigeminal neuralgia, and bipolar disorder.
- It induces its own metabolism, resulting in lower total carbamazepine blood concentrations at higher doses.
- Carbamazepine should not be prescribed for patients with absence seizures because it may cause an increase in seizures .

- 3- Eslicarbazepine:
- Eslicarbazepine acetate is a prodrug that is converted to the active metabolite eslicarbazepine (S-licarbazepine) by hydrolysis.
- 4- Ethosuximide:
- Reduces propagation of abnormal electrical activity in the brain, most likely by inhibiting T-type calcium channels. It is only effective in treating absence seizures.
- 5- Ezogabine:
- Is thought to open voltage-gated M-type potassium channels leading to stabilization of the resting membrane potential. Possible unique side effects are urinary retention, QT interval prolongation, blue skin discoloration, and retinal abnormalities.

- **6- Felbamate:**
- Has a broad spectrum of anticonvulsant action with multiple proposed mechanisms including the **blocking of voltage-dependent sodium channels, competing with the glycine coagonist binding site on the N-methyl-d-aspartate (NMDA) glutamate receptor, blocking of calcium channels, and potentiating GABA action.** It is reserved for use in refractory epilepsies because of the risk of aplastic anemia and hepatic failure.
- **7- Gabapentin:**
- Is an analog of GABA. However, it does not act at GABA receptors, enhance GABA actions or convert to GABA. Its precise mechanism of action is not known.
- It is approved as adjunct therapy for focal seizures and treatment of postherpetic neuralgia.

- Gabapentin is well tolerated by the elderly population with partial seizures due to its relatively mild adverse effects. It may also be a good choice for the older patient because there are few drug interactions.
- **8- Lacosamide:**

Affects voltage-gated **sodium channels, resulting in stabilization of hyperexcitable neuronal membranes and inhibition of repetitive neuronal firing.**

Lacosamide binds to **collapsin** response mediator protein-2 (CRMP-2), a phosphoprotein involved in neuronal differentiation and control of axonal outgrowth.

The role of CRMP-2 binding in seizure control is unknown.

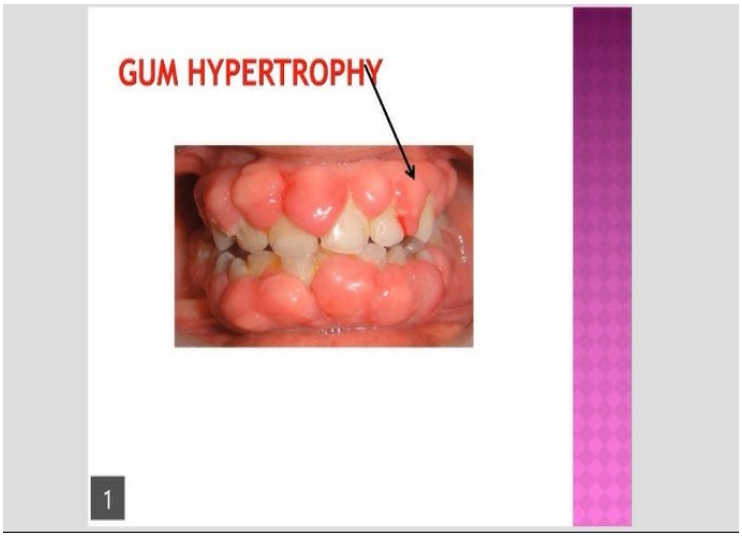
Lacosamide is approved for adjunctive treatment of focal seizures.

The most common adverse events that limit treatment include dizziness, headache, and fatigue.

- **9- Lamotrigine:**
- Blocks **sodium channels, as well as high voltage-dependent calcium channels.** Lamotrigine is effective in a wide variety of seizure types, including focal, generalized, absence seizures, and Lennox-Gastaut syndrome.
- It is also used to treat bipolar disorder.
- Lamotrigine dosages should be reduced when adding valproate to therapy.
- Slow titration is necessary with lamotrigine (particularly when adding lamotrigine to a regimen that includes valproate) **due to risk of rash, which may progress to a serious, life-threatening reaction.**

- **10- Levetiracetam:**
- Is approved for adjunct therapy of focal onset, myoclonic, and primary generalized tonic–clonic seizures in adults and children.
- The exact mechanism of anticonvulsant action is unknown. **It demonstrates high affinity for a synaptic vesicle protein (SV2A).**
- Levetiracetam can cause mood alterations that may require a dose reduction or a change of medication.
- **11- Phenobarbital and primidone:**
- The primary mechanism of action of phenobarbital is enhancement of the inhibitory effects of **GABA-mediated**
- **neurons.**
- Primidone is metabolized to phenobarbital (major) and phenylethylmalonamide, both with anticonvulsant activity.
- Phenobarbital is used primarily in the treatment of **status epilepticus when other agents fail.**

- **12- Phenytoin and fosphenytoin:**
- Phenytoin blocks **voltage-gated sodium channels** by selectively binding to the channel in the inactive state and slowing its rate of recovery.
- It is effective for treatment of **focal and generalized tonic clonic seizures and in the treatment of status epilepticus.**
- Phenytoin induces drugs metabolized by the CYP2C and CYP3A families and the UGT enzyme system.
- Depression of the CNS occurs particularly in the cerebellum and vestibular system, causing nystagmus and ataxia. The elderly are highly susceptible to this effect.
- **Gingival hyperplasia may cause the gums to grow over the teeth. Long-term use may lead to development of peripheral neuropathies and osteoporosis.**
- Although phenytoin is advantageous due to its low cost, the actual cost of therapy may be much higher, considering the potential for serious toxicity and adverse effects.
- **Fosphenytoin is a prodrug that is rapidly converted to phenytoin in the blood within minutes.** Whereas fosphenytoin may be administered intramuscularly (IM), phenytoin sodium should never be given IM, as it causes tissue damage and necrosis.
- ~~Fosphenytoin is the drug of choice and standard of care for IV and IM~~ administration of phenytoin.



- **13- Pregabalin:**
- **Binds to the a2-δ site, an auxiliary subunit of voltage-gated calcium channels in the CNS, inhibiting excitatory neurotransmitter release.**
- **The exact role this plays in treatment is not known, but the drug has proven effects on focal-onset seizures, diabetic peripheral neuropathy, postherpetic neuralgia, and fibromyalgia.**
- **It has no significant metabolism and few drug interactions.**
- **Weight gain and peripheral edema have been reported.**

- **14- Topiramate:**
- **Has multiple mechanisms of action.**
- **It blocks voltage-dependent sodium channels, reduces high-voltage calcium currents (L type), is a carbonic anhydrase inhibitor, and may act at glutamate (NMDA) sites.**
- **Topiramate is effective for use in partial and primary generalized epilepsy. It is also approved for prevention of migraine.**
- **It inhibits CYP2C19 and is induced by phenytoin and carbamazepine.**
- **Adverse effects include somnolence, weight loss, and paresthesias.**
- **Renal stones, glaucoma, oligohidrosis (decreased sweating), and hyperthermia have also been reported.**

VI. STATUS EPILEPTICUS

- In status epilepticus, two or more seizures occur without recovery of full consciousness in between episodes.
- These may be focal or primary generalized, convulsive or nonconvulsive.
- Status epilepticus is life threatening and requires emergency treatment usually consisting of administration of a fast-acting medication such as a benzodiazepine, followed by a slower-acting medication such as phenytoin.

WOMEN'S HEALTH AND EPILEPSY

- Women of childbearing potential with epilepsy require assessment of their antiepilepsy medications in regard to contraception and pregnancy planning.
- Several antiepilepsy medications increase the metabolism of hormonal contraceptives, potentially rendering them ineffective.
- These include phenytoin, phenobarbital, carbamazepine, topiramate, oxcarbazepine, rufinamid , and clobazam.
- These medications increase the metabolism of contraceptives regardless of the delivery system used (for example, patch, ring, implants, and oral tablets). Pregnancy planning is vital, as many antiepilepsy medications have the potential to affect fetal development and cause birth defects.
- All women considering pregnancy should be on high doses (1 to 5 mg) of folic acid prior to conception.

- Divalproex and barbiturates should be avoided. If possible, women already taking divalproex should be placed on other therapies prior to pregnancy and counseled about the potential for birth defects, including cognitive and behavioral abnormalities and neural tube defects.
- The pharmacokinetics of antiepilepsy medications and the frequency and severity of seizures may change during pregnancy.
- Regular monitoring by both an obstetrician and a neurologist is important.