Al-Mustaqbal University College
Department of Pharmacy
4th stage
Pharmacology II
Lecture: 7

Drugs for Epilepsy

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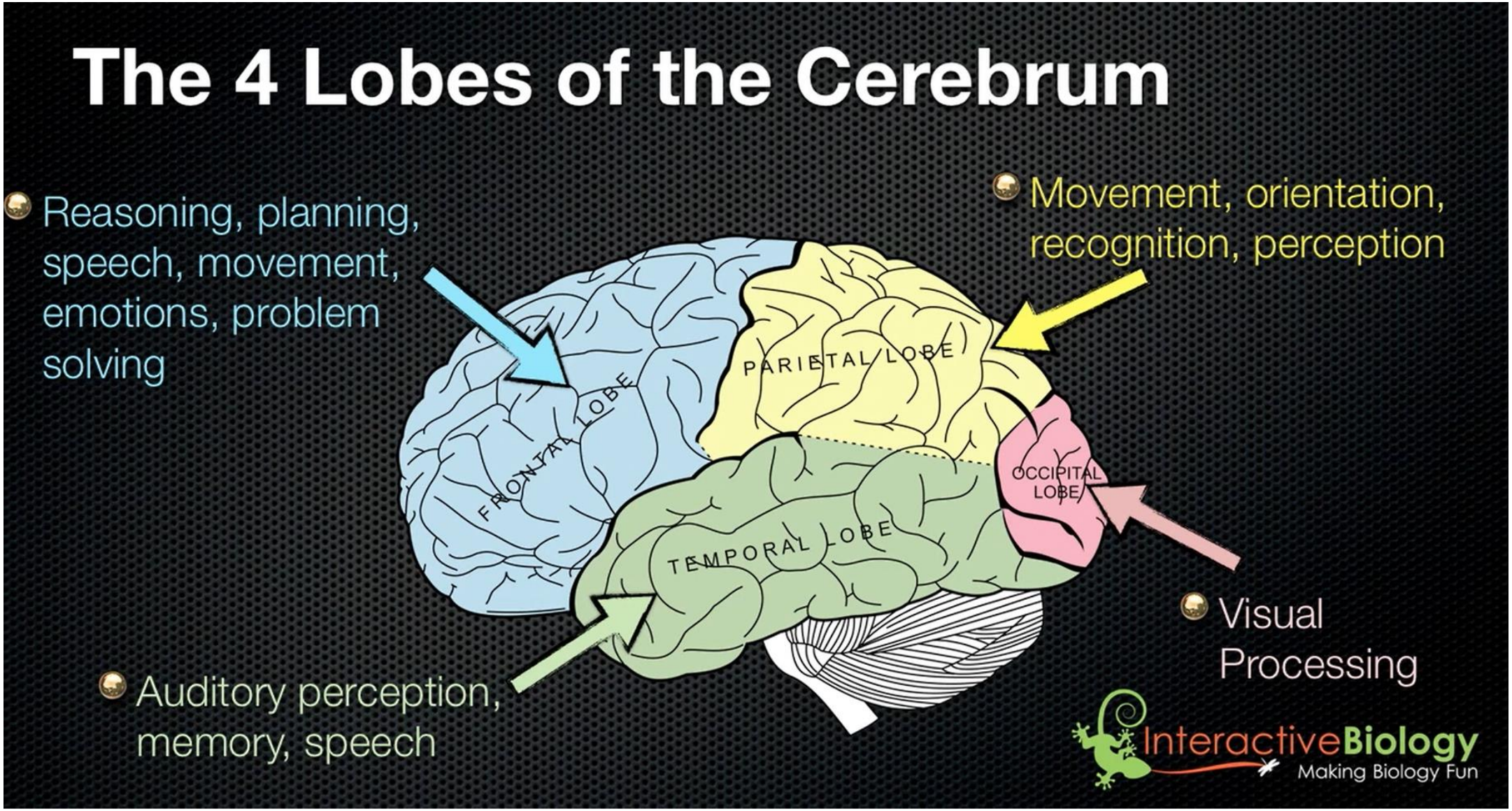
EPILEPSY

- Approximately **10%** of the population has at least **one seizure** in their lifetime.
- **Globally**, epilepsy is the **fourth** most common **neurologic disorder** after migraine, cerebrovascular disease (stroke), and Alzheimer's disease.
- **Epilepsy** is an assortment of **different seizure types** and syndromes that have in **common** the **sudden, excessive, and synchronous discharge** of cerebral neurons.
- This **abnormal electrical activity** may result in:

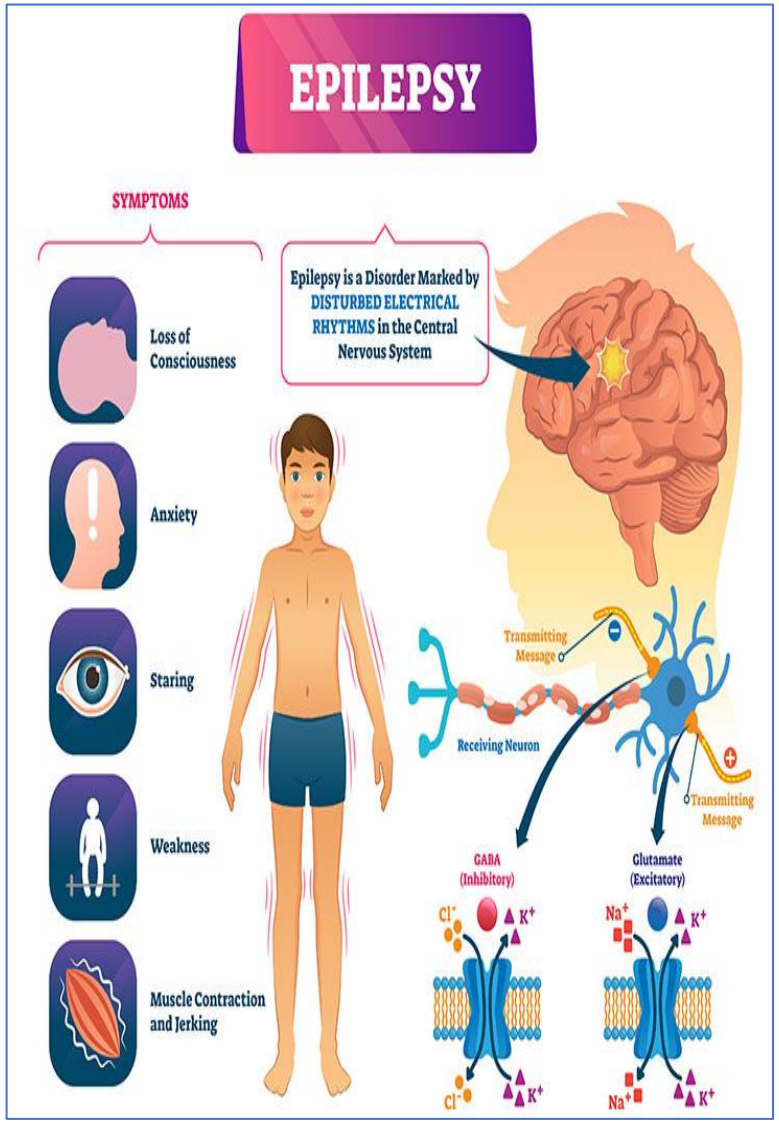
1. Loss of consciousness
2. Abnormal movements
3. Atypical or odd behavior
4. Distorted perceptions


The 4 Lobes of the Cerebrum
Reasoning, planning, speech, movement, emotions, problem solving
Movement, orientation, recognition, perception
FRONTAL LOBE
PARIETAL LOBE
OCCIPITAL LOBE
TEMPORAL LOBE
Auditory perception, memory, speech
Visual Processing
InteractiveBiology
Making Biology Fun

ETIOLOGY OF SEIZURES

- **Epilepsy** can be due to an **underlying (secondary)** genetic, structural, or metabolic cause or an **unknown (idiopathic)** etiology.
- **Epilepsy** results from **firing of a small** population of **neurons** in a specific area of the brain referred to as the "**primary focus**:'
- Focal areas that are functionally abnormal may be **triggered** by:

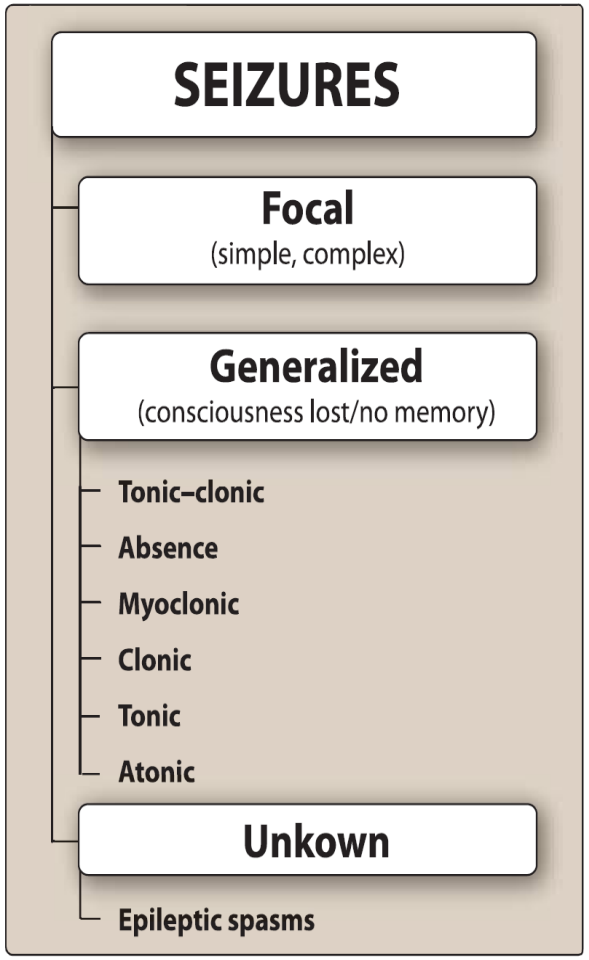
1. **Physiologic factors:** such as an alteration in blood gases, pH, electrolytes, and blood glucose.
2. **Environmental factors:** such as sleep deprivation, alcohol intake, and stress.
3. **Other factors:** such as illicit drug use, tumor, head injury, hypoglycemia, meningeal infection, and the rapid withdrawal of alcohol.



CLASSIFICATION OF SEIZURES

A. Focal (partial, conscious, minor)

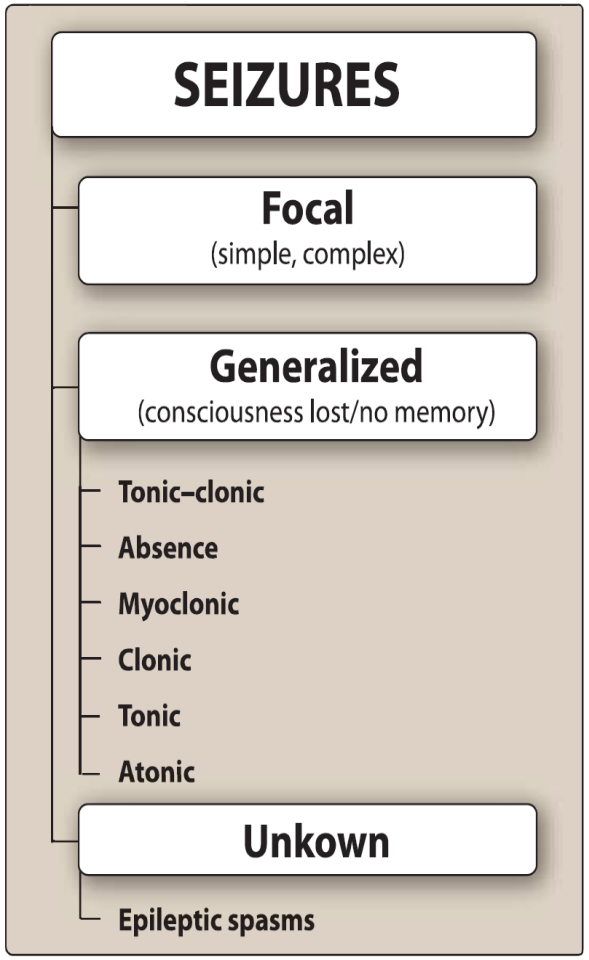
- Focal seizures involve **only** a portion of **one hemisphere** of the brain.
- The **symptoms** depend **on** the site and the extent to which the electrical activity spreads in the brain neurons.
- Focal seizures **may progress** to become bilateral tonic-clonic seizures.
- Patients **may lose** consciousness or awareness.
- This seizure type may begin with a **motor** or **nonmotor** activity.



CLASSIFICATION OF SEIZURES

B. Generalized (unconscious, major)

- It may **begin locally** and then progress to include **both hemispheres** of the brain.
- Primary generalized seizures may be **convulsive** or **nonconvulsive** with an **immediate loss of consciousness**.
- It may include:
  - ✓Tonic-clonic (grand mal seizure)
  - ✓Absence (petit mal seizure)
  - ✓Myoclonic
  - ✓Clonic
  - ✓Tonic
  - ✓Atonic



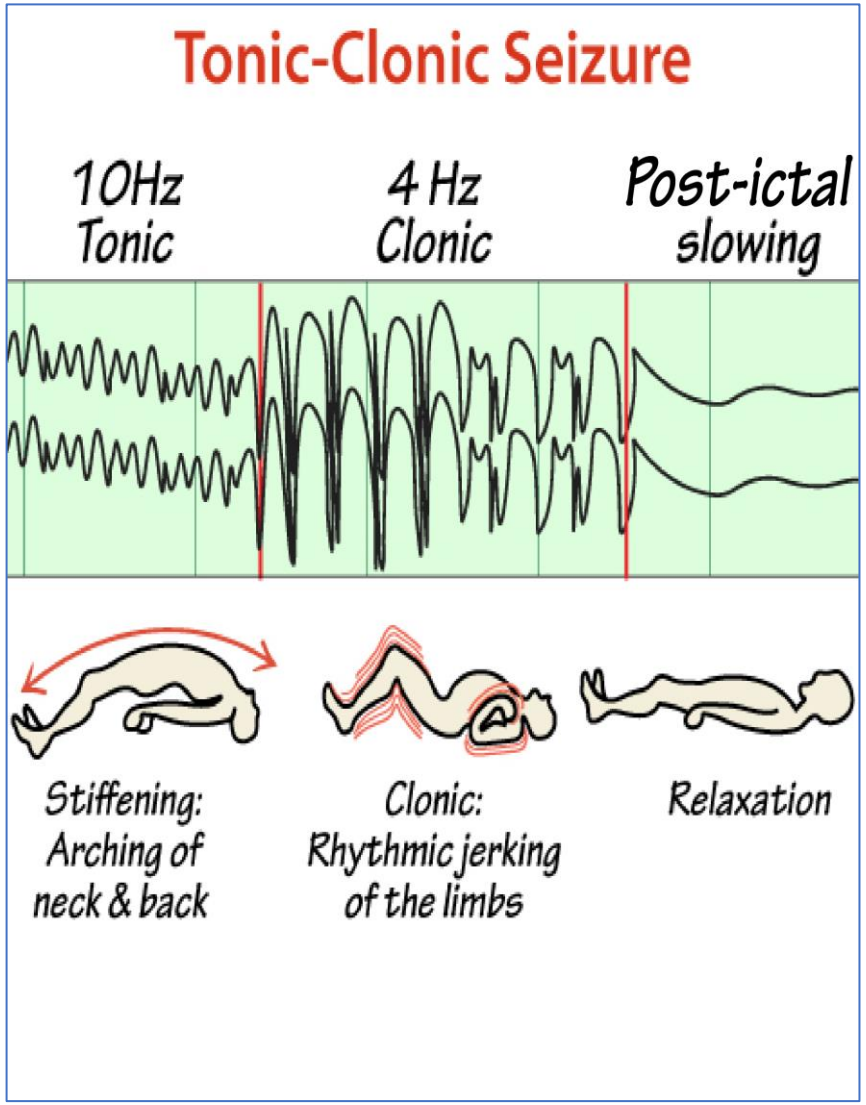
CLASSIFICATION OF SEIZURES

1. Tonic-clonic (grand mal seizure):

- Loss of consciousness, followed by **tonic** (continuous contraction) and **clonic** (rapid contraction and relaxation) phases.
- Followed by a period of **confusion and exhaustion** due to the depletion of **glucose** and energy stores.

2. Absence (petit mal seizure):

- A **brief**, **abrupt**, and **self-limiting** loss of consciousness.
- It occurs about **3 to 5 years** of age and lasts until puberty or beyond.
- The patient stars and exhibits **rapid eye blinking**, which lasts for **3 to 5 seconds**.
- It has a very distinct **three-per-second 2/S spike** waves discharge on **EEG**.



CLASSIFICATION OF SEIZURES

3. Myoclonic:

- These seizures consist of **short episodes of muscle contractions** that may recur for several **minutes**.
- It occurs **after wakening** and exhibits **brief jerks** of the limbs.
- occur at **any age** but usually begin around **puberty or early adulthood**.

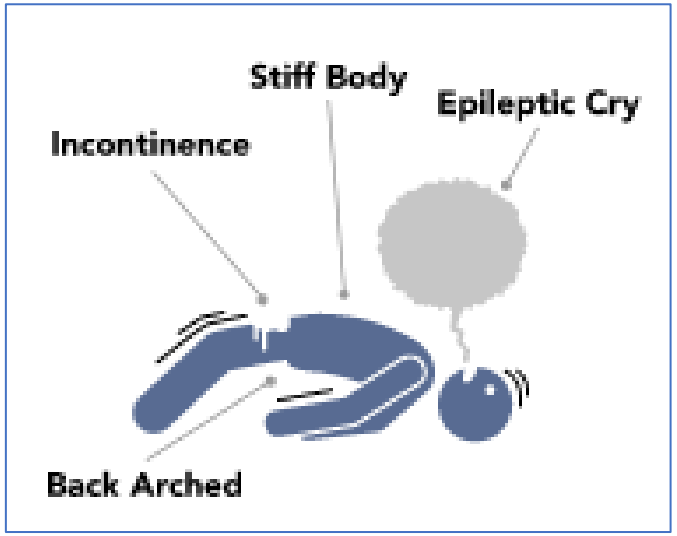
4. Clonic:

- These seizures consist of short **episodes of muscle contractions** that may closely resemble myoclonic seizures.
- **Consciousness** is **more impaired** with clonic seizures as compared to myoclonic.

CLASSIFICATION OF SEIZURES

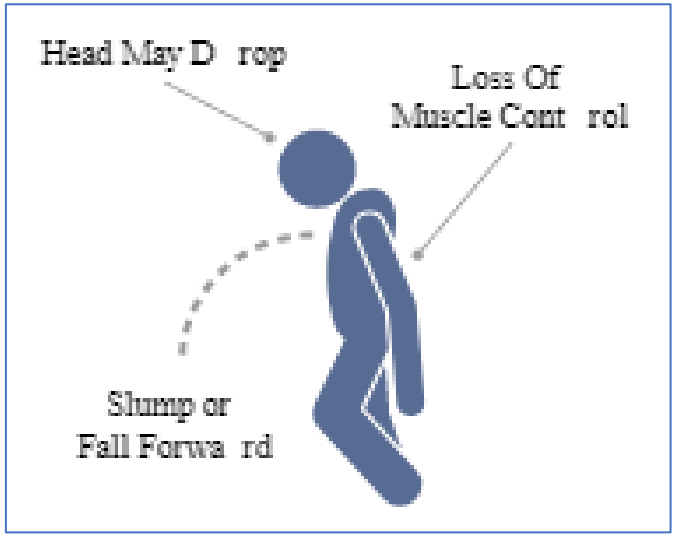
5. Tonic:

- These seizures involve **increased tone** in the extension muscles and are generally **less than 60 seconds**.



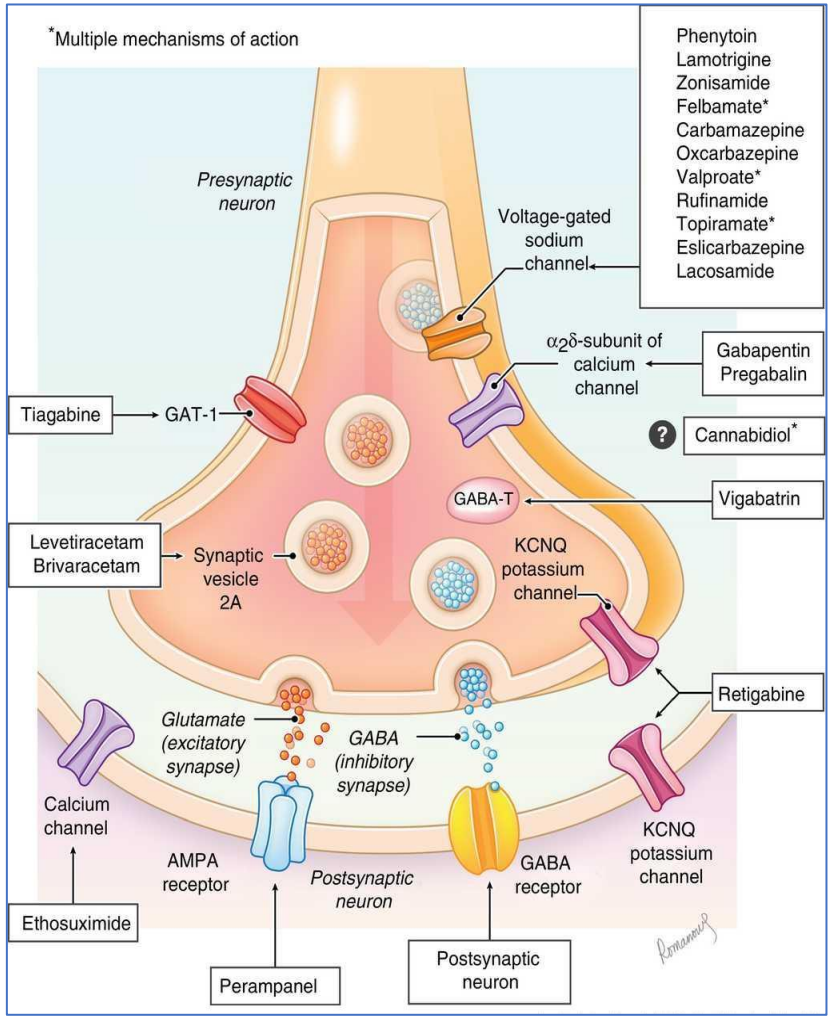
6. Atonic:

- These seizures are also known as **drop attacks** and are characterized by a **sudden loss of muscle tone**.



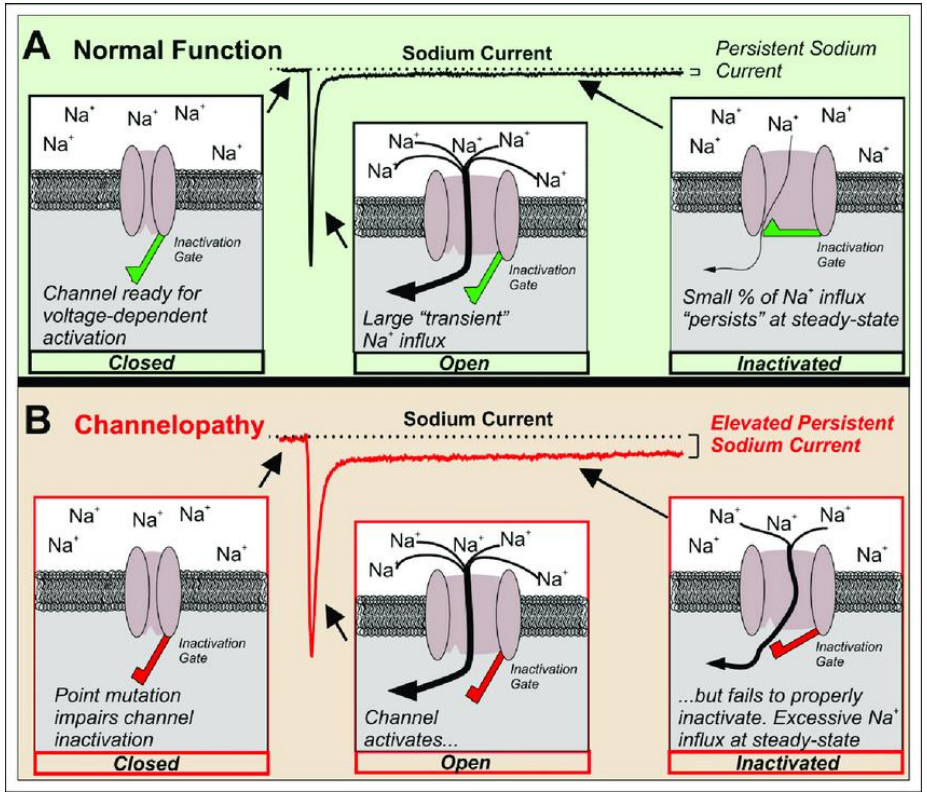
MECHANISM OF ACTION OF ANTISEIZURE MEDICATIONS

- Drugs reduce seizures through **mechanisms** such as:
  1. **Sodium Channel Blockade**
  2. **GABA-Related Targets**
  3. **Calcium Channel Blockade**
  4. **Other Mechanisms**
- Antiseizure medications **suppress** seizures but **do not "cure" or "prevent"** epilepsy.



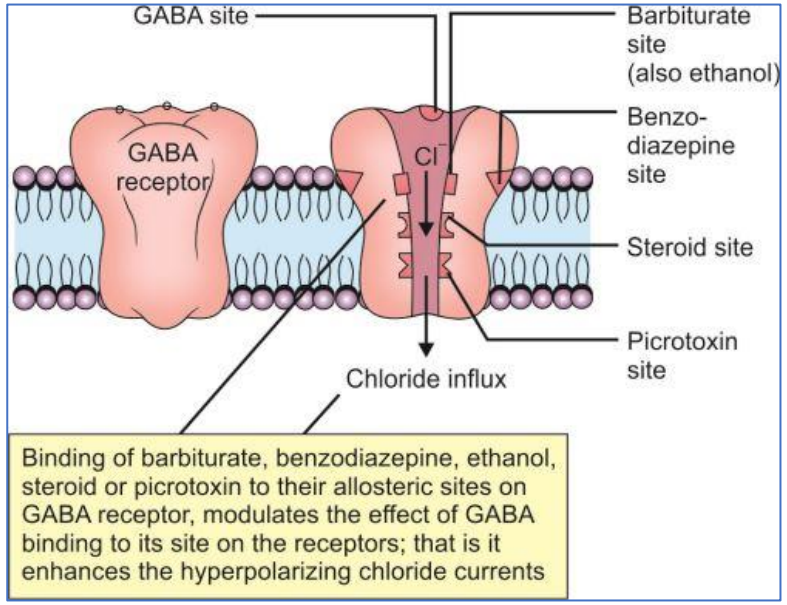
SODIUM CHANNEL BLOCKADE

- At therapeutic conc. **phenytoin**, **carbamazepine, lamotrigine, and zonisamide** block voltage-gated sodium channels in neuronal membranes.
- This action is **rate-dependent** (ie, dependent on the frequency of neuronal discharge).
- It results in the **prolongation** of the inactivated state of the Na+ channel and the refractory period of the neuron.
- **Phenobarbital** and **valproic acid** may exert similar effects at **high doses**.



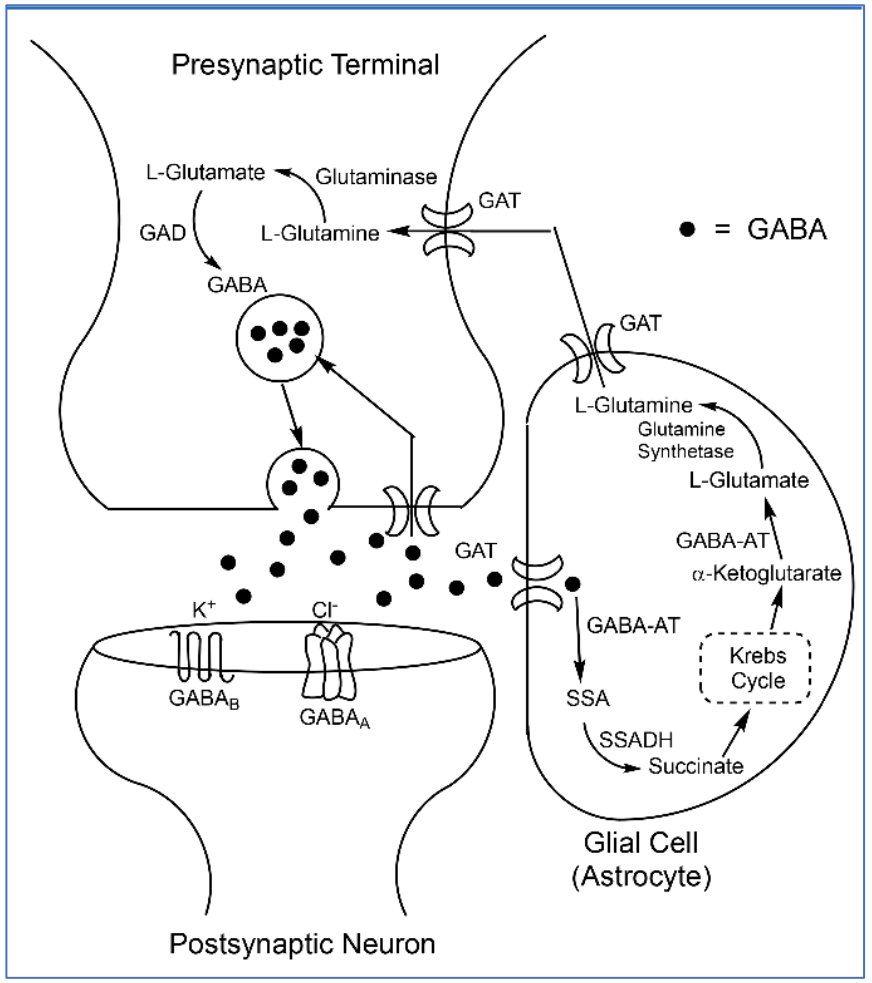
GABA-RELATED TARGETS

- **Benzodiazepines** interact with specific receptors on the **GABA-A** receptor chloride ion channel.
- Benzodiazepines **increase** the **frequency** of chloride ion channel opening; these drugs facilitate the inhibitory effects of GABA.
- **Phenobarbital** and other barbiturates also enhance the inhibitory actions of GABA but interact with a different receptor site on chloride ion channels.
- Barbiturates result in an increased **duration** of chloride ion channel opening.



GABA-RELATED TARGETS

- GABA aminotransaminase (**GABA-T**) is an important enzyme in the **termination** of the action of **GABA**.
- The enzyme is **irreversibly inactivated** by **vigabatrin** at therapeutic plasma levels and can also be inhibited by **valproic** acid at very high concentrations.
- **Tiagabine** inhibits a **GABA transporter** (**GAT-1**) in neurons and glia **prolonging** the action of the neurotransmitter.
- **Gabapentin** is a **structural analog** of GABA, but it does **not activate GABA** receptors directly.
- Other drugs that may **facilitate the inhibitory actions** of GABA include felbamate, topiramate, and valproic acid.



CALCIUM CHANNEL BLOCKADE

- **Ethosuximide** inhibits low-threshold (T type) Ca2+ currents, especially in **thalamic neurons** that act as **pacemakers** to generate rhythmic **cortical discharge**.
- A similar action is reported for **valproic acid**, as well as for both **gabapentin** and **pregabalin**.

OTHER MECHANISMS

- In addition to its action on calcium channels, **valproic acid** causes neuronal membrane **hyperpolarization**, possibly by **enhancing K+ channel permeability**.
- Although **phenobarbital** acts on both **sodium** channels and **GABA-chloride** channels, it also acts as an **antagonist at some glutamate receptors**.
- **Felbamate** blocks **glutamate NMDA** receptors.
- **Topiramate** blocks **sodium channels** and potentiates the actions of **GABA** and may also block **glutamate receptors**.

CLINICAL USES

- **Diagnosis** of a specific seizure **type** is important for prescribing the most **appropriate** antiseizure drug (or combination of drugs).
- **Drug choice is usually made on the basis of:**

1. Established **efficacy** in the specific seizure state that has been diagnosed
2. The prior **responsiveness** of the patient
3. The anticipated **toxicity** of the drug

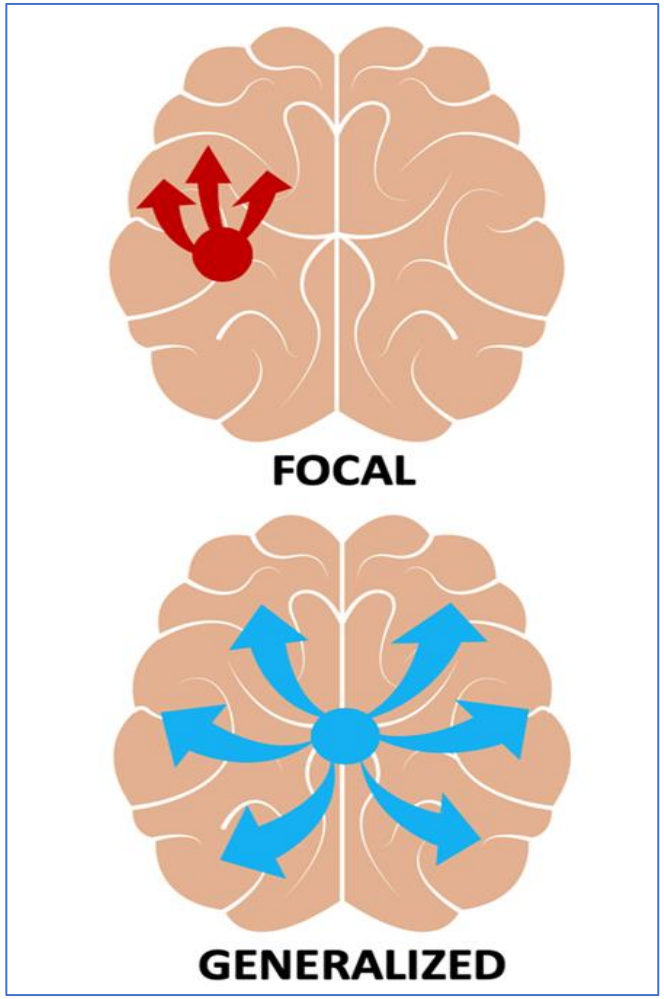
- Treatment may involve **combinations** of drugs, following the principle of adding known effective agents if the preceding drugs are not sufficient.

GENERALIZED TONIC-CLONIC SEIZURES

- **Valproic acid**, **carbamazepine**, and **phenytoin** are the drugs of **choice** for generalized tonic-clonic (grand mal) seizures.
- **Phenobarbital** (or **primidone**) is now considered to be an **alternative** agent in **adults** but continues to be a **primary drug in infants**.
- **Lamotrigine** and **topiramate** are also approved drugs for this indication, and several others may be used adjunctively in refractory cases.

PARTIAL SEIZURES

- The drugs of **first choice** are **carbamazepine** (or oxcarbazepine) or **lamotrigine** or **phenytoin**.
- **Alternatives** include felbamate, phenobarbital, topiramate, and valproic acid.
- Many of the **newer anticonvulsants** can be used **adjunctively** including gabapentin and pregabalin, a structural congener.



ABSENCE SEIZURES

- **Ethosuximide** or **valproic acid** are the **preferred** drugs because they cause **minimal sedation**.
- **Ethosuximide** is often used in **uncomplicated** absence seizures if patients can **tolerate** its **GIT side effects**.
- **Valproic acid** is particularly useful in patients who have **concomitant** generalized tonic-clonic or myoclonic seizures.
- **Clonazepam** is effective as an **alternative** drug but has the **disadvantages** of causing **sedation and tolerance**.
- Lamotrigine, levetiracetam, and zonisamide are also **effective** in absence seizures.

MYOCLONIC AND ATYPICAL ABSENCE SYNDROMES

- **Myoclonic seizure** syndromes are usually treated with **valproic acid**.
- **Lamotrigine** is approved for **adjunctive** use but is commonly used as **monotherapy**.
- **Clonazepam** can be **effective**, but the **high doses** required cause **drowsiness**.
- Levetiracetam, topiramate, and zonisamide are also used as **backup drugs** in myoclonic syndromes.
- **Felbamate** has been used **adjunctively** with the primary drugs but has both **hematotoxic** and **hepatotoxic** potential.

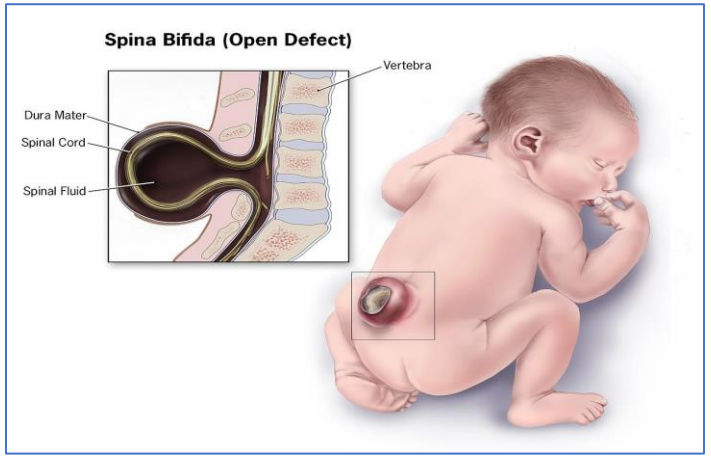
STATUS EPILEPTICUS

- **Intravenous diazepam** or **lorazepam** is usually **effective** in terminating attacks and providing short-term control.
- For **prolonged therapy**, intravenous **phenytoin** has often been used because it is **highly effective** and **less sedating** than benzodiazepines or barbiturates.
- However, **phenytoin** may cause **cardiotoxicity** (perhaps because of its solvent propylene glycol), and *fosphenytoin* (water-soluble) is a **safer** parenteral agent.
- **Phenobarbital** has also been used in status epilepticus, especially in **children**.
- In very **severe status epilepticus** that does not respond to these measures, **general anesthesia** may be used.

TOXICITY OF ANTIEPILEPTICS

Teratogenicity:

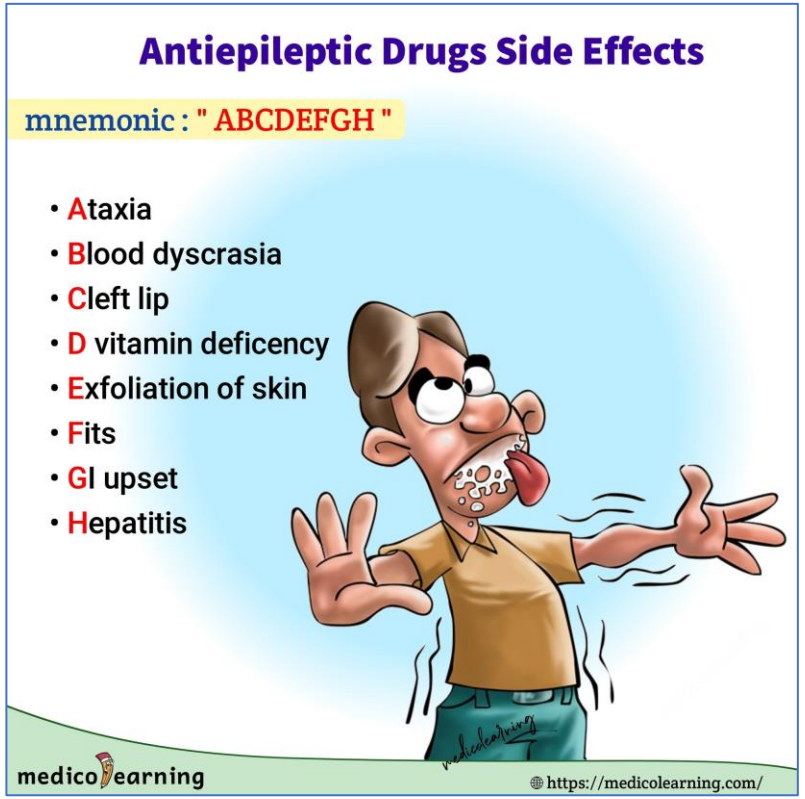
- Children born of mothers taking anticonvulsant drugs have an increased risk of **congenital malformations**.
- **Neural tube defects** (eg, spina bifida) are associated with the use of **valproic acid**.
- **Carbamazepine** has been implicated as a cause of **craniofacial** anomalies and **spina bifida**.
- **Fetal hydantoin syndrome** has been described after **phenytoin** use by pregnant women.



TOXICITY OF ANTIEPILEPTICS

Overdosage Toxicity:

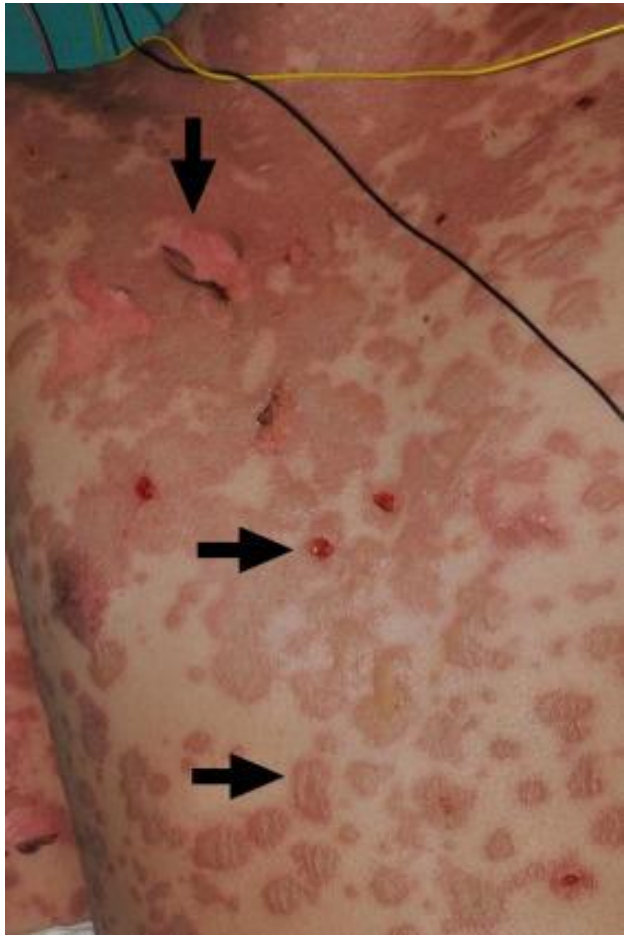
- Most of the commonly used anticonvulsants are **CNS depressants**, and **respiratory depression** may occur with **overdosage**.
- **Management** is **primarily supportive** (airway management, mechanical ventilation).
- **Flumazenil** may be used in **benzodiazepine** overdose.



TOXICITY OF ANTIEPILEPTICS

Life-Threatening Toxicity:

- **Fatal hepatotoxicity** has occurred with **valproic acid**, with the greatest risk to children younger than 2 years and patients taking multiple anticonvulsant drugs.
- **Lamotrigine** has caused skin rashes and life-threatening **Stevens-Johnson syndrome** or **toxic epidermal necrolysis**.
- **Zonisamide** may also cause **severe skin reactions**.
- Reports of **aplastic anemia** and **acute hepatic failure** have limited the use of **felbamate** to severe, refractory seizure states.



WITHDRAWAL OF ANTIEPILEPTICS

- **Withdrawal** from antiseizure drugs should be accomplished **gradually** to avoid increased seizure frequency and severity.
- In general, **withdrawal from anti-absence** drugs is more **easily** accomplished than withdrawal from drugs used in **partial or generalized tonic-clonic seizure** states.

WOMEN'S HEALTH AND EPILEPSY

- Many **antiseizure** 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.
- **Regular monitoring** by both an obstetrician and a neurologist is important.
- **Lamotrigine** (Lamictal®) and **levetiracetam** (Keppra®) are safer to use during pregnancy than other epilepsy medicines.

THANK YOU FOR YOUR ATTENTION