ANTIEPILEPTIC DRUGS

Dr. Yousef Al-saraireh
Associate Professor in Pharmacology
Faculty of Medicine

Epilepsy

- **10 %** of population will have **at least one seizure** in their lifetime
- **Epilepsy** is the **third most common neurologic disorder** after **cerebrovascular (CVA) and Alzheimer's disease**
- **Epilepsy** is different types of **seizures and syndromes** results from **abnormal electrical activity in cerebral neurons associated with prolong depolarization**

- **This abnormal electrical activity** may result in a variety of events, including **loss of consciousness, and abnormal movements**
- **The site of origin of abnormal neuronal firing determines symptoms that are produced**
- For example, **if motor cortex** is involved, patient may experience **abnormal movements or generalized convulsion**

- **Seizures** can be controlled completely in **70 to 80 %** of patients with **one medication**

- **10 to 15** % of patients will require **more than one drug**

- **10 %** may **not achieve complete seizure control**

- **In most cases, epilepsy has no cause**

- Focal areas that are functionally abnormal may be triggered into activity by changes in any of a variety of **environmental factors**, including **alteration in blood gases, pH, electrolytes, blood glucose level, sleep deprivation, alcohol intake, and stress**

Classification of Epilepsy

A. Idiopathic or primary (unknown etiology)

B. Secondary

A. Idiopathic epilepsy

- When **no specific anatomic cause for seizure**, such as **trauma or neoplasm**, is evident, patient may be diagnosed with idiopathic epilepsy
- **Most cases of epilepsy are idiopathic**
- These seizures may result from an **inherited abnormality in CNS**

B. Secondary epilepsy

- Causes, such as **tumors, head injury, hypoglycemia, meningeal infection**, can precipitate seizures

- It is important to classify seizures to determine appropriate treatment
- Seizures have been categorized by **site of origin, etiology & clinical presentation**
- Seizures have been classified into **two broad groups: partial (or focal), and generalized**

A. Partial

- Partial seizures involve only a portion of brain, typically **part of one lobe of one hemisphere**
- Symptoms of each seizure type depend on **site of neuronal discharge** and **on extent to which electrical activity spreads** to other neurons in brain
- **Consciousness is usually preserved**
- Partial seizures may progress, becoming generalized tonic-clonic seizures

1. Simple Partial

- Abnormal electrical activity is **confined to a single locus in brain**
- **Electrical discharge does not spread**
- **Patient does not lose consciousness**
- Patient often exhibits **abnormal activity of a single limb or muscle group**

2. Complex Partial

- These seizures exhibit **complex sensory hallucinations, mental distortion, and loss of consciousness**
- **Diarrhea, and/or urination**

B. Generalized

- Generalized seizures may begin locally, **producing abnormal electrical discharges throughout both hemispheres of brain**
- Patient usually has **an immediate loss of consciousness**

1. Tonic-clonic:

- Seizures result **in loss of** consciousness, followed by **tonic (continuous contraction)** and **clonic (rapid contraction and relaxation)** phases

2. Myoclonic: consists of **short episodes of muscle contractions**. They generally occur after wakening and exhibit as **brief jerks of limbs**

3. Febrile seizures: Young children may develop seizures with illness accompanied **by high fever**. febrile seizures consist of **generalized tonic-clonic convulsions of short duration** and **do not necessarily lead to a diagnosis of epilepsy**

4. Status epilepticus:

- In status epilepticus, **two or more seizures recur without recovery of full consciousness between them**. Status epilepticus **is life-threatening and requires emergency treatment**

Mechanism of action of antiepileptic drugs

- Blockade of voltage-gated Na+ channels (carbamazepine, phenytoin)
- Blockade of voltage-gated Ca 2+ channels (valporic acid)
- Enhancement of inhibitory GABAergic impulses (benzodiazepines, barbiturate)
- Interference with excitatory glutamate transmission (lamotrigine, topiramate)

Choice of drug treatment

- **Classification of seizures** being treated
- **Characteristics of patient** (age, comorbid medical conditions)
- **Characteristics of drug** (toxicity, cost & interactions with other medications)

- **In newly diagnosed patients**, **monotherapy** is instituted with a single agent (exhibit better adherence and fewer side effects)
- If seizures are not controlled with the first drug, monotherapy with **an alternate antiepileptic drug or Combination therapy is used**

- **Older antiepileptics (first generation)**, such as benzodiazepines, phenobarbital, phenytoin, carbamazepine, and valporic acid

- **New drugs (second generation)**, which include gabapentin, lamotrigine, topiramate, and oxcarbazepine

Benzodiazepines

- They act by facilitating the binding of the inhibitory neurotransmitter GABA at various GABA receptors throughout the CNS to reduce firing
- **Diazepam & lorazepam** are most often used as an adjunctive therapy for myoclonic, partial and generalized tonic-clonic seizures, status epilepticus
- **Diazepam** is available for **rectal administration** to avoid prolonged generalized tonic-clonic seizures
- Should be considered for **use only after trials with monotherapy or combinations treatment**

Phenobarbital

- The primary mechanism of action is **enhancement of inhibitory effects of GABA-**mediated neurons
- The primary use in treatment of **status epilepticus**
- Phenobarbital is a cytochrome P450 hepatic enzyme inducer. It binds transcription factor receptors that activate cytochrome P450 transcription, thereby increasing its amount and thus its activity. Due to this higher amount of CYP450, drugs that are metabolized by the CYP450 enzyme system will have decreased effectiveness. This is because the increased CYP450 activity increases the clearance of the drug, reducing the amount of time they have to work

Carbamazepine

- **Tegretol**
- **blocks sodium channels**
- Is effective for treatment of **partial seizures & secondarily generalized tonic-clonic seizures, trigeminal neuralgia & in bipolar disease**
- **Side effects:** Skin rash, hyponatremia

Phenytoin

- **Epanutin**
- **Blocks voltage-gated Na+ channels**
- is effective for treatment of **partial seizures & generalized tonic-clonic seizures & in status epilepticus (IV)**
- Small increases in a daily dose can produce large increases in plasma concentration, resulting in drug-induced toxicity
- Side effects: ataxia, gingival hyperplasia, peripheral neuropathies & osteoporosis

Valproic acid

- **Convulex, Depakine**
- **Block Na+ and Ca+2 channels**
- It is effective for treatment of **partial & generalized tonic-clonicseizures**
- Side effects: hepatic toxicity, teratogenicity (neural tube defects)

Gabapentin

- **Gabatrex, Neurontin**
- Is an analog of GABA
- Its precise mechanism of action is not known
- It is approved as adjunct therapy **for partial seizures and neuropathic pain (postherpetic neuralgia)**
- **Well tolerated by elderly** due to mild adverse effects and limited or no reported drug interactions

Lamotrigine

- **Lamictal**
- blocks **sodium channels & high voltage–calcium channels**
- is effective in a wide variety of seizure disorders, including **partial seizures, generalized seizures, typical absence seizures**
- The half-life **(24–35 hours)**
- Side effects: **rash** (may progress to a serious, life-threatening reaction) **Stevens-Johnson syndrome**

Oxcarbazepine

- Is a **prodrug** that is rapidly reduced **to 10-monohydroxy (MHD) metabolite** which is responsible for its anticonvulsant activity
- It is approved for use in **adults and children with partial seizures**

Pregabalin

- **Lyrica**
- Binds to subunit of voltage-gated calcium channels in the CNS, inhibiting excitatory neu-rotransmitter release
- effective in **partial seizures, neuropathic pain associated with diabetic peripheral neuropathy, post herpetic neuralgia & fibromyalgia**
- Drowsiness, blurred vision, weight gain, peripheral edema

Topiramate

- **Topamax**
- blocks voltage-sodium channels; increases frequency of chloride channel opening by binding to GABA-A receptors
- It is a carbonic anhydrase inhibitor & may act at glutamate (NMDA) sites
- Effective in **partial and primary generalized epilepsies & migraine**
- Somnolence, weight loss, paresthesias, renal stones