DRUGS THAT ACT IN THE CNS

Drugs for Epilepsy 1

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Epilepsy

Approximately **10%** of the population will have at least one seizure in their lifetime.

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.

Epilepsy

The site of origin of the abnormal neuronal firing 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.

In general, seizures can be controlled with one medication in **approximately 75%** of patients.

Patients may require **more than one medication** in order to optimize seizure control, and some patients may never obtain total seizure control.

Epilepsy/ ETIOLOGY OF SEIZURES

Focal areas that are functionally abnormal may be triggered into activity by changes in **physiologic factors**, such as an alteration in blood gases, pH, electrolytes, and blood glucose and changes in **environmental factors**, such as sleep deprivation, alcohol intake, and stress.

The neuronal discharge in epilepsy results from the firing of a small population of neurons in a specific area of the brain referred to as the "primary focus."

Epilepsy can be due to an underlying **genetic, structural, or metabolic cause or an unknown** cause.

Epilepsy/ ETIOLOGY OF SEIZURES

A. Genetic epilepsy

These seizures result from an inherited abnormality in the CNS.

B. 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.

C. Unknown cause

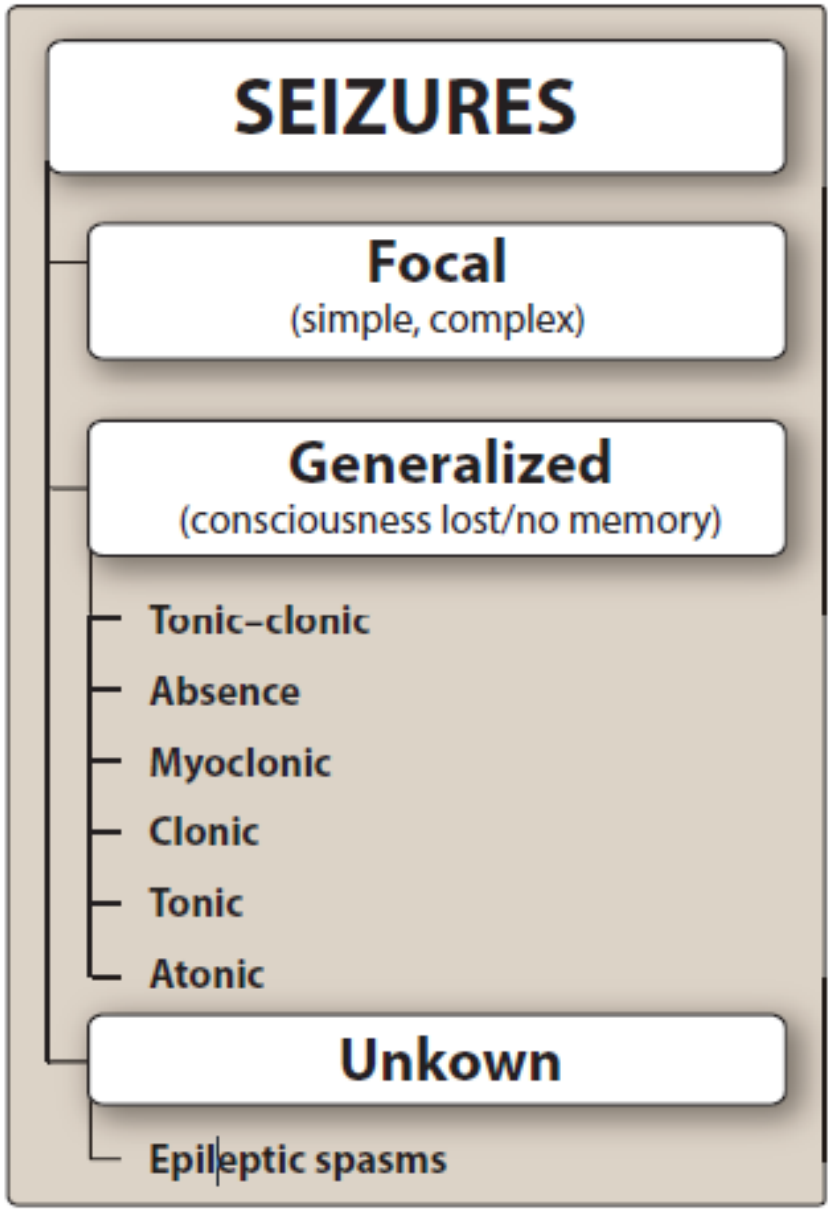
Most cases of epilepsy are due to an unknown cause. Patients can be treated chronically with antiepilepsy medications or vagal nerve stimulation.

Epilepsy/ CLASSIFICATION OF SEIZURES

It is important to correctly classify seizures to determine appropriate treatment.

Seizures have been categorized by **site of origin, etiology, electrophysiologic correlation, and clinical presentation**.

Seizures have been classified into two broad groups: focal and generalized.



Epilepsy/ CLASSIFICATION OF SEIZURES/ A. Focal

Focal seizures involve only **a portion of the brain**, typically part of one lobe of one hemisphere.

The symptoms of each seizure type depend on the site of neuronal discharge and on the extent to which the electrical activity spreads to other neurons in the brain.

Focal seizures may progress to become generalized tonic–clonic seizures.

Epilepsy/ CLASSIFICATION OF SEIZURES/ A. Focal

1. Simple partial:

These seizures are caused by a group of hyperactive neurons exhibiting abnormal electrical activity and are confined to **a single locus** in the brain.

The electrical discharge **does not spread**, and the patient does **not lose consciousness** or awareness.

The patient often exhibits abnormal activity of **a single limb or muscle group** that is controlled by the region of the brain experiencing the disturbance.

The patient may also show **sensory distortions**. This activity may spread.

Simple partial seizures may occur at any age.

Epilepsy/ CLASSIFICATION OF SEIZURES/ A. Focal

2. Complex partial:

These seizures exhibit complex sensory **hallucinations and mental** distortion.

Motor dysfunction may involve chewing movements, diarrhea, and/or urination.

Consciousness is altered.

Simple partial seizure activity may spread to become complex and then spread to a secondarily generalized convulsion.

Complex partial seizures may occur at any age.

Epilepsy/ CLASSIFICATION OF SEIZURES/ B. Generalized

Generalized seizures may begin locally and then **progress** to include abnormal electrical discharges throughout both hemispheres of the brain.

Primary generalized seizures may be convulsive or nonconvulsive, and the patient usually has an **immediate loss of consciousness**.

1. Tonic–clonic:

These seizures result in **loss of consciousness**, followed by **tonic** (continuous contraction) and **clonic** (rapid contraction and relaxation) phases.

The seizure may be followed by a period of confusion and **exhaustion** due to the depletion of glucose and energy stores.

Epilepsy/ CLASSIFICATION OF SEIZURES/ B. Generalized

2. Absence:

These seizures involve a brief, abrupt, and selflimiting **loss of consciousness**.

The onset generally occurs in patients at 3 to 5 years of age and lasts until puberty or beyond.

The patient stares and exhibits **rapid eye-blinking**, which lasts for 3 to 5 seconds.

Epilepsy/ CLASSIFICATION OF SEIZURES/ B. Generalized

3. Myoclonic:

These seizures consist of short episodes of **muscle contractions** that may recur for several minutes.

They generally occur **after wakening** and exhibit as brief jerks of the limbs.

Myoclonic seizures 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.

Epilepsy/ CLASSIFICATION OF SEIZURES/ B. Generalized

5. Tonic:

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

6. Atonic:

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

Epilepsy/ Mechanism of action of antiepilepsy medications

Drugs reduce seizures through such mechanisms as blocking voltage-gated channels **(Na+ or Ca2+),** enhancing inhibitory γ-aminobutyric acid (**GABA**)-ergic impulses and interfering with excitatory **glutamate** transmission.

Some antiepilepsy medications appear to have multiple targets within the CNS, whereas the mechanism of action for some agents is poorly defined.

Epilepsy/ V. ANTIEPILEPSY MEDICATIONS

studies have failed to demonstrate that the newer drugs are significantly more efficacious the older agents.

APPROVED BEFORE 1990

Carbamazepine TEGRETOL
Diazepam VALIUM
Divalproex DEPAKOTE
Ethosuximide ZARONTIN
Lorazepam ATIVAN
Phenobarbital LUMINAL
Phenytoin DILANTIN
Primidone MYSOLINE

APPROVED AFTER 1990

Clobazam ONFI
Eslicarbazepine APTIOM
Ezogabine POTIGA
Felbamate FELBATOL
Fosphenytoin CEREBYX
Gabapentin NEURONTIN
Lacosamide VIMPAT
Lamotrigine LAMICTAL
Levetiracetam KEPPRA
Oxcarbazepine TRILEPTAL
Perampanel FYCOMPA
Pregabalin LYRICA
Rufinamide BANZEL
Tiagabine GABITRIL
Topiramate TOPAMAX
Vigabatrin SABRIL
Zonisamide ZONEGRAN

Epilepsy/ V. ANTIEPILEPSY MEDICATIONS

A. Benzodiazepines

Benzodiazepines bind to **GABA inhibitory** receptors to reduce firing rate.

Most benzodiazepines are reserved for emergency or **acute seizure** treatment due to tolerance.

However, **clonazepam and clobazam** may be prescribed as adjunctive therapy for particular types of seizures.

Epilepsy/ V. ANTIEPILEPSY MEDICATIONS

B. Carbamazepine

Carbamazepine **blocks sodium channels**, thereby inhibiting the generation of repetitive action potentials in the epileptic focus and preventing their spread.

Carbamazepine is effective for treatment of **focal seizures** and, additionally **generalized tonic–clonic seizures, trigeminal neuralgia, and bipolar disorder**.

Carbamazepine is absorbed slowly and erratically following oral administration and may vary from generic to generic, resulting in large variations in serum concentrations of the drug.

It **induces** its own metabolism, resulting in lower total carbamazepine blood concentrations at higher doses.

Epilepsy/ V. ANTIEPILEPSY MEDICATIONS

C. Eslicarbazepine

Eslicarbazepine acetate is a prodrug that is converted to the active metabolite eslicarbazepine (S-licarbazepine) by hydrolysis. S-licarbazepine is the active metabolite of oxcarbazepine

It is a voltage-gated **sodium channel blocker** and is approved for partial-onset seizures in adults.

Eslicarbazepine exhibits linear pharmacokinetics and is eliminated via glucuronidation.

The side effect profile includes dizziness, somnolence, diplopia, and headache. Serious adverse reactions such as rash, psychiatric side effects, and hyponatremia occur rarely.

Epilepsy/ V. ANTIEPILEPSY MEDICATIONS

D. Ethosuximide

Ethosuximide reduces propagation of abnormal electrical activity in the brain, most likely by **inhibiting calcium channels**. It is only effective in treating absence seizures.

E. Ezogabine

Ezogabine is thought to open voltage-gated **potassium channels** leading to **stabilization** of the resting membrane potential.

Ezogabine exhibits linear pharmacokinetics and no drug interactions at lower doses.

Possible unique side effects are urinary retention, QT interval prolongation, blue skin discoloration, and retinal abnormalities.