Antiepileptic Drugs
• Seizures may be partial or generalised depending on the location and spread of the abnormal neuronal discharge. The attack may involve mainly motor, sensory or behavioural phenomena. Unconsciousness occurs when the reticular formation is involved.
Types of Epilepsy

• Two major categories, namely *partial* and *generalised* seizures; there is some overlap and many varieties of each.

**Partial seizures**

– The discharge begins locally, and often remains localised. Produce relatively simple symptoms without loss of consciousness.
Generalised seizures

- Involve the whole brain, including the reticular system, thus producing abnormal electrical activity throughout both hemispheres. Immediate loss of consciousness.
Partial seizures
- Simple partial seizures
- Complex partial seizures
- Partial seizures secondarily generalized

Generalized seizures
- Generalized tonic-clonic (grand mal) seizures
- Absence (petit mal) seizures
- Tonic seizures
- Atonic seizures
- Clonic and myoclonic seizures
- Infantile spasms

\(^1\)
• Two common forms of generalised epilepsy are the tonic-clonic fit (grand mal) and the absence seizure (petit mal). Status epilepticus is a life-threatening condition in which seizure activity is uninterrupted.
Mechanism of Action

- Reducing electrical excitability of cell membranes, possibly through inhibition of sodium channel.

- Enhancing GABA-mediated synaptic inhibition. This may be achieved by an enhanced pre- or post-synaptic action of GABA, by inhibiting GABA-transaminase, or by drugs with direct GABA-agonist properties.
Mechanism of Action

• A few drugs appear to act by a third mechanism, namely inhibition of T-type calcium channels.

• Newer drugs act by other mechanism, yet to be elucidated.

• Drugs that block excitatory amino acid receptors are effective in animal models, but not yet developed for clinical use.
• The main drugs in current use are: phenytoin, carbamazepine, valproate and ethosuximide.

• Secondary drugs include:
  – Phenobarbitone: highly sedative
  – Various benzodiazepines (e.g. clonazepam);
  Diazepam used in treating status epilepticus.
Phenytoin

Mechanism of Action: acts by stabilizing membranes

(1) Blocking voltage-dependence Na\(^+\) channel

(2) Blocking voltage-dependence Ca\(^{2+}\) channel

(3) Inhibiting calcium-induced secretory processes, including release of hormones and neurotransmitters.

(4) Inhibiting post tetanic potentiation (PTP).
Because phentoin is a weak acid, its intestinal absorption is variable and plasma concentration can vary widely. Monitoring is therefore needed.

It is metabolized by the microsomal system and is excreted first in the bile and then in the urine.
• Antiseizure: used in the treatment of grand mal epilepsy and tonic-clonic seizure disorders, not in absence seizures.
• Treatment on peripheral neuralgia.
• Antiarrhythmias

Therapeutic uses
- Gastrointestinal irritation
- Ataxia and diplopia.
- Blood dyscrasias.
- Gingival hyperplasia, hirsutism, increased collagen proliferation.
• Hepatitis.
• Fetal malformations: fetal hydantion syndrome
• Drug interactions: increased plasma concentrations of phenytoin can occur by concurrent administration of chloramphenicol, isoniazid, cimetidine, dicumarol, etc.

Adverse effects
Carbamazepine

- Derivative of tricyclic antidepressants

- Similar profile to that of phenytoin, but with fewer unwanted effects

- Effective in most forms of epilepsy (except absence seizures); particularly effective in psychomotor epilepsy; also useful in trigeminal neuralgia and mania.
Carbamazepine

- Strong inducing agent; therefore many drug interactions

- Low incidence of unwanted effects; principally sedation, ataxia, mental disturbances, water retention

Carbamazepine
Valproate

• Valproate is very effective against absence seizure.
• Mechanism: facilitate glutamic acid decarboxylase; inhibit GABA-transaminase; enhance synaptic responses. some effect on sodium channels
• Relatively few unwanted effects: anorexia, nausea, teratogenicity, liver damage (rare, but serious)
• The main drug used to treat absence seizures, may exacerbate other forms
• Acts by blocking T-type Ca\(^{2+}\)-channels
• Relatively few unwanted effects, mainly nausea and anorexia. (mental disturbances)

Ethosuximide
Benzodiazepine

- Diazepam: preferred drugs for Status epilepticus.
- Nitrazepam: petit mal, especially myoclonic seizures and infantile spasms.
- Clonazepam: is one of the most effective in some cases of myoclonic seizures. Used in petit mal and status epilepticus
• Phenobarbital, Luminal: is useful in the treatment of generalized tonic-clonic seizures and status epilepticus.
• Mechanism: (1) block Ca\(^{2+}\) currents presynaptic membrane and decrease neurotransmitter release. (2) prolong the openings of the Cl\(^{-}\) channel in postsynaptic membrane and decrease its response.
• Adverse effects: sedation, depression, drug interaction.
Clinical Uses of Antiepileptic Drugs

- **Tonic-clonic (grand mal) seizures:** carbamazepine preferred because of low incidence of side-effects, phenytoin, valproate. Use of single drug is preferred when possible, because of risk of pharmacokinetic interactions.
- **Partial (focal) seizures:** carbamazepine, valproate; clonazepam or phenytoin are alternatives.
Clinical Uses of Antiepileptic Drugs

• Absence seizures (petit mal): ethosuximide or valproate. Valproate is used when absence seizures coexist with tonic-clonic seizures, since most drugs used for tonic-clonic seizures may worsen absence seizures.

• Myoclonic seizures: valproate or clonazepam.

• Status epilepticus: must be treated as an emergency, with diazepam intravenously.
• Selection of an appropriate antiseizure agent
• Use of single drug
• Withdrawal
• Toxicity
• Fetal malformations