Antiepileptic Drugs

Treatment

- Try to find a cause. (e.g. fever, head trauma, drug abuse)
  - Recurrent seizures that cannot be attributed to any cause are seen in patients with epilepsy.
- Therapy is aimed at control
  - *drugs do not cure.*
- *The type of seizure determines the choice of drug!*
- More than 80% of patients with epilepsy can have their seizures controlled with medications.

Treatment

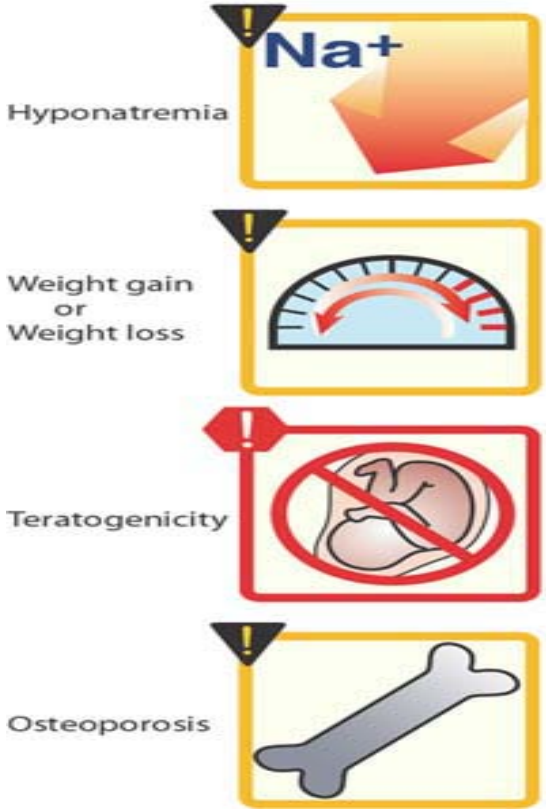
- Monotherapy with anticonvulsant
  - Increase dose gradually until seizures are controlled or adverse effects become unacceptable.
  - Multiple-drug therapy may be required.
- Achieve steady-state kinetics
- Monitor plasma drug levels
- Avoid sudden withdrawal

Pharmacokinetics

- Most classical antiepileptic drugs exhibit similar pharmacokinetic properties.
- Good absorption.
- Low plasma protein binding (except for phenytoin, BDZs, valproate, and tiagabine).
- Conversion to active metabolites (carbamazepine, primidone, fosphenytoin).
- Cleared by the liver but with low extraction ratios.
- Distributed in total body water.
- Plasma clearance is slow.
- At high concentrations phenytoin exhibits zero order kinetics.

Therapeutic Range

Drug	Effective Level (μg/mL)	High Effective Level[2] (μg/mL)	Toxic Level (μg/mL)
Carbamazepine	4–12	7	> 8
Primidone	5–15	10	< 12
Phenytoin	10–20	18	> 20
Phenobarbital	10–40	35	> 40
Ethosuximide	50–100	80	> 100
Valproate	50–100	80	> 100



Notable adverse effects of antiseizure medications.

Treatment of Seizures

Strategies:

- Modification of ion conductances.
- Increase inhibitory (GABAergic) transmission.
- Decrease excitatory (glutamatergic) activity.

Drug treatment of seizures

- Life-long treatment may be necessary.
- It may take weeks to establish adequate drug plasma levels and to determine the adequacy of therapeutic improvement.
- **Lack of compliance** is responsible for many treatment failures.

Classification of epilepsies and drug selection:

1. **Partial seizures**
    1. **Carbamazepine, phenytoin**
    2. Valproic acid, lamotrigine, gabapentin, benzodiazepines, barbiturates
    3. Adjunct: Tiagabine, topiramate, levetiracetam, zonisamide

2. Generalized seizures:

A. Tonic-clonic (grand mal):

1. **Carbamazepine, phenytoin**
2. Valproic acid, lamotrigine, gabapentin, benzodiazepines, barbiturates
3. Adjunct: Topiramate, zonisamide

B. Absence (petit mal):

1. **Ethosuximide**
2. Valproic acid (when absence seizures coexist with tonic-clonic seizures)
3. Clonazepam
4. Adjunct: Lamotrigine, benzodiazepines

C. Myoclonic syndromes:

1. **Valproic acid**
2. Clonazepam and other benzodiazepines
3. Adjunct: levetiracetam

3. Status epilepticus:

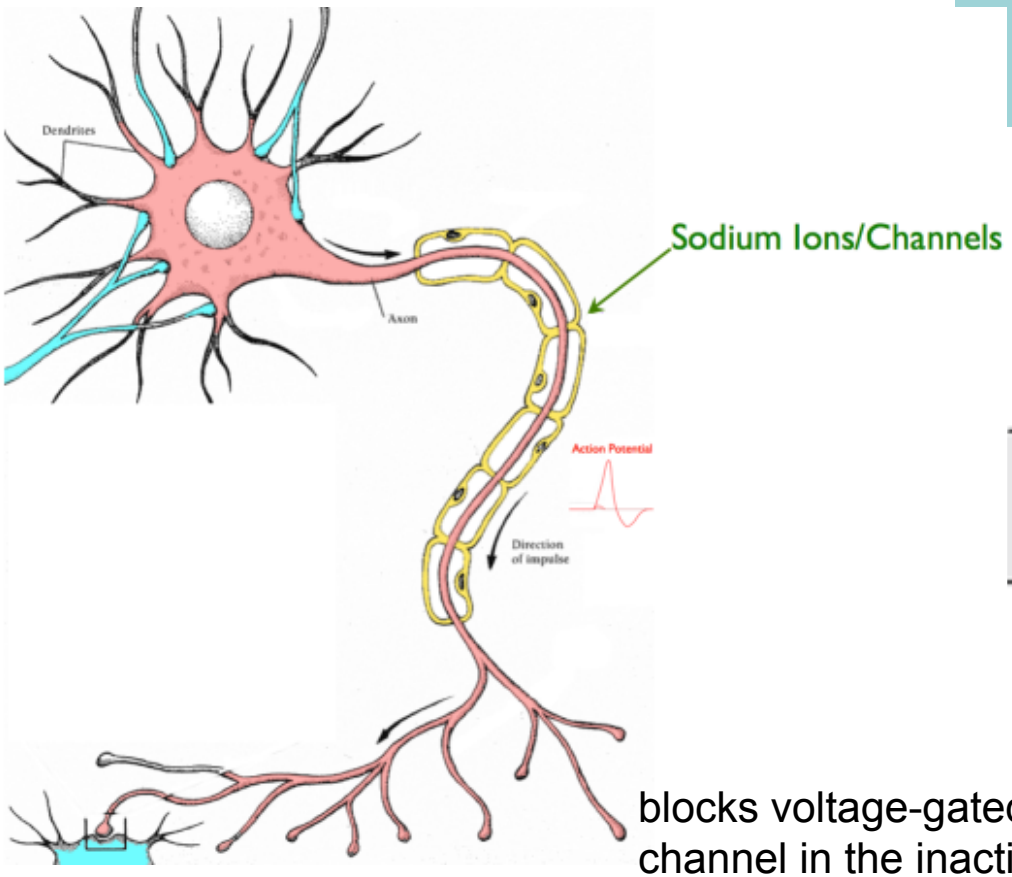
- Treatment is **intravenous diazepam** or **lorazepam** followed by **intravenous fosphenytoin** (or phenytoin) or **phenobarbital.**

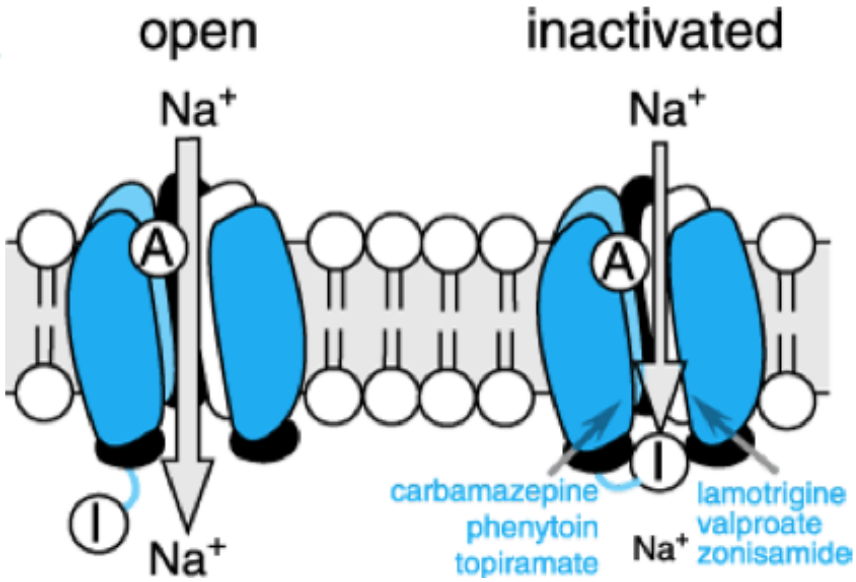
Mechanisms of Action

- 3 main categories of therapeutics:

1. Inhibition of voltage-gated Na+ channels to slow neuron firing.
2. Enhancement of the inhibitory effects of the neurotransmitter GABA.
3. Inhibition of calcium channels.

Na+ Channel Inhibitors





blocks voltage-gated sodium channels by selectively binding to the channel in the inactive state and slowing its rate of recovery

Na+ Channel Inhibitors

- Phenytoin (Dilantin, Phenytek)
- Fosphenytoin (Cerebyx)
- Carbamzepine (Tegretol, Carbatrol)
- Oxcarbazepine (Trileptal)
- Valproic Acid (Valproate; Depakene, Depakote)
- Lamotrigine (Lamictal)
- Topiramate (Topamax)
- Zonisamide (Zonegran)

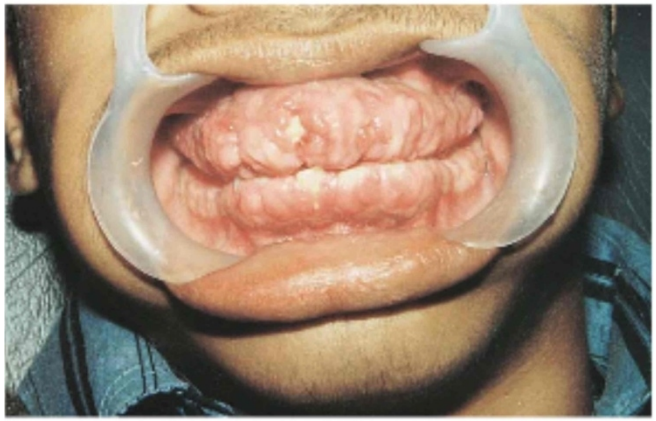
1. Phenytoin (Dilantin, Phenytek):

- Oldest nonsedative antiepileptic drug.
  - Indications:
    - First choice for partial and generalized tonic-clonic seizures
    - Some efficacy in clonic, myoclonic, atonic,
    - No effect on infantile spasms or absence seizures
  - Drug Interactions:
    - Decreases blood levels of many medications
    - Increases blood levels of phenobarbital & warfarin

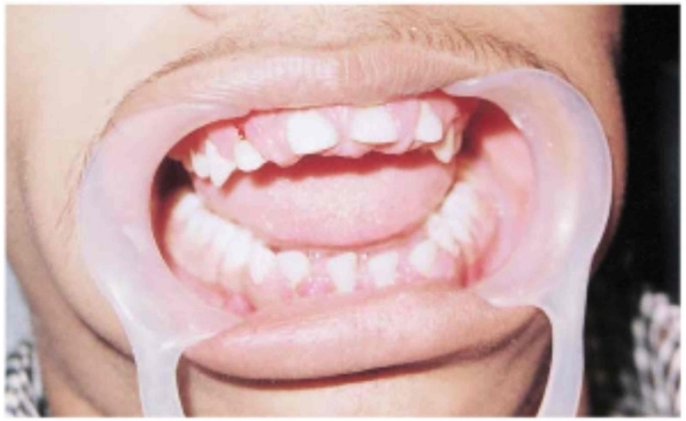
Phenytoin (Dilantin, Phenytek):

- Adverse Effects:
  - Hirsutism & coarsening of facial features
  - Acne
  - Gingival hyperplasia (20-40%)
  - Decreased serum concentrations of folic acid, thyroxine, and vitamin K with long-term use.
- "Fetal hydantoin syndrome":
- includes growth retardation, microencephaly, and craniofacial abnormalities (e.g., cleft palate) and is possibly due to an epoxide metabolite of phenytoin.

Phenytoin Induced Gingival Hyperplasia



17 year old boy treated with 300mg/day phenytoin for 2 years (unsupervised)



Partial recovery at 3 months after discontinuation

- *Fosphenytoin* is a prodrug
- rapidly converted to *phenytoin* in the blood, providing high levels of *phenytoin* within minutes.
- *Fosphenytoin* may also be administered intramuscularly (IM).
- *Phenytoin sodium* should never be given IM because it can cause tissue damage and necrosis.
- Fosphenytoin is the drug of choice and standard of care for IV and IM administration.
- Due to sound-alike and look-alike names, there is a risk for medication error to occur.
  - The trade name of *fosphenytoin* is Cerebyx®
  - Celebrex®, the cyclooxygenase-2 inhibitor
  - Celexa®, the antidepressant.

2. Carbamzepine (Tegretol, Carbatrol):

- Tricyclic, antidepressant (bipolar)
  - Indications:
    - First choice for complex partial and generalized tonic-clonic seizures.
  - Contraindications:
    - May exacerbate absence or myoclonic seizures.
    - Blood disorders
    - Liver disorders

- Phenobarbital (Luminal) & Primidone (Mysoline):

  – Drug Interactions:
    - Other CNS depressants
    - Increased metabolism of vitamin D and K
    - Phenytoin increases the conversion of primidone to phenobarbital.

Enhancement of GABA Inhibition

- Phenobarbital (Luminal) & Primidone (Mysoline):

  – Adverse Effects:
    - Agitation and confusion in the elderly.
    - Worsening of pre-existing hyperactivity and aggressiveness in children
    - Sexual side effects
    - Physical dependence

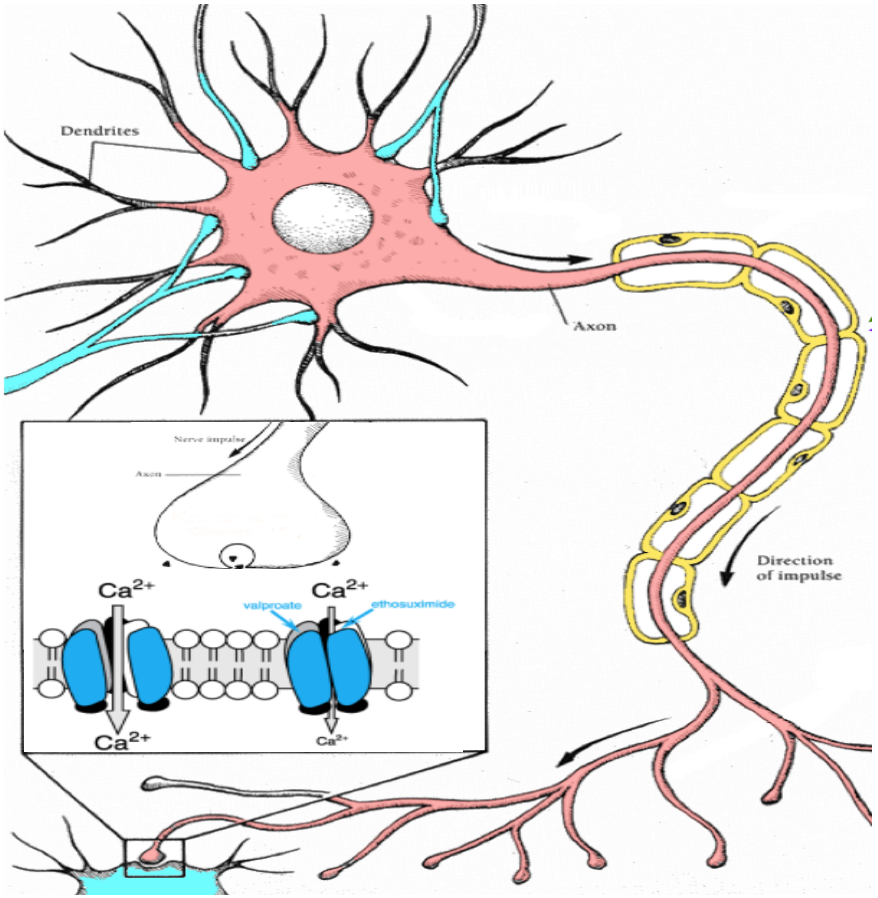
2. Benzodiazepine drugs:

- Diazepam (Valium)
- Lorazepam (Ativan)
- Clonazepam (Klonopin)
- Clorazepate (Transxene-SD)

– Mechanism of Action:

- Increases the frequency of $GABA_A$-activated Cl- channel opening.

inhibit low-threshold (T-type) Ca 2+ currents, especially in thalamic neurons that act as pacemakers to generate rhythmic cortical discharge.



- Levetiracetam (Keppra):
  - Contraindications:
    - Renal dysfunction
  - Adverse Effects:
    - Asthenia
    - Infection
    - Behavioral problems in children

References

https://www.nhs.uk/conditions/epilepsy/treatment/