

# Antiepileptic Drugs

# Objectives

- Classify antiepileptic drugs
- Describe pharmacology of antiepileptic drugs
  - Mechanism of action
  - Relevant pharmacokinetics
  - Indications
  - Adverse drug reactions
  - Important drug interactions
- Explain pharmacological management of epilepsy

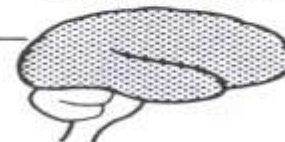
# SEIZURE

## Partial



Seizure activity starts in one part of the brain

## Generalized



Seizure activity involves the whole brain

### Absence



Staring and blinking without falling

### Myoclonic



Jerking movements of the body

### Tonic-clonic



Stiffening, falling and jerking of the body

### Tonic



Falling heavily to the ground

### Atonic



### Simple



Seizure activity while the person is alert

### Complex



Seizure activity with change in awareness of surroundings

### With secondary generalization



Seizure activity begins in one area and spreads

# MECHANISM OF ACTION OF ANTIEPILEPTIC DRUGS

Three main mechanisms –

- Enhancement of GABA action
- Inhibition of sodium channel function
- Inhibition of calcium channel function.

Other mechanisms include -

- Inhibition of glutamate release and
- Block of glutamate receptors.

# Classification of Anticonvulsants

Action on Ion Channels	Enhance GABA Transmission	Inhibit EAA Transmission
<p><b>Na<sup>+</sup>:</b></p> <p>Phenytoin, Carbamazepine, Lamotrigine Topiramate Valproic acid</p> <p><b>Ca<sup>++</sup>:</b></p> <p>Ethosuximide Valproic acid</p>	<p><b>Benzodiazepines</b> (diazepam, clonazepam) <b>Barbiturates</b> (phenobarbital) <b>Valproic acid</b> <b>Gabapentin</b> <b>Vigabatrin</b> <b>Topiramate</b> <b>Felbamate</b></p>	<p><b>Felbamate</b> <b>Topiramate</b></p>

# Mechanism of action of antiepileptic drugs

- ❖ Phenytoin, Carbamazepine, felbamate, lamotrigine, valproic acid
- Block voltage-dependent sodium channels at high firing frequencies

## Mechanism of action of antiepileptic drugs

### ❖ **Barbiturates**

- Prolong GABA-mediated chloride channel openings

### ❖ **Benzodiazepines**

- Increase frequency of GABA-mediated chloride channel openings

# Mechanism of action of antiepileptic drugs(AEDs)

## Valproate

- ❖ May enhance GABA transmission in specific circuits
- ❖ Blocks voltage-dependent sodium channels
- ❖ Blocks T-type calcium currents

## Ethosuximide

- Blocks slow, threshold, “transient” (T-type) calcium channels in thalamic neurons



## Newer AEDs: mechanism of action

**Vigabatrin:** Irreversibly inhibits GABA transaminase

**Tiagabine:** Interferes with GABA re-uptake

**Topiramate:**

- Blocks voltage-dependent sodium channels at high firing frequencies
- Increases frequency at which GABA opens Cl<sup>-</sup> channels (different site from benzodiazepines)
- Antagonizes glutamate actions at receptor subtype

**Gabapentin:** May modulate amino acid transport into brain &  
May interfere with GABA re-uptake

# Phenobarbitone

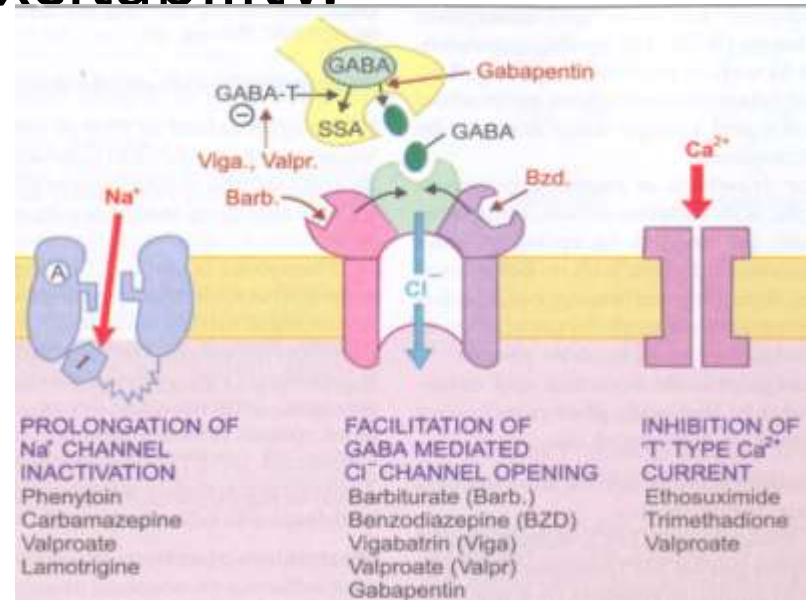
- GABA-facilitatory
- GABA-mimetic
- Adverse effects
  - sedative action.
  - Long term administration - behavioral abnormalities, impairment of learning and memory, hyperactivity in children, mental confusion in older people.
  - Rashes, megaloblastic anaemia and osteomalacia on prolonged use.

# Uses/indications

- Generalized tonic-clonic (GTC), simple partial (SP) and complex partial (CP) seizures:  
60 mg 1-3 times a day in adults; in children (3-6 mg/kg/ day).
- *Status epilepticus*: may be injected i.m. or i.v. but response is slow to develop.
- not effective in absence seizures.

# Phenytoin (Diphenylhydantoin)

- Most commonly used.
- Phenytoin prolongs the inactivated state of voltage sensitive neuronal Na<sup>+</sup> channel and reduces the neuronal excitability.



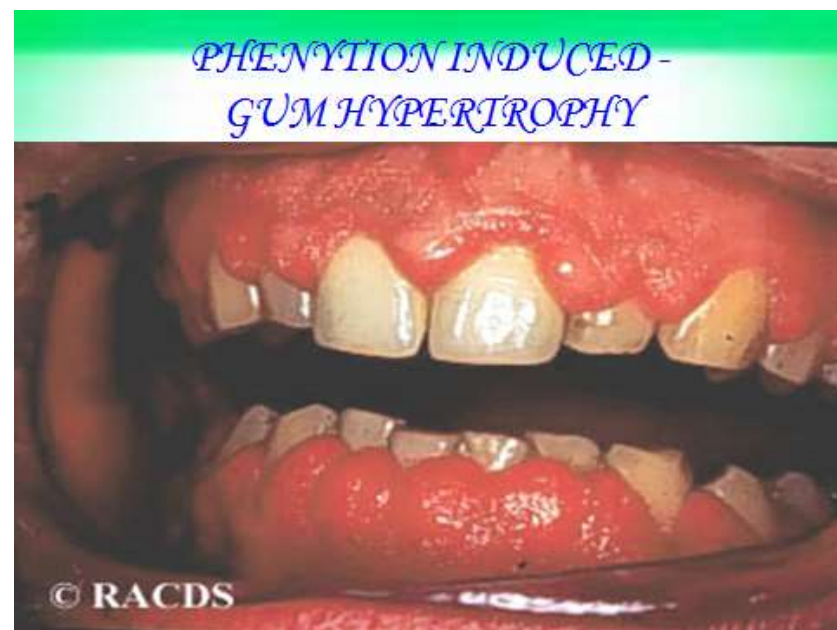
# Pharmacokinetics

- Absorption is formulation dependent
- highly bound to plasma proteins
- fosphenytoin is for IV, IM routes
- The kinetics changes from first order to zero order over the therapeutic range (small increments in dose produce disproportionately high plasma concentrations.)
- The  $t_{1/2}$  - 12-24 hours progressively  $\uparrow$ es upto 60 hr when plasma concentration rises above 10 ug/ml as metabolizing enzymes get saturated.

# Adverse effect

*At therapeutic levels -*

- Gum hypertrophy:
- Hirsutism:
- Hypersensitivity reactions:
- Megaloblastic anaemia:
- Osteomalacia:
- Hyper-glycaemia.
- foetal hydantoin syndrome (hypoplastic phalanges, cleft palate, hare lip, microcephaly), due to its areneoxide metabolite.



Adverse effect

*At high plasma levels (dose related toxicity)*

- CNS- Cerebellar and vestibular manifestations: ataxia, vertigo, diplopia, nystagmus are the most characteristic features.

Drowsiness, behavioral alterations, mental confusion and hallucinations.

- GIT - Epigastric pain, nausea and vomiting: minimised by taking the drug with meals.
- CVS – hypotension & arrhythmias.

# Uses

- Generalized tonic-clonic, simple and complex partial seizures.
- It is ineffective in absence seizures.

Dose: 100 mg BD, maximum 400 mg/day; Children 5-8 mg/kg/day,

- *Status epilepticus*: occasionally used by slow i.v. injection.
- *Trigeminal neuralgia* - second choice drug to carbamazepine.



# Carbamazepine

- Adverse effects
  - Dose related neurotoxicity—sedation, dizziness, vertigo, diplopia and ataxia.
  - Vomiting, diarrhea
  - Acute intoxication - coma, convulsions and cardiovascular collapse.
  - Hypersensitivity reactions:rashes,photosensitivity hepatitis, lupus like syndrome
  - Water retention and hyponatremia in the elderly as it enhances ADH action.
  - Teratogenic

# Uses

- It is the most effective drug for CPS
- First choice drug with phenytoin for GTC and SPS.
- Trigeminal and related neuralgias - is the drug of choice.
- Manic depressive illness and acute mania - as an alternative to lithium

# ETHOSUXIMIDE

- Inhibit T type  $\text{Ca}^{+2}$  current in thalamic neurons.
- Adverse effects
  - GI intolerance, tiredness, mood changes, agitation, headache, drowsiness and inability to concentrate
- Uses
  - Only in ABSENCE SEIZURES but Use has now declined as many consider valproic acid to be superior to it.

# VALPROIC ACID (Sodium Valproate)

Multiple mechanisms of action :

- Phenytoin like frequency dependent prolongation of Na<sup>\*</sup> channel inactivation.
- Attenuation of Ca<sup>2+</sup> mediated 'T' current (ethosuximide like)
- Augmentation of release of inhibitory transmitter GABA by inhibiting its degradation (by GABA-transaminase) & by increasing its synthesis.

# Uses

- Highly effective in absence seizure.
- Alternative /adjuvant drug for GTCS, SPS and CPS.
- Myoclonic and atonic seizures—control is often incomplete, but it is the drug of choice.
- Mania and bipolar illness: as alternative to lithium.

# Adverse effects

- anorexia, vomiting, loose motions, heart burn
- Drowsiness, ataxia, tremors
- Alopecia, curling of hair, increased bleeding tendency
- Fulminant hepatitis (very rare)
- Pancreatitis
- High incidence of PCOD in young girls
- Teraotogenic

# LAMOTRIGINE

Blocks sodium as well as high voltage dependent calcium channels

## Uses

- Broad spectrum antiepileptic.
- Refractory cases of partial seizures and GTCS
- Absence and myoclonic or akinetic epilepsy .
- Lennox-gastaut syndrome

## Adverse effects

- sleepiness, dizziness, diplopia, ataxia and vomiting.
- better tolerated than carbamazepine or phenytoin.
- Rash may be a severe

# GABAPENTIN

- Enhances GABA release in brain.
- does not act as agonist at GABA<sub>A</sub> receptor.
- Reduces seizure frequency in refractory partial seizures with or without generalization.
- Effective in SPS and CPS
- Manic depressive illness and migraine
- first line drug for pain - diabetic neuropathy and postherpetic neuralgia,
- Adverse effects - mild sedation, tiredness, dizziness and unsteadiness.



# VIGABATRIN

- Inhibitor of GABA-transaminase which degrades GABA
- Effective in refractory epilepsy, specially partial seizures with or without generalization.
- Adverse effects- behavioral changes, depression and psychosis . drowsiness, amnesia, visual field contraction, motor disturbances, agitation in children.

# TIAGABINE

- Recently developed anticonvulsant - potentiates GABA mediated neuronal inhibition by depressing GABA transporter GAT-1 which removes synaptically released GABA into neurons & glial cells.
- Uses – add on therapy of partial seizures with or without secondary generalization.
- Adverse effects- mild sedation, nervousness, asthenia, amnesia & abdominal pain.

**Key:** **Drug name**

Consider first based on patient characteristics, diagnosis and symptoms, and concurrent medical problems.

*Drug name*

Consider next if seizures persist or adverse effects of first drug limit therapy.

*Drug name*

Consider as alternative if seizures persist or adverse effects limit therapy.

*Vagal stimulator*

Consider when adherence, drug interaction, or adverse effects limit drug therapy.

## FOCAL EPILEPSY

Simple partial, complex partial with or without secondary generalization

**Lamotrigine**  
**Levetiracetam**  
**Topiramate**

*Carbamazepine*  
*Lacosamide*  
*Pregabalin*  
*Zonisamide*

**Divalproex**  
**Gabapentin**  
**Dicarbazepine**  
**Phenytoin**  
**Tiagabine**

Vagal stimulator

Elderly patients

**Lamotrigine**

*Gabapentin*

**Carbamazepine**

Vagal stimulator

## PRIMARY GENERALIZED EPILEPSY

Absence

**Divalproex**  
**Lamotrigine**

*Ethosuximide*

**Levetiracetam**  
**Topiramate**  
**Zonisamide**

Myoclonic

**Divalproex**  
**Levetiracetam**

*Lamotrigine*  
*Topiramate*

**Benzodiazepines**  
**Zonisamide**

Tonic-clonic

**Lamotrigine**  
**Levetiracetam**  
**Topiramate**

*Divalproex*  
*Zonisamide*

Vagal stimulator

Status epilepticus

**Benzo-diazepines**  
**Fosphenytoin**

*Barbiturates*

# EPILEPSY SYNDROME

**Benign rolandic**

*Gabapentin*  
*Lamotrigine*



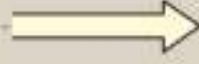
*Carbamazepine*  
*Levetiracetam*  
*Topiramate*



*Divalproex*  
*Oxcarbazepine*

**Infantile spasms  
(West syndrome)**

*Corticotropin*  
*Vigabatrin*



Benzodiazepines  
*Divalproex*  
*Topiramate*



*Lamotrigine*  
*Zonisamide*

**Lennox-Gastaut**

*Divalproex*  
*Lamotrigine*  
*Topiramate*



*Levetiracetam*  
*Vigabatrin*  
*Zonisamide*



Benzodiazepines  
*Felbamate*

**TABLE 410-7** CHARACTERISTICS OF MAJOR ANTIEPILEPTIC DRUGS

NAME	TOTAL MILLIGRAMS PER DAY (USUAL SCHEDULE)	THERAPEUTIC RANGE ( $\mu\text{G/mL}$ )	PROMINENT SIDE EFFECTS	OTHER EFFECTS	OTHER ISSUES
Carbamazepine	400-1600 (bid)	4-12	Diplopia, fatigue, hyponatremia	Mood stabilizer	Enzyme inducer
Ethosuximide	750-1250 (qd, bid)	40-100	Ataxia, lethargy	Skin rash, bone marrow suppression	
Gabapentin	600-6000 (tid, qid)	2-12	Fatigue	Treatment of pain	No drug interactions
Lamotrigine	100-600 (bid)	4-18	Insomnia, headache, tremor, anxiety	Mood stabilizer	Risk for Stevens-Johnson syndrome; slow start-up
Levetiracetam	500-3000 (bid)	3-63	Mood change, irritability, lethargy		No drug interactions
Oxcarbazepine	300-2400 (tid)	6-40	Diplopia, hyponatremia, sedation	Mood stabilizer	
Phenobarbital	60-240 (hs)	15-40	Fatigue, depression, sedation	Joint pain	Enzyme inducer
Phenytoin	200-600 (bid)	10-20	Fatigue, hirsutism, gingival hypertrophy	Treatment of some pain	Enzyme inducer
Topiramate	50-600 (bid)	2-12	Anorexia, weight loss, kidney stones, speech disturbance, distal paresthesias	Headache prophylaxis, mood stabilizer	Enzyme inducer
Valproate	500-6000 (tid)	50-100	Weight gain, hair loss, tremor	Headache prophylaxis, mood stabilizer	Enzyme inhibitor, parkinsonian effects in elderly patients
Zonisamide	100-600 (hs)	10-40	Anorexia, kidney stones, dizziness, distal paresthesias	Mood stabilizer	

# Reference

- Lippincots illustrated pharmacology 6<sup>th</sup> edition page 157-168
- Essentials of Medical Pharmacology 7<sup>th</sup> edition by KD tripathi