Antiepileptic Drugs

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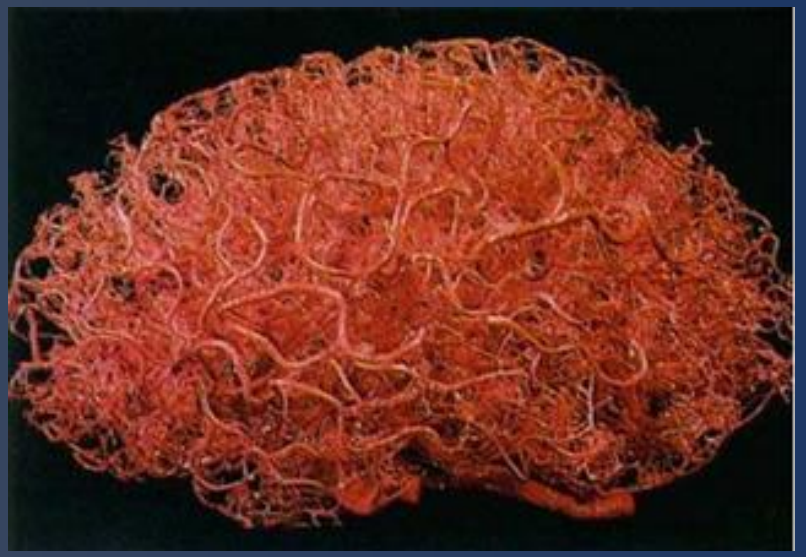
Basic Definitions: Seizure

The clinical manifestation of an **abnormal and excessive** excitation and synchronization of a population of cortical neurons



Basic Definitions: Epilepsy

Epilepsy: a tendency toward **recurrent seizures** unprovoked by any systemic or acute neurologic insults.

Basic Definitions: Epilepsy

Convulsion: **tonic–clonic type of seizure**

characterized by spasmodic contractions of

involuntary muscles

Question

Is the following statement True or False?

Seizure and convulsion are different terms for the same disorder.

Answer

False

Rationale: A seizure is a brief episode of abnormal electrical activity in the brain's nerve cells. A convulsion is a tonic–clonic type of seizure characterized by spasmodic contractions of involuntary muscles.

Normal CNS Function

Excitation

Inhibition

glutamate, aspartate

GABA

CNS Function during seizure

glutamate,
aspartate

Inhibition

Excitation

GABA

Types of Seizures

- Partial Seizures
- Generalized Seizures

SEIZURE

Partial

Seizure activity starts in one part of the brain

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

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

Atonic

Falling heavily to the ground

Antiepileptic Drug

- A drug which decreases the frequency and/or severity of seizures in people with epilepsy
- Treats the symptom of seizures, not the underlying epileptic condition
- Goal—maximize quality of life by minimizing seizures and adverse drug effects
- Currently no “anti-epileptogenic” drugs available

Therapy Has Improved Significantly

"Give the sick person some blood from a pregnant donkey to drink; or steep linen in it, dry it, pour alcohol onto it and administer this".

– Formey, Versuch einer medizinischen Topographie von Berlin 1796, p. 193

Current Pharmacotherapy

- Just under 60% of all people with epilepsy can become seizure free with **drug therapy**
- In another 20% the seizures can be drastically reduced
- ~ 20% epileptic patients, seizures are refractory to currently available AEDs

Choosing Antiepileptic Drugs

- **Seizure type**
- **Epilepsy syndrome**
- **Pharmacokinetic profile**
- **Interactions/other medical conditions**
- **Efficacy**
- **Expected adverse effects**
- **Cost**

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

- Antiepileptics are indicated when there is two or more seizures occurred in short interval (6m -1 y)
- An initial therapeutic aim is to use only one drug (monotherapy)

Advantage of monotherapy:

- fewer side effects,
- decreased drug-drug interactions,
- better compliance,
- lower costs
- Addition of a second drug is likely to result in significant improvement in only approx. 10 % of patients.

- ***when a total daily dose is increased, sufficient time (about 5 t 1l2) should be allowed for the serum drug level to reach a new steady-state level.***

- ***The drugs are usually administered orally***

- ***The monitoring of plasma drug levels is very useful***

- ***Precipitating or aggravating factors can affect seizure control by drugs***

- *The sudden withdrawal of drugs should be avoided*
- *withdrawal may be considered after seizure-free period of 2-3 or more years*
- *Relapse rate when antiepileptics are withdrawn is 20 -40 %*

When to Withdraw Antiepileptic Drugs?

- **Normal neurological examination**
- **Normal IQ**
- **Normal EEG prior to withdrawal**
- **Seizure- free for 2-5 yrs or longer**
- **NO juvenile myoclonic epilepsy**

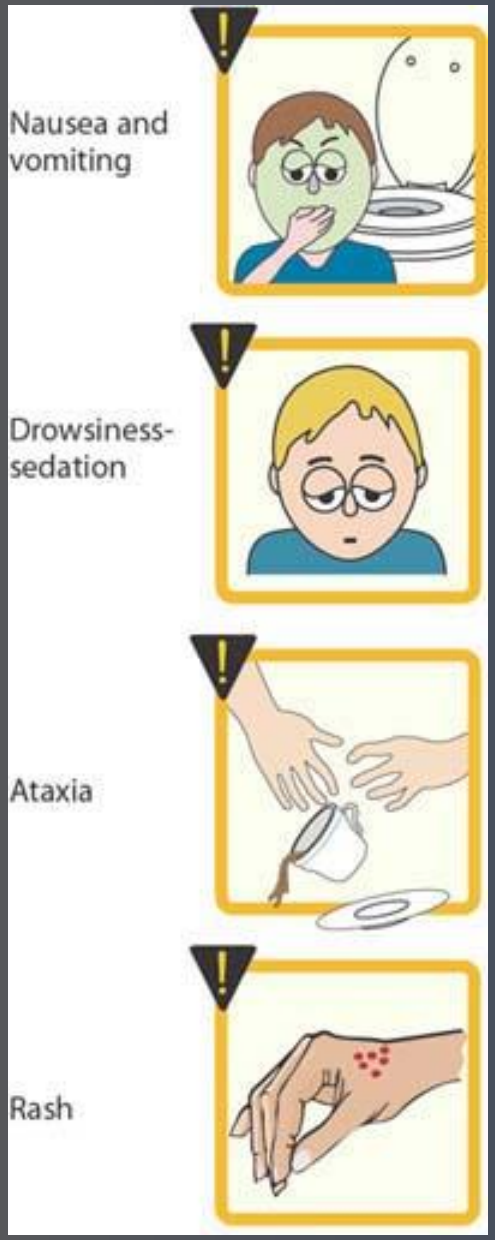
Pts not meeting this ideal profile in all points, withdrawal may be encouraged after careful assessment of the individual patient.

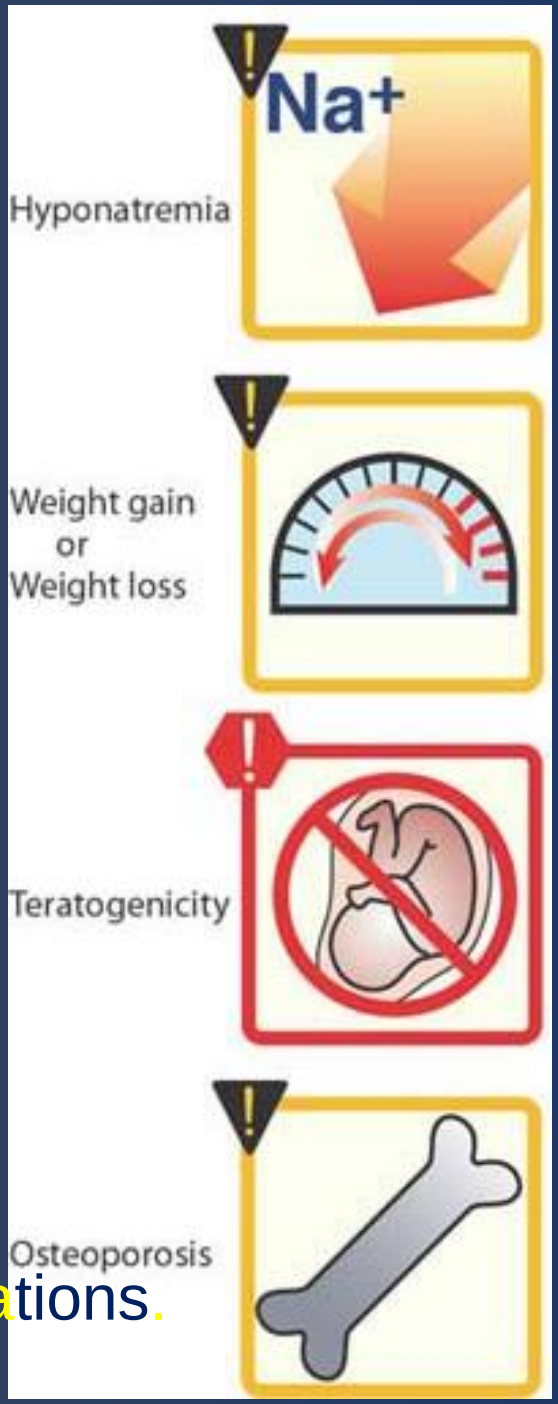
Pharmacokinetics

- 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.

Classification of epilepsies and drug selection

1. Partial seizures

- **Carbamazepine, phenytoin**
- Valproic acid, lamotrigine, gabapentin, benzodiazepines, barbiturates
- Adjunct: Tiagabine, topiramate, levetiracetam, zonisamide

2. Generalized seizures:

A. Tonic-clonic (grand mal):

- **Carbamazepine, phenytoin**
- Valproic acid, lamotrigine, gabapentin, benzodiazepines, barbiturates
- Adjunct: Topiramate, zonisamide

B. Absence (petit mal):

- **Ethosuximide**
- Valproic acid (when absence seizures coexist with tonic-clonic seizures)
- Clonazepam
- 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.**

TREATMENT OF SEIZURES

Seizure disorder	Drugs
Tonic-clonic(Grand mal) Drug of Choice	Carbamazepine or Valproate or Phenytoin or Phenobarbital
Alternatives:	Topiramte Lamotrigine (as adjunct or alone) Gabapentin (as adjunct)
Partial (simple or complex) Drug of choice	Carbamazepine or Topiramte or Phenytoin or Valproate
Alternatives:	Phenobarbital Lamotringine (as adjunct or alone) Gabapentin (as adjunct)

Treatment contd

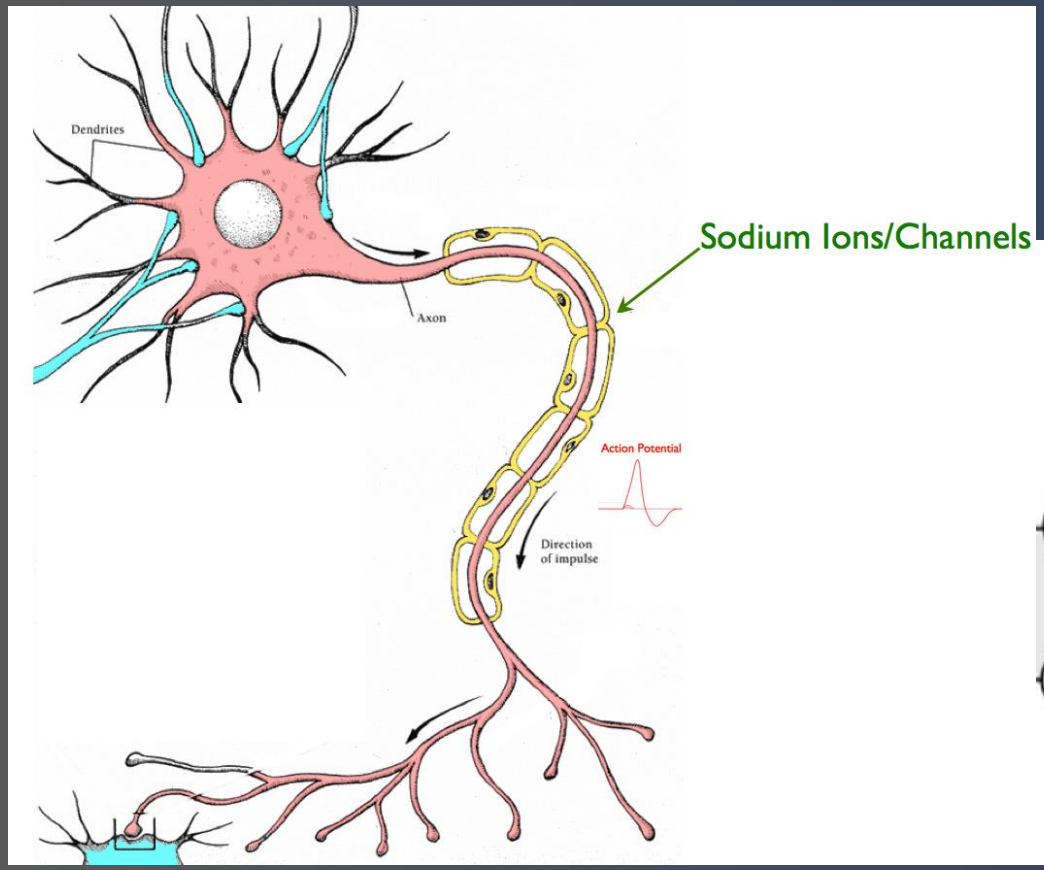
Absence (petit mal) Drug of choice	*Valproate or Ethosuximide*
Alternatives:	*Clonazepam / Lamotrigine*
Myoclonic, Atonic *Drug of choice*	*Valproate*
Alternatives:	*Clonazepam*
Status Epilepticus *Drug of choice*	*Diazepam, i.v. or Phenytoin, i.v. or Vaproate*
Alternatives:	*Phenobarbital, i.v*
Febrile Seizures ** Preferred*	*Diazepam, rectal* or i.v* *Valproate*

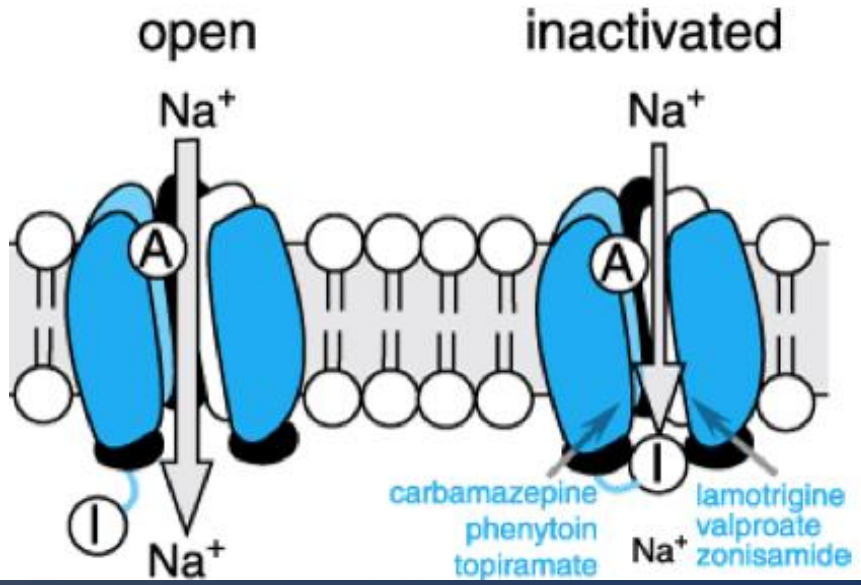
Phenytoin

- 80-90% protein bound
- Induces liver enzymes (Very Important)
- Metabolized by the liver to inactive metabolite
- saturation kinetics and hence t ½ increases as the dose increased
- Excreted in urine as glucuronide conjugate
- Plasma t ½ approx. 20 hours
- Therapeutic plasma concentration 10-20 µg/ml (narrow)

Phenytoin (Cont.)

Mechanism of Action





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

1. Block Na+ channels & inhibit the generation of repetitive action potential. (main action of antiepileptic drugs)
2. Potentiate the GABA system & reduce the glutamic system
3. At higher concentration it can block voltage-dependent Ca ++ channel

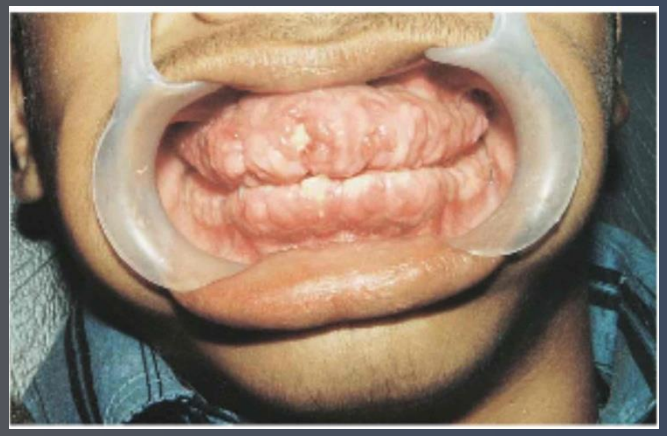
(L-type which is found in cardiac & smooth m. that's why it's ineffective for treating absence epilepsy in which the problem in the T-type & the significance of this action is unclear.)

Oldest nonsedative antiepileptic drug.

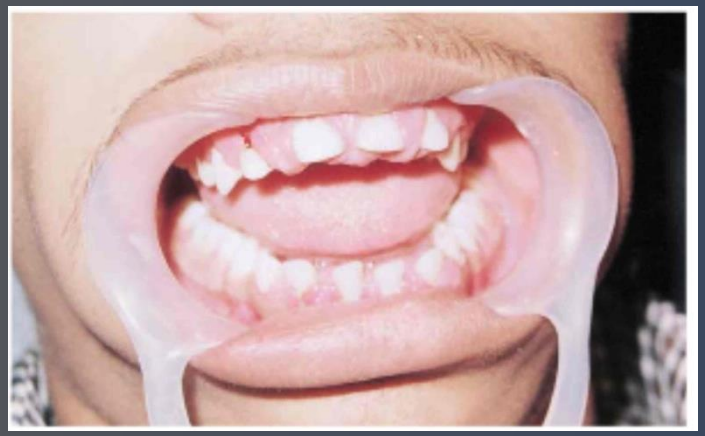
- Indications:
  - First choice for partial and generalized tonic-clonic seizures
  - Some efficacy in clonic, myoclonic, atonic,
  - No effect on infantile spasms or absence seizures

- 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.

CARBAMAZEPINE

Its mechanism of action and clinical uses are similar to that of phenytoin. (No Ca2+ channel block). However, it is also commonly used for Rx of mania and trigeminal neuralgia.

Pharmacokinetics

available as an oral form only

Strong inducing agent including its own (can lead to failure of other drugs e.g. oral contraceptives, warfarin, etc.

Metabolized by the liver

Side Effects of Carbamazepine:

- G.I upset
- Drowsiness, ataxia and headache; diplopia
- Hepatotoxicity- rare
- Congenital malformation (craniofacial anomalies & neural tube defects).
- Hyponatraemia & water intoxication.
- Late hypersensitivity reaction (erythematous skin rashes, mouth ulceration and lymphadenopathy)
- Blood dyscrasias as fetal aplastic anemia (stop medication); mild leukopenia (decrease the dose)

Sodium Valproate or Valproic Acid

Pharmacokinetics :

- Available as capsule, Syrup, I.V
- Metabolized by the liver (inactive)
- Inhibits metabolism of several drugs such as Carbamazepine; phenytoin, Topiramate and phenobarbital.
- Excreted in urine (glucuronide)
- Plasma t1/2 approx. 15 hrs

Sodium valproate (cont.)

Mechanism of action

- Inhibits Na+ channels similar to phenytoin and carbamazepine
- Some inhibition of T-type Ca2+ channels.
- Increases GABA production and decreases GABA metabolism. (Inhibition of GABA transaminase and succinic semialdehyde dehydrogenase)

Sodium Valpraote (cont.)

- **Clinical Use:**
  - Very effective against absence, myoclonic seizures.
  - Also, effective in gen. tonic-clonic siezures (primarly Gen)
  - Less effective as compared to carbamazepine for partial seizures
  - Like Carbamazepine also can be used for Rx of mania

Side Effects of Sod. valproate:

- Nausea, vomiting and GIT disturbances (Start with low doses)
- **Increased appetite & weight gain**
- Transient hair loss.
- **Hepatotoxicity**
- Thrombocytopenia
- **Neural Tube defect** (e.g. Spina bifida) in the offspring of women. (contraindicated in pregnancy)

Ethosuximide

- Mechanism of Action:
  1. block Ca channel (T-Type) mainly thalamic neurons which provide a pacemaker that generate the rhythmic cortical discharge of an absence attack. (main action) (it competes
     with valproic a. in Rx. Of absence seizure & the latter preferred in combination type.)

  2. Na /K ATPase (depress the cerebral metabolic rate).

  3. inhibits GABA aminotransferase.

- Indications:
  - First line for absence seizures
- Contraindications:
  - May exacerbate partial & tonic-clonic seizures

- Adverse Effects:
  - Psychotic behavior
  - Blood dyscrasias
  - Persistent headaches
  - Anorexia
  - Hiccups
  - Lupus-like syndromes

- Toxicity:
  - parkinson-like symptoms
  - photophobia

INTERACTIONS BETWEEN ANTISEIZURE DRUGS

With other antiepileptic Drugs:

- Carbamazepine with

phenytoin	Increased metabolism of carbamazepine
phenobarbital	Increased metabolism of epoxide.

- Phenytoin with

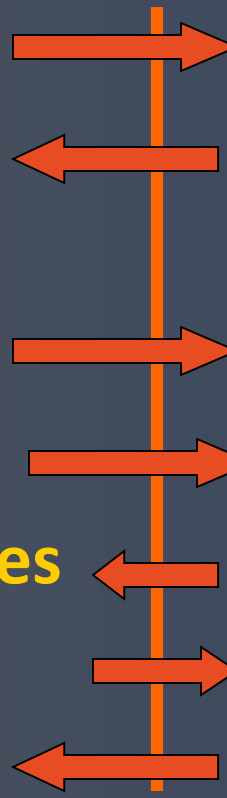
primidone	Increased conversion to phenobarbital.

- Valproic acid with

clonazepam	May precipitate nonconvulsive status epilepticus
phenobarbital	Decrease metabolism, increase toxicity.
phenytoin	Displacement from binding, increase toxicity.

ANTISEIZURE DRUG INTERACTIONS

With other drugs:



antibiotics	↑ phenytoin, phenobarb, carb.
anticoagulants	phenytoin and phenobarb↑ met.
cimetidine	displaces pheny, v.a. and BDZs
isoniazid	↑ toxicity of phenytoin
oral contraceptives	antiepileptics ↑ metabolism.
salicylates	displaces phenytoin and v.a.
theophyline	carb and phenytoin may↓ effect.

Newer Antiepileptic Drugs
(Second- Generation)

1. Vigabatrin 1989
2. Gabapentin 1993
3. Lamotrigine 1994
4. Topiramate 1996
5. Tiagabine 1997
6. levetiracetam 1999
7. Oxcarbazepine 2000 (safety profile similar to CBZ). Hyponatremia is also problem, however it is less likely to cause rash than CBZ.
8. Zonisamide 2000

- **NEWER AGENTS DIFFER FROM OLDER DRUGS BY**

  Relatively lack of drug-drug interaction (simple pharmacokinetic profile) Improved tolerability

  HOWEVER THEY ARE

  Costly with limited clinical experience

Lamotrigine

Pharmacological effects

Resembles phenytoin in its pharmacological effects

Metabolised primarily by glucuronidation

Does not induce or inhibit C. P-450 isozymes (its metabolism is inhibitted by valproate)

Plasma t 1/2 approx. 24 hrs.

Mechanism of Action:

Inhibits excitatory amino acid release (glutamate & aspartate) by blockade of Na channels.

- **Uses**: As add-on therapy or as monotherapy

- **Side effects:**
- Skin rash, somnolence, blurred vision, diplopia, ataxia, headache, aggression, influenza – like syndrome