EPILEPSY AND PHARMACOTHERAPY

EPILEPSY

- Epilepsy is a heterogeneous symptom complex – a chronic disorder characterized by recurrent seizures.

- Seizures are finite episodes of brain dysfunction resulting from abnormal discharge of cerebral neurons

CAUSES FOR ACUTE SEIZURES

- Trauma
- Encephalitis
- Drugs
- Birth trauma
- Withdrawal from depressants
- Tumor
- High fever
- Hypoglycemia
- Extreme acidosis
- Extreme alkalosis
  Hyponatremia
- Hypocalcemia
- Idiopathic

CLASSIFICATION OF EPILEPTIC SEIZURES

- Partial (focal) Seizures
  - Simple Partial Seizures
  - Complex Partial Seizures
  - Partial seizures secondarily generalised

- Generalized Seizures
  - Generalized Tonic-Clonic Seizures
  - Absence Seizures
  - Tonic Seizures
  - Atonic Seizures
  - Clonic and Myoclonic Seizures

PARTIAL (FOCAL) SEIZURES

Simple Partial Seizures (*Jacksonian*)

- Involves one side of the brain at onset.
- Focal motor, sensory or speech disturbances.
- Confined to a single limb or muscle group.
- Seizure-symptoms don't change during seizure.
- No alteration of consciousness.

EEG: Excessive synchronized discharge by a small group of neurons

I. PARTIAL (FOCAL) SEIZURES

Complex Partial Seizures *(Temporal Lobe epilepsy or Psychomotor Seizures)*

- Produces confusion and inappropriate or dazed behavior.
- Motor activity appears as non-reflex actions. Automatisms (repetitive coordinated movements).
- Wide variety of clinical manifestations.
- Consciousness is impaired or lost.

EEG: Bizarre generalized EEG activity with evidence of anterior temporal lobe focal abnormalities. Bilateral.

GENERALIZED SEIZURES

- In Generalized seizures, both hemispheres are widely involved from the outset.
- Manifestations of the seizure are determined by the cortical site at which the seizure arises.
- Present in 40% of all epileptic Syndromes.

II. GENERALIZED SEIZURES (CON'T)

Generalized Tonic-Clonic Seizures

- Recruitment of neurons throughout the cerebrum

- Major convulsions, usually with two phases:
  - Tonic phase
  - Clonic phase

GENERALIZED SEIZURES (CON'T)

Generalized Tonic-Clonic Seizures

- Tonic phase
  - Sustained powerful muscle contraction (involving all body musculature) which arrests ventilation.

- EEG: Rythmic high frequency, high voltage discharges with cortical neurons undergoing sustained depolarization, with protracted trains of action potentials.

GENERALIZED SEIZURES (CON'T)

Generalized Tonic-Clonic Seizures

- Clonic phase:
  - Alternating contraction and relaxation, causing a reciprocating movement which could be bilaterally symmetrical or "running" movements.

- EEG: Characterized by groups of spikes on the EEG and periodic neuronal depolarizations with clusters of action potentials.

GENERALIZED SEIZURES

Absence Seizures (*Petite Mal*)

- Brief and abrupt loss of consciousness.
- Sometimes with no motor manifestations.
- Usually symmetrical clonic motor activity varying from occasional eyelid flutter to jerking of the entire body.
- Typical 2.5 – 3.5 Hz spike-and-wave discharge.
- Usually of short duration (5-10 sec), but may occur dozens of times a day.

GENERALIZED SEIZURES

Absence Seizures (*Petite Mal*) (con't)

- Often begin during childhood (daydreaming attitude, no participation, lack of concentration).
- A low threshold Ca^{2+} current has been found to govern oscillatory responses in thalamic neurons (pacemaker)
- This low threshold probably involve in the generation of these types of seizures.

GENERALIZED SEIZURES (CON'T)

Tonic Seizures

- Opisthotonus, loss of consciousness.
- Marked autonomic manifestations

Atonic Seizures (*atypical*)

- Loss of postural tone, with sagging of the head or falling.
- May loose consciousness.

GENERALIZED SEIZURES (CON'T)

Clonic and Myoclonic Seizures

- Clonic Seizures:
  - Involves rhythmic clonic contractions of all muscles,
  - loss of consciousness and
  - marked autonomic manifestations.

- Myoclonic Seizures:
  - Isolated clonic jerks associated with brief bursts of multiple spikes in the EEG.

GENERALIZED SEIZURES (CON'T)

Infantile Spasms

- An epileptic syndrome.
- Attacks, although fragmentary, are often bilateral.
- Characterized by brief recurrent myoclonic jerks of the body with sudden flexion or extension of the body and limbs.

TREATMENT OF SEIZURES

Goals:

- Block repetitive neuronal firing.
- Block synchronization of neuronal discharges.
- Block propagation of seizure.
- Minimize side effects with the simplest drug regimen.

MONOTHERAPY IS RECOMMENDED IN MOST CASES

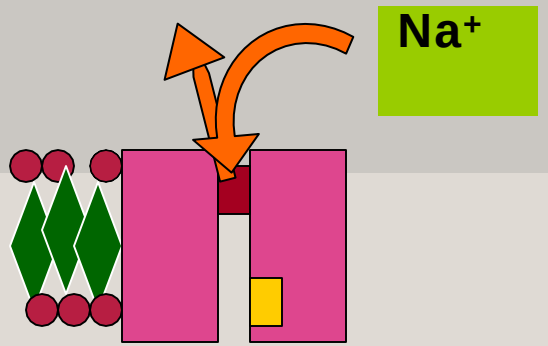
TREATMENT OF SEIZURES

Strategies:

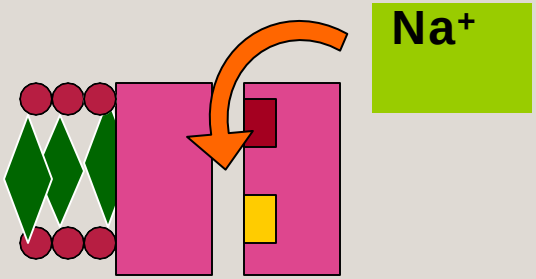
- Modification of ion conductances.
- Increase inhibitory (GABAergic) transmission.
- Decrease excitatory (glutamatergic) activity.

ACTIONS OF PHENYTOIN ON NA^+ CHANNELS

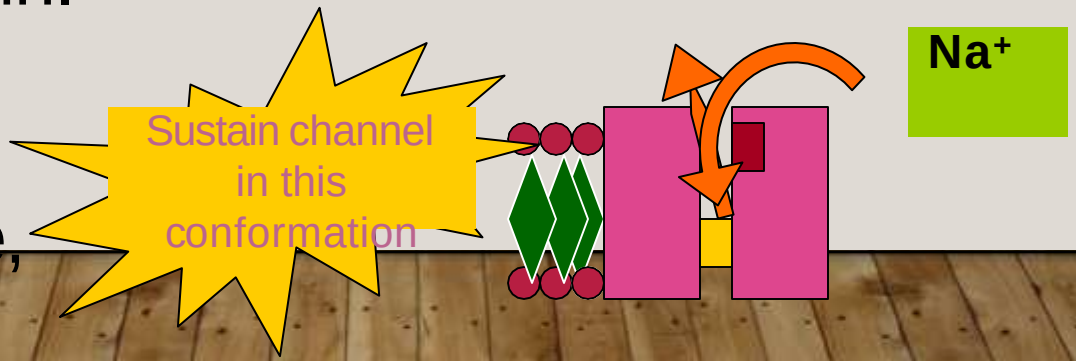
- Resting State



- Arrival of Action Potential causes depolarization and channel opens allowing sodium to flow in.



- Refractory State, Inactivation



GABAERGIC SYNAPSE

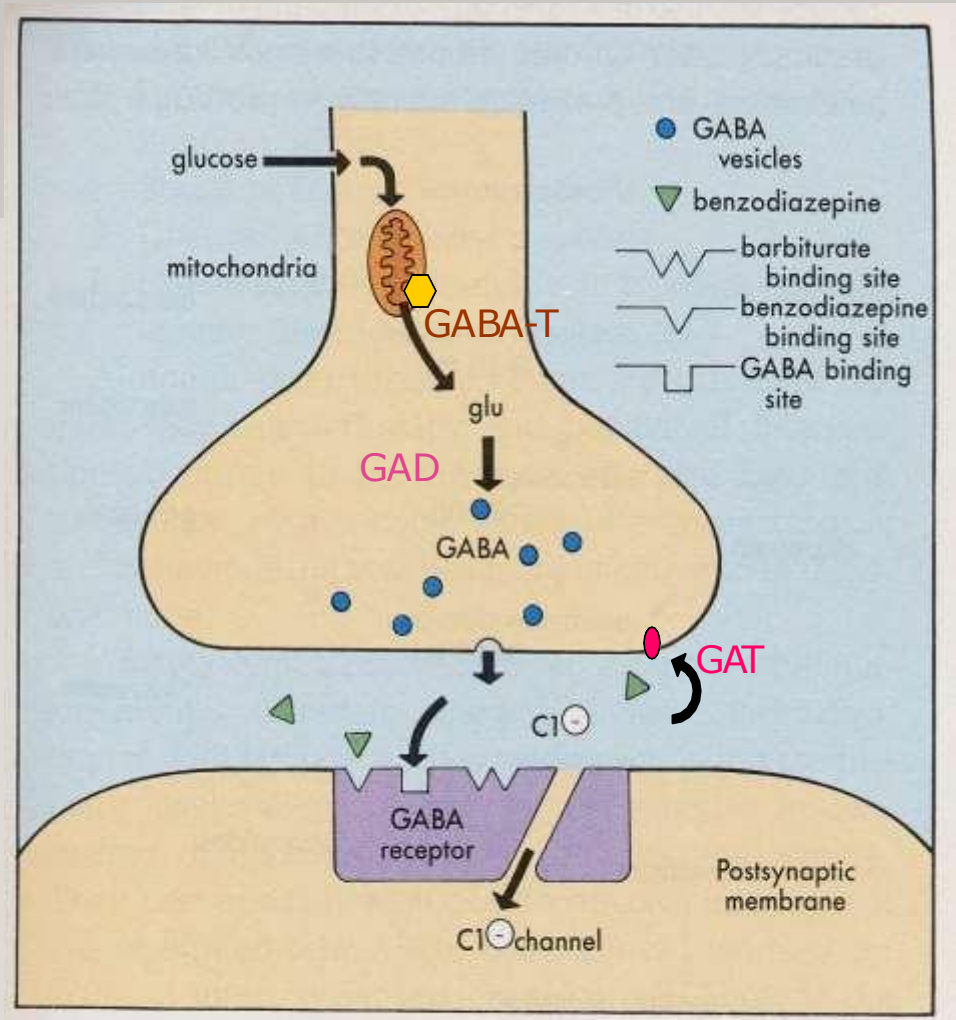
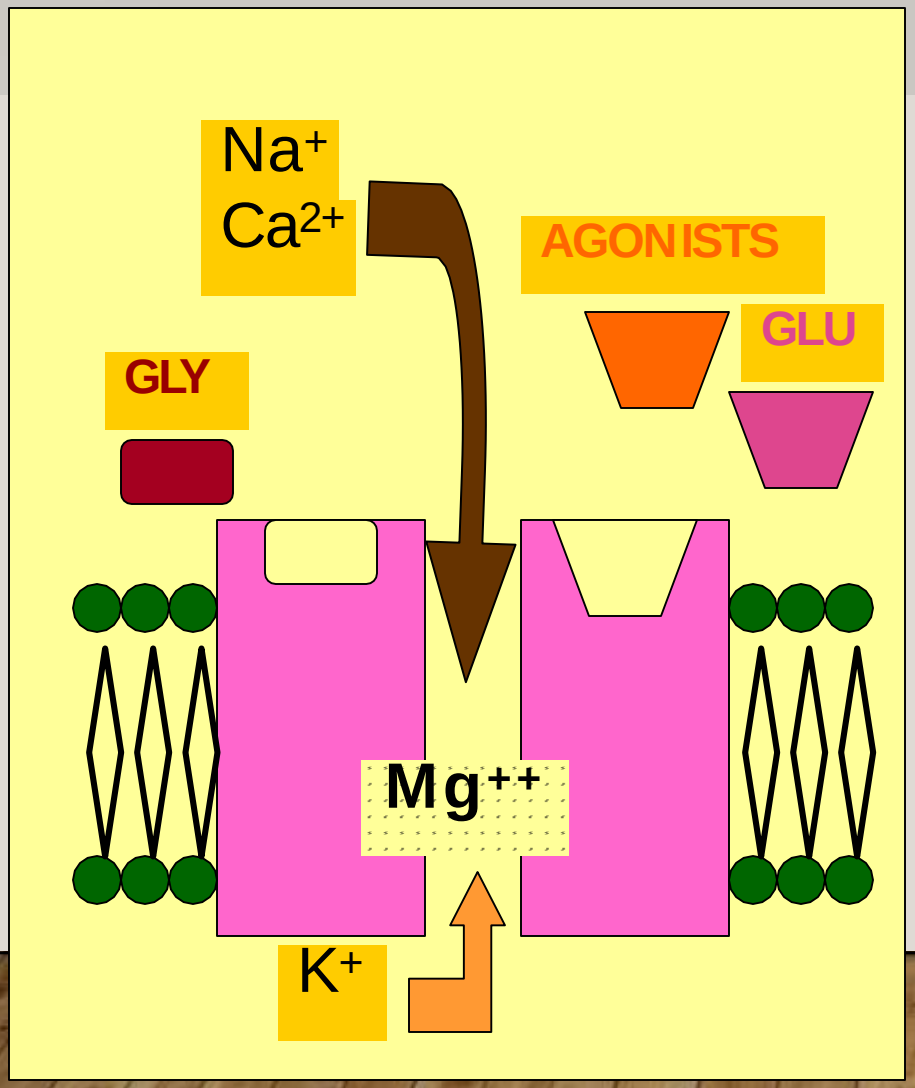


FIGURE 25-2 GABA-benzodiazepine postsynaptic system. Presynaptic system not shown. *Glu*, Glutamic; *GABA*, γ-aminobutyric acid.

Drugs that Act at the GABAergic Synapse

- GABA agonists
- GABA antagonists
- Barbiturates
- Benzodiazepines
- GABA synthesizing enzymes
- GABA uptake inhibitors
- GABA metabolizing enzymes

GLUTAMATERGIC SYNAPSE



- Excitatory Synapse.
- Perme able to Na^+, Ca^{2+} and K^+.
- Magnesium ions block channel in resting state.
- Glycine (GLY) binding enhances the ability of GLU or NMDA to open the channel.
- Agonists: NMDA

TREATMENT OF SEIZURES

1) Hydantoins: phenytoin
2) Barbiturates: phenobarbital
3) Oxazolidinediones: trimethadione
4) Succinimides: ethosuximide
5) Acetylureas: phenacemide
6) Other: carbamazepine, lamotrigine, vigabatrin, etc.
7) Diet
8) Surgery, Vagus Nerve Stimulation (VNS)

TREATMENT OF SEIZURES

- Most classical antiepileptic drugs exhibit similar pharmacokinetic properties.
- Good absorption (although most are sparingly soluble).
- 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.

TREATMENT OF SEIZURES

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HYDANTOINS – PHENYTOIN (DILANTIN)

- Oldest nonsedative antiepileptic drug.
- Fosphenytoin, a more soluble prodrug is used for parenteral

MOA

- It alters Na^{+}, $Ca^{2}+$ and K^{+} conductances.
- Inhibits high frequency repetitive firing.
- Alters membrane potentials.
- Alters amino acid concentration.
- Alters NTs (NE, ACh, GABA)

Pharmacokinetics

- GIT absorption is nearly complete
- IM absorption is unpredictable, precipitation may occur – not recommended
- Fosphenytoin – a more soluble, given IM
- Phenytoin is highly bound to plasma proteins.
- Metabolized in the liver an excreted in urine

Clinical Use

- Phenytoin is effective against partial seizures and generalized tonic-clonic seizures.

- In tonic-clonic seizures it appears to be effective against attacks that are either primary or secondary another seizure type

Toxicity

- Nystagmus
- Diplopia and ataxia are the most common dose-related
- Gingival hyperplasia and hirsutism
- Peripheral neuropathy

- MEPHENYTOIN, ETHOTOIN, & PHENACEMIDE

CARBAMAZEPINE (TEGRETOL)

- Closely related to imipramine and other antidepressants,
- carbamazepine is a tricyclic compound
- 3-D conformation is similar to phenytoin.

CARBAMAZEPINE (TEGRETOL)

MoA

- Similar to phenytoin
- Inhibits high frequency repetitive firing.
- Decreases synaptic activity presynaptically.
- Inh. uptake and release of NE, but not GABA.
- Potentiates postsynaptic effects of GABA.
- Metabolite is active.

- Pharmacokinetics
- Absorption is almost complete absorption but rates of absorption varies
- 70% of the drug is bound to plasma proteins
- Carbamazepine is an enzyme inducer
- Carbamazepine is completely metabolized in the liver.
- Some of the metabolites exhibit activity

- Clinical Use
- drug of choice for both partial seizures and generalized tonic-clonic seizures

- Carbamazepine is not sedative in its usual therapeutic range.

- Effective in management of trigeminal neuralgia

- Carbamazepine is also useful in some patients with mania (bipolar disorder).
- Others: oxcarbazepine

- Toxicity
- Diplopia and ataxia – dose related
- Mild gastrointestinal upsets,
- Unsteadiness
- Drowsiness – at higher doses
- Aplastic anemia and agranulocytosis

BARBITURATES – PHENOBARBITAL (LUMINAL)

- Except for the bromides, it is the oldest antiepileptic drug.
- Although considered one of the safest drugs, it has sedative effects.
- Many consider them the drugs of choice for seizures only in infants.

PHENOBARBITAL (LUMINAL)

MoA

- Prolongs opening of Cl^- channels.
- Blocks excitatory Glutamate responses.
- Blocks Ca^{2+} and Na+ currents
- Inhibits high frequency, repetitive firing of neurons only at high concentrations.

PHENOBARBITAL (LUMINAL)

Clinical uses

- Useful for partial, generalized tonic-clonic seizures, and febrile seizures

PRIMIDONE (MYSOLIN)

- Metabolized to phenobarbital and phenylethylmalonamide (PEMA)

- The three compounds, metabolite and the parent drug are active

MoA

- Although primidone is converted to phenobarb, its MoA is more like that of phenytoin

PRIMIDONE (MYSOLIN)

- **Pharmacokinetics**
- Primidone is completely absorbed
- Low binding to plasma proteins
- Metabolised in the liver to active metabolites
- Should be started slowly to avoid sedation and GI problems.

PRIMIDONE (MYSOLIN)

Clinical Use

- Effective against partial seizures and generalized tonic-clonic seizures
- May be more effective than phenobarbital.
- Carbamazepine and phenytoin are superior to primidone in management of complex partial seizures

PRIMIDONE (MYSOLIN)

- **Toxicity**
- Similar to phenobarbital,
- But drowsiness occurs early in treatment and may be prominent if the initial dose is too large.
- Gradual increments are indicated when starting the drug in either children or adults.

VIGABATRIN (γ-VINYL-GABA)

- Absorption is rapid, bioavailability is ~ 60%, $T_{1/2}$ 6-8 hrs, eliminated by the kidneys.
- Use for partial seizures
- Contraindicated if preexisting mental illness is present.
- Irreversible inhibitor of GABA-amino transferase (enzyme responsible for metabolism of GABA)
- Increases inhibitory effects of GABA.
- S(+) enantiomer is active.

VALPROATE (DEPAKENE)

- Fully ionized at body pH, thus active form is valproate ion.
- One of a series of carboxylic acids with antiepileptic activity.
- Its amides and esters are also active.

VALPROATE (DEPAKENE)

- Mechanism of action
- similar to phenytoin.
- ⇑ levels of GABA in brain.
- Facilitates Glutamic acid decarboxylase (GAD).
- Inhibits the GABA-transporter in neurons and glia (GAT).
- ⇓ $[aspartate]_{Brain}$?
- May increase membrane potassium conductance.

ETHOSUXIMIDE (ZARONTIN)

At high concentrations:

- Inhibits Na^+/K^+ ATPase.
- Depresses cerebral metabolic rate.
- Inhibits GABA aminotransferase.
  - **Phensuximide = less effective**
  - **Methsuximide = more toxic**

ETHOSUXIMIDE (ZARONTIN)

- Drug of choice for absence seizures.
- High efficacy and safety.
- VD = TBW.
- Not plasma protein or fat binding
- Mechanism of action involves reducing low-threshold Ca^{2+} channel current (T-type channel) in thalamus.

BENZODIAZEPINE CLONAZEPAM (KLONOPIN)

- Long acting drug with efficacy for absence seizures.
- One of the most potent antiepileptic agents known.
- Also effective in some cases of myoclonic seizures.
- Has been tried in infantile spasms.
- Doses should start small.
- Increases the frequency of Cl^- channel opening.

LAMOTRIGINE (LAMICTAL)

- Add-on therapy with valproic acid (w/v.a. conc. have be reduced => reduced clearance).
- Almost completely absorbed
- $T_{1/2}$ = 24 hrs
- Low plasma protein binding

LAMOTRIGINE (LAMICTAL)

- Effective in myoclonic and generalized seizures in childhood and absence attacks.
- Involves blockade of repetitive firing involving Na channels, like phenytoin.
- Also effective in myoclonic and generalized seizures in childhood and absence attacks.

FELBAMATE (FELBATROL)

- Effective against partial seizures but has severe side effects.
- Because of its severe side effects, it has been relegated to a third-line drug used only for refractory cases.

- Causes aplastic anemia
- Severe hepatits

TOPIRAMATE (TOPAMAX)

- Rapidly absorbed, bioav. is > 80%, has no active metabolites, excreted in urine. $T_{1/2}$ = 20-30 hrs
- Blocks repetitive firing of cultured neurons, thus its mechanism may involve blocking of voltage-dependent sodium channels
- Potentiates inhibitory effects of GABA (acting at a site different from BDZs and BARBs).
- Depresses excitatory action of kainate on AMPA receptors.
- Teratogenic in animal models.

TOPIRAMATE (TOPAMAX)

Toxicity:

- Somnolence
- Fatigue
- Dizziness
- Cognitive slowing
- Parenthesis
- Nervousness
- Confusion
- Weak carbonic anhydrase inhibitor
- Urolithiasis

TIAGABINE (GABATRIL)

- Derivative of nipecotic acid.
- 100% bioavailable, highly protein bound.
- $T_{1/2}$ = 5 -8 hrs
- Effective against partial seizures in pts at least 12 years old.
- Approved as adjunctive therapy.
- GABA uptake inhibitor γ aminibutyric acid transporter (GAT) by neurons and glial cells.

TIAGABINE (GABATRIL)

Toxicity:

- Abdominal pain and nausea (must be taken w/food)
- Dizziness
- Nervousness
- Tremor
- Difficulty concentrating
- Depression
- Asthenia
- Emotional liability
- Psychosis
- Skin rash

GABAPENTIN (NEURONTIN)

- Used as an adjunct in partial and generalized tonic-clonic seizures.
- Does not induce liver enzymes.
- not bound to plasma proteins.
- drug-drug interactions are negligible.
- Low potency.
- An a.a.. Analog of GABA that does not act on GABA receptors, it may however alter its metabolism, non-synaptic release and transport.

GABAPENTIN (NEURONTIN)

Toxicity:

- Somnolence.
- Dizziness.
- Ataxia.
- Headache.
- Tremor.

STATUS EPILEPTICUS

- Occurs when seizures recur within a short period of time, such that baseline consciousness is not regained between the seizures.
- They last for at least 30 minutes.
- Can lead to
  - systemic hypoxia,
  - acidemia,
  - hyperpyrexia,
  - cardiovascular collapse
  - renal shutdown.

STATUS EPILEPTICUS

- The most common, generalized tonic-clonic status epilepticus is life-threatening

- Must be treated immediately with concomitant cardiovascular, respiratory and metabolic management.

TREATMENT OF *STATUS EPILEPTICUS* IN ADULTS

Initial

- Diazepam, i.v. 5-10 mg (1-2 mg/min)

  repeat dose (5-10 mg) every 20-30 min.
- Lorazepam, i.v. 2-6 mg (1 mg/min)

  repeat dose (2-6 mg) every 20-30 min.

Follow-up

- Phenytoin, i.v. 15-20 mg/Kg (30-50 mg/min).

  repeat dose (100-150 mg) every 30 min.
- Phenobarbital, i.v. 10-20 mg/Kg (25-30mg/min).

  repeat dose (120-240 mg) every 20 min.

TREATMENT OF SEIZURES

Partial seizures

- Simple and Complex, including secondarily generalized

- Drugs of choice
  - Carbamazepine
  - Phenytoin
  - Valproate

TREATMENT OF SEIZURES

Partial seizures

- Alternatives:
  - Lamotrigine,
  - phenobarbital,
  - primidone,
  - oxcarbamazepine.
- Add-on therapy
  - Gabapentin,
  - topiramate,
  - tiagabine,
  - levetiracetam,
  - zonisamide.

TREATMENT OF SEIZURES

Primary generalized tonic-clonic seizures (*grand mal*)

- drugs of choice:
  - Carbamazepine
  - Phenytoin
  - Valproate*

*not approved except if absence seizure is involved

TREATMENT OF SEIZURES

Primary generalized tonic-clonic seizures (*grand mal*)

- alternatives:
  - lamotrigine,
  - phenobarbital,
  - topiramate,
  - Oxcarbazepine,
  - primidone,
  - levetiracetam.

TREATMENT OF SEIZURES

Generalized absence seizures

- drugs of choice
  - ethosuximide
  - valproate*
- alternatives:
  - lamotrigine,
  - clonazepam,
  - zonisamide,
  - topiramate (?).

* first choice if primary generalized tonic-clonic seizure is also

TREATMENT OF SEIZURES

Atypical absence, myoclonic, atonic* seizures

- Drugs of choice
  - Valproate
  - Clonazepam
  - Lamotrigine

- <u>Alternatives:</u>
  - Topiramate,
  - clonazepam,
  - zonisamide,
  - felbamate.

TREATMENT OF SEIZURES

Infantile spasms

- drugs of choice
  - corticotropin (im) or
  - corticosteroids (prednisone)
  - zonisamide

- Alternatives
  - clonazepam,
  - nitrazepam,
  - vigabatrin,
  - phenobarbital.