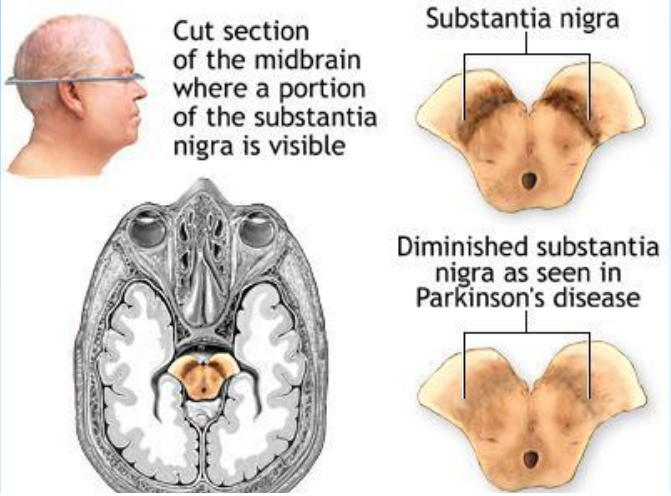


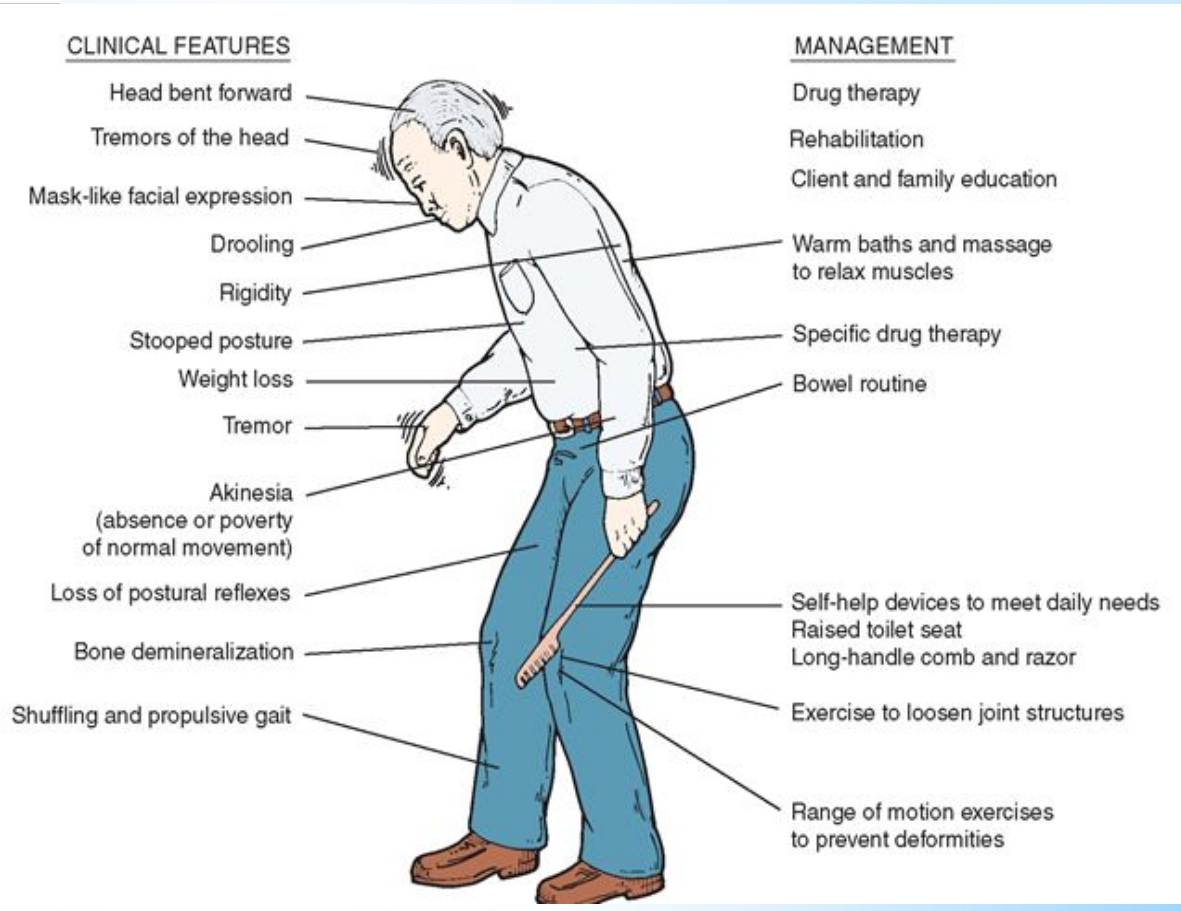
Zaporizhzhia State Medical University
Pharmacology Department

Lecture № 6

HYPNOTIC, ANTIEPILEPTIC and ANTIPARKINSONIAN DRUGS

Parkinson's Disease

- Chronic, progressive neurodegenerative disease
- Slow and selective loss of substantia nigra dopaminergic neurons
- Clinical features
  - Tremor, rigidity, bradykinesia and postural instability in later stages of disease
  - Autonomic dysfunction
    - Orthostatic hypotension
    - Constipation and bladder dysfunction
    - Sexual dysfunction
  - Neuropsychiatric disturbances
    - Depression
    - Dementia
    - Psychosis



SEDATIVE-HYPNOTIC DRUGS

I. Benzodiazepine Receptor Agonists

1. BZD compounds:

Diazepam -Tab. 5 mg; amp. 0.5%-2 ml

Nitrazepam - Tab. 5 and 10 mg

Lorazepam - Tab. 1 and 2 mg, amp. 0. 2% - 1ml

Phenazepam – Tab. 0.5 and 1 mg

Alprazolam (*Xanax*) – Tab. 0.25 and 0.5 mg

Chlordiazepoxide

Nozepam (*Oxazepam*, *Tazepam*) – Tab. 10 mg

2. Agents of other chemical groups:

Zolpidem - Tab. 10 mg

Zopiclone - Tab. 7.5 mg

II. Hypnotics with Narcotic Effect

1. Barbiturates:

- Long-acting: 1 - 2 days

Phenobarbital (*Luminal*) – Tab. 0.005, 0.05 and 0.1 g

- Short-acting: 3 - 8 hours

Amobarbital – *Tab*. 0.03, 0.05, 0.1 g; *Vial* 0.5 g

Secobarbital – *Caps*. 0.05 and 0.1 g; syringe 5% - 2 ml

Pentobarbital

- Ultra-short acting: 20 min

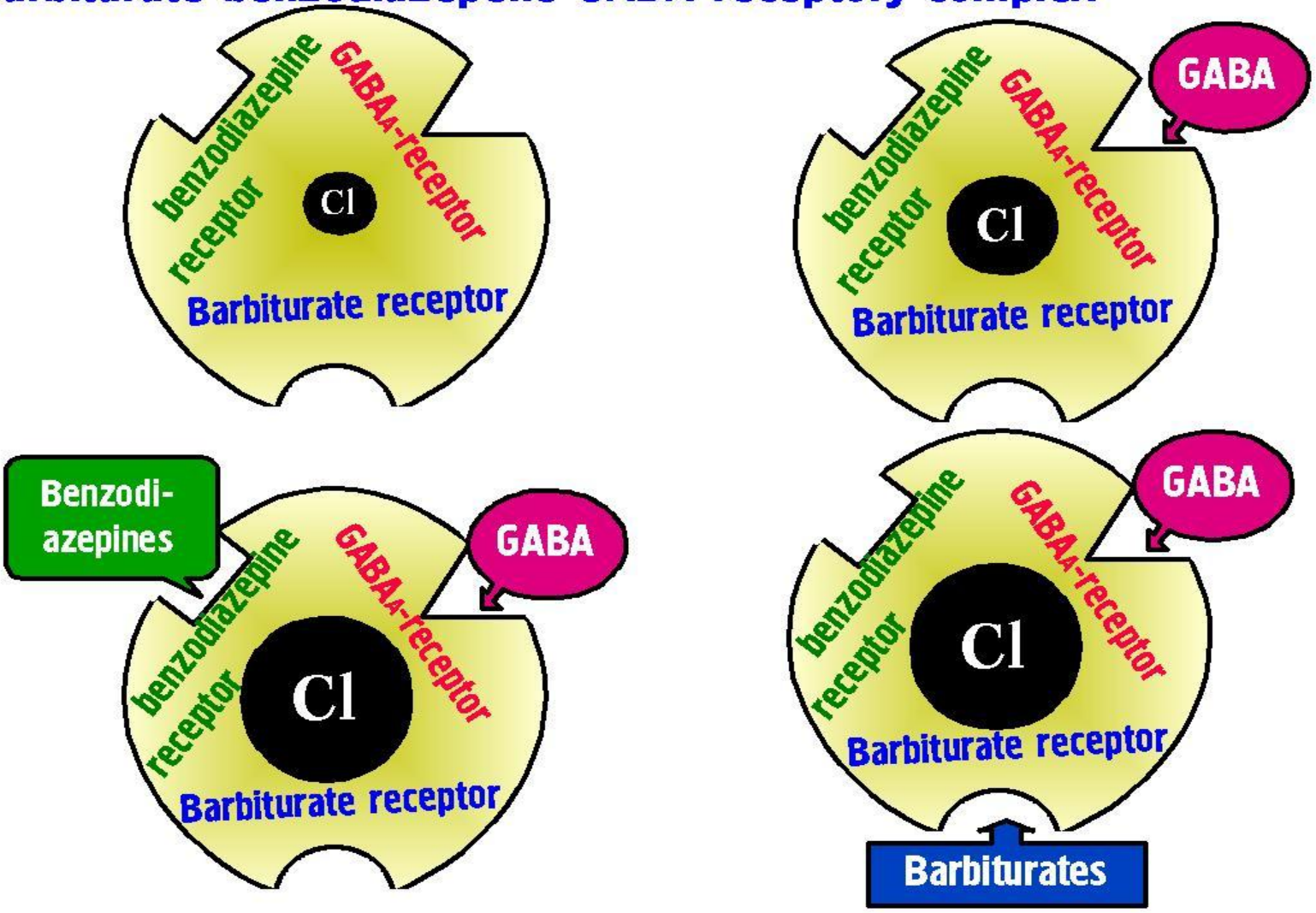
Thiopental sodium (*Aethaminalum-natrium*, *Nembutal*)

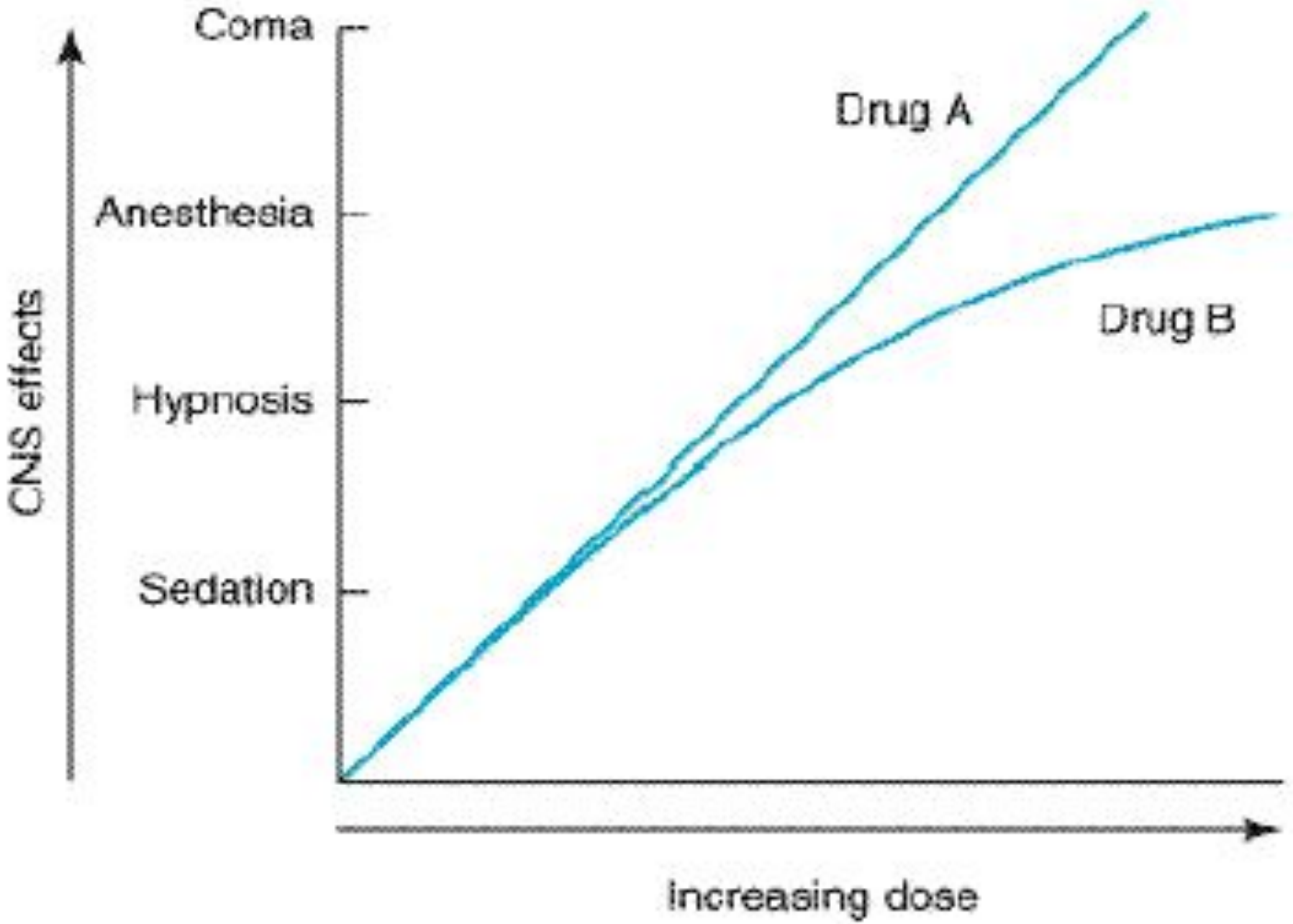
2. Non-barbiturate hypnotics:

Chloral hydrate - powder

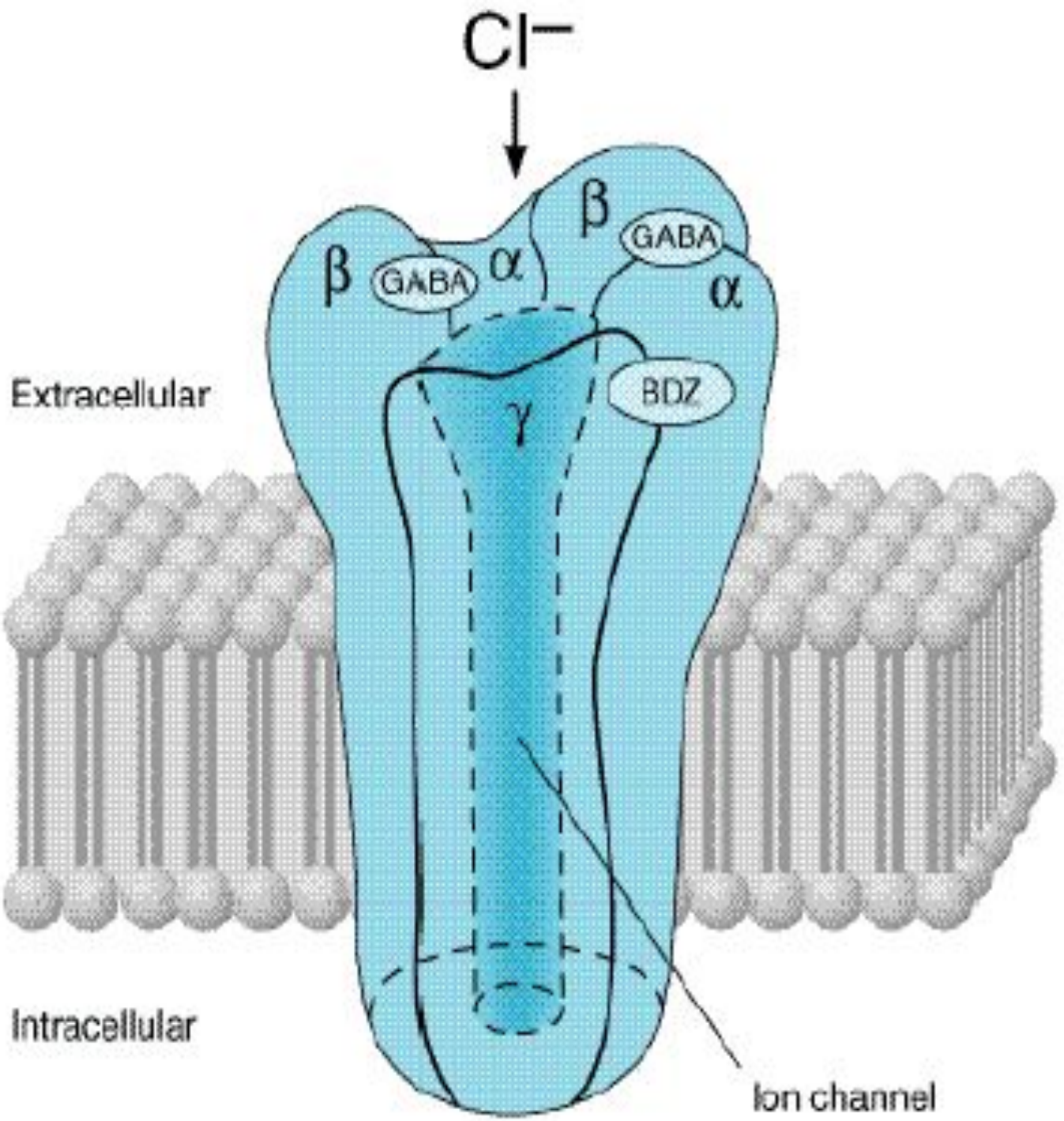
Mechanism of action of barbiturates and benzodiazepines

Barbiturate-benzodiazepene-GABA-receptory complex





Dose-response curves for two hypothetical sedative-hypnotics.


Cl⁻
β
GABA
α
β
GABA
α
γ
BDZ
Extracellular
Intracellular
Ion channel

MECHANISM OF ACTION of BZDs

- **Bind to the α-subunit of the $GABA_A$ Rs**
  surrounding the **Cl^-** channels
  Designated as BZD Rs (omega-receptors)
  - Affinity of GABA receptors
  - Frequency of Cl^- channel opening
  - Cl^- conductance => **HYPERPOLARIZATION**

  INHIBITION of **ACTION POTENTIAL** formation and further NEURONAL FIRING
- BZDs turnover of **5-HT** and NORADRENALINE

- Antispasticity Effect:

- action on $GABA_A$ Rs in the Brain Stem
Spinal Chord

- Sedative and Anticonvulsant effects:
  - are localized to the Limbic System.
- Seadtive-hypnotic Effect:
  - is due to their actions on the omega-1 Rs
- Impairment of Memory:
  - action on the omega-2 Rs

MECHANISM OF ACTION of Barbiturates

- Bind to the **β-subunit** of **the $GABA_A$ Receptor** surrounding the **Cl^-** channels.
- They facilitate the actions of GABA at multiple sites in the CNS and **hyperpolarize** the post-synaptic cell,
- Duration of **the GABA-gated** Chloride Channel openings.
- At lower doses they enhance the action of GABA whereas in larger doses they may also be GABA-mimetic, directly activating Chloride Channels.

Barbiturates also **inhibit** the excitatory AMPA-glutamate receptors. They are less selective than BZDs, since they also depress the actions of excitatory neurotransmitters (e.g., glutamic acid)

Rapid Eye Movement (REM)

During sleep, the brain generates a rhythmic activity.

Internal sleep cycles recur 4-5 times per night, each cycle being interrupted by a **Rapid Eye Movement** sleep phase.

The REM stage is characterized by EEG activity similar to that seen in **the waking state**, **Rapid Eye Movements**, **Vivid Dreams**, and occasional **twitches** of **individual muscle groups** against a **background** of **generalized atonia** of skeletal musculature.

The **REM stage** is entered after a **non-REM cycle** (NREM).

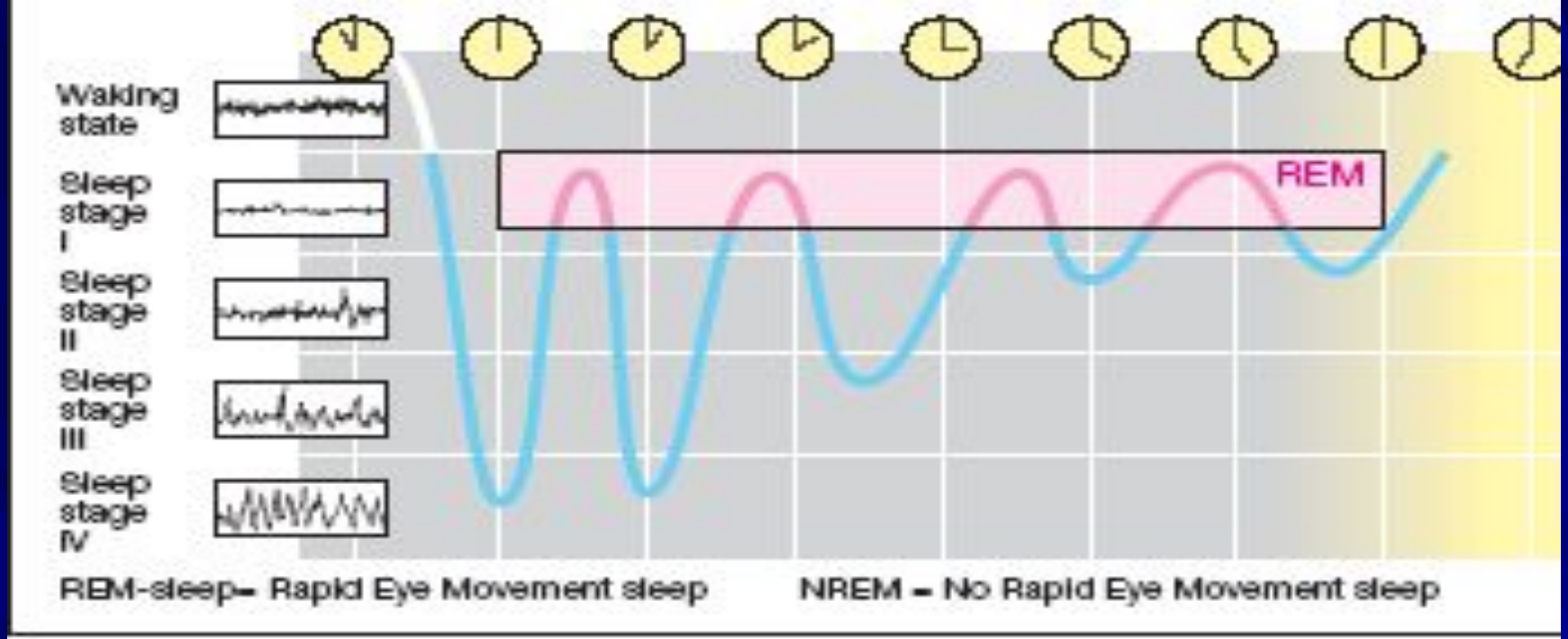
All hypnotics shorten the time spent in the REM stages !!

With repeated ingestion of a hypnotic for several successive days, the proportion of time spent in REM vs. non-REM sleep returns to normal despite continued drug intake.

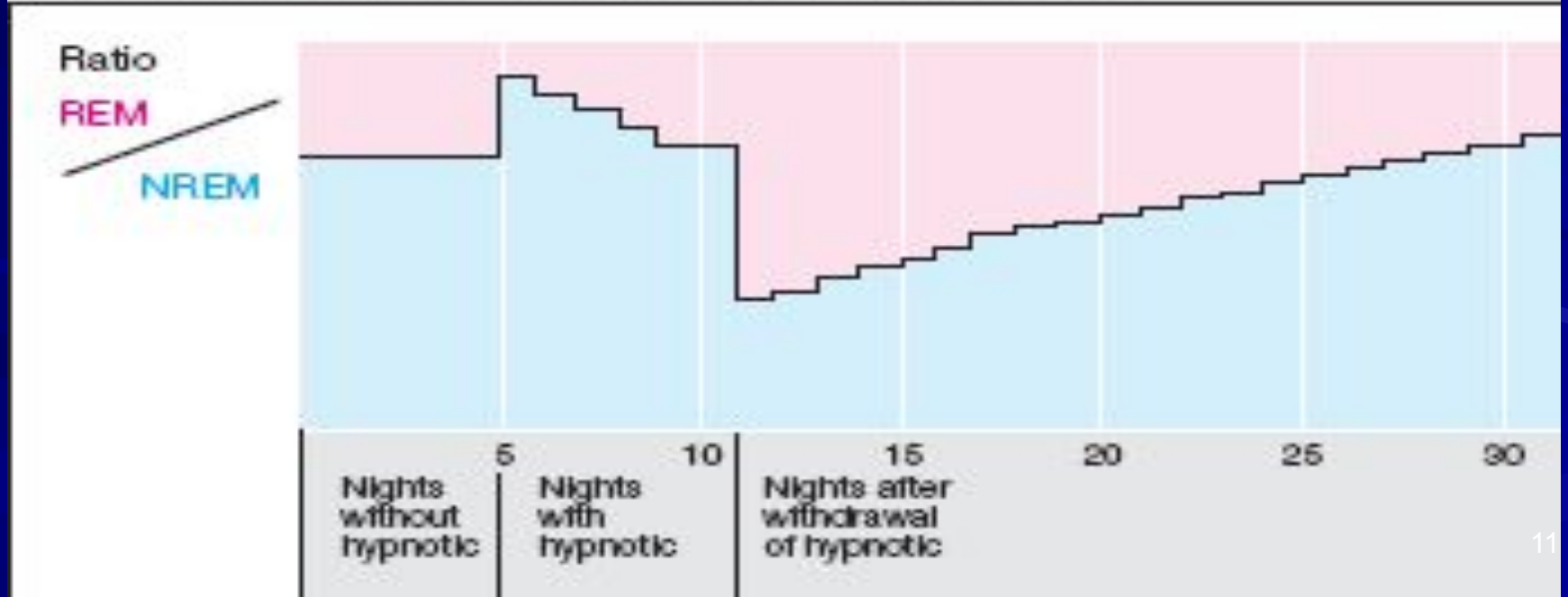
Withdrawal of the hypnotic drug results in **REM rebound**, which tapers off over many days.

Since REM stages are associated with vivid dreaming, sleep with excessively long REM episodes is experienced as unrefreshing.

The attempt to discontinue use of hypnotics may result in the impression that refreshing sleep calls for a hypnotic, promoting **Hypnotic Drug Dependence**.



A. Succession of different sleep phases during night rest



PHENOBARBITAL (*Luminal*)

Tab. 0.005, 0.05 and 0.1 g

- Bind to β-subunit of the $GABA_A$ Rs

  => Facilitate the actions of GABA

- **DURATION** of the GABA-gated

  Cl^- channel openings

- is a potent inducer of the *P-450* system, and it enhances the metabolism of other agents

Pharmacological Effects of Barbiturates

- 1. Depression of the CNS
- 2. Respiratory Depression
- 3. Enzyme Induction:

Barbiturates induce *P-450* microsomal enzymes in the liver.

Clinical Uses of Barbituretes:

- 1. Anesthesia:

  Thiopental Sodium IV to induce general anesthesia.

- 2. Anticonvulsant:

  Phenobarbital - in long-term management of Tonic-clonic Seizures

  Status Epilepticus

  Eclampsia.

- 3. Insomnia.
- 4. Preoperative sedation

Adverse Effects of Barbiturates:

- 1. Drowsiness, impaired concentration, mental and physical sluggishness
- 2. Drug hangover: a feeling of tiredness after the patient awakes
- 3. Barbiturates induce *the P-450* system and may □the effect of drugs that

are metabolized by these hepatic enzymes

Poisoning with Barbiturates

- **I Stage** (Falling Asleep): slurred speech, sustained Nystagmus, Somnolence; Apathy, Miosis,
  Bradycardia, Hypersalivation.
- II **Stage** (Superficial Coma): unconsciousness, Tachycardia,
  Muscle Hypotonia or Hypertonia,
  Decrease or Increase of Reflexes,
  Miosis. Rare and Superficial Breathing,
  Weak Pulse, Cyanosis, Oliguria
- III **Stage** (Deep Coma): Areflexia,
  Absence of Reaction to Painful Stimulation.
- IV **Stage**: (Post Comatose Period): Ptosis, Unsteady Gate,
  Emotional Lability, Depression.

Treatment of Poisoning with Barbiturates

- Forced Alkaline Diuresis,

Adequate Fluids, Acid-base Balance Correction

Mannitol, Furosemide (*Lasix*)

Sodium Bicarbonate 4% 500 ml IV

- Intensive Infusion Therapy with

Polyglucin, Rheopolyglucin, Hemodes

- Antidote Therapy:

Bemegrid 0.5% 5-10 ml IV or IM

Sulfacamphocaine

Coffeine-sodium bensoate

Ephedrine hydrochloride

Cordiamine

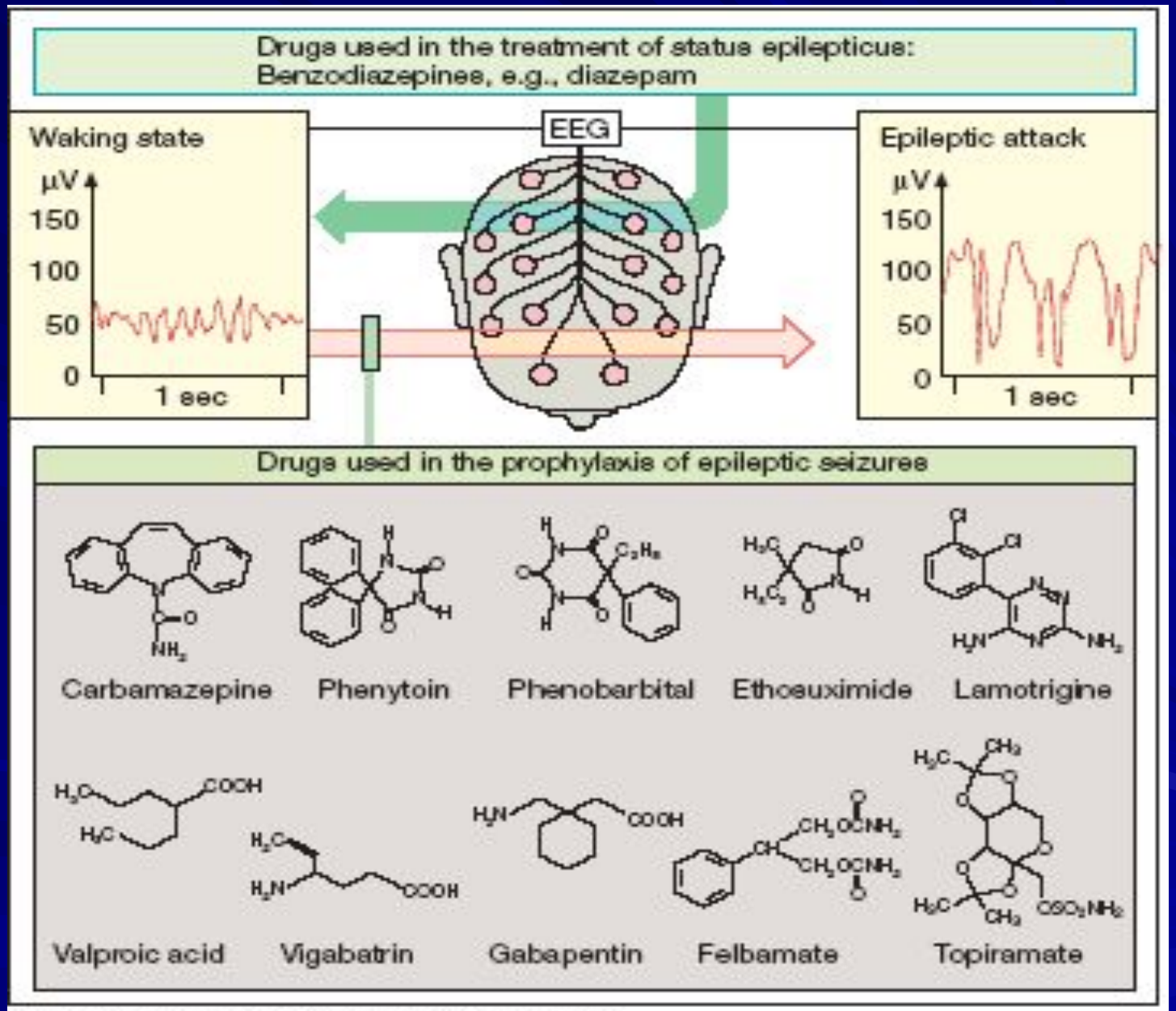
- VITAMINS:
  - B_1 6% 5 ml,
  - B_6 5% 6-8 ml,
  - B_{12} 600 μg
  - C 5% 5-10 ml.
- ATP 1% - 6 ml
- Noradrenaline hydrotartrate 0.2% - 1 ml

combined with

- Dopamine 4% - 5 ml

in *Polyglucin (Macrodex)* 400 ml IV infusion

Drugs Used to Treat Epilepcy



A. Epileptic attack, EEG, and antiepileptics

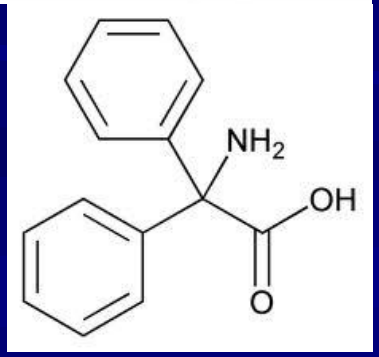
Antiepileptic Drugs

I. Delaying the recovery from inactivating Na^+ channels:

Carbamazepine (*Finlepsin*)

Oxcarbazepine

Diphenin (*Phenytoin*)



- Carbamazepine - tab. 0.2 g, 0.4 g

Mechanism of action: It blocks Na^+ channels =>

- Propagation of abnormal impulses
- Generation of repetitive action potentials in the Epileptic Focus

Clinical Uses:

- **Partial Seizures** (Simple and Complex) - is the Drug of 1st Choice.
- Tonic-Clonic Seizures
- Trigeminal Neuralgia

- Diphenin (*Phenytoin*, *Hydantoin*)

- Tab 0.117 g; amp. 5%-5 ml

Mechanism of action: ▫ Influx of Na^+ across cell membranes in the motor cortex during generation of nerve impulses

Adverse effects:

Gingival Hyperplasia,

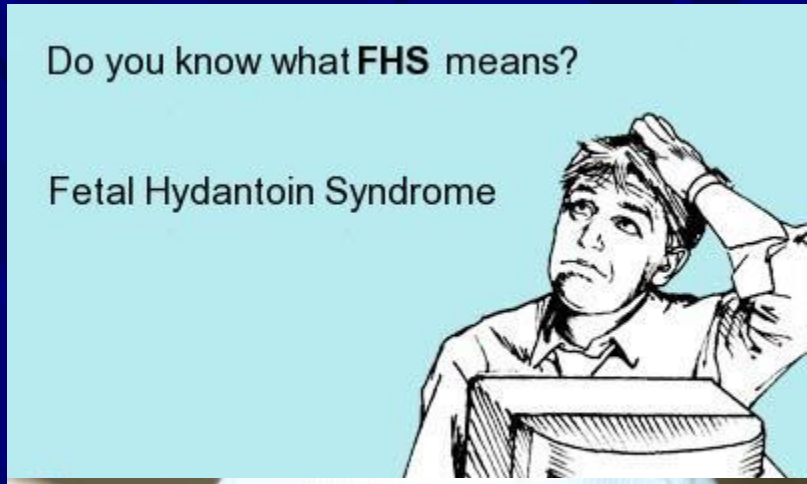
us,

Ataxia.

Nystagmus - involuntary movement of the eye comprising a Smooth Drift followed by a Flick Back

Teratogenic Effects of *Diphenin*

- Fetal Hydantoin Syndrome:
  - Cleft Lip (hare lip)
  - Cleft Palate
  - Congenital Heart Disease
  - Slowed Growth
  - Mental Deficiency



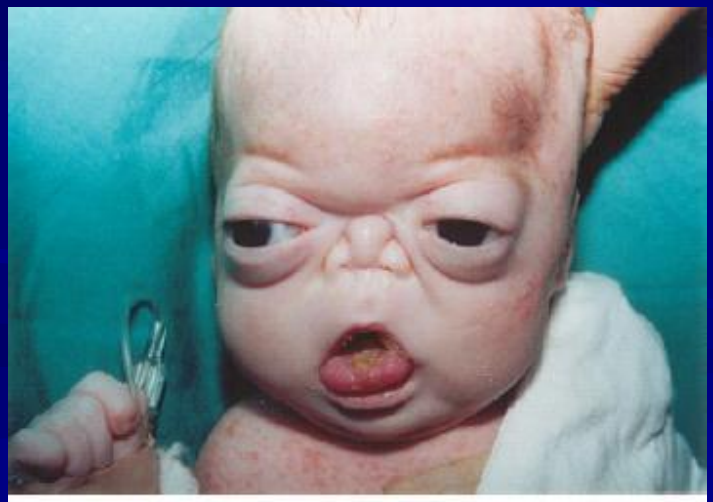
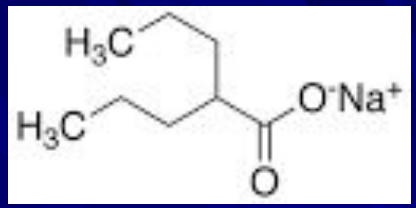


Fig. 1. Frontal view of the patient's head with proptosis, depressed nasal bridge and triangular mouth.

II. GABA-mimetics:

1. Stimulating GABA-ergic transmission:
   Sodium Oxybutyrate (*Sodium oxybate*)
2. Activating GABA Receptors:
   BARBITURATES, BENZODIAZEPINES
3. Inhibiting GABA-transferase and ▫GABA synthesis:
   Sodium Valproate
4. Releasing GABA from neuronal endings:
   Gabapentin
5. Inhibiting GABA transaminase:
   Vigabatrine
6. Inhibiting GABA reuptake:
   Tiagabine

- Valproate Sodium (*Depakin)*



Tab. 0.3 g; amp. 10% - 5 ml;
Syrup 5%-120 ml
a Stimulator of GABA-ergic Processes

Mechanism of action:

- Inhibits GABA-transferase
- GABA synthesis =>

 Brain Levels of GABA

 Propagation of *abnormal electrical discharge*

Adverse effects: ataxia, tremor, rash,
Hepatic toxicity,
Alopecia,
Bleeding time

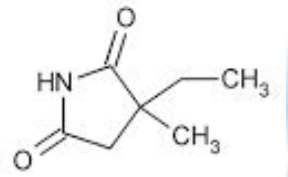
III. Inhibiting Excitatory Neurotransmitters and NMDA-receptors:

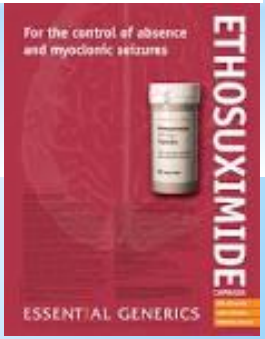
Lamotrigine

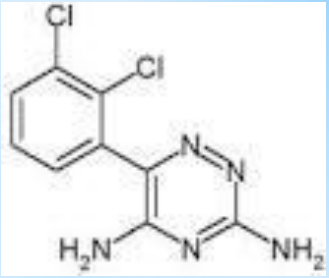
IV. Inhibitig **Low threshold** (*T-current*) Ca^{2+} channels in the thalamic neurons:

Ethosuximide

Trimethine (*Trimethadione*)







Lamotrigine - *Tab. 0.05 and 0.1 g*
an Inhibitor of Exciting Amino Acids – *Glutamate* and *Asparginate*

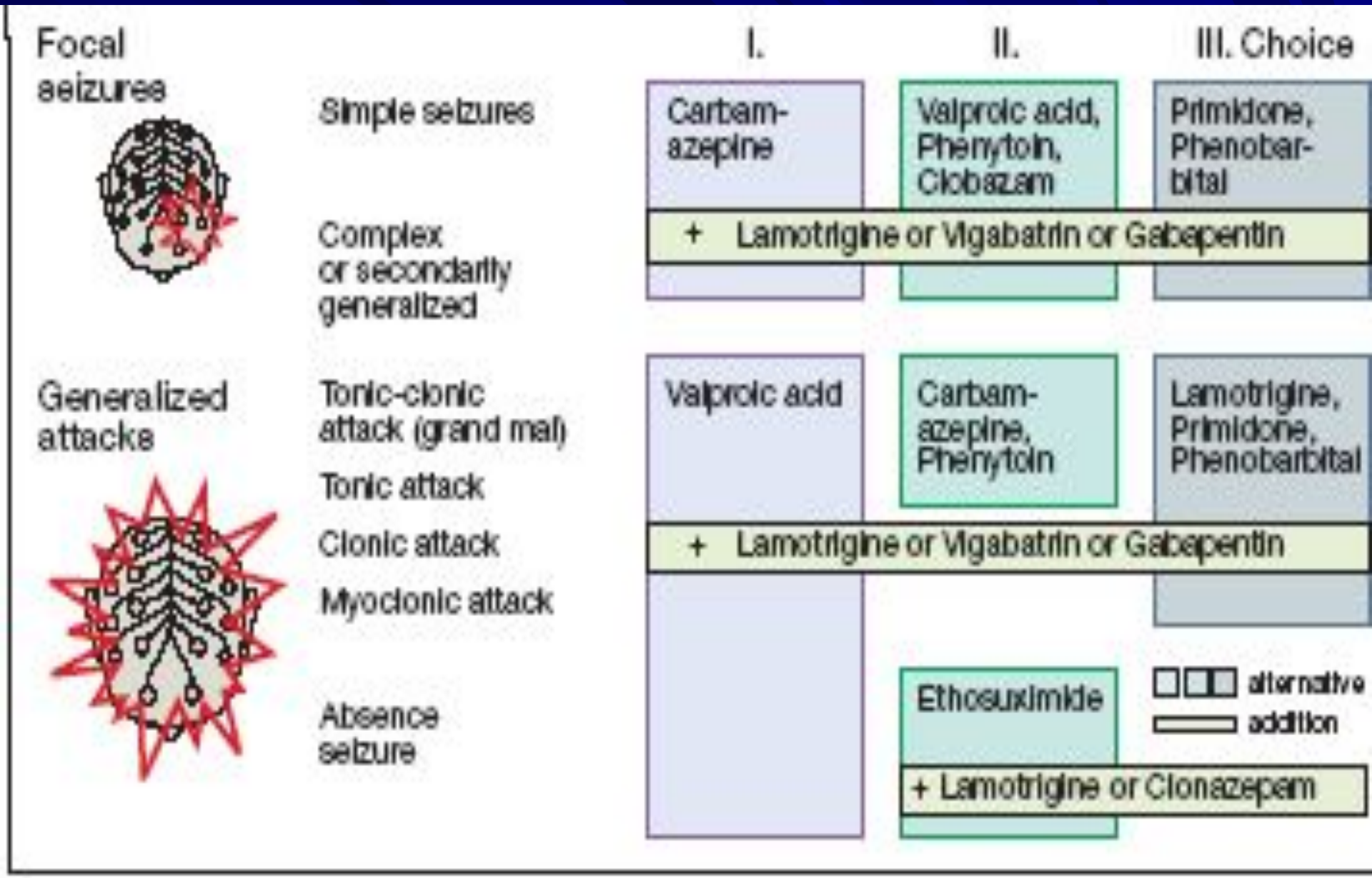
Mechanism of action:
inactivates voltage-sensitive Na^+ Channels =>
inhibits the Release of *Glutamate* and *Asparginate* - Exciting Neurotransmitters

Clinical uses: partial and secondarily generalized seizures that are resistant to other drugs.

Adverse effects: nausea, headache, rash, diplopia, ataxia, hepatotoxicity, aggressiveness.

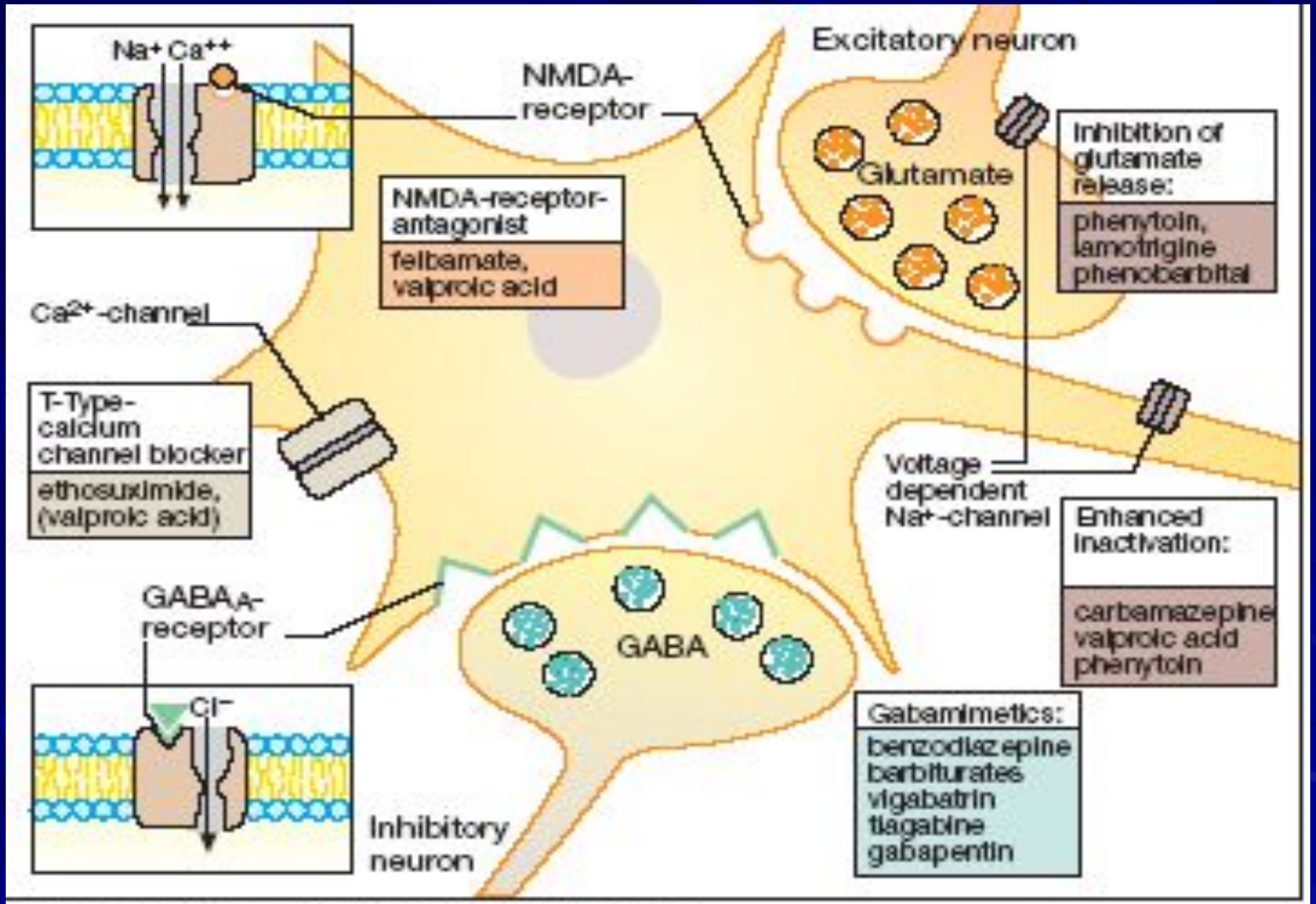
Classification of Epilepsy

- 1. PARTIAL:
  - a. Simple Partial
  - b. Complex Partial
- 2. GENERALIZED:
  - **a.** Tonic-clonic (Grand mal)
  - b. Absence (Petit mal)
  - c. Myoclonic
  - d. Febrile Seizures
  - e. Status Epilepticus



B. Indications for antiepileptics

Seizure Type	1st Choice	2nd Choice
Focal Seizures	Carbamazepine Difenin	Clonazepam Lamotrigine Valproate Na
Generalized Seizures (GRAND MAL)	Carbamazepine Diphenin Valproate Sodium	Clonazepam Lamotrigine
Status Epilepticus	Diazepam Diphenin Sodium Oxybutyrate	Phenobarbital
Absence (PETIT MAL)	Ethosuximide Valproate Sodium	Lamotrigine Trimethine



A. Neuronal sites of action of antiepileptics

Antiparkinsonian Drugs

I. Activating Dopaminergic Influences:

1. Precursors of Dopamine:

Levodopa (*Tab. 0.25 and 0.5 g*)

· Combined agents:

Sinemet (*Nakom*)

Madopar

2. D-receptor agonist:

Bromocriptine (*tab. 2.5 mg*)

Pergolide (*tab. 0.25 mg* and *1 mg*)

Cabergolin (*tab. 0.5 mg*)

3. MAO-B inhibitors:

Deprenil (*Selegiline – tab. 5 mg*)

II. Inhibiting Glutamatergic Influences:

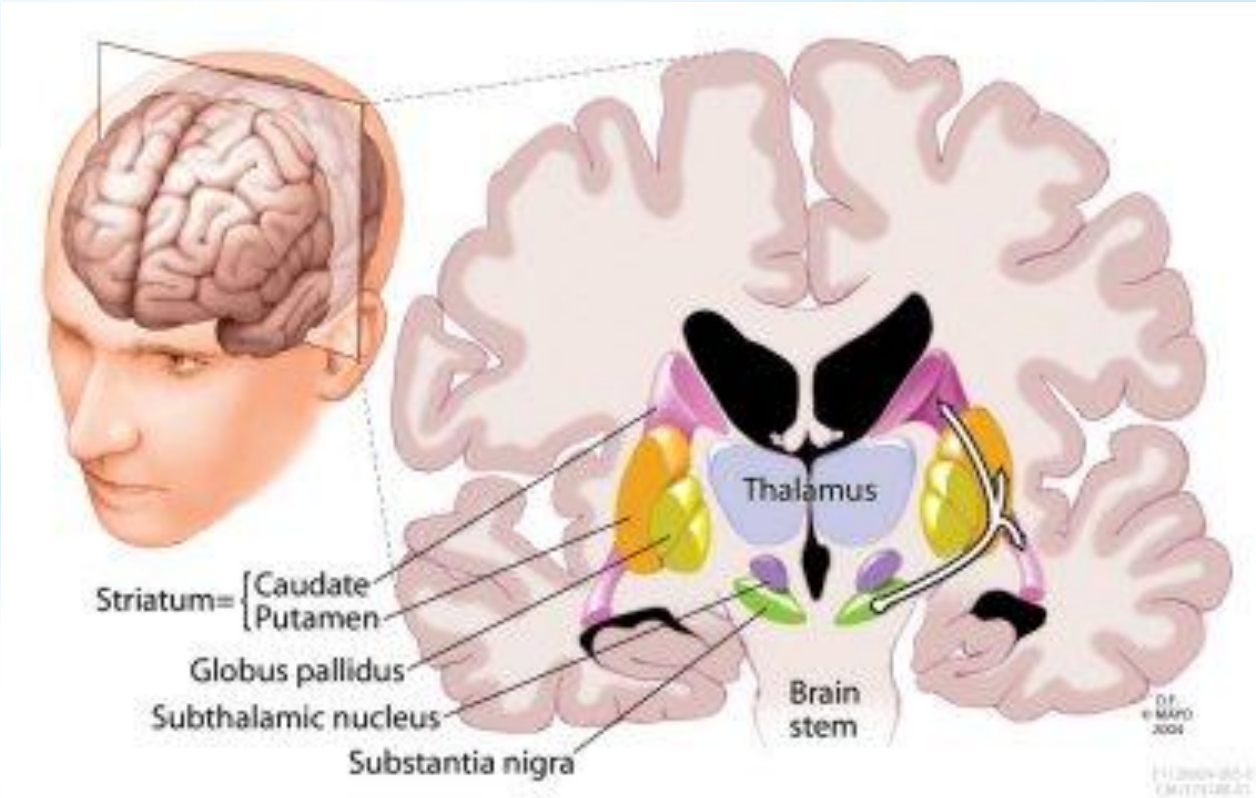
Amantadine (*Midantane – tab. 0.1 g*)

III. Inhibiting Cholinergic Influences:

Cyclodol (*tab. 1 mg, 2 mg and 5 mg*)

Benztropine

Tropacine



Levodopa (*L-DOPA, Dopar*) -

a Laevorotatory Isomer of DOPA (Dihydroxy-Phenylalanine) – a precursor of Dopamine

MA: Stimulates the D_2 receptors in the basal ganglia

=> Improves modulation of Voluntary Nerve Impulses transmitted to the motor cortex

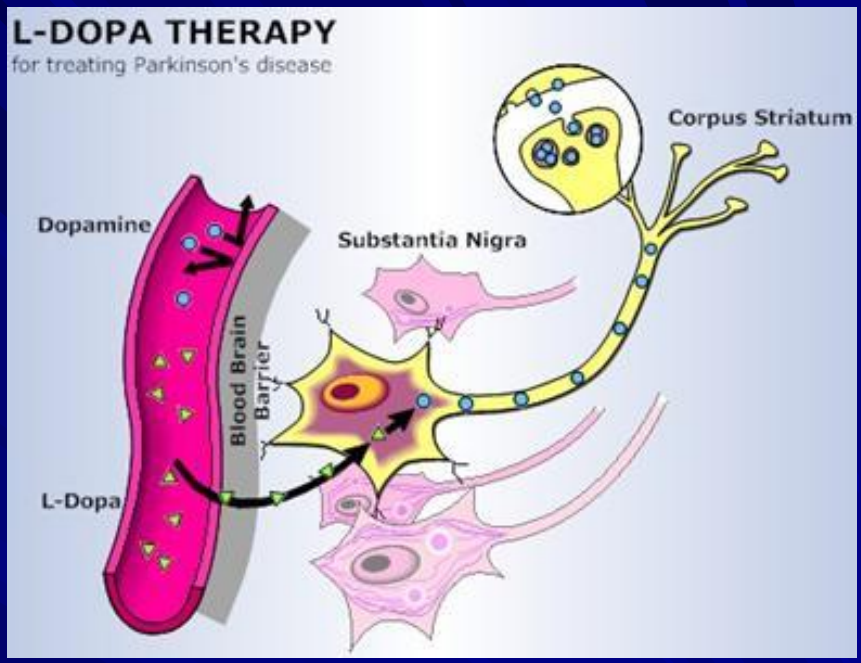
=> Relieves all major symptoms, esp.:

- Akinesia (inability of voluntary movement)
- Rigidity and Bradykinesia (Slowness of movement)
- Akathisia (the inability to sit still because of uncontrollable movement)
- Tremors

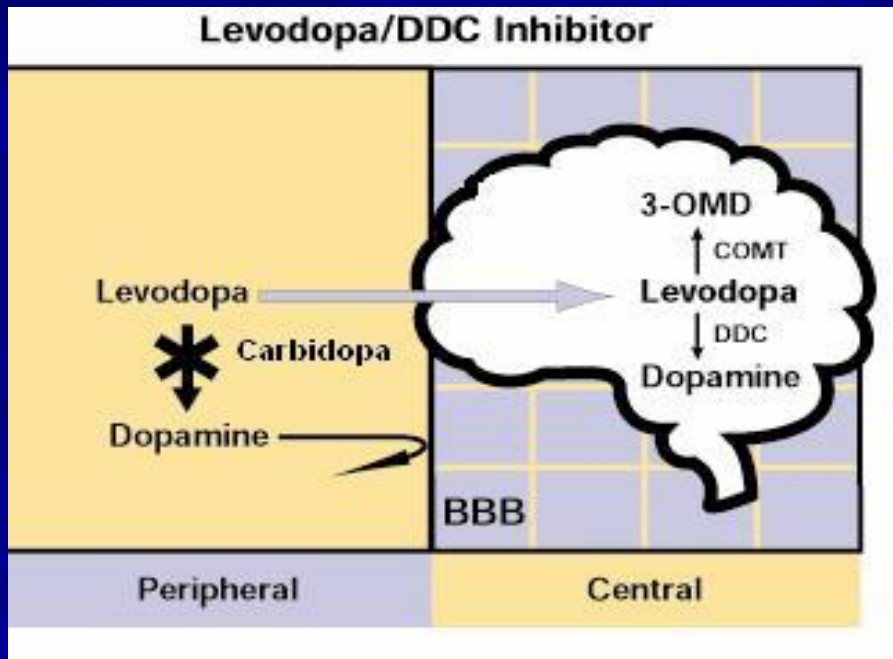
=> Improves Mood and Memory

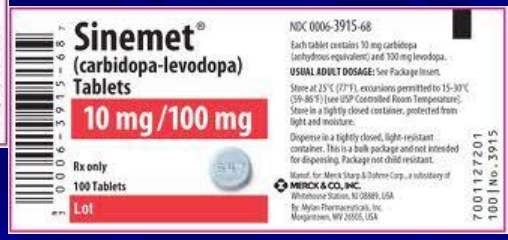
Adverse effect of Levodopa:

- Anorexia, Vomiting
- Cardiac Arrhythmias
- Orthostatic Hypotension
- Aggressive Behavior
- Seizures
- Hallucinations, Confusion, Delirium
- Dyskinesia – **Involuntary** Repetitive Movements
  - in up to 80% of patients



- Carbidopa and Benserazide -
  inhibitors of *DOPA decarboxylase* –
  do not penetrate the Blood-Brain barrier
  => less Levodopa is decarboxylated
  in peripheral tissues
  => more Levodopa reaches the brain where
  it is decarboxylated to DOPAMINE
  => much smaller doses
  of Levodopa can be given.





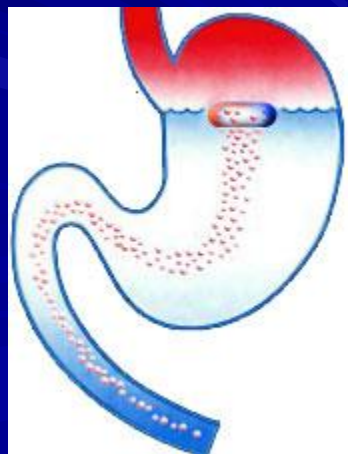
- Sinemet (Nakom) :

  Levodopa 100 mg + *Carbidopa* 25 mg

- Madopar :

  Levodopa 100 or 200 mg +

  Carbidopa 25 mg or 50 mg respectively



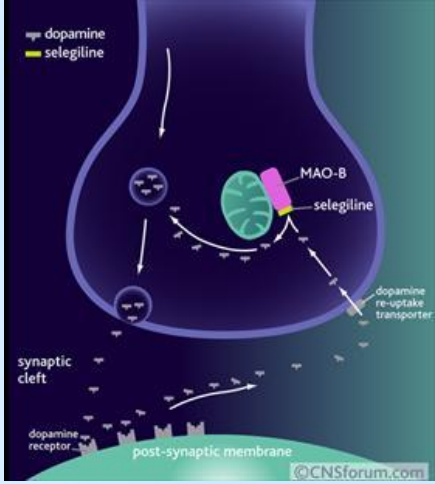
Bromocriptine, an *ergotamine* derivative,
is a Dopamine Receptor Agonist.

- The actions are similar to those of *Levodopa*,
except that

Hallucinations, Confusion, Delirium, Nausea, and Orthostatic Hypotension are more common,
whereas **Dyskinesia** is less prominent.

- In psychiatric illness it causes the mental condition to worsen.
- In patients with Peripheral Vascular Disease
a worsening of the vasospasm occurs.
- In patients with Peptic Ulcer, there is a worsening of the ulcer.

Selegiline (*Deprenil*) - MAO-B inhibitor



Mechanism of Action: This is a selective, irreversible inhibitor of Monoamine Oxidase type B, thus decreasing the metabolism of Dopamine by preventing inter-neuronal degradation.

Inhibition of this enzyme slows the breakdown of Dopamine in the striatum.

Adverse reactions: can potentiate dyskinesia, mental and psychiatric adverse effects, and nausea due to *levodopa* dose.

If selegiline is administered in high doses, the selectivity of the drug is lost, and the patient is at risk for severe hypertension.

Selegiline increase the peak effect of L-DOPA and can worsen preexisting dyskinesia or psychiatric symptoms such as delusion and hallucination.

Contraindication: Selegiline should be avoided in patients with known falls, hallucinations, confusion and postural hypotension.

Thank You for Attention!