

**HYPNOTIC AND**

**ANTI CONVULSANT DRUGS**

# SLEEP

**Sleep** is associated with a state of muscle relaxation and reduced perception of environmental stimuli

During sleep, most of the body's system are:

- ❖ in an anabolic state
- ❖ helping to restore the immune nervous, skeletal, and muscular systems these are vital processes that maintain mood memory
- ❖ cognitive function
- ❖ play a large role in the function of the endocrine and immune systems

# SLEEP

**Sleep deprivation tends to cause:**

- ❖ **slower brain waves in the frontal cortex**
- ❖ **shortened attention span, higher anxiety, impaired memory, and a grouchy mood**
- ❖ **conversely, a well-rested organism tends to have improved memory and mood.**

# SLEEP

sleeping **6–7 hours** each night correlates with longevity and cardiac health in humans

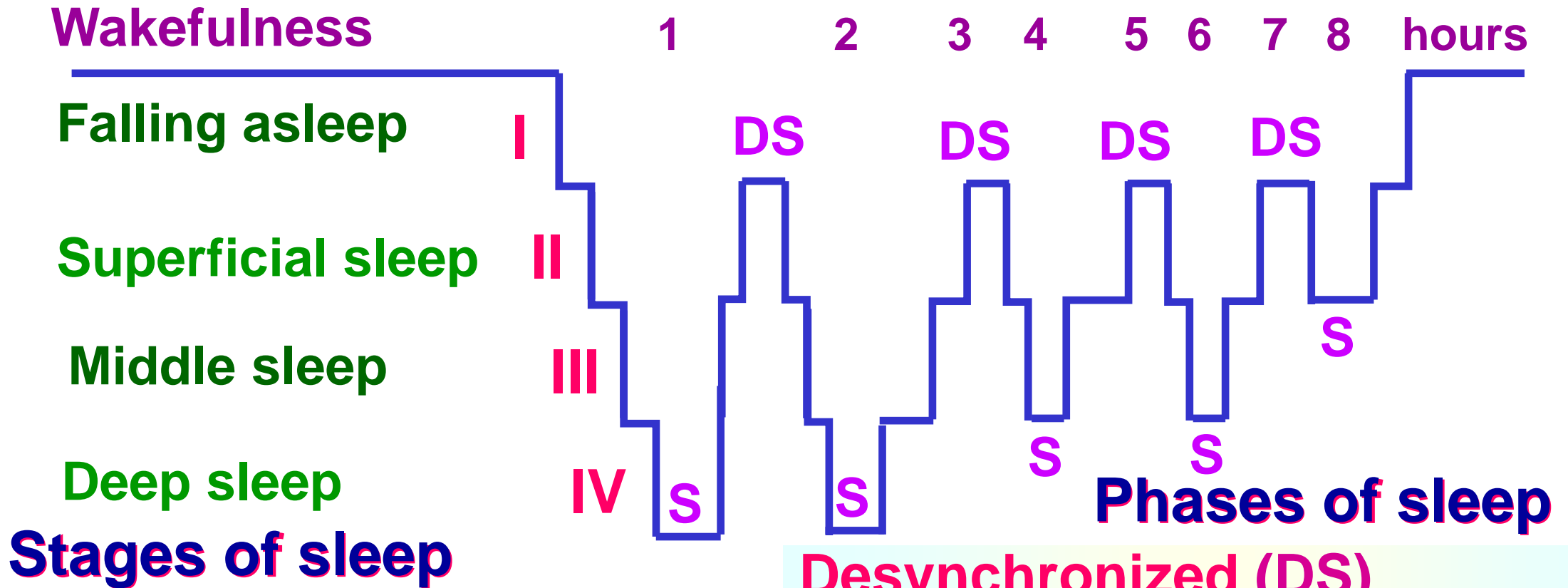
## **Sleep DISORDERS CAN COUSE:**

- ❖ psychiatric disorders (depression, psychosis)
- ❖ alcoholism, and bipolar disorder
- ❖ negatively affects learning processes, short-term and long-term memory
- ❖ Increased risk of developing cardiovascular disease (myocardial infarction)
- ❖ decrease process of formation of bone tissue
- ❖ Increase weight

# SUBSTANCES AFFECTING CNS

- ◆ **Depressing functions of CNS:**
  - **general anaesthetic drugs**
  - **hypnotics**
  - **anticonvulsants**
  - **non-narcotic analgesics**
  - **psychotropic drugs (narcotic analgesics, psychodysleptics, neuroleptics, tranquilizers, psychosedatives)**
- ◆ **Stimulating functions of CNS:**
  - **psychotropic (psychostimulants, antidepressants)**
  - **nootrops, adaptogens**
  - **analeptics**

# PHYSIOLOGICAL SLEEP STRUCTURE



**Synchronized (S)**  
or **slow sleep (75%) non-REM-phase (non-rapid eye movement) EEG — slow correct high-voltage activity muscular twitching, n. vagus predominance**

**Desynchronized (DS)**  
or **fast sleep (25%) REM-phase (rapid eye movement) EEG — rapid wrong low-voltage activity, presence of dreams, rapid eye movement, rise of sympathetic innervation**



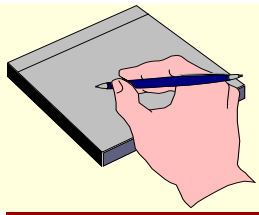
# TYPES OF INSOMNIA

- **Emotional (juvenile)** — a process of falling asleep is broken (neurasthenia, overstrain)
- **Senile** — short sleep (2–5 hrs), after which a patient can not fall asleep (sclerosis of cerebral vessels)
- **Pathological** — phases and stages of sleep are broken (pain, neurosis, etc.)

# DEMANDS TO HYPNOTIC DRUGS

- ❖ An ability to **fast provoking physiological-like sleep** without disturbing its structure and night awaikenning
- ❖ **Preserving wakefulness** all the day long (absence of cumulating and aftereffect)
- ❖ Absence of **tolerance** and drug **dependence**
- ❖ **Low organotoxicity**, including absence of negative influence on the moving activity, memory, somatic and reproductive functions
- ❖ **Absence** of adverse **interaction** with other drugs
- ❖ Absence of unpleasant odour, taste and irritating influence

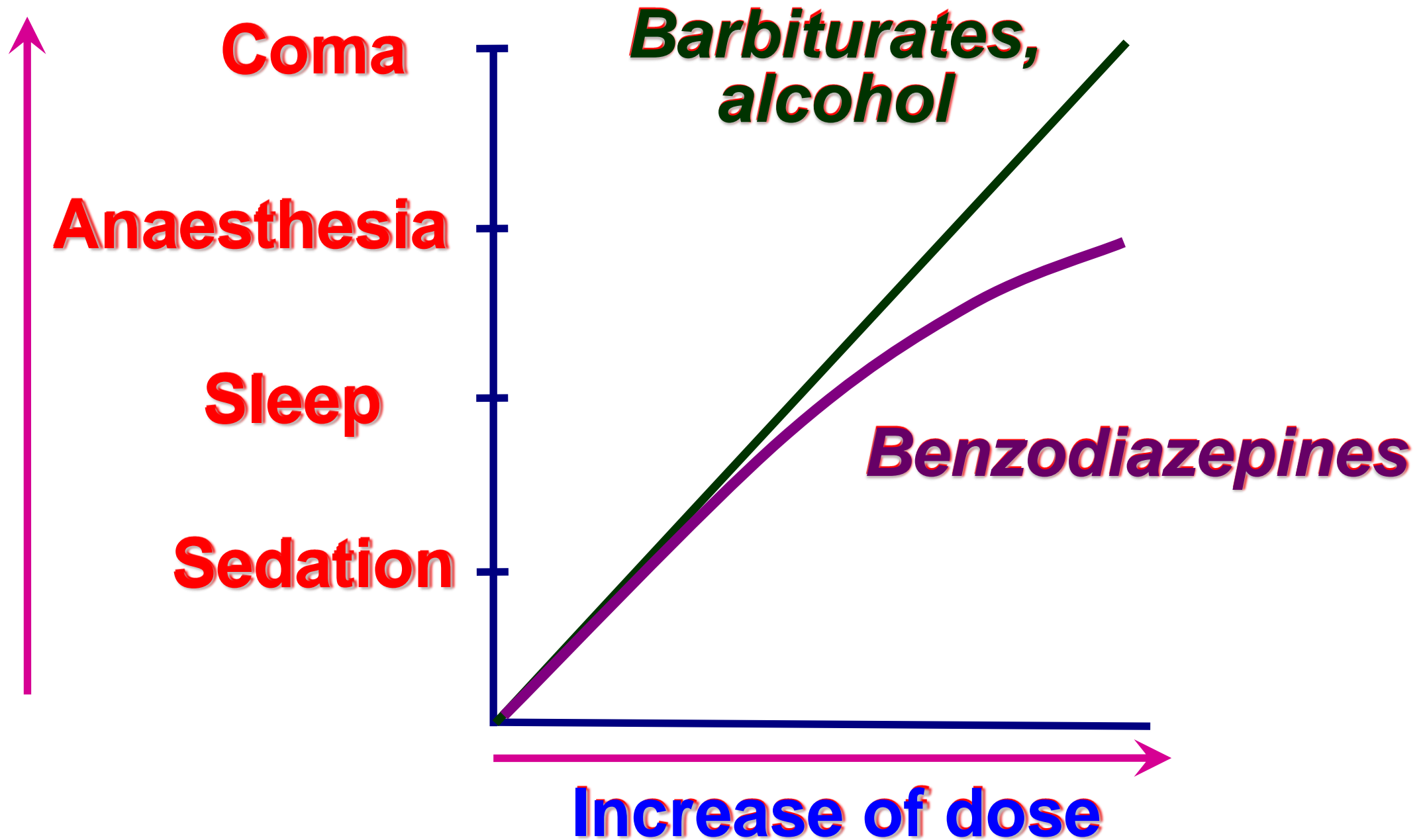




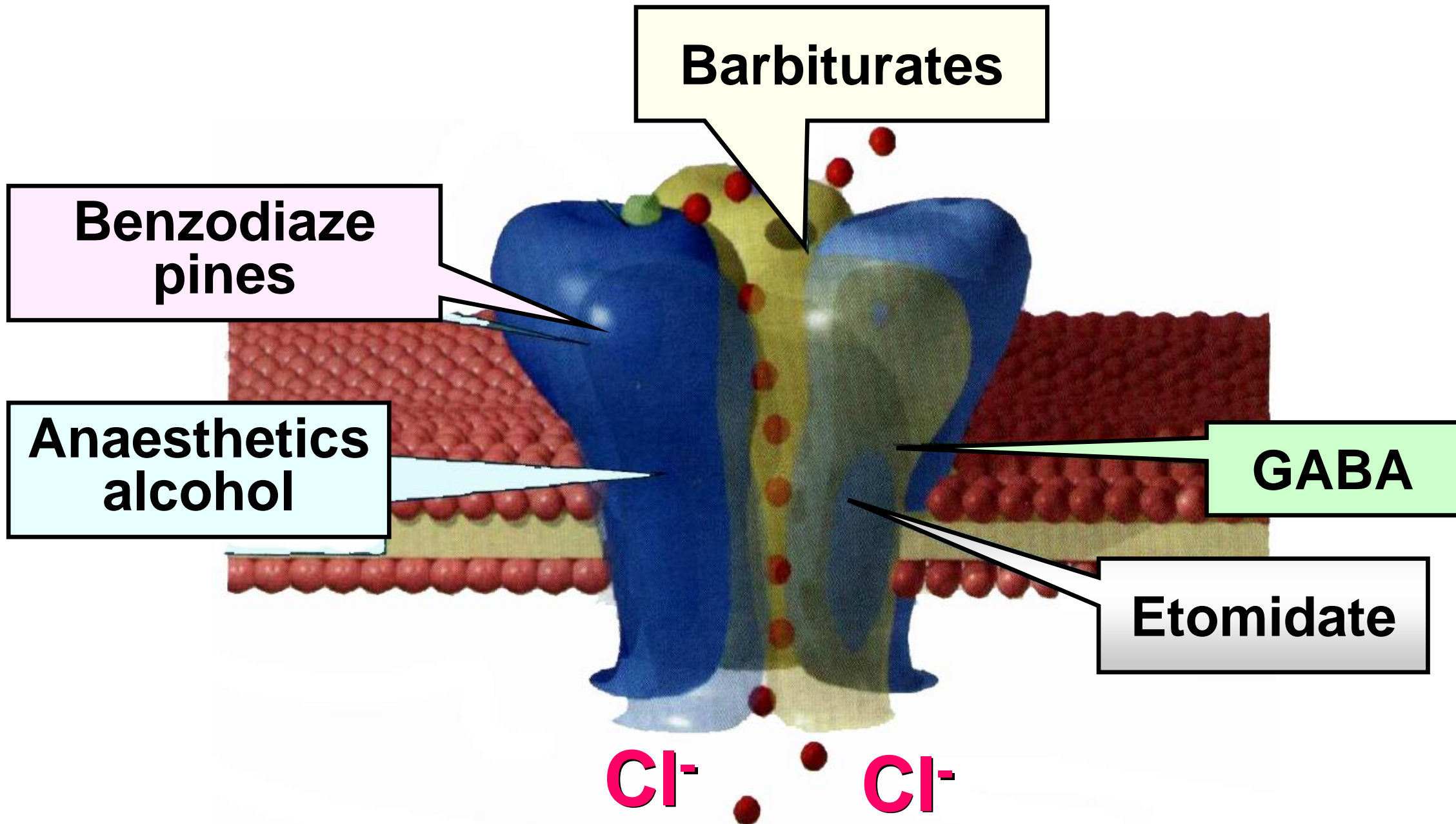
# CLASSIFICATION OF HYPNOTIC DRUGS

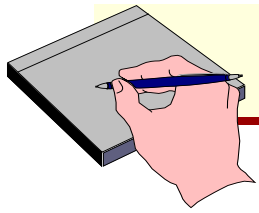
- **Derivatives of benzodiazepine (tranquilizers):** nitrazepam, phenazepam, flunitrazepam, alprazolam, triazolam
- **Derivatives of barbituric acids (barbiturates):** phenobarbital (luminal), relanorm (cyclobarbital+diazepam)
- **Derivatives of different chemical groups:**
  - cyclopirrilones** — zopiclone (imovan)
  - imidazopiridins** — zolpidem
  - pyrazolopirimidins** — zaleplone (andante)
  - ethanolamines** — doxylamine (donormil)
  - tiazoles** — clomethiazole (hemineurin)
  - aliphatics** — chloralhydrate, bromisoval

# DOSE-EFFECT DEPENDENCE FOR HYPNOTIC AND SEDATIVE DRUGS



# MODEL OF COMPLEX GABAA-RECEPTOR-CHLORIONIC CHANNEL





# BARBITURATES

## Classification

- long-acting (6–10 hrs) — phenobarbital
- middle-acting (4–6 hrs) — cyclobarbitol
- ultrashort-acting (30–40 min) — thiopental, hexenal

## Mechanism of action

- ✓ **GABA-mimetic action:**
  - interaction with barbituric receptors of GABAA-receptor-chlorionic channel ⇒
  - affinity of GABA to GABAA-receptors and the term of opening of chloride channels ⇒ ↑ inhibition influence of GABA in the CNS
- ✓ ↓ liberation of excitatory neurotransmitters (glutaminic, asparginic acids)
- ✓ ↓ system of wakefulness — reticular formation of the mesencephalone (sleep coming)
- ✓ ↓ hypnogenic zone of the hindbrain (fast sleep)



# PHARMACODYNAMICS OF BARBITURATES

## Influence on sleep structure

- ✓ ↓ process of falling asleep
- ✓ ↑ general term of sleep
- ✓ Substantially change sleep structure — ↑ duration of slow sleep, causing deficit of fast sleep — ↑ II and III stage due to reduction of I and IV stages of
- ✓ ↓ frequency and completeness of awakenings

**sedative** → **hypnotic** → **anaesthesia**

*doses smal*

*middle*

*large*

Cause also **anticonvulsive, myorelaxant action**



# PHARMACOKINETICS OF BARBITURATES

**Introduction:** peroral, absorption **in the stomach** (weak acids)

**Bioavailability:** depends on diseases of the liver

**Binding with proteins:** **5–75%**

**Distribution:** well penetrate through BBB, placenta!

**Biotransformation:** **strong inductors of enzymes of microsomal oxidation of liver!**

**Excretion:** by kidneys, partially with bile. The speed of inactivation depends on the structure of drug and functional state of the liver:  **$T_{1/2}$  cyclobarbital — 18 and 48 hrs in different people, phenobarbital — 4–5 days**

**Cumulation is pronounced!**



# ADVERSE EFFECTS OF BARBITURATS

- **Afteraction syndrome (hangover)**  
(apathy, drowsiness, weakness)
- **Somatic and neurological disturbances**  
(apnoea, ↓ ABP during sleep, depressions, disturbances of coordination, neurotrophic injury of joints, allergic reactions)
- **Tolerance**
- **Accelerated metabolism of other drugs**
- **Rebound syndrome**
- **Drug dependence (physical and psychical)**



# ACUTE POISONING BY BARBITURATES



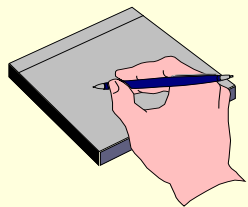
- **CNS** (depression of respiratory and vasomotor centers, coma)
- **System of respiratory organs** (bronchorrhea, pulmonary edema)
- **CVS** (heart failure, collapse)
- **Acid-base disturbance** (acidosis)
- **The urinary system** (anuria)
- **Other diagnostic symptoms** (miosis, then mydriasis, areflexia, hypothermia)

**Death from paralysis of the respiratory center!**

# EMERGENCY IN CASE OF POISONING BY BARBITURATES

- **Prevention of further absorption and acceleration of excretion (gastric lavage, adsorbents, salt laxatives, forced diuresis)**
- **Maintenance of basic vital function (i.v. introduction of sodium hydrocarbonate, adrenomimetics, dopamine, etc.)**
- **If necessary — AVL, hemosorption, hemodialysis**





# CLASSIFICATION OF BENZODIAZEPINES

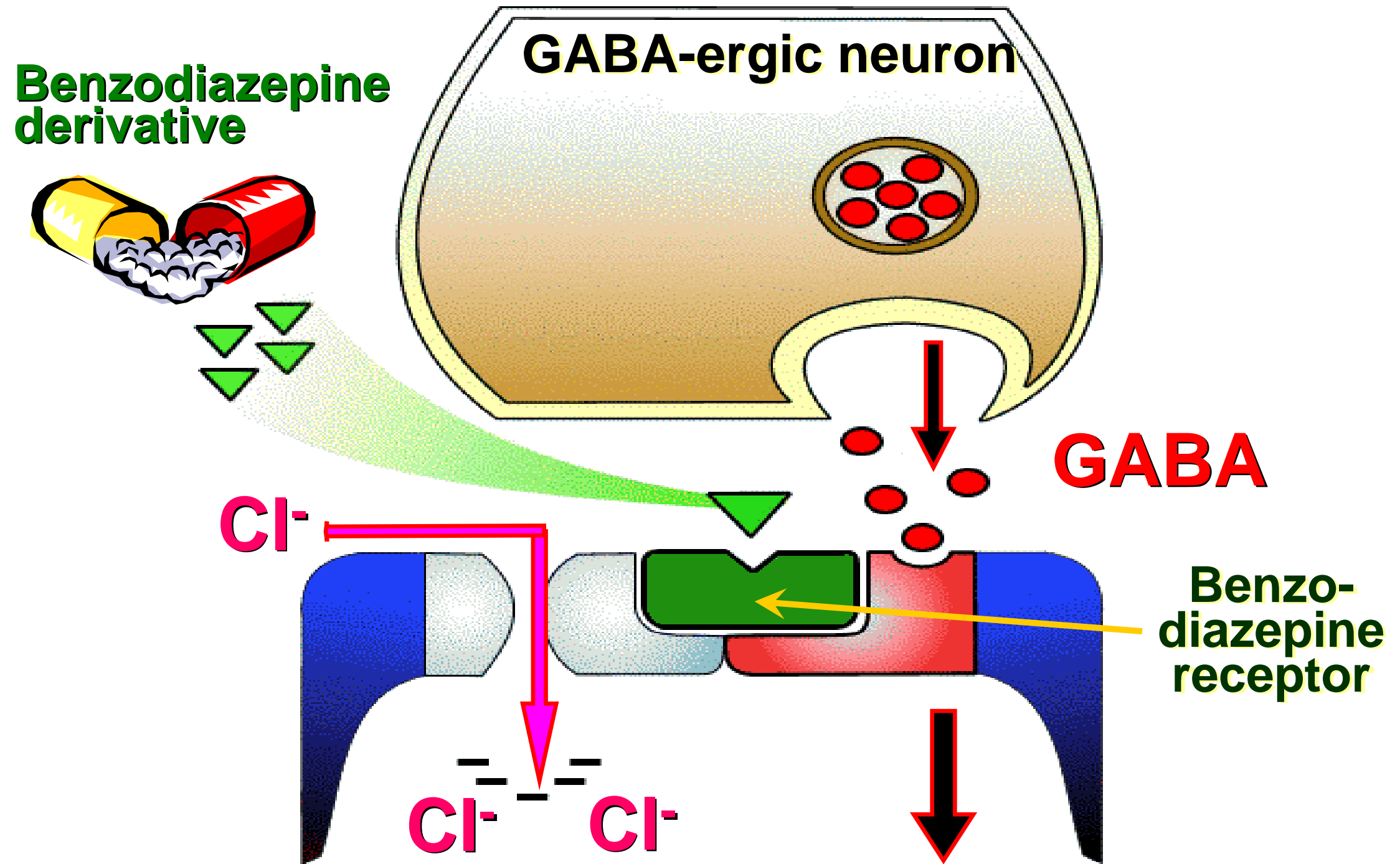
## According to chemical structure:

- **Derivatives of 1,4-benzodiazepine (typical)** — clordiazepoxide, diazepam (sibazon, seduxen), phenazepam, lorazepam, flurazepam, alprazolam, triazolam, etc.
- **Derivatives of different chemical groups (atypical)** — mebikar, grandaxin, amizil, lironit, phenibut

## According to spectrum of the sedative-hypnotic action:

- **Sedative (“large”, night)** — nitrazepam, flurazepam, diazepam, phenazepam, etc.
- **• Day (“small”), having stress-protecting activity with activating component** —

# MECHANISM OF BENZODIAZEPINES ACTION





# TRANQUILIZERS AS HYPNOTICS

## Influence on sleep structure

- ✓ ↓ a process of falling asleep
- ✓ ↑ general term of sleep
- ✓ ↓ fast phase of sleep
- ✓ In the part of slow sleep the II (non-deep) stage prevails due to reduction of the I, III and IV stages
- ✓ ↓ frequency and completeness of awakenings

## Advantages over barbiturates

- Less pronounced suppression of fast phase of sleep
- Sleep is more superficial than with intake of barbiturates, ↓ probability of apnoea and other complications

# PHARMACOKINETICS OF BENZODIAZEPINES

**Absorption:** in the duodenum (weak bases); time of absorption with **per oral and i/m intake** is almost the same! (peak of concentration is in 0.5–4 hrs)

**Binding with proteins:** 60–95%

**Distribution:** penetrates well through **BBB, placenta!**

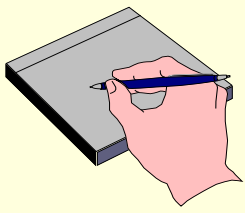
**Biotransformation in the liver:**

— **short-acting (triazolam):** conjugation with glucuronides formation;

— **long-acting (diazepam):** at first they undergo the microsomal oxidization of the liver (**N-dealcylicizing and hydroxylizing**) with formation of active metabolites (diazepam → ordiazepam → oxazepam), then conjugation → lucuronides

**Excretion:** as glucuronides by kidneys **T<sub>1/2</sub>:**  
**triazolam** — 1.5–3 hrs, **diazepam** — about 40 hrs





# CLASSIFICATION OF BENZODIAZEPINES

## According to the term of action

- **Short-acting ( $T_{1/2}$  up to 6 hrs):**  
triazolam
- **Intermediate-acting ( $T_{1/2}$  = 6–24 hrs):**  
lorazepam, nozepam (oxazepam),  
flunitrazepam, etc.
- **Long-acting ( $T_{1/2}$  = over 24 hrs):**  
nitrazepam, fenazepam, diazepam,  
flurazepam, etc.

# COMPARATIVE CHARACTERISTICS OF HYPNOTIC DRUGS

<b>Drug</b>	<b>Ways of introduction</b>	<b>Additional application</b>	<b>Durations, hrs</b>
<b>Nitrazepam</b>	<b>Per os</b>	<b>Neurosis, alcoholic abstinence</b>	<b>6-8</b>
<b>Zolpidem</b>	<b>Per os</b>	<b>-</b>	<b>2-3</b>
<b>Zopiclon</b>	<b>Per os</b>	<b>-</b>	<b>4-5</b>
<b>Phenobarbita</b>	<b>Per os</b>	<b>Prophylaxis of seizures, epilepsy</b>	<b>6-8</b>
<b>Chloralhydrate (rarely)</b>	<b>Per os, rectal (coating)</b>	<b>Seizures</b>	<b>8-10</b>

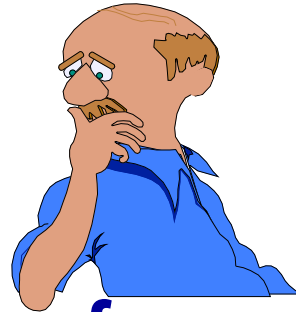
# APPLICATION OF HYPNOTIC DRUGS

- ✓ **Insomnias**
- ✓ **Neuroses and psychopathies**
- ✓ **The abstinence syndrome**
- ✓ **Symptomatic therapy  
of seizures, epilepsy**
- ✓ **Premedication**
- ✓ **Postoperative period**
- ✓ **For potentiating effects of analgesics  
and other substances which depress CNS**



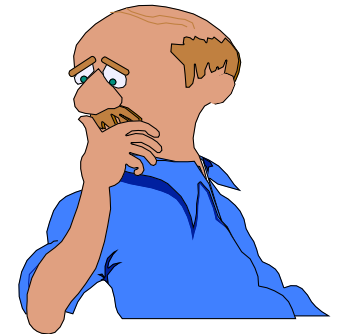
# FUNDAMENTALS OF HYPNOTIC DRUGS PHARMACOLOGY

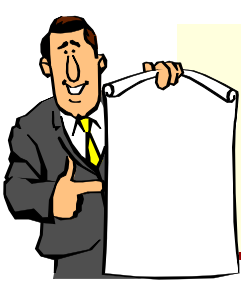
- Hypnotic drugs cause **sleep cycles disturbances** by way of ↓ of the REM-phase, as well as the delta-sleep
- Stoppage of the hypnotic drugs intake leads to ↑ REM-phase (**rebound phenomenon**). During REM-phase vegetative and hormonal phases of an organism ↑ ⇒ **risk of stroke and myocardial infarction** ↑
- **With regular intake** of hypnotic drugs periods of falling asleep and night awakening ↑ ⇒ **the general duration of insomnias** ↑, which is more than that one in patients who don't take hypnotic drugs
- As a rule, the affect of hypnotic drugs ↓ in 2 weeks ⇒ patients increase the dose for themselves, intake additional medicines or stimulate the affect of hypnotic drugs by **alcohol addiction**, which sharply ↑



# FUNDAMENTALS OF HYPNOTIC DRUGS PHARMACOLOGY

- Drug **dependence** appears in case of prolonged intake of hypnotic drugs
- Some hypnotic drugs (barbiturates) excrete from an organism fast. With repeated intake their **cumulation** takes place. The risk of intoxication ↑ with the age ⇒ barbiturates are contraindicated after 60 years old
- A majority of hypnotic drugs have **aftereffect**, or hangover (fatigue, feeling jaded, working ability ↓, etc.)
- **Drivers** should be especially **careful** with hypnotic drugs
- Alcohol ↑ hypnotic drugs effect ⇒ simultaneous intake of these medicines and alcohol is **contraindicated**





# BASIC PRINCIPLES OF HYPNOTIC DRUGS

- **Emotional** — psychosedatives, benzodiazepines of short action
  - **Geriatric** — benzodiazepines of middle and short action, ZZZ-preparations (zopiklon, zolpidem, zaleplon)
  - **Pathological** — therapy of the basic disease
- 
- ✓ Duration of treatment course is no more than 3 weeks (**optimally 10–14 days**)
  - ✓ The presence of pauses in the medical treatment is necessary (**“medicinal vacations”**)
  - ✓ The patients of elderly age are appointed **a half dose**
  - ✓ With apnoe in sleep **ZZZ-preparations** are better

# CLASSIFICATION OF ANTICONVULSANT DRUGS

**For reduction of seizures** — **barbiturates** (phenobarbital, hexenal), **benzodiazepines** (diazepam, phenazepam), **chloralhydrate**, **sodium oxybutyrate**, **lidocaine**, **magnesium sulfate**, **nitrous oxide**, **myorelaxants**

**Antiepileptic** — **valproats** (sodium valproat), **benzodiazepines** (clonazepam, diazepam), **barbiturates**, **suximides** (etosuximide), **carbamazepine**, **diphenine** (phenytoin), **trimetine**

**Antiparkinsonic** — **central M-cholinolytics** (cyclodol, tropacin), **dopaminomimetics** (levodopa, nacom, sinemet, bromocriptine)

**For treatment of spasticity** — **benzodiazepines** (diazepam, fenazepam), **GABA-ergic** (fenibut, baclofen), **dantrolen**, **midocalm**

# BASIC MECHANISMS OF ANTICONVULSANT DRUGS

- ✓ **Facilitation of the GABA-dependent (inhibitor) transmission — barbiturates, benzodiazepines, valproate**
- ✓ **Depression of excitant (usually glutamatergic) transmission**
- ✓ **Modification of ionic currents — magnesium sulfate, lidocaine, suximides, difenine, carbamazepine**

# EPILEPSY

– Group of chronic convulsive pathology with sudden attacks (fits) with the loss or disorder of consciousness accompanied with convulsions and spontaneous hyper reactivity

Generalized attacks		Partial (focal) seizures
large	small	
<p><b>Tonicoclonic seizures</b> with the sudden loss of consciousness up to 10–15 min (<b>grand mal</b>)</p>	<p><b>Absans</b> — sudden short-term loss of consciousness (<b>petit mal</b>)</p> <p><b>Akinetic</b> — sharp short-term decrease of muscular tone</p> <p><b>Myoclonic</b> — small rhythmic twitches of muscles</p> <p><b>Hypertensive</b> — short-term tonic tension of muscles</p> <p><b>Infantile spasms</b> — epileptic syndrome</p>	<p><b>Simple</b> — forms:</p> <ul style="list-style-type: none"> <li>motive</li> <li>sensitive</li> <li>psychic</li> <li>vegetative-</li> <li>visceral</li> </ul> <p><b>Complex (mixed)</b></p> <p><b>Secondary generalized</b></p>

**Epileptic status** — prolonged attacks or those following in sequence with small intervals

# GENERAL PRINCIPLES OF EPILEPCY TREATMENT

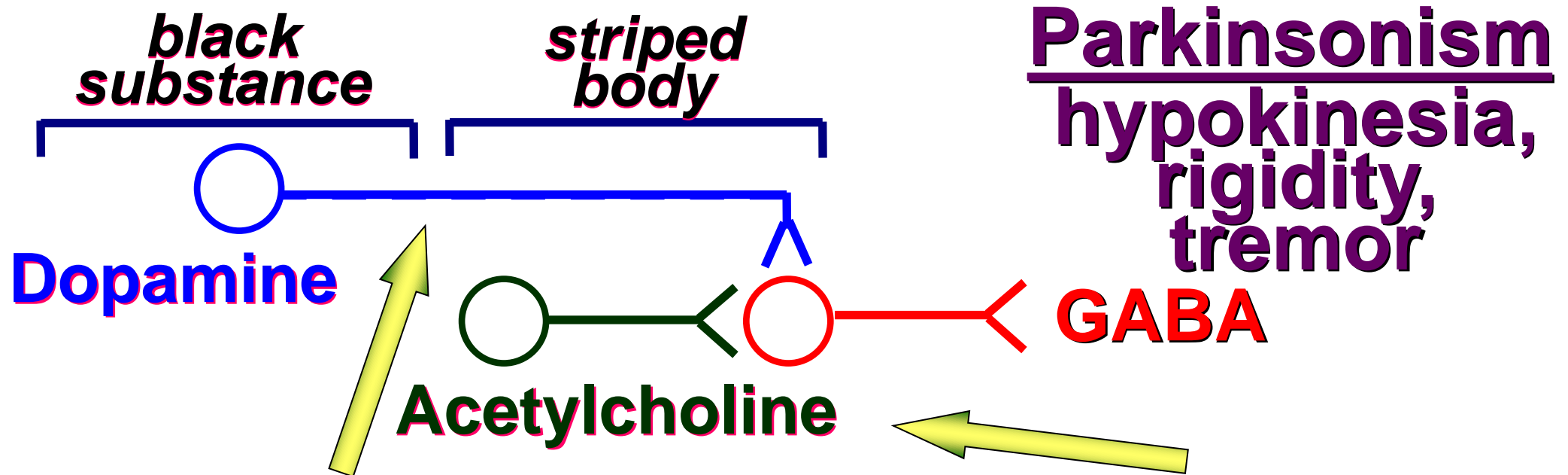
- **In-time diagnosis and early (strictly) individual (!) pharmacotherapy, especially in children**
- **If possible monotherapy**
- **Strict following the dosages and rhythm of drugs introduction (combination); transition from one to another takes place step by step**
- **Uninterrupted treatment continues for 3–4 years after disappearance of clinical signs of epilepsy; then during 1–2 years long gradual withdrawal**

# COMPARATIVE EFFICIENCY OF ANTIEPILEPTIC DRUGS

Drug	Generalized attacks		Parttial attacks
	large	small	
Sodium valproat	+++	+++	++
Clonazepam	+++	+++	++
Phenobarbital	+++	+	++
Phenytoin	+++	-	+++
Carbamazepine	+++	-	+++
Etosuximide	-	+++	-

**With epileptic status —** i.v. introduction of diazepam (10–30 mg), phenytoin (13–18 mg/kg), phenobarbital (500 mg), lidocaine, etc.

# ANTIPARKINSONIC DRUGS



## Dopaminomimetics

## Central M-cholinergic antagonists

*indirect*

*direct*

Levodopa and combined with periph. inhibitor of dopa-decarboxylase (nacomsinemet), midantan, selegidin

Bromocriptine, apomorphine

Cyclodol, norakin, tropacin