PSYCHOTROPIC AGENTS

NEUROLEPTICS.
TRANQUILIZERS.
PSYCHSEDATIVES

NEUROLEPTICS (ANTIPSYCHOTICS) –

neuron – nerve; lepticos – hold

Psychosis is a form of disorder in which the patient's mental reactions are strongly contrary to reality.

- **Psychoses are classified according to their origin (etiology) and causes (pathogenetic mechanisms of development)**

- **endogenous (including endogenous psychoses include schizophrenia, schizoaffective disorder, some psychotic forms of affective disorders)**
- **organic, somatogenic, psychogenic (reactive, situational), intoxication, withdrawal and post-withdrawal symptoms.**

NEUROLEPTICS (ANTIPSYCHOTICS) –

neuron – nerve; lepticos – hold

Psychotropic agents that inhibit CNS, remove hallucinations, delusion without inhibition of conciseness

5 signs (J. Delay and P. Deniker):

- remove psychosis (antipsychotic action)
- abort psychomotor excitement of different origin
- predominantly influence on subcortex structures of the brain
- possible psychodysleptic action without hypnotic action
- oftenly produce neurologic and neurovegetative reactions

(3 «H»: hypodynamia, hypothermia, hypotension)

HISTORY OF NEUROLEPTICS DISCOVERY

1950 y. in Paris was synthesized a derivative of phenothiazine – chlorpromazine

1952 y. J. DELAY, P. DENIKER showed its effectivnes

1957 y. they proposed a name «neuroleptic» («that take nerve»), decribed its actions

1958 y. was discovered first antipsychtic neuroleptic – haloperidol

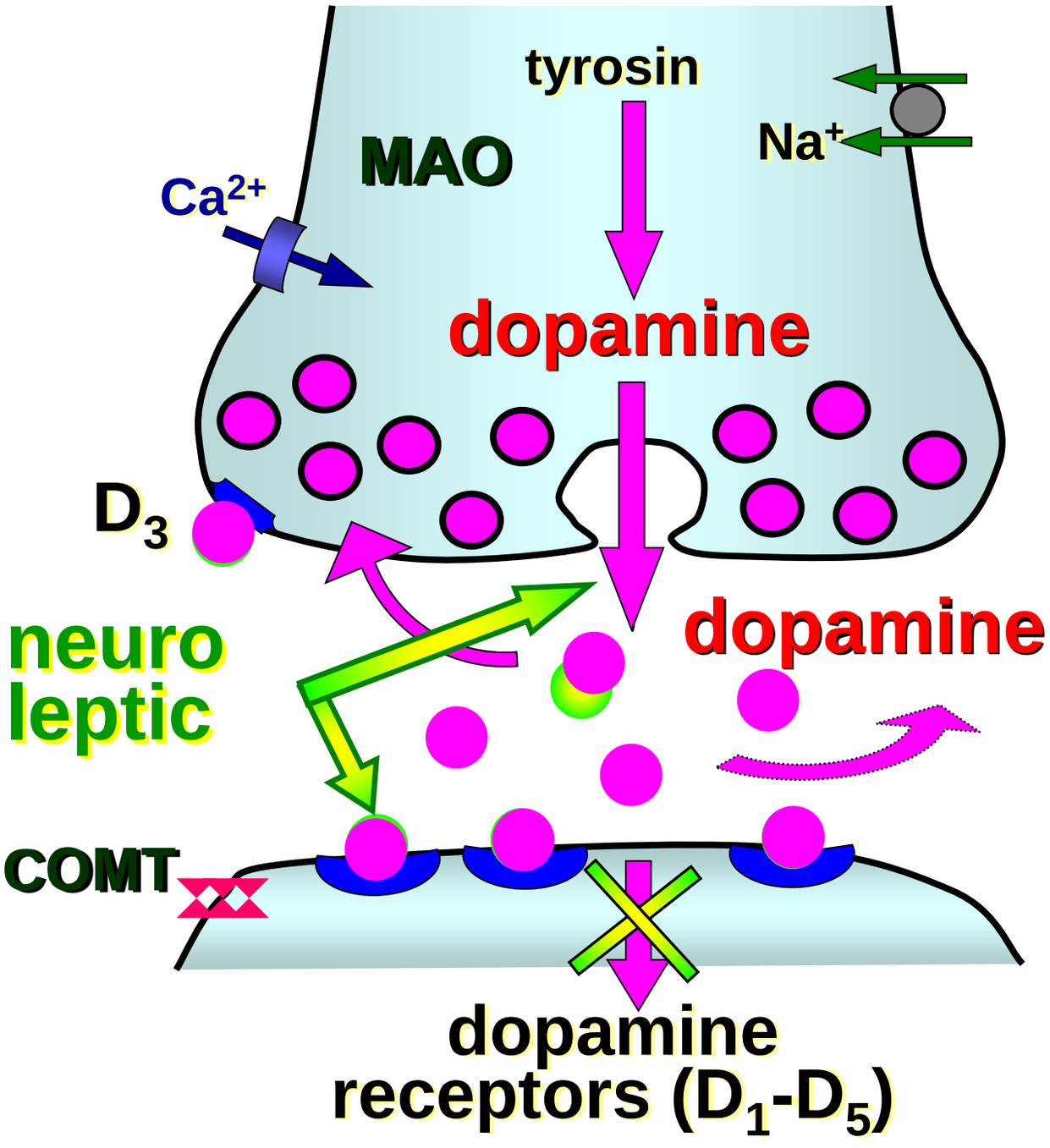
1966 y. was synthesized founder of benzamids - sulpirid

1968 y. first atypical neuroleptic – clozepin (free from extrapyramidal disturbances)

CLASSIFICATION OF NEUROLEPTICS

- derivatives of **phenothiazins** (typical neuroleptics)
  - ✓ ***alyphyatic*** – chlorprominazin (aminazin), levomepromazin
  - ✓ ***piperazin*** – ethaperazinн, triphtazin
  - ✓ ***piperidin*** – neuleptil
- derivatives of **buterophenone** – haloperidol, droperidol
- derivatives of **benzamid** – sulpirid, metoclopramid
- derivatives of **piperidin** – fluspirilen, pimosid
- derivatives of **different chemical groups** – reserpin, clozepin, olenzepin etc

MECHANISM OF ACTION OF NEUROLEPTICS



Main dopaminergic routes
Mesolimbic and mesocortical systems (antipsychotic action, mental depression)
Hypothalamus-pituitary (hypothermia, ↑ prolactin)
Extrapyramidal system (symptoms of parkinsonism)
Trigger zone of vomiting center (antiemetic effect)

SPECTRUM OF PSYCHOTROPIC ACTION OF NEUROLEPTICS

chlorpromazin – $\alpha > 5\text{-}HT_2 \geq D_2 > D_1$

haloperidol – $D_2 > D_1 = D_4 > \alpha_1 > 5\text{-}HT_2$

antipsychotic

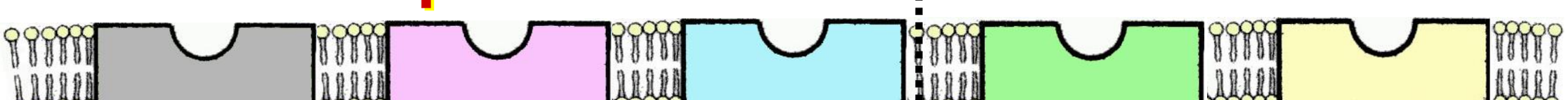
sedatives:

droperidol > aminazin > chlorprotixen > clozepin > neuleptil

antipsychotics:

haloperidol > pimozid > fluspirilen > triftazin > etaperazin > sulpirid

neuroleptic



H_1- M- α- $D_{1,2,3,4,5}$- $5HT_2$-

PHARMACODYNAMICS OF NEUROLEPTICS

neuroleptic (sedative)

- ✓ apathy, drowsiness, lethargy
- ✓ depression of initiative, “paralysis” of will, emotional indifference to environment
- ✓ inhibition of motor activity
- ✓ quick onset of action
- ✓ vegetative disturbances (collaptoid reaction etc), especially at the beginning of treatment

antipsychotic

- ✓ removing of persistent changes of personality and asocial features of behaviour
- ✓ removing of hallucination, delirium
- ✓ enhancement of motives and initiative, interest to surrounding
- ✓ develops in 1–2 weeks
- ✓ extrapyramidal disorders (increasing during the therapy course)

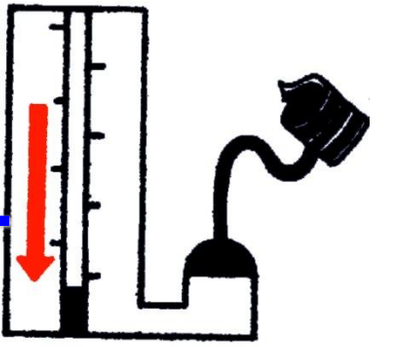
PHARMACODYNAMICS OF NEUROLEPTICS

CNS:

- **hypothermia** (↓ the center of heat release because of blockade of α-adreno- and serotonin receptors of hypothalamus + dilatation of the skin vessels)
- **hypodynamia** (muscular tone as a result of activating influence of reticular formation and spinal cord through α-adrenoblockade)
- **antivomiting** (anti-emetic) **and antihiccup effects** (blockade of D_2-receptors of the trigger zone of the vomiting center)
- **disorders in the motor sphere with systematic intake:** parkinsonism, acute dystonia, tardive dyskinesia, etc. (D_2-receptors blockade of extrapyramidal system)
- **potentiation of anaesthesia and analgesia, especially with sedatives** (blockade of α-adrenoreceptors of the reticular formation and ↓activating influence on the cerebral cortex)

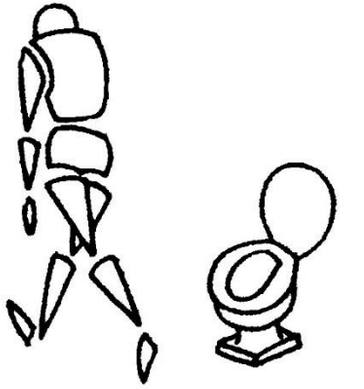
PHARMACODYNAMICS OF NEUROLEPTICS

Vegetative reactions:



- acute hypotension, ↑ HR
- ↓ tone of hollow organs, motility and GIT secretion
- disturbance of accommodation, dry mouth

Endocrinic and other disorders:



- ↑ prolactin, ↓ gonadotropins, estrogens, gestagens
- in women — amenorea, ↑ libido; in men — gynecomastia, impotence
- ↓ STH, ACTH, ADH, oxytocin
- ↑ melanostimulating hormone
- ↑ appetite and body weight antiallergic and antipruritic action (H_1-receptors blockade)

PHARMACOKINETICS OF NEUROLEPTICS

Administration: **with oral administration absorption is unpredictable (first pass metabolism, change of GIT motility because of cholinolytic action; partial biotransformation in the intestine), bioavailability – 30-60 %; at I.M. – ↑ in 10-40 times, but also is unpredictable (precipitation in the muscle)**

Plasma protein binding: **90-95 %**

Distribution: **accumulate in tissues of the brain, lungs and other well vascularized organs; penetrate well through the BBB, placenta; penetrate well through the BBB, placenta!**

Biotransformation: **takes place by various ways (oxidization, conjugation) not only in the liver, but also in the lungs, brain, kidneys and intestine with formation of active and nonactive metabolites**

Excretion: **via the kidneys and bile mainly as nonactive metabolites; *T ½:* in majority – 20-40 hrs ⇒ there are slow-release forms –flushpirilen, pimozide (4-20 days)**

APPLICATION OF NEUROLEPTICS

- schizophrenia
- attack (relapse) of endogenous psychoses with delirium, hallucinations, aggressiveness
- acute psychical disorders (psychologic traumatic situations, traumas)
- delirium, abstinence syndrome — haloperidol, sedative neuroleptics
- neuroleptanalgesia — haloperidol, droperidol in combination with opioids (fentanyl) and premedication
- vomiting of the central origin, hiccup (chemotherapy of oncologic patients) — pimozide, haloperidol, etaperazine

APPLICATION OF NEUROLEPTICS

- shock (traumatic and burn) — droperidol, aminazine
- hypertensive crisis — levomepromazine, droperidol, aminazine
- hyperthermia (resistant to NSAIDs) — aminazine
- vegetoneuroses (ischemic heart disease (IHD), peptic ulcer, climax) — sulpiride, thioridazine
- neurodermatosis (pruritis) — aminazine, levomepromazine, chlorprotixen
- migraine — sulpiride
- in gastroenterology — metoclopramide

ADVERSE EFFECTS OF NEUROLEPTICS

- “behavioral” affects like “pseudodepressions” (flaccidity, lack of initiative, indifference, etc.)
- as a result of dopamine blockade extrapyramidal disorders (neuroleptic syndrome):

  at the early stages: parkinsonism (rigidity, tremor)

  at the late stages (in months and years), tardive dyskenesis (winking, spasm of eyelids, choreoatetosis as usual in women)

- malignant neuroleptic syndrome (malignant hyperthermias) — rigidity of muscles, high temperature, arrhythmia, coma

ADVERSE EFFECTS OF NEUROLEPTICS

- collapse (α-adrenoblockage)
- M-cholinolytic action (dryness of mouth, mydriasis, urine retention, constipation etc.)
- endocrinic disturbance:
  - ✓ «castration effect» (dopamine blockade ⇒ ↑ prolactin,↓ gonadotropic hormones, in women galactorrhea, amenorrhea, in men gynecomastia, ↓ libido, importance)

- hepatotoxicity (cholestatic hepatitis)
- cardiotoxicity
- allergic reaction (rush, hemolysis, agranulocytosis)
- corneal and lenticular opacity (20-30 %)
- teratogenic, embryo-, fetotoxic action
- local irriation (phenothiazinese)

A PERFECT NEUROLEPTIC

- a broad spectrum of clinical action
- efficiency with different variants and stages of schizophrenia
- rapid relief of psychomotor excitation with normal wakefulness of patients
- long-term application without development of tolerance
- administration 1 time a day or rarer (for long-acting drugs)
- low toxicity (absence of extrapyramidal and other somatoneurologic effects)
- minimal number of drug interactions

TRANQUILIZERS (ANXIOLYTICS)

tranquillium — rest; *anxious* — warried, frightened
ataractics (ataraxia — coolness*)*

– depriming psychotropic drugs, selectively removing emotional instability, anxiety, fear (phobia), tension

HISTORY OF CREATION

1954 г. a new tranquilizer meprobamate was introduced in the USA

1957 г. swiss scientists synthesized the first tranquilizer from a series of derivatives of 1,4-benzodiazepine — chlordiazepoxide (elenium)

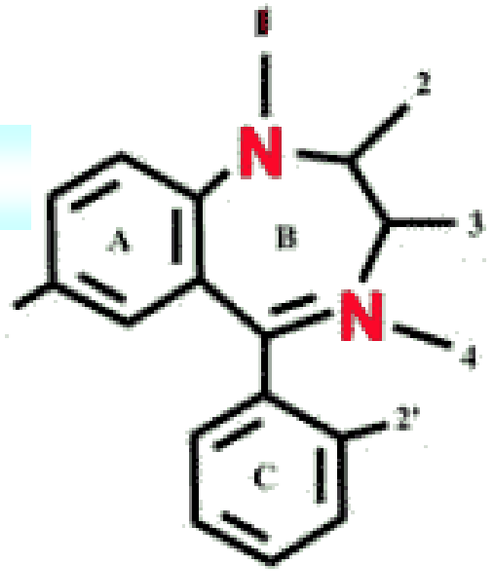
1963 г. diazepam (valium) was applied

CLASSIFICATIONS OF TRANQUILIZERS

historically:

- **I generation**: meprobamate, hydroxizine (atharax), amizil, (benactizine), mebicar, etc.
- **II generation**: benzodiazepine derivatives (chlordiazepoxide, diazepam, etc.)
- **III generation**: buspirone, etc.

according to chemical structure:



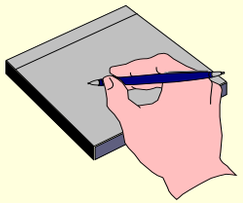
- **benzodiazepine derivatives (typical)**– chlordiazepoxide, diazepam, phenazepam, lorazepam, flunitrazepam, alprazolam, etc.)
- **different chemical groups (atypical)** – buspirone, mebicar, amizyl, trioxaxine, oxalidine, meprobamate, etc

SPECTRUM OF TRANQUILIZERS' PHARMACOLOGICAL EFFECTS

- anxiolytic (reduction of anxiety + stress-protective + antiphobic)
- sedative
- hypnotic
- myorelaxant
- anticonvulsant
- vegetostabilizing
- amnestic (anterograde amnesia)
- activate action of hypnotics, narcotic analgesics, alcohol

according to spectrum of action:

- sedative («major», night) – nitrazepam, flurazepam, diazepam, phenazepam, etc.
- daily («minor») – mezapam, gidazepam, buspirone, mebicar

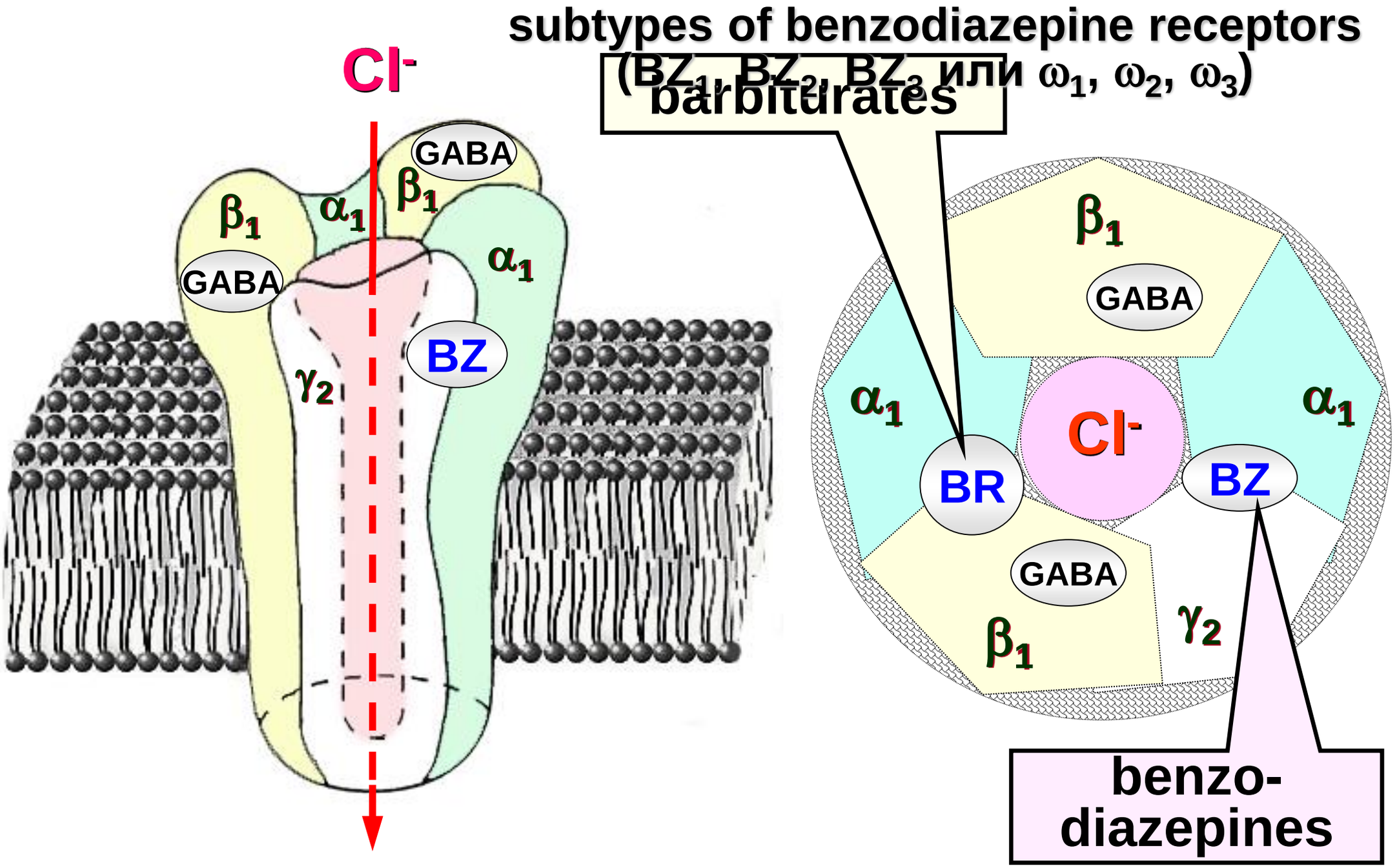


CLASSIFICATIONS OF TRANQUILIZERS

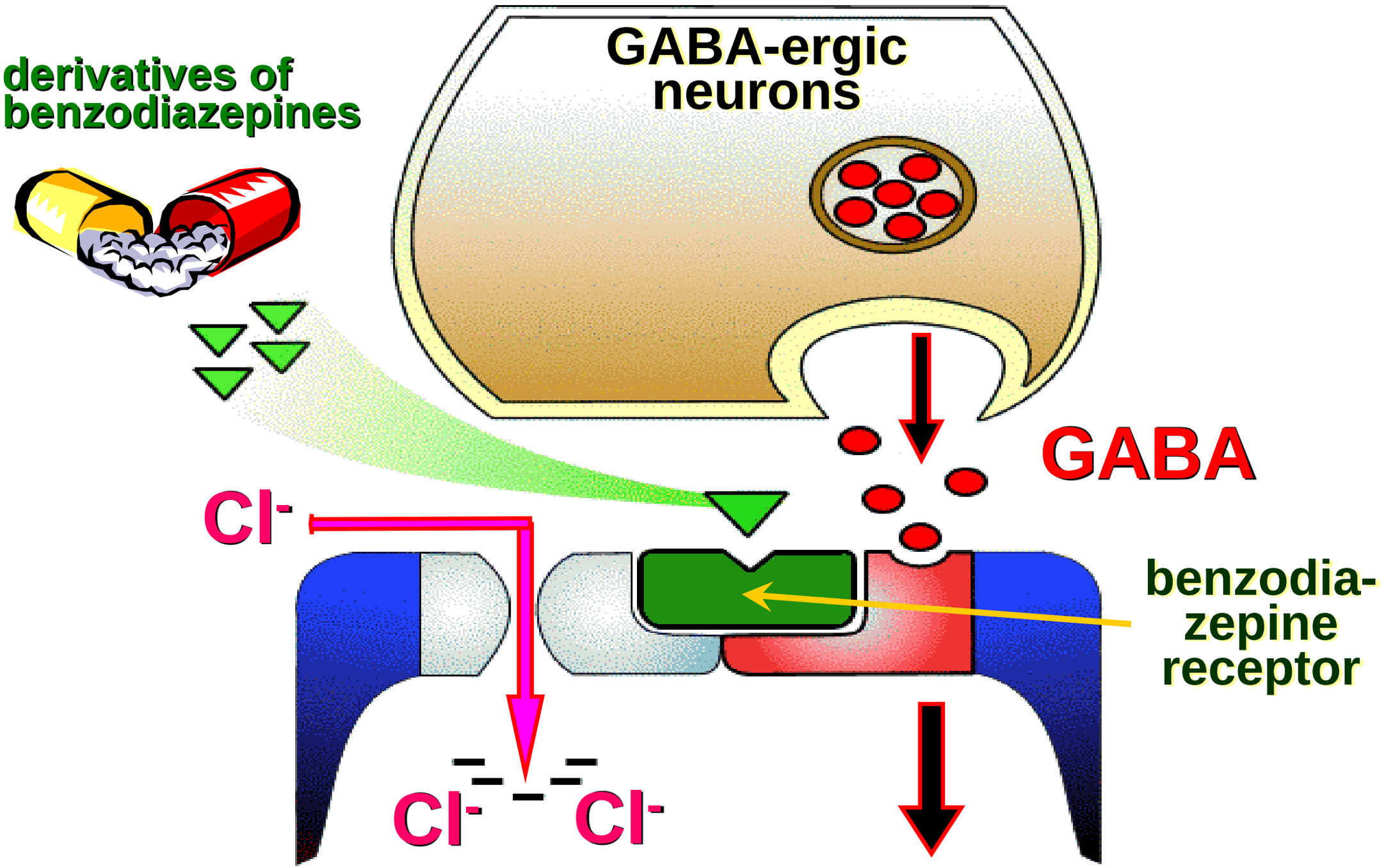
according to mechanism of action:

- direct agonists of benzodiazepine receptors* of the $GABA_A$-receptor-chlorionic channal – derivatives of benzodiazepine (diazepam, oxazepam, lorazepam, etc.)
- direct agonists of serotonine receptors– buspirone and others
- different mechanism of action– meprobamate, mebicar, trioxazine, oxilydin, etc.

MODEL OF THE COMPLEX GABA$_A$-RECEPTOR- CHLORIONIC CHANNEL



MECHANISM OF BENZODIAZEPINES ACTION



PHARMACODYNAMICS OF BENZODIAZEPINES

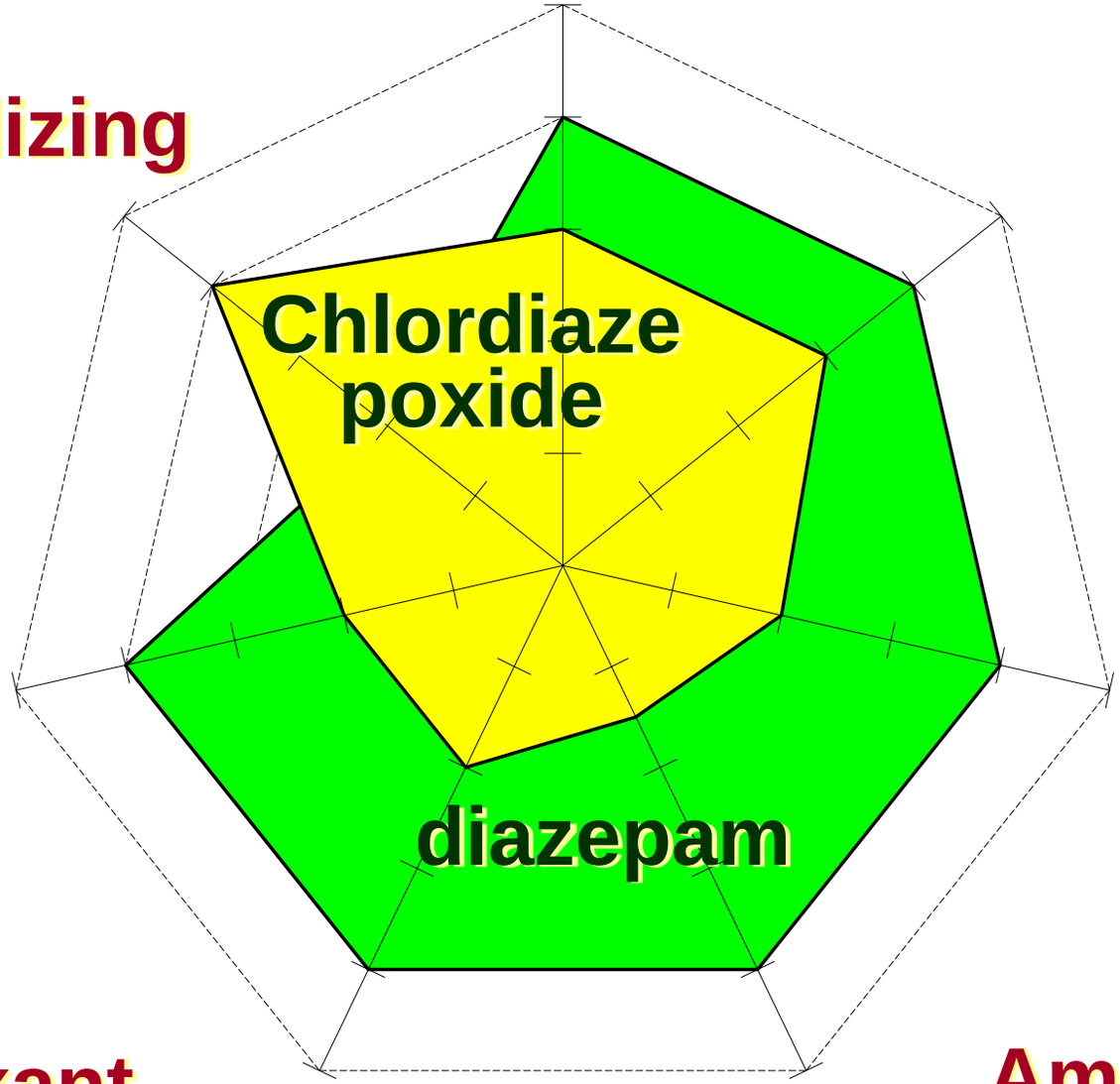
- benzodiazepine → stimulation of BZ-receptor of the
- complex GABAA-receptor-chlorionic channel ⇒
- ↑ sensitivity of GABA-receptors to GABA ⇒
- ↑ the rate of chlorine channels opening, which ↑ the entering current of Cl- ⇒
- hyperpolarization of the neuron postsynaptic membrane ⇒
- ↑GABA-transmission ⇒ inhibition process development in definite departments of the CNS (limbic system, cerebral cortex, hypothalamus, thalamus, reticular formation, spinal cord, etc.)
- ⇒suppressing effect on the emotional sphere (anxiolytic, sedative-hypnotic, amnestic), motor and vegetative systems (myorelaxation, relief of seizures, vegetostabilization)

SPECTRUM OF BENZODIAZEPINES' PHARMACOLOGICAL EFFECTS

Anxiolytic ***(reduction of anxiety + stress-protective + antiphobic)***

Vegetostabilizing

Sedative



Anticonvul-sive

Hypnotic

Myorelaxant

Amnestic

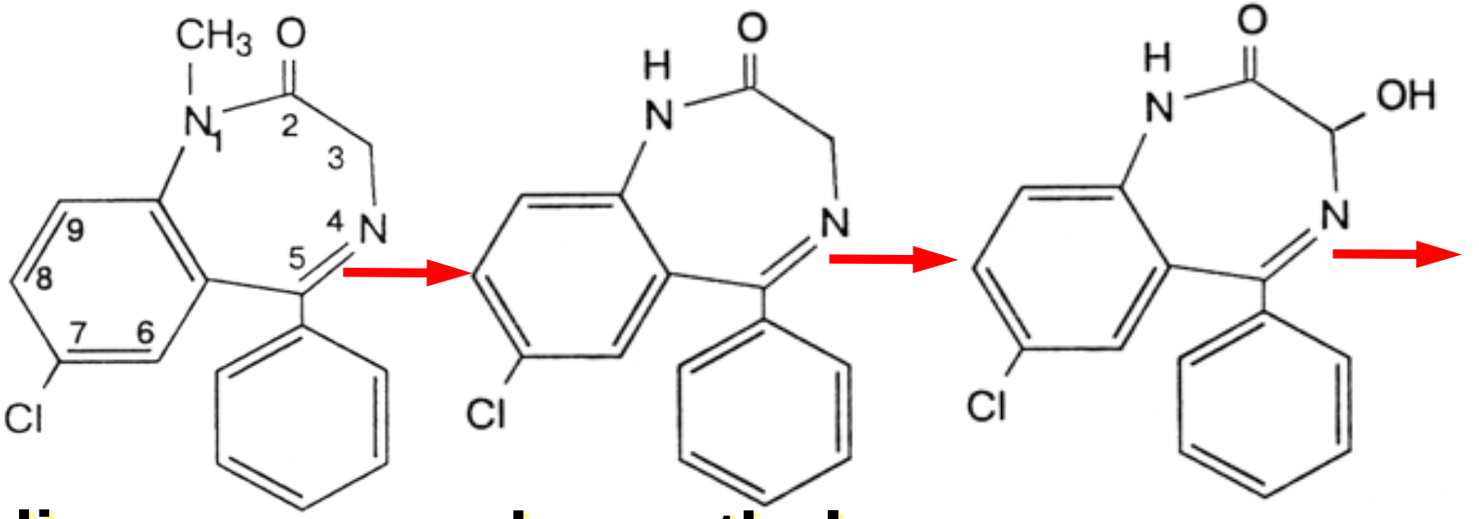
PECULIARITIES OF BENZODIAZEPINES' CLINICAL ACTION

- **with pronounced anxiolytic effect — phenazepam, diazepam, lorazepam, alprazolam, etc.; *moderate* — chlordiazepoxide, gidazepam, oxazepam, etc.; *"daily"* (anxioselectivity with activating component) — medazepam, tophizopam, gidazepam, etc.**
- **with pronounced hypno-sedative effect — nitrazepam, flunitrazepam, phenazepam, diazepam, lorazepam, chlordeazepoxide, oxazepam, triazolam, midazolam, etc.**
- **with pronounced anticonvulsant effect — clonazepam, diazepam, phenazepam, lorazepam, nitrozepam;**
- **with pronounced myorelaxant effect — diazepam, chlordeazepoxide, lorazepam, etc.**

PHARMACOKINETICS OF BENZODIAZEPINES

Phase I – microsomal oxidation

Phase II – conju-gation



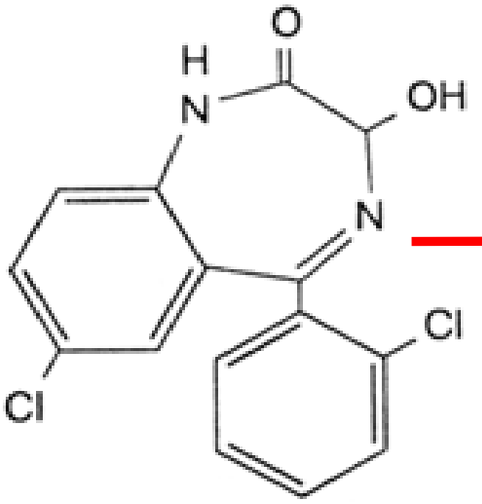
diazepame

desmethyl-diazepam

oxazepame

glucuro nides

Excreti on via urine



lorazepame

+ other metabolites via intestine

PHARMACOKINETICS OF BENZODIAZEPINES

Absorption: **in duodenum; time of absorption at oral and I.M. administration almost the same (peak of concentration after 0,5-4 hrs)**

Plasma protein binding: **60-95 %**

Distribution: **well cross placenta, BBB!**

Biotransformation: ***metabolized***

Excretion: **excreted mainly in the urine (about 70%) in the form of active or inactive metabolites. T½ may increase in newborns, elderly and senile patients, and in patients with liver or kidney disease.**

PHARMACOKINETICS OF BENZODIAZEPINES

T ½ depend on:

- ✓ **age (in newborns — 31, infants — 8–14, a 24–72, aged — 100 hrs)**
- ✓ **concomitant diseases of the liver, kidneys, etc.**

according to duration of action:

- **short acting ($T_{1/2}$ up to 6 hrs): triazolam, medazolam**
- **intermediate ($T_{1/2}$ – 6-24 hrs): lorazepam, oxazepam, flunitrazepam, etc.**
- **long acting ($T_{1/2}$ more than 24 hrs): nitrazepam, phenazepam, diazepam, flurazepam (prodrug, T1/2 ≈ 100 hrs), etc.**

APPLICATION OF TRANQUILIZERS

- all the kinds of phobic disorders (neuroses, psychopathy, accompanied with alertness, fear, emotional stress, etc.) - phenazepam, alprazolam, lorazepam
- anxiety with a background of depressive conditions of various genesis — with antidepressants alprazolam, lorazepam, oxazepam
- endogenic psychiatric diseases (schizophrenia) — diazepam, phenazepam, etc.
- acute conditions (psychomotor agitation, alcohol abstinence, delirium) — diazepam, phenazepam
- in somatic diseases therapy (IHD, peptic ulcer, hypertension, cholecystitis, bronchial asthma, etc.)

APPLICATION OF TRANQUILIZERS

- sleep disorders — nitrazepam, phenazepam
- epilepsy, epileptic status, seizures of various genesis, tetanus — clonazepam, diazepam, etc.
- neurologic disorders accompanied with muscular hypertonus — diazepam, lorazepam
- for premedication and anesthesia (atharalgesia — diazepam + phentanyl), during the postoperative period — flunitrazepam, midazolam, diazepam, etc.
- acute reactive stress conditions in healthy people in extreme situations (but not with everyday stress)

ADVERSE EFFECTS OF TRANQUILIZERS

- **"behavioral" reactions:** ↓ apprehensive and psychomotor processes, disturbance of orientation, anterograde amnesia
- **after-effect (hangover), especially in elderly people** (dose-dependent hypersedation, dysco-ordination of movement)
- **"paradoxal" reactions:** movement anxiety, nightmares, ↑ aggressiveness, inadequate conduction **(in children, elderly and mentally ill patients)**
- **tolerance**
- **drug dependence** (psychic and/or physical) neuroses-like. The risk of arising with administration for more than 6 months, especially high doses

ADVERSE EFFECTS OF TRANQUILIZERS

- rebound syndrome
- ↓ myocardial contractility, hypotension (diazepam, lorazepam with parenteral introduction in elderly people)
- moderate depressive influence on the respiratory center (in pulmonary patients)
- dry mouth, dyspepsia, ↑ appetite, ↑ intraocular pressure, impotence; seldom allergy, hematologic changes (leukopenia)
- teratogenic, embryo- and fetotoxic action

CLASSIFICATION OF PSYCHOSEDATIVES

- **plant-origin: valeriana, common motherwort, passiphlora**
- **bromides: potassium and sodium bromide**
- **combined:**

valocardin, corvalol (ethyl ether of bromine isovaleric acid + phenobarbital + oil of peppermint + ethanol),

valocormid (extract of valeriana, lily of the valley, belladonna, sodium bromide, mentol),

novopassit etc.

valeriana

motherwort

PLANT-ORIGIN PSYCHOSEDATIVES

pharmacodynamics

- ↓ excitability of reticular structure, medulla
- oblongata and hypothalamus
- ↑ threshold of neuronal excitability
- ↓ emotional and motive excitation
- ↓ threshold of convulsive activity
- (especially in children)
- adrenolytic activity (↓ ABP, “-” ino-, chronotropic
- effects)
- ↓ afferent impulsation to the cerebral cortex
- spasmolytic action (↓ vessels of the heart and brain,
- ↓ tone of smooth muscles of the intestine)
- potentiation of action of hypnotic drugs

PLANT-ORIGIN PSYCHOSEDATIVES

indications

- **insomnia** (caused by vegetative disorders)
- **emotional overexcitation**
- **neurotic disorders**
- **angina pectoris with background of neurotic disorders**
- **arrhythmias** (extrasystole, paroxysmal tachycardia)
- **initial stage of hypertension**
- **climacteric disorders**
- **intestinal colic** (especially in children) **insomnia** (due to vegetative disorders)

PLANT-ORIGIN PSYCHOSEDATIVES

Side effects

- Drowsiness
- depression,
- decreased performance
- with prolonged use – constipation
- Rarely - allergic reactions
- Enhances the effect of hypnotics and sedatives, antispasmodics

BROMIDES

pharmacodynamics

- facilitate all types of the internal (conditional) inhibition
- restore the mosaic of excitative and inhibition processes
- ↑ inhibition processes in the cortex
- facilitate differentiation, restore conditional-reflex activity
- ↓ excitability of motive neurons of the cortex and prevent from exhaustion (for example, at epilepsy)
- prevent or remove dysrhythmia of the brain, render an antiepileptic effect
- according to I. P. Pavlov: “strengthen assimilation processes in the neurons of cortex”
- the effects depend on the nervous activity type and its functional condition

BROMIDES

pharmacokinetics

Absorption: **well absorbed in the GIT; strong irritating effect on the mucous ⇒ as solutions, mixtures with starch; therapeutic effect comes in 2–3 days**

Distribution: **extracellularly; concentration in the brain is 3–4 times less than in the blood**

Excretion: **by the kidneys, and also by the glands (sweat, lacrimal, bronchial, salivary, mammary)**

T ½: **12 days, traces after a month; strong cumulation!**

indications

- **vegetative disorders**
- **emotional excitation**
- **neurasthenia, neuroses, hysterias**
- **spontaneous tachycardia**
- **convulsive states, in large doses at epilepsy**

BROMIDES

adverse effects

- general weakness, fatigue, indifference to surrounding,
- weakening of memory, drowsiness
- irritation of gastric mucous, anorexia, constipation
- excessive sweating
- sexual dysfunction (↓ libido, potentia)
- cumulation ⇒ acute and chronic poisoning (bromism): sleep, apathy, hallucinations, delirium, tremor of eyelids, tongue, hands, speech disorder, conjunctivitis, rhinitis, bronchitis, acne-like rash

bromism treatment

- withdrawal of drug
- antidote — sodium chloride (5–10 g on 3–4 l of liquid)
- diuretics (aminophyllin, ammonium chloride)
- hemodialysis
- symptomatic treatment