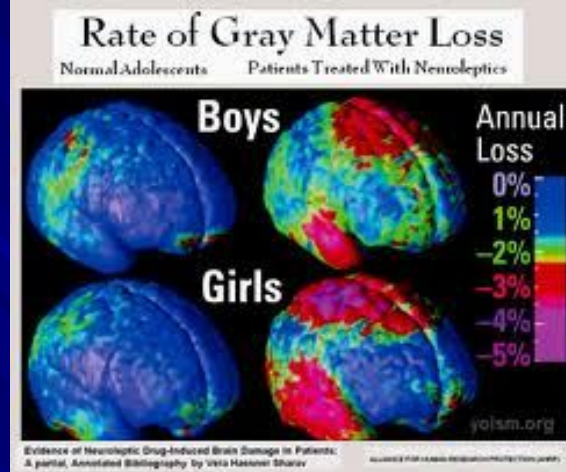


ZAPORIZHZHIA STATE MEDICAL UNIVERSITY
PHARMACOLOGY DEPARTMENT



Lecture № 5

**Neuroleptics, Lithium,
Tranquilizers, Sedatives.**

Lecturer – Associate Professor Irina Borisovna Samura



Neuroleptics (Antipsychotic Drugs)

I. Typical

- 1. PHENOTHIAZINES:

Aminazine (*Chlorpromazine*)

Triftazine

Fluphenazine (*Trifluoperazine*)

Thioridazine (*Sonapax*)

- 2. THIOXANTHENES:

Chlorprothixene

- 3. BUTYROPHENONES:

Droperidol

Haloperidol

II. Atypical

- 1. BENZAMIDES:

Sulpiride (*Eglonil*)

Tiapride

- 2. DIBENZODIAZEPINES:

Clozapine (*Leponex*)

- 3. OTHERS:

Risperidone



MECHANISM OF ACTION:

blockade of dopamine D₂-receptors

IN PERIPHERY :

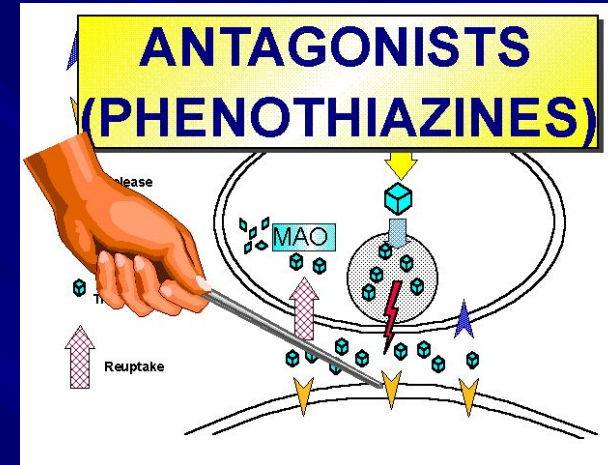
BLOCK :

M - Cholinoreceptors

α - Adrenoreceptors

H₁- Histamine Receptors

Serotonin (5-HT) Receptors



DIRECT SPASMOLYTIC ACTION

Pharmacological Effects:

Antipsychotic Actions:

↓ Hallucination and Agitation

Antiemetic Effects

Extrapyramidal Effects:

D₂-Rs blockade in the **Nigrostriatal Pathways** =>
=> **Parkinsonian Symptoms**

Anti-muscarinic Effects:

Blurred Vision, Dry Mouth, Sedation, Confusion,
Inhibition of GIT and Urinary Smooth Muscles

Mechanism of action and pharmacological effects of neuroleptics

→ **D₂-dopamine receptors blocking** -

▶ **in mesolimbic and mesocortical systems:**

- Antipsychotic effect.
- Emotional indifference.
- Depression.

▶ **Hypothalamus - hypophysis:**

- Decreasing of body temperature (hypotermia).
- Galactorrhea (increasing of prolactine production).

▶ **Extrapyramidal system:**

- Symptomatic parkinsonism, late (tarvide) dyskinesia.

▶ **Triger-zone of vomitive centre:**

- Anti-vomitive effect



Mechanism of action and pharmacological effects of neuroleptics

→ **H₁-histamine receptors blocking** -

- Sedative effect.
- Anti-vomitive effect.

→ **α₁-adrenoreceptors blocking** -

- Dilatation of blood vessels - decreasing of blood pressure, ortostatic collapse.

→ **5-HT-receptors blocking** -

- Bulemia - increasing of appetite, increasing of body weight.

→ **M-cholinoreceptors blocking** -

- Increasing of intraocular pressure.
- Decreasing of glands' secretion.
- Relacsation of smooth muscles, constipation.
- Decreasing of extrapyramidal side effects.

Extrapyramidal Effects:

due to **Blocking of D₂ receptors** in the **Nigrostriatal Pathway**:

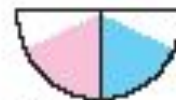
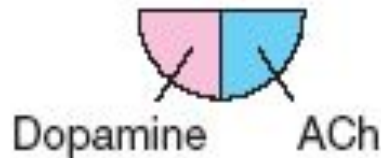
- **Parkinsonian Symptoms**
- **Akathisia** (Motor Restlessness) - the inability to sit still because of Uncontrollable Movement
- **Tardive Dyskinesia**: Inappropriate Postures of the Neck, Trunk, and Limbs
- **Malignant Neuroleptic Syndrome**:
Skeletal Muscle Rigidity, Hyperthermia, Stupor



less

sedating

strongly



Dopamine- = ACh effect



Dopamine- < ACh effect
→ extrapyramidal disturbances

Neuroleptics: Antipsychotic potency, sedative, and extrapyramidal motor effects

Clinical Uses of Neuroleptics



- 1. SCHIZOPHRENIA:

Positive Symptoms of Schizophrenia : DELUSIONS, HALLUCINATIONS and THOUGHT DISORDERS

Negative Symptoms of Schizophrenia: withdrawal, blunted emotions, reduced ability to relate to people

- 2. PREVENTION OF SEVERE NAUSEA and VOMITING:

Drug-induced nausea

- 3. OTHER USES: treatment of DRUG ADDICTION, ***NEUROLEPTANESTHESIA***, hypertensive crises

- Aminazine (Chlorpromazine) -**
blocks CNS D₂ receptors
- **α-Recetor** and **GANGLIONIC BLOCKADE**
 - □ **HISTAMINE-** and **SEROTONIN** -mediated activity.

It has great:

Sedative,
Hypotensive,
Antiallergic,
Anticonvulsant activity

It may produce **Galactorrhea** (excessive production of milk – due to □Prolactin release)

Clinical uses: Schizophrenia,
Acute Psychosis in Severely Agitated Patients

DROPERIDOL amp. 0.25%-10 ml –

a BUTYROPHENONE derivative,
more potent and to have fewer autonomic effects than other
typical neuroleptics.

It blocks subcortical D_2 and α -adrenergic receptors, and
blocks CNS receptors at the CTZ.

It has **no CholinoBlock action**.

The drug produces marked sedation and has an antiemetic
effect.

IM injection: Sedation begins in 3-10 min,
peaks at 30 min, and lasts for 2-4 hrs.

CLINICAL USE: a drug of choice at

NEUROLEPTANESTHESIA –the combination of neuroleptics
with opioid analgesics, **FENTANYL**.

Anesthetic Premedication,
Maintenance of General Anesthesia.

Lithium Salts

Lithium Carbonate – Caps. 0.15 and 0.3 g; Tab. 0.3 g

Lithium Citrate – Syrup – 300 mg/5 ml (6% Syrup)

- “Anti-Manic” drugs, also considered as “mood-stabilizing” agents because of their primary action of preventing MOOD SWINGS in patients with

Bipolar Affective (*Manic-Depressive*) Disorder.

- Antimanic Action: antipsychotic and antimanic effects - by competing with other cations for exchange at the Na⁺/ K⁺ ion pump, thus altering cation exchange at the tissue level.
- Noradrenaline and Dopamine turnover

CLINICAL USES

- Bipolar Affective Disorders
- Major Depression
- Schizoaffective Disorder
- Alcohol Dependence

ADVERSE EFFECTS

- Psychomotor retardation
- Lethargy
- Epileptiform seizures
- Impaired Speech
- Muscle Weakness
- Arrhythmias
- HYPOTENSION
- Dry Mouth
- Nausea, Vomiting
- Polyuria
- Leukocytosis
- Hypothyroidism

TRANQUILIZERS (ANXIOLYTIC DRUGS)

I. Benzodiazepines (BZDs):

Diazepam (*Sibazon*) – amp. 0.5%-2 ml; Tab. 0.005 g

Chlordiazepoxide (*Chlozepide*) – Tab. 0.005 g

Nozepam (*Oxazepam, Tazepam*) – Tab. 0.01 g

Lorazepam – Tab. 1 and 2 mg

Phenasepam – Tab 0.5 and 1 mg

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

Mezapam (*Rudotel*) – Tab. 10 mg

Tofizopam (*Grandaxin*) – Tab. 50 mg

II. Other Anxiolytics

Buspirone – Tab. 5 and 10 mg

Amyzyl – Tab. 1 and 2 mg

Hydroxyzine – amp. 5%-2 ml; Tab. 10 and 25 mg

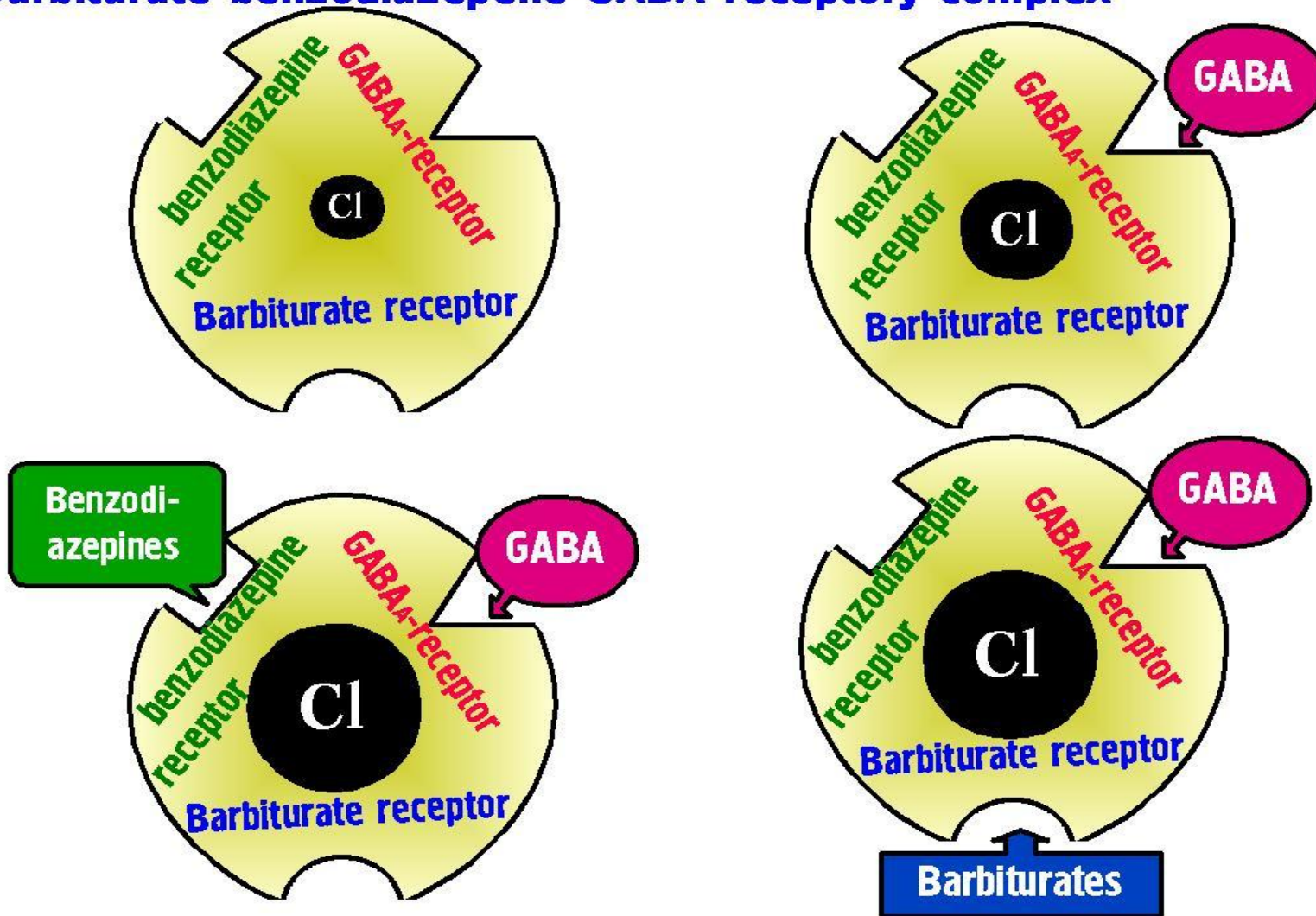
BENZODIAZEPINES

according to their Duration of Action:

- 1. Long-acting (24-48 hours):
 - Diazepam
 - Phenasepam
 - Chlordiazepoxide
- 2. Intermediate-acting (6-24 hours):
 - Alprazolam
 - Nozepam
 - Lorazepam
- 3. Short-acting (< 6 hours):
 - Midazolam (*Dormicum*)
 - Gidazepam

Mechanism of action of barbiturates and benzodiazepines

Barbiturate-benzodiazepene-GABA-receptor complex



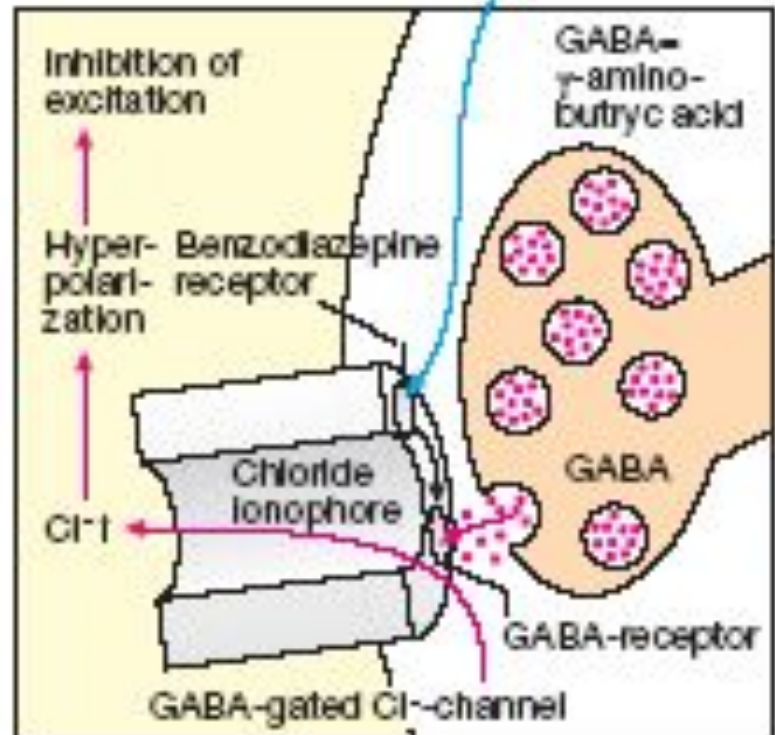
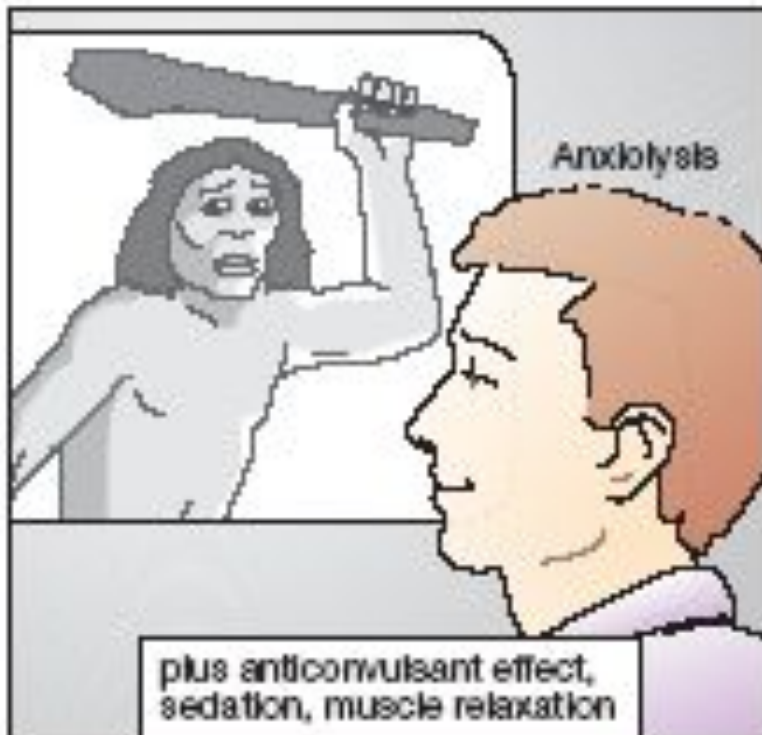
MECHANISM OF ACTION of BZDs:

Bind to the α -subunit of the GABA_A Rs surrounding the Cl⁻ channels designated as BZD Rs (omega-Receptors)

- ▶ □ Affinity of GABA Rs
- ▶ □ Frequency of Cl⁻ channel opening
- ▶ □ Cl⁻ Conductance => Hyperpolarization

=> Post-synaptic Potential away from its Firing Threshold =>

- ▶ Inhibition of Action Potential Formation and Further Neuronal Firing



CLINICAL USES of BZDs

- **1. ANXIETY and PANIC DISORDERS**
- **2. MUSCULAR DISORDERS:**
 - *DIAZEPAM* –
 - Skeletal Muscle SPASMS in Muscle Strain
 - SPASTICITY from degenerative disorders, such as Multiple Sclerosis
- **3. SEIZURES:**
 - *CLONAZEPAM* – Epilepsy
 - *DIAZEPAM* – Grand Mal Epileptic Seizures
Status Epilepticus
 - *CHLORDIAZEPOXIDE, DIAZEPAM,*
NOZEPAM (OXAZEPAM) – Alcohol Withdrawal
- **4. SLEEP DISORDERS**

ADVERSE EFFECTS of BZDs:

- **DROWSINESS**
- **CONFUSION**
- **ATAXIA**
- **COGNITIVE IMPAIRMENT:**
 - **LONG-TERM RECALL**
 - **ACQUISITION of NEW KNOWLEDGE**
- **Early Morning Insomnia**
- **Daytime anxiety with AMNESIA and CONFUSION**

Psychological and Physical Dependence -
if high doses are given over a prolonged period

- BZD Antagonist:

FLUMAZENIL –

a GABA receptor competitive antagonist that can rapidly reverse the effects of BENZODIAZEPINES.

Blocks actions of BZDs

(and imidazopyridines) but does not antagonize the CNS effects of other sedative-hypnotic, ethanol, opioid, or general anesthetics

DIAZEPAM (Sibazon) amp. 0.5%-2 ml; Tab. 0.005 g

is a Tranquilizer, a LONG ACTING BENZODIAZEPINE

MECHANISM OF ACTION: binds to **BDZ** receptors, which are separate from but adjacent to the **GABA** receptors, trigger an opening of a **Cl⁻ channel** =>

=> \square in **Cl⁻ Conductance** =>

=> **HYPERPOLARIZATION** that moves the postsynaptic potential away from its firing threshold and inhibits the Formation of Action Potentials.

PHARMACOLOGIC EFFECTS: \square anxiety, sedative and hypnotic action, anticonvulsant and myorelaxant action.

CLINICAL USES: neurotic and neurosis-like conditions with symptoms of anxiety and phobia, increased irritability; epilepsy and status epilepticus, alcohol withdrawal, muscle spasm, as adjunct to anesthesia and endoscopic procedures.

Gidazepam Tab. 0.02 g; 0.05 g –

DAY TRANQUILIZER – has ACTIVATING EFFECT
a **SHORT ACTING BZD** with anxiolytic, anticonvulsive and weakly expressed myorelaxant action.

It also stabilizes the functions of the Vegetative NS.

MECHANISM OF ACTION:

□ the effect of the GABA in the **ASCENDING RETICULAR ACTIVATING SYSTEM**, => **increases inhibition** and **blocks cortical and limbic arousal**.

INDICATIONS:

Neurotic and Neurosis-like conditions with symptoms of anxiety and phobia, increased irritability; Acute alcohol withdrawal, Muscle spasm,

Convulsive disorders.

Buspirone - Tab. 10 mg - an non-BZD anxiolytic

MECHANISM OF ACTION:

- Blocks **5-HT_{1A} Serotonin** receptors and presynaptic **Dopamine** receptors
- □ **Norepinephrine** biotransformation

=> Indirect effect on **BZD-GABA-CHLORINE** receptor complex or GABA receptors

=> has no anticonvulsant or muscle relaxant activity and **does not appear to cause physical dependence**

The drug is **95% protein-bound**;

onset of therapeutic effect may require **1 - 2 weeks**.

INDICATIONS:

Anxiety disorders, major depression, parkinsonian syndrome, premenstrual syndrome, drug addiction.

Sedative Drugs:

1. BROMINE SALTS:

Sodium Bromide - *NaBr*

Potassium Bromide - *KBr*

2. VALERIAN'S PREPARATIONS:

(*Valeriana officinalis*)

Infusion, Tincture, Extract from
Rhizome and Root of *VALERIAN*



3. MOTHERWORT'S PREPARATIONS:

(*Leonurus cardiaca*)

Tincture from Plant Grass

(*Tinctura Leonuri*)

Mechanism of Action:

□ Intensification of slowdown processes in the brain

Clinical Uses: Neurosis

Adverse Effects: Skin Rashes, Sedation,
Behavioral Changes.



BROMISM – chronic intoxication with BROM salts.

Bromides eliminate slowly ($T_{1/2}=12$ days),

MANIFESTATION: total retardation, apathy,
memory disorders, skin rashes

The IRRITATIVE ACTION of bromides induces

Mucous Inflammations along with
COUGH, RHINITIS, CONJUNCTIVITIS, DIARRHEA.

TREATMENT: the drug should be discontinued and its elimination must be accelerated.

Bromide excretion may be enhanced by using of :

Sodium Chloride, NaCl

abundant drinking, and diuretics (saluretics).

Valerian's and Motherwort's Preparations - are widely used sedative drugs.

VALERIAN'S preparations - Infusion, Tincture, Extract – are produced from Rhizome and Root of **VALERIANA OFFICINALIS** which contain:
valerian acid, organic acids, alkaloids, tannic substances

MOTHERWORT'S PREPARATIONS - Infusion and Tincture from plant **Grass** - contain:

ether oils, alkaloids, saponins, tannic substances.

- **SEDATIVE and WEAK TRANQUILIZING EFFECTS**
- do not cause myorelaxation, ataxia, psychologic and physical dependence.

CLINICAL USES: Light Neurosis,
Somatic Diseases with Neurotic Syndrome

ADVERSE EFFECTS: Allergic Reactions.



Thank You for Attention!

