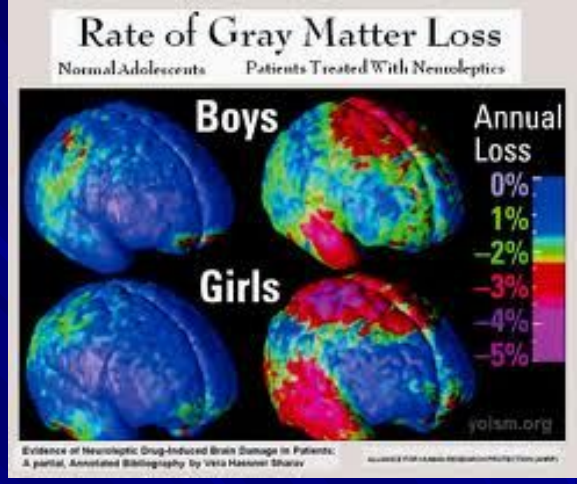
ZAPORIZHZHIA STATE MEDICAL UNIVERSITY
PHARMACOLOGY DEPARTMENT



Lecture № 5

Neuroleptics, Lithium, Tranquilazers, 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

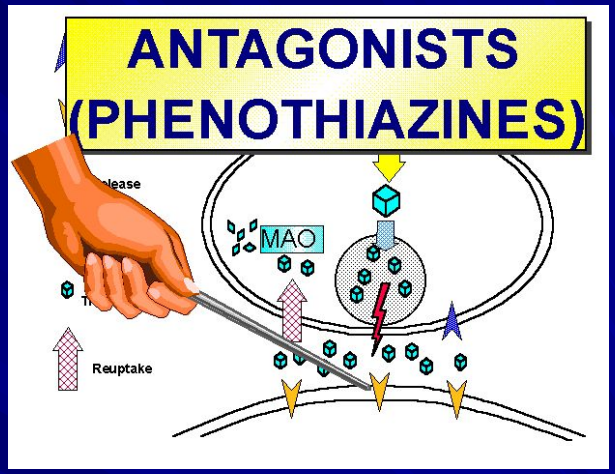
MECHANISM OF ACTION:

blockade of dopamine D_2-receptors

IN PERIPHERY :

BLOCK :

- M - Cholinoreceptors
- α - Adrenoreceptors
- H_1- Histamine Receptors
- Serotonin (5-HT) Receptors



DIRECT SPASMOLYTIC ACTION

Pharmacological Effects:

***Antipsychotic Actions*:**

⇓ Hallucination and Agitation

Antiemetic Effects

***Extrapyramidal Effects*:**

D_2-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

➡ D_2-dopamine receptors blocking -

- ► in mesolimbic and mesocortical systems:
  - Antipsyhotic effect.
  - Emotional indifferency.
  - Depression.
- ► Hypothalamus - hypophysis:
  - Decreasing of body temperature (hypotermia).
  - Halactorrea (increasing of prolactine production).
- ► Extrapyramidal system:
  - Symptomathetic parkinsonism, late (tarvide) dyskinesia.
- ► Triger-zone of vomitive centre:
  - Anti-vomitive effect

Mechanism of action and pharmacological effects of neuroleptics

➡ H_1-histamine receptors blocking -

- Sedative effect.
- Anti-vomitive effect.

➡ α_1-adrenoreceptors blocking -

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

➡ 5-HT-receptors blocking -

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

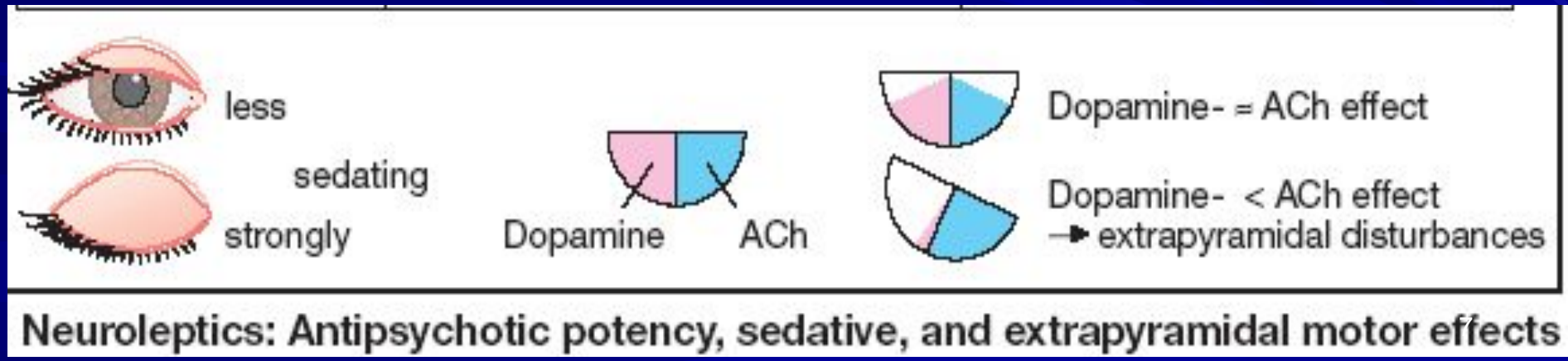
➡ M-cholinoreceptors blocking -

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

Extrapyramidal Effects:

due to Blocking of D_2 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



Neuroleptics: Antipsychotic potency, sedative, and extrapyramidal motor effects

Clinical Uses of Neuroleptics

- **1. <u>SCHIZOPHRENIA</u>:**

Positive Symptoms of Schizophrenia **: DELUSIONS, HALLUCINATIONS and THOUGHT DISORDERS**

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

- **2. <u>PREVENTION OF SEVERE NAUSEA and VOMITING</u>: Drug-induced nausea**
- **3. <u>OTHER USES</u>: treatment of DRUG ADDICTION, *NEUROLEPTANESTHESIA*, hypertensive crises**

Aminazine (*Chlorpromazine*) -
blocks CNS D_2 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

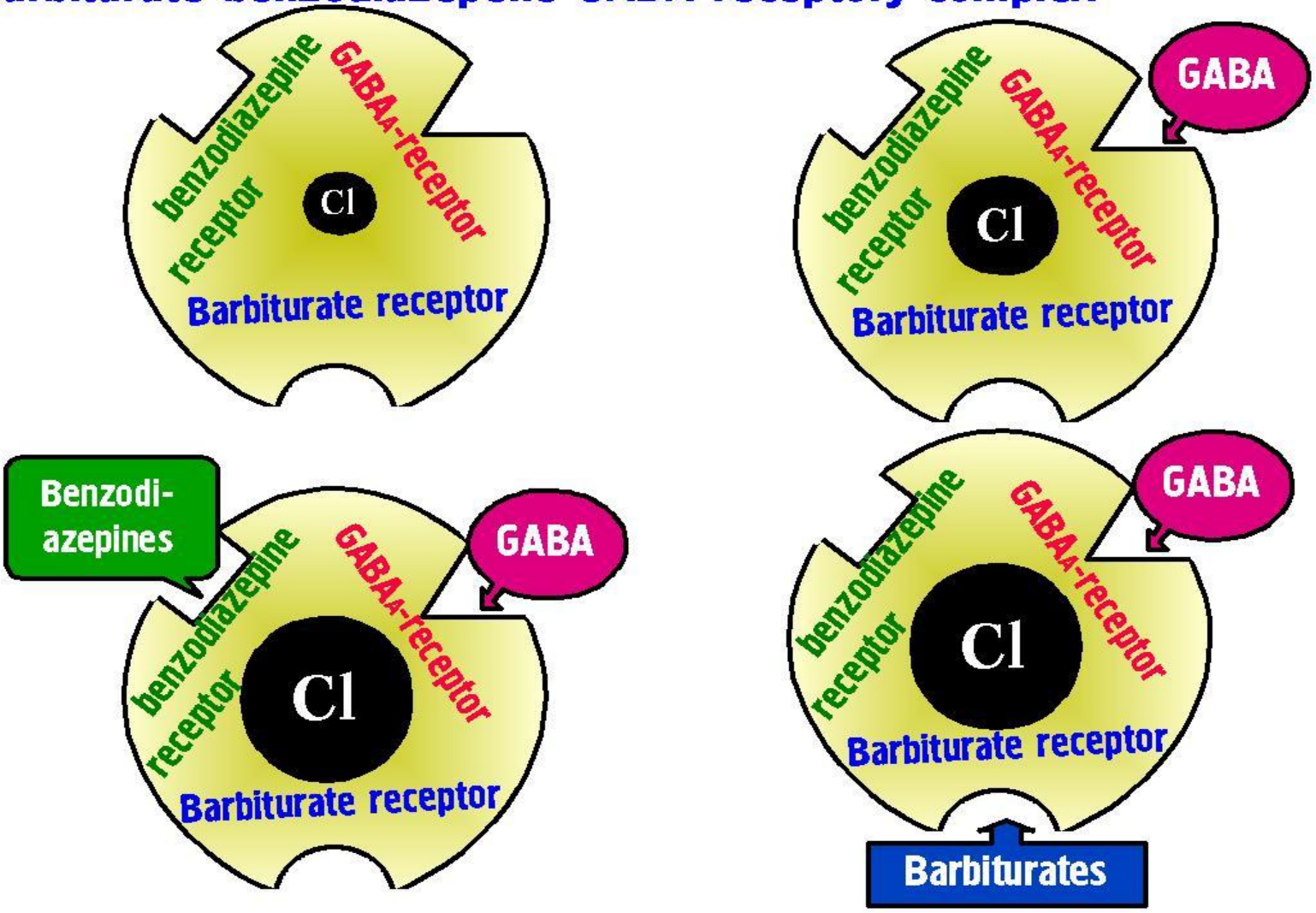
BENZODIAZEPINES

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-receptory complex



MECHANISM OF ACTION of BZDs:

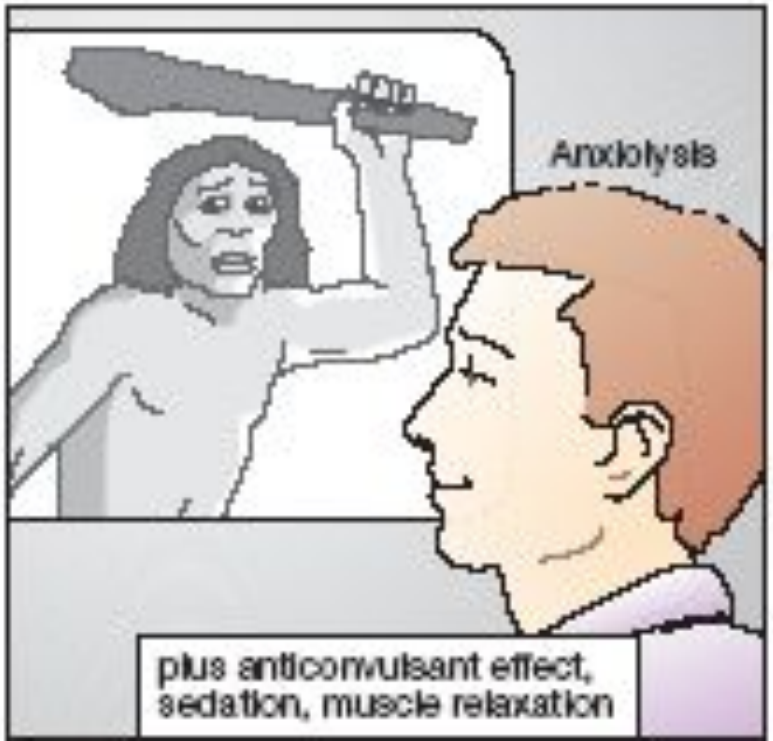
Bind to the α-subunit of the $GABA_A$ Rs surrounding the Cl^- channels designated as BZD Rs (omega-Receptors)

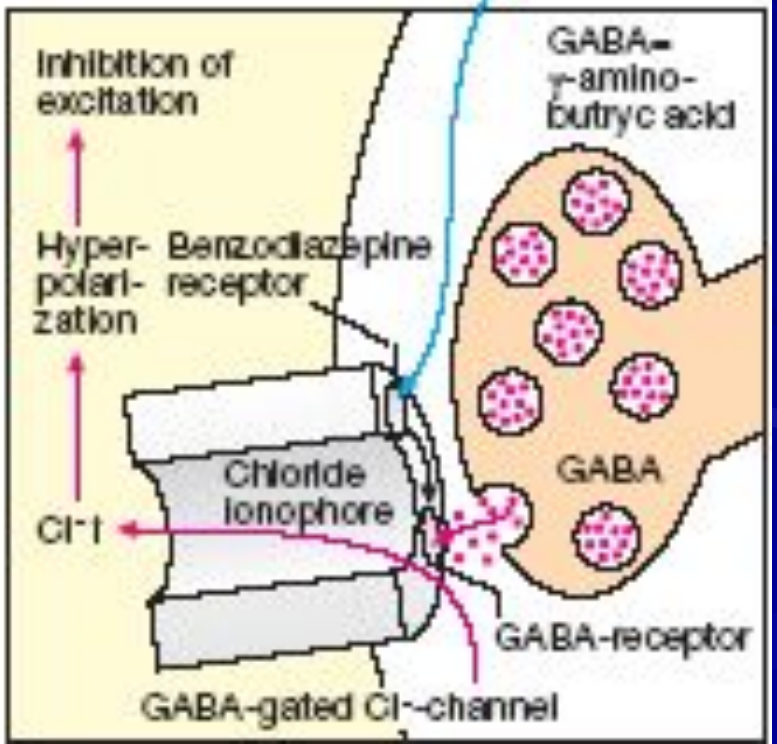
- ↑ Affinity of GABA Rs
- ↑ Frequency of Cl^- channel opening
- ↑ Cl^- Conductance => Hyperpolarization

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

- Inhibition of Action Potential Formation and Further Neuronal Firing


R2
O
N
Benzo
diaz
R3
epine
N
R1
R4
R1 = Cl
R2 = CH3
R3 = R4 = H
Diazepam


Anxiolysis
plus anticonvulsant effect,
sedation, muscle relaxation


Inhibition of
excitation
GABA=
γ-amino-
butryc acid
Hyper-
polari-
zation
Benzodiazepine
receptor
Chloride
ionophore
GABA
Cl-
GABA-receptor
GABA-gated Cl--channel

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 =>

=> ↑ in Cl- Conductance =>

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

PHARMACOLOGIC EFFECTS: ↓ anxiety, sedative and hypnotic action, anticonvulsunt 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.

Busbirone **- 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 Efects: **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, psyhologic and physical dependence.

CLINICAL USES: Light Neurosis,
Somatic Diseases with Neurotic Syndrome

ADVERSE EFFECTS: Allergic Reactions.

Thank You for Attention!