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ANTIPSYCHOTICS. TRANQUILIZERS. HYPNOTICS SEDATIVES. NORMOTHYMICS

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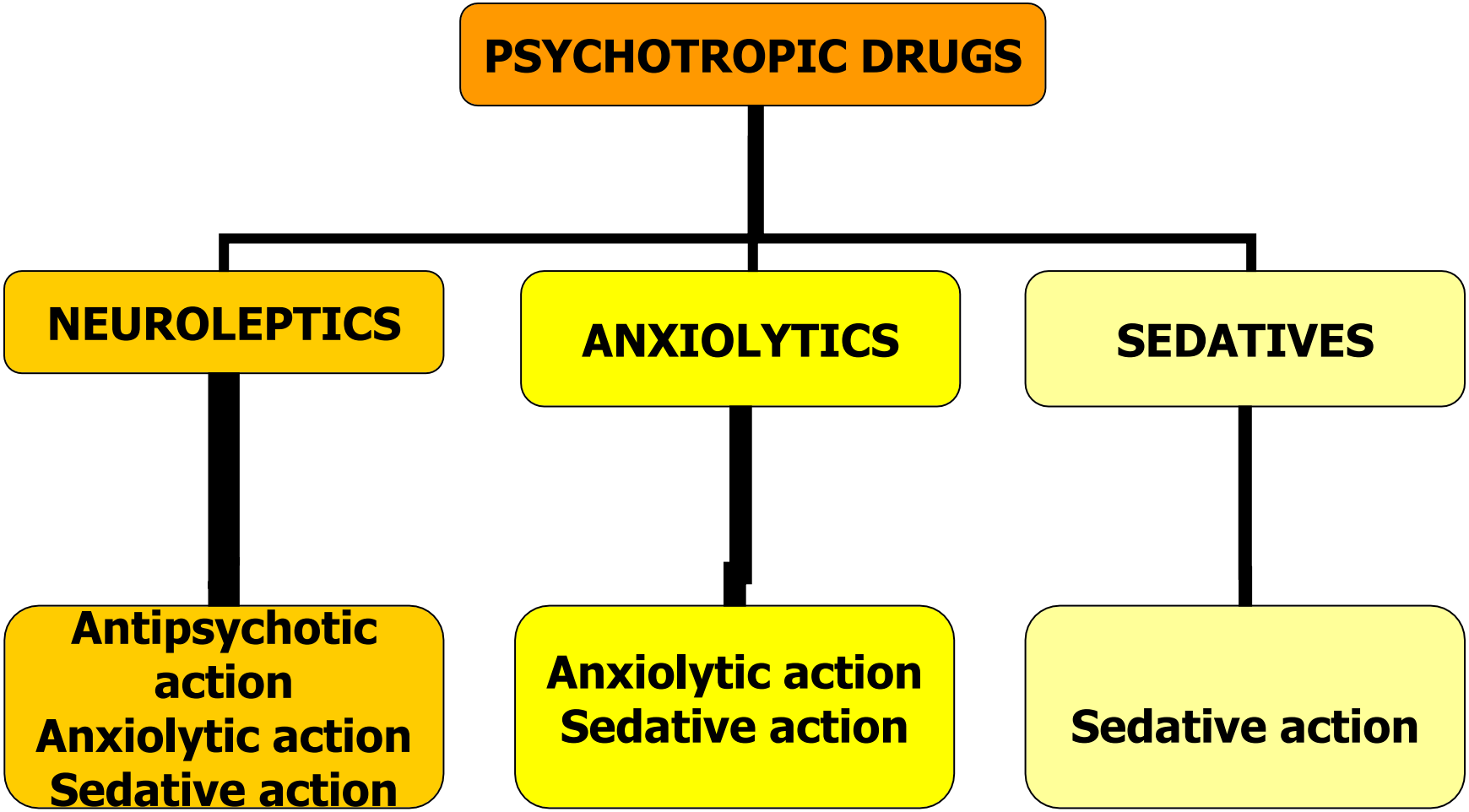
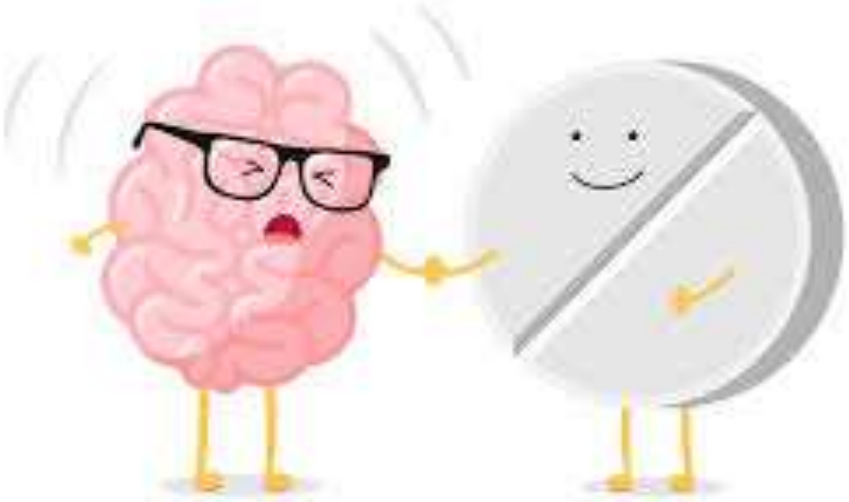
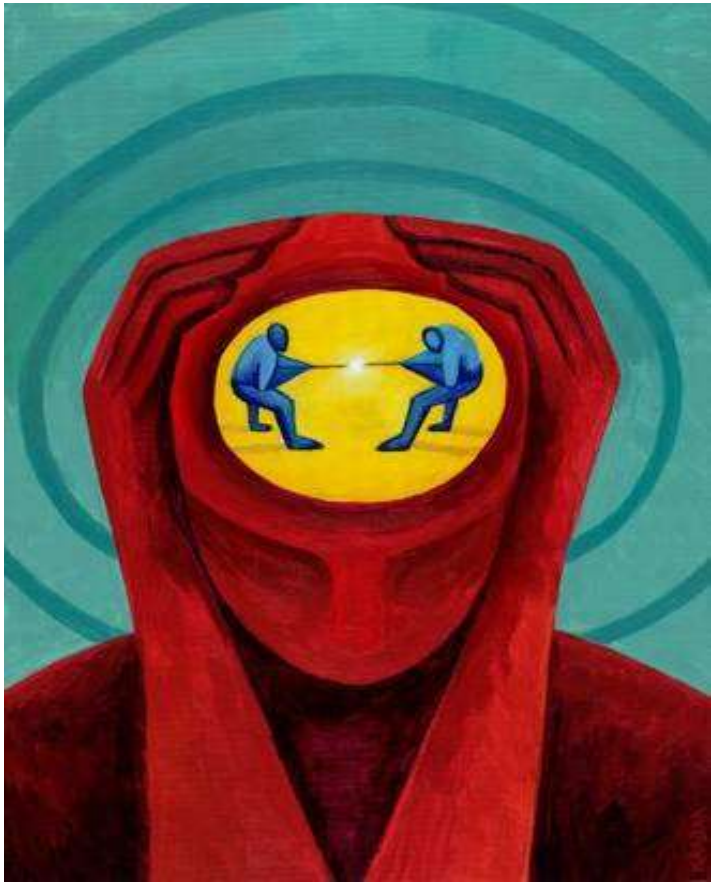
MAIN GROUPS OF PSYCHOTROPIC DRUGS



ANTIPSYCHOTIC DRUGS



SCHIZOPHRENIA



Schizophrenia is the type of psychosis characterized by delusions, hallucinations, thinking and speech disturbances. The illness often initially affects people during adolescence and is chronic and disabling disorder. It has genetic component and reflect biochemical abnormality in brain, possibly an overactivity of the mesolimbic dopaminergic neurons.

NEUROLEPTICS

Neuroleptics are drugs which are used to treat schizophrenia and some other psychotic states, such as manic states and delirium.

Typical neuroleptics block D2-, D1-, D3- and D4-dopamine receptors; cause extrapyramidal disturbances (drug parkinsonism)

Atypical neuroleptics block 5-HT2- receptors, α2-adrenoceptors, D4-dopamine receptors, have weak action on D2-dopamine receptors, do not cause extrapyramidal disturbances.

NEUROLEPTICS: classification

A. Typical neuroleptics

1. Phenothiazines

– Chlorpromazine (Aminazinum)
– Trifluoperazine (Triftazinum)
– Flunazine (Phthorphenazinum)

2. Butyrophenones

– Haloperidol
– Droperidol

3. Thioxanthenes

– Chlorprothixene

B. Atypical neuroleptics

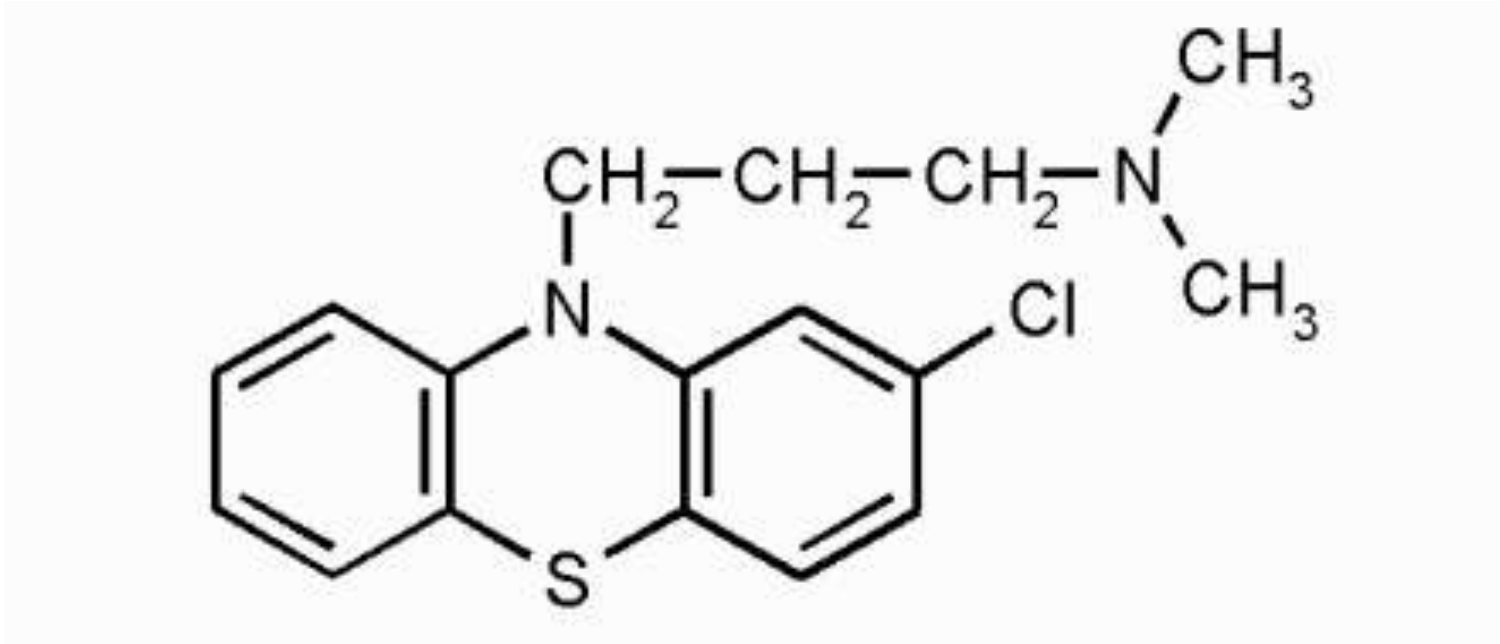
1. Dibenxzodiazepines

– Clozapine

2. Benzamides

– Sulpiride.

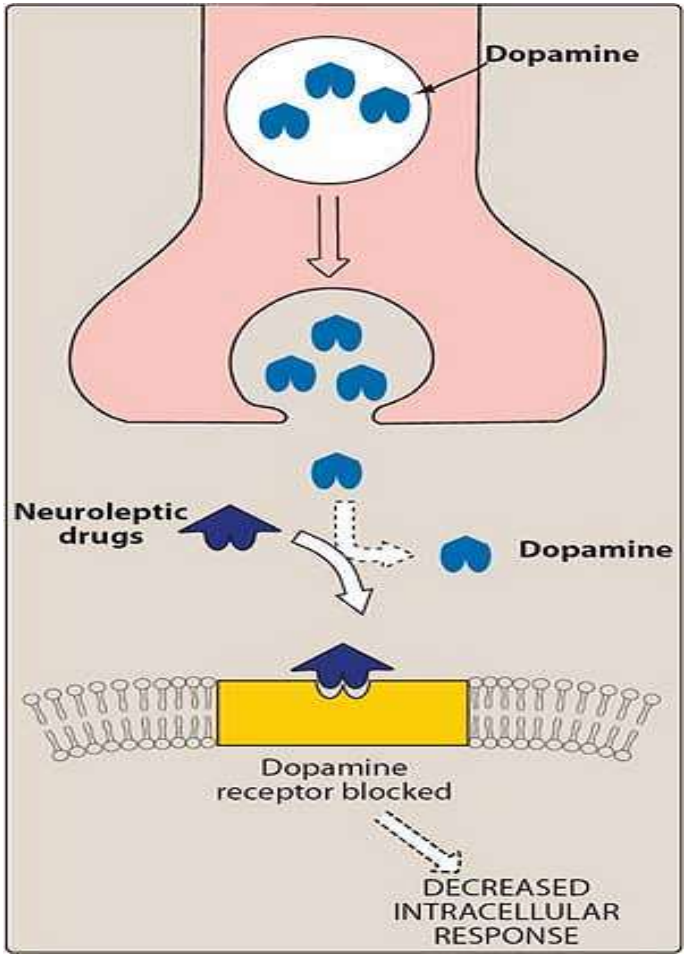
CHLORPROMAZINE (AMINAZINUM): chemical structure



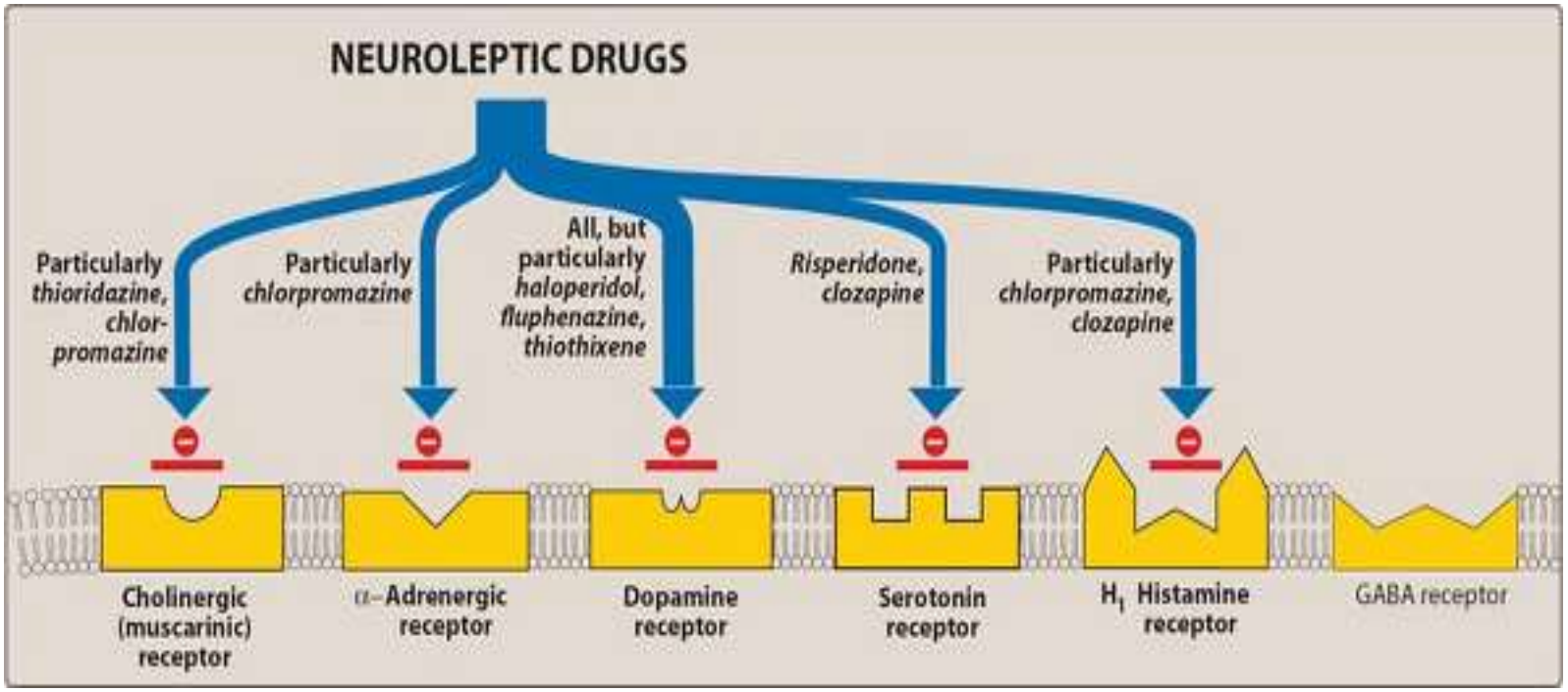
CHLORPROMAZINE: pharmacokinetics

- is administered orally, IM, IV
- is absorbed in the GI tract, but absorption is poor
- maximal concentration is determined in 2-4 hrs
- penetrates CNS and placenta
- binds with albumins in blood plasma (95-98%)
- is metabolized in the liver
- is the inductor of microsomal oxidation
- is excreted by urine, bile, and mothers' milk
- acts during 6-8 hrs, T ½ = 30 hrs
- accumulates.

CHLORPROMAZINE: mechanism of action



CHLORPROMAZINE: mechanism of action

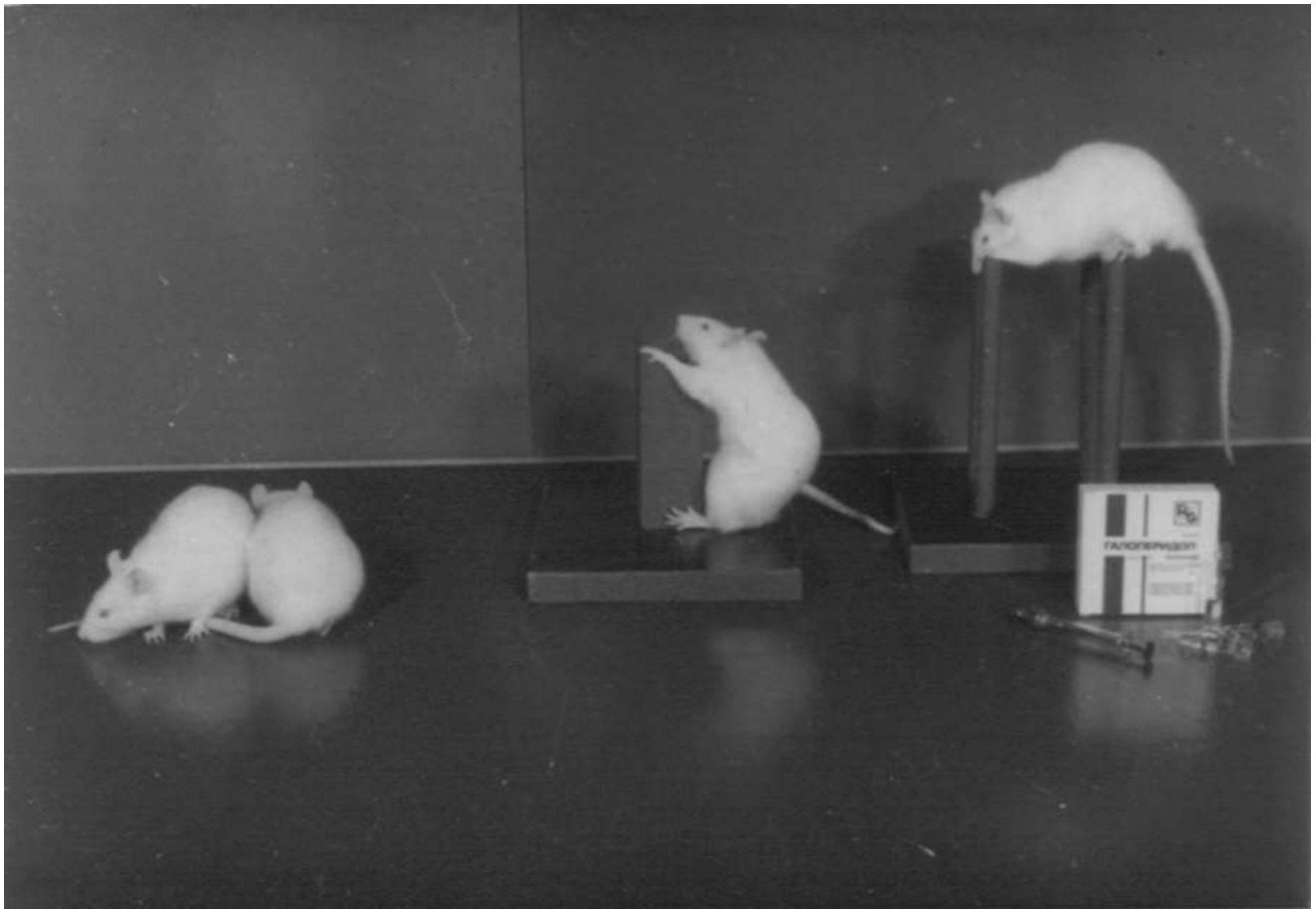


CHLORPROMAZINE: pharmacodynamics and indications

Pharmacodynamics	Indications
1. Antipsychotic action (a decrease in hallucinations and agitation) 2. Anxiolytic action 3. Sedative action 4. A decrease in psycho-motor excitement 5. Hypnotic action 6. Anti-seizure action 7. Cataleptic effect 8. Anti-emetic action 9. Antihypertensive effect 10. Hypothermia and poikilothermia 11. Potentiative action 12. Weak anti-inflammatory and anti-allergic actions	1. Psychosis, schizophrenia 2. Psycho-motor excitement 3. Seizures attack 4. Premedication 5. Severe vomiting of central origin 6. Hypertensive crisis 7. Hyperthermia 8. Hibernation (a decrease in normal body temperature during surgeries on the brain or on the heart) 9. Combined therapy of pain syndromes 10. Skin diseases accompanied by severe itch.

CHLORPROMAZINE:

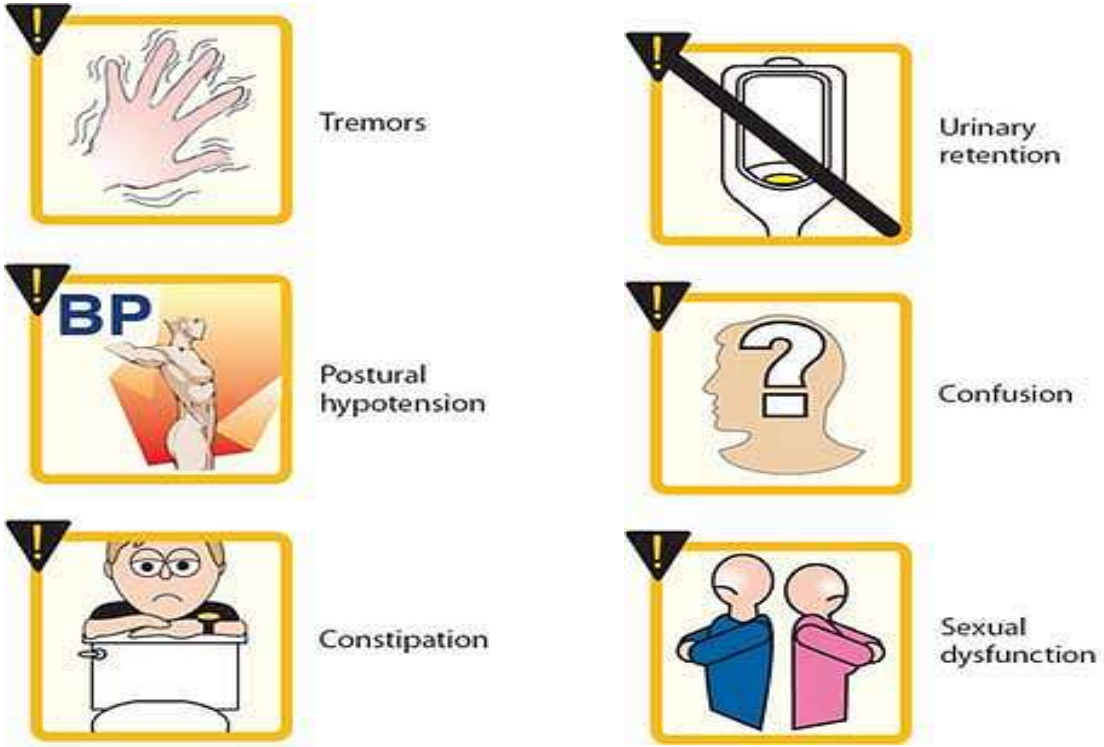
cataleptic action (absence of active movements under the conditions of normal muscle tone)



CHLORPROMAZINE: side effects

1. Irritation in the place of injection
2. Pain in the stomach
3. Irritation of the skin and mucous membranes
4. Confusion, blurred vision, dry mouth, hyposecretion in the stomach, constipation, urinary retention (due to M-cholinoblockage)
5. Hypotension, orthostatic reactions, lightheadedness (due to blockage of α-adrenoceptors)
6. Liver lesions, icterus
7. Inhibiting in hemopoiesis (leukopenia, agranulocytosis)
8. Dermatitis, phototoxicity
9. Parkinsonian symptoms, such as akathisia and tardive dyskinesia (due to blockage of dopaminoreceptors in the nigrostriatal pathway)
10. Neuroleptic syndrome (apathy, depression, parkinsonism)
11. Aggravation of acute agitation accompanying withdrawal from alcohol
12. Aggravation of epilepsy
13. Amenorrhea, galactorrhea, infertility, impotence
14. Allergy
15. Tolerance, drug dependence.

CHLORPROMAZINE: side effects



CHLORPROMAZINE: contraindications

- Diseases of the liver and kidney
- Diseases of blood
- Hypothyroidism
- Thromboembolism
- Organic diseases of the brain and spinal cord (trauma, cancer, stroke)
- Gastric ulcer
- Pregnancy and lactation.

PECULIARITIES OF PREPARATIONS

Typical neuroleptics

Trifluorperazine (Triftazinum) contains fluorine; is more active in its anti-emetic action and in the influence on extrapyramidal system; is less active in potentiation, anti-seizure, and antihistamine actions; may cause sedative or stimulating effect according to the form of disease.

Flunazine (Phthorphenazinum) contains fluorine; has strong antipsychotic and anti-emetic actions; manifests stimulating action in lower doses and sedative action in bigger doses; is effective for the treatment of long durative schizophrenia; may be used in neurosis (lower doses).

Haloperidol is from butyrophenone derivatives; has strong antipsychotic, potentiative, anti-emetic, and sedative actions, denominated catalepsy; is effective for the treatment of acute psychosis; may be used for neuroleptanalgesia; often causes extrapyramidal disturbances.

Droperidol has strong and short action; has not cholinoblocking activity; has anti-shock, anti-arrhythmic, antihypertensive actions; strong catalepsy; is used for neuroleptanalgesia, before, during and after operations, in shock and myocardial infarction.

Chlorprothixene is a thioxanthene derivative; has sedative action, decreases depression; has weak anti-seizure effect; does not cause catalepsy; is used in psychoses accompanied by depression, in neurosis (lower doses).

PECULIARITIES OF PREPARATIONS

Atypical neuroleptics

Clozapine (Asaleptin) has an antipsychotic action with sedation; does not cause catalepsy and extrapyramidal disturbances; does not cause apathy; is effective in the resistance to other preparations.

Sulpiride has a strong anti-emetic action and weak cataleptic action; has not sedative, anti-seizure, and potentiative effects; has antidepressive action; is used for treatment of psychic diseases accompanied by apathy, as well as of psycho-somatic diseases.

COMPARATIVE DISCRIPTION OF NEUROLEPTICS

	Drug	Therapeutic notes
TYPICAL NEUROLEPTICS	*Fluphenazine*	Available as slow-release depot form
	Thioridazine	Strong muscarinic antagonist
	Haloperidol	Little adrenergic or muscarinic activity; available as slow-release depot form; High potential for extrapyramidal effects
ATYPICAL NEUROLEPTICS	*Aripiprazole*	Low potential for extrapyramidal effects; Used in treatment of bipolar depression
	Clozapine	Few extrapyramidal effects; causes a potentially fatal agranulcytosis in 1–2% of patients; weight gain, seizures, nocturnal salivation, myocarditis, anticholinergic symptoms; hypotension; sedation
	Olanzapine	Low potential for extrapyramidal effects; weight gain; Used in treatment of bipolar depression
	Quetiapine	Low potential for extrapyramidal effects; Used in treatment of bipolar depression
	Risperidone	Low potential for extrapyramidal effects; minimal sedation; Used in treatment of autism, bipolar depression
	Ziprasidone	Low potential for extrapyramidal effects; contraindicated in patients with history of cardiac arrhythmias; weight gain minimal; Used in treatment of bipolar depression

Tremors

Parkinsonian effects commonly seen with typical neuroleptics

Weight g ain

Weight gain commonly occurs with atypical neuroleptics

CONCEPT OF NEUROLEPTANALGESIA

Neuroleptanalgesia is a kind of general anesthesia when neuroleptic (droperidol) and narcotic analgesic (fentanyl) are administered together (IV). In this case neuroleptic produces psychic oppression and narcotic analgesic causes abolishing of pain. Co-administered, they display synergic action.

ANXIOLYTICS

ANXIETY

Anxiety is a state of tension, apprehension or uneasiness.

The symptoms of severe anxiety are mental disturbances accompanied by tachycardia, sweating, trembling, palpitation. Episodes of mild anxiety are common life experiences and do not warrant treatment.

The symptoms of severe or chronic anxiety should be treated with anti-anxiety drugs.

ANXIOLYTICS

Anxiolytics are drugs to treat anxiety and stress. They also are named ***minor tranquilizers, ataractics.***

ANXIOLYTICS: classification

1. Benzodiazepines

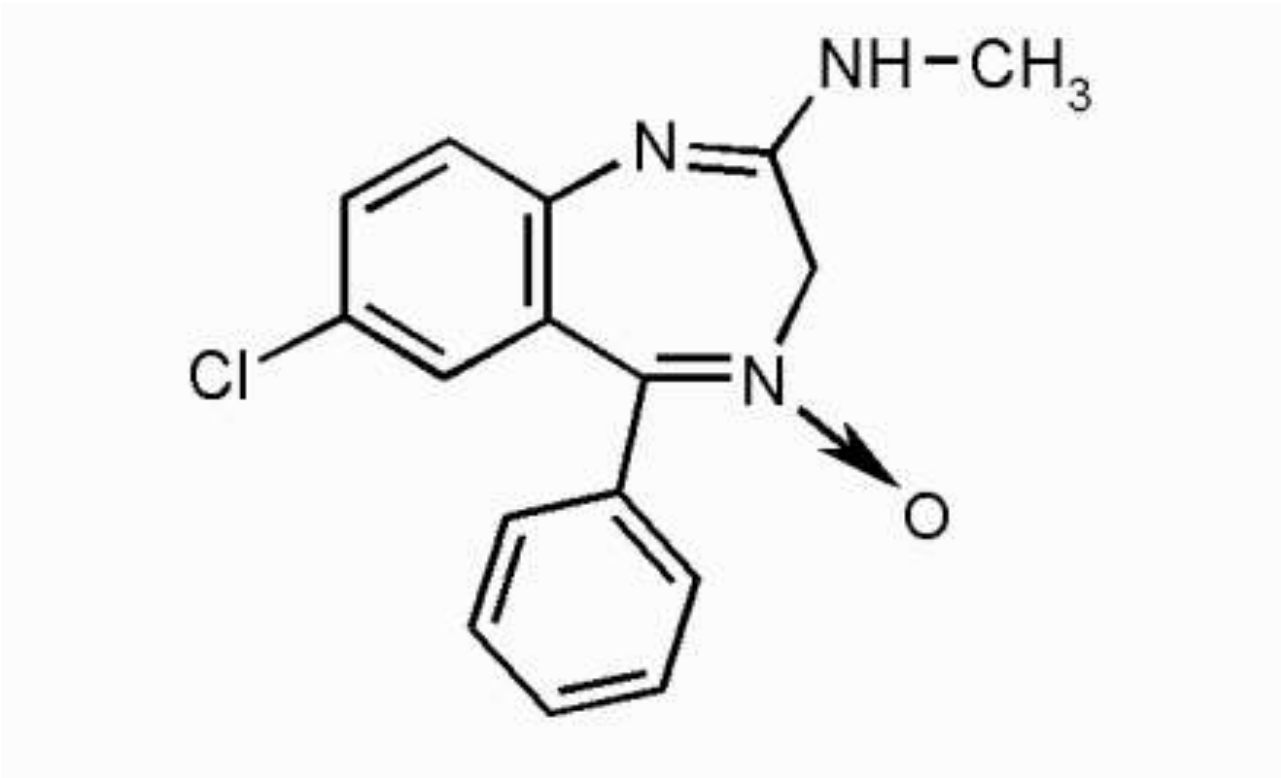
- Chlordiazepoxide (Chlosepidum)
- Diazepam (Sibasonum)
- Phenazepam
- Medazepam (Mezapam, Rudotel)
- Gidazepam

2. Preparatioins of other chemical structure

- Buspirone
- Benactyzime (Amizilum)
- Meprobamate (Meprotanum).

Antagonist of benzodiazepines is Flumazenil.

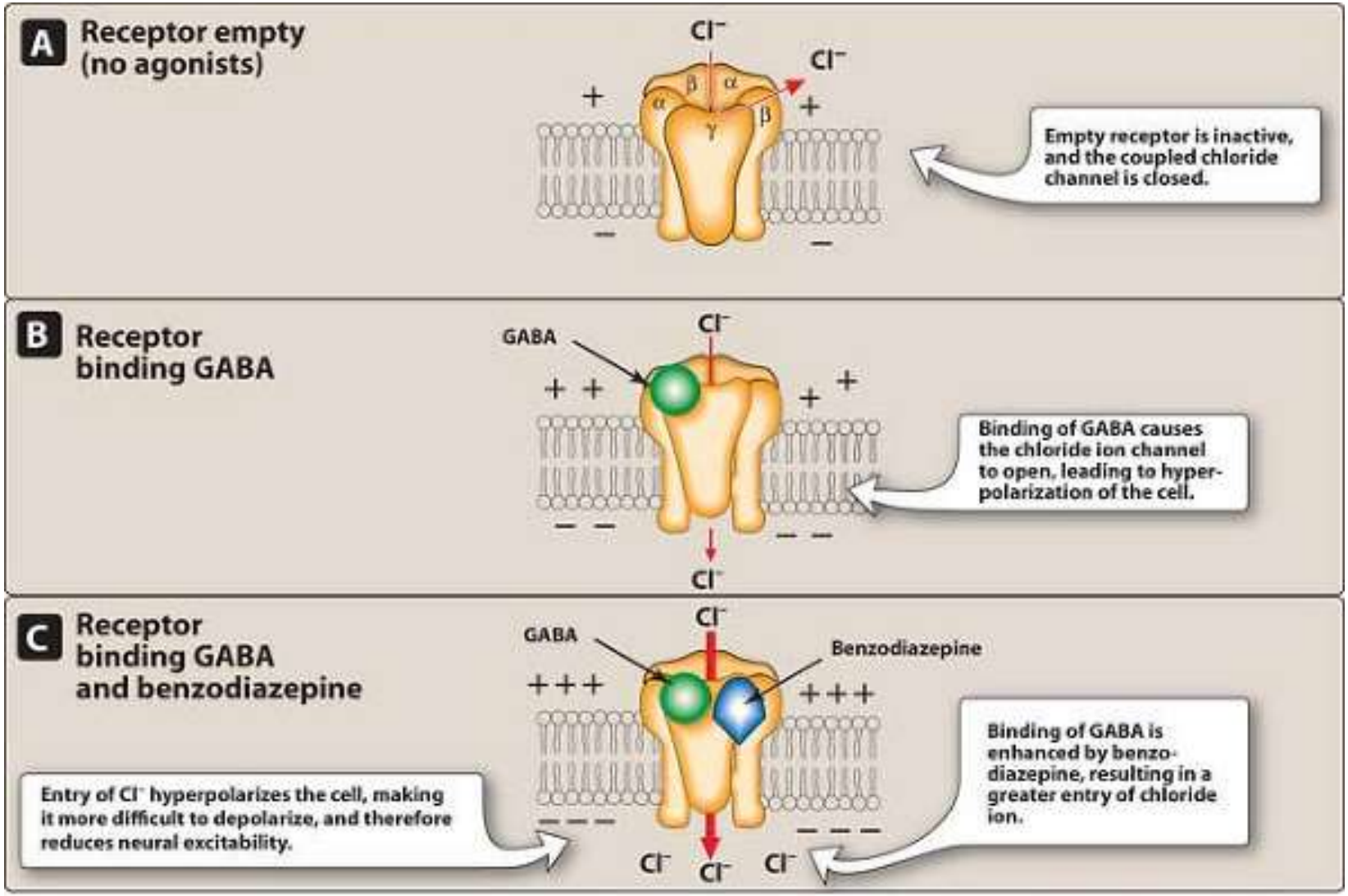
CLORDIAZEPOXIDE: chemical structure



CLORDIAZEPOXIDE: **pharmacokinetics**

- is administered orally, IM, IV
- is absorbed in the GI tract
- penetrates CNS
- is metabolized in the liver
- is excreted by urine
- has long-durative action, T½= 24-48 hrs.

CLORDIAZEPOXIDE: mechanism of action



CHLORDIAZOPOXIDE: pharmacodynamics and indications

Pharmacodynamics	Indications
1. Anxiolytic action (a decrease in anxiety, panic, and stress) 2. Sedative action 3. Hypnotic action 4. Central myorelaxative action (due to the action on spinal polysynaptic reflexes) 5. Anti-seizure action 6. Potentiative action (drug addition if analgesics, general anesthetics or other CNS inhibitors are administered together with this drug).	1. Neuroses 2. Stress, emotional overstrain 3. Sleeping disorders induced by emotional overstrain 4. Neurological diseases with muscle spasticity 5. Seizures 6. Abstinence in chronic alcoholics 7. Psychosomatic diseases 8. Premedication.

CHLORDIAZOPOXIDE: side effects and contraindications

Side-effects	Contraindications
1. Weakness 2. Drowsiness 3. Decrease in attention and rapidness of motor reactions 4. Ataxia 5. Skin itch 6. Amenorrhea 7. Impotence 8. Drug addition 9. Drug dependence.	1. Jobs that needs increased attention 2. Myasthenia 3. Diseases of the liver and kidney 4. Pregnancy.

PECULIARITIES OF OTHER ANXIOLYTICS

Diazepam (Sibazonum) is administered orally, IM, IV; maximal concentration after oral administration develops in 30-90 min; elimination is characterized by two phases (the 1st short phase with distribution of the drug in tissues during 3 hrs and the 2nd long-lasting phase with T½= 48 hrs); is more potent than clordiazepoxide, especially in anti-seizure effect; causes decrease in night gastric secretion and arrhythmia; is suitable to treat seizure attack; may be used in combined therapy of ulcerative disease and heart arrhythmia.

Phenazepam is administered orally; maximal concentration is in 1-2hrs; has T½ = 6-10 hrs; is stronger than clordiazepoxide or diazepam; has strong hypnotic action and muscle relaxation.

Medazepam is taken orally; is less potent but does not cause hypnotic effect and myorelaxation (so named "day-time" tranquilizer); may be used in patients who need increased attention for their jobs.

Gidazepam is a "day-time" tranquilizer; is taken by mouth; begins to act in 30-60 min and acts during 1-4 hrs; has T½ = 87 hrs; has anxiolytic action, psychostimulating and antidepressant effects; has not hypnotic effect; is well tolerated; is used to treat neuroses accompanied by asthenia and depression.

SEDATIVES

SEDATIVES:
definition and classification

Sedatives are drugs to treat restlessness and light forms of anxiety.

CLASSIFICATION

1. Non-organic preparations

– Sodium bromide

– Potassium bromide

2. Vegetable preparations

– Tincture from valerian

– Tincture from Leonurum

3. Combined preparations

– Corvalol

– Valocormid

SODIUM BROMIDE

Pharmacokinetics

It is taken orally in the form of solution or mixture, quickly penetrates CNS, is excreted by urine, saliva, and sweat, excretion depends on concentration of chloride-ions in blood plasma, accumulates in the body.

Mechanism of action

It increases inhibition in CNS. Effective dose depends on the type of higher nervous activity.

Pharmacodynamics

- sedative action (decrease in restlessness and anxiety)
- hypnotic action
- anti-epileptic action.

Indications

Light forms of neuroses, neurasthenia, hysteria, restlessness, insomnia,

epilepy, light forms of hypertension.

Side-effects

Accumulation of bromides results in ***bromism.*** ***Main signs:*** drowsiness, weakness, apathy, memory disturbances, skin rash, rhinitis, cough. ***Treatment:*** to drink much liquid, sodium chloride with meals, diuretics, especially ethacrynic acid.

SEDATIVES OF VEGETABLE ORIGIN

Sedatives of vegetable origin are galenic preparations from medicinal plants, such as valerian, Leonurum and some other plants.

They have common pharmacological properties:

- are taken orally
- mechanism of action is not known
- main effects are sedative, hypnotic, spasmolytic
- indications to use are light forms of neurosis, neurasthenia, insomnia, cardioneurosis, somatic diseases with neurotic syndrome, spasms of stomach and intestine.

MEDICINAL PLANTS CONTAINING SEDATIVES

Valeriana

Leonurus

HYPNOTICS

INSOMNIA

•***Insomnia*** is characterized by poor sleep, with difficulty either in initiating sleep or maintaining sleep throughout the night

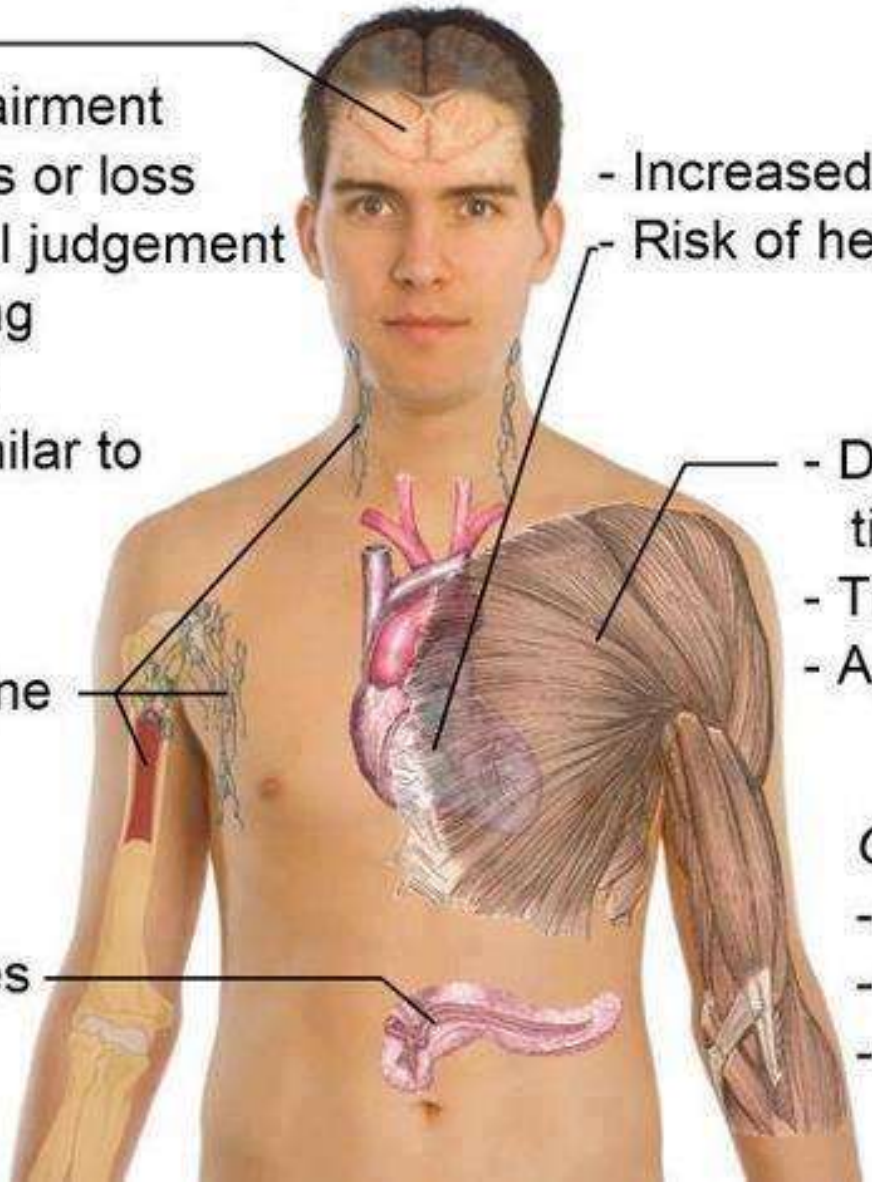
• It can occur in the course of another physical disorder such as pain, depression, or sleep apnoea.

•In a large proportion of patients it is a primary sleep disorder and causes significant impairment in social, occupational or other important areas of functioning.

•One survey showed similar ***deficits in quality of life in insomniacs*** as in patients with long-term disorders such as diabetes.

Effects of

Sleep deprivation



- Irritability
- Cognitive impairment
- Memory lapses or loss
- Impaired moral judgement
- Severe yawning
- Hallucinations
- Symptoms similar to ADHD

- Impaired immune system

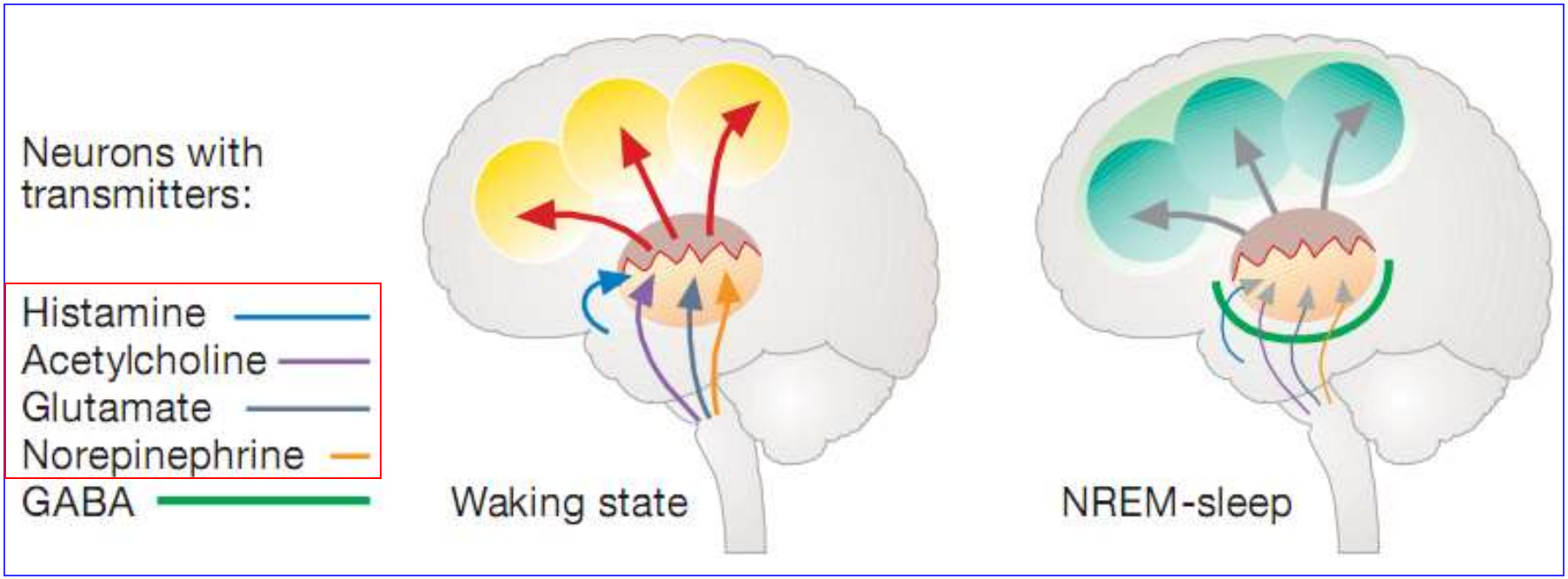
- Risk of diabetes Type 2

- Increased heart rate variability
- Risk of heart disease

- Decreased reaction time and accuracy
- Tremors
- Aches

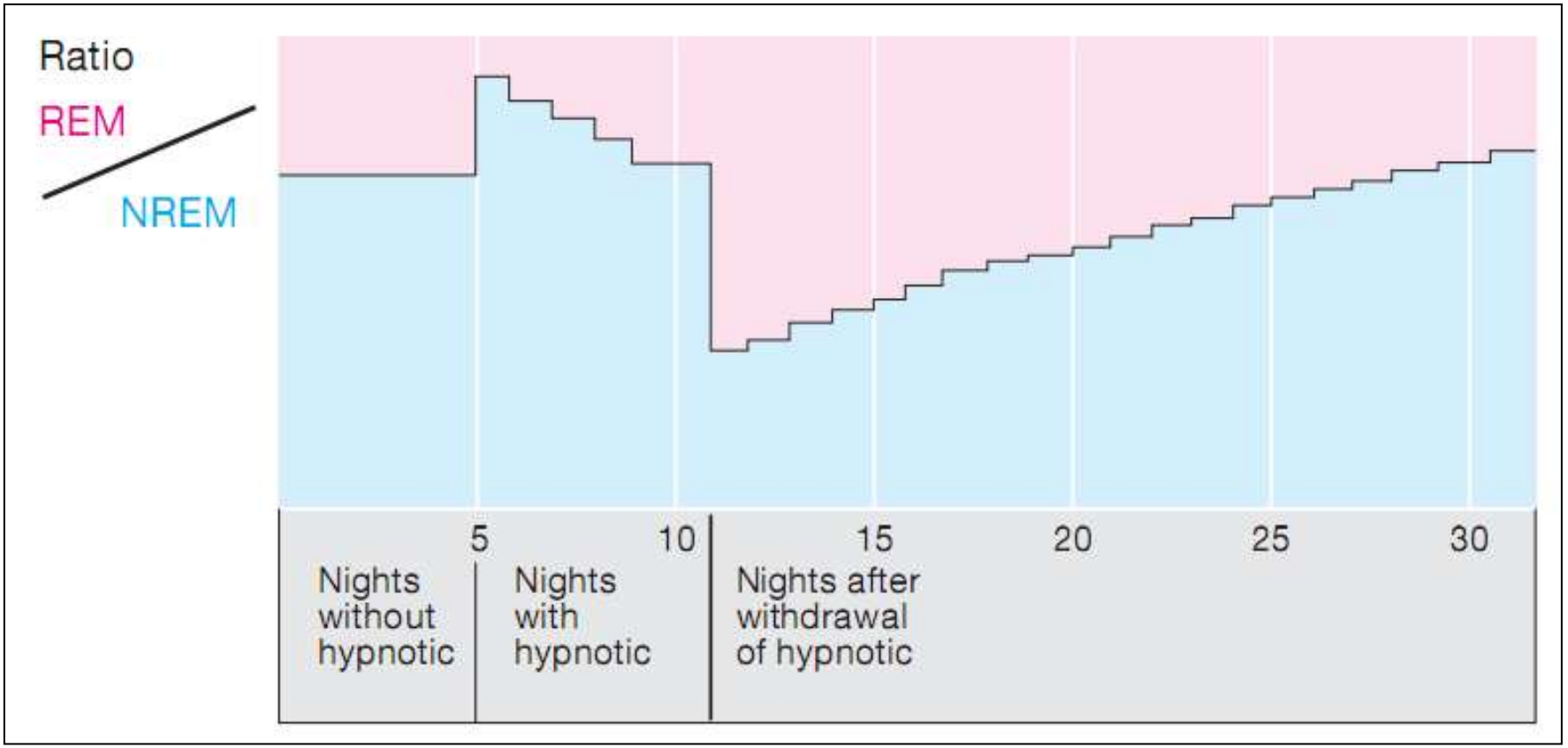
Other:

- Growth suppression
- Risk of obesity
- Decreased temperature



Transmitters: waking state and sleep.
During the sleep dominates GABA.

SLEEP STRUCTURE AND HYPNOTICS



Effect of hypnotics on proportion of REM/NREM

PRINCIPLES OF INSOMNIA TREATMENT

The approaches are to:

1. Treat any precipitating cause
2. Educate about trigger factors for sleep and reassure that sleep will improve
3. Establish good sleep hygiene
4. Consider hypnotic medication

CLASSIFICATION OF HYPNOTICS

1. Benzodiazepines:

Bromazepam, Flurazepam, Nitrazepam, Triazolam

2. Benzodiazepine like drugs (Z-drugs):

Zaleplon, Zolpidem, Zopiclone

3. Barbiturates:

-***Very short-acting*** *(i.v. anaesthetics):* Thiopental

- ***Intermediate-acting***: Cyclobarbital

- ***Long-acting***: Phenobarbital

4. H1-blockers: Diphenhydramyne, Promethazine

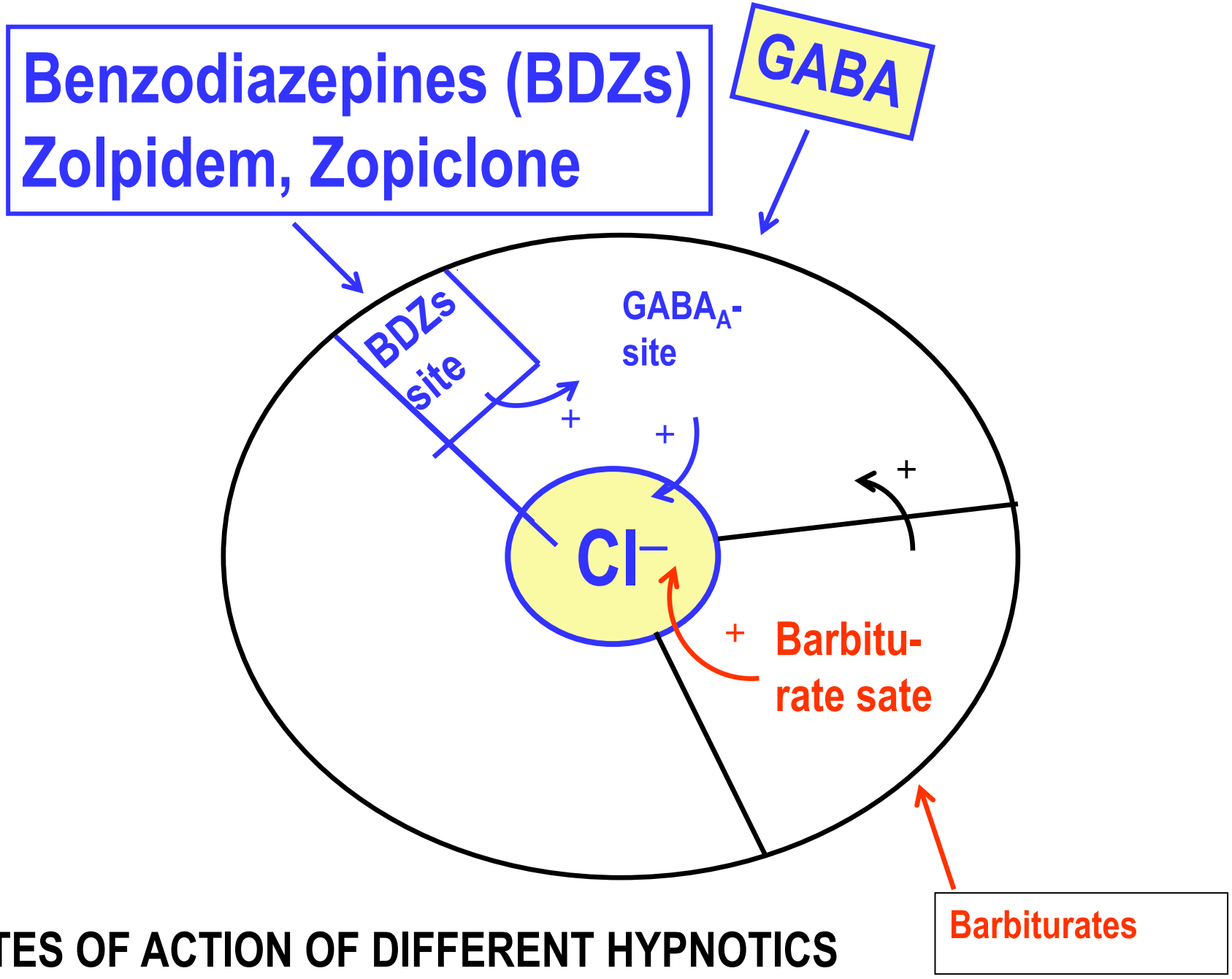
5. Piperidinediones: Gluithetimide

6. Phenothiazines: Thioridazine

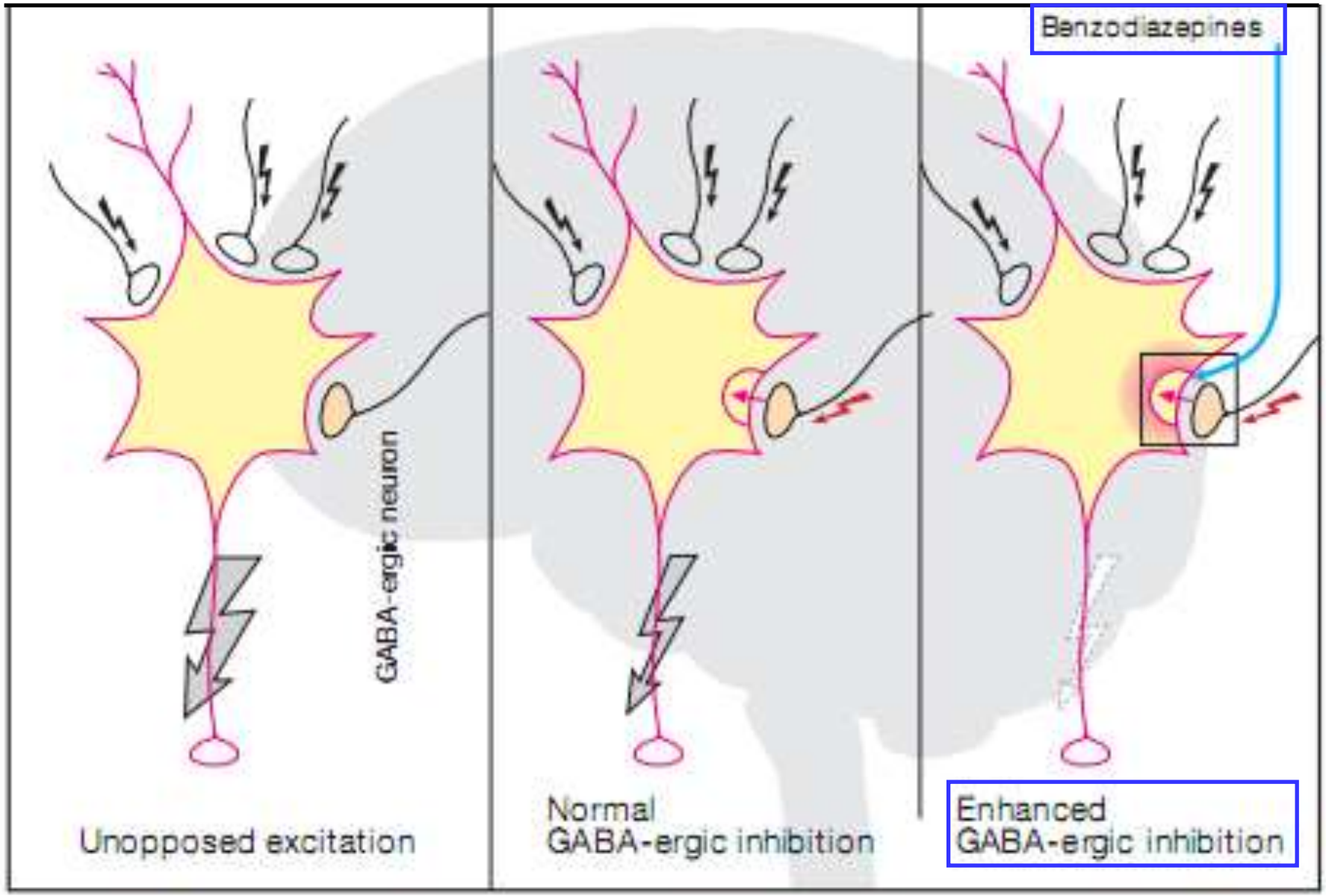
7. Melatoninergic hypnotics: Ramelteon

8. Combined preparations: Reladorm (cyclobarbital+diazepam)

9. Herbal preparations: Valerian



SITES OF ACTION OF DIFFERENT HYPNOTICS



BENZODIAZEPINES ENHANCE GABA-ERGIC INHIBITION.

BENZODIAZEPINES AND BENZODIAZEPINE-LIKE HYPNOTICS

- All BDZs and benzodiazepine-like drugs are safe and effective for insomnia, if the compound with the right timing of onset of action and elimination is chosen
- Objective measures of sleep show that BDZs decrease time to sleep onset and waking during the night
- Subjective effects of improved sleep are usually greater than the objective changes because of their anxiolytic effects.

BENZODIAZEPINE-LIKE HYPNOTICS ACTING AT GABA-BZD RECEPTOR

Zopiclone is a cyclopyrrolone in structure. It has a fairly fast (about 1 h) onset of action which lasts for 6–8 h, making it an effective drug both for initial and maintenance insomnia. Its duration of action is prolonged in the elderly and in hepatic insufficiency. About 40% of patients experience a metalic aftertaste.

Zolpidem is an imidazopyridine in structure and has a fast onset (30–60 min) and short duration of action. Patients over 80 years have slower clearance of this drug.

BARBITURATES

The use of ***intermediate-acting drugs*** (cyclobarbital) is now limited to severe intractable insomnia in patients already taking barbiturates (they should be avoided in the elderly).

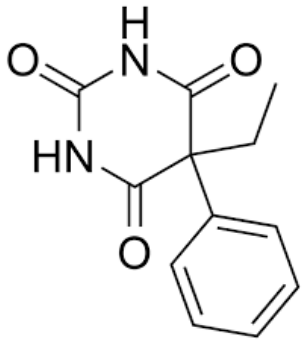
The **l*ong-acting*** phenobarbital is used for epilepsy, and ***very short-acting*** **t**hiopental and methohexital for anaesthesia.

The barbiturates are enzyme inducers.

They can cause rachitis in children and osteomalacia in elderly. They cross the placenta and have teratogenic activity.

Phenobarbital may produce tolerance and drug dependence.

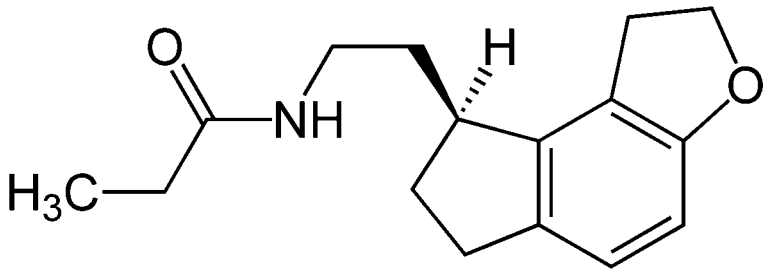
An overdose (acute poisoning with barbiturates) may have severe features including hypotension (may lead to renal failure), hypothermia, respiratory depression, and coma. Supportive measures are i.v. fluid, activated charcoal, urine alkalinization, hemodialysis.



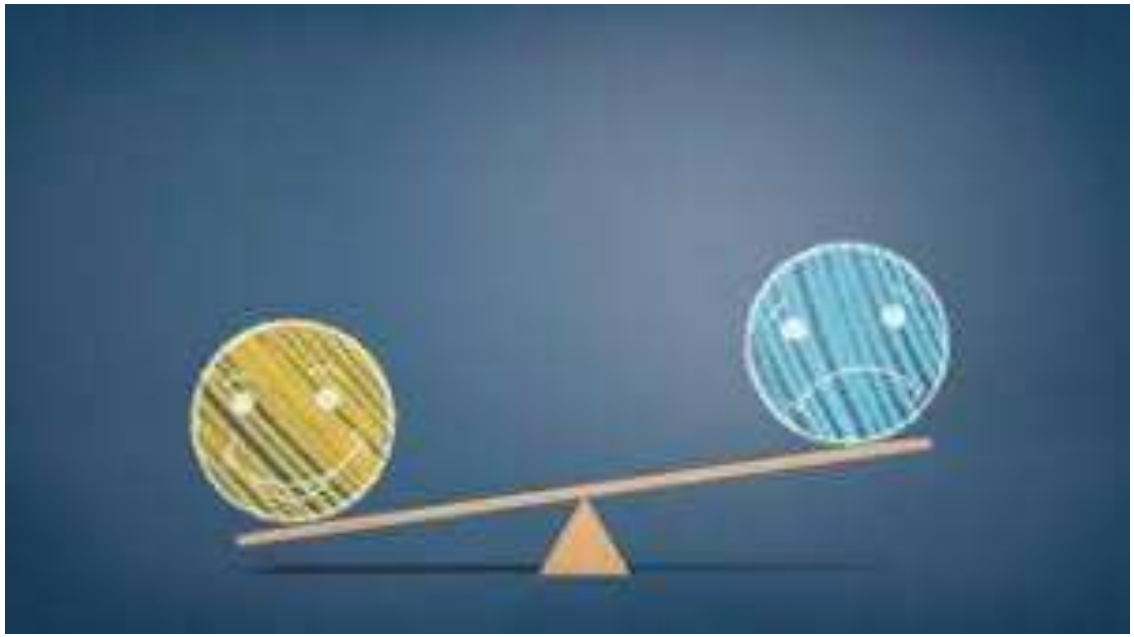
MELATONINERGIC HYPNOTICS

Melatonin is a hormone produced by the pineal gland during darkness. It has been investigated for insomnia. There is interest in its use therapeutically to reset circadian rhythm to prevent jet-lag on long-haul flights and for blind people who cannot use daylight to synchronize their natural rhythm.

Ramelteon is an analogue of melatonin



NORMOTHYMICS



MANIA AND BIPOLAR (MANIC-DEPRESSIVE) DISORDER

Mania is affective disorder characterized by elevated, expansive, or irritable mood, accompanied by increased activity, pressure of speech, flight of ideas, decreased need for sleep, distractibility, or involvement in activities that have high potential for painful consequences.

Patients that cycle between depression and mania have the diagnosis of ***bipolar affective disorder***.

LITHIUM CARBONATE

Pharmacokinetics

It is taken orally, is absorbed in the gut completely, absorption lasts during 8 hrs; maximal concentration develops in 2-4 hrs; does not bind to plasma proteins; 95% of the dose is excreted with urine and 5% – with sweat; T½ = 19 hrs; therapeutic effect develops in 1-3 weeks after the start of treatment.

Mechanism of action

Lithium disturbs sodium transport and inhibits Ca-dependent liberation of norepinephrine and dopamine in synapses of the brain.

Lithium salt also inhibits re-uptake of norepinephrine and dopamine.

Pharmacodynamics

a decrease in manic behavior

stabilization of mood, reduce in frequency and magnitude of mood swings

prevention of phase of mania in patients with bipolar disorder.

Indications

Bipolar affective disorder (manic-depressive disease). Manias

Side effects

Weakness, tremor, ataxia, pseudotumor of brain, hyperreflexia, extrapyramidal disturbances, headache, vision disturbances. Nausea, vomiting, diarrhea, abdominal pain, increase in size of salivary glands, dry mouth. Renal dysfunction (glucosuria, proteinuria, creatinuria). Thyroid enlargement, hypo- or hyperthyroidism. Skin rash. Teratogenous action (congenital cardiac anomalies).

OTHER MOOD STABILIZERS

- ***Anticonvulsants*** (valproate, lamotrigine, carbamazepine)
- ***Antipsychotics*** (atypical neuroletics: aripiprazole, asenapine, cariprazine, quetiapine, ris peridone, and ziprasidone)
- ***Omega-3-fatty acids*** (additional agents which reduce depressive symptoms of bipolar disease)
- ***L-thyroxine*** (improves response to the mood stabilizers)

USE OF PSYCHOTROPIC DRUGS AND HYPNOPTICS IN DENTISTRY. ORAL SIDE EFFECTS

Anxiolytics, sedatives, some hypnotics are used for a decrease of restlessness, anxiety, and insomnia before visit to the dental clinic

Oral diseases such as bruxism, orofacial dystonia, oromandibular dyskinesia, and rabbit syndrome are related to extrapyramidal effects of ***antipsychotic drugs***. Drugs with anticholinergic effects may cause dry mouth and related complications (candidiasis, oral infections).

Lithium treatment induces dry mouth, sialorrhea, infections, and ulceration of the oral cavity.

Z-drugs may cause metallic aftertaste.

CONTROL TASKS

- Diazepam is prescribed to the patient who is in the panic state before dental treatment. What is the mechanism of anxiolytic action of this drug?

  A. Stimulation of GABA -benzodiazepine receptor complex B. Blockage of D2-dopamine receptors C. Blockade of serotonin receptors D. Blockade of central M-cholinoreceptors E. Stimulation of barbiturate receptors. (A)

- A patient with emotional overstrain complains of anxiety and insomnia. Which benzodiazepine hypnotic can be used in this case?

  A. Chlorpromazine B.Diphenhydramine C. Sodium bromide D. Nitrazepam E.Carbamazepine. (B)

CONTROL TASKS

- A patient is prepared to the surgery in the maxilla-facial area. It should be under the neuroleptanalgesia. Which typical neuroleptic is the best choice in this case?

  A. Droperidol B. Chlopromazine C. Phenobarbital
  D. Gidazepam E. Diazepam (A)

- A patient with acute psychosis has been injected wth chlorpromazine. His attempt to stand up quickly was complicated by severe lowering of blood pressure. Which receptors blocked by the drug are responsible for such side effect?

  A. D2-dopaminoreceptors B.M-cholinoreceptors C. Alpha-adrenoceptors D. Histaminoreceptors E. Serotoninoreceptors

  (C)