PSYCHOTROPIC DRUGS

Drugs of this group are used for the treatment of mental illness:

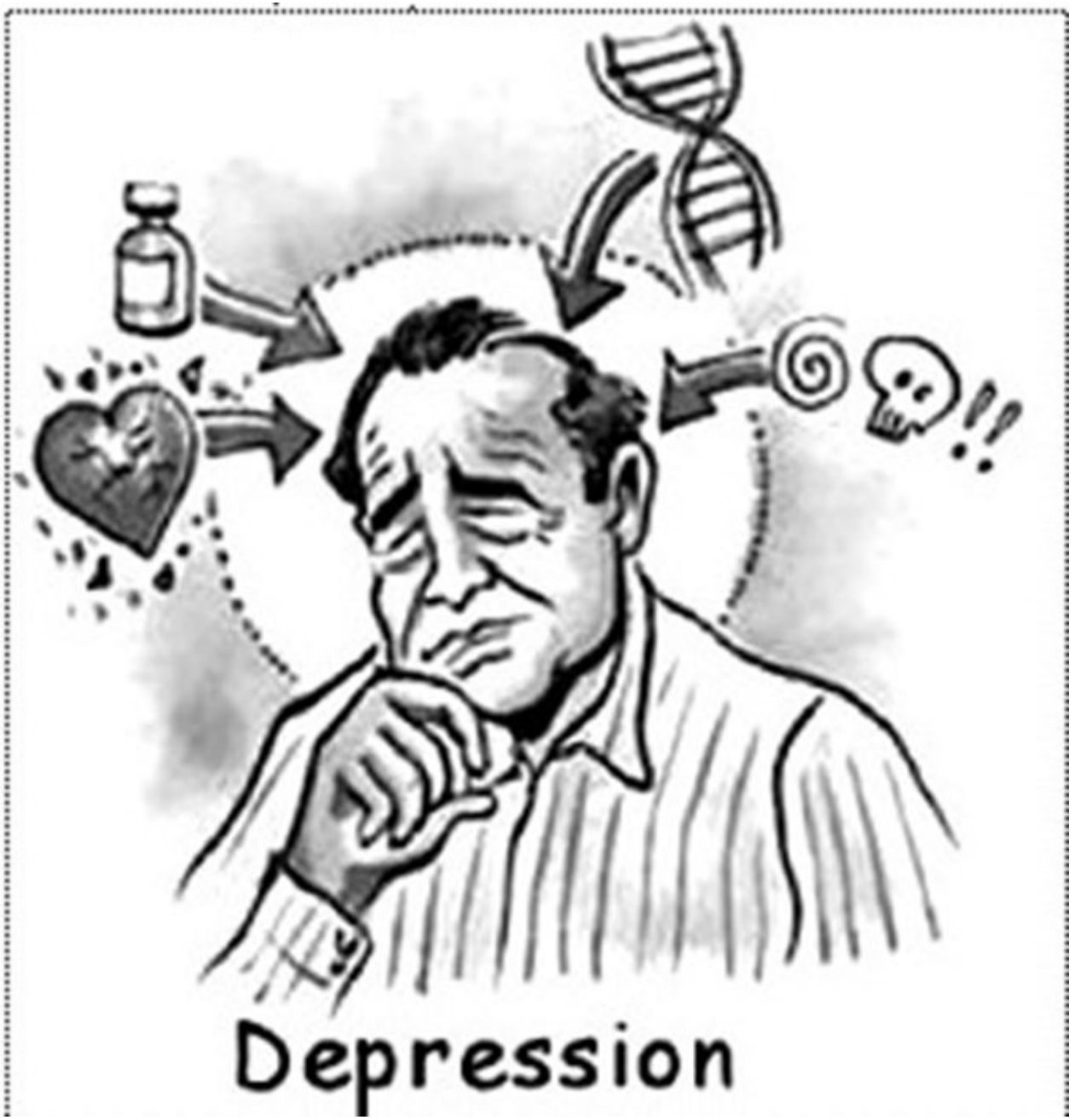
- Psychoses,
- Neurotic and pseudoneurotic disoders, associated with stress, nervousness, fear, anxiety.

Antidepressants
Psychostimulants
Nootropics
Analeptics

Depression (from lat. deprimo - "push", "suppress") is a mental disorder characterized by a “depressive triad”:

- Decrease in moods, inability to experience joy;
- Thinking disorders, negative judgments;
- Motor retardation

There are disturbances of a somatic nature (insomnia, loss of appetite, constipation, palpitations, loss of libido, impotence) also.


Depression

Therapeutic agents are divided into two groups:

- **Thymoleptics ,** possessing a pronounced ability to re-elevate depressed mood e.g., the tricyclic antidepressants;
- **Thymeretics,** having a predominant activating effect on psychomotor drive, e g., monoamine oxidase inhibitors.

Classification

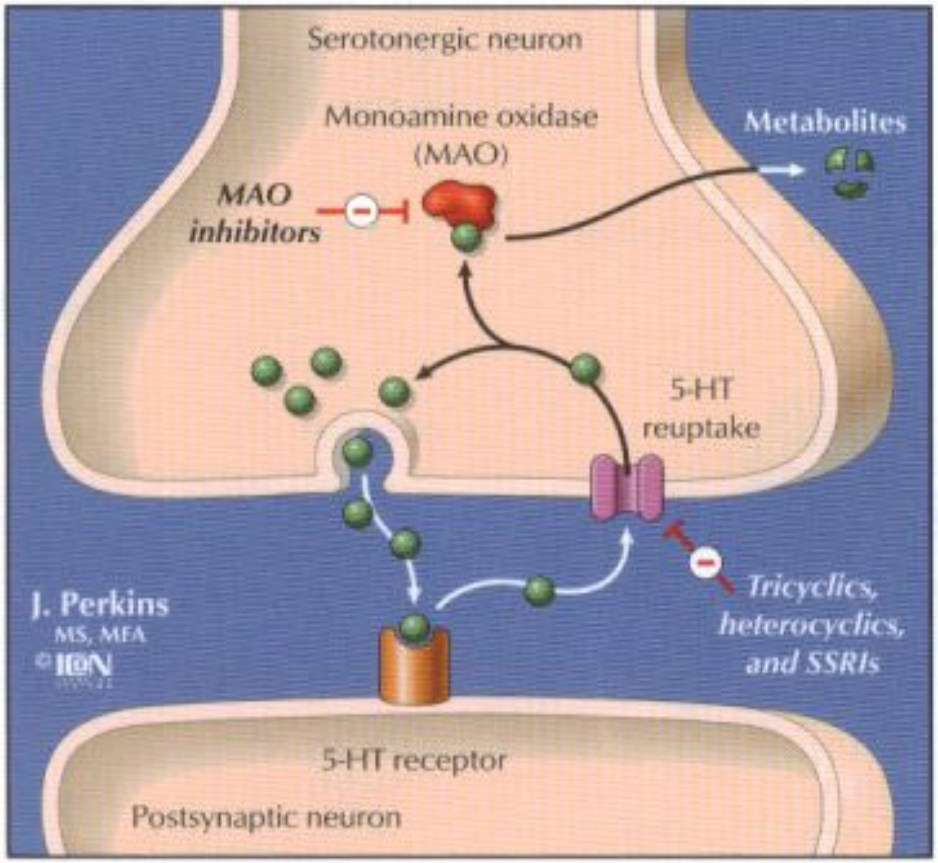
A. Drugs blocking neuronal uptake of monoamines

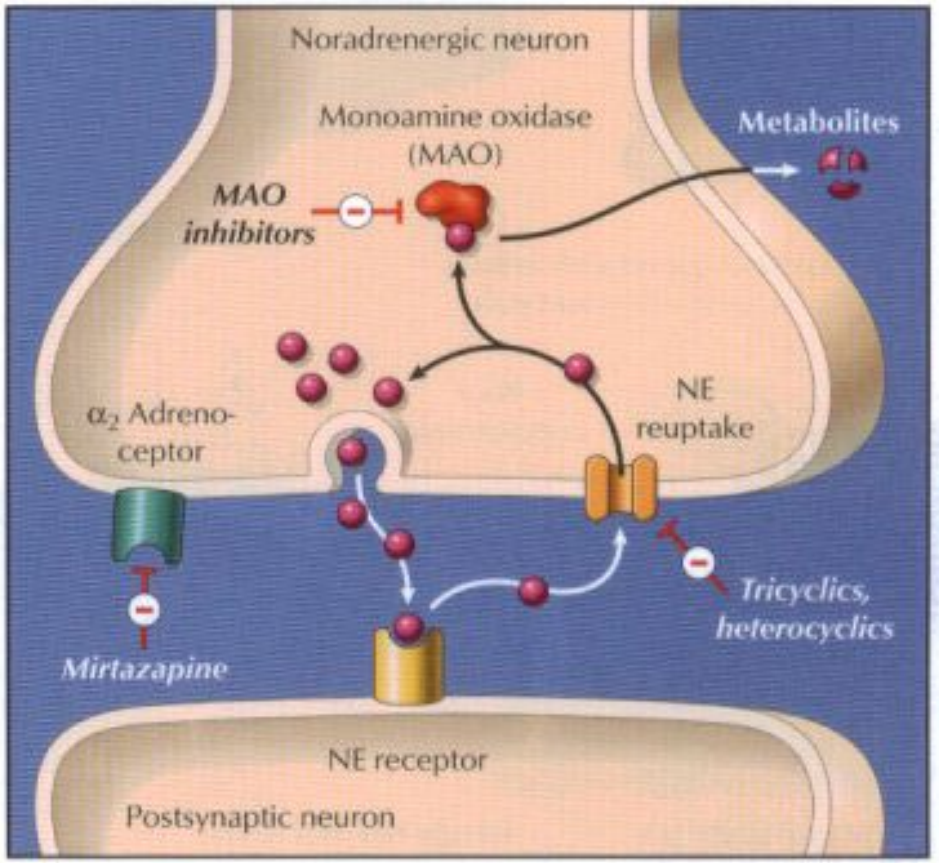
1. Drugs possessing nonselective action, blocking neuronal uptake of serotonin and norepinephrine: Imipramine; Amitriptyline
2. Drugs possessive selective action

- Blocking neuronal uptake of serotonin: Fluoxetine
- Blocking neuronal uptake of norapinephrine: Maprotiline

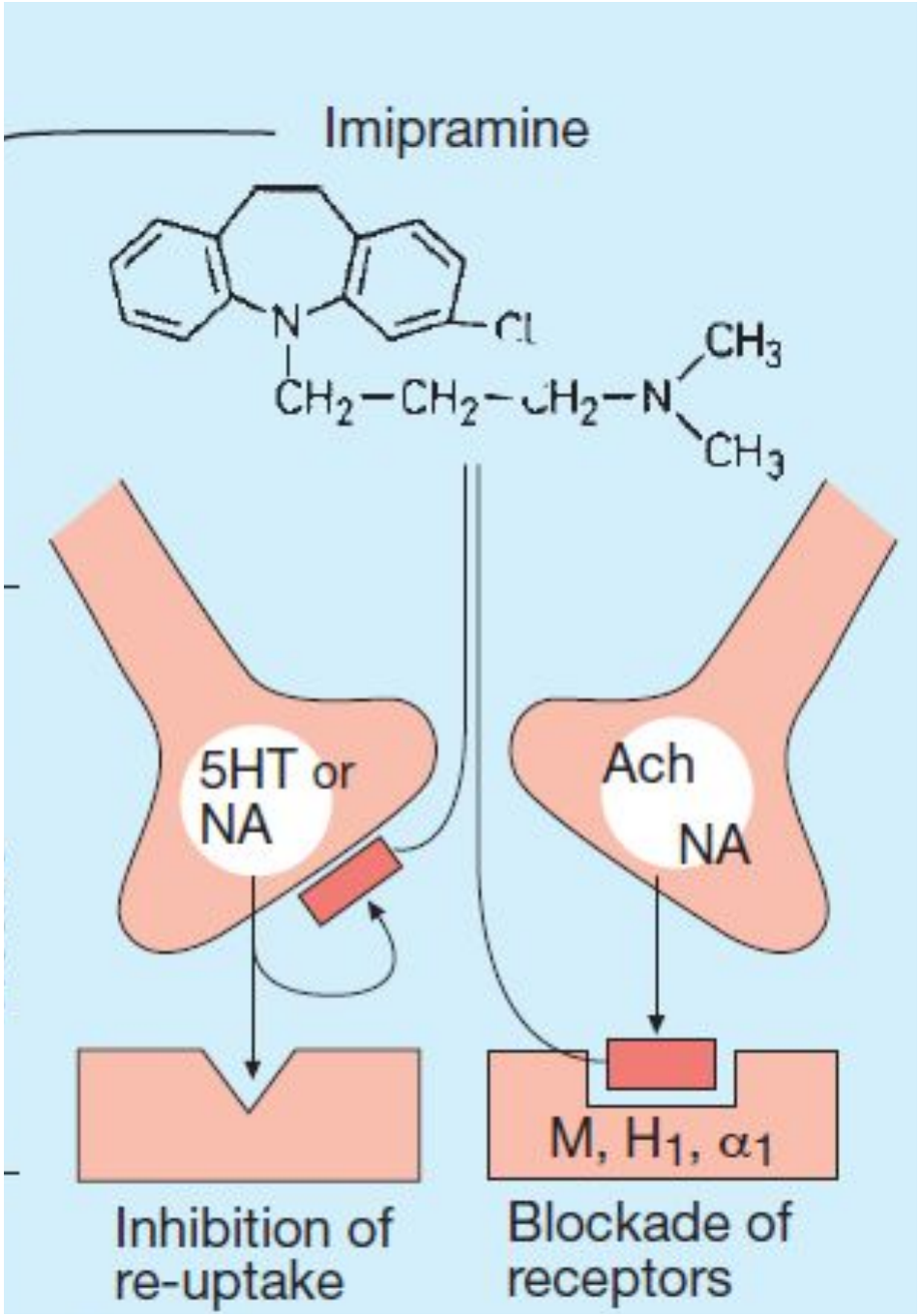
B. Monoamine oxidase inhibitors (MAO)

1. Nonselective action (MAO-A and MAO-B inhibitors): Nialamide
2. Selective action (MAO-A inhibitors): Moclobemide, Pirlindol (Pirazidol)


Serotonergic neuron
Monoamine oxidase
(MAO)
Metabolites
MAO
inhibitors
5-HT
reuptake
Tricyclics,
heterocyclics,
and SSRIs
J. Perkins
MS, MFA
5-HT receptor
Postsynaptic neuron


Noradrenergic neuron
Monoamine oxidase
(MAO)
Metabolites
MAO
inhibitors
α2 Adreno-
ceptor
NE
reuptake
Tricyclics,
heterocyclics
Mirtazapine
NE receptor
Postsynaptic neuron

- Tricyclic antidepressants or antidepressants of nonselective action block neuronal reuptake of serotonin and norepinephrine.
- Imipramine has marked antidepressant properties, a weak psychostimulating and sedative effects. I. blocks the presynaptic α_2-AR, serotonin (5-HT) and histamine receptors.
- It blocks peripheral M-ChR, α1-AR, H1-R; it has papaverin-like effect.


Imipramine
N
Cl
CH2–CH2–CH2–N
CH3
CH3
5HT or
NA
Ach
NA
M, H1, α1
Inhibition of
re-uptake
Blockade of
receptors

- I. is metabolized in the liver and its metabolite (desmethylimipramine or desipramine) is used in clinical practice as an antidepressant.
- The therapeutic effect of I. sets in after 2-3 weeks.
- Amitriptyline has marked sedative effect. It is connected with blockade of M-ChR and H1-R. It develops in 1-2 days.

- The stimulating effect is associated with the accumulation of norepinephrine in the synapses of the reticular formation of the brain stem. It develops 5-7 days.
- Symptoms: decreased inhibition, increased reaction rate, the recovery of facial expressions.
- Antidepressants have analgesic, hypothermic, antiemetic effects also.

- Side effects of tricyclic antidepressants: tachycardia, hypotension, mydriasis, increased intraocular pressure, impaired accommodation, dry mouth, constipation, difficulty in urination, allergic reactions, jaundice, leukopenia.
- They are contraindicated in glaucoma and hypertrophy of prostate gland.
- They are not be combined with non-selective MAO inhibitors due to the risk of toxic effects. The interval between administration of 2 groups should not be less than 1.5-2 weeks.

- Fluoxetine has high antidepressant activity. The effect develops gradually (1-4 weeks).
- It has no sedative, anticholinergic and adrenergic action. Fluoxetine causes loss of appetite and weight reduction.
- Its main adverse effects include appetite disorders (anorexia), nausea, nervousness, headache, sleeplessness, skin rashes, “serotonin syndrome” (in a case of accumulation of excessive of serotonin): psychomotor agitation, tremor, chills, hyperthermia, collapse, diarrhea.

- Maprotiline has antidepressant and sedative effect. It selectively blocks neuronal uptake of norepinephrine.

MAO is a mitochondrial enzyme involved in the oxidative deamination of biogenic amines (Adr, NA, DA, 5-HT). Two isoenzyme forms of MAO have been identified.

- MAO-A preferentially deaminates 5-HT and NA, and is inhibited by moclobemide.
- MAO-B preferentially deaminates phenylethylamine and is inhibited by selegiline.
- Dopamine is degraded equally by both isoenzymes.
- Their distribution also differs. Peripheral adrenergic nerve endings, intestinal mucosa and human placenta contain predominantly MAO-A, while MAO-B predominates in certain areas (mainly serotonergic) of brain and in platelets.

- The active metabolites of nonselective MAO inhibitors inactivate the enzyme irreversibly. The drugs themselves stay in the body for relatively short periods, but their effects last for 2–3 weeks after discontinuation.
- Return of MAO activity depends on synthesis of fresh enzyme; tissue monoamine levels remain elevated long after the drug has been largely eliminated.

- These drugs inhibit a number of other enzymes and interact with many food constituents and drugs **(tricyclic antidepressants, Levodopa)** .
- **Cheese reaction.** Certain varieties of cheese, beer, wines, pickled meat and fish, contain large quantities of tyramine, dopa, etc. In MAO inhibited patients these indirectly acting sympathomimetic amines escape degradation in the intestinal wall and liver → reaching into systemic circulation they displace and release large amounts of NA from transmitter loaded adrenergic nerve endings → **hypertensive crisis, cerebrovascular accidents.**

- **Moclobemide is a reversible and selective** MAO-A inhibitor with short duration of action; full MAO activity is restored within 1–2 days of stopping the drug. Assignment does not require a special diet.
- Adverse effects are nausea, dizziness, headache, insomnia, rarely excitement and liver damage.

- Pirazidolum is a tricyclic compound, a derivative of indole.
- Antidepressant effect of pirazidolum can occur together with sedative (on the background of anxiety, nervousness) or stimulating (on the background of depression) effects, depending on the patient' condition.
- The mechanism of its antidepressant effect is linked to the reversible inhibition of MAO-A and neuronal uptake of norepinephrine.
- The drug is well tolerated.

Indication for use of Antidepressants:

- Depression with motor excitation, aggressiveness, delirium;
- D. with lethargy, apathy;
- Chronic somatic diseases with depressive component (diabetes mellitus, neurodermatitis, cancer, heart failure, myocardial infarction);
- Chronic pain symptoms accompanied by depression: migraine, cardialgia, back pain, pain in cancer;
- Bed-wetting.

- Psychostimulants-drugs that increase physical and mental performance, restoring functional activity in fatigue, apathy, psychomotor retardation in hypochondria.
- Phenylalkylamine derivative- Amphetamine (Phenamine)
- Sydnonimin derivative - Mesocarb
- Methylxanthine derivative -Caffeine
- Adamantane derivatives - Bromantan

- They have an exciting effect on the cerebral cortex, reticular formation, thalamus, hypothalamus, limbic system.
- They increase the release of dopamine, serotonin, norepinephrine, reduce neuronal uptake of mediators, block MAO. They indirectly stimulate adrenergic receptors.
- They decrease fatigue, drowsiness, need for sleep, improve vision, hearing, smell, touch. They cause the desire to work, ↑ initiative, physical and mental performance, memory, improve mood.

- Amphetamine acts quickly and strongly after 30-60 minutes.
- It affects the food center located in hypothalamus and inhibits hunger.
- It stimulates the respiratory center (as an analeptic).
- It affects the peripheral innervations.
- Adverse effects: hypertension, tachycardia, arrhythmia, nausea, chill, giddiness, excitation, anxiety, sleeplessness, euphoria, drug dependence and tolerance. Thus, it is not used now in medical practice.

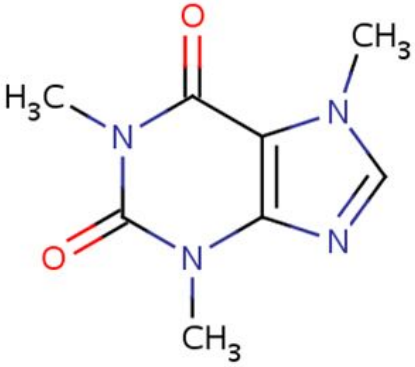
- Mesocarb does not work in the area of dopaminergic synapses. It acts gently after 2-3 days.
- It does not cause anorexigenic action.
- It weakly increases blood pressure.
- Does not cause euphoria.
- It is used for asthenia, depression, narcolepsy, enuresis, neuroses, after encephalitis, meningitis, abstinence. It is used together with Bromantan.
- Side effects: excitation, anxiety, sleeplessness, slight rise in arterial pressure.

There are 2 main groups of methylxanthines.

Caffeine is 3-methylxanthine, but theophylline and aminophylline are 2-methylxanthine.

Mechanism of action of methylxanthines:

- Blockade of adenosine receptors
- Blockade of phosphodiesterase, which leads to the accumulation of cAMP
- Increased output of neurotransmitters (dopamine, serotonin, norepinephrine. acetylcholine)



- Adenosine is intermediate metabolite produced from cAMP under the influence of enzyme PDE (phosphodiesterase).
- Adenosine is endogenous ligand (neuromediator) of A_1 and A_2 receptors localized in the CNS and on periphery.
- Adenosine is inhibitory neuromediator of the CNS. The activation of adenosine receptors causes inhibition, sleepiness, a sense of tiredness.

Direction of action	**Methylxanthines**	**Adenosine**
The CNS	Excitation	Inhibition
Catecholamines release	Increased	Decreased
Rate and force of the cardiac contraction	Increased	Decreased
Renal flow and renin production	Increased	Decreased
Histamine release from the mast cells	Decreased	Increased
Lipolysis in the fatty tissue	Increased	Decreased

- Caffeine is alkaloid contained in tea leaves, beans of coffee, cacao, cola.

It produces the following central effects, - psychotropic and non-psychotropic ones:

- Psychotropic effect - p*sychostimulant effect* (direct stimulating action on brain cortex): it increases mood, temporarily relieves tiredness and sleepiness, stimulates cognitive activity, increases mental and physical efficiency, motor activity and shortens reaction time.
- Non-psychotropic ones (a*naleptic (life-enhancing) effect)* –stimulates vagus, respiratory and vasomotor center of medulla oblongata and activates respiration and cardiovascular system.

Caffeine has both central and peripheral action. These effects can be opposite.

1.Action on the heart

- Direct - stimulant due to direct action on adenosine receptors of myocardium (increase in rate and contractility)
- Central - inhibitory (action on vagus center).

2.Action on vascular tone and BP

- Direct myotropic spasmolytic action on smooth muscles of blood vessels (inhibition of PDE and increase in cAMP) - dilation of vessels
- Central action (activation of vasomotor center) - narrowing of vessels

- Final Caffeine action on vessels is determined by their initial state and depends on their localization.
- Coronary blood vessels, renal artery, skeletal muscle blood vessels are mainly dilated.
- Cerebral blood vessels are narrowed more frequently. So Caffeine is effective in migraine.
- Commonly Caffeine does not change or little increase normal BP.
- It increases BP at hypotension.
- High of doses can stimulate release of adrenalin from adrenals and increase BP.

- Cafeine has bronchodilatory action (direct myotropic spasmolytic).
- Dimethylxanthines (aminophylline, teophylline, theobromine) have mainly peripheral action.
- Caffeine increases diuresis because it dilates renal arteries and increases filtration
- Caffeine stimulates secretion of pepsinogen and hydrochloric acid.
- Caffeine stimulates glycogenolysis and lipolysis.

	Aminophylline	Caffeine
Stimulation of the CNS	+	3+
Stimulation of the heart	2+	2+
Dilation of coronary vessels	2+	+
Relief of bronchospasm	3+	±
Increase in diuresis	2+	±

- Indications: C. is used to stimulate cognitive activity, in fatigue, migraine, headaches (together with non-narcotic analgesics) and hypotension.
- The side effects: tolerance, psychological dependence (theism), nausea, vomiting, anxiety, excitation, sleeplessness, paradoxical sleepiness, tachycardia, cardiac arrhythmias.

Nootropic drugs (Greek *noos* – mind, thinking, *tropos* – direction, relativity) - cognition enhancers.

They are able to activate higher psychic functions of brain (memory, learning, mental activity).

They influence on metabolism in brain (neurometabolic stimulants).

- Derivatives of pyrrolidone (a cyclic derivative of GABA) - **Piracetam, Phenotropil**
- GABA derivatives – **Phenibut**
- Derivatives of aminoacetic acid - **Glycine**
- The analog of the fragment ACTH – **Semax**
- Preparation of plant origin - Ginkgo biloba leaf extract (**Bilobil, Tanakan**)

Nootropic effect:

- **Improving learning and memory**-in the pathology of vascular, traumatic, infectious, toxic genesis and aging.
- **Strengthening of brain functions after loss** - recovery and stabilization of mental functions (amnesia, speech loss after stroke)
- **Facilitation of interhemispheric and intrahemispheric communication.**
- **Increasing the tone of the cerebral cortex.**

- Stimulating effect: Piracetam, Phenotropil, Piriditol
- Sedative-tranquilizing effect: Phenibut, Glycine
- Anticonvulsant
- Somnolent
- Anti-asthenic (Phenibut, Phenotropil)
- Vasovegetative
- Antiplatelet, angioprotective (Bilobil, Tanakan)
- Adaptogenic and anti-psychotic

The main mechanisms of nootropic drug action

- Stimulate energetic and plastic processes;
- Increase activity of enzymes of respiratory chain and tricarboxylic acid cycle (Krebs cycle);
- Increase uptake and consumption of glucose by brain cells;
- Increase ATP synthesis;
- Increase the resistance of brain cells to adverse factors, including hypoxia
- Improve blood supply of brain;
- Increase synthesis of proteins, nucleic acids and membrane phospholipids;
- Stabilize damaged cell membranes, reduce the formation of free radicals.

Indications for the use

- Mental disorders of children: developmental delay, cerebral palsy, birth trauma;
- Atherosclerosis of cerebral vessels, post-stroke states, encephalopathy;
- Brain injury;
- Senile dementia, depression, asthenia;
- Neurotic conditions, severe stress with fatigue, violation of social adaptation;
- Coma (vascular, traumatic or toxic etiology).

- They are used for long courses. They are injected and administered orally. Effect develops slowly.

They are well tolerated but can cause:

- ❑ Anxiety;
- ❑ Irritability;
- ❑ Insomnia;
- ❑ Allergy;
- ❑ Dyspepsia.

ANALEPTICS (Respiratory stimulants)

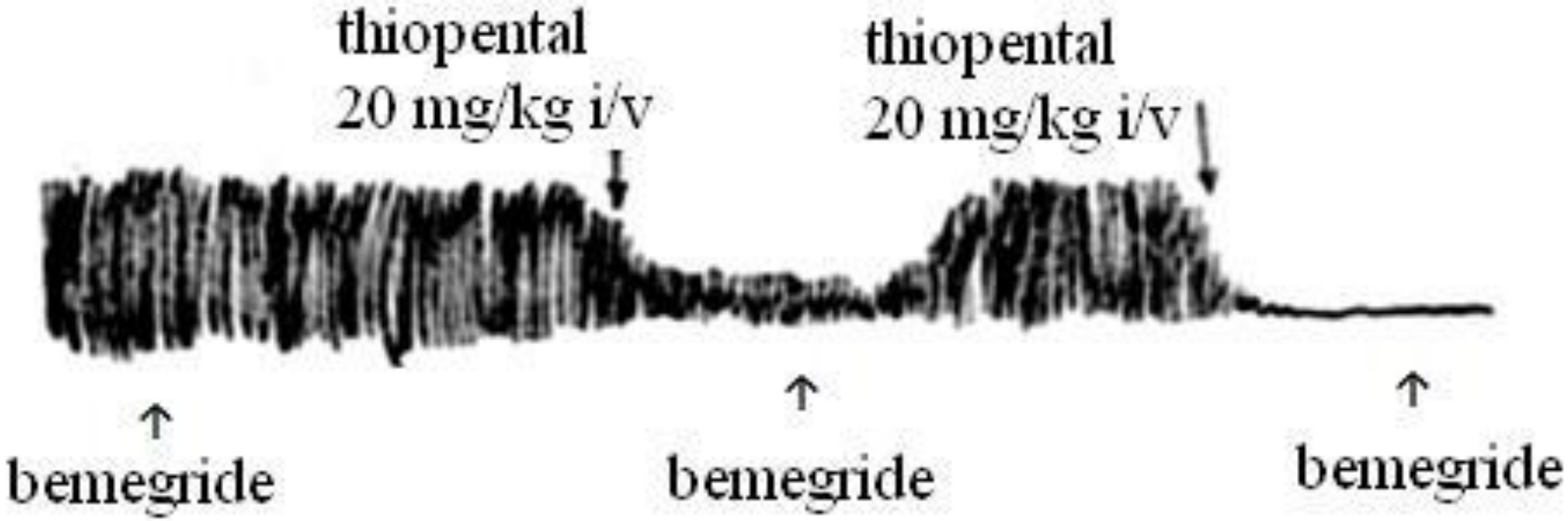
Classification

- Direct acting drugs: **Caffeine, Bemegrid**
- Direct and reflex action (through carotid and aortic body chemoreceptors): **Doxapram, Camphor, Nikethamide** (25% solution of nicotinic acid diethylamide)
- Reflex action (through carotid and aortic body chemoreceptors): **Cytisine, Lobeline**

Effects

- Excitation of the respiratory center - ↑ frequency and depth of breathing
- Excitation of vasomotor center - ↑ vascular tone, elevation of blood pressure;
- Stimulation of the cerebral cortex (only in high doses) - awakening and convulsive effect;
- Cardiac stimulating effect (Caffeine, Camphor);
- Locally irritating effect (Camphor).

The most powerful respiratory analeptic – Bemegrid


thiopental
20 mg/kg i/v
thiopental
20 mg/kg i/v
bemegride
bemegride
bemegride

Indications for the use

- Overdose of sleeping pills and anesthetics (only direct analeptics are effective);
- Collapse of the Central Genesis;
- Acute heart failure (Caffeine, Camphor);
- The easing breathing in infectious diseases and during convalescence, in shock, asphyxia (severe breathing disorders);
- Asphyxia of newborns;
- Locally as an irritant (Camphor).

- Camphor has a local action - irritation of the skin and mucous membranes (distracting, trophic effect). It is used with bedsores, myalgia, arthritis.
- In addition, camphor has expectorant, deodorizing, and antimicrobial (anti-pneumococcal) effect.

Side effects of analeptics: nausea and vomiting; convulsion; restlessness, dizziness, insomnia; infiltrates (oleomas), pain at the injection site; allergic reaction.