

Lecture. PSYCHOTROPIC DRUGS

I. NEUROLEPTICS. ANXIOLYTICS. SEDATIVES. LITHIUM SALTS

PSYCHOTROPIC DRUGS

Neuroleptics, tranquilizers and sedatives are drugs for treatment of psychic disorders of different severity. Neuroleptics (major tranquilizers) are the strongest among these preparations and have antipsychotic action (fig.1.1). Tranquilizers are characterized by anxiolytic and sedative effects. Sedative drugs are the least active and have only sedative effect. Lithium salts are specific agents to treat mania.

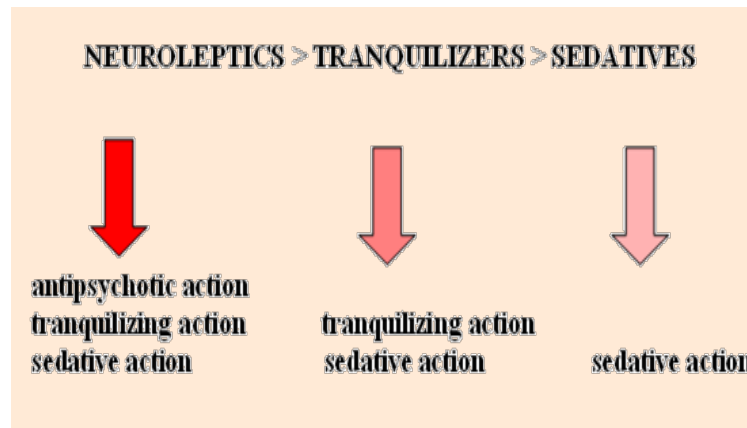


Fig.1.1. Main groups of psychotropic drugs.

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.

Classification

A. Typical neuroleptics

1. Phenothiazines
 - Chlorpromazine (Aminazinum)
 - Trifluoperazine (Triftazinum)
 - Flunazine (Phthorphenazinum)
2. Butyrophenones
 - Haloperidol
 - Droperidol
3. Thioxanthenes
 - Chlorprothixene

B. Atypical neuroleptics

1. Dibenzodiazepines
 - Clozapine
2. Benzamides
 - Sulpiride

Differences between typical and atypical neuroleptics

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

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

CHLORPROMAZINE (AMINAZINUM)

It is 2-chlorine-10-(3-dimethylaminopropyl)-phenothiazine hydrochloride

Pharmacokinetics

- is administered orally, IM, IV
- is absorbed in GI tract, but absorption is poor
- maximal concentration is determined in 2-4 hrs
- penetrates CNS and placenta, concentration in brain is more than in plasma
- binds with albumins in blood plasma (95-98%)
- is metabolized in liver
- is the inductor of microsomal oxidation
- is excreted by urine, bile and mothers' milk
- acts during 6-8 hr, T_{1/2} = 30 hrs
- is accumulated

Mechanism of action

It blocks dopamine receptors; exert preference for D₂-dopamine receptors (fig.1.2), serotonin receptors, cholinergic receptors, α-adrenoceptors, H₁-histamine receptors (fig.1.3).

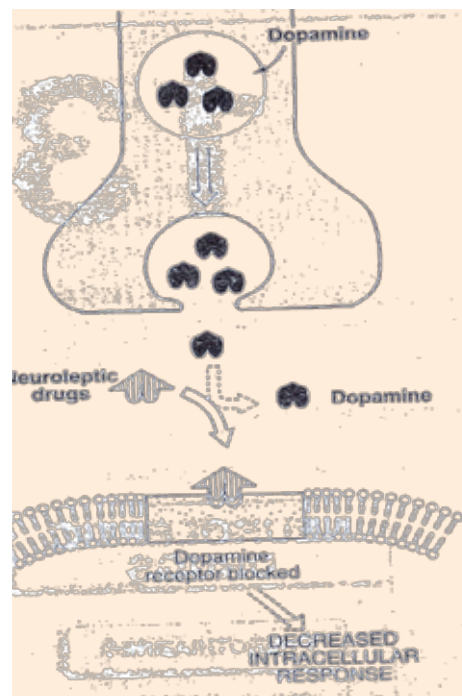


Fig.1.2. Dopamine-blocking mechanism of action of neuroleptics.

Chlorpromazine acts in mesolimbic system, hypothalamus, extrapyramidal system, trigger zone of emetic center, ascending reticular system of brain. It has peripheral action (antimuscarinic, antiadrenergic and antihistamine).

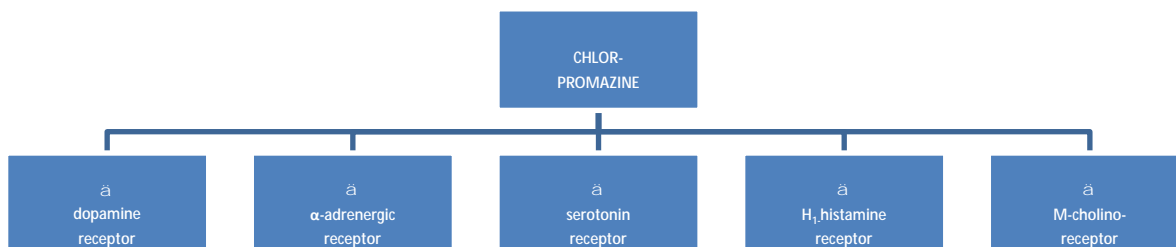


Fig.1.3. Receptors, which are blocked by chlorpromazine.

Pharmacodynamics

- antipsychotic action (decreasing in hallucinations and agitation)
- anxiolytic action (decreasing in anxiety and stress)
- sedative action (decreasing in restlessness)
- decrease in psycho-motor excitement
- hypnotic action
- antiseizure action
- cataleptic effect (absence of active motions under the conditions of normal muscle tone)
- antiemetic action (decreasing in nausea and vomiting caused by cancer chemotherapy or radiation)
- antihypertensive effect
- hypothermia and poikilothermia (decreasing in high body temperature as well as normal temperature)
- otentative action
- weak anti-inflammation and anti-allergic actions

Indications

1. Psychosis, schizophrenia
2. Psycho-motor excitement
3. Seizures attack
4. Premedication
5. Severe vomiting
6. Hypertensive crisis
7. Hyperthermia
8. Hibernation (decreasing 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

Side-effects	Contraindications
1. Irritation in the place of injection 2. Pain in stomach 3. Irritation of skin and mucous membranes 4. Confusion, blurred vision, dry mouth, hyposecretion in stomach, constipation, urinary retention (due M-cholinoblockage) 5. Hypotension, orthostatic reactions,	1.Diseases of liver and kidney 2.Diseases of blood 3.Hypothyroidism 4.Thromboembolism 5.Organic diseases of brain and spinal cord (trauma, cancer, insult) 6.Gastric ulcer

lightheadedness (due to blockage of α -adrenoceptors) 6. Liver lesions, icterus 7. Inhibiting in hemopoiesis (leucopenia, agranulocytosis) 8. Dermatitis, increasing in sensitivity to sun radiation, 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 (due depression of hypothalamus) 14. Allergy 15. Tolerance	7. Pregnancy and lactation
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Peculiarities of other preparations

Typical neuroleptics

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

Phthorphenazinum contains fluorine; has strong antipsychotic and antiemetic actions; may manifest 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, antiemetic and sedative action, 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 thioxanthene derivative; has sedative action; decrease depression; antiseizure effect is weak; does not cause catalepsy; is used in psychoses accompanied by depression, in neurosis (lower doses).

Atypical neuroleptics

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

Sulpiride has strong antiemetic action and weak cataleptic action; has not sedation, antiseizure and potentiative effects; has antidepressive action; is used for treatment of psychic diseases accompanied by apathy as well as for psycho-somatic diseases.

Concept about neuroleptanalgesia

Neuroleptanalgesia – is the kind of general anaesthesia when neuroleptic (Droperidol) and narcotic analgesic (Phentanyl) are administered together (IV).

ANTI-ANXIETY DRUGS

ANXIETY

Anxiety is the state of tension, apprehension or uneasiness. The symptoms of severe anxiety are mental disturbances accompanied by tachycardia, sweating, trembling, palpitations.

Episodes of mild anxiety are common life experiences and do not warrant treatment. The symptoms of severe or chronic anxiety may be treated with anti-anxiety drugs.

ANXIOLYTICS

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

Classification

1. Benzodiazepines
 - Chlordiazepoxide (Chlosepilum)
 - Diazepam (Sibasonum)
 - Phenazepamum
 - Medazepam (Mezapam, Rudotel)
 - Gidazepam
2. Preparations of other chemical structure
 - Buspirone
 - Benactyzime (Amizilum)
 - Meprobamate (Meprotranum)

Antagonist of benzodiazepines is Flumazenil

CLORDIAZEPOXIDE

It is benzodiazepine derivative (fig.1.4).

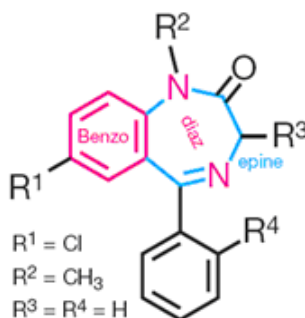


Fig. 1.4. Chemical structure of benzodiazepines.

Pharmacokinetics

- is administered orally, IM, IV
- is absorbed in GI tract
- penetrates CNS
- is metabolized in liver
- is excreted by urine
- has long-durative action, $T_{1/2} = 24-48$ hr

Mechanism of action

Benzodiazepine-receptor is the part of benzodiazepine-GABA-chloride ion channel complex. The drug binds with benzodiazepine receptors of Cl^- ion channels and opens them (fig.1.5). Cl^- ions entry is increased, that leads to hyperpolarization of cell membranes. Depolarization gets worse and decreasing of neurons excitement in limbic system and midbrain is developed. It is resulting in anxiolytic action.

Pharmacodynamics	Indications
1. Anxiolytic action (decrease in anxiety, panic and stress)	1. Neuroses
2. Sedative action	2. Stress, emotional overstrain
3. Hypnotic action	3. Sleeping disorders induced by emotional overstrain
4. Central myorelaxative action (due to action on spinal polysynaptic reflexes)	4. Neurological diseases with muscle spasticity
5. Anti-seizure action	5. Seizures
	6. Abstinence in chronic alcoholics

6. Potentiative action (drug addition if analgesics, general anesthetics or other CNS inhibitors are administered together with this drug)	7. Psychosomatic diseases 8. Premedication
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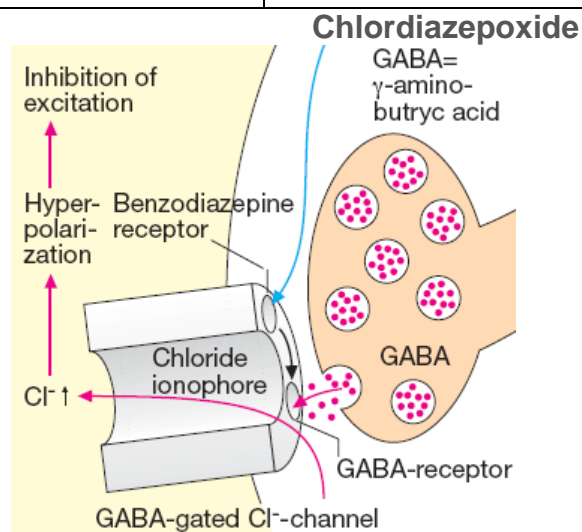


Fig. 1.5. Mechanism of action of chlordiazepoxid.

Side-effects	Contraindications
<ol style="list-style-type: none"> 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 	<ol style="list-style-type: none"> 1. Jobs that needs increased attention 2. Myasthenia 3. Diseases of liver and kidney 4. Pregnancy

Peculiarities of other preparations

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 T_{1/2} = 48 hrs); is more active than clordiazepoxide, especially in anti-seizure effect; causes decrease in night gastric secretion and in arrhythmia; has all typical indications; is suitable to treat seizure attack; may be used in combined therapy of ulcerative disease and heart arrhythmia.

Phenazepamum is administered orally; maximal concentration is in 1-2 hrs; T_{1/2} = 6-10 hrs; is stronger than clordiazepoxide or diazepam; has strong hypnotic action and muscle relaxation.

Medazepam is taken orally; is less active, but does not cause hypnotic effect and myorelaxation (so named "day" tranquilizer); may be used in patients, which are needed increased attention for their jobs.

Gidazepam is "day" tranquilizer; is taken by mouth; therapeutic action begins in 30-60 min and lasts 1-4 hrs; T_{1/2} = 86,7 hrs; has anxiolytic action, psychostimulating and antidepressant actions; has not hypnotic effect; is well tolerated; is used to treat neuroses accompanied by asthenia and depression.

Concept about ataractanalgesia

Ataractanalgesia is the kind of general anaesthesia when tranquilizer and narcotic analgesic are administered together (IV).

SEDATIVES

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
 - Corvalolum
 - Valocormidum

SODIUM BROMIDE

Pharmacokinetics

- 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 (decreasing in restlessness and anxiety)
- hypnotic action
- antiepileptic action

Indications

1. Light forms of neuroses, neurasthenia, hysteria
2. Restlessness
3. Insomnia
4. Epilepsy
5. Light forms of hypertension

Side-effects

Accumulation of bromides results in *bromism*.

Main signs:

drowsiness, weakness, apathy, memory disturbances, skin rash, rhinitis, cough.

Treatment of bromism:

- to drink much of liquid
- sodium chloride with meals
- diuretics, especially ethacrynic acid

Vegetable preparations

Sedatives of vegetable origin are galenic preparations from medicinal plants such as valerian, Leonurum and some other plants (fig 1.6).

They have common pharmacological properties:

- are taken orally
- mechanism of action is not known
- main effects are sedative, hypnotic, spasmolytic

- indications use are: light forms of neurosis, neurasthenia, insomnia, cardioneurosis, somatic diseases with neurotic syndrome, spasms of stomach and intestine

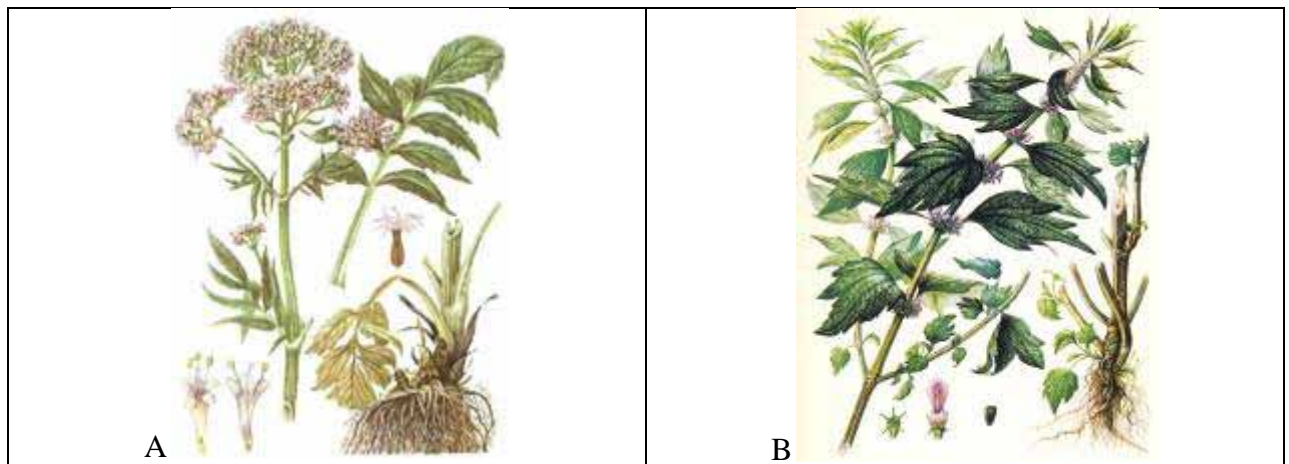


Fig.1.6. Medicinal plants for sedatives: A – valerian; B – Leonurum.

Combined sedative preparations

Corvalolum is mixture for oral administration, which is dosed by drops and contains ethylic ester of bromine-isovalerianic acid, 2% of phenobarbital, 3% of oil of menthe, sodium hydroxide, alcohol and water. It has sedative, spasmolytic and light hypnotic action and is used in neuroses, spasms of coronary blood vessels, tachycardia, spasms in the gut.

Valocormidum contains tincture from valerian, tincture from the lily of the valley, tincture from Belladonna, sodium bromide, menthol and distil water; is used in neuroses accompanied by bradycardia.

DRUGS USED TO TREAT MANIA

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 carry the diagnosis of bipolar affective disorder.

DRUGS USED IN MANIAS

Classification

1. Lithium salts
 - Lithium carbonate
 - Lithium oxibutyrate
2. Other preparations
 - Carbamazepine
 - Clonazepam
 - Valproic acid

LITHIUM CARBONATE

Pharmacokinetics

- is taken orally
- is absorbed in the gut completely, but absorption lasts during 8 hrs
- maximal concentration is developed in 2-4 hrs
- does not bind to plasma proteins
- 95% of the dose is excreted with urine and 5% – with sweat
- $T_{1/2} = 19$ hrs
- therapeutic effect is developed 1-3 weeks after the start of treatment

Mechanism of action

Lithium disturbs sodium transport and in such way inhibits Ca-dependent liberation of noradrenalin and dopamine in synapses of brain. At the same time it does not influence on serotonin. Lithium salts also inhibits re-uptake of noradrenalin and dopamine.

Pharmacodynamics

- 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

1. Bipolar affective disorder (manic-depressive disease)
2. Manias

Small therapeutic index of the drug necessitates frequent monitoring of lithium level in blood serum

Side-effects

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

II. ANTIDEPRESSANTS

DEPRESSION

Depression is mood altering disease, affective disorder.

Signs of depression: hopelessness, despair, inability to experience pleasure in ordinary life, loss of interest to usual activity, suppression of appetite, sleep disturbance.

There are three types of depressions: 1) reactive (or secondary); 2) endogenous; 3) manic-depressive disease.

According to **biogenic monoamine theory** development of depression is resulting from deficiency of monoamines (norepinephrine and serotonin) in certain areas of brain.

ANTIDEPRESSANTS

Antidepressants are the drugs for treatment of depression.

Classification

On mechanism of action

A. Inhibitors of monoamine re-uptake

1. Non-selective inhibitors of monoamines re-uptake
 - Imipramine (Imizinum)
 - Amitriptyline
2. Selective inhibitors of serotonin re-uptake
 - Fluoxetine
3. Selective inhibitors of norepinephrine re-uptake
 - Maprotiline

B. MAO inhibitors

1. Non-selective (MAO-A and MAO-B)
 - Phenelzine
 - Tranylcypromine
 - Nialamidum
2. Selective (MAO-A)
 - Pirlindole (Pirazidolum)
 - Moclobemide

C. Atypical antidepressants

- Trazodone
- Tianeptine
- Mianserin

On additional action

A. Thymoleptics (+ sedative effect)

- Amitriptyline

B. Thymoerectics (+ psychostimulating effect)

- Nialamidum

C. Mixed acting

- Imizinium
- Pirlindole

IMIPRAMINE

It has tri-cyclic structure.

Pharmacokinetics

- is administrated orally or IM
- is well absorbed in GI tract
- penetrates CNS
- is metabolized in liver and excreted with urine and bile
- has half-life of 4-17 hrs
- has latent period; therapeutic effect is developed slowly in 2-3 weeks after beginning of the treatment

Mechanism of action

It includes inhibition of norepinephrine re-uptake resulting in increase in adrenergic processes in brain structures (fig.2.1).

Mechanism of action is also connected with inhibition of serotonin re-uptake resulting in increase in serotonin amount in synapses, that leads to increase in serotonin inhibiting influence in limbic system (fig.2.1).

Imipramine and other tri-cyclic antidepressants block central and peripheral M-cholinoreceptors. Sedation and antimuscarinic action is due to such blockade.

It also blocks α -adrenergic receptors and histamine receptors.

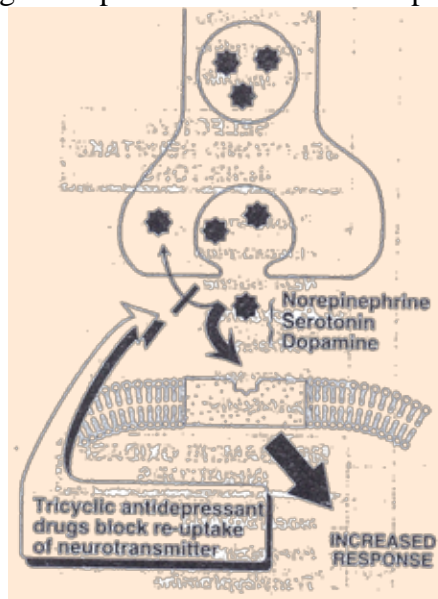


Fig.2.1. Mechanism of action of imipramine.

Pharmacodynamics

- anti-depressive action
- in emotional sphere may manifest sedative or weak psychostimulant action

- does not produce CNS stimulation or mood elevation in normal individuals
- peripheral M-cholinoblocking action
- antihistamine action

Indications

1. Severe major depression
2. Enuresis (in children older than 6 years)

Side-effects	Contraindications
1.Excitement 2.Insomnia 3.Inbcrease in agitation and hallucination 4.Headache 5.Tremor 6.Lowerinn of BP, orthostatic hypotension 7.Tachycardia, arrhythmia 8.Allergy 9.Changes in blood film 10.Dry mouth 11.Disturbances of accomodation 12.Increase in intraocular pressure 13.Retention of urine 14.Contipation 15.Physical and psychological dependence	1.Psychic excitement 2.Schizophrenia 3.Glacouma 4.Adenoma of prostate 5.Atony of urinary bladder 6.Diseases of blood 7.Diabetes mellitus 8.Tuberculosis 9.Infections 10.Severe diseases of heart, liver, kidney 11.Should not be taken in the evening 12.Should not be taken together or after withdrawal of MAO-inhibitors (fig2.2).

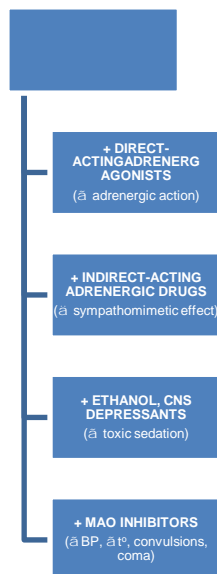


Fig.2.2. Drugs interactions of imipramine and other tri-cyclic antidepressants.

Peculiarities of other re-uptake inhibitors

Amitriptyline has tri-cyclic structure; is administered orally or IM, antidepressant action manifests 10-14 days after the start of treatment; is non-selective inhibitor of monoamines re-uptake; is thymoleptic; does not provoke agitation and hallucinations, does not cause insomnia; may be taken in the evening; is indicated to patients in whom depression is accompanied by panic and anxiety; has M-cholinoblocking action and side-effects resulting from antimuscarinic effect.

Fluoxetine contains fluorine; is taken orally; half-life is 1-10 days; latent period lasts 1-4 weeks; is selective serotonin re-uptake inhibitor (SSRI); possesses psychostimulation effect; has not M-cholinoblocking effect; has not adrenoblocking effect; is widely used to treat depression,

neurotic bulimia, neurotic anorexia, panic disorders, some pain syndromes, premenstrual syndrome; has low toxicity but may cause headache, nervousness, insomnia, appetite disturbances, skin rash, sexual disturbances; should not be combined with non-selective MAO-inhibitors(may cause serotonin syndrome).

NIALAMIDUM

- is taken orally, latent period lasts 12-14 days
- is non-selective MAO-inhibitor: inhibits both MAO-A and MAO-B. In such way prevents inactivation of monoamines within neuron and increases the release of monoamines into synaptic space. That is why increases neurotransmission in certain areas of brain (fig.2.3)
- is thymoerectic
- increases effects of adrenomimetics and sympathomimetics, is reserpine antagonist
- decreases pain syndromes
- indications: depressions unresponsive to tricyclic antidepressants, depressions accompanied by severe anxiety, phobic states, pain syndromes, neuralgia of n.trigeminus
- side-effects: insomnia, headache, hypotension, dry mouth, constipation, cheese syndrome (occurs in patients treated with MAO-inhibitors after use of cheese, beer and other products containing tyramine; manifests by hypertensive crisis and cerebro-vascular accidents; emergence help should be IV injection of α -adrenoblocker)

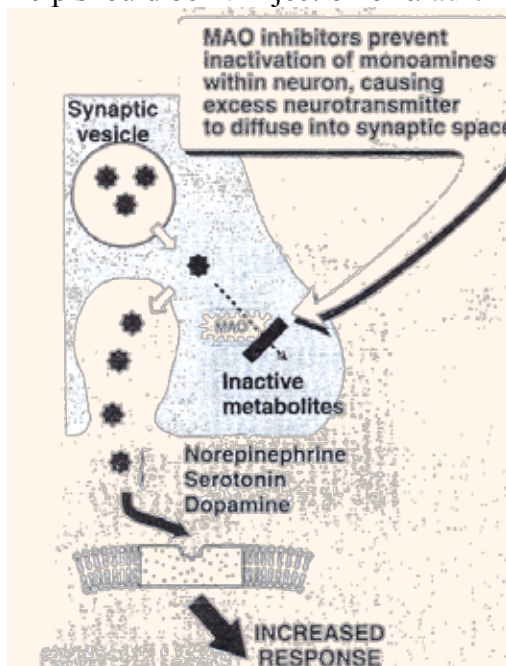


Fig.2.3. Mechanism of action of MAO-inhibitors.

Peculiarities of other MAO-inhibitors

Pirlindole has tetra-cyclic structure; is selective inhibitor MAO-A with reversible action; has regulatory influence on emotions: it causes psychostimulation under the conditions of fatigue and dormancy as well as sedation under the conditions of anxiety; has not M-cholinoblocking properties; is indicated in depressions, manic depressive disease, some types of schizophrenia, has low toxicity; may be used in patients with glaucoma, adenoma of prostate, myocardial infarction

Concept about atypical antidepressants

Atypical antidepressants are modern preparations differ from typical antidepressants on their mechanism of action. It may be blockage of α_2 -receptors and increase in norepinephrine release or inhibition of serotonin receptors.