**Lecture 4**

**Drugs used in mental illness. Drugs of abuse inducing euphoria and psychotomimetics.**

## I. Drugs used in mental illness

The term "psychosis" denotes a variety of mental disorders in which a person has lost some contact with reality. Specific psychotic symptoms include delusions, hallucinations, ideas of reference, and disorders of thought.

- **Schizophrenia** is a disorder usually present between late adolescence and the third decade, in which patients have psychotic symptoms that persists for at least 6 months. It is characterized by delusions, hallucinations (often in the form of voices), marked thinking or language disturbances, inappropriate affect and bizarre disorganized behavior.

- **Paranoia** (chronic systematized delusions) is a personality disorder characterized by systematized delusions of persecution or grandeur usually without hallucinations, with exaggerated self-reference, a tendency to construe independent events and acts as pertaining to him- or herself. Paranoia was formerly classified as a distinct psychosis, but is now considered as one of several varieties of schizophrenia or of personality disorder.

- **Bipolar disorder** (manic depressive illness) is a mood disorder in which episodes of major depression are interspersed with episodes of mania or hypomania. Mania is characterized by increased motor activity and restlessness, unusual talkativeness, flight of ideas and racing thoughts, decreased need for sleep and appetite, excessive involvement in risky activities. Hypomania is characterized by attenuated manic symptoms.

**Neuroleptic drugs (antipsychotic drugs)** are a group of drugs that have been used mainly for treating schizophrenia but are also effective in some other psychoses and conditions marked by severe agitation.

### 1. NEUROLEPTIC DRUGS (ANTIPSYCHOTIC AGENTS)

**Classification and mechanisms of action of neuroleptics:**

1. **Phenothiazines:**
   - Aliphatic side chain \( =\alpha_1 = M = H_1 > 5HT2 \geq D_2 > D_1 \): Chlorpromazine, Levomepromazine
   - Piperidine side chain \( =\alpha_1 = M = H_1 > 5HT2 \geq D_2 > D_1 \): Thioridazine
   - Piperazine side chain \( =D_2 > D_1 = D_4 > \alpha_1 > 5HT2 \): Fluphenazine, Trifluoperazine, Perphenazine

2. **Thioxanthenes:** Thiothixene, Chlorprothixene

3. **Butyrophenones** \( =D_2 > D_1 \geq D_4 \geq \alpha_1 > 5HT2 \): Haloperidol, Droperidol

4. **Diphenylbutilpiperidine** \( =D_2 \): Pimozide

5. **Other structures atypical neuroleptics:** Risperidone \( =D_2 = 5HT2 \), Clozapine \( =D_4 = H_1 > \alpha_1 > 5HT2 > D_2 > D_1 \), Quetiapine \( =D_2 = \alpha_1 = \alpha_2 = H_1 = 5HT2 \), Olanzapine \( =5HT2 > H_1 > \alpha_1 = D_2 = D_1 \), Sertindole \( =5HT2 > D_2 = \alpha_1 \), Molindone, Sulpiride, Loxapine, Remoxipride, Ziprasidone

**Effects of blocking dopamine receptors:**
- from the mesolimbic area → improvement in symptoms of schizophrenia;
- from the nigrostriatal area → pseudoparkinsonism;
- from the tuberoinfundibular area → hyperprolactinemia.
Antipsychotic drugs that selectively block dopamine receptors does not cause ataxia, dysarthria, narcosis.

**Pharmacodynamic effects of Antipsychotics (neuroleptics) in mental illness:**
- reduction of hostility, of aggression, of anxiety;
- attenuation of the dynamics of mental processes;
- inhibition of autism, the delusional ideation, hallucinations.

**Pharmacodynamic effects of Antipsychotics (neuroleptics) in healthy humans:**
- discomfort; drowsiness;
- anxiety, psychomotor agitation;
- vegetative effects (particularly phenothiazines);
- answers correctly to questions;
- decreased physical ability and intellectual capacity;
- indifference to the environment;
- inhibition of conditioned reflexes and unconditioned reflexes maintenance.

**Indications common for all neuroleptics:**
- **psychotic disorders**
  - schizophrenia;
  - mania;
  - chronic systematized delusions;
  - manic periods of bipolar psychosis;
  - Alzheimer dementia
  - behavioral disorders in psychomotor agitation.
- **Other particular indications for some neuroleptics:**
  - Chlorpromazine:
    - antiallergic (hay fever, pruritus, rash);
    - antiemetic and treatment of motion sickness;
    - anxiolytic-sedative-hypnotic;
  - Haloperidol: neuroleptanalgesia

**Adverse reactions common to all antipsychotics:**
- **neuropsychiatric disorders:**
  - "pseudodepressions" because akinesia;
  - pseudoparkinsonism;
  - tardive dyskinesia;
  - confusional state (with antimuscarinic effects);
  - ataxia (with the exception of selective antidopaminergic neuroleptics);
- **hyperprolactinemia:** syndrom amenorrhea – galactorrhea, infertility, decreased libido, impotence;
- **hypotension, the inhibition of ejaculation (anti-adrenergic α1 effects);**
- **antimuscarinic effects;**
- **immunological reactions → agranulocytosis, cholestatic jaundice, rashes;**
- **neurovegetative dystonia;**
- **teratogenic effects;**
- **weight gain (probably by blocking H1 receptors and 5-HT2) → mild for ziprasidone and aripiprazole and severe for olanzapine;**
- **hyperglycemia and diabetes mellitus (secondary to dyslipidemic syndrome associated with insulin resistance) → more common for clozapine and olanzapine.**
- **The neuroleptic malignant syndrome occurs in patients chronically treated with neuroleptics. The syndrome is characterized by muscle rigidity which results in a**
dangerous increase in body temperature and leukocytosis (the latter two effects require a differential diagnosis with infectious processes). Other symptoms are alterations in blood pressure and pulse; increase the creatine kinase (reflecting muscle injuries). The treatment of neuroleptic malignant syndrome is with:

- antiparkinsonian drugs → dopamine receptor agonists (bromocriptine);
- skeletal muscle relaxants → Dantrolene, Diazepam
- treatment of fever.

- Other particular adverse effects for some neuroleptics:
  - Chlorpromazine: accumulation of pigment in the anterior chamber (cornea, crystalline);
  - Thioridazine accumulation of pigment in the retina;
  - Thioridazine determines quinidine-like effects (in large doses determines arrhythmias, T wave changes in the EKG, ventricular fibrillation).
  - Ziprasidone: cardiotoxicity.

Pharmacological characteristics of different groups of neuroleptics

- Phenothiazines with aliphatic side chain (Chlorpromazine, Levomepromazine) and the side chain piperidine (Thioridazine)
  - Pharmacodynamic effects:
    - weak antipsychotic effects;
    - powerful sedative effects;
    - These phenothiazines determine mild antipsychotic effects and strong sedative effects. These drugs have the advantage of much lower incidence pseudoparkinsonism and hyperprolactinemia.
    - Thioridazine has also thymoleptic effect (favorably modifies mood in serious affective disorders such as depression or mania);
    - Chlorpromazine has also anti-allergic, anti-inflammatory, anxiolytic-sedative-hypnotics, anti-emetic effects.
  - Pharmacokinetics:
    - Chlorpromazine and Thioridazine are liposoluble; are bound to plasma proteins (92%-99%); after oral administration present intense first-pass hepatic and enterohepatic circulation; they are metabolized to active metabolites → chlorpromazine metabolites are eliminated through urine, several weeks after administration; thioridazine metabolite (mesoridazine) is very active and determines concentrations with significant antipsychotic effects.
  - Indications:
    - Chlorpromazine:
      - antiallergic (hay fever, pruritus, the hives, rash);
      - antiemetic and treatment of motion sickness;
      - anxiolytic-sedative-hypnotic;
      - antipsychotic (schizophrenia, mania, manic periods of bipolar psychoses, dementia from Alzheimer, psychomotor restlessness);
    - Levomepromazine: antipsychotic (schizophrenia);
    - Thioridazine: antipsychotic (schizophrenia, mania, psychomotor agitation).
  - Contraindications:
    - Similar to antimuscarinic drugs (glaucoma; angina; heart failure, arrhythmias; peptic ulcer; prostate hyperplasia; children under 12 years; sun exposure;
    - combination with tricyclic antidepressants (particularly for thioridazine, which has quinidine-like effects);
• old persons.

  • **Adverse effects:**
    o excessive sedation;
    o the confusional state;
    o antimuscarinic effects: dry mouth (dryness of mucousa); difficulty for urination (acute retention of urine), constipation, and unclear view;
    o hypotension, inhibition of ejaculation (by blocking adrenergic α1);
    o the level of eye:
      ▪ Chlorpromazine: accumulation of pigment in the anterior chamber (cornea, crystalline);
      ▪ Thioridazine accumulation of pigment in the retina;
    o Thioridazine determines quinidine-like effects (in large doses determines arrhythmias, T wave changes in the EKG, ventricular fibrillation).

  ➢ **Phenothiazines piperazine side chains and butyrophenone**
    • **Pharmacodynamic effects:**
      o strong antipsychotic effects (these drugs are called "major antipsychotics").
      ▪ These drugs determine pseudoparkinsonism and they have the advantage of lower sedative effects.

    • **Pharmacokinetics →** Haloperidol has important hepatic first pass effect.

    • **Indications:**
      o antipsychotic (schizophrenia, mania, manic periods of bipolar psychoses, behavioral disturbances in psychomotor restlessness);
      o neuroleptanalgesia (Droperidol/Haloperidol in association with Fentanyl).

    • **Adverse effects:**
      o orthostatic hypotension;
      o reduced sedation;
      o extrapyramidal side effects;
      o teratogenic effects (especially the piperazine phenothiazines).

  ➢ **Diphenylbutylpiperidines (Pimozide)**
    • **Pharmacodynamic effects:** antipsychotic effects are very strong.
    • **Adverse effects:** pseudoparkinsonism; tardive dyskinesia.

  ➢ **Thioxanthenes (Thiothixene, Chlorprothixene)**
    • high clinical efficacy;
    • extrapyramidal effects; they have also sedative effects; moderate hypotension;
    • these drugs also have antidepressant effect.

  ➢ **Other structures (atypical neuroleptics)**
    o Antipsychotics from this group are called "atypical antipsychotics" because of their partial action on dopamine receptors and stronger action on receptors other than dopamine receptors.

    ❖ **Risperidone**
    • **Pharmacodynamic effects:** antipsychotic effects are very strong.
    • **Adverse effects:** reduced sedation; reduced extrapyramidal side effects; hypotension with low intensity.

    ❖ **Clozapine**
    • **Pharmacodynamic effects:** moderate antipsychotic effects.
    • **Adverse effects:** reduced extrapyramidal side effects; reduced sedative effects; agranulocytosis; marked weight gain; increased frequency syndrome dyslipidemia and diabetes mellitus.

    ❖ **Quetiapine**
• **Pharmacodynamic effects**: antipsychotic effects very strong.
• **Adverse effects**: pseudoparkinsonism drug; tardive dyskinesia; moderate sedative effects;
  - **Olanzapine**
  • **Pharmacodynamic effects**: antipsychotic effects very strong.
  • **Adverse effects**: moderate sedative effects; mild hypotension; marked weight gain; increased frequency of dyslipidemic syndrome and diabetes mellitus.
  - **Sertindole**
  • **Pharmacodynamic effects**: antipsychotic effects very strong.
  • **Adverse effects**: reduced extrapyramidal side effects; reduced sedative effects; hypotension in very low intensity.
  - **Ziprasidone, Aripiprazole, Molindone, Sulpiride, Loxapine, Remoxipride**
  • **Pharmacodynamic effects**: moderate antipsychotic effects.
  • **Adverse effects**: moderate extrapyramidal effects; moderate sedative effects; moderate hypotension; Ziprasidone → cardiotoxicity; Ziprasidone, Aripiprazole → reduced frequency of weight gain, dyslipidemia syndrome and diabetes mellitus.

2. LITHIUM AND OTHER MOOD STABILIZING DRUGS (antimaniac drugs)

**Classification of mood stabilizing agents**

2.1. **Lithium salts**: Lithium acetate, Lithium carbonate

2.2. **Tricyclic compounds**: Carbamazepine

2.3. **Carboxilic acids**: Valproic Acid, Sodium valproate

- **Pharmacodynamic effects of lithium**: increase intervals between periods of mania, sometimes complete;
  - effect is installed after 2-3 weeks of administration (during this period, lithium salts are associated with neuroleptics). Determine lethargy, cyanosis, hepatomegaly, Moro reflex in the newborn.
  - The therapeutic index is low.
- **Pharmacokinetics of lithium salts**: good absorption after oral administration; lithium is not bound to plasma proteins; Lithium is not metabolized; elimination through urine (elimination is reduced by dietary salt restriction, thiazide administration); cross the placenta, are concentrated in the milk;
- **Indications of lithium salts**: manic periods (treatment of choice).
- **Adverse effects of lithium salts**:
  - hematological effects: **leukocytosis**;
  - neurological effects: tremors of the extremities, dizziness, confusional states, choreoathetoid crises, convulsions;
  - renal effects: polyuria and polydipsia (decrease the ability of the collector tube to retain water, which is followed by dehydration = the nephrogenic diabetes insipidus, which is resistant to treatment with vasopressin), interstitial nephritis chronic lesions in the glomeruli in nephrotic syndrome decreased glomerular filtration with increasing azotemia, edema with sodium retention;
  - cardiovascular effects: sick sinus syndrome (bradycardia/tachycardia syndrome), flattening of the T wave on ECG;
  - teratogenic effects (cardiac dysmorphogenesis);
  - diarrhea;
• decreased thyroid function;
• more rarely, acneiform eruptions (early treatment).

Contraindications of lithium salts:
• pregnancy; breastfeeding;
• renal failure;
• heart failure; coronary artery disease; hypotension;
• organic diseases of the brain;
• sodium diet / salt-free diet;
• treatment with thiazides (thiazides reduce the elimination of lithium).

3. ANTIDEPRESSANT DRUGS

Classification of antidepressant drugs
3.1. Tricyclic antidepressants (1st generation)
3.2. Heterocyclic antidepressants (2nd and 3rd generation)
3.3. Selective serotonin reuptake inhibitors (SSRI)
3.4. Inhibitors of monoamine oxidase (IMAO):
3.5. Selective noradrenaline reuptake inhibitors: Reboxetine

Indications for antidepressants
• depression;
• enuresis (for tricyclic antidepressants);
• chronic pain.

TRICYCLIC ANTIDEPRESSANTS (first generation of antidepressants)

These drugs are divided into 3 structural-related groups:
• Imipramine; Desipramine; Clomipramine; Trimipramine.
• Amitriptyline; Nortriptyline; Butriptiline.
• Doxepin; Protriptyline.

Mechanisms of action:
• block the reuptake of noradrenaline and serotonin;
• block muscarinic receptors;

Pharmacokinetics: these drugs are highly lipophilic; present hepatic first-pass effect; strong binding to plasma proteins; the volume of distribution is high; metabolism by hydroxylation and then by glucuron conjugation, demethylation; desipramine and nortriptyline are metabolized to active substances.

Adverse effects:
• antimuscarinic effects;
• sedation / insomnna;
• negative inotropic effect (prolongaton of PR and QRS on ECG), conduction disorders, arrhythmias;
• orthostatic arterial hypotension;
• tremors, convulsions;
• endocrine effects: weight gain, disorders of sexual function.

Contraindications:
• ischemic heart disease, congestive heart failure;
• hyperthyroidism;
• antimuscarinic contraindications.
HETEROCYCLIC ANTIDEPRESSANTS (second and third generation)

Classification
- Non selective (block noradrenaline and serotonin reuptake):
  - With cholinergic effects: Maprotiline, Amoxapine, Nomifensine
  - Without cholinergic effects: Venlafaxine, Bupropion
- Antagonists on 5-HT2A/5-HT2C receptors: Trazodone, Nefazodone, Mirtazapine

Mechanisms of action:
- Heterocyclic Antidepressants with antimuscarinic effects:
  - block the reuptake of noradrenaline and serotonin;
  - block muscarinic receptors;
  - amoxapine also determines the blocking of dopamine receptors and block the reuptake of dopamine;
  - maprotiline selective block the reuptake of noradrenaline;
- Heterocyclic Antidepressants without antimuscarinic effects:
  - venlafaxine block the reuptake of serotonin, norepinephrine and low block of the reuptake of dopamine;
  - bupropion block the reuptake of serotonin, norepinephrine;
  - antagonists on receptor 5-HT2A / 5-HT2C.

Pharmacokinetics is similar to that of tricyclic antidepressants.

Adverse effects:
- antimuscarinic effects for Heterocyclic Antidepressants with antimuscarinic effects:
  - venlafaxine: nausea, drowsiness, sweating, sexual dysfunction, hypertension, anxiety;
  - bupropion: dizziness, dry mouth, sweating, tremors, convulsions;
  - receptor antagonists 5-HT2A / 5-HT2C: sleepiness / insomnia, dizziness, nausea, psychomotor agitation;
  - mirtazapine: drowsiness, increased appetite, weight gain, dizziness.

SELECTIVE INHIBITORS OF SEROTONIN REUPTAKE INHIBITORS (SSRIs): Fluoxetine, Sertraline, Paroxetine, Fluvoxamine, Citalopram, Escitalopram


Pharmacokinetics: these drugs are enzyme inhibitors of hepatic metabolism of drugs; paroxetine and sertraline → T1 / 2 is short; fluoxetine → an active metabolite, T1 / 2 = 7-9 days.

Adverse effects:
- gastrointestinal symptoms; decreased libido; acute anxiety; insomnia; tremors;
- association of selective inhibitors of serotonin reuptake with MAOIs can determine serotoninergic syndrome (hyperthermia, muscle rigidity, myoclonus, rapid changes in the mental state + / - vital signs).

MAO inhibitors

Classification
- Non selective: - Hydrazines: Phenelzine, Isocarboxazid
  - Nonhydrazines: Tranylcypromine, Dextroamphetamine
- Isoenzyme MAO-A selective: Moclobemide, Brofaromine, Toloxatone

Mechanisms of action:
- non-selective inhibition of MAO-A and MAO-B → non-selective MAO;
- selective inhibition of MAO-A → selective MAO-A.
• **Pharmacokinetics:** rapid absorption; metabolism by acetylation (there are rapid acetylators / intermediate acetylators / slow acetylators); determine the accumulation of tyramine and the decrease in hepatic first-pass effect → hypertension in case of consumption of foods containing tyramine. The pharmacodynamic effect persists 7 days after the last dose of tranylcypromine and 2-3 weeks after the last dose of phenelzine.

• **Adverse effects:** sleep disorders; weight gain; orthostatic arterial hypotension; Phenelzine → sexual disorders.

• **Contraindications:** arterial hypertension; tachyarrhythmias.

4. **ANXYOLITIC DRUGS**
- Benzodiazepines
- Antidepressant drugs
- Anxoylotic drugs without sedative effects (Serotonin receptor 5HT1A agonists: Buspirone, Ipsapirone, Gepirone, Tandospirone)
- ß-blocking drugs

5. **PSYCHOMOTOR STIMULANTS:** Methylxanthines (Caffeine), Amphetamine, Cocaine

6. **RESPIRATORY STIMULANTS:** Doxapram

- **Indications:**
  - lung disease (including respiratory failure, accompanied of hypoxemia and hypercapnia);
  - resuscitation after general anesthesia.

- **Adverse effects:** cough, nausea, vomiting, agitation, hypertension, tachycardia, arrhythmias, headache, sensation of heat, sweating, tremor, muscle hypertonia, clonic convulsions.

- **Contraindications:**
  - epilepsy;
  - bronchial asthma;
  - recent stroke.

7. **NOOTROPE DRUGS:** Meclofenoxat, Meclosulfonat, Piracetam, Piritinol, Gingko Biloba, Lecitine

- **Mechanisms of action:** increase glucose metabolism promoting the use of glucose by neurons.

- **Indications:**
  - sequelae after stroke, post-traumatic syndromes;
  - precoma, coma;
  - behavior disorders in epileptics;
  - encephalopathies, dizziness;
  - neuropsychiatric disorders in chronic alcoholism;
  - delay in the psychic development in children.

- **Adverse effects:**
- Piracetam: at the beginning of treatment → agitation, anxiety; for people with mental illness → aggressiveness, agitation; for people with epilepsy → decrease seizure threshold;
- pyritinol: irritability, anxiety, insomnia, headache, "burns" epigastric; nausea, rash (blistering rashes in people with rheumatoid arthritis → interruption of treatment); rarely, agranulocytosis, proteinuria.

- **Contraindications nootropics**: epilepsy and renal failure.

8. NON-SELECTIVE AND SELECTIVE β-BLOCKING DRUGS USED IN PSYCHIATRY AND NEUROLOGY: Propranolol, Oxprenolol, Sotalol, Metoprolol.

9. IMMUNOMODULATOR DRUGS USED IN SCHIZOPHRENIA: Levamisole.

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<td>1. Drugs of abuse inducing euforia</td>
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<td>1.1. <strong>CNS depressants</strong>: opioids (natural or synthetic sources), benzodiazepines, barbiturates, ethanol and other structures (Meprobamate, Glutethimide, Methyprilon, Methaqualone, Chloral hydrate, Paraldehyde)</td>
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<td>1.2. <strong>CNS stimulants</strong>: Caffeine, Nicotine, Amphetamines, Cocaine</td>
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<td>1.3. <strong>Inhalants</strong>: inhalatory general anesthetics (nitrous oxide, ether, chlorophorm), industrial solvents (gasoline, toluene, benzene, trichloroethylene), aerosol propellants.</td>
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<td>2. <strong>Psychotomimetics (Hallucinogens, Psychodysleptics)</strong></td>
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<td>2.1. <strong>Lysergic acid diethylamide (LSD) and related compounds</strong> (Dimethyltriptamine, Diethyltriptamine, Dipropiltriptamine, Para-clor-phenylalanine)</td>
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<td>2.2. <strong>Mescaline and related compounds</strong> (Methylenedioximetamphetamine = MDMA = “Ecstasy”)</td>
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<td>2.3. <strong>Psilocybin and related compounds</strong></td>
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<td>2.4. <strong>Phencyclidine (PCP)</strong></td>
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<td>2.5. <strong>Cannabinoids</strong>: Marijuana, Hashis, tetrahydrocannabinol (THC)</td>
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<td>2.6. <strong>Anticholinergic hallucinogens</strong> (natural or synthetic sources).</td>
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