Learning objectives

- to review psychopharmacotherapy
- to explain basics of electroconvulsive therapy
- to introduce other biological therapeutic methods in psychiatry
PSYCHOPHARMACOTHERAPY

ELECTROCONVULSIVE THERAPY

OTHER BIOLOGICAL THERAPIES

History of psychopharmacotherapy

- Medication used for modulation of psychic state
- 1900 use of opium
- 1903 use of barbiturates, amphetamines
- 1949 Cade – use of lithium (to treat mania)
- 1950s Deley, Deniker – use of chlorpromazine – (as antipsychotic)
- 1957 Kuhn – use of imipramine (TCA) (to treat depression)
- 1958 Kline – use of monoamine inhibitors (MAO), haloperidol
- 1960s use of first anxiolytics, carbamazepine, valproic acid
- 1970s use of long acting injections (antipsychotics), second generation antipsychotics (atypical - clozapine), fluoxetine (first SSRI)
- 1990s use of RIMA, NaSSA, atypical antipsychotics (risperidone, olanzapine), use of cholinesterase inhibitors
- 2002 use of memantine

Mechanisms of action in psychopharmacotherapy

Effect on:
- Dopamine receptors: D2 (1,3,4) – antipsychotic effect
- Serotonin receptors: 5HT-1A, 5HT-2 – antidepressive effect
- Monoamine transporters (antidepressants)
- GABA-A receptors: anxiolytic and hypnotic effect
- Acetylcholine, glutamate – cognitives
- α1, histamine (H1), muscarine (M1) receptors and other: mix of therapeutic effect and side effects
Psychopharmacotherapy

Focus on:
- efficacy
- safety
- tolerability
- side effects

Main drug classes:
- antipsychotics
- antidepressants
- mood stabilizers
- anxiolytics
- hypnotics
- cognitives and neuroprotectives
- psychostimulants

Antipsychotics – definition
- medicaments that affect integration of psychic functions (antipsychotic effect)
- pacification / sedation effect (unspecific)
- forms:
  - tablets, drops, injections, long acting injections (LAI)
Antipsychotics – effects

- **antipsychotic** (primary)
- other effects
  - antidepressive
  - antimanic
  - anxiolytic
  - mood stabilizing
  - antiaggressive
  - antisuicidal
  - hypnotic
  - antiimpulsive

Antipsychotics – classes

**Typicals** (1. generation)
- **Basal** (sedative / low potency)
  - Chlorpromazine
  - Leporpromazine
- **Incisive** (high potency)
  - Fluphenazine
  - Flupenthixol
  - Zuclopenthixol

**Atypicals** (2. generation)
- **DSA** (Dopamine Selective Antagonists)
  - Amisulpride
  - Sulpiride
  - Tiapride
- **MARTA** (Multi Acting Receptor Targeted antipsychotics)
  - Clozapine
  - Quetiapine
  - Olanzapine
  - Zotepine
- **SDA** (Serotonine and Dopamine Antagonists)
  - Paliperidone
  - Risperidone
  - Sertindole
  - Ziprasidone
- **DPA** (Dopamine Partial Antagonists)
  - Aripiprazole
  - Cariprazine

Antipsychotics – indications

- psychotic disorders
  - schizophrenia, schizoaffective disorder, delusional disorder, bipolar affective disorder, toxic psychosis, organic psychosis
- affective disorders
  - treatment resistant, psychotic depression, mania
- qualitative disturbances of consciousness
- behavioral disturbances in dementia, mental retardation
- tics
Antipsychotics – contraindications

ABSOLUTE:
- severe intoxication with alcohol or other sedative substances

RELATIVE:
- Parkinson syndrome (typical antipsychotics)
- neuroleptic malignant syndrome in history
- chronic kidney diseases
- disturbances in blood count especially white cells (clozapine)

Common side effects in typicals

Blockade of D2 receptors in nigrostriatal system leads to extrapyramidal syndrome:
- acute dystonia – contraction of muscle group to the maximal limit: sternocleidomastoid and tongue, oculogyric crisis
- parkinsonism – tremor, rigidity, bradykinesia
- akathisia – restlessness (usually legs)
- tardive dystonia – continuous slow writhing movements + sudden movements

M blockade: dry mouth, blurred vision, urinary retention, constipation
α blockade: postural hypotension, tachycardia, sexual dysfunction
H blockade: sedation, weight gain

Common side effects in atypicals

Risperidone, Amisulpiride, Sulpiride
hyperprolactinemia

Olanzapine, Clozapine
weight gain, metabolic syndrome, diabetes mellitus

Sertindole, Ziprasidone
ECG prolongation of QT interval, potential cardiac problems

Clozapine
leukopenia, agranulocytosis

Quetiapine
postural hypotension
Antidepressants – definition

- medicaments primary used for treatment of depression

Antidepressants – indications

- depressive disorders
- anxiety disorders
  - obsessive compulsive disorders, panic disorder, social anxiety disorder, generalized anxiety disorder
- impulsivity
- sleep disorders
- pain syndromes
- eating disorders

Antidepressants – classes

<table>
<thead>
<tr>
<th>Name of group/main mechanism of action</th>
<th>Example</th>
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<tr>
<td>Tricyclic antidepressants (TCA)</td>
<td>imipramine, desipramine, amitriptyline</td>
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<td>Monoamine oxidase inhibitors (MAO)</td>
<td>fenelzine, tranylcypromine</td>
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<td>Serotonin selective reuptake inhibitors (SSRI)</td>
<td>citalopram, escitalopram</td>
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<td>mirtazapine, mianserine</td>
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<td>Stimulator of serotonin receptors</td>
<td>tiagabine</td>
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<td>Antidepressant and selective serotonin antagonists (ASSA)</td>
<td>agomelatine</td>
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<tr>
<td>Serotonin Modulator and Stimulator (SMS)</td>
<td>vortioxetine</td>
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</table>
Antidepressants – common side effects

TCA: sedation, orthostatic hypotension
IMAO, RIMA: hypertensive crisis (tyramine - cheese), hepatotoxicity, weight gain, edema, sexual dysfunction
SSRI: serotonin syndrome, gastrointestinal problems, headaches, agitation, sexual dysfunction
SNRI: see SSRI + hypertension
SARI: sedation, fatigue, priapism
NaSSA: sedation, increased appetite, weight gain
MASSA: hepatotoxicity
SMS: nausea

Mood stabilizers – definition

Medicaments primary used for antimanic, antidepressive and mood stabilizing effect

Mood stabilizers

Medicaments:

- Lithium
- Valproate / valproic acid
- Carbamazepine
- Lamotrigine
- Atypical antipsychotics (quetiapine)
**Mood stabilizers – effects**

- antimanic medication
  - lithium, valproate, carbamazepine
- mood stabilizing medication – prophylaxis of depressive, manic or mixed episodes
  - lithium, valproate, lamotrigine
- antisuicidal effect
  - lithium
- antiagnostic effect
  - lithium, valproate, carbamazepine

**Mood stabilizers – indications**

- bipolar affective disorder
- schizoaffective disorder
- recurrent depression

**Mood stabilizers – common side effects**

- **Lithium:** diarrhea, nausea, vomiting, edema, polyuria, polydipsia, tremor, weight gain, increase of thyroid gland, hypothyreosis
- **Valproate:** polycystic ovaries, teratogenity, tremor, weight gain, pancreatitis
- **Carbamazepine:** agranulocytosis, aplastic anemia, hepatotoxicity, dermatitis, pancreatitis
- **Lamotrigine:** skin rash
Anxiolytics – definition

- medicaments used for relieving or elimination of anxiety of various origin

Anxiolytics – mechanisms of action

- benzodiazepine (BZD)
  - by acting on GABA receptors
- non-benzodiazepine (non-BZD)
  - by acting on different receptor systems

BZD Anxiolytics – effects

- anxiolytic
- sedative
- myorelaxant
- anticonvulsant
- amnestic
BZD Anxiolytics – duration of activity

- long-term (half-time of elimination > 24 hours): diazepam, clonazepam
- intermediate-term (half-life of elimination 6-24 hours): alprazolam, lorazepam, bromazepam
- short-term (half-life of elimination < 6 hours): oxazepam, midazolam, cinolazepam

BZD Anxiolytics – indications

- anxiety disorders
  - anxiety in depression
  - stress related disorders
  - psychosomatic disorders
- alcohol, drug, hypnotics withdrawal syndrome
  - alcohol delirium
- sleep disturbances
- increased myotonus and muscle spasms

BZD Anxiolytics – other indications

- Internal medicine: acute cardiovascular problems, endocrine disturbances with anxiety, febrile convulsions
- Anesthesiology: premedication in short surgical interventions, cardioversion, endoscopic investigations
- Neurology: epilepsy, dystonia, vertebropathy with muscle spasms, neuralgia, tetania
**BZD Anxiolytics – contraindications**

- pregnancy, breast feeding
- myastenia gravis
- alcohol intoxication – risk of suppression of breathing center → coma → death

**BZD Anxiolytics – side effects**

- sedative
- myorelaxant
- amnestic
- paradoxical reactions
- risk of BZD dependence

**non-BZD Anxiolytics – effects**

- anxiolytic effect
- myorelaxant effect
- non sedative

**Buspirone** (selective partial agonist of 5HT-1A receptors)

**Hydroxyzine** (antihistaminic)
Hypnotics – definition

- Medicaments used for sleep disorders
  - Initiation of sleep, sleep sustainment, early morning awakening

Hypnotics – mechanisms of action

- Mechanism through GABAergic system
- Benzodiazepine (BZD)
- Non-benzodiazepine (non-BZD)
  - Do not change the architecture of sleep and do not cause daytime sleepiness, wider indications – zopiclone, zolpidem, zaleplon, eszopiclone
- Melatonin – modification of biorhythms
- Promethazin – antihistaminic
- Sedative antidepressants – by sedative side effects
- Antipsychotics – by sedative side effects

Hypnotics – treatment

- Initiation of sleep and sleep sustainment: short-term BZD (midazolam, cinolazepam), zopiclone, zolpidem
- Early morning awakening: long-term BZD (diazepam)
Hypnotics – precautions

- length of treatment < 1 month
- contraindications: sleep apnoe, respiratory insufficiency, pregnancy, breast feeding, myastenia gravis, alcohol intoxication – risk of supression of breathing center → coma → death
- side effects: daily tiredness, amnestic effect, paradox reactions, dependence, „rebound“ insomnia

Cognitives – definition

- medicaments used for long-term treatment of dementia (especially Alzheimer)
- stabilization/deceleration of degradation of cognitive functions, effect on non-cognitive symptoms, improvement of memory, attention, learning ability

Types:
- Cholinesterase inhibitors – increase the level of acetylcholine (donepezil, rivastigmin, galantamin)
- NMDA receptor antagonists – regulate the level of glutamate (memantine)

Cognitives – contraindications & side effects

Contraindications:
- gastric and duodenal ulcer disease, cardiac problems

Side effects:
- nausea, diarrhea, vertigo, excitation
Neuroprotectives – definition

- medicaments used for organic impairment of the brain, usually ischemic – qualitative and quantitative disturbances of consciousness, vascular dementia, cerebral stroke
- protection of neurons (hypoxia and ischemia)
- decrease of free oxygen radicals
- decrease of intraneuronal calcium toxicity
- increase of cerebral metabolism
- vasodilatation of brain vessels
- improvement of rheologic properties of blood

Neuroprotectives – groups

- nootropics: piracetam, pyritinol, extract from Ginkgo biloba - EGb 761
- antioxidants: selegilin, E-vitamine
- central vasodilatants: pentoxifylin, nicergolin
- inhibitors of inflammation: NSAID
- decrease of Calcium intraneuronal activity: nimodipin, cinnarizin, flunarizin

Psychostimulants – definition

- medicaments used for treatment of ADHD (Attention deficit hyperactivity disorder) and narcolepsy
- increase of noradrenalin and dopamine
- methylphenidate, atomoxetine, modafinil

Side effects: insomnia, dysphoria, irritability, anxiety, hypertension, tachycardia, tremor, hyporexia

Contraindications: drug dependence, anxiety, suicidal behavior, delirium, schizophrenia, ischemic heart disease, hypertension, hypothyreosis
Electroconvulsive therapy

Meduna (1934) – use of chemical induced epileptic seizure (camphor, metrazol)
- schizophrenia vs. epilepsy

Cerleti, Bini (1938) – use of „electric shock“ to induce seizures – frequent injuries (luxations, fractures), fear
- use of anesthesia, myorelaxation

ECT – mechanisms of action

- mode of action not fully known
  - effect on monoamine system (NA, 5-HT, DA), GABA, Ach, endogenous opioids, adenosine
  - effect on neuroendocrine system (hypopituitary, pituitary, adrenal hormones)
  - increase of brain metabolism
  - increase of brain blood flow
  - increase of gene expression
ECT – indications

Highly effective treatment for:
- treatment resistant, severe, psychotic depression
  - treatment resistant, catatonic psychosis (schizophrenia, schizoaffective disorder, delusional disorder)
  - treatment resistant, prolonged, severe mania, mixed episodes in bipolar affective disorder
    - psychosis, depression, mania in pregnancy
    - neuroleptic malignant syndrome
    - obsessive-compulsive disorder

ECT – contraindications

- cerebral/aortal aneurysm
- intracerebral hemorrhage
- increased intracranial pressure
- brain tumor
- recent brain stroke
- recent myocardial infarction
- cardiac arrhythmias
- phaeochromocytoma
- demyelinization diseases
- allergy on used medication during ECT

ECT – side effects

- headache
- muscle aches
- dizziness
- short-term memory loss (usually resolves completely)
- nausea
- post-seizure confusion
- mortality not greater than usual in minor surgery anesthesia – cardiac complications due to cardiac disease
Assessments prior to ECT

- General medical history of the patient
- Blood count, blood biochemistry
- ECG
- Physical examination
- Medication check
- other upon request of anesthesiologist

ECT – administration

- patient is fasting minimum 8 hours
- premedication with atropine (to reduce salivation, cardioprotection) i.m.
- monitoring of blood pressure, heart rate, blood oxygen, EEG
- establish intravenous access
- short-term acting anesthetics (thiopental) i.v.
- muscle relaxant (succinylcholine) – i.v.
- ventilation of patient via face mask with pure oxygen
- insertion of bite-block between patient teeth to protect tongue and teeth from jaw clenching

ECT – administration

ECT electrodes placement

- Bilateral
- Right unilateral
- Left unilateral

Faster response
mood memory side effects
ECT – administration

- bilateral application of electrodes (bitemporal)
- administer dose (begins with lower dose, different dose and time duration of impulse in men and woman)
- monitoring of length of convulsions (usual duration 20-150 seconds)
- ventilation of patient via face mask until the patient starts to breath spontaneously
- set the patient to stabilized (recovery) position
- recording of dose, duration and complications
- usual repetition 6-15 times (3 times per week)

Other biological therapeutic methods

- Phototherapy (light therapy)
- Sleep deprivation
- Repetitive transcranial magnetic stimulation
- Psychosurgery
- Vagal nerve stimulation
- Deep brain stimulation
**Phototherapy (light therapy)**

- applying bright light
- **mechanism of action**: stabilization of circadian rhythms mediated by melatonin
- **device**: light box producing 2500-10000 Lux
- every morning / 30 minutes / 2 weeks

- **indications**: depressive disorders (especially seasonal), SAD, dementia with sleep disturbances
- **adverse effects**: headache, visual problems
- **contraindications**: agitation, insomnia

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**Sleep deprivation**

- **partial or total sleep deprivation** (24 hours)
- **mechanism of action**: increase of level of tryptophan (serotonin precursor), modification of circadian rhythms

- **indications**: depression, premenstrual tension, sleep disturbances
Repetitive transcranial magnetic stimulation

- **electromagnetic induction** – magnetic impulse induce electric field
- **mechanism of action**: depolarization of cortical neurons
  - high frequency stimulation > 1 Hz
  - low frequency stimulation < 1 Hz
- **indications**: depression, negative symptoms in schizophrenia, chronic hallucinations, OCD, tinnitus
- **contraindications**: cardiostimulator, metal implants in the brain
- **side effects**: headache

Deep brain stimulation

- invasive neurosurgical intervention by implanting electrode arrays into a specific region of the brain using neuroimaging-guided stereotactic neurosurgical techniques
- **mechanism of action**: electric stimulation of targeted neurons
- **indications**: Parkinson’s disease, treatment-resistant depression, intractable obsessive-compulsive disorder, Tourette’s Syndrome
Deep brain stimulation

Holtzheimer & Mayberg, 2011

Psychosurgery
- destruction or stimulation of specific brain structures
- stereotactic surgery (precise localization) – electrocauagulation, freezing, radiation
- methods: anterior cingulotomy, capsulotomy, subcaudate tractotomy, limbic leucotomy, amygdalotomy
- indications: chronic long-lasting (years) depression, OCD refractory to other kind of therapy
- side effects: disturbances of consciousness, apathy, exhaustion, enuresis, epileptic seizures

Vagal nerve stimulation
- surgical implant of electrode on nervus vagus
- 15-30 second impulses, full therapeutic effect after 1-2 years
- mechanism of action: increased metabolism in limbic structures, increase of monoamine transmission
- indications: chronic depression resistant to other types of therapy
- side effects: nausea, arrhythmia, cough
Any questions?