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 chlorpromazin – (as antipsychotic)
- 1957 Kuhn – use of imipramin (TCA) (to treat depression)
- 1958 Kline – use of monoamine inhibitors (IMAO), haloperidol
- 1960s use of first anxiolytics, carbamezepine, valproic acid
- 1970s use of long acting injections (antipsychotics), second generation antipsychotics (atypical - clozapin), 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
  - antiagressive
  - antisuicidal
  - hypnotic
  - antiimpulsive

Antipsychotics – classes

<table>
<thead>
<tr>
<th></th>
<th>1. generation (Basal low potency)</th>
<th>1. generation (Incisive high potency)</th>
<th>2. generation (Atypicals)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chlorpromazine</td>
<td>Chlorpromazine</td>
<td>DSA (Dopamine Selective Antagonists)</td>
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<td></td>
<td>Levothroxol</td>
<td>Fluphenazine</td>
<td>Tiaprid</td>
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<td>Flupenthixol</td>
<td>Zuclopenthixol</td>
<td>Sertindole</td>
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<td>Chlorprothixene</td>
<td>Haloperidol</td>
<td>Ziprasidone</td>
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<td>Paliperidone</td>
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<td>Ziprasidone</td>
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</tbody>
</table>

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

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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 primarily 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/active mechanism of action</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricyclic antidepressants (TCA)</td>
<td>Imipramine, clomipramine, desipramine, doxepin, amitriptyline, nortryptiline, clomipramine, desipramine</td>
</tr>
<tr>
<td>Serotonin selective reuptake inhibitors (SSRI)</td>
<td>Citalopram, escitalopram, paroxetine, fluoxetine, fluvoxamine, sertraline</td>
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<tr>
<td>Monoamine oxidase inhibitors (MAO)</td>
<td>Tryptophan, tyramine, fenelzine, tranylcypromine</td>
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<td>Reversible monoamine oxidase inhibitors (RIMA)</td>
<td>Moclobemide</td>
</tr>
<tr>
<td>Serotonin/norepinephrine reuptake inhibitors (SNRI)</td>
<td>Venlafaxine, duloxetine, milnacipran</td>
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<tr>
<td>Noradrenergic and specific serotonergic antidepressants (NaSSA)</td>
<td>Mirtazapine, maprotiline, nefazodone, mianserin</td>
</tr>
<tr>
<td>Serotonin and norepinephrine reuptake inhibitors (SNRI)</td>
<td>Duloxetine, milnacipran</td>
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<tr>
<td>Norepinephrine reuptake inhibitors (NRI)</td>
<td>Reboxetine</td>
</tr>
<tr>
<td>Serotonine antagonist/reuptake inhibitors (SARI)</td>
<td>Tianeptine, nefazodone, trazodone</td>
</tr>
<tr>
<td>Serotonin agonist and selective serotonin antagonist (SMAS)</td>
<td>Agomelatine, vortioxetine</td>
</tr>
<tr>
<td>Serotonin MODulator and Stimulator (SMS)</td>
<td>Vortioxetine</td>
</tr>
</tbody>
</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

- **Antiagressive effect**
  - lithium, valproate, carbamazepine

**Mood stabilizers – indications**

- bipolar affective disorder
- schizoaffective disorder
- recurrent depression

**Mood stabilizers – common side effects**

**Lithium:** diarrhea, nausea, vomiting, edemas, 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 rush
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
- amnesic
- 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 – zopiclon, zolpidem, zaleplon, eszopiclon ("Z-drugs")
- 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), zopiclon, 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

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Electroconvulsive therapy – history

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
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  - obsessive-compulsive disorder
- psychosis, depression, mania in pregnancy
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ECT – contraindications

- cerebral/aortal aneurysm
- intracerebral hemorrhage
- increased intracranial pressure
- brain tumor
- recent brain stroke
- recent myocardial infarction
- cardiac arrhythmias
- phaeochromocytoma
- demyelinating 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: Faster response, more memory side effects

Right unilateral

Left unilateral

Lisanby, 2007
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 > 1Hz
  - low frequency stimulation < 1Hz
- **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

Psychosurgery
- destruction or stimulation of specific brain structures
- stereotactic surgery (precise localization) – electrocoagulation, 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?