ANTIDEPRESSANT AND ANTIMANIC AGENTS

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• The most common psychiatric disorder
• 5-6% of the population is affected
1). Unipolar - endogen
   - secunder

2). Bipolar

Mania
Hypomania
Euthymia
Dysthymia
Depression
Symptoms of depression

- marked lack of feeling joy
- pessimism
- feeling of worthlessness or exaggerated consciousness of guilt
- decrease of ability to concentrate
- decision making problems
- insomnia or sleepiness, fatigue
- returning thoughts in relation to death and suicide
- loss of appetite
Symptoms of mania

- hyperactivity
- increased self confidence
- excitement, impulsivity
- aggression, diminished need for sleep
- increased communicative competence
- grandiose ideas/plans
Schildkraut: - depression-deficiency of monoamin transmission (mania - overactivated)

- RESERPIN – blocks the uptake of biogenic amines into the storage vesicles (depression developed in 50% of the patients)
**Pathophysiology**

**PRO**
- effective drugs
  - MAO-inhibitors
    → increased MA in storage vesicles
  - TCA- inhibit the reuptake of MA
  - $\alpha_2$ – antagonists

**CONTRA**
- pharmacologic effect develops immediately
- relief of symptoms takes min. 2-3 weeks

**ADAPTIVE CHANGES**
- desensitization and decreased number of $\alpha_2$, $\beta$ and 5-HT$_2$ receptors
I. REUPTAKE INHIBITORS

1). TCA (tri- and tetracyclic antidepressants)

Inhibit the reuptake of NE and 5-HT

*imipramine, amitriptyline, clomipramine*

Inhibits mainly the NE reuptake

*maprotiline*
Adverse effects

$H_1$ antagonism  - sedation, dizziness, confusion  
                 - weight gain

$\alpha_1$ blockade  - dizziness, orthostatic hypotension, reflex tachycardia,

Anticholinergic  - dry mouth, constipation, urinary retention, blurred vision  
                 - confusion, impaired cognitive functions

*Ventricular arrhythmias*: blockade of HERG type $K^+$ channels in the heart
Pharmacokinetics

Long elimination half life, $t_{1/2}=25-35$ óra

Interactions

- Potentiate the effect of alcohol – respiratory depression

- Together with MAO inhibitors → **Serotonin Syndrome** (hyperpyrexia, seizures, coma)
Indications

- depression
- panic disorders - IMIPRAMINE, CLOMIPRAMINE
- Nocturnal enuresis (nighttime urinary incontinance)
- neuropathic pain: AMITRIPTYLINE, CLOMIPRAMINE
- migraine profilaxis: AMITRIPTYLINE
I. REUPTAKE INHIBITORS

2). **SSRI** *(selective serotonine reuptake inhibitors)*

selective inhibition of 5-HT reuptake

*fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram*
Adverse effects

Lack of TCA like adverse effects!

5-HT$_2$ receptor stimulation
- anxiety (begin of the treatment), insomnia, loss of libido, delayed orgasm

5-HT$_3$ receptor stimulation
- nausea, vomit, GI problems, diarrhea, headache
SEROTONIN SYNDROME

- SSRI + MAO- inhibitors → increased 5-HT level

- Symptoms: muscle rigidity, cramps, hyperthermia, hypertension

- Attention! – when we switch the drug FLUOXETIN – elimination requires 4-6 weeks
Pharmacokinetics

• **FLUOXETIN** long duration of action (active metabolite: NORFLUOXETINE, \( t_{1/2} = 7-9 \) days)

• **PAROXETINE, SERTRALINE**, shorter duration of action (\( t_{1/2} = 25-35 \) hours)
INDICATIONS

• Depression (1st choice drugs)

• Anxiety disorders, OCD

• Eating disorders: bulimia nervosa, but not anorexia

• premenstrual dysphoric disorder
II. ATYPICAL OR NEWER REUPTAKE INHIBITORS

- SNRI (selective 5-HT and NE reuptake inhibitors)
  
  *venlafaxine* – common use
  
  - 2× day, $t_{1/2} = 5-11$ h

- *duloxetine*

- NRI (selective NE reuptake inhibitor)
  
  *reboxetine*
II. ATYPICAL OR NEWER REUPTAKE INHIBITORS

- DA and NE reuptake inhibitor
  \textit{bupropion} – contraindicated in epilepsy
  (might cause seizures)

- reuptake enhancer of 5-HT

  \textit{tianeptin}
  - not known mechanism of action, has significant \textit{anxiolytic} effect

- Indication: to treat depression and anxiety during alcohol withdrawal syndrome
II. ATYPICAL OR NEWER REUPTAKE INHIBITORS

- 5-HT reuptake inhibitors and 5-HT$_{2A}$ receptor antagonists: *trazodone, nefazodone*

- $\alpha_2$ and 5-HT$_{2,(3)}$ antagonists
  *mirtazapine, mianserine*

5-HT$_2$ inhibition: anxiolytic, sedative effect, better sleeping, does not modulate libido

5-HT$_3$ inhibition: antiemetic effect
III. MONOAMINO-OXIDASE INHIBITORS

norepinephrine  dopamine  serotonin  tiramine  fenilethylamine

MAO-A

GI-tract nerve endings

CLORGYLIN  MOCLOBEMID

MAO-B

platelets  glial cells

SELEGILIN
III. MONOAMINO-OXIDASE INHIBITORS

non-selective irreversible MAO inhibitors

depression (very severe cases)

phenelzine

selective reversible MAO-A inhibitors (RIMA)

depression

moclobemid

selective irreversible MAO-B inhibitors

Parkinson disease

selegiline
Adverse effects

- „cheese reaction" – dietary restrictions (primarily in case of irreversible MAOIs)
- insomnia, agitation
- sexual disturbances
• **INTERACTIONS:**
  1) increase the effect of sympathomimetics;
  2) *Serotonin Syndrome* given together with TCA or SSRI;
  3) with Pethidin—respiratory depression, seizures

• **INDICATIONS:** depression, social phobias

• **THERAPY:** *Moclobemid*, 2-3×/day, start with small dose and gradual increase
THERAPEUTICAL GUIDELINE

• SSRI, 1st choice

• Monotherapy, if it is possible (cumulating adverse effects)

• Therapeutical effect: min. 2-4 weeks
IV. MOOD STABILIZING, ANTIMANIAC DRUGS

- **Lithium**: mood stabilizer, prevents the maniac phase
- **Carbamazepine, Valproate** (antiepileptics)
- Antipsychotics
- **BZD**, high potency drugs, ex. **Clonazepam**
Influence on the Na\textsuperscript{+} permeability

inhibition of adenylate cyclase

uncouple G proteins from their receptors

Other possible mechanism of actions:

- Influence on the Na\textsuperscript{+} permeability
- inhibition of adenylate cyclase
- uncouple G proteins from their receptors
PHARMACOKINETICS

- excellent absorption from the gastrointestinal tract
- excreted unchanged by the urine
- half life is about 24 hours

<table>
<thead>
<tr>
<th>Serum level</th>
<th>profilactic</th>
<th>0.6-1 mol/l</th>
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<tbody>
<tr>
<td></td>
<td>acute maniac phase</td>
<td>1.0-1.2 mol/l</td>
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<tr>
<td>toxic level</td>
<td></td>
<td>1.5-1.7 mol/l</td>
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Adverse effects

- Tremor, sedation, nausea, vomit
- Hypothyreosis
- Polyuria, polydipsia - nephrogenic diabetes insipidus
- Terratogenic
- Hyperactivity, seizures, coma (toxicity)
INDICATIONS

• *Bipolar affective disorder*

  In severe maniac phase: Li is given together with an antipsychotic. After mania is controlled, the antipsychotic drug can be discontinued.

    Li is administrated profilactically during the depressive phase of the bipolar disorder as well.

• *Recurrent endogenous depression*

  Li potentiates the effect of antidepressants