Pharmacology of antidepressants & Li

László Drimba MD
University of Debrecen
Department of Pharmacology & Pharmacotherapy

„commonly used drugs”

- MDD (major depressive disorder)
- BD (bipolar disorder / manic-depressive disorder)

- Other indications of antidepressants
  - GAD (generalised anxiety disorder)
  - PTSD (post-traumatic stress disorder)
  - OCD (obscessive-compulsive disorder)
  - PMDD (premenstrual dysphoric disorder)
  - Enuresis/Incontinence

Hypothesis of MDD

- Neurotrophic hypothesis:
  - BDNF
  - neural plasticity, resilence, neurogenesis
  - prefrontal cortex, hippocampus, anterior cingulate
  - Findings in depressed state vs. treated state???
  - Intracerebral inf. of BDNF……
- Monoamine hypothesis
  - 5HT, NE, D (cortical, limbic) ↓

Antidepressant agents

- **SSRIs (Selective Serotonin Reuptake Inhibitors)**
    - fluoxetine
    - citalopram (+escitalopram)
    - paroxetine
    - sertraline
- **SNRIs (Serotonin-Norepinephrine Reuptake Inhibitors)**
  - ***SSNRI (Selective Serotonin-Norepinephrine Reuptake Inhibitors)***
    - venlafaxine (+desvenlafaxine)
    - duloxetine
  - ***TCA (Tricyclic antidepressants)***
    - imipramine
    - desipramine
    - amitriptyline
- **5-HT_2 antagonists**
    - trazodone
    - nefazodone
- **Tetracyclic and Unicyclic Antidepressants**
    - bupropion
- **Monoamine Oxidase Inhibitors**
    - selegiline
    - moclobemide

SSRIs

- MOA:
  - selective inhibition of SERT
  - CNS stimulation
  - fluoxetine
    - „most commonly prescribed drug”
    - norfluoxetine (long half life) - + MAO inh. → „serotonin syndrome”
- Adverse effects:
  - seizures, convulsions
  - sexual dysfunctions (effect on spinal neurons)
  - QT prolongation (citalopram)
- Clinical indication
  - MDD, sleep disorders
  - OCD, bulimia
  - GAD, panic attacks, social phobias

SNRIs

SSNRIs (Selective Serotonin-Norepinephrine Reuptake Inhibitors)

- MOA.:
    - selective inhibition of SERT & NET
  - venaflaxine
    - weak inhibitor of NET
  - duloxetine
    - balanced inhibitor of SERT & NET

- Adverse effects:
    - narrow adverse effect profile (<TCAs)
    - BP↑, HR↑ (venaflaxine)

- Clinical indication:
  - MDD
  - pain syndromes (diabetic neuropathy, fibromyalgic pain)

SNRIs

TCAs (Tricyclic antidepressants)

- MOA.:
    - inhibition of SERT & NET
  - imipramine, desipramine, amitiptyline

- Adverse effects:
  - anticholinergic effect
  - orthostatic hypotension - α-blocking effect
  - weight gain sedation - H1R blocking effect
  - cardiac toxicity, QT prolongation

- Clinical indication:
  - MDD
  - OCD (clomipramine)

5-HT_2 antagonists

- MOA.:
    - antagonism on 5-HT_{2A} receptors
        - (lysergic acid, mescaline are agonists…)
    - inhibition of SERT & NET
  - trazodone, nefazodone
    - antidepressant, antipsychotic, antianxiety effect

- Adverse effects:
  - sedation
  - orthostatic hypotension – αR blocking
  - GIT disturbances

- Clinical indication:
    - sleeplessness (trazodone)

Tetracyclic and Unicyclic Antidepressants

- MAO.:
    - modest inhibition of NET and dopamin reuptake
    - antagonism on α_2R, presynaptically

  – bupropion, amoxapine, mirtazapine

- Adverse effect
  – sedation (mirtazapine – H_1R blocking effect)
  – pseudoparkinsonism (amoxapine – D_2R blocking effect)

- Clinical indication:
  – smoking cessation
  – reduce the symptoms of nicotin withdrawal

MAO inhibitors

- MOA.:
    - selective blockade of MAO-A/MAO-B

    - phenelzine (irreversible nonselective MAO inhibitor)
    - moclobemide (selective, reversible MAO-A inhibitor)
    - selegiline (selective, irreversible MAO-B inhibitor)

- Adverse effects:
    - abrupt cessation – hypotonia, orthostatic collapse
    - with SSRI – „serotonin syndrome”
    - with tyramine – „cheese reaction”

- Clinical indication:
    - MDD
    - anxiety, phobias
    - parkinsonism (selegiline)

Li^+

- monovalent cation
- anti-maniac/mood stabilizing agent
- prophylaxis/treatment of BD

- MOA.:
  - effects on ion transport
    - substitution for Na^+ in neural cells
  - effects on second messengers
    - inhibition of recycling enzymes converting IP_1, IP_2
  - effects on neurotransmitters
    - ↑action of serotonin
    - ↓NE, dopamine turnover

Li^+

- Excretion: kidneys!
- serum cc.: 0,6-0,9 mmol/L
- Side effects:
  - tremor
  - ↓ thyroid function: uncoupling of TSH receptors
  - renal failure: diabetes insipidus
  - oedema
  - SA node depression
- Clinical indication
  - Bipolar disorders
    - (+ antipsychotics)
  - Schizoaffective disorder
  - Unipolar depression
    - unresponsive cases + SSRIs, TCAs