Antidepressants

Notes for Pharmacology II Practical

This study material is exclusively for students of general medicine and dentistry in Pharmacology II course. It contains only basic notes of discussed topics, which should be completed with more details and actual information during practical courses to make a complete material for test or exam studies. Thus, without your own notes from the lesson this presentation is NOT SUFFICIENT. This presentation alone can not serve as the only study material for preparation for tests in practicals, nor for the final exam.

Classification of psychotropics drugs

- New classification of psychotropics drugs based on main mechanisms of action
- Neuroscience based nomenclature - ECNP (European College of Neuropsychopharmacology)
- Axis 1, 2, 3, 4, 5

https://www.ecnp.eu/~/media/Files/ecnp/Projects%20and%20initiatives/Nomenclature/140214%20Nomenclature%20list.pdf

Alprazolam

Axis 1: class neurotransmitter: GABA
  Relevant mechanism: positive allosteric receptor modulator

Axis 2: receptor subclass: positive allosteric modulation of GABA-A

Axis 3: neurobiological description
  Benzodiazepine receptor agonist

Axis 4: effects: anxiolytic, myorelaxant, anticonvulsive, hypnotedative

Axis 5: indication (FDA/EMA approval)
  GAD; panic attacks; short-term therapy of anxiety, alcohol abstinent syndrome (France)
Antidepressants - definition

- substances that are used to improve pathological depressive mood and other symptoms associated (anxiety, sleep disturbances, suicidal thoughts, psychomotor inhibition, etc.)
- typical delayed onset of antidepressant action (after 1-3 weeks)
- used also in other conditions (phobias, anorexia nervosa, etc.)

Classification of antidepressants according to their

- chemistry (tricyclic, tetracyclic)
- pharmacological profile (MAO-I's, SSRI's, etc.) and their influence on neurotransmitters and receptors in the CNS (DA-ergic, etc.)
- clinical effect (activating, anxiolytic, etc.)

Antidepressants - pharmacokinetics

- well absorbed upon oral administration
- relatively long half-lives
- steady-state plasma concentration has interindividual variability
- correlation with the therapeutic response (TDM)
- readily cross the placenta
- metabolized in the liver via cytochromes P450 (2D6 and 3A4)
  - inhibition of CYP 1A2: SSRI (fluvoxamine)
  - induction of CYP 1A2: cigarette smoke, caffeine, atypical antipsychotics (clozapine, olanzapine)

Antidepressant classes:

- monoamine oxidase inhibitors (MAOIs)
- tricyclic antidepressants (TCAs)
- tetracyclic antidepressants (TeCAs)
- selective serotonin reuptake inhibitors (SSRIs)
- serotonin and noradrenaline reuptake inhibitors (SNRIs)
- noradrenergic and specific serotonergic antidepressant (NaSSAs)
- melatonin agonist and selective serotonin antagonist (MASSA)
- serotonin antagonist, reuptake inhibitor (SARI)
- noradrenaline reuptake inhibitor (NARI)
- noradrenaline and dopamine reuptake inhibitor (NDRI)
- selective serotonin reuptake enhancer (SSRE)
- selective modulators of serotonin (SMS)
- and others (St. John's wort)
Monoamine oxidase inhibitors (MAO-I)

- history of MAO-I - nonselective, irreversible - therapy of pulmonary tuberculosis with hydrazine derivatives of isonicotinic acid (1952)
- risk of hypertensive crisis, hepatotoxicity, dietary restriction

MAO inhibitors - inhibitors of degradation of neurotransmitters

1st GENERATION - nonselective (tranylcypromine) irreversible

2nd GENERATION

- MAOI-A selective moclobemide reversible
- MAOI-B selective selegilin irreversible

(COMT inhibitors)

MAO-inhibitors – adverse effects

- delirium, paranoid psychosis, agitation, aggressivity, thyreotoxicosis
- risk of hypertensive crisis - pressoric effect of tyramine
- drowsiness, fatigue, blurred vision, dizziness, nausea
- gastrointestinal problems (diarrhea/constipation)
- increased appetite, weight gain
- reduced sexual desire and impaired function
- decreased urine output
- sleep disturbances (insomnia)
- muscle twitching (involuntary muscle jerks)

interactions: serotonin syndrome - [GIT and neurological symptoms, muscle rigidity, myoclonus, hyperthermia, cardiovascular side effects, vegetative symptoms, seizures, confusion, delirium, coma]
MAO-A selective inhibitor

**Moebelamide** (AURORIX) competitive inhibitor of MAO-A - reversible (RMA)

- positive effect on cognitive functions
- I: depressive elderly patients, atypical depression, dysthymia, social phobias, PSTD, positive effect on anxiety
- drug interactions – SSRI’s or and MAOI’s - risk of serotonin syndrome
- inhibition of CYP2D6, CYP2C19, CYP1A2

MAO-B selective inhibitor

**Selegilin** (up to 10mg/day - selective and irreversible MAO-B inhibitor)

- at the dose of 20-60 mg. 50-70% - antidepressant effect
- increase of DA concentration in the synaptic cleft
- I: Parkinson’s disease (Alzheimer’s disease, atypical depression)

### MONOAMINE REUPTAKE INHIBITORS

**Older classification**

1\(^{st}\) GENERATION  tricyclic AD, tetracyclic AD

2\(^{nd}\) GENERATION  heterocyclic AD (violation)

3\(^{rd}\) GENERATION  SSRI  SARI (trazodone, nefazodone)
NARI (reboxetine)

4\(^{th}\) GENERATION  SNRI (venlafaxine, milnacipran)
NDRI (bupropion)

5\(^{th}\) GENERATION

**Tricyclic antidepressants (TCA)**

- history - **imipramine**
- mechanism of action
- indication
- adverse reactions
TCA - adverse reactions

- **anticholinergic** effect – xerostomia, blurred vision, constipation, urine retention, etc.
- **antihistamine** effect – (H1)
  - sedation, body weight gain
- **antidrenergic** effect – α1 receptors
  - postural hypotension
- **antiserotonergic** effect – 5-HT2
  - body weight gain (anxiolytic effect)
- **arhythmogenic** effect (M, α1)

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**Tricyclic antidepressants (TCA)**

- **imipramine** (MELIPRAMIN)
  I: depression, enuresis nocturna, chronic pain
  anxiolytic effect: amitriptyline > dosulepine > imipramine
- **clomipramine**
  derived from imipramine
  5-HT and NA reuptake inhibition
  I: depression, chronic pain, OCD
- **amitriptyline** (AMITRIPTILIN – SLOVAKOFARMA)
  strong anticholinergic and antihistamine effects
  AE: sedation, body weight gain, cardiotoxicity
- **nortriptyline** (NORTRILEN)
- **dibenzipen** (NOVERIL)
- **dosulepine** - dothiepin (PROTHIADEN) - sedative, antiH1, antiAch effect

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**Tetracyclic antidepressants (TeCA)**

- **maprotiline** (LUDIOMIL)
  inhibition of NA reuptake, weak effect on 5-HT
  lower efficacy in anxious patients
  suitable for elderly, but careful in patients with cardiovascular disease
  adverse effects similar to those of amitriptyline
  Ki MAO-I, epilepsy, overdose – convulsions, glaucoma
  CYP2D6 interactions (toxicity)
- **mianserine** (MIABENE, LERIVON) 2nd generation AD
  inhibitor of NA and 5-HT reuptake
  minimal anticholinergic effects, weak sedation
  blockade of α2 receptors
  blockade of 5-HT2 receptors
  I: suitable for elderly, safer when overdosed
- **mirtazapine** (see NASSA)
Selective serotonin reuptake inhibitors (SSRI)

3rd generation AD
different chemical structure
different pharmacokinetic properties
alteration of SSRI's in the case of therapeutic failure after 4-6 weeks

1st choice in elderly patients
1st choice in cardiac patients
1st choice in patients with suicidal risks
disadvantage: higher price
advantages: low incidence of side effects - good compliance
low teratogenic risk
other indications:
anxiety, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), therapy of drug addiction, eating disorders (anorexia, bulimia), adjuvant in migraine, in chronic and psychosomatic pain

SSRI – selective serotonin reuptake inhibitors

citalopram (SEROPRAM)
available also in the i.v. pharmaceutical drug dosage form
low risk of pharmacokinetic interactions compared to other SSRI's

escitalopram (CIPRALEX)

fluoxetine (PROZAC, DEPREX LÉČIVA)
long elimination half life (3 days, its metabolite norfluoxetine 7 days)
slow onset of action
inhibitor of CYP2D6, norfluoxetine - inhibitor of CYP3A4

fluvoxamine (FEVARIN)
inhibitor of CYP1A2, 3A4 a 2C19

paroxetine (SEROXAT)
strong inhibitor of CYP2D6 ze všech SSRI

sertralin (ZOLOFT)
potent inhibition of the 5-HT reuptake, minimal CYP2D6 inhibition
antimicrobial activity – potentiates the ATB efficacy
SSRI – side effects

- usually disappear in 4 weeks (adaptation)
- less severe compared to MAO-I and TCA
- risk of sudden withdrawal – vertigo, nausea, fatigue, weakness, insomnia, anxiety, dysforia
- GIT adverse effects
- somnolence, vivid dreams, anhedonia, cefalea, tremor
- sexual dysfunctions, petechiae (minor bleedings, into the skin)
- mild hypotension (but they are not cardiotoxic)

interactions with other serotonergic drugs (MAO-I, SNRI, SARI, tramadol, pentazocine, triptans, etc.) - risk of serotonin syndrome

CYP interactions

SARI - Serotonin Antagonist, Reuptake Inhibitor

trazodone (TRITTICO)

5-HT reuptake inhibitor
5-HT2 receptor antagonist - antidepressant effect
positive effect on sleep architecture (use in insomnia)
positive effect on sexual functions
5-HT1A autoreceptor agonist - anxiolytic effect
alpha 1-adrenolytic effect
no affinity to muscarinic and dopamine receptors
side effects:
- hypotension, somnolence, nausea, vertigo
- agitation, irritability
- hepatotoxicity
- arrhythmias
interactions: CYP2D6 substrate, CYP3A4 inhibitor

NARI - NorAdrenaline Reuptake Inhibitor

reboxetine

- not marketed in the Czech Republic
- selective inhibitor of NA reuptake
- weak inhibition of 5-HT reuptake
- no inhibition of DA reuptake
- muscarinic receptor antagonist
- α1-adrenergic receptor antagonist
- histaminic receptor antagonist
adverse effects: insomnia, anxiety, tachycardia
- blood pressure changes, constipation, sexual dysfunctions
- hyperprolactinemia
interactions: CYP3A4 substrate
SNRI – Serotonin and Noradrenaline reuptake inhibitors

**Venlafaxine** (ARGOFAN, EFECTIN, ELIFY, VELAXIN)
DA reuptake inhibition in sufficient doses - advantage in patients with hypobulia and with inhibited psychomotor performance
weak antagonistic activity on 5HT2A and M1 receptors
lowers β-adrenergic response
O-demethylvenlafaxine active metabolite

adverse effects:
- nausea, vomiting, anorexia
- anxiety,
- hypertension,
- sweating
- tremor
- sexual dysfunctions

SNRI – Serotonin and Noradrenaline reuptake inhibitors

**Milnacipran**
not marketed in the Czech Republic
non sedative
not metabolised in the liver, no active metabolites

better AD effect compared to SSRI's, comparable with TCA's
lower side effects compared to TCA's (nausea, anxiety, hypertension)
Ki: digoxin, MAO-I risk of serotonin syndrome

**Duloxetine** (CYMBALTA, ARCICLAIM)
inhibition of DA reuptake in higher doses
weak antagonistic effect on 5-HT1A, 5-HT2A, H1 receptors
potentiation of analgesic effects

NASSA – NorAdrenergic and Specific Serotonergic Antidepressants

**Mirtazapine** (REMERON, ESPRITAL, MIRTAZEN)
nondirect agonistic effect on 5-HT1A
antagonistic effect on 5-HT2A, 5-HT3, H1, α1 (weak)
antagonistic effect on presynaptic α2 receptors (increase of NA and 5-HT neurotransmission)
no inhibition of monoamine reuptake
no anticholinergic effects
2 active enantiomers, S(+) enantiomer inhibits α2 and 5-HT2; R(-)
inhibits 5-HT3 receptors
positive effect on insomnia
risk of increased appetite and body weight
linear pharmacokinetics,
low incidence of sexual dysfunctions (like bupropion, trazadone)
drug interactions via CYP3A4
Ki: MAO-I, patients under the age of 18
hepatal and renal insufficiency, epilepsy, patients with suicidal tendencies

**Mianserin** (LERIVON, MIABENE) (see TeCA) - 2nd generation AD
NDRI - Noradrenaline-Dopamine reuptake inhibitor

bupropion (ELONTRIL, WELLBUTRIN SR)

- minimal inhibition of 5-HT reuptake
- lower incidence of anticholinergic side effects compared to TCA's
- lower risk of cardiovascular side effects compared to TCA's
- lower anti H1 activity (BW increase)
- risk of epileptic convulsions

Indication: nicotine dependence (anti-craving drug)

SSRE – Selective Serotonin Reuptake Enhancer

tianeptin (COAXIL, ANTINEPTE)

- stimulates 5-HT reuptake in hippocampus and brain cortex
- stimulates spontaneous activity of pyramidal cells in hippocampus
- increases their regeneration following functional inhibition
- affinity to NMDA, AMPA, μ, δ receptors
- mechanism of action is not fully elucidated
- abusus – alteration for opioids ?!

Melatonergic: MASSA - Melatonin Agonist and Selective Serotonin Antagonist

agomelatine (THYMANAX, VALDOXAN)

- agonist of MT1 and MT2 receptors
- antagonist of 5-HT2C receptors
- no influence on monoamine reuptake
- no affinity to α, β adrenergic receptors
- no affinity to H1, M, DA, BZD receptors

administration in the evening, short t1/2
- I: depression with many symptoms (insomnia, anxiety, body weight changes, etc.)
- metabolism via CYP1A2, 1st pass effect
- side effects: elevation of the liver enzymes
- Ki: CYP1A2 inhibitors (fluvoxamine, ciprofloxacin)
SMS – Selective Modulators of Serotonin

new class of antidepressants

vortioxetine
5-HT reuptake inhibitor
no effect on NA, DA transport
effect on 5-HT receptors: not only antagonistic as SARI’s, but also partial and full agonistic activity on 5-HT receptors

antagonistic effect on 5-HT3 (antiemetic), 5-HT1D, 5-HT7
agonistic effect on 5-HT1A (antidepressant, anxiolytic)
parcial agonistic activity on 5-HT1B receptors

mechanism of action is not fully elucidated

Augmentation of antidepressant therapy

Thymostabilisers
therapy of bipolar disorder
lithium
valproic acid
carbamazepine
lamotrigine
other agents

Phytofarmaceuticals
St. John’s Wort
Valeriana, lavender, hops, ...
anxiolytic/antidepressant effect
CYP interactions
Non-pharmacological therapies

Recommended literature

Rang & Dale’s Pharmacology, 8th ed (Humphrey P. Rang et al.), 2015
available on-line

Students should come prepared for practical lessons. Please, read the relevant chapter in the recommended textbook.