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Antidepressants

Depression

- the most common affective disorder
- pesimistic mood with feelings of dejection, low self-worth or guilt for at least two weeks
- different grades of severity
- world-wide one of the most common causes of premature death
- emotional and biological symptoms

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Depression

- loss of interest, happiness and motivation
- loss of self-confidence, remorse, feeling of guilt
- suicidal tendencies (in 2/3 patients)
- loss of energy and tiredness
- attention deficit, indecision
- agitation (if anxiety is present)
- sleep disorder (characteristic is early wake-up)
- change in appetite
- decrease of libido

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Depression

https://www.youtube.com/watch?v=wCd6LPzWscc

https://www.youtube.com/watch?v=2VRRx7Mtep8

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Monoamine theory of depression

- depression = monoamine deficit in particular parts of the brain
- mania = hyperactivity of monoamines in the CNS
- clinical evidence – substances decreasing monoamine activity = mood aggravation
- the specific roles of 5-HT and NA are not clear
- antidepressants directly or indirectly increase the monoamine activity

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Depression

Mild depression

- lost of interest and enjoyment in usual activities, patient are able to perform usual daily activities/duties
- outpatient treatment

Moderate depression

- deep sadness, unability to work, loss of enjoy
- outpatient/inpatient treatment

Severe depression

- severe inhibition, person také can care about him/herself, general „slowlness“, just lying surrounded by his/her dark thoughts...
- inpatient treatment

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Depression

Goldberg Depression Questionnaire

https://www.gracepointwellness.org/5-depression-depression-related-conditions/article/973-goldberg-depression-questionnaire

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Other possible factors:

Brain neuroplasticity deficit in depression

HPA axis activation in depression

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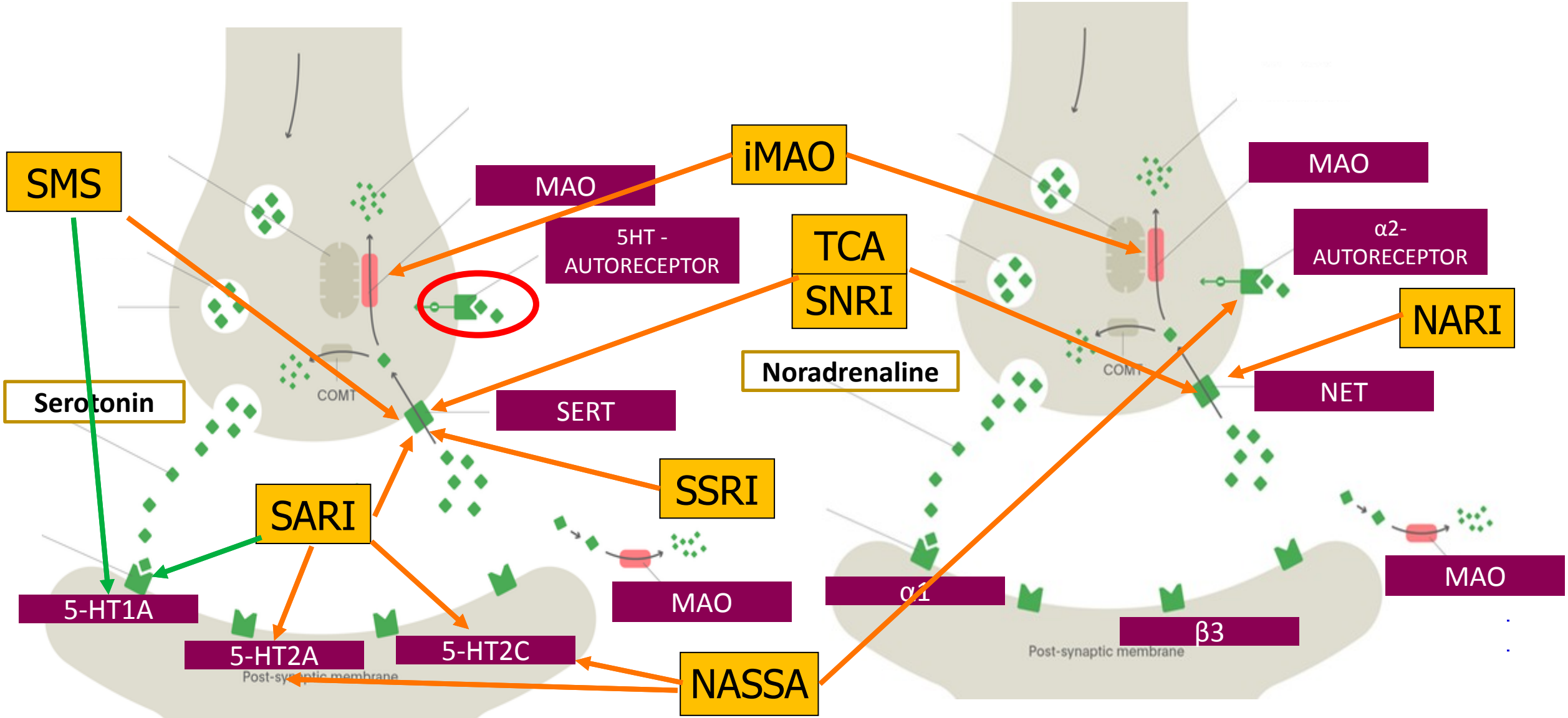
Mode of action of antidepressants



Mode of action of antidepressants

- most AD increase 5-HT, NA or D activity

General modes of action of antidepressants:

- MAO inhibition (selective MAO A/ nonselective)
- reuptake inhibition (SERT, NAT)
- desensitisation/antagonism of presynpatic autoreceptors (5-HT_{1D}, α_2)

→ increase of 5-HT and/or NA

- agonism on receptors 5-HT_{1A}
- antagonism on receptors 5-HT_{2A}

→ increased BDNF activity

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Efficacy of antidepressants

- in general partial response or remission in 60-70% of patients
- „only 30 %“ in the first line of antidepressant treatment
- significant interindividual differences in treatment response
- the efficacy of distinct groups of AD is equipotential

= criterions of AD selection

1. depression side symptoms (agitation, anxiety, insomnia)
2. decrease of adverse reactions risk

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SSRI – selective serotonin reuptake inhibitors 

- inhibit also NAT, but more selective for SERT
- PK and PD differences between single agents = one SSRI can be replaced by other in case of therapy failure
- drugs of choice in most patients
- great safety profile – but not tolerability
- ↑ risk of suicide in tennagers
- risk of drug-drug interactions (iCYP 2D6 and 3A4 inhibitors)

I: depression, anxiety, OCD, PTSD, migraine, pain

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SSRI

AE

- GIT irritation
- ↑ bleeding, sex. dysfunction, anhedonia

Serotonin syndrome

- induced by hyperactivity of serotonine in the CNS
- high risk in combinations of serotonergic drugs (AD, triptans, opioids)

Antidepressant discontinuation syndrome - FINISH

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SSRI

fluoxetine

- 5-HT_{2A}antagonist, CYP2D6 strong inhibitor

sertraline

- the strongest SERT inhibitor
- weak DAT inhibitor, anxiolytic activity

paroxetine

- weak antimuscarinic effect = sedative; CYP2D6 strong inhibitor

citalopram

- the lowest risk of drug-drug interactions

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SNRI – serotonin and noradrenaline reuptake inhibitors

MofA – nonselective blockade of 5-HT and NA

- „activating“ drugs

AE

- stimulation of adrenergic receptors = insomnia, sex. impairment,

  ↓ apetite, hypertension

- increased risk of suicide, discontinuation sydrome
- **venlafaxine** + **desvenlafaxine**
- **duloxetine** – also for neuropathic pain, hepatotoxic

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NDRI – noradrenaline and dopamine reuptake inhibitors

bupropion

- little effect on 5-HT
- in comparison to other DAT and NAT inhibitors does not cause euphoria
- in the treatment of smoking cessation

AE

- risk of seizures
- aggravation/development of psychotic signs

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NARI – noradrenaline reuptake inhibitor

reboxetine

MofA – blockade of NAT: SERT = 20:1

- M, H1 and α_1 antagonist

AE

- stimulation of adrenergic receptros = insomnia, restlessness, anxiety
- constipation, sex. dysfunction
- **atomoxetine** –ADHD therapy

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SARI – serotonine antagonist and reuptake inhibitor

trazodone

MofA

- SERT inhibition
- 5-HT_{1A} agonism
- 5-HT_{2A} and $_{2C}$ antagonis
- H_1 and $\alpha_1$antagonismus

AE: hypotension, sleepiness

- CYP2D6 substrate, 3A4 inhibitor

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NASSA – noradrenergic and specific serotonergic antidepressants

mirtazapine

- is not reuptake inhibitor
- α_2 antagonist
- 5-HT_{2A}, 5-HT_{2C} and 5-HT_3 antagonist
- H_1 and weak α_1 antagonist
- increased apetite and weight gain
- suitable in depression with sleep disorder, low risk of sex. impairment

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SMS – serotonin modulator and stimulator

vortioxetine

MofA: inhibice SERT

5-HT_{1A}agonism

5-HT_{1D}, 5-HT_3 antagonism

AE: pruritus, nausea, live dreams

- risk of serotonine syndrome
- CYP2D6 substrate

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MASSA-melatonine agonist and serotonin selective antagonist

MofA: MT_1 and MT_2 agonist

5- HT_{2C} antagonist

- increased melatonin release and resynchronizes circadian rhythm
- CYP1A2 substrate
- risk of hepatotoxicity = monitoring of transaminases
- in single dose when going to bed

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TCA

MofA: 5-HT, NA and D reuptake inhibition

+ 5-HT_{2A} antagonism and 5-HT_{1A} agonism

+ antagonism of H_1, M, α_1 and 5-HT_{2C} => AE

serotonergic

clomipramine

adrenergic

imipramine, desipramine

amitriptyline, nortriptyline

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TCA

AE:

antiM – confusion, cognitive deficit, peripheral effects

antiH_1 – sedation, weight gain

antiα_1 – ortostatic hypotension

anti $5HT_{2C}$ - weight gain

proarrhythmogenic

- significant acute toxicity
- initial dose usualy titrated

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TCA

- liver metabolism - CYP2D6 and 3A4
- plasma protein binding
- long $t_{1/2}$ = risk of drug accummulation

- „older“ drugs, still in use

I: resistant depression

co-analgesics

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iMAO

- ireversible inhibitors today obsolete
- reversible selective iMAO A – **moclobemide**
- the strongest effect on 5-HT > NA > D
- „cheese reaction“
- positive effect on cognition
- inhibitor of CYP2D6, 2C19 and 1A2

AE: hypotension, CNS stimulation, weight gain

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Esketamine

- NMDA antagonist
- intranasally, supervision needed
- in combination with SSRI or SNRI in resistant depression
- blood pressure monitoring necessary
- fast onset of action
- AE: dissociation incl. hallucinations, sedation, somnolence, BP changes

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Side effects of antidepressant therapy

Nonselective serotonergic activity (SSRI, iMAO, TCA, SNRI)

+ anxiolytic and antidepressant activity

- sex. impairment, emotional flatness, serotonin syndrome

Nonselective noradrenergic activity (TCA, NARI)

+ „activation“ of patient, antidepressant activity

- tremor, tachycardia, hypertension

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Side effects of antidepressant therapy

Antihistaminergic activity = sedation, weight gain

$\alpha_1$lytic activity = ortostatic hypotension and risk of falls

Antimuscarinic activity = cognitive deficit and peripheral effects

QT interval prolongation

- SSRI, TCA

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activating x sedative AD

fluoxetine	trazodone
nortriptyline	mirtazapine
venlafaxine	agomelatine
	paroxetine, fluvoxamine, citalopram
	dosulepine, maprotiline

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How long should be antidepressant treatment continued?

Pharmacotherapy shouldbe continued:

- after 1st episode min. 6 -12 months
- after 2nd episode 2 years
- after 3rd episode 5 years
- after 4th episode lifelong treatment

- the efficacy could be evaluated after 4-6 weeks
- the first step is the dose increase

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Antidepressant discontinuation

- after remission is reached and maintained for specific time
- if discontinued to soon = high risk of relapse
- in some risk of discontinuation syndrome (venlafaxin, paroxetin)

Antidepressant substitution

- some AD has long elimination halftime = „wash out“ period

  (moclobemide, imipramine, clomipramine and fluoxetine)
- gradual dose decrease and titration of new AD

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Augmentation of antidepressant therapy

Antipsychotics

- separately or in combination with antidepressants
- in depression with psychotic symptoms, and in prophylaxis
- atypical antipsychotics

Anxiolytics

- in the begining of therapy of depression with significant anxiety component to decrease the risk of suicide

Phytopharmacology

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Nonpharmacologigal antidepressive measures

- psychotherapy
- physical exercise
- phototherapy
- rTMS (transcranial magnetic stimulation)
- ECT

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