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Antidepressants

Depression

- loss of interest, happiness and motivation
- loss of self-confidence, remorses, 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 apettite
- decrease of libido

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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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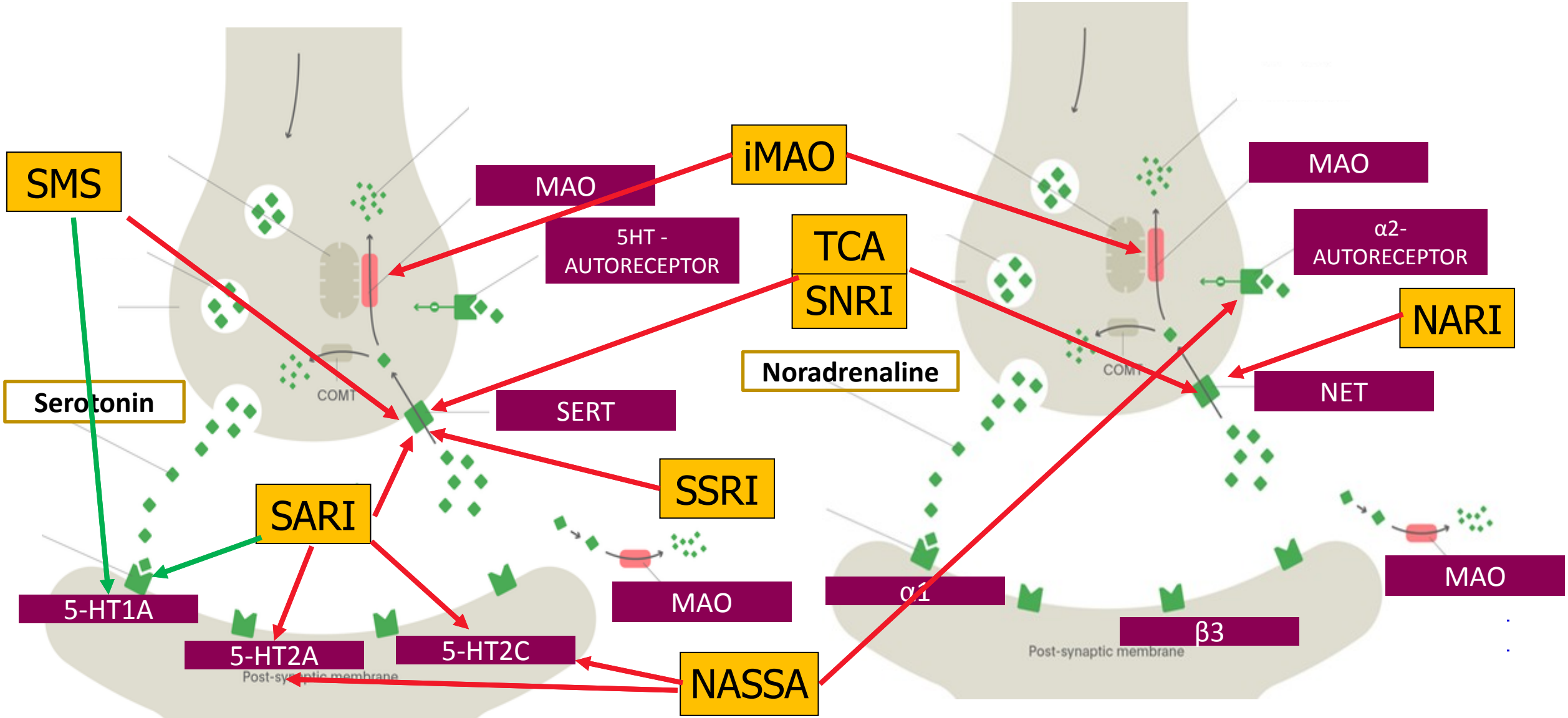
Mechanismus účinku antidepresiv



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 of postsynaptic receptors 5-HT_{1A}
- antagonism of postsynaptic receptors 5-HT_{2A}

→ increased BDNF activity

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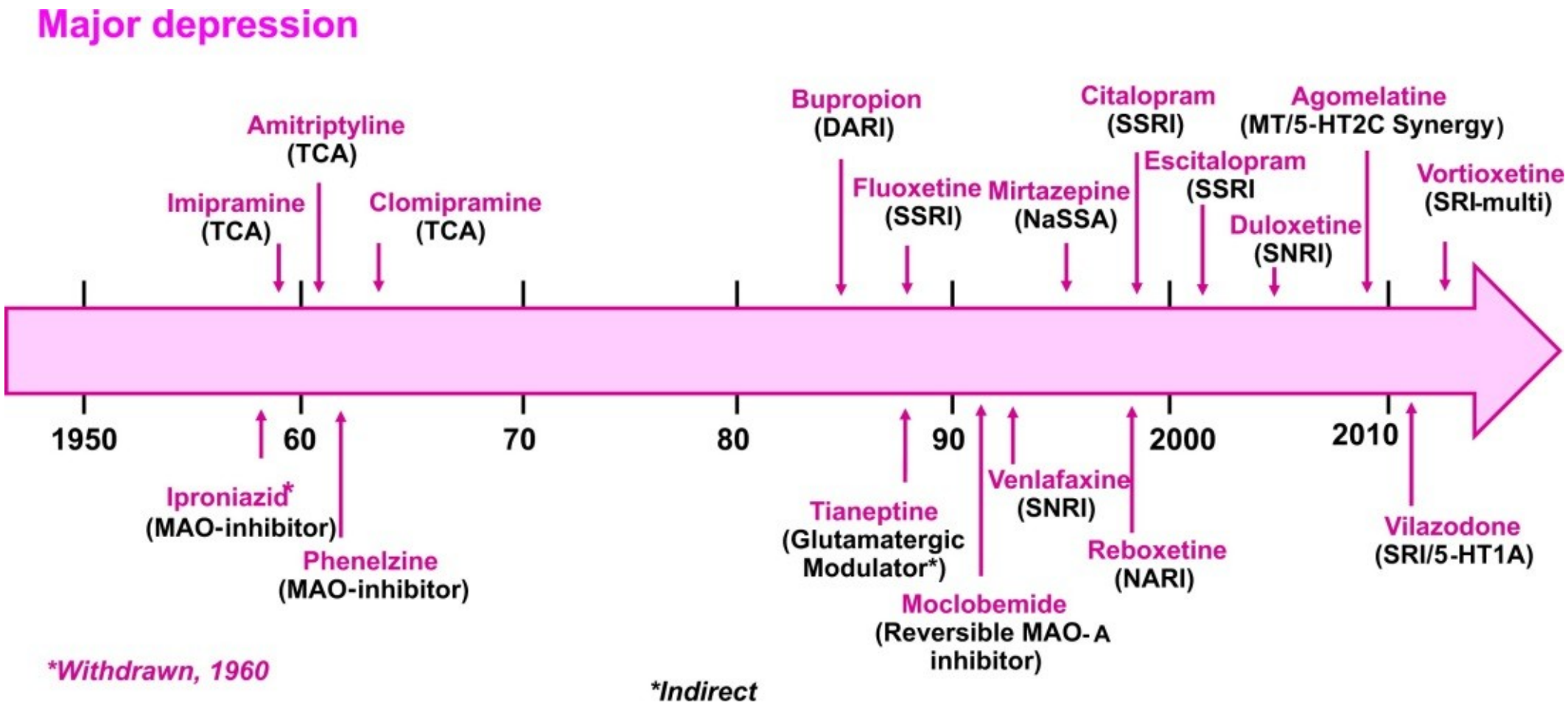
History of antidepressants



MILLAN, Mark J., et al. **Learning from the past and looking to the future: Emerging perspectives for improving the treatment of psychiatric disorders.** *European Neuropsychopharmacology*, 2015, 25.5: 599-656.

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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

= criteria 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, analgesics)

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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SSRI - escitalopram

MofA: SERT selective inhibition

Indications: depression, anxiety

Administration: per os

PK: good absorption from GIT, low protein binding, complete biotransformation in liver (CYP2C19), active metabolites, dominantly excreted into urine

AE: prolongation of QT, serotonine syndrome

DDI: iMAO ↑risk of serotonine syndrome, CYP inhibitors

KI: till 18 years, gravidity, lactation

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SNRI – serotonin and noradrenaline reuptake inhibitors

MofA – nonselective blockade of 5-HT and NA reuptake

- „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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mirtazapine

NASSA – noradrenergic and specific serotonergic antidepressants

MofA: block of presynaptic α_2 + postsynaptic 5-HT_{2A}, 5-HT_{2C} and 5-HT_3

stimulation of 5-HT_1

block of H1 and weak antagonism of α1

Administration: per os

PK: F from GIT app. 50%, protein binding, substrate of CYP3A4, CYP2D6 and CYP1A2, complete metabolization, some metabolites are active

AE: serotonine syndrome, sedation, ↑ weight

Interactions: serotonergic drugs, including St. John‘s wort, CYP inducers/inhibitors

KI: till 18 years, combination with iMAO

- drug discontinuation– slow dose decrease
- suitable in depression with insomnia, low risk of sex. disorders

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SMS – serotonin modulator and stimulator

vortioxetine

MofA: inhibice SERT

$5\text{-}HT_{1A}$agonism

$5\text{-}HT_{1D}$, $5\text{-}HT_{3}$ antagonism

AE: pruritus, nausea, live dreams

- risk of serotonin 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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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		paroxetine, fluvoxamine, citalopram
nortriptyline		dosulepin, maprotiline
venlafaxine		trazodone
		mirtazapine
		agomelatine

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Augmentation of antidepressant terapy

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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