

Serotoninerđični sistem 2

Antidepresivi

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18. april 2013

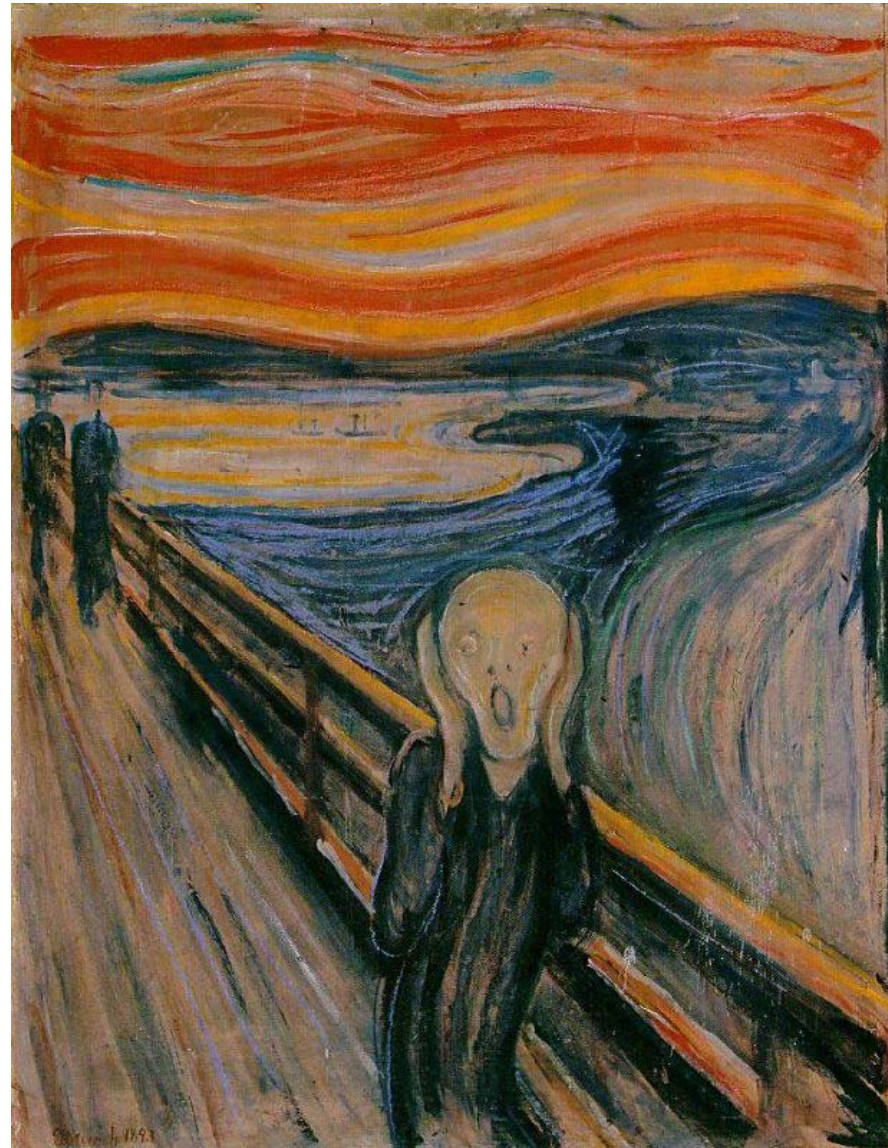
Depresija

- Kaj so to “zdravi možgani”?

Depresija?

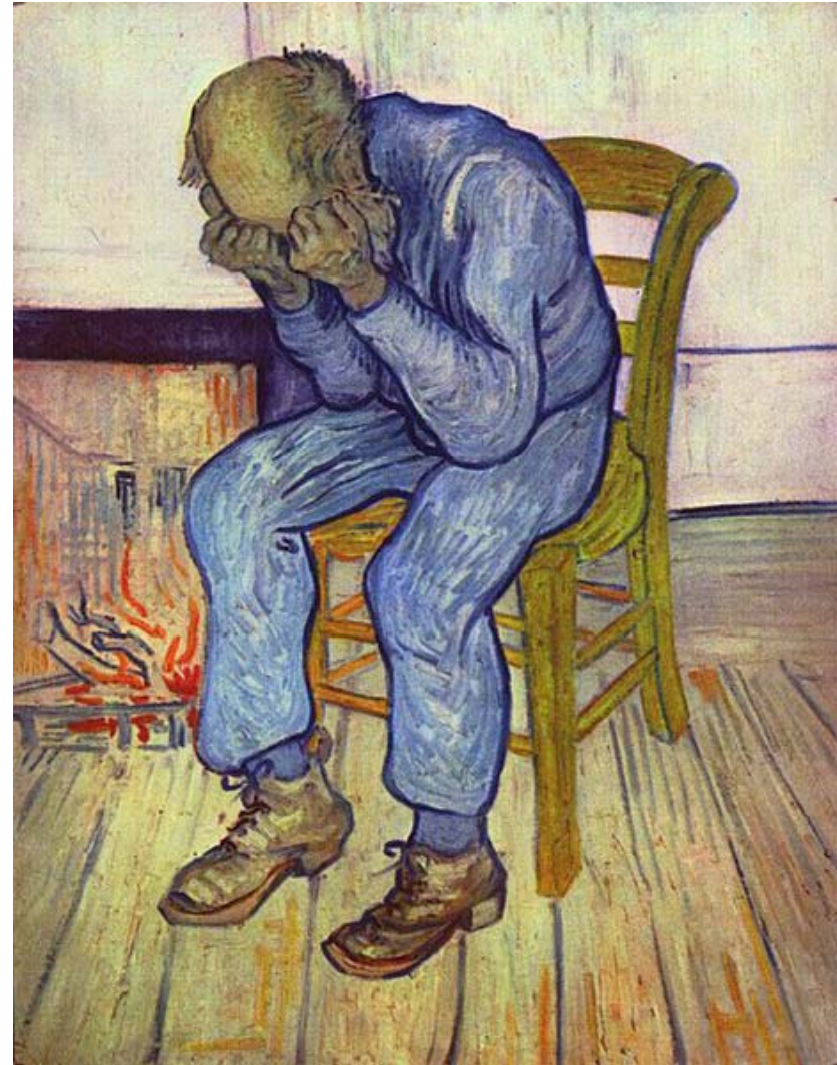
Edvard Munch (1893): “Skrik”

"One evening I was walking along a path, the city was on one side and the fjord below. I felt tired and ill. I stopped and looked out over the fjord—the sun was setting, and the clouds turning blood red. I sensed a scream passing through nature; it seemed to me that I heard the scream. I painted this picture, painted the clouds as actual blood. The color shrieked. This became *The Scream*."



Depresija?

**Vincent van Gogh
(1882): “Na vratih
večnosti”**



Depresija?

**Vincent van Gogh (1885-
1886): “Lobanja z
gorečo cigareto”**



Depresija - Anksioznost

Depresija

- **duševna motnja, ki jo označujejo žalostno razpoloženje, pobitost, pesimizem, obupanost, pomanjkanje notranjih spodbud, včasih tesnoba in samomorilna nagnjenja**
- Kronična, recidivirajoča, epizoda
- Distimija (kronična)
- Bipolarna (manično depresivna)

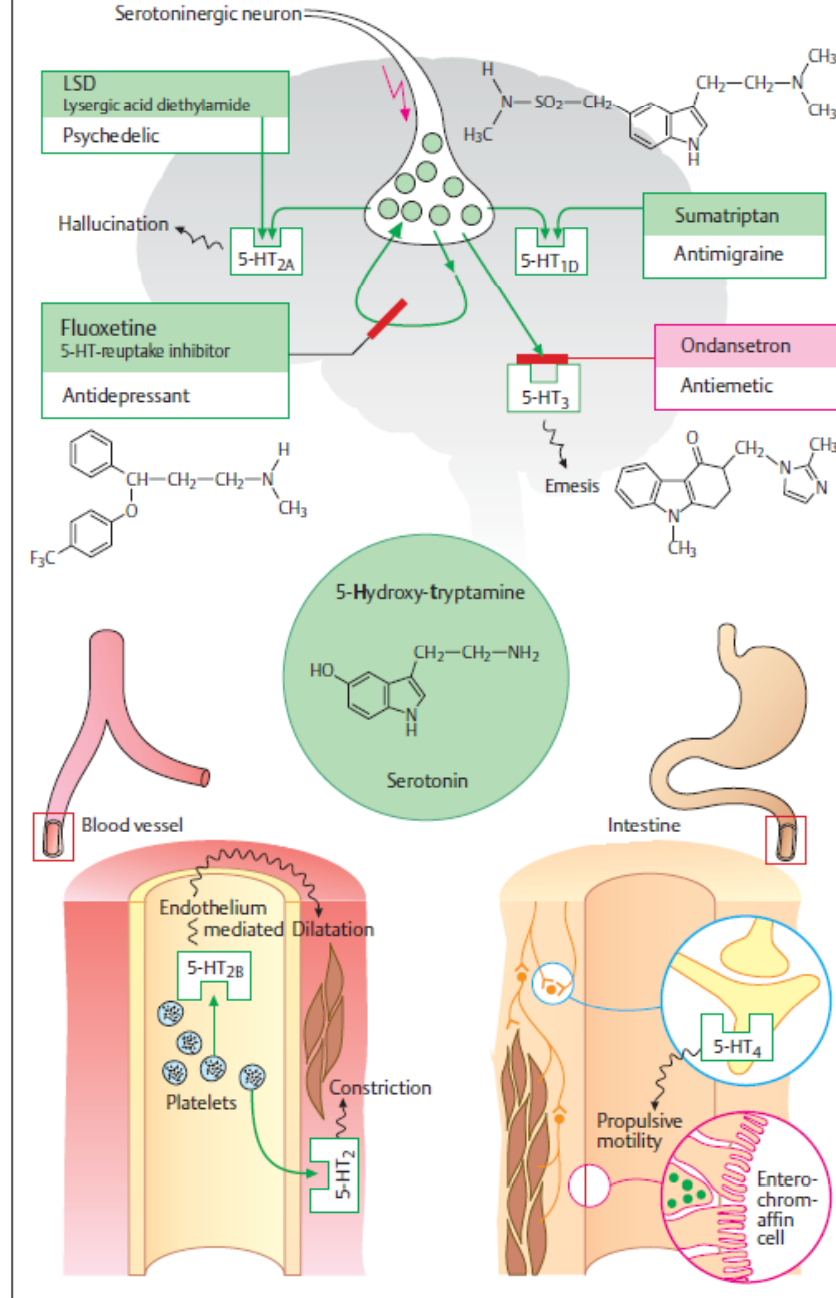
Anksioznost

- **Tesnoba:** občutje negotovosti, pričakovanja česa neugodnega, brez stvarnega zunanjega razloga, spremljano z vegetativnimi pojavi (npr. pospešen srčni utrip in pospešeno dihanje, drhtenje); sin. Anksioznost
- Generalizirana anksiozna motnja
- Panična motnja
- Socialna anksiozna motnja (socialna fobija)
- Akutna stresna reakcija
- Posttravmatska stresna motnja
- Obsesivno-kompulzivna motnja

Depresija

- Izguba “energije”
 - Težave pri koncentraciji
 - Brezvoljnost
 - Motnje spanja
 - Motnje teka in telesne teže
 - Izguba veselja do aktivnosti
 - Samomorilske misli
 - Žalostno počutje
 - Občutek krivde
 - Fizična neaktivnost
-
- **Vsaj 5 od vseh navedenih znakov traja 5 tednov ali več – depresija!**

A. Serotonin actions as influenced by drugs



Hipoteze nastanka depresije

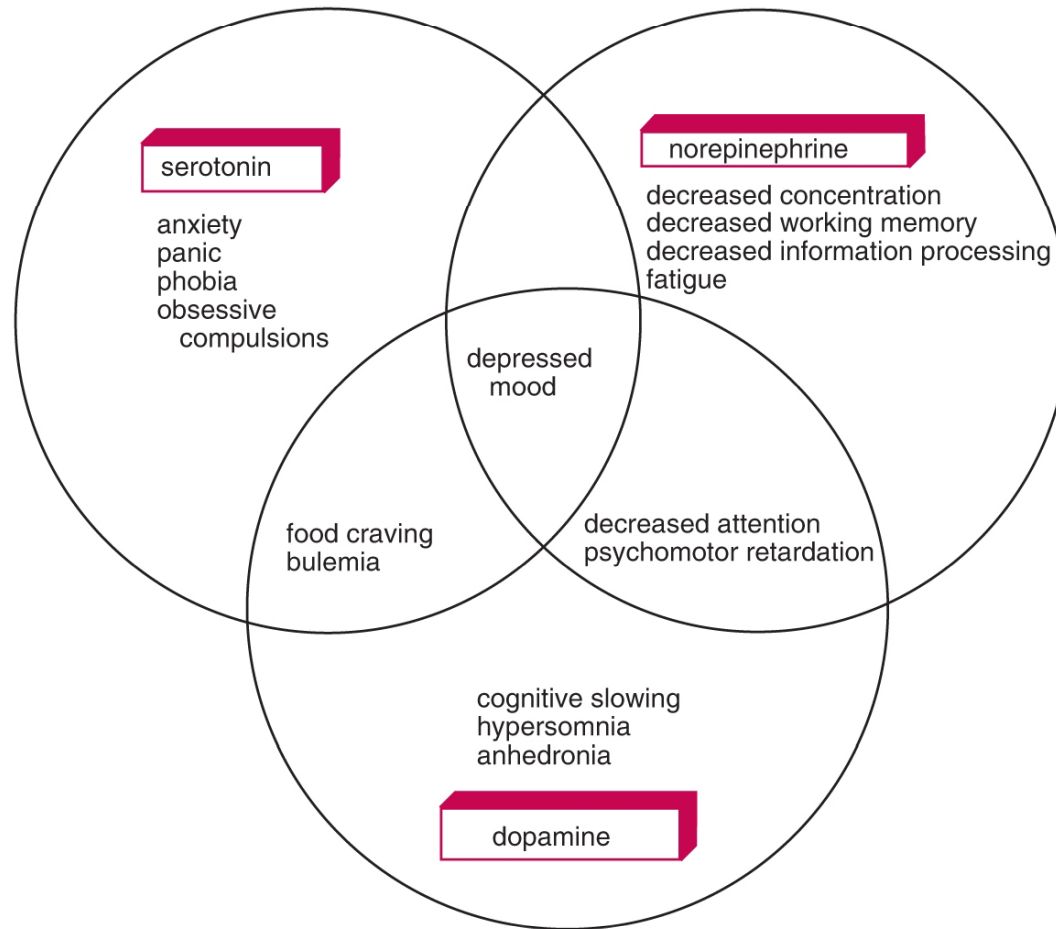
Hipoteza monoaminskega pomanjkanja:

- pomanjkanje monoaminskih prenašalcev (MAP) serotonina, noradrenalina, dopamina v centralnem živčevju
- Serotonin (5-HT): v *Raphe nuclei*, uravnavanje razpoloženja, spanja in v spolnosti
- Noradrenalin: v *Locus coeruleus*, uravnava procese budnosti, pozornosti in koncentracije, učinkuje na krvni pritisk in pulz, vpliva na občutke zadovoljstva in z nagrado pogojeno vedenje
- Dopamin: v *Substantia nigra*, kognitivne funkcije, učenje, razpoloženje, občutek ugodja, evforije

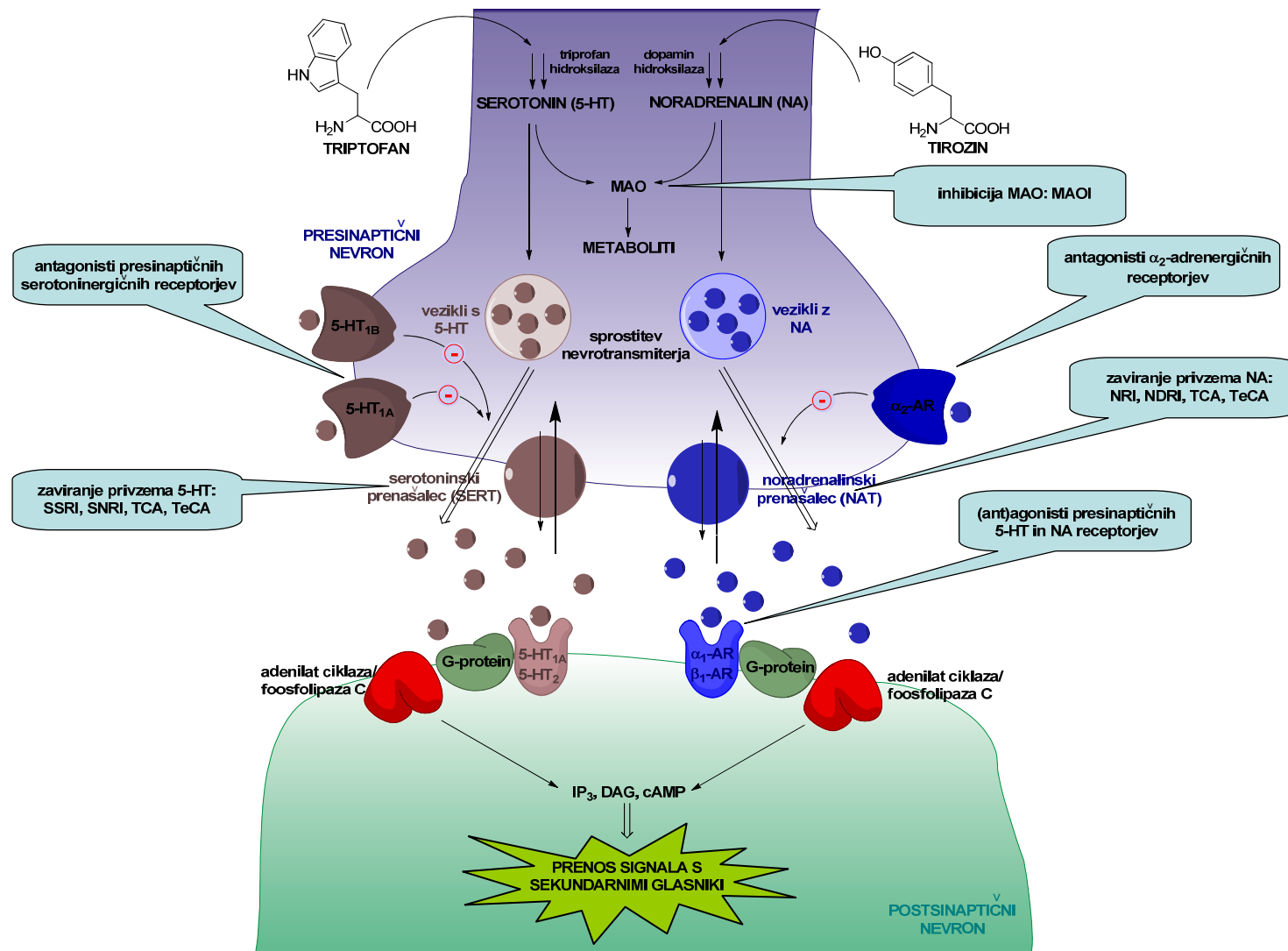
Hipoteza nevrottransmiterskih receptorjev:

- Povečano/zmanjšano število in občutljivost (downregulation) serotoninergičnih in adrenergičnih receptorjev
- posledica adaptacije na znižane nivoje MAP v sinaptični špranji

Hipoteze nastanka depresije



Molekularni nivo nastanka depresije



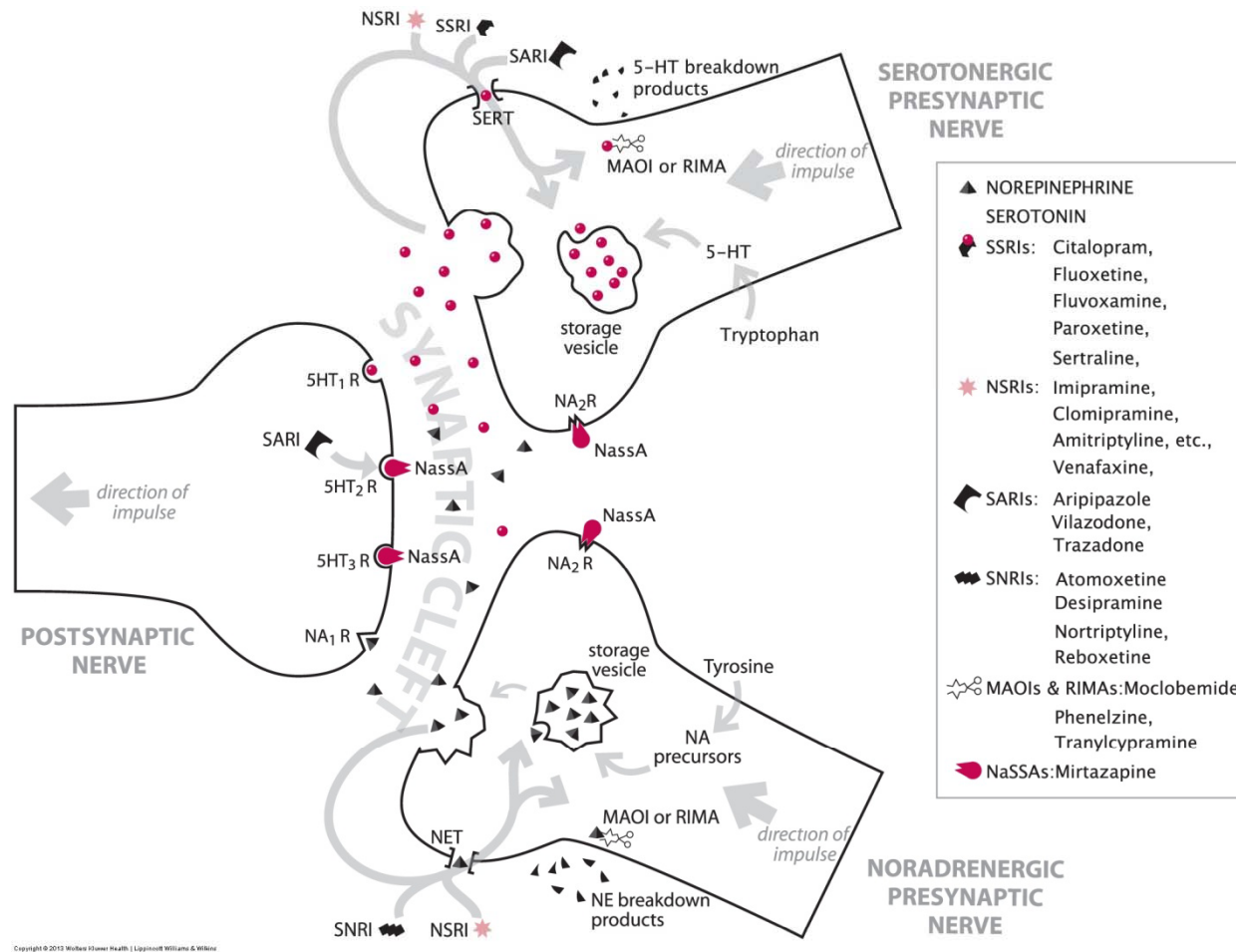
Antidepressivi

- Triciklični antidepressivi = SNRI = Neselektivni zaviralci privzema 5-HT in NA
- SSRI = Selektivni zaviralci privzema 5-HT
- NRI = selektivni zaviralci privzema NA
- NDRI = Neselektivni zaviralci privzema NA in DA
- NaSSA = NA in 5-HT antidepressivi
- MAOI = inhibitorji MAO

A. Antidepressants: activity profiles

	Indication	Adverse effects
Tricyclic Antidepressants		
<p>Amitriptyline <chem>CCN(C)CCc1ccc2c(c1)ccc3c2c1</chem></p>	Patient: Anxious, agitated	Parasympatholytic effects: e.g., tachycardia, dry mouth, constipation, difficult urination Caution: closed-angle glaucoma
<p>Imipramine <chem>CCN(C)CCc1ccc2c(c1)ccc3c2c1</chem></p>	Patient: Drive normal	α_1 -Blockade: orthostatic hypotension
<p>Desipramine <chem>CCN(C)CCc1ccc2c(c1)ccc3c2c1</chem></p>	Patient: Psychomotor inhibition	In high dose: cardiodepression
Selective Serotonin Reuptake Inhibitors (SSRI)		
<p>Fluoxetine <chem>CCN(C)CCc1ccc2c(c1)ccc3c2c1</chem></p>	Patient: Psychomotor inhibition	Akathisia, insomnia, loss of appetite, weight loss, suicidal ideation
MAO _A Inhibitors		
<p>Moclobemide <chem>CCN(C)CCc1ccc2c(c1)ccc3c2c1</chem></p>	Patient: Psychomotor inhibition	In hypertonic patients: Caution: biogenic amines in food

Antidepressivi

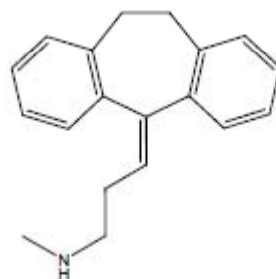
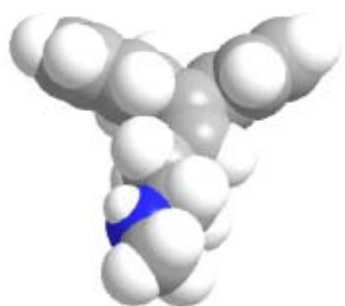


Triciklični antidepresivi (TCA) = NSRI

- podobno kot MAOI ena prekretnic v farmakoterapiji depresivnih motenj, imipramin že leta 1957
- dve skupini:
 - **terciarni amini** (amitriptilin, imipramin, doksepin, klomipramin) – zavirajo predvsem **privzem serotonina** v presinaptične nevrone
 - **sekundarni amini** (desimipramin, nortriptilin, protriptilin) – zavirajo predvsem **privzem noradrenalina** v presinaptične nevrone

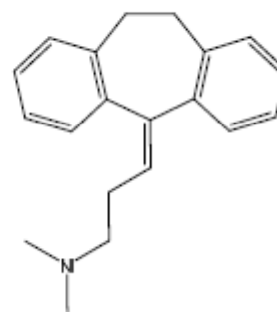
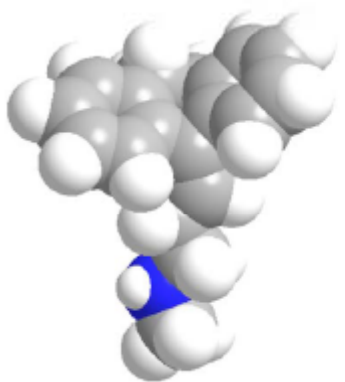
Tricikliční antidepresivi

Nortriptilin 30-40 mg/dan



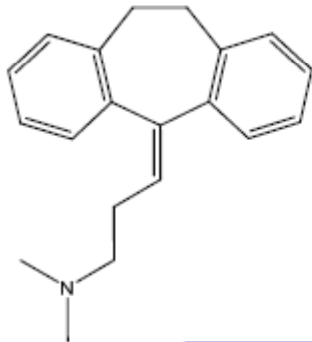
Tricikliční antidepresivi

Amitriptilin 25-150 mg/dan

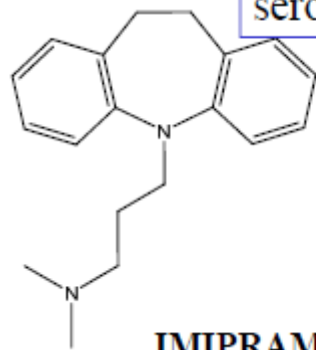


Triciklični antidepresivi

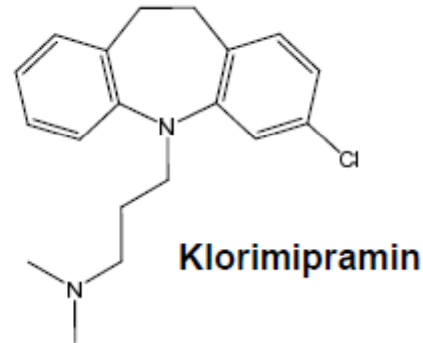
AMITRIPTILIN



Ovira vraćanje
serotonina

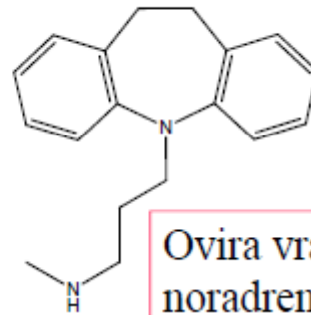


IMIPRAMIN

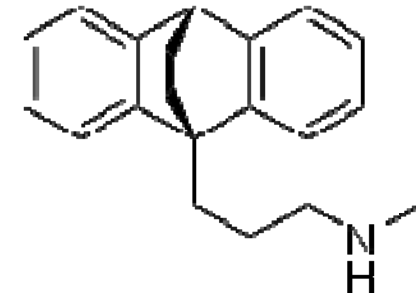


Klorimipramin

DESIPRAMIN



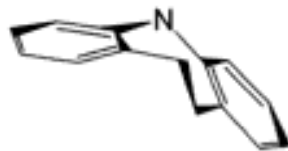
Ovira vraćanje
noradrenalina



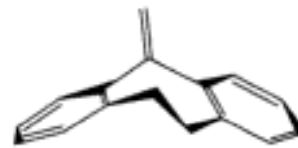
MAPROTILIN

Triciklični antidepresivi

- Primerjava z antispilotiki (fenotiazini) – večji kot med aromatomoma – vzrok za 5-HT + NA vs. DaA selektivnost



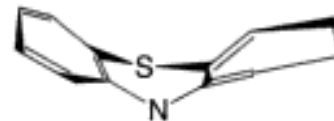
Dihydrodibenzazepine



Dibenzocycloheptene



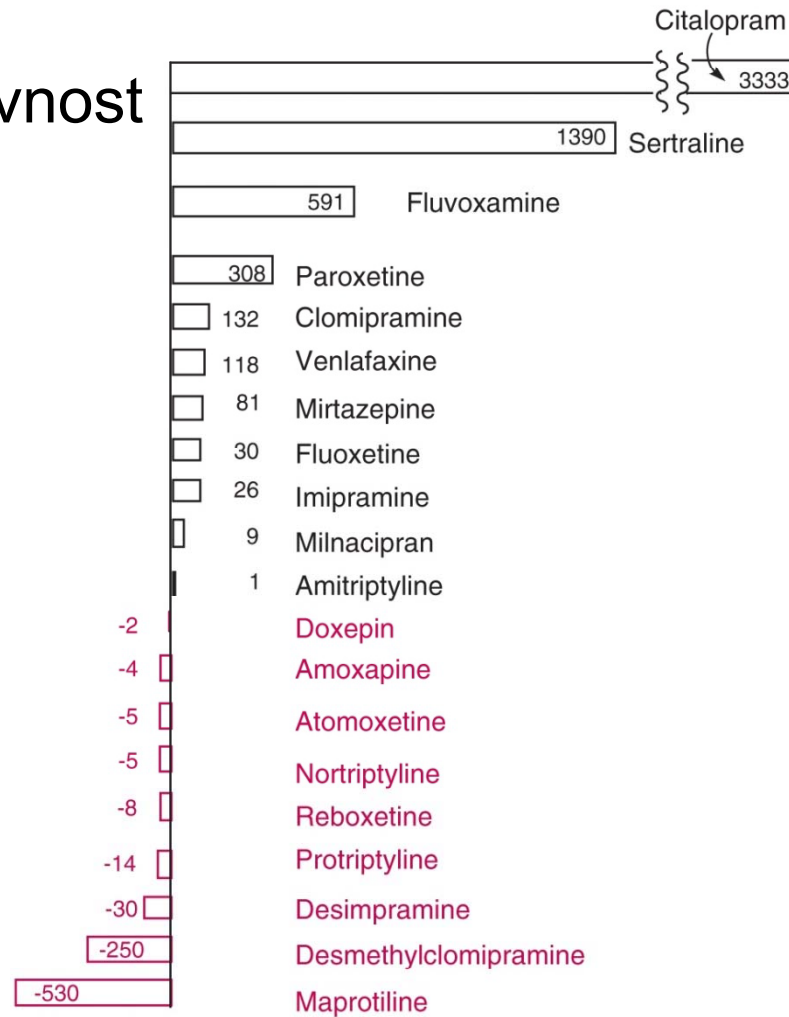
Dibenzobicyclooctadiene



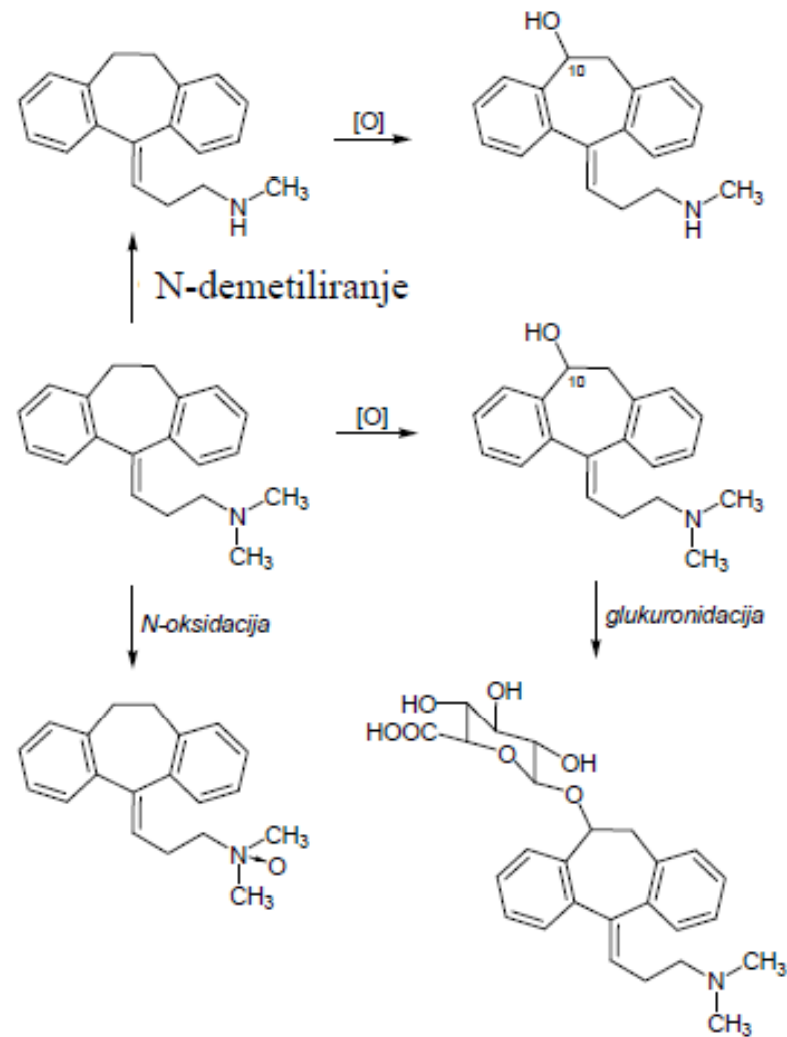
Phenothiazine

Triciklični antidepresivi

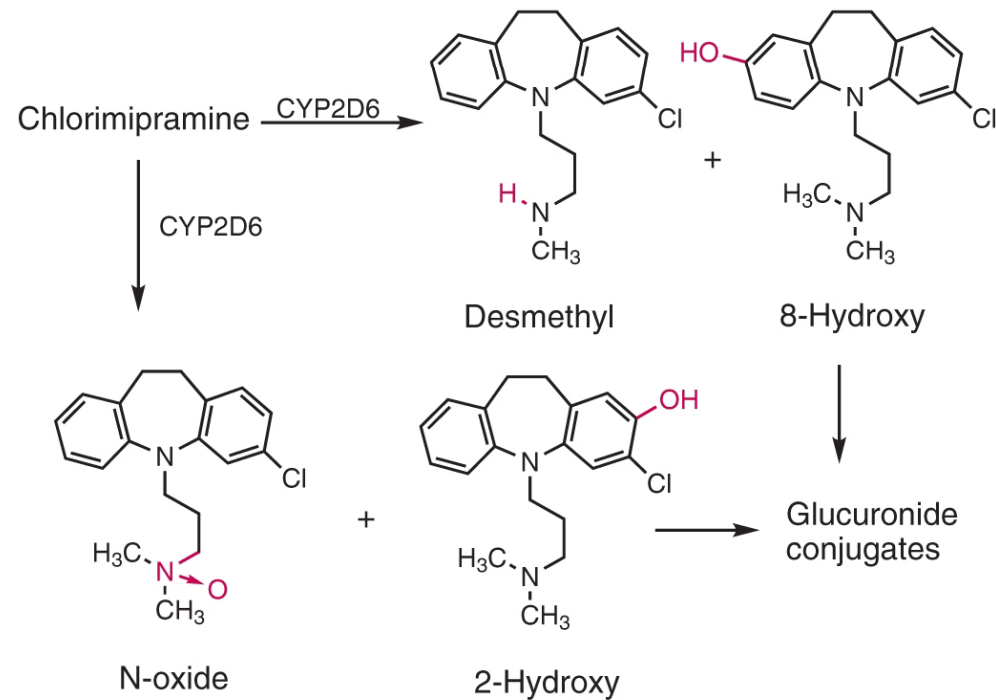
5-HT/NA selektivnost



Triciklični antidepresivi - metabolizam

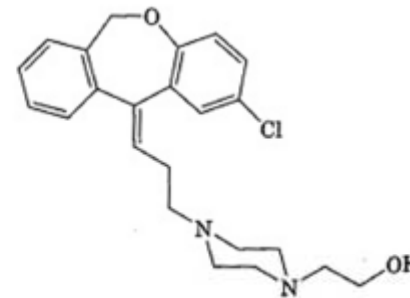
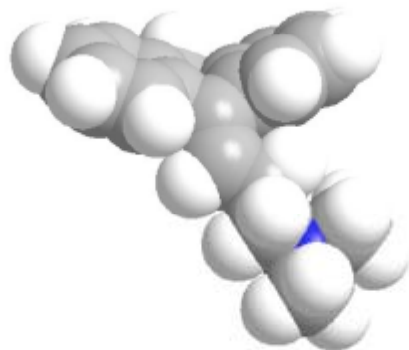
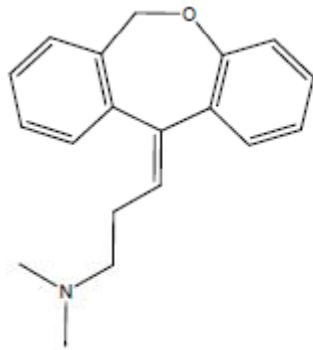


Triciklični antidepresivi - metabolizem



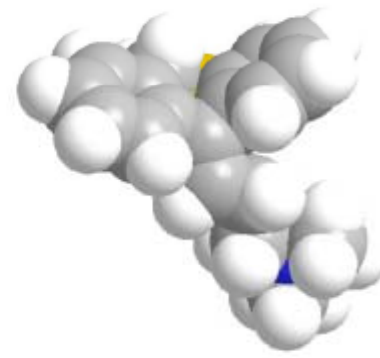
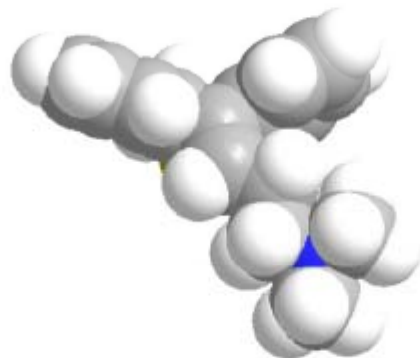
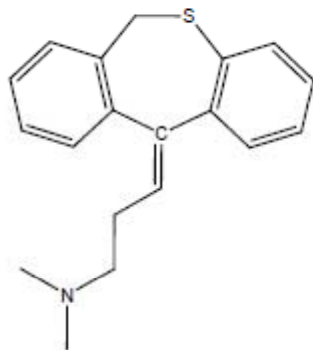
Tricikliční antidepresivi

DOKSEPIN



PINOKSEPIN

PROTIADEN



Stranski učinki TCA

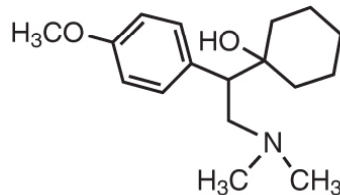
- Antiholinergični – H1
- Antihistaminergični - muskarinski
- Kardiotoksični (adenergični $\alpha 1$)
- CNS

TABLE 18.4 Common Side Effects with Secondary Amine Tricyclic Antidepressants and Recommendations

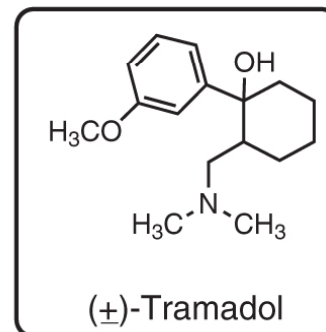
Side Effects	Treatment Recommendations
Dry mouth	Drink sips of water; chew sugarless gum; clean teeth daily
Constipation	Diet rich in bran cereals, prunes, fruit, and vegetables
Bladder complaints (weak urine stream, emptying difficulty, painful urination)	Consult physician
Sexual problems	Consult physician
Blurred vision	Should pass with time
Dizziness	Rise slowly from the bed or chair
Daytime drowsiness	Do not drive; take medication at bedtime; commonly will pass with time

Ostali NSRI

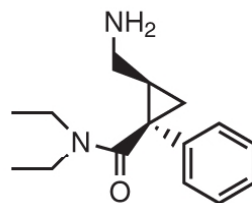
- selektivneje kot triciklični antidepresivi, ni zaviranja privzema dopamina
- močnejši učinek in pogostejše remisije, manj str. učinkov



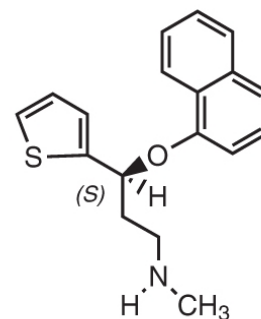
(±)-Venlafaxine



(±)-Tramadol



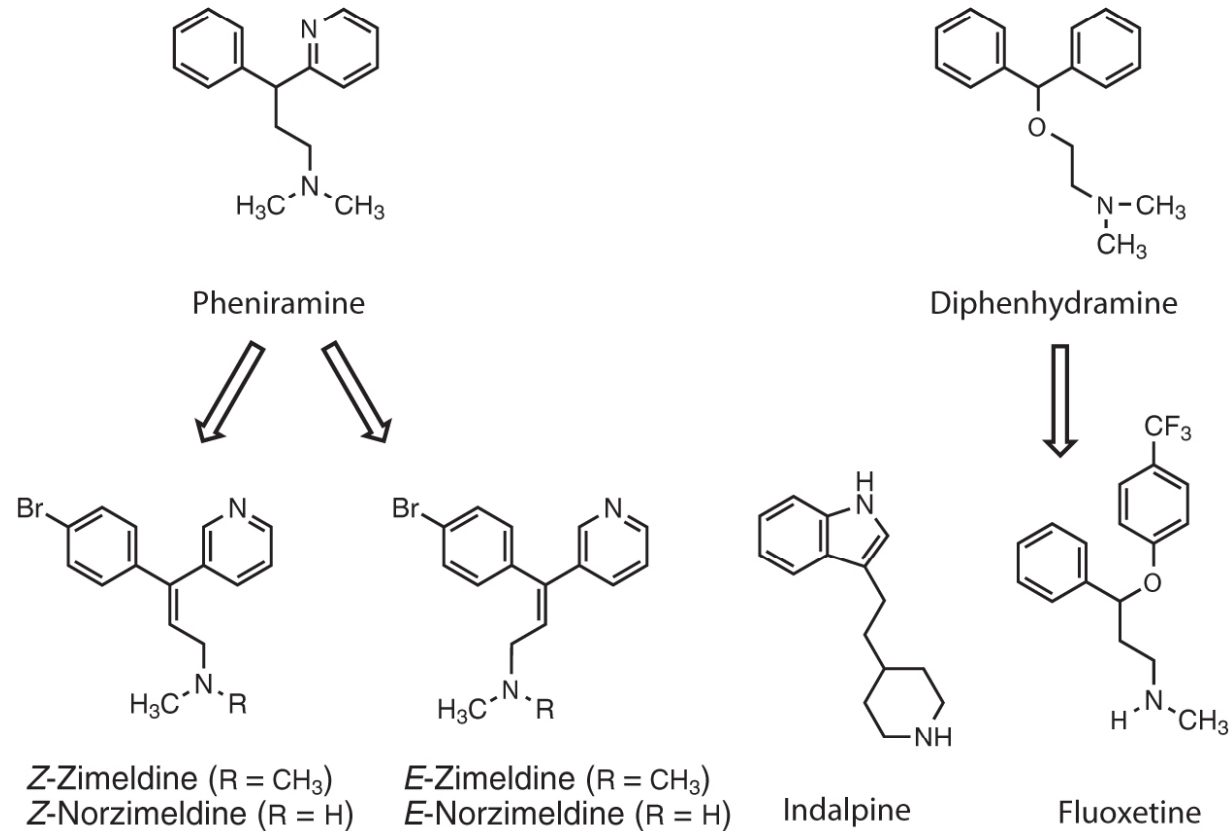
(±)-*cis*-Milnacipran



S(+)-Duloxetine

SSRI = Selektivni zaviralci privzema 5-HT

- načrtovanje



SSRI = Selektivni zaviralci privzema serotonina

- fenoksifenilalkilamini
- najpogosteje predpisovani antidepresivi, zlati standard terapije depresivnih motenj - začetek zdravljenja ravno s SSRI
- Zapozneno delovanje!?

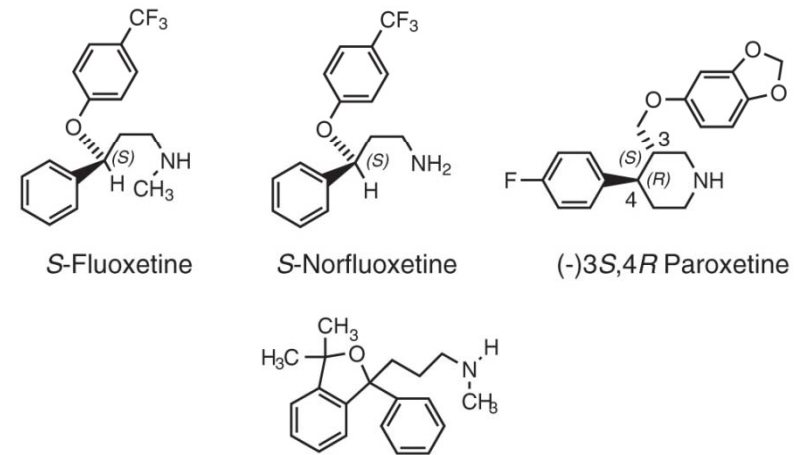
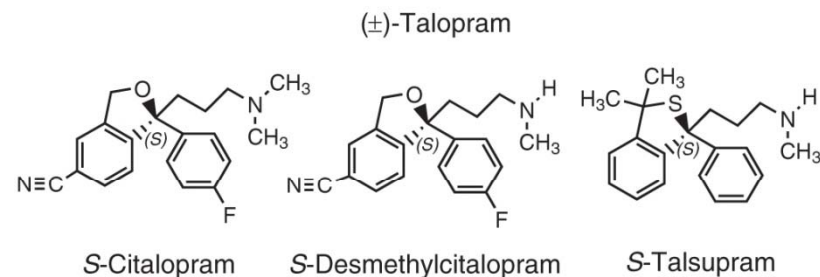


TABLE 18.7 Relationship Between Dose, Plasma Level, Potency, and Serotonin Uptake

SSRI	Dose (mg/d)	Plasma Level	In Vitro Potency (IC ₅₀)	Inhibition of SERT
Citalopram	40	85 ng/mL (260 nM)	1.8	60%
Fluoxetine	20	200 ng/mL (300 nM/L) ^a	3.8	70%
Fluvoxamine	150	100 ng/mL (300 nM/L)	3.8	70%
Paroxetine	20	40 ng/mL (130 nM/L)	0.29	80%
Sertraline	50	25 ng/mL (65 nM/L)	0.19	80%

^aPlasma level for fluoxetine represents the total of fluoxetine plus norfluoxetine given comparable effects on SERT; parent SSRI alone shown for all others. Also, plasma levels are a total of both enantiomers for citalopram and fluoxetine. Values for the parent drug and for the respective major metabolite are in parentheses.



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SSRI = Selektivni zaviralci privzema serotonina

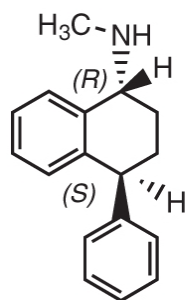
- Farmakokinetični parametri

Parameters	(±)-Fluoxetine	(-)-Sertraline	(-)-Paroxetine	<i>E</i> -Fluvoxamine	(±)-Citalopram [(+)-Escitalopram]
Oral bioavailability (%)	70	20–36	50	>50	80 (51–93)
Lipophilicity (logD _{7.4})	2.38	3.03	1.49	1.21	1.52
Protein binding (%)	95	96–98	95	77	~56 (70–80)
Volume of distribution (L/kg)	12–18	17 (9–25)	25 (12–28)	15–31	12–16
Elimination half-life (h)	50	24 (19–37)	22	15–20	36 (27–32); elderly ~48
Cytochrome P450 major isoform	2D6	3A4	2D6	2D6	2C19, 2D6, and 3A4
Major active metabolites	<i>O</i> -Desmethyl-fluoxetine (240 h) Norfluoxetine (96–364 h)	<i>N</i> -Desmethyl (62–104 h)	None	None	<i>N</i> -Desmethylcitalopram (30 h)
Peak plasma concentration (h)	6–8	4–8	2–8	3–8	4 (1–6)
Excretion (%)	Urine 25–50 Feces minor	Urine 51–60 Feces 24–32	Renal ~50 Feces minor	Urine ~40 (24 h) Feces minor	Feces 80–90 Urine <5
Plasma half-life (h)	1–4 d (norfluoxetine 7–15 d)	22–35	24	7–63	36 (23–75)
Time to steady-state concentration	~4 wk	7–10 d; elderly 2–3 wk	7–14 d	10 d	7 d

“Očiščenje” pred uvedbo MAOI po terapiji s SSRI!

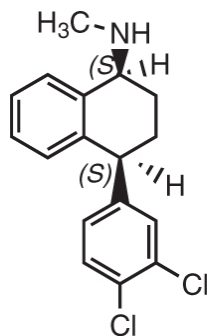
SSRI = Selektivni zaviralci privzema serotonina

- fenilalkilamini

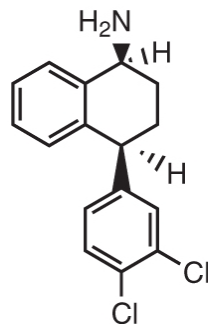


Tametraline

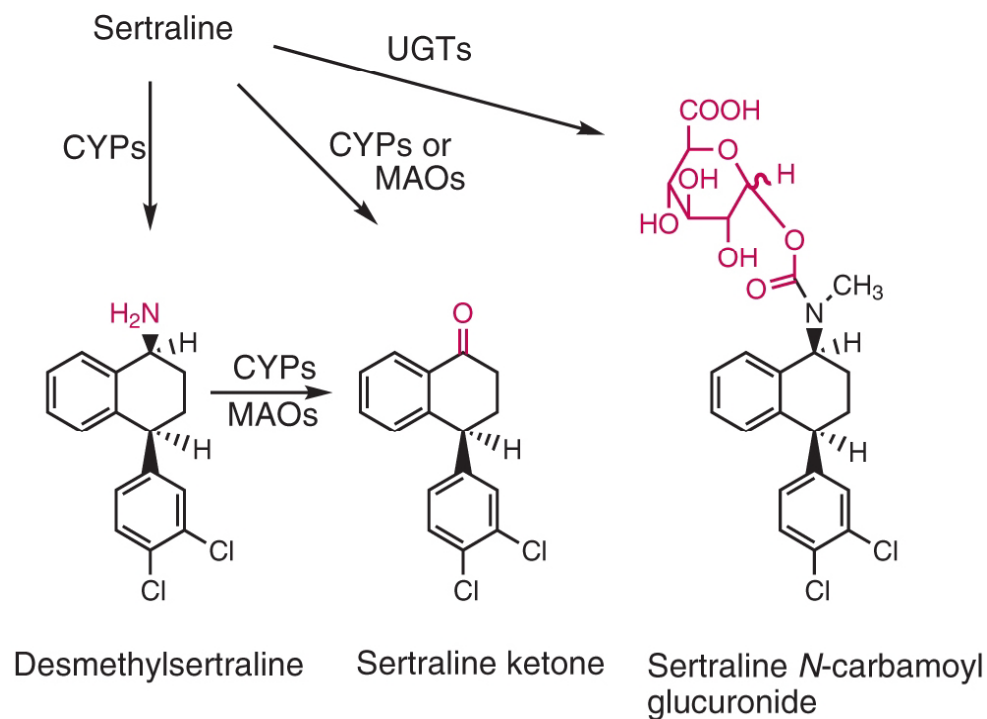
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1*S*,4*S*-Sertraline



1*S*,4*S*-*N*-Desmethyl-sertraline

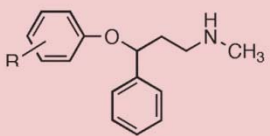


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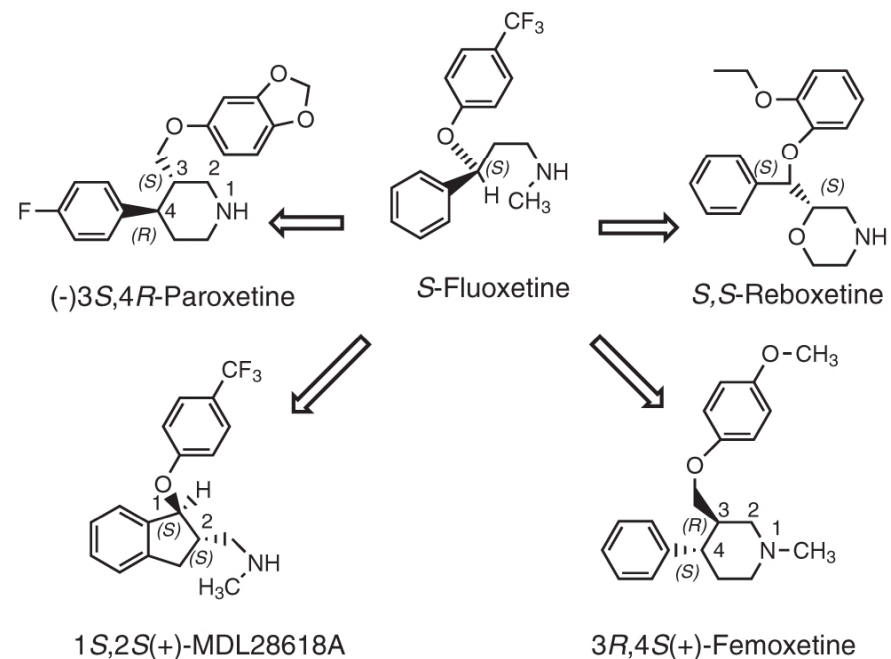
Selektivni zaviralci privzema NA/5-HT

- SAR

TABLE 18.6 Structure–Activity Relationships for Phenoxyphenylpropylamines



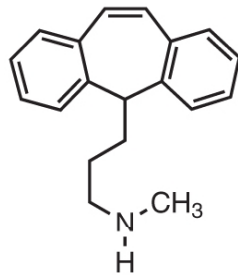
R (drug)	Inhibition of Reuptake (K_i , nM) (20)	
	5-HT	NE
H	102	200
2-OCH ₃ (nisoxetine)	1,371	2.4
2-SCH ₃ (thionisoxetine)	130	0.2
2-CH ₃ (atomoxetine)	390	3.4
2-F	898	5.3
2-I	25	0.4
2-CF ₃	1,489	4,467
3-CF ₃	16	1,328
4-CF ₃ (fluoxetine)	17	2,703
4-CF ₃ (norfluoxetine, NH ₂)	17	2,176
4-CH ₃	95	570
4-OCH ₃	71	1,207
4-Cl	142	568
4-F	638	1,276



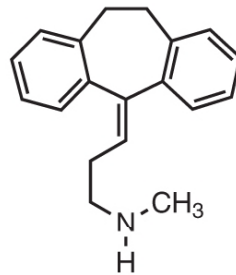
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SNRI = selektivni zaviralci privzema noradrenalina

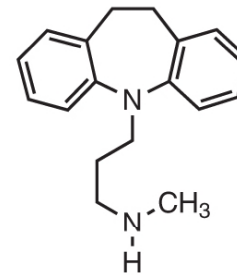
- Po mehanizmu neselektivni: delujejo selektivneje kot triciklični antidepresivi, ni zaviranja privzema dopamina



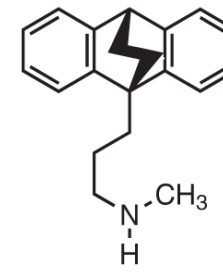
Protriptyline



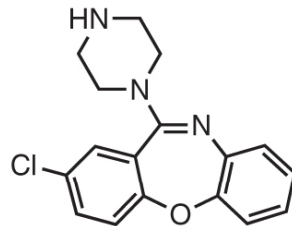
Nortriptyline



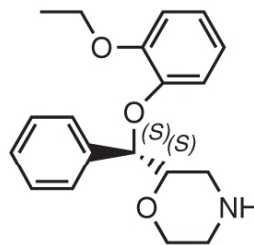
Desipramine



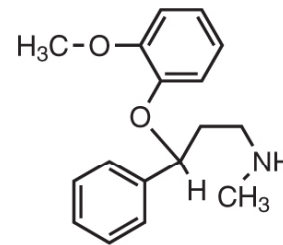
Maprotiline



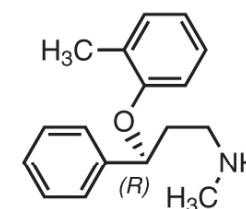
Amoxapine



S,S-Reboxetine



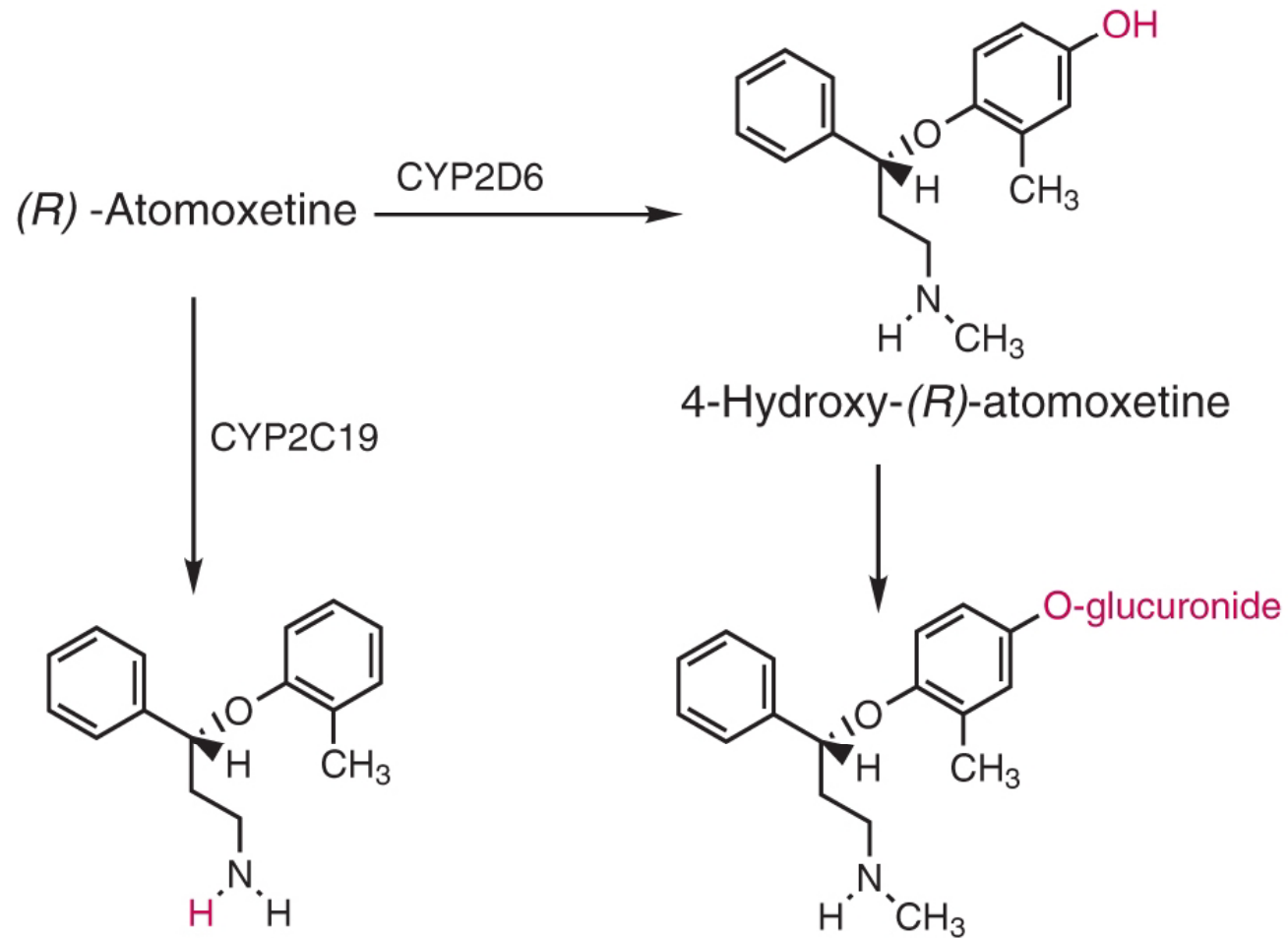
(±)-Nisoxetine



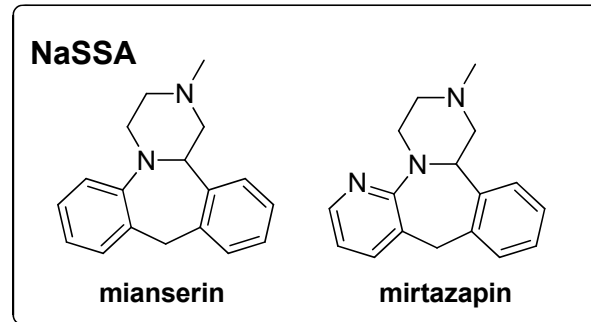
R(-)-Atomoxetine

SNRI = selektivni zaviralci privzema noradrenalina

- metabolizem



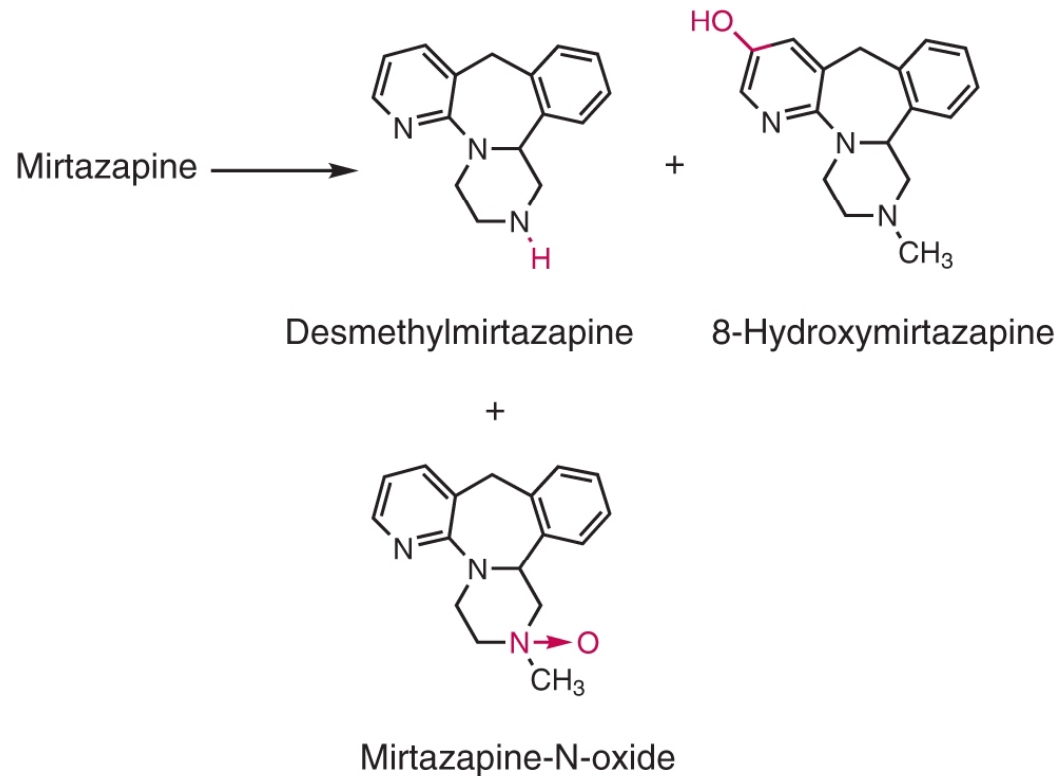
Noradrenergični in selektivni serotoninergični antidepresivi (NaSSA)



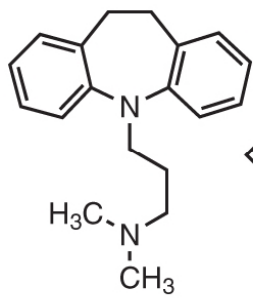
- Tetraciklični antidepresiv mianserin in novejši mirtazapin
- delujejo zaviralno na $\alpha 1$ - in $\alpha 2$ -adrenergične receptorje ter praktično vse serotoninergične receptorje, na delovanje

Noradrenergični in selektivni serotoninergični antidepresivi (NaSSA)

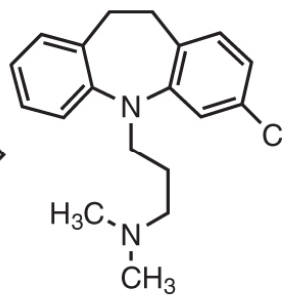
- Metabolizem



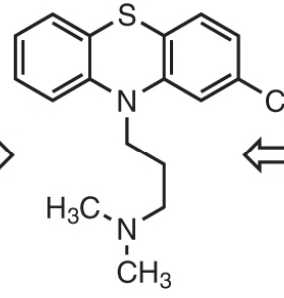
Primerjava struktur



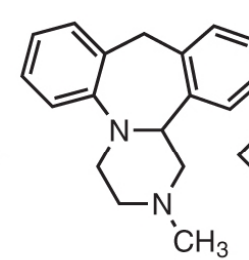
Imipramine



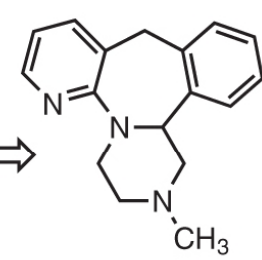
Chlorimipramine



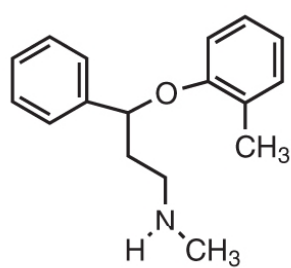
Chlorpromazine



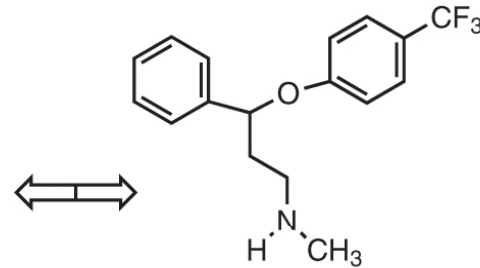
Mianserin



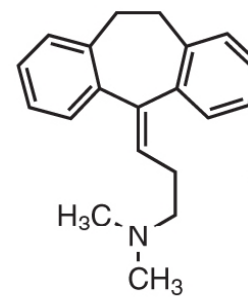
Mirtazapine



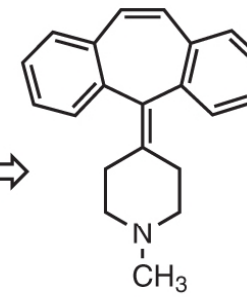
Atomoxetine



Fluoxetine



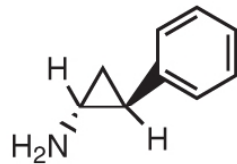
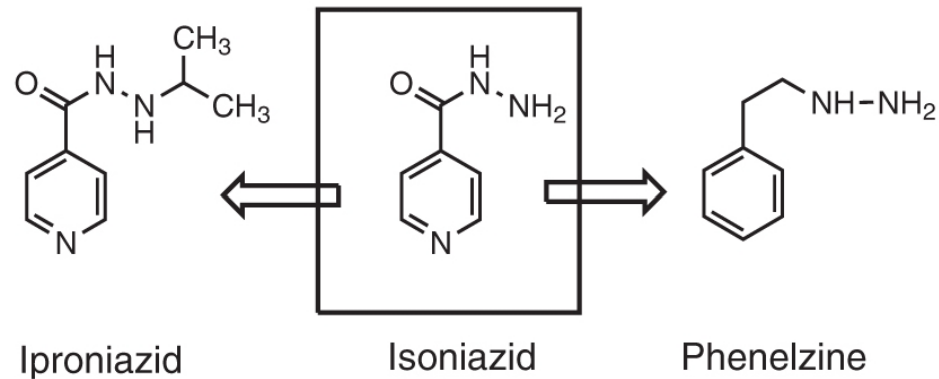
Amitriptyline



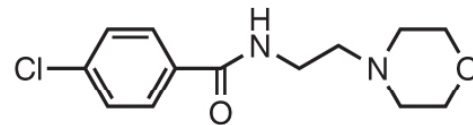
Cyproheptadine

Zaviralci monoaminooksidaz (MAOI)

- prvi klinično uporabljeni antidepressivi: izoniazid in iproniazid



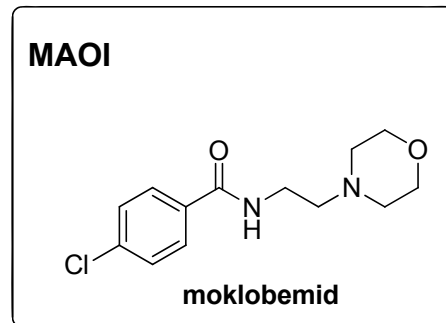
Tranylcypromine



Moclobemide

Zaviralci monoaminooksidaz (MAOI)

- Večinoma neselektivni – več str. učinkov.
- Moklobemid – reverzibilen in MAO-A selektiven



Zaviralci monoaminooksidaz (MAOI)

- Potencialna nevarnost? Hipertenzivna kriza

TABLE 18.13 Foods to Be Avoided Due to Potential Monoamine Oxidase Inhibitor–Food Interactions

Cheeses

Cheddar
Camembert
Stilton
Processed cheese
Sour cream

Meats

Chicken livers
Genoa salami
Hard salami
Pepperoni
Lebanon bologna

Spirits

Chianti
Champagne
Alcohol-free/reduced wines

Fruit

Figs (overripe/canned)
Raisins
Overripe bananas

Fish

Pickled herring
Anchovies
Caviar

Dairy product

Yogurt

Miscellaneous

Shrimp paste
Chocolate
Meat tenderizers (papaya)

Vegetable products

Yeast extract
Pods-broad beans
Bean curd
Soy sauce
Avocado

Literatura predavanj

Foye's Principles of Medicinal Chemistry, 6.
izdaja:

- 14., 21. poglavje