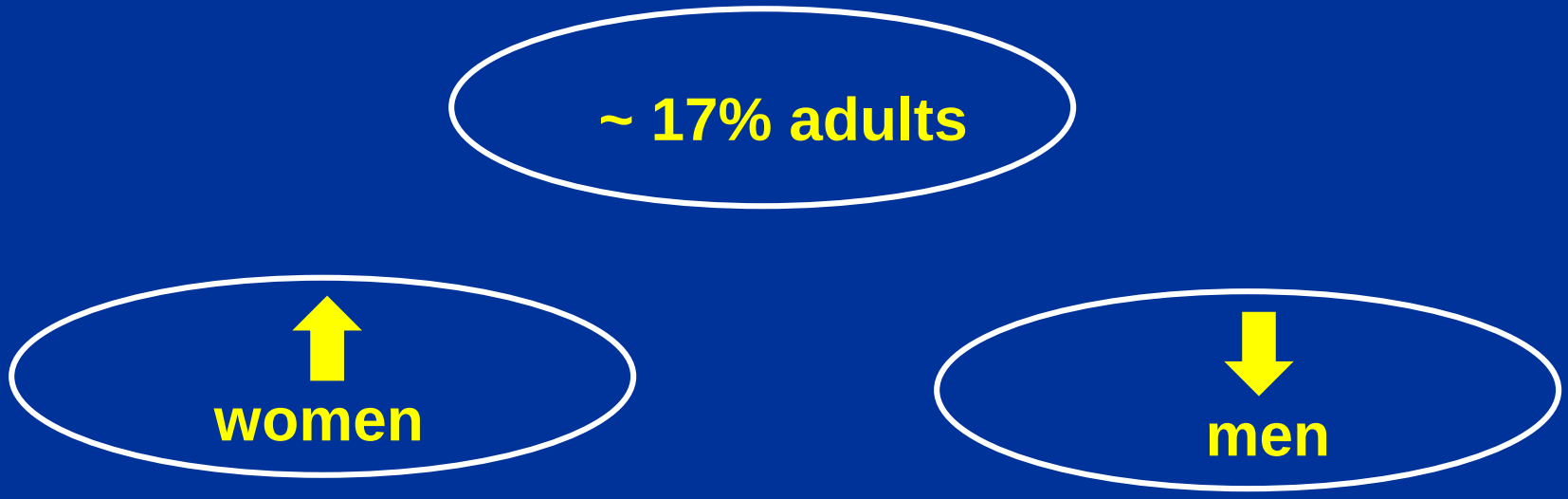
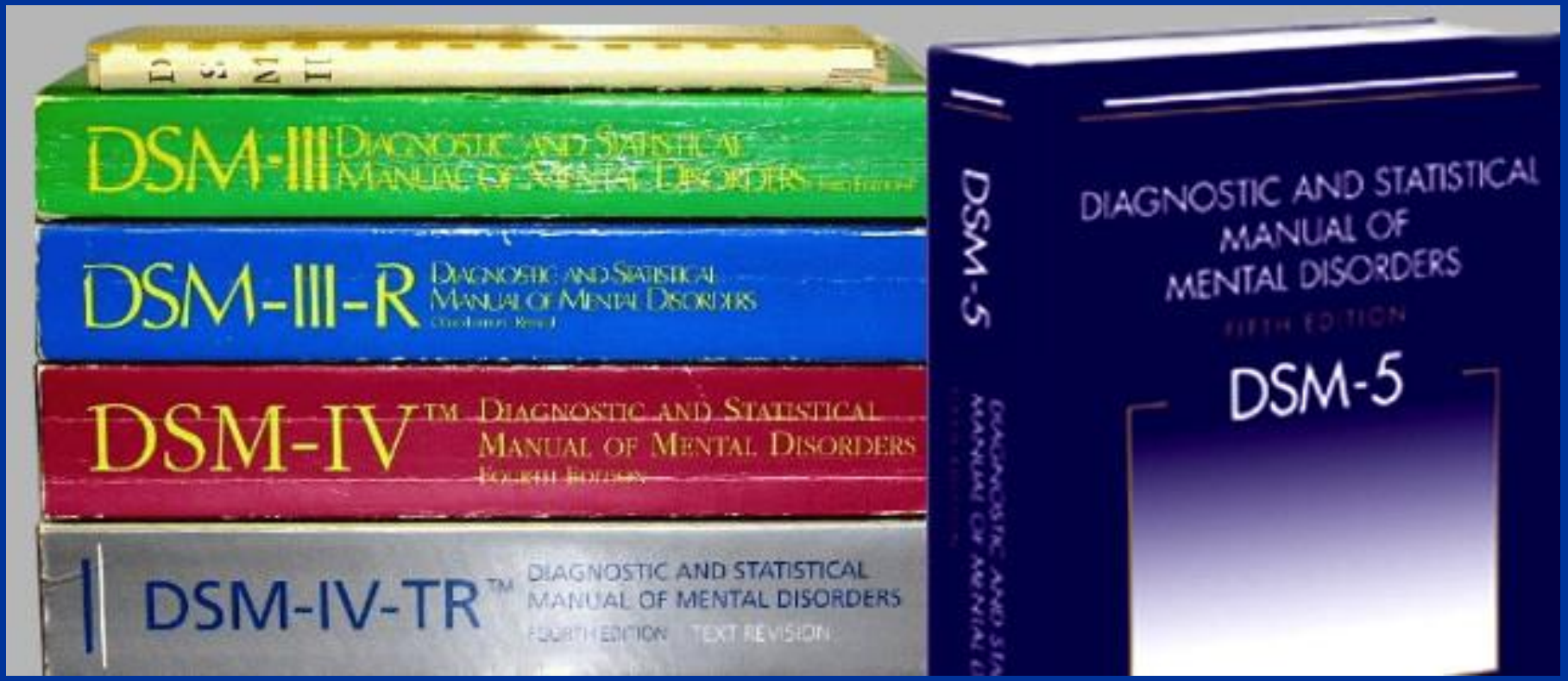
ANTIDEPRESSANT DRUGS

Incidence of the major depression in the U.S.



~ 32 million of people

- Most common affective disorder
- Premature death
- Multifactorial etiology
- Environmental origin
- Heterogeneous disease


DSM-III
DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS
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Major Depressive Disorder

Diagnostic Criteria

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly attributable to another medical condition.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (**Note:** In children and adolescents, can be irritable mood.)
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (**Note:** In children, consider failure to make expected weight gain.)
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

1951-52 Iproniazide (Delay; Zeller) MAO inhibitors

1949-52 Litium – bipolar disorder (Cade; Schou)
1955-57 Antidepressant (Crane et al.)

1957-58* Imipramine (dibenzazepina) (Kuhn et al.)

1970-75* 5-HT e NA reuptake inhibitors (Carlsson et al.) Zimelidina (fluoxetina, fluvoxamina)

* discovery

Theories of depression

Symptoms controlled by monoaminergic systems

Selectivity of antidepressants towards uptake transportes for

serotonin (5-HT)

noradrenaline (NA)

dopamine (DA)

Proposed origin of depression

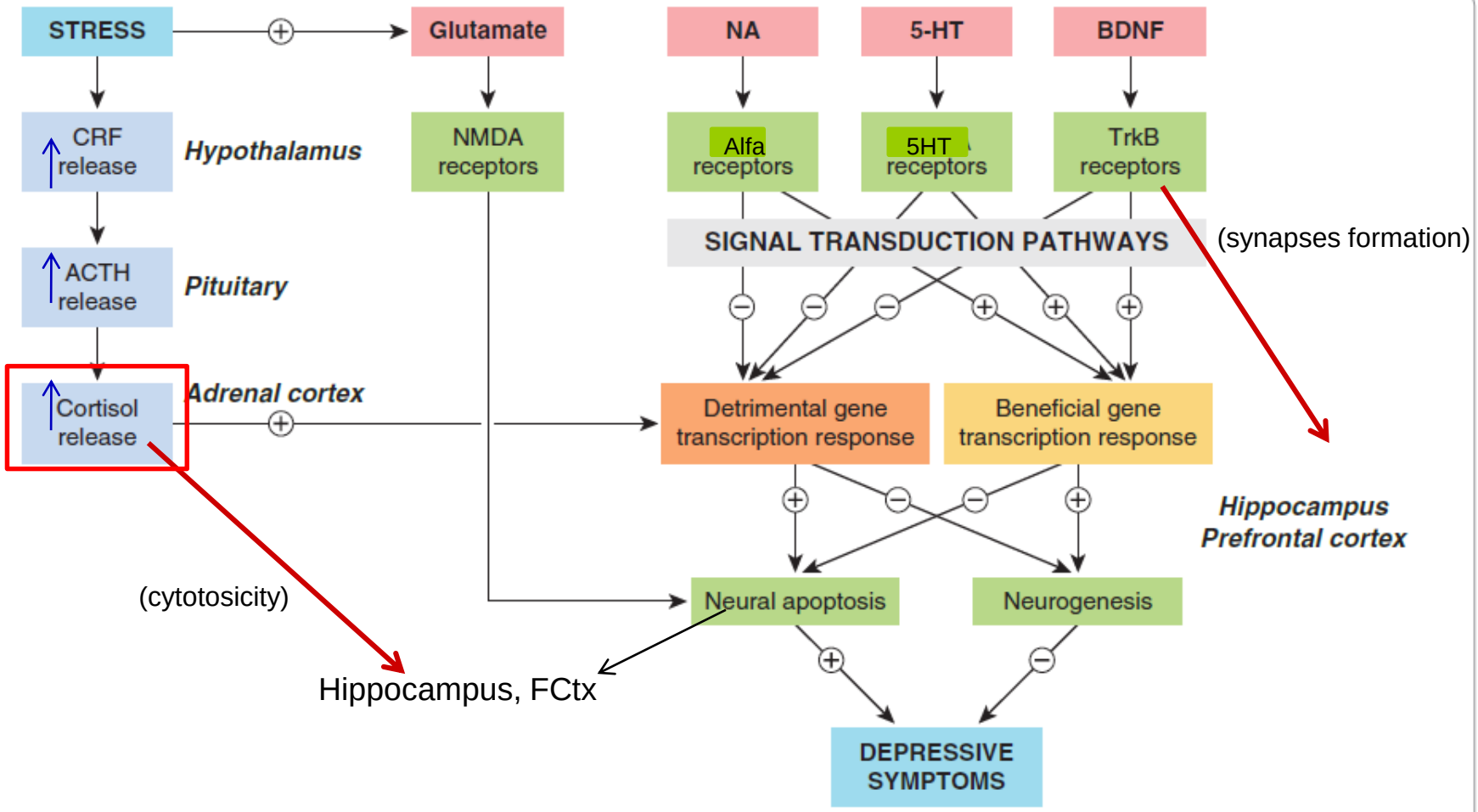


Fig. 47.1 Simplified diagram showing mechanisms believed to be involved in the pathophysiology of depression. The main prodepressive pathways involve the hypothalamic–pituitary–adrenal axis, which is activated by stress and in turn enhances the excitotoxic action of glutamate, mediated by NMDA receptors (see Ch. 38), and switches on the expression of genes that promote neural apoptosis in the hippocampus and prefrontal cortex. The antidepressive pathways involve the monoamines noradrenaline (NA) and 5-hydroxytryptamine (5-HT), which act on G protein-coupled receptors, and the brain-derived neurotrophic factor (BDNF), which acts on a kinase-linked receptor (TrkB), switching on genes that protect neurons against apoptosis and also promote neurogenesis. For further detail, see Charney & Manji (2004). ACTH, adrenocorticotrophic hormone; CRF, corticotrophin-releasing factor.

Evolution of antidepressant drugs

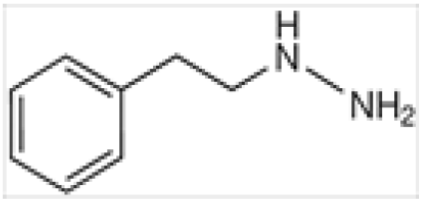
1950 1960 1970 1980 1990 2000 2010 2015 2019

MAO-I

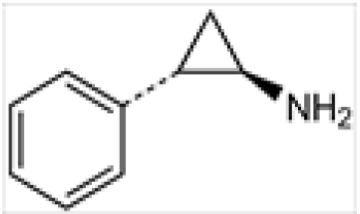
TCA

Serendipity

MAO inhibitors

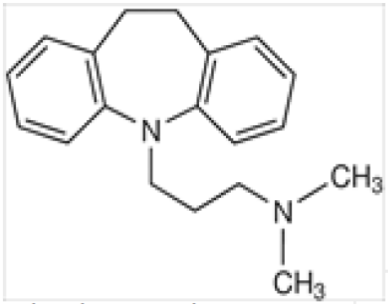


phenelzine

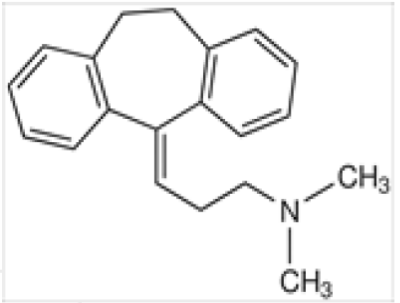


tranylcypromine

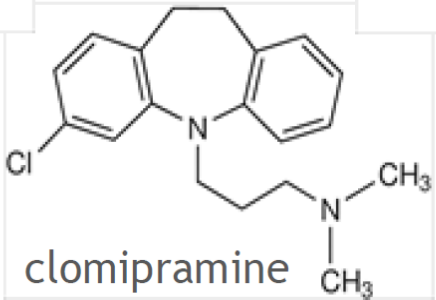
Tricyclic antidepressants



imipramine

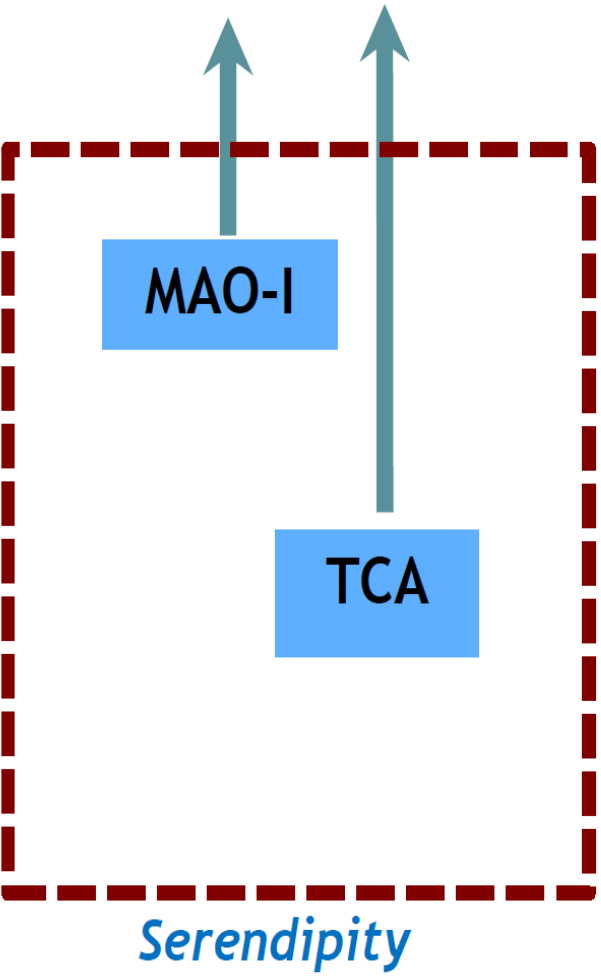


amitriptyline



clomipramine

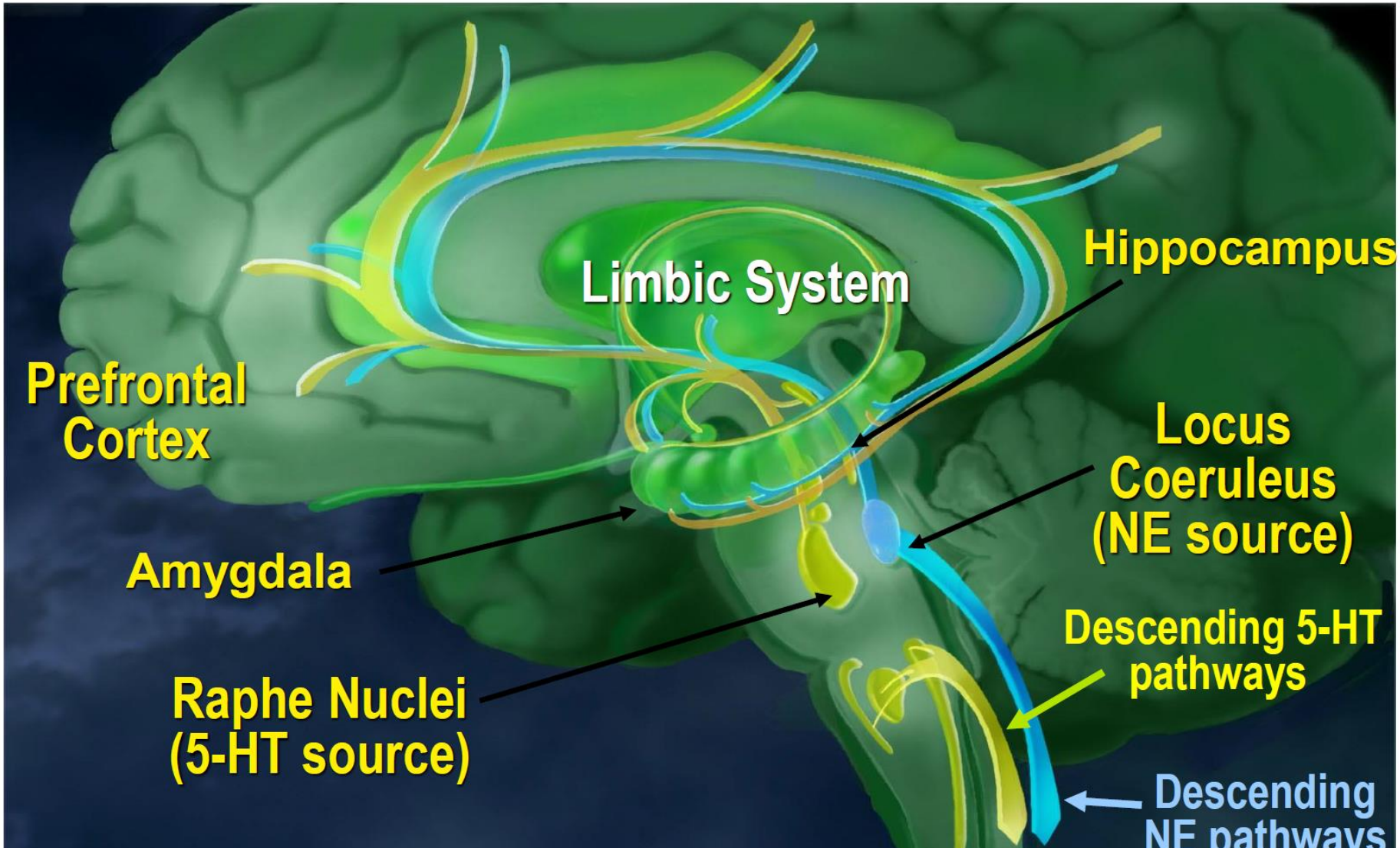
Evolution of antidepressant drugs



Monoamine hypothesis of depression

- Depletion of catecholamines results in induction of depression
- Inhibition of neurotransmitter reuptake or degration improves symptoms of depression
- Depression might be caused by a deficiency of monoaminergic neurotransmitters
  - serotonin
  - noradrenaline
  - dopamine

Serotonin (5-HT) and Norepinephrine (NE) Pathways in the Human Brain



Antidepressant Drugs

INIBITORI SELETTIVI DELLA RICAPTAZIONE DELLA SEROTONINA

- *Citalopram*
- *Escitalopram*
- *Fluoxetina*
- *Fluvoxamina*
- *Paroxetina*
- *Sertralina*

INIBITORI DELLA RICAPTAZIONE DI SEROTONINA/NORADRENALINA

- *Venlafaxina*
- *Duloxetina*

- Milnacipran

ANTIDEPRESSIVI ATIPICI

- *Bupropione* **(DAT)**
- *Mirtazapina* **(α_2, $5HT_{2A}$)**
- *Nefazodone* (reptake, 5HT1/2A)
- *Trazodone* **($5HT_1$)**

ANTIDEPRESSIVI TRICICLICI/POLICICLICI

- *Amitriptilina*
- *Amoxapina*
- *Clomipramina*
- *Desipramina*
- *Doxepina*
- *Imipramina*
- *Maprotilina*
- *Nortriptilina*
- *Protriptilina*
- *Trimipramina*

INIBITORI DELLA MONOAMINOSSIDASI

- *Fenelzina*
- *Tranilcipromina*, *Moclobemide*

FARMACI USATI NELLA MANIA

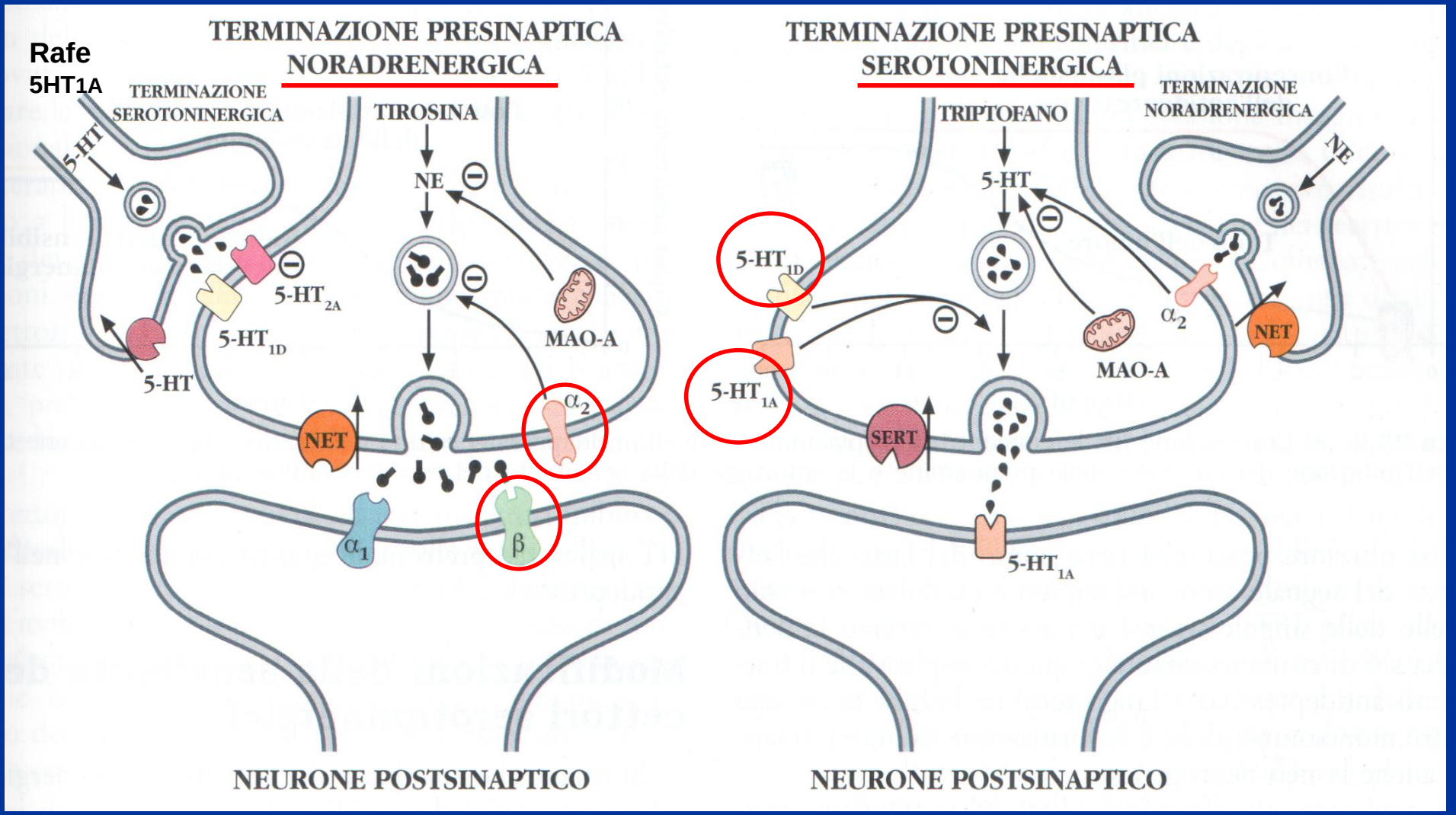
- *Carbamazepina*
- *Sali di litio*
- *Acido valproico*

Inibitori selettivi della ricaptazione della NA

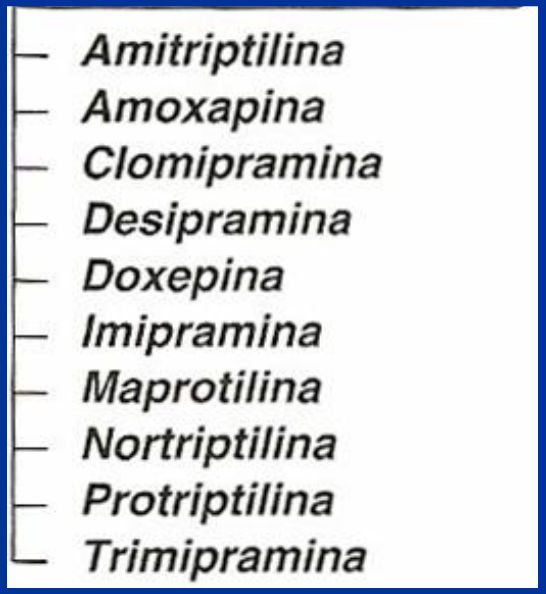
Atomoxetina
Levoprotalina
Lofepramina
Maprotilina
Nisoxetina
Oxaprotilina
Reboxetina
Viloxazina

* ECT

Mechanisms of action of antidepressants: NA and 5-HT



Tricyclic Antidepressants



Antidepressivo	Ki 5-HT uptake / Ki NA uptake
S-Citalopram	0,0001
R,S-Citalopram	0,0003
Sertralina	0,0007
Paroxetina	0,0031
Fluvoxamina	0,0017
Fluoxetina	0,0033
Clomipramina	0,0076
Venlafaxina	0,0086
Nor1-Citalopram	0,0095
Nor2-Citalopram	0,0160
Zimelidina	0,0167
Trazodone	0,0193
Imipramina	0,0381
Norfluoxetina	0,0609
Amitriptilina	0,1092
Milnacipran	0,1255
Duloxetina	0,1384
Bupropione	0,1730
Norsertralina	0,1809
Dotiepina	0,1831
Trimipramina	0,6250
Doxepina	2,2687
Nefazodone	3,3333
Amoxapina	3,6335
Nortriptilina	4,2528
Reboxetina	8,2353
Atomoxetina	12,1519
Lofepramina	13,4717
Protriptilina	14,0000
Norclomipramina	16,4000
Mirtazapina	21,0084
Desipramina	21,0840
Mianserina	56,0224
Nomifensina	64,1026
Viloxazina	108,9743
Maprotilina	531,5315
Oxaprotilina	800,0000

Antidepressivo	Ki 5-HT uptake / Ki DA uptake
R,S-Citalopram	0,00005
S-Citalopram	0,00011
Milnacipran	0,00013
Clomipramina	0,00013
Imipramina	0,00017
Fluoxetina	0,00023
Paroxetina	0,00025
Venlafaxina	0,0010
Amitriptilina	0,0013
Dotiepina	0,0016
Fluvoxamina	0,0017
Lofepramina	0,0038
Reboxetina	0,0051
Doxepina	0,0055
Desipramina	0,0055
Protriptilina	0,0092
Sertralina	0,0120
Zimelidina	0,0126
Amoxapina	0,0134
Nortriptilina	0,0162
Norfluoxetina	0,0227
Atomoxetina	0,0338
Trimipramina	0,1500
Viloxazina	0,1700
Norsertralina	0,1727
Trazodone	0,2240
Mianserina	0,4396
Nefazodone	0,5555
Oxaprotilina	0,9195
Mirtazapina	1,0000
Maprotilina	5,9000
Bupropione	17,3003
Nomifensina	17,9856

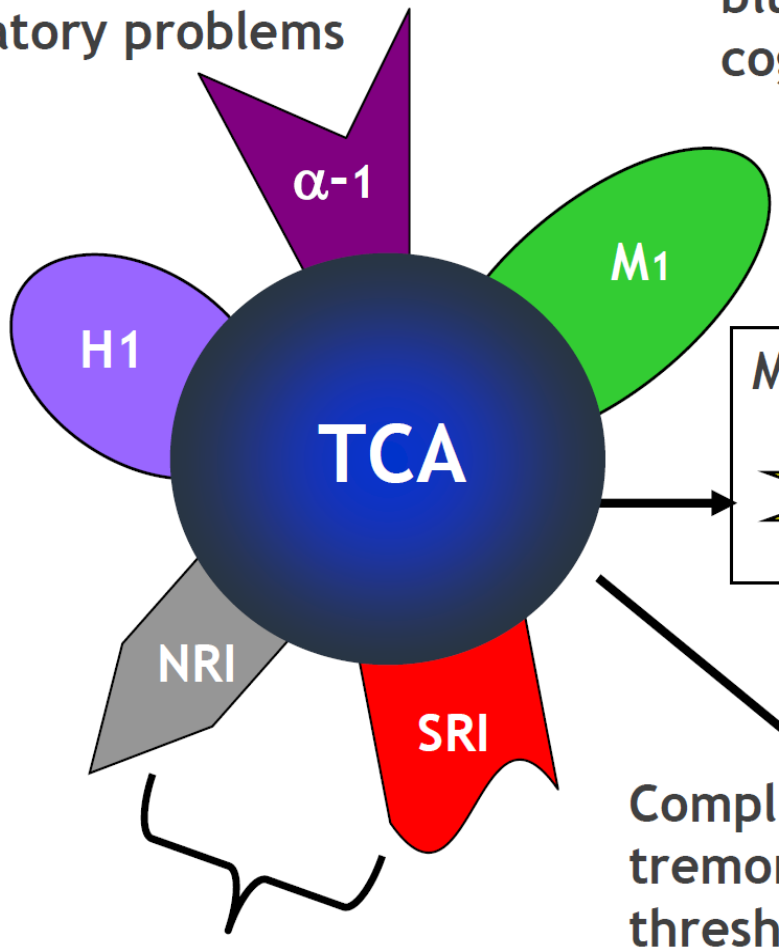
Tricyclic (TCA)
side effects

Tricyclic antidepressants

Dizziness
Orthostatic hypotension
Ejaculatory problems

Dry mouth, constipation
urinary retention
blurred vision, tachicardia,
cognitive disturbances

Weight gain
Drowsiness
Dizziness

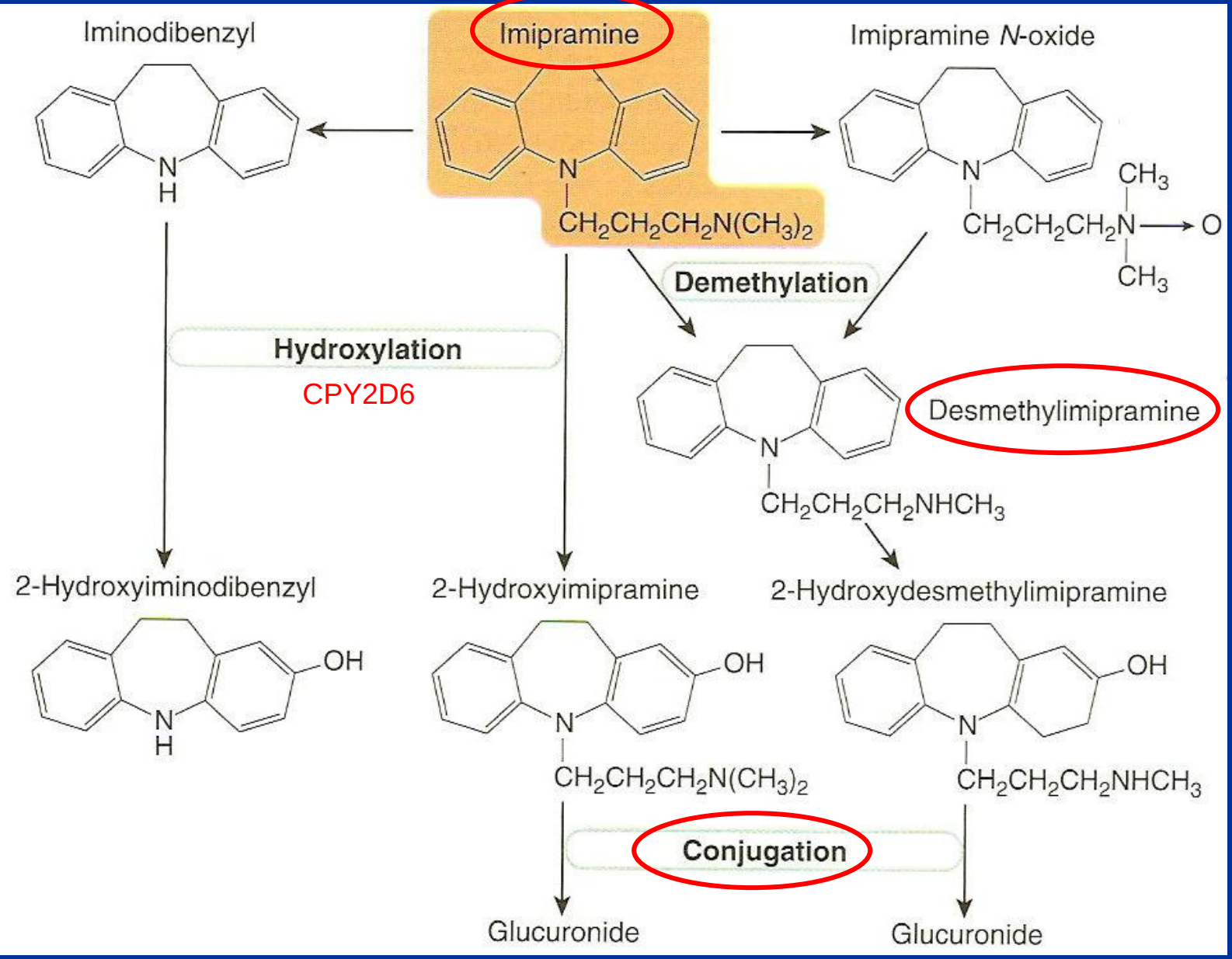


Membrane stabilization:
A-V conduction
ventricular arrhythmias

ANTIDEPRESSIVE EFFECT

Complex effects:
tremor, reduction seizure threshold, (mioclonus, epilepsy)
manic switch

Metabolism of imipramine



lipophilicity
SNC

LIver

Kidney

Drug interactions

Antidepressivo	Interazioni pericolose	Interazioni di modesta rilevanza
IMAO	amfetamine, TCA, atomoxetina, β_2-agonisti, brimonidina, bupropione, buspirone, carbamazepina, ciproeptadina, cocaina, destrometorfano, dopamina e dopaminomimetici, droperidolo, efedrina, entacapone, fenfluramina, iperico, levodopa, litio, mazindol, meperidina, metildopa, metilfenidato, morfina, nefazodone, nefopam, sibutramina, SSRI, tolcapone, tramadolo, triptani	antidiabetici, barbiturici
TCA	analgesici oppiacei,anestetici generali alogenati, antiaritmici di classe I e III, SSRI, antiipertensivi, antimicotici imidazolici, antipsicotici, antivirali, chinolonici, antibiotici macrolidici, cotrimossazolo, IMAO, linezolid, octreotide, primidone, rifampicina, simpaticomimetici, triptani, alcool	clonidina, alfametildopa, ansiolitici, ipnotici, β_2-agonisti, anticoagulanti orali, antiepilettici, antimuscarinici, primidone, β-bloccanti, calcio-antagonisti, cannabinoidi, carbamazepina, cimetidina, iperico, miorilassanti, nitroderivati
SSRI	analgesici oppiacei, desfenfluramina, destrometorfano, droperidolo, IMAO, iperico, sibutramina, tramadolo, trazodone, triptofano, triptani	alcool, anestetici, antiaritmici, anticoagulanti orali, antiepilettici, antipsicotici (escluso il droperidolo), anti-H2, barbiturici, β-bloccanti, bupropione, buspirone, cannabinoidi, ciproeptadina, clozapina, litio, teofillina, TCA

Hydroxylation Methylation

CYP 3A4, 2D6, 2C19

Inhibitors:

Itraconazolo
Eritromicina
Fluoxetina

Inductors:

Rifampicina
Fenitoina
Carbamazepina
Alcool

Inhibitors of the reuptake of 5HT/NA

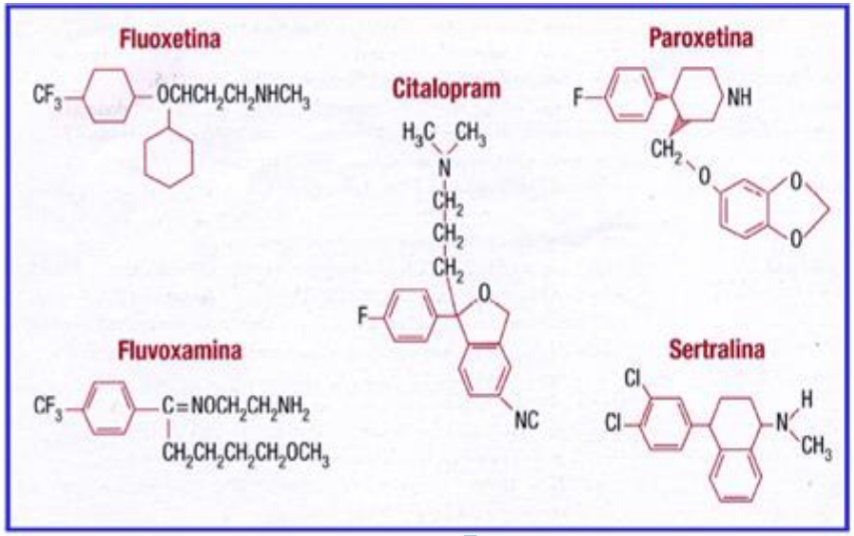
Evolution of antidepressant drugs

1950 1960 1970 1980 1990 2000 2010 2015 2019

MAO-I

TCA

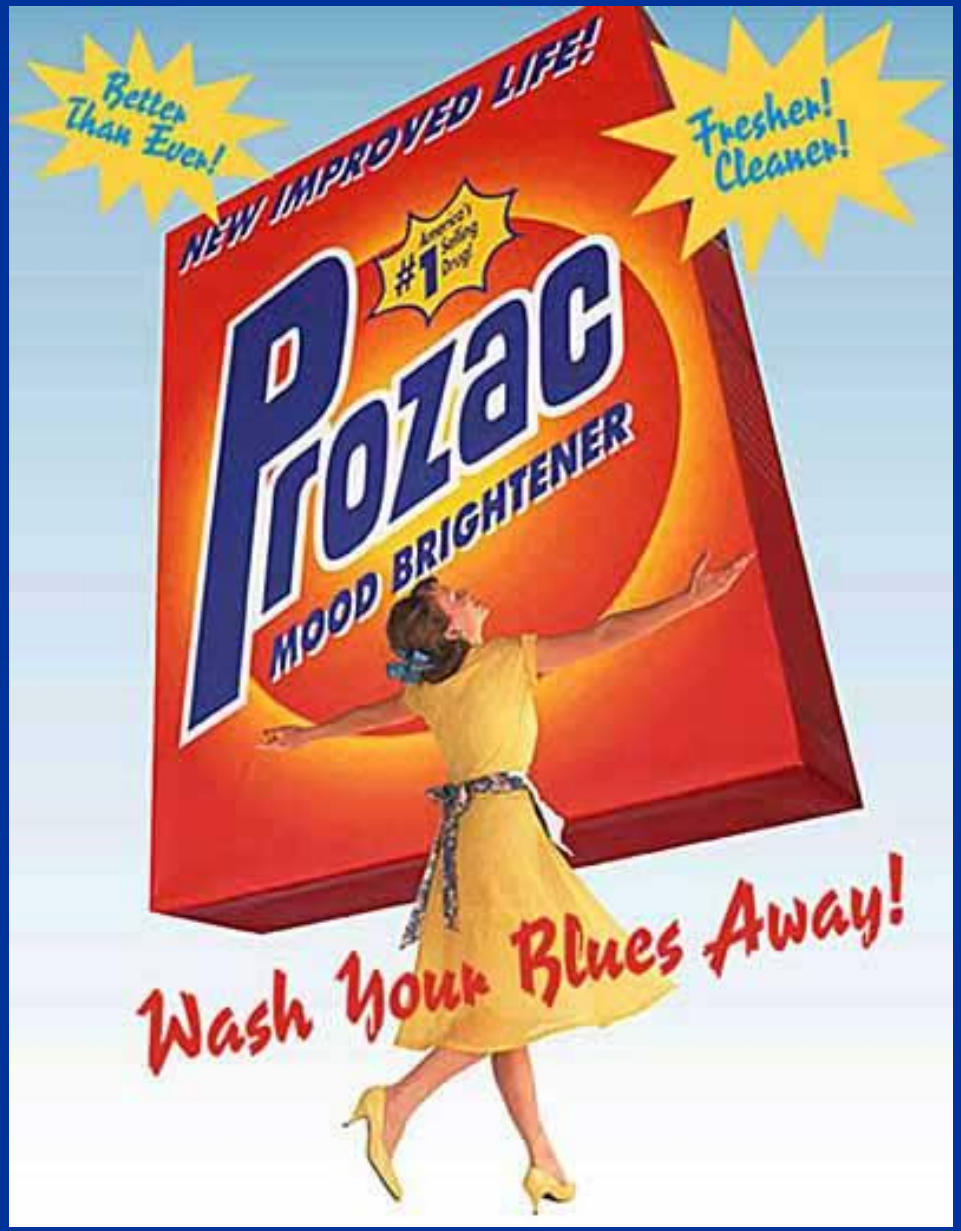
SSRI



Serendipity

Refinement

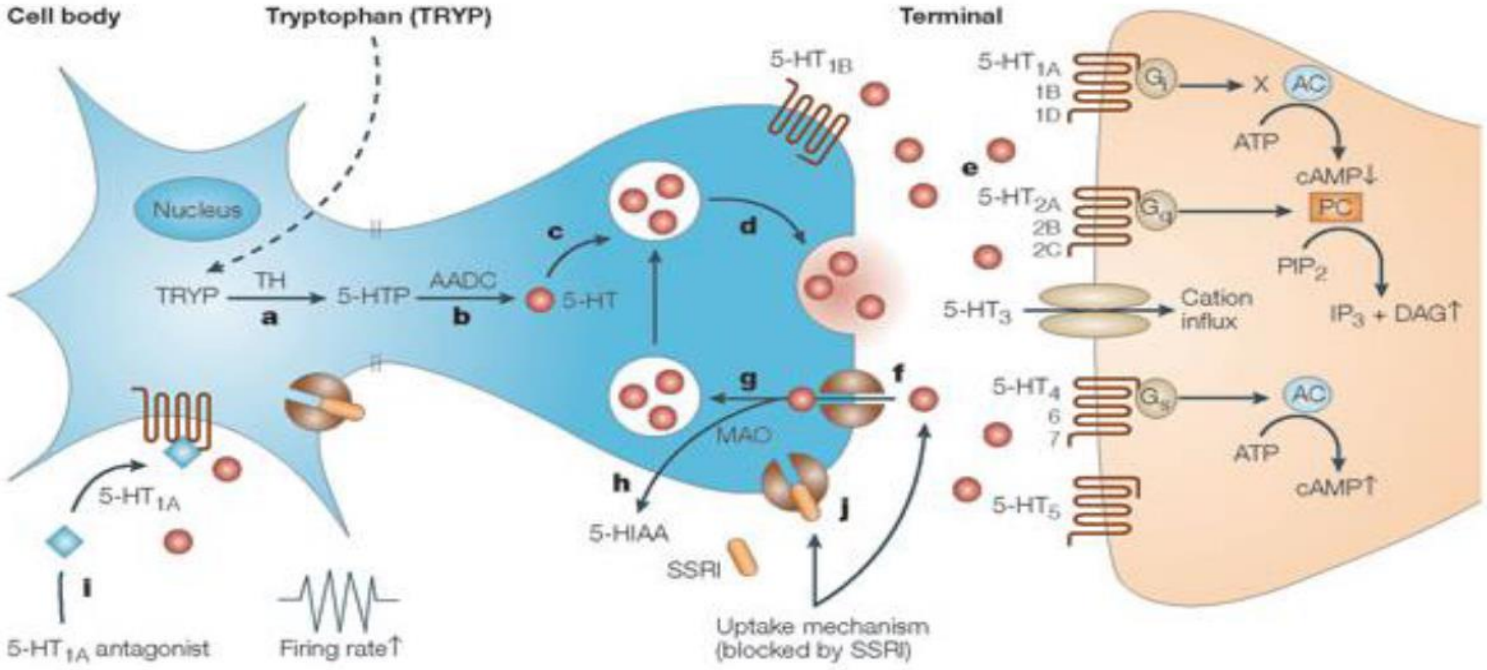
Selective inhibitors for the reuptake of serotonin (SSRI)


Better Than Ever!
NEW IMPROVED LIFE!
Fresher! Cleaner!
America's Selling Drug!
#1
Prozac
MOOD BRIGHTENER
Wash Your Blues Away!

Escitalopram

Antidepressivo	Ki 5-HT uptake / Ki NA uptake	Antidepressivo	Ki 5-HT uptake / Ki DA uptake
S-Citalopram	0,0001	R,S-Citalopram	0,00005
R,S-Citalopram	0,0003	S-Citalopram	0,00011
Sertralina	0,0007	Milnacipran	0,00013
Paroxetina	0,0031	Clomipramina	0,00013
Fluvoxamina	0,0017	Imipramina	0,00017
Fluoxetina	0,0033	Fluoxetina	0,00023
Clomipramina	0,0076	Paroxetina	0,00025
Venlafaxina	0,0086	Venlafaxina	0,0010
Nor1-Citalopram	0,0095	Amitriptilina	0,0013
Nor2-Citalopram	0,0160	Dotiepina	0,0016
Zimelidina	0,0167	Fluvoxamina	0,0017
Trazodone	0,0193	Lofepramina	0,0038
Imipramina	0,0381	Reboxetina	0,0051
Norfluoxetina	0,0609	Doxepina	0,0055
Amitriptilina	0,1092	Desipramina	0,0055
Milnacipran	0,1255	Protriptilina	0,0092
Duloxetina	0,1384	Sertralina	0,0120
Bupropione	0,1730	Zimelidina	0,0126
Norsertralina	0,1809	Amoxapina	0,0134
Dotiepina	0,1831	Nortriptilina	0,0162
Trimipramina	0,6250	Norfluoxetina	0,0227
Doxepina	2,2687	Atomoxetina	0,0338
Nefazodone	3,3333	Trimipramina	0,1500
Amoxapina	3,6335	Viloxazina	0,1700
Nortriptilina	4,2528	Norsertralina	0,1727
Reboxetina	8,2353	Trazodone	0,2240
Atomoxetina	12,1519	Mianserina	0,4396
Lofepramina	13,4717	Nefazodone	0,5555
Protriptilina	14,0000	Oxaprotilina	0,9195
Norclomipramina	16,4000	Mirtazapina	1,0000
Mirtazapina	21,0084	Maprotilina	5,9000
Desipramina	21,0840	Bupropione	17,3003
Mianserina	56,0224	Nomifensina	17,9856
Nomifensina	64,1026		
Viloxazina	108,9743		
Maprotilina	531,5315		
Oxaprotilina	800,0000		

Mechanism of action of SSRI



Advantages of SSRI

- low acute toxicity
- no reaction with diet component
- lack of collateral cardiovascular effect

Evolution of antidepressant drugs

1950 1960 1970 1980 1990 2000 2010 2015 2019

MAO-I

TCA

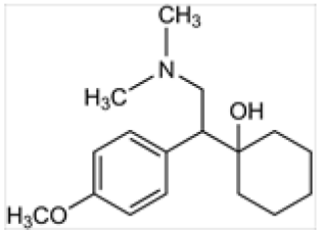
Serendipity

SSRI

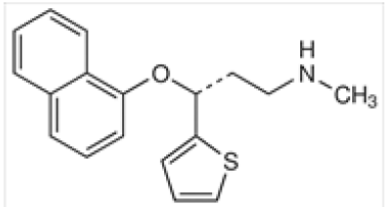
venlafaxine*
mirtazapine

escitalopram
duloxetine*

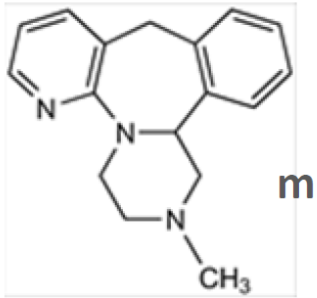
Refinement



venlafaxine



duloxetine



mirtazapine

Antidepressivo	Ki 5-HT uptake / Ki NA uptake
S-Citalopram	0,0001
R,S-Citalopram	0,0003
Sertralina	0,0007
Paroxetina	0,0031
Fluvoxamina	0,0017
Fluoxetina	0,0033
Clomipramina	0,0076
Venlafaxina	0,0086
Nor1-Citalopram	0,0095
Nor2-Citalopram	0,0160
Zimelidina	0,0167
Trazodone	0,0193
Imipramina	0,0381
Norfluoxetina	0,0609
Amitriptilina	0,1092
Milnacipran	0,1255
Duloxetina	0,1384
Bupropione	0,1730
Norsertralina	0,1809
Dotiepina	0,1831
Trimipramina	0,6250
Doxepina	2,2687
Nefazodone	3,3333
Amoxapina	3,6335
Nortriptilina	4,2528
Reboxetina	8,2353
Atomoxetina	12,1519
Lofepramina	13,4717
Protriptilina	14,0000
Norclomipramina	16,4000
Mirtazapina	21,0084
Desipramina	21,0840
Mianserina	56,0224
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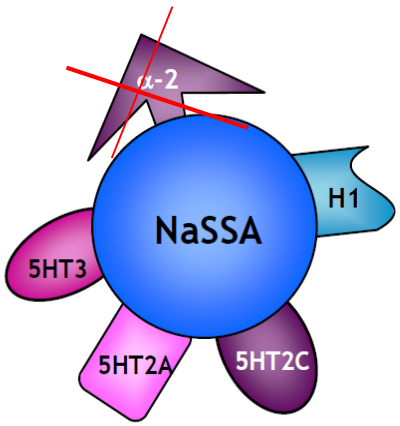
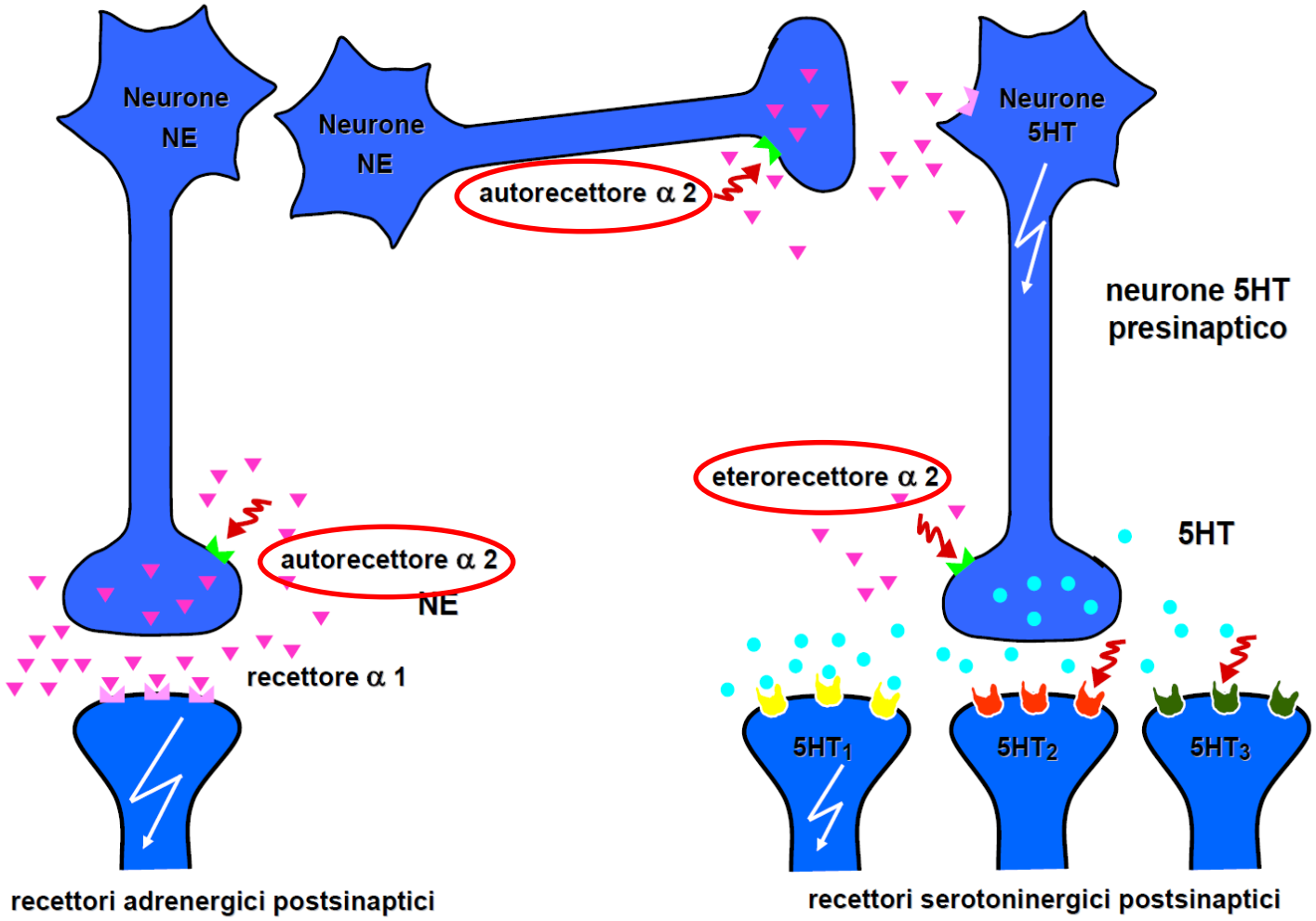
Viloxazina	108,9743
Maprotilina	531,5315
Oxaprotilina	800,0000

Antidepressivo	Ki 5-HT uptake / Ki DA uptake
R,S-Citalopram	0,00005
S-Citalopram	0,00011
Milnacipran	0,00013
Clomipramina	0,00013
Imipramina	0,00017
Fluoxetina	0,00023
Paroxetina	0,00025
Venlafaxina	0,0010
Amitriptilina	0,0013
Dotiepina	0,0016
Fluvoxamina	0,0017
Lofepramina	0,0038
Reboxetina	0,0051
Doxepina	0,0055
Desipramina	0,0055
Protriptilina	0,0092
Sertralina	0,0120
Zimelidina	0,0126
Amoxapina	0,0134
Nortriptilina	0,0162
Norfluoxetina	0,0227
Atomoxetina	0,0338
Trimipramina	0,1500
Viloxazina	0,1700
Norsertralina	0,1727
Trazodone	0,2240
Mianserina	0,4396
Nefazodone	0,5555
Oxaprotilina	0,9195
Mirtazapina	1,0000
Maprotilina	5,9000
Bupropione	17,3003
Nomifensina	17,9856

Noradrenergic and Specific Serotonergic Antidepressant



mirtazapine

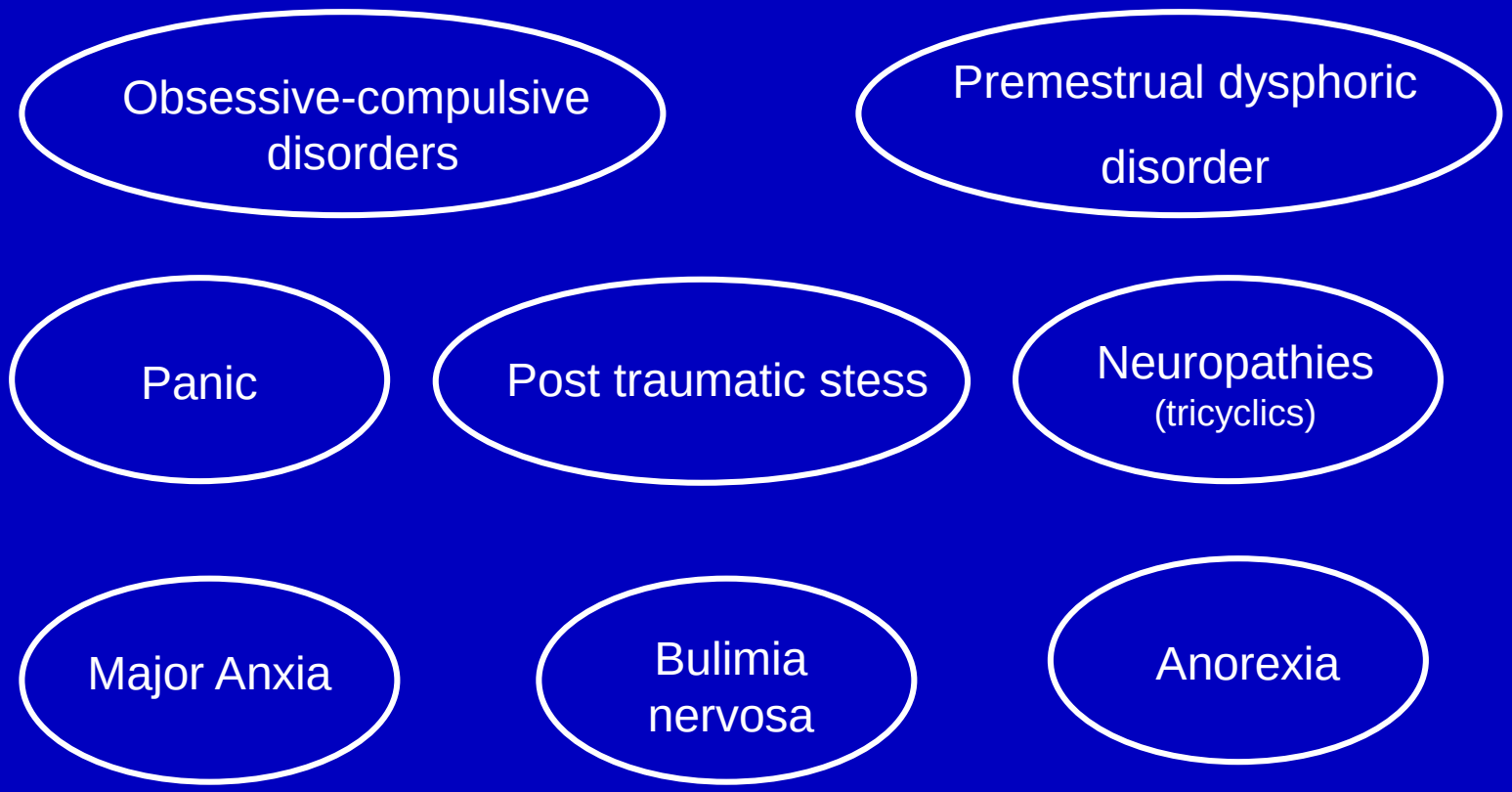


$5HT_{2A}$ antagonism = no sexual disturbances

$5HT_3$ antagonism = antiemetic effect

$5HT_{2C}$ + H1 antagonism = sedation and weight gain

Other therapeutic applications



Pharmacokinetic of antidepressants

Farmaco	Dose (mg/die)	Biodisponibilità	Tmax (min)	Emivita di eliminazione (ore)		Latenza della della risposta clinica (giorni)
				Farmaco	Metaboliti attivi	
Amineptina	100-200		60	0,8	2,5	Entro 7 gg
Amitriptilina	100-200	48%	240	15 (range 9-25)	16 (range 15-39) (Protriptilina)	20-30
Amoxapina	100-300	35% (range 18-54%)	60-120	8	4-6,5 (7-OH-amoxapina) 30 (8-OH-amoxapina)	Entro 14 gg (nell'80% dei casi)
Atomoxetina	40-80	EM: 63% PM: 94%	120 120	EM: 5.3 PM: 20		
Bupropione	200-300	80%	90	14-21	20-37	24
Citalopram	20-40	80-95%	120-240	33-37		14
Clomipramina	100-200	20-78%	280	32 (range 19-37)	69 69 (range 54-77) (Desmetilclomipramina)	14
Desipramina	100-200			17 (range 14-25)	22 (2-OH-desipramina)	21
Dibenzepina	240-280			4	4	7
Dotiepina	75-150	30%	120-240	14-45	19-33	7
Doxepina	100-200	30%	30-60	17 (range 8-25)	51 (range 33-80) (Desmetildoxepina)	14-21
Duloxetina	40-60	70%	360-600	11-16		21
Escitalopram	20-40	80%	180-360	22-32	59 (desmetilcitalopram)	7-14
Fenelzina	30-60		120-240	2-4		14
Fluoxetina	20-40	80-100%	360-480	24-96	168-380 (norfluoxetina)	7-14
Fluvoxamina	100-300	53%	300-360	16 (range 9-28)		4-7
Imipramina	100-200	42%	60	6-18	12-36 (desipramina)	7-21
Isocarbossazide	30-60			12		7-42
Lofepramina	140-210	7%	60	2	12-24 (desipramina)	7-21
Maprotilina	100-150	100%	720	43 (range 27-58)		3-7
Mianserina	30-90	20-30%	60-180	1,4 (fase iniz. rapida) 10-41 (fase tard. lenta)		1-14
Mirtazapina	15-45	50%	60-120	20-40	25 (demetilmirtazapina)	7
Moclobemide	150-300	55-95%	60-120	2		7-21

Farmaco	Dose (mg/die)	Biodisponibilità	Tmax (min)	Emivita di eliminazione (ore)		Latenza della della risposta clinica (giorni)
				Farmaco	Metaboliti attivi	
Nefazodone	200-400	20%	30-120	2-5	2,4 (OH-nefazodone) 18-33 (desetil-OH-n.) 4-9 (clorofenilpiperazina)	7
Nortriptilina	75-150	60% (55-80%)	60	15-39		14
Opipramolo	50-300			6-9		14
Paroxetina	20-40	65%	180-480	15-22		14
Protriptilina	15-40		480-720	54-198		7
Reboxetina	8-10	95%	120-240	12		
Sertralina	50-150	44-100%	360-480	24	62-104 (desmetilsertralina)	14
Tianeptina	25-37.5	99%	60	3	7-8 (MC 5)	7-14
Tranilcipromina	20-30		38-210	1,5-3,5		10
Trazodone	150-200	81%	30-120	7	(clorofenilpiperazina)	7
Trimipramina	75-200		120	23		
Venlafaxina	75-225	10-45%	120	5	10 (*O*-demetilvenlafaxina)	

Pharmacokinetic parameters

	FLUOXETINA	SERTRALINA*	PAROXETINA	FLUVOXAMINA	CITALOPRAM
Plasma half-lives	fluoxetina 6 gg norfluoxetina 19 gg	26 hours	21 hours	16 hours	33 hours
Washout periods	5 weeks	2 weeks	2 weeks	2 weeks	2 weeks

Peak concentration 5 hours.

* First-pass metabolism

Renal excretion (paroxetina and sertralina faeces)

SSRI: SIDE EFFECTS

Side effects	Fluvoxamine (%)	Fluoxetine (%)	Sertraline (%)	Paroxetine (%)	Citalopram (%)	Escitalopram (%)
Nausea	26	11	14.3	16.4	10	5
Dry mouth	4	3.5	7	6	8	1
Diarrhoea	4	5.3	8.4	4	4	3
Anejaculation	7	1.9	13.3	12.9	6	8
Drowsiness	14	5.9	7.5	14.3	9	1
Weight gain	< 1	7	5	25	< 5	< 1

Major interactions with other drugs

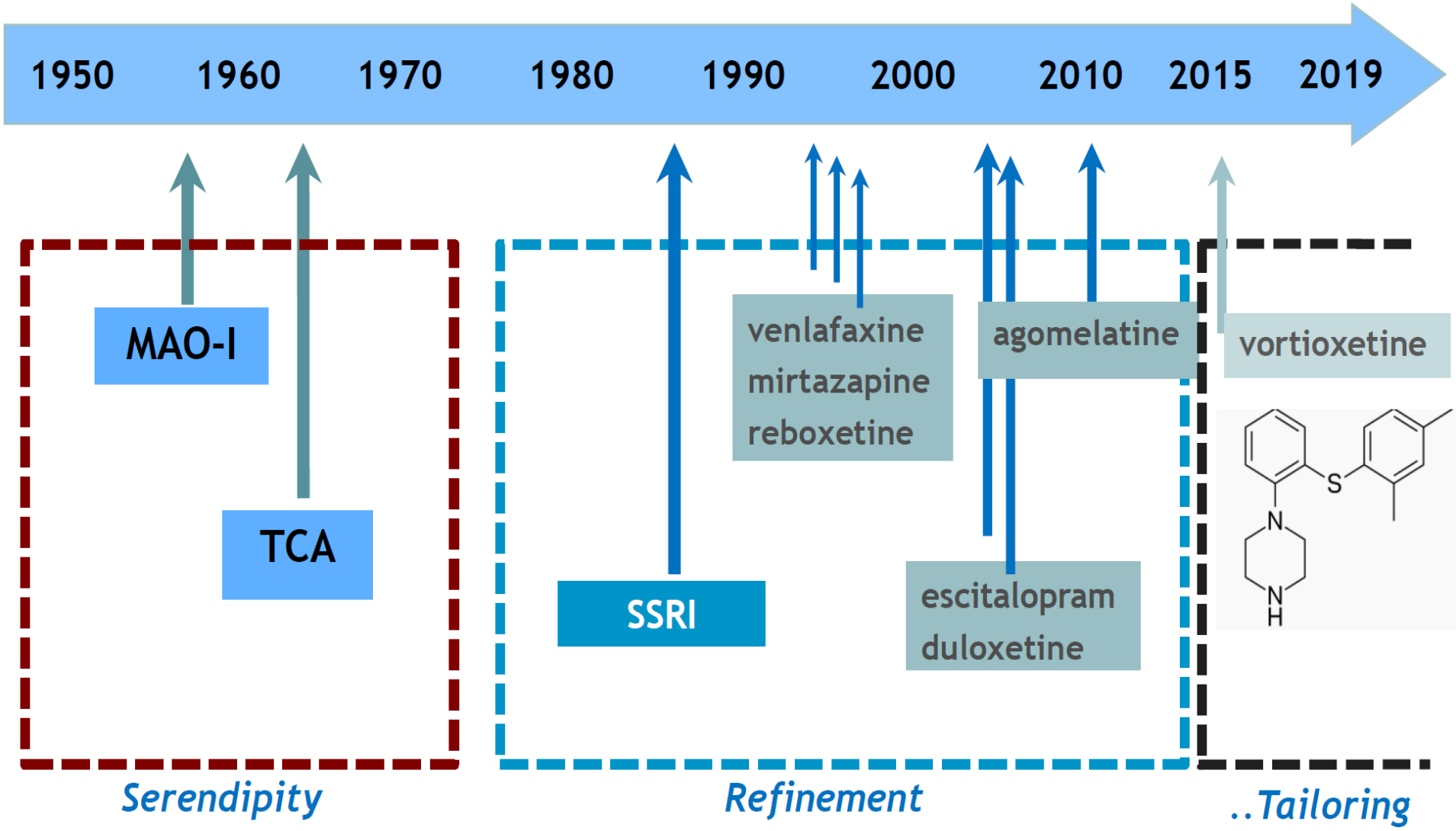
Antidepressivo	Interazioni pericolose	Interazioni di modesta rilevanza
IMAO	amfetamine, TCA, atomoxetina, β_2-agonisti, brimonidina, bupropione, buspirone, carbamazepina, ciproeptadina, cocaina, destrometorfano, dopamina e dopaminomimetici, droperidolo, efedrina, entacapone, fenfluramina, iperico, levodopa, litio, mazindol, meperidina, metildopa, metilfenidato, morfina, nefazodone, nefopam, sibutramina, SSRI, tolcapone, tramadolo, triptani	antidiabetici, barbiturici
TCA	analgesici oppiacei,anestetici generali alogenati, antiaritmici di classe I e III, SSRI, antiipertensivi, antimicotici imidazolici, antipsicotici, antivirali, chinolonici, antibiotici macrolidici, cotrimossazolo, IMAO, linezolid, octreotide, primidone, rifampicina, simpaticomimetici, triptani, alcool	clonidina, alfametildopa, ansiolitici, ipnotici, β_2-agonisti, anticoagulanti orali, antiepilettici, antimuscarinici, primidone, β-bloccanti, calcio-antagonisti, cannabinoidi, carbamazepina, cimetidina, iperico, miorilassanti, nitroderivati
SSRI	analgesici oppiacei, desfenfluramina, destrometorfano, droperidolo, IMAO, iperico, sibutramina, tramadolo, trazodone, triptofano, triptani	alcool, anestetici, antiaritmici, anticoagulanti orali, antiepilettici, antipsicotici (escluso il droperidolo), anti-H2, barbiturici, β-bloccanti, bupropione, buspirone, cannabinoidi, ciproeptadina, clozapina, litio, teofillina, TCA

Drug-drug interactions through CYP 450 inhibition

		Venlafaxine	Fluoxetine	Sertraline	Paroxetine	Citalopram	Escitalopram
CYP 1A2	Caffeina, teofillina, aminofillina, paracetamolo, fenacetina, clozapina, propranololo, R-warfarin, imipramina, triciclici	0	+	++	++	0	0
CYP 2C9	Ibuprofene, naprossene, fenitoina, S-warfarin, tolbutamide	0	++	++	++	0	0
CYP 2C19	S- mefenitoina, omeprazolo, propranololo, diazepam, citalopram, triciclici	0	++	++	++	0	0
CYP 2D6	Codeina, destrometorfano, triciclici, captopril, flecainide, encainide, tioridazina, perfenazina, clozapina, risperidone, aloperidolo, propranololo, timololo, metoprololo, paroxetina, fluoxetina	+/++	++++	++	++++	+	0/+
CYP 3A4	Cisapride, terfenadina, astemizolo, pimozide, loratadina, ciclosporina, triciclici, nefazodone, sertralina, zolpidem, corticosteroidi, eritromicina, carbamazepina, lidocaina, chinidina, triazolam, midazolam, alprazolam	+	+	+	++	0	0

0= absent += weak ++= mild +++= moderate ++++= high

Evolution of antidepressant drugs



Other antidepressants

CYP 3A4, 2D6

<u>Inibitori:</u>
Itraconazolo
Eritromicina
Fluoxetina

<u>Induttori:</u>
Rifampicina
Fenitoina
Carbamazepina
Alcol

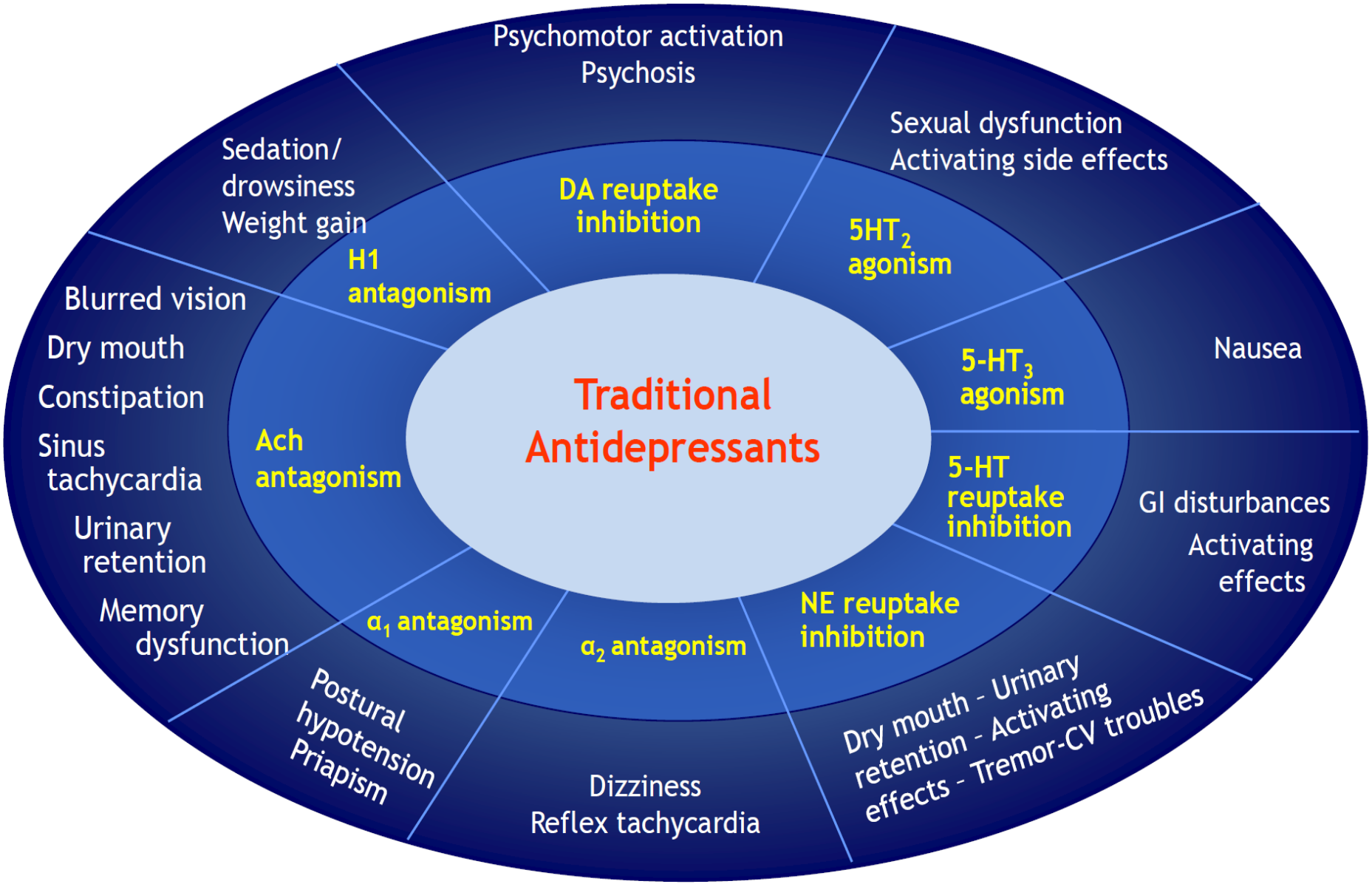
Antidepressivo	Ki 5-HT uptake / Ki NA uptake
S-Citalopram	0,0001
R,S-Citalopram	0,0003
Sertralina	0,0007
Paroxetina	0,0031
Fluvoxamina	0,0017
Fluoxetina	0,0033
Clomipramina	0,0076
Venlafaxina	0,0086
Nor1-Citalopram	0,0095
Nor2-Citalopram	0,0160
Zimelidina	0,0167
Trazodone	0,0193
Imipramina	0,0381
Norfluoxetina	0,0609
Amitriptilina	0,1092
Milnacipran	0,1255
Duloxetina	0,1384
Bupropione	0,1730
Norsertralina	0,1809
Dotiepina	0,1831
Trimipramina	0,6250
Doxepina	2,2687
Nefazodone	3,3333
Amoxapina	3,6335
Nortriptilina	4,2528
Reboxetina	8,2353
Atomoxetina	12,1519
Lofepramina	13,4717
Protriptilina	14,0000
Norclomipramina	16,4000
Mirtazapina	21,0084
Desipramina	21,0840
Mianserina	56,0224
Nomifensina	64,1026
Viloxazina	108,9743
Maprotilina	531,5315
Oxaprotilina	800,0000

Antidepressivo	Ki 5-HT uptake / Ki DA uptake
R,S-Citalopram	0,00005
S-Citalopram	0,00011
Milnacipran	0,00013
Clomipramina	0,00013
Imipramina	0,00017
Fluoxetina	0,00023
Paroxetina	0,00025
Venlafaxina	0,0010
Amitriptilina	0,0013
Dotiepina	0,0016
Fluvoxamina	0,0017
Lofepramina	0,0038
Reboxetina	0,0051
Doxepina	0,0055
Desipramina	0,0055
Protriptilina	0,0092
Sertralina	0,0120
Zimelidina	0,0126
Amoxapina	0,0134
Nortriptilina	0,0162
Norfluoxetina	0,0227
Atomoxetina	0,0338
Trimipramina	0,1500
Viloxazina	0,1700
Norsertralina	0,1727
Trazodone	0,2240
Mianserina	0,4396
Nefazodone	0,5555
Oxaprotilina	0,9195
Mirtazapina	1,0000
Maprotilina	5,9000
Bupropione	17,3003
Nomifensina	17,9856

Major interactions with other drugs

Antidepressivo	Interazioni pericolose	Interazioni di modesta rilevanza
IMAO	amfetamine, TCA, atomoxetina, β_2-agonisti, brimonidina, bupropione, buspirone, carbamazepina, ciproeptadina, cocaina, destrometorfano, dopamina e dopaminomimetici, droperidolo, efedrina, entacapone, fenfluramina, iperico, levodopa, litio, mazindol, meperidina, metildopa, metilfenidato, morfina, nefazodone, nefopam, sibutramina, SSRI, tolcapone, tramadolo, triptani	antidiabetici, barbiturici
TCA	analgesici oppiacei,anestetici generali alogenati, antiaritmici di classe I e III, SSRI, antiipertensivi, antimicotici imidazolici, antipsicotici, antivirali, chinolonici, antibiotici macrolidici, cotrimossazolo, IMAO, linezolid, octreotide, primidone, rifampicina, simpaticomimetici, triptani, alcool	clonidina, alfametildopa, ansiolitici, ipnotici, β_2-agonisti, anticoagulanti orali, antiepilettici, antimuscarinici, primidone, β-bloccanti, calcio-antagonisti, cannabinoidi, carbamazepina, cimetidina, iperico, miorilassanti, nitroderivati
SSRI	analgesici oppiacei, desfenfluramina, destrometorfano, droperidolo, IMAO, iperico, sibutramina, tramadolo, trazodone, triptofano, triptani	alcool, anestetici, antiaritmici, anticoagulanti orali, antiepilettici, antipsicotici (escluso il droperidolo), anti-H2, barbiturici, β-bloccanti, bupropione, buspirone, cannabinoidi, ciproeptadina, clozapina, litio, teofillina, TCA
SNaRI	antiaritmici di classe I e III, antibiotici macrolidici, antipsicotici, astemizolo, bepredil, chinolonici, cisapride, cotrimossazolo, droperidolo e aloperidolo, enflurano, fenfluramina, fluconazolo, foscarnet, IMAO, mesoridazina, pimozide, probucolo, sibutramina, terfenadina, tramadolo	cannabinoidi, cimetidina, metoclopramide, zolpidem
NaRI	IMAO, TCA, antimicotici azolici, antipsicotici, ciclosporina, ergotamina, macrolidi, sibutramina	
Bupropione	antipsicotici, corticosteroidi, teofillina, tramadolo, meperidina	antiepilettici, antivirali, dopaminergici, alcool
Nefazodone-trazodone	antiipertensivi, droperidolo, terfenadina	alcool, antimicotici imidazolici, carbamazepina, digitalici, fenitoina, benzodiazepine

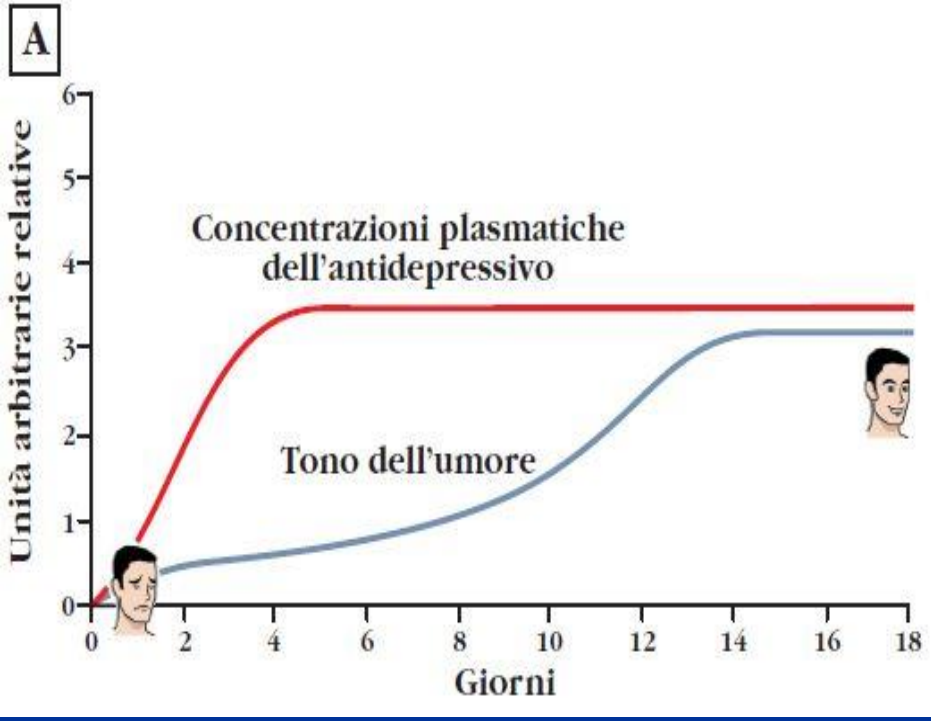
ADVERSE EFFECTS LINKED WITH PHARMACOLOGICAL PROFILE

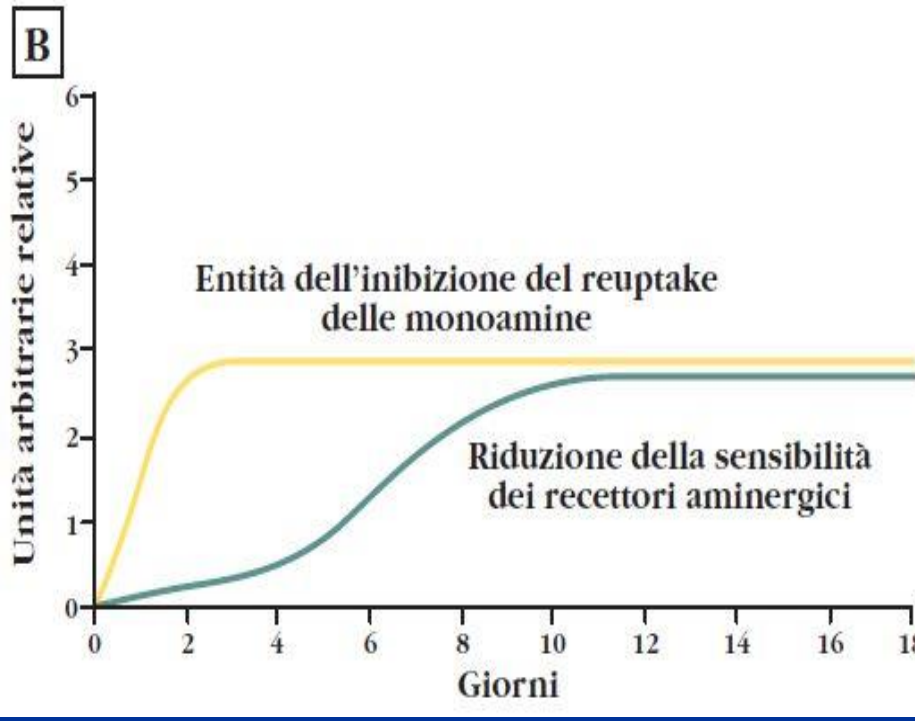


Delayed therapeutic Effects

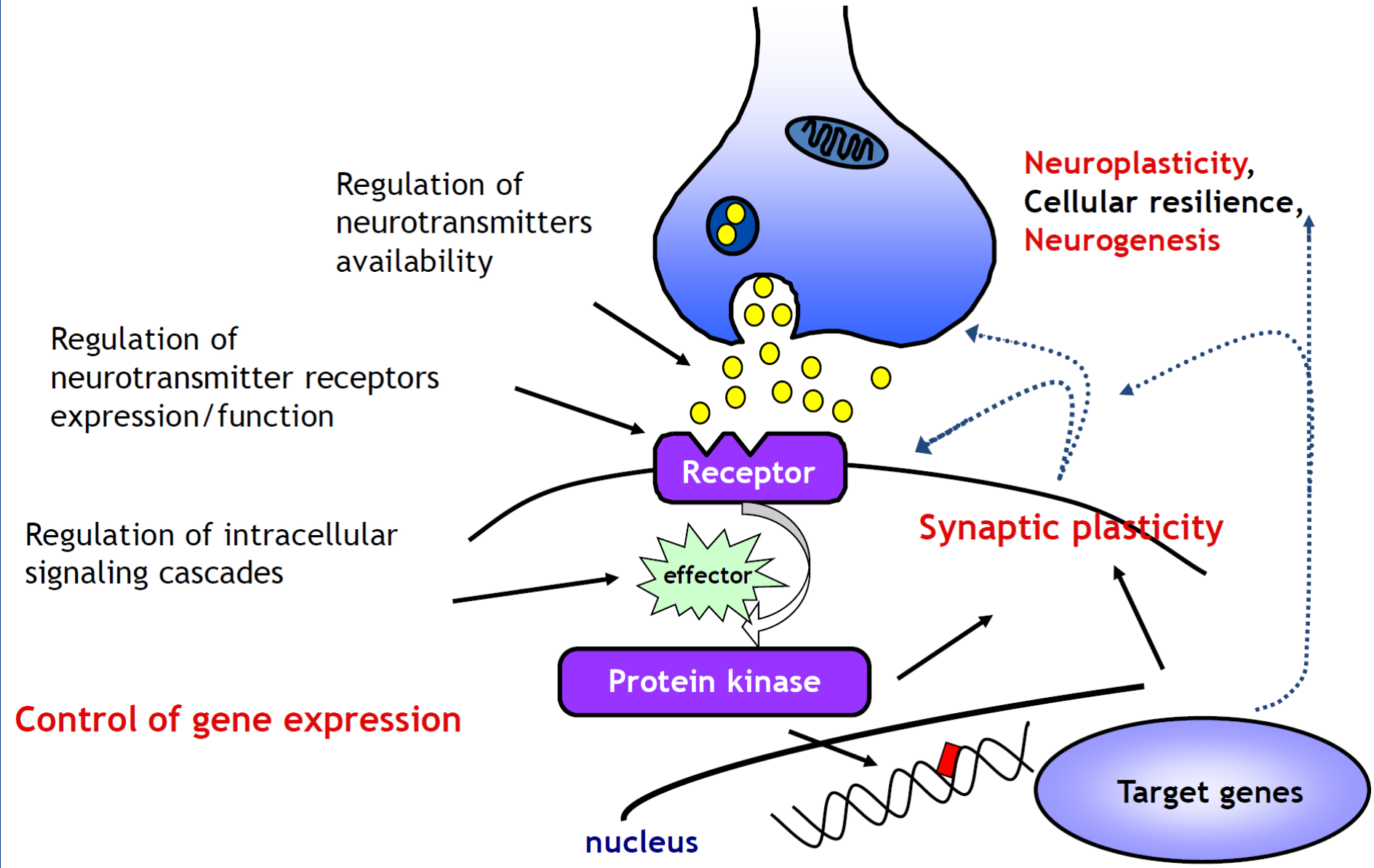
(Mechanism of action)

Therapeutic effects

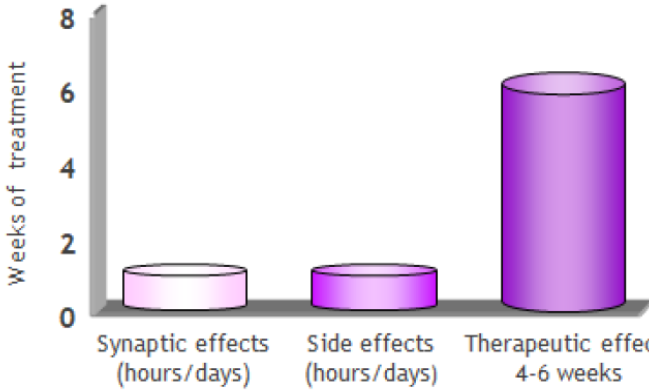




Antidepressant mechanism
A cascade of neuroplasticity events



Evolution of hypotheses on pathophysiology/ pharmacotherapy of mood disorders



- ***Monoaminergic hypothesis (1960-70s)***

  Depression is caused by a decreased availability of monoaminergic neurotransmitters. Antidepressants boost monoamine levels.

- ***Monoaminergic receptor hypothesis (1980s)***

  Depression is caused by abnormalities in monoamines receptors. Chronic antidepressants alter sensitization state of receptors.

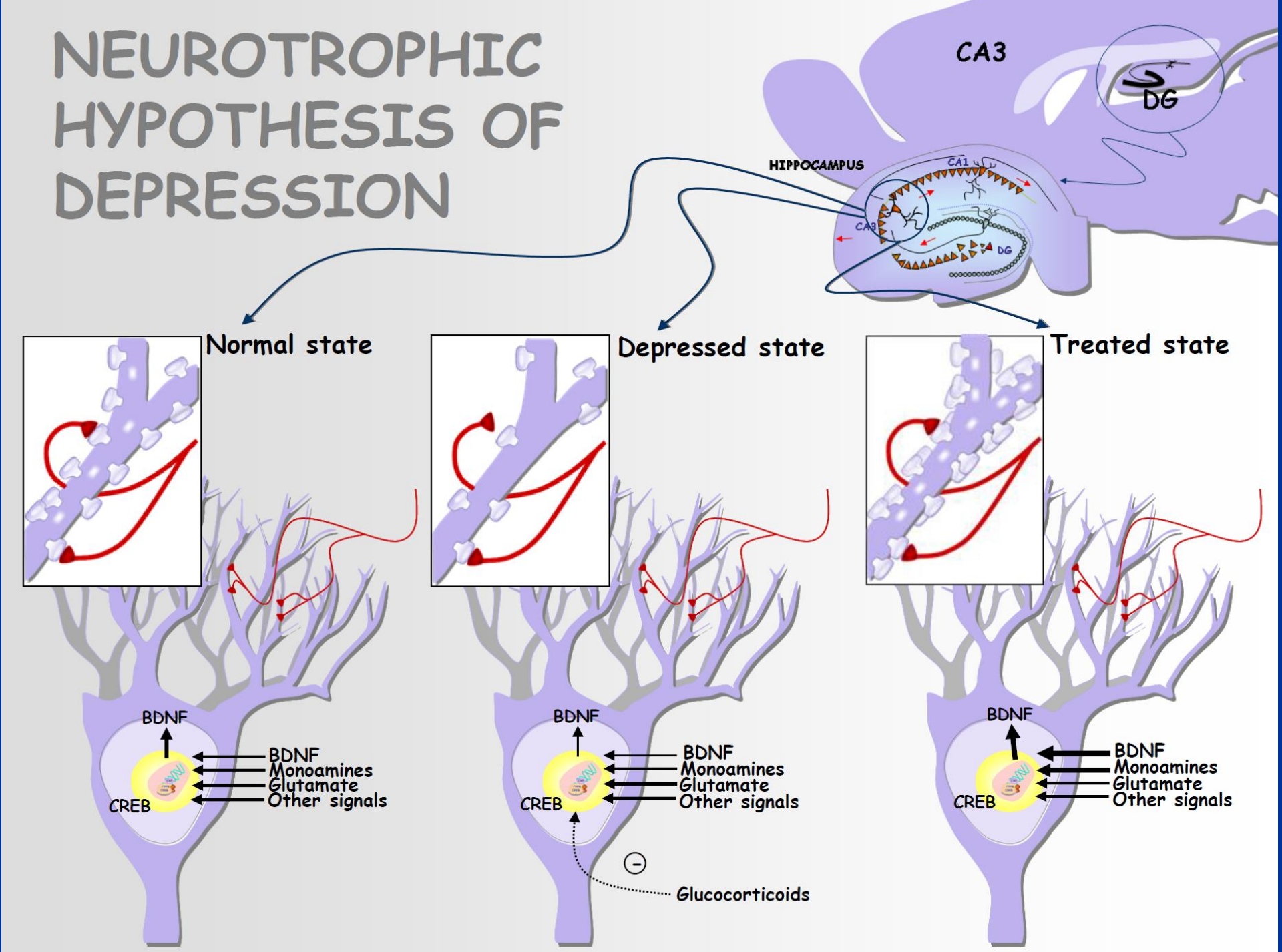
- ***Hypothesis of signaling adaptation (1990s)***

  Chronic antidepressants induce adaptive changes in post-receptor signaling cascades, and in gene expression.

- ***Hypothesis of neuroplasticity (2000s)***

  Chronic antidepressants change neuroplasticity, cellular resilience and synaptic plasticity.

NEUROTROPHIC HYPOTHESIS OF DEPRESSION



Neurotrophic hypothesis of depression

- Atrophy of selected brain structures can be associated with depression.
- These changes may represent the consequence of genetic dysfunction and/or the result of adverse life experiences (stress).
- Structural and functional impairment is the consequence of altered expression and function of proteins involved in synaptic plasticity and cellular resiliency.
- Chronic administration of antidepressants induces ↑ BDNF in hippocampus.
- Time course of response for antidepressants corresponds to delay of trophic factor synthesis (much more than to receptor modifications).
- The neurotrophin BDNF appears to be a key element in this context and a potential target for long-term pharmacological intervention.

Evolution of antidepressant drugs