Pharmacology of CNS
Antidepressants and antimanics

Depression – emotion, symptom, syndrome

- **depression**

  - a persistent of low mood and aversion to activity that can affect a person's thoughts, behaviour, feelings and physical well-being

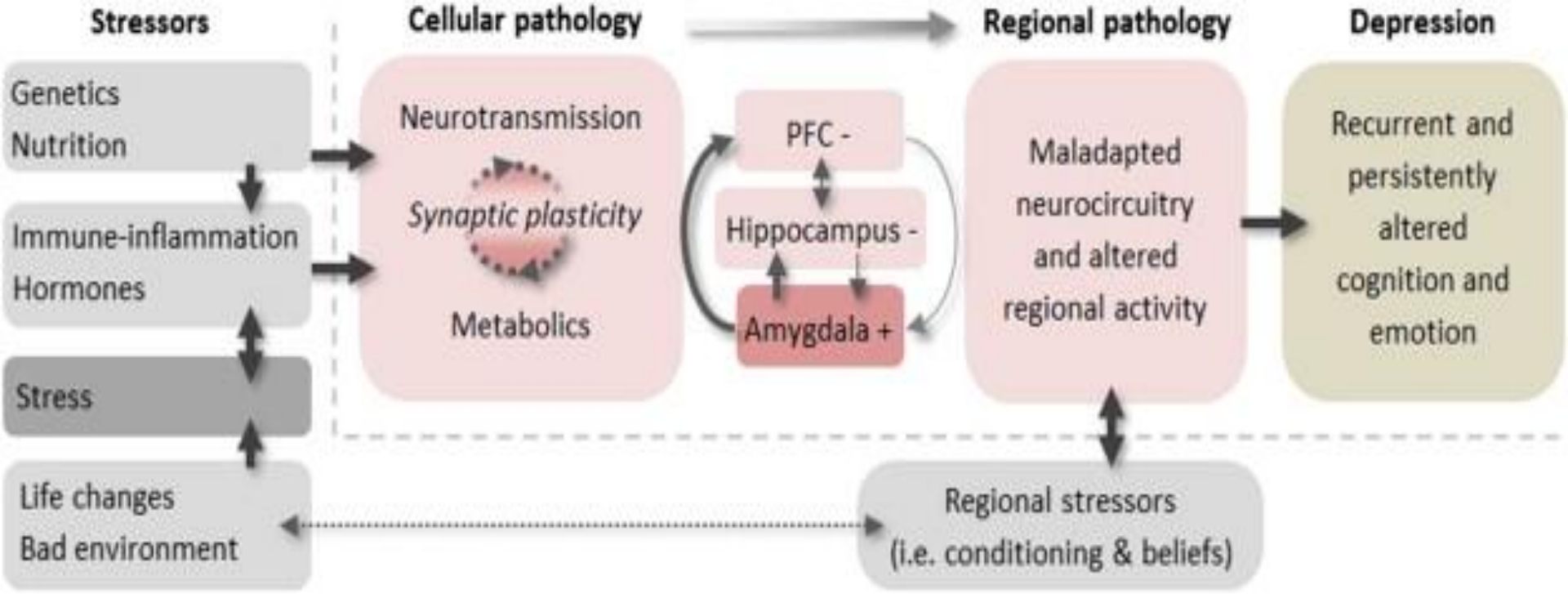
- **manifestations**

  - moodiness, anger or irritability; anhedonia; sadness; guilt feelings; low self confidence; social isolation; changes in sleep and appetite; somatic complaints

- **„ I have no friends."**
- **„ Life is boring."**
- **„ There is nothing I can**
- **do to make things better"**
- **„ I wish I were dead"**

Depression – theories, hypothesis

- **Monoamines NA, 5-HT, (DA)**
- Corticoids
- Cytokines, macrophages
- **Neurotrophic, neuroplastic**
- Cholinergic
- Vascular
- Homocysteinic....



A basic hierarchical scheme for the pathogenesis of depression. A variety of physical and psychological stressors associate with neuropsychiatric disorders. These stressors differentially affect the state and function of neurons and neuron...(PFC - Prefrontal cortex)

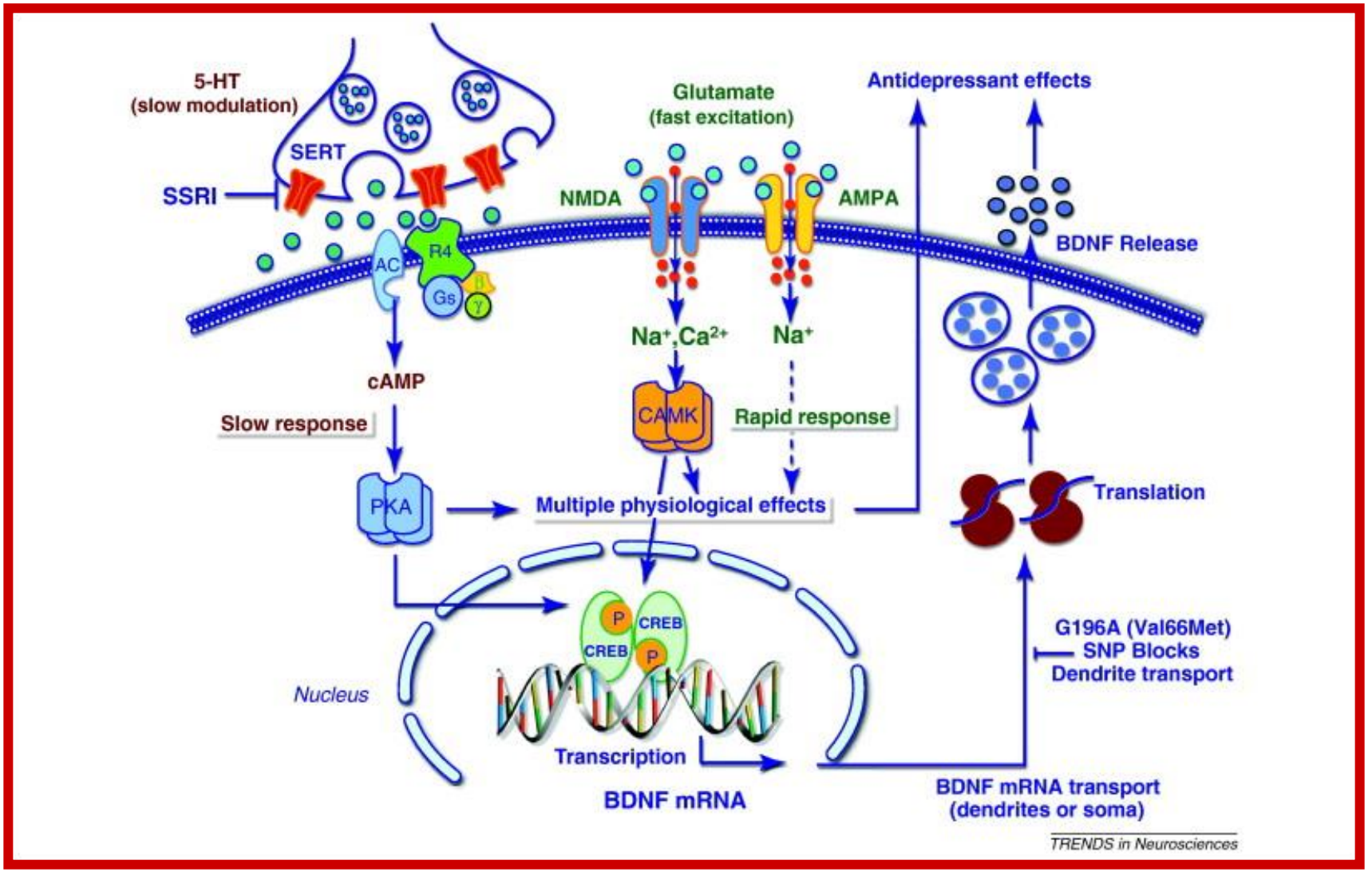
W.N. Marsden

Synaptic plasticity in depression: Molecular, cellular and functional correlates

Progress in Neuro-Psychopharmacology and Biological Psychiatry Volume 43 **2013** 168 - 184

http://dx.doi.org/10.1016/j.pnpbp.2012.12.012

Signaling pathways of depression



Duman RS, Voleti B. Trends Neurosci, 2012, 35: 47–56

Monoamine theory of depression

Serotonin (5-HT)

Norepinephrine (NE,NA)

Dopamine (DA)

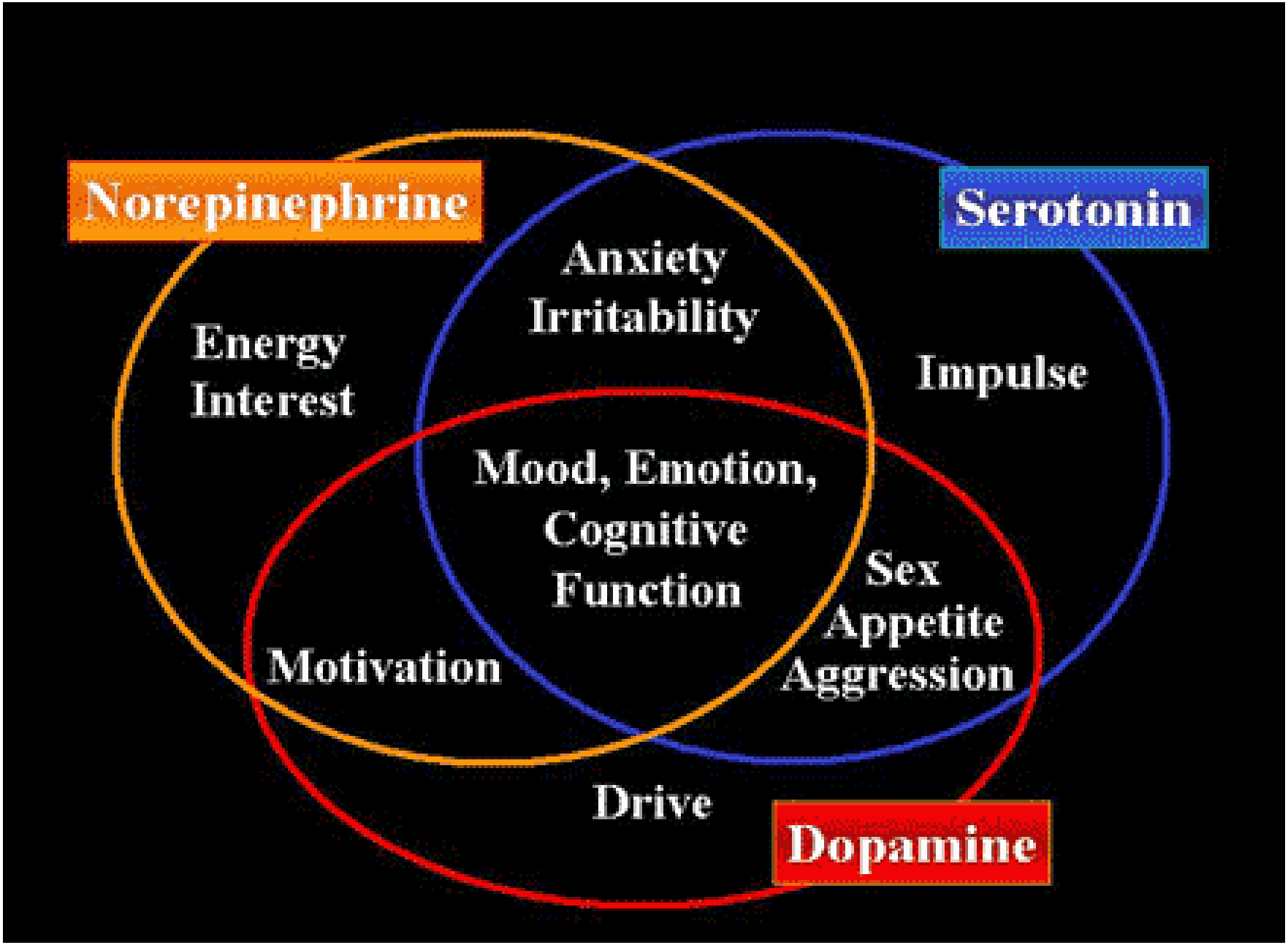
↓ level of 5-HT

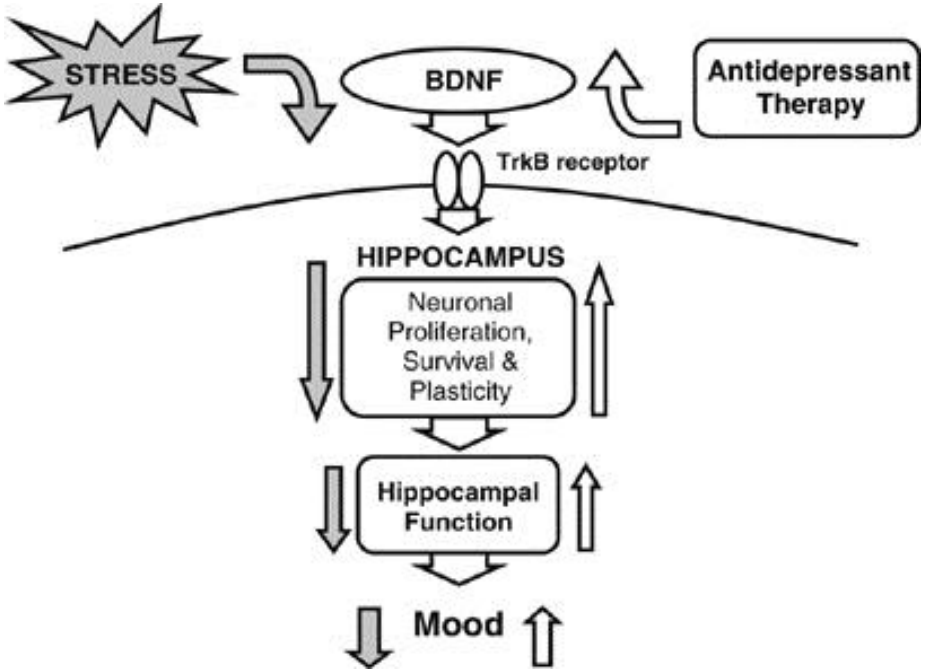
↓ level of NA

DA - level

↑ > mania

↓ > depression

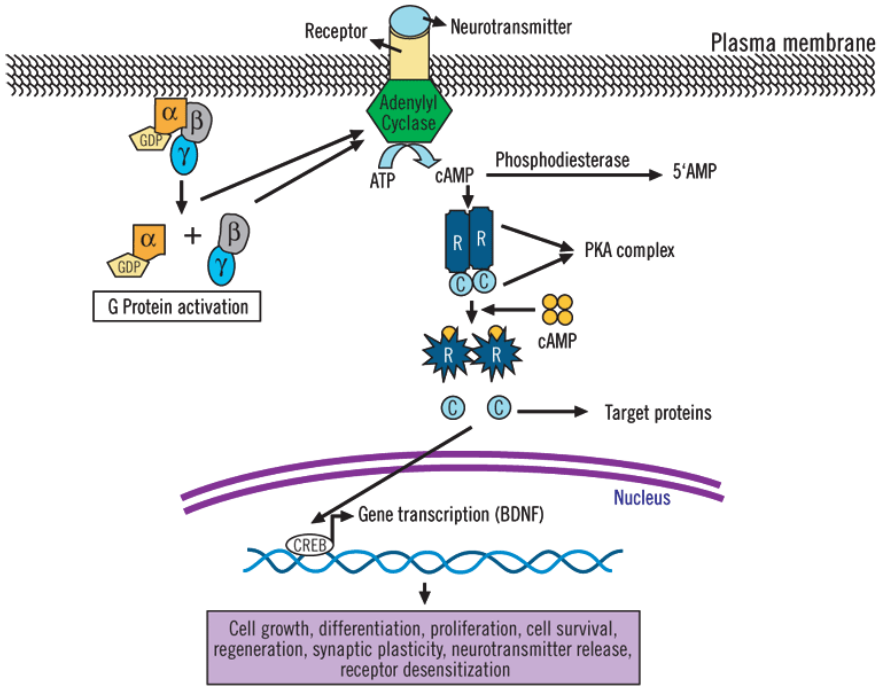

Norepinephrine
Serotonin
Anxiety
Irritability
Energy
Interest
Impulse
Mood, Emotion,
Cognitive
Function
Sex
Appetite
Aggression
Motivation
Drive
Dopamine



Simplified model outlining the opposing roles of stress and antidepressant therapy on hippocampal BDNF expression, hippocampal function, and mood. Abbreviations: BDNF, brain-derived neurotrophic factor; TrkB, tyrosine kinase receptor B.

Groves JO, *Molecular Psychiatry* (2007) **12,** 1079–1088

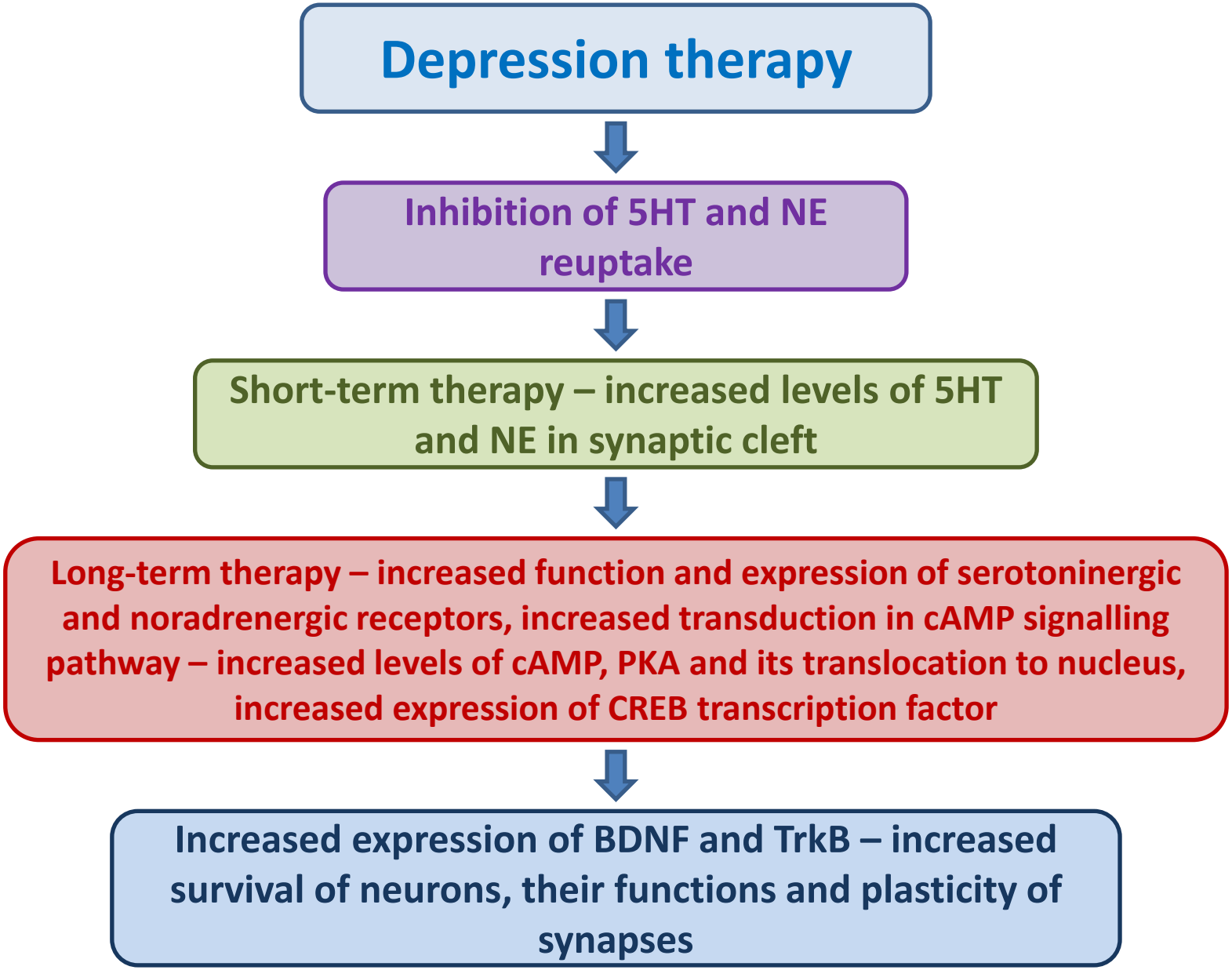
ADENYLYL CYCLASE–CYCLIC ADENOSINE MONOPHOSPHATE SIGNALING PATHWAY



Binding of a neurotransmitter to its specific receptors leads to activation of heterotrimeric guanosine nucleotide-binding protein (G proteins; α, β, and γ subunits), which in turn causes dissociation of the α subunit from the β, γ complex. This results in activation of the enzyme adenylyl cyclase. Adenylyl cyclase then converts ATP to cAMP. cAMP binds to regulatory subunits of tetrameric PKA holoenzymes. This releases free catalytic subunits, which phosphorylate cytoplasmic, as well as nuclear, substrates (eg, CREB). One of the genes whose transcription is regulated by PKA/CREB is BDNF. cAMP is degraded by cAMP-specific phosphodiesterases.

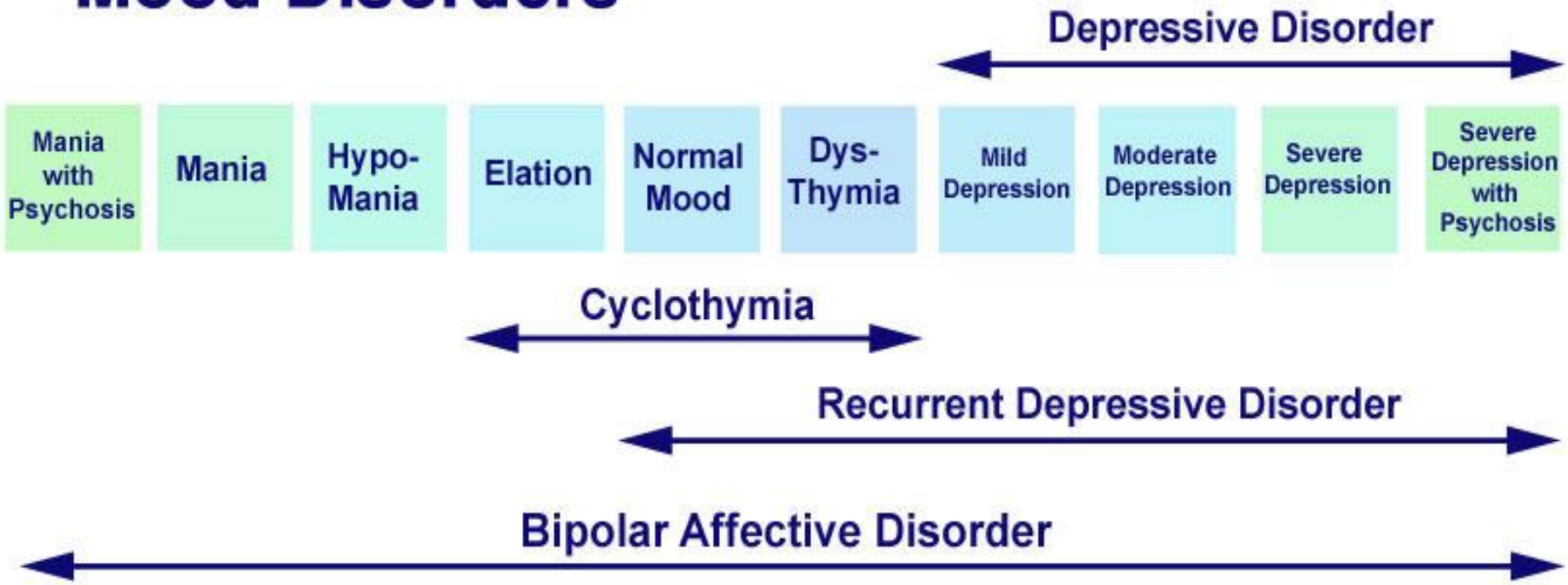
GDP=guanine nucleotide diphosphate; ATP=adenosine triphosphate; R=regulatory subunits; PKA=protein kinase A; C=catalytic subunits; cAMP=cyclic adenosine monophosphate; BDNF=brain-derived neurotrophic factor; CREB=cAMP response element binding protein.

Dwiwedi Y, Pandey GN. *Primary Psychiatry.* Vol 14, No 11. 2007.



Hrubý and Nosáľová, 2011

Mood Disorders



Therapeutic use of antidepressants

- **depression**
- panic, generalized anxiety, social phobia
- obsessive-compulsive disorders
- enuresis
- bulimia nervosa, anorexia nervosa, gambling
- chronic algic syndromes – neuropatic,

  myofascial pain (TCA, SSRI, SNRI)

History of antidepressants

2000s
Generics and new prescriptions

Patents run out, and FDA approves older drugs for new uses in treating depression.

2002 to 2007

Augmenting treatment

Many older drugs are re-approved for new uses in treating depression. These drugs are used to augment existing pharmacological treatments.

2002 – Mertazapine (Remeron)
2006 – Bupropion (Wellbutrin XL)
2007 – Aripiprazole (Abilify)

2006 to 2010

Drug patents expire

During this period, 9 of the 10 patented antidepressants face a patent loss, which represents a large financial hit to the pharmaceutical companies.

Antidepressants: mechanisms of action

- ↓ biodegradation of neurotransmitters
  - thymoeretics

- ↓ transport of neurotransmitters
  - thymoleptics

- ↓ density of receptors - both groups

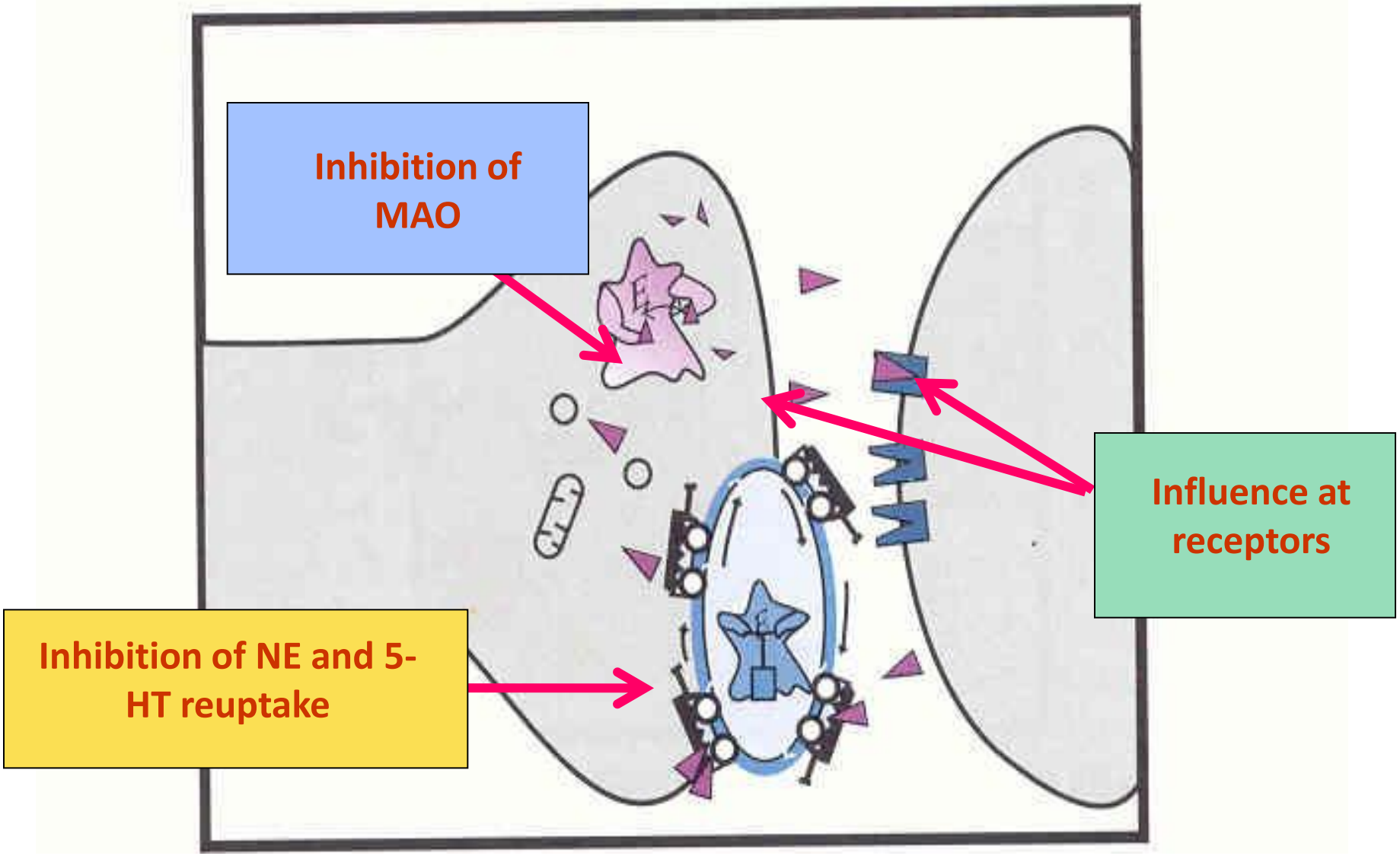
Antidepressants: mechanisms of action

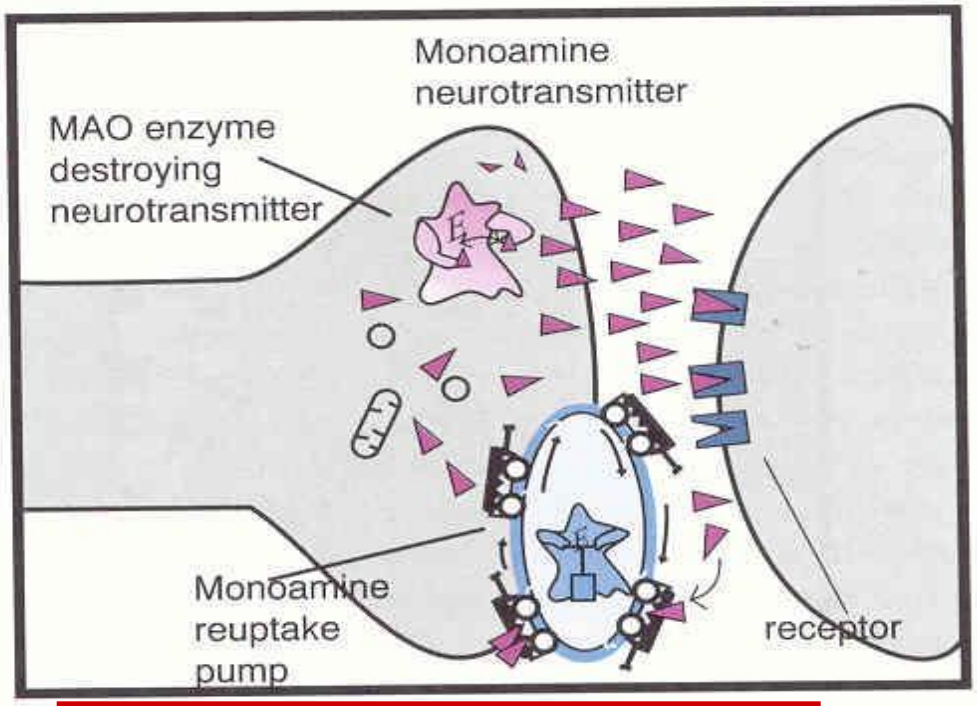
Inhibition of MAO enzymes

Inhibition of NE, 5-HT reuptake by inhibition of transporters

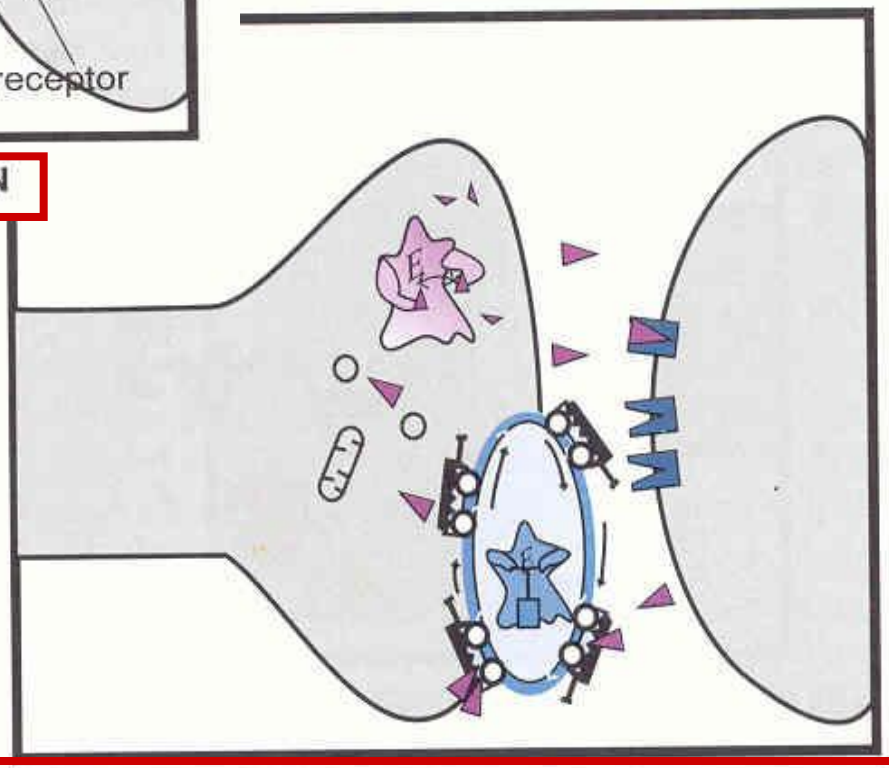
- **serotonin transporter – SERT**
- **norepinephrine transporter – NET**
- **(dopamine transporter – DAT)**

Influence at 5-HT_{1A},5-HT_{2C} , α_2 receptors


Inhibition of MAO
Influence at receptors
Inhibition of NE and 5-HT reuptake



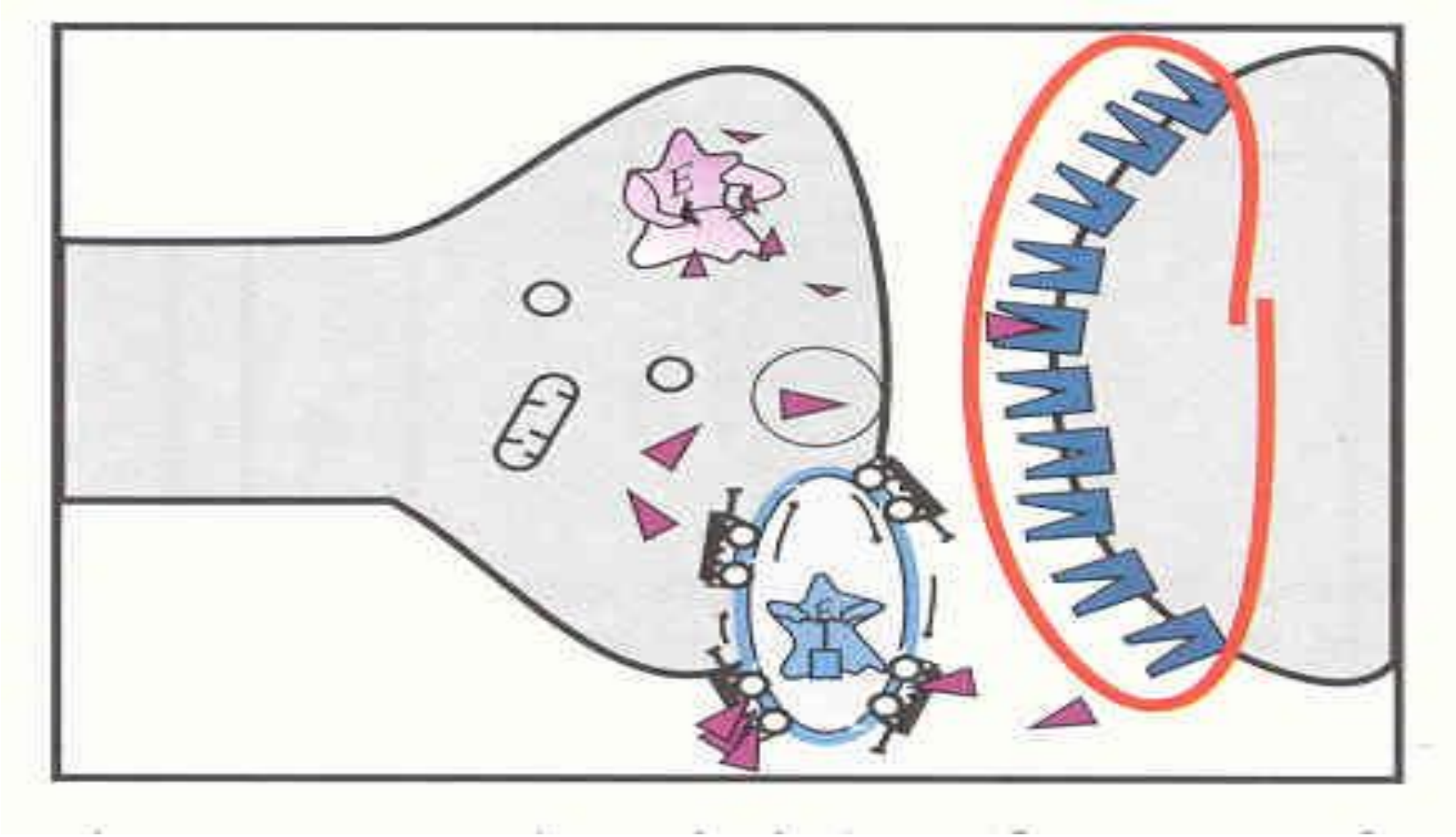
NORMAL STATE - NO DEPRESSION



DEPRESSION: CAUSED BY NEUROTRANSMITTER DEFICIENCY

Deficiency of the neurotrasmitter

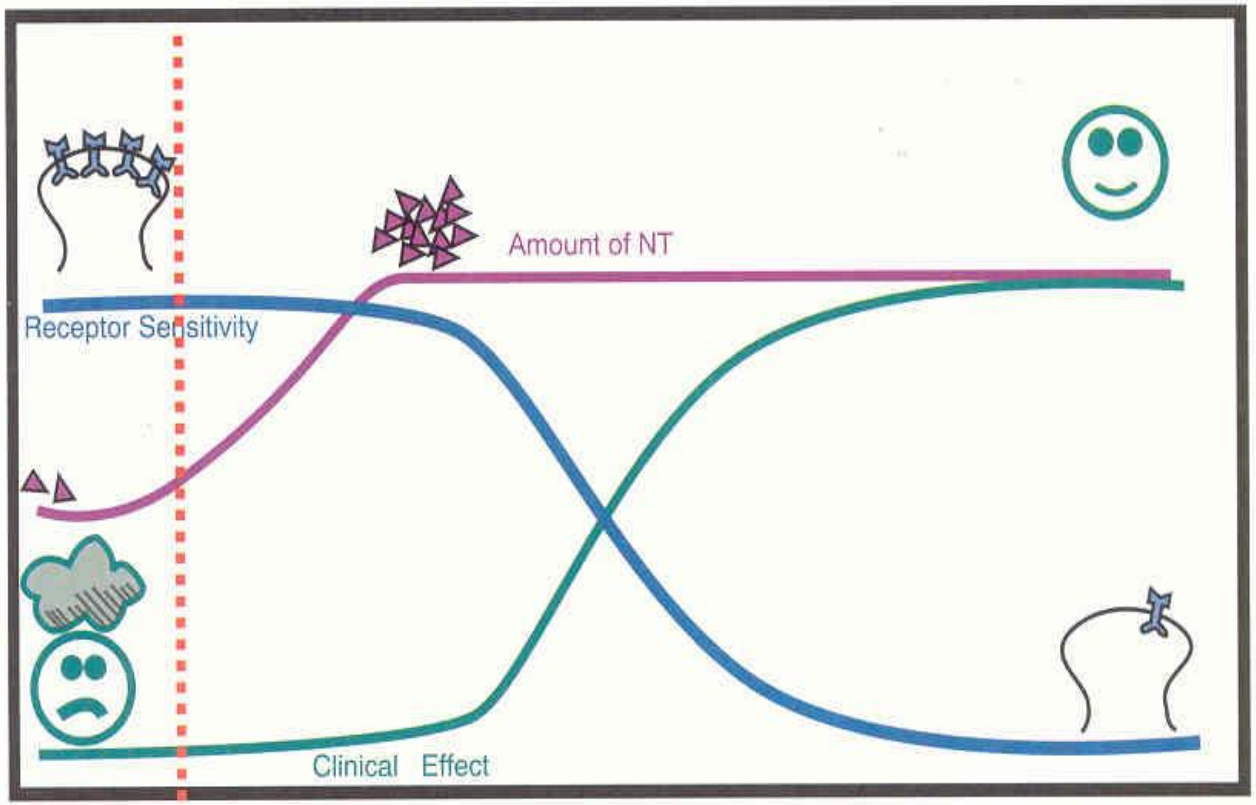
„up-regulation “ of receptors



antidepressants

↓

↑ neurotransmitrers and „down-regulation“of receptors



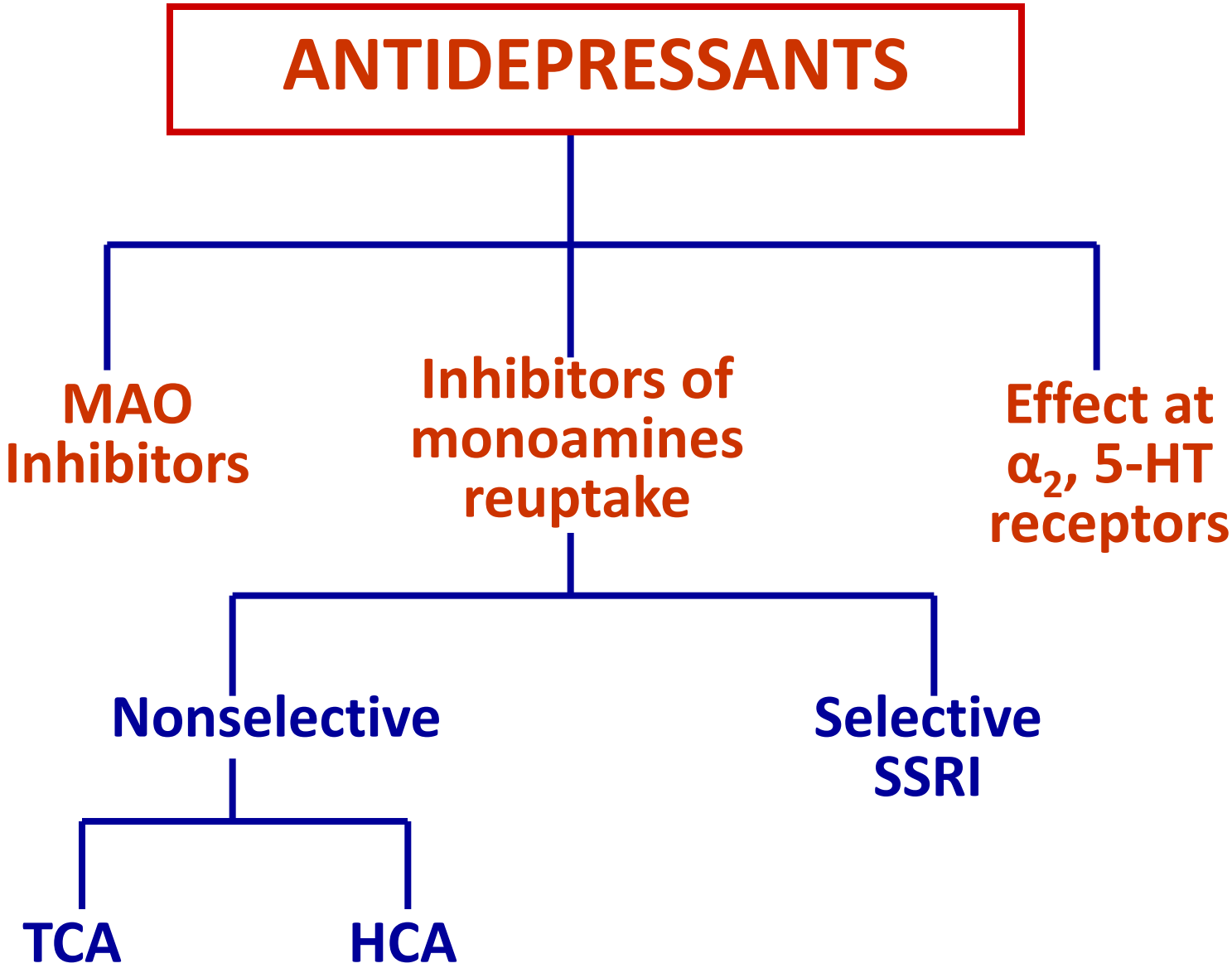
— down-regulation

— ↑ neurotransmitter

— patient improvement

ANTIDEPRESSANTS

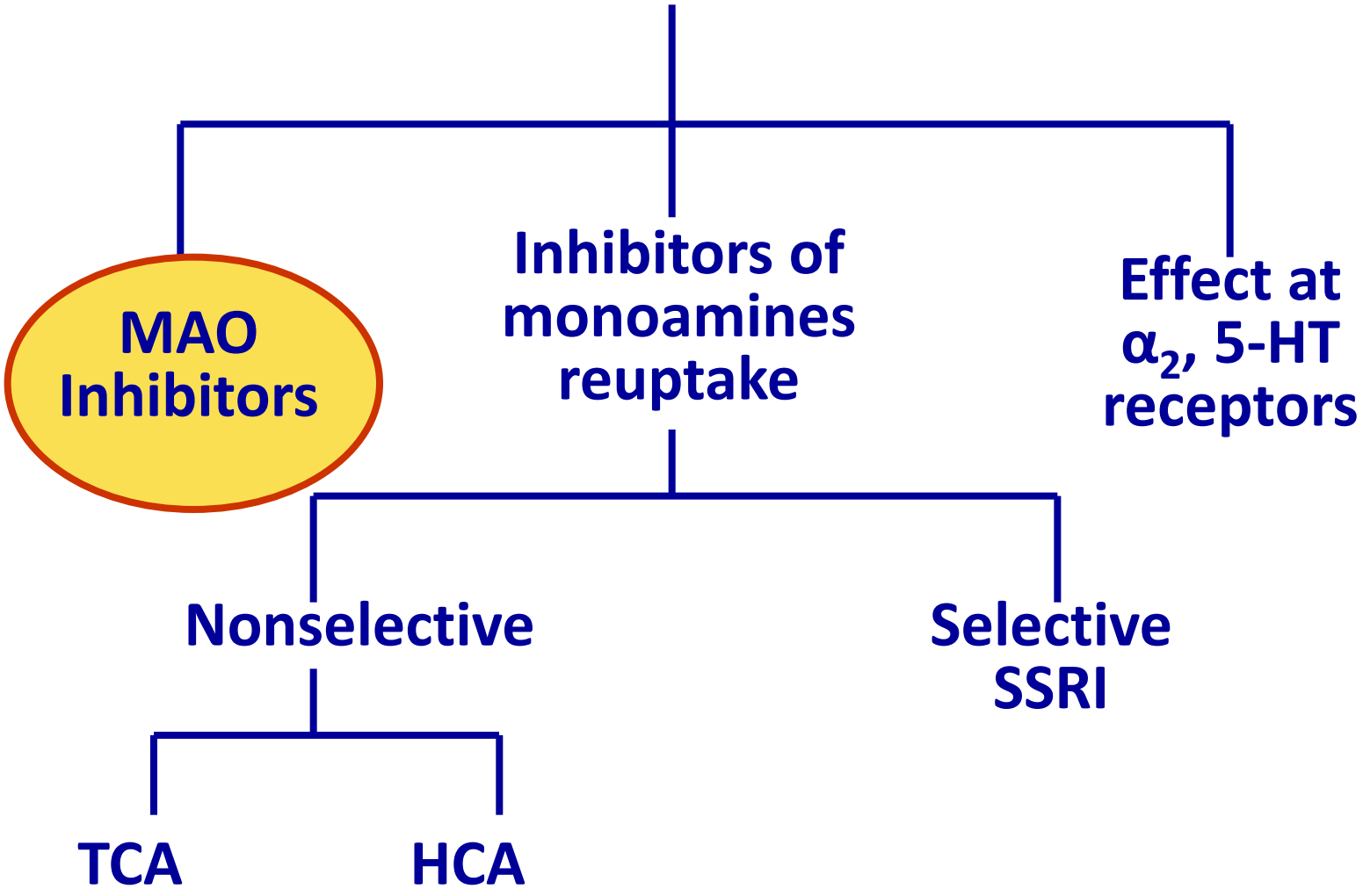
First generation	Second generation		Third generation
MAOI RIMA	**SSRI**	**SNRI**	**Melatonergic**
Phenelzine Tranylcypromine Selegiline patch Moclobemide	Citalopram Fluoxetine Fluvoxamine Paroxetine CR Sertraline	Venlafaxine XR Milnacipran Duloxetine	Agomelatine
TCA	**ASRI**	**NDM**	
Amitriptyline Clomipramine Nortriptyline and others	Escitalopram	Bupropion SR/XL	
	NRI	**NaSSA**	
	Reboxetine	Mirtazapine	


ANTIDEPRESSANTS
MAO Inhibitors
Inhibitors of monoamines reuptake
Effect at α_2, 5-HT receptors
Nonselective
Selective SSRI
TCA
HCA

Inhibitors of monoaminoxidase

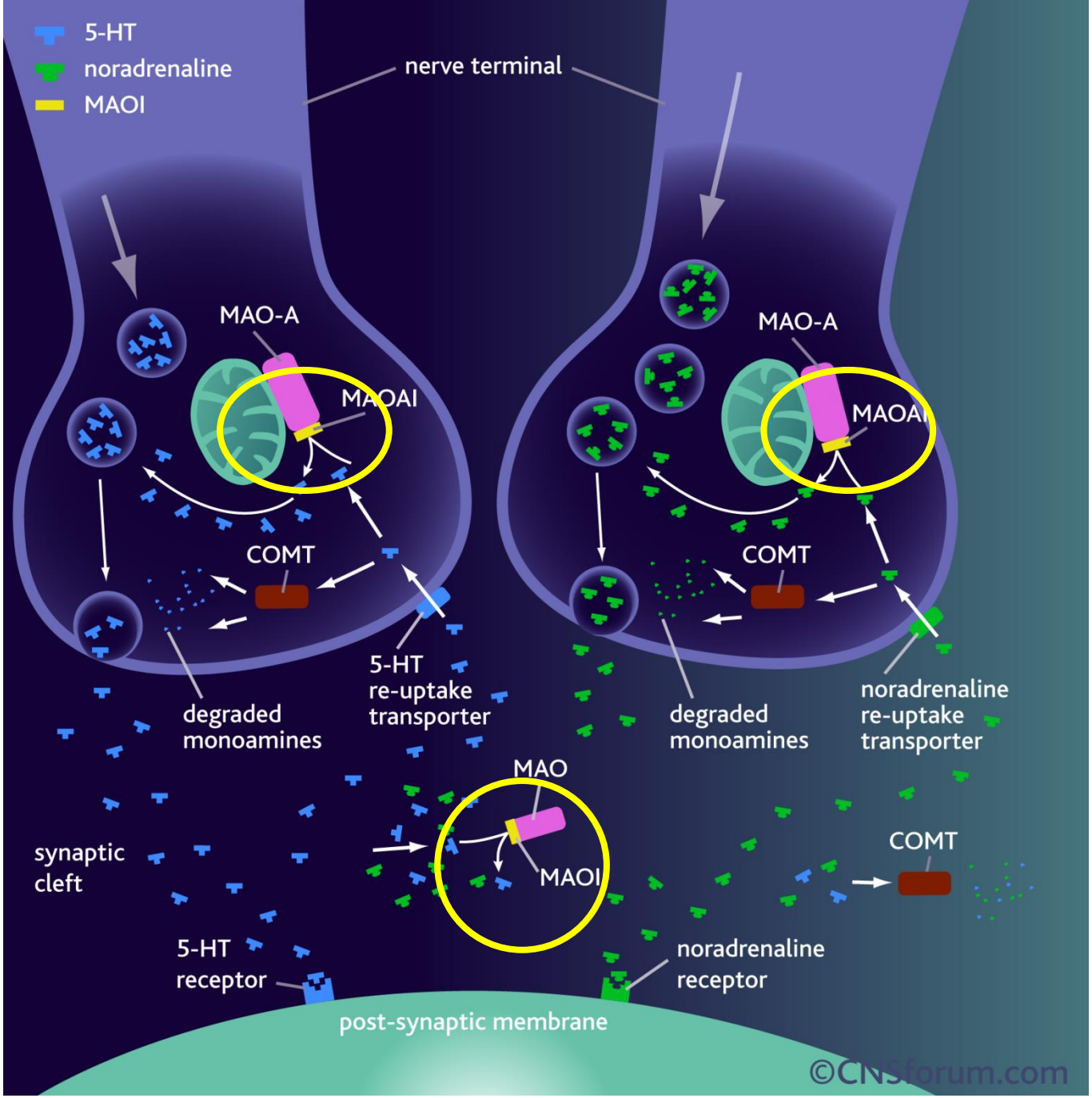
(thymoeretics)

ANTIDEPRESSANTS



MAOI

- for atypical depression
- as a last line of treatment when other classes have failed
- rapid, good GIT absorption
- good distribution
- liver metabolism
- $T_{1/2}$ – short relatively



Mechanism of action - MAOI

http://www.cnsforum.com/imagebank/item/Drug_MOAI_2/default.aspx

MAO-A inhibition reduces the breakdown of primarily serotonin, epinephrine, norepinephrine - a higher risk of serotonin syndrome and/or a hypertensive crisis.
Tyramine is broken down by MAO-A, therefore inhibiting its action may result in excessive build-up of it, so diet must be monitored for tyramine intake. This risk is generally not present with RIMAs

MAO-B inhibition reduces the breakdown mainly of dopamine and phenethylamine so there are no dietary restrictions associated with this.
Two such drugs, selegiline and rasagiline

Patients on MAO inhibitors must completely avoid foods and beverages containing tyramine

Aged cheese and meats
Smoked meats or pickled meats
Liver
Anchovies
Sauerkraut
Avacado
Bananas
Pepperoni
Salami
Raisons
Caffeine should be used sparingly
Avoid wine, sherry, beer, and hard liquor

MAO inhibitors (MAOI)

phenelzine (NARDIL)

isocarboxazid (MARPLAN)

tranylcypromine (PARNATE)

non-selective (irreversible)

moclobemide (AURORIX)

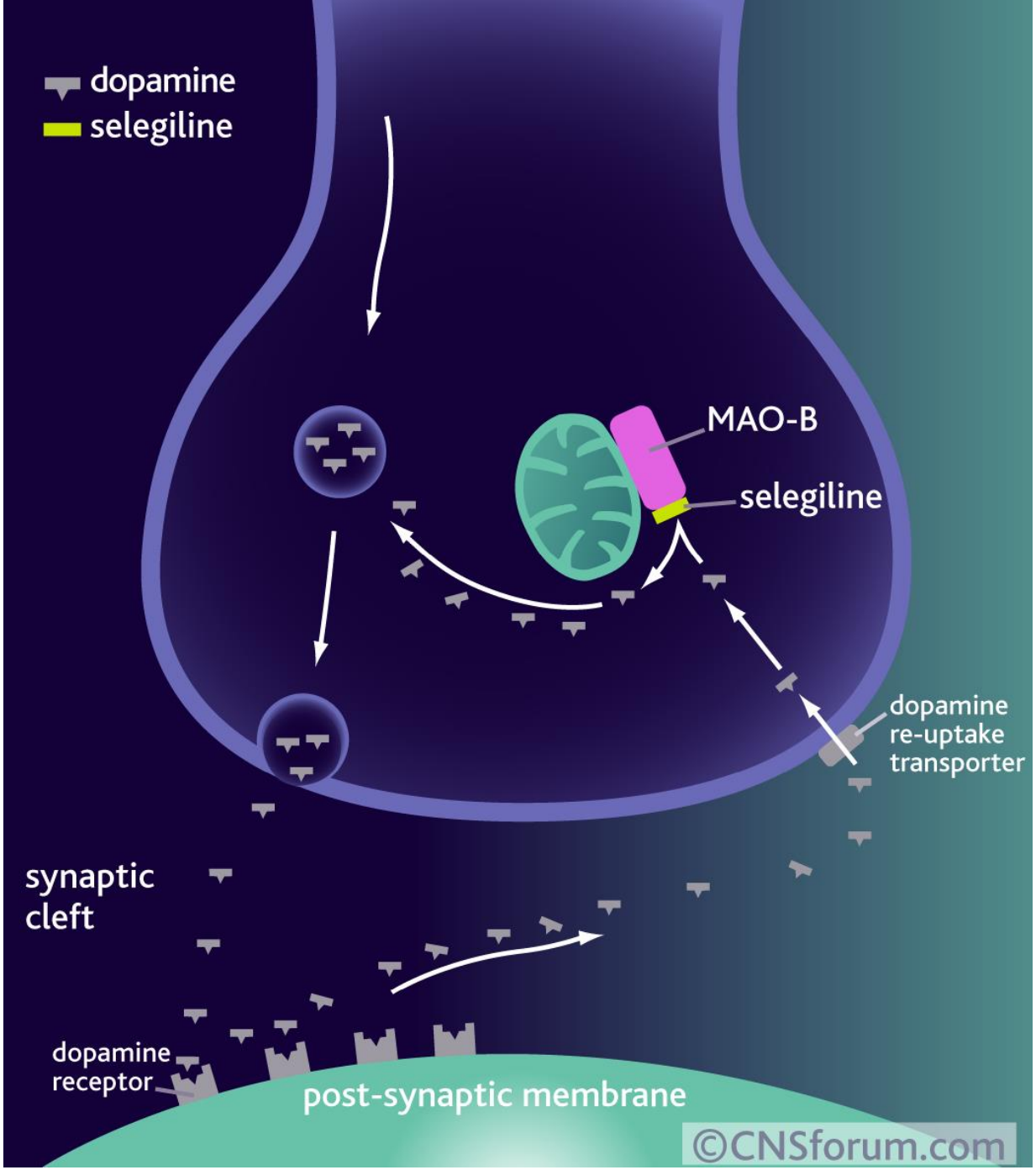
pirlindole (PIRAZIDOL)

MAO-A selective (reversible RIMA)

selegiline (DEPRENYL)

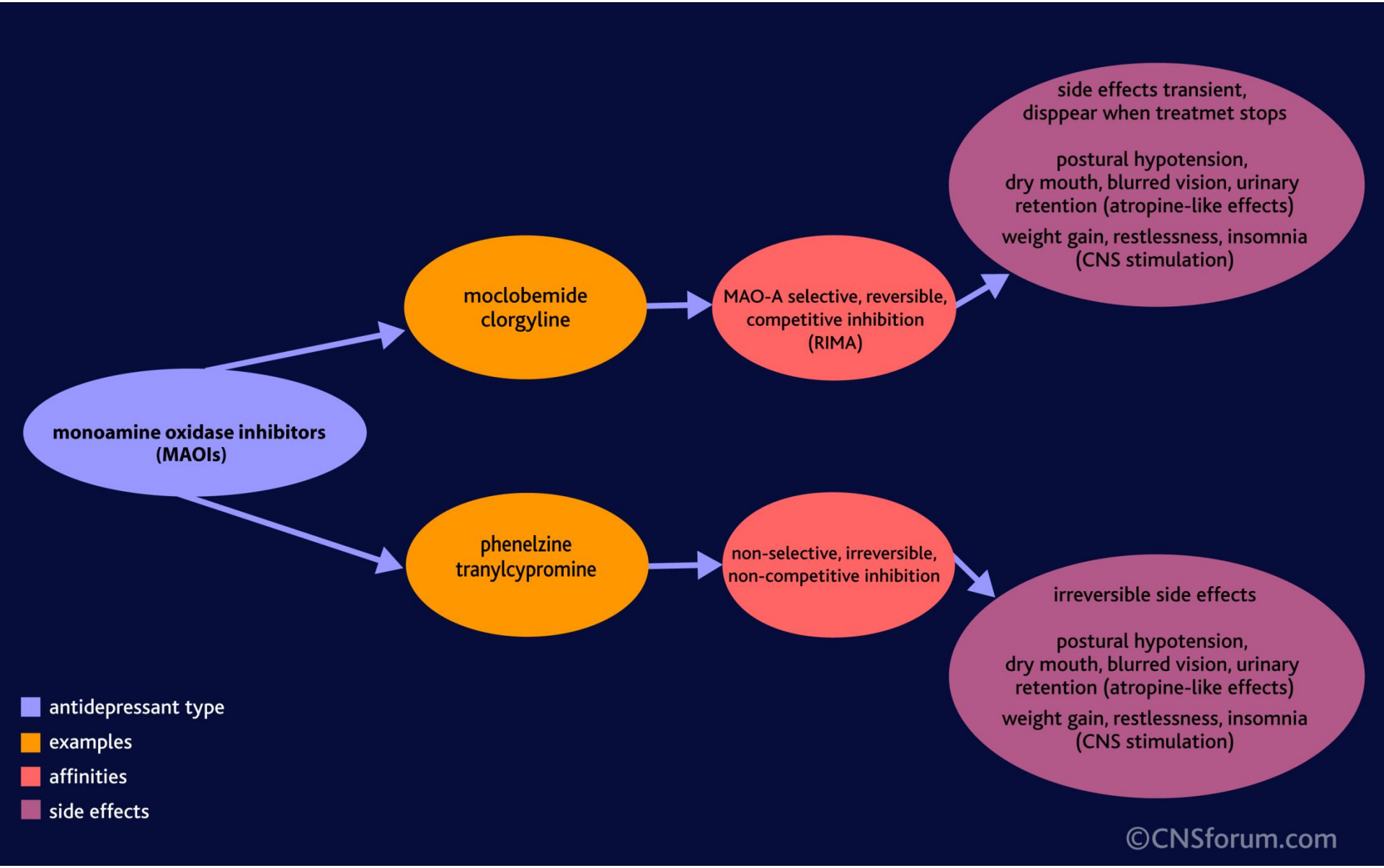
rasagiline (AZILECT)

MAO-B selective



Mechanism of action - MAO B I

http://www.cnsforum.com/imagebank/item/MAOB_inhib/default.aspx



http://www.cnsforum.com/imagebank/item/Properties_MAOIs/default.aspx

MAOI - adverse effects

- dizziness, fainting, headache, tremors, muscle twitching, confusion, memory impairment, anxiety, agitation, insomnia, weakness, drowsiness, chills, blurred vision, xerostomia, sexual dysfunction, heart palpitations....

MAOIs – adverse effects

- **hypertensive crisis ("cheese reaction")**

  - **tyramine** (↑ BP) – metabolized by MAO in GIT

- **moclobemide** does not cause the cheese reaction because it is a selective inhibitor of MAO type A, which inactivates noradrenaline and 5-HT

Note!

patients must wait for 14 days following discontinuation of an MAO inhibitor before they can safely consume any of these foods

or

drugs enhancing NE

MAOI - drug interactions

- sympathomimetics
- DA agonists (Bupropion)
- SSRIs, Venlafaxin, TCA
- L-Tryptophan
- Analgesics (tramadol, dextromethorphan..)

Inhibitors of monoamine reuptake (thymoleptics)

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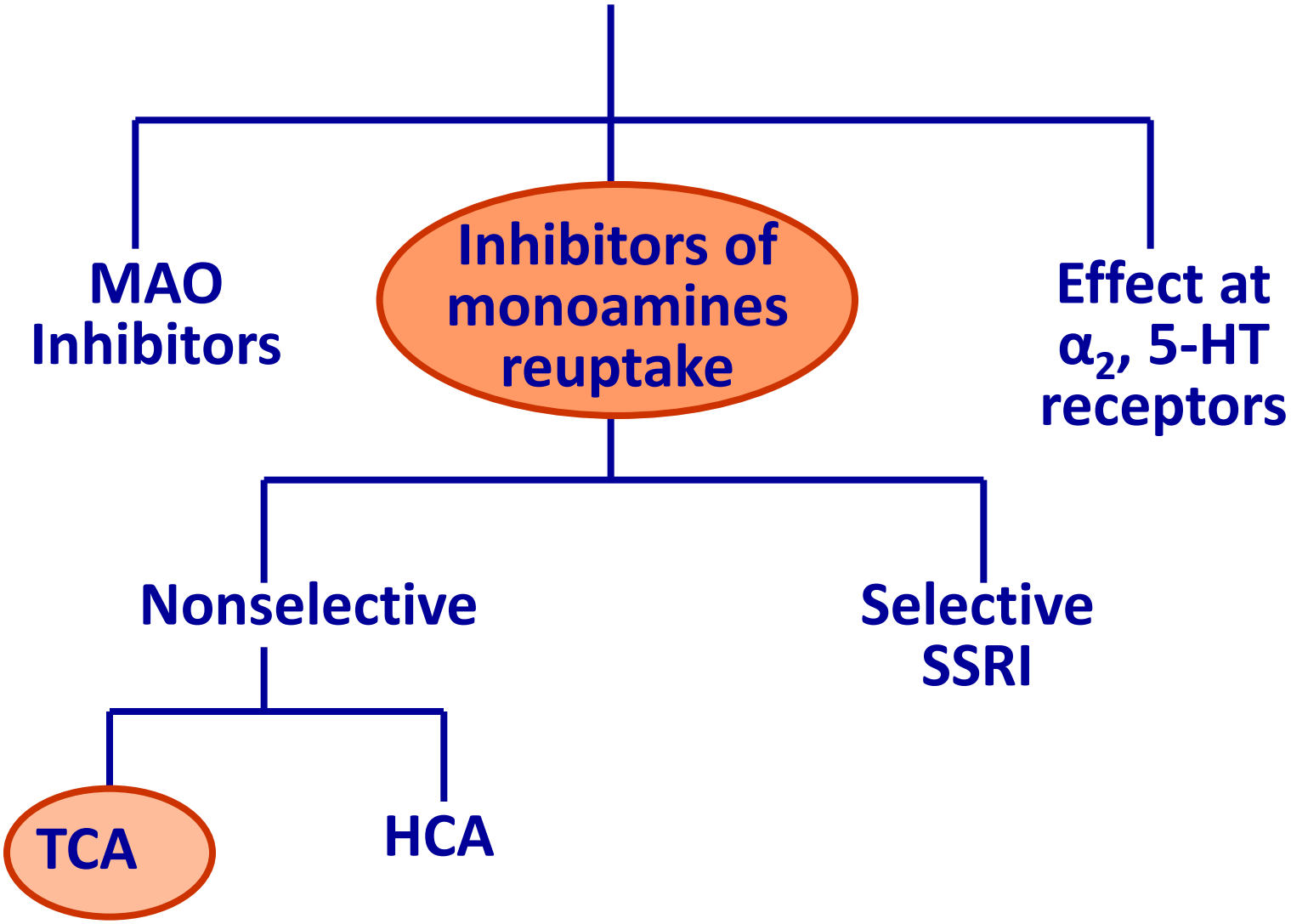
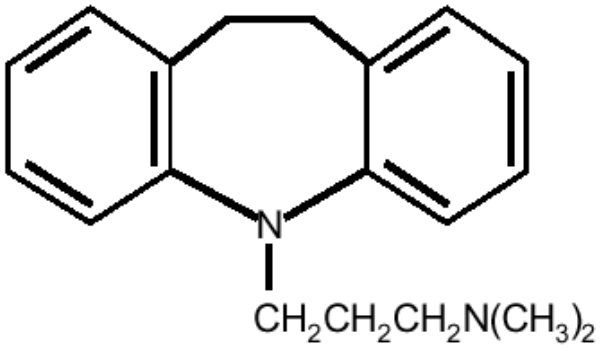
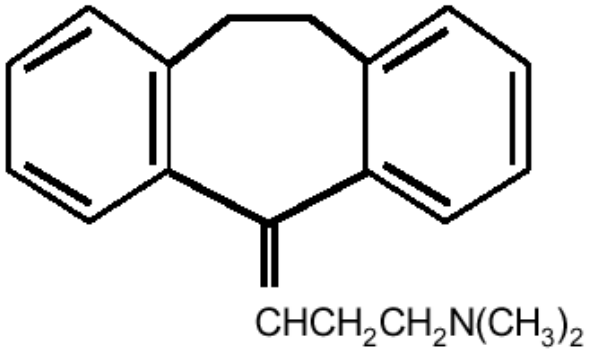


1st generation

Tricyclic antidepressants - TCAs

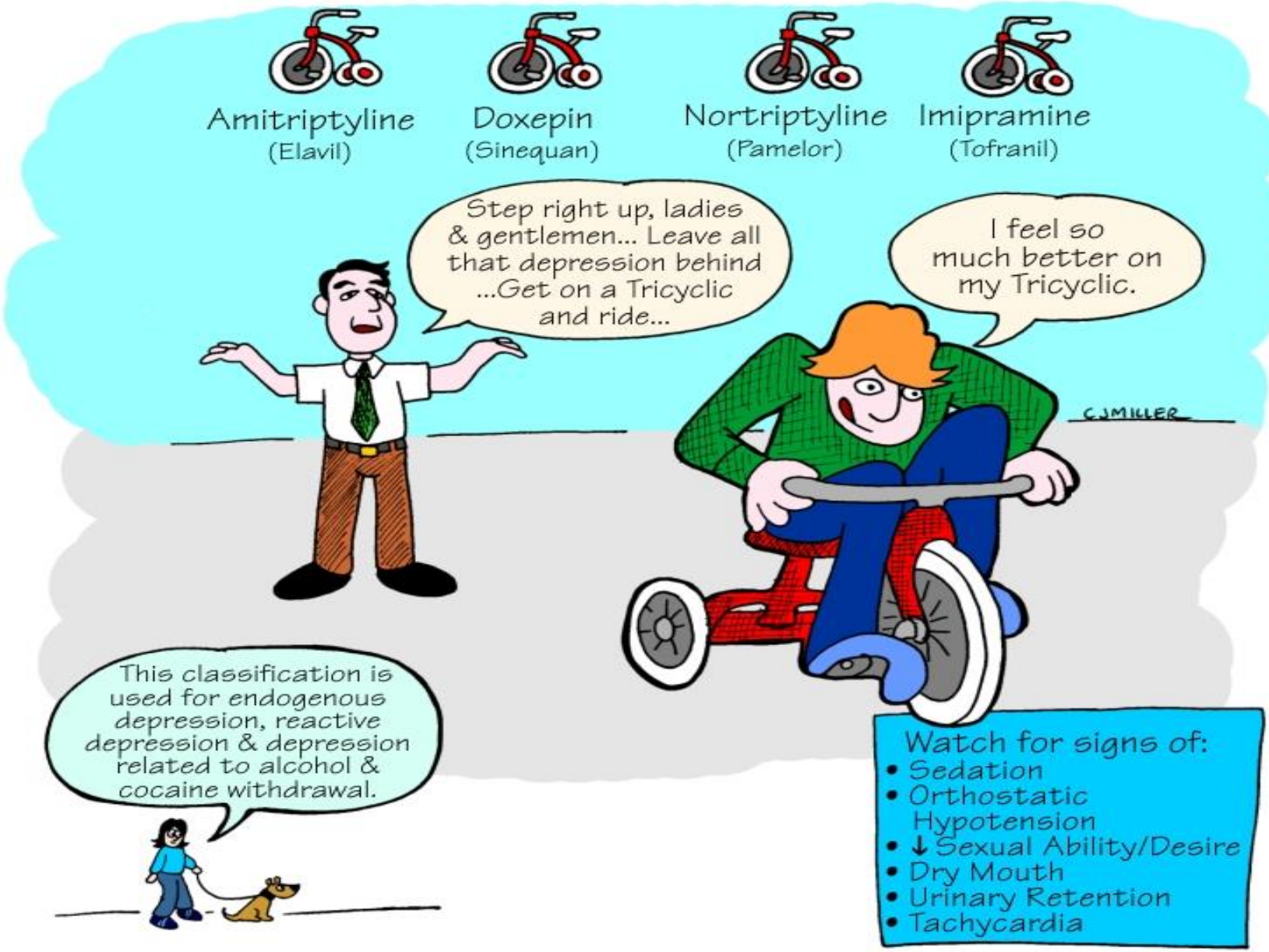


Imipramine



Amitriptyline

Tricyclic Antidepressants



Tricyclic Antidepressants

Amitriptyline (ELAVIL, ENDEP)

Clomipramine (ANAFRANIL)

Desipramine (NORPRAMIN)

Doxepin (ADAPIN, SINEQUAN)

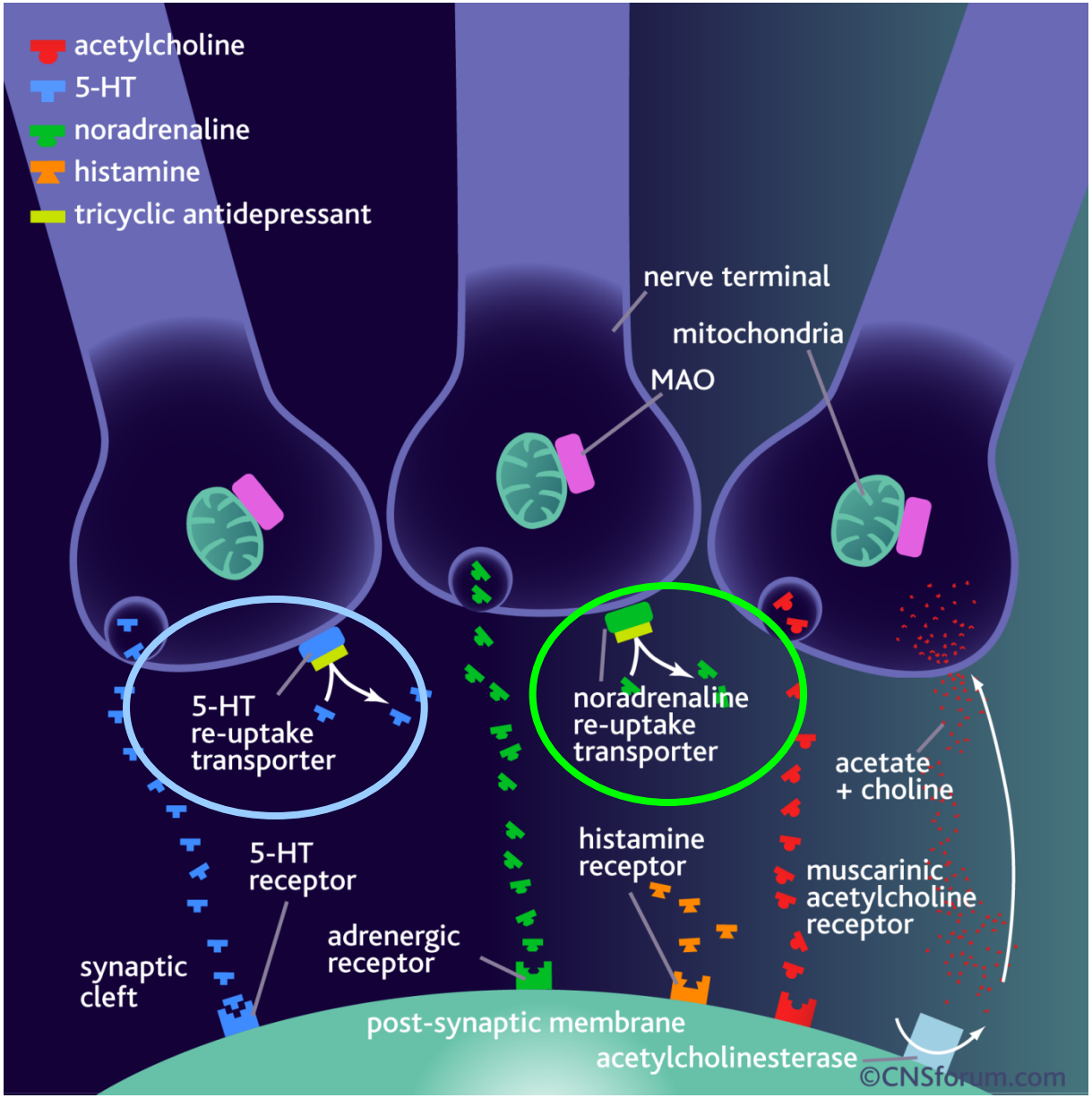
Imipramine (TOFRANIL)

Nortriptyline (PAMELOR)

Protriptyline (VIVACTYL)

Trimipramine (SURMONTIL)

The mechanism of TCA action



http://www.cnsforum.com/imagebank/item/Drug_TCA_efficacy/default.aspx

TCAs - mechanism of action

- **inhibition of NT reuptake** (NET, SERT)
- immediate action - ↑ **NE** and **5-HT** in synapse
- chronic treatment (2 - 4 weeks)

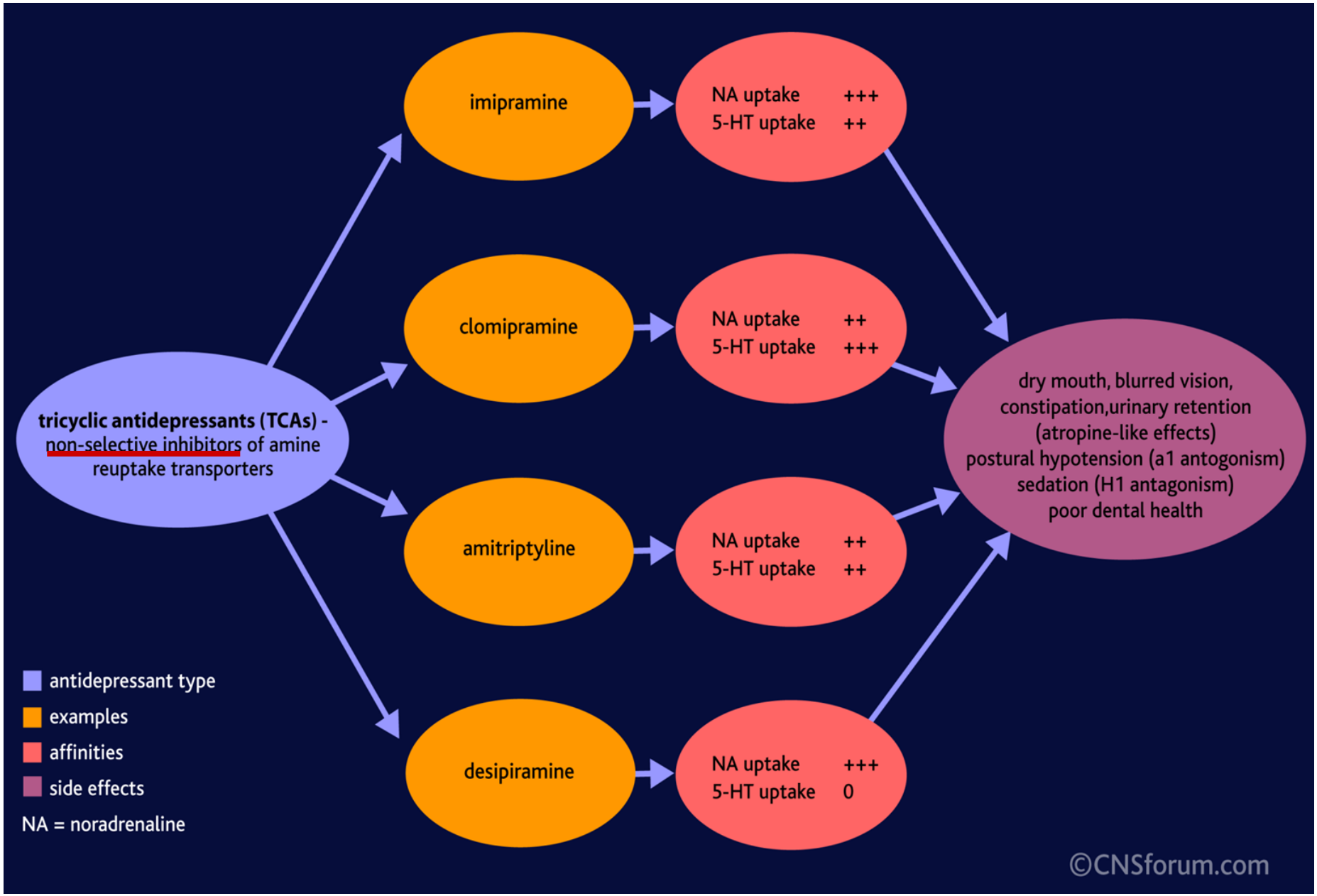
↓NE-R and ↓5-HT_2R

↑ sensitization of 5-HT receptors

↓ NE release and turnover

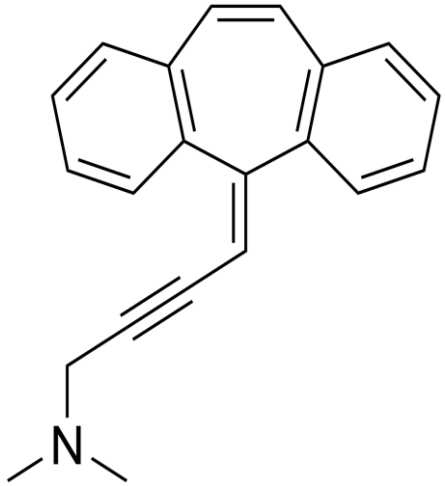
↓ NE-stimulated cAMP in brain

- effect of all TCA antidepressants – within 4 weeks



http://www.cnsforum.com/imagebank/item/properties_TCAs/default.aspx

TCAs - pharmacokinetics



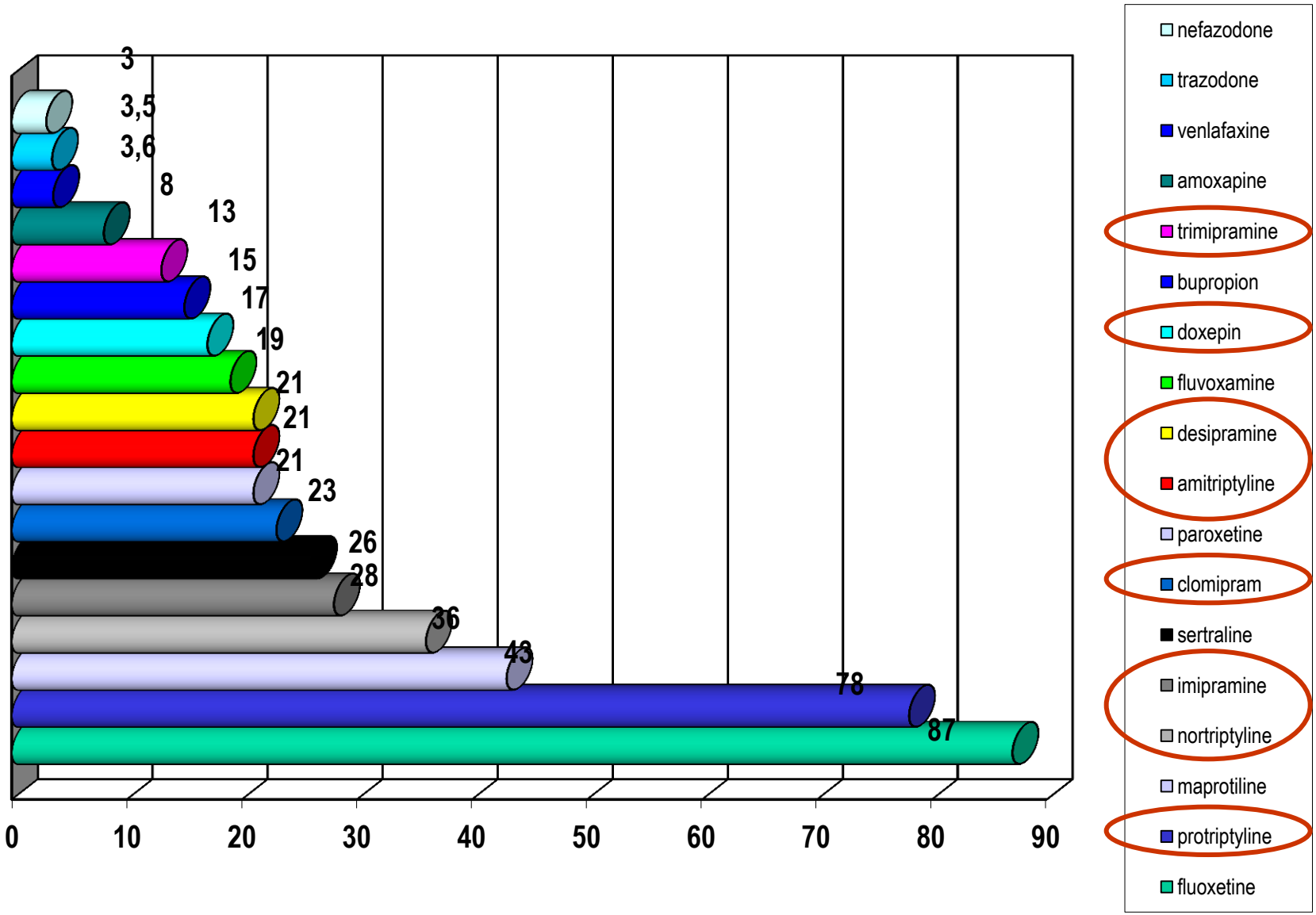
- characteristic three ring nucleus
- most are incompletely absorbed
- all are metabolized in liver - high first pass effect

    1) transformation to glucoronides

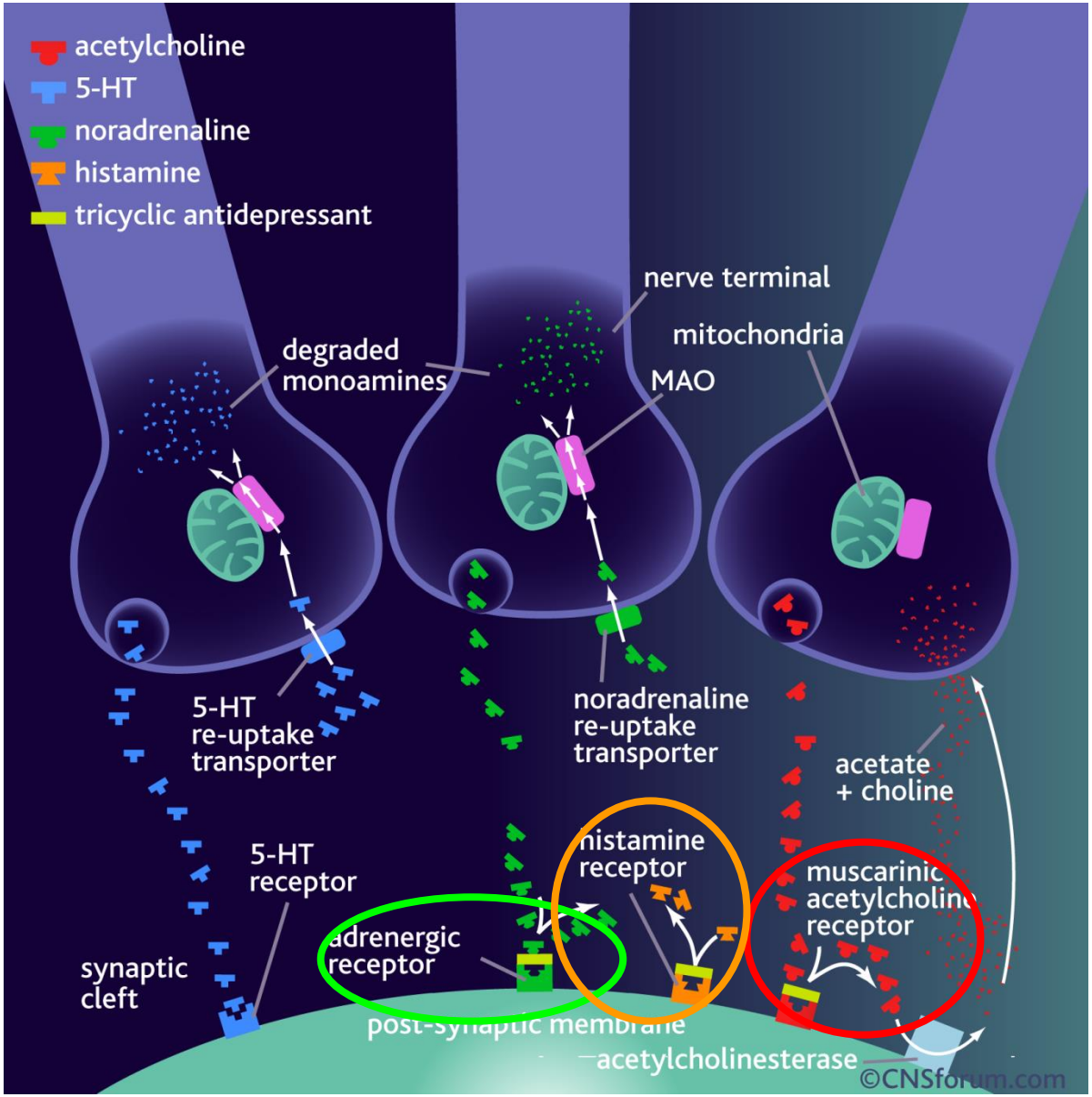
    2) alteration to active metabolites

- high protein binding, high lipid solubility

Antidepressant half-lives (hrs)



TCAs adverse effects



http://www.cnsforum.com/imagebank/item/Drug_TCA_AE/default.aspx

TCAs adverse effects

- **atropine-like side effects** - dry mouth,
  - paradoxical excessive perspiration, constipation,
  - blurred vision, mydriasis, metallic taste, urine
  - retention => muscarinic blockade.
- **orthostatic hypotension** => α_1 and possibly α_2-blockade

TCAs adverse effects

- drowsiness, sedation, weight gain - H_1 blockade
- **cardiotoxicity** - arrhythmias, palpitations, tachycardia, congestive heart failure, ↑ QT interval
- **sexual dysfunction** - loss of libido, impaired erection and ejaculation and anorgasmia
- all potentiate CNS depressants => coma and death

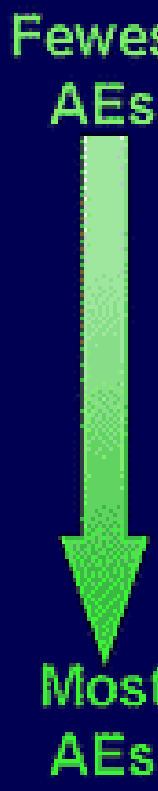
↓ COMPLIANCE

drugs of the second-line

(first-line in severe depression)

Tricyclic Antidepressants: Adverse Effects

- Commonly reported AEs (generally anticholinergic):
  - blurred vision
  - cognitive changes
  - constipation
  - dry mouth
  - orthostatic hypotension
  - sedation
  - sexual dysfunction
  - tachycardia
  - urinary retention



- Desipramine
- Nortriptyline
- Imipramine
- Doxepin
- Amitriptyline

Risk of weight gain

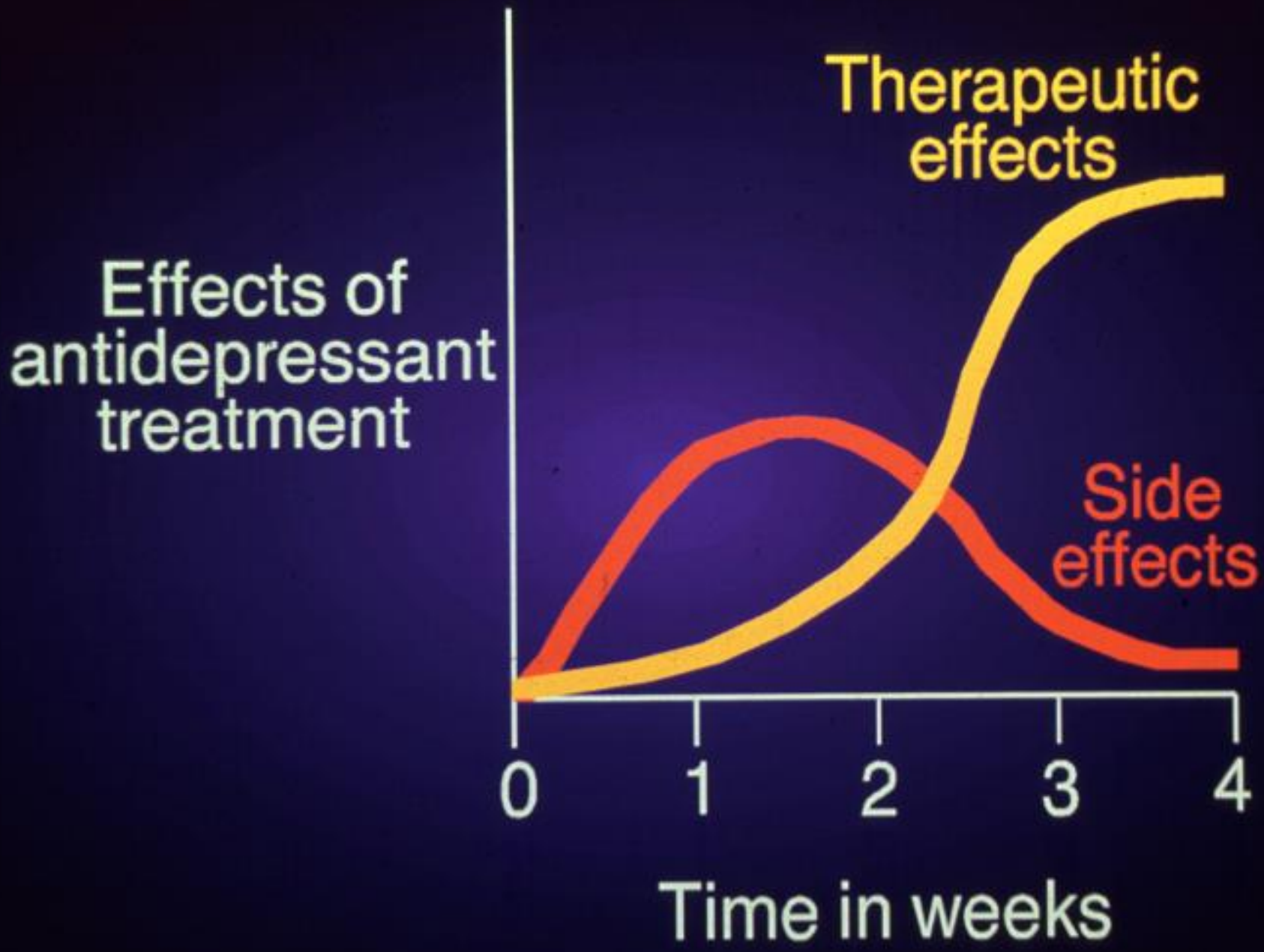
↓ body weight ↑ body weight ↑ body weight

bupropion venlafaxin fluoxetin paroxetin mirtazapin

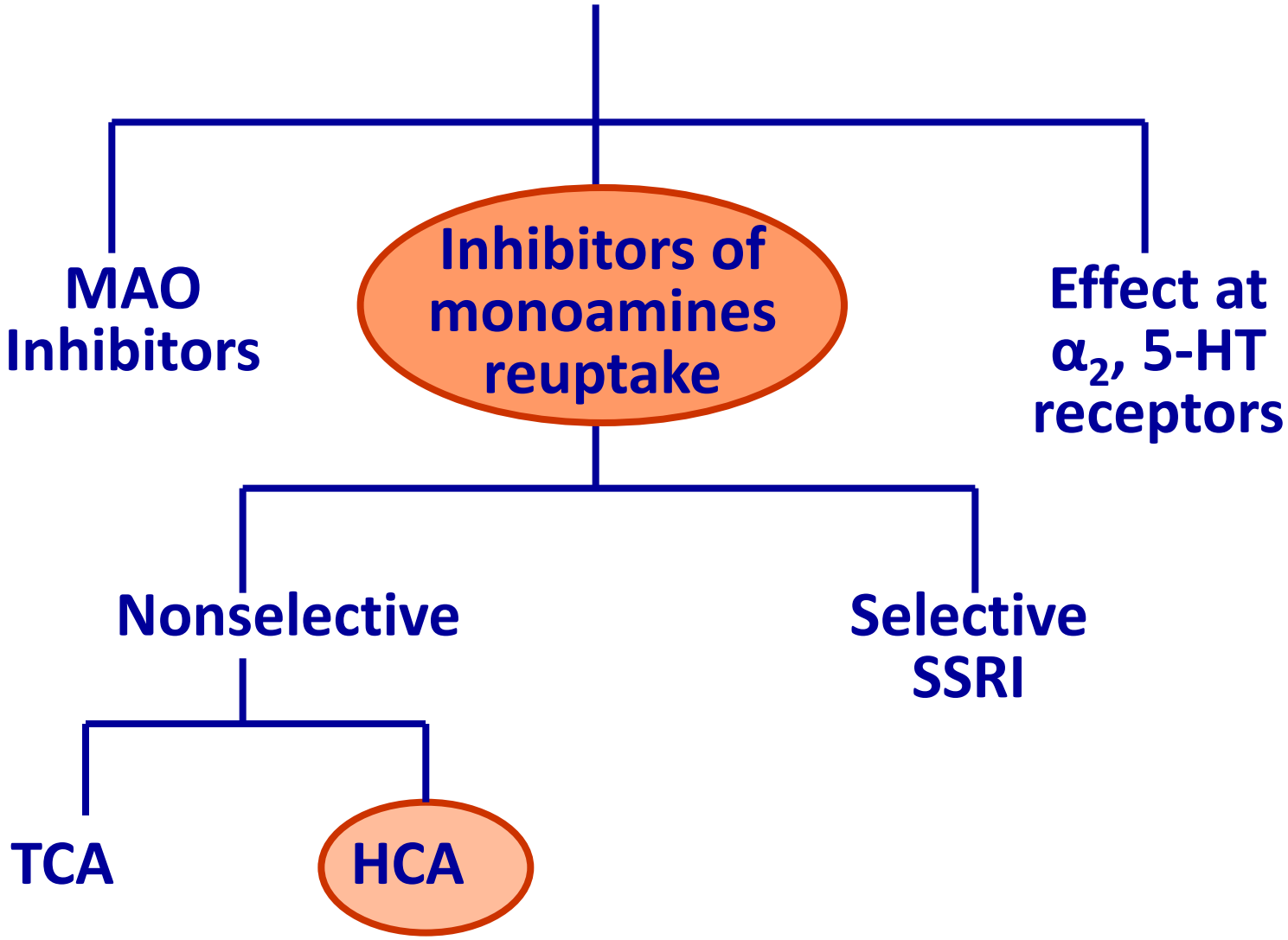
tranylcypromin sertralin some of IMAO

citalopram

TCA

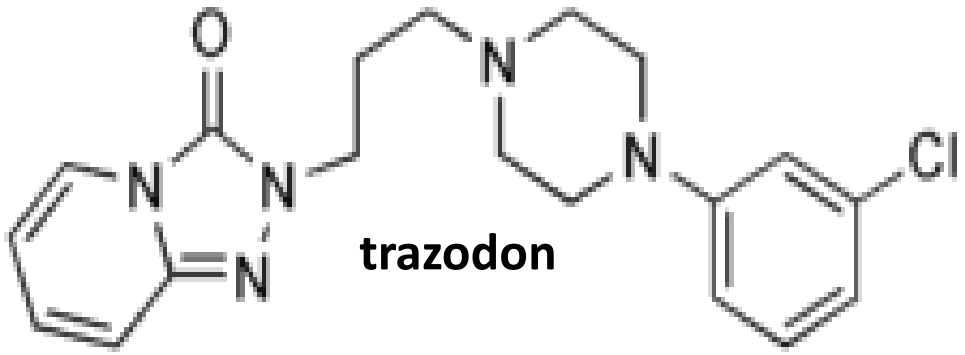

Therapeutic effects
Effects of antidepressant treatment
Side effects
0
1
2
3
4
Time in weeks

ANTIDEPRESSANTS

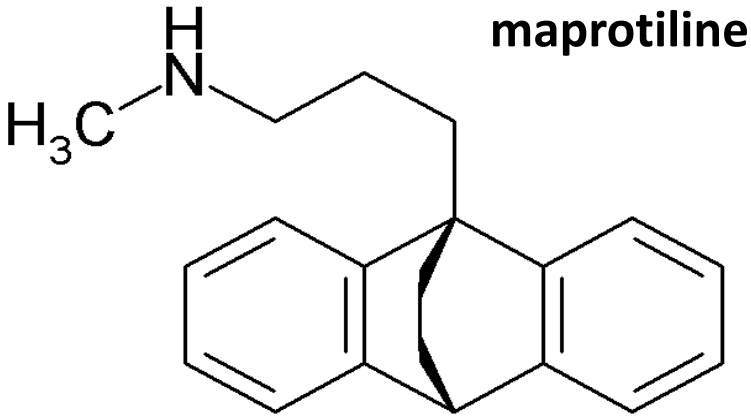


2nd generation

Heterocyclic antidepressants
HCAs



trazodon



maprotiline

Mechanism of Action

- bicyclic, tetracyclic

1. NT reuptake inhibition
2. 5-HT receptor antagonism (5-HT_{2A} or HT_{2C}) or other receptors
3. alteration of NE output

Heterocyclic antidepressants

1st group

- amineptine (SURVECTOR)
- bupropion (ZYBAN, WELLBUTRIN)
- maprotiline (LUDIOMIL)
- trazodone (DESYREL)
- viloxazine (VIVALAN)

2nd group

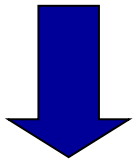
- amoxapine (MOXADIL)
- duloxetine (CYMBALTA)
- mianserine (NORVAL)
- mirtazapine (REMERON)
- nefazodone (SERZONE)
- reboxetine (EDRONAX)
- tianeptine (COAXIL)
- venlafaxine (EFECTIN, ALVENTA)

1st group of HCA

↓reuptake - predominantly 1 monoamine

- serotonine (SSRI, SARI)
- noradrenaline (NARI)
- dopamine (DARI)

minimal affinity at other receptors - **muscarinic**



less adverse effects

1st group of HCA

SARI (**S**erotonin **A**ntagonist and 5-HT **R**euptake **I**nhibitor) – „double“ 5-HT effect - **trazodone**

DARI (**D**op**A**mine **R**euptake **I**nhibitor) - selective inhibitors of DA reuptake – **amineptine**

NARI (**N**or**A**drenaline **R**euptake **I**nhibitor) selective inhibitors of NE reuptake – **viloxazine, reboxetine**

2nd group

Antidepressants with double effect

SNRI (**S**erotonine and **N**oradrenaline **R**euptake **I**nhibitors) - **milnacipram, venlafaxin, duloxetine**

DNRI (**D**opamine and **N**oradrenaline **R**euptake **I**nhibitor) – **bupropion**

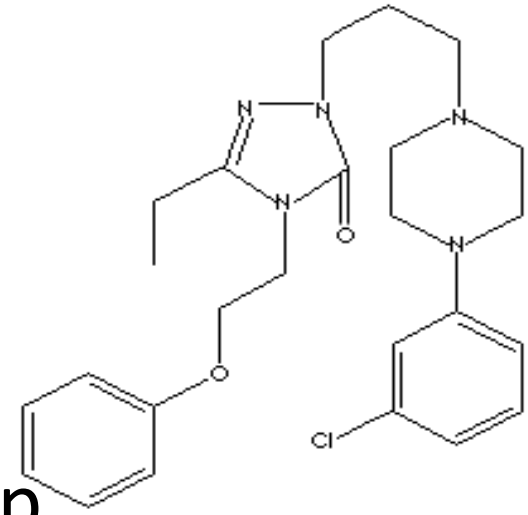
- effective in the patients resistant to SSRI or for SSRI side effects
- more rapid onset of the action

New classes of antidepressants

- **SNDRI** (**S**erotonin–**N**orepinephrine–**D**opamine **R**euptake **I**nhibitor (**SNDRI**)
  or **triple reuptake inhibitor** (**TRI**)
  - broad-spectrum antidepressants (**bicifadine, tesofensine**)
  - more rapid onset, better efficacy
  - ideal rank N>D >S ???
  - under development, in clinical trials

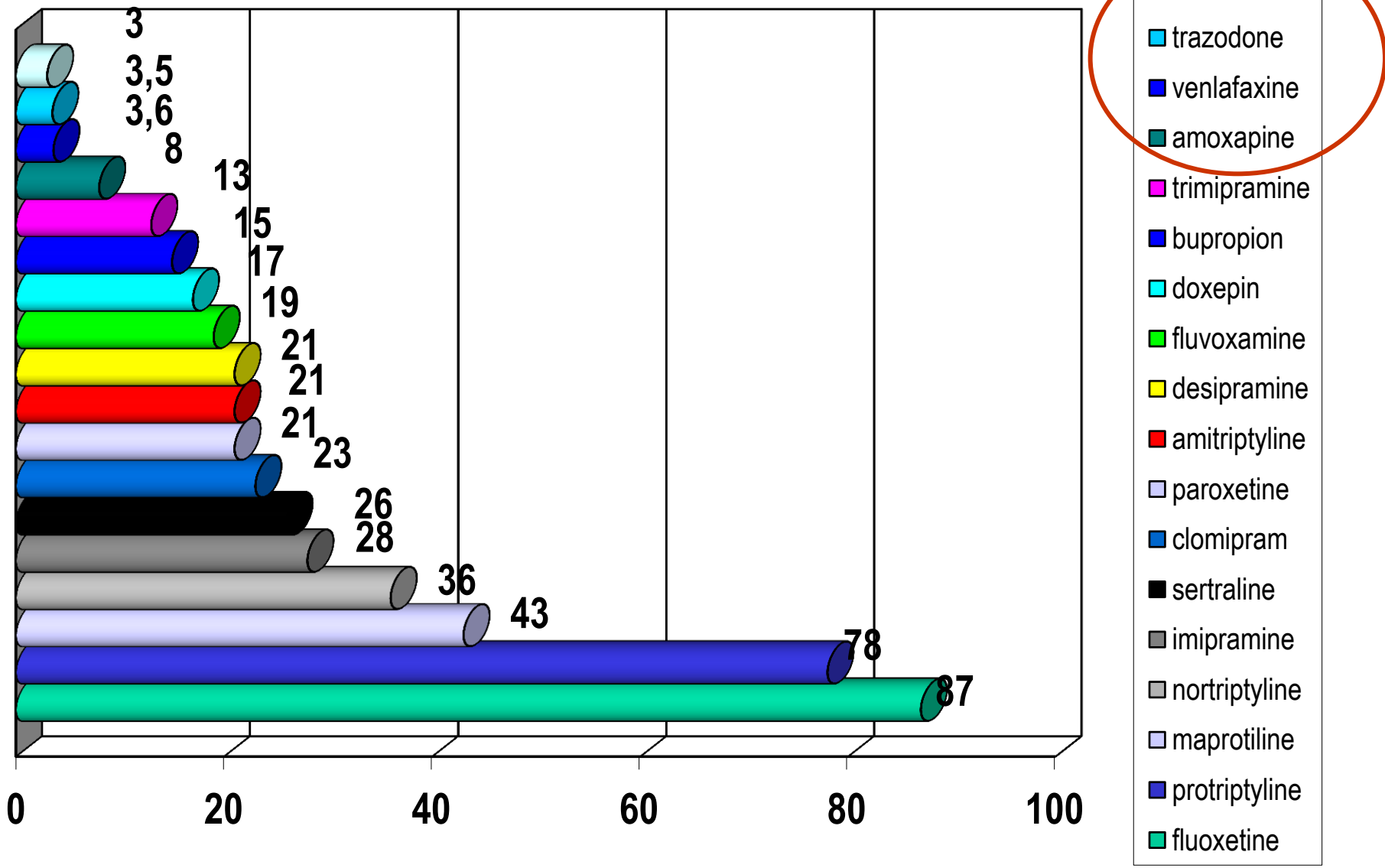
- **SRS** (**S**timulation **R**euptake **S**erotonine) or selective serotonin reuptake enhancer (SSRE) (opposite effect to SSRI)
  - alteration of AMPA glutamate receptor activity (**tianeptine**)

HCA - pharmacokinetics



- no means a homogeneous group
- they all have variable bioavailability
- high protein binding
- some have active metabolites
- some have the short plasma half-lives

Antidepressants T½ (h)



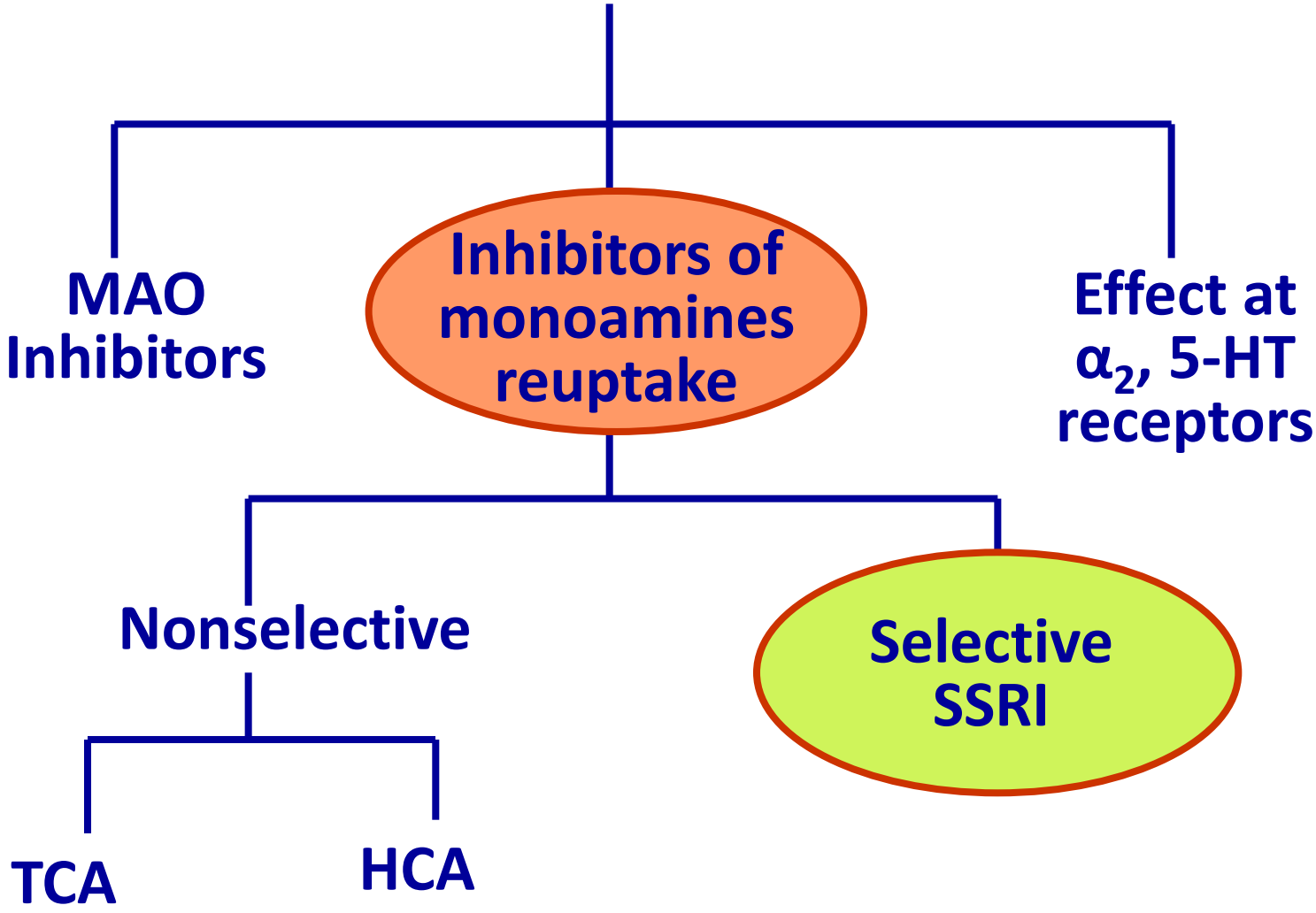
HCA – adverse effcets

- similar to SSRI
- anorexia, ↓ body weight, insomnia
- sexual dysfunction (↓ libido, anorgasmia)

  weaker than SSRI
- dizziness, fatigue, headache, mydriasis,

  nausea, urine retention
- ↑ NA - anxieta, ↑ BP, tachycardia,
- „ discontinuation syndrome“

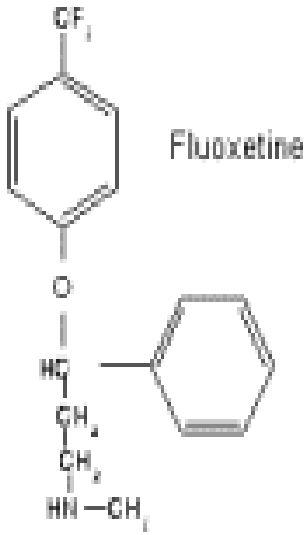
ANTIDEPRESSANTS

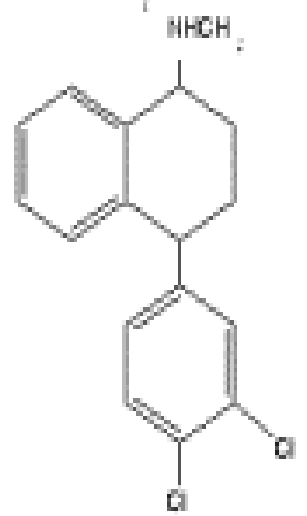


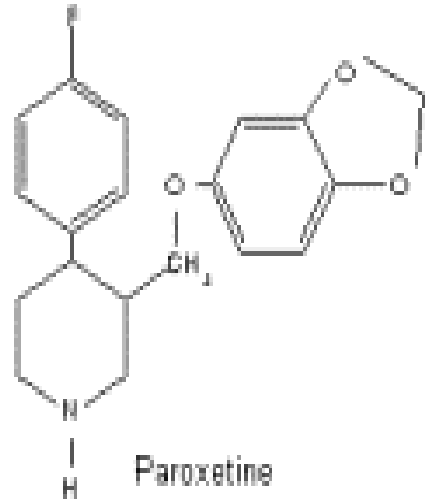
3rd generation

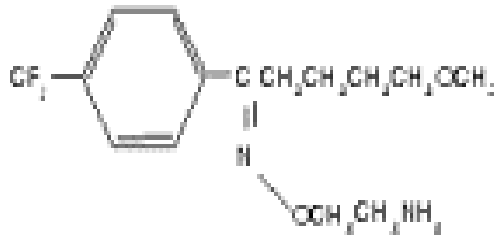
Selective Serotonine Reuptake Inhibitors

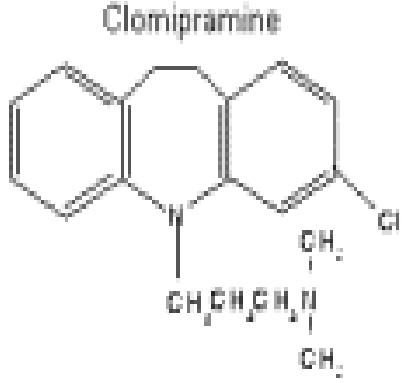
SSRI







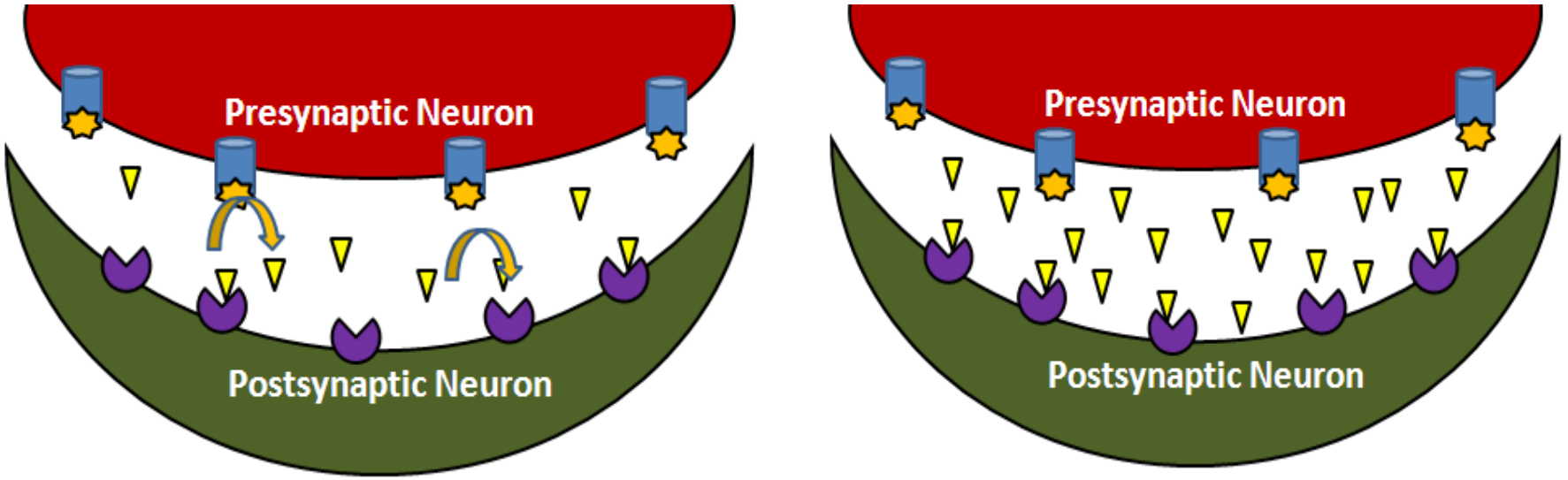




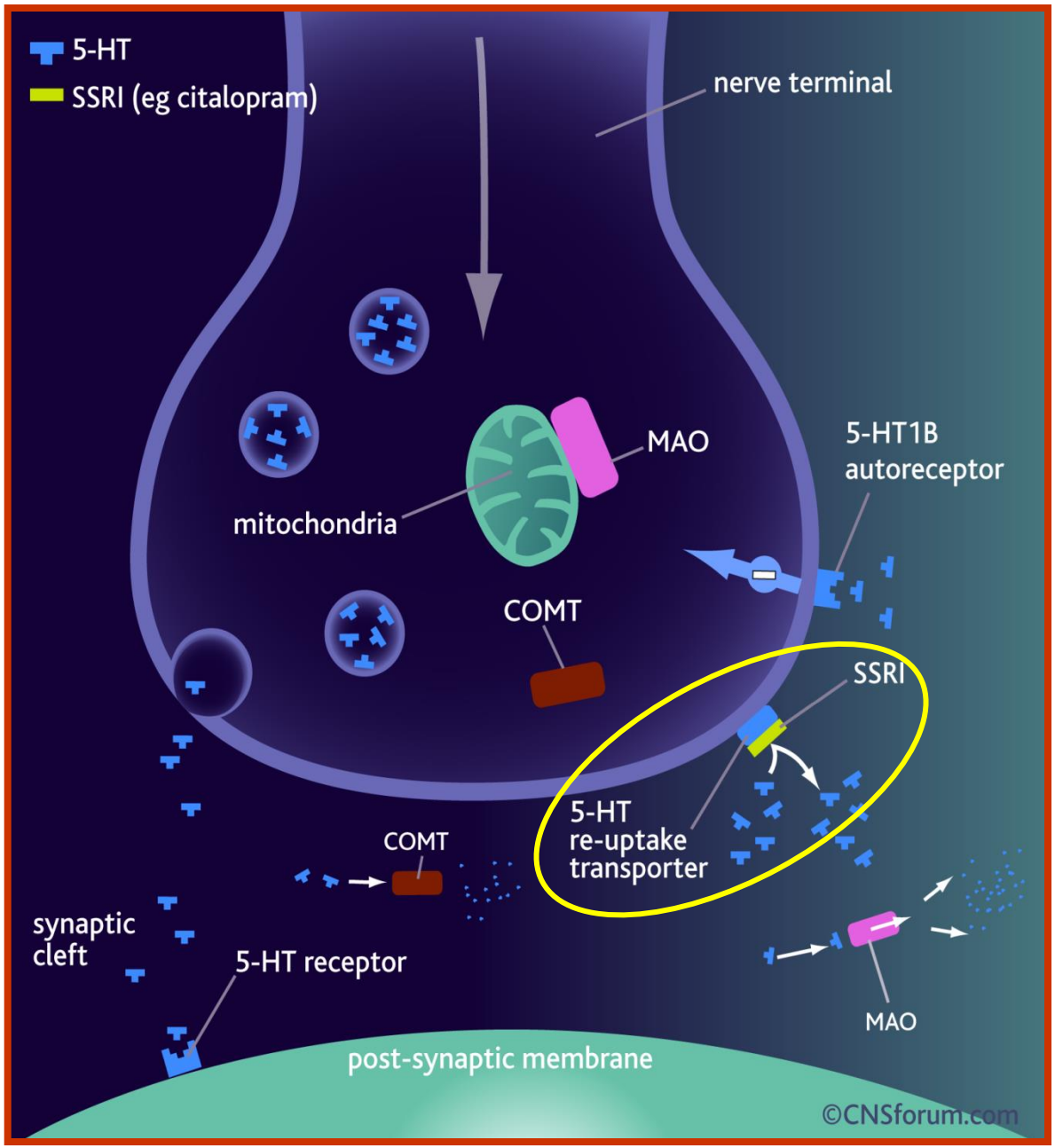
Main similarities and differences SSRIs and TCAs

- SSRIs are more commonly prescribed than TCAs
- SSRIs and TCAs have similar efficacy
- SSRIs have different molecules, it is possible to substitute their one another
- SSRIs have fewer anticholinergic and cardiovascular side effects
- TCA have fewer sexual and gastrointestinal side effects
- SSRIs are better tolerated by patients
- TCAs are associated with more frequent treatment discontinuations (i.e. more people dropping out tricyclics than SSRIs)
- SSRIs are safer in overdose than TCAs

Mechanism of SSRI action



- is BLOCKADE of the serotonin transporter



Mechanism of SSRI action

- inhibition of 5-HT reuptake
- ↑ of postsynapt. 5-HT_{1A} sensitivity

http://www.cnsforum.com/imagebank/item/Drug_SSRI_2/default.aspx

Selective Serotonin Reuptake Inhibitors (SSRIs)

Citalopram (CELEXA)

Dapoxetine (PRILIGY)

Escitalopram (LEXAPRO)

Fluoxetine (PROZAC)

Fluvoxamine (LUVOX)

Paroxetine (PAXIL)

Sertraline (ZOLOFT)

Vilazodone (VIIBYRD)

SSRIs - pharmacokinetics

inhibition of cytochrome P-450

- interactions, toxicity

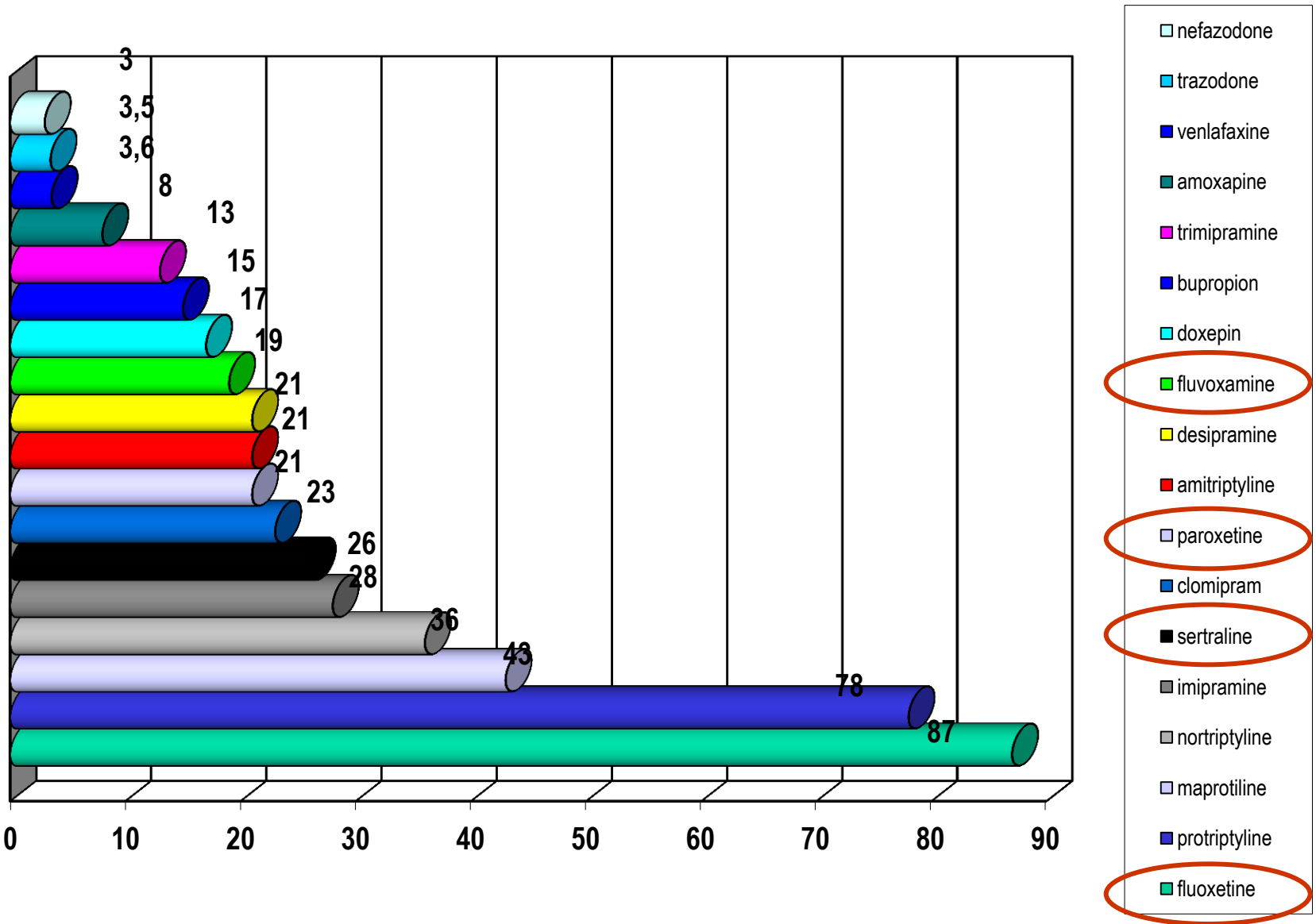
$T_{1/2}$ – variable - 2-3, 7-9 days

↑ protein binding

Inhibition of CYP450

cytochrom P450	2C9	2D6	3A4
fluoxetine	+++	+++	++
paroxetine	0/+	+++	0/+
sertraline	+	0/+	++
citalopram	0/+	0/+	0/+
fluvoxamine	++	0	++
venlafaxine	0/+	0/+	0/+
milnacipran	0	0	0
duloxetine	?	+++	?
mirtazapine	0	+	0
bupropion	0/+	++	0/+

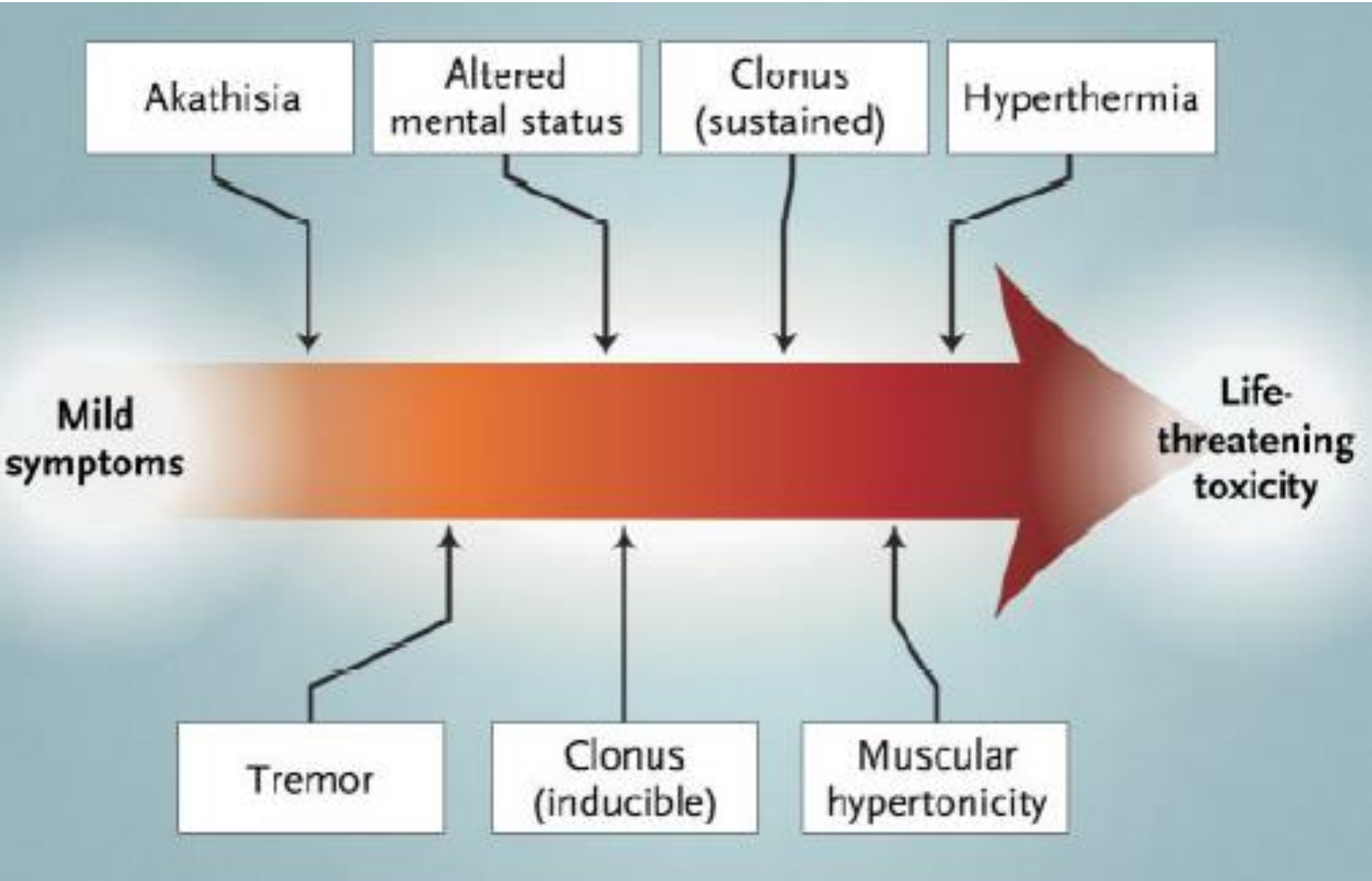
Antidepressant half-lives (hrs)

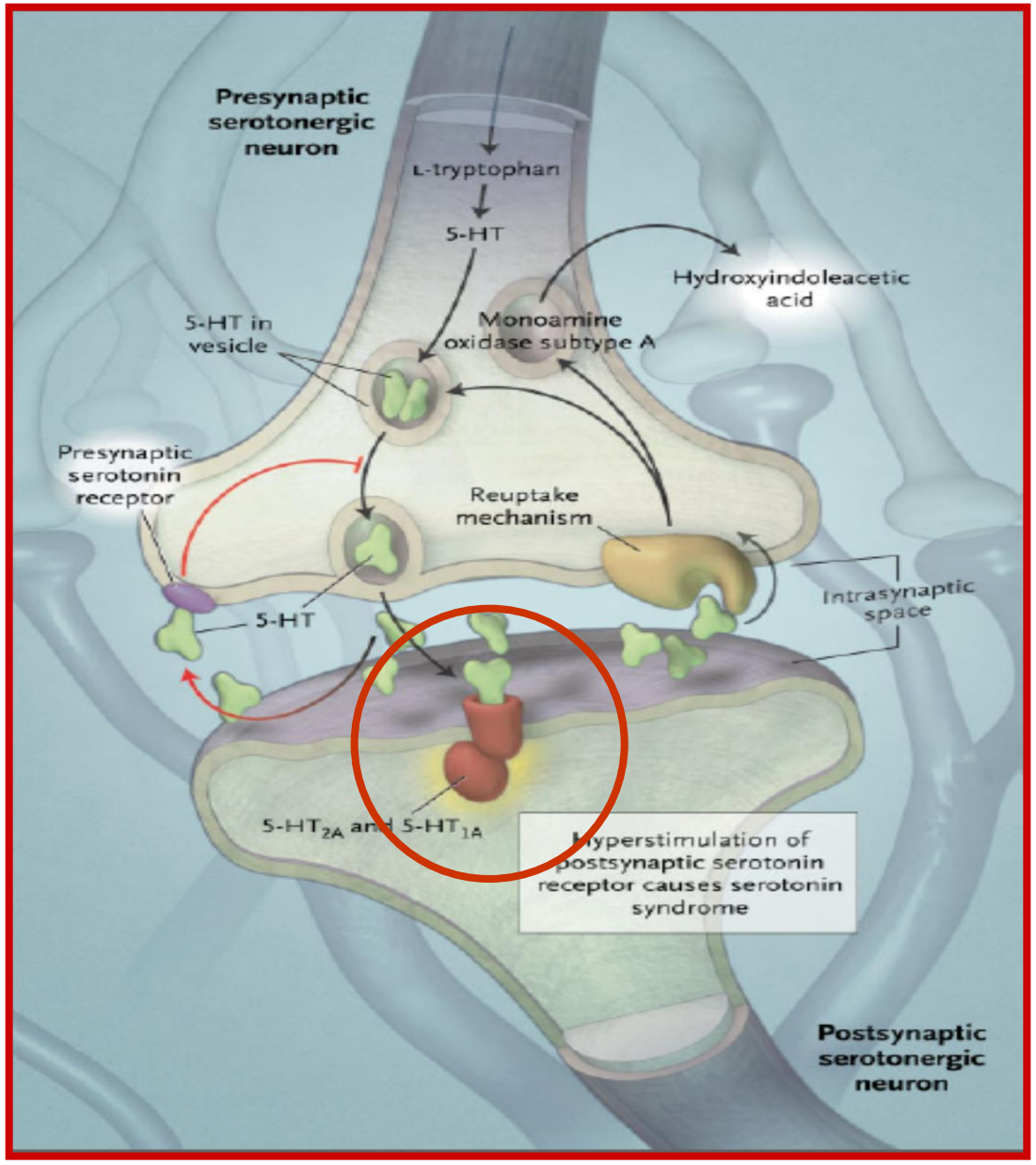


SSRIs - adverse effects

- nausea, vomitus, diarrhoe
- tremor, muscle rigidity, myoclonus
- disturbances of the sexual functions
  - anorexia
  - agitation, insomnia
- Hyperthermia
- risk of bleeding – antiplatelets
- rapid changes in mental status and vital signs
  - suicide as an adverse effect?

Serotonine syndrom





Serotonine syndrom

- it is important to wait up to 6 weeks after medication is stopped, before starting with another drug

- treatment
  - **cyproheptadine**
    5-HT_2 antagonist

SSRI/SNRI Discontinuation Syndrome

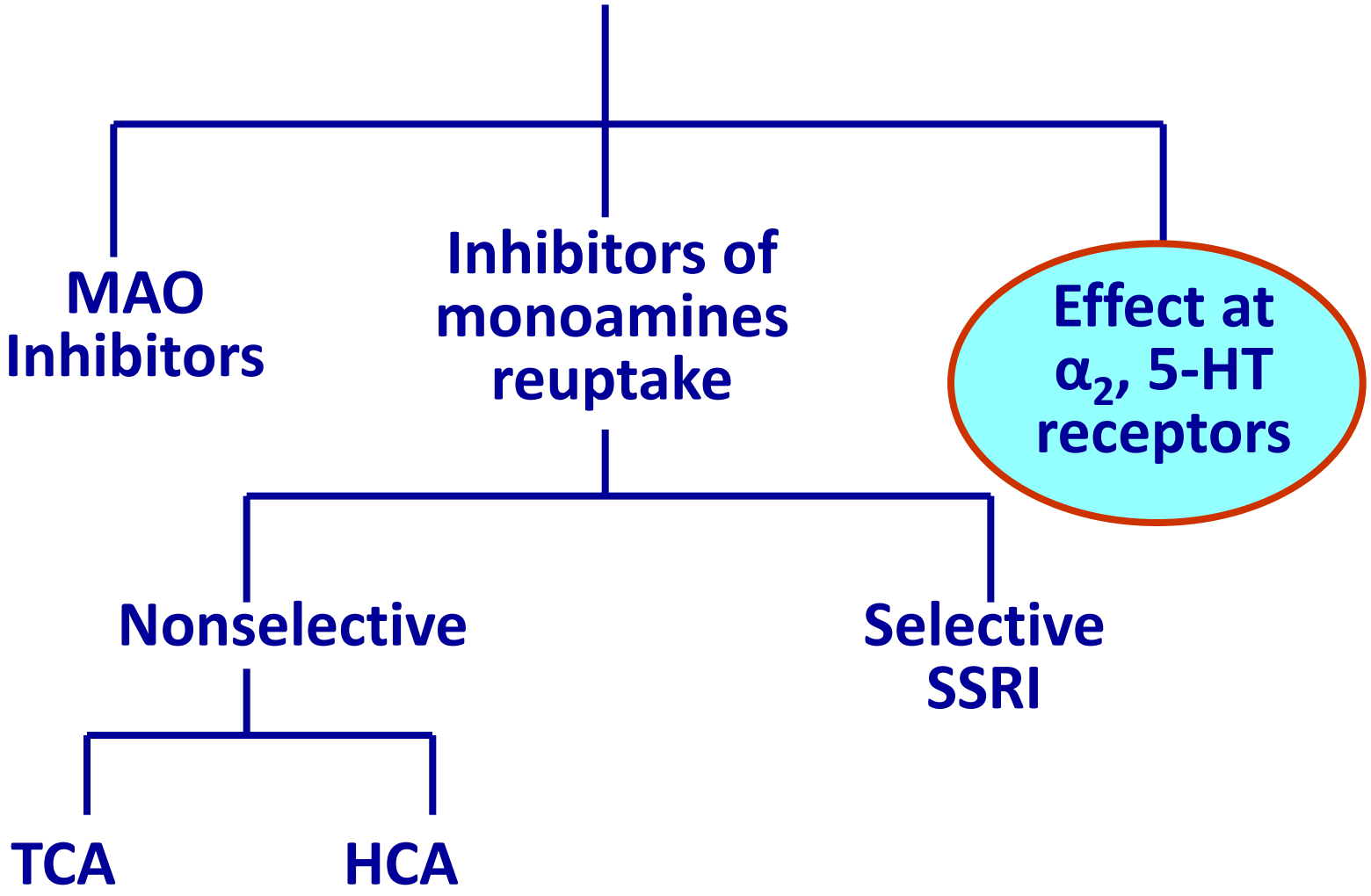
F.I.N.I.S.H.

- **F**lu-like : fatigue, muscle aches, headache, diarrhea
- **I**nsomnia: vivid or disturbing dreams
- **N**ausea
- **I**mbalance: gait instability, lightheadedness, vertigo
- **S**ensory disturbance: paresthesia, “electric shock” sensation, visual disturbance
- **H**yperarousal: anxiety, agitation

- Onset: 24-72 hours + Resolution: 1-14 days
- Incidence: ~ 20 - 40 % (treated at least 6 weeks)

Antidepressants with the influence at receptors

ANTIDEPRESSANTS



Influence also on the NT reuptake

- mianserin

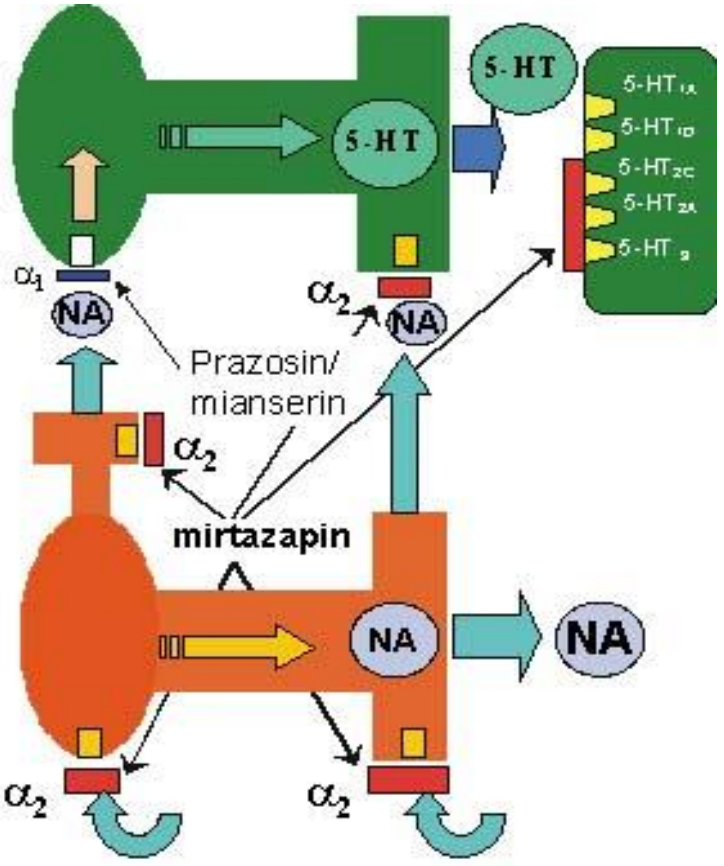
  - it blocks H_1,5-$HT_{1D,2A,2C,3,6,7}$, α_1,α_2

- mirtazapin (NaSSA)

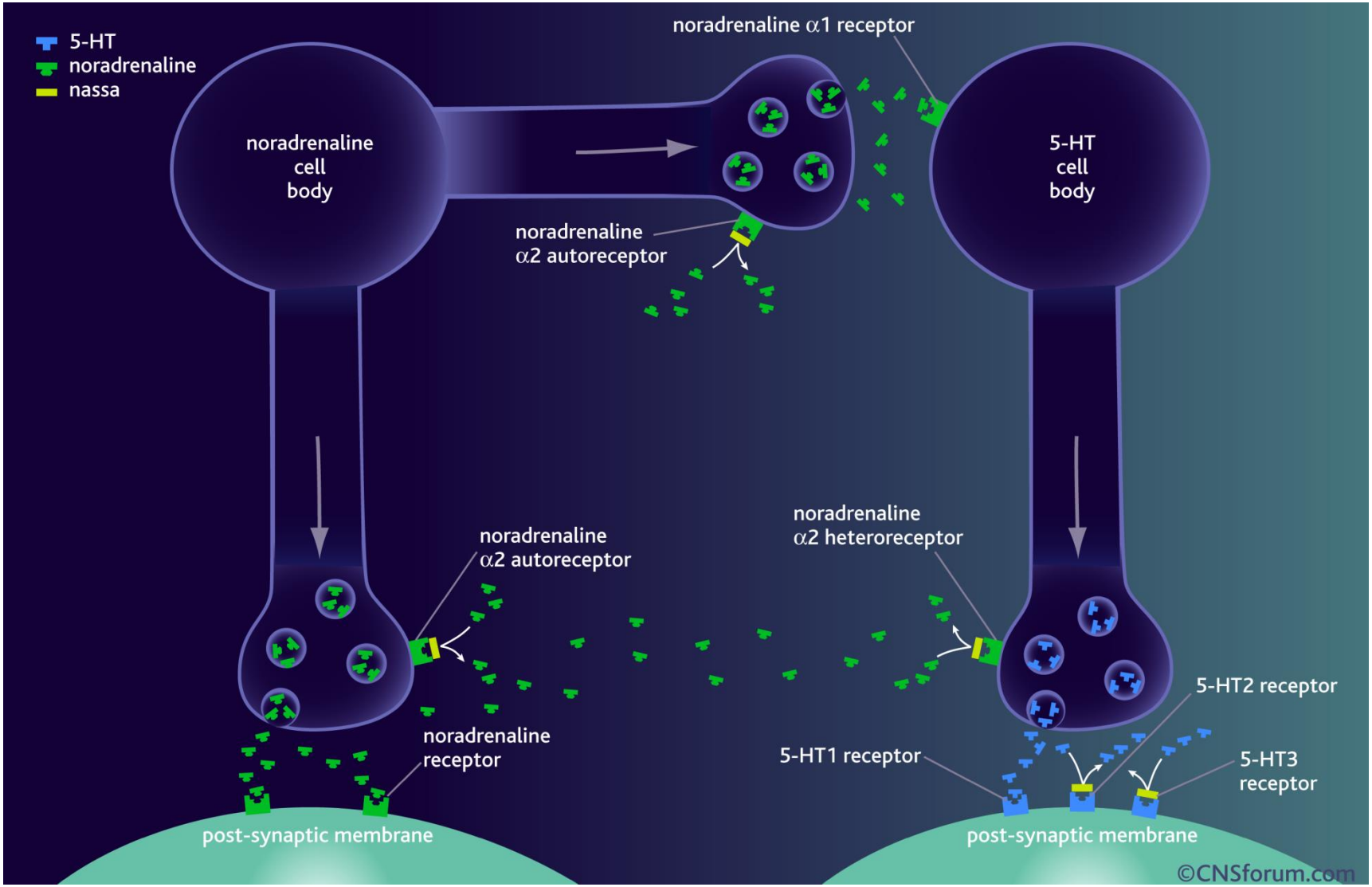
- nefazodone

  - antagonist at 5-HT_2 ,

    5-HT_{1A} , (α_1, α_2, D_2)



NaSSA – mirtazapine – mechanism of action



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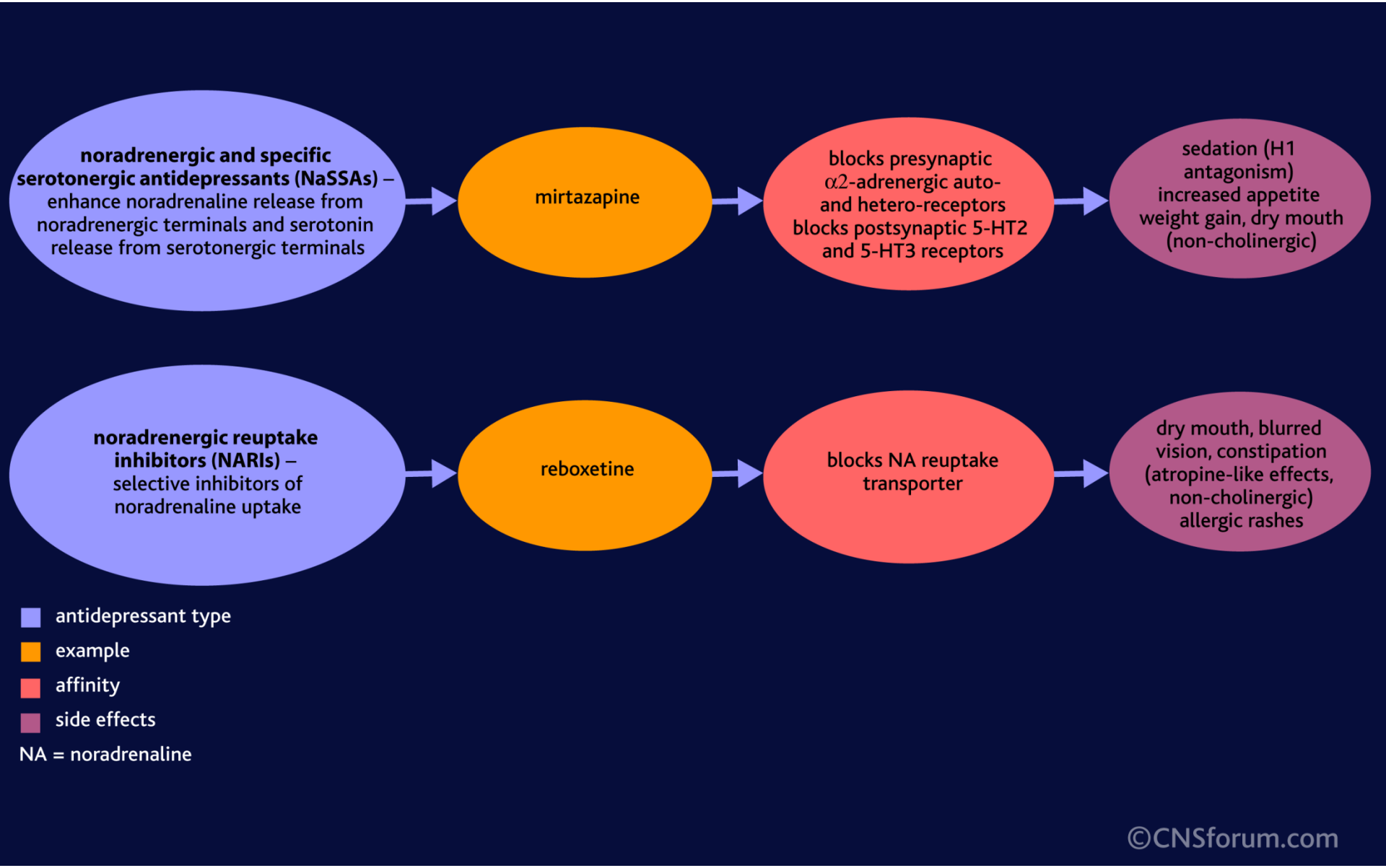

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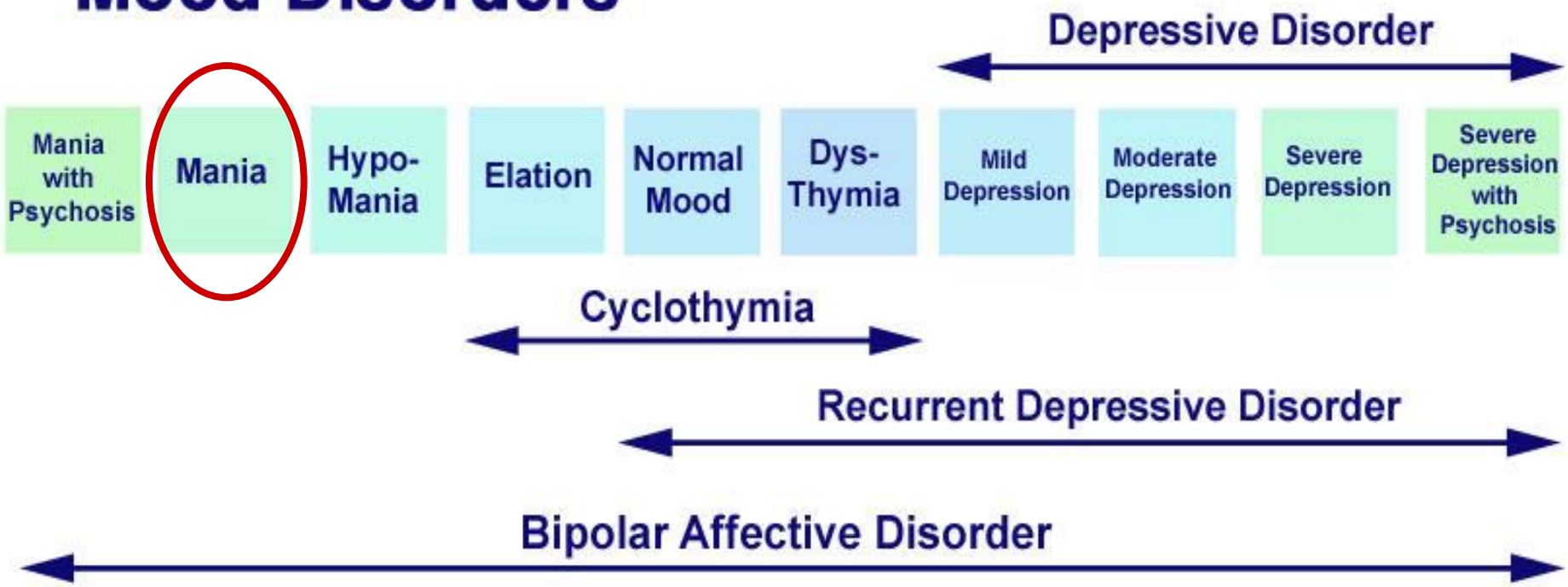
Antimanics or

Mood Stabilizers

Mood Disorders



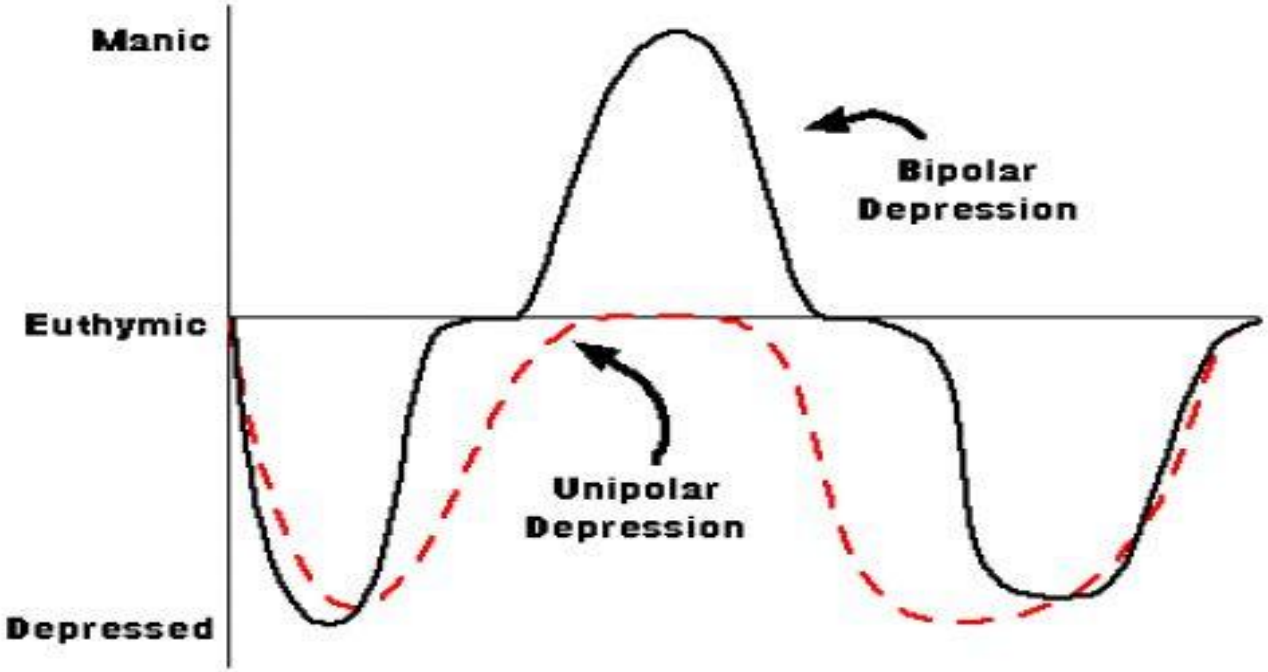
Antimanics or Mood Stabilizers

- are used to treat bipolar disorder
- mood stablizers - decreases not only the manic phase but also the depressed phase of bipolar disorder
- for many years - **lithium**
- more recently – some **antiepileptics**, e.g. carbamazepine and valproic acid
- Atypical neuropetics were also approved (**risperidone, olanzapine, ziprasidone**, etc.)

Antimanics or Mood Stabilizers

Lithium

(CARBOLITH, ESKALITH, LITHONATE, LITHOTABS)



Antimanics or Mood Stabilizers

Anticonvulsants

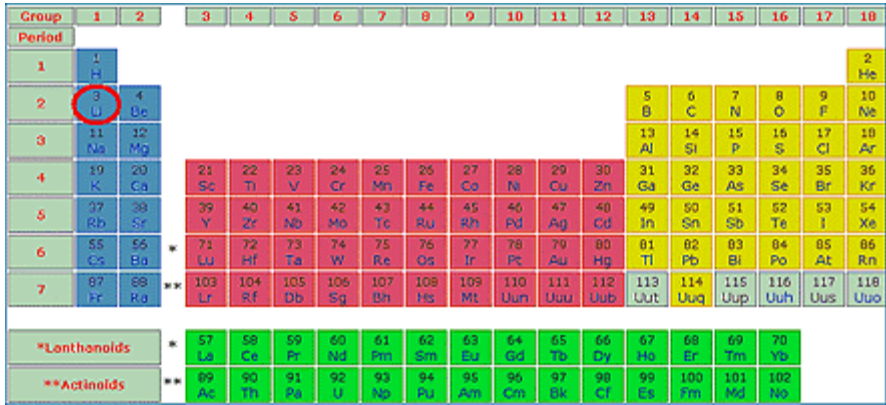
- Valproic acid
- Carbamazepine
- Oxcarbazepine
- Lamotrigine
- Topiramate
- Zonisamide
- Gabapentin and pregabalin
- Levetiracetam

Lithium

1940s - an Australian psychiatrist John Cade - lithium salt would calm his manic patients

Li - was not available commercially till the 1970s because it was an element and could not be patented.

Li - as a *mood stabilizer* or an *antimanic* rather than an antidepressant because it will relieve manic symptoms and block both mania and depression but it cannot treat depression



Lithium - Pharmacokinetics

- rapid absorption - can be a problem
- peak 30 min-2 hrs
- most Li is now in a slow release forms
- a low therapeutic index - blood levels need to be carefully monitored
- is excreted unchanged
- half-life of 12-21 hrs (36 hrs)

Possible mechanisms of Li action

-alteration of the balance of ions Cl- and K+

-stabilizes membranes – less excitable

-alteration of the function of 5-HT, NE, DA, ACh, and GABA

-inhibition of the second-messenger cAMP

-down-regulation of NE receptors

-alteration of gene expression

Lithium – adverse effcets

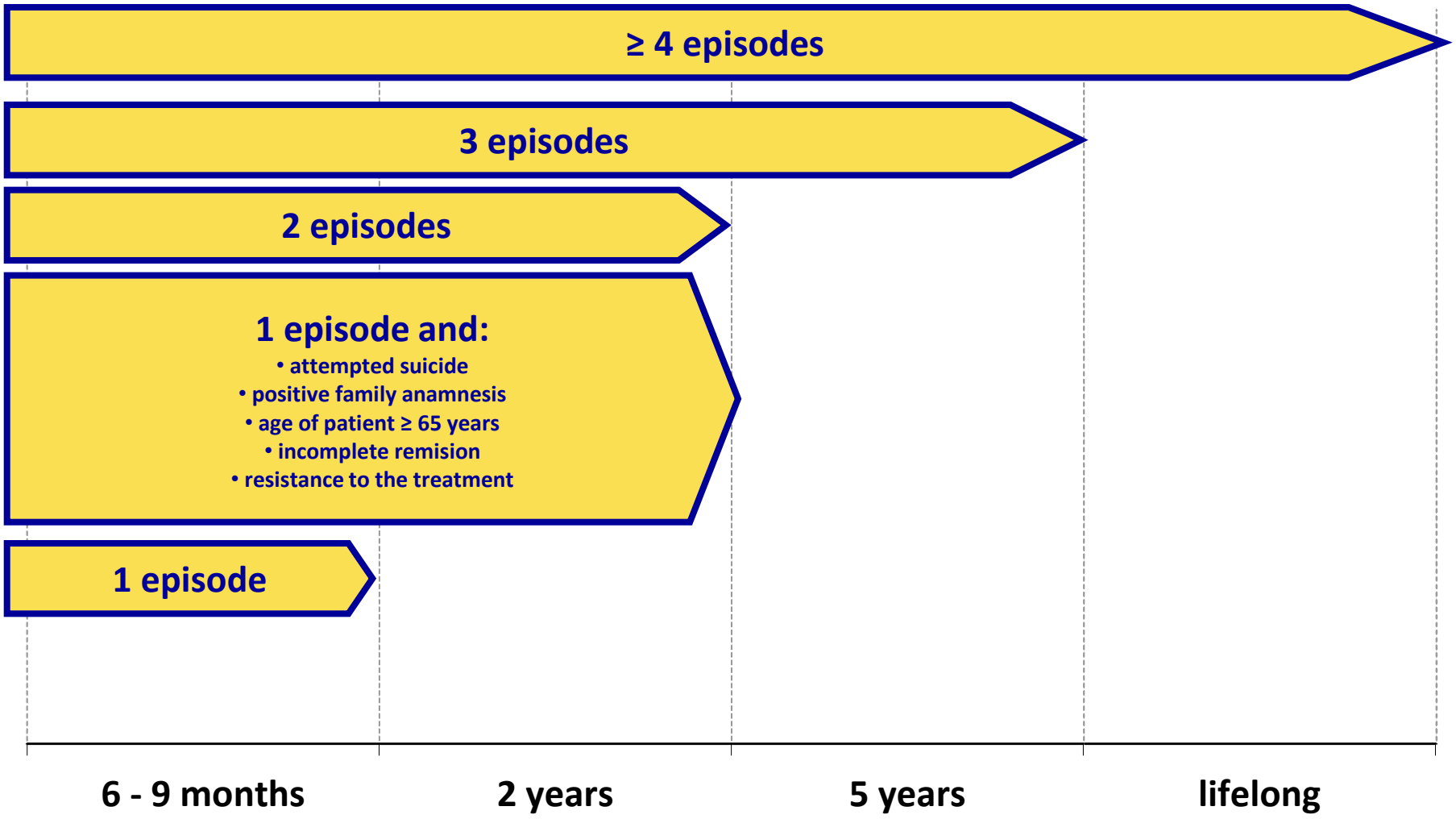
- hand tremors
- increased thirst
- nausea and vomiting
- diarrhea
- swelling
- weight gain
- fatigue
- muscle weakness
- hypothyroidism
- strong teratogen
- long-term use - kidney damage or failure

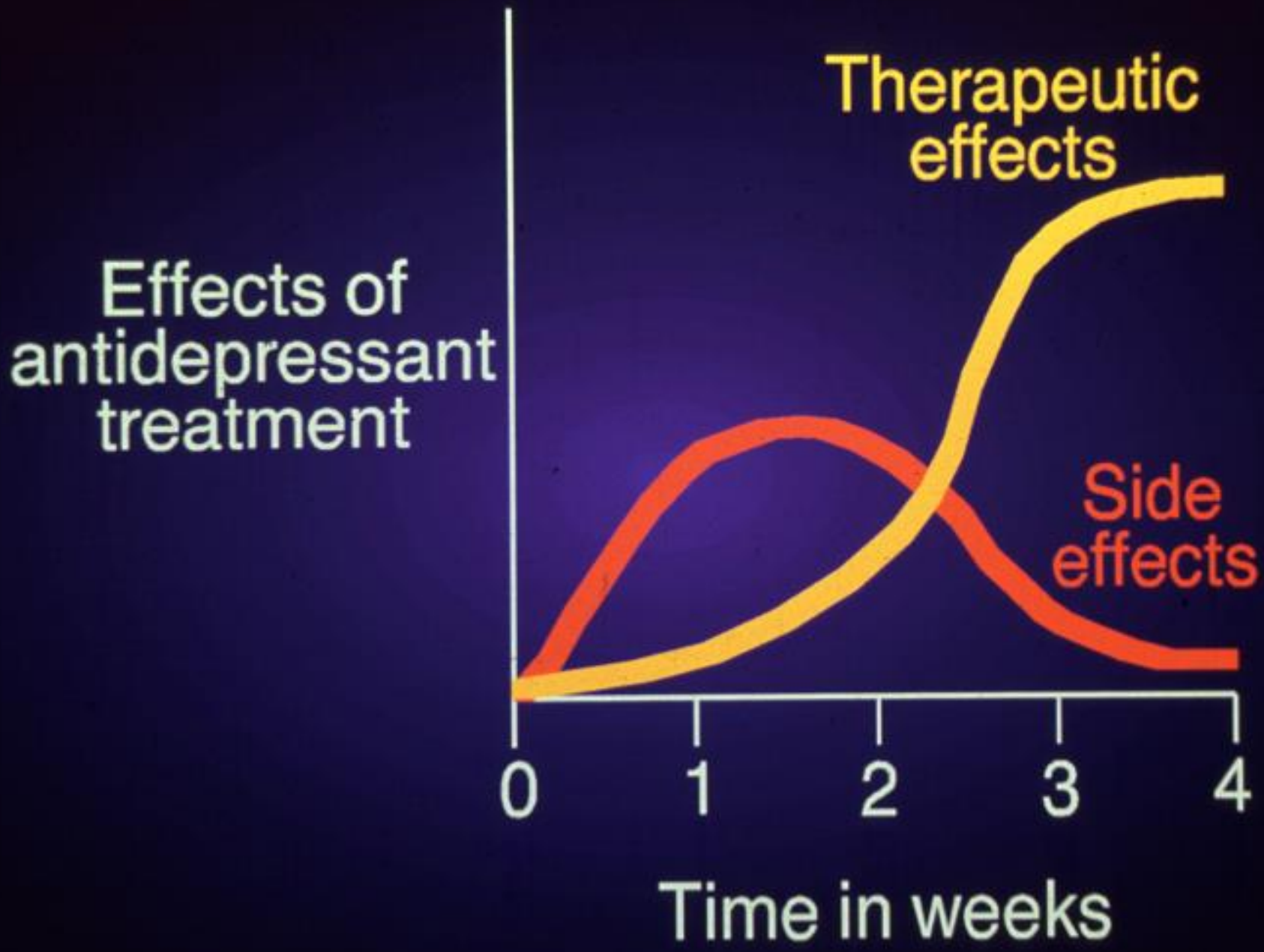
Li - toxic drug - adverse reactions are dose- and concentration-dependent

Depression therapy

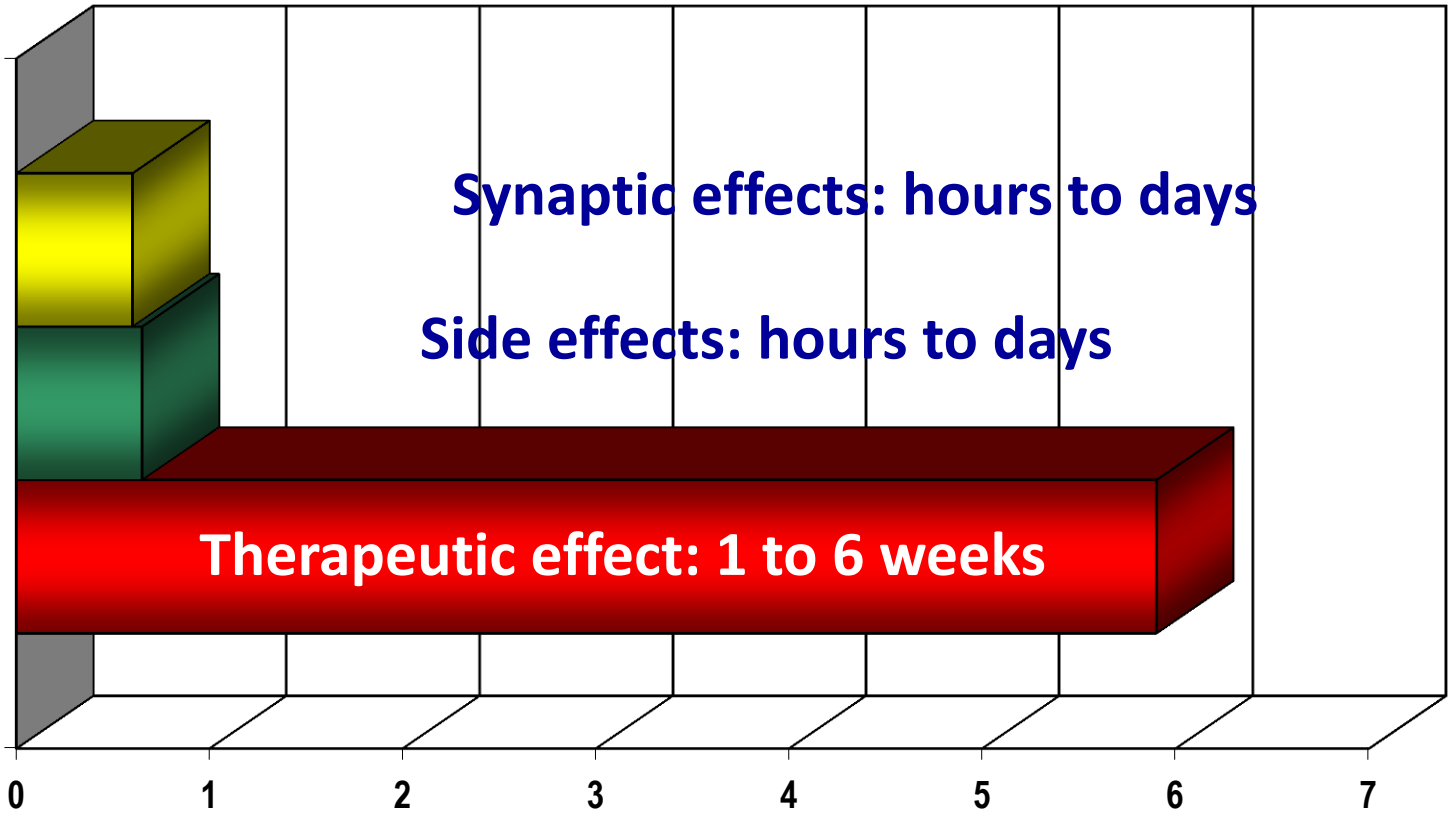
pharmacotherapy - antidepressants

Recommended duration of the treatment




Therapeutic effects
Effects of antidepressant treatment
Side effects
0
1
2
3
4
Time in weeks

After Dosing Antidepressants (days)



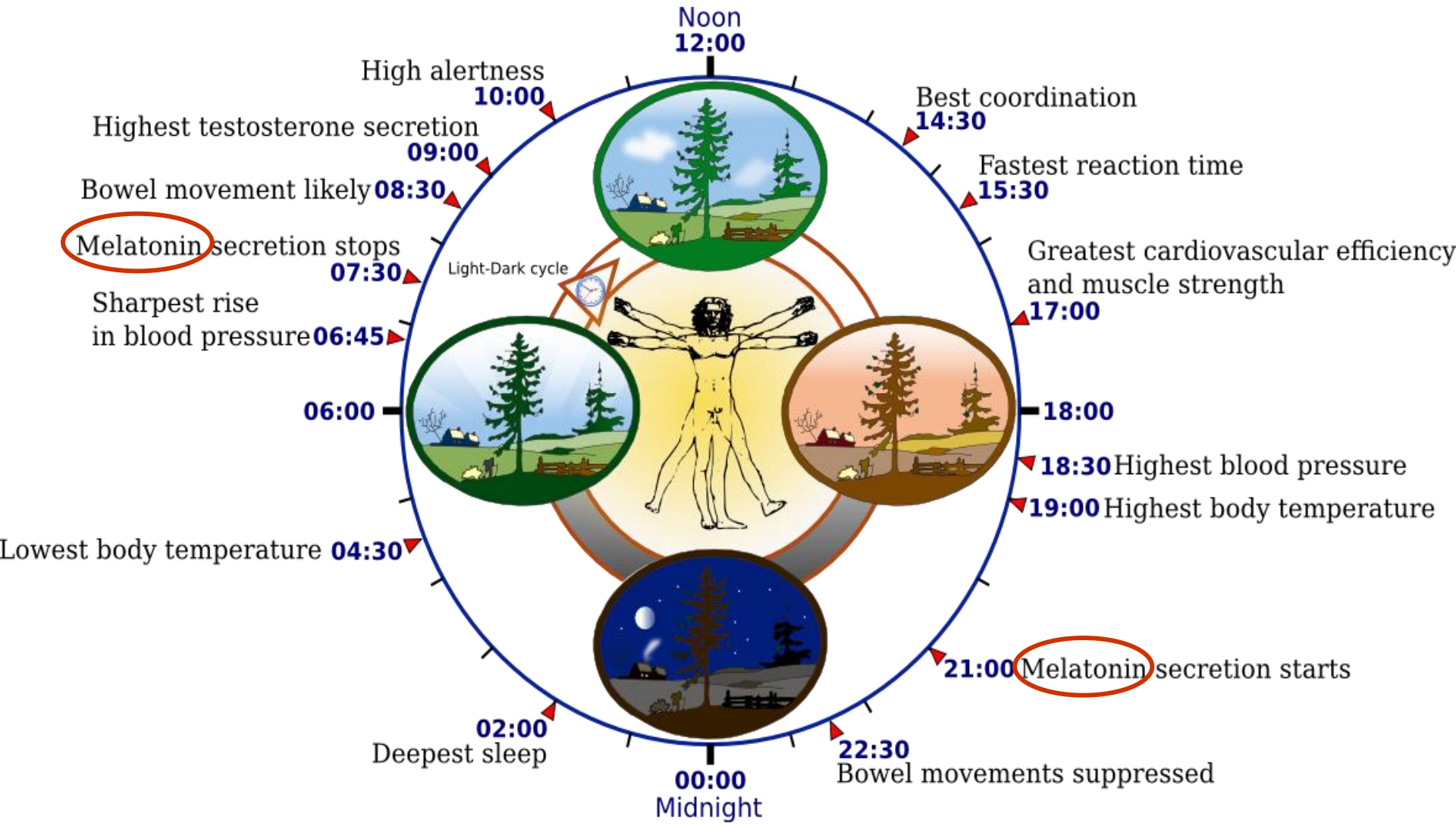
Other ways of depression therapy

- psychotherapy
- phytotherapy
- phototherapy
- sleep therapy
- electroconvulsive treatment

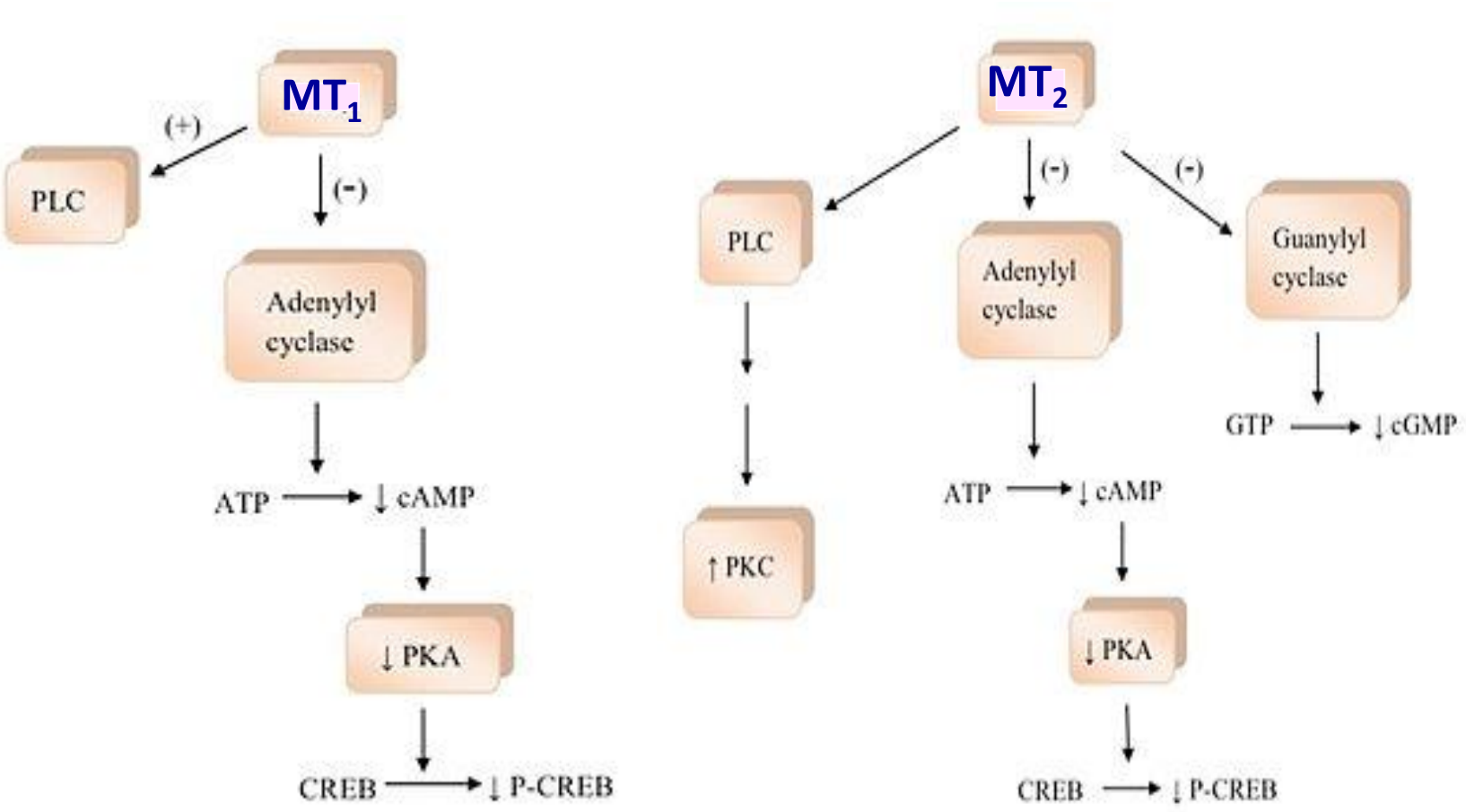
HYPERICUM PERFORATUM
St. John's wort

- hypericine, hyperphorine
- acts on 5-HT, NA, DA, GABA
- it also has anti-viral and anti-inflammatory effects
- inducer of P-450
- photosensitivity!!

Depression and sleep therapy



Melatonin receptors



Depression and sleep therapy

- depression - ↓↓ levels of melatonin

- **melatonergic agonists**

- resynchronization of the circadian rhythm

- **melatonin** (CIRCADIN)

- **ramelteon** (ROZEREM)

  - agonist of MT_1/MT_2 melatonin receptors

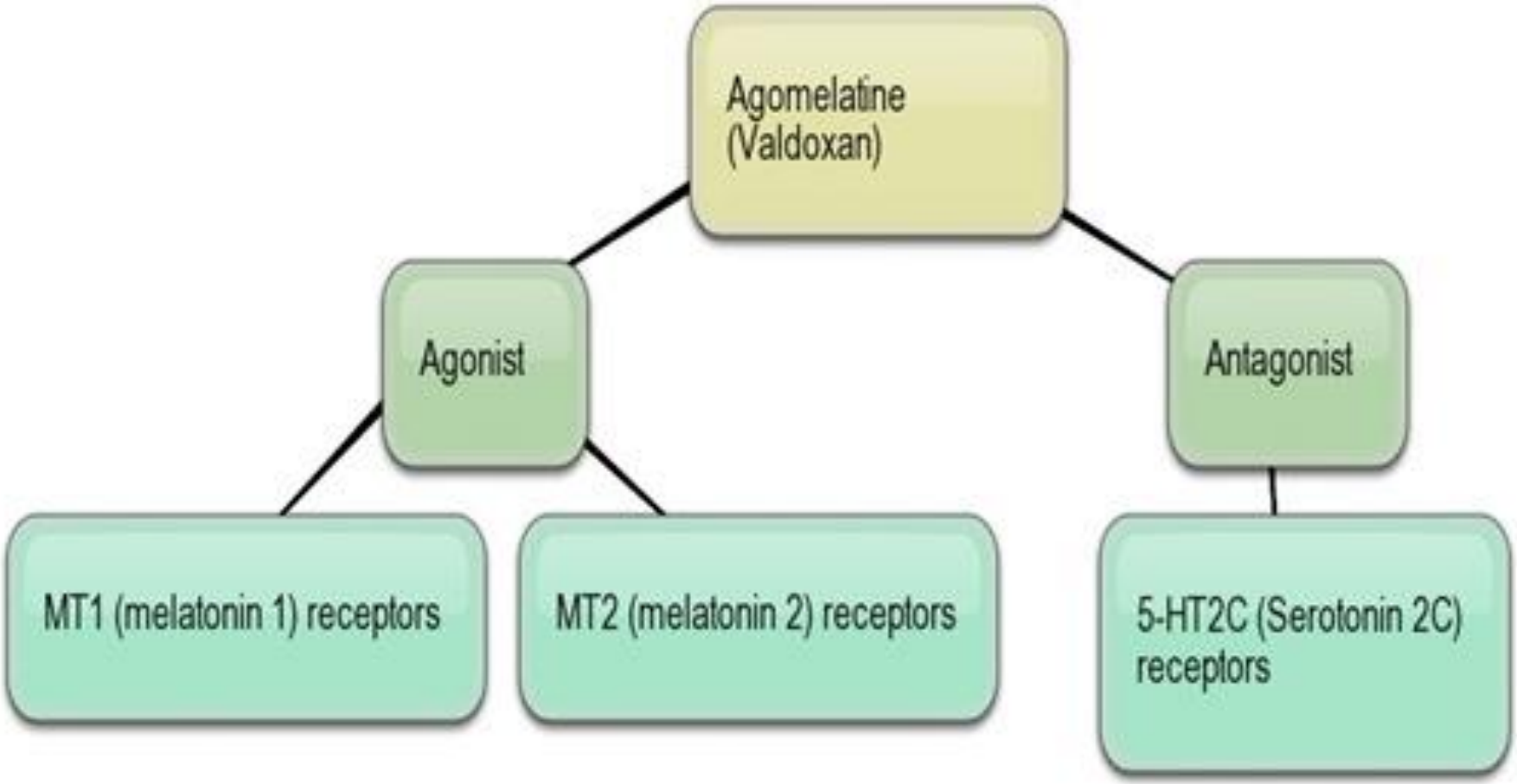
  - induction of sleep, ↑ time of sleep

Depression and sleep therapy

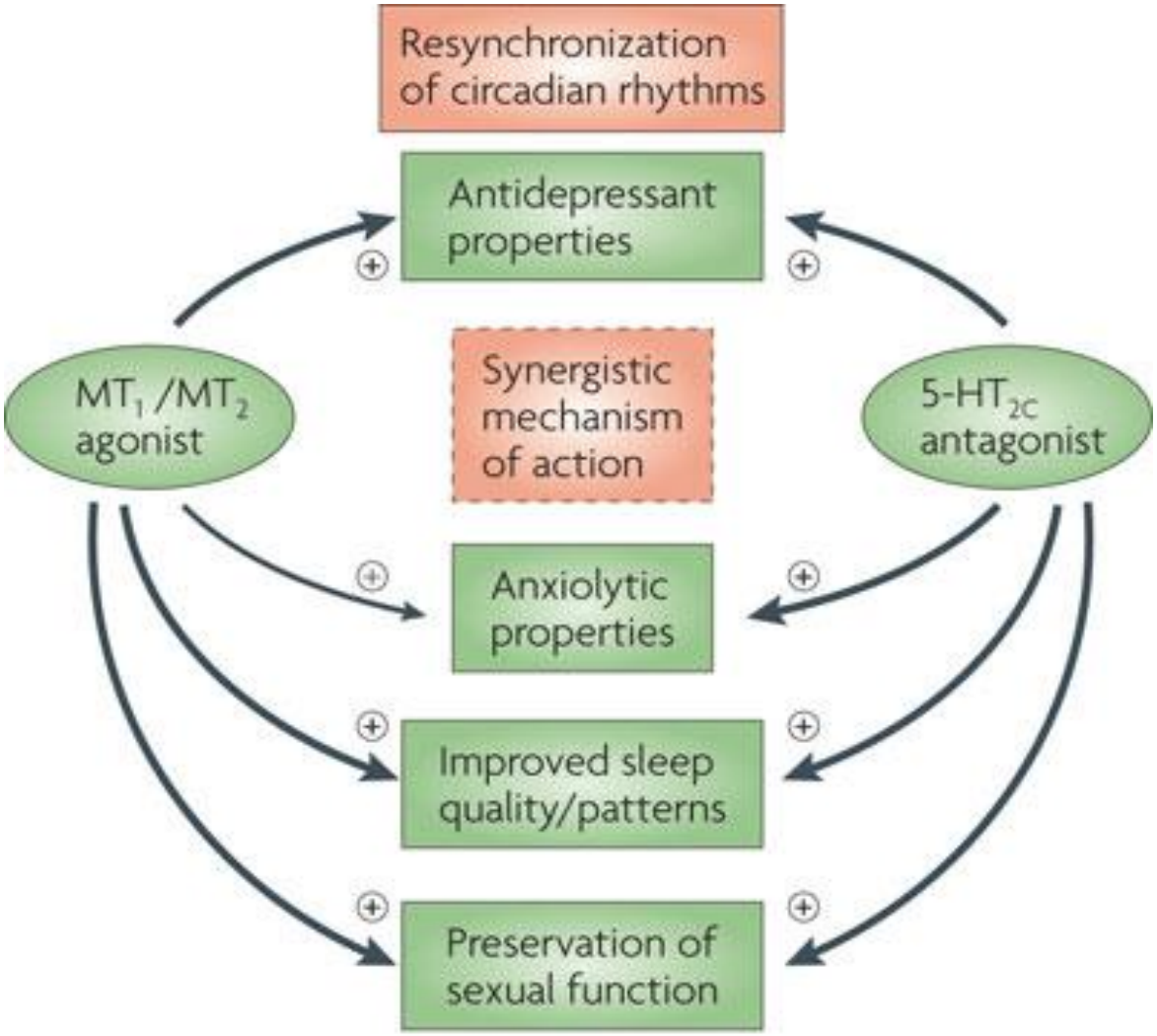
- **agomelatine** (VALDOXAN, THYMANAX)
  - ↑ NA, DA level and neurotransmission
  - antagonistic activity at 5-HT_{2C}
  - effect on the transcription factors

    "clock genes"
  - excellent safety profile

Agomelatine



Agomelatine



Nature Reviews | Drug Discovery

Some practical hints about antidepressants

- **Imipramine** (TCA) can be used for **enuresis nocturna** (bed-wetting in children older than 6 years), as well as for management of **chronic pain** and **ADHD**
- **Prevent use of TCAs in bipolar disorder** (manic-depressive patients) – risk of switching to manic behavior)
- **Prevent use of TCAs in depressed patients with suicidal risk** – to narrow therapeutic index (5x maximal daily dose can lead to death)
- **Prevent use of TCAs in patients with glaucoma, and urinary retention**
- If **neuropathic pain** accompanies depression, **duloxetine** can be used
- If **obsesive-compulsive disorder** is a problem, **SSRIs** can be used (e.g. **fluvoxamine**); effective can be also one of TCAs - **clomipramine**
- **SSRIs and MAOI** need **wash-out period** for min 2 weeks (6 weeks for **fluoxetine**)
- If **sexual dysfunction** is a problem in depression therapy, **mirtazapine** or **bupropion** are preferred (**bupropion** is effective also in nicotine dependence withdrawal)
- **Discontinuation syndrome** by SSRI and SNRI is more prominent in drugs with shorter half-life and with inactive metabolites
- Be careful with **SSRI** in children and teenagers – increased **risk of suicidium**
- **Trazodone** can be useful in depressed patients with **insomnia**