OBAT ANTIDEPRESI

Unipolar Depression (Major Depression)

Bipolar Disorder (Manic Depression)

DEPRESI

- Definisi:gangguan alam perasaan (mood) yang ditandai dengan kemurungan dan kesedihan yang mendalam dan berkelanjutan sehingga hilangnya kegairahan hidup.
- Bisa mrpk ggn.psikosomatik murni maupun ko-morbiditas (bersamaan peny.medis atau kondisi medik sebelumnya).

Prevalensi Depresi pada Beberapa Penyakit

Penyakit	Prevalensi
Penyakit Jantung koroner	18 – 23%
Stroke	23 – 29%
Diabetes mellitus	9 – 27%
Parkinson disease	2 – 51%
HIV	4 – 18%
Arthritis reumatoid	12 – 28%
Kanker	6 – 25%

Etiologi Depresi: NEUROTRANSMITTER

- Menurunnya pelepasan dan transport serotonin, atau menurunnya kemampuan neurotransmitter serotonergik.
- Menurunnya pelepasan atau produksi epinefrin; terganggunya regulasi aktivitas norepinefrin dan meningkatnya aktivitas alfa 2 adrenoreseptor presinaptik.
- Menurunnya aktivitas dopamin.
- Meningkatnya aktivitas asetilkolin.

Etiologi depresi

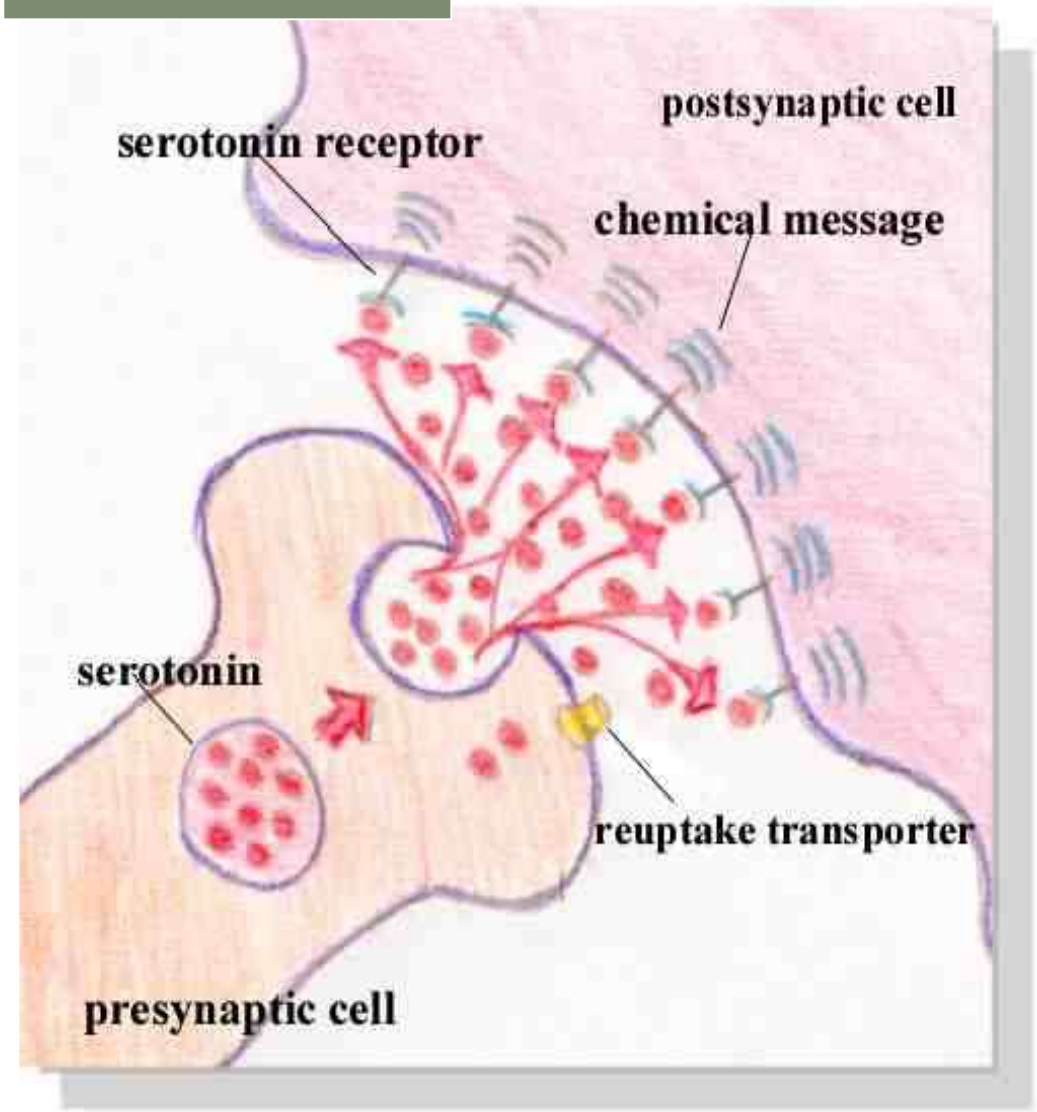
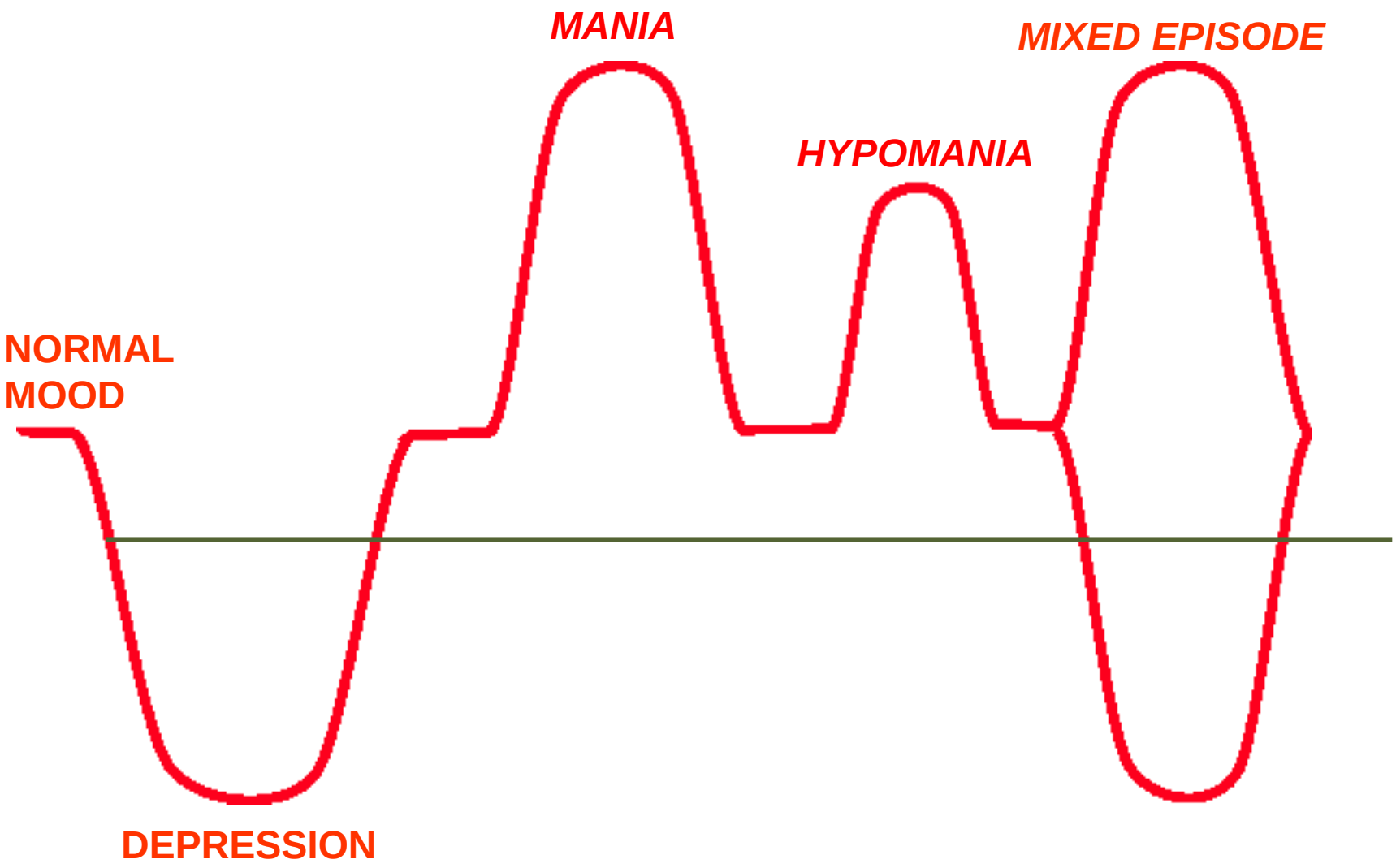


Figure 1
Image by Nancy Schimelpfening

- Serotonin yang diproduksi tidak cukup
- reseptor yang menerima serotonin tidak cukup (sdkt)
- Serotonin diambil kembali (re-uptake)terlalu cepat sebelum dapat mencapai reseptornya
- Preskusor kimia untuk membentuk serotonin mungkin juga kurang
- Molekul yang membantu produksi serotonin mungkin juga terlalu sedikit jumlahnya.

DIAGNOSIS DEPRESI

Kriteria Depresi DSM-IV
Lima atau lebih dari gejala berikut tampak hampir tiap hari selama minimal 2 minggu dan menunjukkan perubahan fungsi dibanding sebelumnya: Mood depresi Kehilangan perhatian atau minat terhadap sesuatu yang menyenangkan Kehilangan atau penambahan berat badan Insomnia atau hipersomnia Agitasi atau retardasi psikomotor Fatig atau kurang energi Merasa tidak berguna atau rasa bersalah berlebihan Penurunan konsentrasi/sulit membuat keputusan Pikiran tentang kematian/ide bunuh diri



Stahl S M, Essential Psychopharmacology (2000)

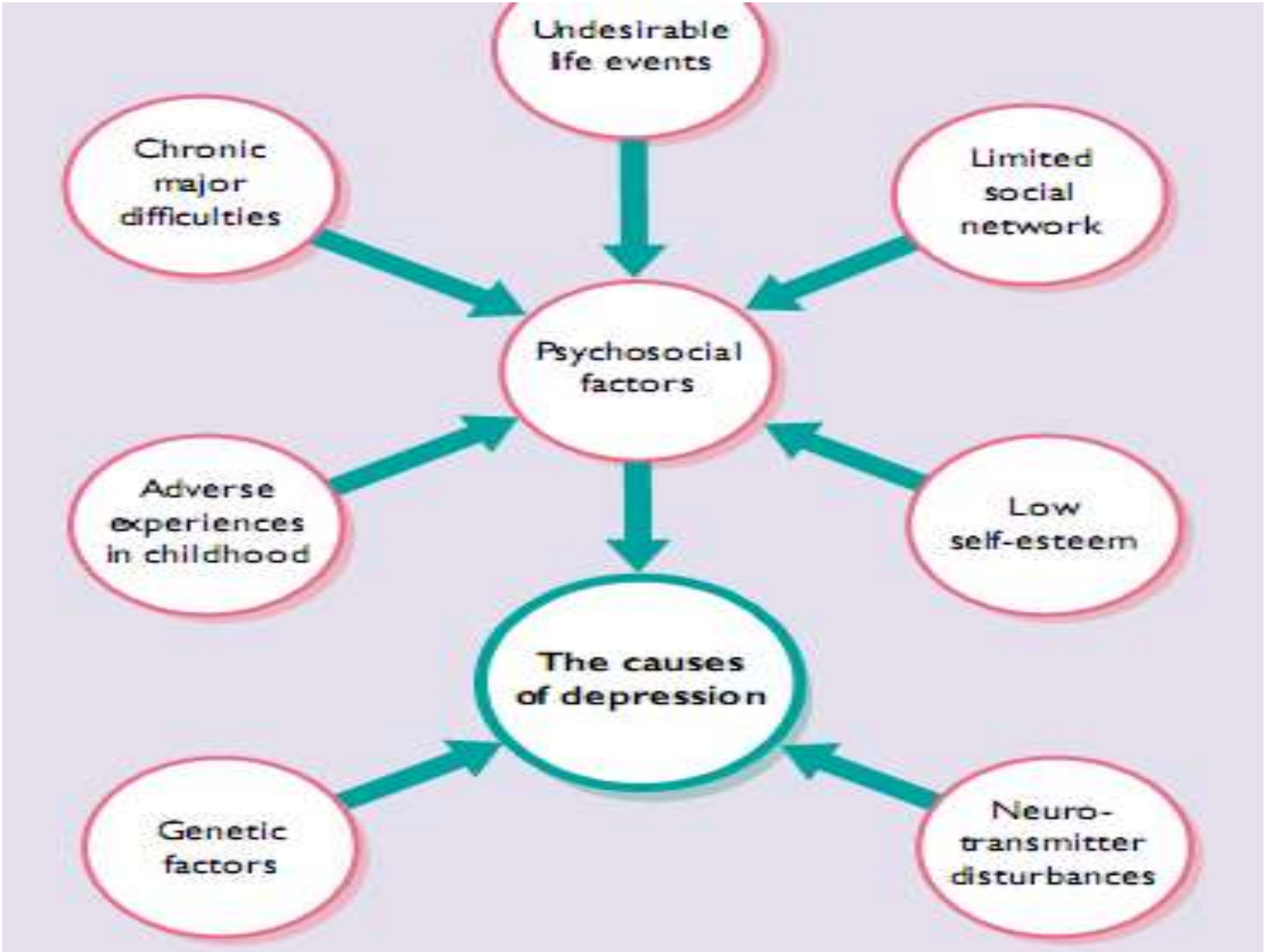
Symptoms of Depression

- Changes in mood, sleep, cognition
- Depressed mood (in children may be irritability
- Diminished Interest or pleasure in activities (Anhedonia)
- Significant weight loss or gain
- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Fatigue or loss of energy
- Feelings of worthlessness or inappropriate guilt
- Diminished ability to think of concentrate
- Suicidal thoughts or behavior
- Appetite Disturbance

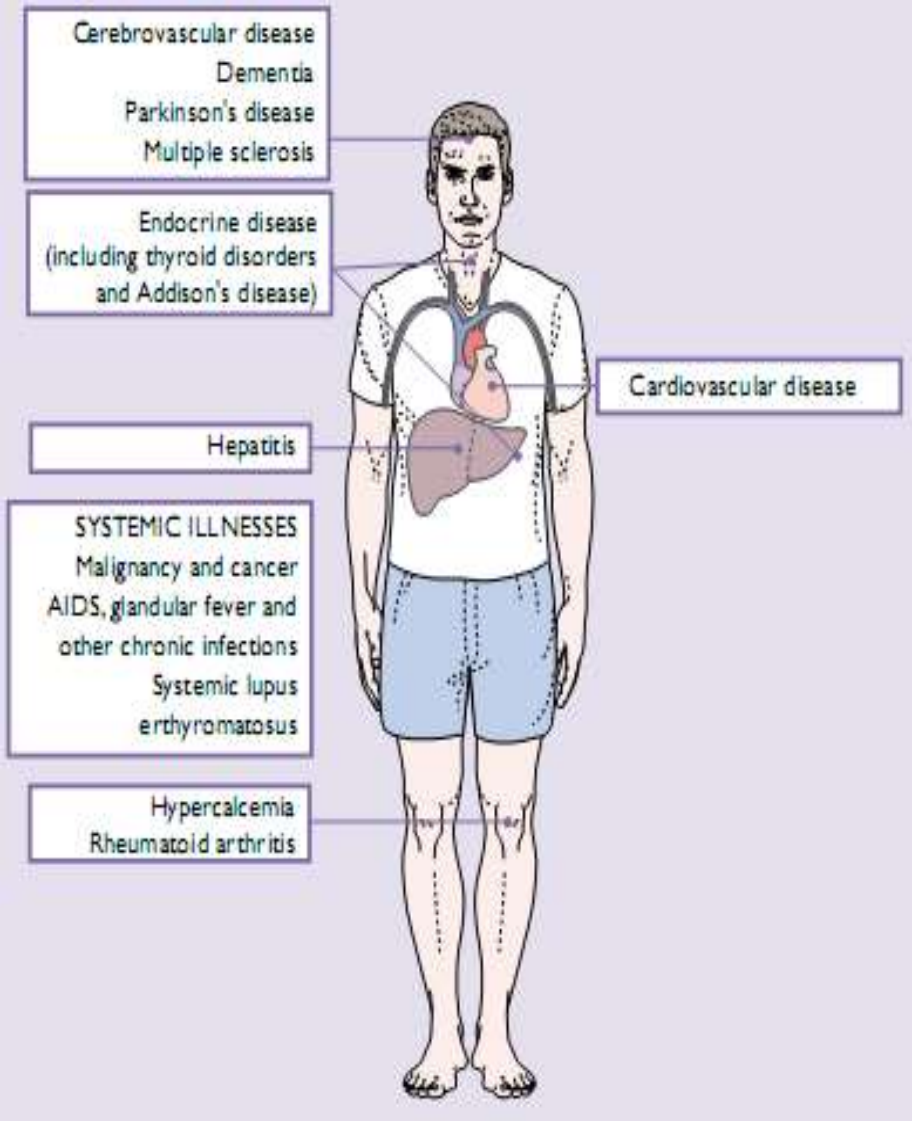
Symptoms of Mania

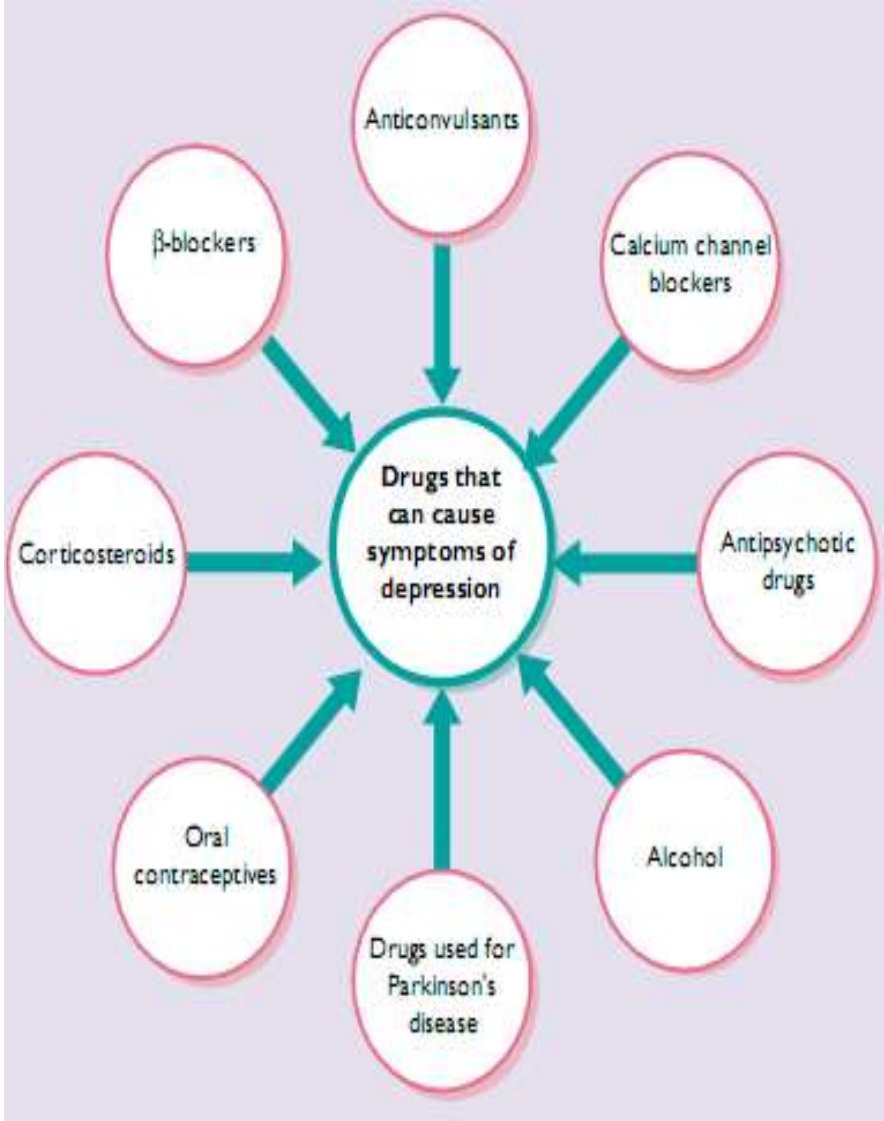
- Abnormally and persistently elevated mood
- Inflated self-esteem or grandiosity
- Decreased need for sleep
- Talkativeness or pressure to keep talking
- Flight of ideas
- Distractibility
- Increase in goal-directed behavior
- Excessive involvement in pleasurable activities

Penyebab Depresi

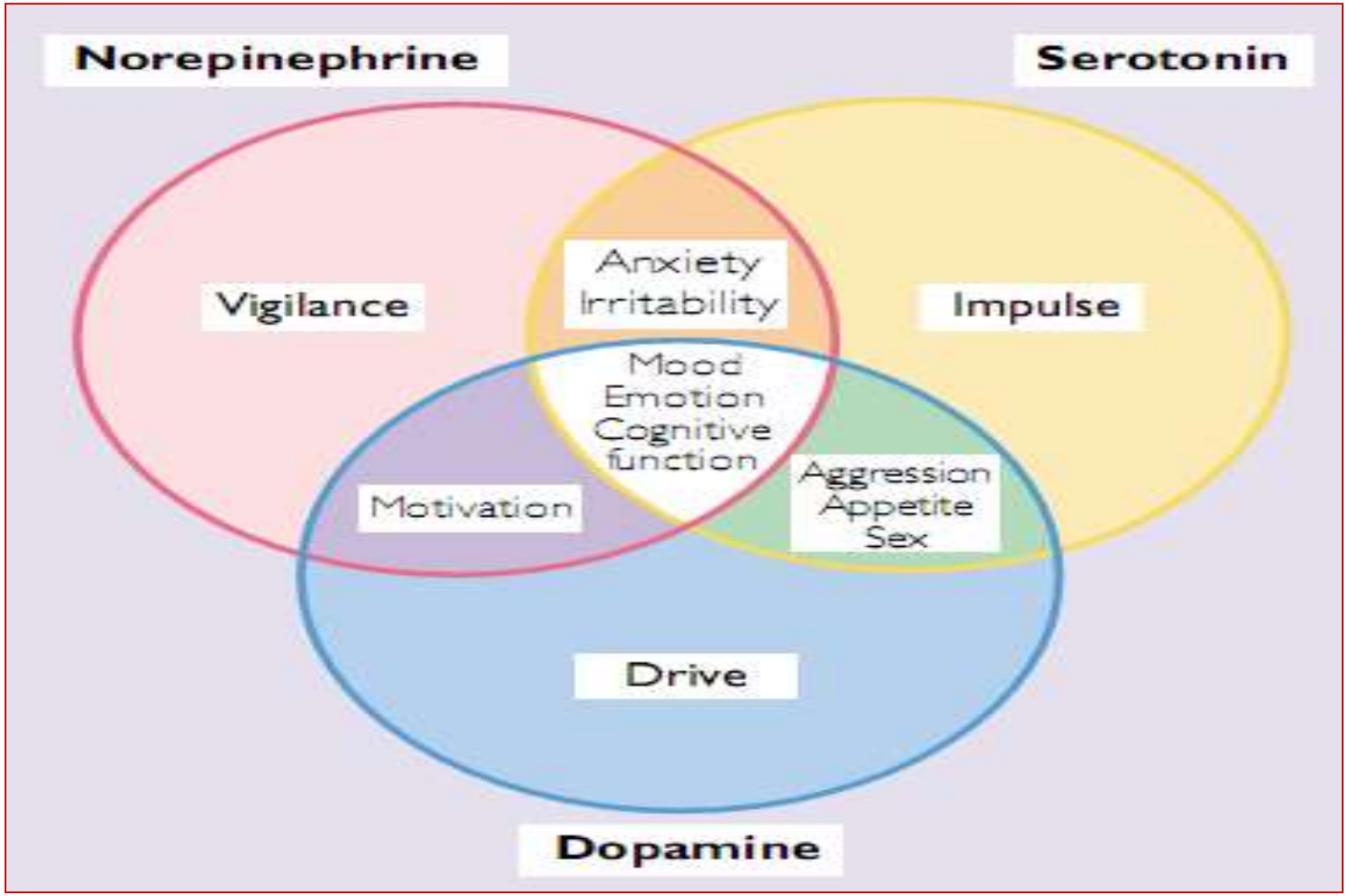


Physical illness & Drug that associated with depression





Neurotransmitter yg berperan dalam psikopatologi

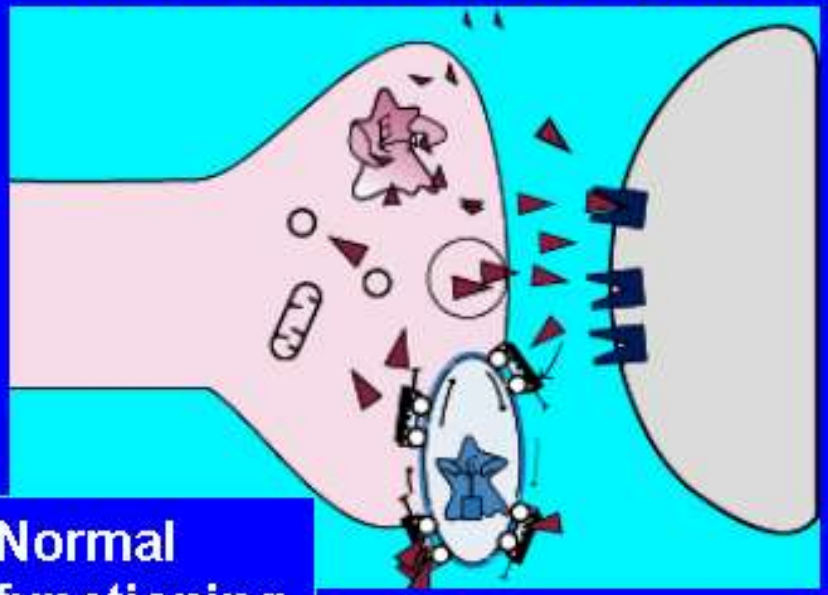


Catecholamine Hypothesis dari gangguan affective

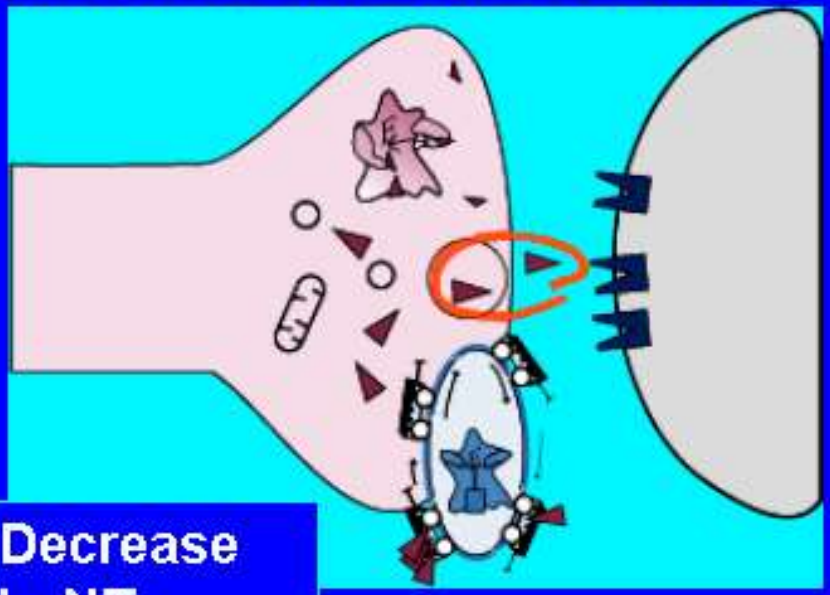
- Meningkatnya aktifitas catecholaminergic berkaitan dengan elevated mood
- Agonists (e.g., amphetamine) → menaikkan mood
- Amine-depleting drugs (e.g., reserpine)→ menekan mood

Depresi berkaitan dengan menurunnya aktifitas catecholaminergic

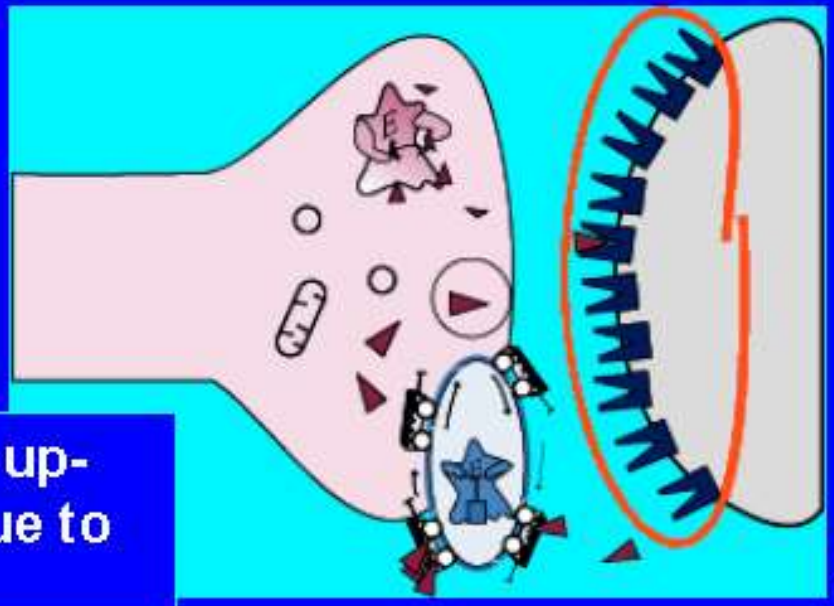
Monoamine Receptor Hypothesis of Depression



Normal functioning



Decrease in NT



Receptors up-regulate due to lack of NT

Stahl S M, Essential Psychopharmacology (2000)

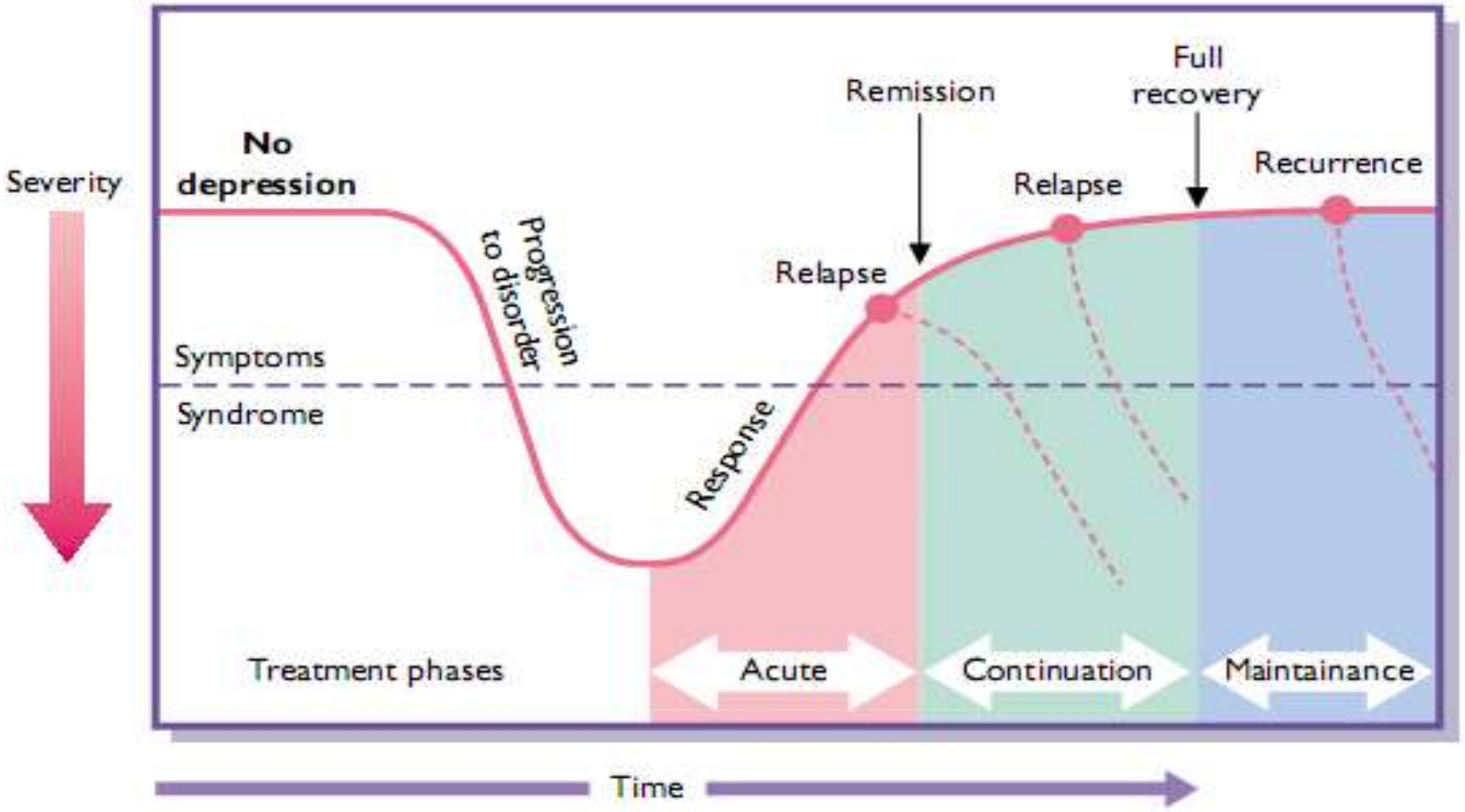
Penatalaksanaan Depresi

- Psikoterapi
  - Terapi yang digunakan untuk menghilangkan keluhan dan mencegah kambuhnya gangguan psikologik atau pola perilaku mal adaptif
- Psikofarmaka
  - Dengan menggunakan antidepresan:
    - SSRI
    - Gol Trisiklik
    - MAOI
    - dll

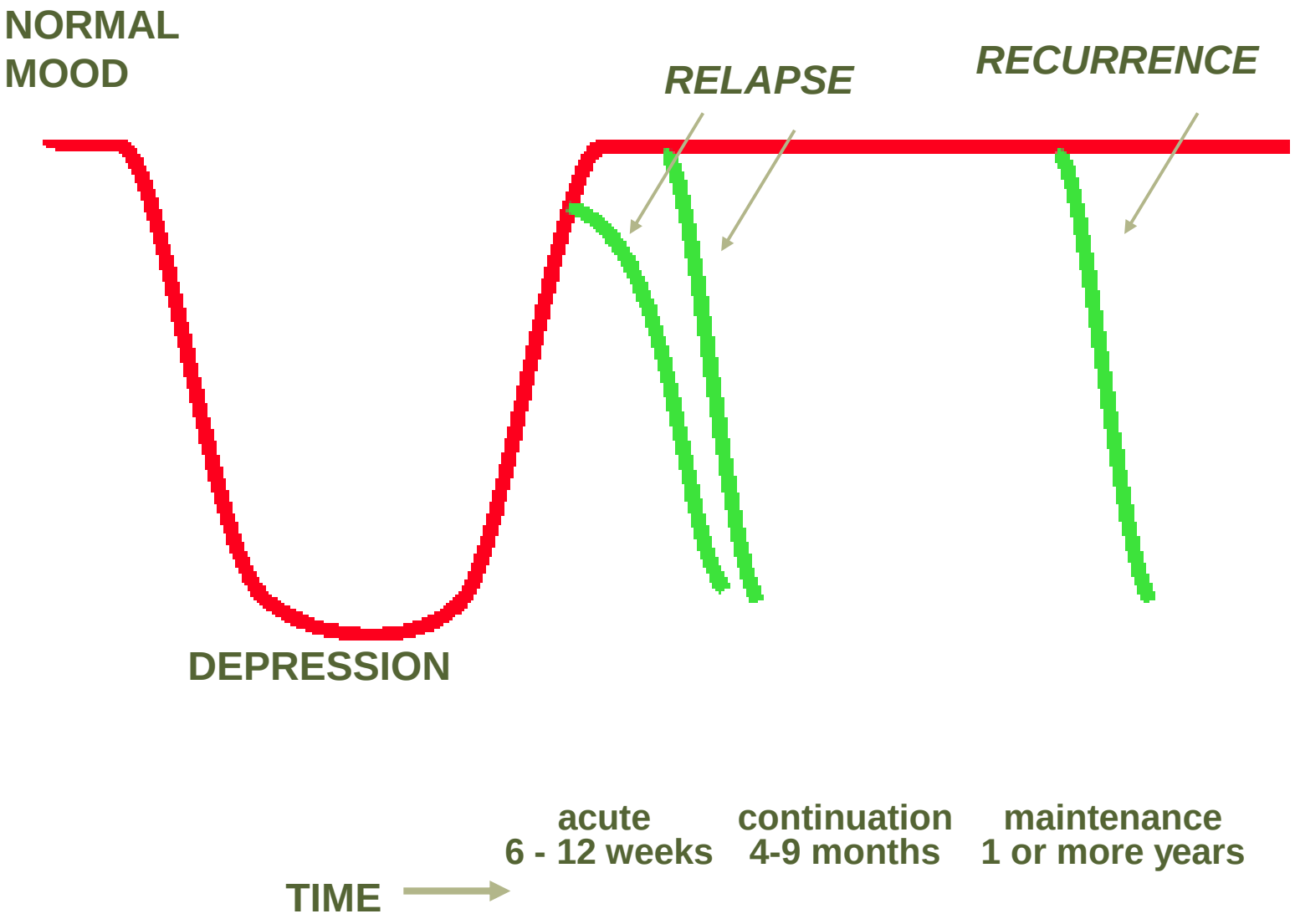
Fase Pengobatan Depresi

- Fase akut: awal pengobatan sampai tjd remisi total.
- Fase lanjutan: dimulai saat remisi dan berlangsung 2 - 4 bulan.
- Fase pemeliharaan: segera setelah terapi fase lanjutan dan lamanya bervariasi.

Treatment phases in depression



Adapted with permission from Kupfer DJ.Long-term treatment of depression.J Clin Psychiatry 1991;52 (suppl):28ñ34



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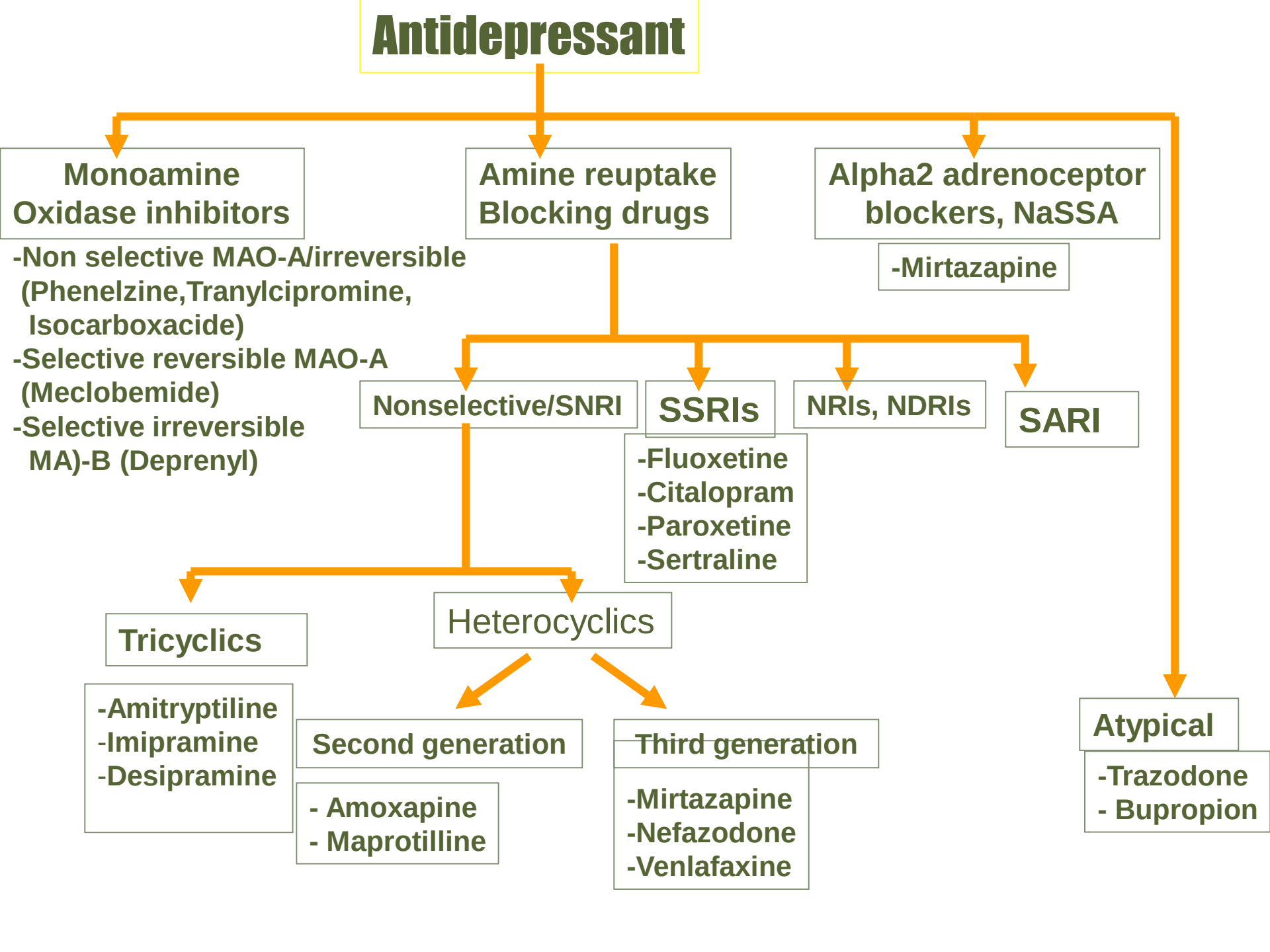
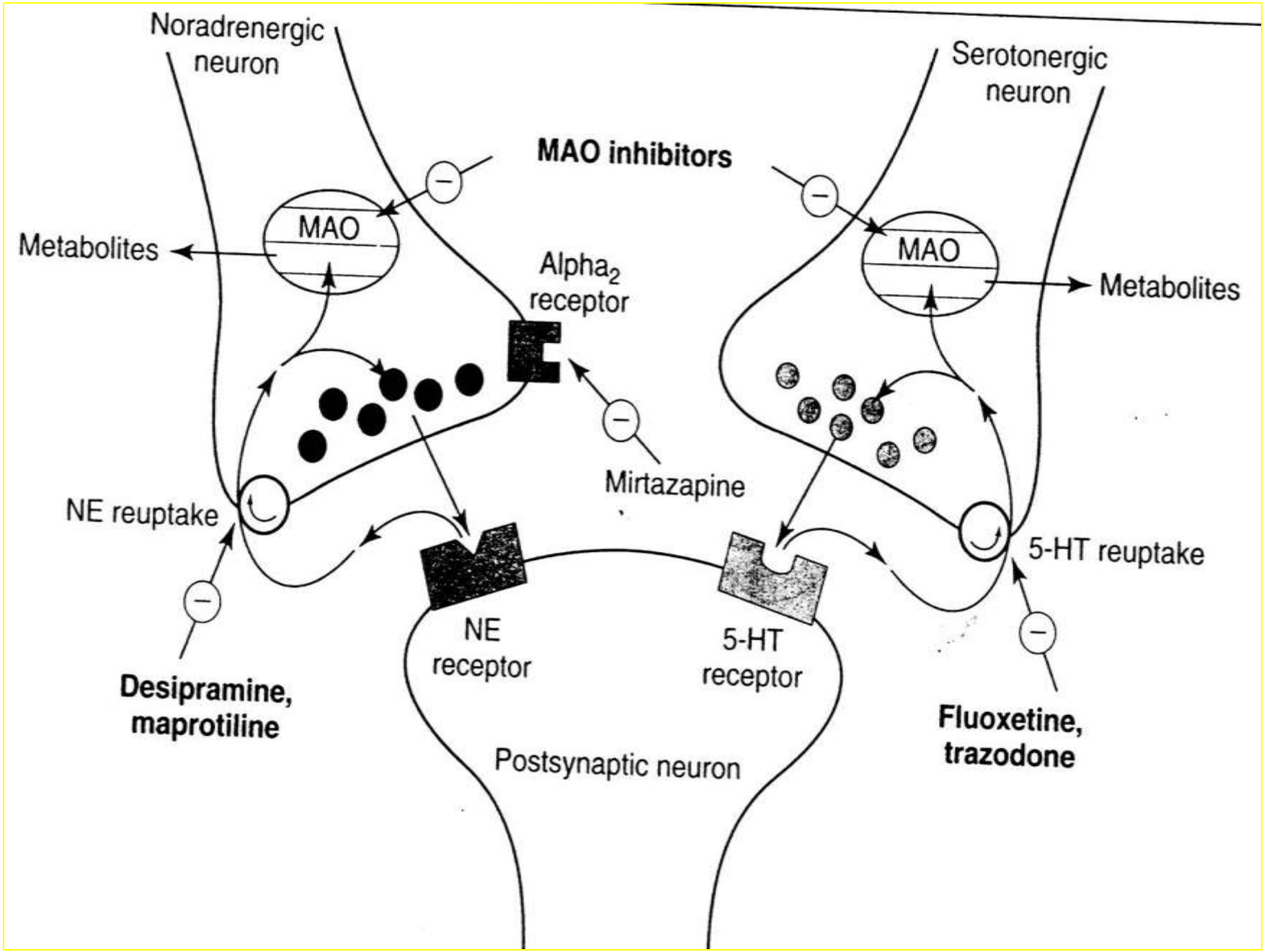
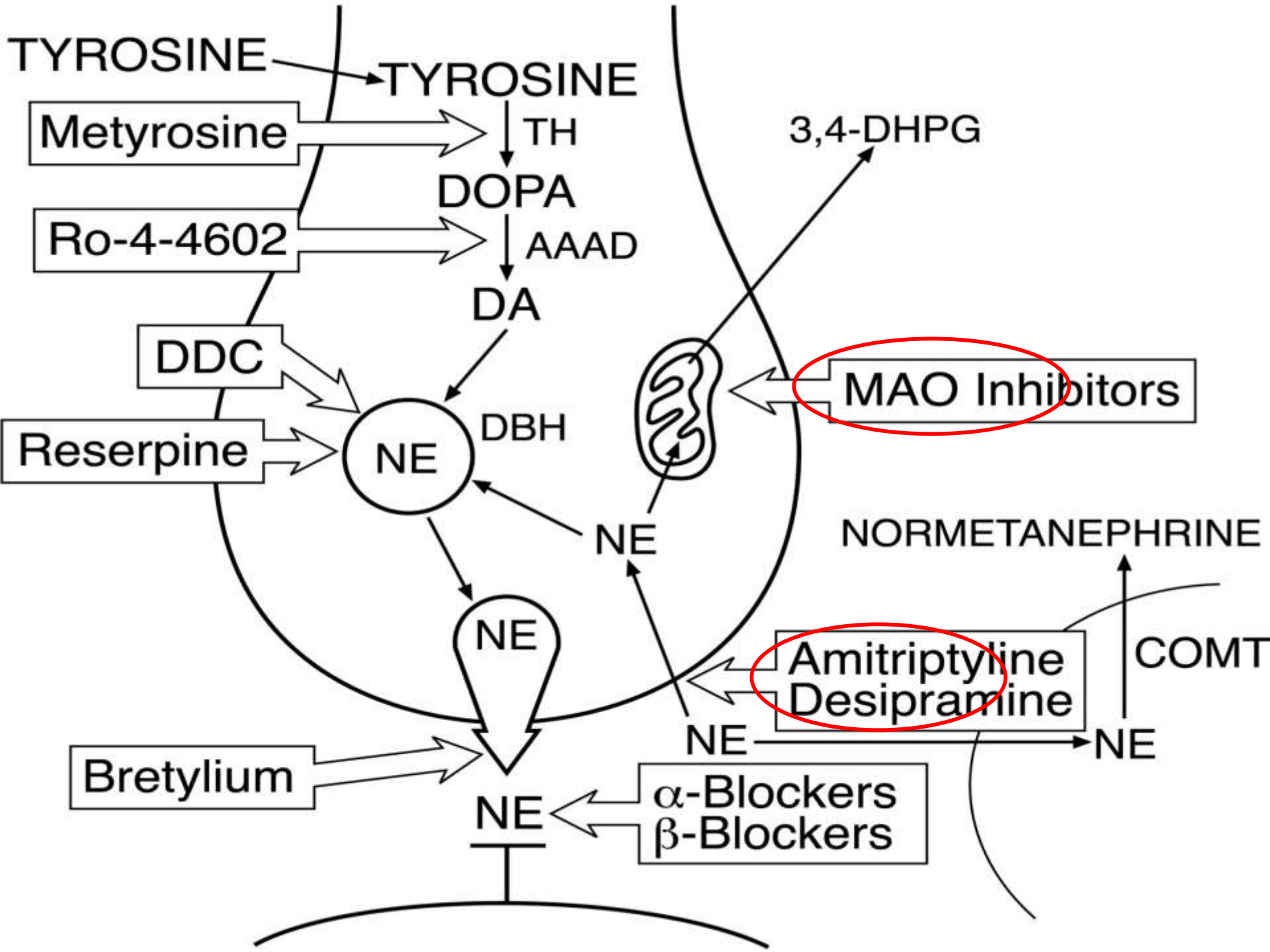
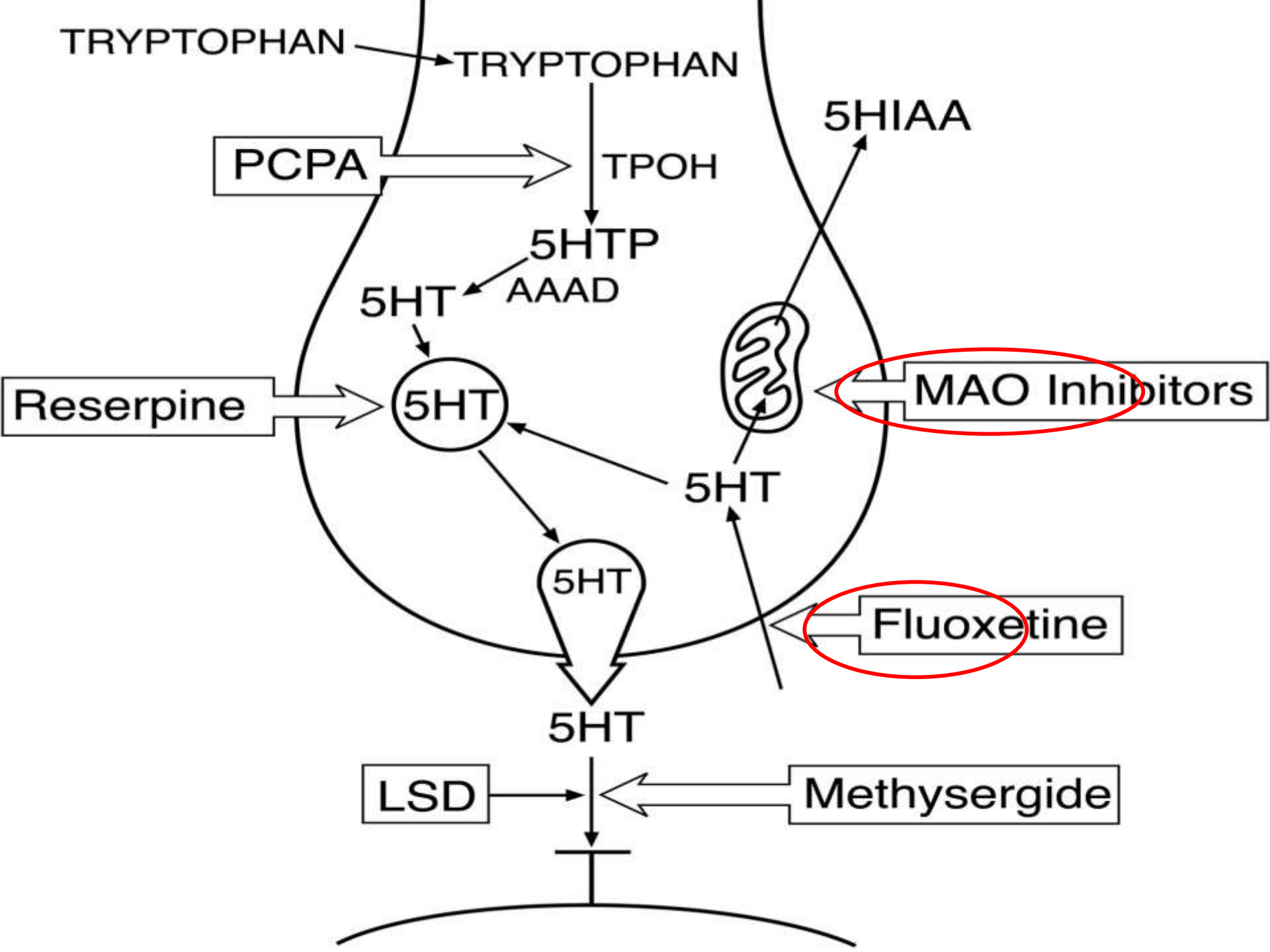

Antidepressant
Monoamine Oxidase inhibitors
-Non selective MAO-A/irreversible (Phenelzine,Tranylcipromine, Isocarboxacide)
-Selective reversible MAO-A (Meclobemide)
-Selective irreversible MA)-B (Deprenyl)
Amine reuptake Blocking drugs
Alpha2 adrenoceptor blockers, NaSSA
-Mirtazapine
Nonselective/SNRI
SSRIs
-Fluoxetine
-Citalopram
-Paroxetine
-Sertraline
NRIs, NDRIs
SARI
Tricyclics
-Amitryptiline
-Imipramine
-Desipramine
Heterocyclics
Second generation
- Amoxapine
- Maprotilline
Third generation
-Mirtazapine
-Nefazodone
-Venlafaxine
Atypical
-Trazodone
- Bupropion

Classification of Antidepressants

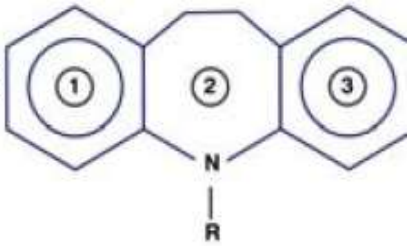
- Tricyclics
- Selective Serotonin Reuptake Inhibitors (SSRIs)
- Norepinephrine-Selective Reuptake Inhibitors (NRIs)
- Norepinephrine/Dopamine Reuptake Inhibitors (NDRIs)
- Mixed Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs)
- Monoamine Oxidase Inhibitors (MAOIs)
- Noradrenergic and Specific Serotonergic Antidepressant (NaSSA)
- Serotonin$_{2A}$ Antagonist/Serotonin Reuptake Inhibitors (SARI)


Noradrenergic neuron
Serotonergic neuron
MAO inhibitors
MAO
Metabolites
Alpha2 receptor
MAO
Metabolites
Mirtazapine
NE reuptake
5-HT reuptake
NE receptor
5-HT receptor
Desipramine, maprotiline
Fluoxetine, trazodone
Postsynaptic neuron


TYROSINE
TYROSINE
Metyrosine
TH
DOPA
Ro-4-4602
AAAD
DA
DDC
DBH
Reserpine
NE
NE
NE
3,4-DHPG
MAO Inhibitors
NORMETANEPHRINE
COMT
Amitriptyline
Desipramine
NE
NE
Bretylium
NE
α-Blockers
β-Blockers


TRYPTOPHAN
TRYPTOPHAN
5HIAA
PCPA
TPOH
5HTP
AAAD
5HT
Reserpine
5HT
MAO Inhibitors
5HT
5HT
Fluoxetine
5HT
LSD
Methysergide

A. Tricyclics AntiDepressant (TCA)



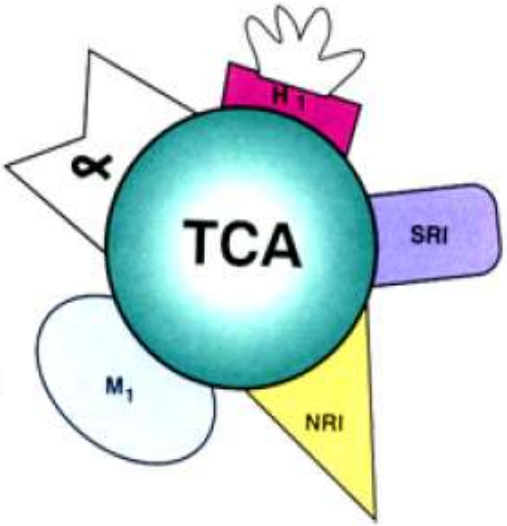
- All tricyclics block reuptake pumps for both 5HT and NE and they work negative allosteric modulators of neurotransmitter uptake process

- Some have more potency for inhibition of 5HT uptake pump (e.g. clomipramine, imipramine, amitryptyline)

- Others have more potency for inhibition of NE uptake pump (nortriptyline, desipramine)

- All tricyclics block α_1 adrenergic, histaminergic, and M1 cholonergic receptors (causes side effects, e.g., weight gain, drowsiness, blurred vision)

- Tricyclics also block Na^+ channels, thus may cause cardiac arrythmia

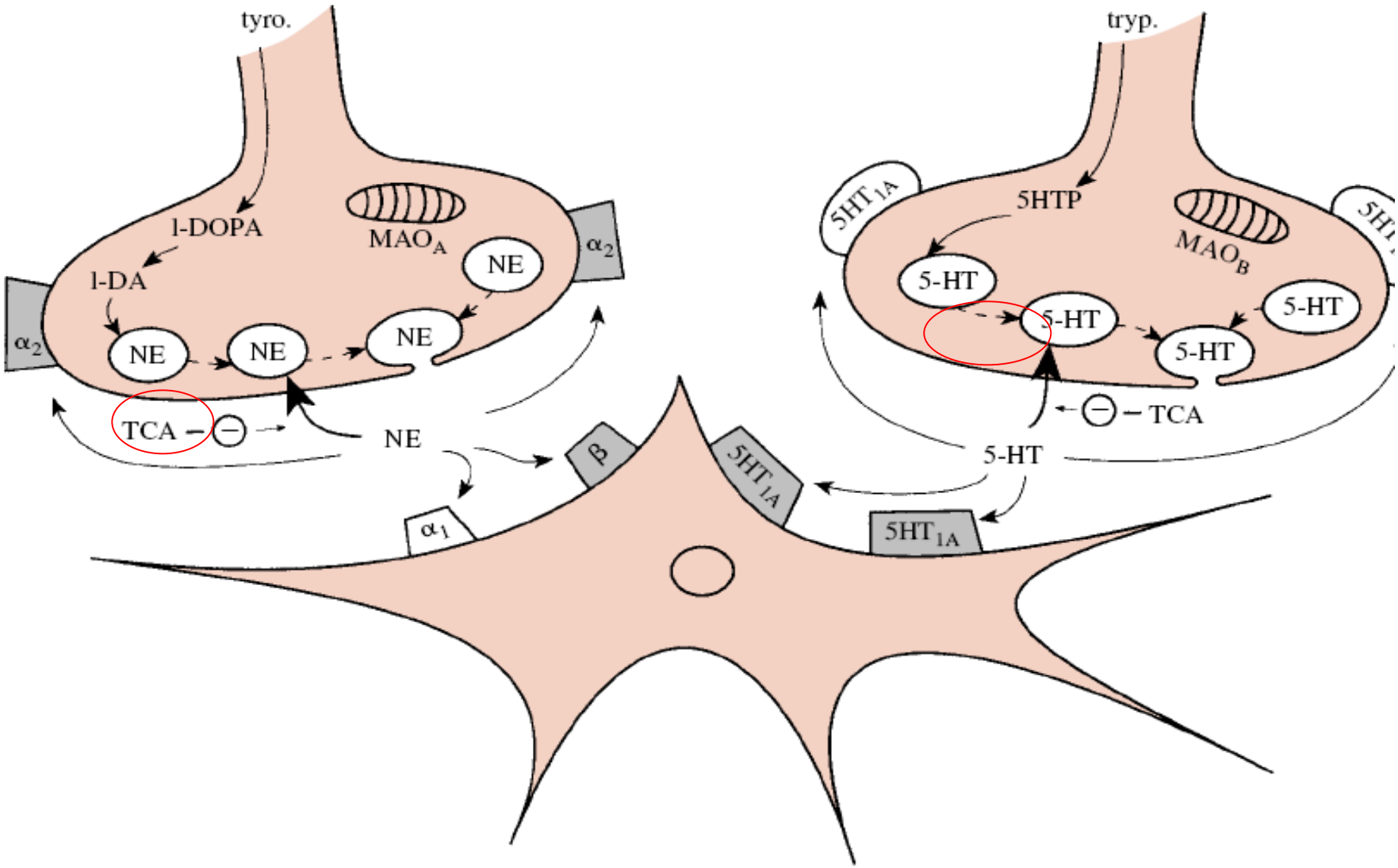


(Stahl, 2002)

A. Tricyclics AntiDepressant (TCA)

- Tricyclic antidepressants: generasi I (oldest)
- Mekanisme kerja :
  - down-regulation reseptor β-adrenergic,5-HT_{2A}
  - perubahan dari signal transduction
  - modulasi gene transcription (terutama BDNF, trkB)
- KI : prostatism, Glaukoma sdt sempit, jantung
- Hati-hati : peny jantung (abN kondksi), epilepsi (me↓ ambang kejang)
- Interaksi : potensiasi alkohol, antikolinregik, NE

A. Tricyclics AntiDepressant (TCA)



Cascade of adaptive changes occurring at norepinephrine(NE) synapses following chronic TCA drug treatment

Inhibition of nerve terminal NE neuronal uptake system

↓

Increase in synaptic concentrations of NE

↓

Desensitization of nerve terminal α_2-adrenoceptors

↓

Increase in neuronal NE release

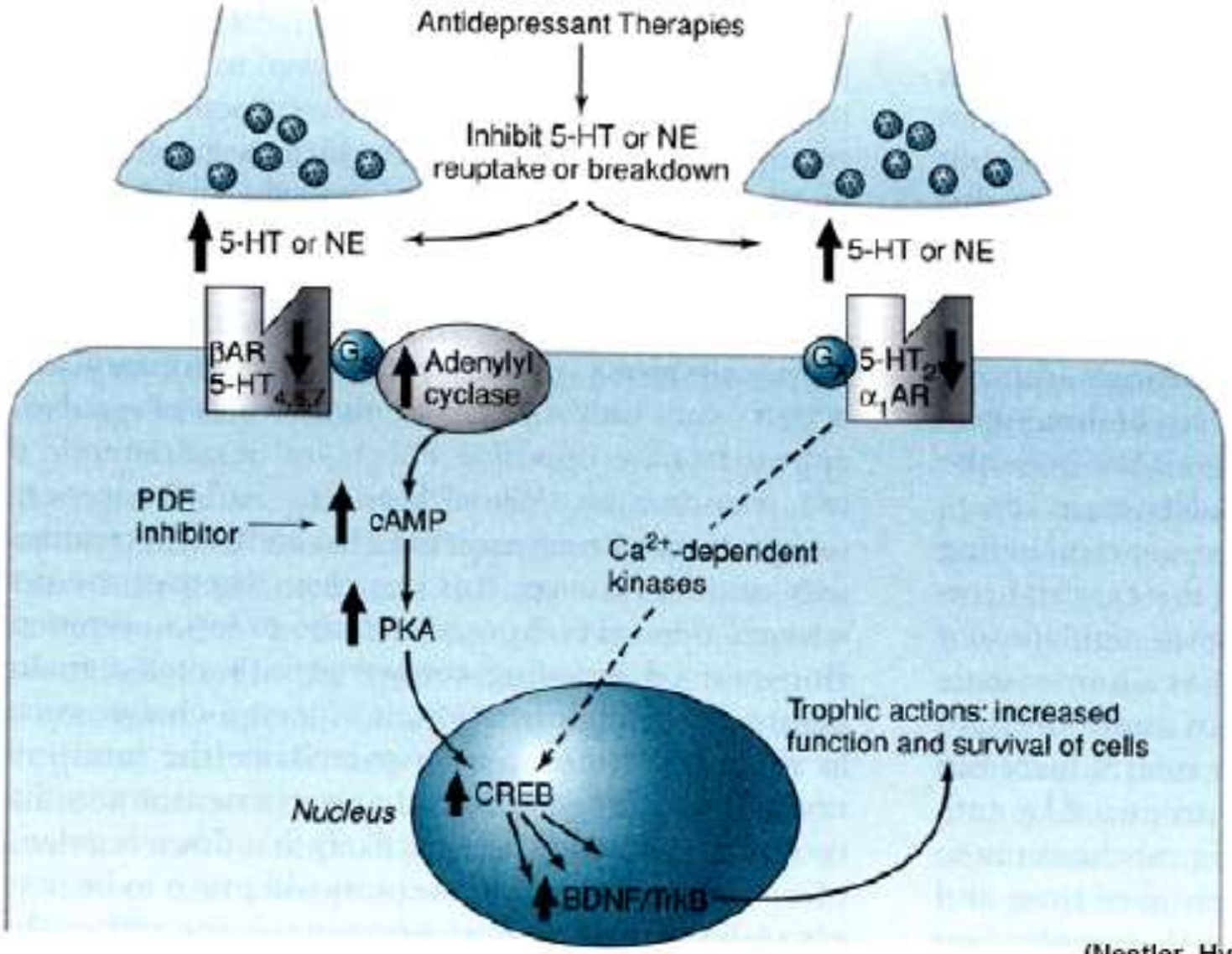
↓

Further increase in synaptic concentrations of NE

↓

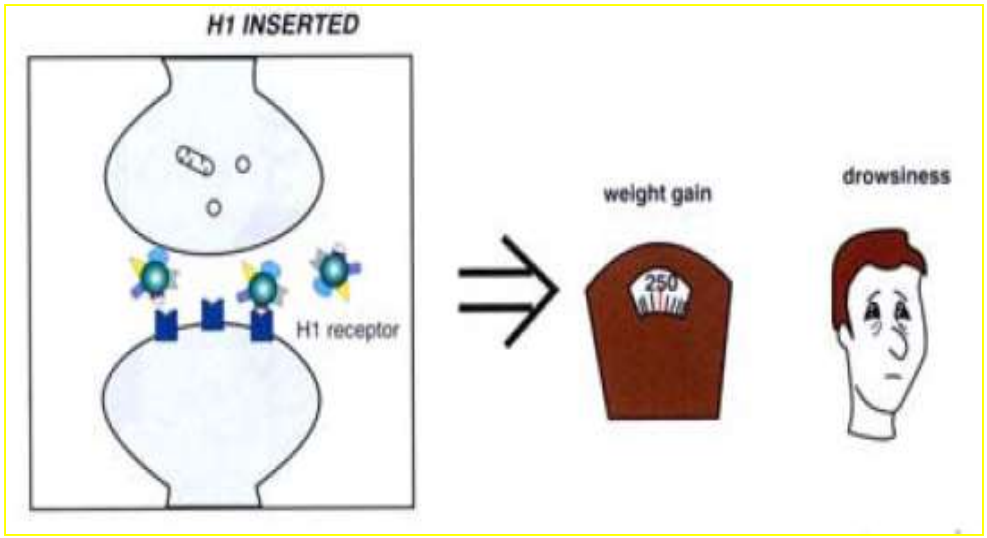
Desensitization of postsynaptic β-adrenoceptors with no change in postsynaptic α_1-adrenoceptor sensitivity

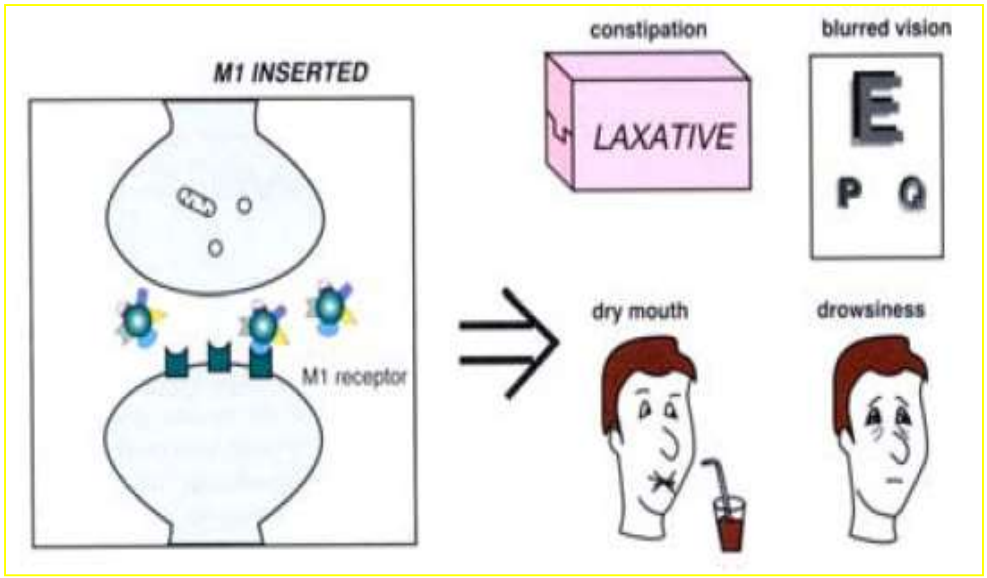
Postulated Adaptive Mechanisms at Gene Exprerssion

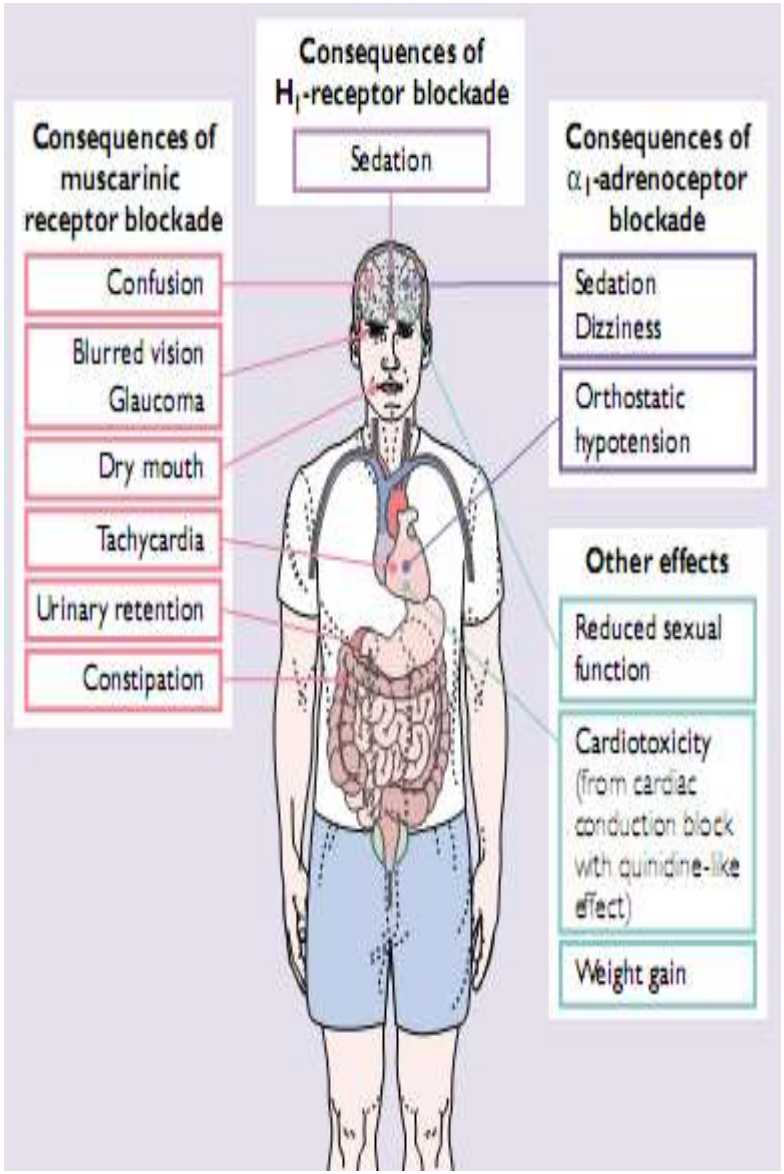


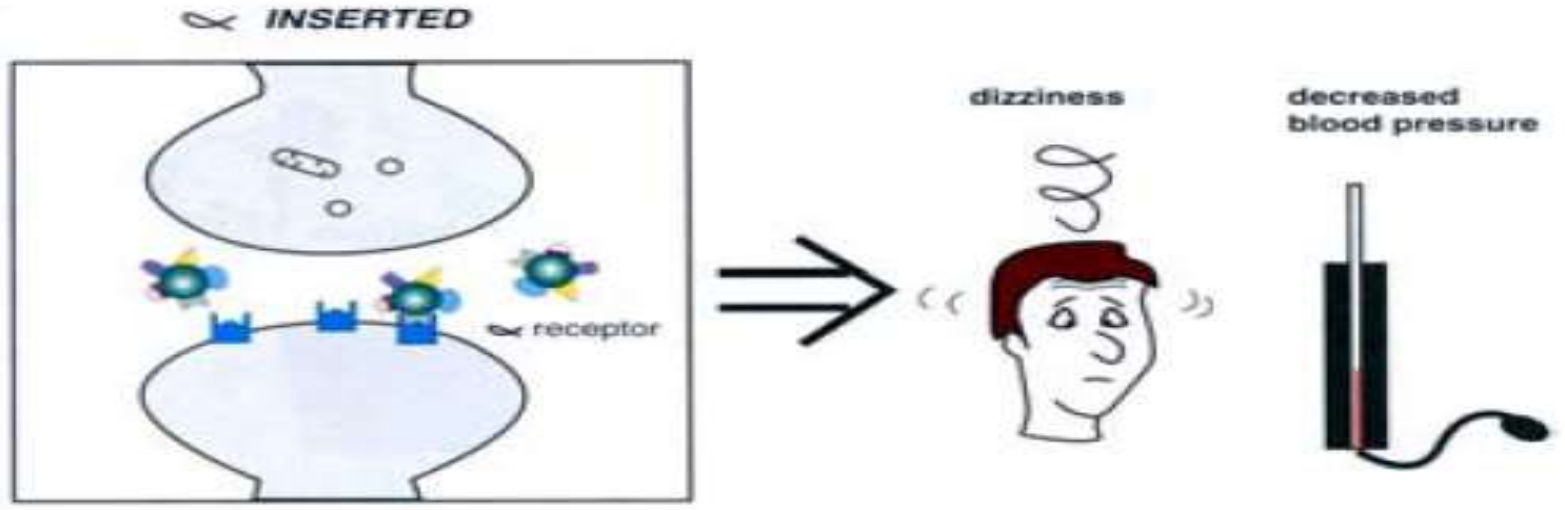
(Nestler, Hyman, Malenka)

Side Effects of TCA









TCA	Sedasi	Antimuscarinic
Imipramine	++	++
Desipramine	+	+
Amitriptyline	+++	++
Nortriptyline	++	+
Protriptyine	+/-	+++
Doxepin	++++	++

TOKSISITAS GOLONGAN TRISIKLIK

- Efek simpatomimetik:
  tachycardia,agitasi,berkeringat,insomnia
- Over dosis Trisiklik berakibat fatal:
  Agitasi,delirium,neuromuscular, irritability, convulsi, coma, depresi pernafasan,circulatory collaps,hyperpyrexia,gangguan konduksi jantung, arrhytmia berat
  → Three Cs : Coma, convulsion, cardiotoxicity
- Interaksi Obat-obat:
  1. kombinasi dgn Barbiturate,Ethanol,benzodiazepine, Opioid → depresi SSP bersifat aditif
  2. kombinasi dgn Guanethidine → antagonisme (hambatan transport Guanethidine menuju neuron simpatik)
  3. kombinasi dgn methylnorepinephrine, clonidine → antagonisme

b. Monoamine Oxidase Inhibitors (MAOIs)-I

Two types of MAO

- **MAO-A --- metabolizes 5HT and NE selectively**

  --- metabolizes certain amines, linked to blood pressure

- **MAO-B --- protects neurons by metabolizing certain amines such as protoxins into toxins that may cause neuronal damage**

b. Monoamine Oxidase Inhibitors (MAOIs)-I

MAO-A (jar perifer & otak – intracellular): merusak NE dan 5-HT

Inhibitor MAO-A : pargyline, Phenylzine,Tranylcypromine, Isocarboxazid (Marplan), Meclobemide

Iproniazid merupakan obat antitubercular MAOI → hepatotoxic

Menghambat enzim MAO di ujung saraf → kdr NT meningkat → kdr dlm vesikel meningkat → pelepasan meningkat

- MAO-B (otak – extracellular): merusak Dopamine

  Inhibitor MAO-B : deprenyl (selegiline)

  Tidak mempunyai efek antidepressant
- Interaksi yang fatal dengan makanan yang kaya *tyramine* (cheese, yeast products, fermented sausages, guacamole dip, fava beans, chianti wine)→efek sympathomimetic tyramine meningkat. Tyramine dirusak oleh MAO di liver
- Kombinasi dgn SSRI → Serotonin syndrome

b. Monoamine Oxidase Inhibitors (MAOIs)-I

- **Classic MAOIs--irreversible and nonselective**

(MAO-A and B enzyme activity can not be restored unless new enzyme is synthesized)

Phenelzine
Tanylcypromine
Isocarboxazid

- **Reversible and selective inhibitors of MAO-A (RIMAs)**

Moclobemide (antidepressant action)

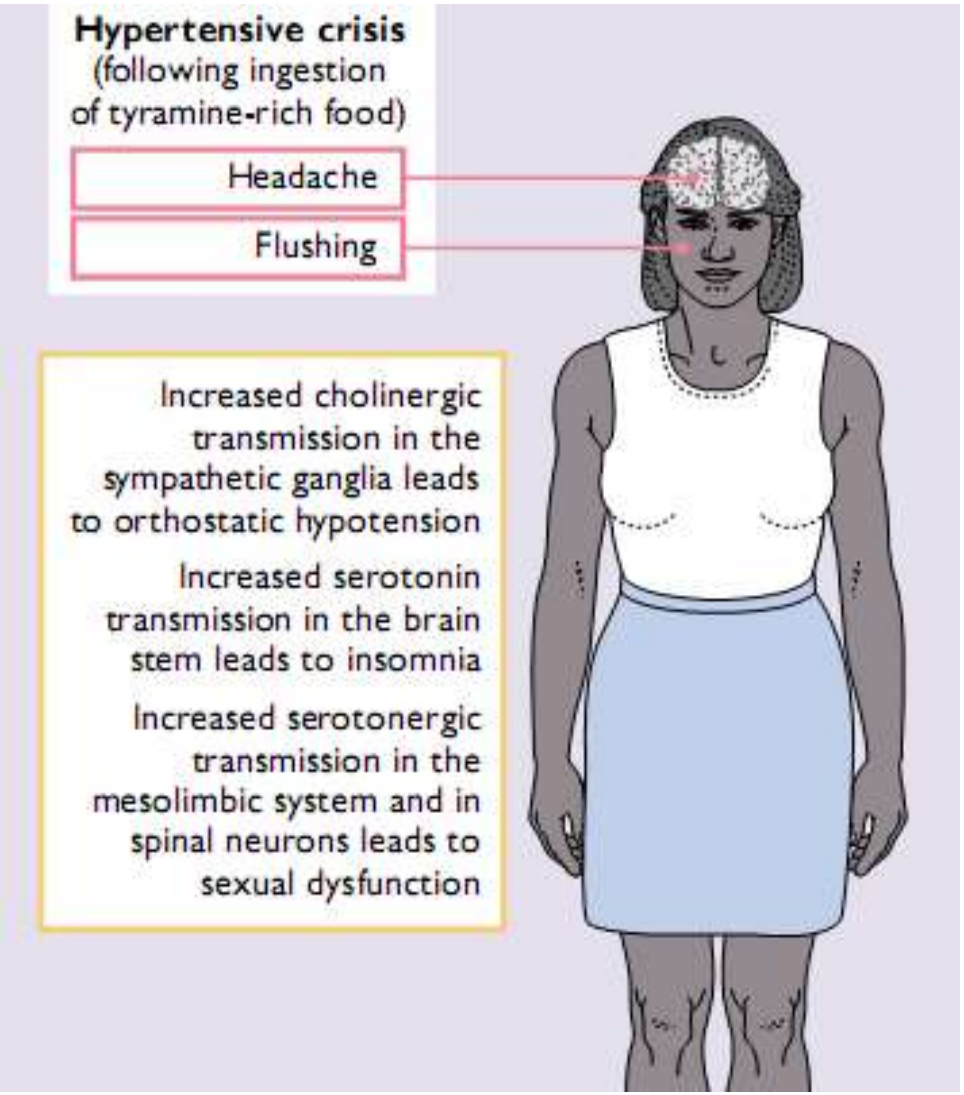
- **Selective inhibitor of MAO-B**

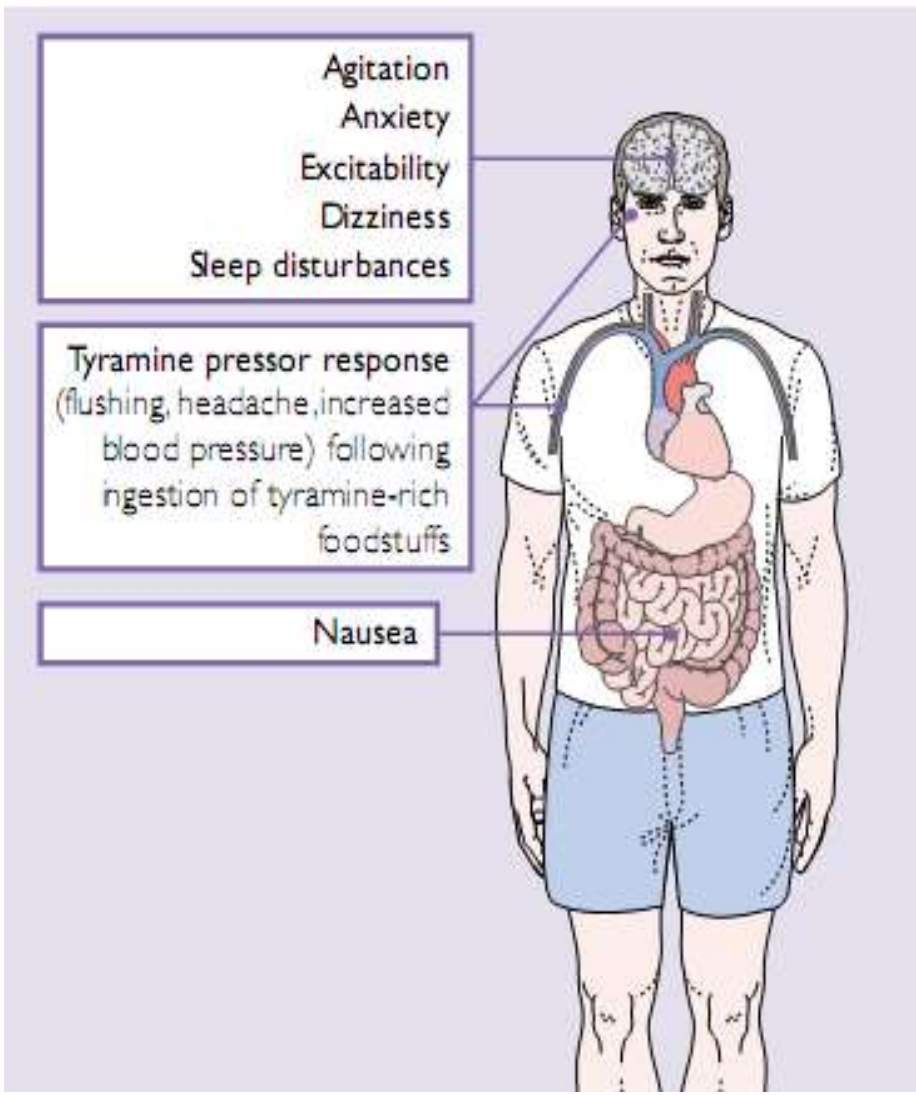
Deprenyl (neurodegenerative disorder)

- MAOI+Antikolinergik : efek meningkat
- MAOI+TCAs, Sympathomimetik → cardiovascular effects, seizures
- MAOI+ SSRIs: Serotonin Syndrome
- MAOI+Meperidine (Demerol ®):

  → pembentukan neurotoxic metabolite, seizures dan fatal (death)
- MAOI+tyramine-containing foods: →hypertensive crisis

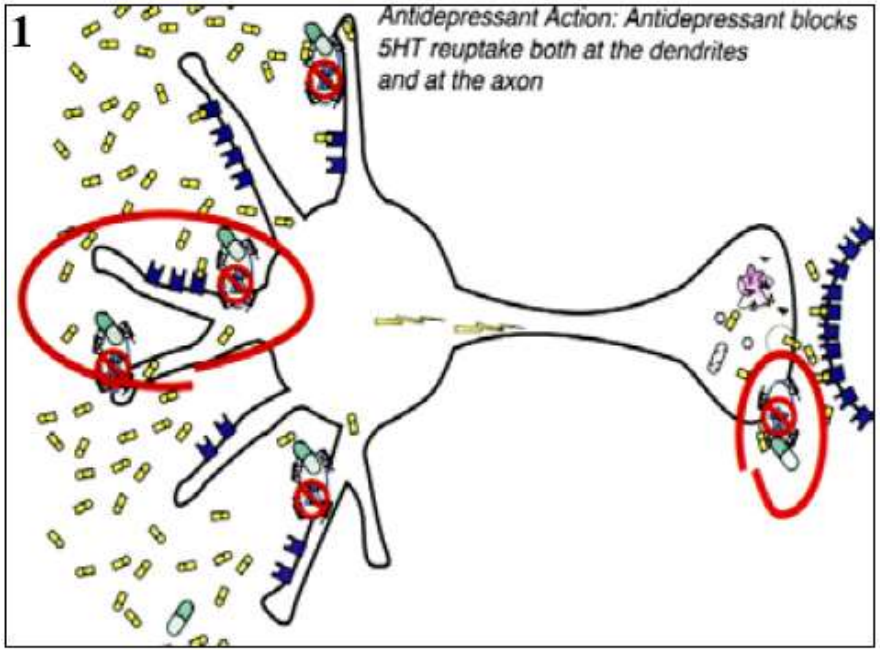
Side Effects of MAOi

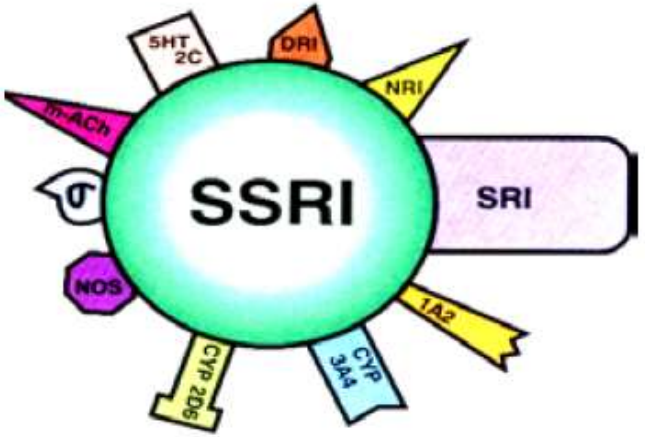




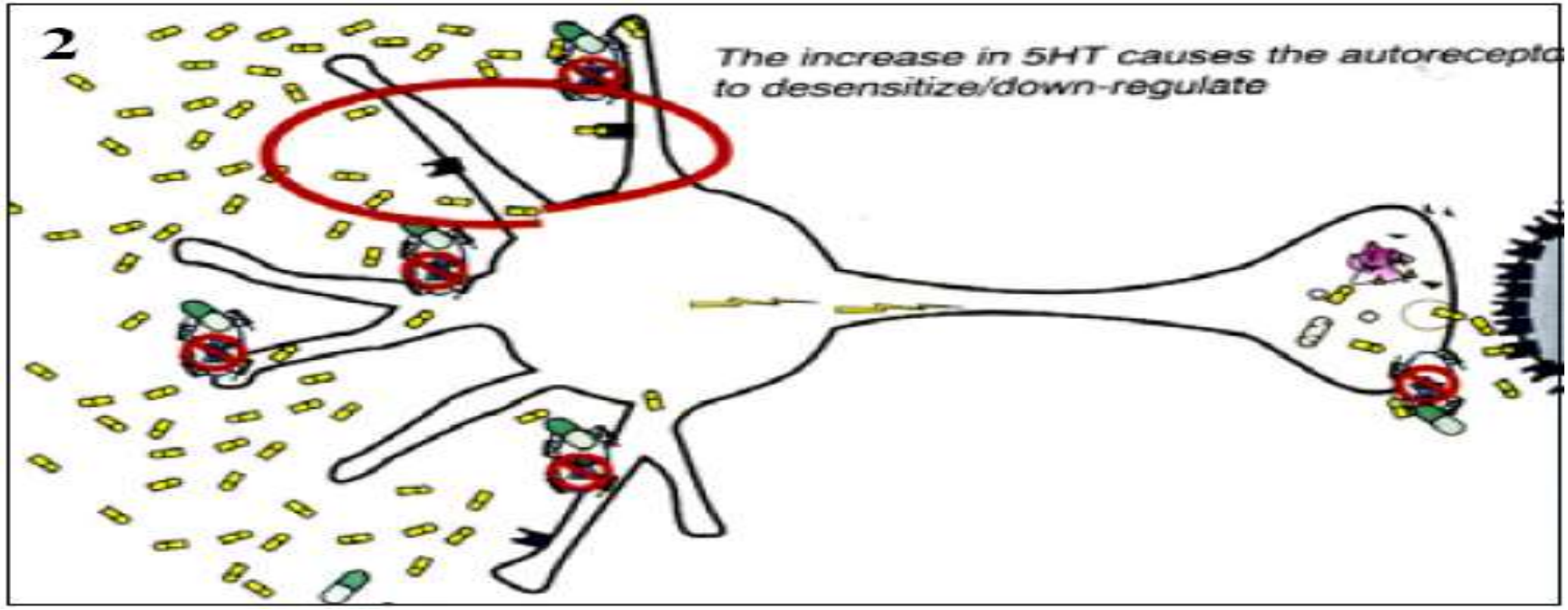
C. Selective Serotonin Reuptake Inhibitors (SSRI)

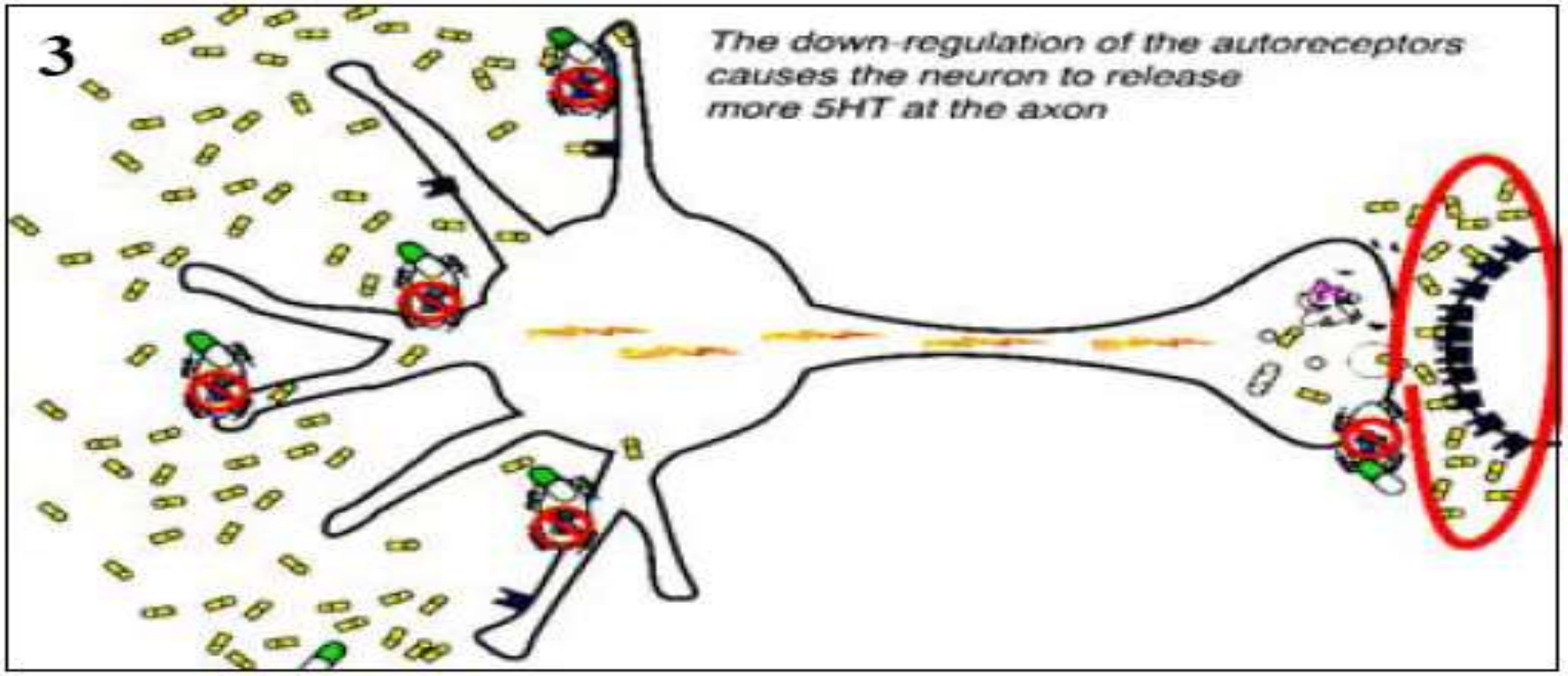
- Selective and more potent inhibitors of serotonin uptake than tricyclics (fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram)
- No blockade of α_1, histamine or M cholinergic receptors or Na^+ pump

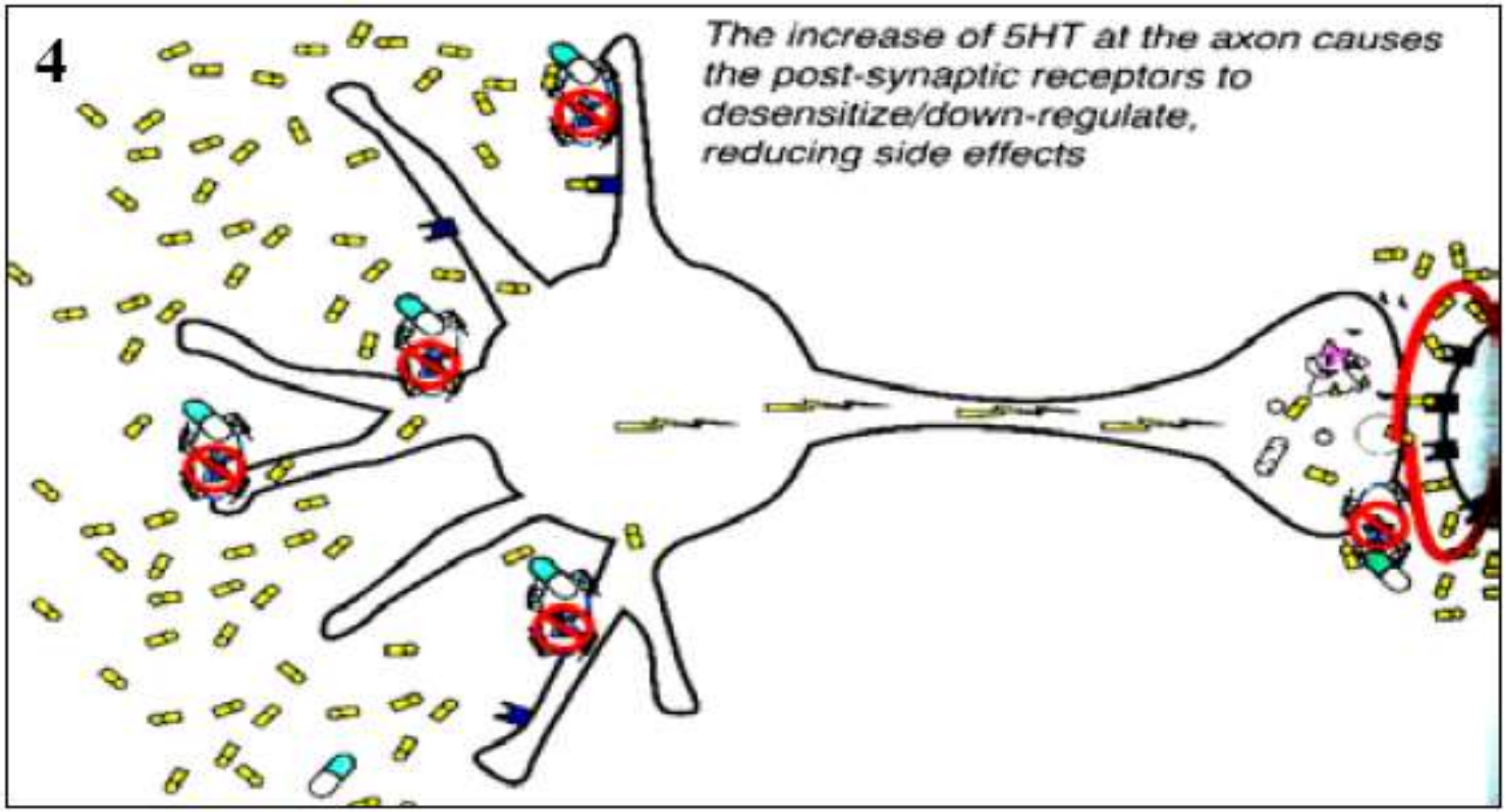




(Stahl, 2002)


2
The increase in 5HT causes the autorecepto
to desensitize/down-regulate

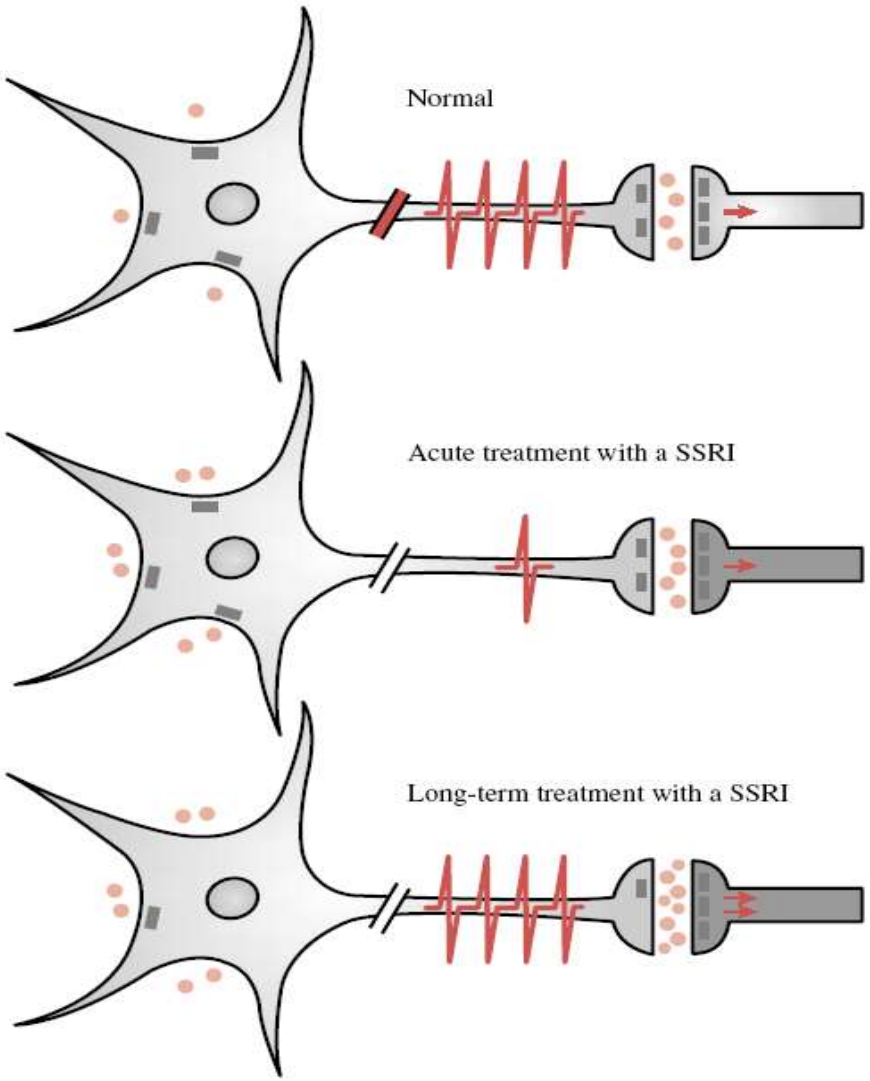

3
The down-regulation of the autoreceptors
causes the neuron to release
more 5HT at the axon


4
The increase of 5HT at the axon causes the post-synaptic receptors to desensitize/down-regulate, reducing side effects

C. Selective Serotonin Reuptake Inhibitors (SSRI)

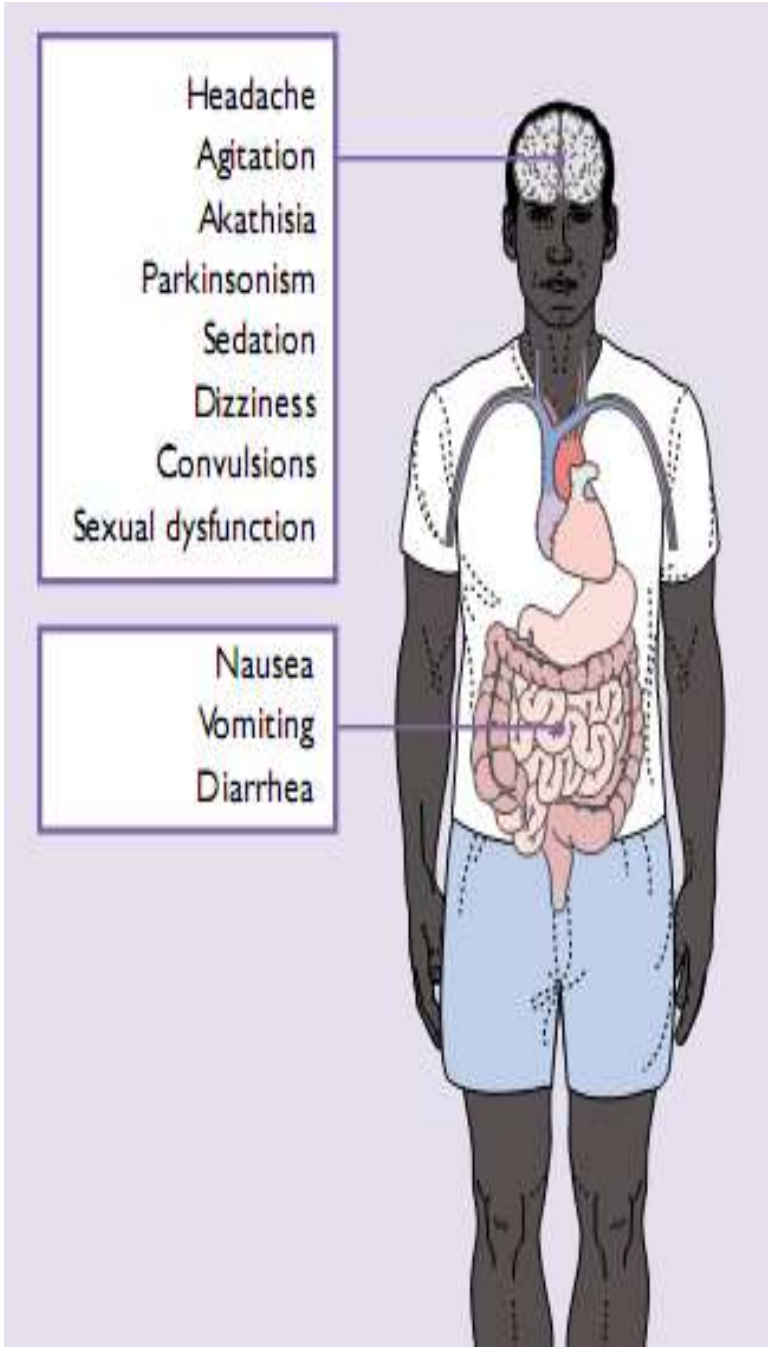
- Secara Selektif memblokade reuptake 5-HT
- Menyebabkan perubahan compensatory neurotransmisi 5-HT (desensitisasi autoreceptors →potensiasi 5-HT neurotransmission)
- Menyebabkan perubahan compensatory gene transcription (BDNF, trkB, CREB) → efek therapeutic
- Efek terapi 2 – 3 minggu
- Efek samping lebih ditolerir dari pada TCA
- Kombinasi dgn MAO-I → Serotonin syndrome (fatal)
- Umumnya merupakan inhibitor cyt P 450 di hepar

SSRI



Efek Samping :

- anxiety / agitation → reducing the dose and titrating upward more slowly.
- Insomnia → require the addition of a sedating agent at bedtime.
- Nausea and loose stools → taking the medication with food
- sexual dysfunction (decreased libido, delayed ejaculation, and anorgasmia.
- No correlation has been made between plasma levels of the SSRIs and efficacy.


Headache
Agitation
Akathisia
Parkinsonism
Sedation
Dizziness
Convulsions
Sexual dysfunction
Nausea
Vomiting
Diarrhea

C. Selective Serotonin Reuptake Inhibitors (SSRI)

	Fluoxetin	Sertraline	Paroxetine	Citalopram
Ikatan dg prot	kuat			
Sitokrom P450	Inhibitor kuat	Inhibitor lemah	Inhibitor kuat	Kurang pengaruhi
Potensi	++	+	+++	++++
ES	GIT	GIT ++	BB↑, sedasi, antikolinerg+ Perlu tappering off	

d. NE Selective Reuptake Inhibitors (NRIs)

(reboxetine, 1555U88*, tomoxetine*)

- Selective to NE uptake
- May be more effective in noradrenaline deficiency syndrome (e.g., depression associated with fatigue, apathy, cognitive disturbances), or nonresponders to SSRIs
- Also act at presynaptic α_2, postsynaptic α_1, α_2 and β adrenergic receptors (tremor, agitation, blood pressure)
- No blockade of histamine, M cholinergic receptors or Na^+ pump as with tricyclics

*under clinical trial

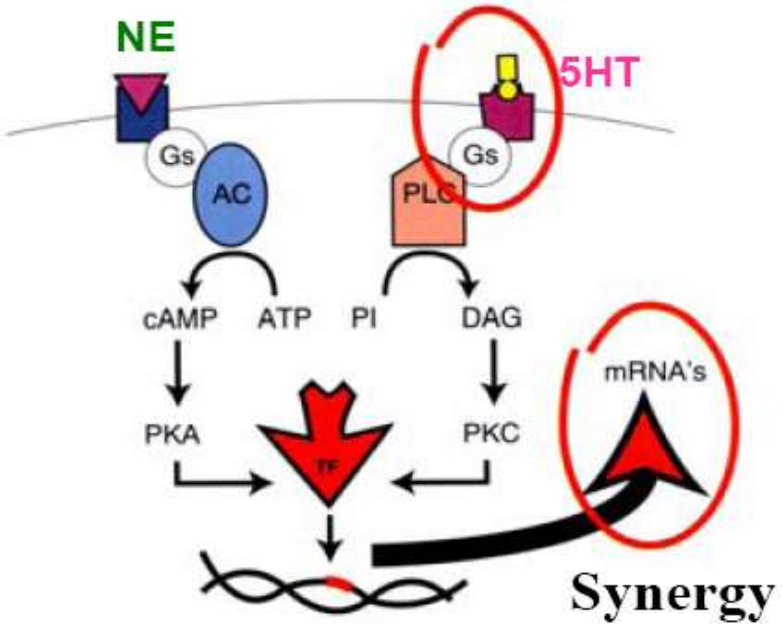
e. NE/DA Reuptake Blockers (NDRIs)

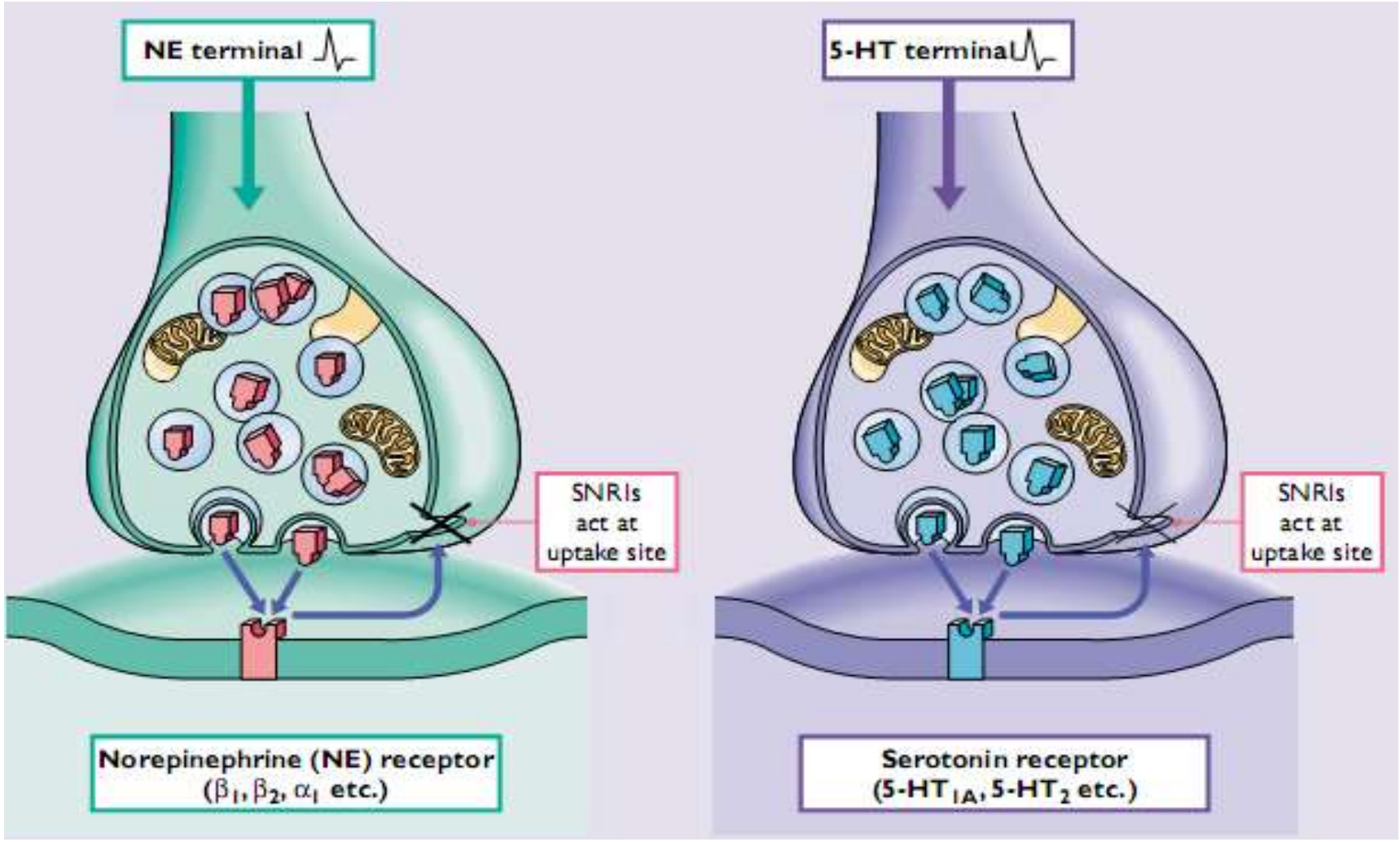
(Bupropion)

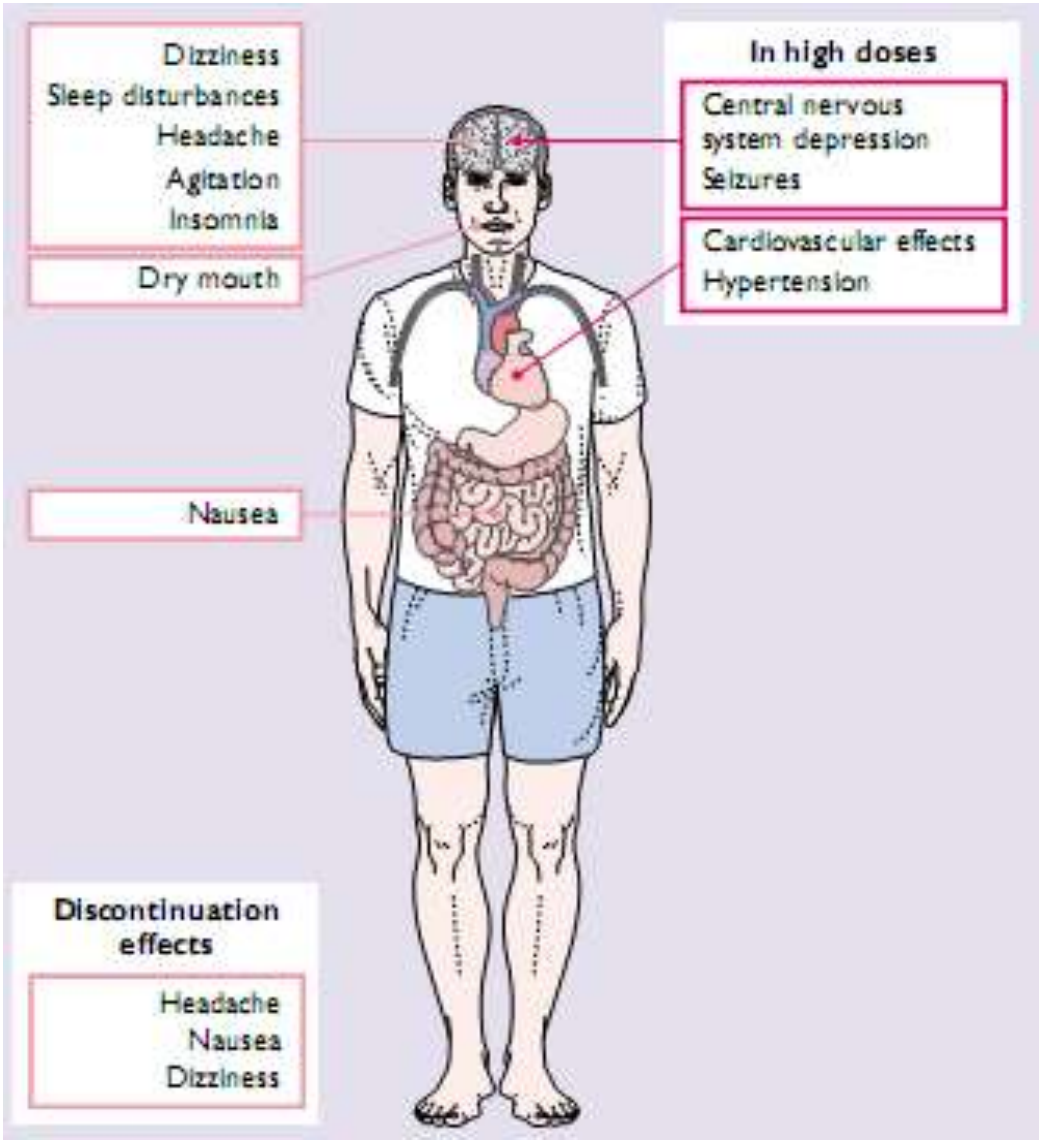
- Weak dopamine and weak NE reuptake blocker But is potent blocker of NE and dopamine neurotransmission
- Bupropion is metabolized into its hydroxylated active metabolite, which is a potent NE reuptake blocker
- Effective for patients who can not tolerate side effects of SSRIs such as sexual dysfunction or nonresponders of SSRIs

f. Mixed 5HT/NE Reuptake Inhibitors (SNRIs)
(venlafaxine)

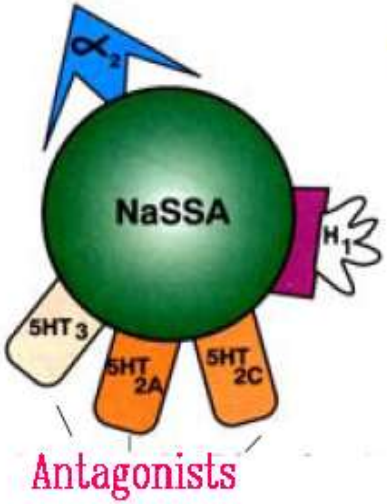
- Combines the action of SSRI and NRI
- Selective 5HT and NE uptake blockers
- Weak DA uptake blocker as with TCA
- But without α_1, M_1 cholinergic or H receptor blocking properties
- Causes dual action on serotonin and adrenergic systems, thus amplifying these two systems synergistically
- Greater NE action at higher doses, thus greater efficacy at increased doses, as opposed to other antidepressants which have little difference in efficacy at higher doses
- Effective in patients who are responders but not remmiters to SSRIs



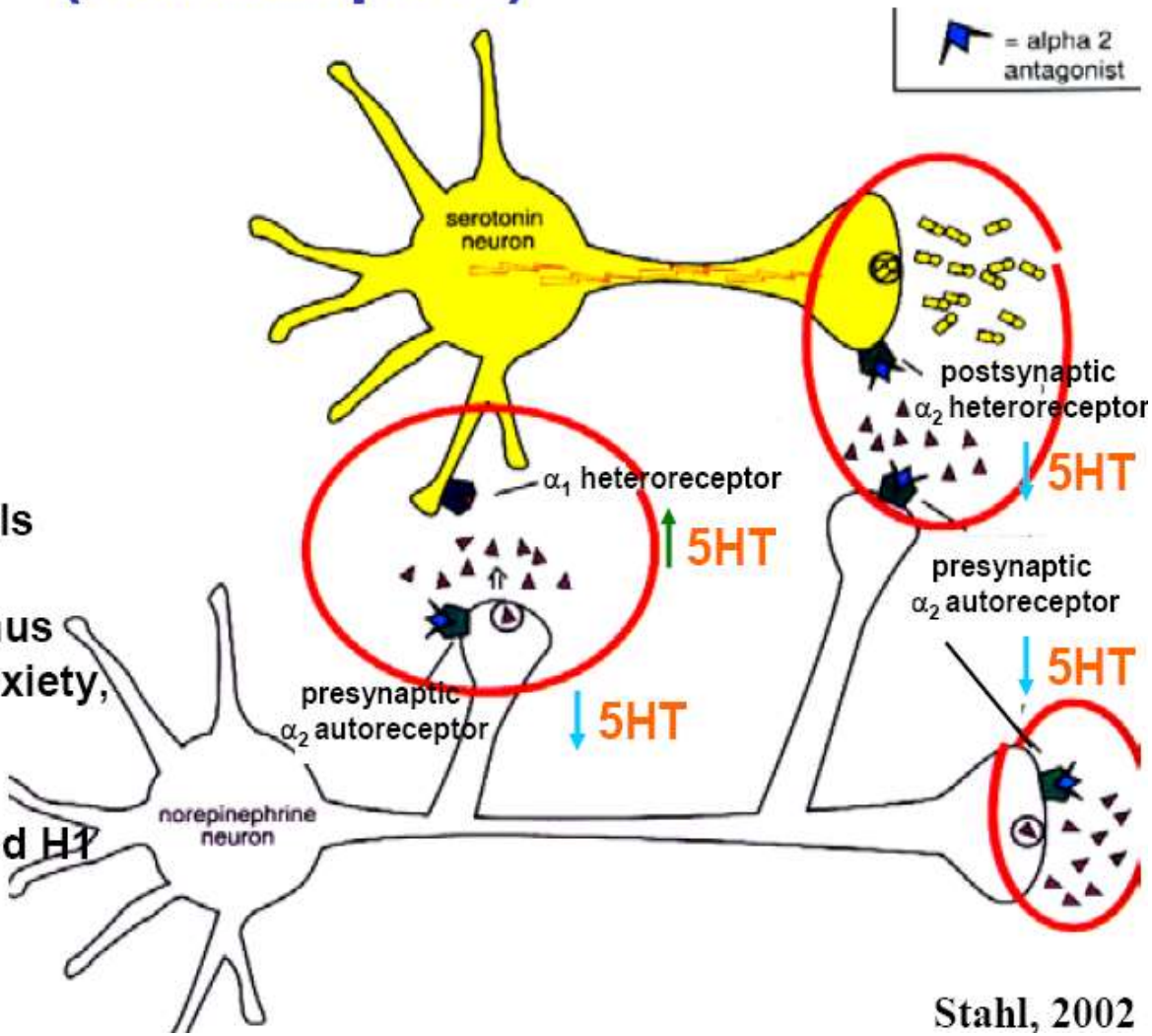

NE terminal
SNRIs act at uptake site
Norepinephrine (NE) receptor (β_1, β_2, α_1 etc.)
5-HT terminal
SNRIs act at uptake site
Serotonin receptor (5-HT_{1A}, 5-HT_2 etc.)


Dizziness
Sleep disturbances
Headache
Agitation
Insomnia
Dry mouth
Nausea
In high doses
Central nervous system depression
Seizures
Cardiovascular effects
Hypertension
Discontinuation effects
Headache
Nausea
Dizziness

g. Noradrenergic and specific Serotonergic Antidepressant (NaSSA) (mirtazapine)



- α_2 receptor antagonist
- Increase NE and 5HT levels
- Blocks $5HT_{2A}$, $5HT_3$ and thus reduces side effects of anxiety, and sexual dysfunction
- But by blocking $5HT_{2C}$, and H1 receptors cause side effects: sedation, and weight gain

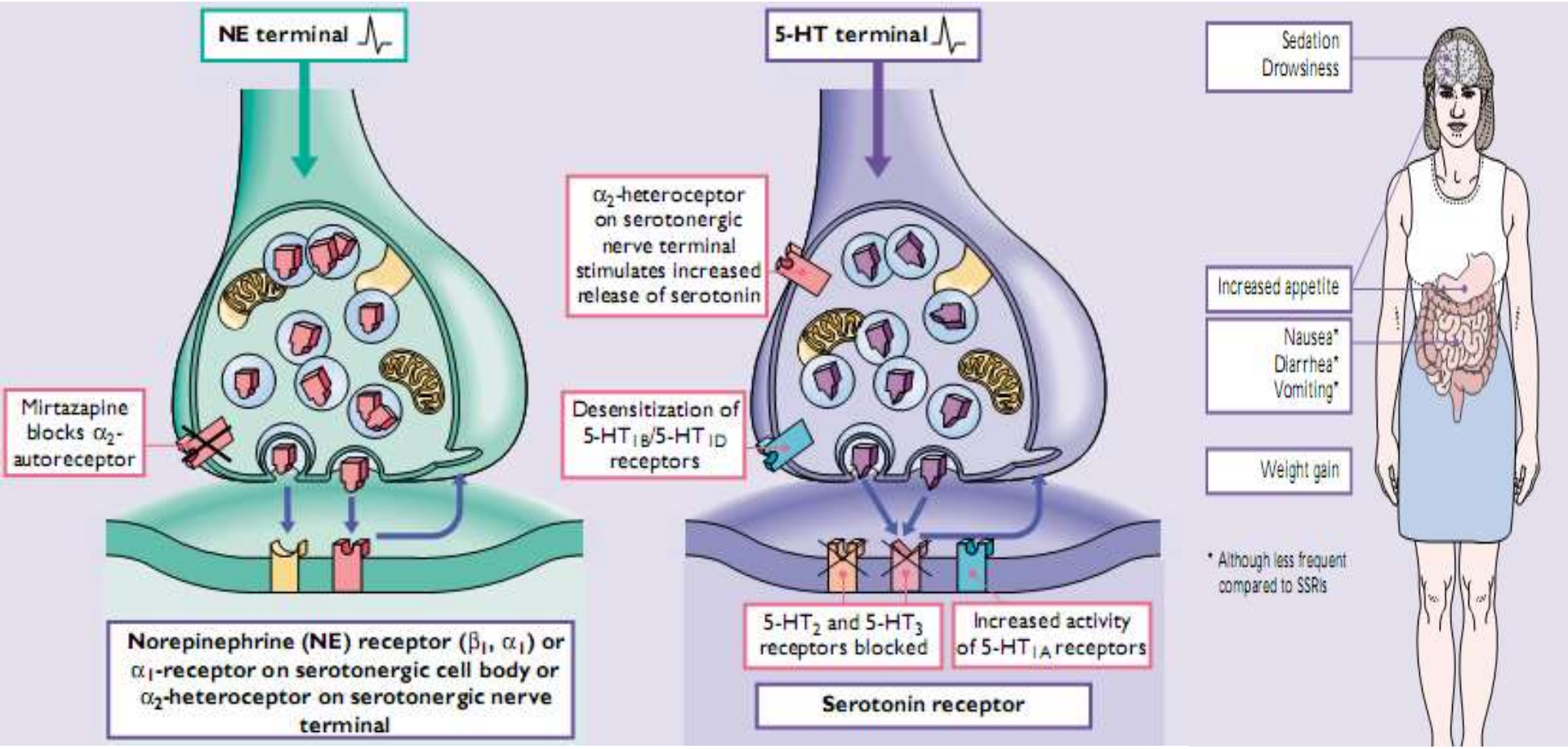


Stahl, 2002

g. NaSSA

- Hamb R/ α2 autoreseptor ➔me↑ transmisi NE
- Hamb R/ α2 heteroreceptor pd sel bodi neuron serotonergik ➔me↑ 5-HT di sinap
- Antagonis R/ 5-HT2a, 5-HT3, M, H1
- ES : mual, skt kepala,cemas << SSRI

  me ↑ appetite, BB, ngantuk


NE terminal
Mirtazapine blocks α_2-autoreceptor
Norepinephrine (NE) receptor (β_1, α_1) or α_1-receptor on serotonergic cell body or α_2-heteroceptor on serotonergic nerve terminal
5-HT terminal
α_2-heteroceptor on serotonergic nerve terminal stimulates increased release of serotonin
Desensitization of 5-HT_{1B}/5-HT_{1D} receptors
5-HT_2 and 5-HT_3 receptors blocked
Increased activity of 5-HT_{1A} receptors
Serotonin receptor
Sedation
Drowsiness
Increased appetite
Nausea*
Diarrhea*
Vomiting*
Weight gain
* Although less frequent compared to SSRIs

h. Serotonin2A Antagonist/ Serotonin Reuptake Inhibitors (SARI) (nefazodone, trazodone)

- Blocks 5HT uptake selectively but in a less potent manner than tricyclics
- This helps reduces depression
- However, they are powerful $5HT_{2A}$ antagonists
- $5HT_{2A}$ antagonists are not potent antidepressants
- But blockade of $5HT_{2A}$ receptors stimulate $5HT_{1A}$ receptors, which may help reduce depression
- $5HT_{2A}$ antagonism also reduces the risk of anxiety, sedation or sexual dysfunction which is normally associated with SSRIs

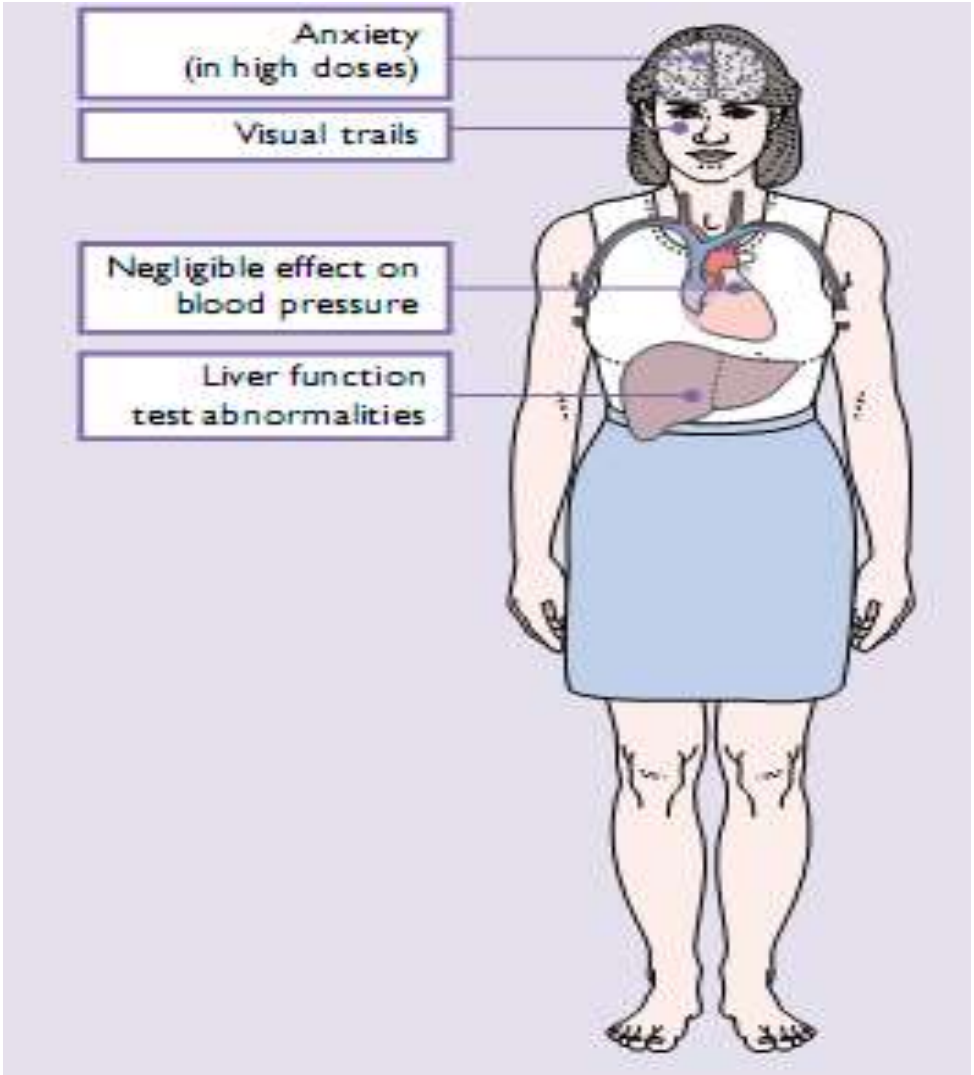

Anxiety
(in high doses)
Visual trails
Negligible effect on
blood pressure
Liver function
test abnormalities

Table 13-5. EFFECTS OF VARIOUS ANTIDEPRESSANTS ON DIFFERENT RECEPTORS*

	β-ADRENERGIC† STIMULATION	SEROTONIN 2 RECEPTOR† STIMULATION	α_1-ADRENERGIC BLOCKADE	α_2-ADRENERGIC BLOCKADE	MUSCARINIC BLOCKADE	DOPAMINE 2 BLOCKADE	HISTAMINE 1 BLOCKADE
Tricyclics							
Imipramine	++	++	+++	+	++	+	++
Desipramine	+++	0	++	±	+	+	+
Amitriptyline	++	+++	+++	++	+++	+	+++
Nortriptyline	++	++	+++	+	+	+	+
Doxepin	++	++	+++	++	++	+	++++
Second-Generation							
Amoxapine	++	++	+++	±	+	++	++
Maprotiline	+++	+	+++	±	+	+	+++
Trazodone	±	++	++++	++	0	+	+
Fluoxetine	±	+++	±	±	±	0	±
Buproprion	±	±	±	0	0	?†	±

* Data obtained from a variety of sources as well as clinical estimates of side effects.

† β-Adrenoreceptor (norepinephrine) and serotonin 2 receptor are stimulated because of uptake inhibition; all others represent blockade of receptors.

Table 29–3. Pharmacologic differences among several antidepressants.[1]

			Block of Amine Pump for:		
Drug	**Sedative**	**Antimuscarinic**	**Serotonin**	**Norepinephrine**	**Dopamine**
Amitriptyline	+++	+++	+++	+	0
Amoxapine	++	++	+	++	+
Bupropion	0	0	+,0	+,0	?
Desipramine	+	+	0	+++	0
Doxepin	+++	+++	++	+	0
Fluoxetine	+	+	+++	0,+	0,+
Imipramine	++	++	+++	++	0
Maprotiline	++	++	0	+++	0
Nortriptyline	++	++	+++	++	0
Paroxetine	+	0	+++	0	0
Protriptyline	0	++	?	+++	?
Sertraline	+	0	+++	0	0
Trazodone	+++	0	++	0	0

[1]0 = none; + = slight; ++ = moderate; +++ = high; ? = uncertain.

Table 30–2. Pharmacodynamics of common tricyclic antidepressants, heterocyclic agents, and selective serotonin reuptake inhibitors.[1,2]

Drug	Sedation	Muscarinic Receptor Block	NE Reuptake Block	5-HT Reuptake Block
Tricyclics				
Amitriptyline, doxepin	+++	+++	++	+++
Desipramine, protriptyline	+	+	+++	–
Imipramine, nortriptyline	++	++	++	+++
Heterocyclics (second generation)				
Amoxapine	++	++	++	+
Bupropion	–	–	–	–
Trazodone	+++	–	–	++
Maprotiline	++	++	+++	–
Heterocyclics (third generation)				
Mirtazapine	+++	–	–	–
Nefazodone	++	+++	–	+
Venlafaxine	–	–	+++	++
SSRIs				
Fluoxetine, citalopram, paroxetine, sertraline	–	+	–	+++

[1]Similar drugs have been grouped together for study purposes even though they may not be identical in their ac-

EFEK SAMPING ANTIDEPRESSANT

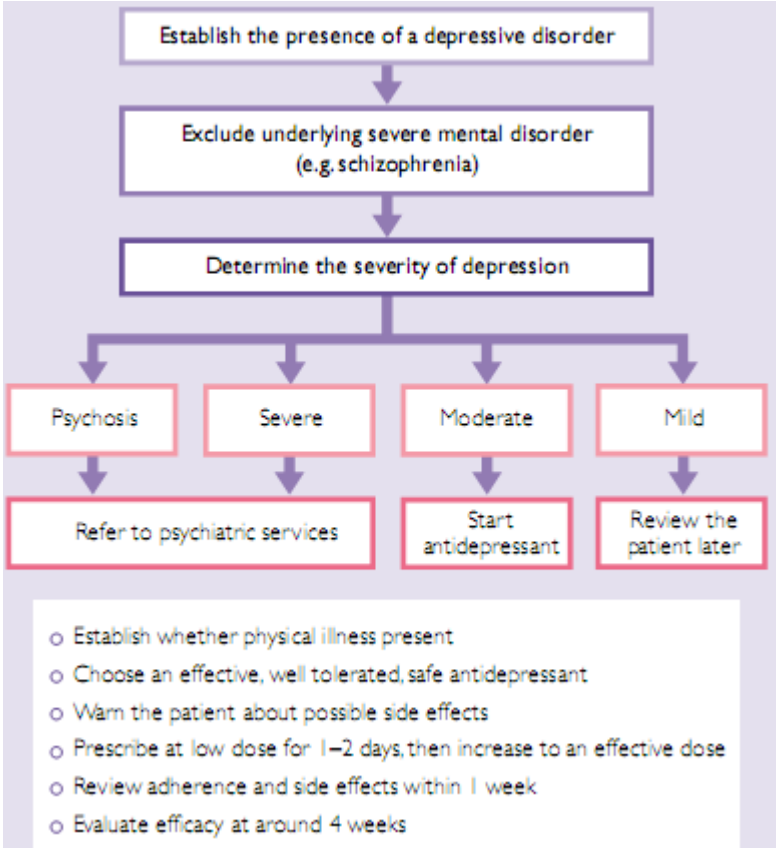
Agent	Sedation	Anticholinergic	Orthostasis	Weight Gain	Sexual Dysfunction
SSRIs	+/−	0	0	+/−	+++
TCAs	+ + +	+ + +	+ + +	++	++
Miscellaneous					
Trazodone	+++	0	++	++	+[a]
Bupropion	0	0	0	0	0
Nefazodone	++	0	0	0	0
Venlafaxine	+/-	0	0[b]	0	++
Mirtazapine	++	0	0	++	0
MAOIs	0	+	+++	++	+

TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; MAOI, monoamine oxidase inhibitor.
0, no effect; +, + +, +++ indicate increasing effect.
[a]Priapism.
[b]Venlafaxine can cause a dose-dependent increase in blood pressure.

Table 29–5. Adverse effects of antidepressants.

Tricyclics	
Sedation	Sleepiness, additive effects with other sedative drugs
Sympathomimetic	Tremor, insomnia
Antimuscarinic	Blurred vision, constipation, urinary hesitancy, confusion
Cardiovascular	Orthostatic hypotension, conduction defects, arrhythmias
Psychiatric	Aggravation of psychosis, withdrawal syndrome
Neurologic	Seizures
Metabolic-endocrine	Weight gain, sexual disturbances
Monoamine oxidase inhibitors	Headache, drowsiness, dry mouth, weight gain, postural hypotension, sexual disturbances
Amoxapine	Similar to the tricyclics with the addition of some effects associated with the antipsychotics (Chapter 28)
Maprotiline	Similar to tricyclics; seizures dose-related
Trazodone, venlafaxine	Drowsiness, dizziness, insomnia, headache, weight loss
Bupropion	Dizziness, dry mouth, sweating, tremor, aggravation of psychosis, potential for seizures at high doses
Fluoxetine and other serotonin reuptake inhibitors	Anxiety, insomnia, asthenia, tremor, sweating, gastrointestinal symptoms, rashes

Criteria for starting patient on antidepressants



PEMILIHAN ANTIDEPRESSAN

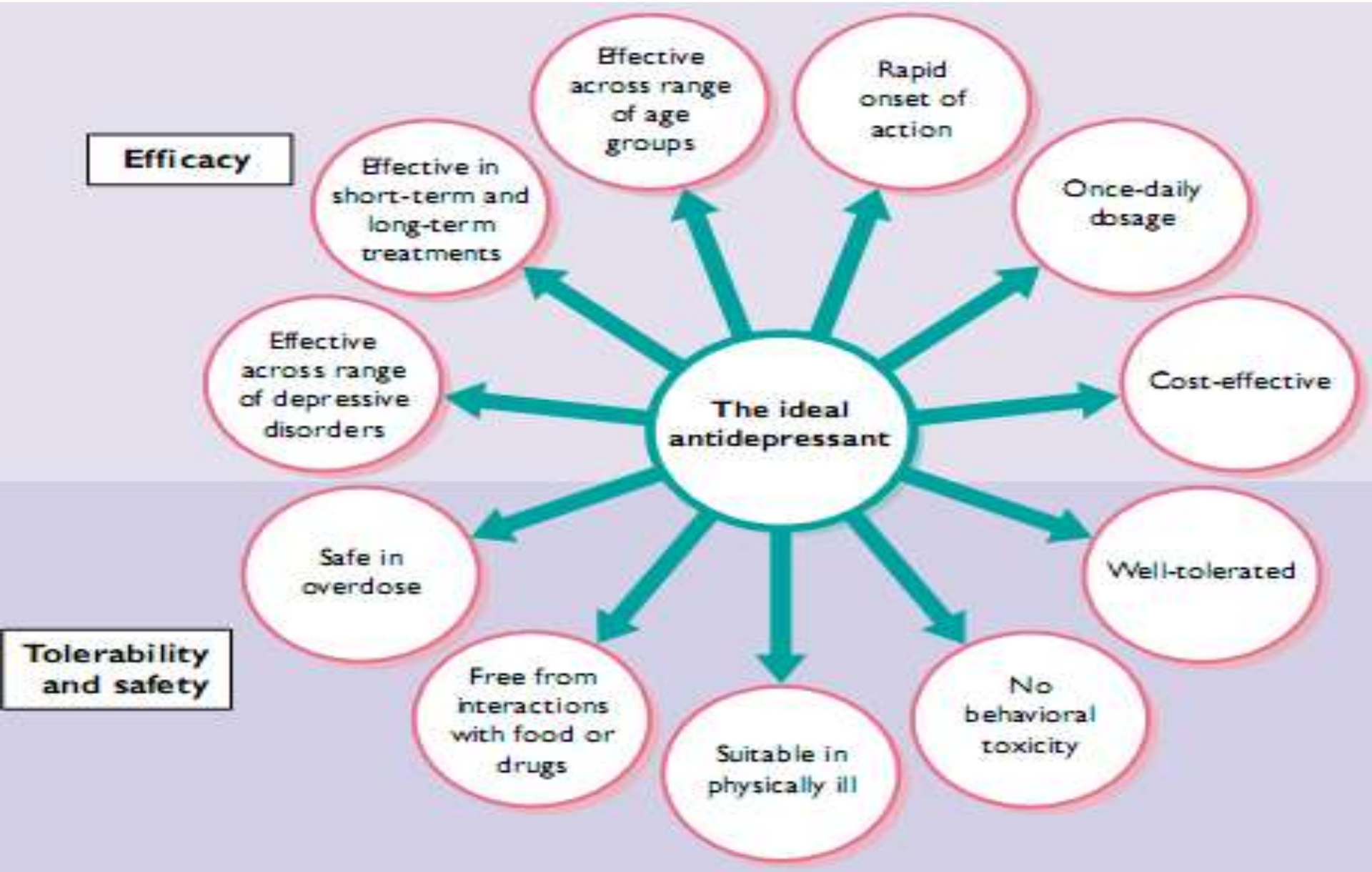
Tgt

- Karakter penyakit pasien
- ES obat
- Bahaya overdosis
- Tx sblmnya

Sec umum, jk KI(-), butuh efek sedatif → TCA

Tdk toleran dg TCA → SSRI, SNRI, NaSA, dll

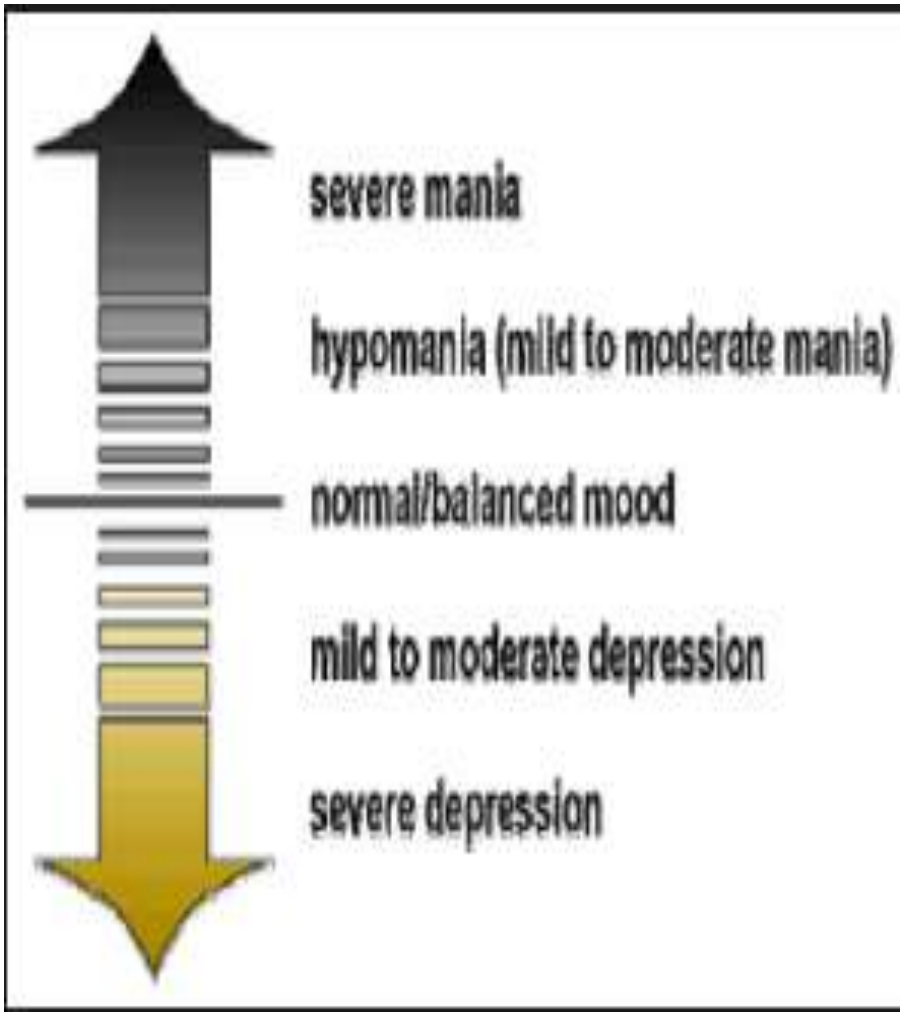
THE IDEAL ANTIDEPRESSANT



MANIC DEPRESSIVE / BIPOLAR

Definisi

- merupakan gangguan mood yang bersifat siklik dengan fluktuasi perasaan, energi, dan kelakuan dari ujung-ujung yang ekstrim



Teori Neurotransmitter

- Gangguan mood disebabkan krn ketidakseimbangan neurotransmiter di SSP
- Kelebihan senyawa amin (NE dan dopamin) →mania;
- kekurangan NE, Dopamin, 5-HT →depresi
- ketidakseimbangan antara aktivitas/rasio DA dan NE →
- perubahan mood dari depresi ke mania
- Jika NE turun→dopamin mendominasi →switch ke hipomania atau mania

Teori Kation dan Membran

- perubahan keseimbangan elektrolit, terutama Ca dan Na, diduga terkait dgn fluktuasi mood pada bipolar
- perubahan [Ca] ekstrasel dan intrasel dpt mempengaruhi pelepasan dopamin, NE dan 5-HT→eksitabilitas saraf → mempengaruhi variasi perasaan dan switch dari depresi ke mania atau sebaliknya
- Pasien bipolar yang tidak diobati memiliki konsentrasi Ca intrasel yang lebih tinggi pada limfosit dan plateletnya dibanding orang normal
- Obat-obat Ca bloker: memblok kanal Ca (L-type) → menurunkan Ca intraseluler → memblok aktivitas 5-HT, dopamin, dan endorfin → mengurangi mania
- Lamotrigin : memblok kanal Na → menghambat pelepasan glutam at
- danaspartat, danmenurunkan aktivitas Ca

Tx Farmakologis

Classic Mood Stabilizer:

Lithium

Anticonvulsants:

Valproic acid
Carbamazepine
Lamotrigine
Gabapentin
Topiramate

- **Lini pertama :**Lithium, Valproat,
- **Lini kedua/alternatif:** Carbamazepin, Gabapentin, lamotrigin, topiramat (antikonsvulsan), nimodipin, verapamil (Ca bloker), olanzapin, risperidon (antipsikotik atipikal)

Pilihan Mood Stabilizer pd Kondisi Khusus

Kondisi	Lini pertama	Lini kedua
Pasien dgn agitasi atau kekerasan	VPA atau Li, lalu Li/VPA + ApAt	VPA ± Li ± ApAt ± BZD
Gangguan jantung/gagal jantung	VPA	Ca bloker
Penyalahguna obat: kokain atau alkohol	VPA atau Li	CBZ, VPA+Li, CBZ+Li, CBZ+VPA
Pasien geriatri	VPA atau Li	CBZ, VPA+Li, CBZ+Li, CBZ+VPA
Gangguan liver	Li	CBZ, VPA, Ca bloker, antipsikotik → 25-50% dose reduction
Gangguan ginjal	VPA atau CBZ	Okskabarzepin
Gangguan neurologis	VPA	CBZ atau Oxcabarzepin
Kehamilan	Antipsikotik, BZD, Ca bloker; Li mungkin bisa diberikan pada trimester I	Li atau VPA setelah trimester I, Klonazepam atau CBZ digunakan sbg lini ketiga setelah trimester I, Gabapentin, lamotrigin, topiramat

Prinsip Tx Bipolar

- pengobatan gangguan bipolar harus dilakukan secara individual karena gambaran klinis, keparahan, dan frekuensi kejadian yang sangat bervariasi antar pasien
- episode hipomanik mungkin tidak perlu pengobatan, kecuali jika pasien memiliki sejarah pernah mengalami episode manik
- episode manik pertamakali umumnya diobati dengan lithium (Li) dan Tx tambahan seperti benzodiazepine untuk membantu tidur
- episode manik kambuhan dapat diobati dengan Li, atau valproat (VPA), bersama dengan benzodiazepine untuk insomnia-nya

- jika episode mania diikuti dengan psikosis→terapi yang sama dapat diperpanjang sampai mania berkurang
- jika pasien tdk berespon dalam 2-3 minggu → bisa ditambah obat-obat stabilizer mood yang lain (kombinasi)
- jika masih tidak ada respon → perlu dilakukan ECT
- sekali pasien sembuh, diperlukan terapi pemeliharaan untuk mencegah terjadinya kekambuhan → terapi pemeliharaan yang skrg direkomendasikan (2005) : Litium atau lamotrigin jangka panjang
- monoterapi lebih disukai untuk terapi pemeliharaan jangka panjang, tetapi kombinasi mungkin dibutuhkan bagi pasien dengan episode campuran

Mild to moderate symptoms of mania or mixed episod

1. Mulai dg Litium atau valproat atau antipsikotik atipikal (olanzapin, quetiapin, risperidon)
Alternatif antikonvulsan: karbamazepin, lamotrigin, atau oxcabarzepin
2. Jika respon tidak adekuat: tambah benzodiazepin (lorazepam atau klonazepam) jika perlu (utk agitasi atau insomnia)
3. Jika respon tdk adekuat, pertimbangkan
- kombinasi Li + antikonvulsan or antipsikotik atipikal
- kombinasi antikonvulsan + antikonvulsan or antipsikotik atipikal

Moderate to severe symptoms of mania or mixed episode

1. Mulai dg kombinasi 2 obat : Litium atau valproat plus antipsikotik atipikal (olanzapin, quetiapin, risperidon)
Alternatif antikonvulsan : karbamazepin, lamotrigin, atau oxcabarzepin
2. Jika respon tidak adekuat: tambah benzodiazepin (lorazepam atau klonazepam) jika perlu (utk agitasi atau insomnia)
3. Jika respon tdk adekuat, pertimbangkan kombinasi 3 obat:
- Li + antikonvulsan + antipsikotik atipikal
- antikonvulsan + antikonvulsan + antipsikotik atipikal
4. Jika respon tdk adekuat, pertimbangkan ECT utk mania dg psikosis atau katatonia, atau tambahkan klozapin

Mild to moderate symptoms of depressive episode

Mulai dg atau optimasi penggunaan mood stabilzer : Litium atau lamotrigin

Alternatif : karbamazepin, atau oxcabarzepin

Moderate to severe symptoms of depressive episode

1. Mulai dg kombinasi 2 obat : Litium atau lamotrigin plus antidepresan; atau Li + lamotrigin

Alternatif antikonvulsan : karbamazepin, lamotrigin, atau oxcabarzepin

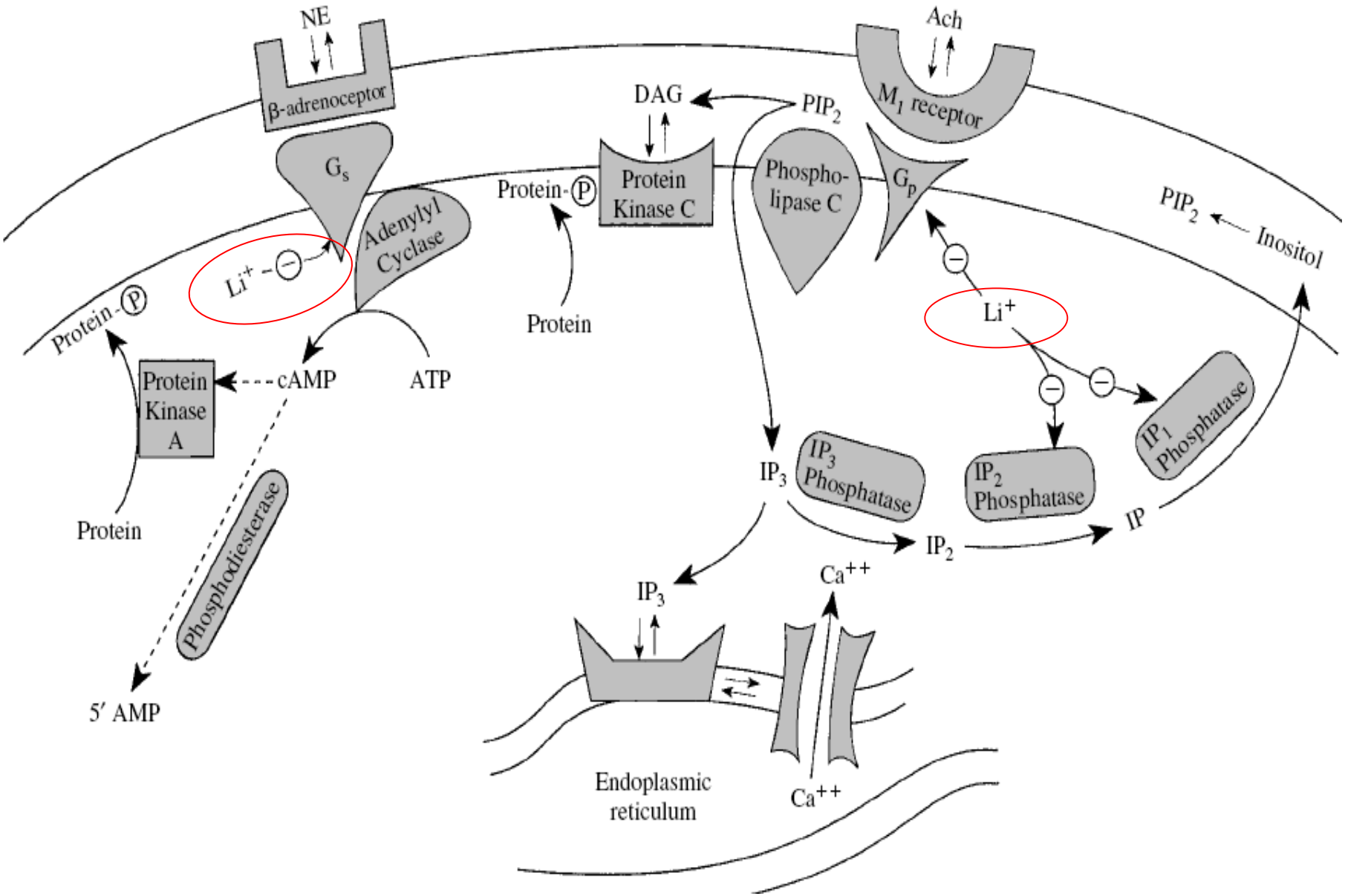
2. Jika respon tidak adekuat, tambah antipsikotik atipikal jika ada tanda-tanda psikotik (halusinasi, delusi)

3. Jika respon tdk adekuat, pertimbangkan kombinasi 3 obat:

- Li + antikonvulsan + antidepresan
- Lamotrigin+ antikonvulsan + antidepresan

4. Jika respon tdk adekuat, pertimbangkan ECT

LITHIUM


NE
β-adrenoceptor
Ach
M1 receptor
DAG
PIP2
Gs
Protein-P
Protein Kinase C
Phospho-lipase C
Gp
PIP2
Inositol
Adenylyl Cyclase
Li+
Protein-P
Protein
Li+
Protein Kinase A
cAMP
ATP
Protein
IP3
IP3 Phosphatase
IP2 Phosphatase
IP1 Phosphatase
IP2
IP
Phosphodiesterase
5′ AMP
IP3
Ca++
Endoplasmic reticulum
Ca++

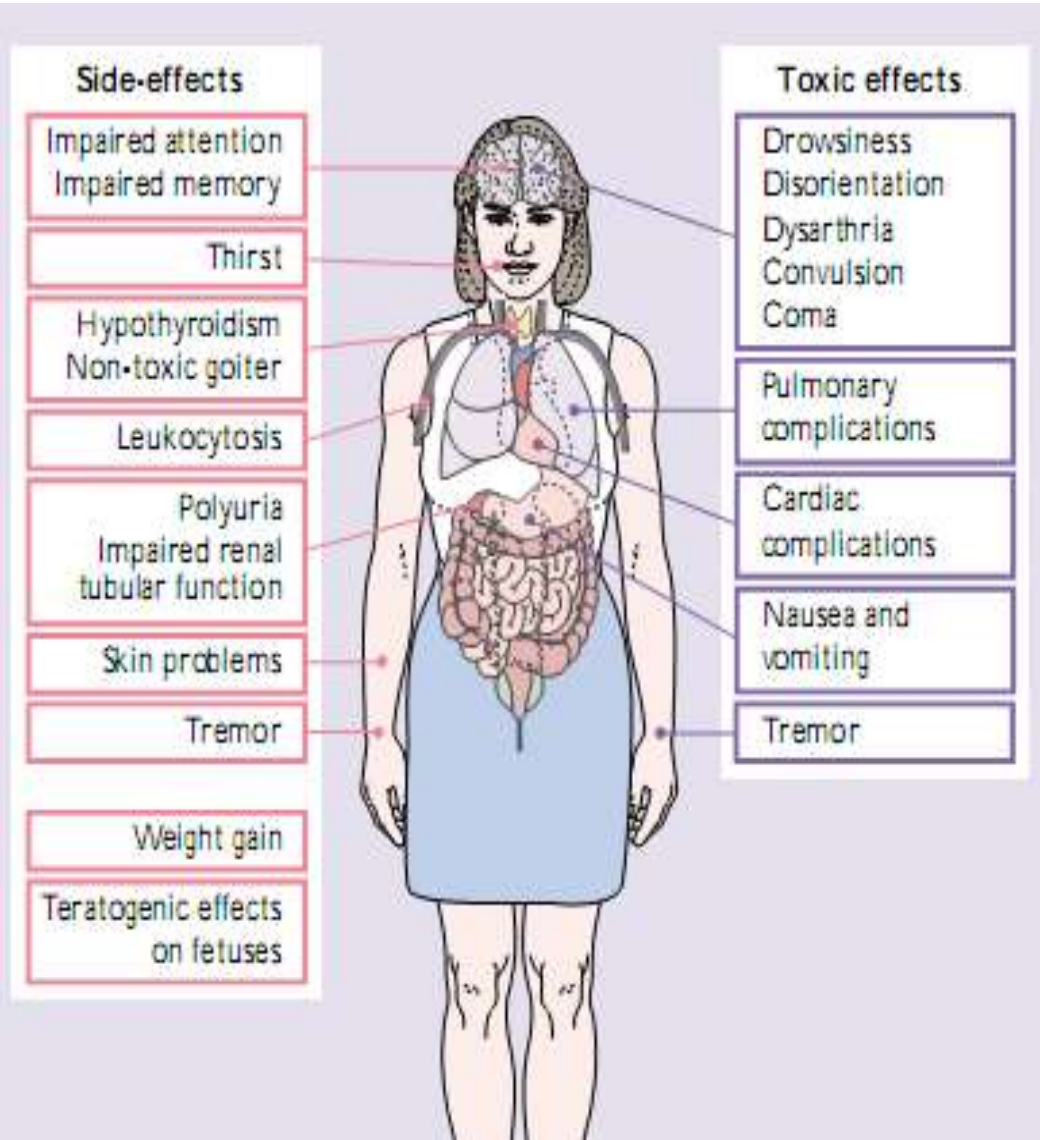
- The actions of Li on postsynaptic receptor-mediated second-messenger signaling systems.

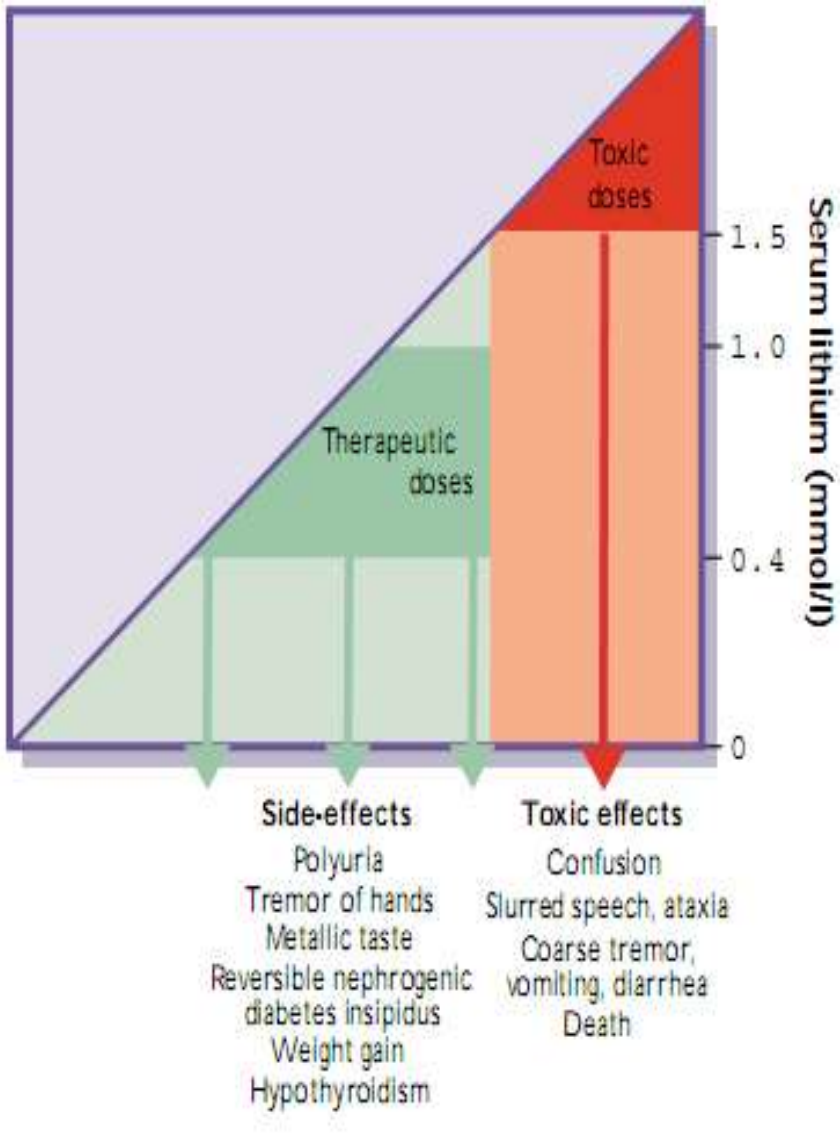
- Lithium can simultaneously alter the flow of synaptic information through several receptor mediated systems by diminishing coupling between the receptor recognition site and its specific G proteins. This model explains the stabilizing actions of Li at both ends of the mood spectrum through a single action at the G-protein level. Attenuating actions of Li have been demonstrated through G-protein interactions at the β-adrenoceptor and the acetylcholine M1 muscarinic receptor systems of the CNS.

- A second action of Li as an inhibitor of inositol diphosphate (IP2) phosphatase may further attenuate the flow of synaptic information through the M1 muscarinic receptor by the eventual depletion of membrane phosphatidyl inositol-bis-phosphate (PIP2).
- IP3, inositol triphosphate; DAG, diacylglycerol; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; 5-AMP, 5-adenosine monophosphate; NE, norepinephrine; ACh, acetylcholine.

LITHIUM

- Berupa garam litium yaitu Li-carbonat , relatif teratogenik (dose-dependent), boleh utk anak > 12 th
- Indeks terapi sempit
- ES awal Tx : haus, mual, tremor halus, poliuria
- ES jangka panj : diabetes insipidus → polidipsi
- Hamb kerja vasopressin di ginjal →obligat water loss
- Ggn fs thyroid →goiter, hipotiroid
- Mencapai steady state stl 2-3 mgg


Side-effects
Impaired attention
Impaired memory
Thirst
Hypothyroidism
Non-toxic goiter
Leukocytosis
Polyuria
Impaired renal tubular function
Skin problems
Tremor
Weight gain
Teratogenic effects on fetuses
Toxic effects
Drowsiness
Disorientation
Dysarthria
Convulsion
Coma
Pulmonary complications
Cardiac complications
Nausea and vomiting
Tremor


Toxic doses
Therapeutic doses
1.5
1.0
0.4
0
Serum lithium (mmol/l)
Side-effects
Polyuria
Tremor of hands
Metallic taste
Reversible nephrogenic diabetes insipidus
Weight gain
Hypothyroidism
Toxic effects
Confusion
Slurred speech, ataxia
Coarse tremor, vomiting, diarrhea
Death

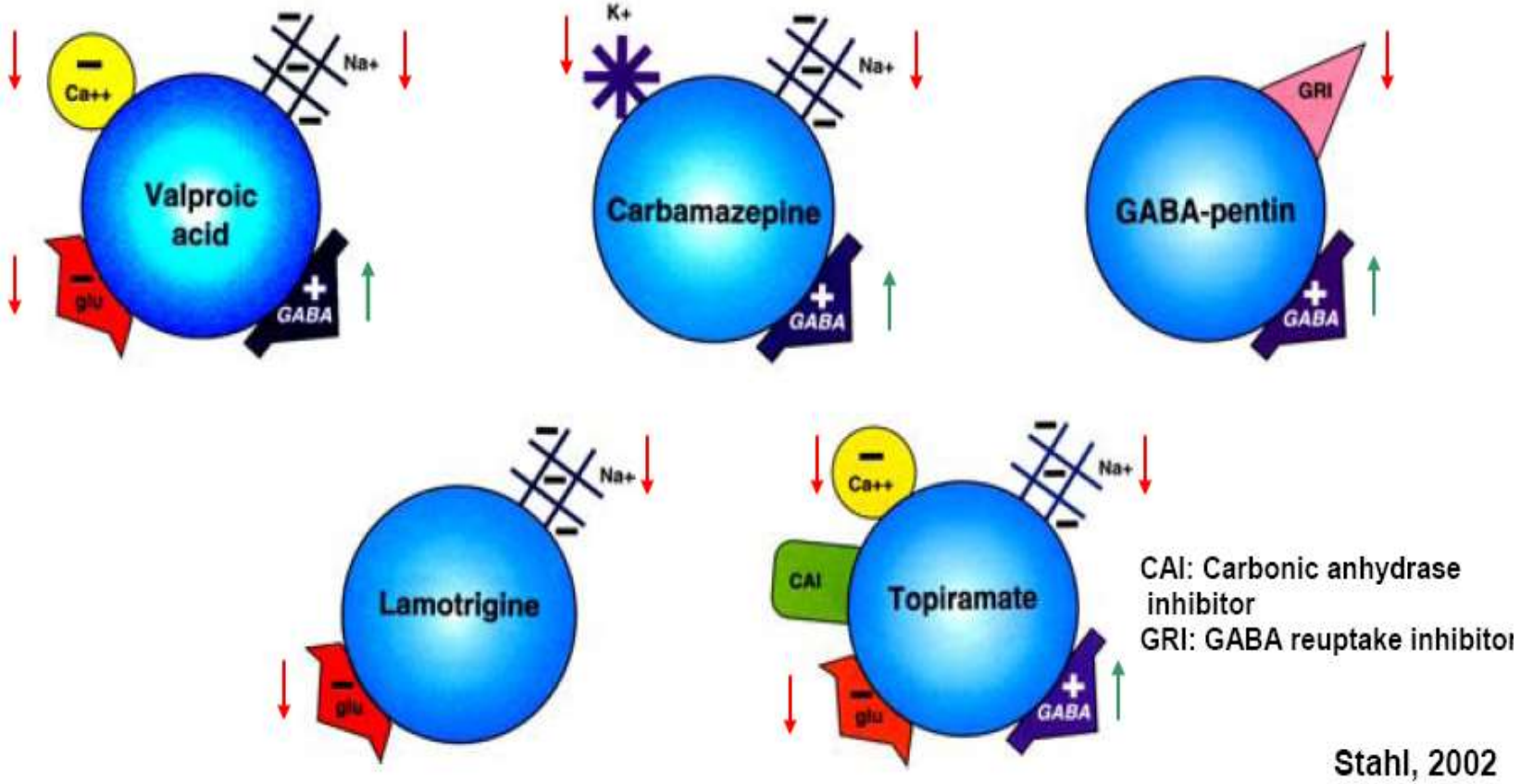
Anticonvulsants

Reduces neuronal activity by:

-Reducing flux of ions through voltage-gated ion channels, such as Na^+, K^+, Ca^{2+}

-Enhancing inhibitory neurotransmission with GABA, by increasing its synthesis, release, or inhibiting its breakdown

-Reducing excitatory neurotransmission with glutamate by reducing its release



Stahl, 2002

Other Mechanisms of Action of Anticonvulsants

- Inhibit PKC (carbamazepine)
- Inhibit adenylyl cyclase activity (carbamazepine)
- Decreases inositol monophospahte activity (carbamazepine)
- Increase neurogenesis (valproic acid)
- Increase expression of Bcl-2, thus cause neuroprotection (valproic acid)

Na VALPROAT

- 1st line drug atau adjunct pd kasus refrakter
- Mek kerja tdk jelas
- Me ↑sintesa, turn-over & release GABA
- Hamb influk Ca mel R/ NMDA
- me ↑ fs serotonergik & me↓ fs dopaminergik

CARBAMAZEPIN

- Efektif cegah relaps BPAD =Li
- Efek pd 2^{nd} messenger
- Hamb Ca influk mel R/ NMDA, GABAb
- Stabilisasi kanal Na
- Potensiasi R/$\alpha 2$
- ES : diplopi, ataksia, mual, nyeri kepala, ggn hematologi (agranulositosis, lekopeni)
- Perlu cek kdr CBZ & DL stp 2 mgg pd 2 bln pertama Tx

Drug associated with manic reaction

Dopaminomimetic: levodopa, bromocriptine, metoclopramide

Sympathomimetic: phenylephrine, theophylline, yohimbine, reserpine (withdrawal)

Antidepressant: tricyclics (also withdrawal); MAO inhibitors (also withdrawal); second-generation—amoxapine, trazodone, fluoxetine, alprazolam, buproprion

Gastrointestinal: cimetidine

Corticosteroid: prednisolone, others

Miscellaneous: fenfluramine, antimalarials, muscle relaxants, metrizamide, carbamazepine indomethacin, AZT (azidothymidine), penicillin IV

ALHAMDULILLAH.....