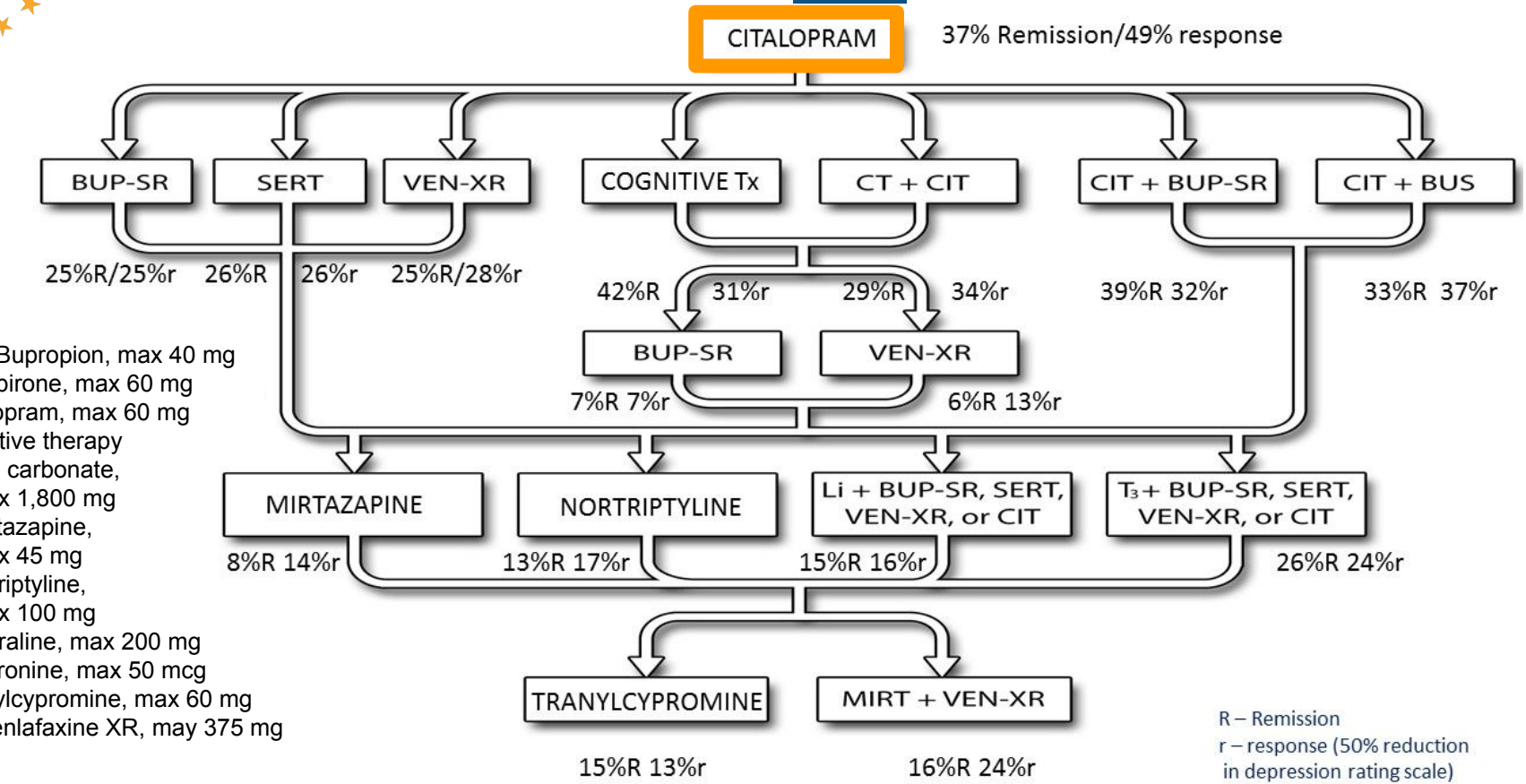
STAR*D Meds

Jason Cafer MD

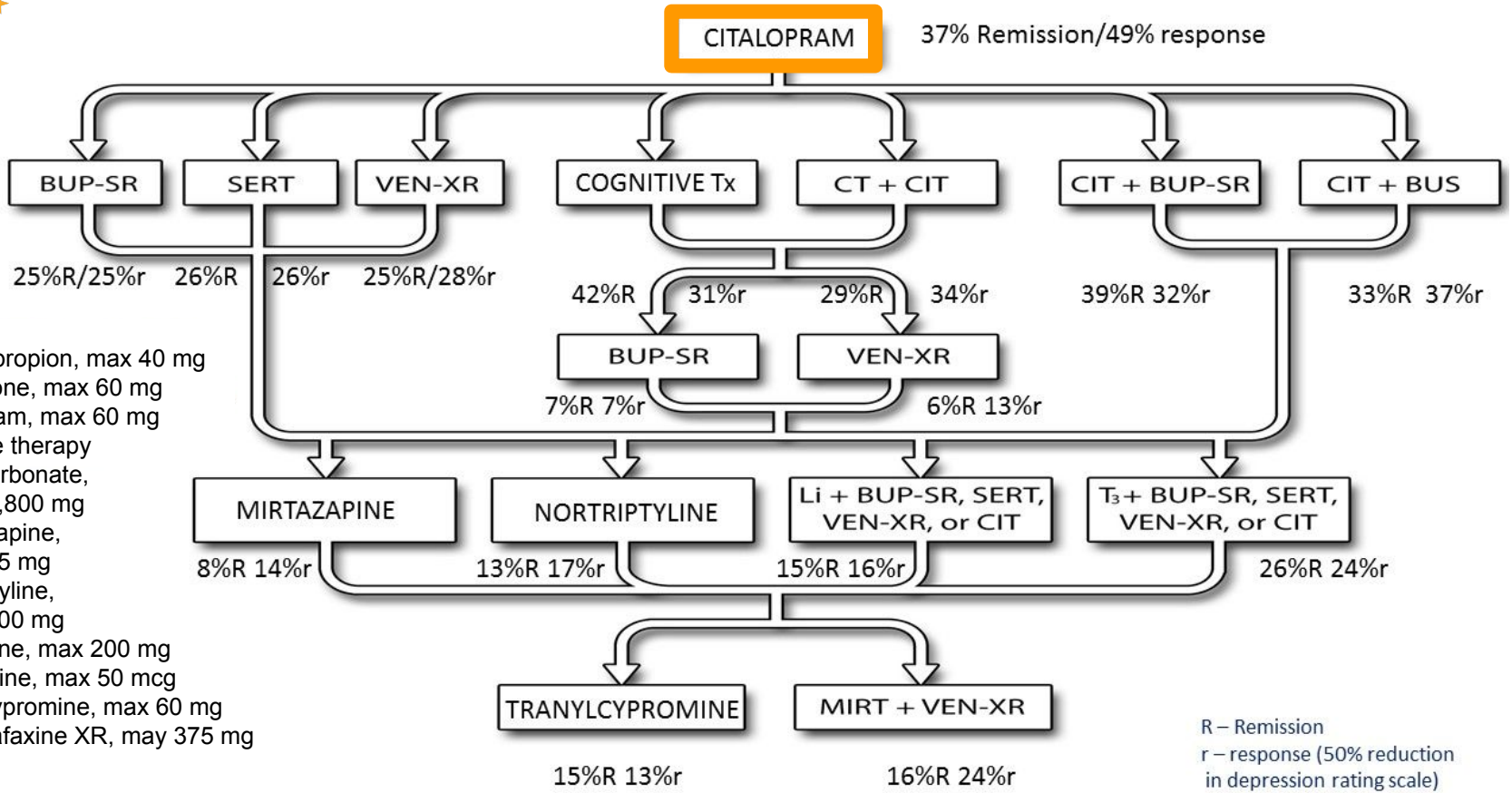
STAR*D medications were chosen in the year ?



BUP-SR – Bupropion, max 40 mg
BUS – Buspirone, max 60 mg
CIT – Citalopram, max 60 mg
CT – Cognitive therapy
Li – Lithium carbonate, max 1,800 mg
MIRT – Mirtazapine, max 45 mg
NTP – Nortriptyline, max 100 mg
SER – Sertraline, max 200 mg
T3 – Liothyronine, max 50 mcg
TCP – tranylcypromine, max 60 mg
VEN-X – venlafaxine XR, may 375 mg

R – Remission
r – response (50% reduction in depression rating scale)

STAR*D medications were chosen in the year 1999 (before the 2nd gen antipsychotic boom)



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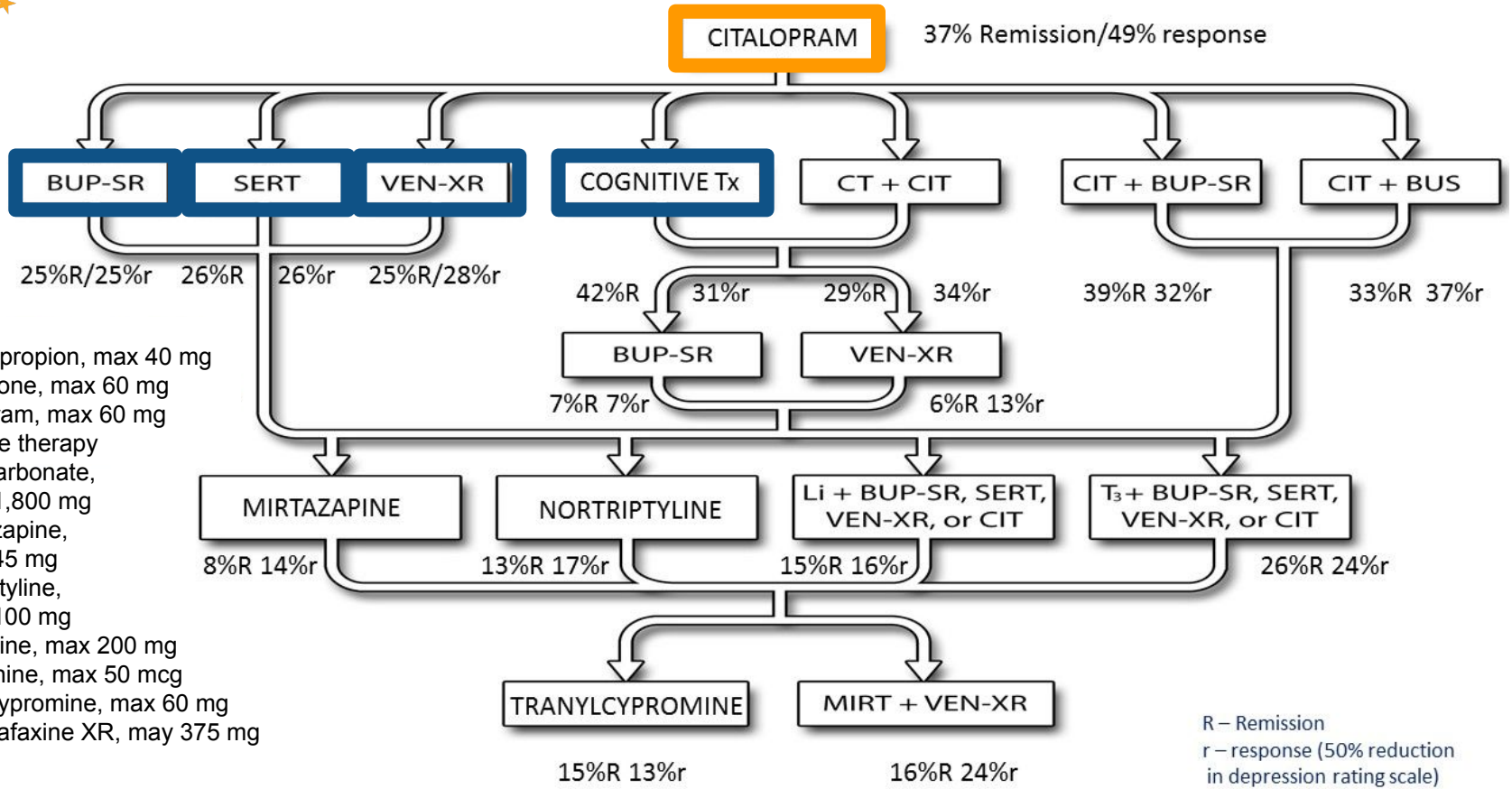

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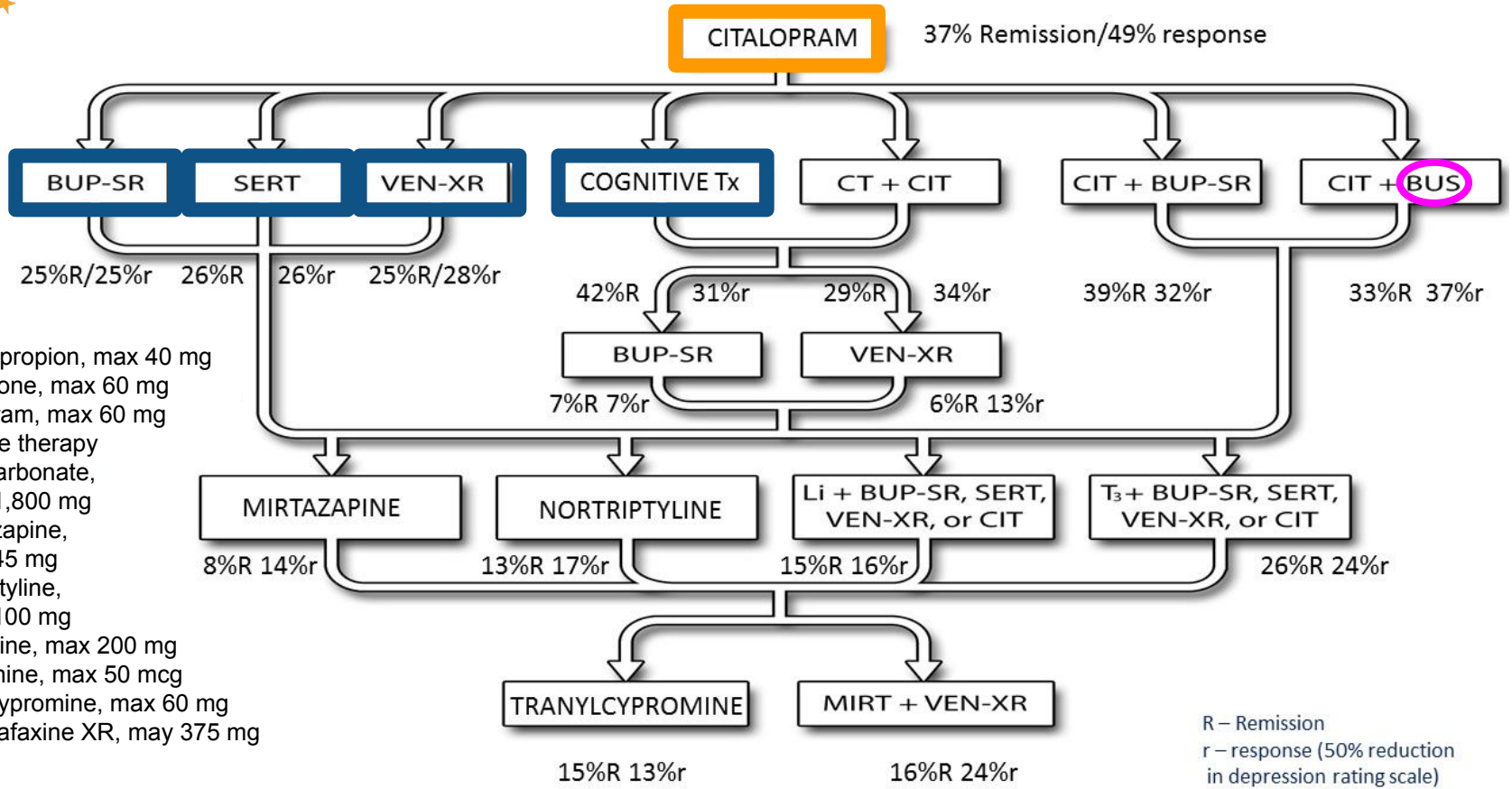

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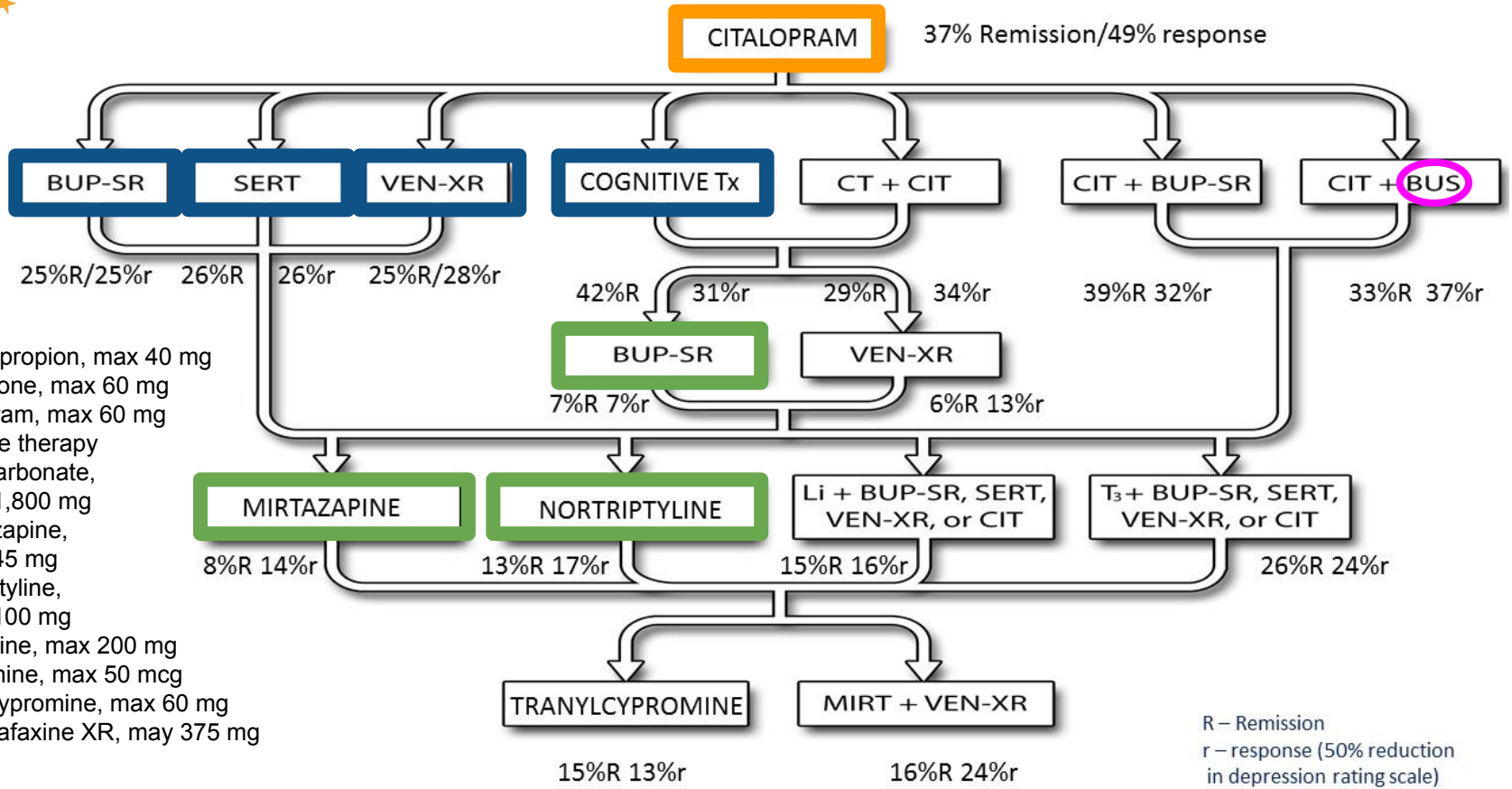

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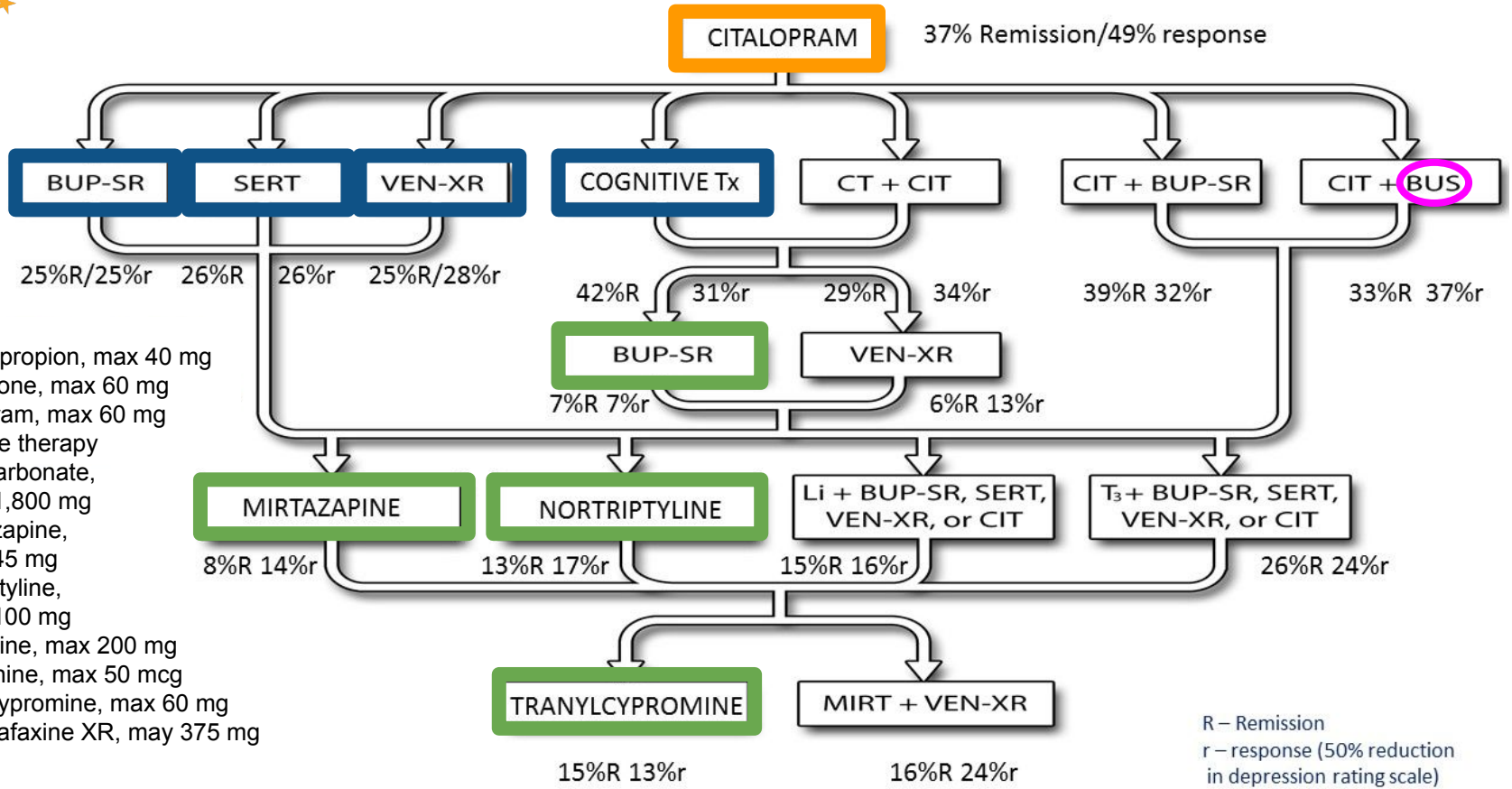

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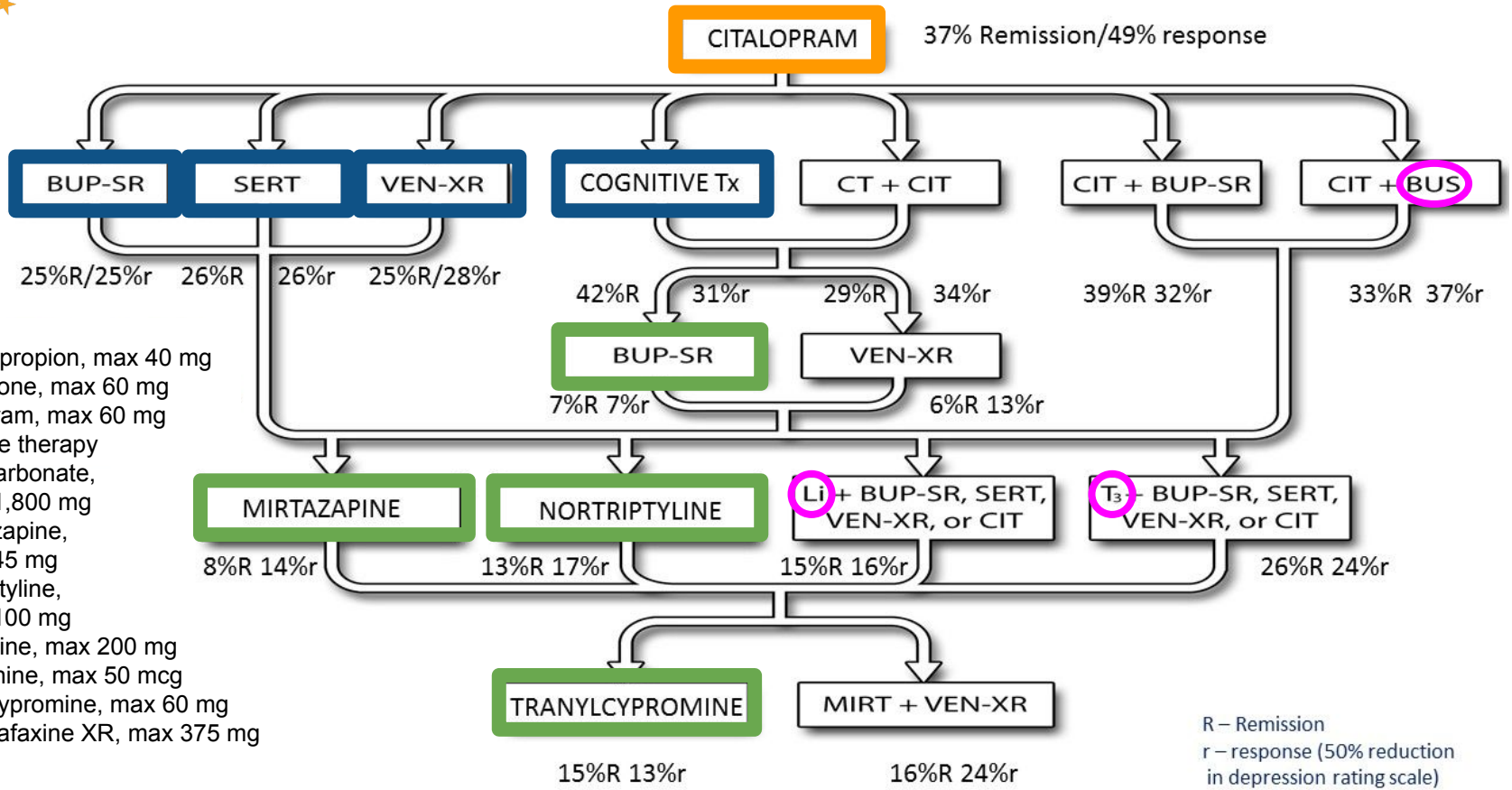

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= 10 meds, 7 of which are “antidepressants”

Neuroscience-based Nomenclature (NbN)

Pharmacological domains:

- Serotonin
- Dopamine
- Norepinephrine
- GABA
- Glutamate
- Histamine
- Acetylcholine
- Opioid
- Orexin
- Melatonin
- Adenosine
- Cannabinoid

Modes of action:

- Receptor agonist
- Receptor antagonist
- Receptor partial agonist
- Receptor inverse agonist
- Positive allosteric modulator
- Enzyme inhibitor
- Enzyme modulator
- Reuptake inhibitor
- Neurotransmitter releaser
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- Ion channel blocker
- Transcription activator

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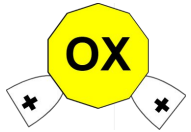

Orexin

Melatonin

Adenosine

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Neuroscience-based Nomenclature (NbN)

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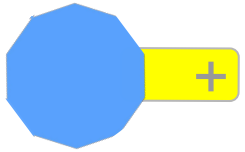
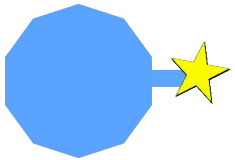
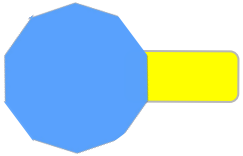
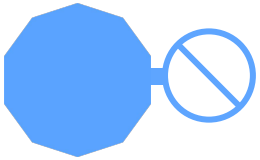
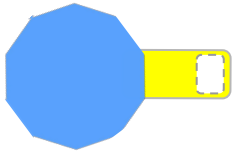


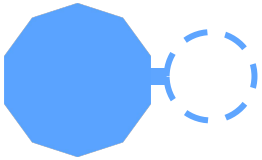
Agonist

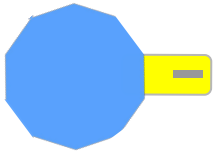

Positive allosteric modulator


Antagonist


Enzyme inhibitor


Partial agonist


Enzyme modulator

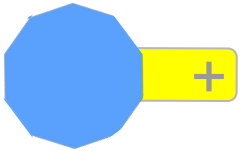


Inverse agonist

Neuroscience-based Nomenclature (NbN)

Modes of action:

- Receptor agonist
- Receptor antagonist
- Receptor partial agonist
- Receptor inverse agonist
- Positive allosteric modulator
- Enzyme inhibitor
- Enzyme modulator
- Reuptake inhibitor
- Neurotransmitter releaser
- Neurotransmitter depletor
- Ion channel blocker
- Transcription activator



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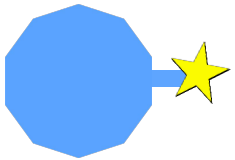
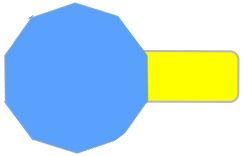
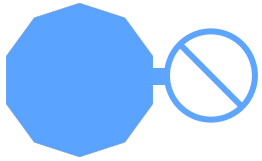


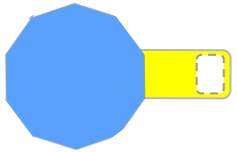
Positive allosteric modulator



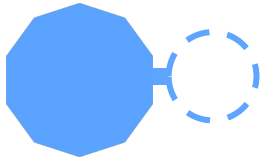
Antagonist



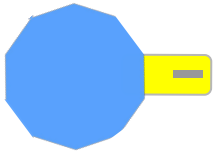
Enzyme inhibitor



Partial agonist



Enzyme modulator



Inverse agonist

Neuroscience-based Nomenclature (NbN)

Modes of action:

- Receptor agonist
- Receptor antagonist
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- Enzyme inhibitor
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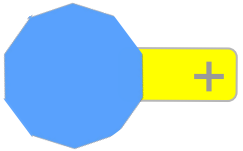
- Neurotransmitter releaser
- Neurotransmitter depletor
- Ion channel blocker
- Transcription activator



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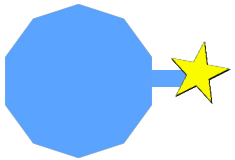
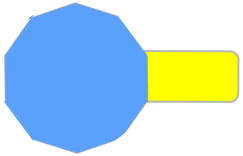
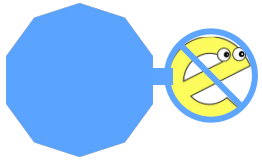


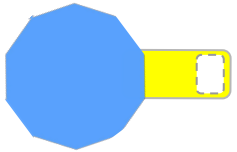
Positive allosteric modulator



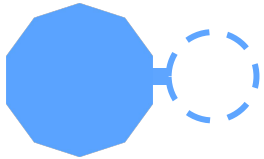
Antagonist



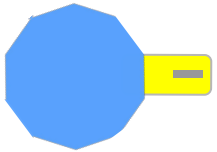
Enzyme inhibitor



Partial agonist



Enzyme modulator



Inverse agonist

Neuroscience-based Nomenclature (NbN)

Modes of action:

- Receptor agonist
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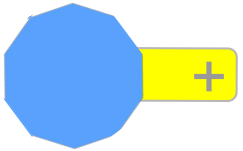

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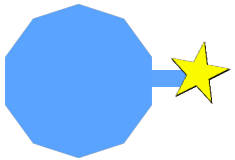
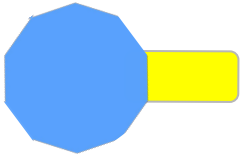
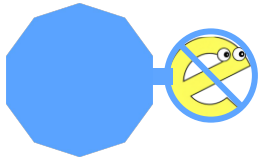


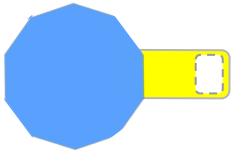
Positive allosteric modulator



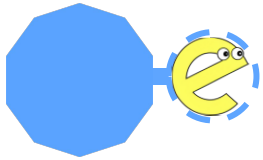
Antagonist



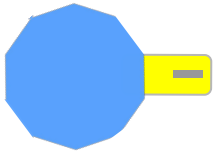
Enzyme inhibitor



Partial agonist



Enzyme modulator



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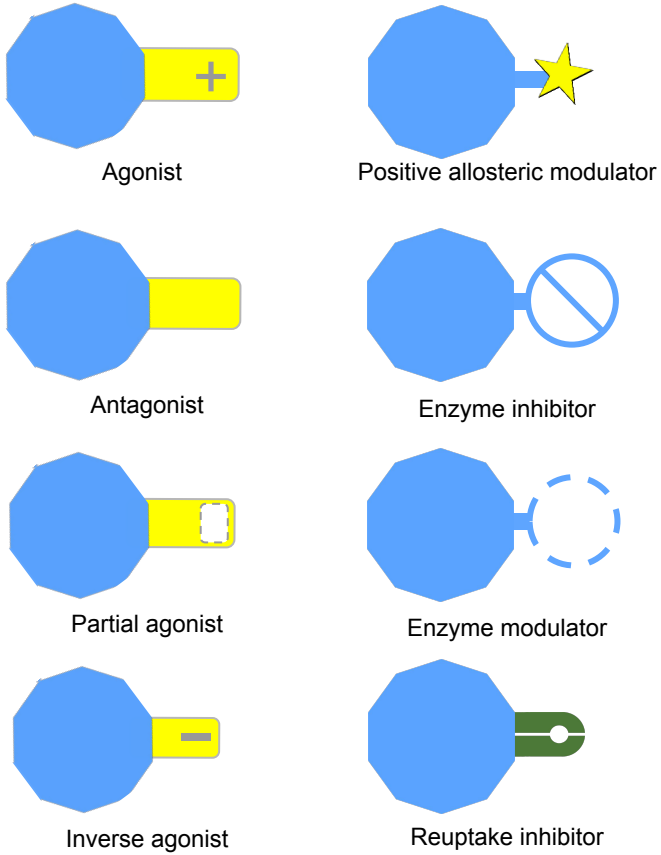

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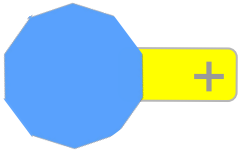
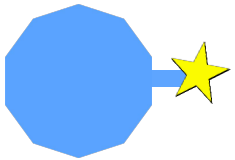
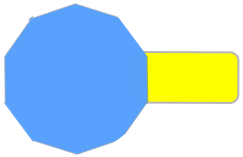
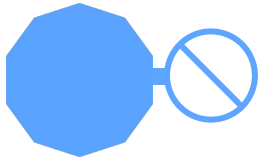


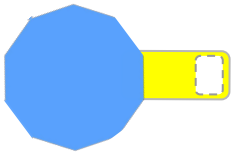
Agonist

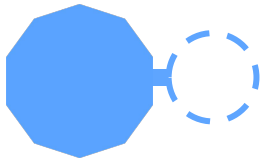

Positive allosteric modulator

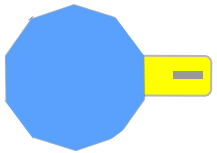
Neurotransmitter releaser


Antagonist

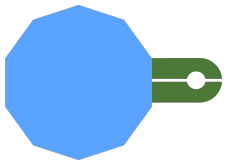

Enzyme inhibitor


Partial agonist


Enzyme modulator



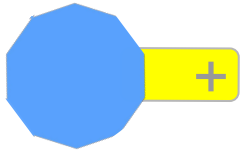
Inverse agonist


Reuptake inhibitor

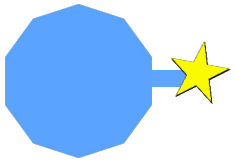
Neuroscience-based Nomenclature (NbN)

Modes of action:

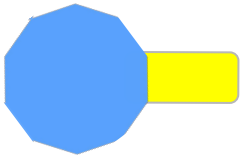
- Receptor agonist
- Receptor antagonist
- Receptor partial agonist
- Receptor inverse agonist
- Positive allosteric modulator
- Enzyme inhibitor
- Enzyme modulator
- Reuptake inhibitor
- Neurotransmitter releaser
- Neurotransmitter depletor
- Ion channel blocker
- Transcription activator

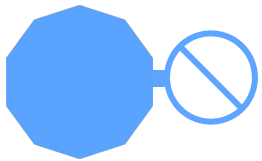


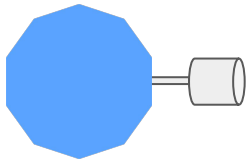
Agonist

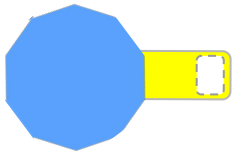

Positive allosteric modulator

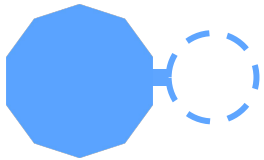
Neurotransmitter releaser

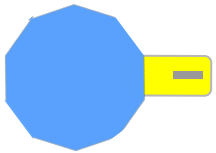

Antagonist


Enzyme inhibitor

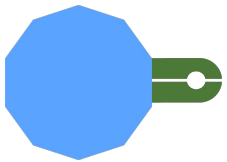

Ion channel blocker


Partial agonist


Enzyme modulator



Inverse agonist


Reuptake inhibitor

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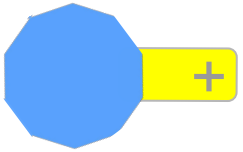
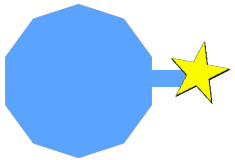
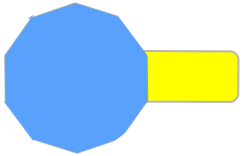
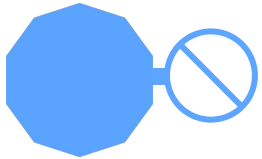


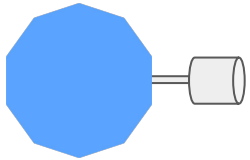
Agonist

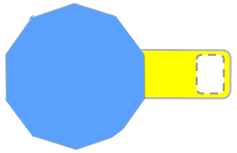

Positive allosteric modulator

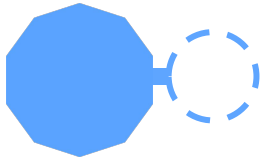
Neurotransmitter releaser


Antagonist

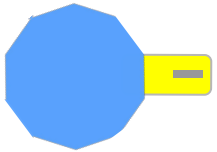

Enzyme inhibitor


Ion channel blocker

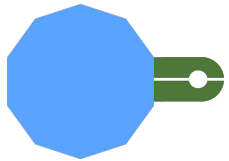

Partial agonist


Enzyme modulator


Transcription activator

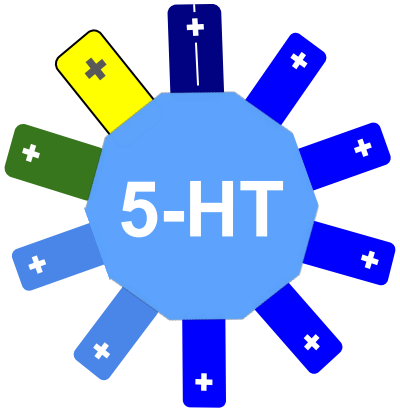


Inverse agonist

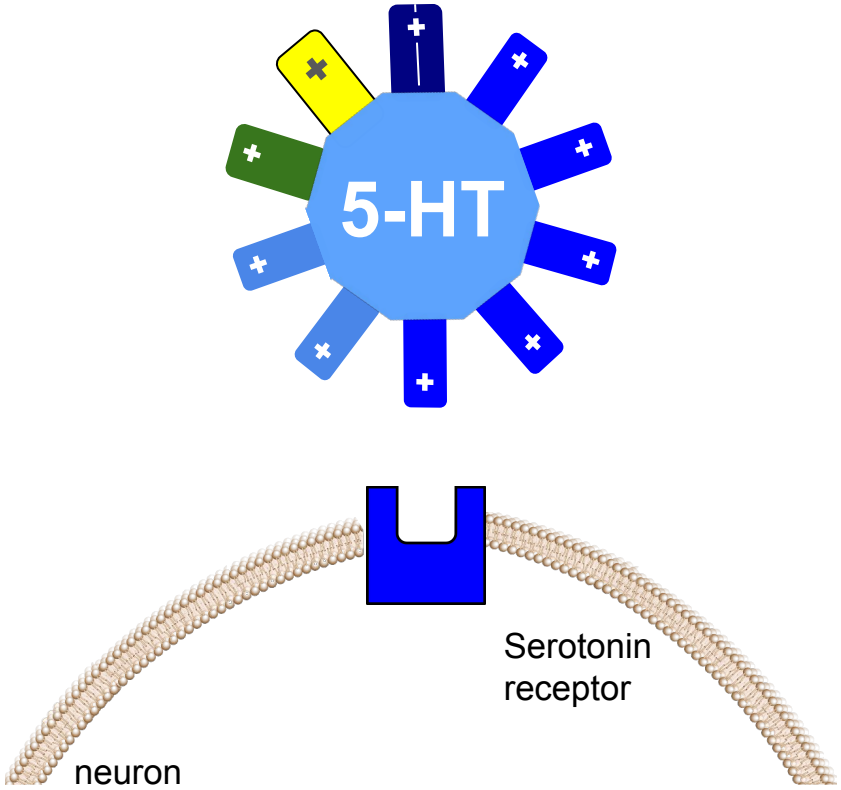

Reuptake inhibitor

Intracellular messenger

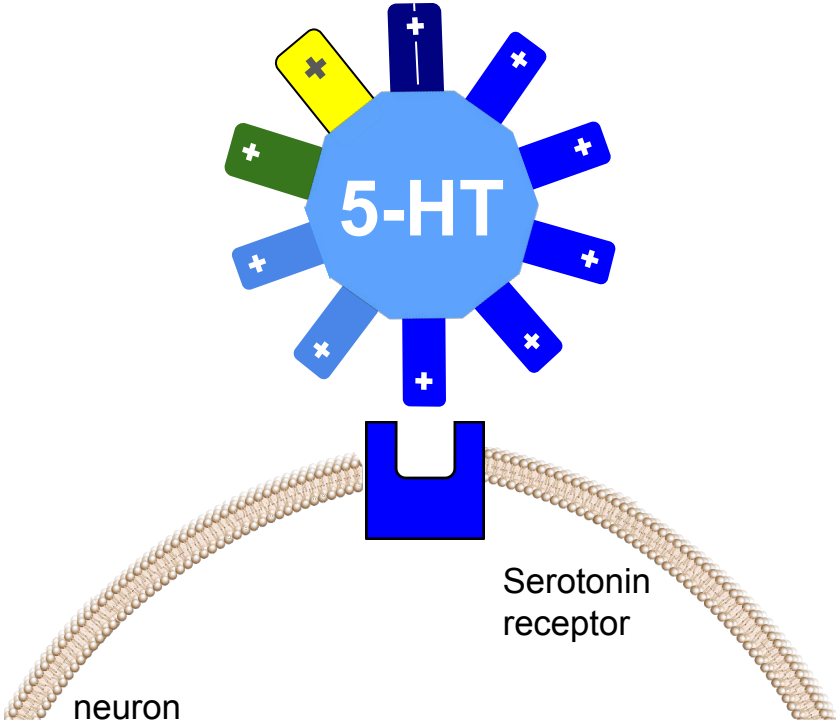
Serotonin – 5-HT receptor agonist



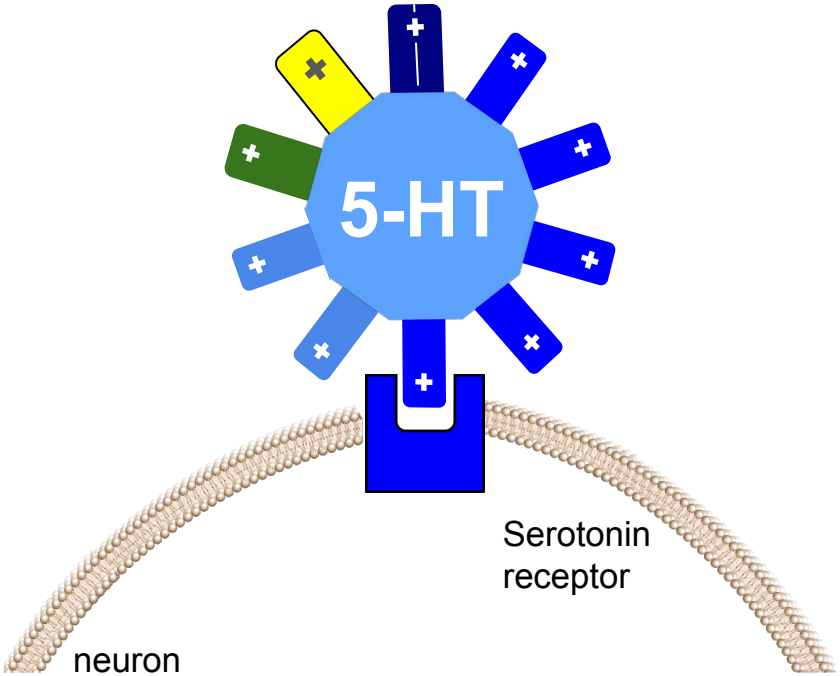
Serotonin – 5-HT receptor agonist



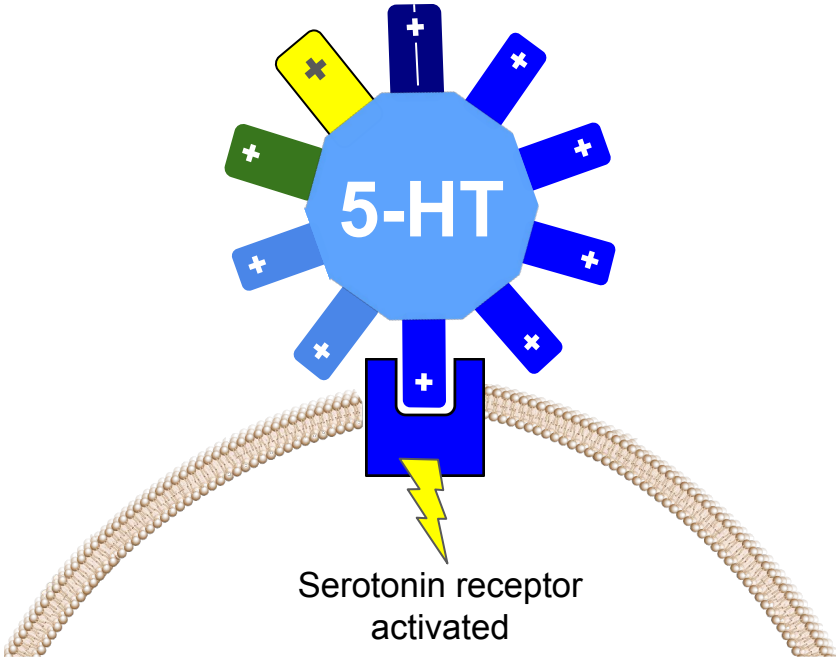
Serotonin – 5-HT receptor agonist



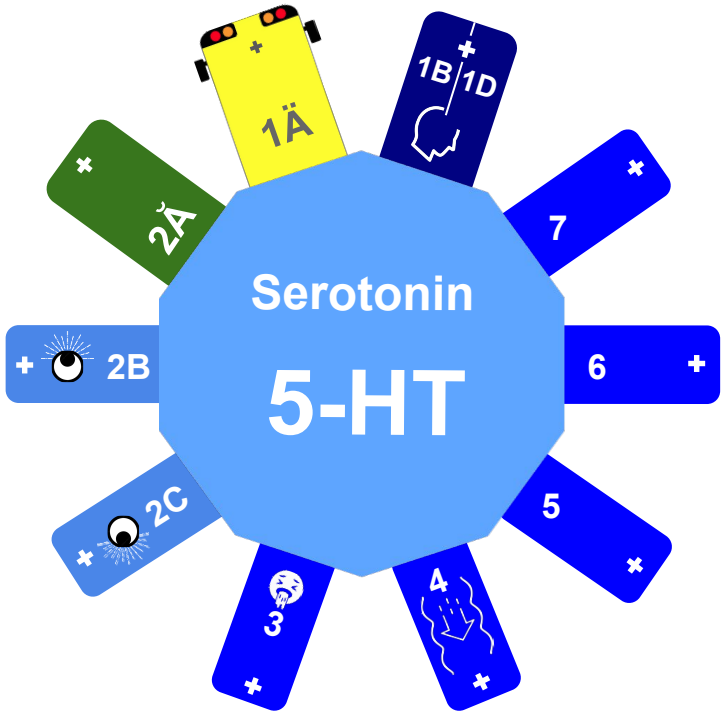
Serotonin – 5-HT receptor agonist

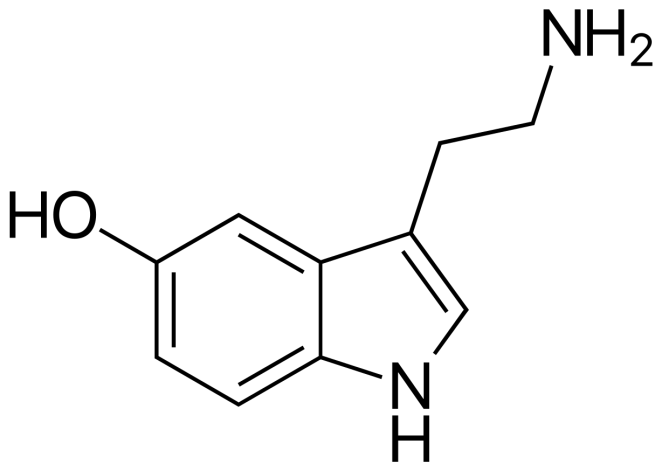


Serotonin – 5-HT receptor agonist



Serotonin – 5-HT receptor agonist



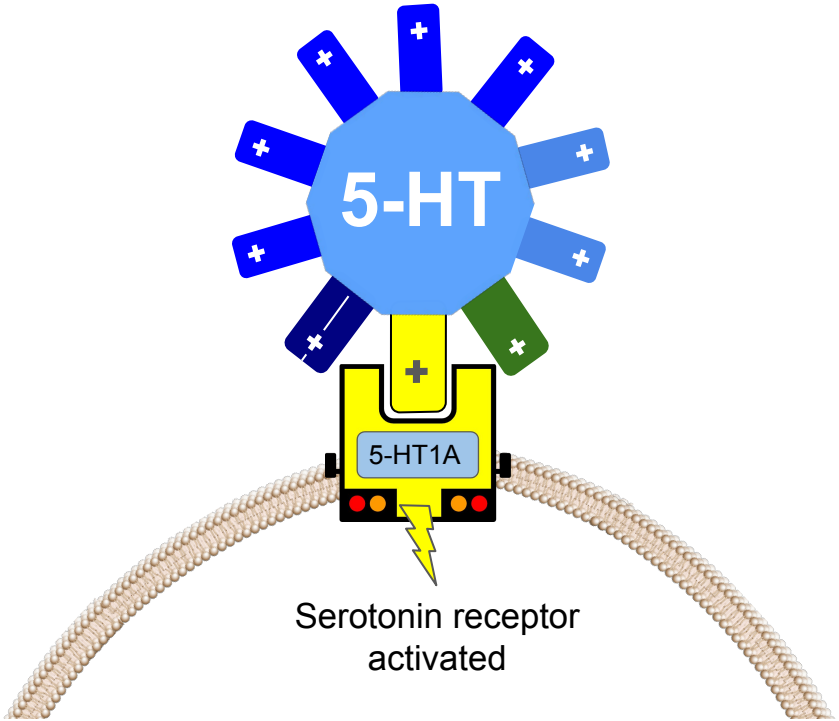


Serotonin – 5-HT receptor agonist

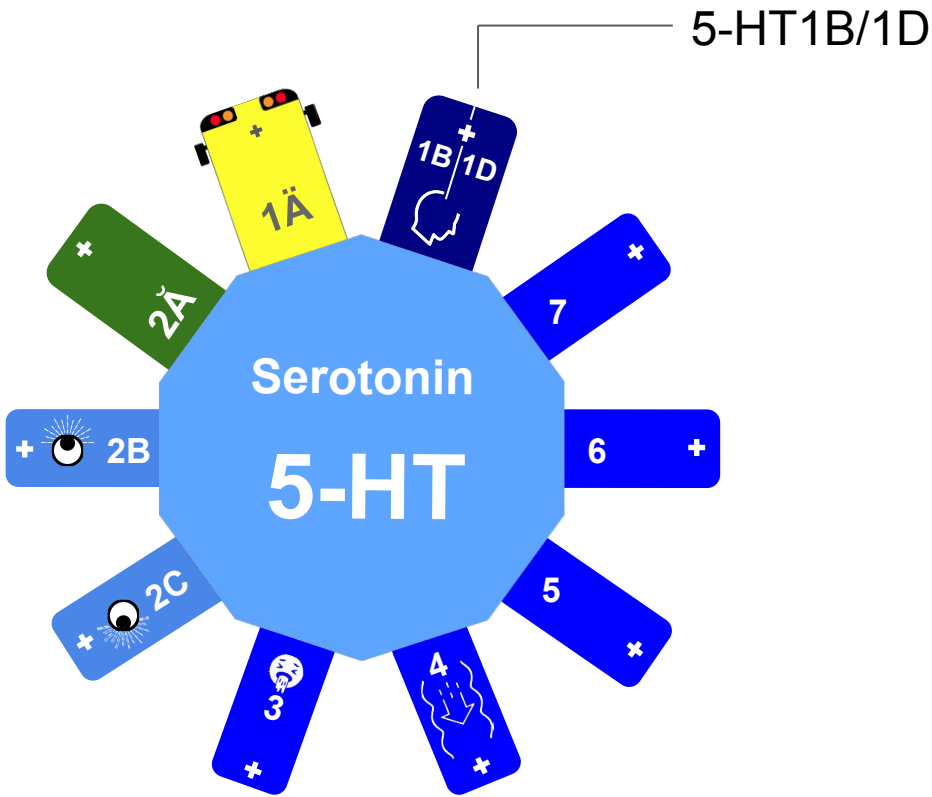
Buspirone (BUSPAR)

“Bus spear”

Serotonin – 5-HT receptor agonist



Serotonin – 5-HT receptor agonist



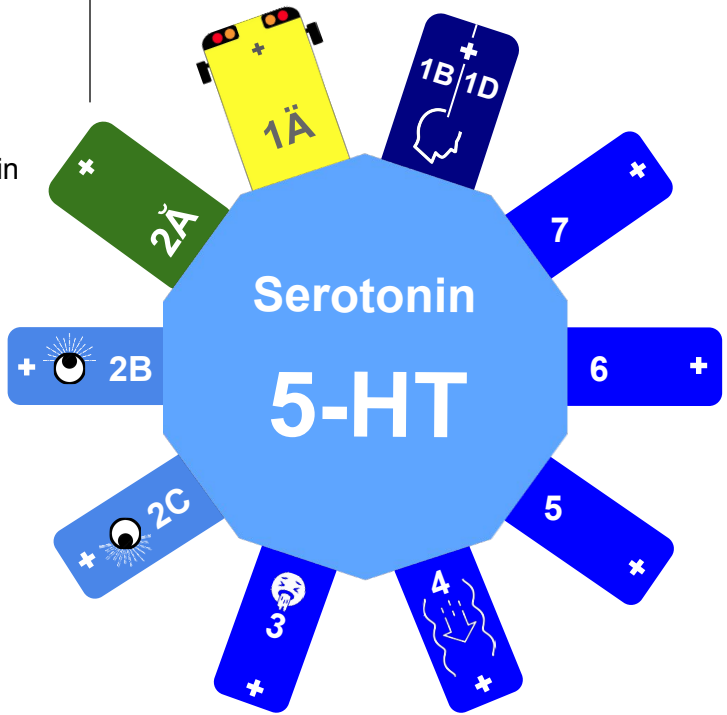
Sumatriptan (IMITREX)

“Sumo tripped (in my tracks)”

Serotonin – 5-HT receptor agonist

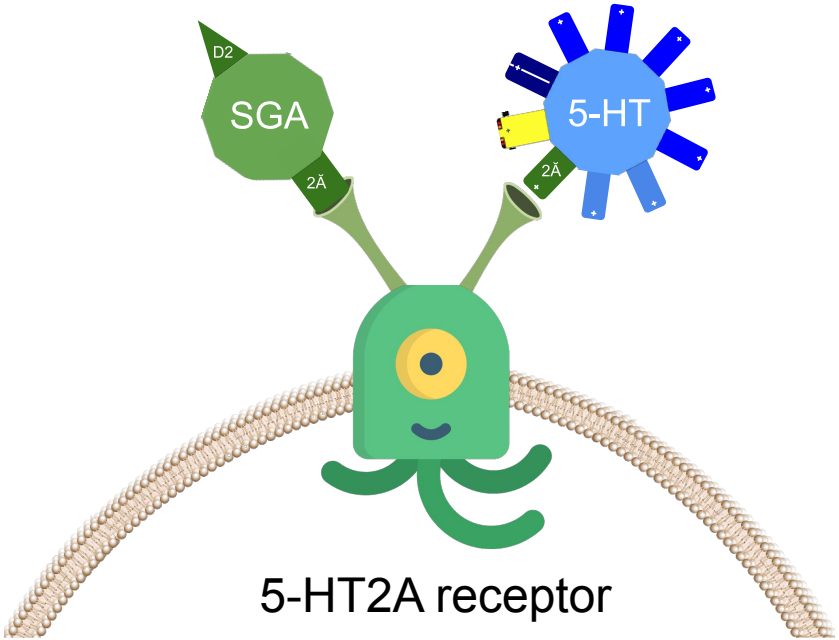
5-HT2A

The effect of psilocybin



"**2**nd generation **A**ntipsychotics"

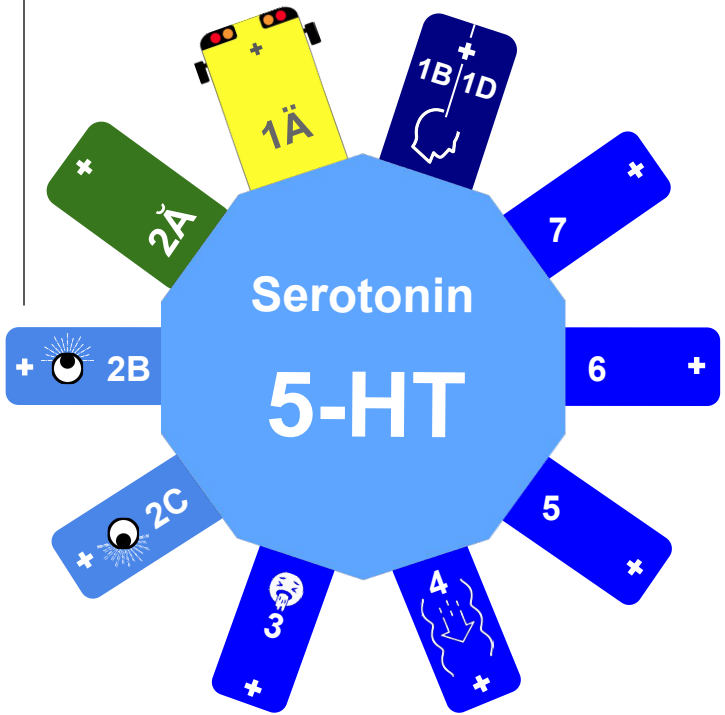
"**2** **A**ntennae"

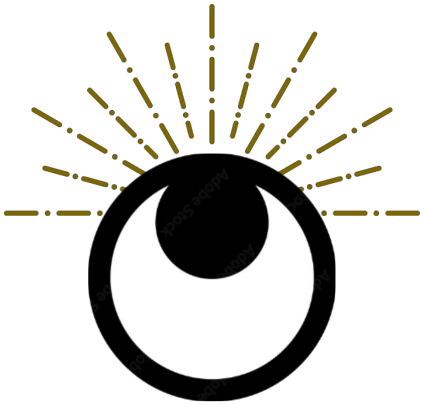


Serotonin – 5-HT receptor agonist

5-HT2B – weight loss

The effect of fenflur-amine

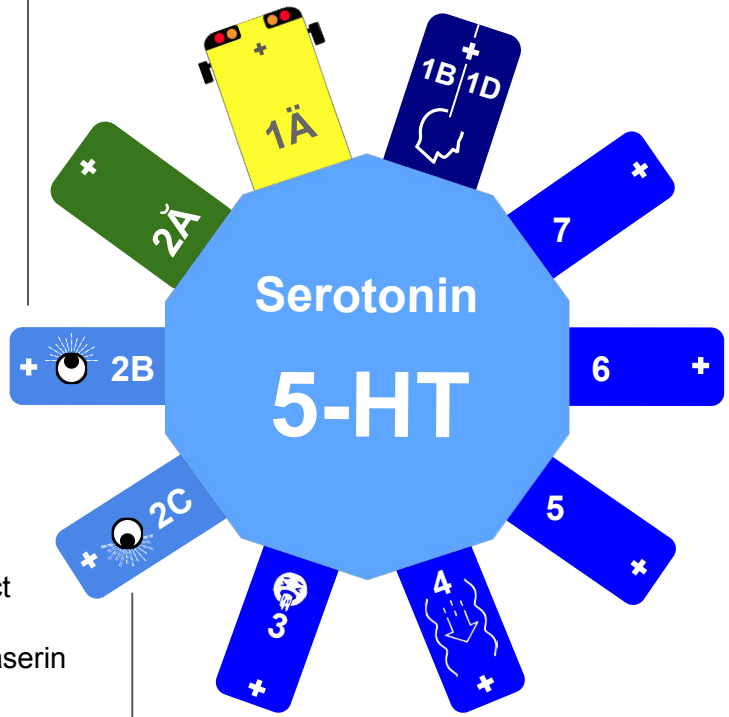




“I’d pray **2B** thin, but it would hurt my heart”

Serotonin – 5-HT receptor agonist

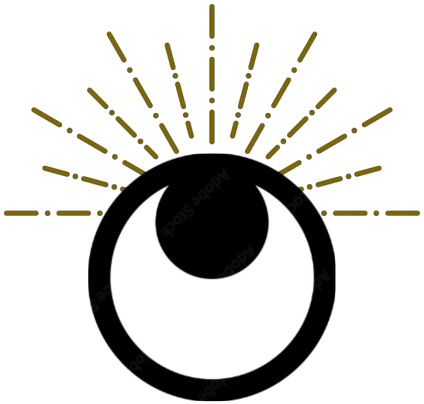
5-HT2B – weight loss



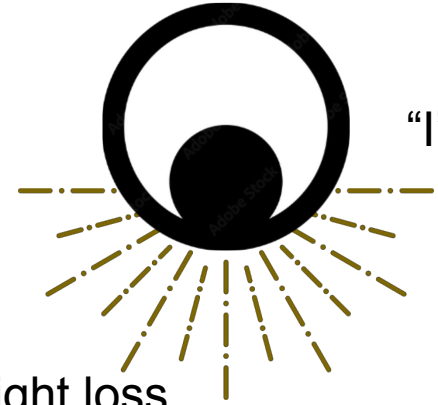
The effect of fenflur-amine

The effect of lorcaserin

5-HT2C – weight loss

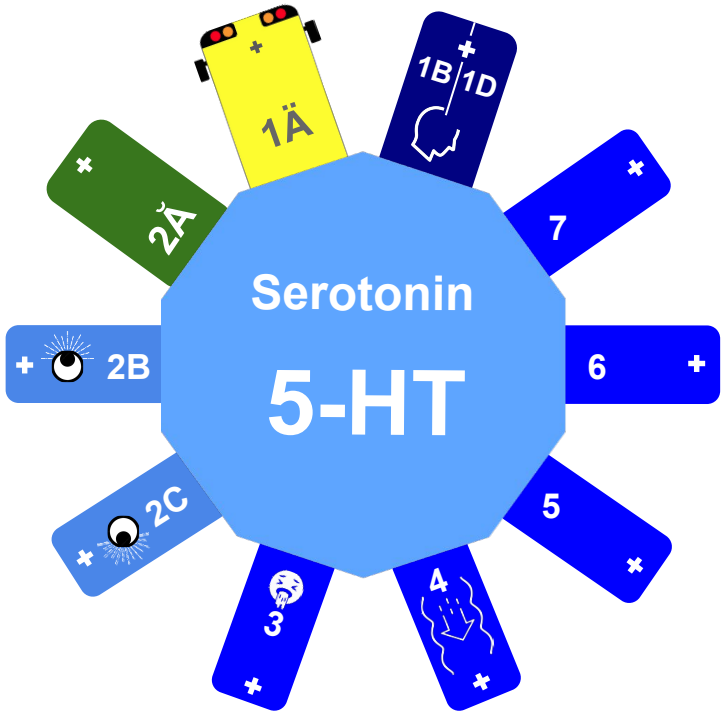


“I’d pray **2B** thin, but it would hurt my heart”



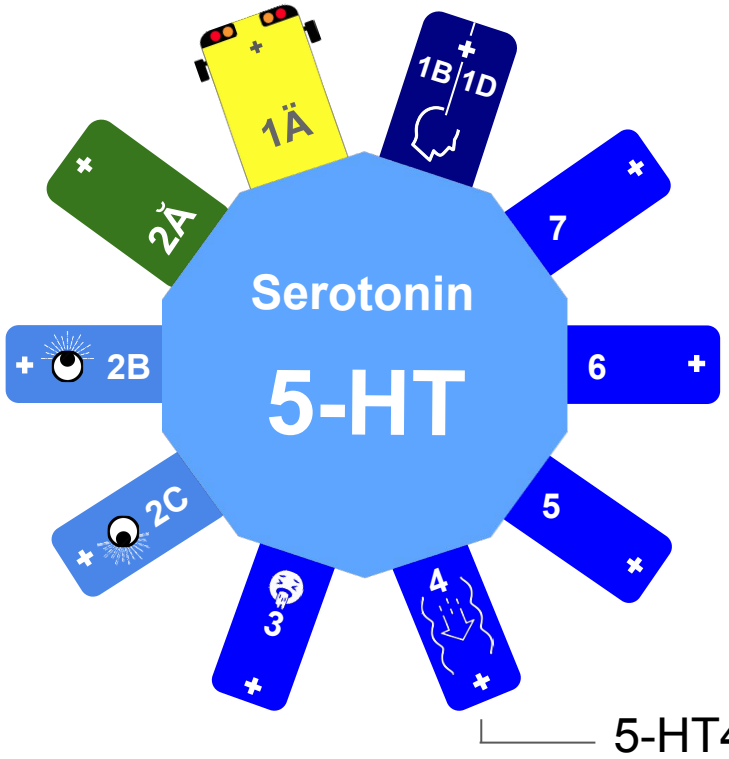
“I’d like **2C** my feet”

Serotonin – 5-HT receptor agonist



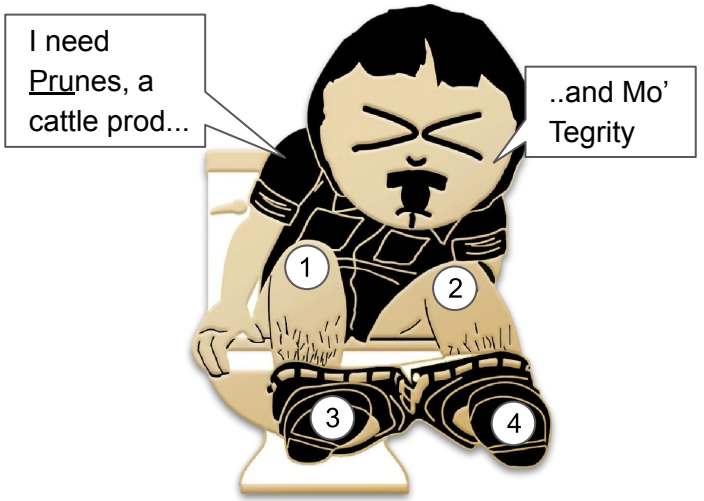
5-HT3 is *blocked* by ondansetron (Zofran)

Serotonin – 5-HT receptor agonist



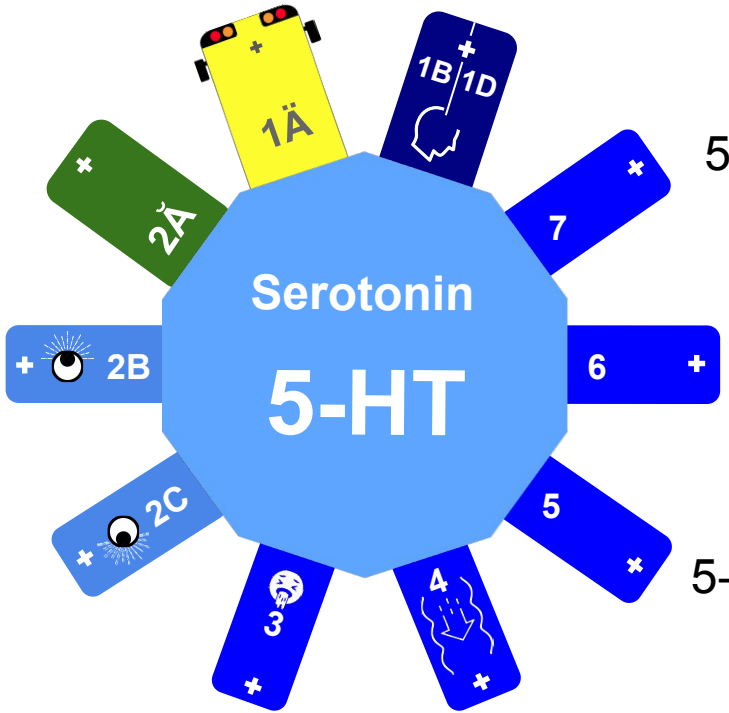
5-HT4

Prucalopride (MOTREGRITY)



"Prunes, cattle prod, & Mo' Tegrity"

Serotonin – 5-HT receptor agonist



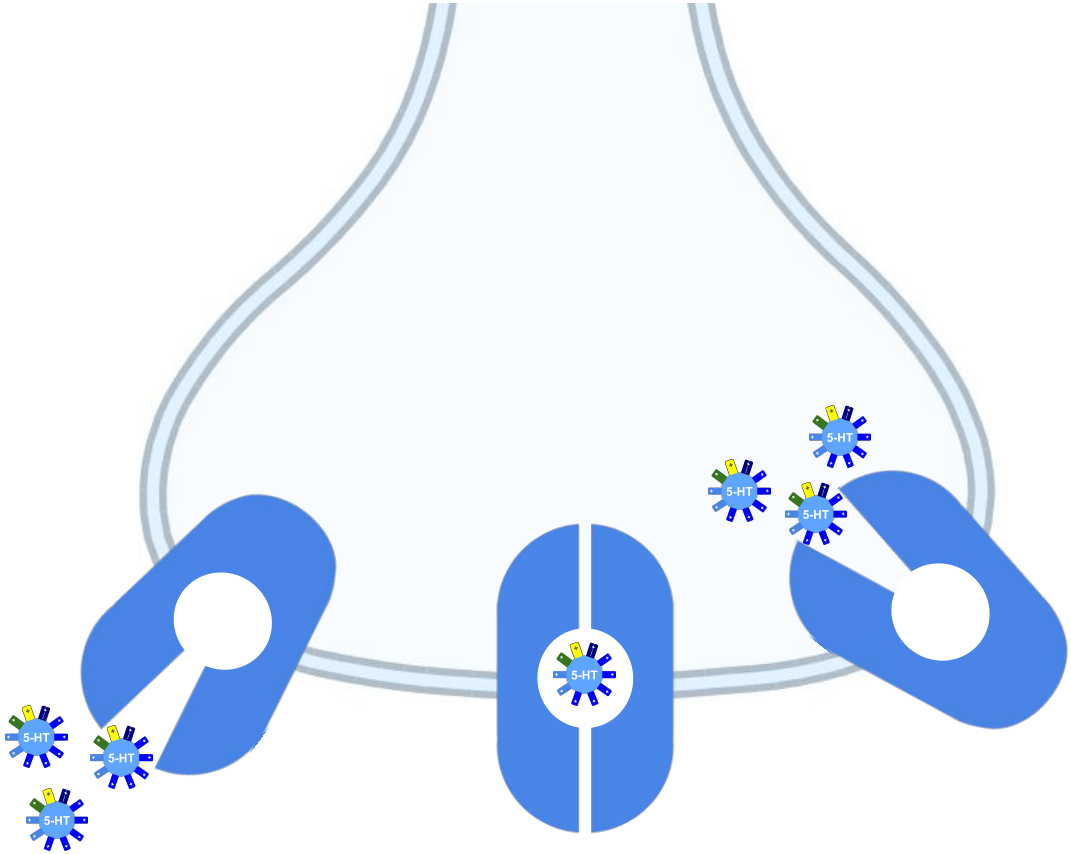
5-HT7

5-HT6

psychiatric relevance but nothing specific to memorize

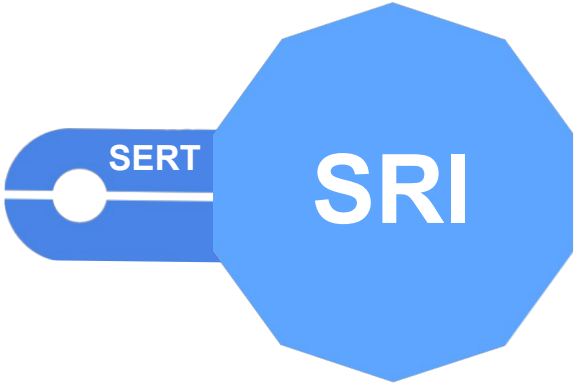
5-HT5 — little is known

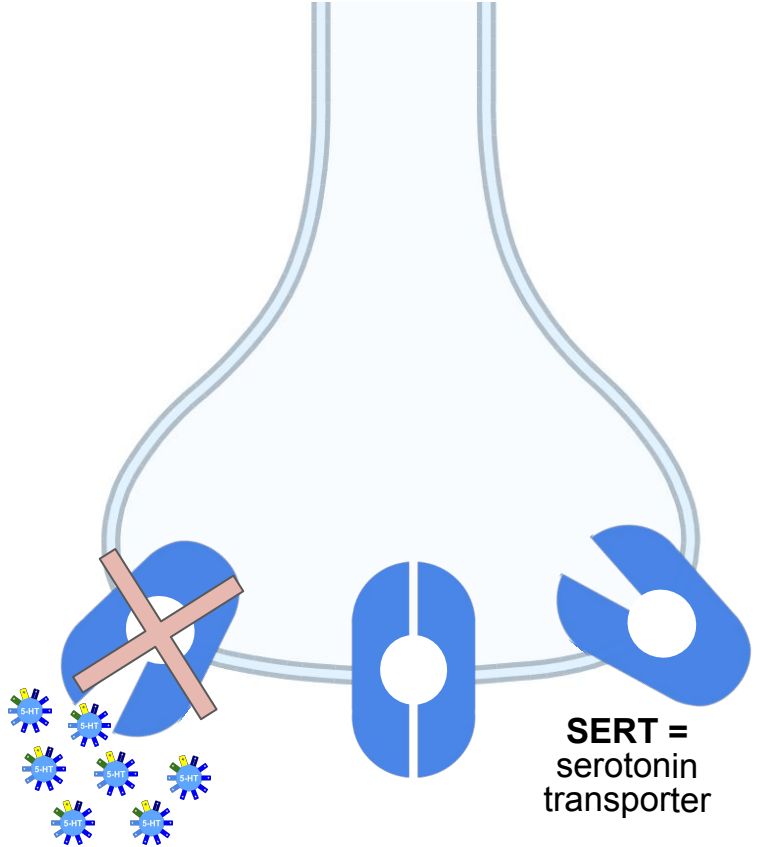
Serotonin transporter (SERT)



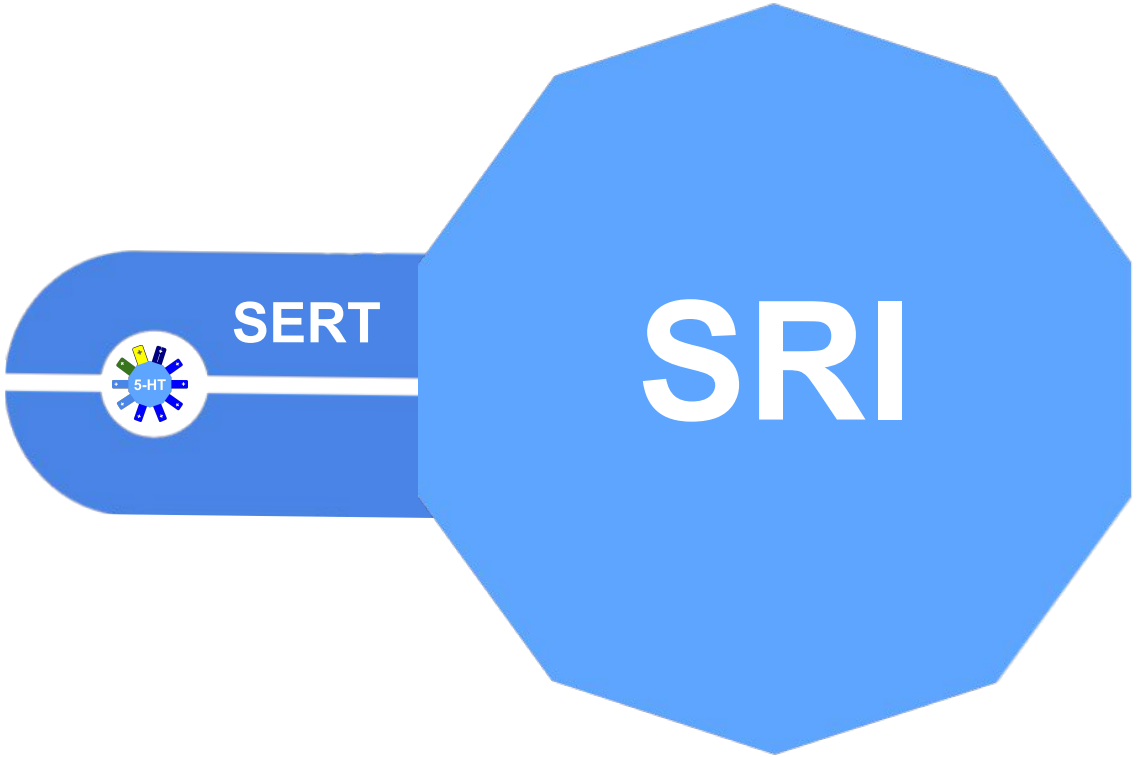
SERT = serotonin transporter

Serotonin reuptake inhibitor (SRI)

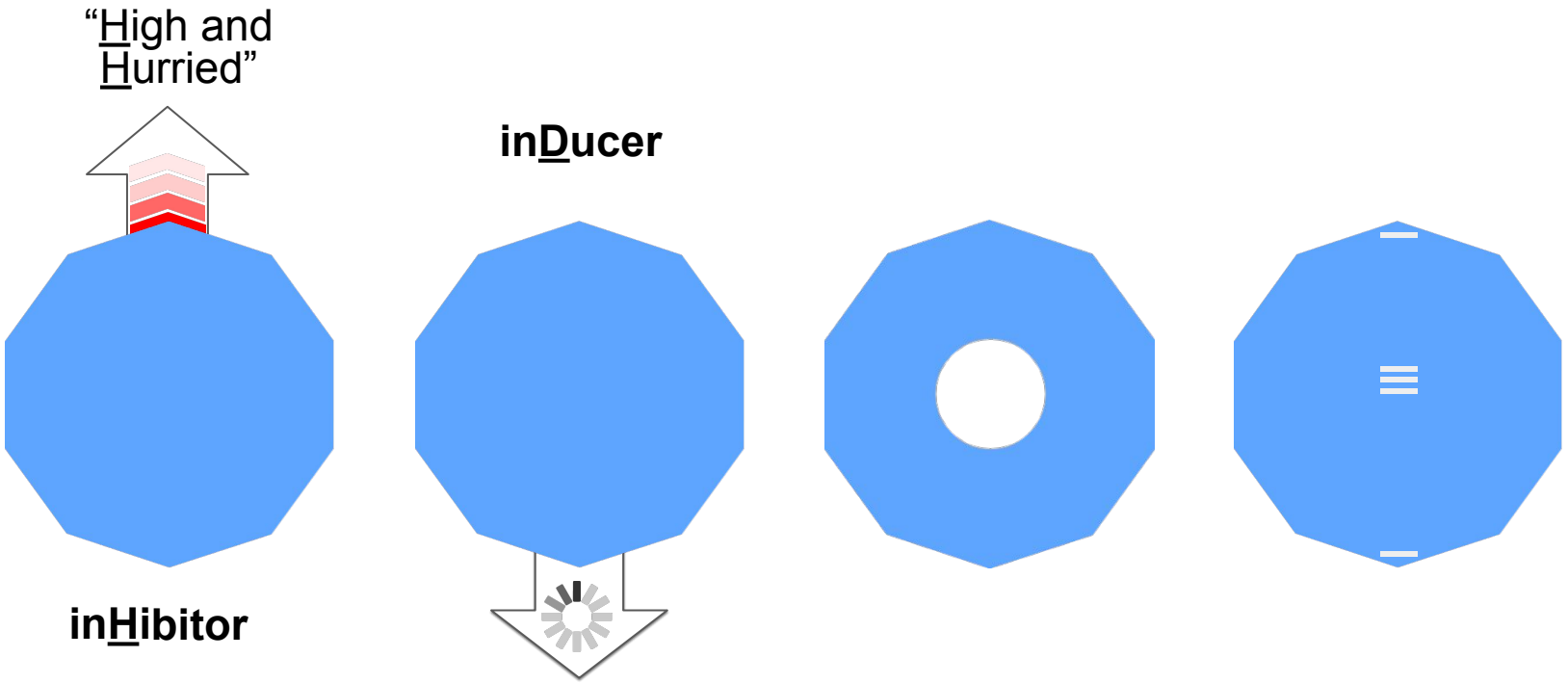




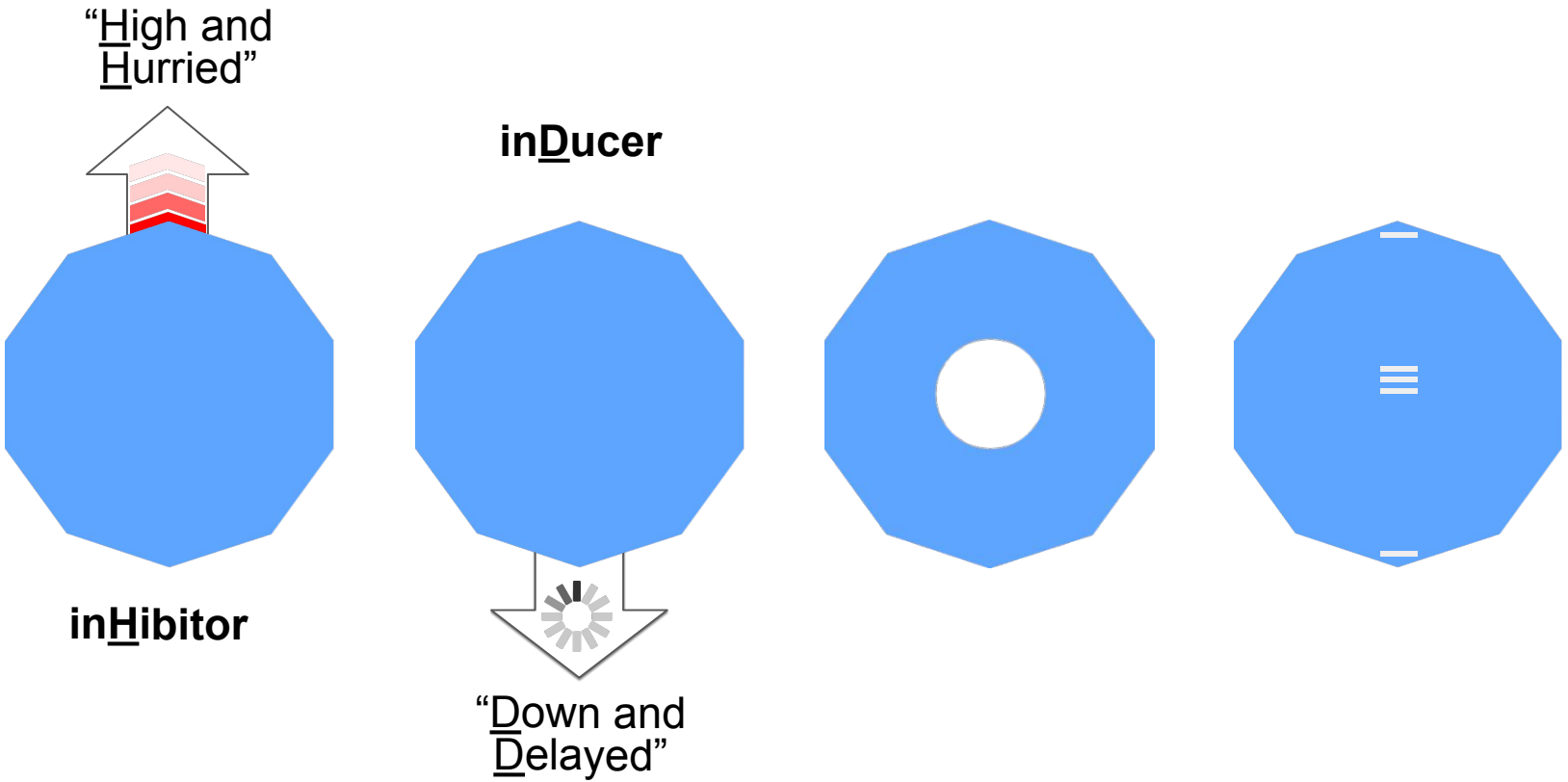
Serotonin reuptake inhibitor (SRI)



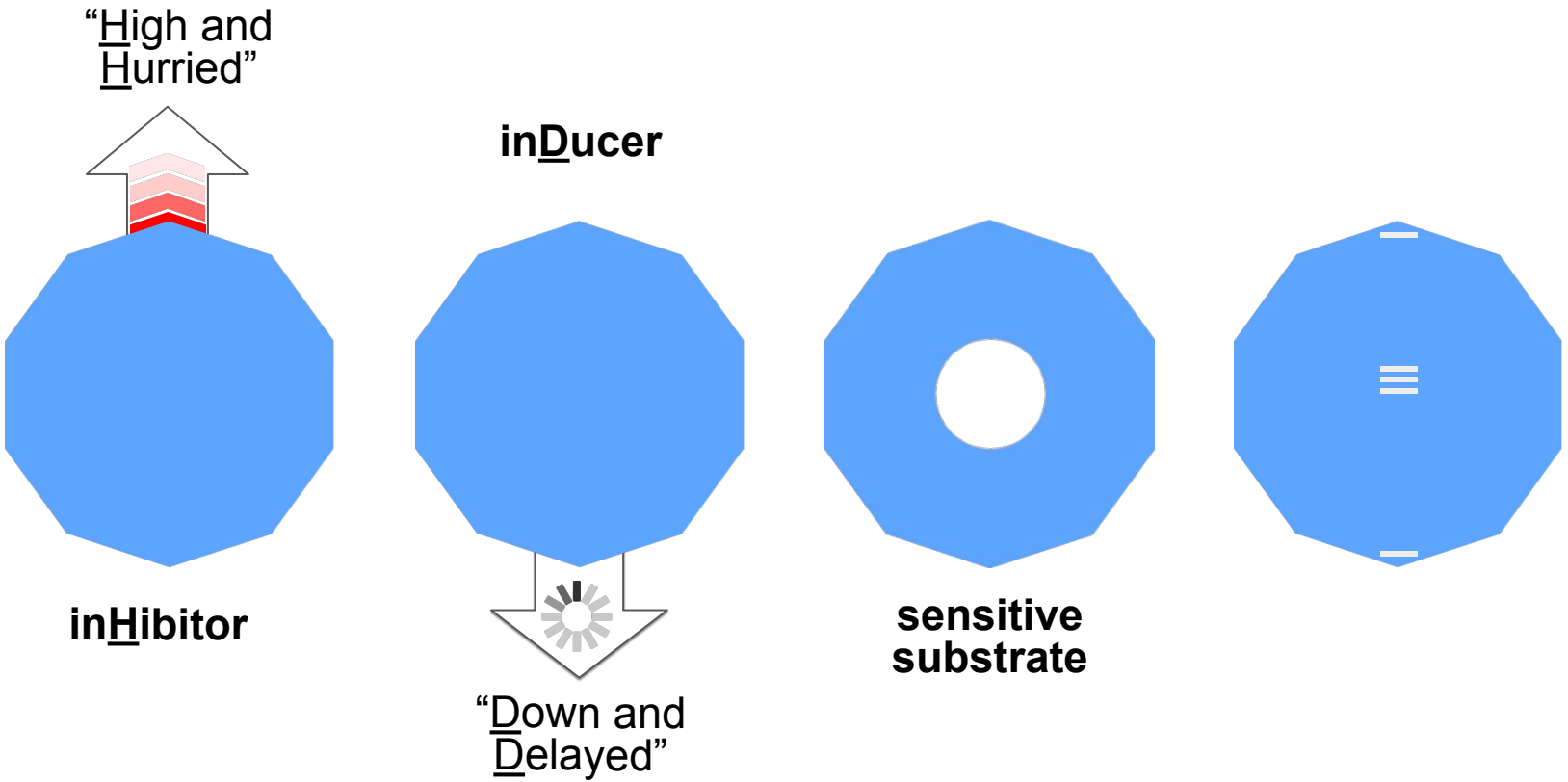
Pharmacokinetic interaction visuals



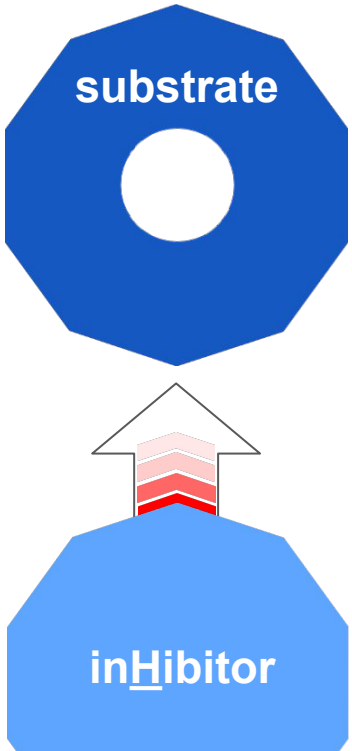
Pharmacokinetic interaction visuals



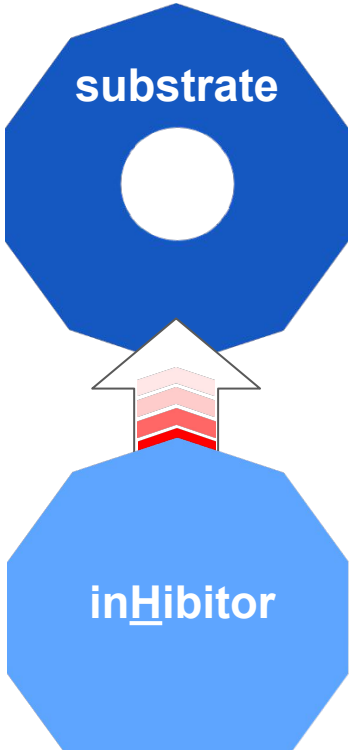
Pharmacokinetic interaction visuals



Pharmacokinetic interaction visuals

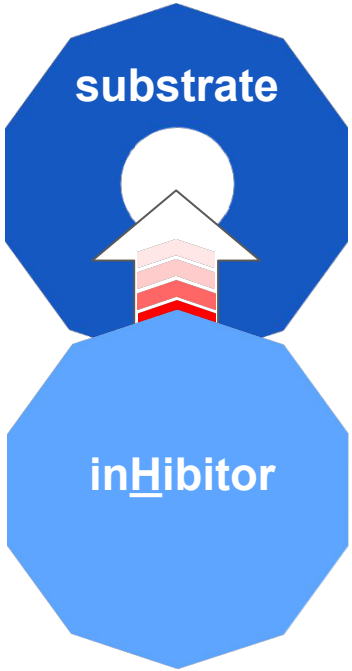


Pharmacokinetic interaction visuals



Pharmacokinetic interaction visuals

Pharmacokinetic interaction visuals



Pharmacokinetic interaction visuals

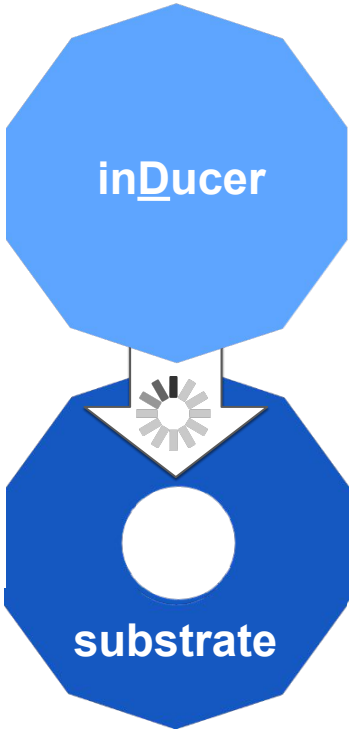
Pharmacokinetic interaction visuals

Pharmacokinetic interaction visuals

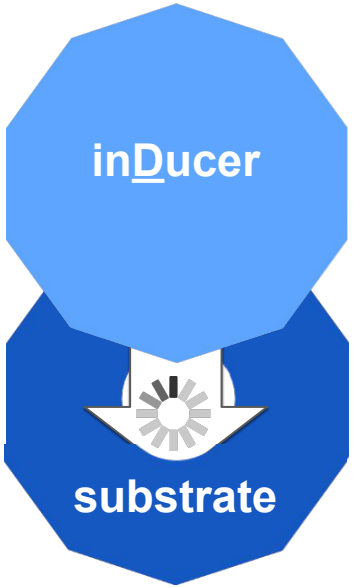
Pharmacokinetic interaction visuals

“High and Hurried”

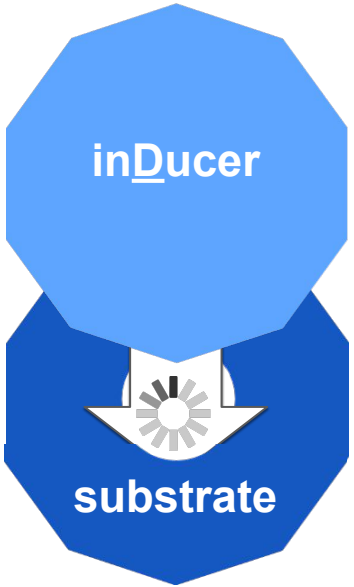
Pharmacokinetic interaction visuals



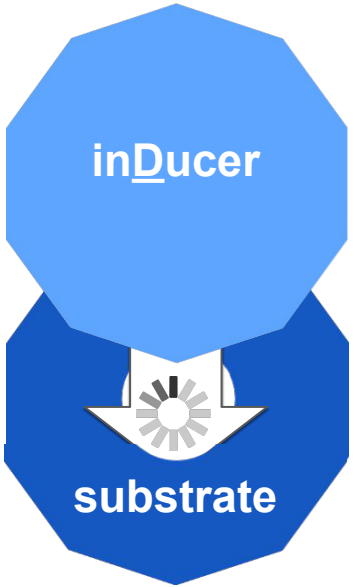
Pharmacokinetic interaction visuals



Pharmacokinetic interaction visuals

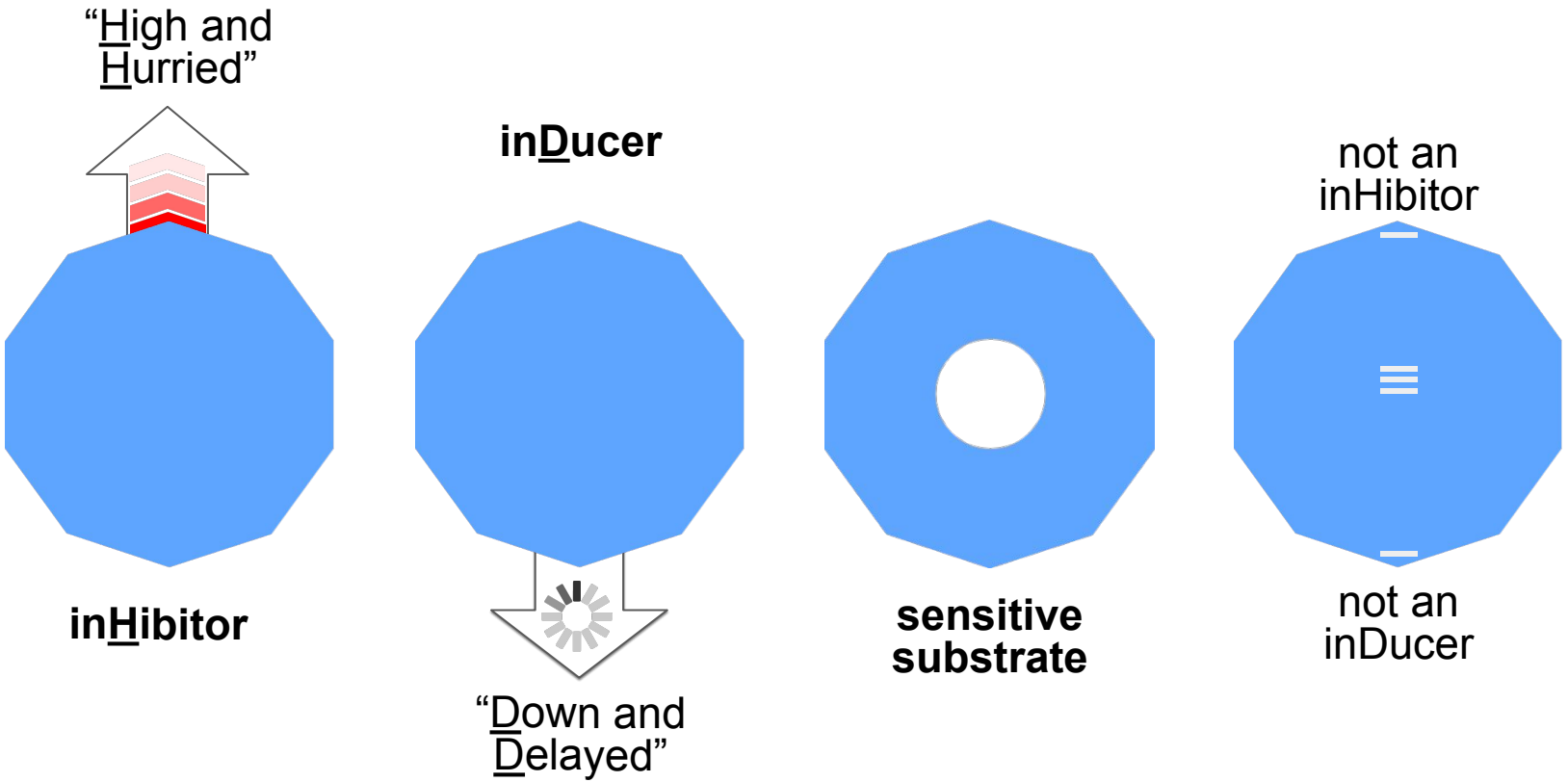


Pharmacokinetic interaction visuals

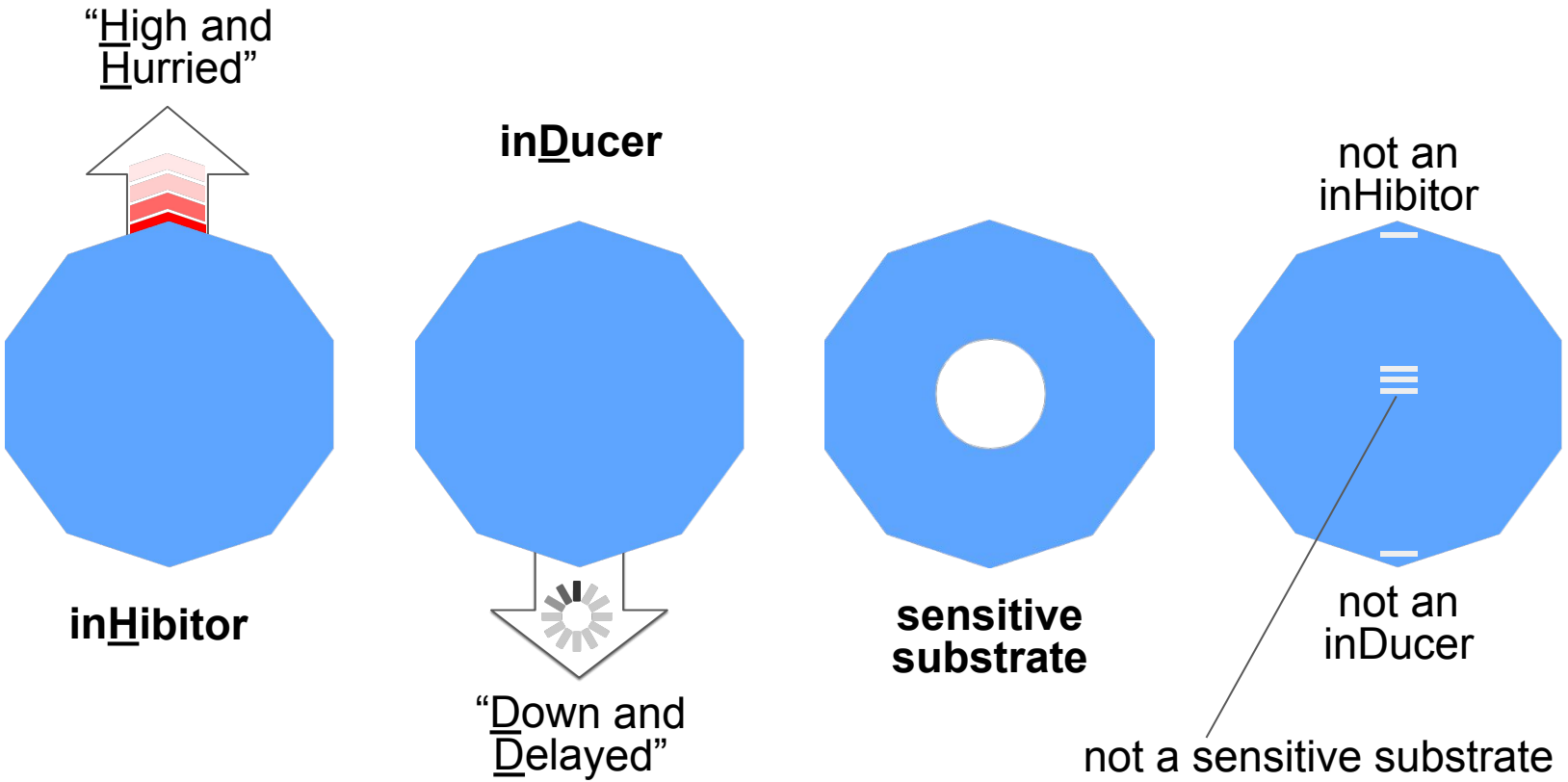


“Down and Delayed”

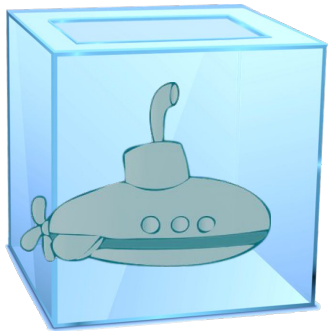
Pharmacokinetic interaction visuals



Pharmacokinetic interaction visuals



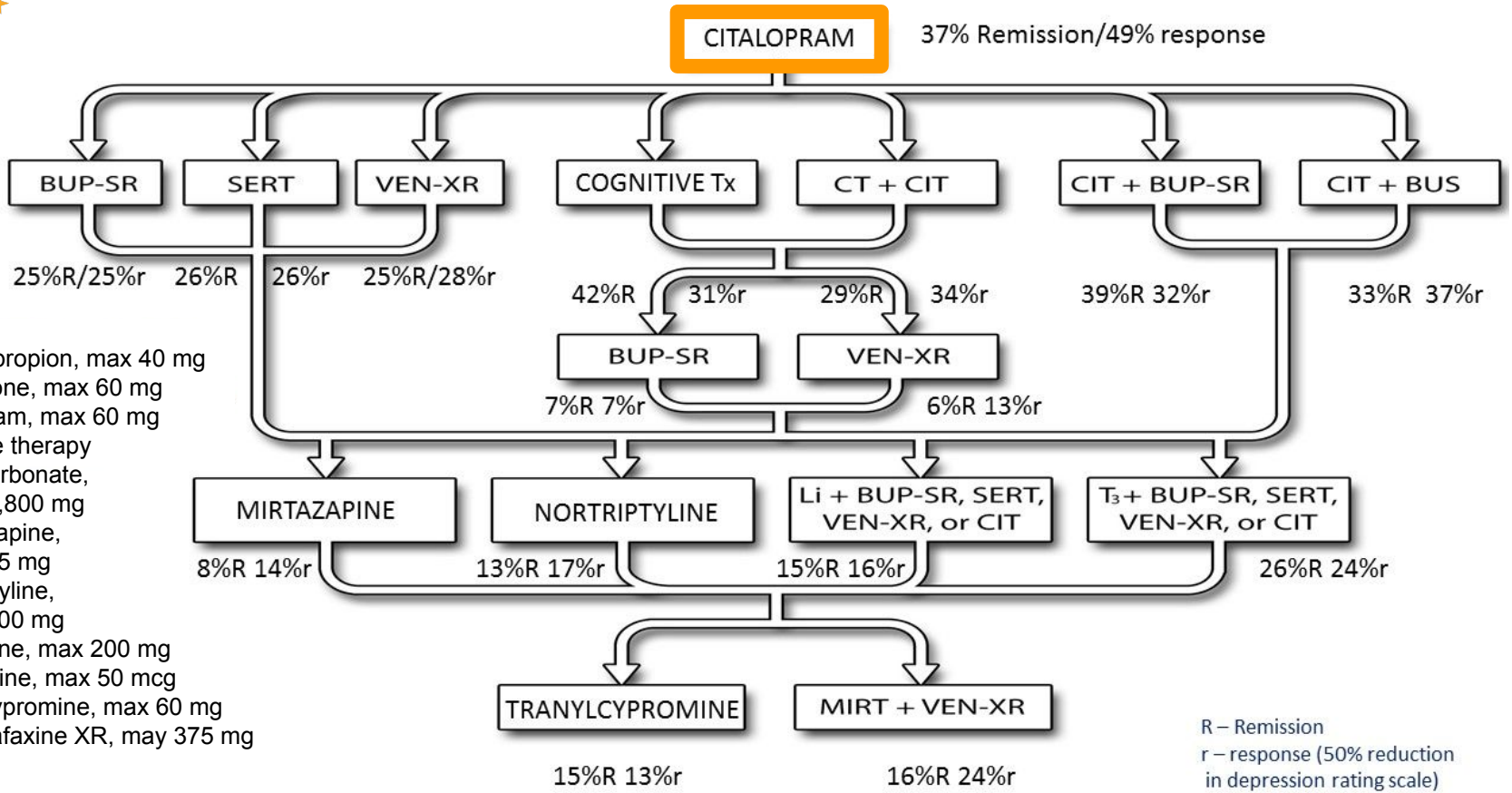
Pharmacokinetic interaction visuals



not an
inHibitor

not an
inDucer

not a sensitive
substrate



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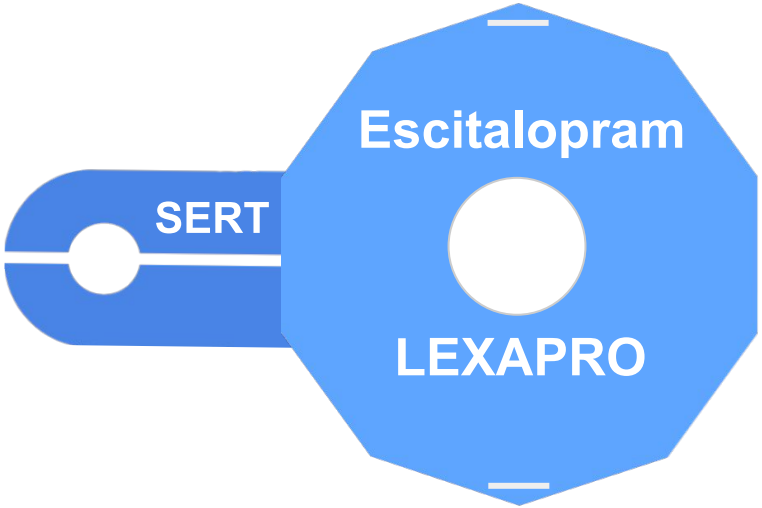
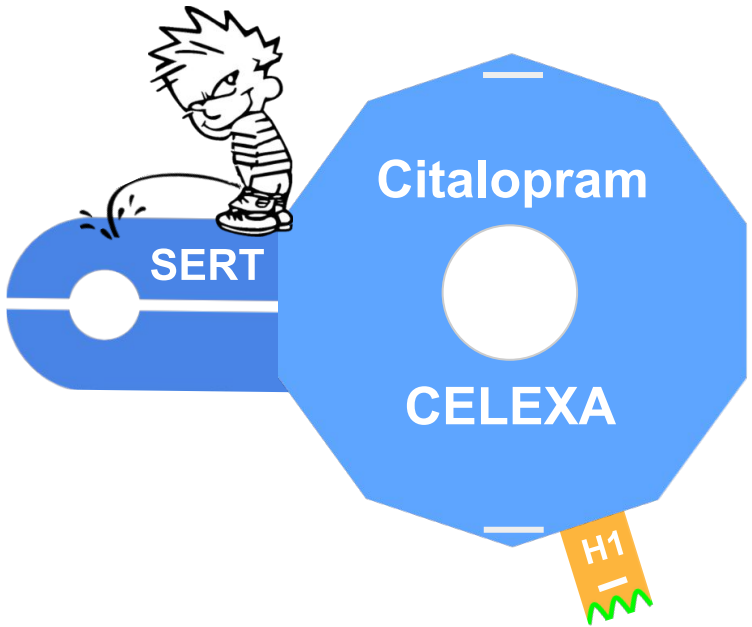
VEN-X – venlafaxine XR, may 375 mg

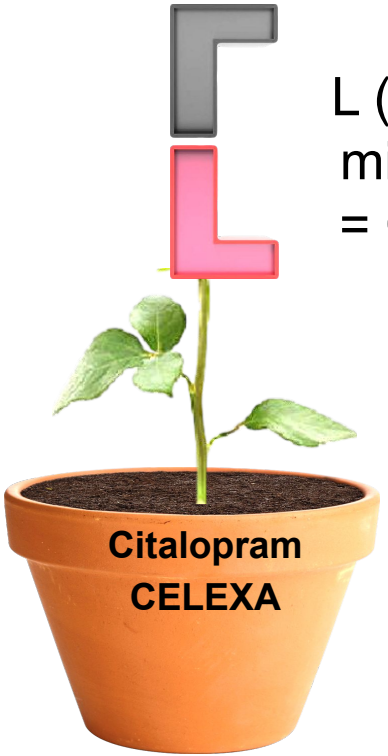
R – Remission
r – response (50% reduction in depression rating scale)

Escitalopram (LEXAPRO) – SSRI



Citalopram (CELEXA) – SSRI

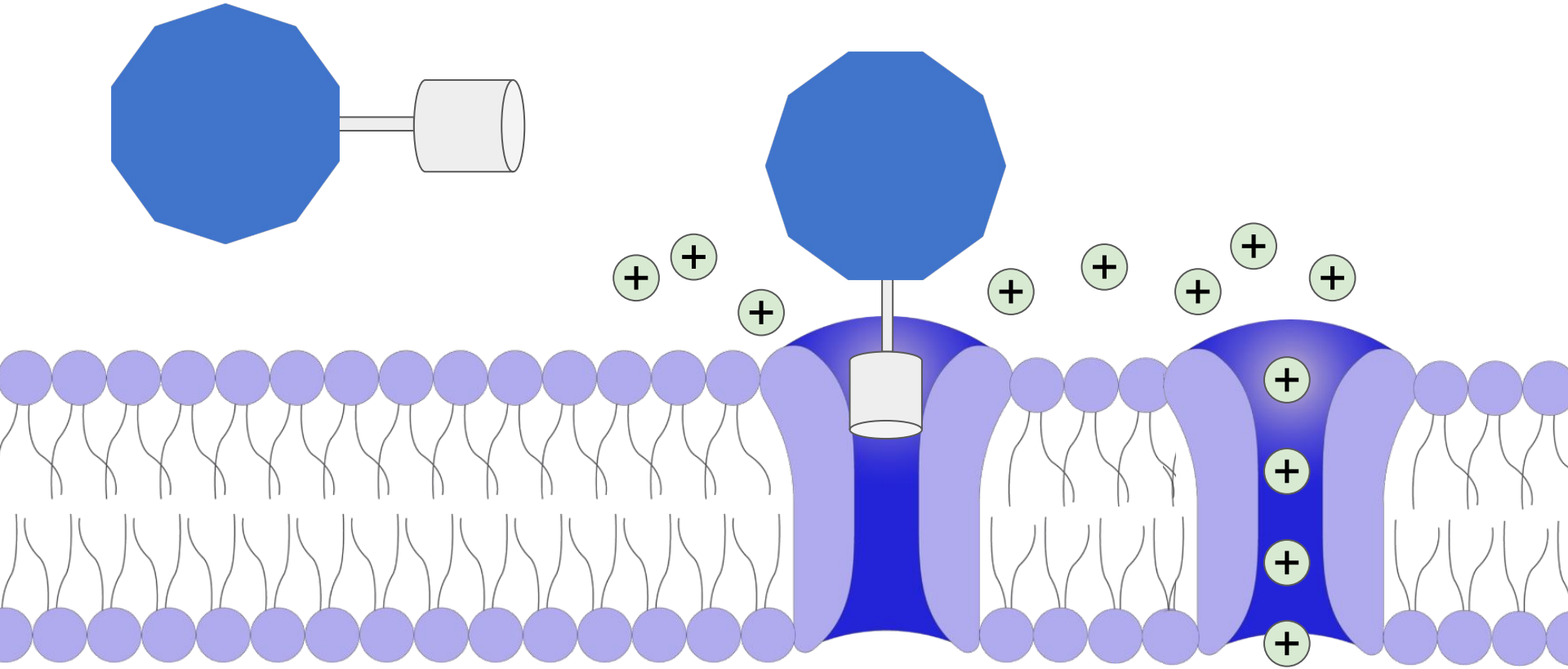




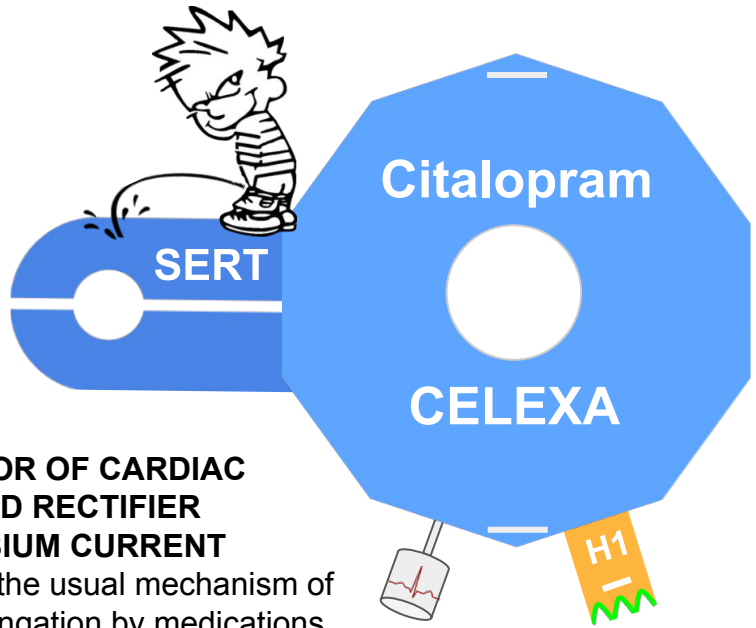
L (Lexapro) + mirror image = C (Celexa)

Used in STAR*D because cheaper than Lexapro and they didn't know about...

Ion channel blocker

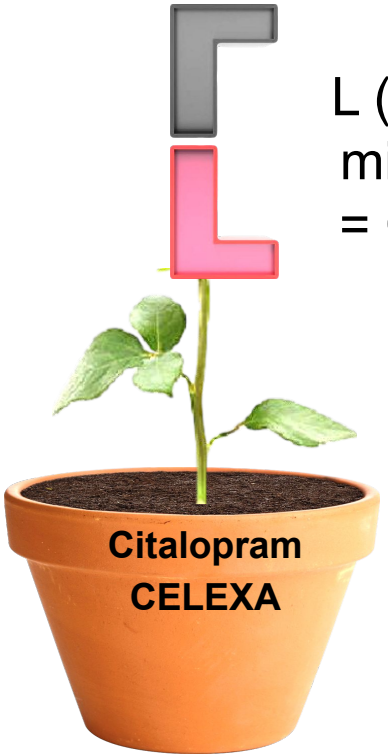


Citalopram (CELEXA) – SSRI



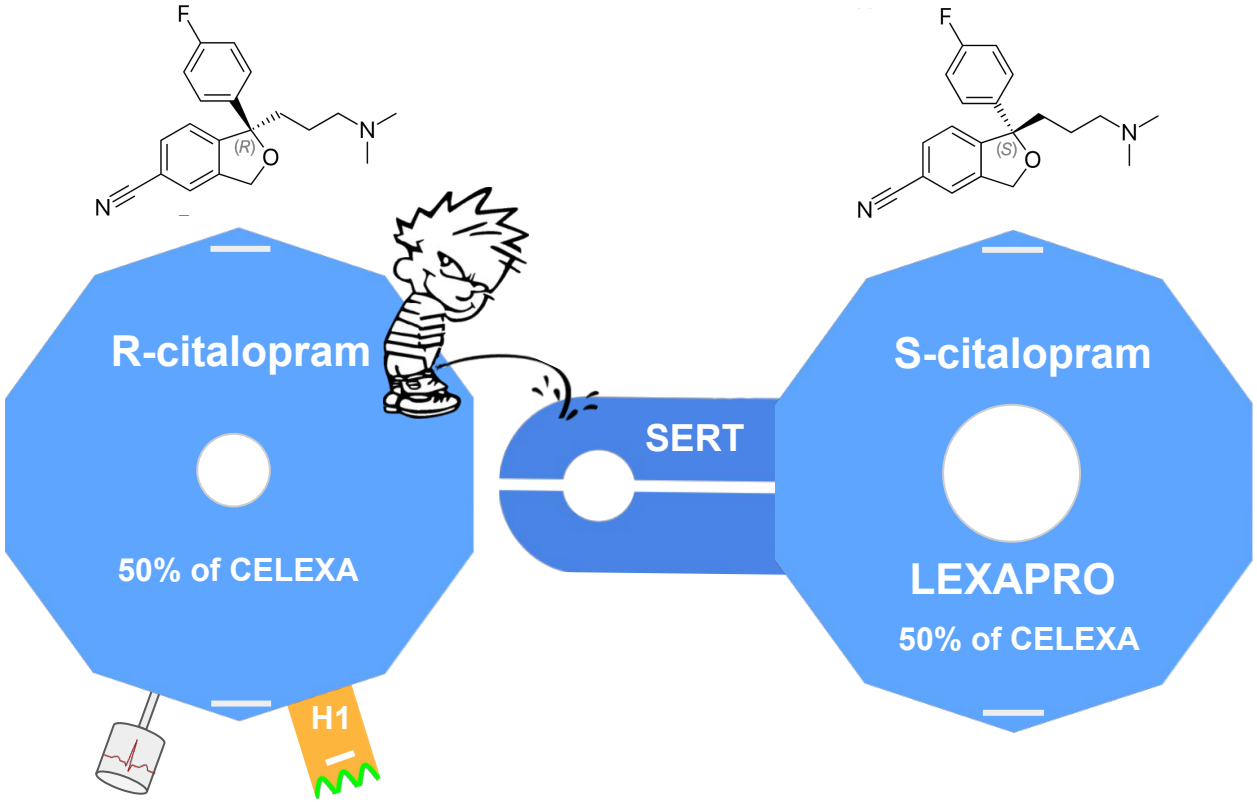
INHIBITOR OF CARDIAC DELAYED RECTIFIER POTASSIUM CURRENT
which is the usual mechanism of QT prolongation by medications.

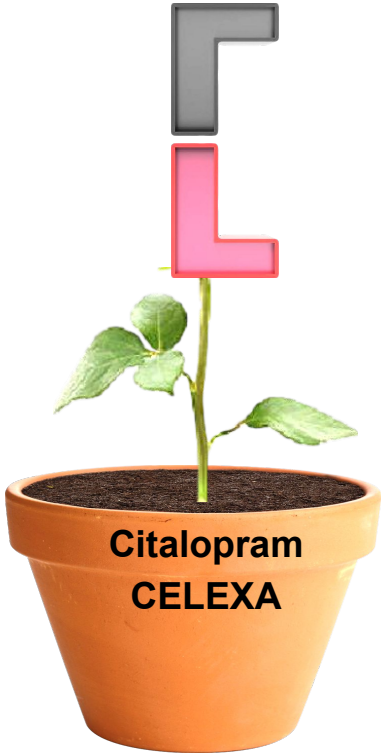
Why the max dose was decreased from 60 mg to 40 mg.



L (Lexapro) + mirror image = C (Celexa)

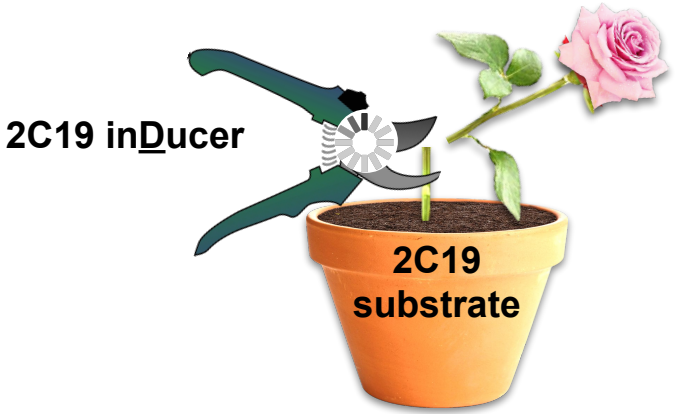
Citalopram (CELEXA) – SSRI





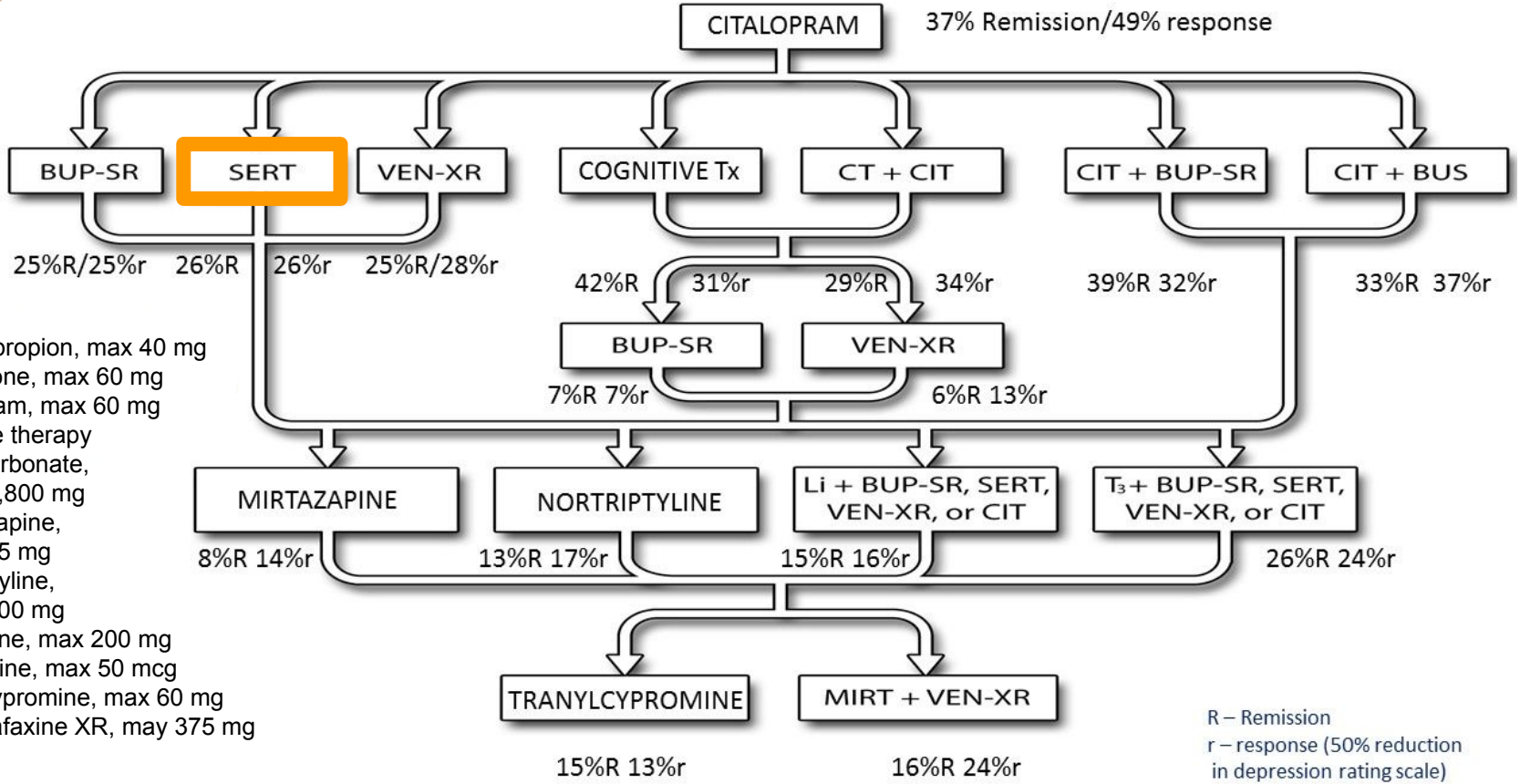
Cytochrome P450 2C19 (CYP2C19)

"To See Nice Things (grow)"



"Down and Delayed"

"High and Hurried"



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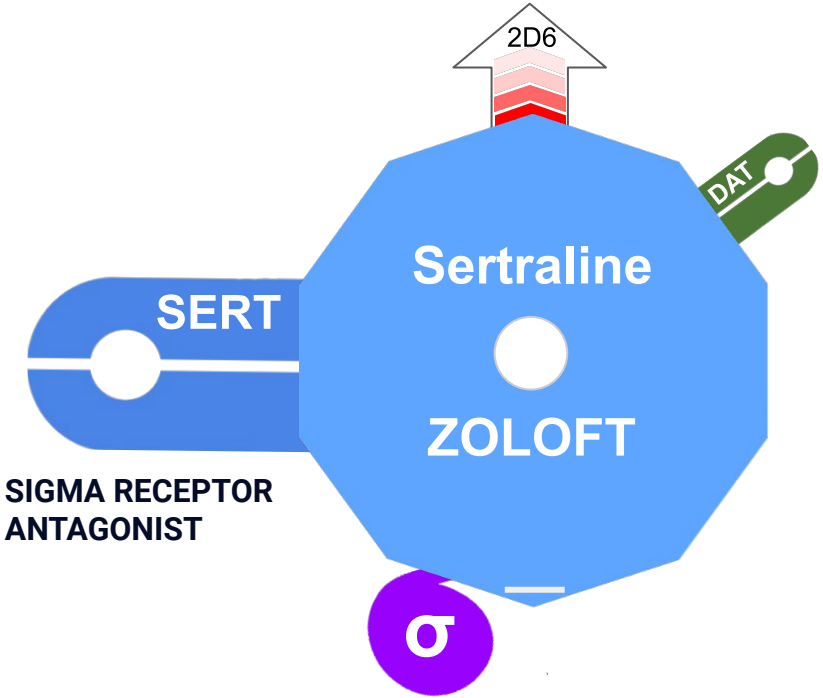
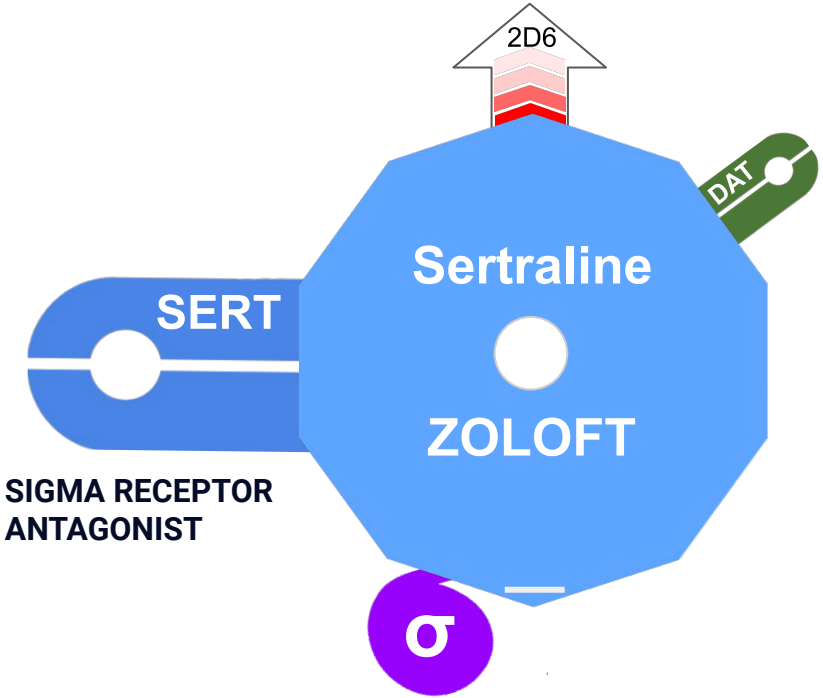
Sertraline (ZOLOFT) – SSRI



"So soft (on the) Shirt line"

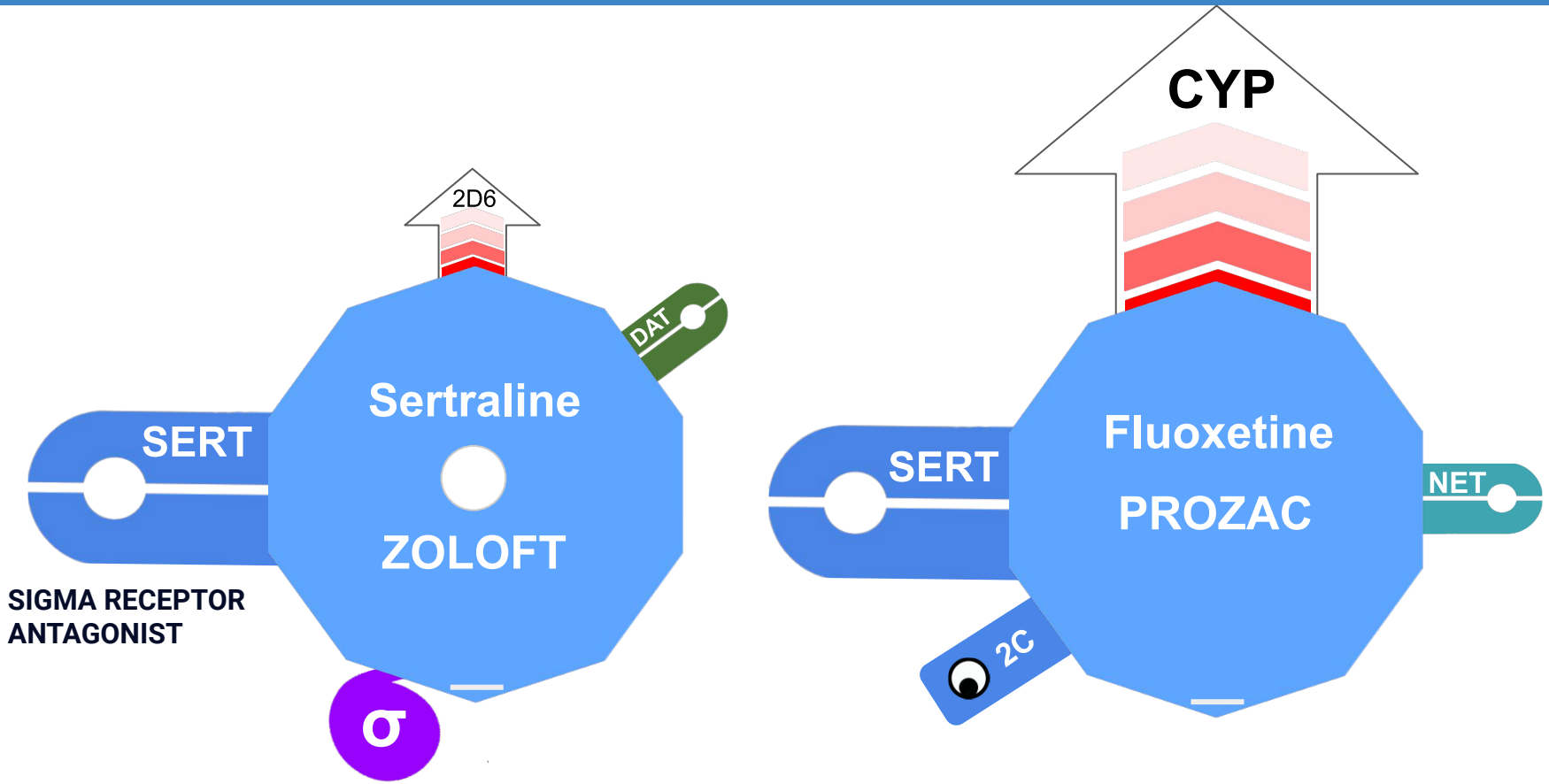
Sertraline is the preferred antidepressant for pregnancy and breastfeeding.

Sertraline (ZOLOFT) – SSRI

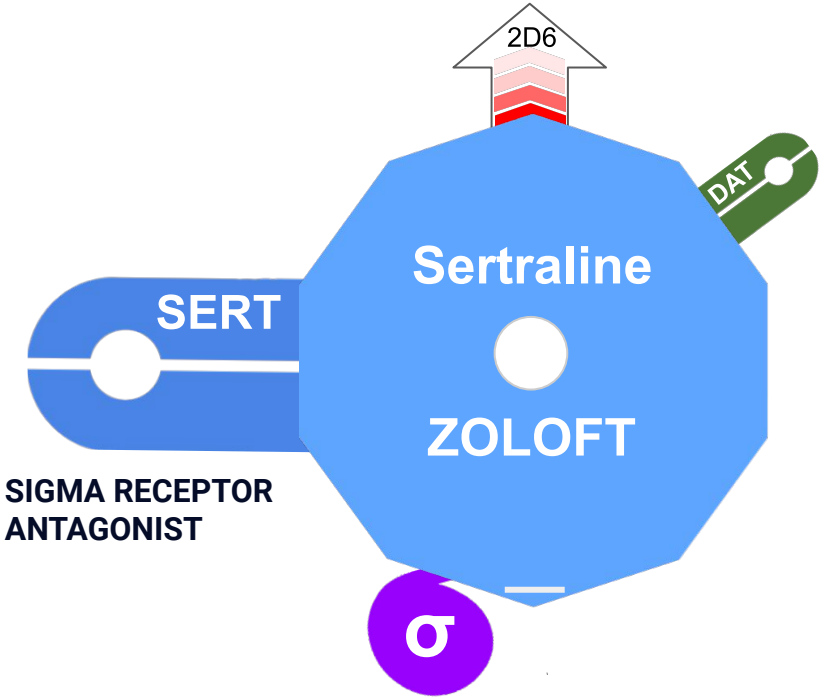


How does it compare to fluoxetine (Prozac)?

Sertraline (ZOLOFT) – SSRI

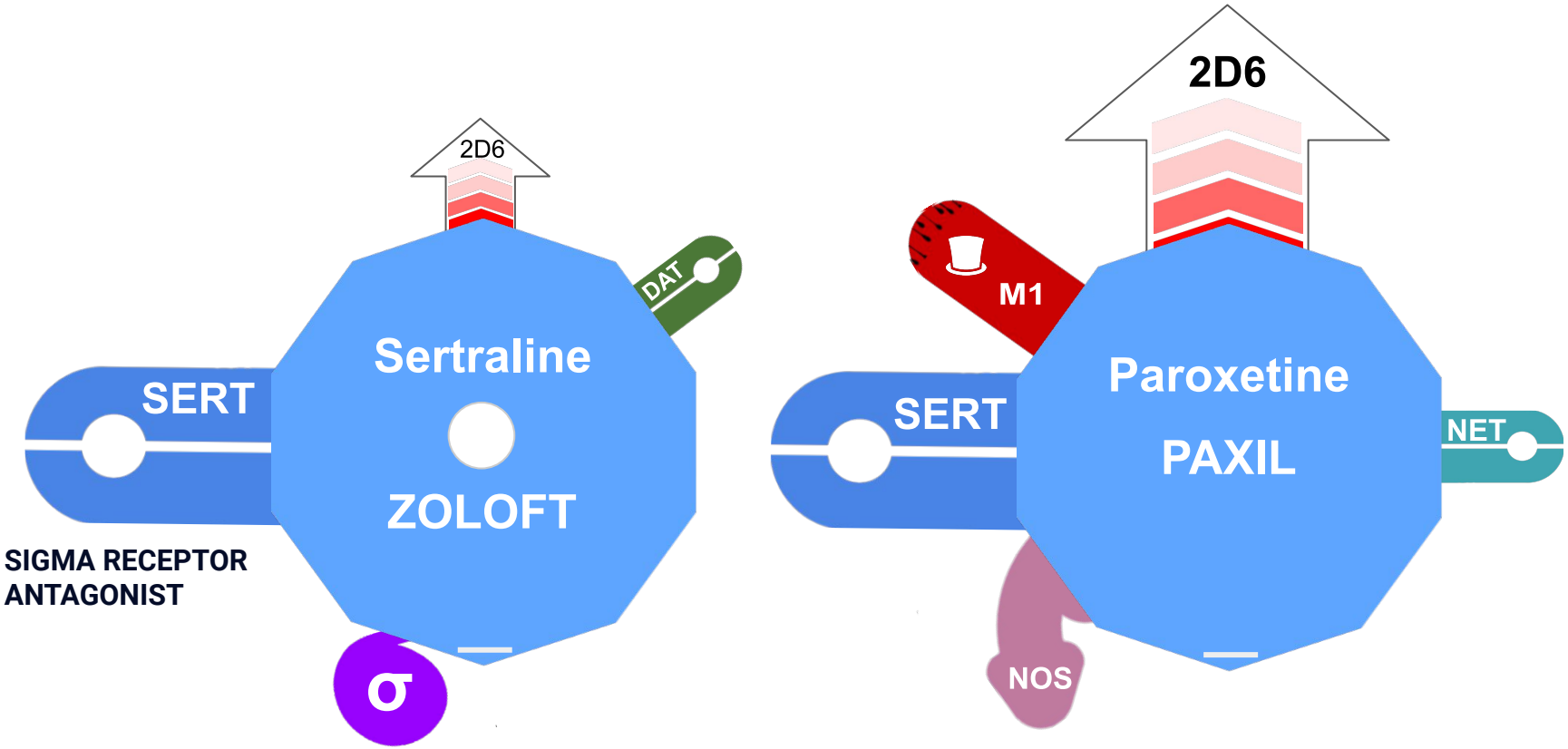


Sertraline (ZOLOFT) – SSRI

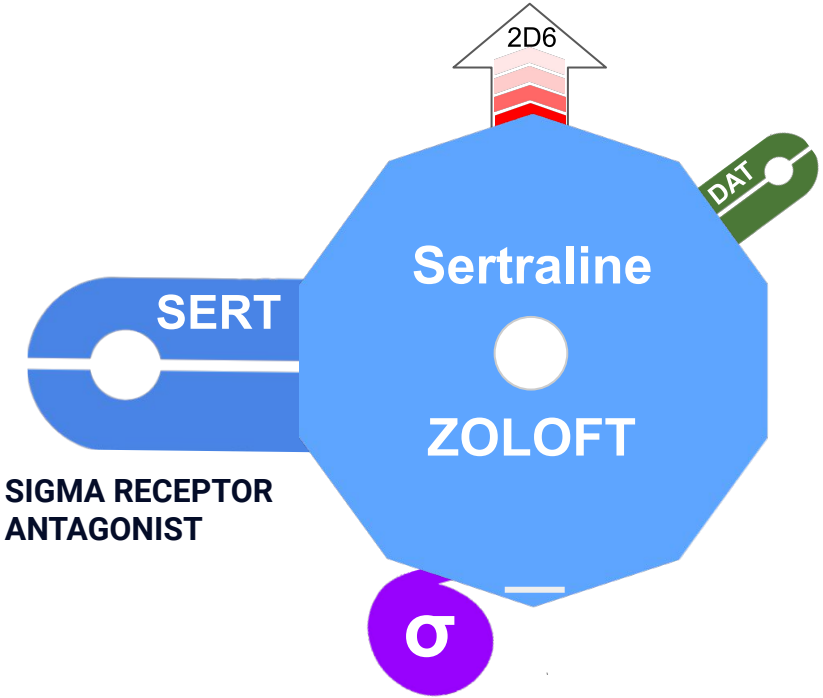


How does it compare to paroxetine (Paxil)?

Sertraline (ZOLOFT) – SSRI

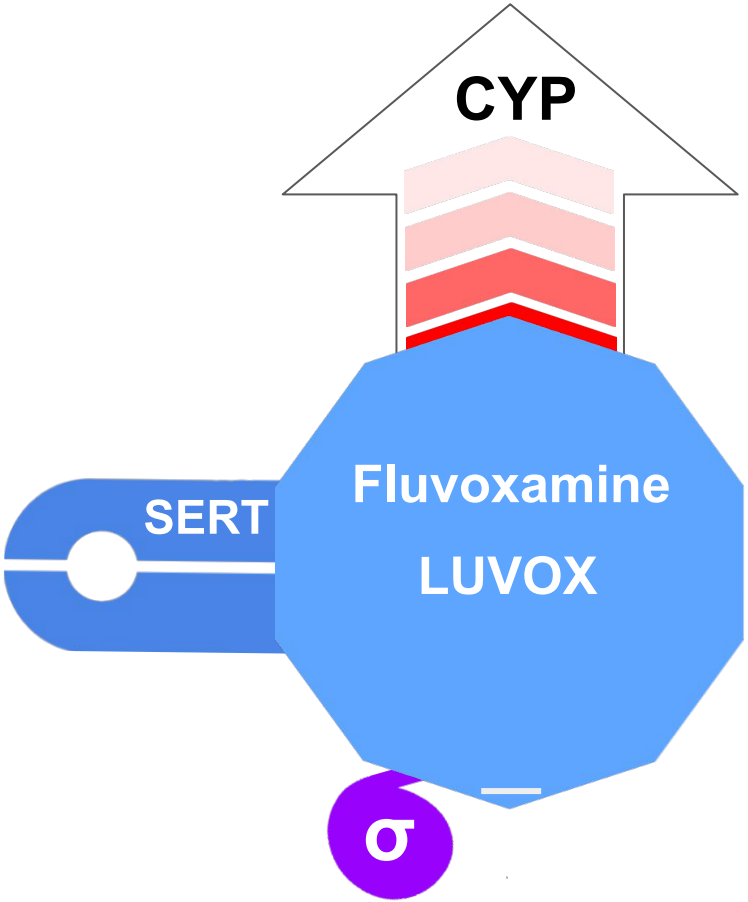


Sertraline (ZOLOFT) – SSRI



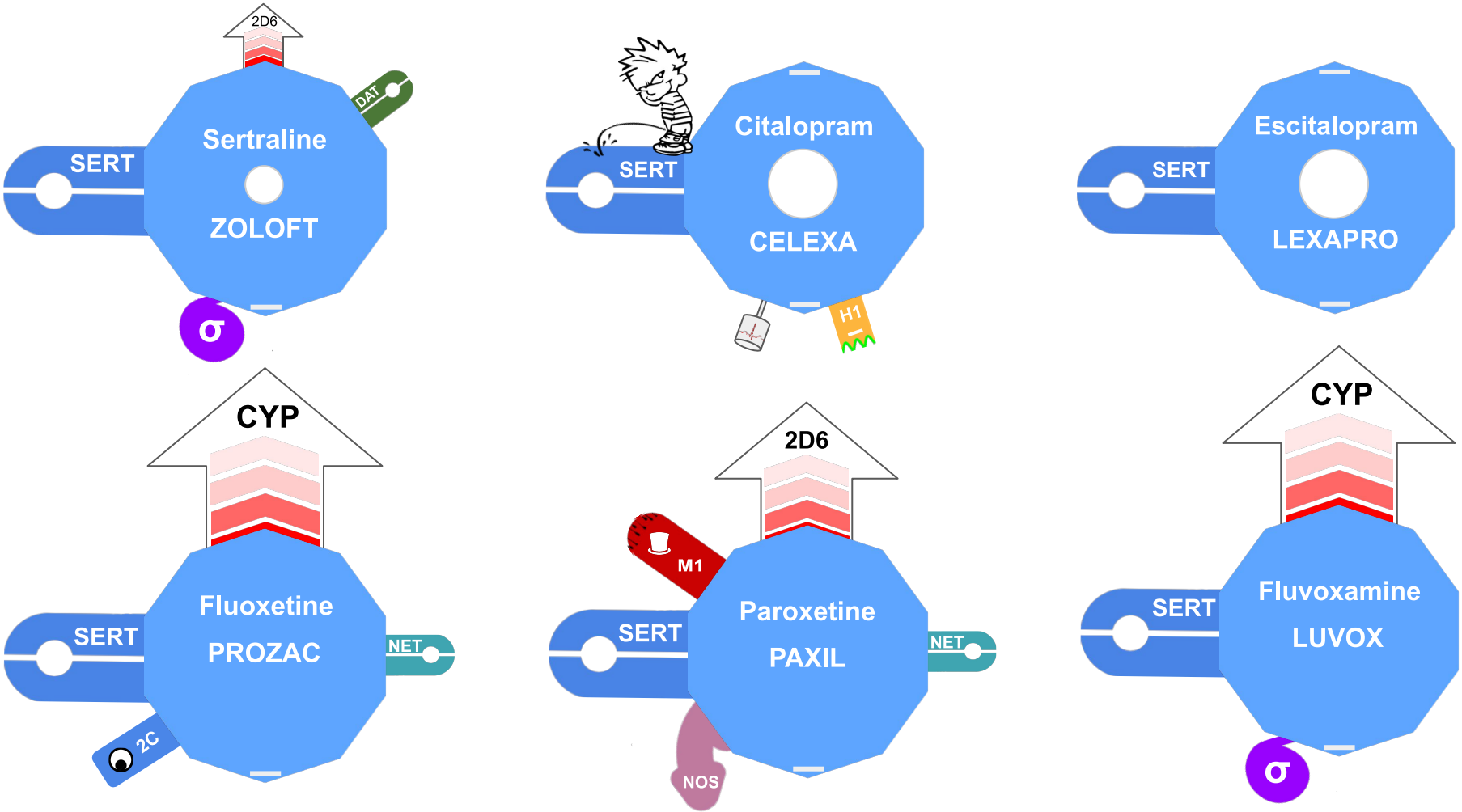
How does it compare to fluvoxamine (Luvox)?

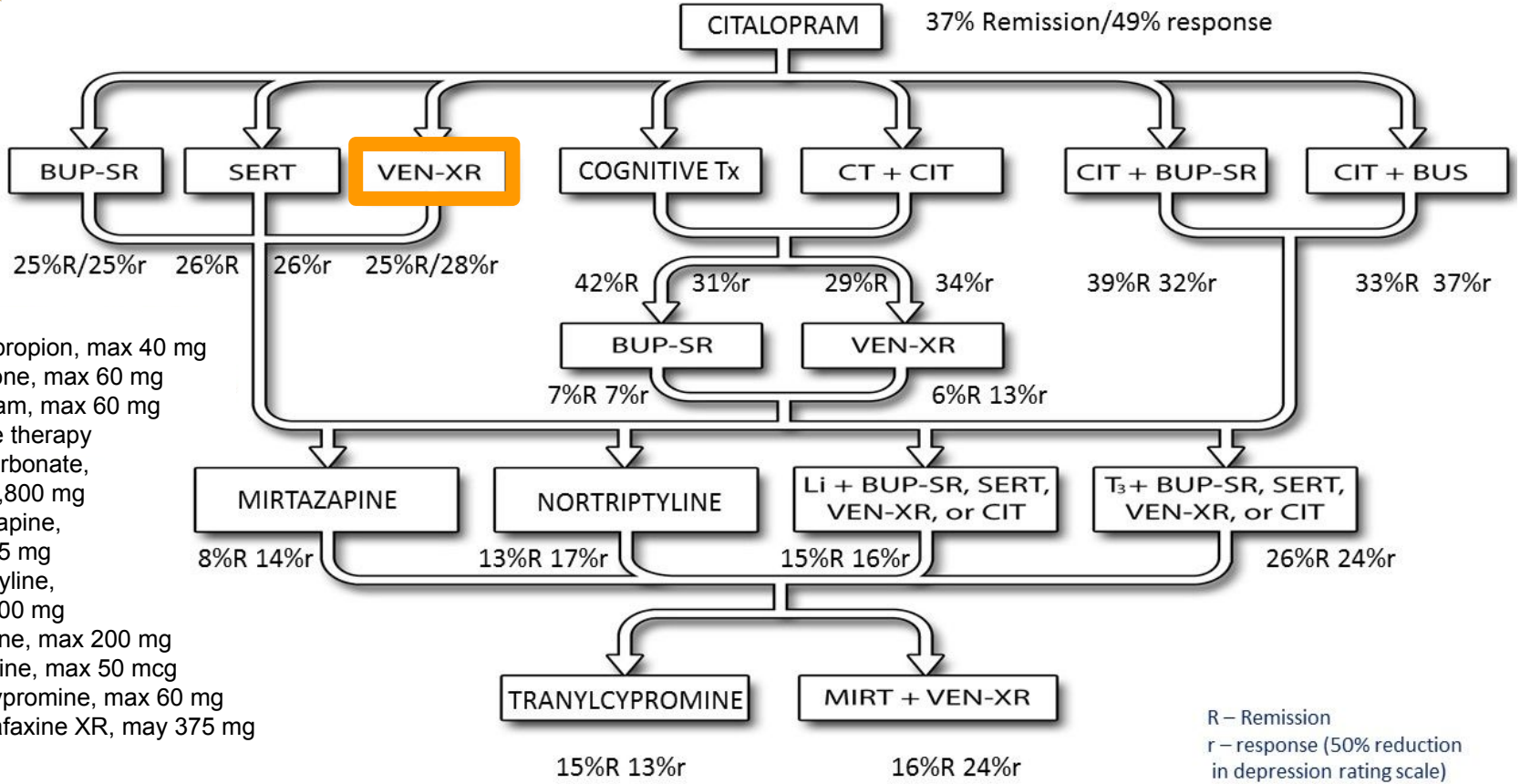
Fluvoxamine (Luvox) – SSRI



“glove-ox”

SSRIs


2D6
DAT
SERT
Sertraline
ZOLOFT
σ
SERT
Citalopram
CELEXA
H1
SERT
Escitalopram
LEXAPRO
CYP
SERT
Fluoxetine
PROZAC
NET
2C
2D6
M1
SERT
Paroxetine
PAXIL
NET
NOS
CYP
SERT
Fluvoxamine
LUVOX
σ



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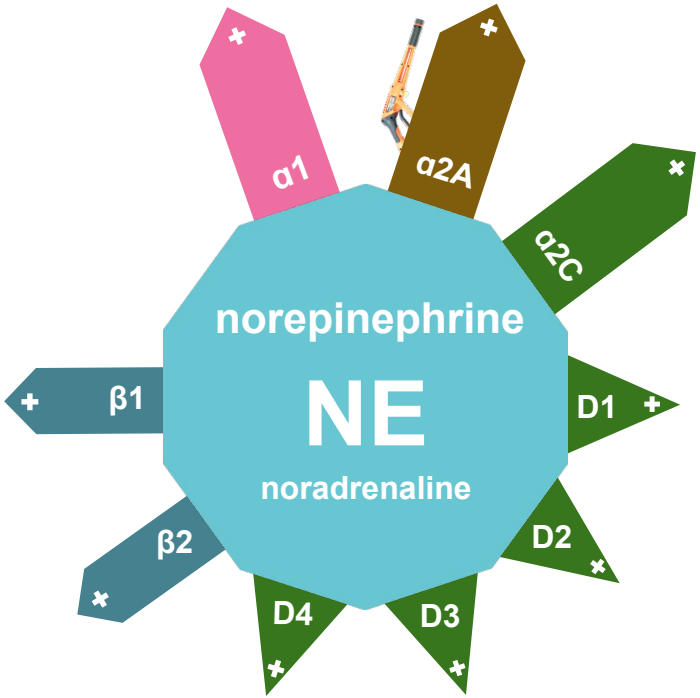
Norepinephrine

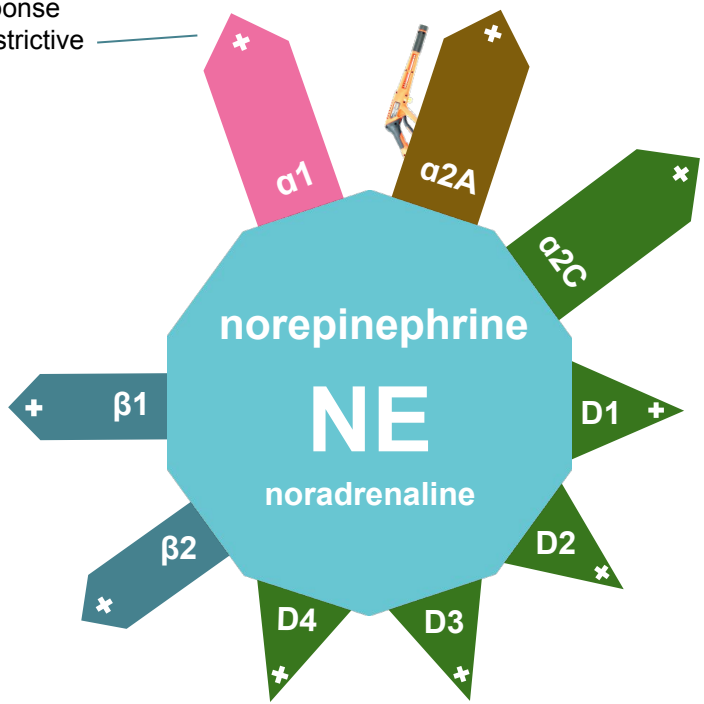


DA receptors are activated by NE, although at 50 to 100-fold higher concentrations than DA

Norepinephrine

α1A AGONIST

- ❖ “Fight or flight” sympathetic response
- ❖ The vasoconstrictive effect of effect of midodrine and phenylephrine



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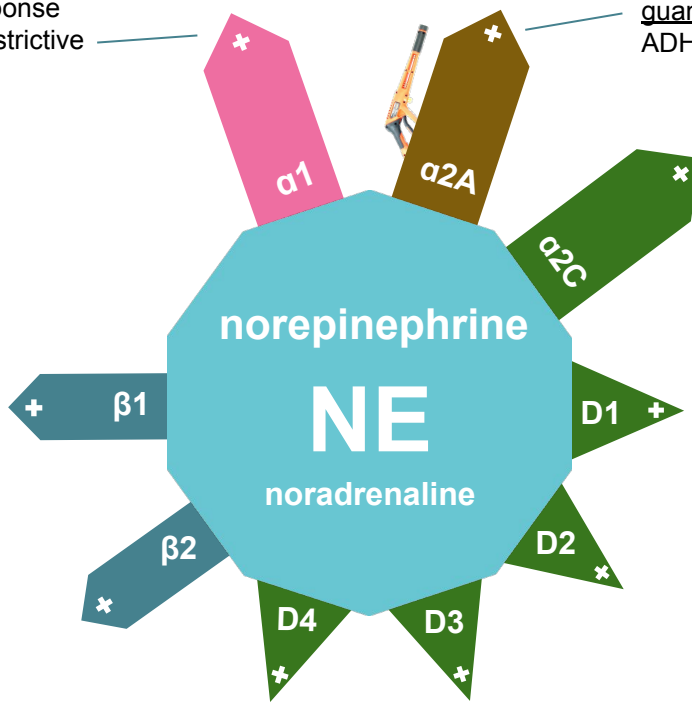
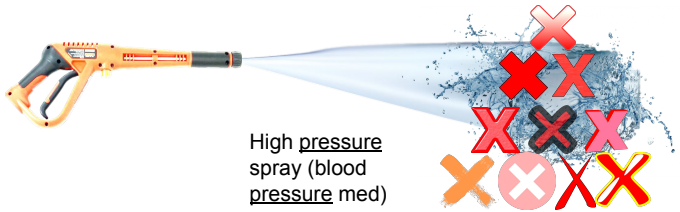
Norepinephrine

α1A AGONIST
- ❖ "Fight or flight" sympathetic response
- ❖ The vasoconstrictive effect of effect of midodrine and phenylephrine

α2A AGONIST
- ❖ The effect of guanfacine in treating ADHD



Guanfacine (TENEX)



High pressure spray (blood pressure med)

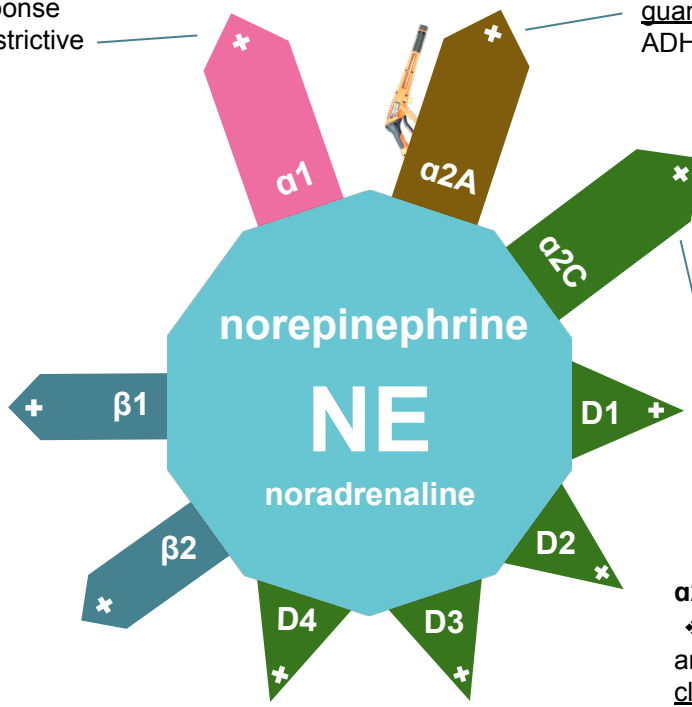
"Gun facing Ten X's"

Selective (centrally acting) alpha-2A agonist

Norepinephrine

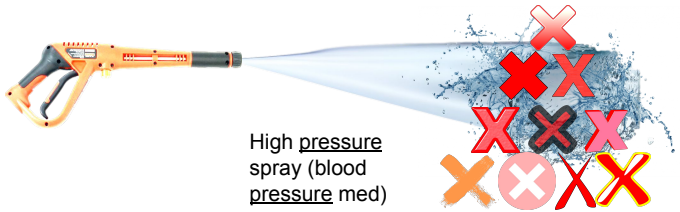
α1A AGONIST
- ❖ "Fight or flight" sympathetic response
- ❖ The vasoconstrictive effect of effect of midodrine and phenylephrine

α2A AGONIST
- ❖ The effect of guanfacine in treating ADHD



α2C AGONIST
- ❖ Sedative and analgesic effect of clonidine and dexmedetomidine (Precedex, Igalmi)

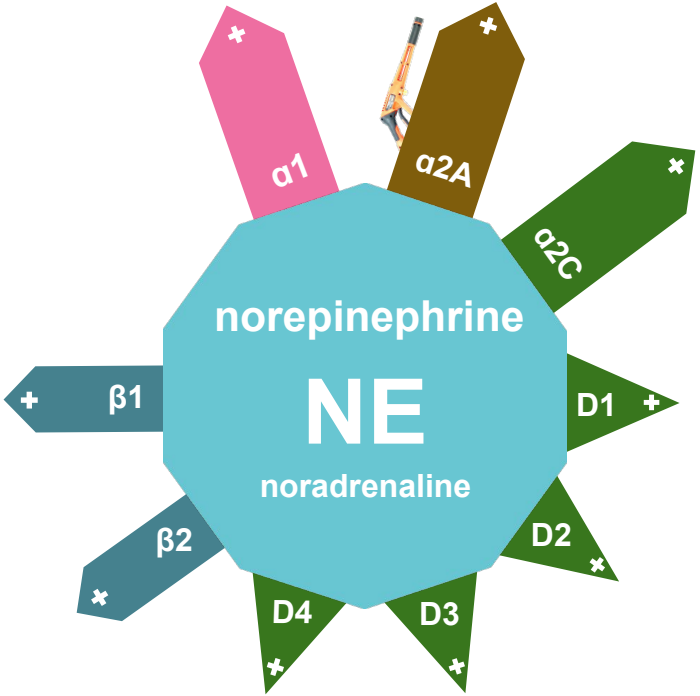
Guanfacine (TENEX)

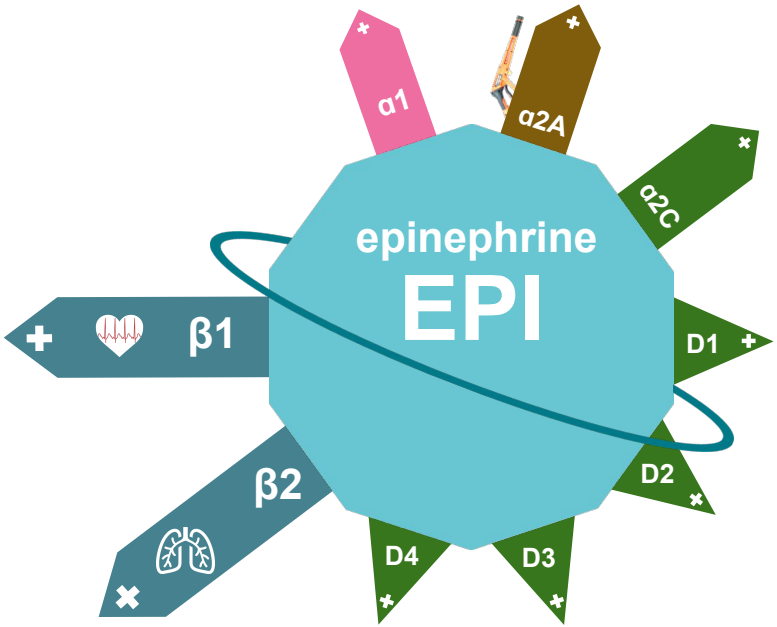


"Gun facing Ten X's"

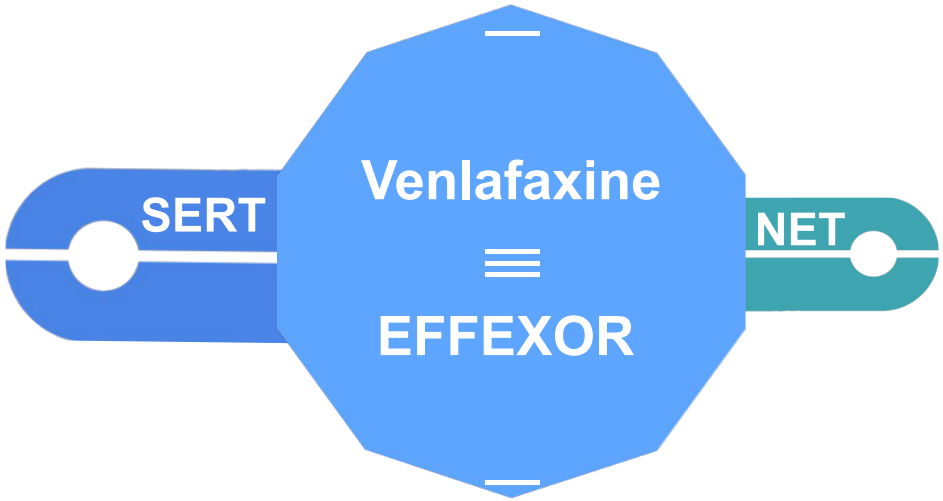
Selective (centrally acting) alpha-2A agonist

Norepinephrine

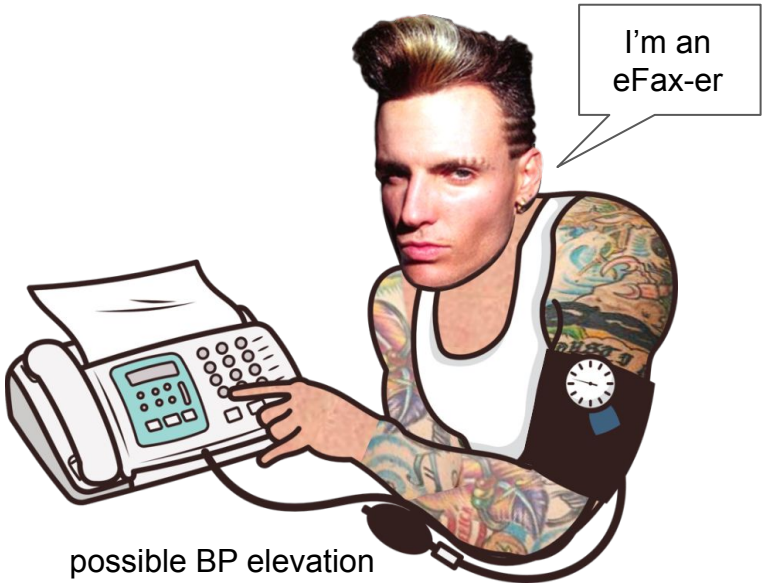




Venlafaxine (EFFEXOR) – SNRI

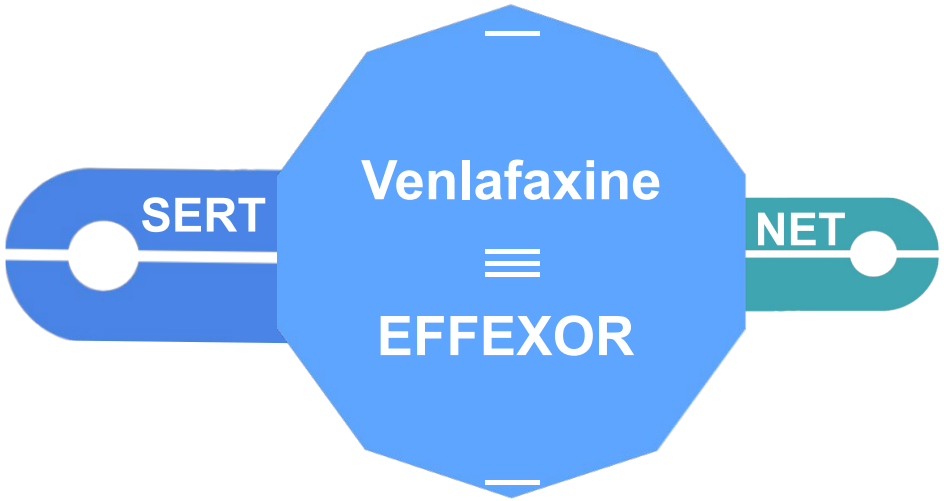


“Vanilla faxing”



possible BP elevation

Venlafaxine (EFFEXOR) – SNRI

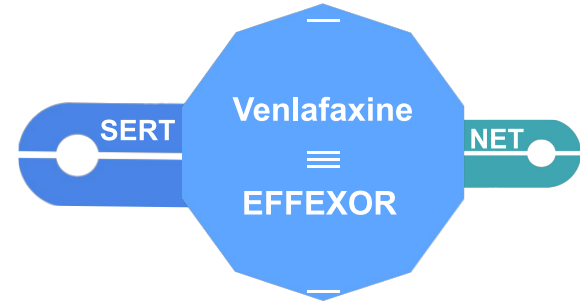


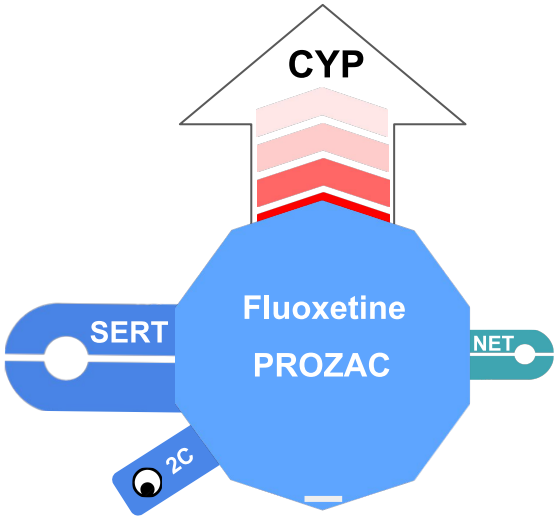
Effexor XR

37.5 mg	75 mg	150 mg
		
“S**S**RI”	“S**S**RI”	S**N**RI

Under 150 mg, it’s just an SRI.

Venlafaxine (EFFEXOR) – SNRI





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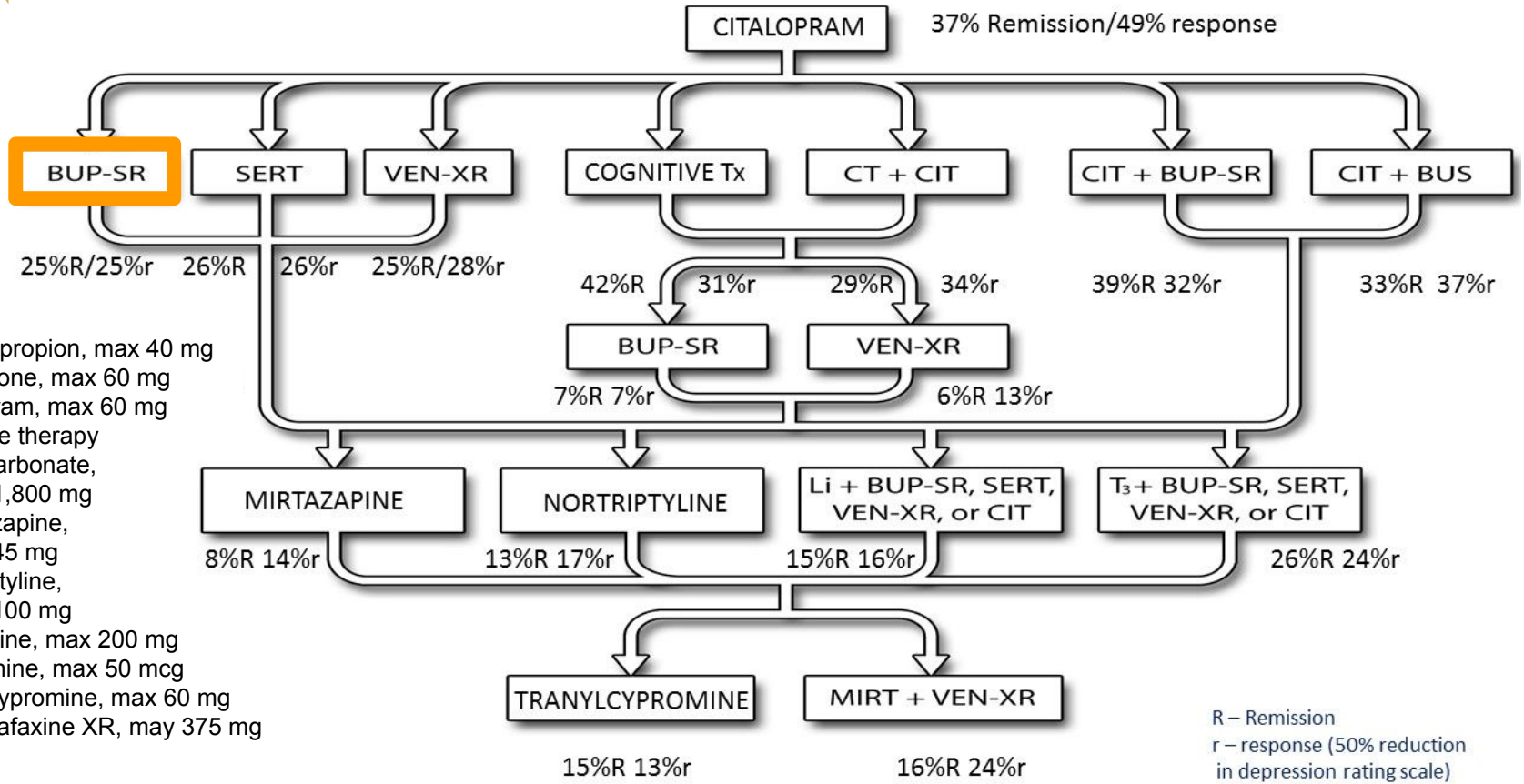

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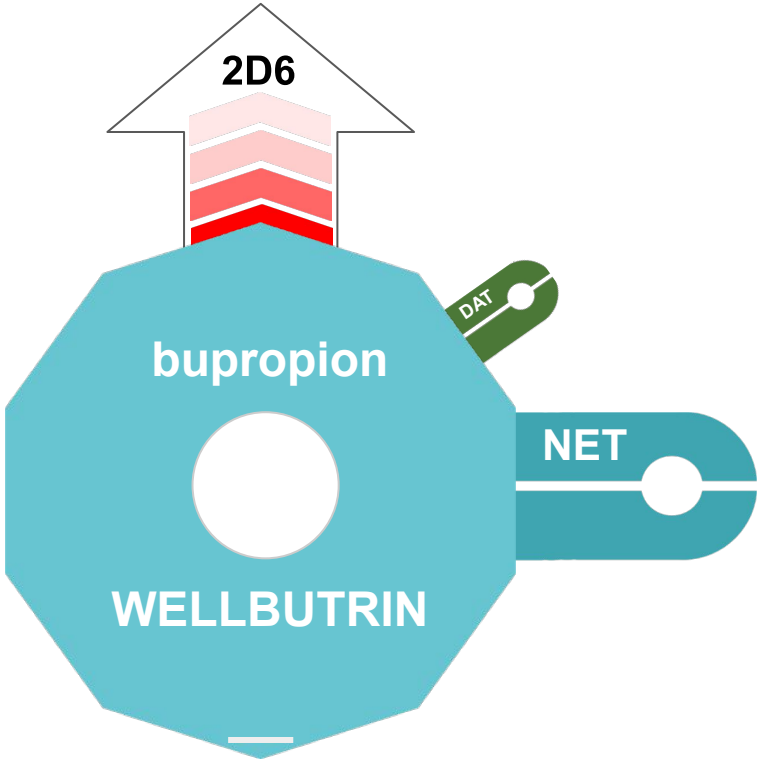
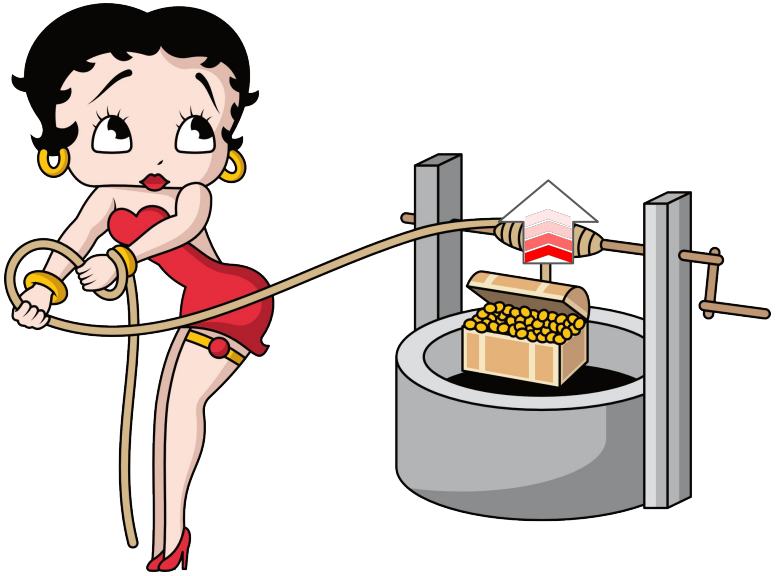
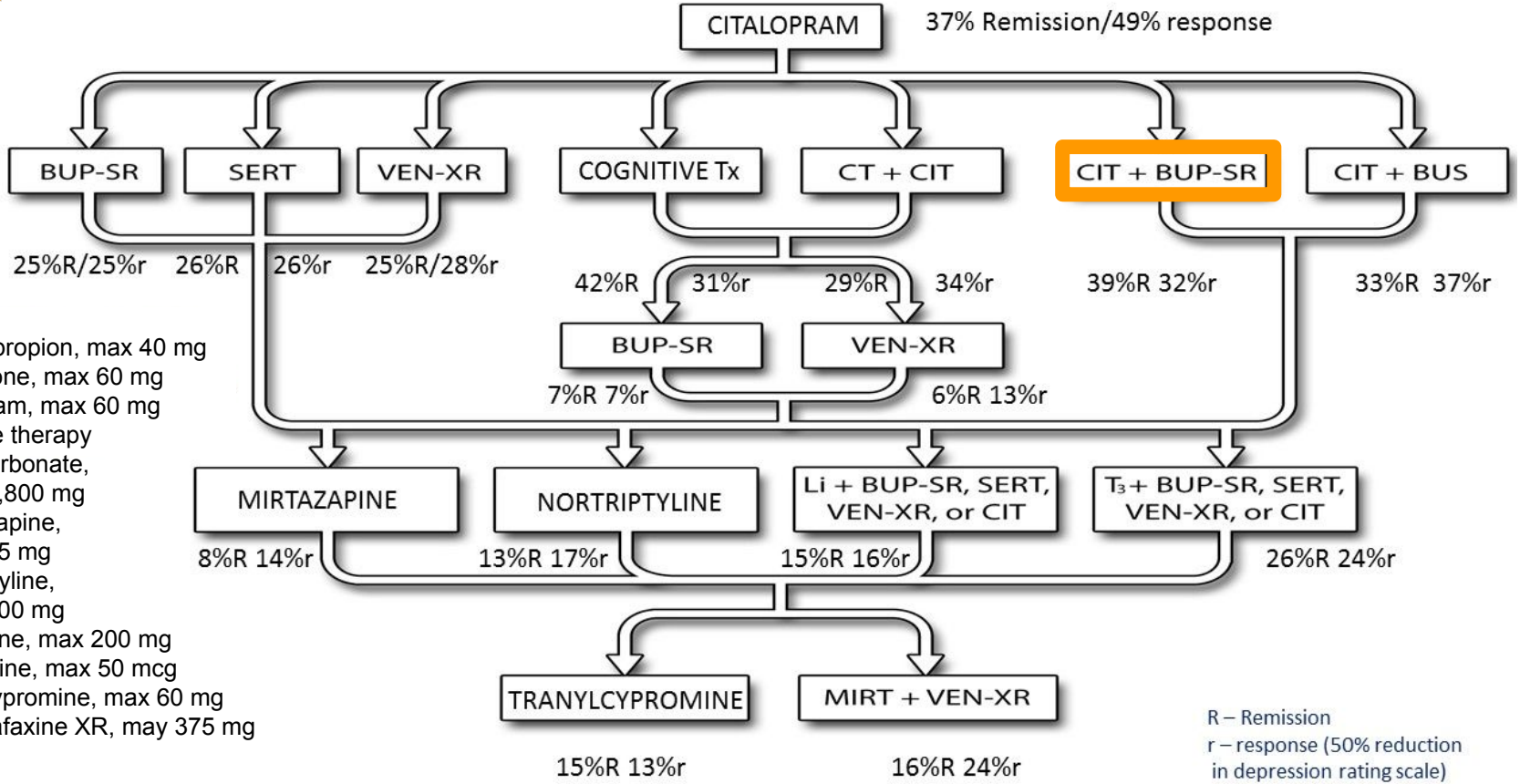
Bupropion (Wellbutrin) – NDRI





“Boop ropin’ Well booty”



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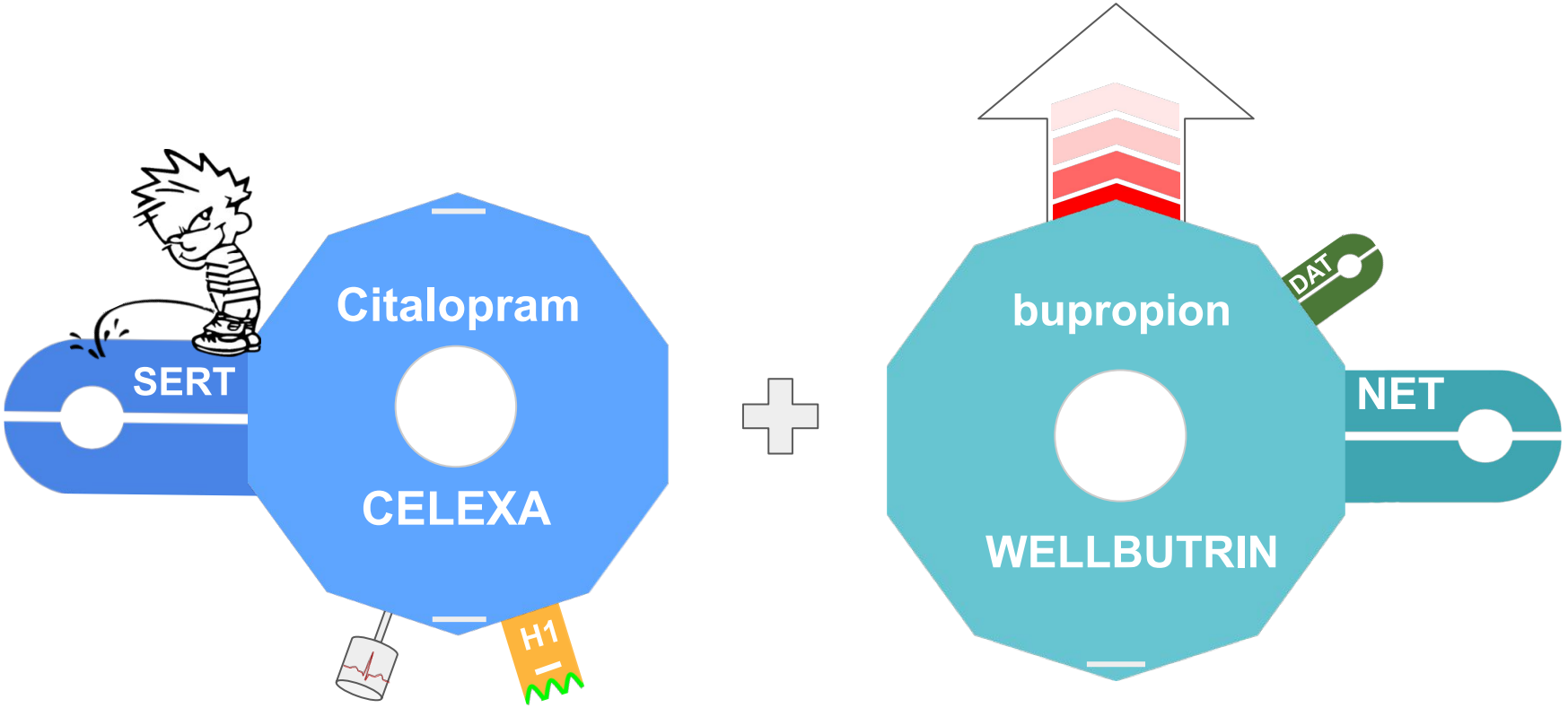
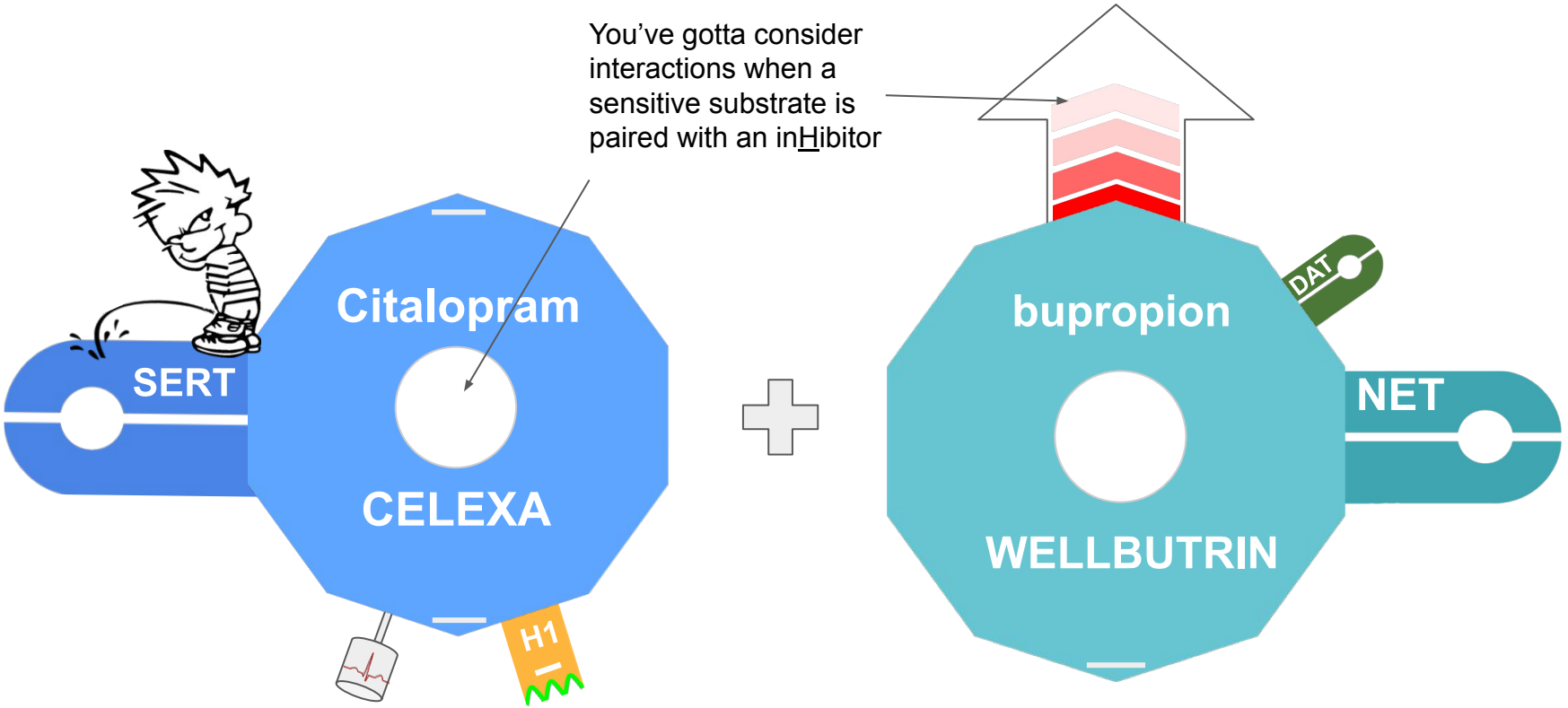
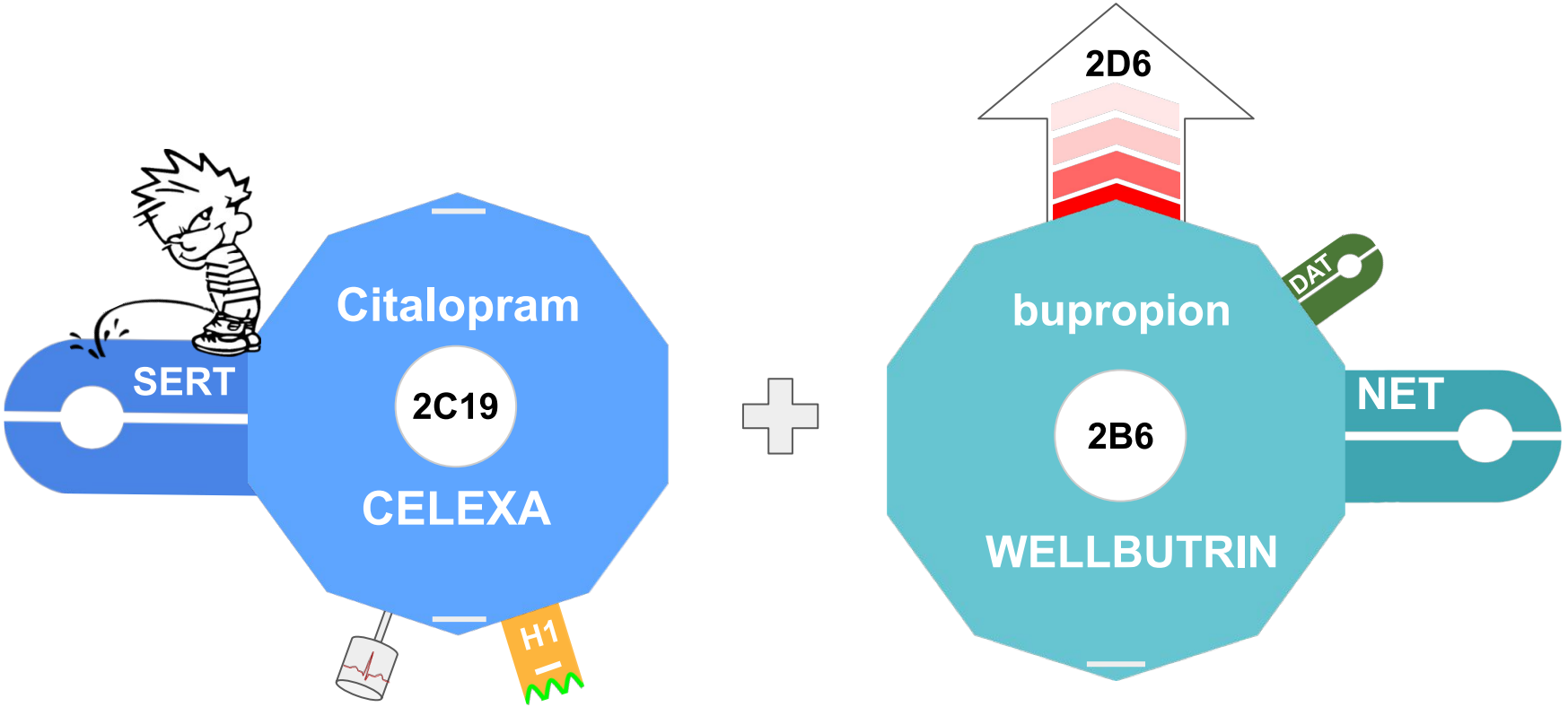
Citalopram + bupropion SR



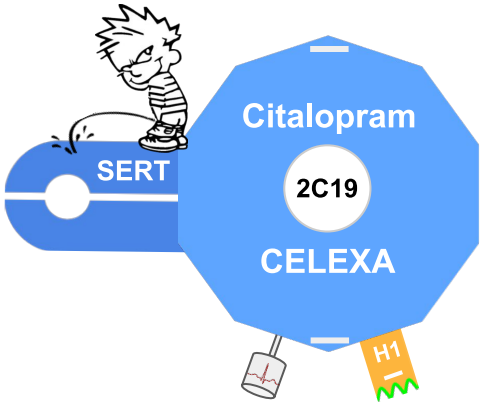
Citalopram + bupropion SR

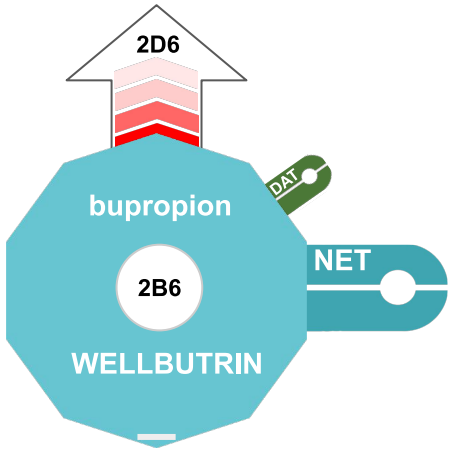


Citalopram + bupropion SR

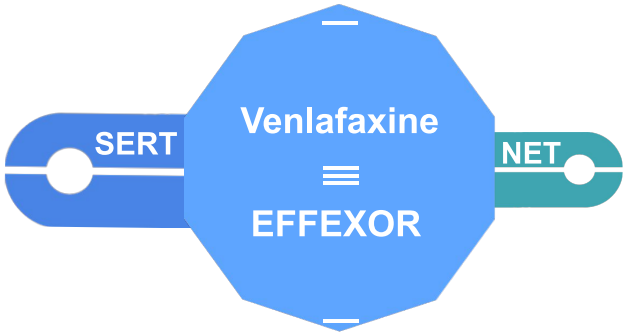


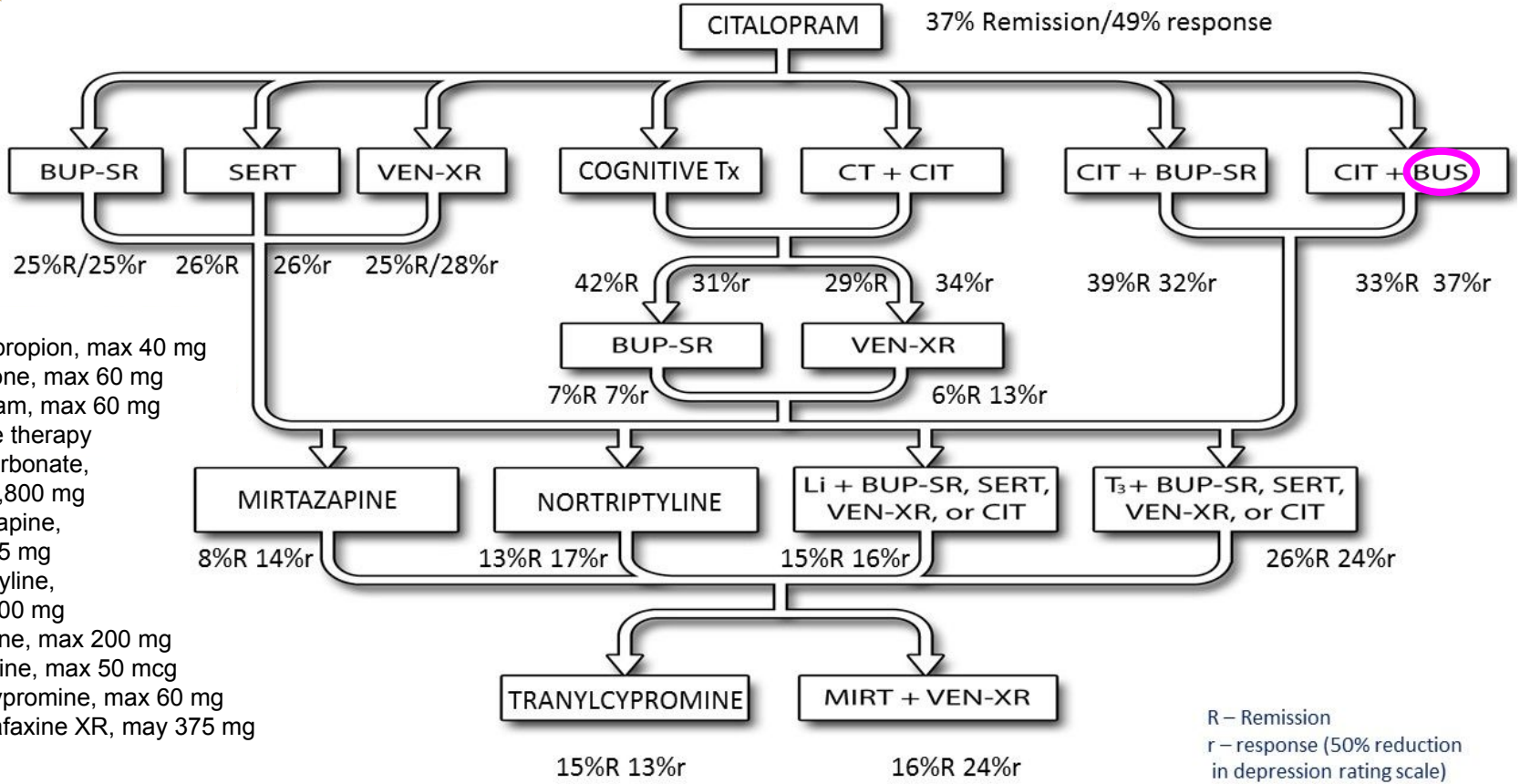
Citalopram + bupropion SR





VS



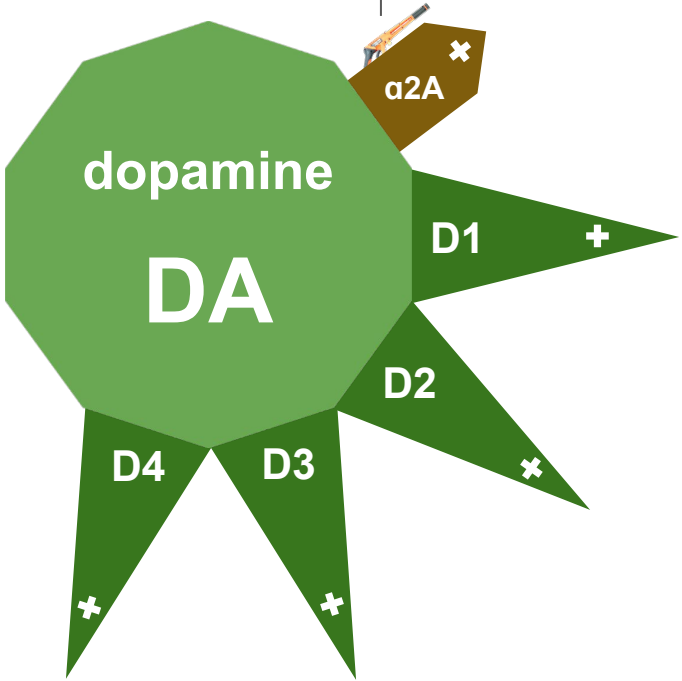


BUP-SR – Bupropion, max 40 mg
BUS – Buspirone, max 60 mg
CIT – Citalopram, max 60 mg
CT – Cognitive therapy
Li – Lithium carbonate, max 1,800 mg
MIRT – Mirtazapine, max 45 mg
NTP – Nortriptyline, max 100 mg
SER – Sertraline, max 200 mg
T3 – Liothyronine, max 50 mcg
TCP – tranylcypromine, max 60 mg
VEN-X – venlafaxine XR, may 375 mg

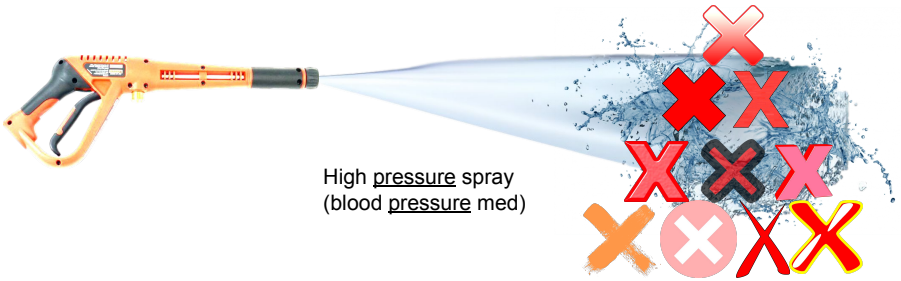
R – Remission
r – response (50% reduction in depression rating scale)

Dopamine – DA receptor agonist

DA binds the norepinephrine receptor responsible for pro-cognitive effect of guanfacine



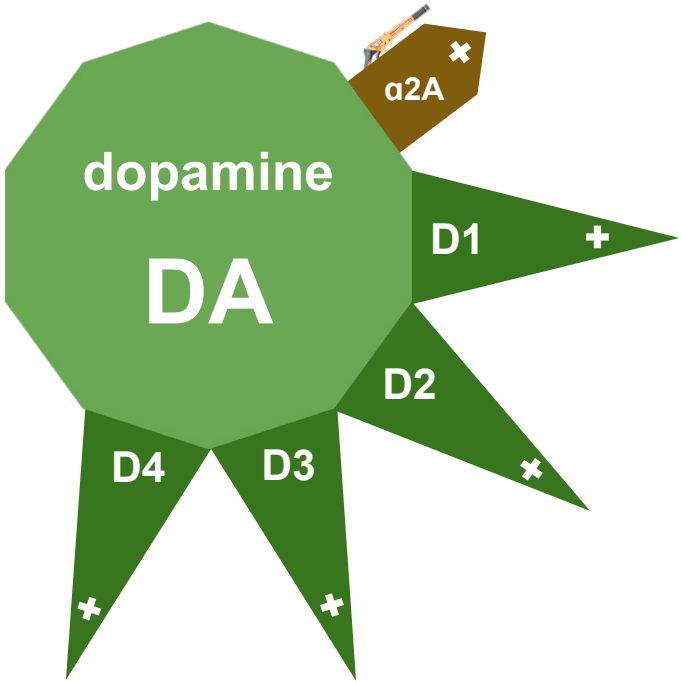
Guanfacine (TENEX)

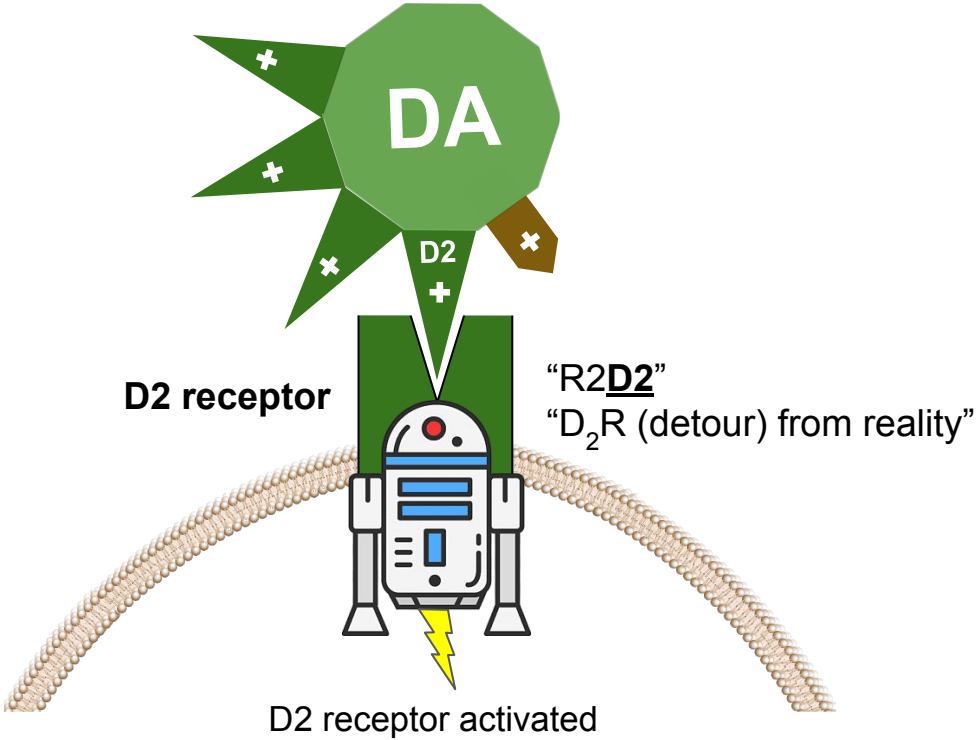


"Gun facing Ten X's"

Selective (centrally acting) alpha-2A agonist

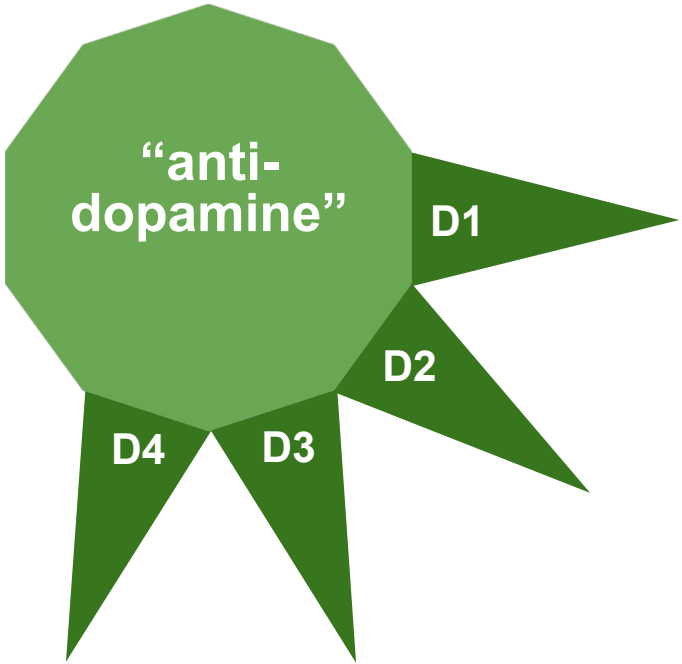
Dopamine – DA receptor agonist

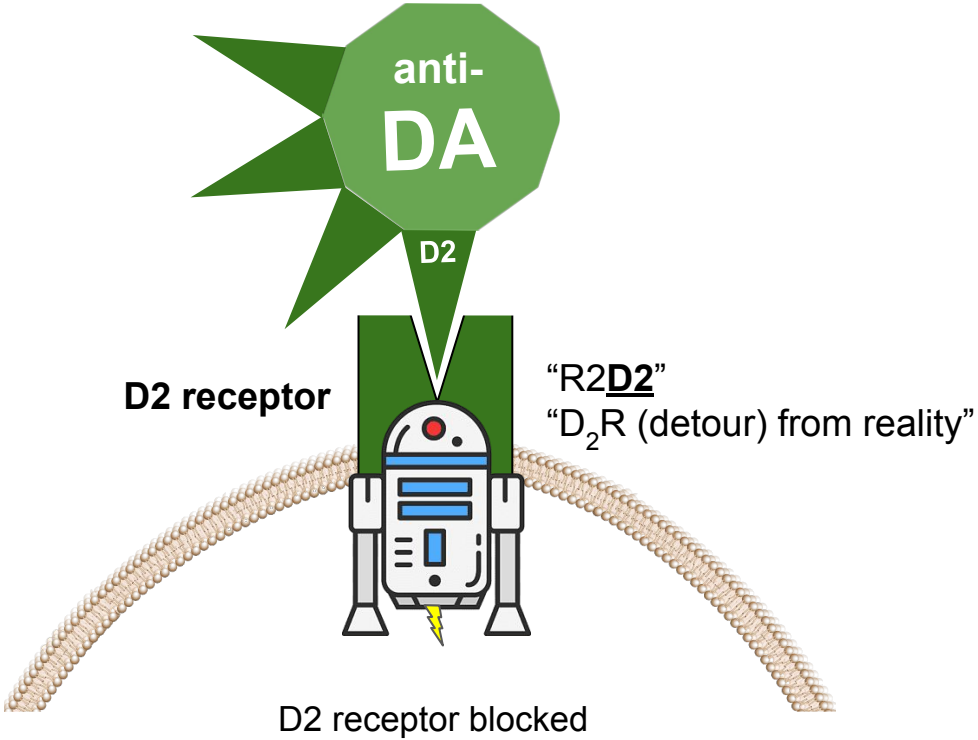




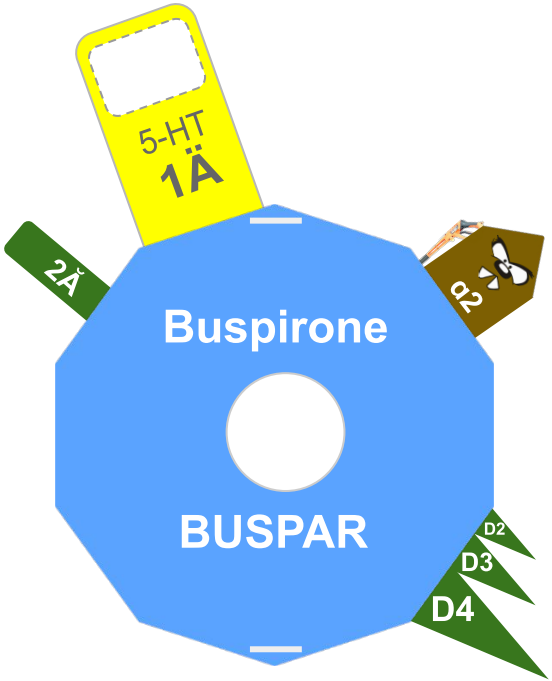
“Anti-dopamine” - DA receptor antagonist

There were no antipsychotics in STAR*D, but we’re about to add a pinch of DA receptor blockade...



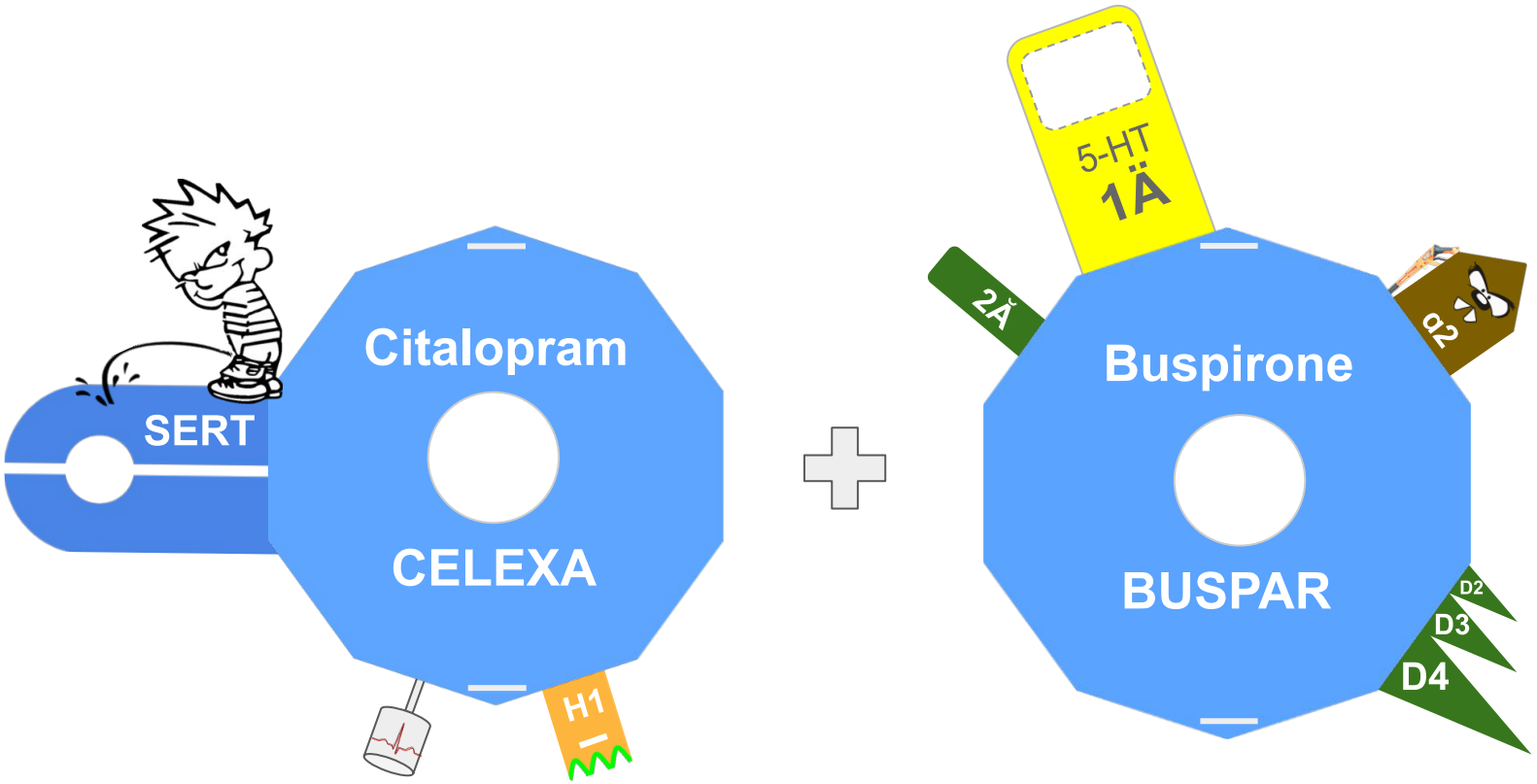


Buspirone (BUSPAR) – 5-HT1A partial agonist

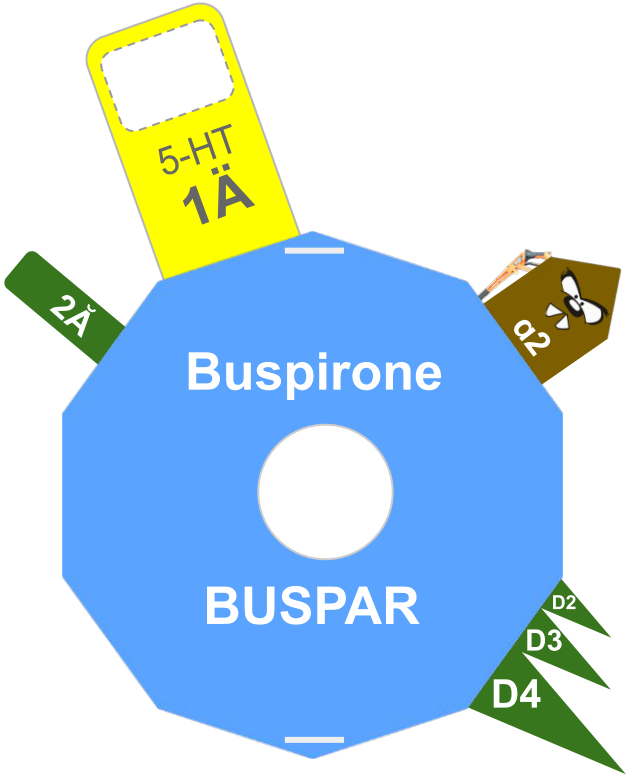


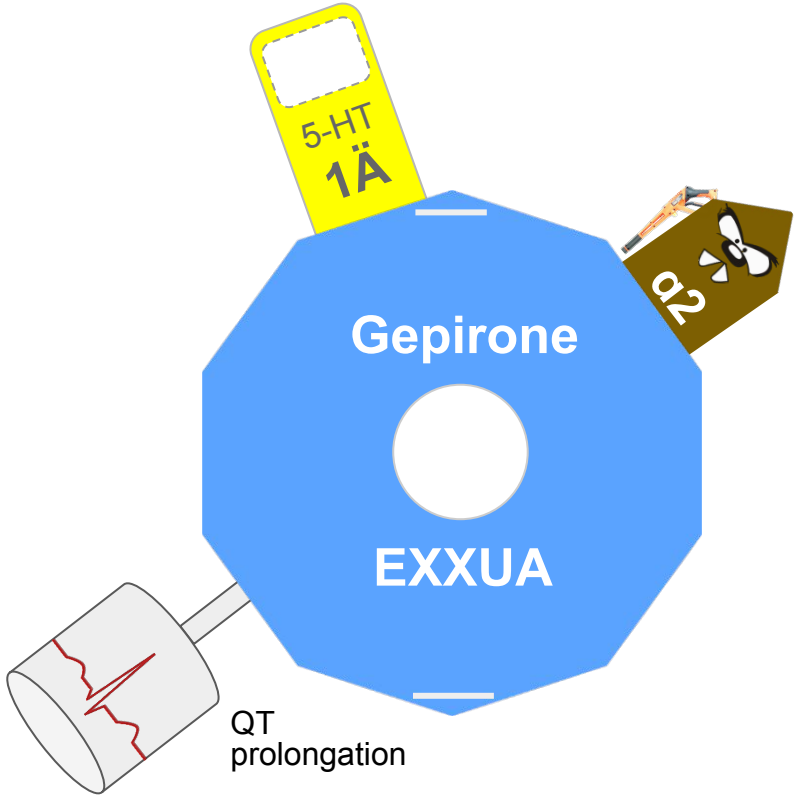
“Bus spear”

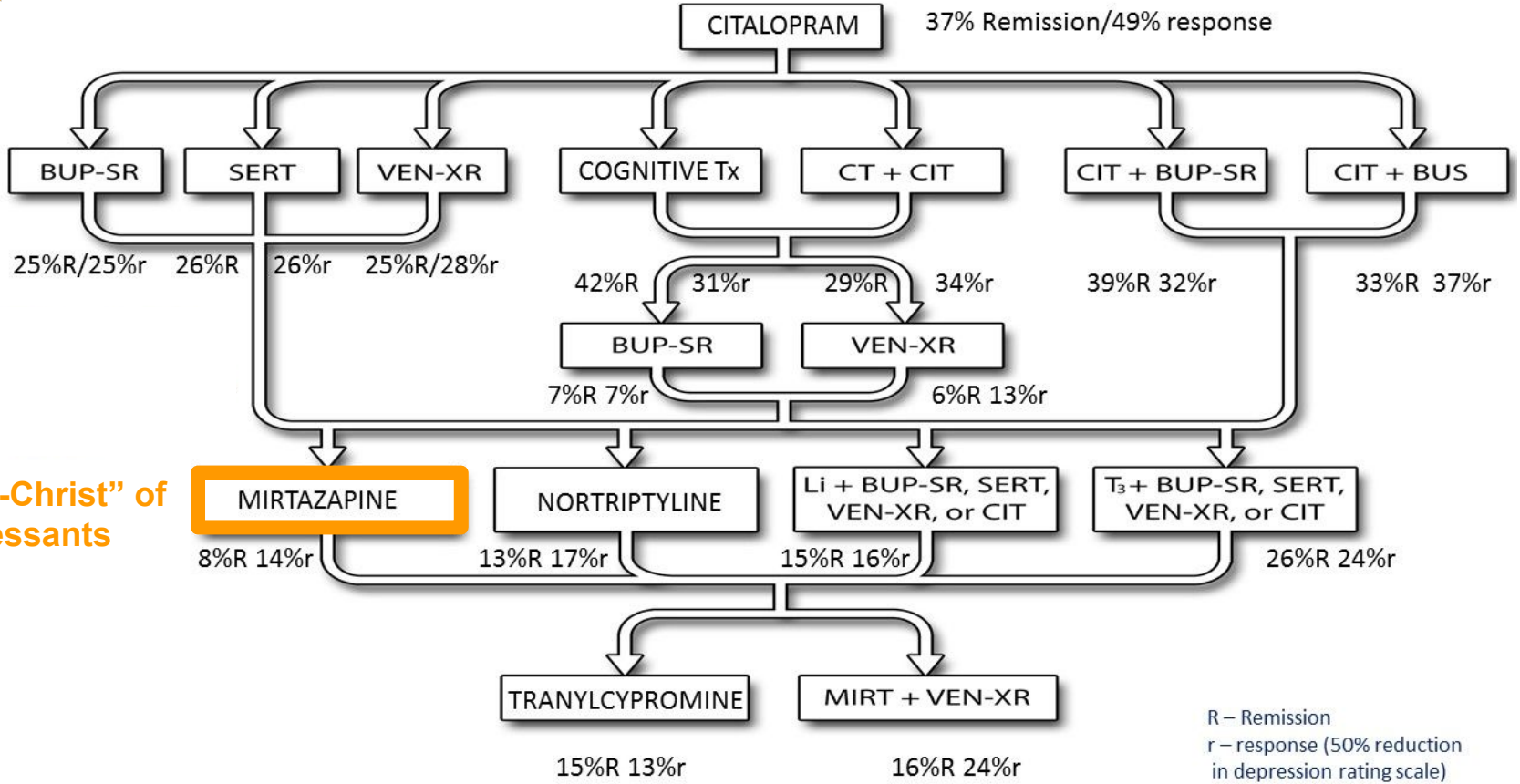
Citalopram + buspirone



Buspirone (BUSPAR) – 5-HT1A partial agonist

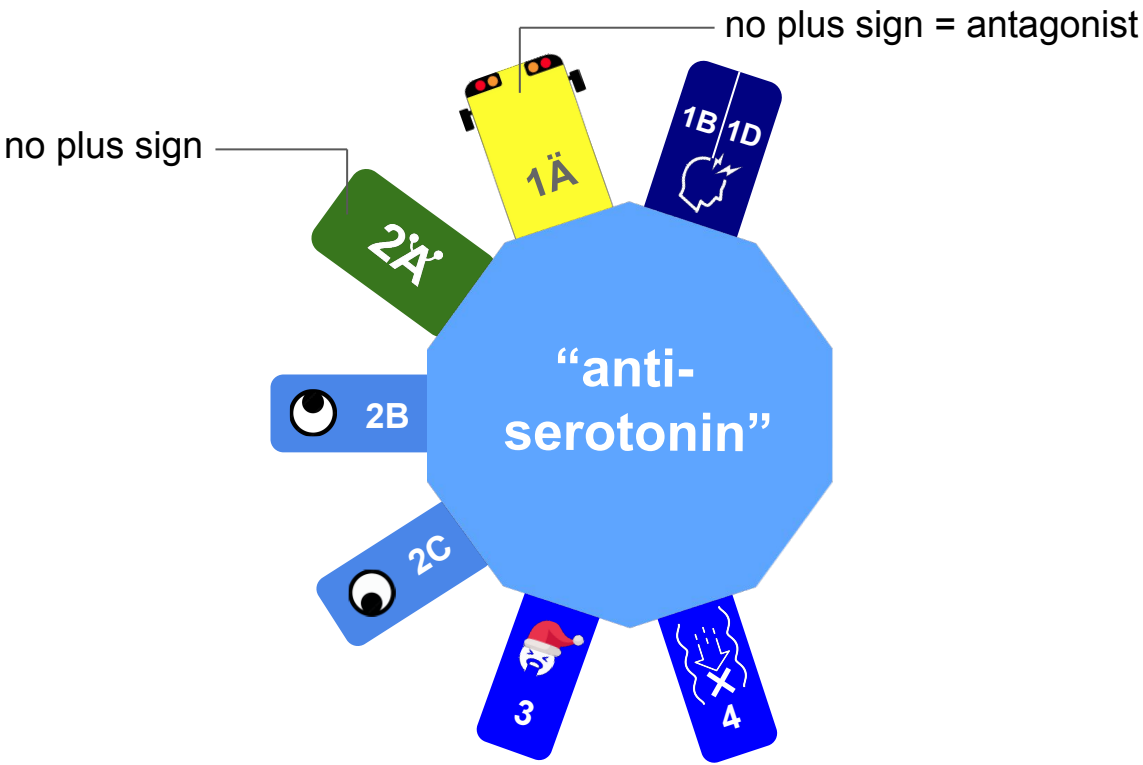




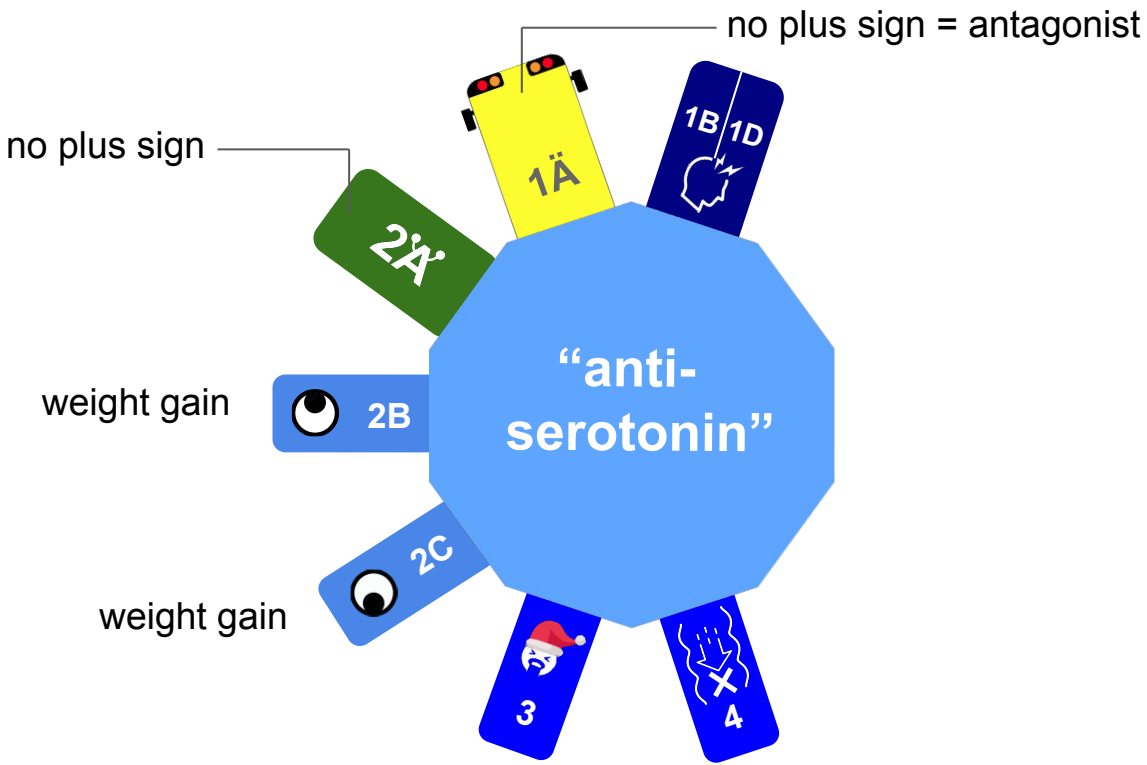


The "anti-Christ" of antidepressants

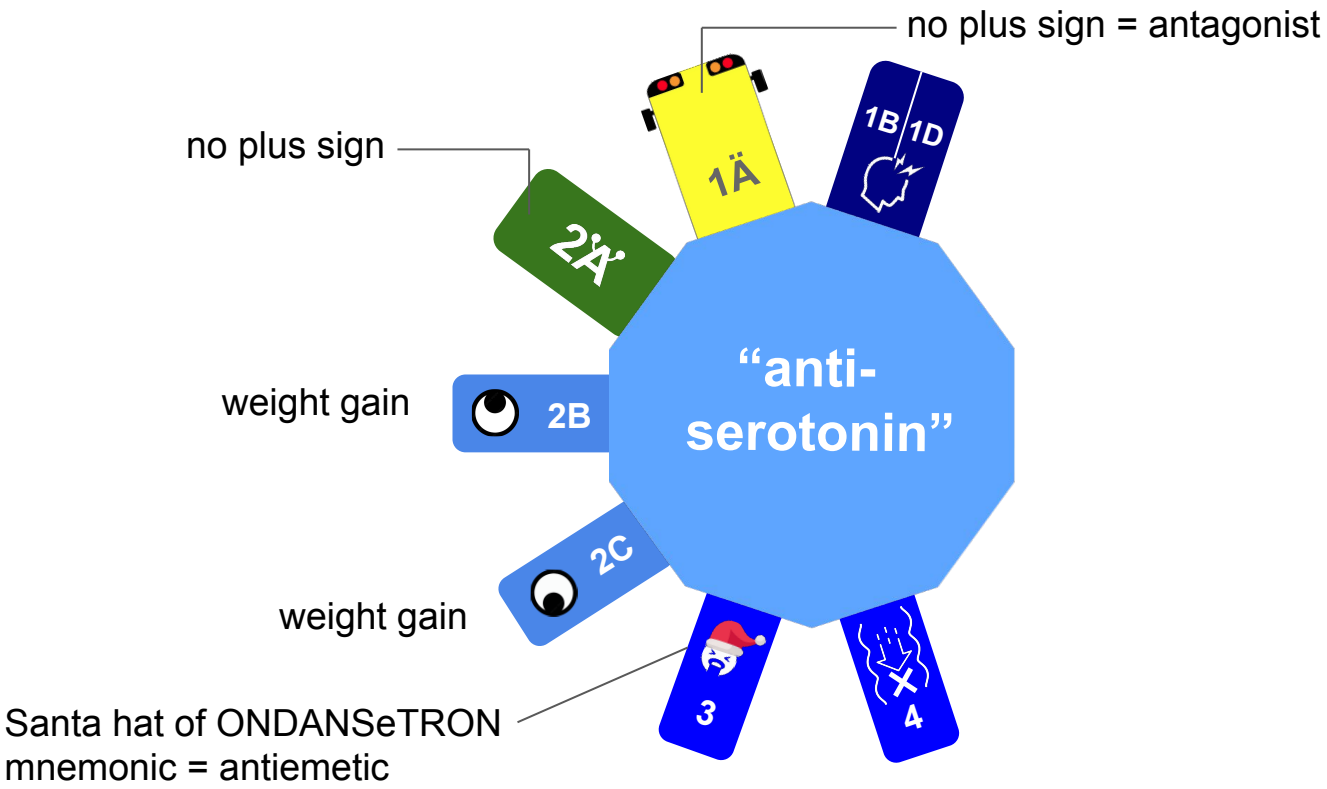
“Anti-serotonin” – 5-HT receptor antagonist



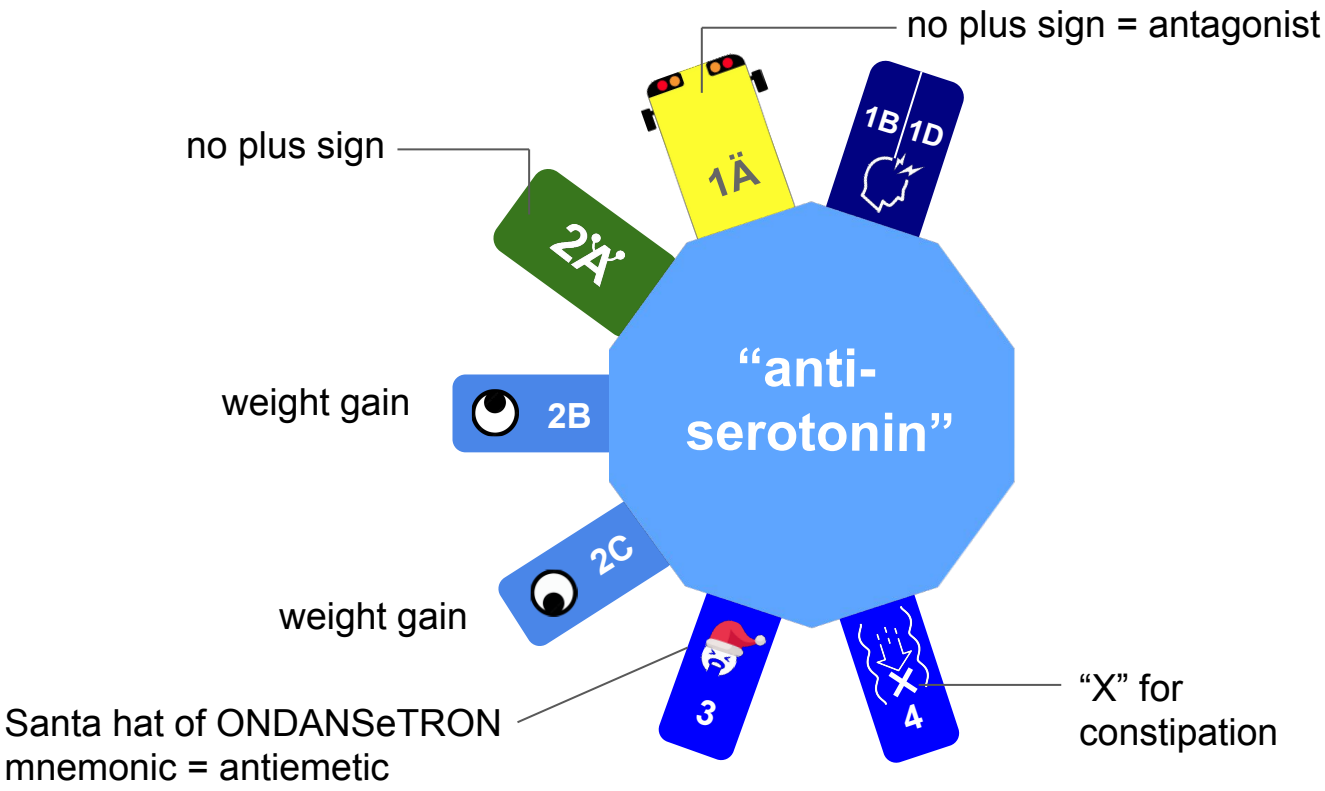
“Anti-serotonin” – 5-HT receptor antagonist



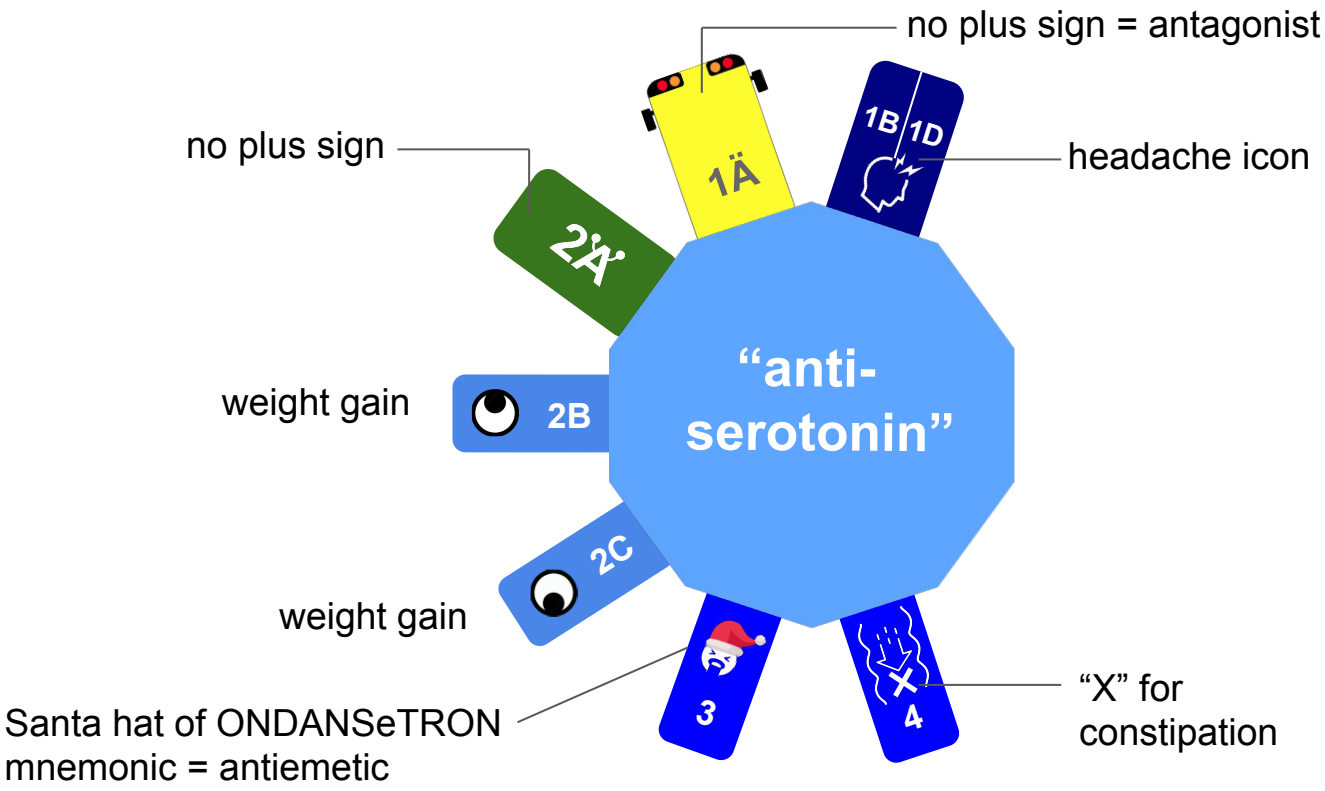
“Anti-serotonin” – 5-HT receptor antagonist



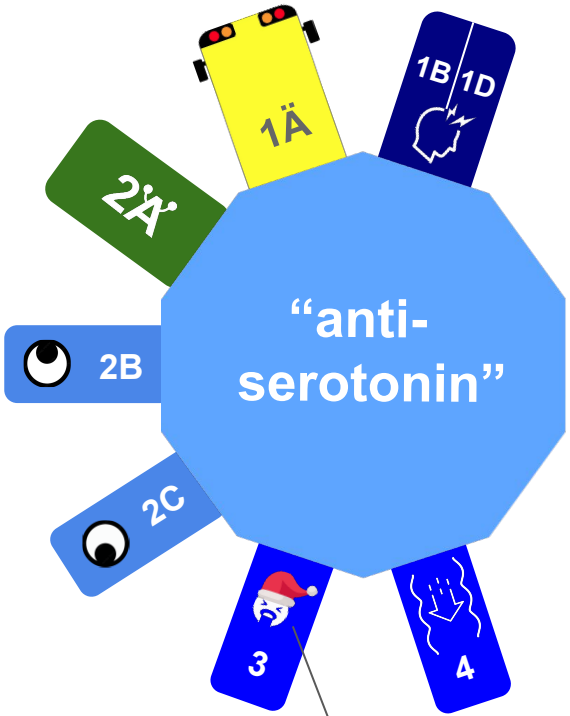
“Anti-serotonin” – 5-HT receptor antagonist



“Anti-serotonin” – 5-HT receptor antagonist

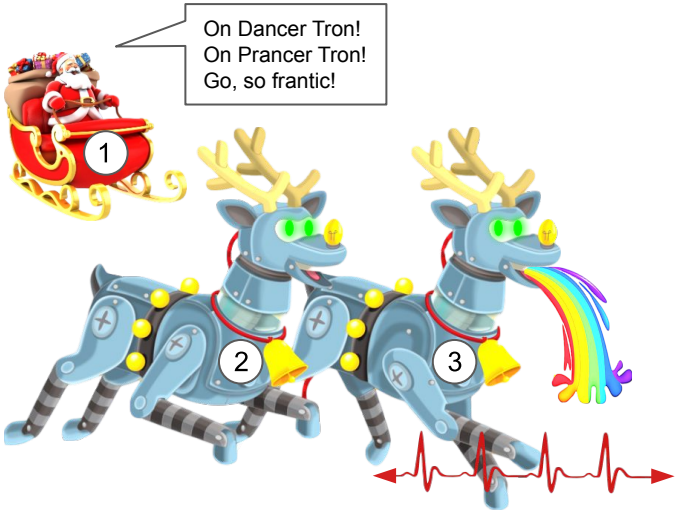


“Anti-serotonin” – 5-HT receptor antagonist



Santa hat of ONDANSETRON mnemonic = antiemetic

ONDANSETRON (ZOFRAN)



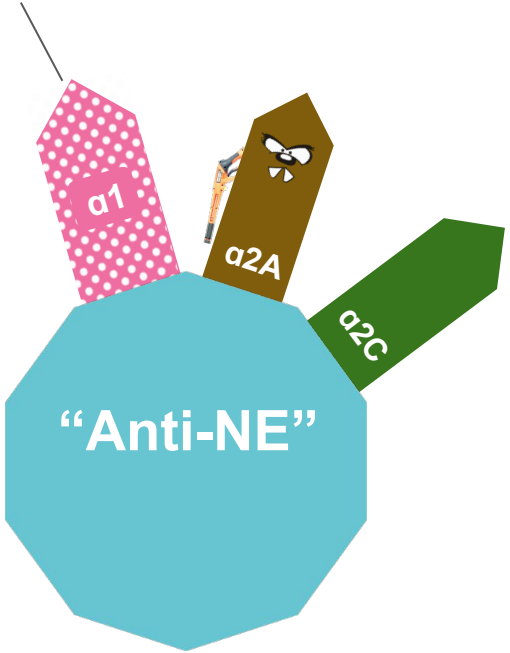
“On Dancer Tron!”

“Anti-norepinephrine” – adrenergic receptor antagonist

“Anti-norepinephrine” – adrenergic receptor antagonist

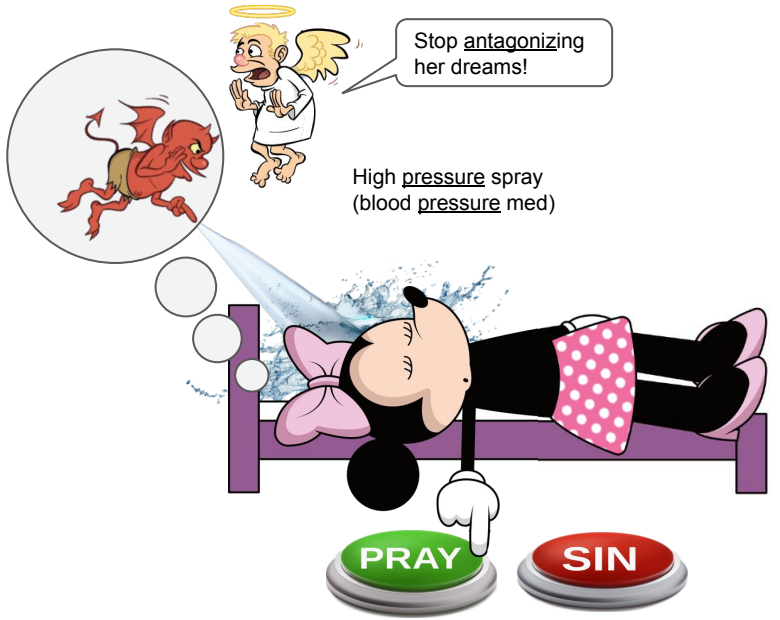
α1 ANTAGONIST

❖ The effect of prazosin (Minipress) in lowering blood pressure and improving PTSD-related nightmares



Prazosin (MINIPRESS)

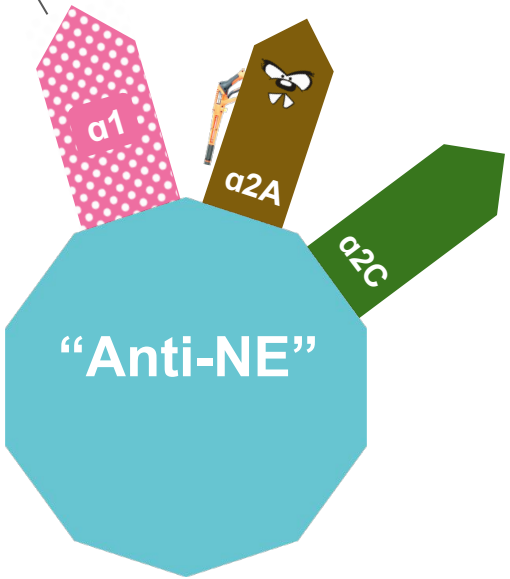
“Minnie press (Prays or sins)”



“Anti-norepinephrine” – adrenergic receptor antagonist

α1 ANTAGONIST

❖ The effect of prazosin (Minipress)



α2A ANTAGONIST

❖ Principal antidepressant effect of mirtazapine (Remeron), with downstream release of serotonin

❖ Mirtazapine blocks the antihypertensive effect of clonidine, potentially precipitating hypertensive crisis

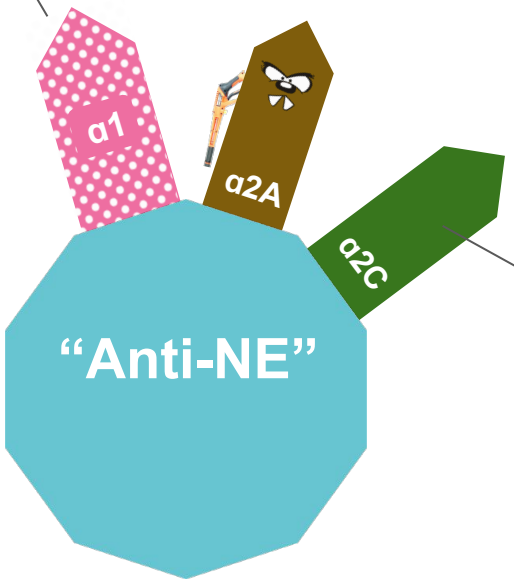
Mirtazapine (REMERON)

“Mr Taz zapping”

“Anti-norepinephrine” – adrenergic receptor antagonist

α1 ANTAGONIST

❖ The effect of prazosin (Minipress)



α2A ANTAGONIST

❖ Principal antidepressant effect of mirtazapine (Remeron), with downstream release of serotonin

❖ Mirtazapine blocks the antihypertensive effect of clonidine, potentially precipitating hypertensive crisis

α2C ANTAGONIST

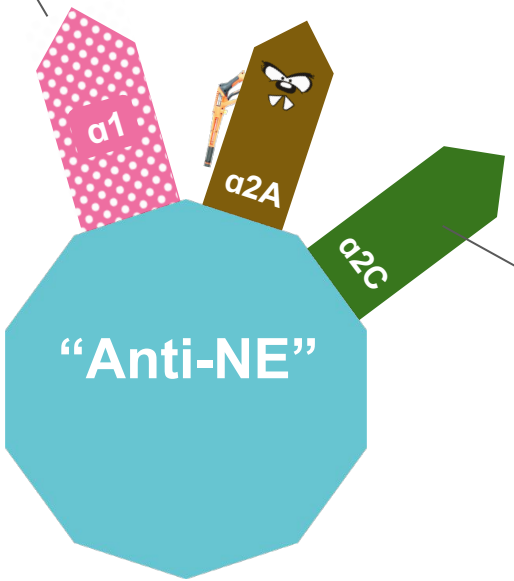
❖ May contribute substantially to antipsychotic effects of clozapine, olanzapine, risperidone, paliperidone, and brexpiprazole.

(green for “little green men”)

“Anti-norepinephrine” – adrenergic receptor antagonist

α1 ANTAGONIST

❖ The effect of prazosin (Minipress)



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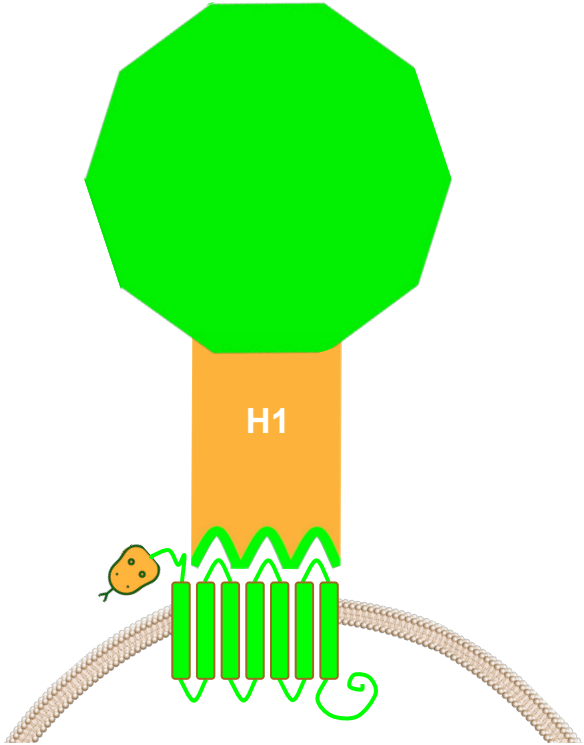
(green for “little green men”)

Histamine

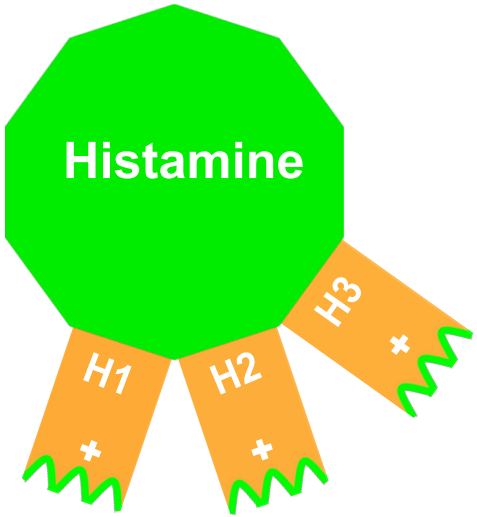


“Hissed”-amine receptor

Histamine

HISTAMINE H1 RECEPTOR AGONIST

- ❖ Acute allergic response
- ❖ Wake-promoting
- ❖ Pro-cognitive
- ❖ Anticonvulsant
- ❖ Anorectic

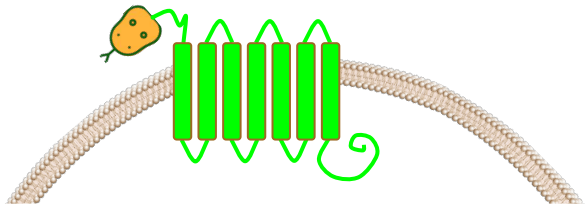


H2 AGONIST

- ❖ Gastric acid secretion

H3 AGONIST

- ❖ Inhibition of histamine release, as negative feedback



“Hissed”-amine receptor

Anti-histamine

Virtually all antihistamines are inverse agonists (minus sign on peg) rather than neutral antagonists.

HISTAMINE H1 RECEPTOR INVERSE AGONIST

- Sedation
- Anxiolytic effects
- Relief of allergic conditions
- Antiemetic
- Increased appetite and weight gain

H2 INVERSE AGONIST

- Decreased gastric acid secretion: ranitidine (Zantac), famotidine (Pepcid), etc

H3 INVERSE AGONIST

- The wake-promoting effect of pitolisant (Wakix)

Pitolisant (WAKIX)

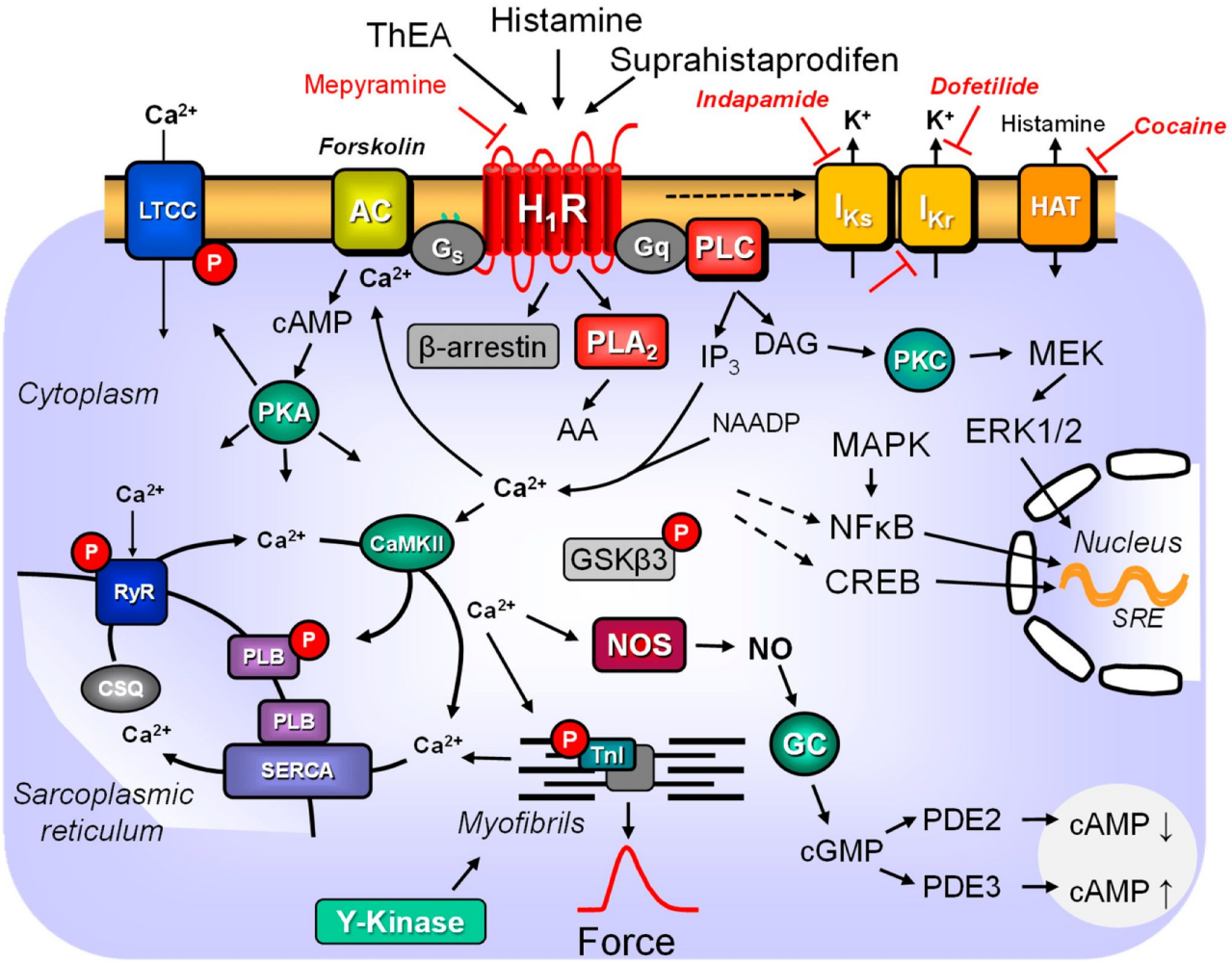
pi TOL i sant / way kicks

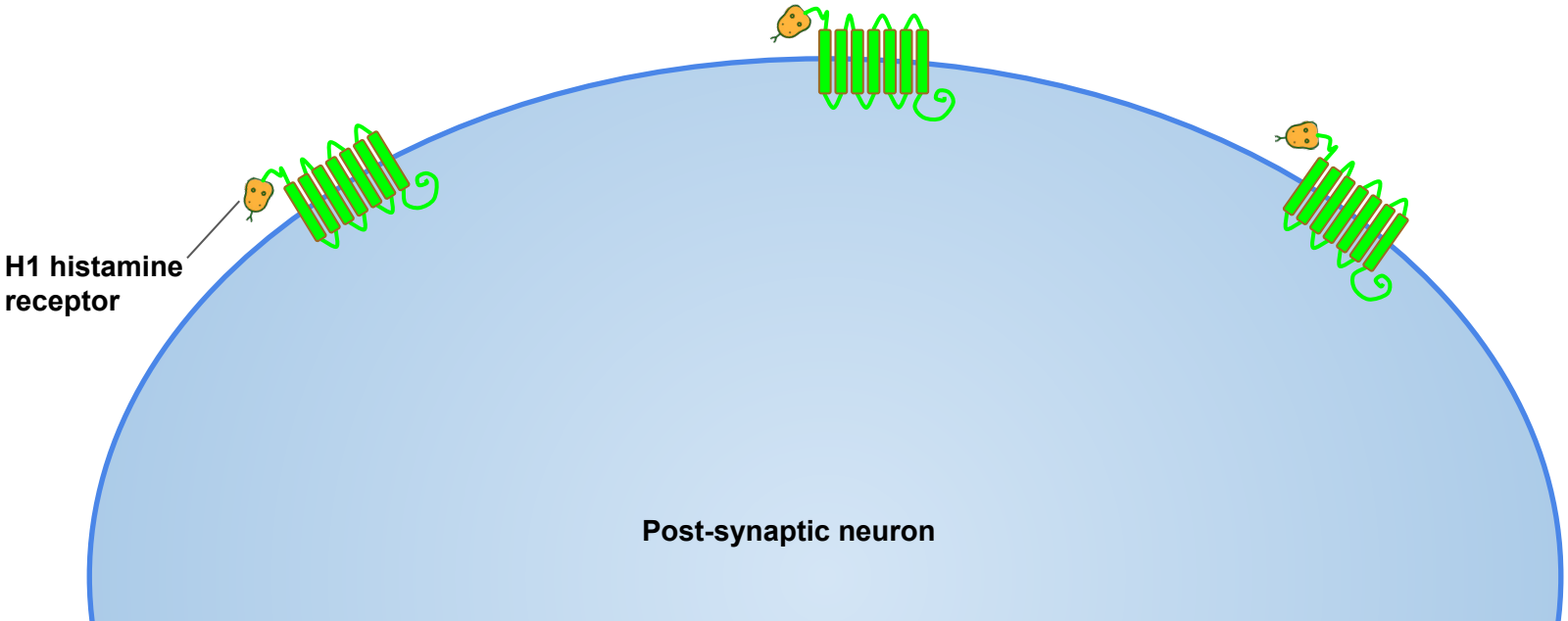
“Wacky Pitstop”

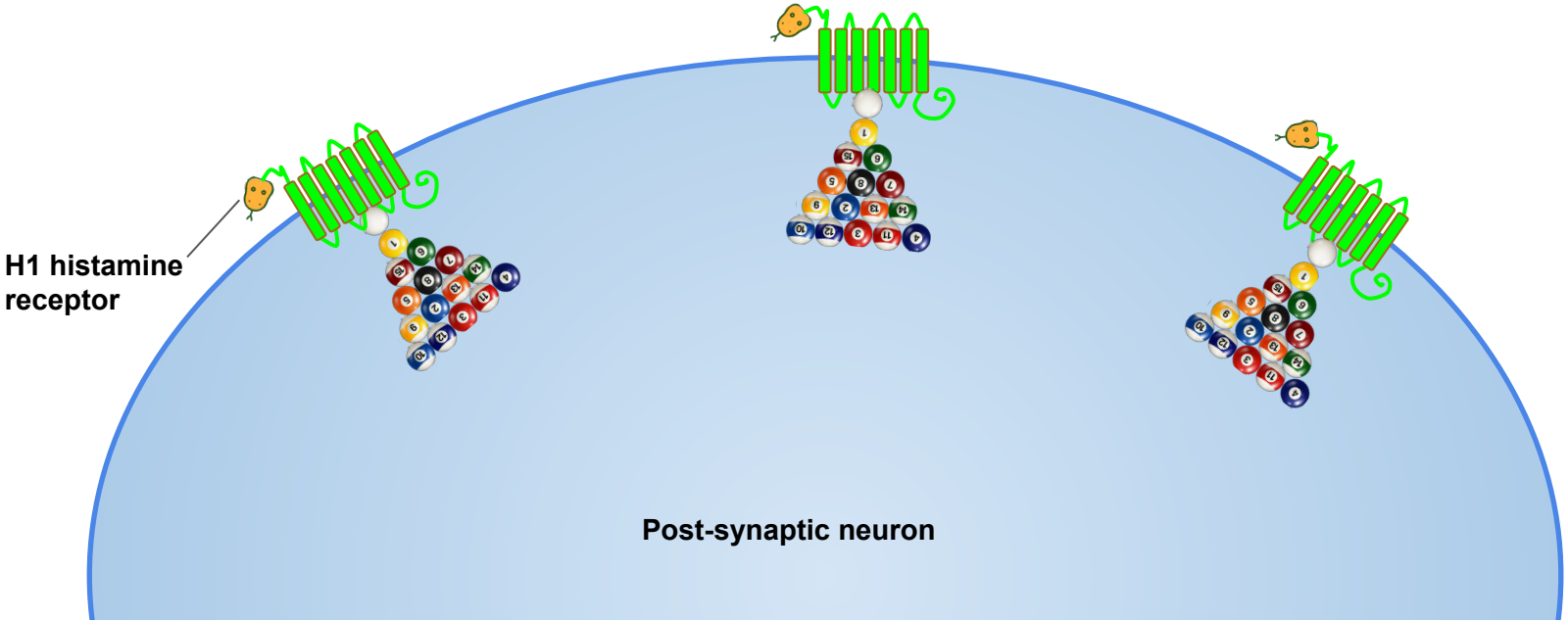
FDA-approved for:

- Excessive daytime sleepiness (EDS) with narcolepsy
- Cataplexy with narcolepsy
- Idiopathic hypersomnia – “Wakix keeps you awake”

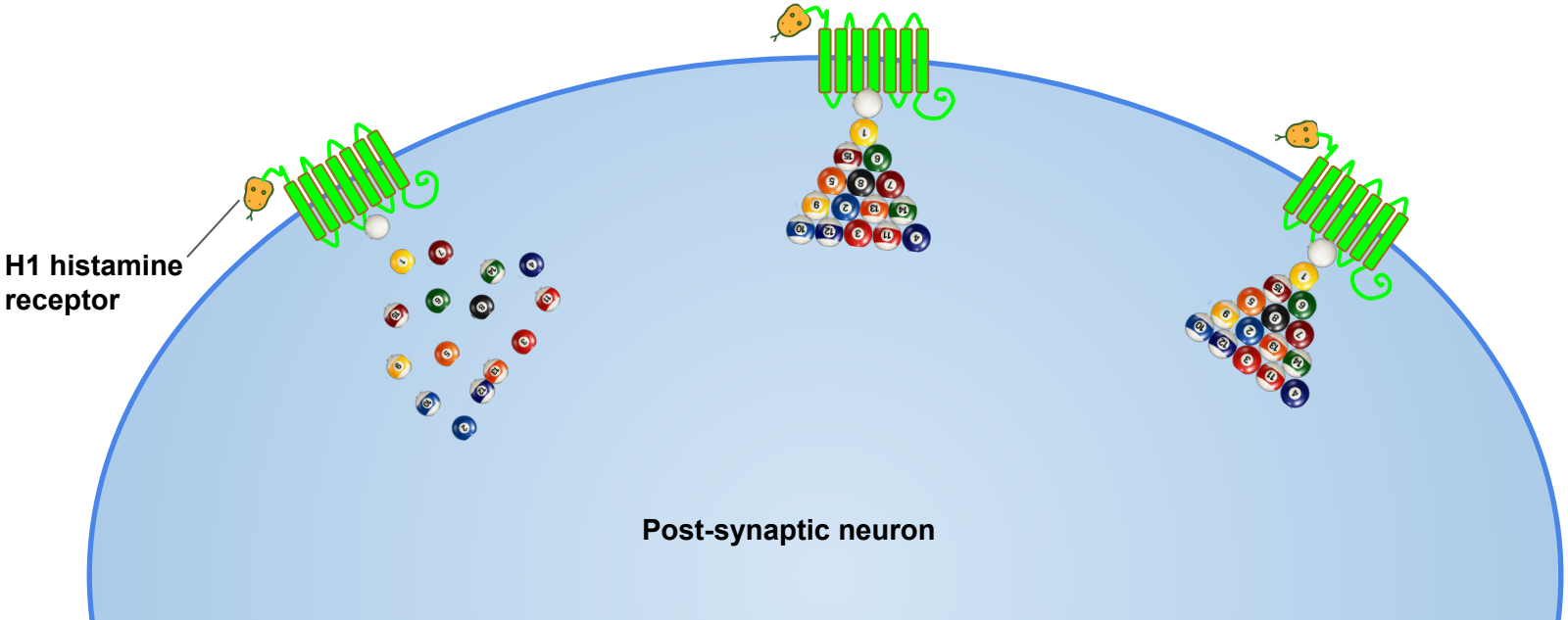
Penelope Pitstop's car (the Compact Pussycat) from the Hanna-Barbera animated series Wacky Races (1968)


ThEA
Histamine
Suprahistaprodifen
Mepyramine
Indapamide
Dofetilide
Cocaine
Forskolin
Ca2+
K+
K+
Histamine
LTCC
AC
H1R
IKs
IKr
HAT
Gs
Gq
PLC
P
Ca2+
cAMP
β-arrestin
PLA2
IP3
DAG
PKC
MEK
Cytoplasm
PKA
AA
NAADP
MAPK
ERK1/2
Ca2+
Ca2+
NFκB
Nucleus
P
RyR
Ca2+
CaMKII
GSKβ3
P
CREB
Ca2+
NOS
NO
SRE
P
PLB
CSQ
PLB
Ca2+
SERCA
Ca2+
P
TnI
GC
Sarcoplasmic
reticulum
Myofibrils
cGMP
PDE2
cAMP ↓
PDE3
cAMP ↑
Y-Kinase
Force

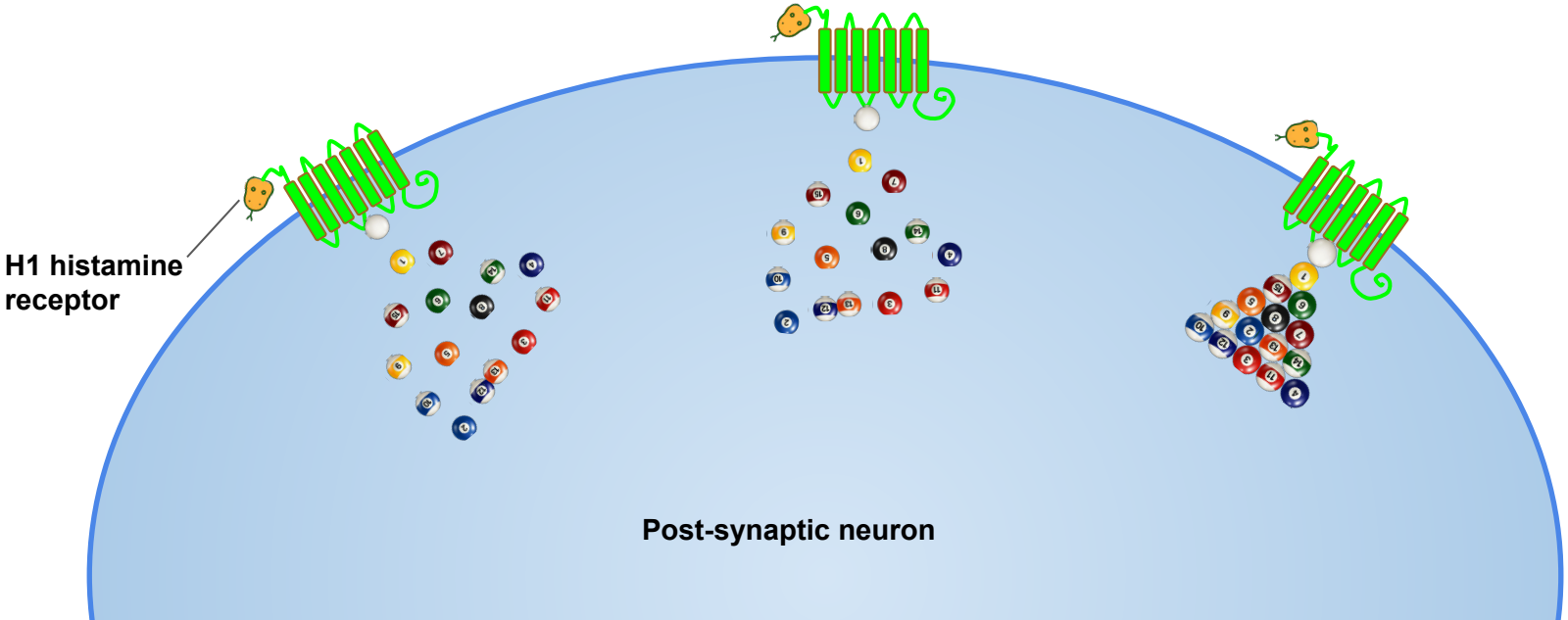

H1 histamine receptor
Post-synaptic neuron


H1 histamine receptor
Post-synaptic neuron

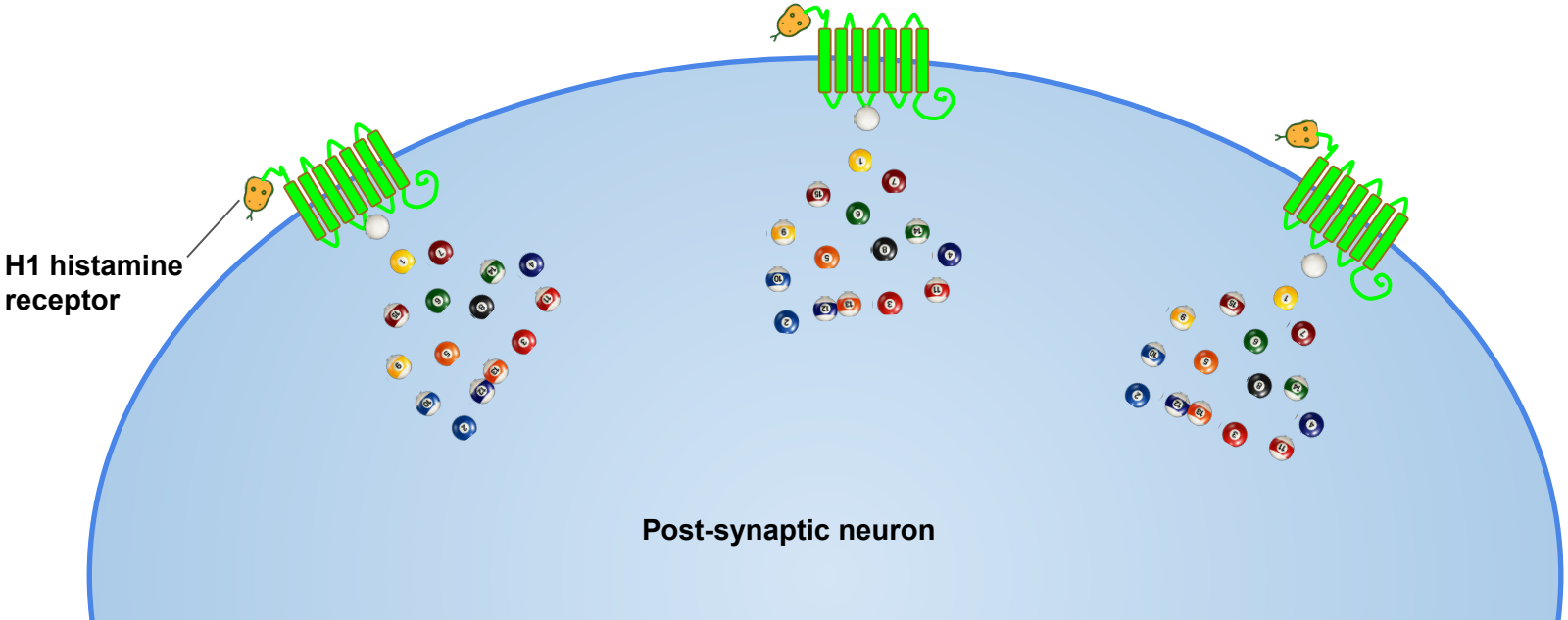
Constitutive activity in absence of histamine

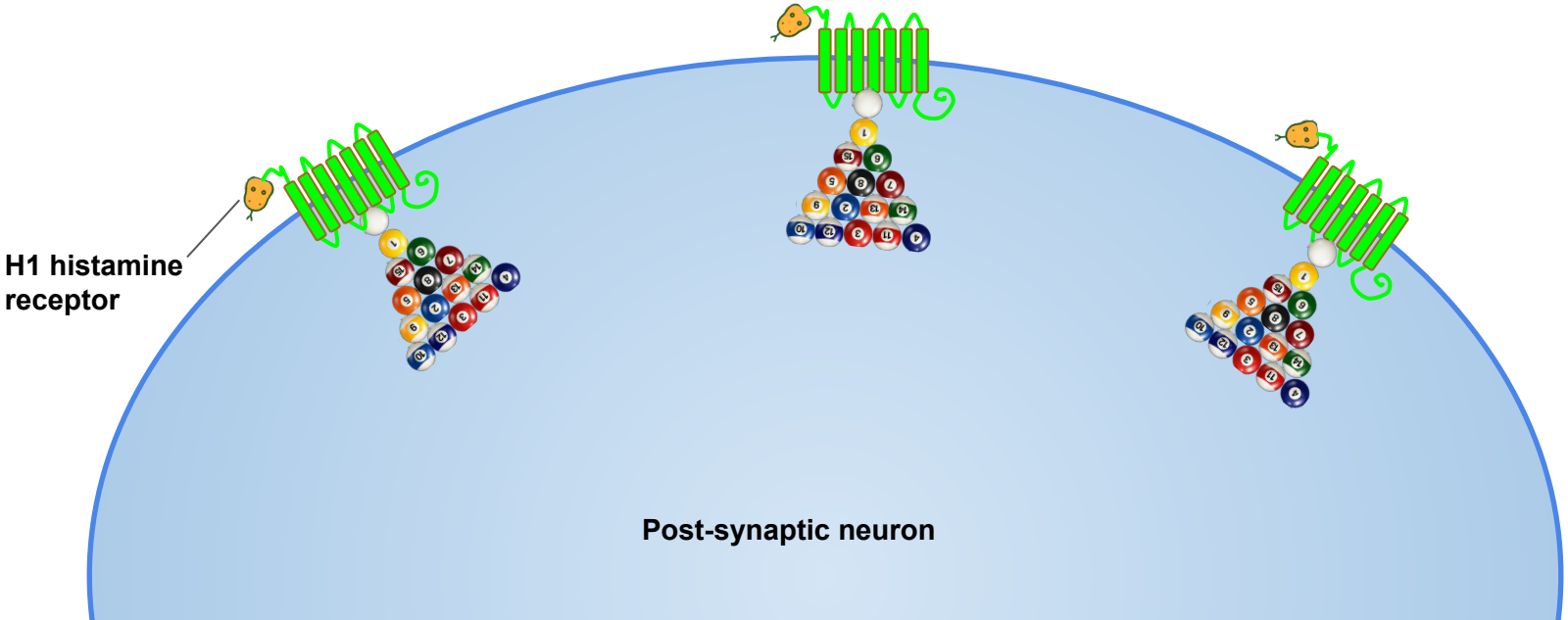


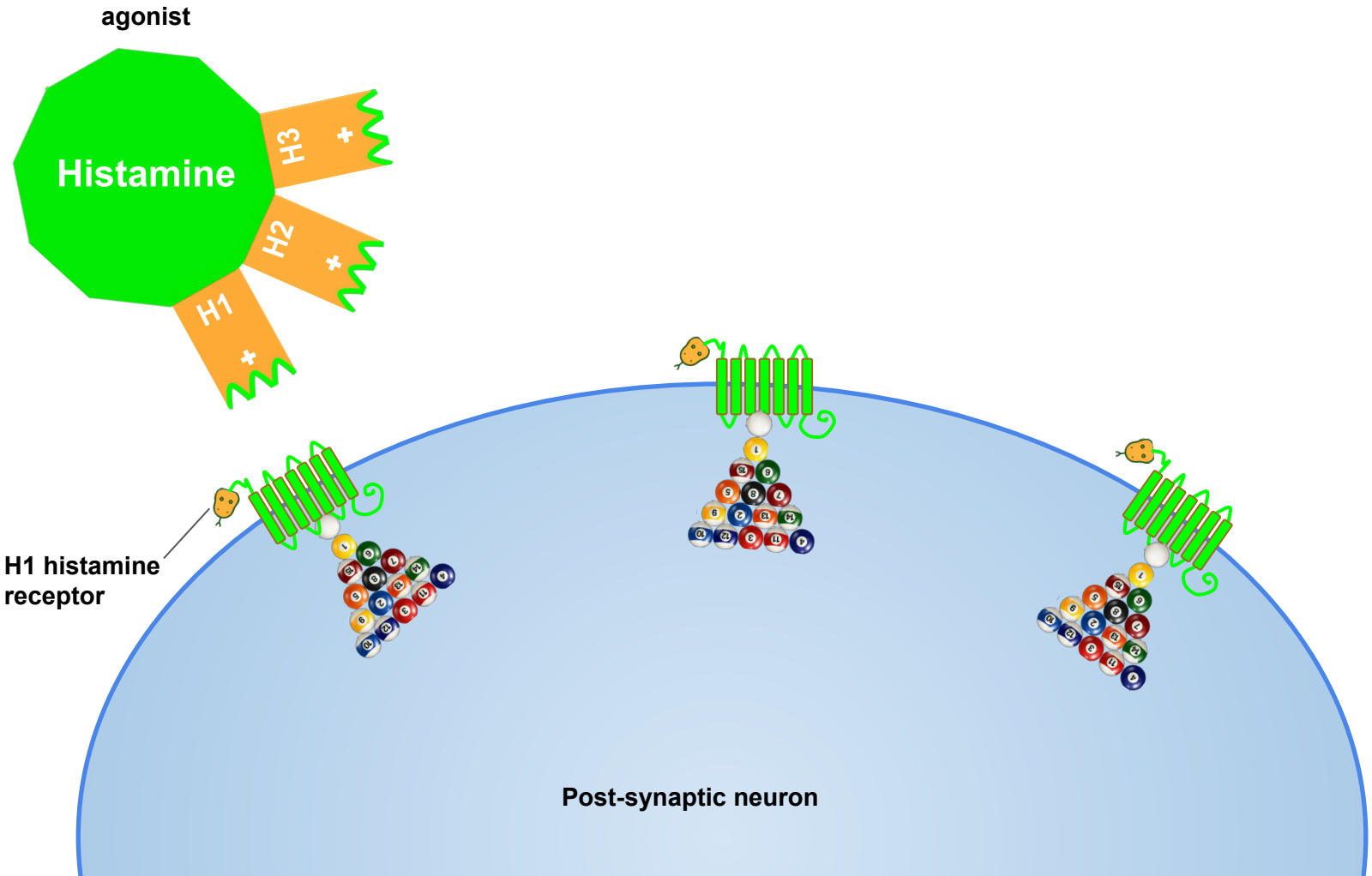
Constitutive activity in absence of histamine

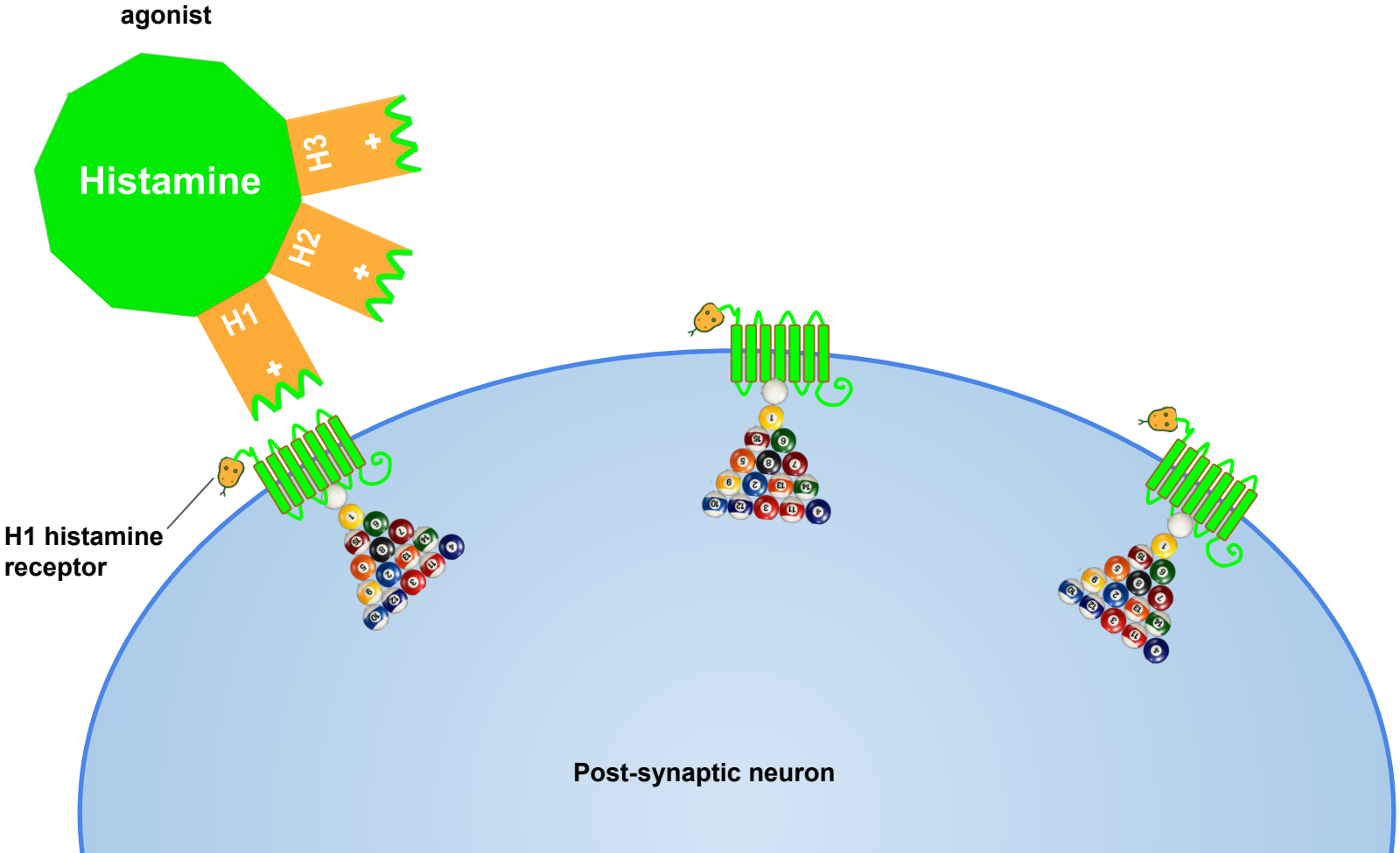


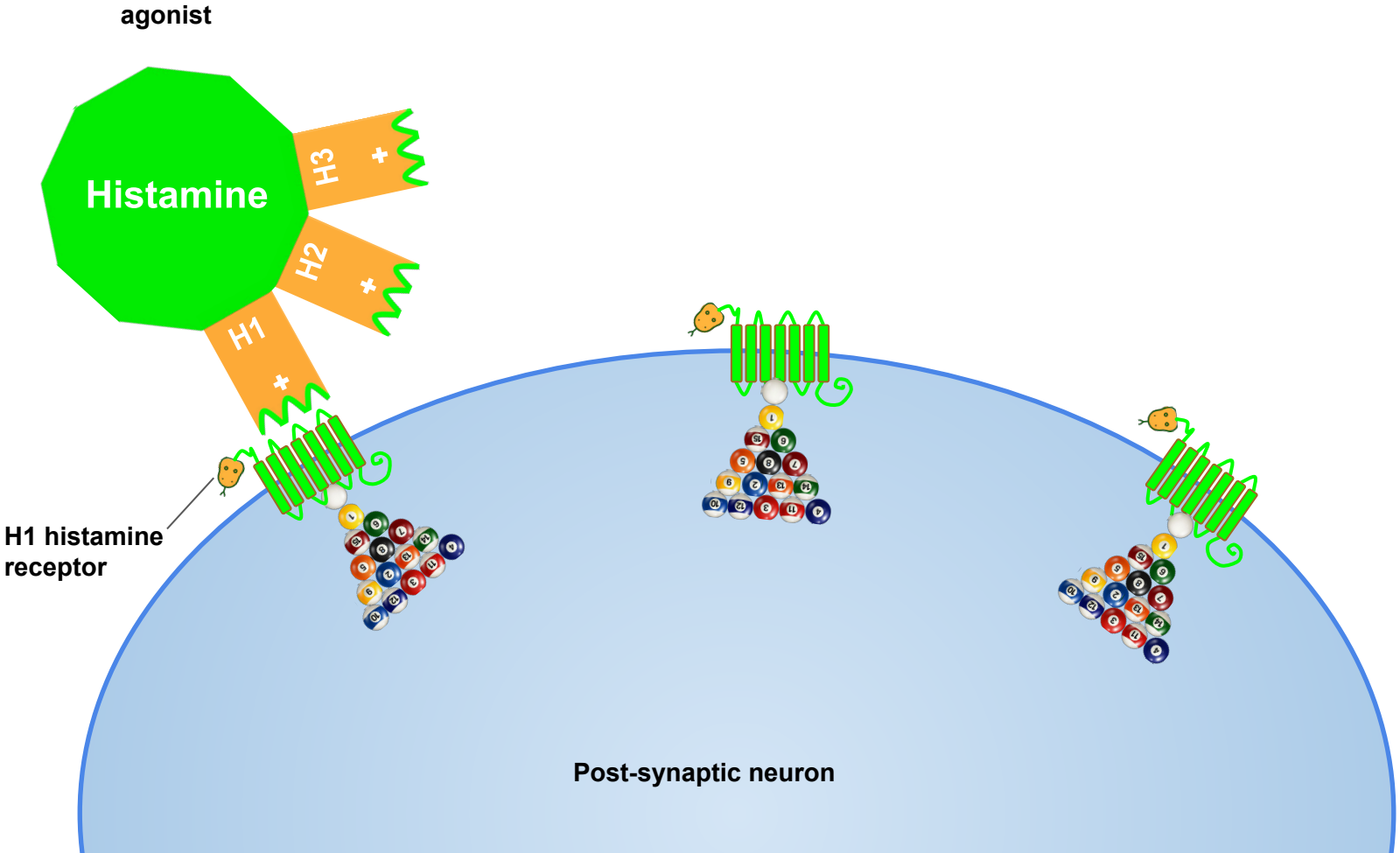
Constitutive activity in absence of histamine

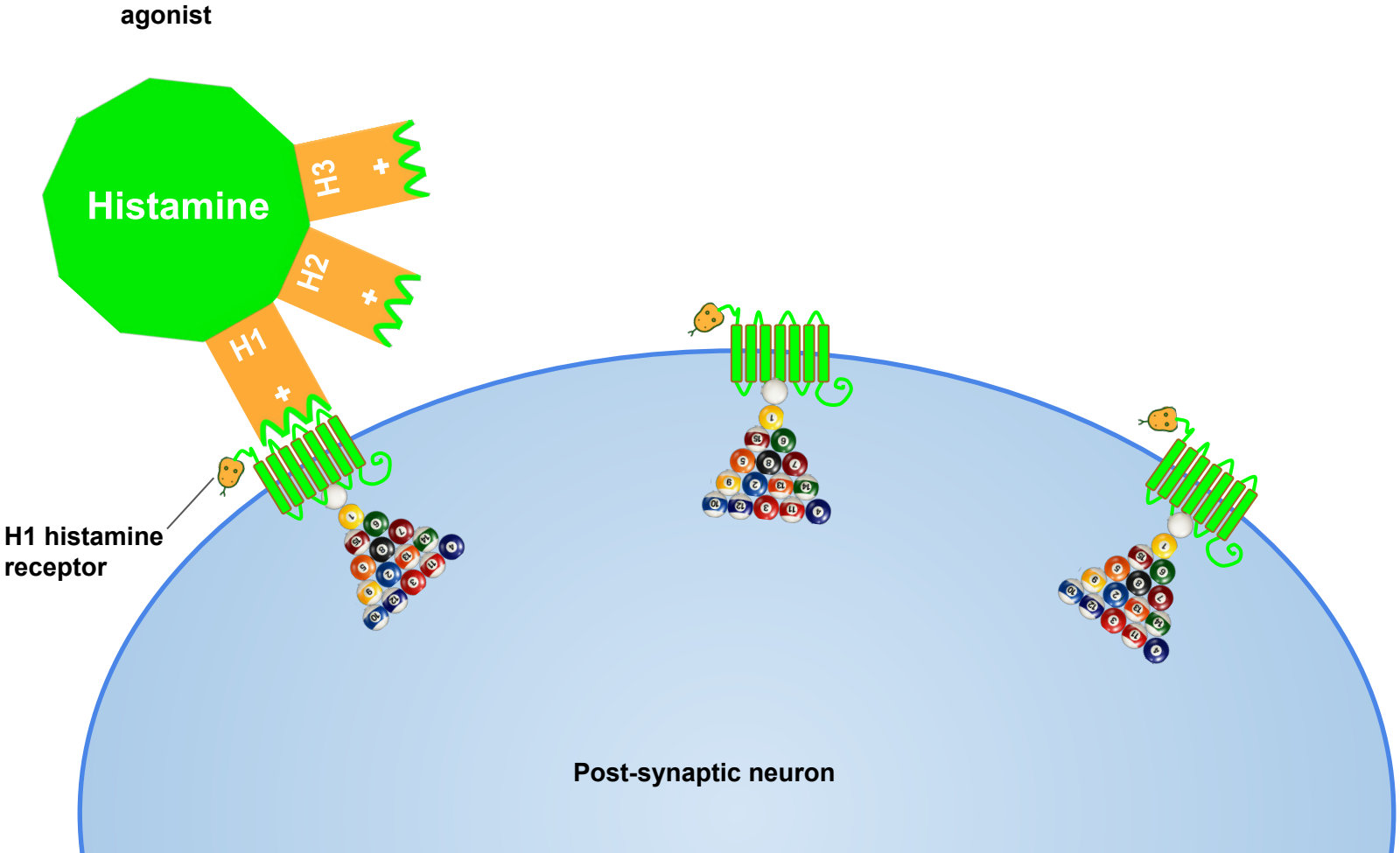


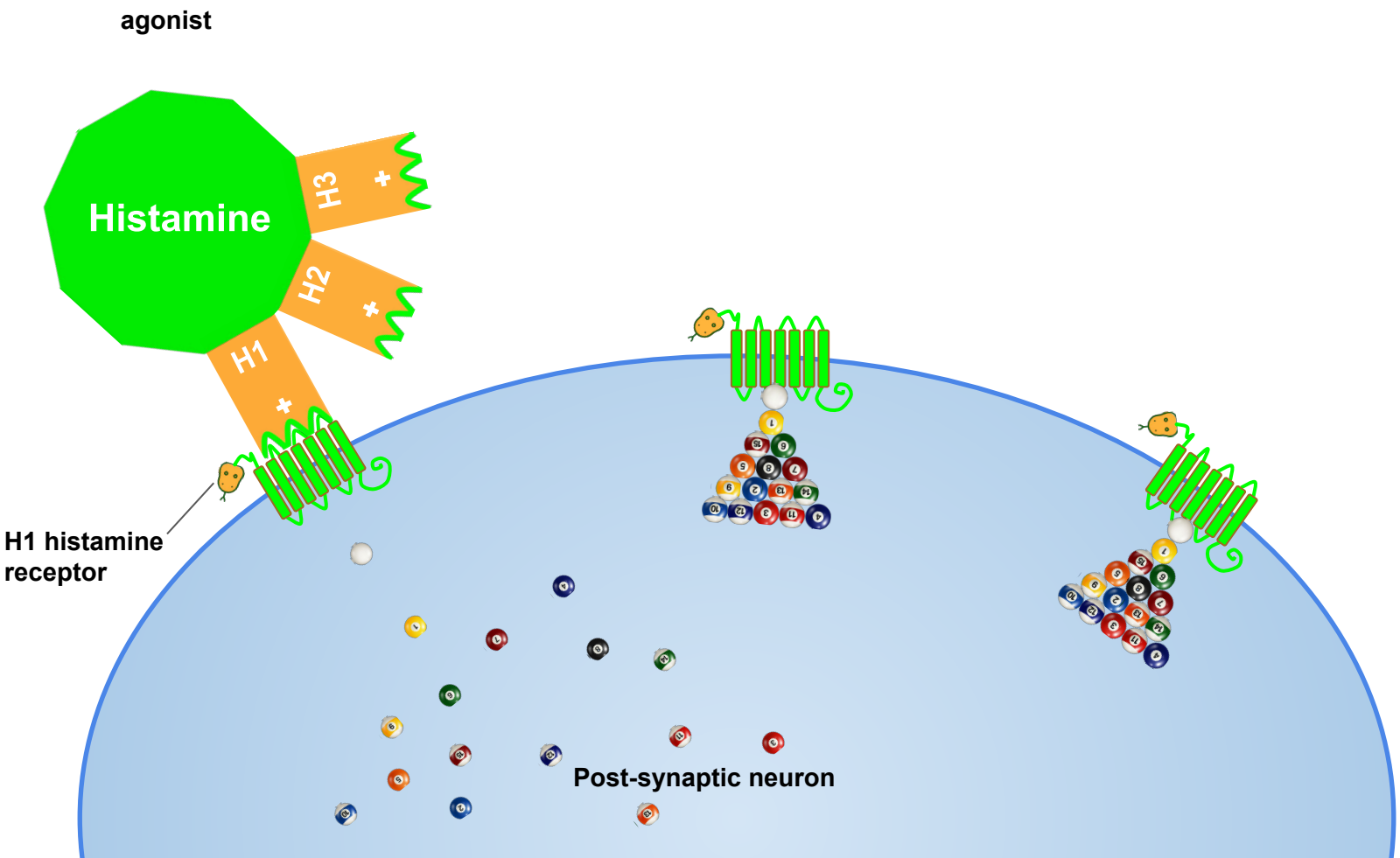

H1 histamine receptor
Post-synaptic neuron

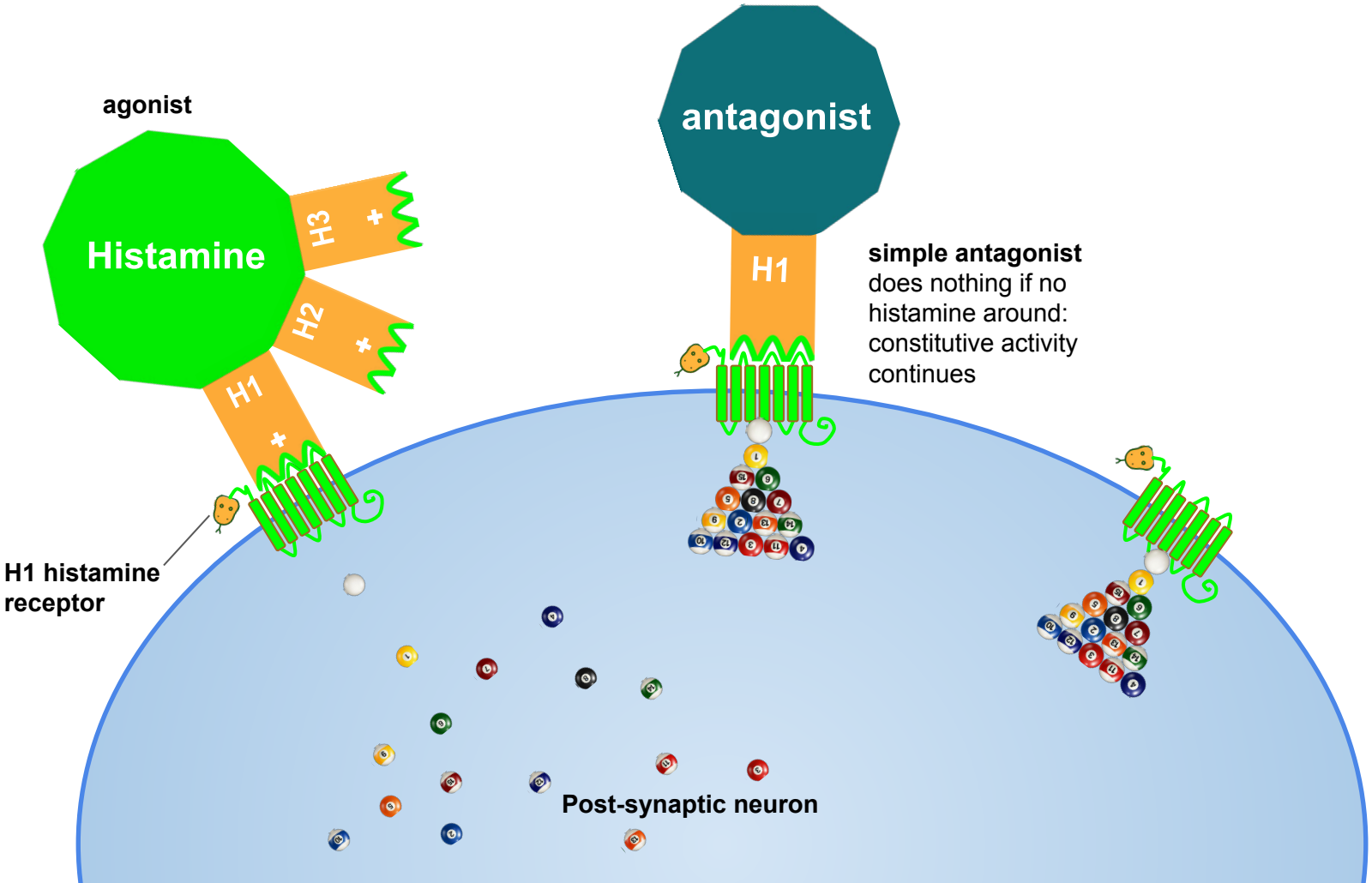

agonist
Histamine
H3
+
H2
+
H1
+
H1 histamine receptor
Post-synaptic neuron

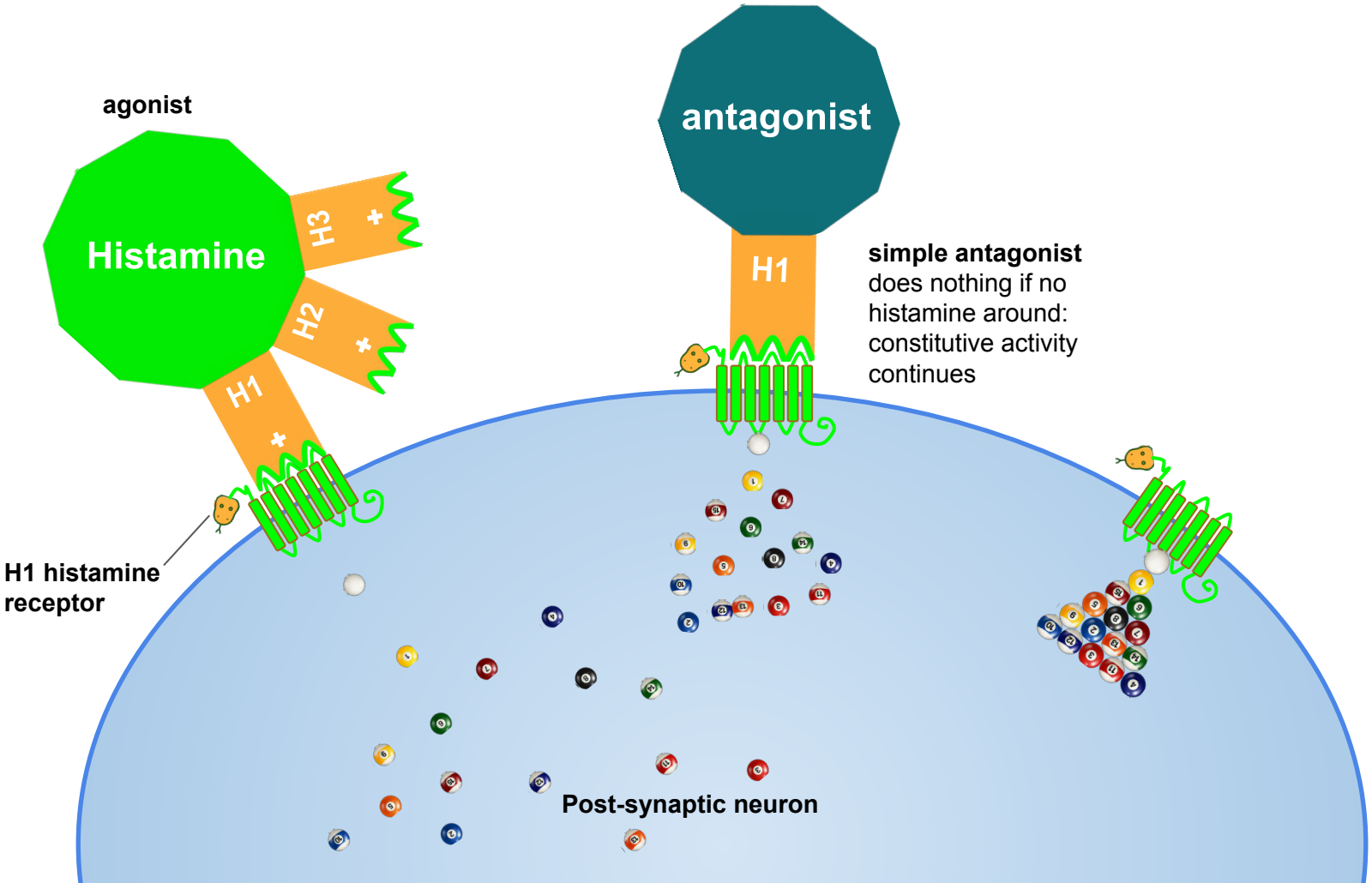

agonist
Histamine
H3
+
H2
+
H1
+
H1 histamine receptor
Post-synaptic neuron

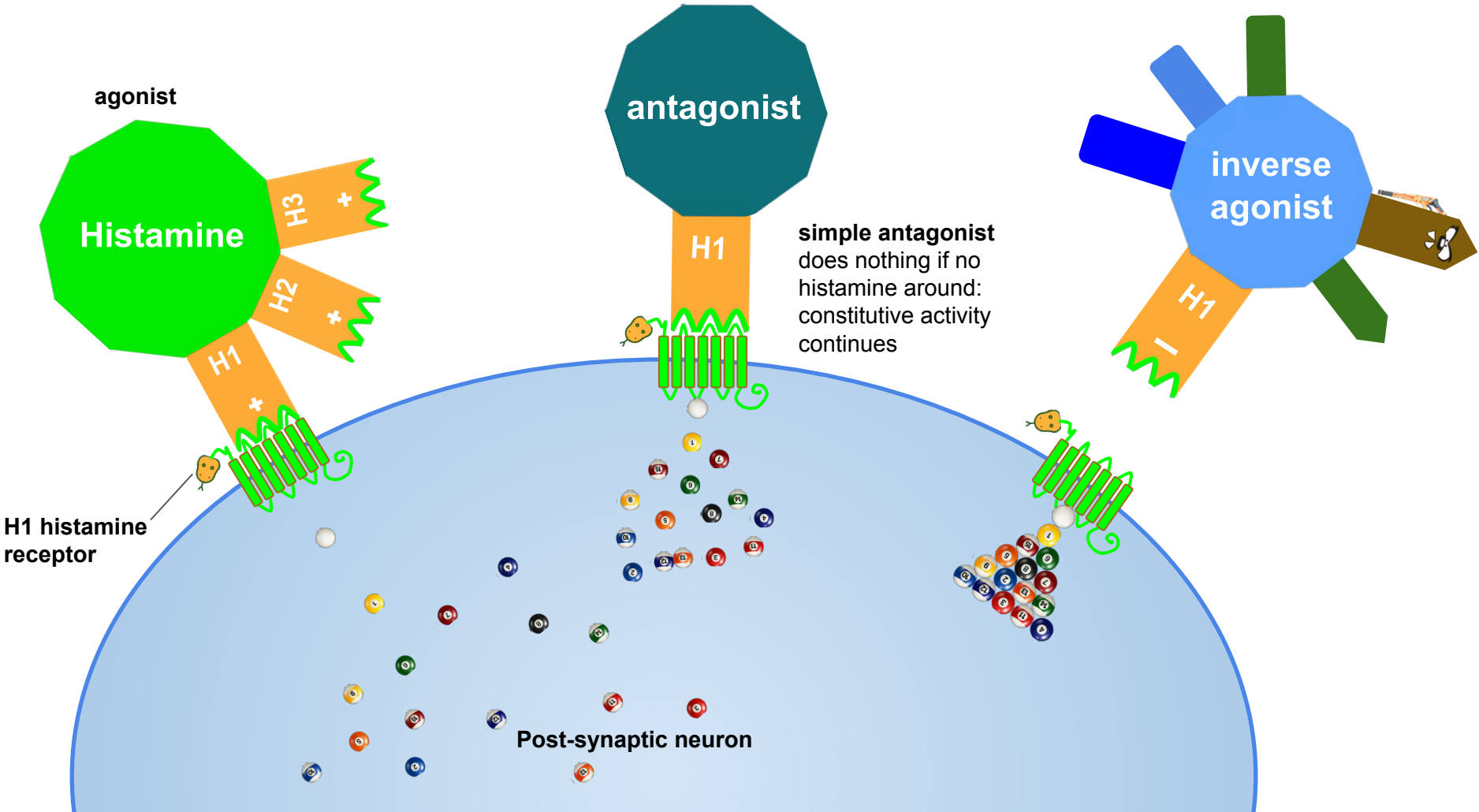

agonist
Histamine
H3
+
H2
+
H1
+
H1 histamine receptor
Post-synaptic neuron

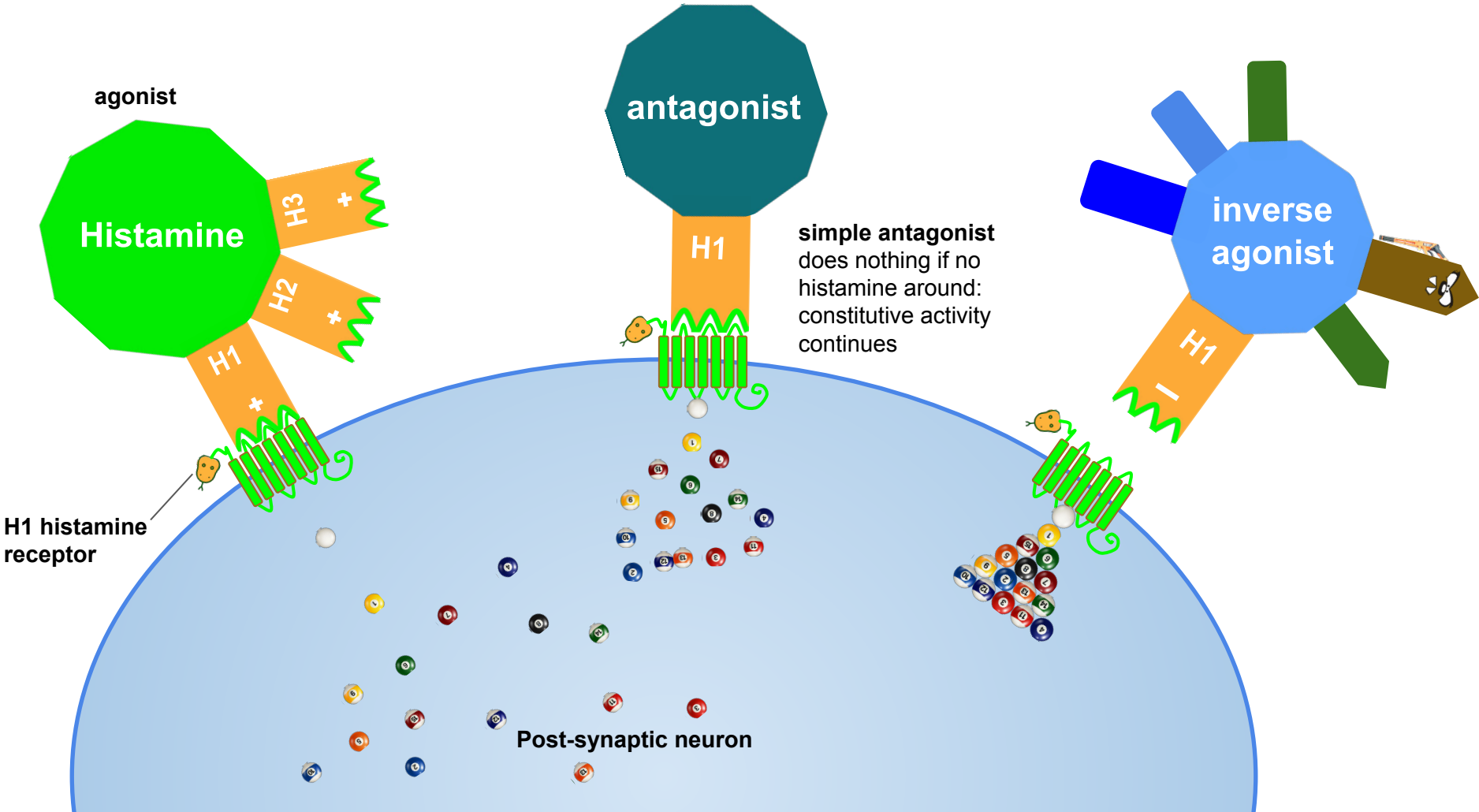

agonist
Histamine
H3
+
H2
+
H1
+
H1 histamine receptor
Post-synaptic neuron

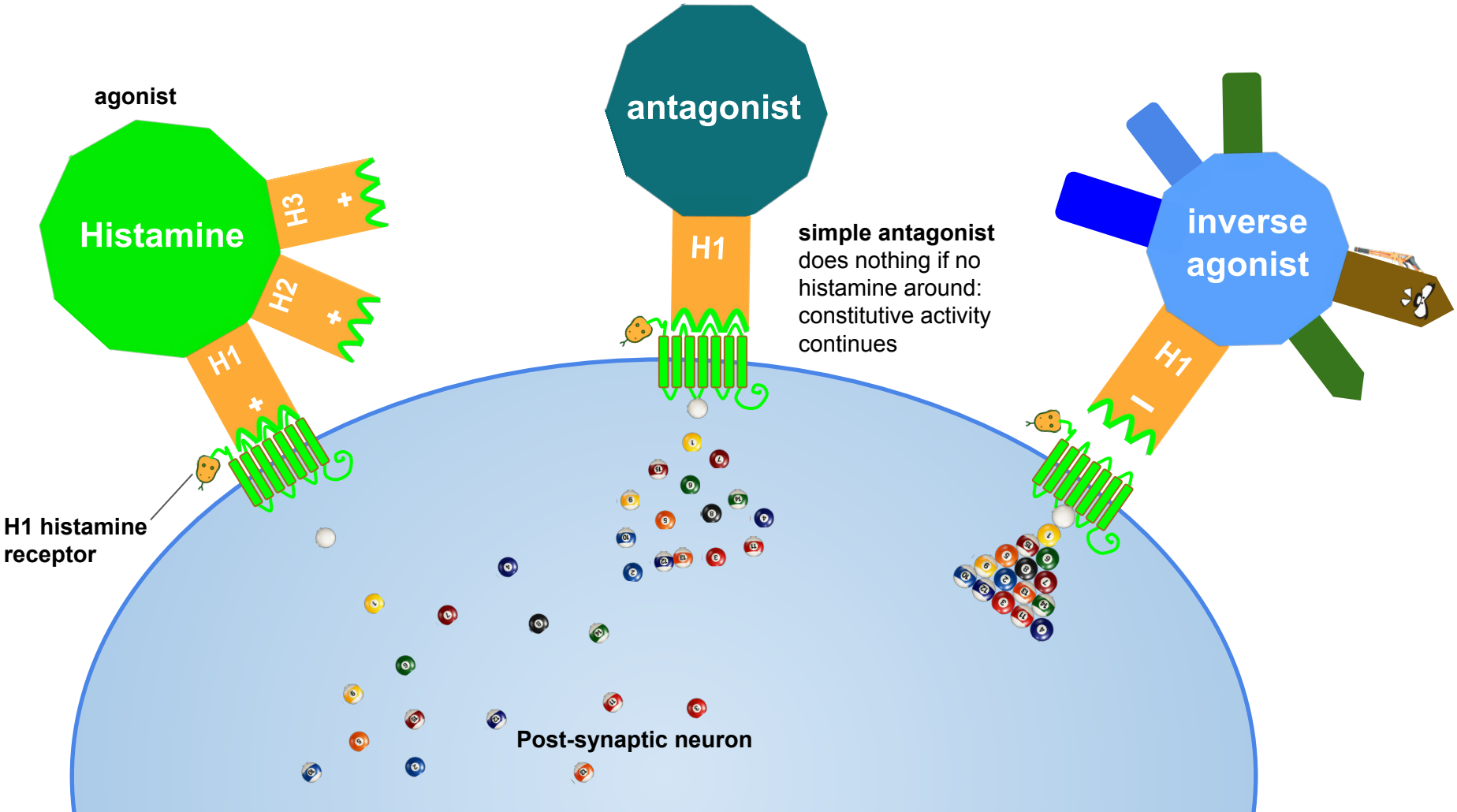

agonist
Histamine
H3
H2
H1
H1 histamine receptor
Post-synaptic neuron


agonist
Histamine
H3
H2
H1
antagonist
H1
simple antagonist
does nothing if no
histamine around:
constitutive activity
continues
H1 histamine
receptor
Post-synaptic neuron


agonist
Histamine
H3
H2
H1
antagonist
H1
simple antagonist
does nothing if no
histamine around:
constitutive activity
continues
H1 histamine
receptor
Post-synaptic neuron


agonist
Histamine
H3
H2
H1
H1 histamine receptor
antagonist
H1
simple antagonist does nothing if no histamine around: constitutive activity continues
inverse agonist
H1
Post-synaptic neuron


agonist
Histamine
H3
+
H2
+
H1
+
H1 histamine receptor
antagonist
H1
simple antagonist
does nothing if no histamine around:
constitutive activity continues
inverse agonist
H1
–
Post-synaptic neuron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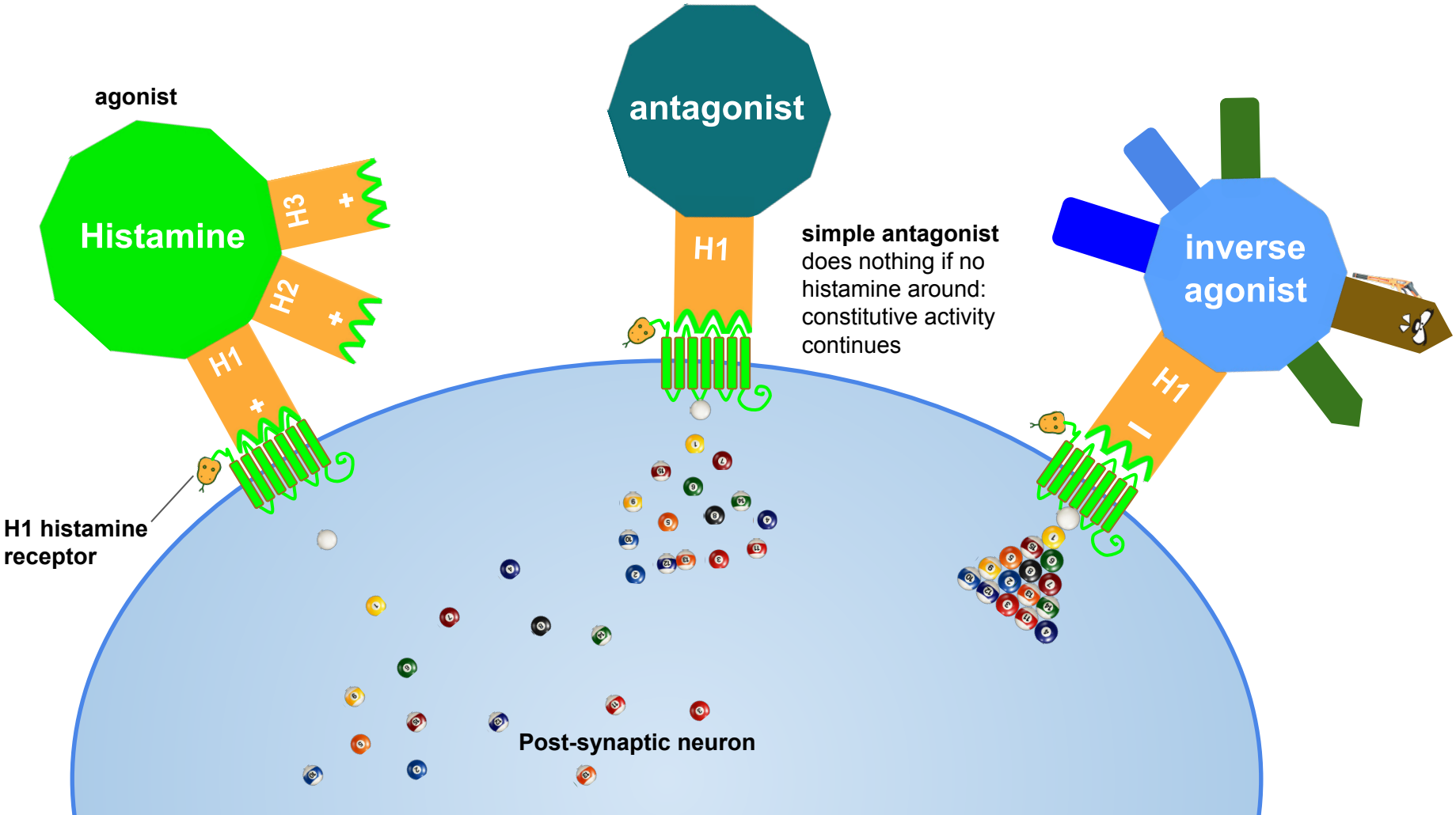
Post-synaptic neuron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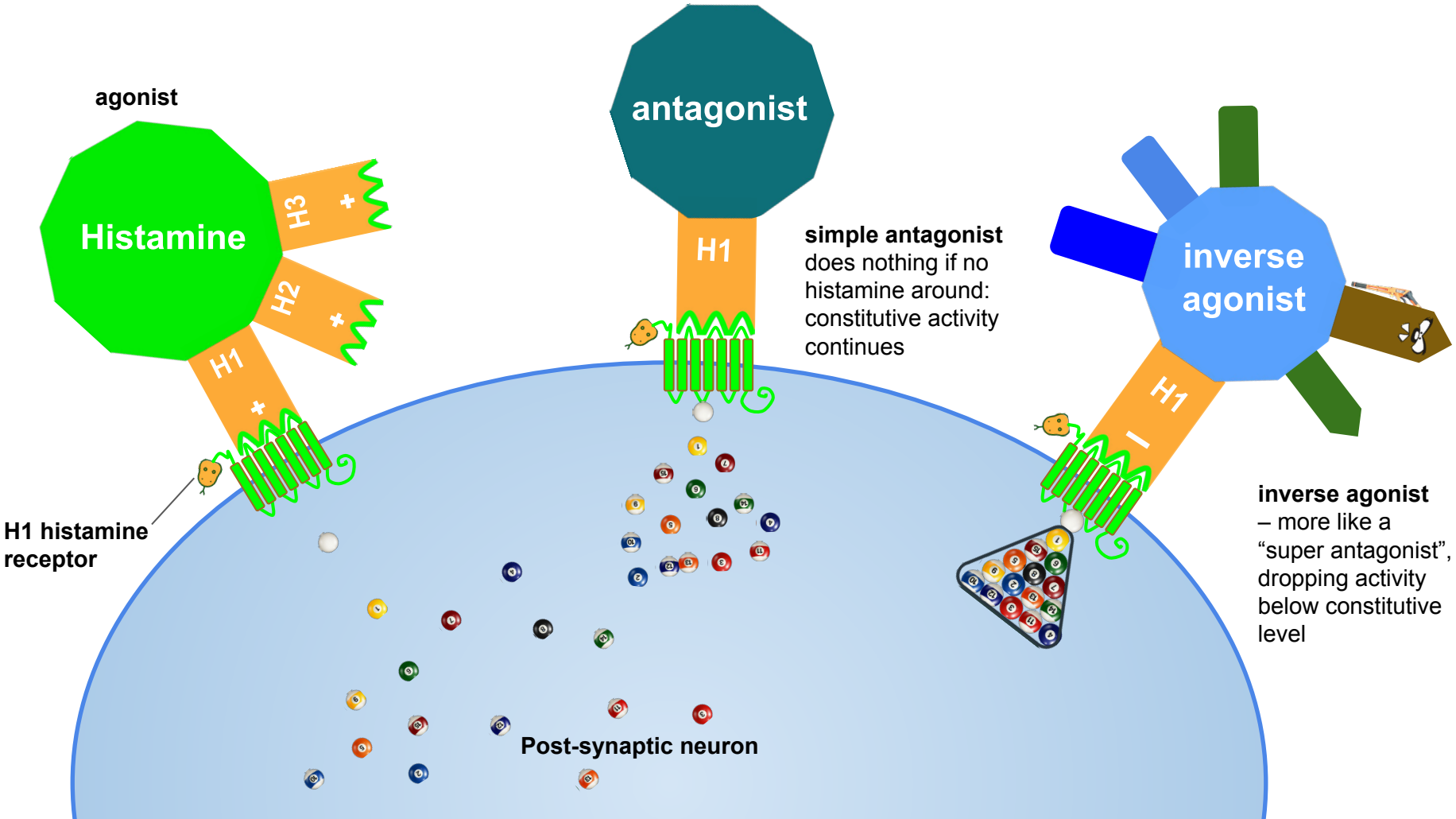
−
Post-synaptic neuron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simple antagonist
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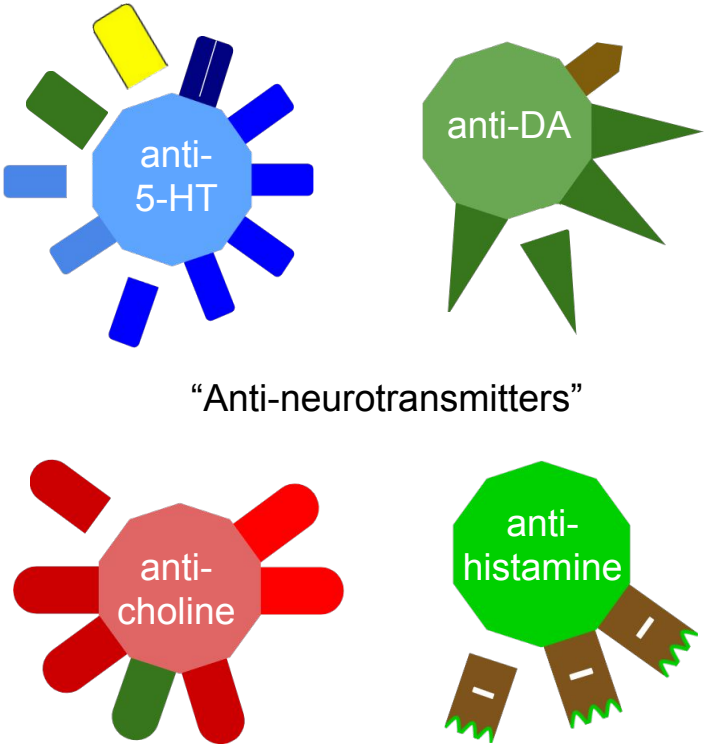
inverse agonist
H1
−
inverse agonist
– more like a "super antagonist", dropping activity below constitutive level
Post-synaptic neuron

How to bioengineer an antipsychotic

Relevant to mirtazapine, I promise

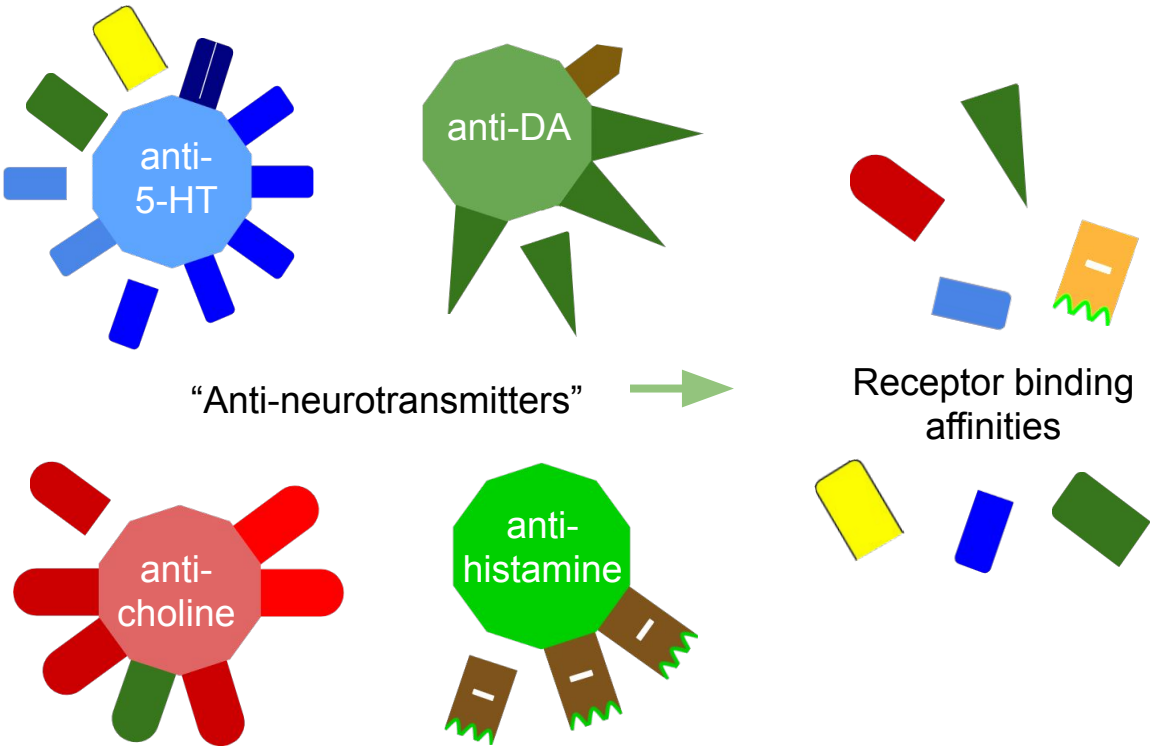
How to bioengineer an antipsychotic

Relevant to mirtazapine, I promise



“Anti-neurotransmitters”

How to bioengineer an antipsychotic



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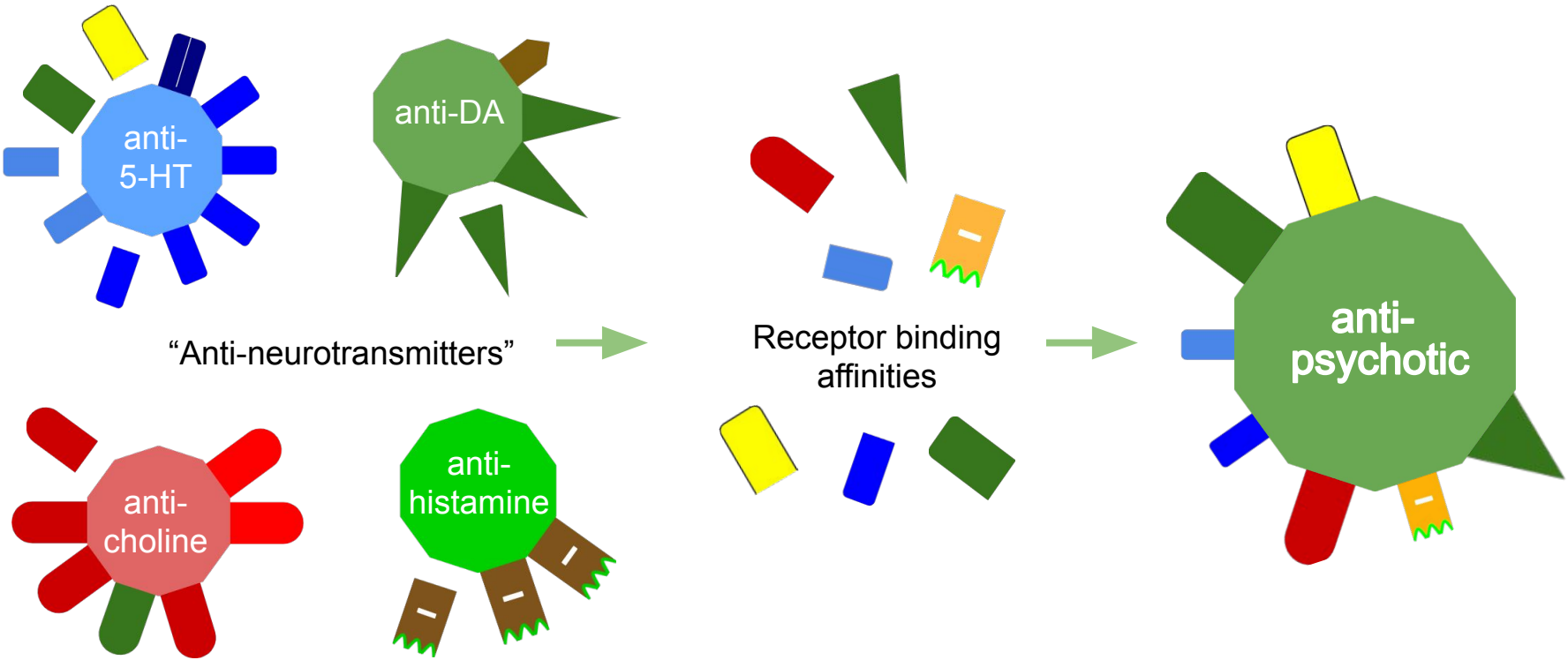
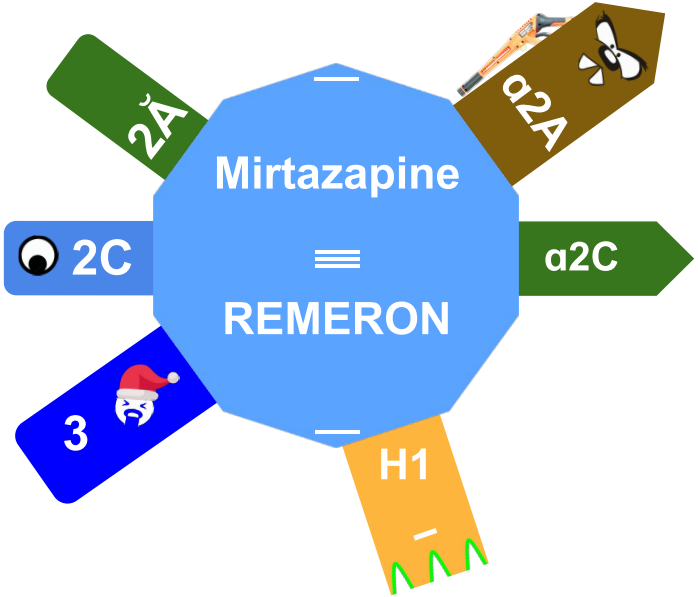


Mirtazapine (REMERON) – Receptor antagonist (NbN)

- The only commonly-prescribed antidepressant that is not a reuptake inhibitor! (gepirone)
- It's built like an antipsychotic (without anti-D2)



"Mr Taz zapping"

Noradrenergic and Specific Serotonergic Antidepressant (NaSSA)

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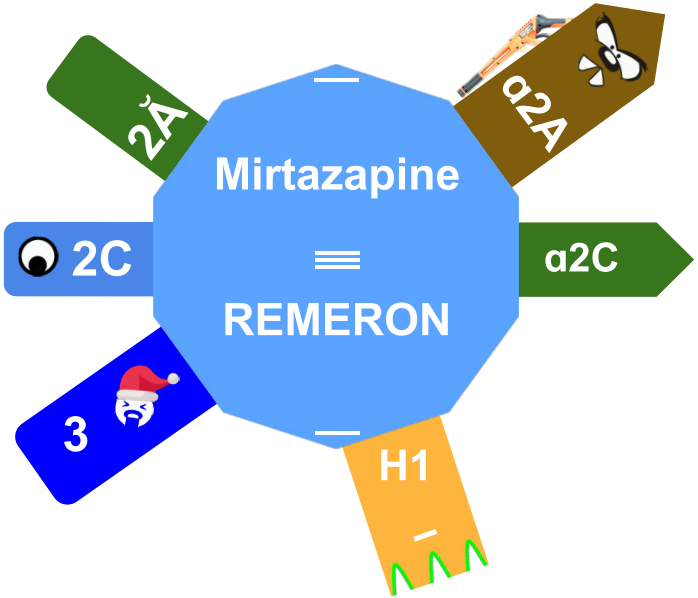


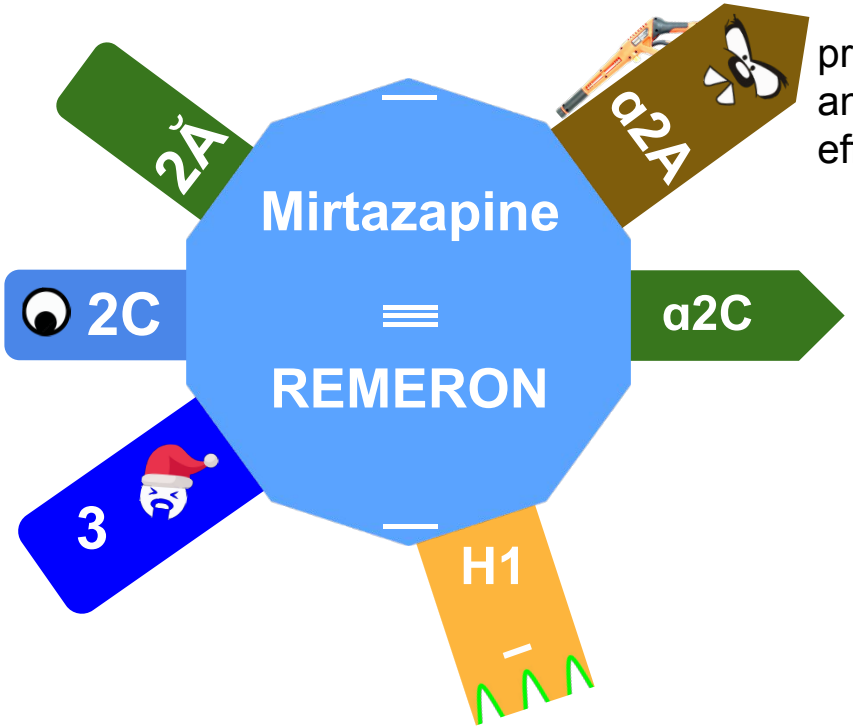
"Mr Taz zapping"

Noradrenergic and Specific Serotonergic Antidepressant (NaSSA)

"The Antichrist of antidepressants"

Receptor antagonist supreme

Mirtazapine (REMERON) – Receptor antagonist (NbN)



principal antidepressant effect

"Mr Taz zapping"

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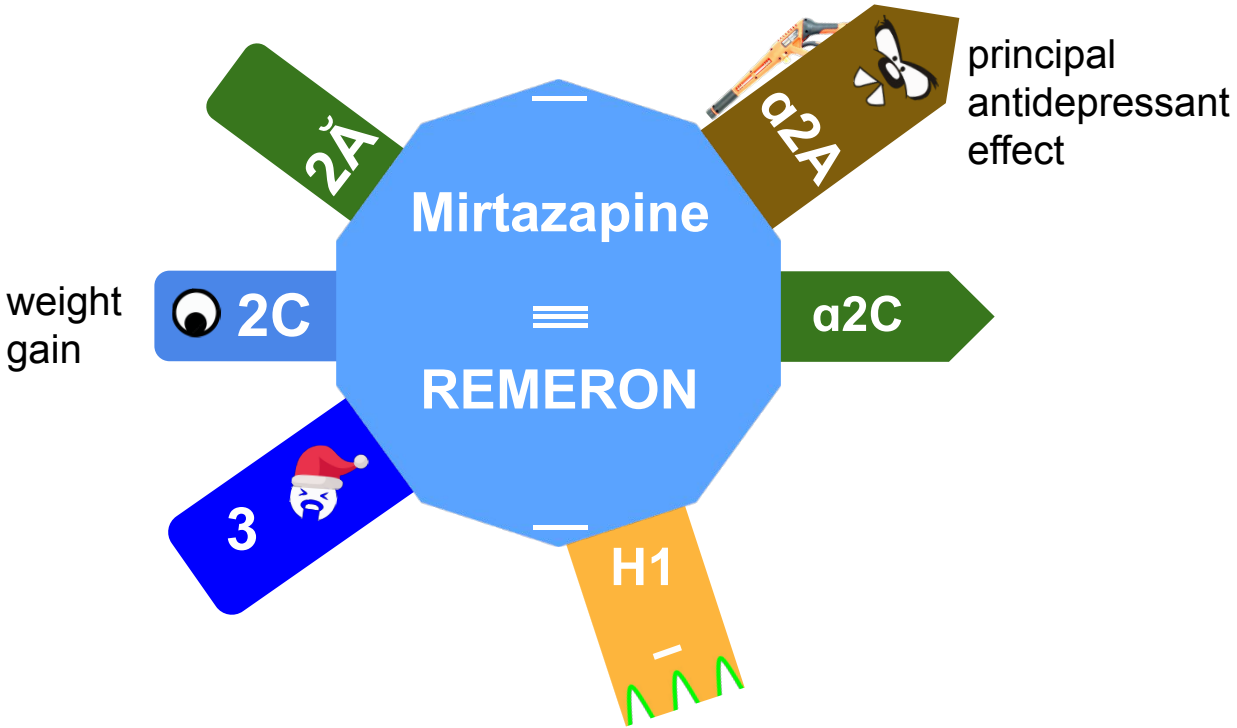

principal antidepressant effect

weight gain

“Mr Taz zapping”

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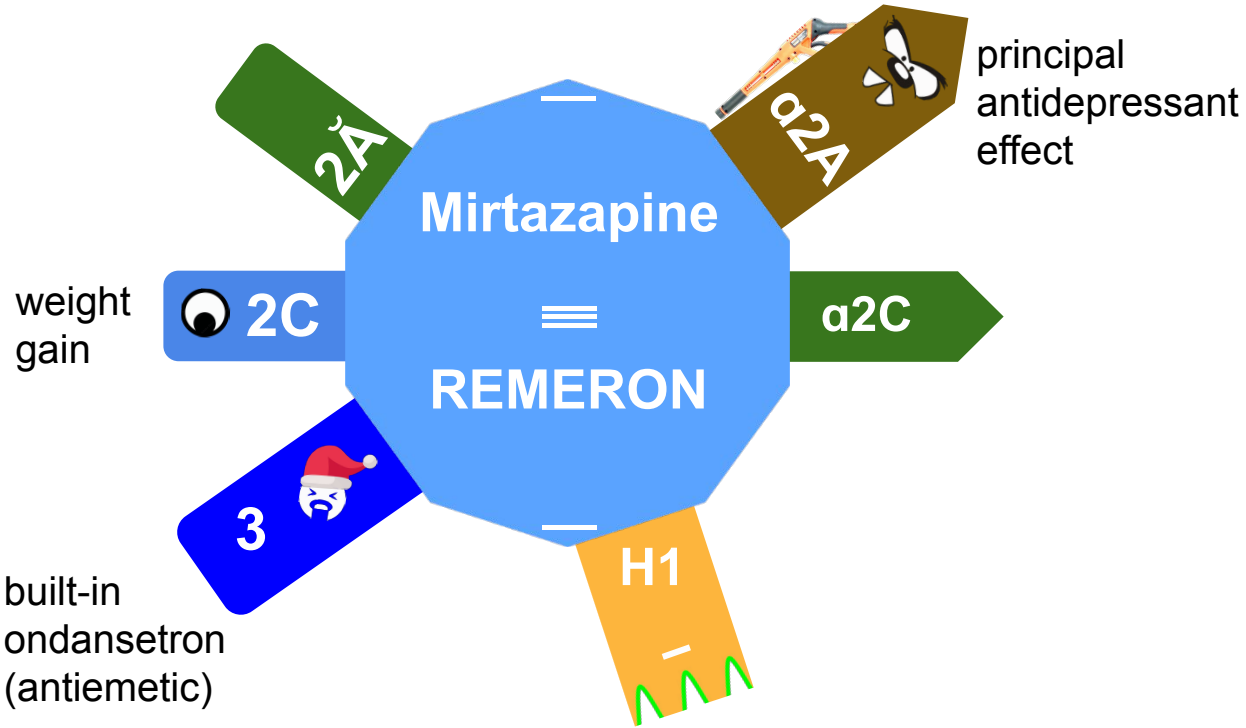

principal antidepressant effect

weight gain

built-in ondansetron (antiemetic)

"Mr Taz zapping"

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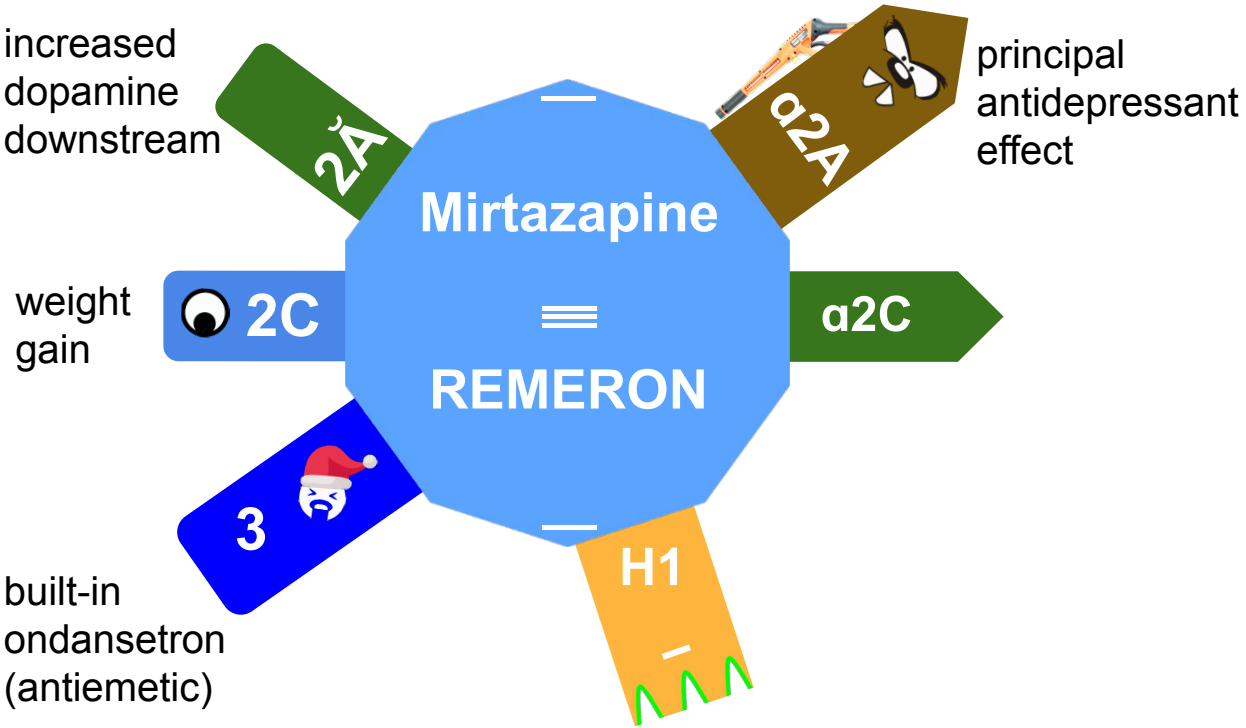

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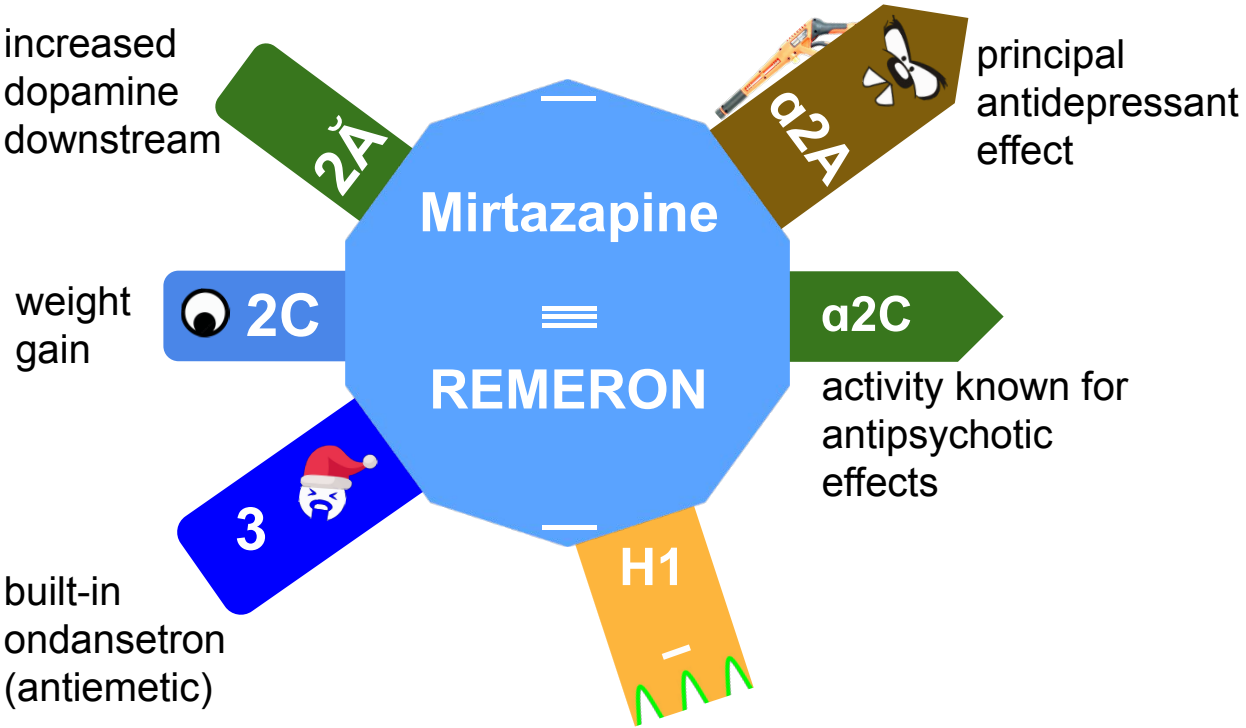

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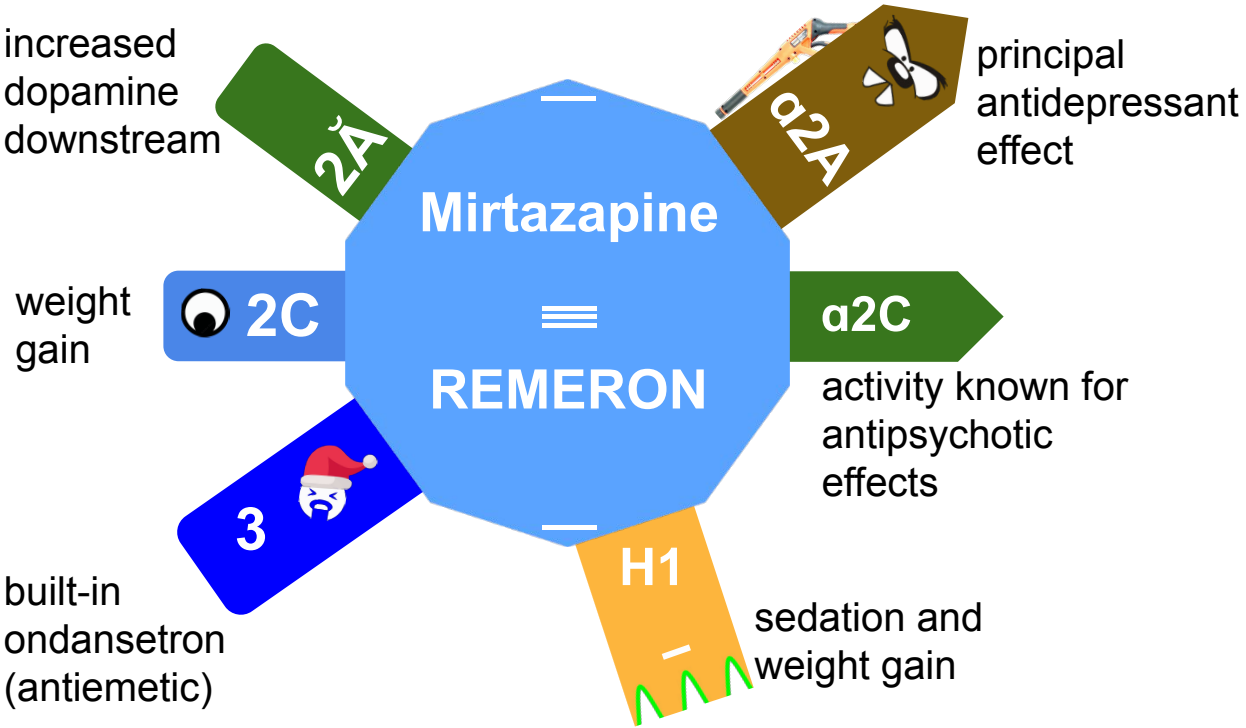

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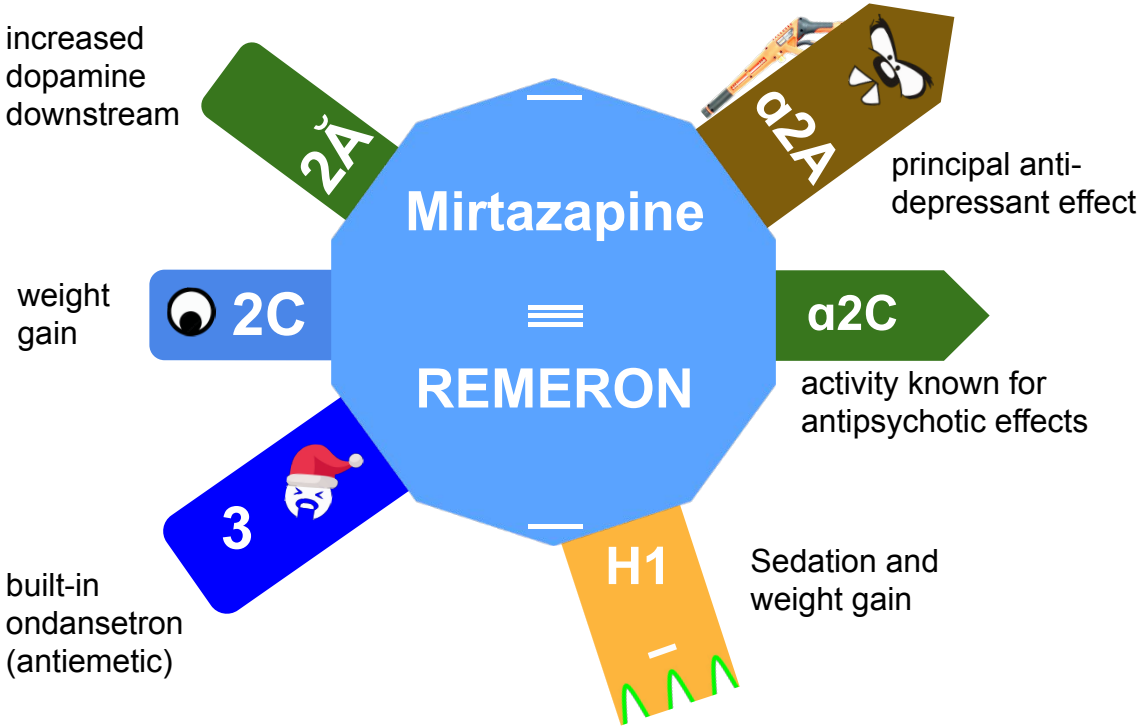


The Mental Health Clinician

Ment Health Clin. 2019 Jan; 9(1): 41–47. PMCID: PMC6322815
Published online 2019 Jan 4. doi: 10.9740/mhc.2019.01.041 PMID: 30627503

Relationship between mirtazapine dose and incidence of adrenergic side effects: An exploratory analysis

Michael Shuman, PharmD, BCPP,[1] Athena Chukwu, PharmD,[2] Nathan Van Veldhuizen, PharmD,[3] and Steven A. Miller, PhD[4]

"This study failed to support the hypothesis that mirtazapine is more activating at higher doses".

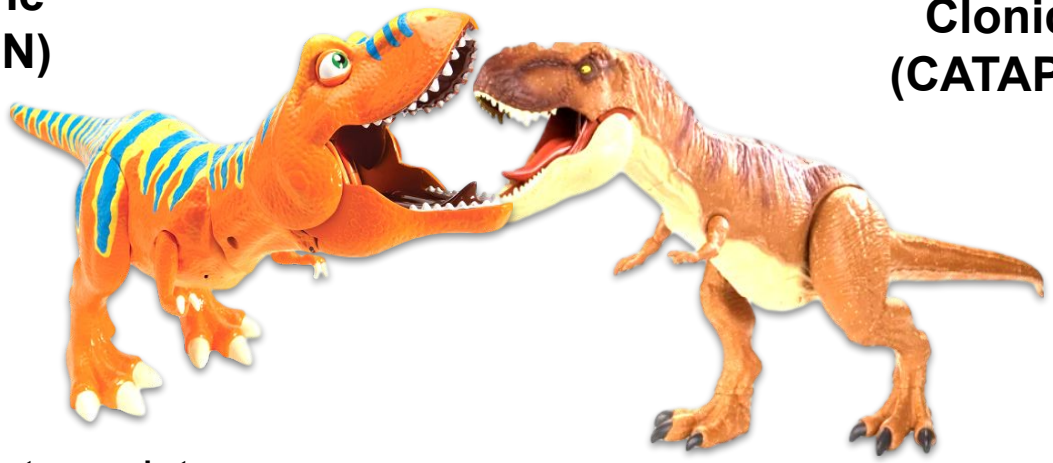
It's called a Noradrenergic and Specific Serotonergic Antidepressant (NaSSA), but it's **anti**-noradrenergic.

Mirtazapine (REMERON) – Receptor antagonist (NbN)

Antagonistic pharmaco**DYN**amic interaction:

Fightin' **DYN**os with opposing mechanisms

Mirtazapine (REMERON)



Clonidine (CATAPRES)

Alpha-2 antagonist

Alpha-2 agonist

Mirtazapine (REMERON) – Receptor antagonist (NbN)

Antagonistic pharmaco**DYN**amic interaction:

Fightin' **DYN**os with opposing mechanisms

Mirtazapine (REMERON)

Clonidine (CATAPRES)

Potential hypertensive crisis

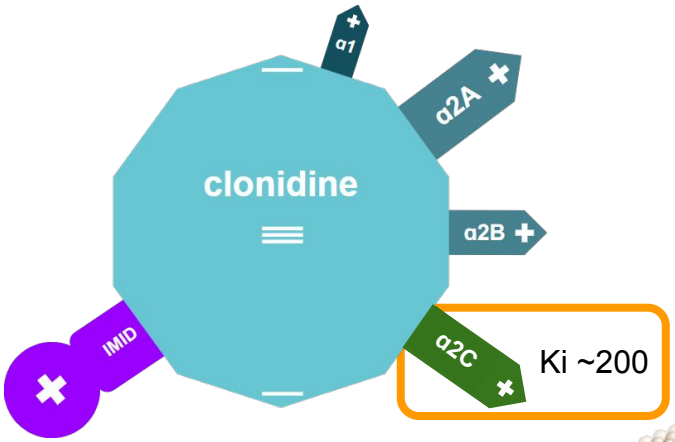
Alpha-2 antagonist

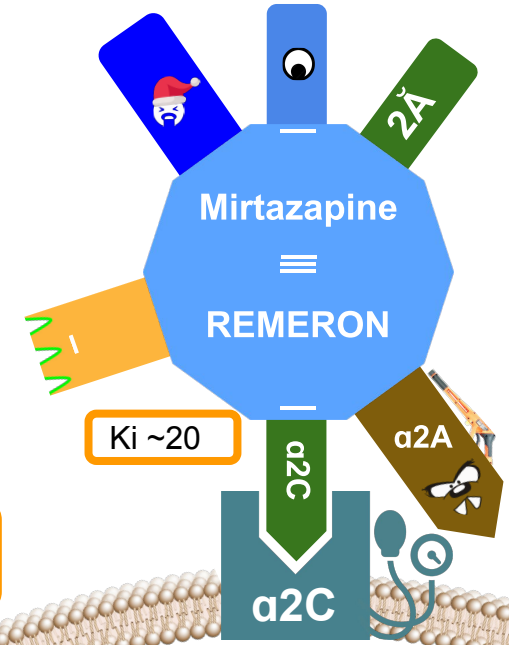
Alpha-2 agonist

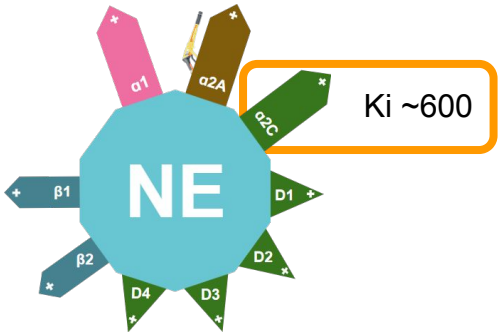
All actions are antagonism (blocking).

All actions are agonism (activation).

All actions are agonism (activation).

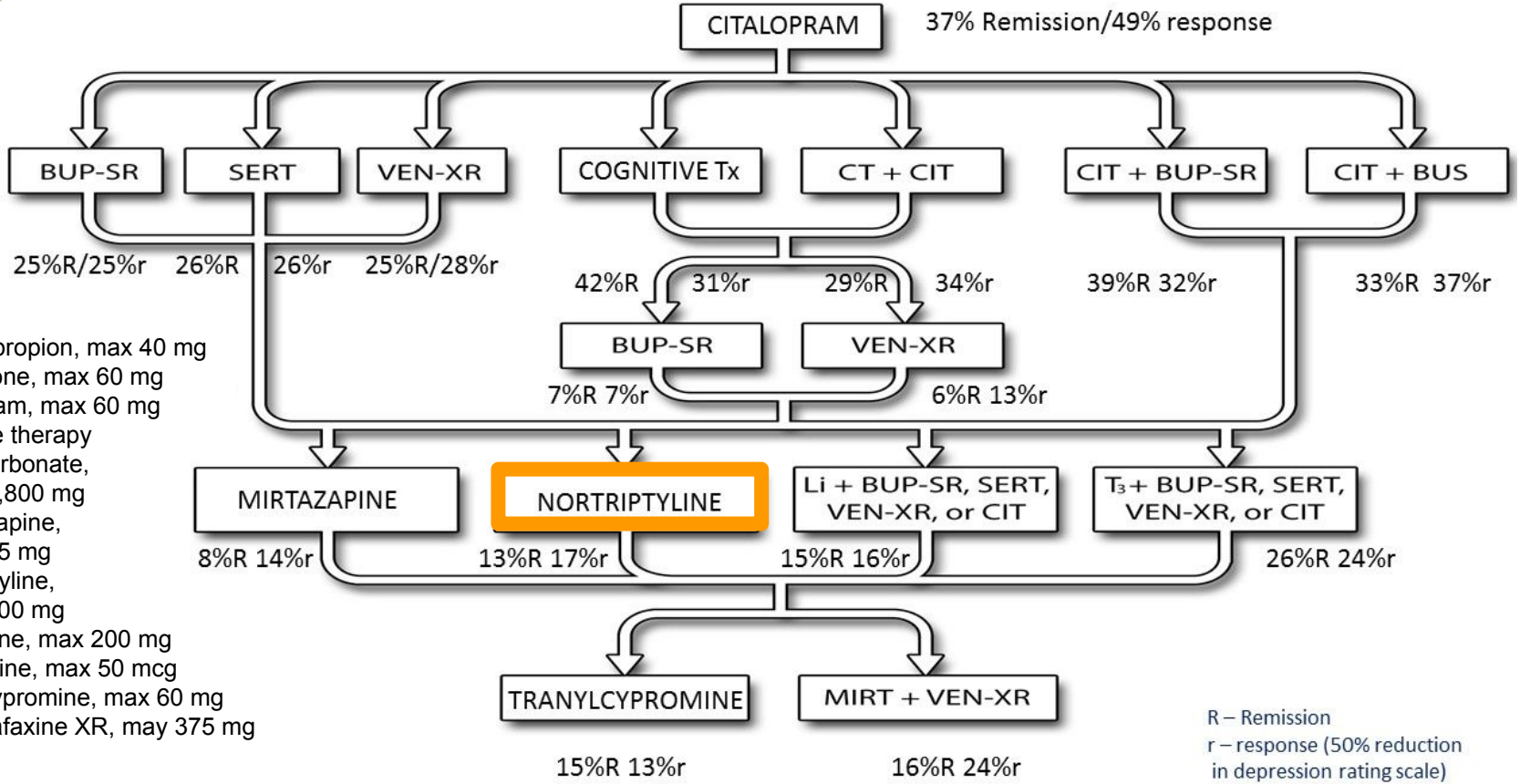






α2C
adrenergic receptor

Binding affinity: The smaller the **Ki** value, the more strongly the drugs binds to the receptor.



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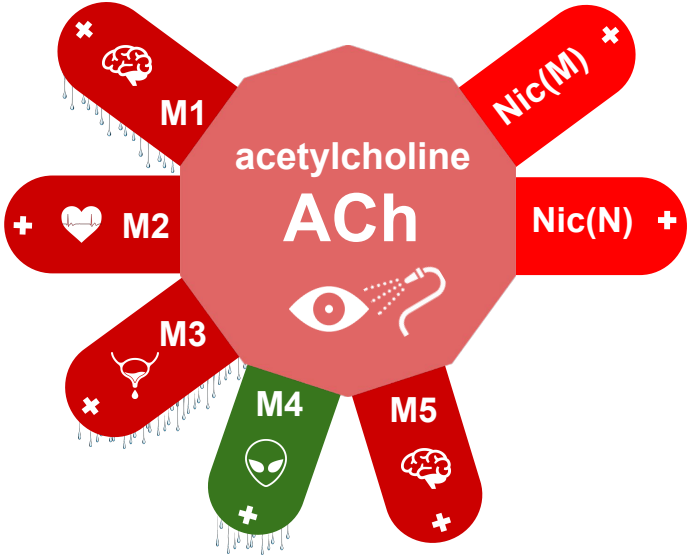
VEN-X – venlafaxine XR, may 375 mg

R – Remission
r – response (50% reduction in depression rating scale)

Acetylcholine - cholinergic receptor agonist

"Everything wet"

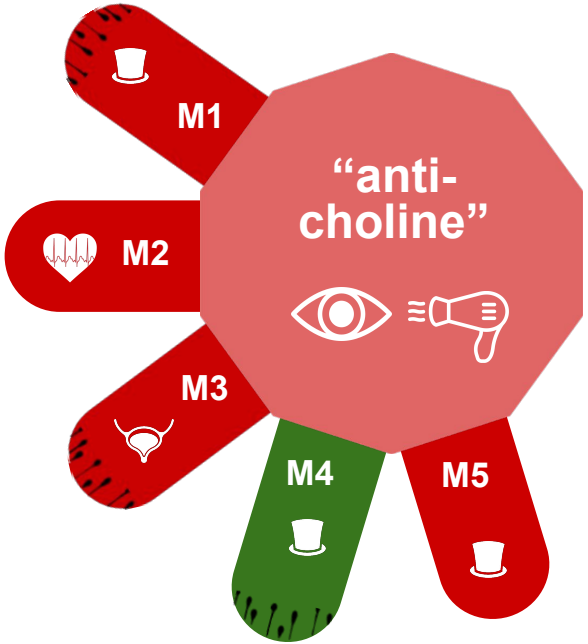


M4 AGONIST – antipsychotic effect of xanomeline

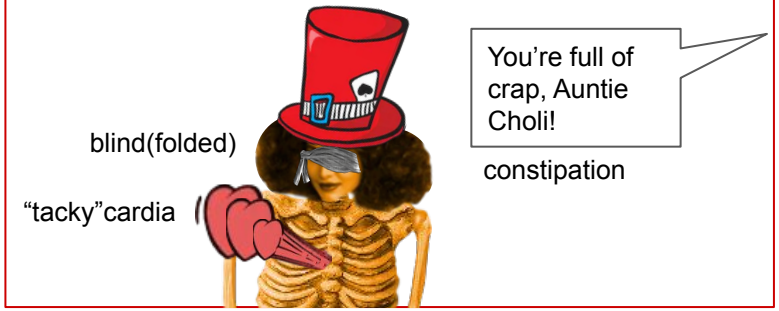
When we saw cholinergic, we usually mean muscarinic.

“Anti-choline” - cholinergic receptor antagonist

“Everything dry”



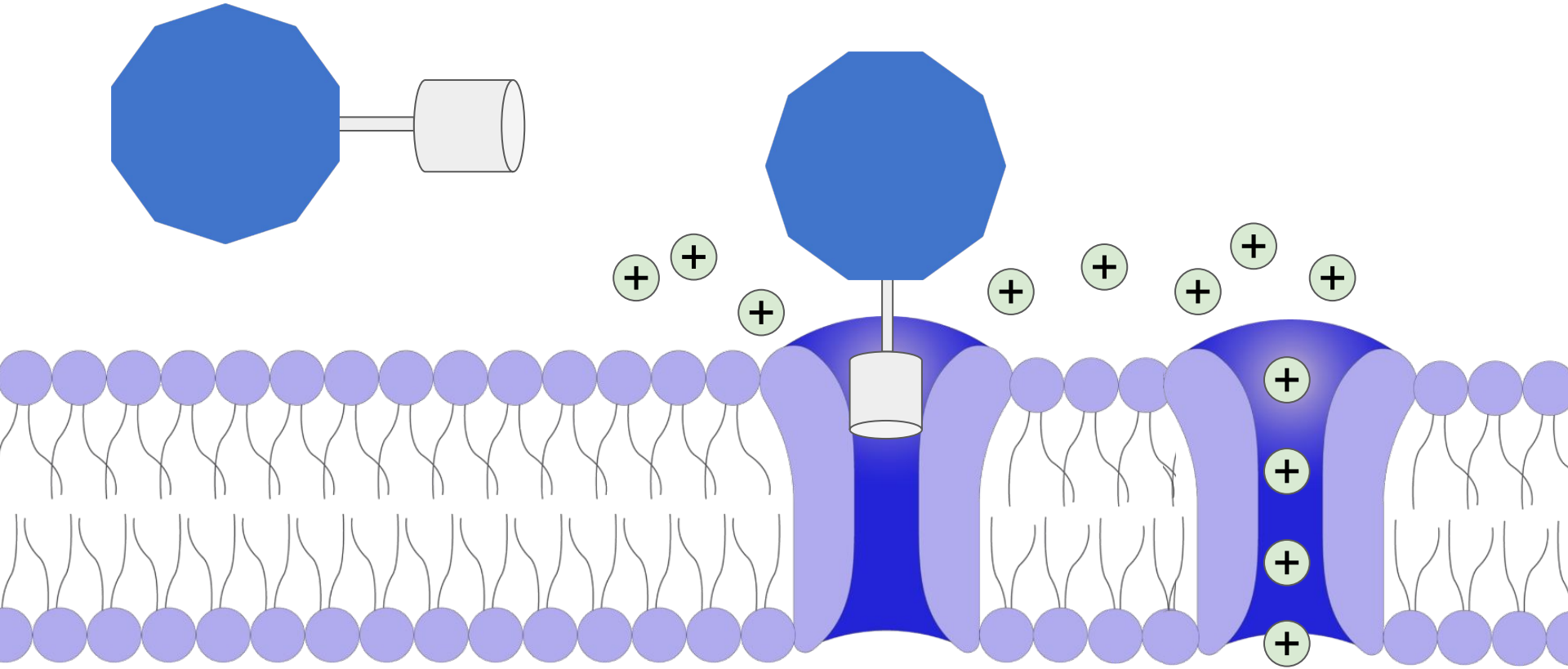
“Anticholinergic”



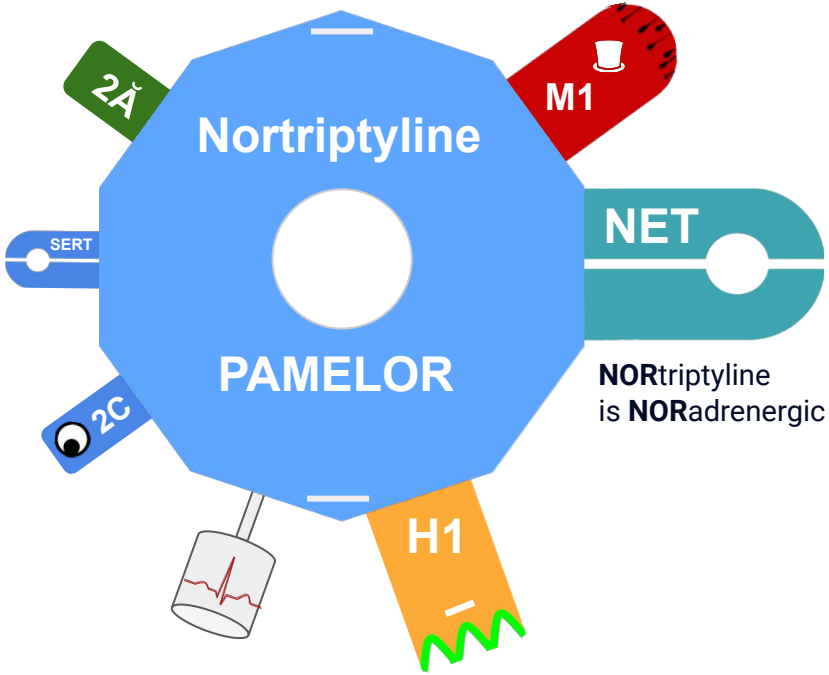
“Antimuscarinic”

Synonym of anticholinergic in common use. More precise because it excludes nicotinic.

Ion channel blocker



Nortriptyline (PAMELOR) – TCA – NRI per NbN



NORtriptyline
is **NOR**adrenergic

Tricyclic (TCA)

“North trippin’ Pam”

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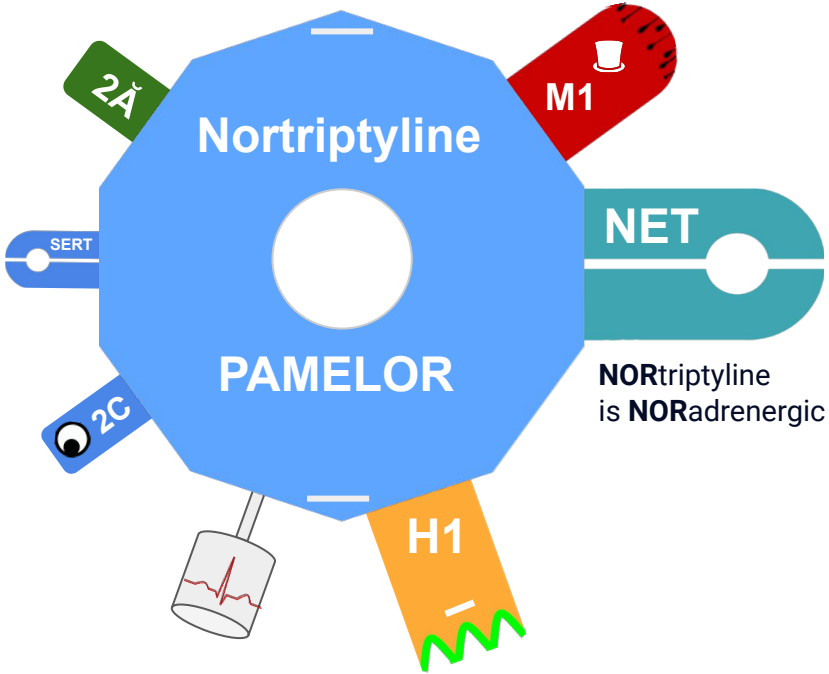


NORtriptyline
is **NOR**adrenergic

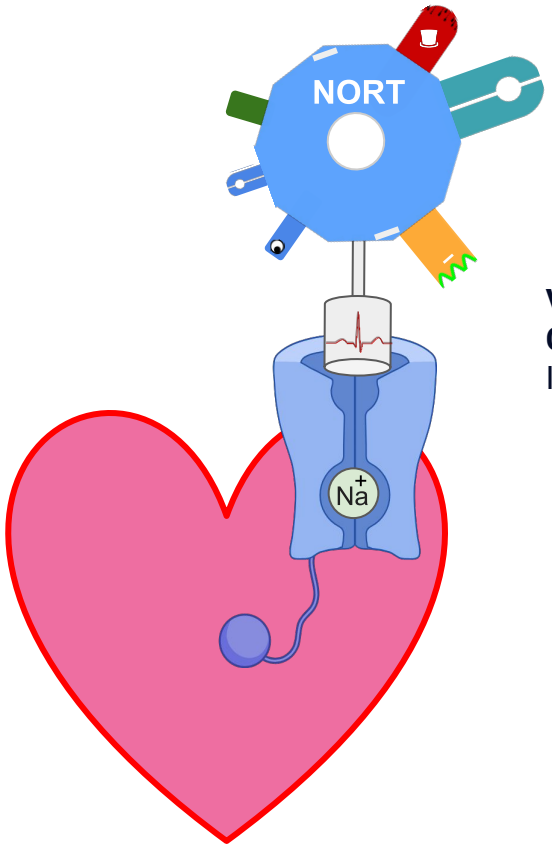
VOLTAGE-SENSITIVE SODIUM CHANNEL BLOCKER

- In brain → coma, seizure in overdose
- In heart → arrhythmia in overdose

Tricyclic (TCA)

“North trippin’ Pam”

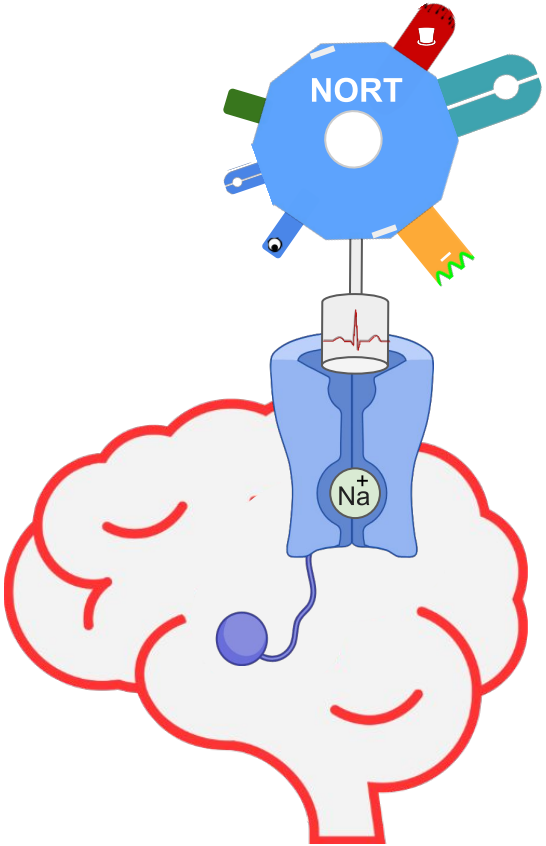
Nortriptyline (PAMELOR) – tricyclic NRI



VOLTAGE-SENSITIVE SODIUM CHANNEL BLOCKER

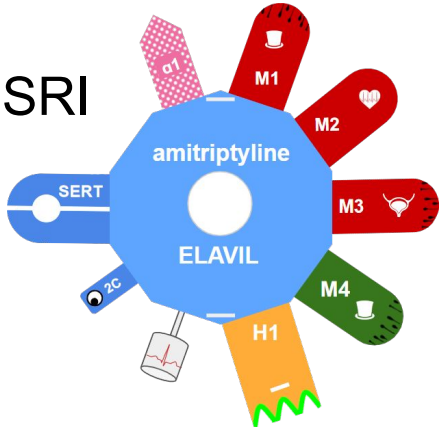
In overdose:

- In brain
  → coma, seizure
- In heart
  → arrhythmia



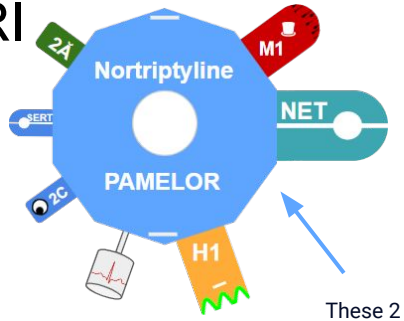
Nortriptyline (PAMELOR) – TCA – NRI per NbN

SRI



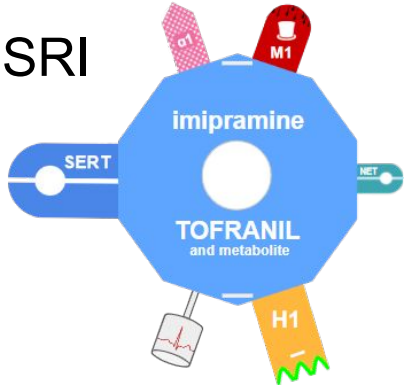
metabolized to

NRI



These 2 *could* be combined with an MAOI

SRI



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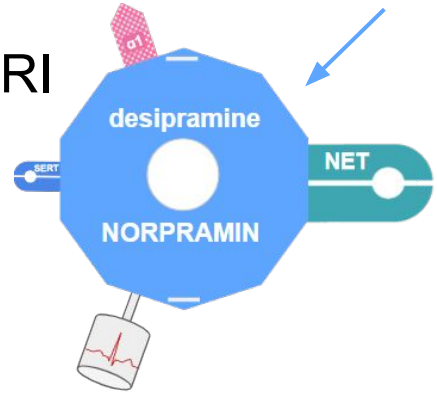

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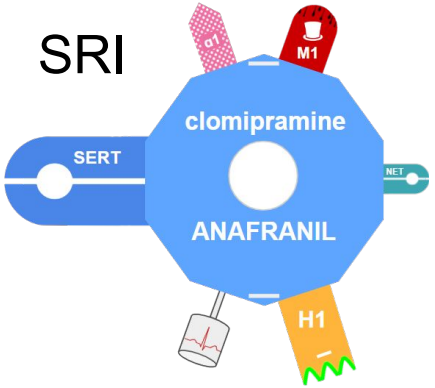

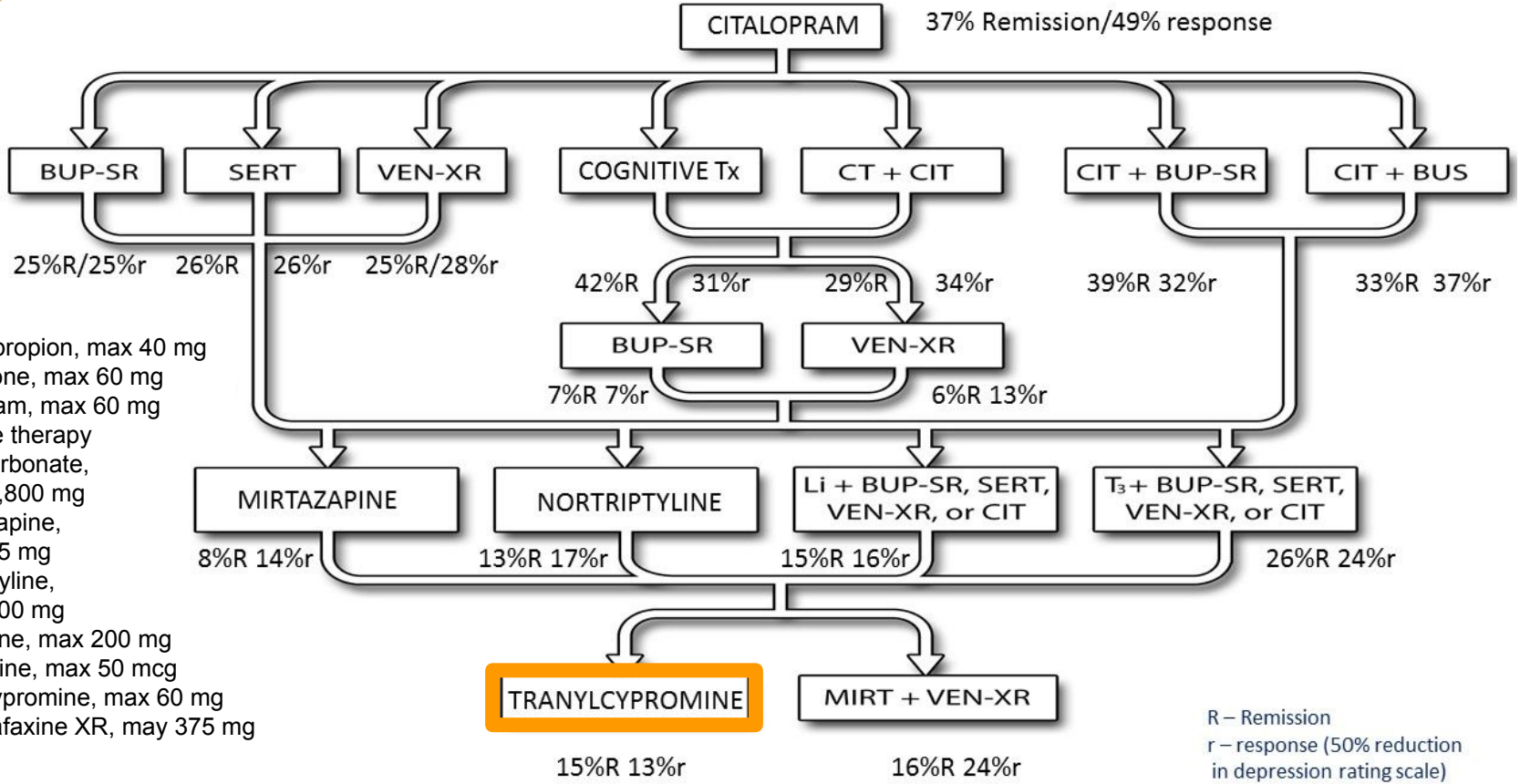

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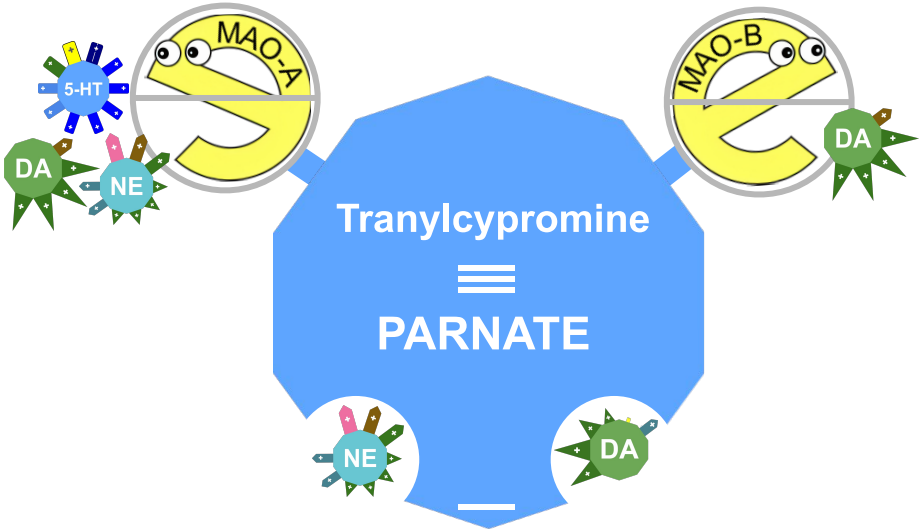
Tranylcypromine (PARNATE) – MAOI

tran yl CY pro meen

Neuroscience-based nomenclature (NbN):

- Enzyme inhibitor (MAO-A, MAO-B)
- Neurotransmitter releaser (DA, NA)



Short half-life but this is irrelevant because inhibition of MAO is irreversible

"(Mao's) Trans prom Partner"

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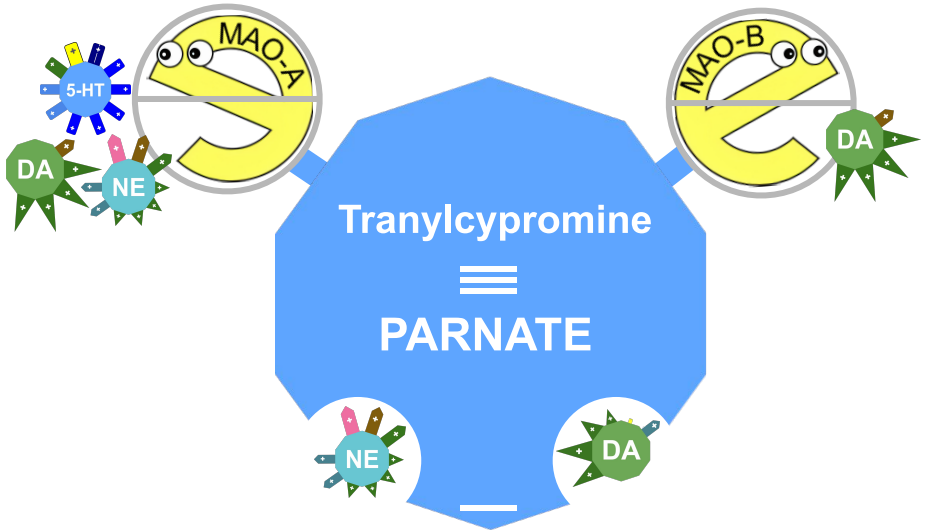

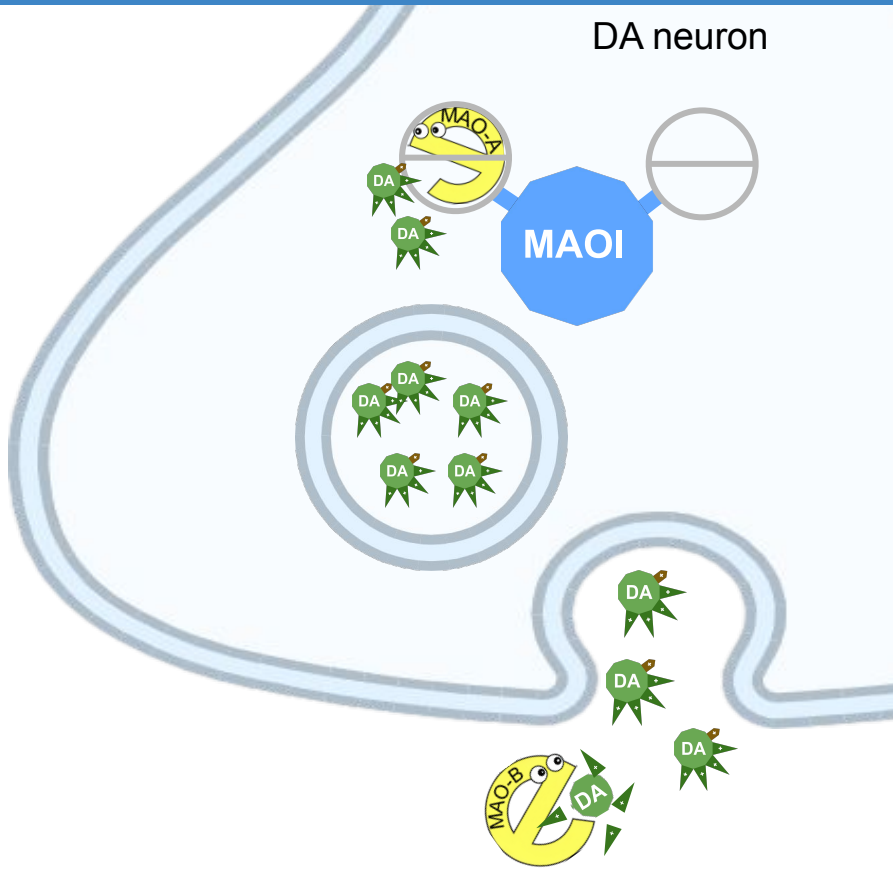

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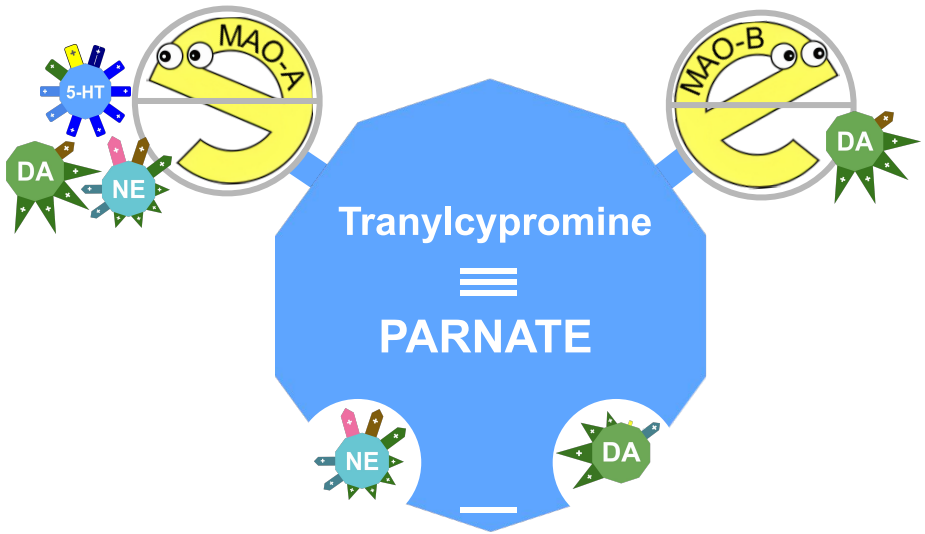


Metabolized to methamphetamine.

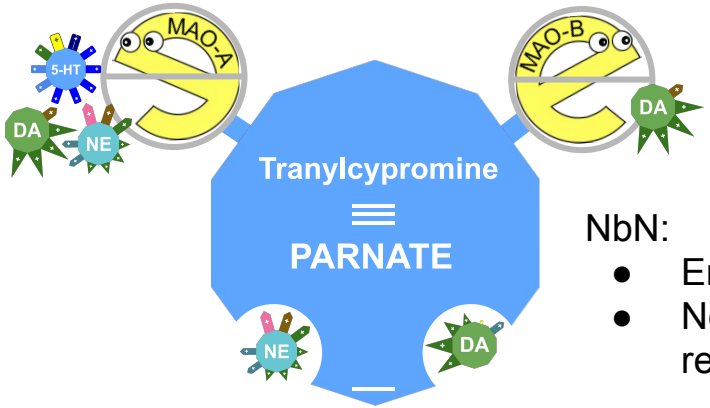
Tranylcypromine abuse has been reported at 120 – 600 mg per day. FDA max is 60 mg.

inhibition of MAO is irreversible and the effect continues for up to 2 weeks after the medication is discontinued.

Risk of serious outcome from a single-drug overdose of tranylcypromine is about 40%, which is one of the highest morbidity rate among antidepressants.

There was 1 death out of 330 single-drug overdoses.

Tranylcypromine (PARNATE) – MAOI

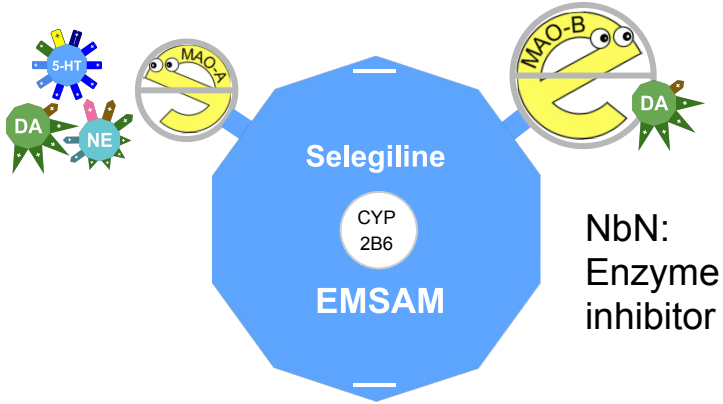


NbN:

- Enzyme inhibitor
- Neurotransmitter releaser

NbN:
Enzyme inhibitor

NbN:
Enzyme inhibitor



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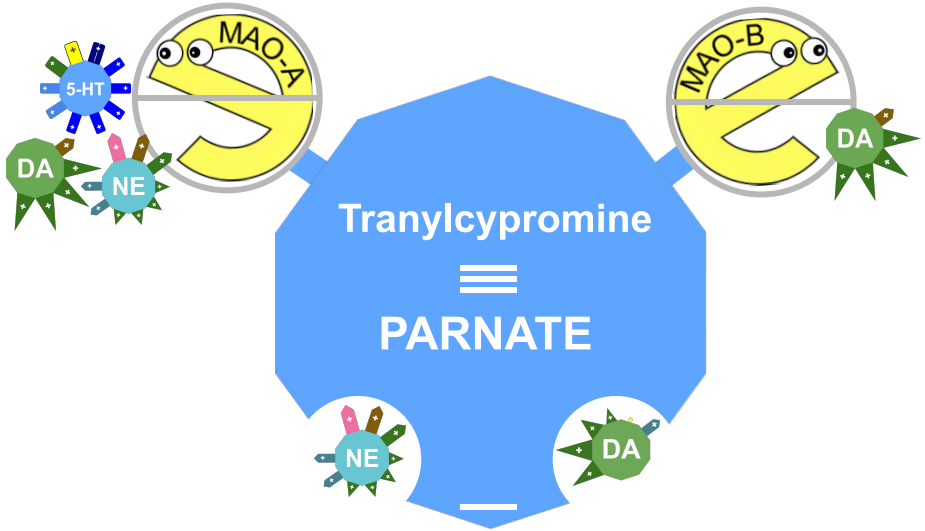
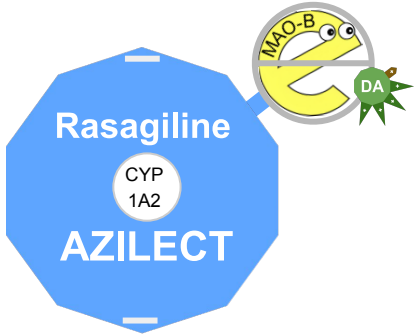
- Enzyme inhibitor (MAO-A, MAO-B)
- Neurotransmitter releaser (DA, NA)



Rasagiline (AZILECT)



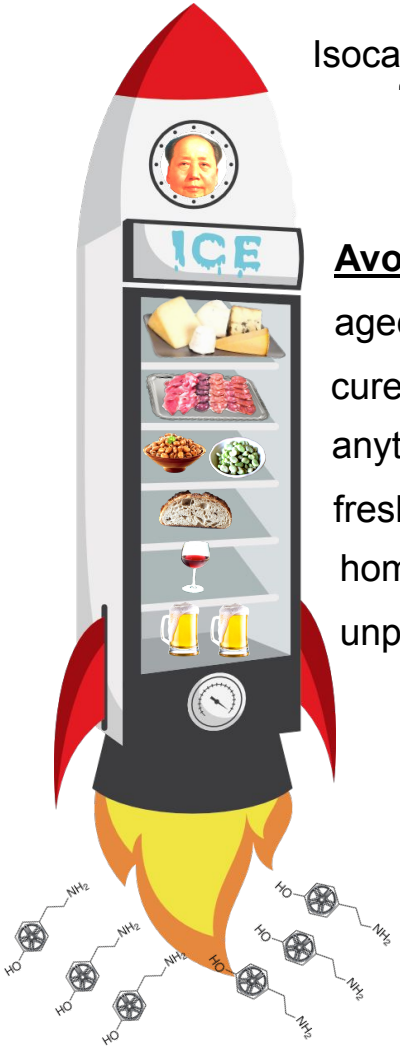
"Raise a lean Aztec"

for Parkinson's disease


You could eat this while taking an MAOI

Avoid completely	Highly aged cheeses and aged beef (eg, charcuterie boards) Freshly baked sourdough bread Fermented soy bean products (found in Asian foods like tempeh, miso, pickled tofu, and bean paste) Fermented meat or fish Raw meat or fish that has not been refrigerated properly or is past its use-by date Homemade beer or wine
OK in small portions (less than a typical serving size)	Specialty soy sauce Dried, aged sausage and salami (prosciutto is OK) Sauerkraut Beer that is microbrewed, on tap, or requires refrigeration (no more than 1 standard drink)
OK in normal portions (but don't overindulge)	Cheeses that are not highly aged Chocolate Caffeinated beverages Wine from a commercial producer (no more than 2 glasses) Beer that is shelf-stable or pasteurized (no more than 2 pints) Fresh beef or fish Fava beans Bananas and avocados that aren't overly ripe Soy sauce or fish sauce from grocery store brands Worcestershire sauce Kimchi Commercially produced sourdough bread Fermented yeast products (Marmite and Vegemite)
No restrictions (barely any tyramine here)	Milk, yogurt, cream Non-matured, soft cheese (mozzarella, American, ricotta, cottage cheese, cream cheese) Dry, cured meats (prosciutto, pepperoni) Smoked or pickled fish Fresh chicken, duck, pork, and sausage Stock cubes, powder, or bullion Non-fermented soy bean products

Sources: psychotropical.com; Finberg JPM and Gillman K, *Int Rev Neurobiol* 2011;100:169–190



Isocarboxazid (MARPLAN)
"Ice box Mars plan"

Avoid completely with MAOIs:

aged cheese

cured meats

anything fermented

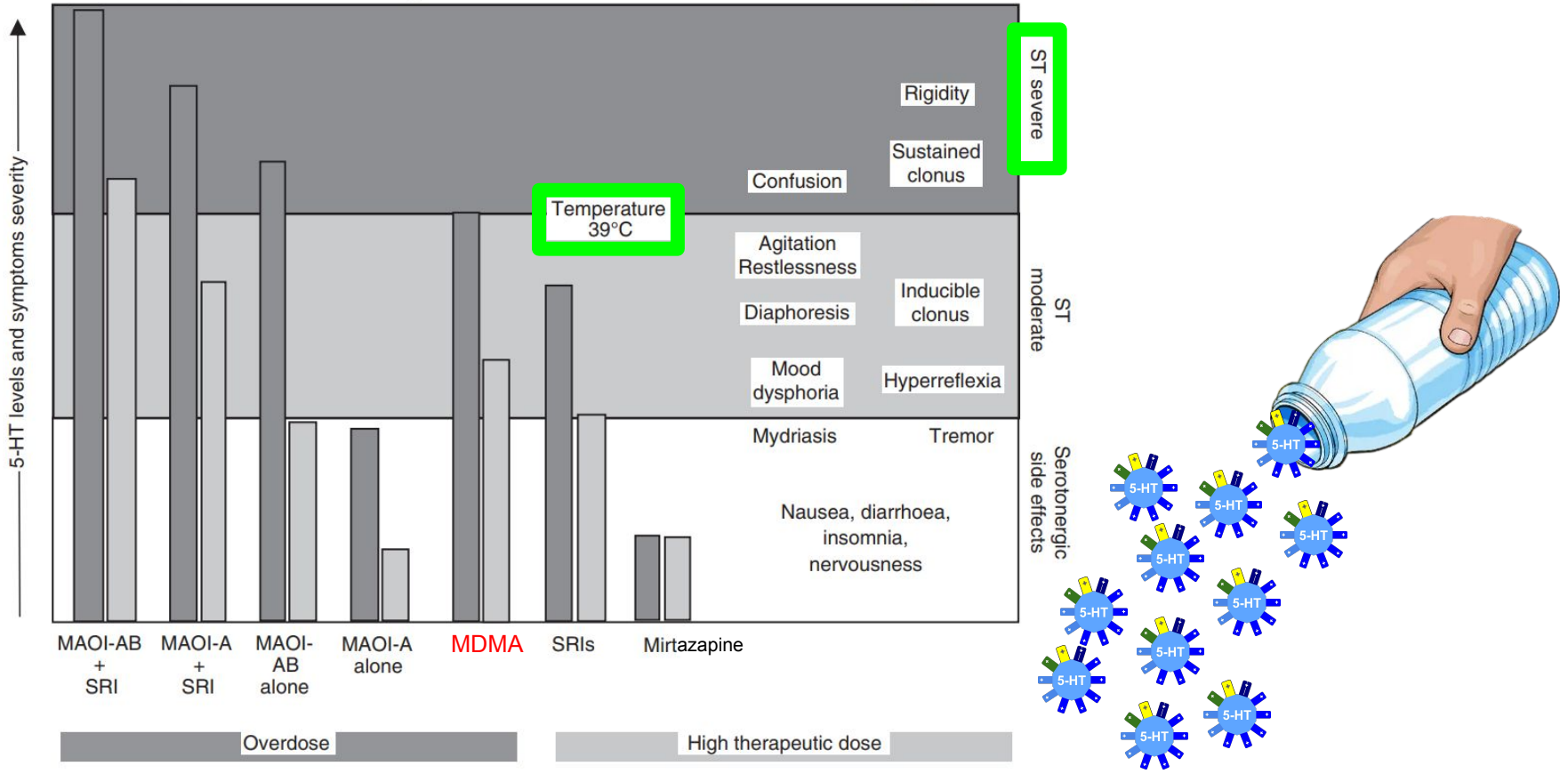
freshly baked sourdough bread

homemade wine

unpasteurized beer

Tyramine accumulates, causing hypertensive crisis.

Serotonin toxicity - don't say "serotonin syndrome"



Gillman, P. K. (2011). CNS toxicity involving methylene blue: the exemplar for understanding and predicting drug interactions that precipitate serotonin toxicity. *Journal of psychopharmacology*, *25*(3), 429-436.

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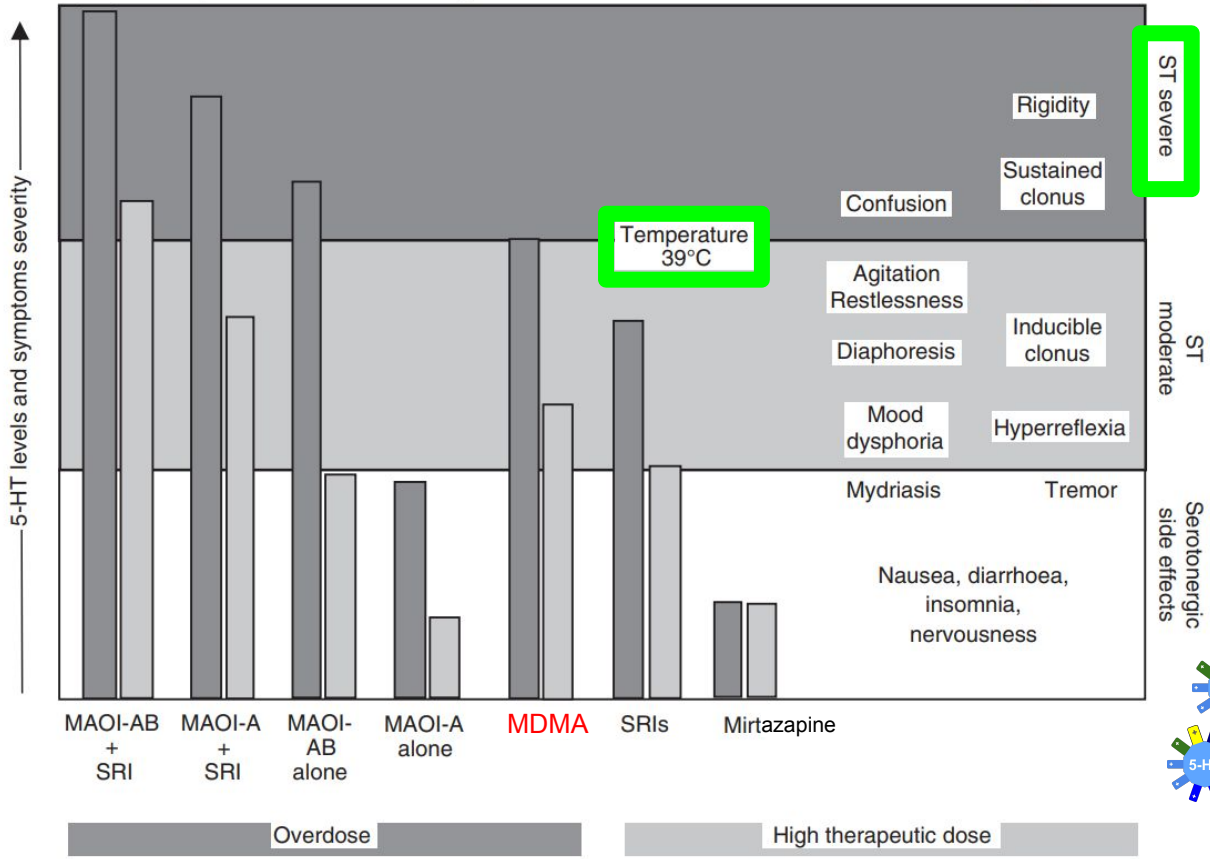
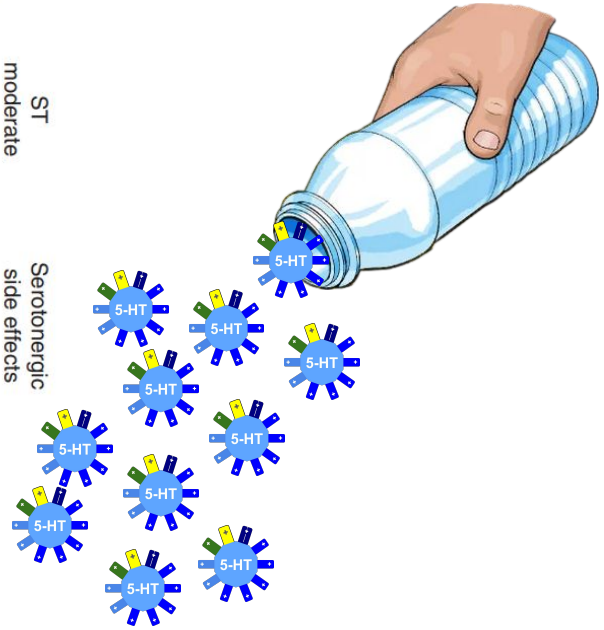


~the only ways to develop life-threatening serotonin toxicity

➤ Combine a MAOI with an SRI

➤ Overdose on an MAOI



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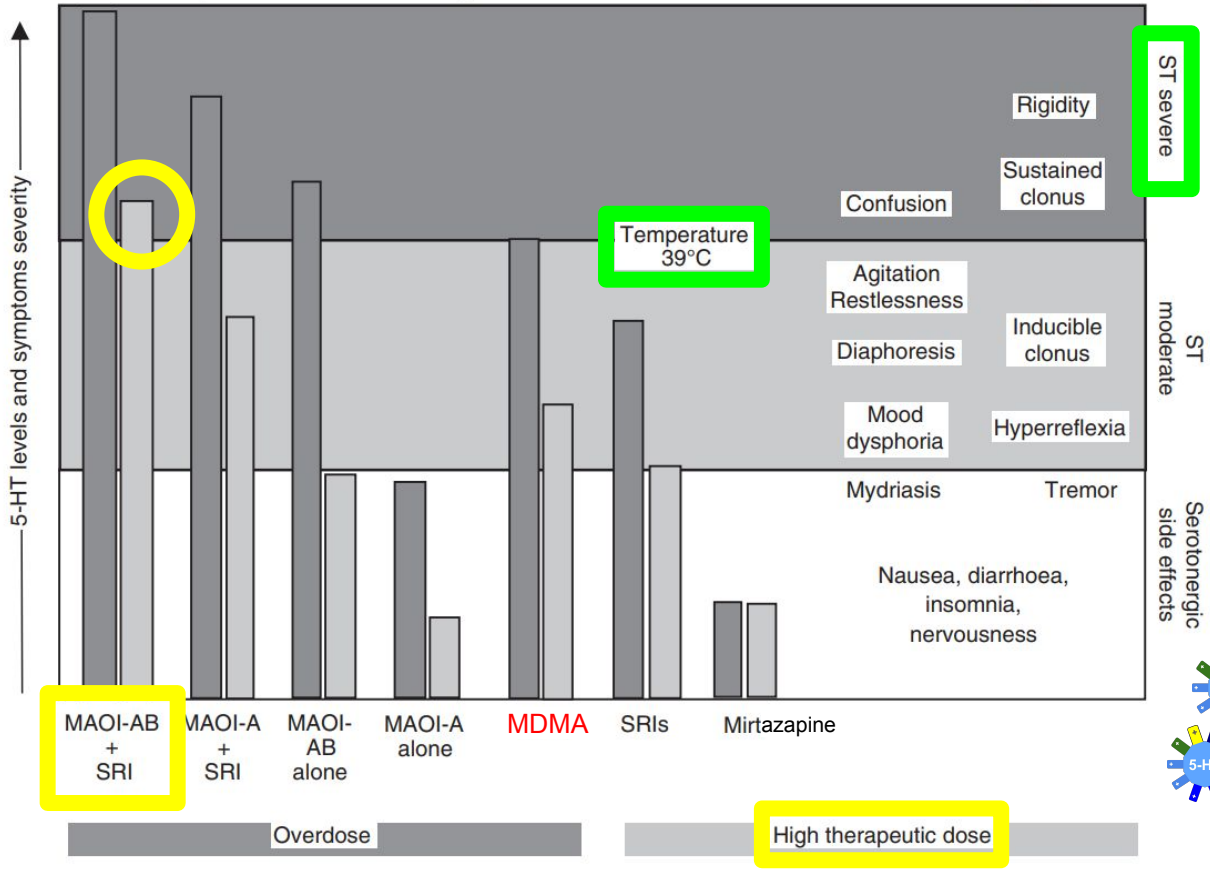

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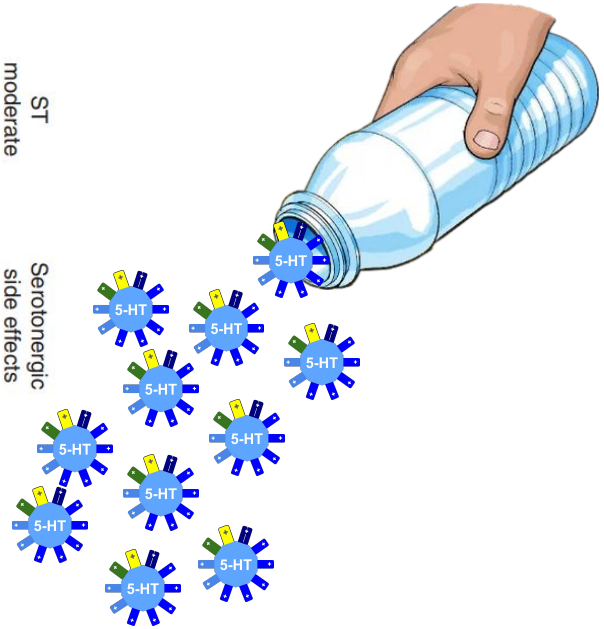

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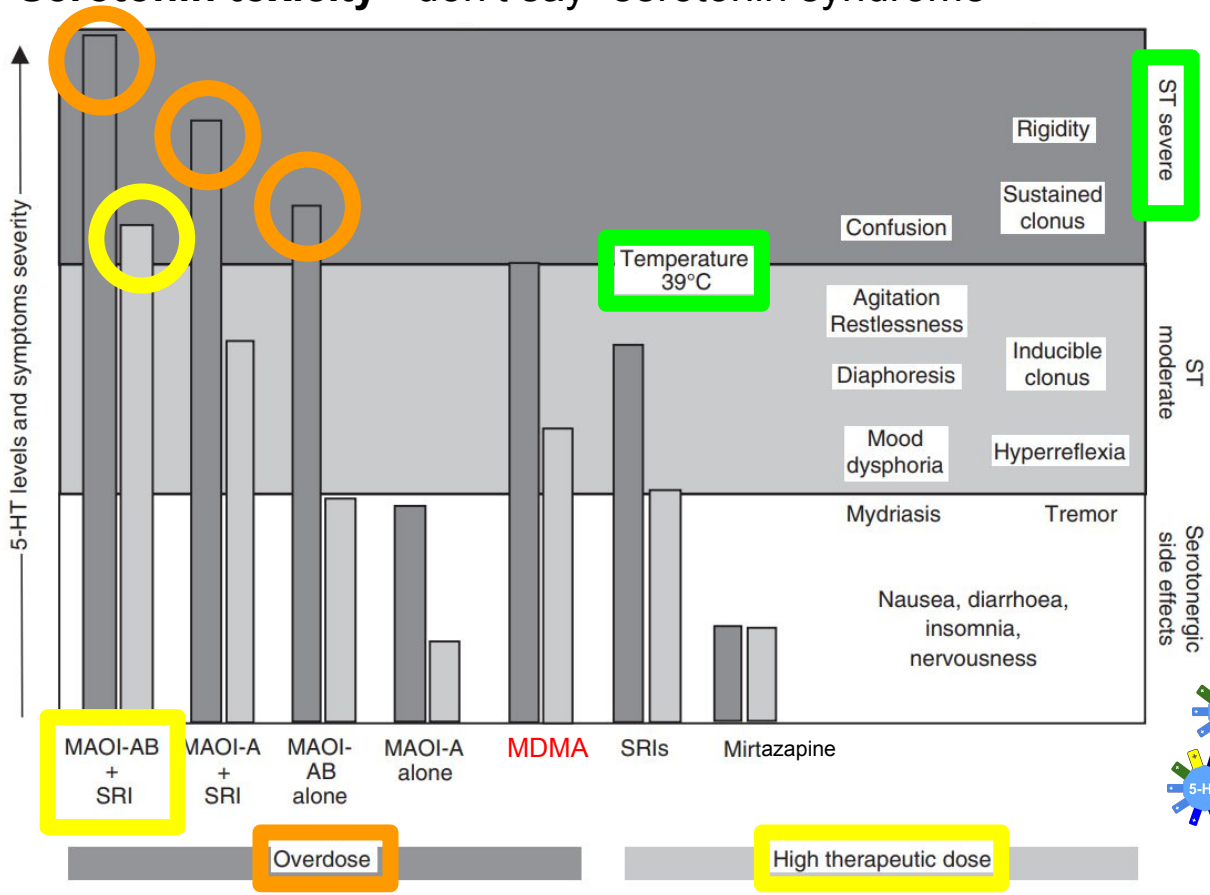

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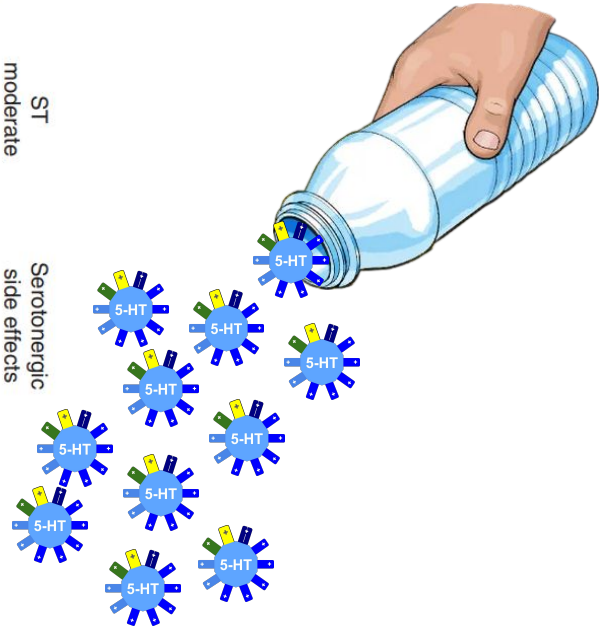

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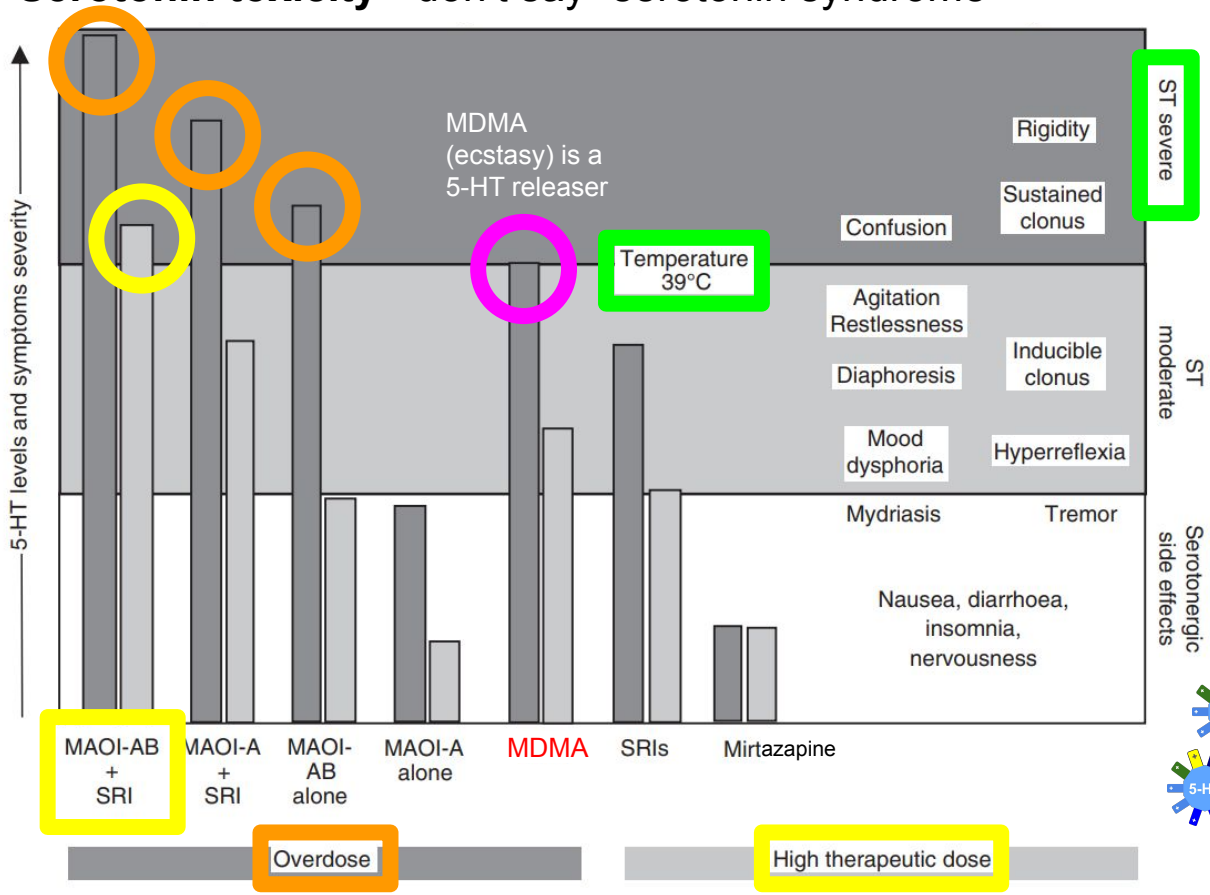
Serotonin toxicity - don't say "serotonin syndrome"



~the only ways to develop life-threatening serotonin toxicity

➤ Combine a MAOI with an SRI

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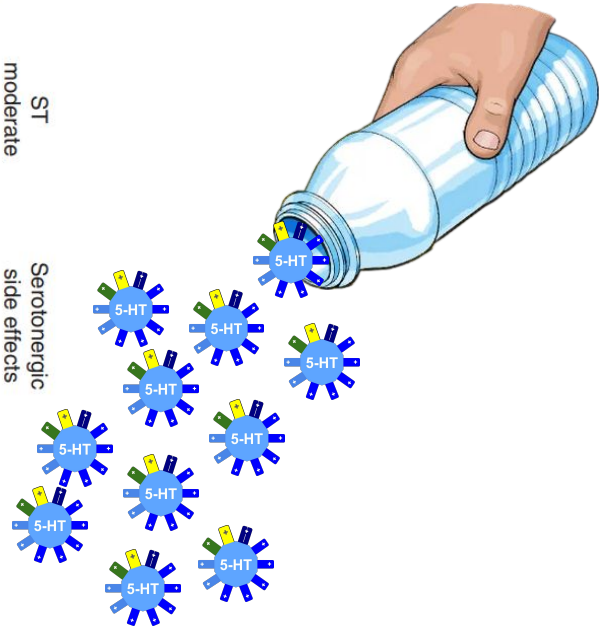

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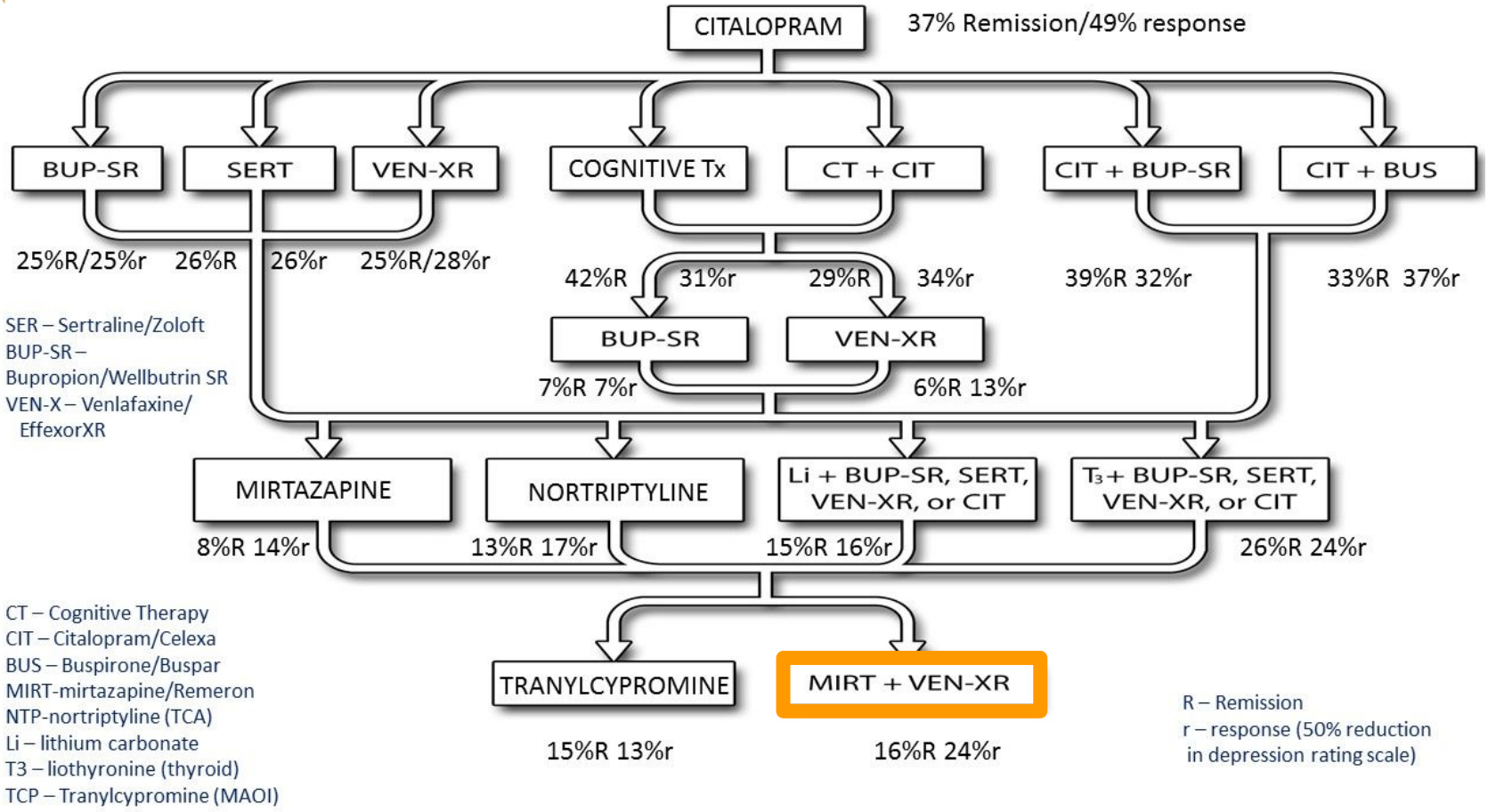


SER – Sertraline/Zoloft
BUP-SR – Bupropion/Wellbutrin SR
VEN-X – Venlafaxine/ EffexorXR

CT – Cognitive Therapy
CIT – Citalopram/Celexa
BUS – Buspirone/Buspar
MIRT-mirtazapine/Remeron
NTP-nortriptyline (TCA)
Li – lithium carbonate
T3 – liothyronine (thyroid)
TCP – Tranylcypromine (MAOI)

R – Remission
r – response (50% reduction in depression rating scale)

Venlafaxine + Mirtazapine – “California Rocket Fuel”

Strategic pharmaco**DYN**amic interaction:

Like-minded “**DYN**os”

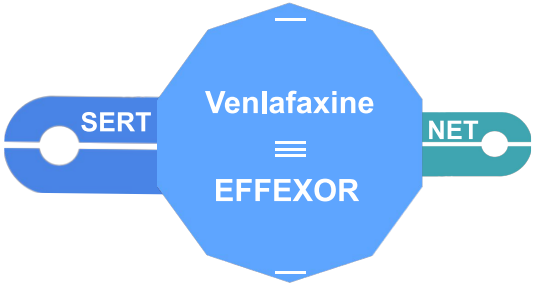
Mirtazapine (REMERON)

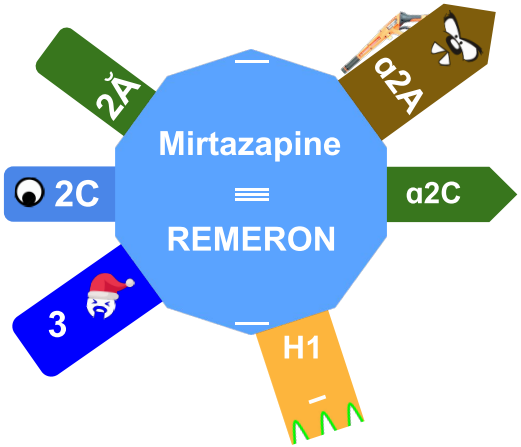
Venlafaxine (EFFEXOR)

NaSSA / receptor antagonist

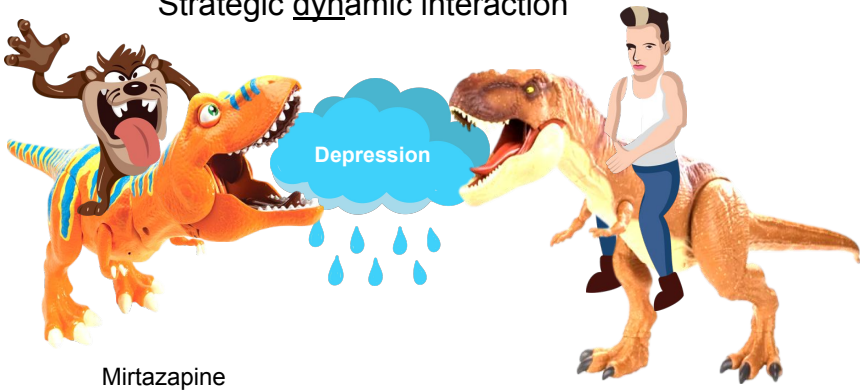
SNRI

Venlafaxine + Mirtazapine – “California Rocket Fuel”





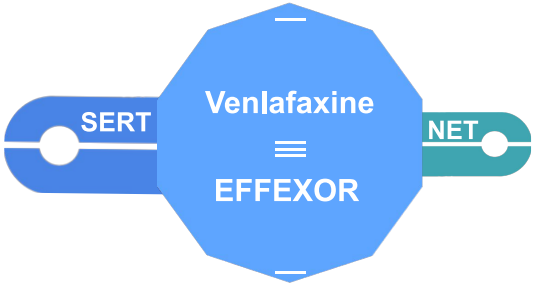
Strategic dynamic interaction

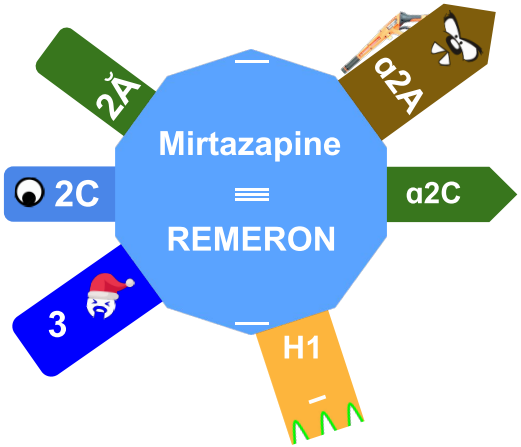


Mirtazapine
NaSSA

Venlafaxine
SNRI

Venlafaxine + Mirtazapine – “California Rocket Fuel”



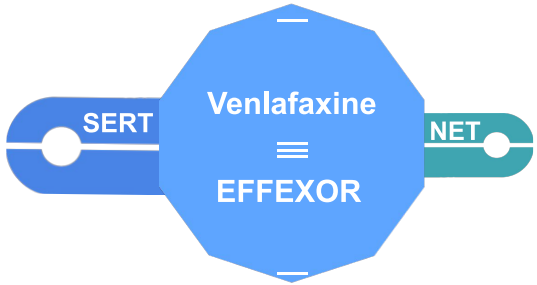


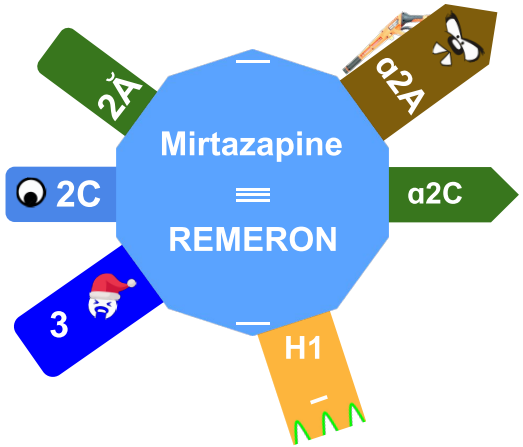
Nothing magical about this combo

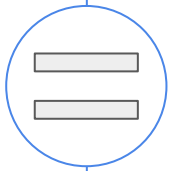
CO-MED study (N=665, randomized, single-blind, 12 wk)

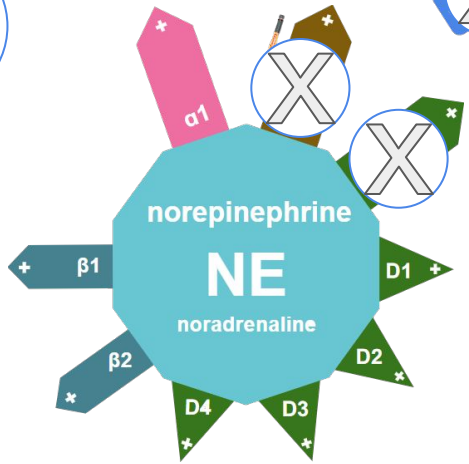
- escitalopram + placebo → 39% remission
- escitalopram + bupropion → 39%
- venlafaxine + mirtazapine → 38%

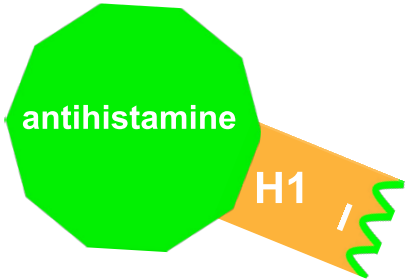
Venlafaxine + Mirtazapine – “California Rocket Fuel”

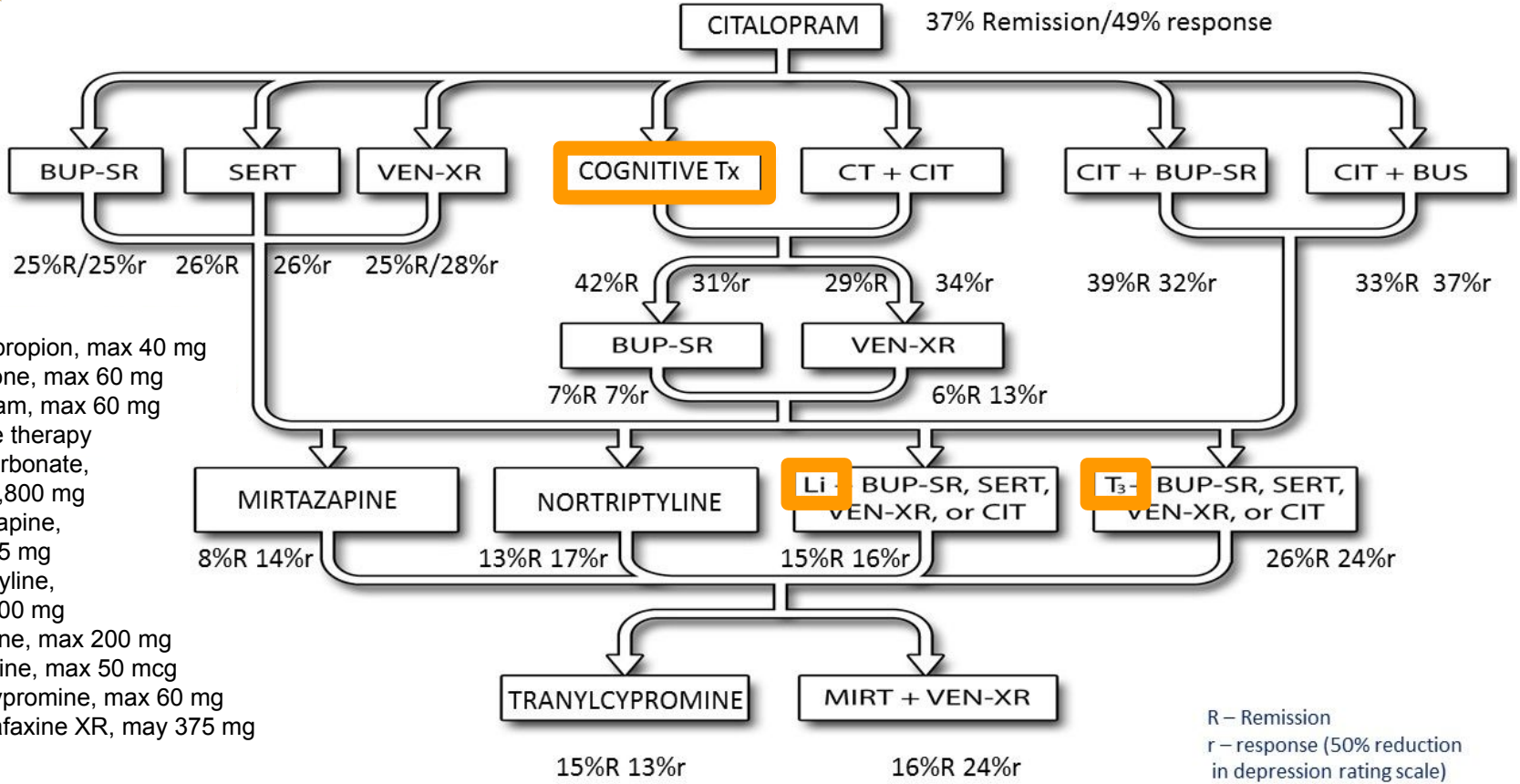






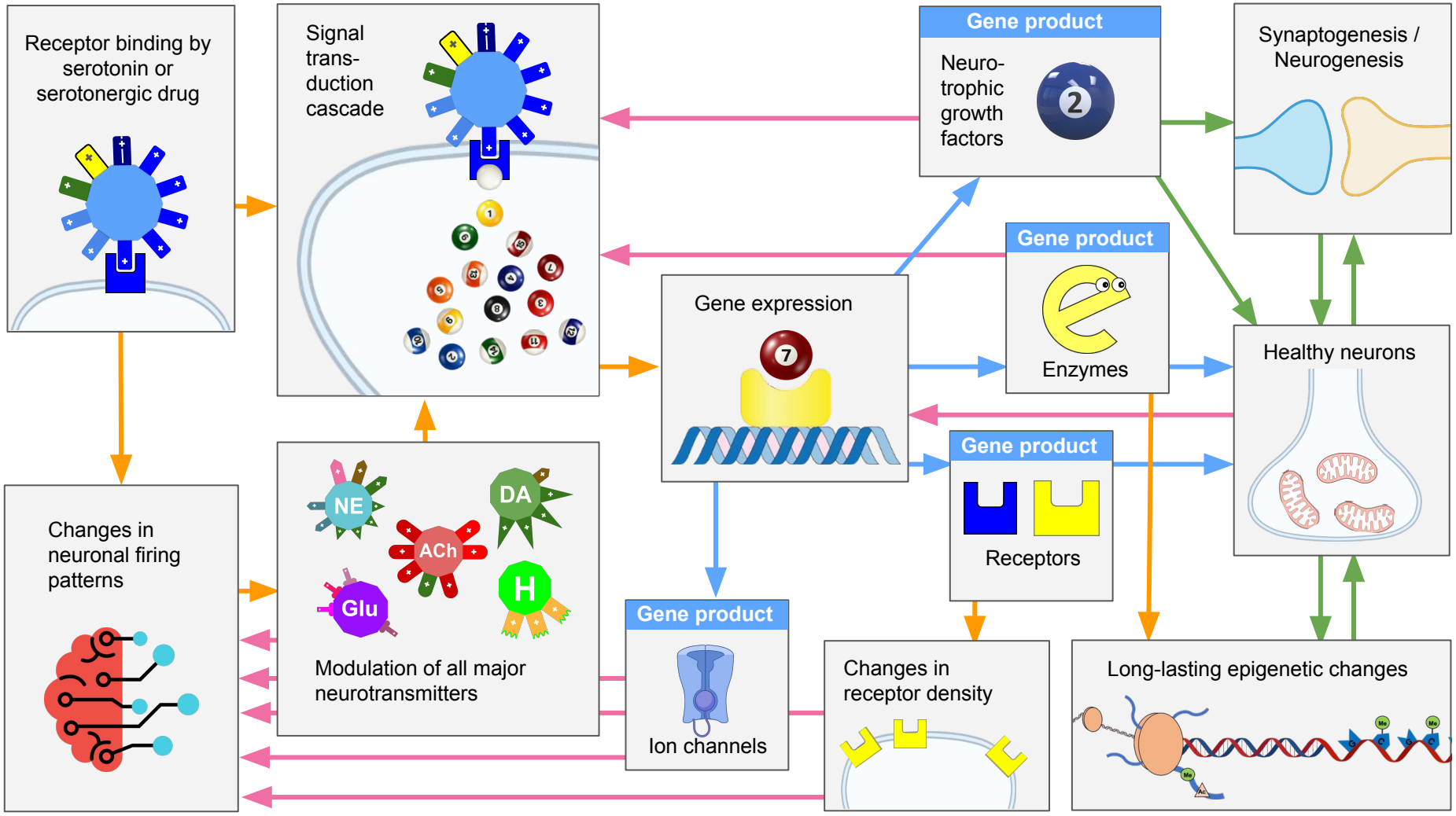


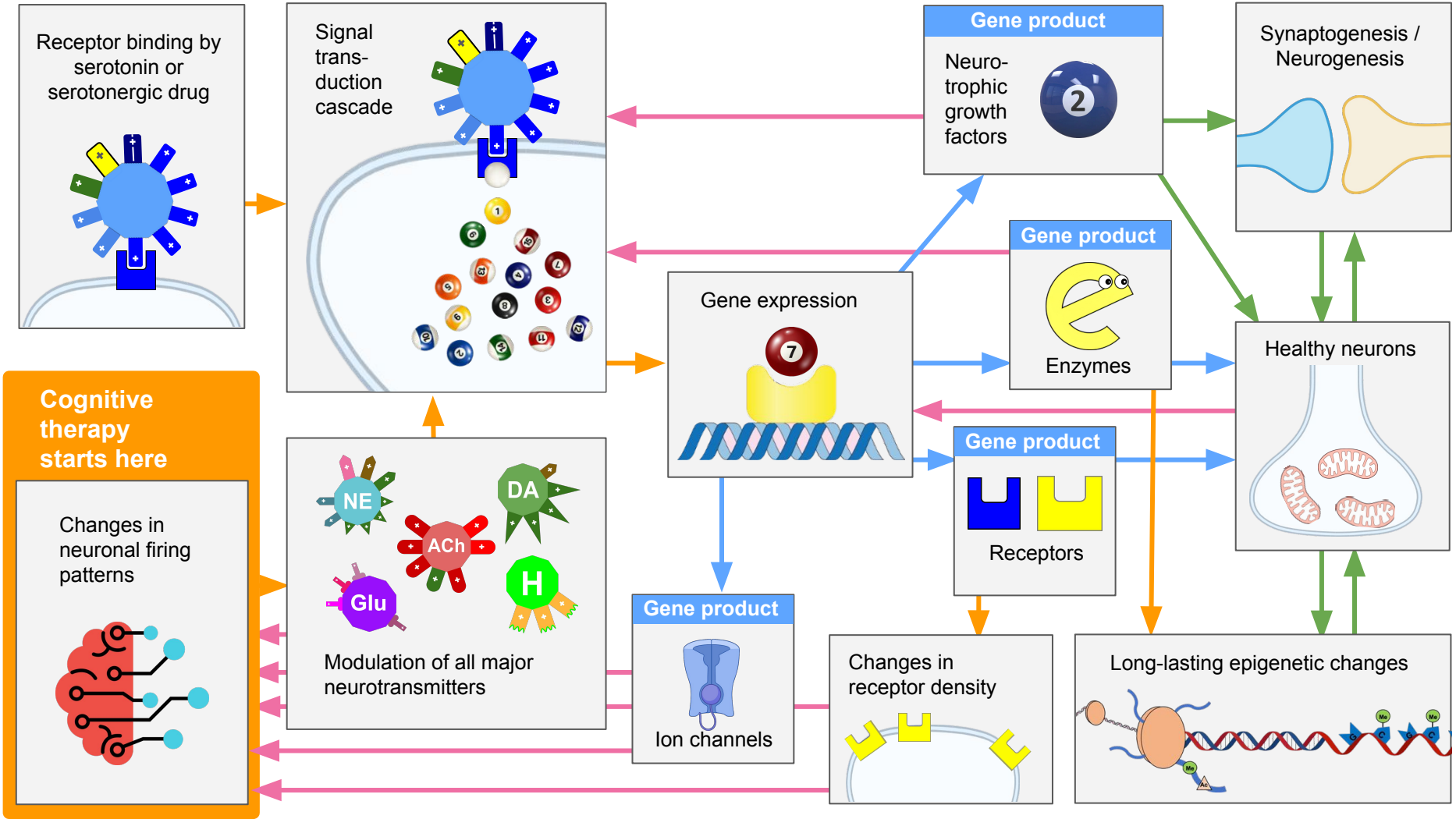




BUP-SR – Bupropion, max 40 mg
BUS – Buspirone, max 60 mg
CIT – Citalopram, max 60 mg
CT – Cognitive therapy
Li – Lithium carbonate, max 1,800 mg
MIRT – Mirtazapine, max 45 mg
NTP – Nortriptyline, max 100 mg
SER – Sertraline, max 200 mg
T3 – Liothyronine, max 50 mcg
TCP – tranylcypromine, max 60 mg
VEN-X – venlafaxine XR, may 375 mg

R – Remission
r – response (50% reduction in depression rating scale)


Receptor binding by serotonin or serotonergic drug
Signal trans-duction cascade
Gene product
Neuro-trophic growth factors
2
Synaptogenesis / Neurogenesis
Gene product
Enzymes
Gene expression
7
Healthy neurons
Gene product
Receptors
Changes in neuronal firing patterns
NE
DA
ACh
H
Glu
Modulation of all major neurotransmitters
Gene product
Ion channels
Changes in receptor density
Long-lasting epigenetic changes


Receptor binding by serotonin or serotonergic drug
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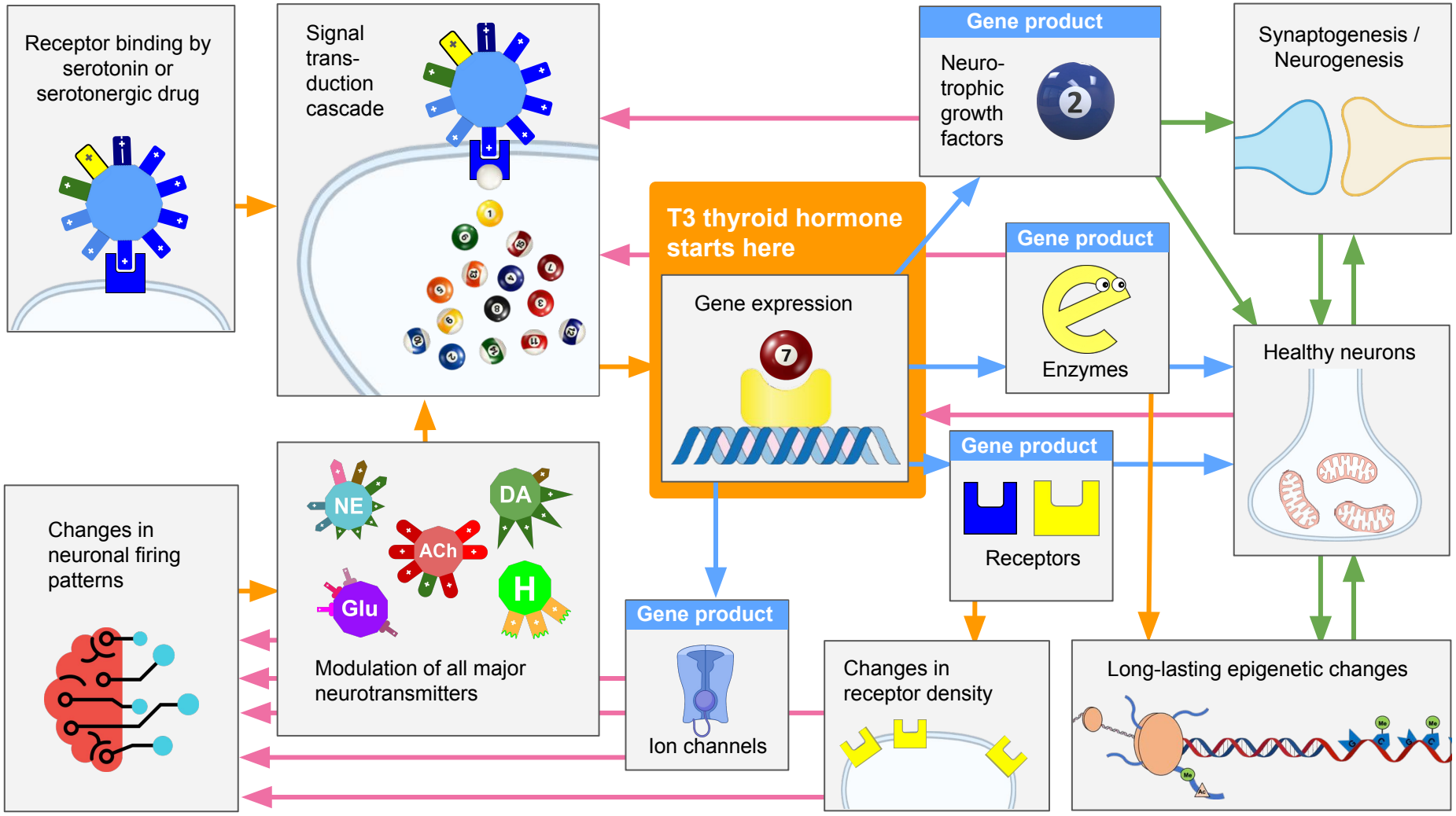
Gene expression
Healthy neurons
Gene product
Receptors
Cognitive therapy starts here
Changes in neuronal firing patterns
NE
DA
ACh
H
Glu
Modulation of all major neurotransmitters
Gene product
Ion channels
Changes in receptor density
Long-lasting epigenetic changes


Receptor binding by serotonin or serotonergic drug
Signal trans-duction cascade
Gene product
Neuro-trophic growth factors
Synaptogenesis / Neurogenesis
T3 thyroid hormone starts here
Gene expression
Gene product
Enzymes
Healthy neurons
Gene product
Receptors
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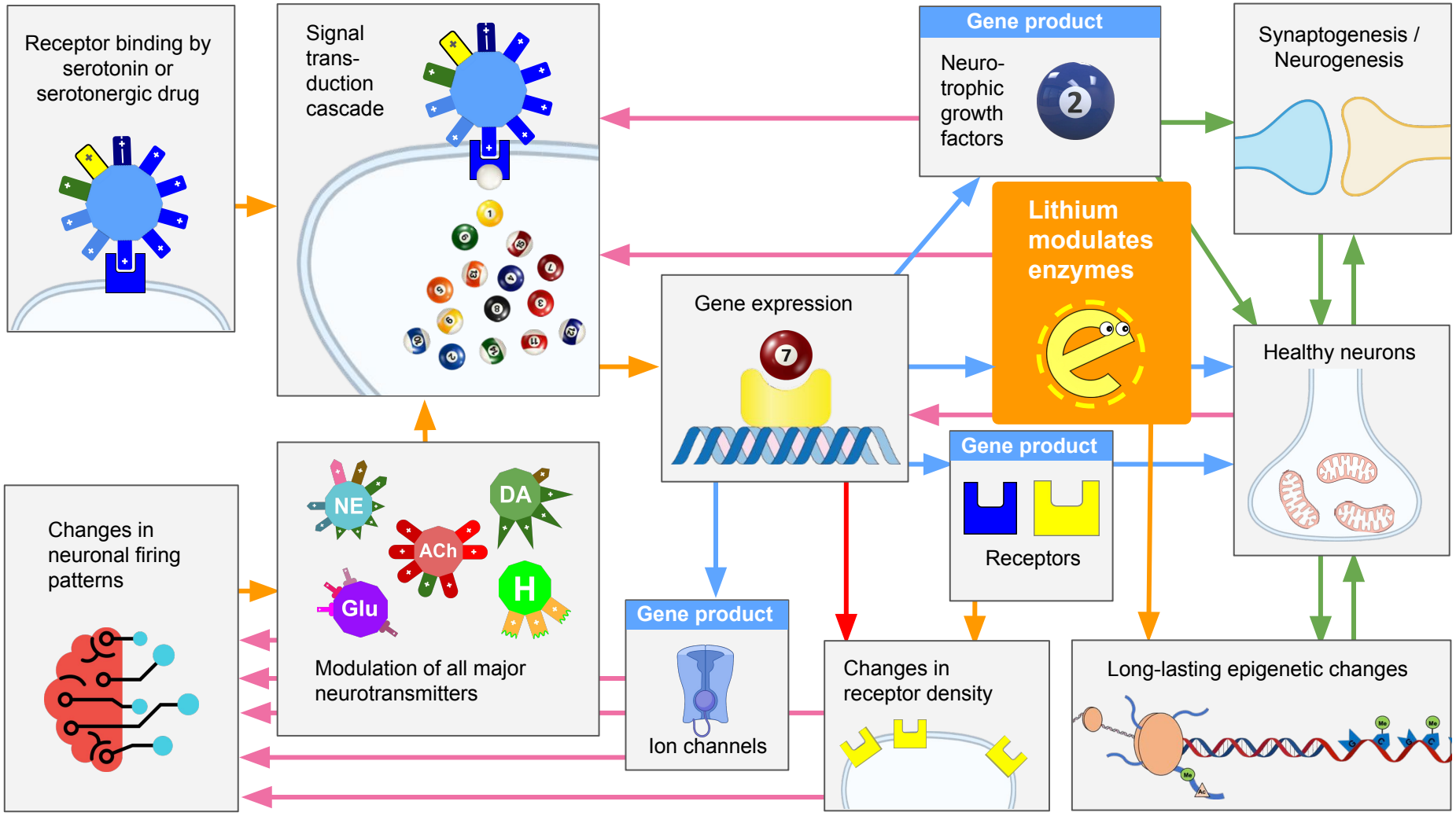
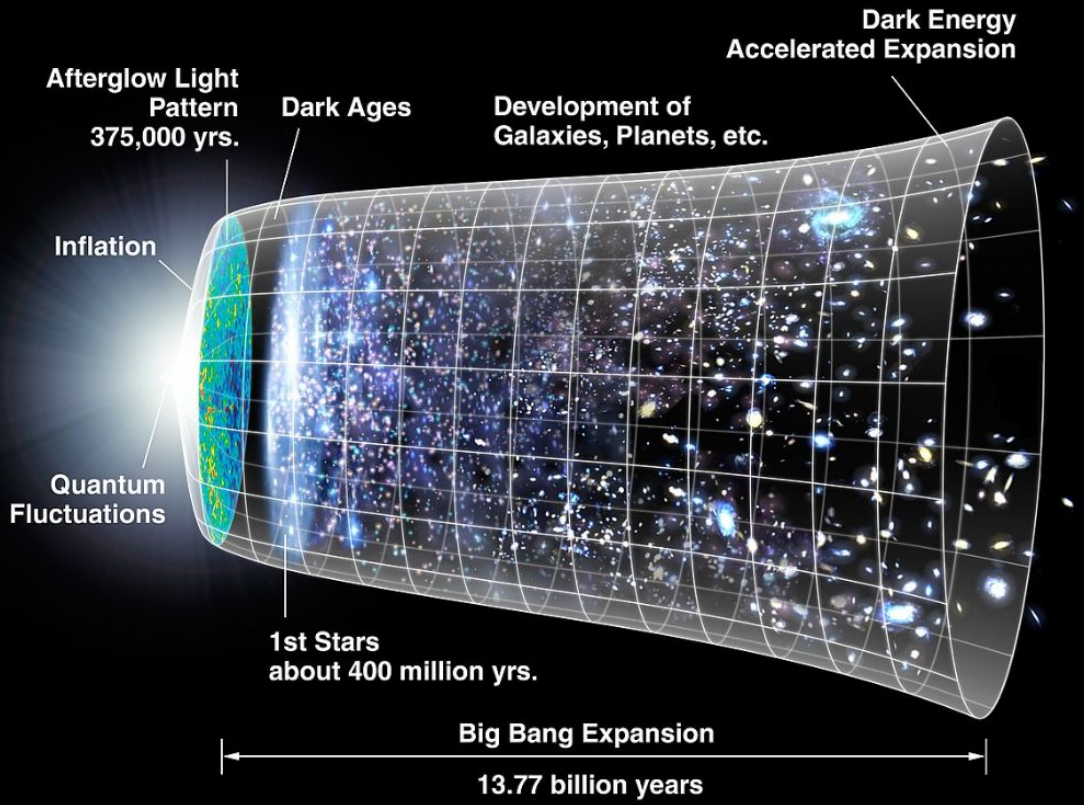
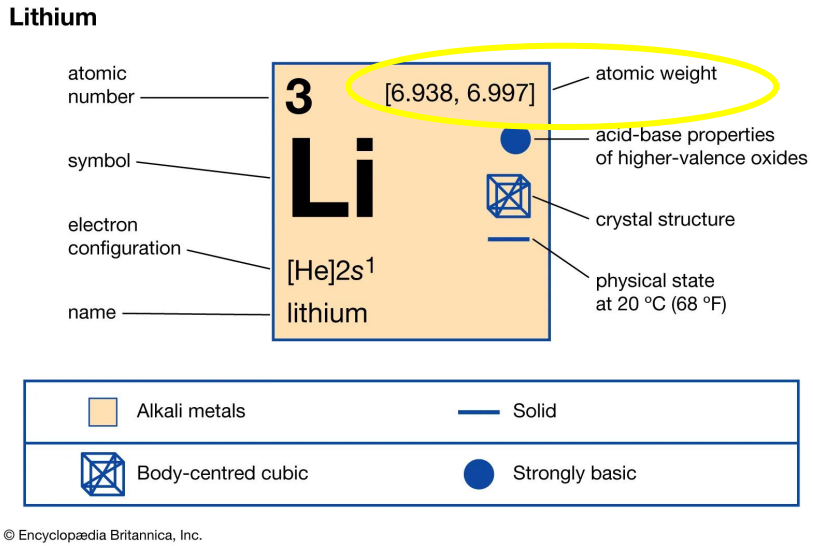
ACh
H
Glu
Modulation of all major neurotransmitters
Gene product
Ion channels
Changes in receptor density
Long-lasting epigenetic changes

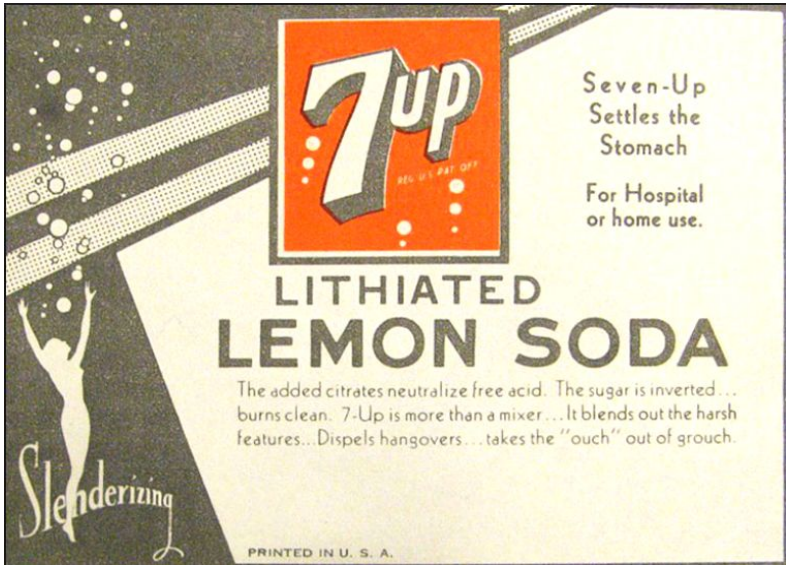

Receptor binding by serotonin or serotonergic drug
Signal trans-duction cascade
Gene product
Neuro-trophic growth factors
Synaptogenesis / Neurogenesis
Lithium modulates enzymes
Gene expression
Healthy neurons
Gene product
Receptors
Changes in neuronal firing patterns
NE
DA
ACh
Glu
H
Modulation of all major neurotransmitters
Gene product
Ion channels
Changes in receptor density
Long-lasting epigenetic changes

Lithium


Dark Energy
Accelerated Expansion
Afterglow Light
Pattern
375,000 yrs.
Dark Ages
Development of
Galaxies, Planets, etc.
Inflation
Quantum
Fluctuations
1st Stars
about 400 million yrs.
Big Bang Expansion
13.77 billion years

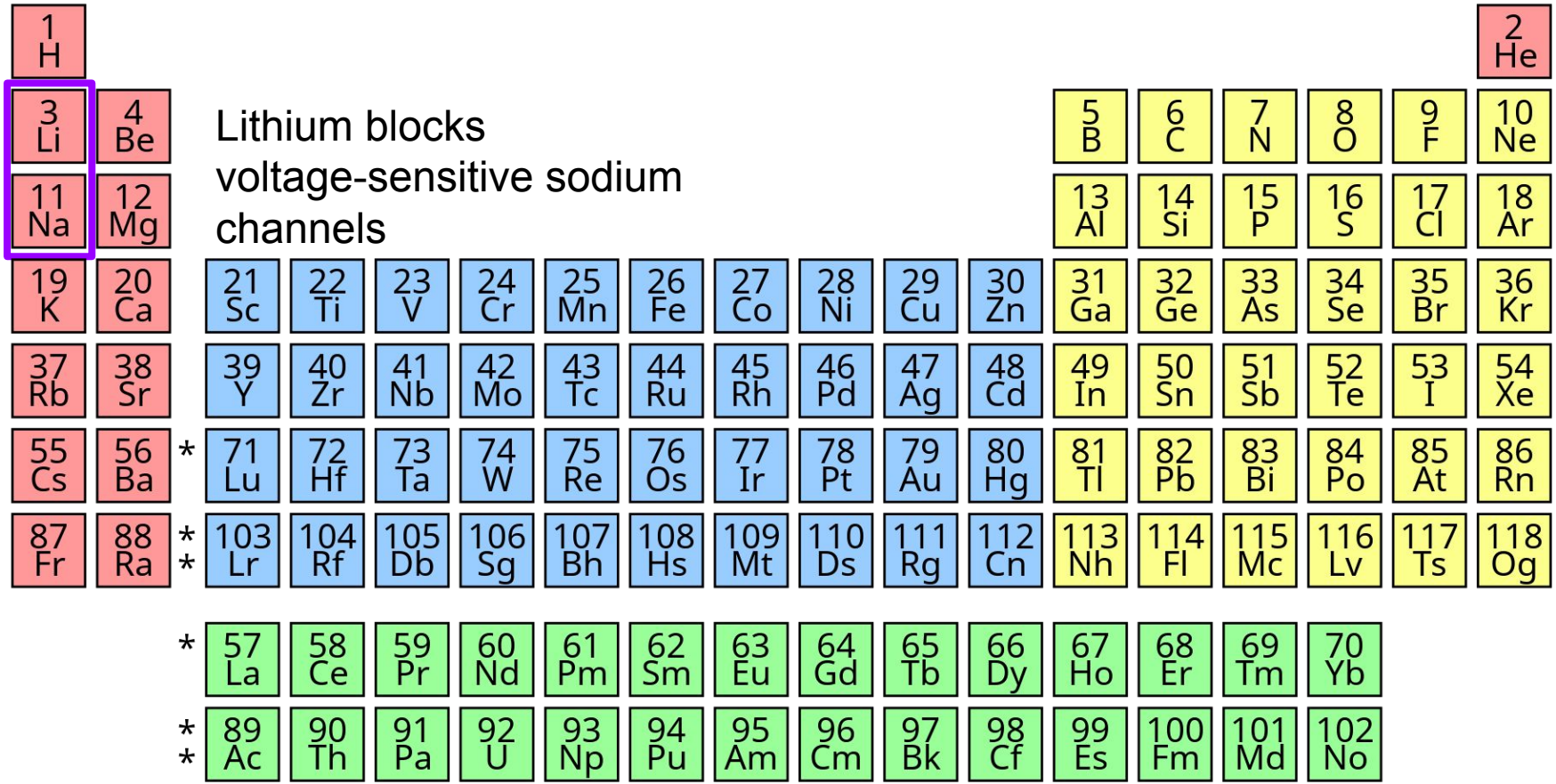
Lithium



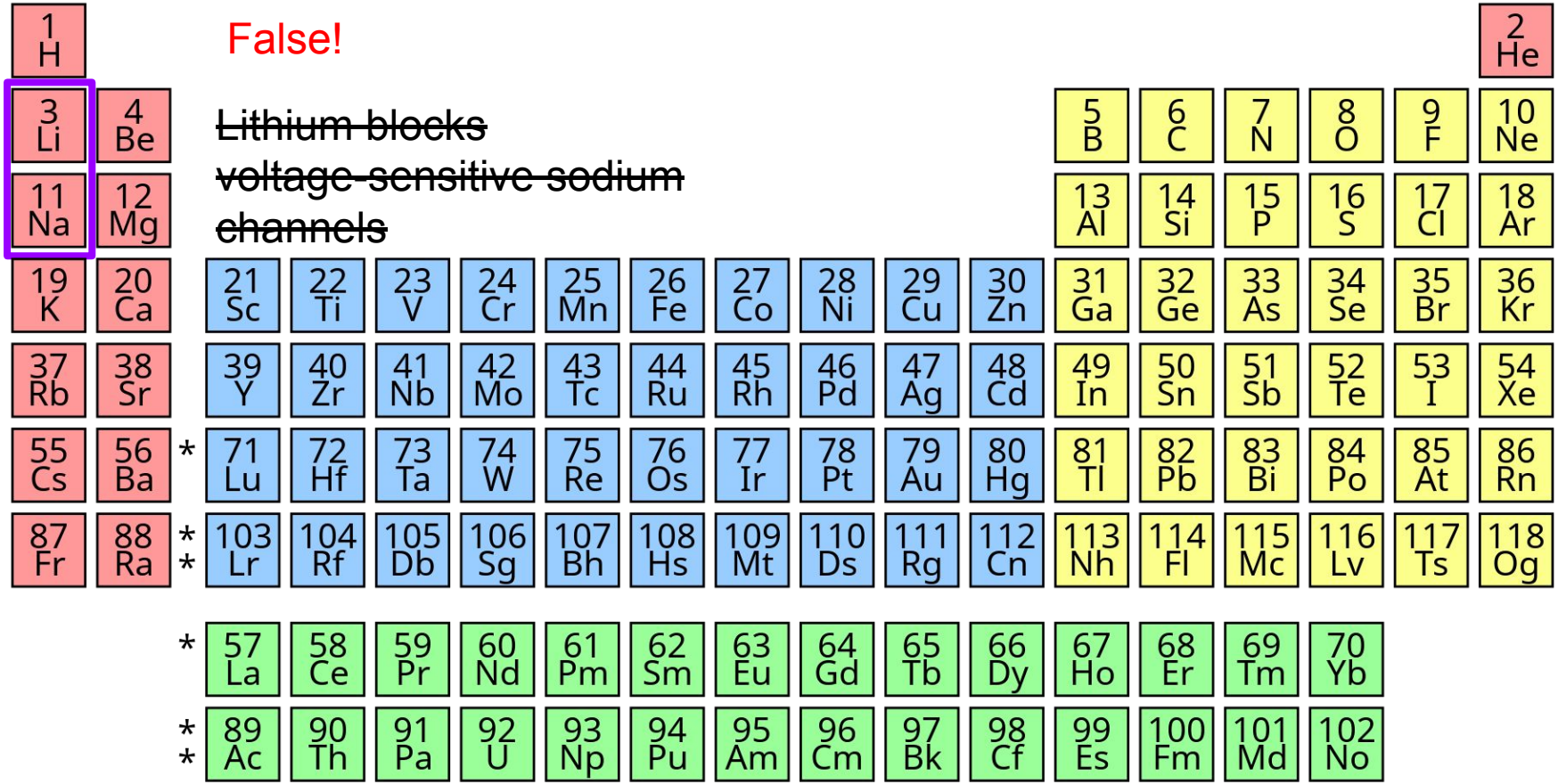


7-up contained lithium until 1950

Lithium


Lithium blocks voltage-sensitive sodium channels
1 H
2 He
3 Li
4 Be
5 B
6 C
7 N
8 O
9 F
10 Ne
11 Na
12 Mg
13 Al
14 Si
15 P
16 S
17 Cl
18 Ar
19 K
20 Ca
21 Sc
22 Ti
23 V
24 Cr
25 Mn
26 Fe
27 Co
28 Ni
29 Cu
30 Zn
31 Ga
32 Ge
33 As
34 Se
35 Br
36 Kr
37 Rb
38 Sr
39 Y
40 Zr
41 Nb
42 Mo
43 Tc
44 Ru
45 Rh
46 Pd
47 Ag
48 Cd
49 In
50 Sn
51 Sb
52 Te
53 I
54 Xe
55 Cs
56 Ba
* 71 Lu
72 Hf
73 Ta
74 W
75 Re
76 Os
77 Ir
78 Pt
79 Au
80 Hg
81 Tl
82 Pb
83 Bi
84 Po
85 At
86 Rn
87 Fr
88 Ra
** 103 Lr
104 Rf
105 Db
106 Sg
107 Bh
108 Hs
109 Mt
110 Ds
111 Rg
112 Cn
113 Nh
114 Fl
115 Mc
116 Lv
117 Ts
118 Og
* 57 La
58 Ce
59 Pr
60 Nd
61 Pm
62 Sm
63 Eu
64 Gd
65 Tb
66 Dy
67 Ho
68 Er
69 Tm
70 Yb
** 89 Ac
90 Th
91 Pa
92 U
93 Np
94 Pu
95 Am
96 Cm
97 Bk
98 Cf
99 Es
100 Fm
101 Md
102 No

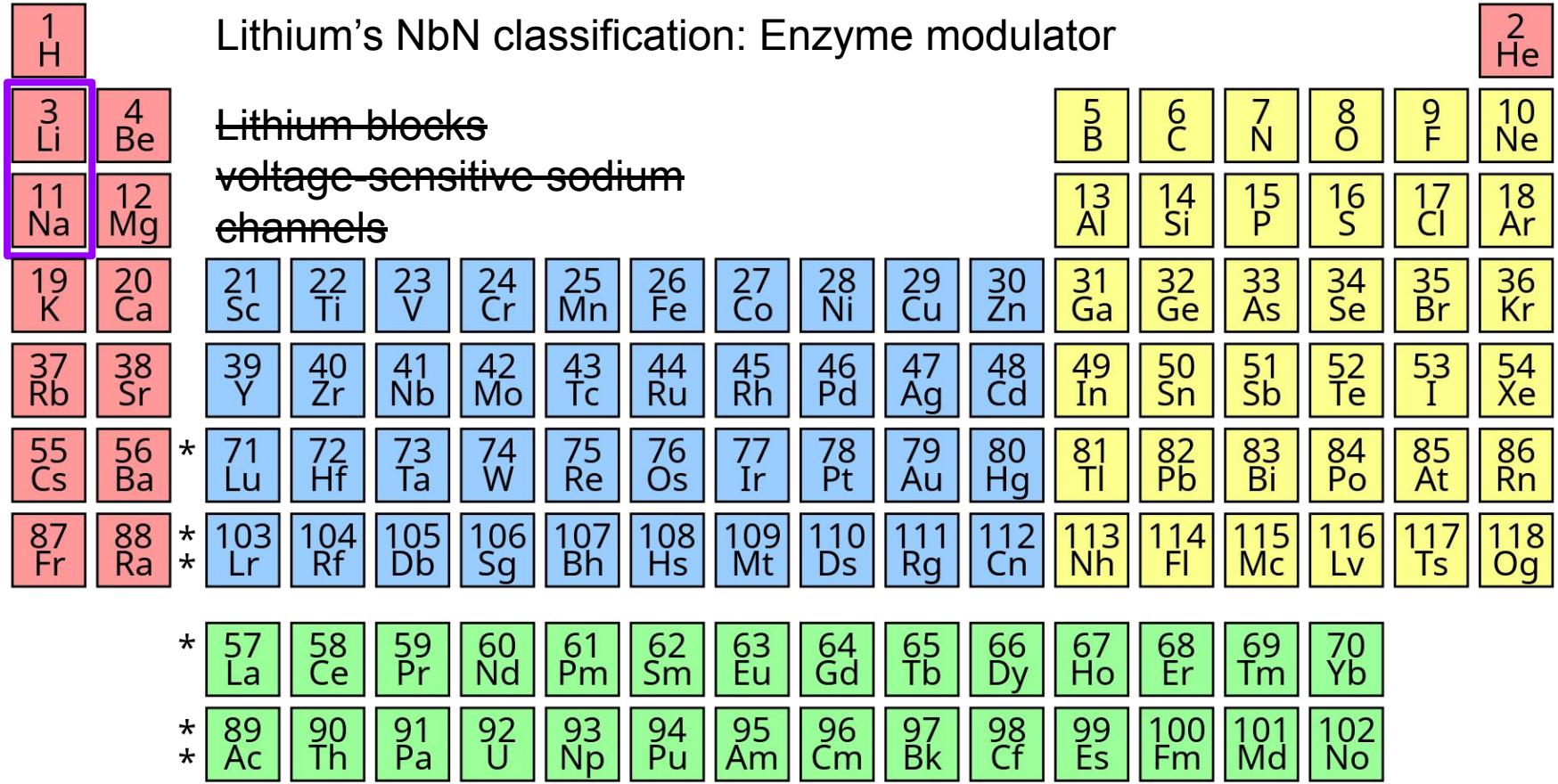
Lithium



Lithium

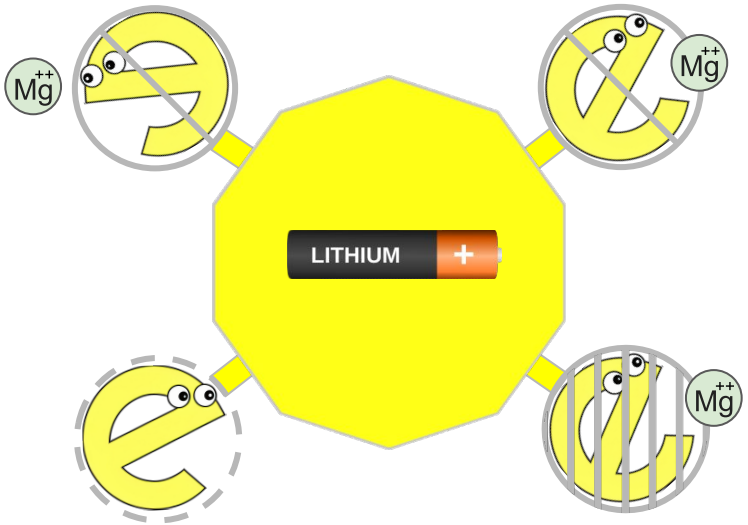
Lithium's NbN classification: Enzyme modulator

~~Lithium blocks voltage-sensitive sodium channels~~

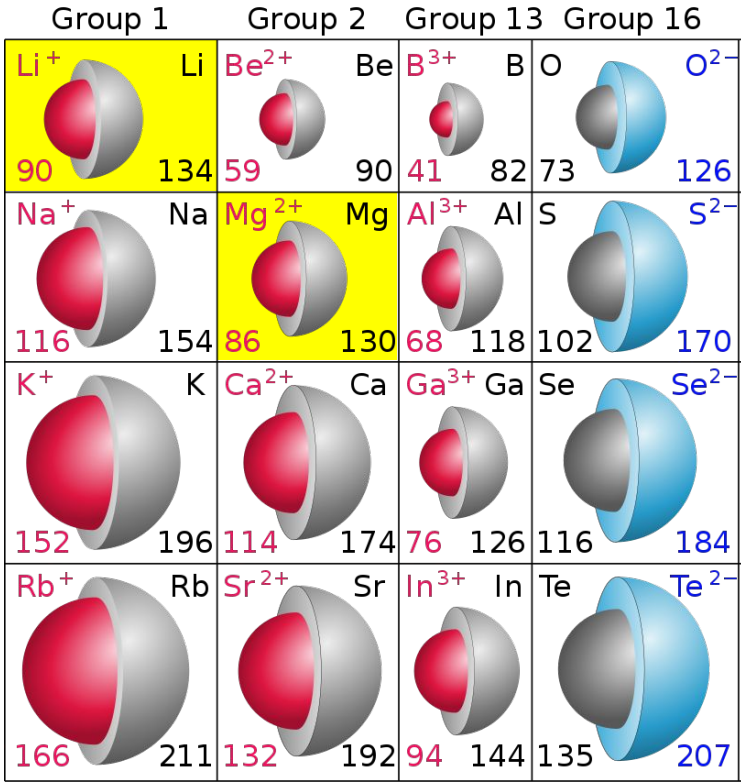


Lithium – enzyme modulator

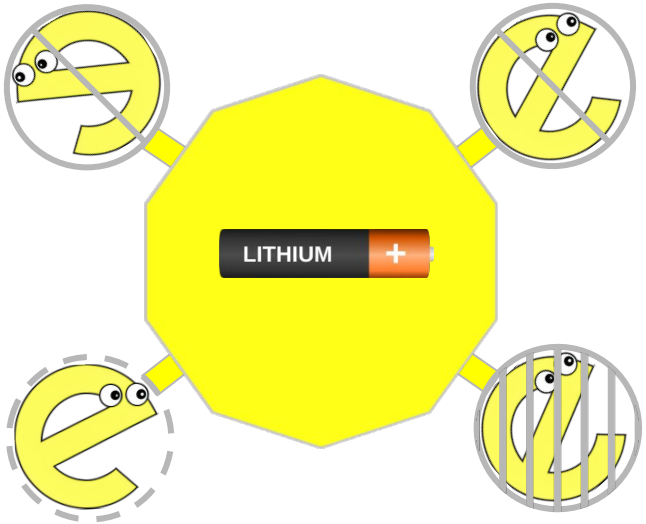
Lithium competes with magnesium as an enzyme co-factor.



Sizes of atoms and their ions



Lithium – enzyme modulator

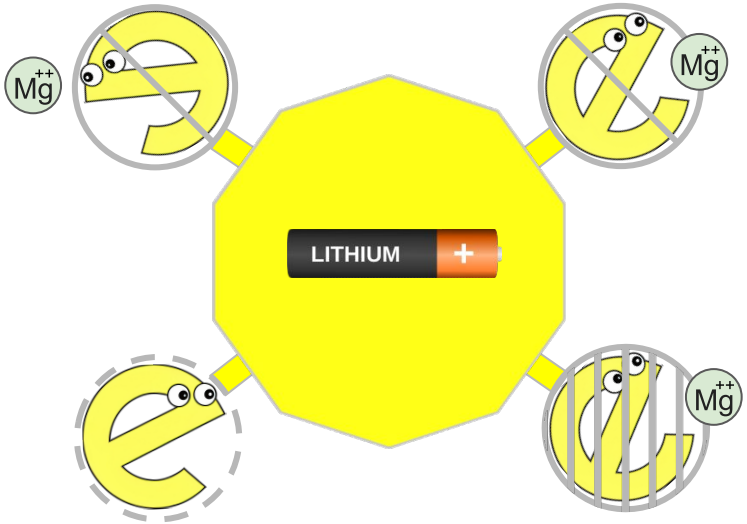


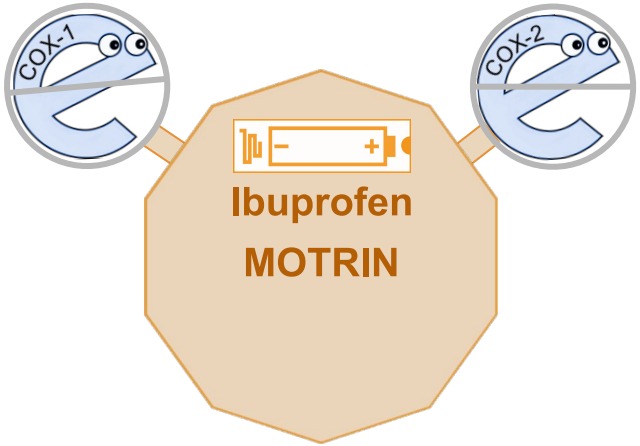
Lithium competes with **sodium** for renal reabsorption.

That's why hyponatremia can lead to lithium toxicity—more lithium is reabsorbed when less sodium is around.

Group 1	Group 2	Group 13	Group 16
Li^+ Li 90 134	Be^{2+} Be 59 90	B^{3+} B 41 82	O O^{2-} 73 126
Na^+ Na 116 154	Mg^{2+} Mg 86 130	Al^{3+} Al 68 118	S S^{2-} 102 170
K^+ K 152 196	Ca^{2+} Ca 114 174	Ga^{3+} Ga 76 126	Se Se^{2-} 116 184

Lithium – enzyme modulator





Lithium toxicity

Lithium levels increased by:

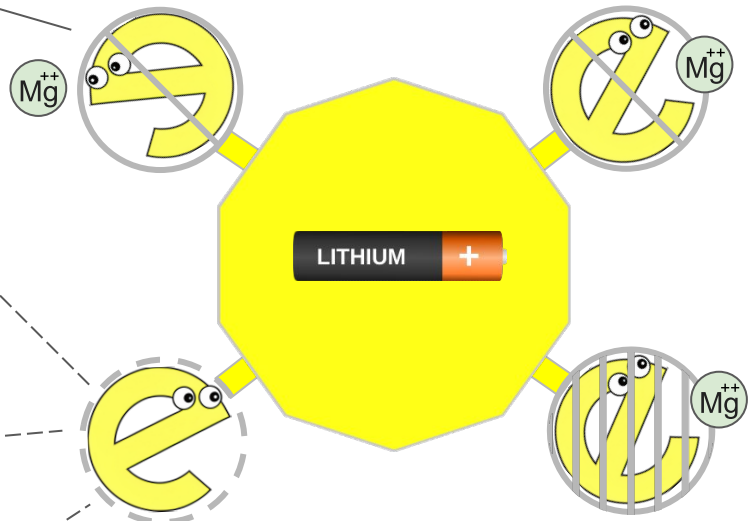
- The “N said” lithium toxicity
- “Tie-dyed diuretics”

Lithium – enzyme modulator

Lithium is an modulator of enzymes involved in signal transduction pathways.

"Better arrest imported gaskets"

inhibitor of glycogen synthase kinase 3 (GSK3) → anti-aging effects



inositol monophosphatase (IMPase) inhibitor

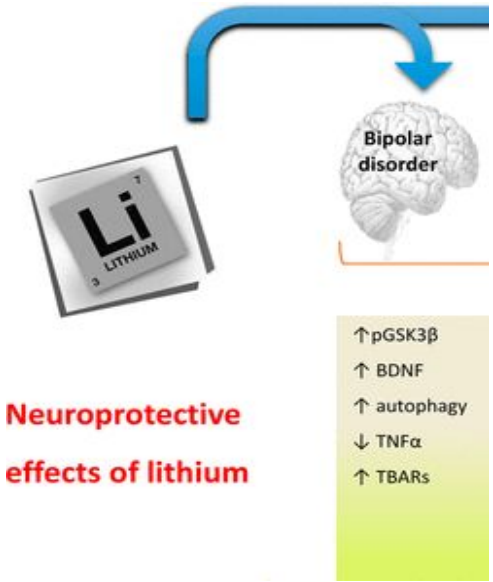
Lithium stimulates production of granulocyte colony stimulating factor (G-CSF), which leads to increased neutrophil counts starting 1 to 2 weeks after initiation.

Lithium indirectly inhibits protein kinase C (PKC). Tamoxifen, which directly inhibits PKC, was effective for mania with large effect size.

Lithium indirectly inhibits mTOR (molecular target of rapamycin), countering mTOR-driven quasi-programmed cellular aging.

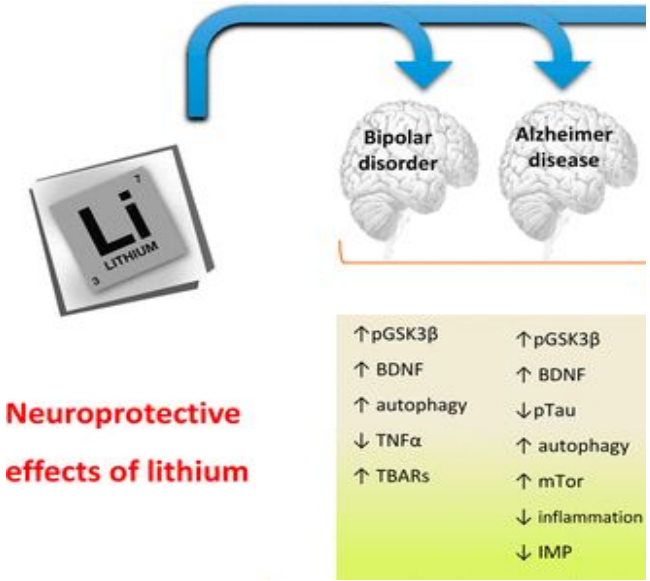
Lithium destabilizes the beta-arrestin complex, resulting decreased signal transduction from activation of D2 receptors → antimanic effects.

Lithium – neuroprotection



Neuroprotective Effects of Lithium: Implications for the Treatment of Alzheimer's Disease and Related Neurodegenerative Disorders O. V. Forlenza et al. ACS Chemical Neuroscience 2014.

Lithium – neuroprotection



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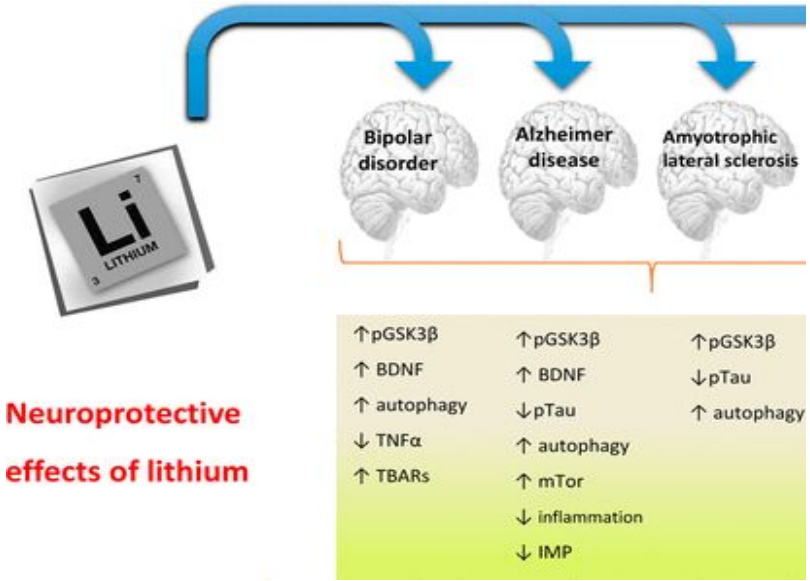
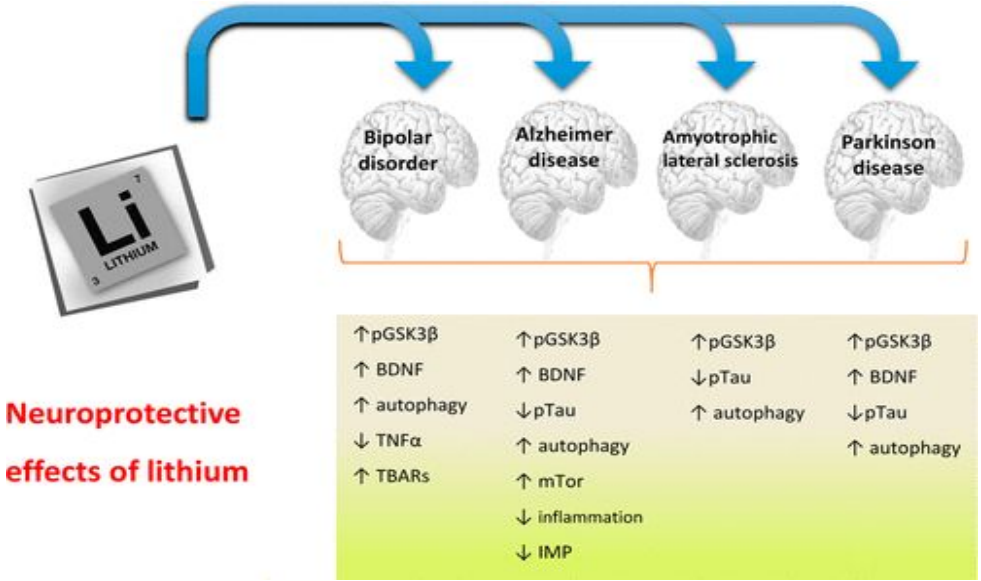
Lithium – neuroprotection



Neuroprotective Effects of Lithium: Implications for the Treatment of Alzheimer's Disease and Related Neurodegenerative Disorders O. V. Forlenza et al. ACS Chemical Neuroscience 2014.

Lithium – neuroprotection



Neuroprotective Effects of Lithium: Implications for the Treatment of Alzheimer's Disease and Related Neurodegenerative Disorders O. V. Forlenza et al. ACS Chemical Neuroscience 2014.

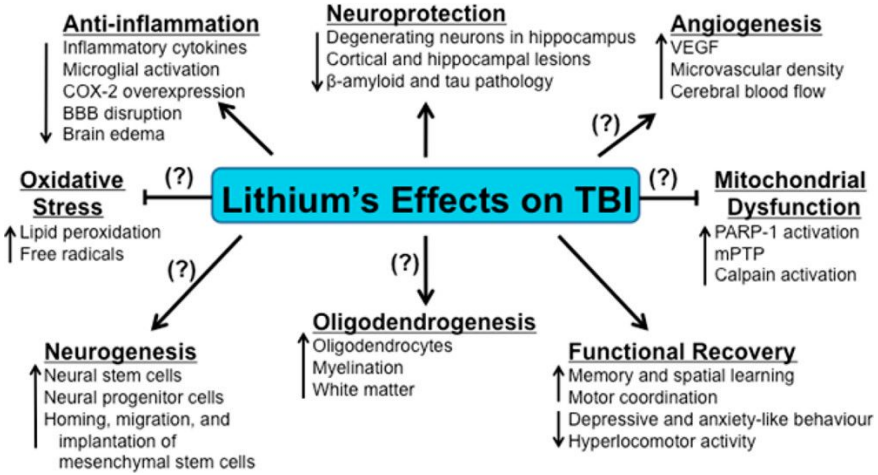
Lithium – neuroprotection post-TBI

ACS Chemical Neuroscience
Review
pubs.acs.org/chemneuro

A New Avenue for Lithium: Intervention in Traumatic Brain Injury

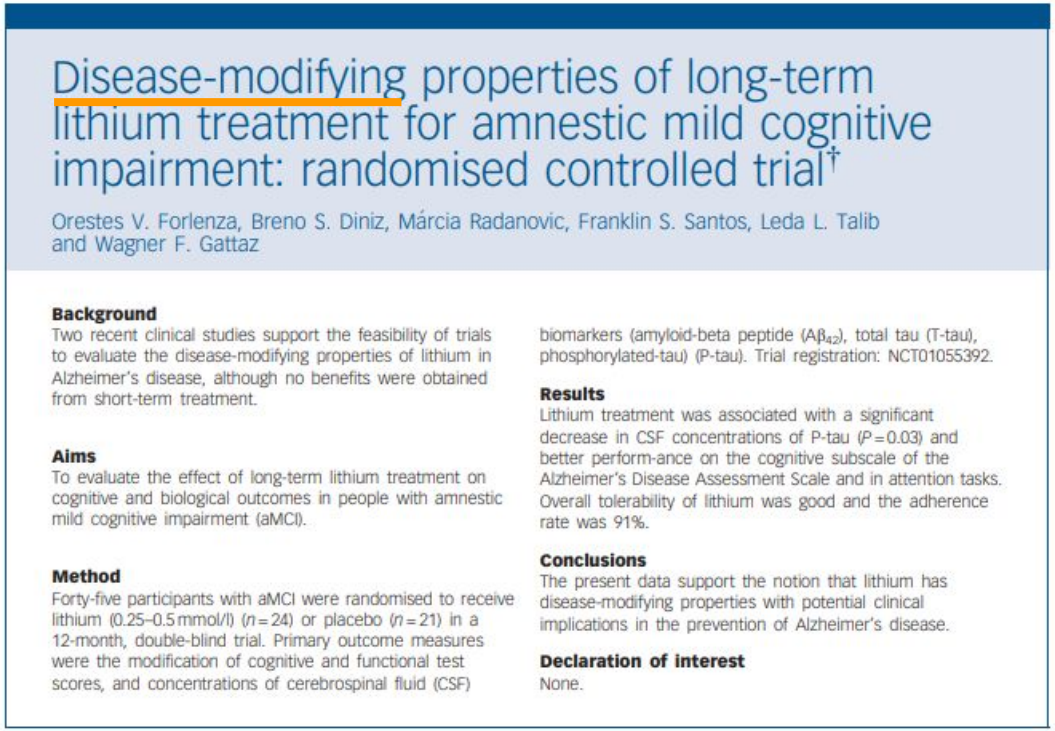
Peter R. Leeds,[†] Fengshan Yu,[†,‡] Zhifei Wang,[†] Chi-Tso Chiu,[†] Yumin Zhang,[‡,§] Yan Leng,[†] Gabriel R. Linares,[†] and De-Maw Chuang*[,†,‡]

[†]Molecular Neurobiology Section, National Institute of Mental Health, National Institutes of Health, 10 Center Drive, MSC 1363, Bethesda, Maryland 20892-1363, United States



ACS Chem. Neurosci. 2014, 5, 6, 422–433 Publication Date:April 3, 2014 https://doi.org/10.1021/cn500040g

Lithium – prevention of dementia



Disease-modifying properties of long-term lithium treatment for amnestic mild cognitive impairment: randomised controlled trial†

Orestes V. Forlenza, Breno S. Diniz, Márcia Radanovic, Franklin S. Santos, Leda L. Talib and Wagner F. Gattaz

Background
Two recent clinical studies support the feasibility of trials to evaluate the disease-modifying properties of lithium in Alzheimer's disease, although no benefits were obtained from short-term treatment.

Aims
To evaluate the effect of long-term lithium treatment on cognitive and biological outcomes in people with amnestic mild cognitive impairment (aMCI).

Method
Forty-five participants with aMCI were randomised to receive lithium (0.25–0.5 mmol/l) ($n=24$) or placebo ($n=21$) in a 12-month, double-blind trial. Primary outcome measures were the modification of cognitive and functional test scores, and concentrations of cerebrospinal fluid (CSF) biomarkers (amyloid-beta peptide ($A\beta_{42}$), total tau (T-tau), phosphorylated-tau) (P-tau). Trial registration: NCT01055392.

Results
Lithium treatment was associated with a significant decrease in CSF concentrations of P-tau ($P=0.03$) and better perform-ance on the cognitive subscale of the Alzheimer's Disease Assessment Scale and in attention tasks. Overall tolerability of lithium was good and the adherence rate was 91%.

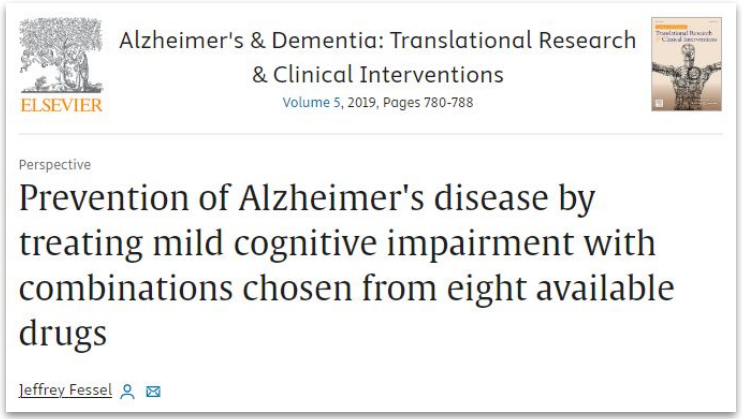
Conclusions
The present data support the notion that lithium has disease-modifying properties with potential clinical implications in the prevention of Alzheimer's disease.

Declaration of interest
None.

- Lithium level 0.25 - 0.5
- 1 year
- Improved cognition
- Decrease in tau proteins

Forlenza OV, Diniz BS, Radanovic M, et al. Disease modifying properties of long-term lithium treatment for amnestic mild cognitive impairment: randomised controlled trial. Br J Psychiatry. 2011;198(5):351-356.

Lithium – Just how special is it?



Alzheimer's & Dementia: Translational Research & Clinical Interventions
Volume 5, 2019, Pages 780-788

Perspective

Prevention of Alzheimer's disease by treating mild cognitive impairment with combinations chosen from eight available drugs

Jeffrey Fessel

There are approximately **25 pathways** at fault in development of dementia.

Lithium targets 16 of the 25, more than any other chemical.

Dantrolene	Ca^{2+} release↓; memory↑; synaptic transmission↑; neural regeneration↑; neuronal apoptosis↓; amyloid load↓; BCl2↑
Erythropoietin	Memory↑; synaptic plasticity↑; neural regeneration↑; AKT activated; BCl2↑; Bax↓; pTau↓; EPCs↑; astrocytes↑; insulin resistance↓.
Lithium	Neuronal excitability↓; synaptogenesis↑; plasticity↑; IMP-ase↓; unfolded protein response↑; autophagy↑; NF tangles↓; BCl2↑; VEGF↑; TGF-β↑; activated Wnt/β-catenin↑; oxidative stress↓; amyloid load↓; mitochondrial function↑; insulin resistance↓. **16 of the 25 pathways**
Memantine	Ca^{2+}-induced excitotoxicity↓; NO-induced excitotoxicity↓; mitochondrial function↑.
Minocycline	JNK↓; amyloid↓; insulin resistance↓; mitochondrial function↑; brain immunity↓; transmitted systemic immunity↓.
Piracetam	Mitochondrial fusion/function↑; neuronal excitability↓; synaptic markers↑; plasticity↑; neurite outgrowth↑; cognition↑; oxidative stress↓; cerebral microcirculation↑.
Riluzole	Hyper-pTau↓; cognitive decline↓; excessive glutamate release & excitotoxicity↓; EEAT↑; $A\beta_{40-42}$↓; synaptic transmission↑ (downregulated genes for neurotransmission become upregulated).
Silymarin/ silybin (milk thistle)	Memory↑; dendritic spines↑; learning↑; soluble and insoluble Aβ↓; JNK↓; ERK↓; antioxidative enzymes↑; insulin resistance↓; decreased dopamine in PFC↓; brain immunity↓; transmitted systemic immunity↓.

Lithium in drinking water

Meta-Analysis > Aust N Z J Psychiatry. 2021 Feb;55(2):139-152. doi: 10.1177/0004867420963740. Epub 2020 Oct 13.

The association between lithium in drinking water and neuropsychiatric outcomes: A systematic review and meta-analysis from across 2678 regions containing 113 million people

Brenton Eyre-Watt [1], Eesharnan Mahendran [2], Shuichi Suetani [1 2 3 4], Joseph Firth [5 6], Steve Kisely [2 7], Dan Siskind [2 3 7]

Higher lithium concentrations were associated with

Lithium in drinking water

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Higher lithium concentrations were associated with

- reduced suicide rates

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Higher lithium concentrations were associated with

- reduced suicide rates
- reduced homicide rates

Lithium in drinking water

October 2017

Association of Lithium in Drinking Water With the Incidence of Dementia

Lars Vedel Kessing, MD, DMSc[1]; Thomas Alexander Gerds, MSc, PhD[2]; Nikoline Nygård Knudsen, MSc[3]; et al

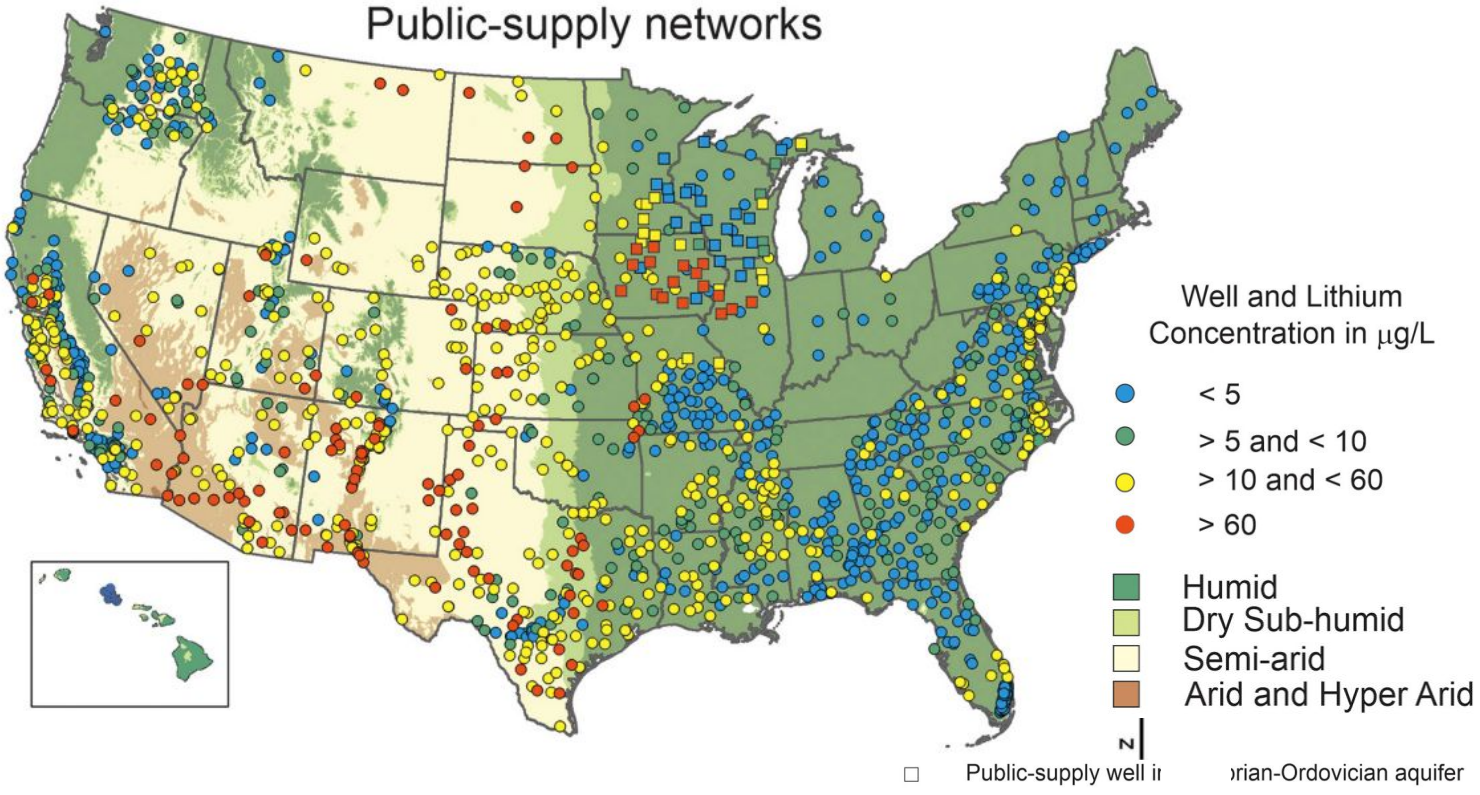
» Author Affiliations | Article Information

JAMA Psychiatry. 2017;74(10):1005-1010. doi:10.1001/jamapsychiatry.2017.2362

Higher lithium concentrations were associated with

- reduced suicide rates
- reduced homicide rates
- reduced all-cause dementia

Lithium in drinking water

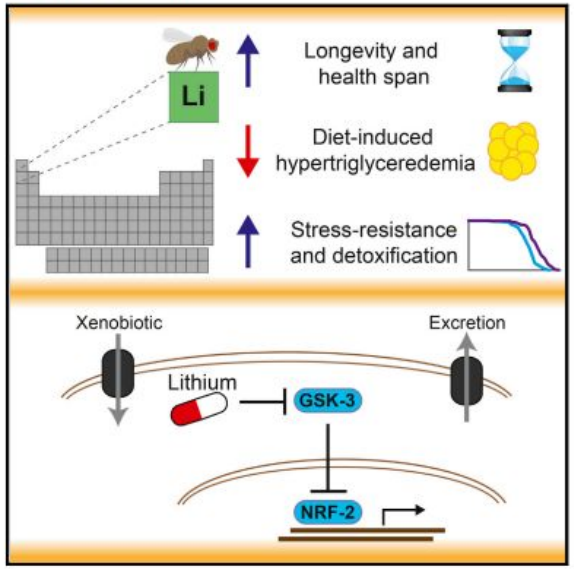


Bruce D. Lindsey, et al. Lithium in groundwater used for drinking-water supply in the United States,Science of The Total Environment,Volume 767, 2021.

Lithium – anti-aging

Lithium Promotes Longevity through GSK3/NRF2-Dependent Hormesis

Graphical Abstract



Authors

Jorge Iván Castillo-Quan, Li Li, Kerri J. Kinghorn, ..., John Hardy, Ivana Bjedov, Linda Partridge

Correspondence

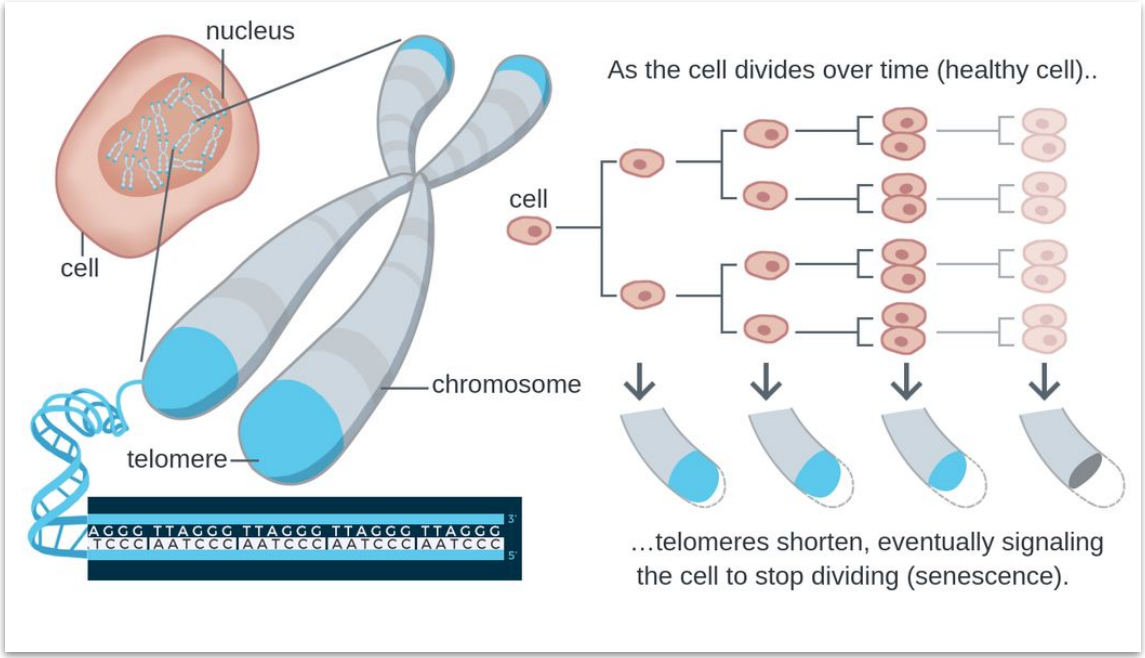
l.partridge@ucl.ac.uk

In Brief

The mood stabilizer lithium has been shown to extend lifespan in organisms ranging from yeast to flies. Castillo-Quan et al. show that lithium promotes longevity through GSK-3 inhibition and subsequent NRF-2 activation, suggesting that GSK3 is a possible drug target that might affect aging.

Castillo-Quan et al., Lithium Promotes Longevity through GSK3/NRF2-Dependent Hormesis, Cell Reports (2016) http://dx.doi.org/10.1016

Lithium – anti-aging



Telomere shortening is a biomarker of aging.

https://theory.labster.com/telomere-length/

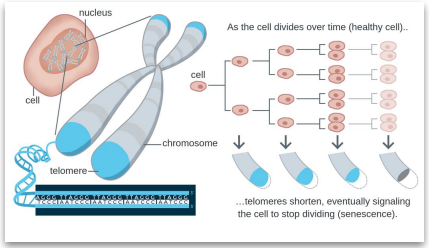
Lithium – anti-aging

frontiers in Psychiatry

REVIEW
published: 29 September 2020
doi: 10.3389/fpsyt.2020.586083

Lithium and the Interplay Between Telomeres and Mitochondria in Bipolar Disorder

Martin Lundberg[1,2], Vincent Millischer[1,2], Lena Backlund[1,2], Lina Martinsson[3], Peter Stenvinkel[4], Carl M. Sellgren[3,5], Catharina Lavebratt[1,2] and Martin Schalling[1,2]*



(Leukocytes of) lithium-treated bipolar patients had **35% longer telomeres** than controls.

Lundberg M, Millischer V, Backlund L, Martinsson L, Stenvinkel P, Sellgren CM, Lavebratt C, Schalling M. Lithium and the Interplay Between Telomeres and Mitochondria in Bipolar Disorder. Front Psychiatry. 2020 Sep 29;11:586083.
Martinsson L, Wei Y, Xu D, Melas PA, Mathé AA, Schalling M, et al. Long-term lithium treatment in bipolar disorder is associated with longer leukocyte telomeres. Transl Psychiatry (2013) 3(5):e261. 10.1038/tp.2013.37

Lithium – cardioprotection

Cardioprotective potential of lithium and role of fractalkine in euthymic patients with bipolar disorder

Pao-Huan Chen[1,2,3], Cheng-Yi Hsiao[4,5,6,7], Shuo-Ju Chiang[8], Ruei-Siang Shen[9], Yen-Kuang Lin[10], Kuo-Hsuan Chung[1,2,3] and Shang-Ying Tsai[1,2,3]

Australian & New Zealand Journal of Psychiatry
2023, Vol. 57(1) 104–114
DOI: 10.1177/00048674211062532

Lithium may **protect cardiac structure and function** in patients with bipolar disorder.

Lithium – improved bone mineral density

Literature Review | Article | Full-text available

The Skeletal-Protecting Action and Mechanisms of Action for Mood-Stabilizing Drug Lithium Chloride: Current Evidence and Future Potential Research Areas

April 2020 · Frontiers in Pharmacology 11 · Follow journal

DOI: 10.3389/fphar.2020.00430

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Sok Kuan Wong · Kok Yong Chin · Soelaiman Ima-Nirwana

- Lithium regulates expression of osteoblastic- and osteoclastic-specific genes
- Improved bone density
- Fewer fractures

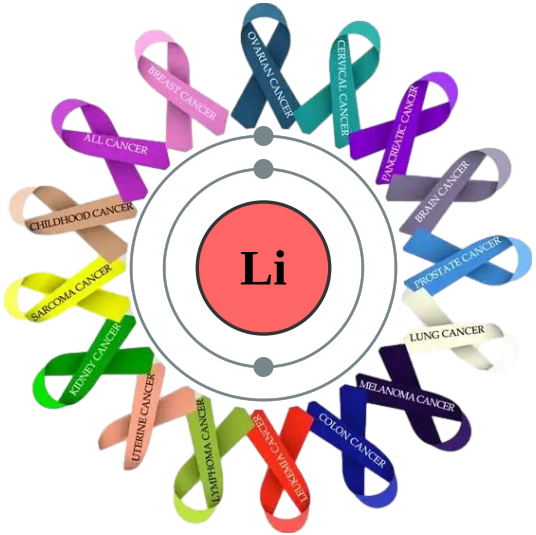
Lithium – anti-tumor effects

Cancers (Basel). 2023 Feb; 15(4): 1095.
Published online 2023 Feb 8. doi: 10.3390/cancers15041095

Lithium in Cancer Therapy: Friend or Foe?

Chunhao Yang,[1,†] Bo Zhu,[1,*†] Mingjie Zhan,[1] and Zi-Chun Hua[1,2,*]

Alfonso Baldi, Academic Editor



- Much evidence shows lithium **prevents** the development of different cancers, including leukemia, melanoma, lung cancer, and pancreatic cancer.
- Lithium **prevents tumor metastasis**
- Lithium may increase cancer treatment efficacy while reducing side effects, suggesting that it can be used as an **adjunctive therapy**.

Yang C, Zhu B, Zhan M, Hua ZC. Lithium in Cancer Therapy: Friend or Foe? Cancers (Basel). 2023 Feb 8;15(4):1095.

Lithium – renal risk

Long-term effect of lithium maintenance therapy on estimated glomerular filtration rate in patients with affective disorders: a population-based cohort study

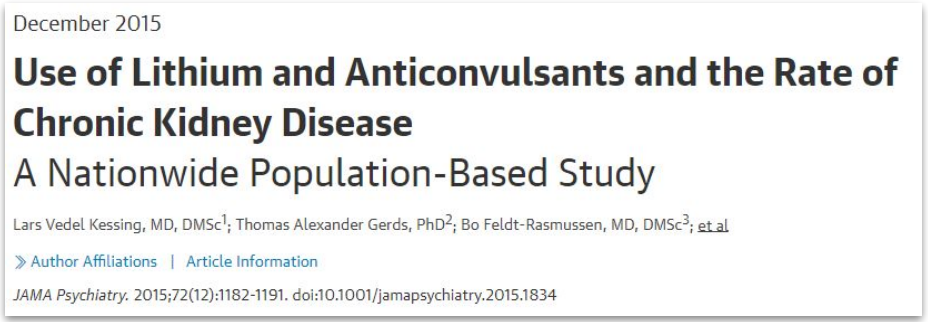
Dr Stefan Clos MSc [a], Petra Rauchhaus ClinStat [b], Alison Severn PhD [c], Lynda Cochrane PhD [d], Prof Peter T Donnan PhD [d]

Our analysis suggests **no effect** of stable lithium maintenance therapy (lithium levels in therapeutic range) on the rate of change in **eGFR** over time.

Our results therefore contradict the idea that long-term lithium therapy is associated with nephrotoxicity in the absence of episodes of acute intoxication.

Stefan Clos, Petra Rauchhaus, Alison Severn, Lynda Cochrane, Peter T Donnan, Long-term effect of lithium maintenance therapy on estimated glomerular filtration rate in patients with affective disorders: a population-based cohort study, The Lancet Psychiatry, Volume 2, Issue 12, 2015.

Lithium – renal risk



December 2015

Use of Lithium and Anticonvulsants and the Rate of Chronic Kidney Disease

A Nationwide Population-Based Study

Lars Vedel Kessing, MD, DMSc[1]; Thomas Alexander Gerds, PhD[2]; Bo Feldt-Rasmussen, MD, DMSc[3]; et al

» Author Affiliations | Article Information

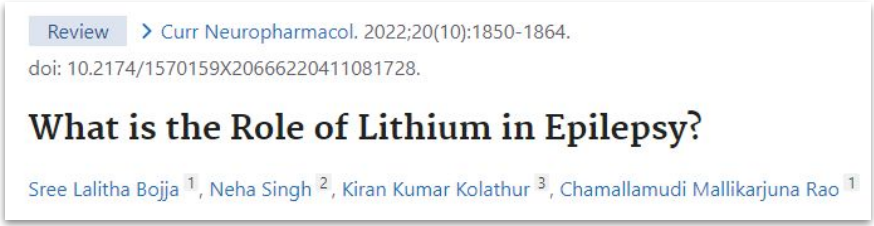
JAMA Psychiatry. 2015;72(12):1182-1191. doi:10.1001/jamapsychiatry.2015.1834

Maintenance treatment with lithium or anticonvulsants as practiced in modern care is associated with an increased rate of chronic kidney disease (CKD).

However, use of **lithium is <u>not</u> associated with** an increased rate of **<u>end-stage</u>** CKD.

Kessing LV, Gerds TA, Feldt-Rasmussen B, Andersen PK, Licht RW. Use of Lithium and Anticonvulsants and the Rate of Chronic Kidney Disease: A Nationwide Population-Based Study. JAMA Psychiatry. 2015;72(12):1182–1191. doi:10.1001/jamapsychiatry.2015.1834

Lithium – antiepileptic effects



Review > Curr Neuropharmacol. 2022;20(10):1850-1864.
doi: 10.2174/1570159X20666220411081728.

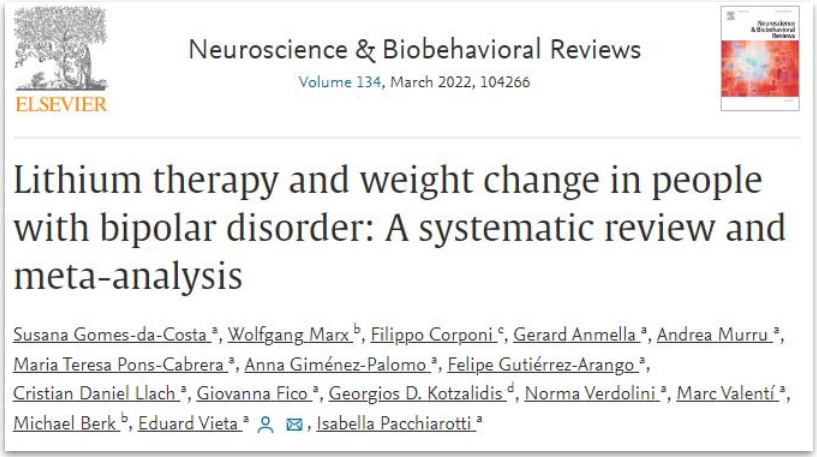
What is the Role of Lithium in Epilepsy?

Sree Lalitha Bojja [1], Neha Singh [2], Kiran Kumar Kolathur [3], Chamallamudi Mallikarjuna Rao [1]

Lithium holds a significant interest in epilepsy, where the past reports expose its non-specific proconvulsant action, followed lately by **numerous studies for anticonvulsant action**.

Lithium does cause seizures in overdose.

Lithium – weight gain?



Neuroscience & Biobehavioral Reviews
Volume 134, March 2022, 104266

Lithium therapy and weight change in people with bipolar disorder: A systematic review and meta-analysis

Susana Gomes-da-Costa [a], Wolfgang Marx [b], Filippo Corponi [c], Gerard Anmella [a], Andrea Murru [a], Maria Teresa Pons-Cabrera [a], Anna Giménez-Palomo [a], Felipe Gutiérrez-Arango [a], Cristian Daniel Llach [a], Giovanna Fico [a], Georgios D. Kotzalidis [d], Norma Verdolini [a], Marc Valentí [a], Michael Berk [b], Eduard Vieta [a], Isabella Pacchiarotti [a]

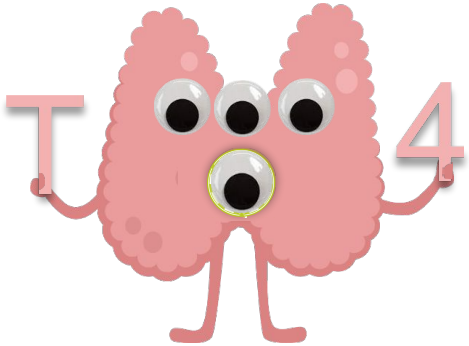
Weight change with lithium was **not clinically or statistically significant**.

Weight change with lithium did not differ from placebo.

Lithium for depression

Evidence for lithium as adjunctive therapy for unipolar depression is stronger than its evidence for bipolar depression.

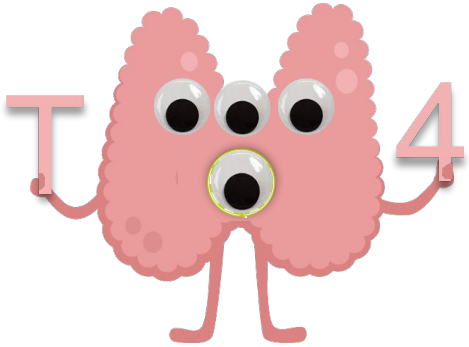
Triiodothyronine (CYTOMEL) – T3 thyroid hormone



“Four-I’d monster”

“Three-I’d monster”

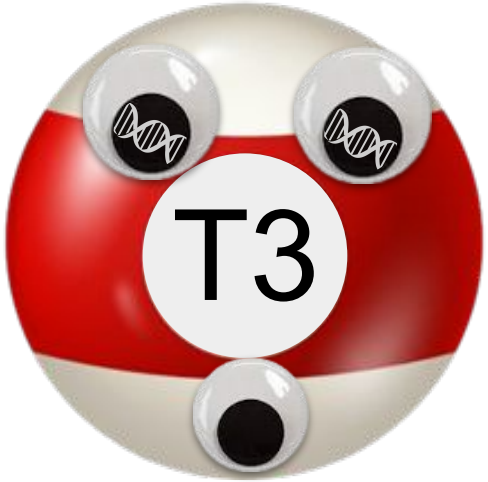
Triiodothyronine (CYTOMEL) – T3 thyroid hormone



“Four-I’d monster”

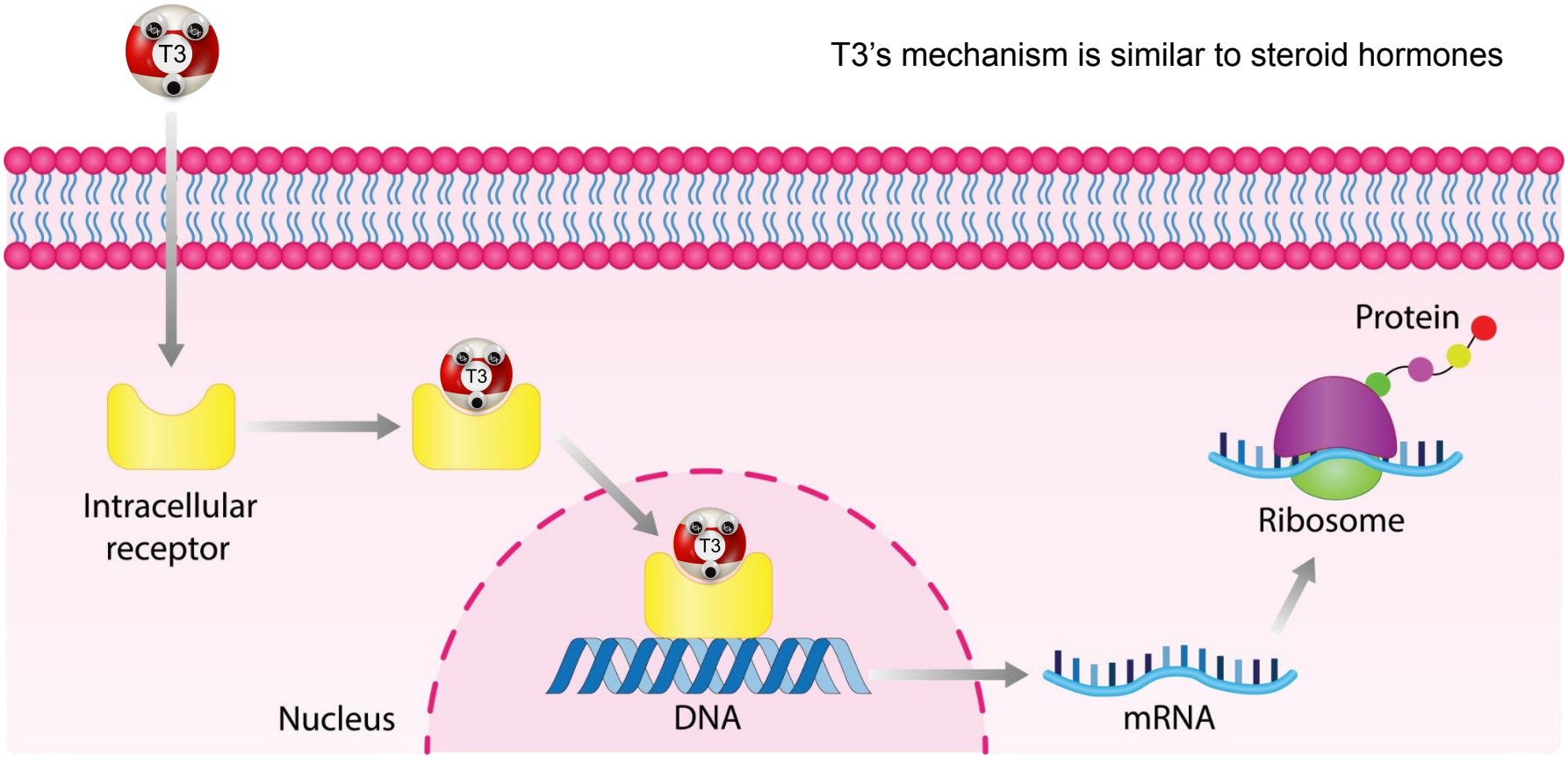
“Three-I’d monster”

Transcription activator

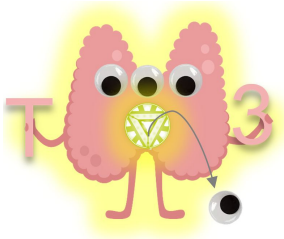


Triiodothyronine (CYTOMEL) – T3 thyroid hormone

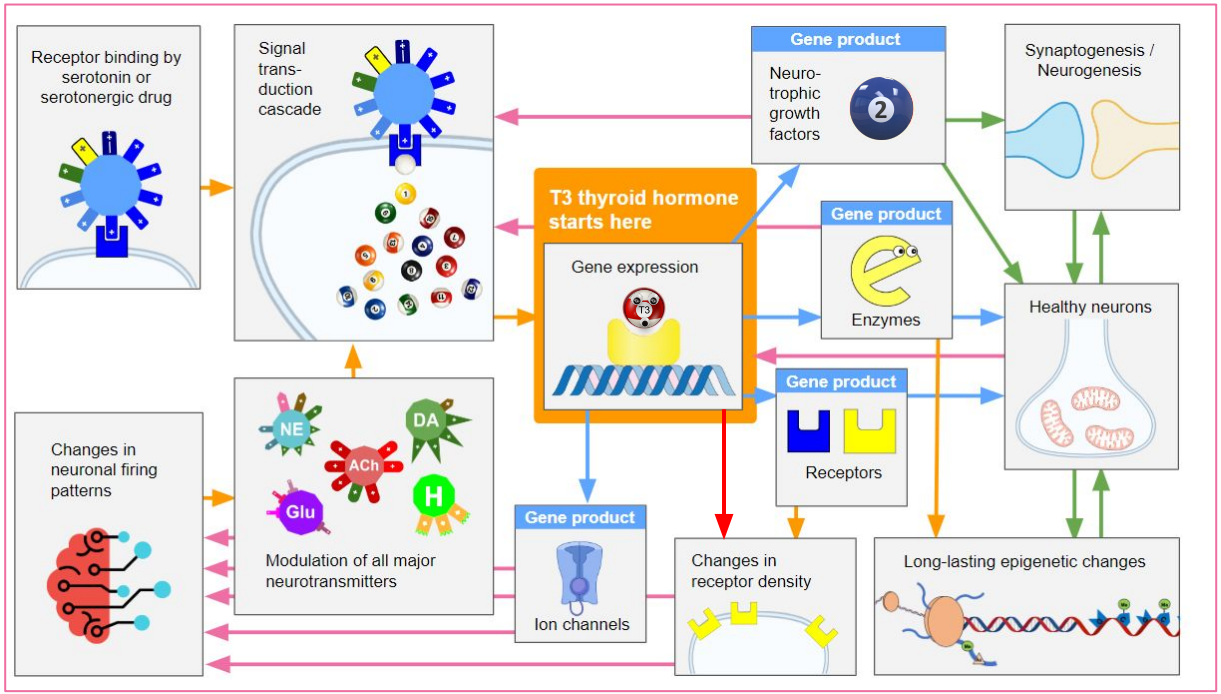
T3's mechanism is similar to steroid hormones



Triiodothyronine (CYTOMEL)



"Three-I'd monster"



Depression is associated with neuronal death, so it follows that decreasing neuronal stress, atrophy, and death would be associated with an antidepressant effect.

T3 has been shown to increase brain derived neurotrophic factor (BDNF).

There are changes in sensitivity and transcription of serotonin (5-HT) receptors (red arrow added).

Neuroscience-based Nomenclature

Pharmacological domains:

- Serotonin
- Dopamine
- Norepinephrine
- GABA
- Glutamate
- Histamine
- Acetylcholine
- Opioid
- Orexin
- Melatonin
- Adenosine
- Cannabinoid

Modes of action:

- Receptor agonist
- Receptor antagonist
- Receptor partial agonist
- Receptor inverse agonist
- Positive allosteric modulator
- Enzyme inhibitor
- Enzyme modulator
- Reuptake inhibitor
- Neurotransmitter releaser
- Neurotransmitter depletor
- Ion channel blocker
- Transcription activator

There’ll be ballicule of it