Psicosis

PARANOIDE	DESORGANIZADA	DEPRESIVA
-Proyec Paranoides	- Desorganiz conceptual	- Retraso psicomotor
-Actitud hostil	- Desorientación	- Apatía
- Act grandiosa y expans	- Desorientación/excitac	- Autocastigo/ans/culp

Psicosis: Vías de neurotransm

Teoría dopaminérgica

Hiperactividad en recep D2 vía mesolímbica

Hipoactividad en vía mesocortical

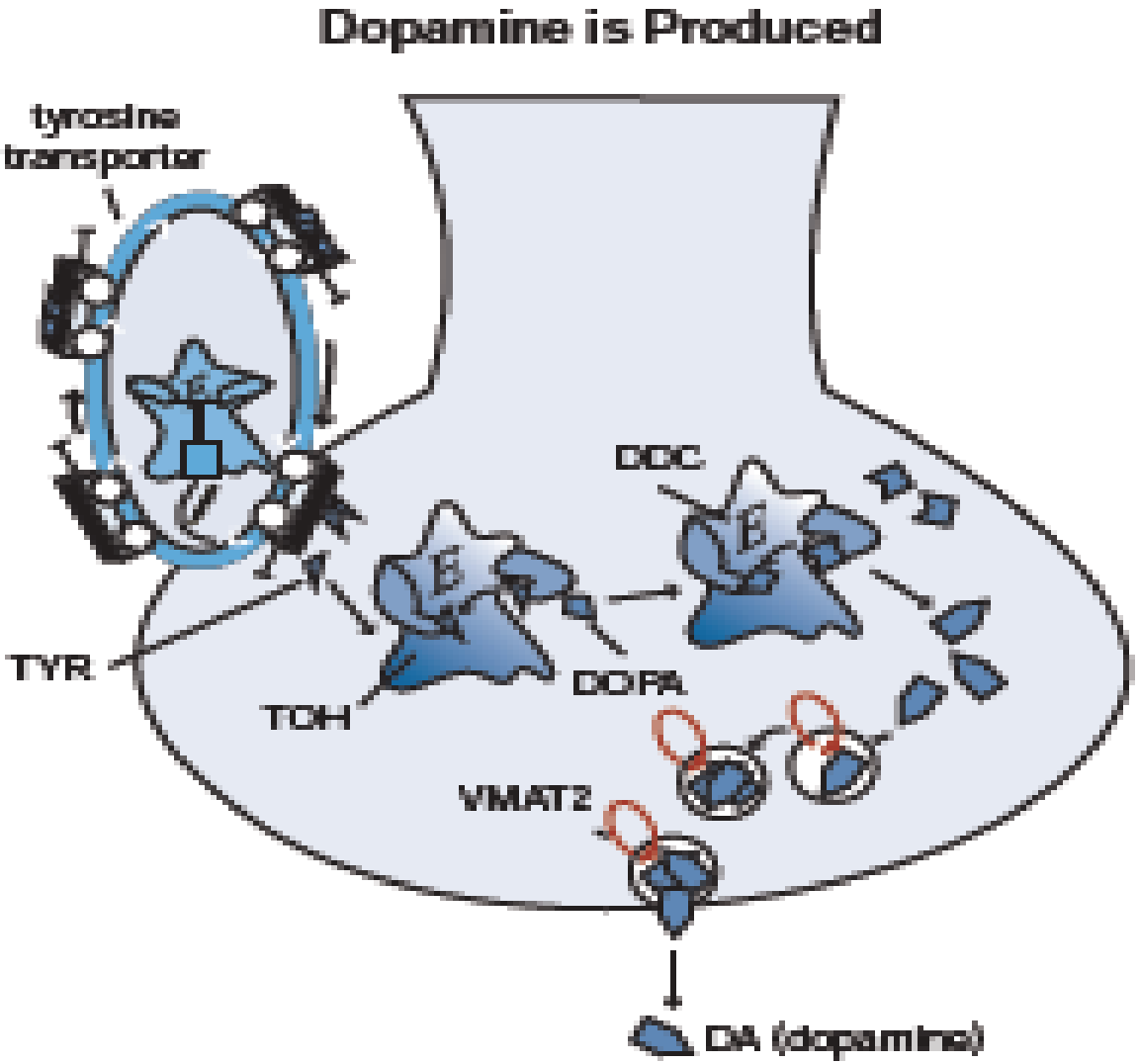
Teoría glutamatérgica

Hipofunción recep NMDA en neuronas GABA

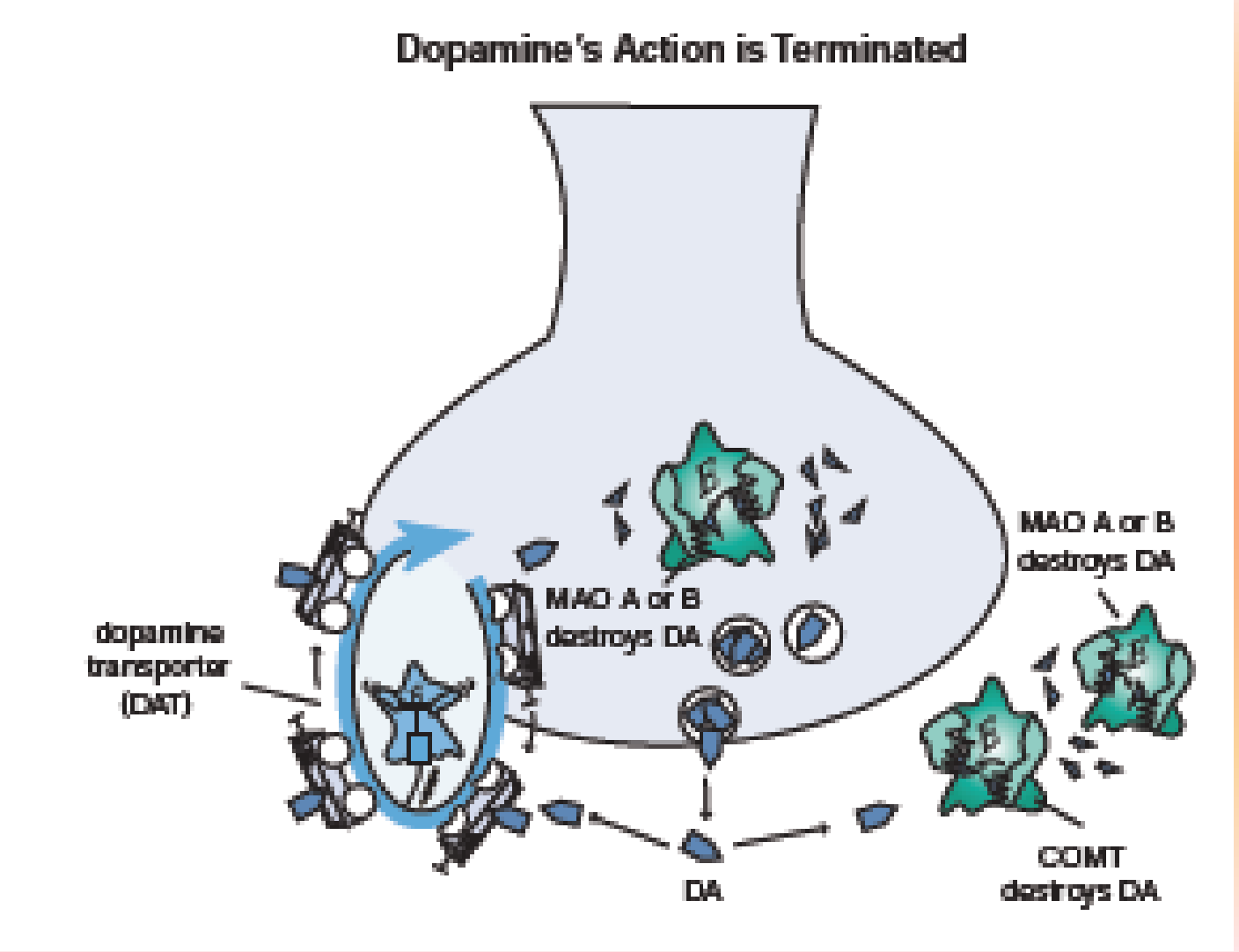
Teoría serotoninérgica

Hiperfunción recep 5HT2A en el córtex

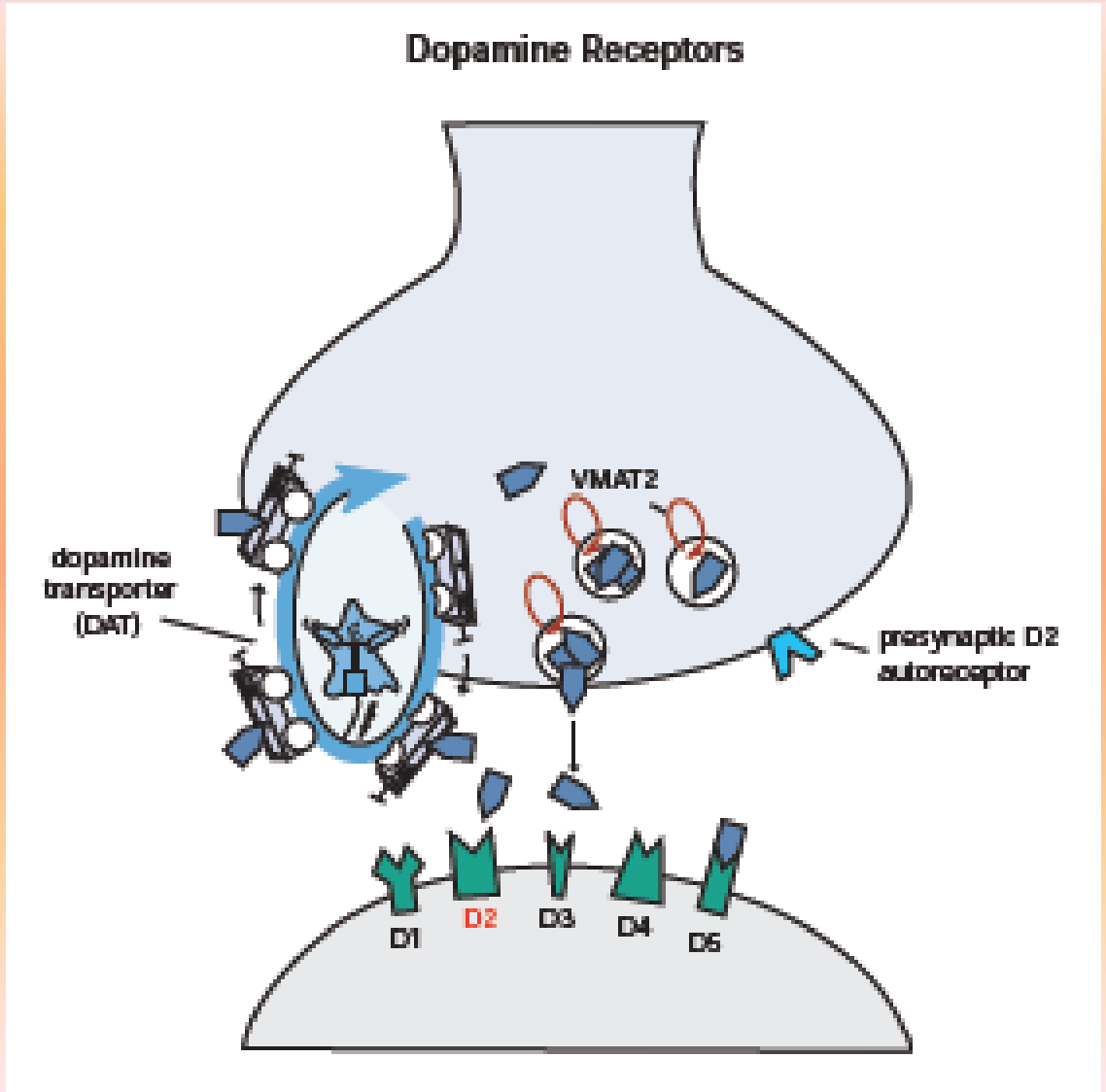
SÍNTESIS DE DOPAMINA



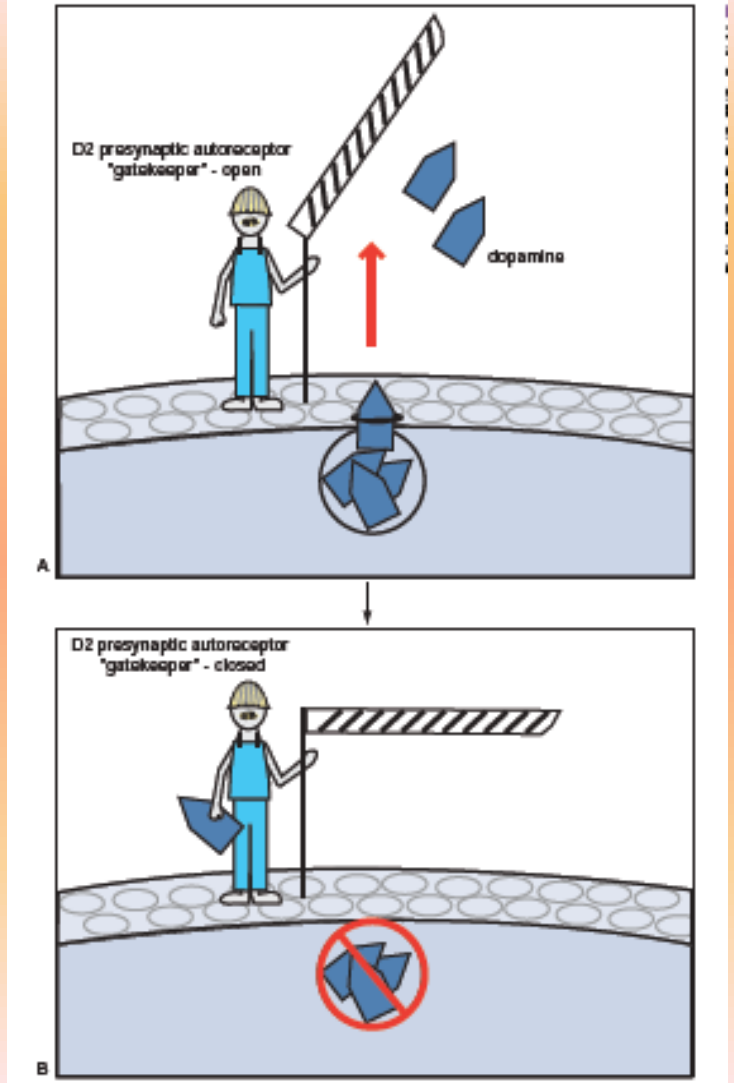
DEGRADACIÓN DE LA DOPAMINA



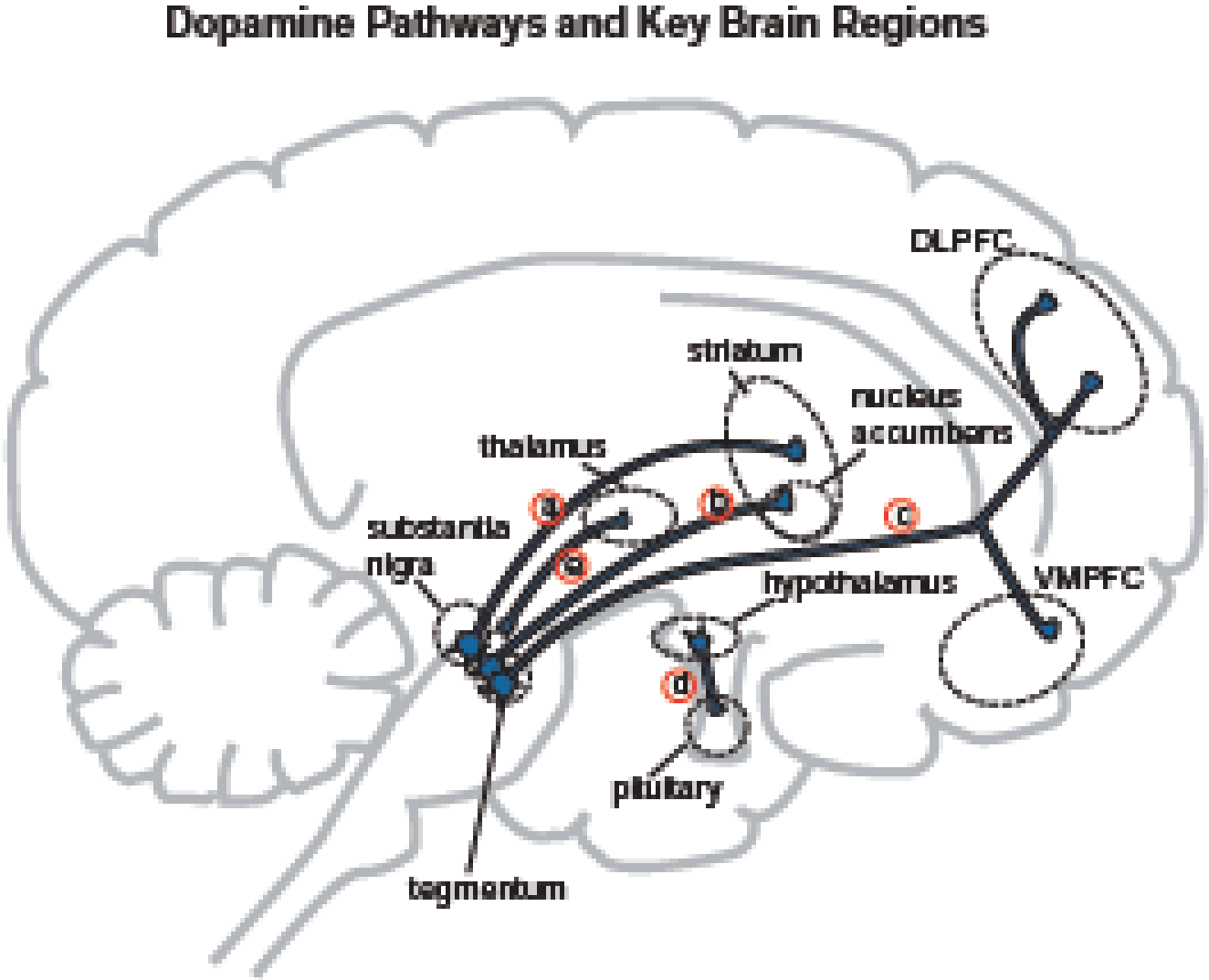
RECEPTORES DE DOPAMINA



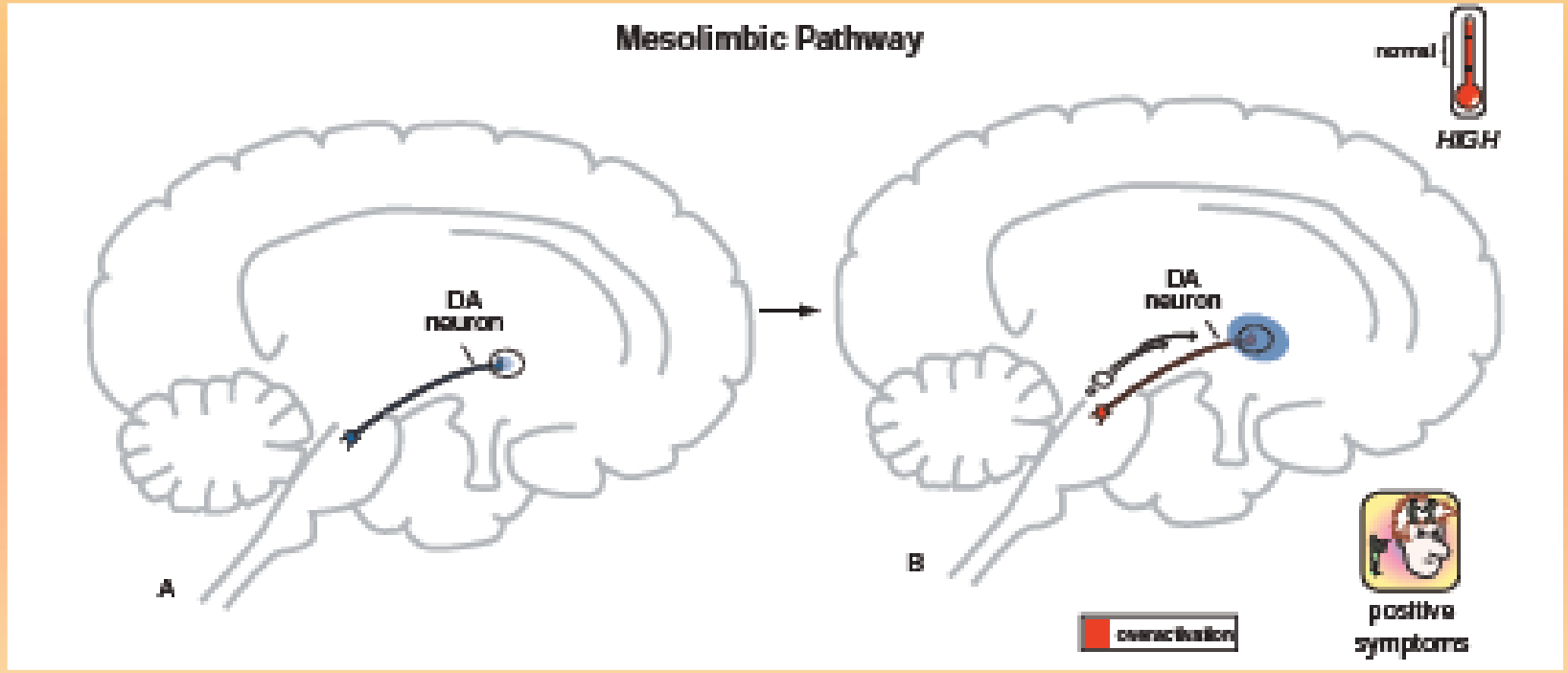
AUTORRECEPTOR D2



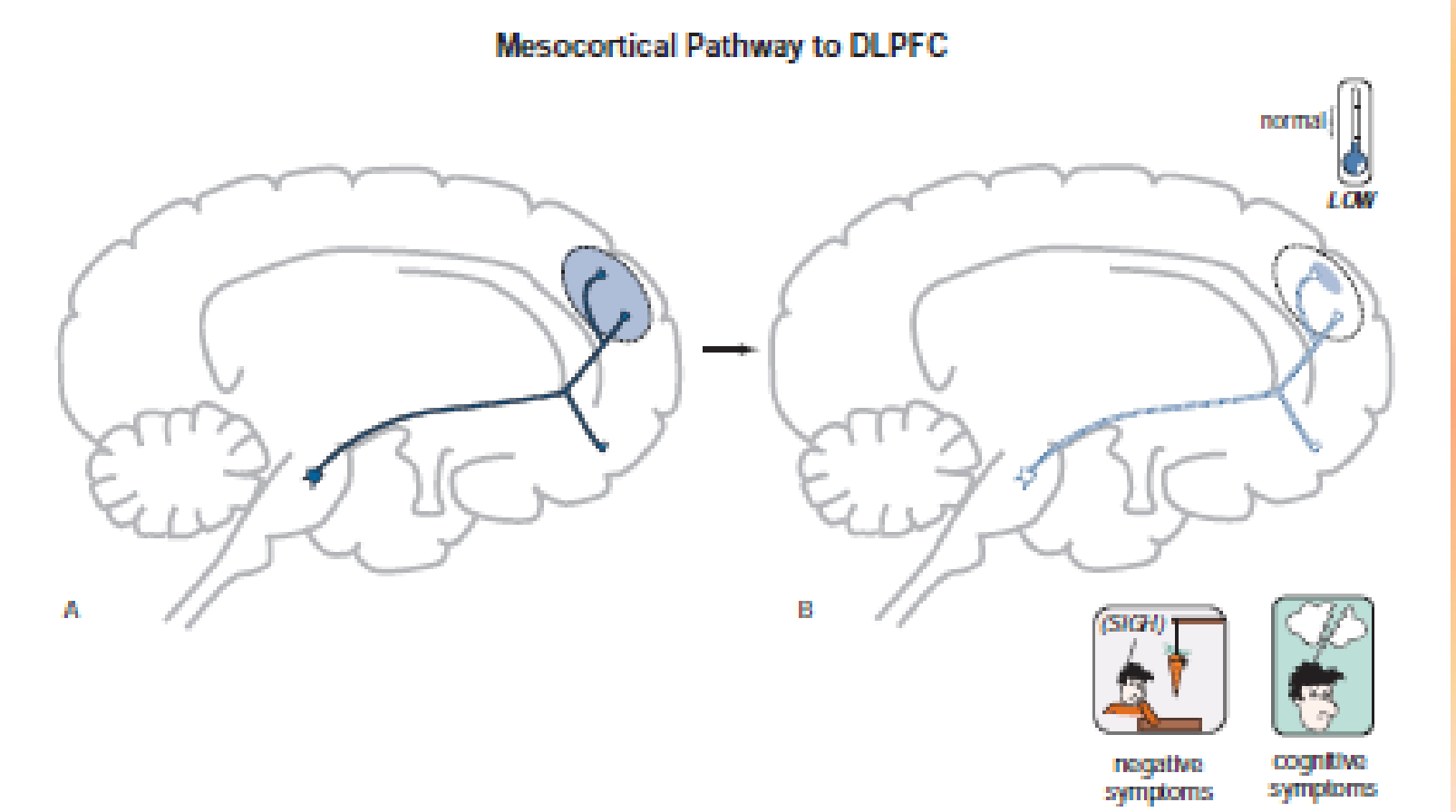
VÍAS DOPAMINÉRGICAS



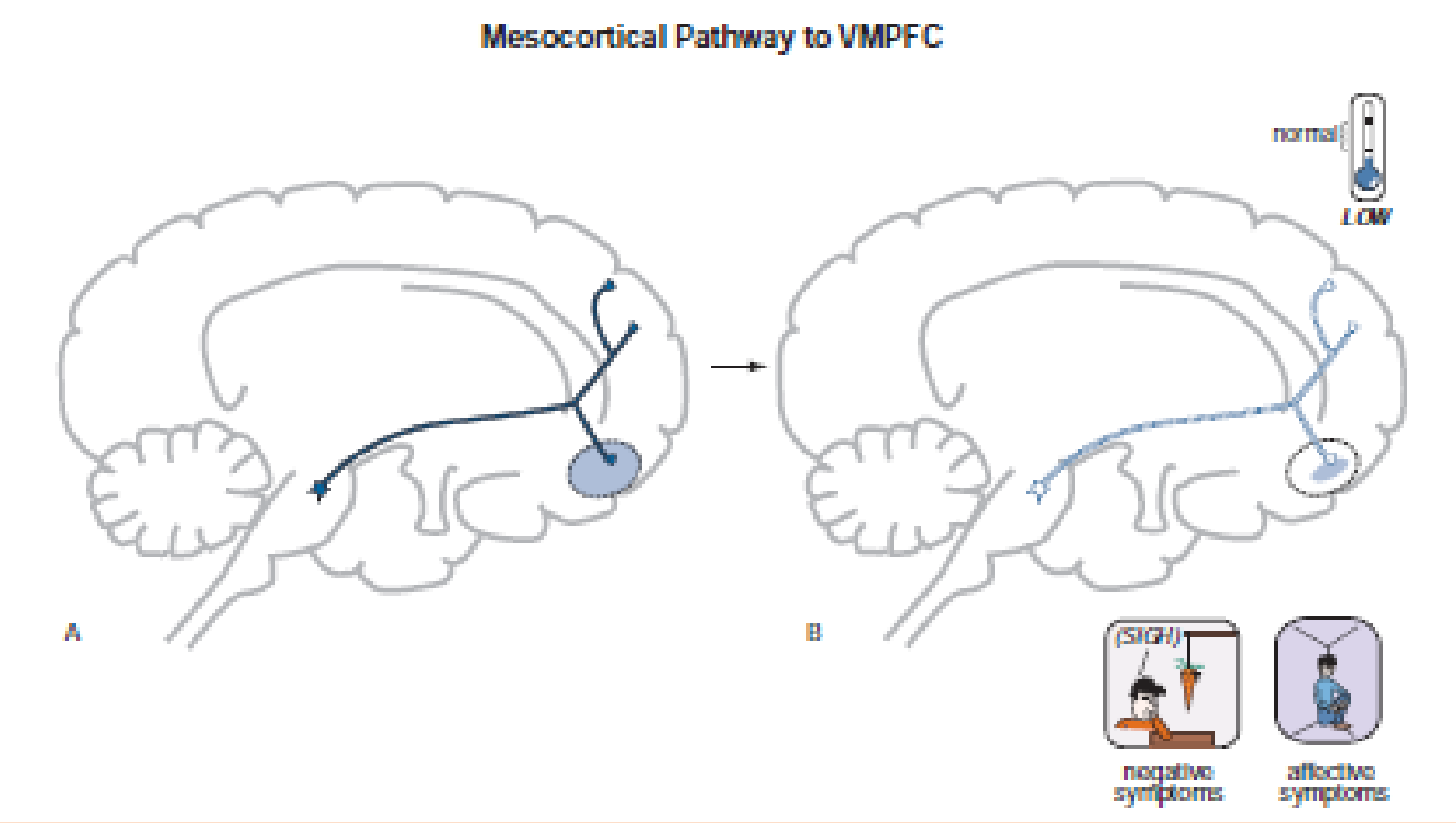
HIPERACTIVACIÓN VÍA M-L



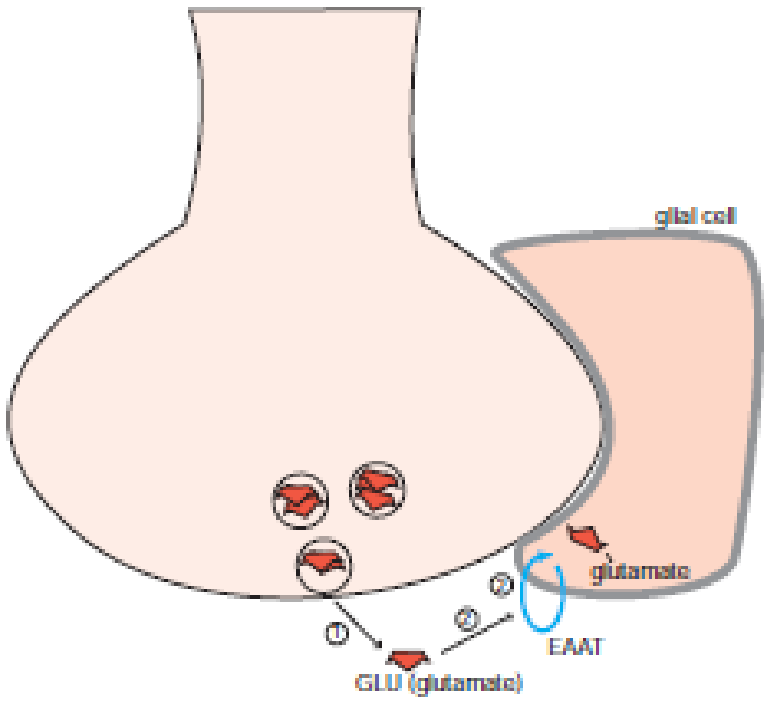
HIPOACTIVACIÓN VÍA M-C

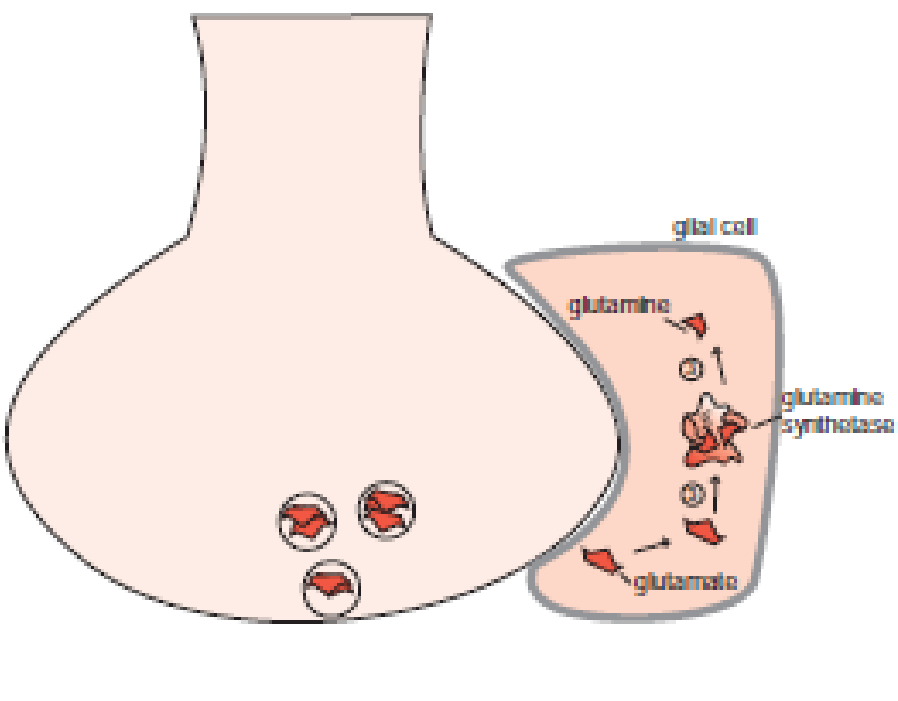


HIPOACTIVACIÓN VÍA M-C

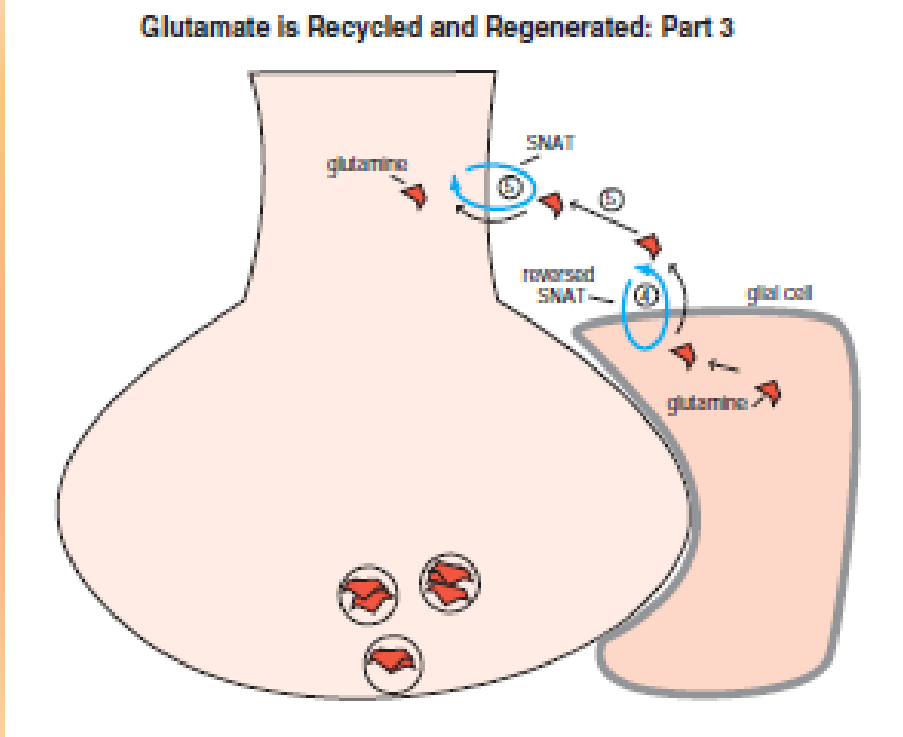


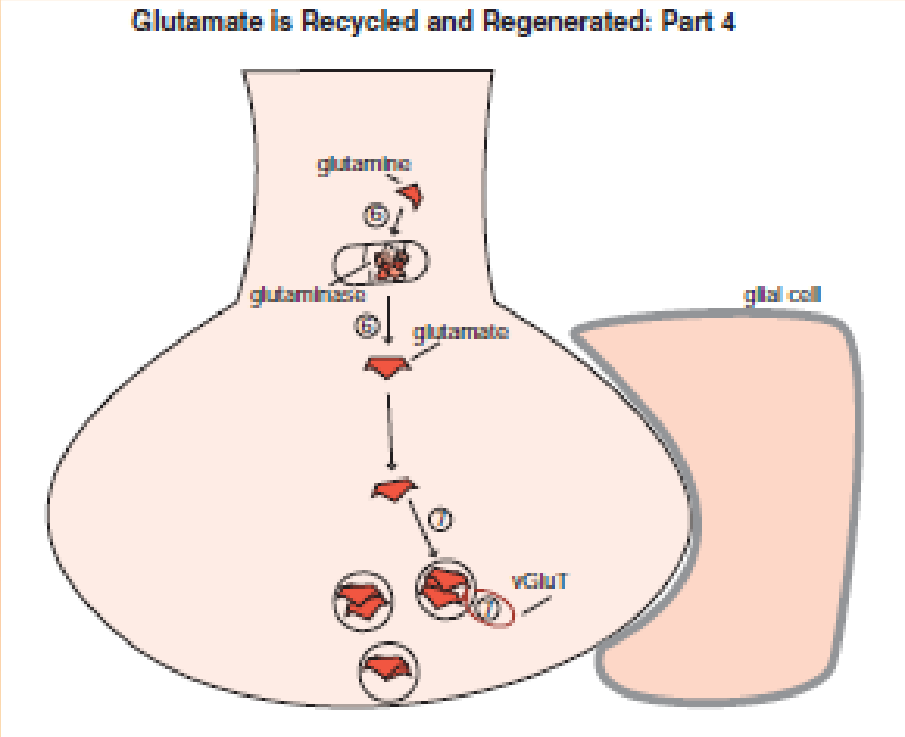
SÍNTESIS DE GLUTAMATO



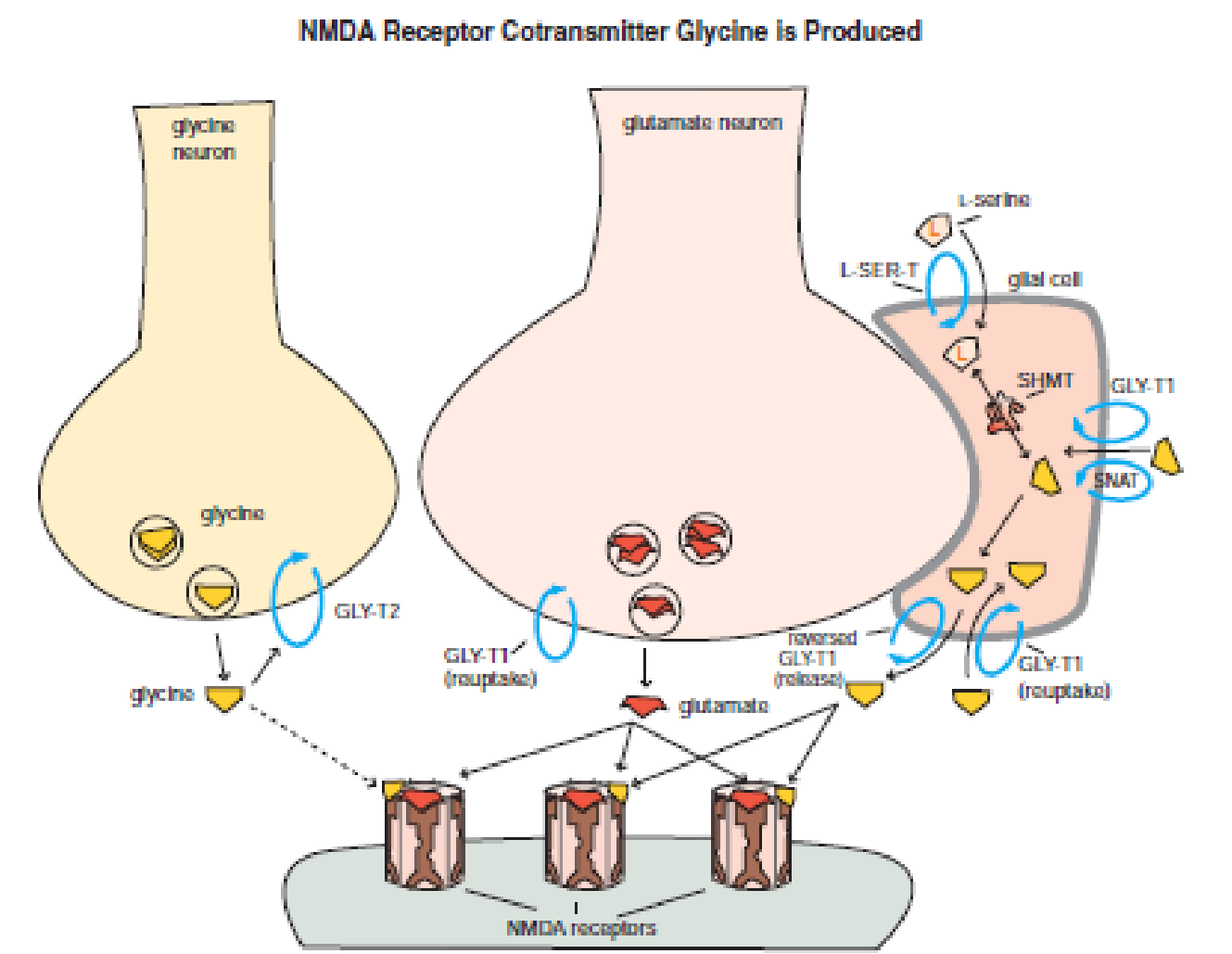


SÍNTESIS DE GLUTAMATO

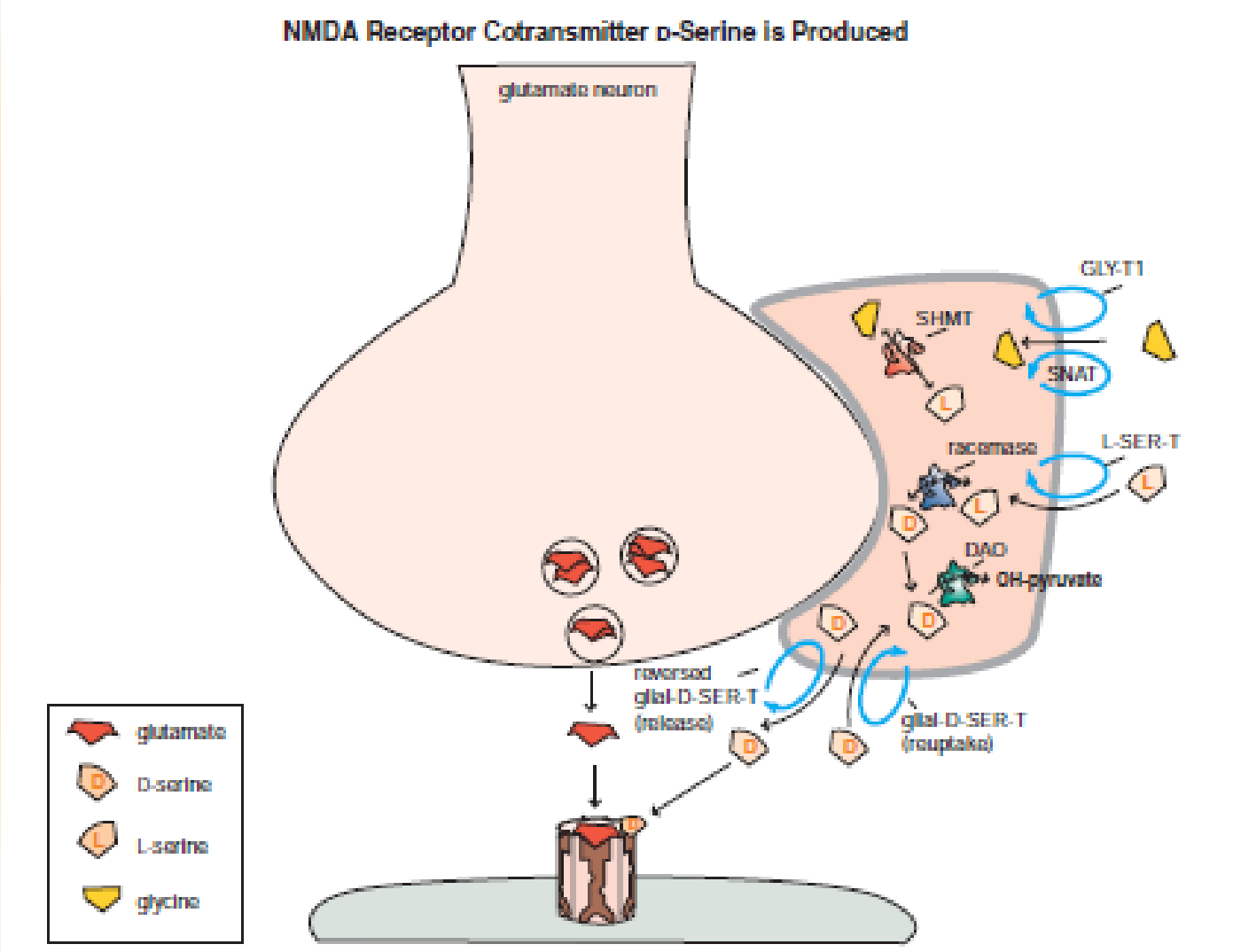




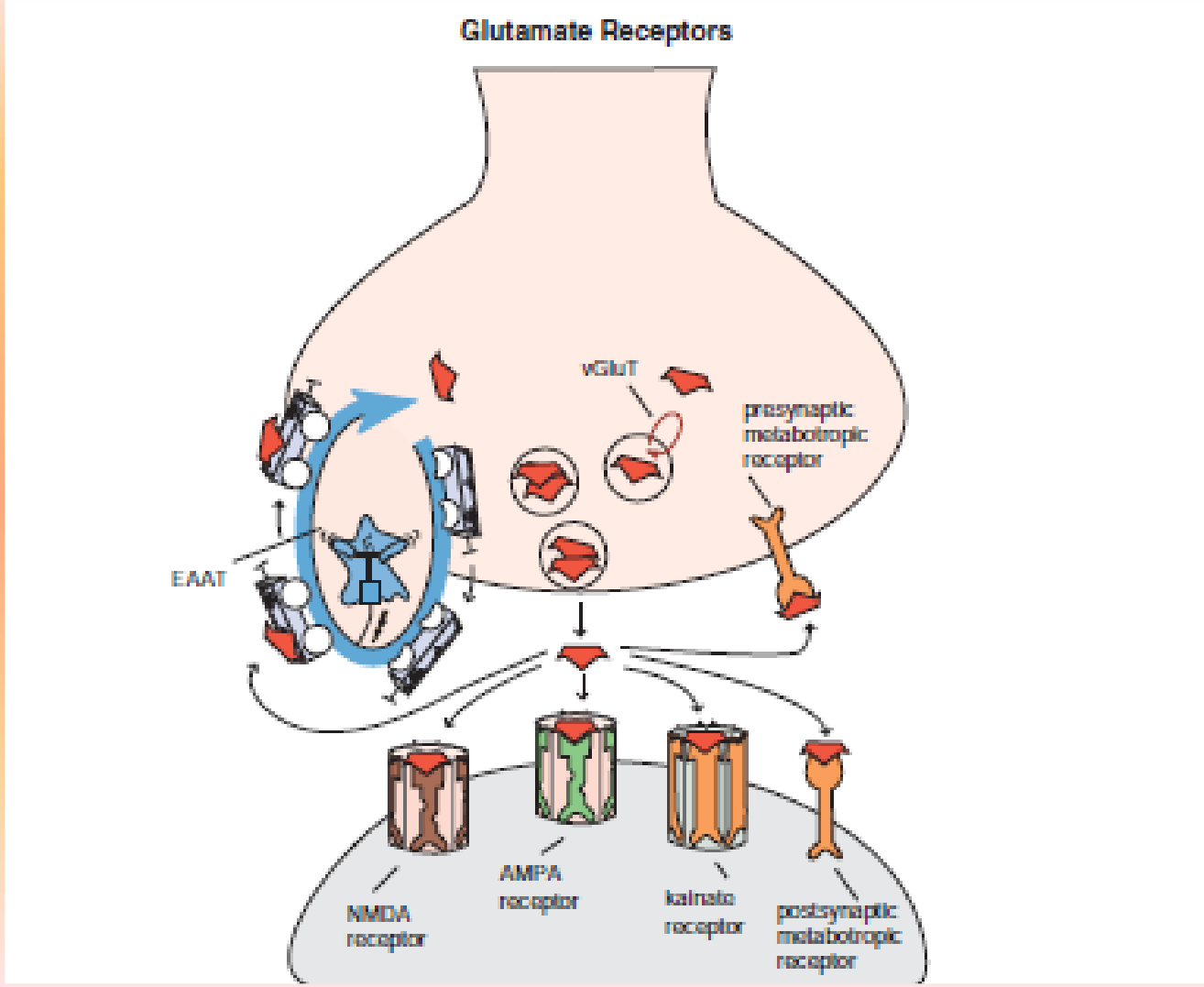
COTRANSMISIÓN RECEPTOR NMDA



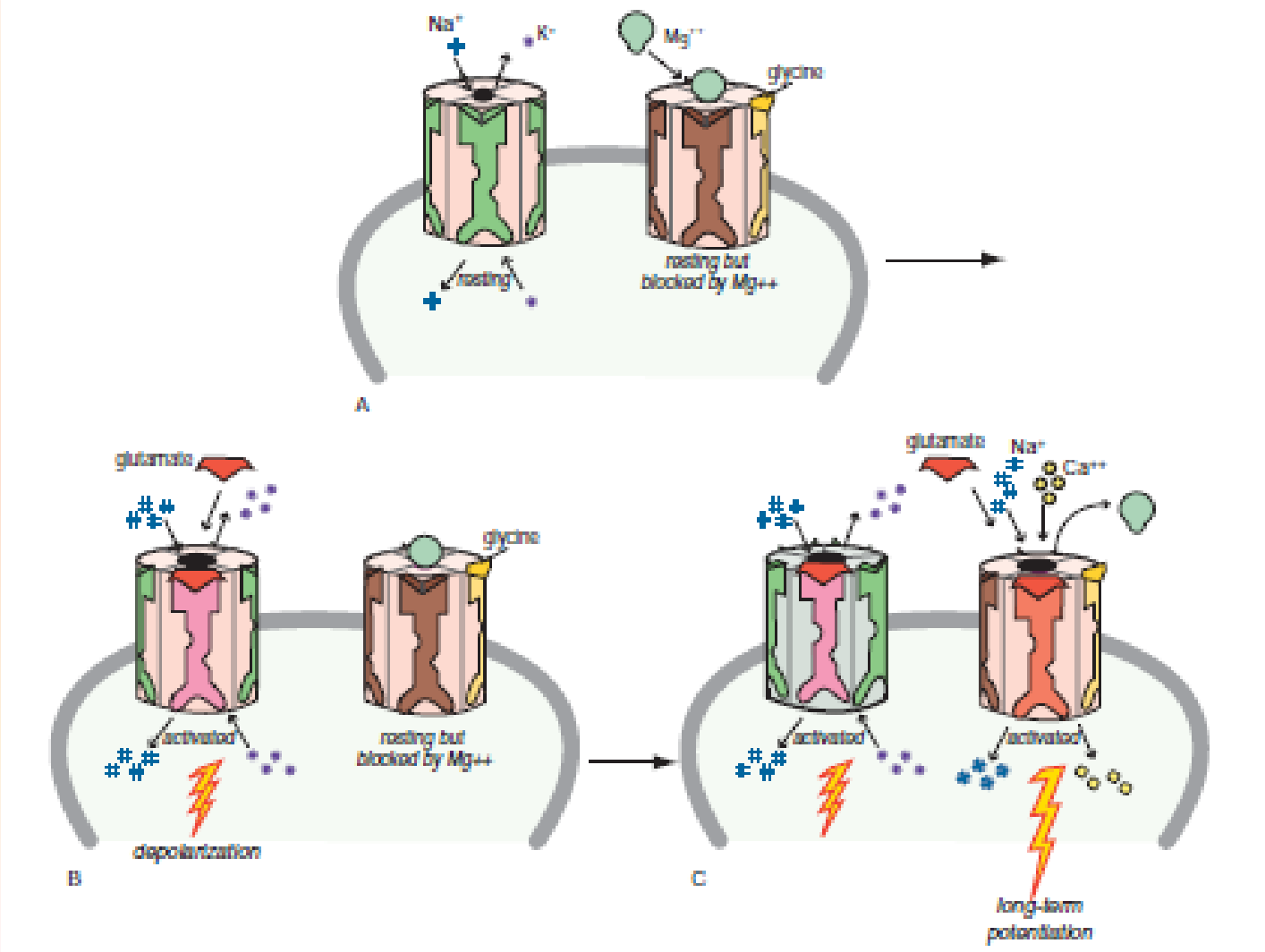
SÍNTESIS D-SERINA



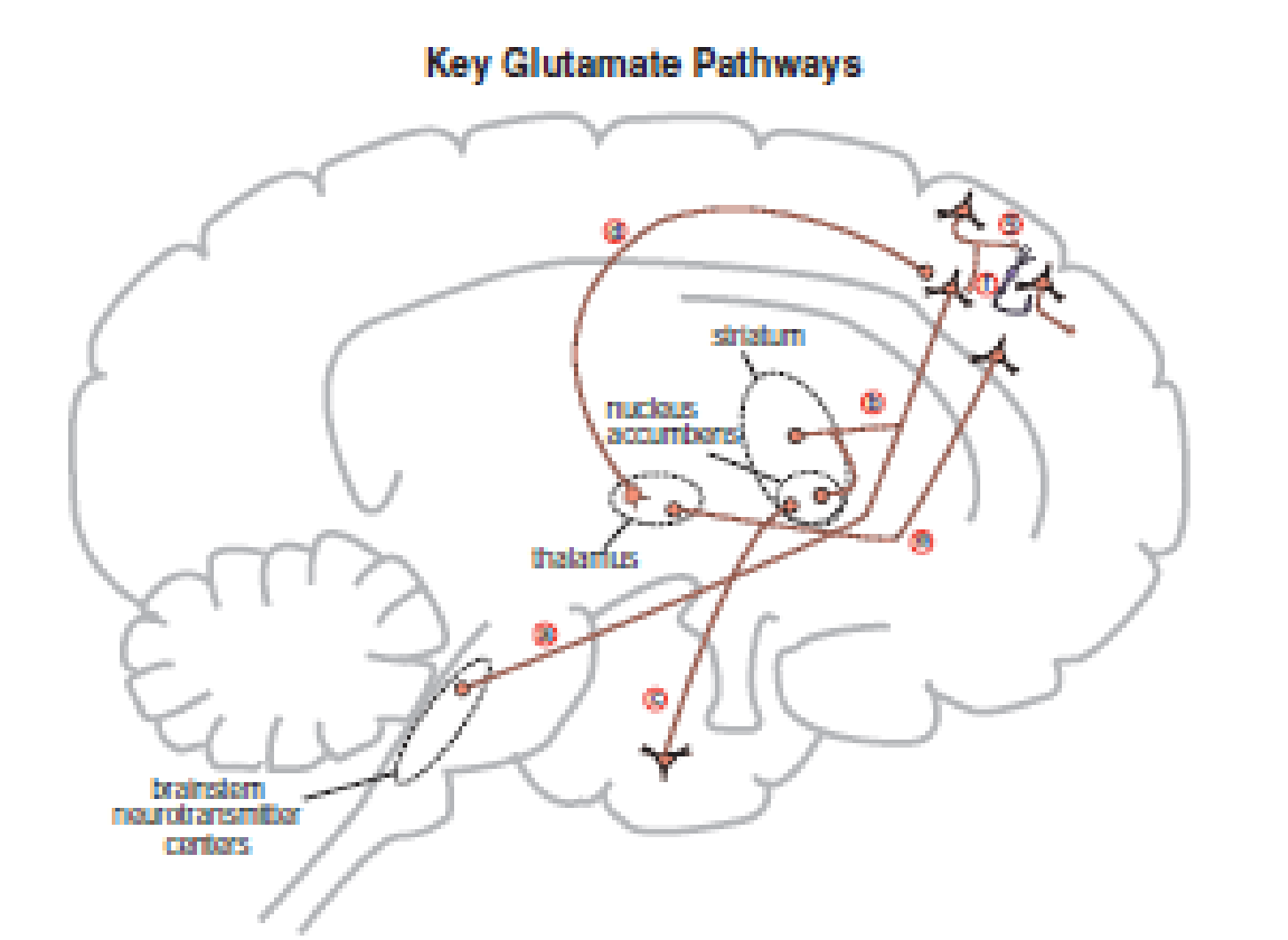
RECEPTORES DE GLUTAMATO



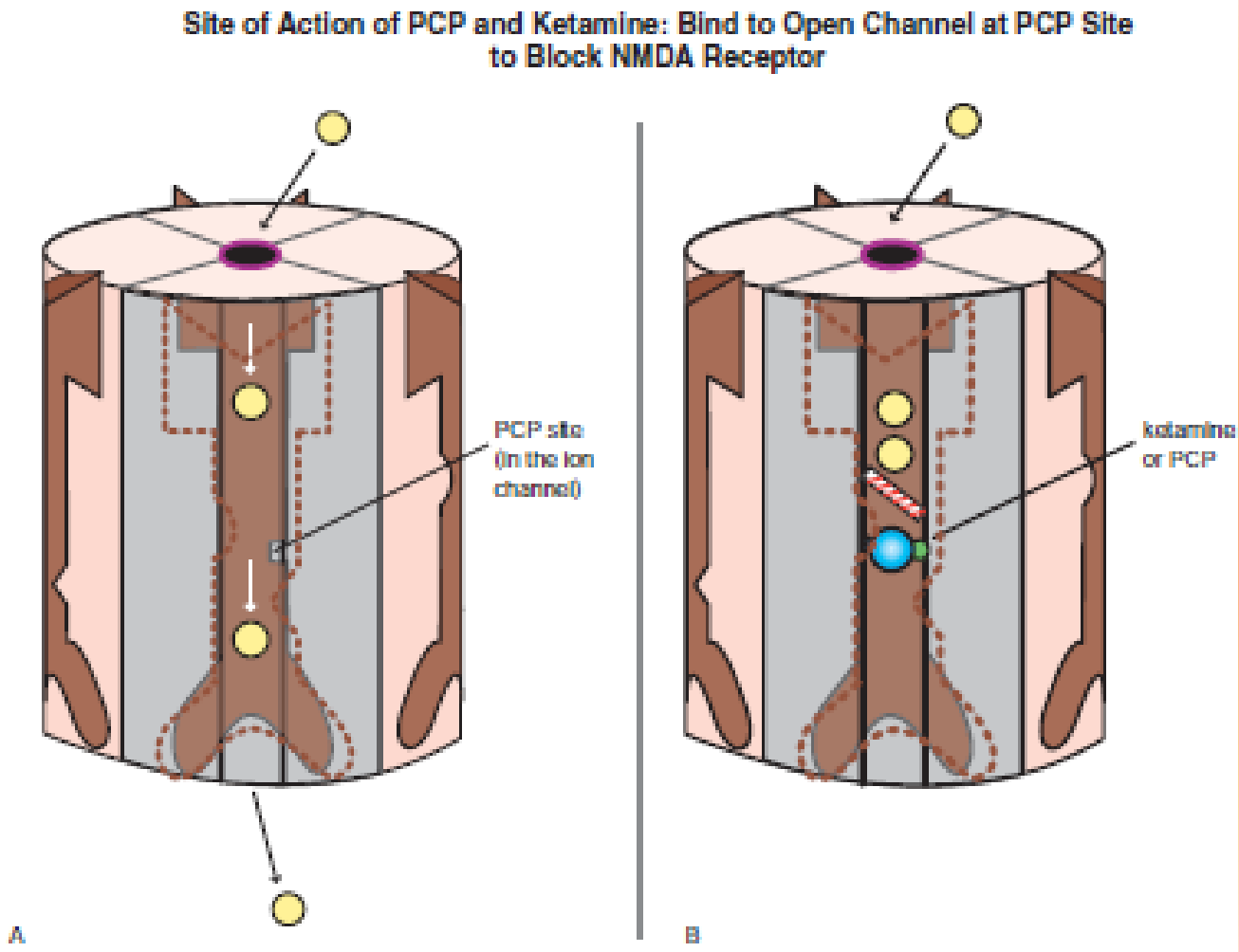
RECEPTORES AMPA Y NMDA



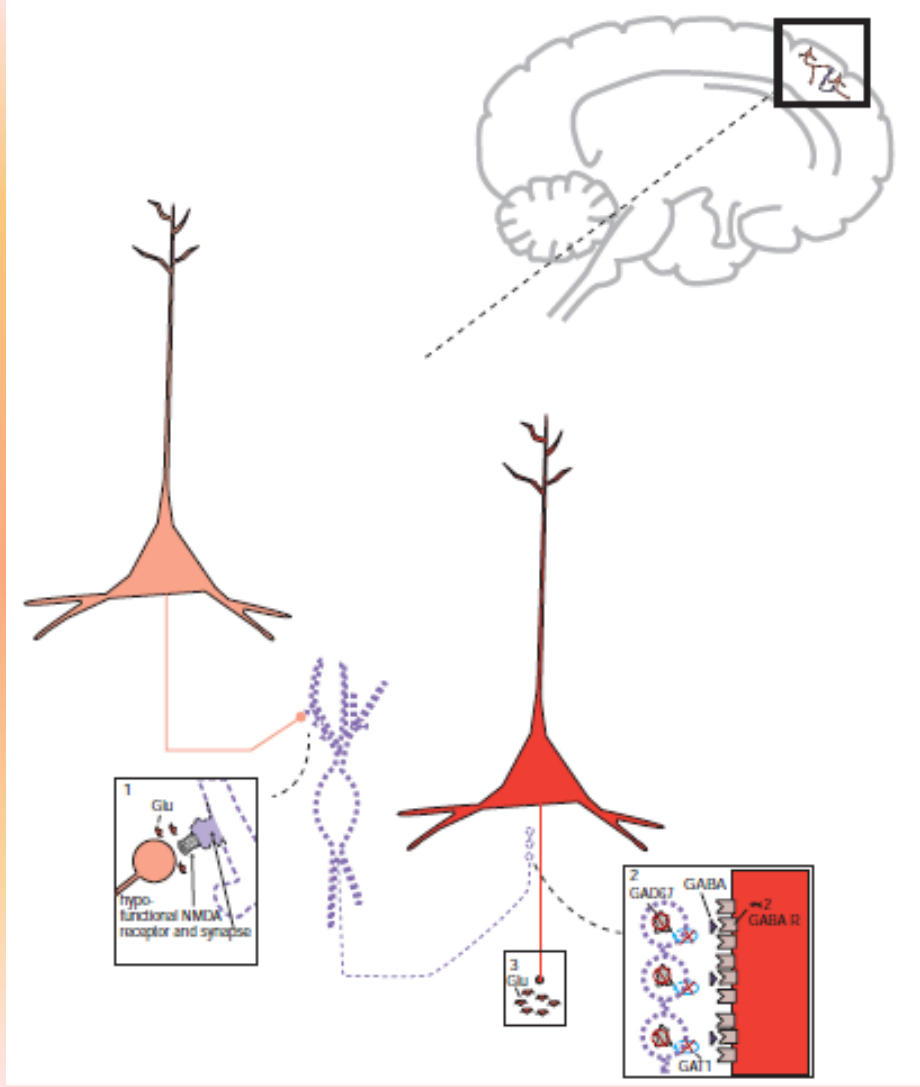
VÍAS GLUTAMATÉRGICAS



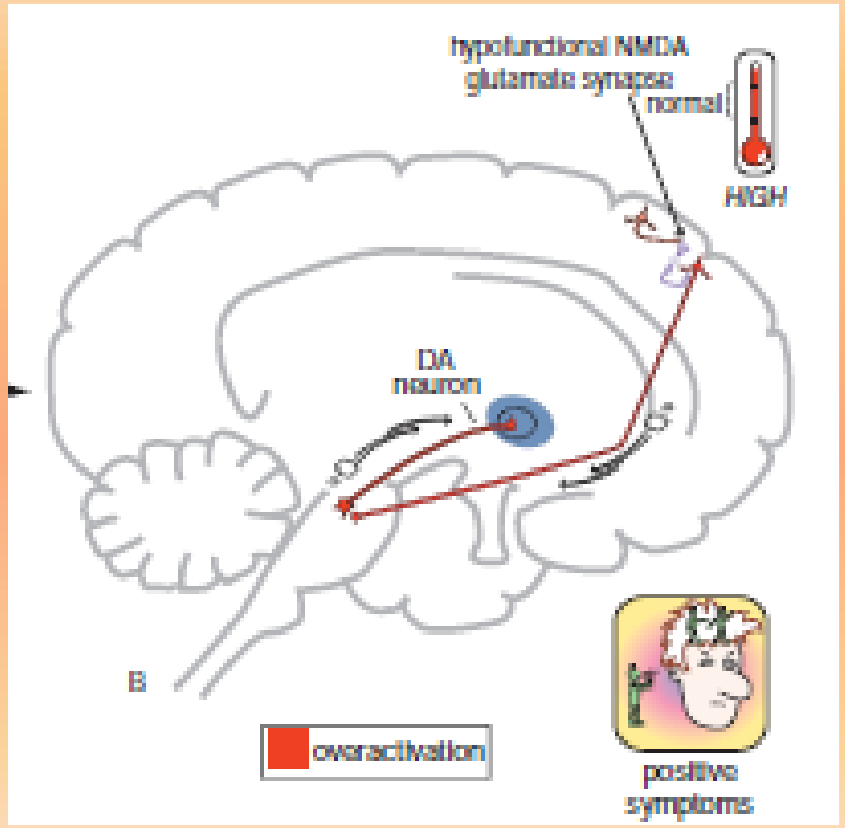
PCP Y SÍNTOMAS DE LA ESQUIZOFRENIA

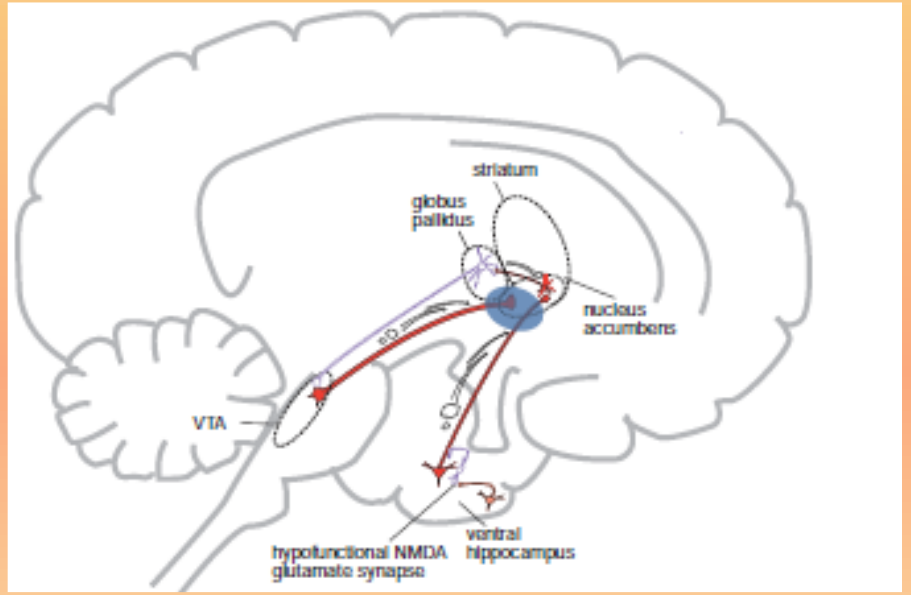


HIPÓTESIS HIPOFUNCIÓN NMDA

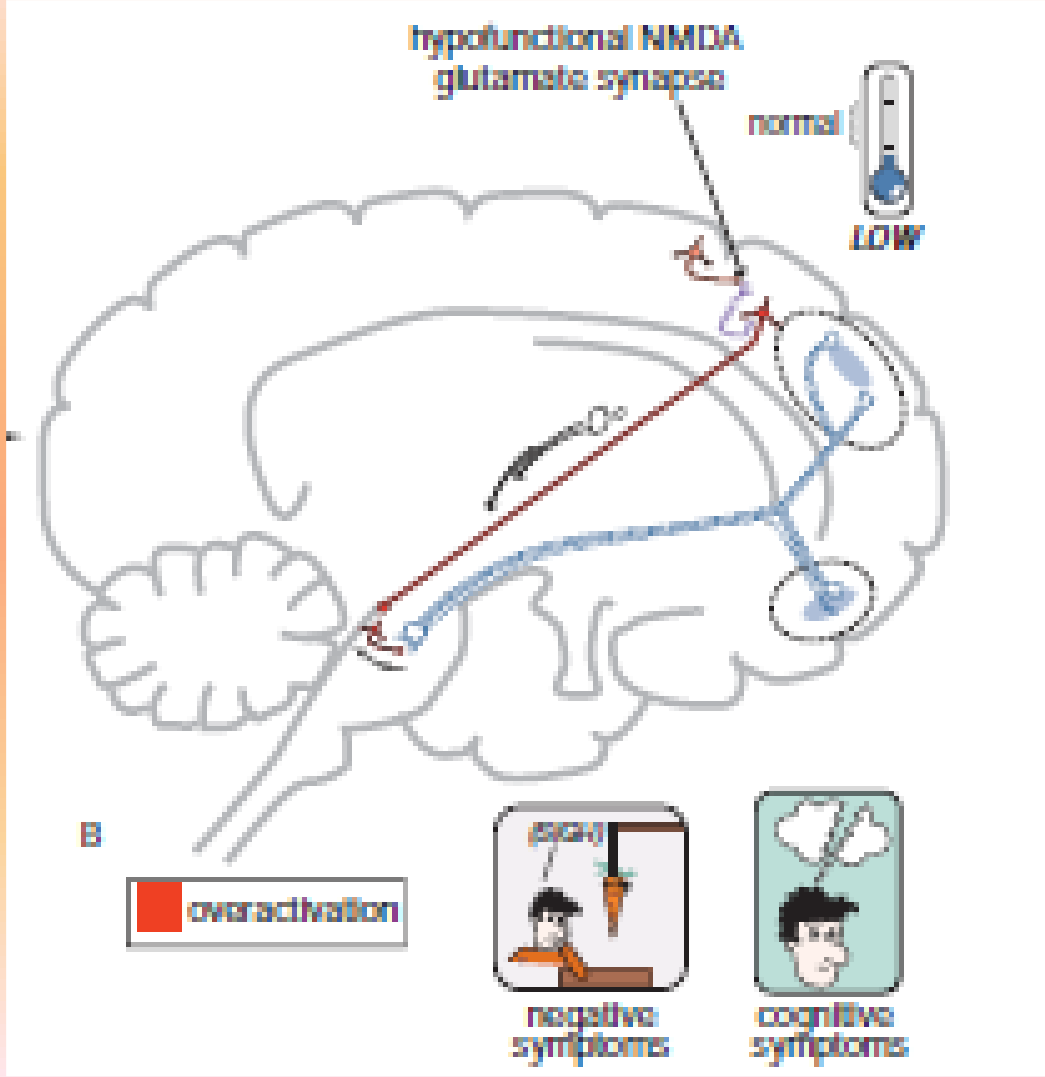


HIPÓTESIS HIPOFUNCIÓN NMDA SÍNTOMAS POSITIVOS





HIPÓTESIS HIPOFUNCIÓN NMDA SÍNTOMAS NEGATIVOS



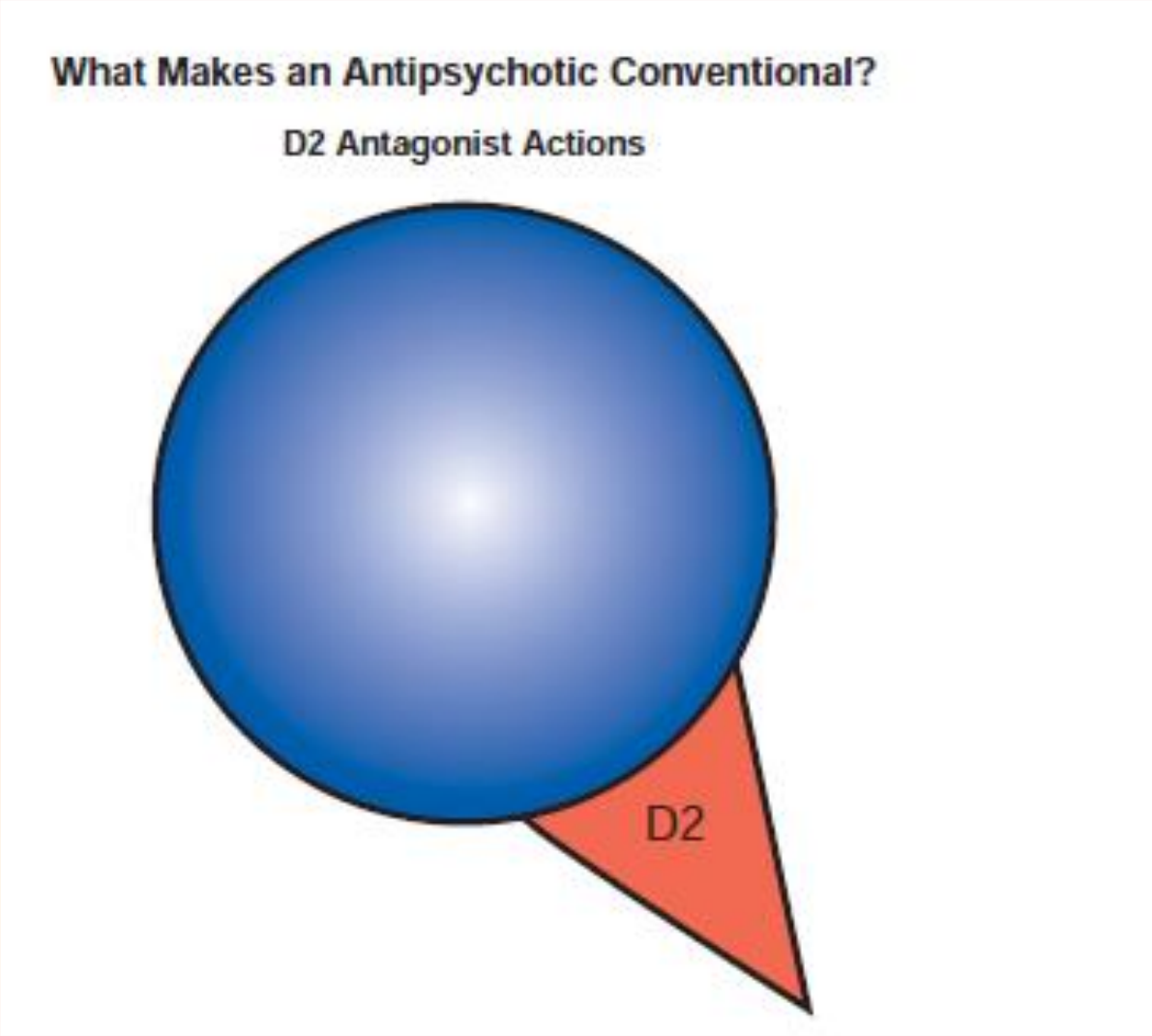
Equizofrenia

- Importancia síntomas negativos ➔ Entre episodios y pródromo
- No deterioro memo corto plazo ➔ Sí en demencia
- Sínt afectivos ➔ Difícil distinguir de transt humor y ans ➔ Importante tratarlos ➔ 5% suicidio ➔ añadir fárm epec
- Agresividad➔ Psicótica // Impulsiva // Organizada (psicopática)
- La mayoría no son violentos
- Causa ➔ Conspiración muchos genes y estrés ambiental
- Se hereda el riesgo de enfermedad, no la enfermedad

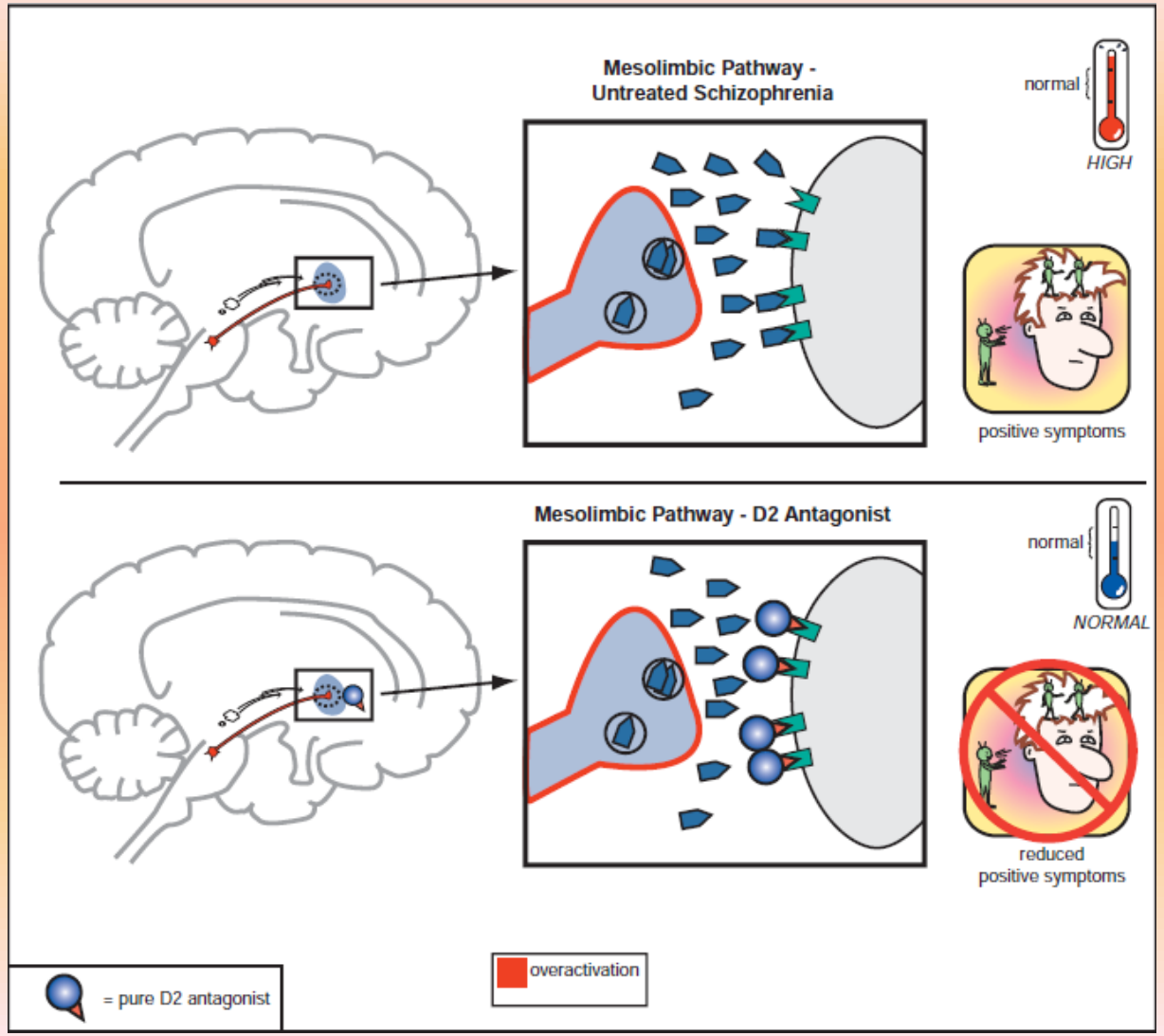
Fármacos para Psicosis

- Antagonistas D2
- Antagonistas D2 y 5HT2A
- Antagonistas 5HT2A
- Agonistas parciales D2 y 5HT1A

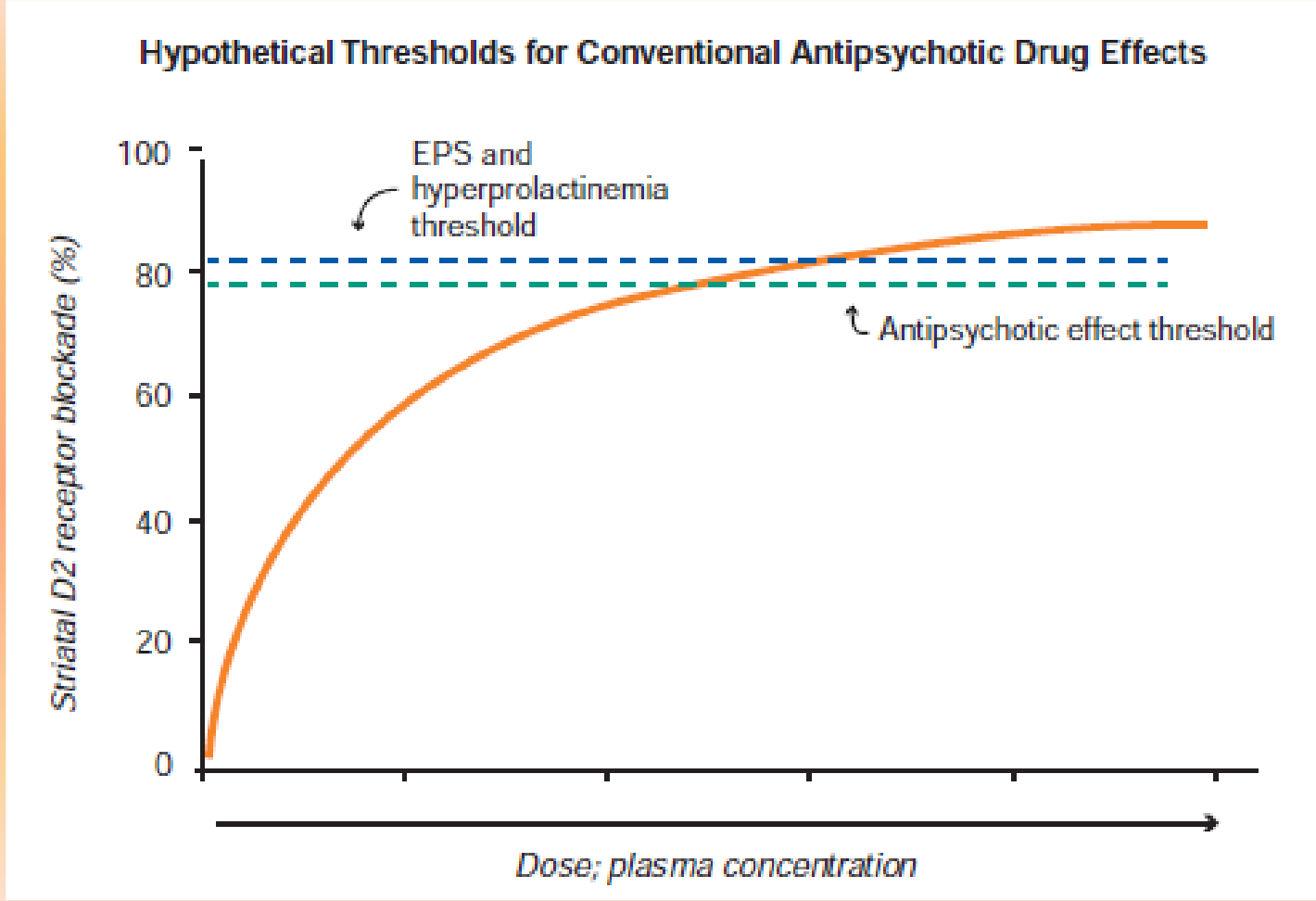
Antipsicóticos convencionales



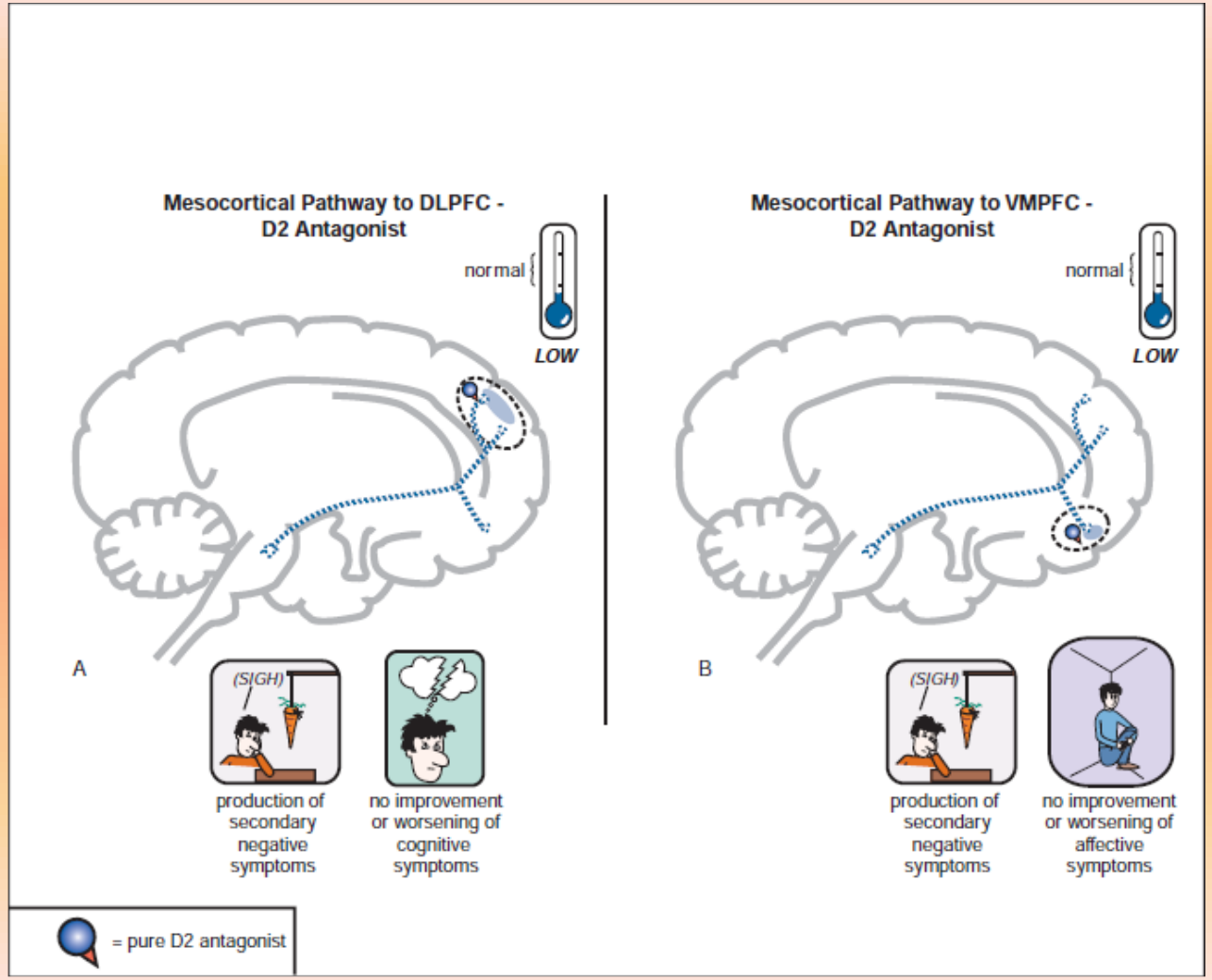
Antipsicóticos convencionales



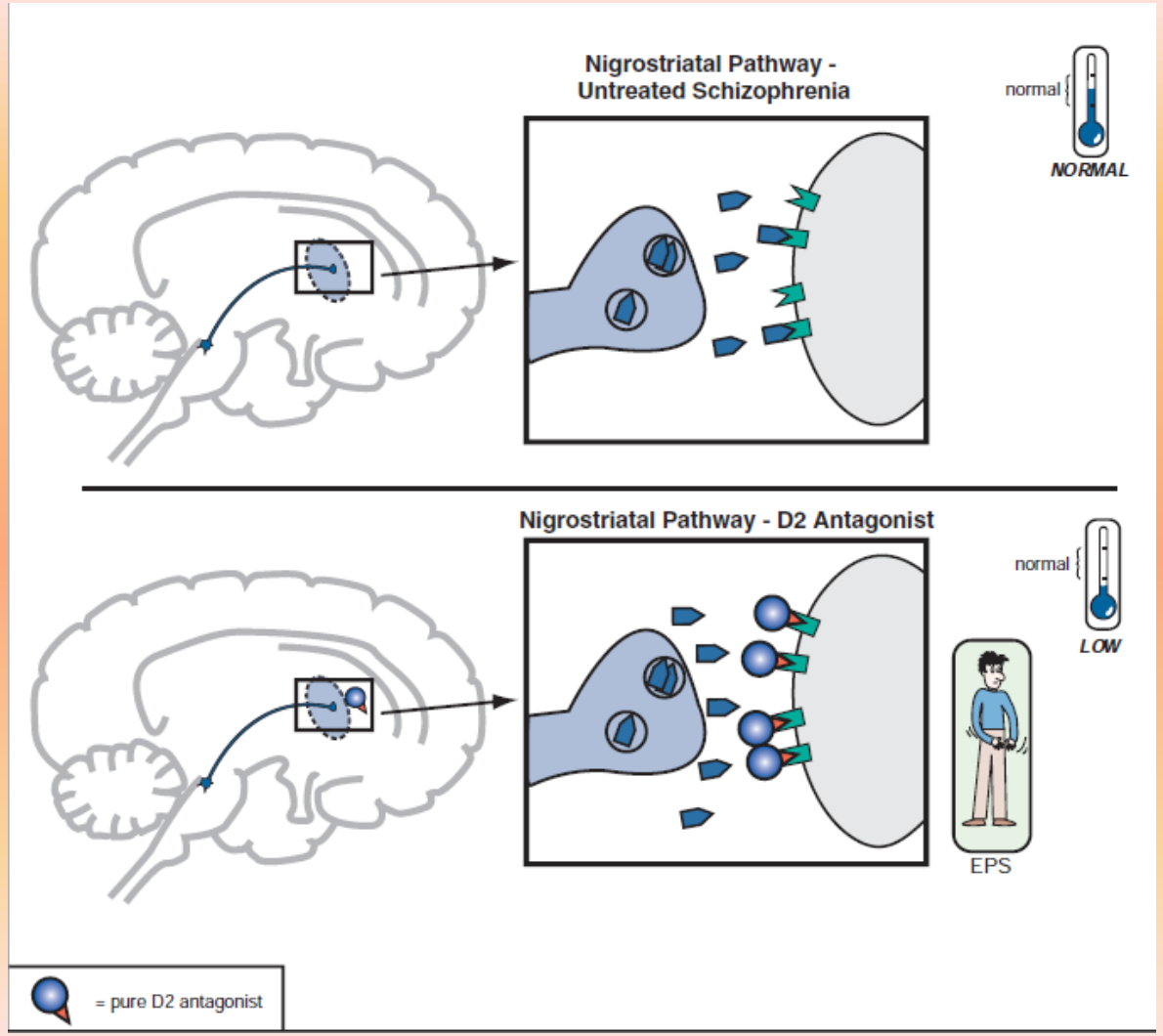
Antipsicóticos convencionales



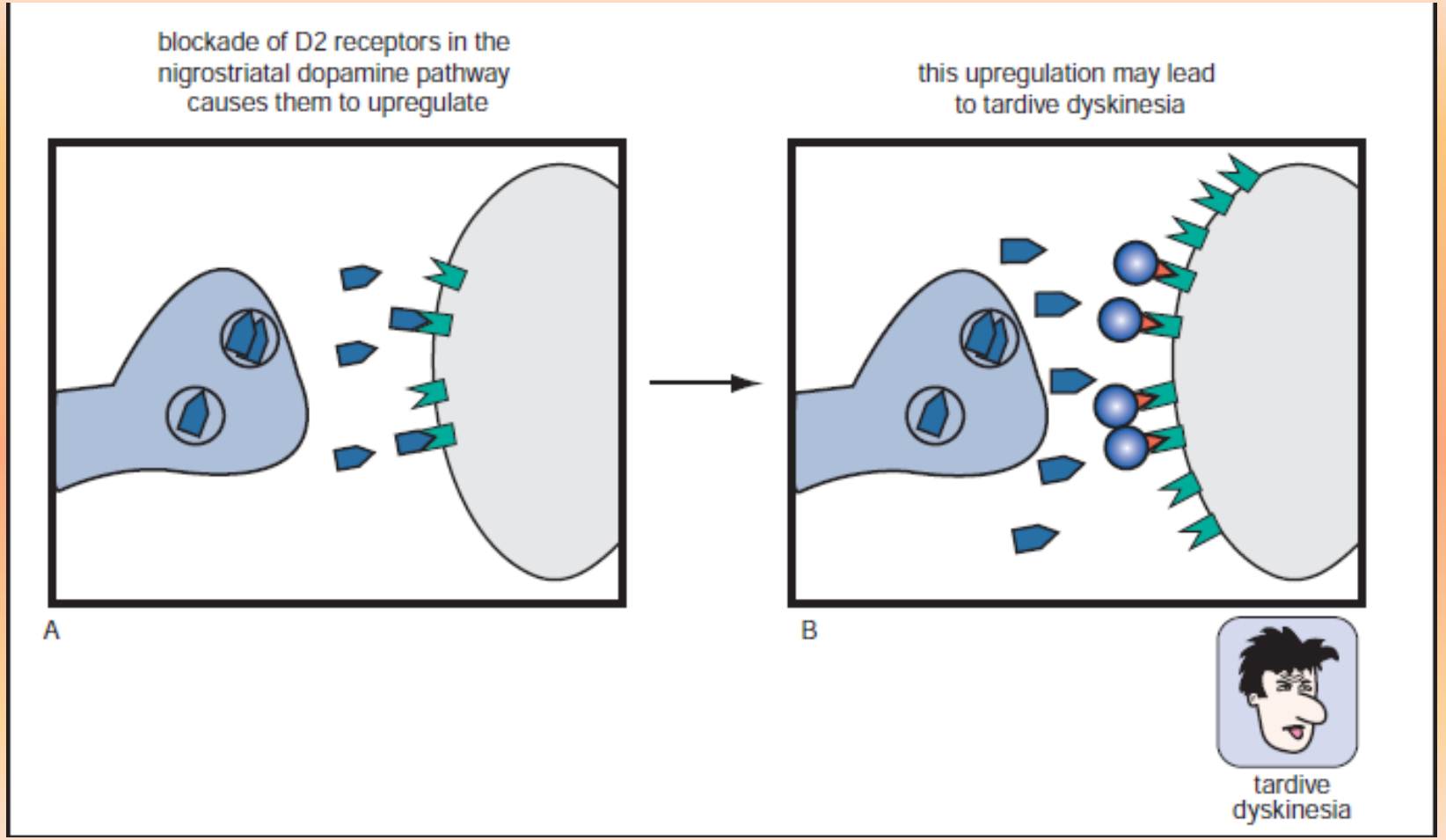
Neurolepsis



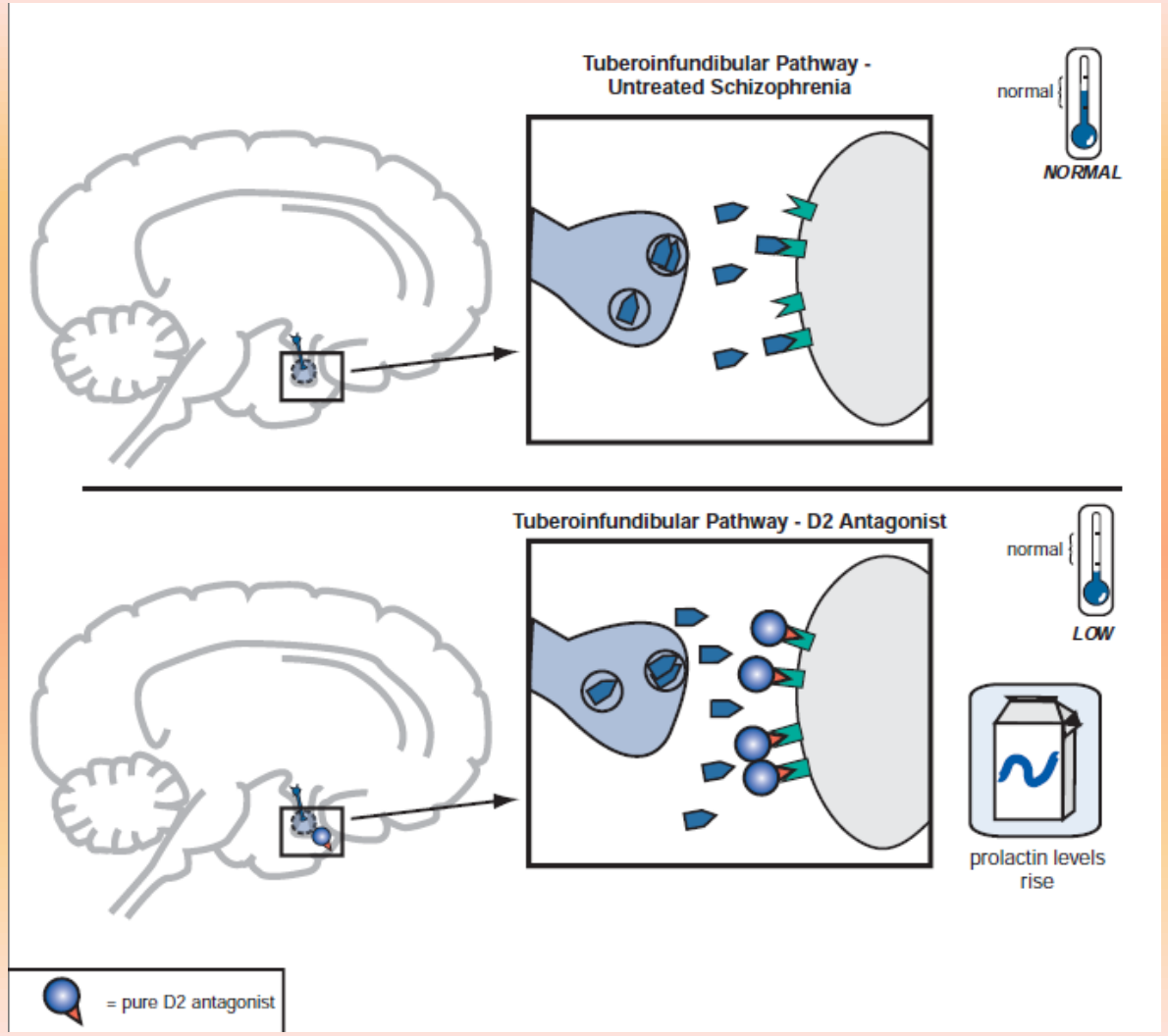
´Síntomas extrapiramidales



Disquinesia tardía



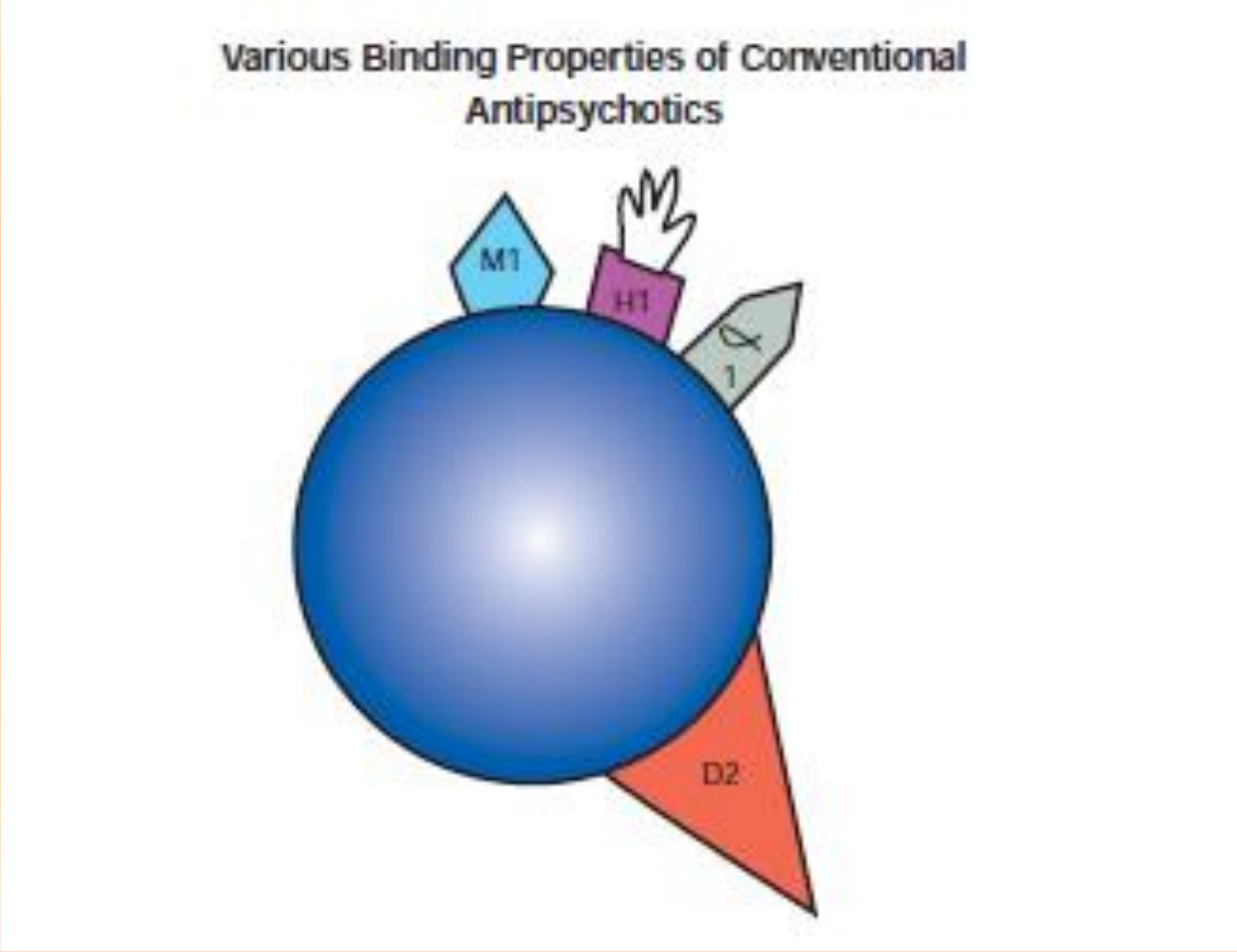
Hiperprolactinemia



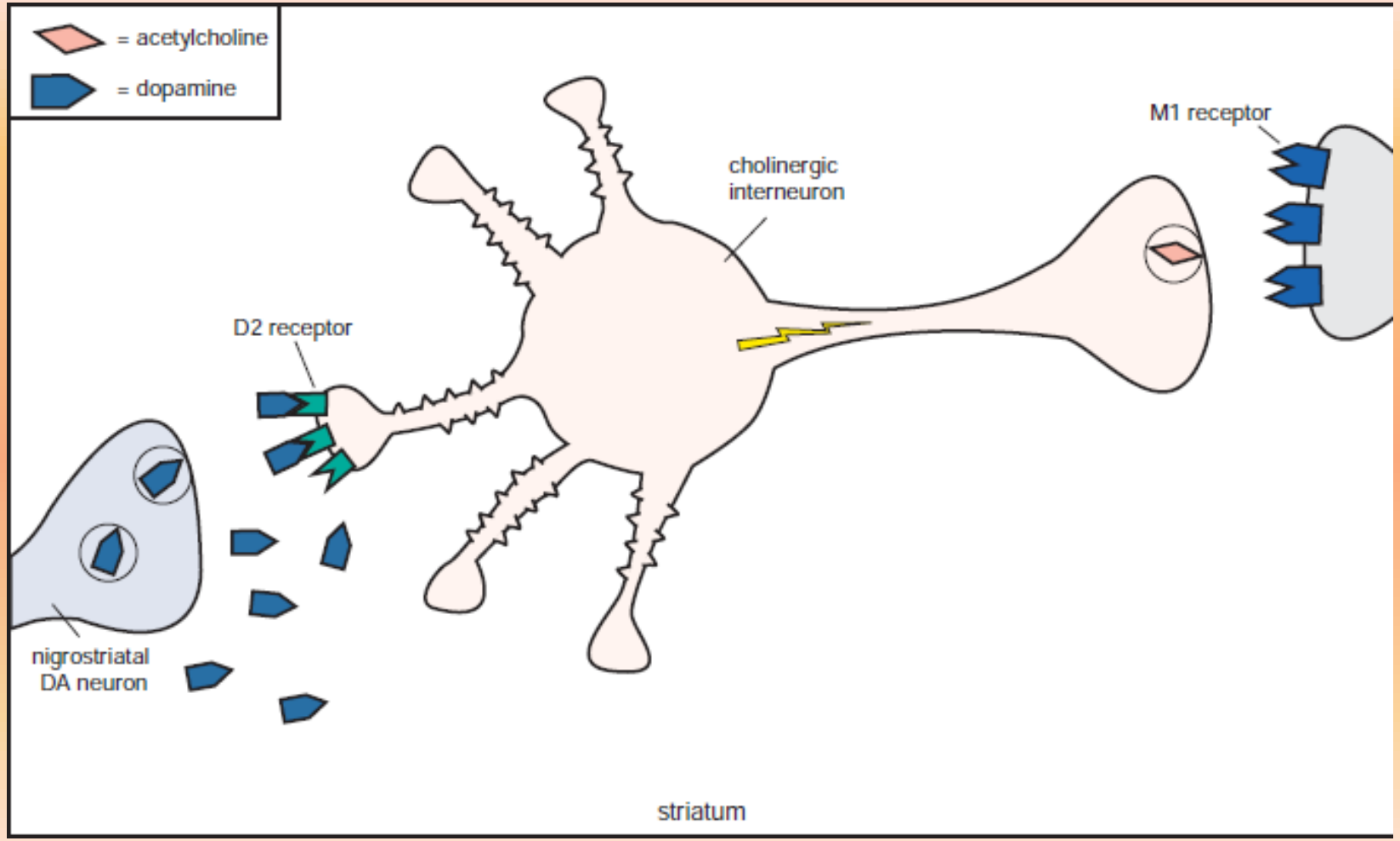
Otros efectos secundarios

- Distonía aguda → Anticolinérg intramusc
- Acatisia → Badrenérg // Benzos // 5HT 2ª
- S Neuroléptico Maligno → Retirada // dantroleno // Agonistas DA

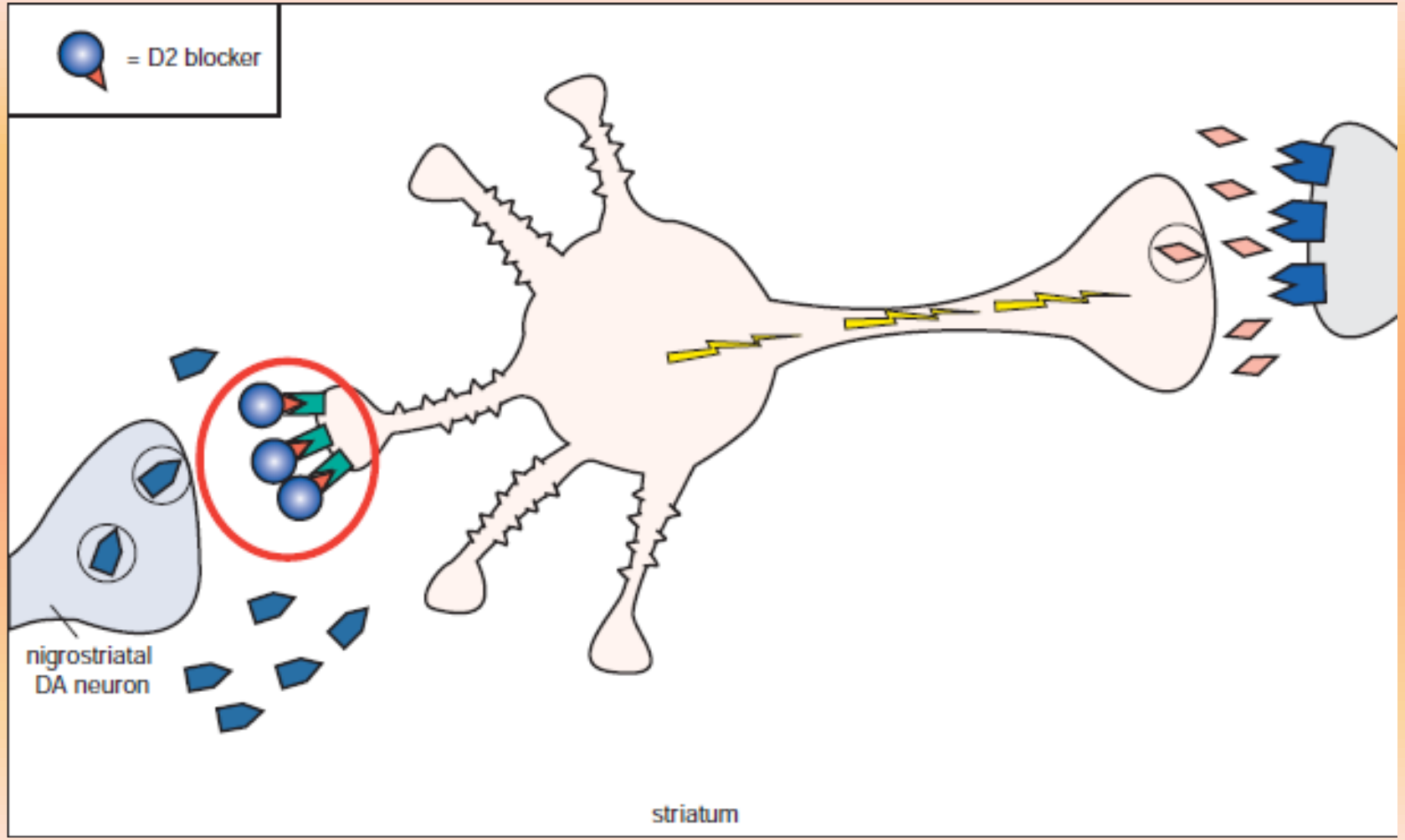
Antipsicóticos convencionales: propiedades adicionales



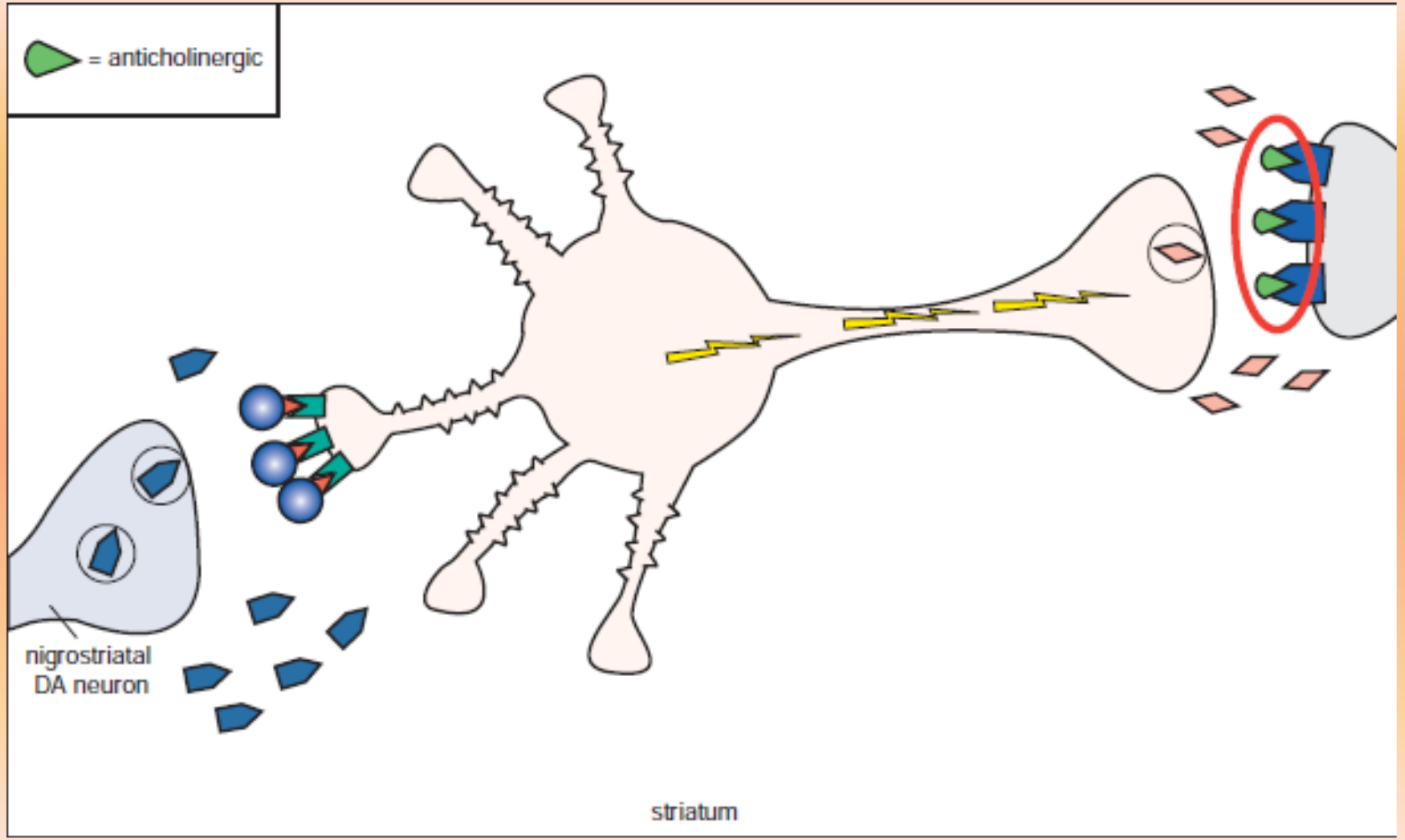
Interacción dopamina-acetilcolina (vía nigroestriada)



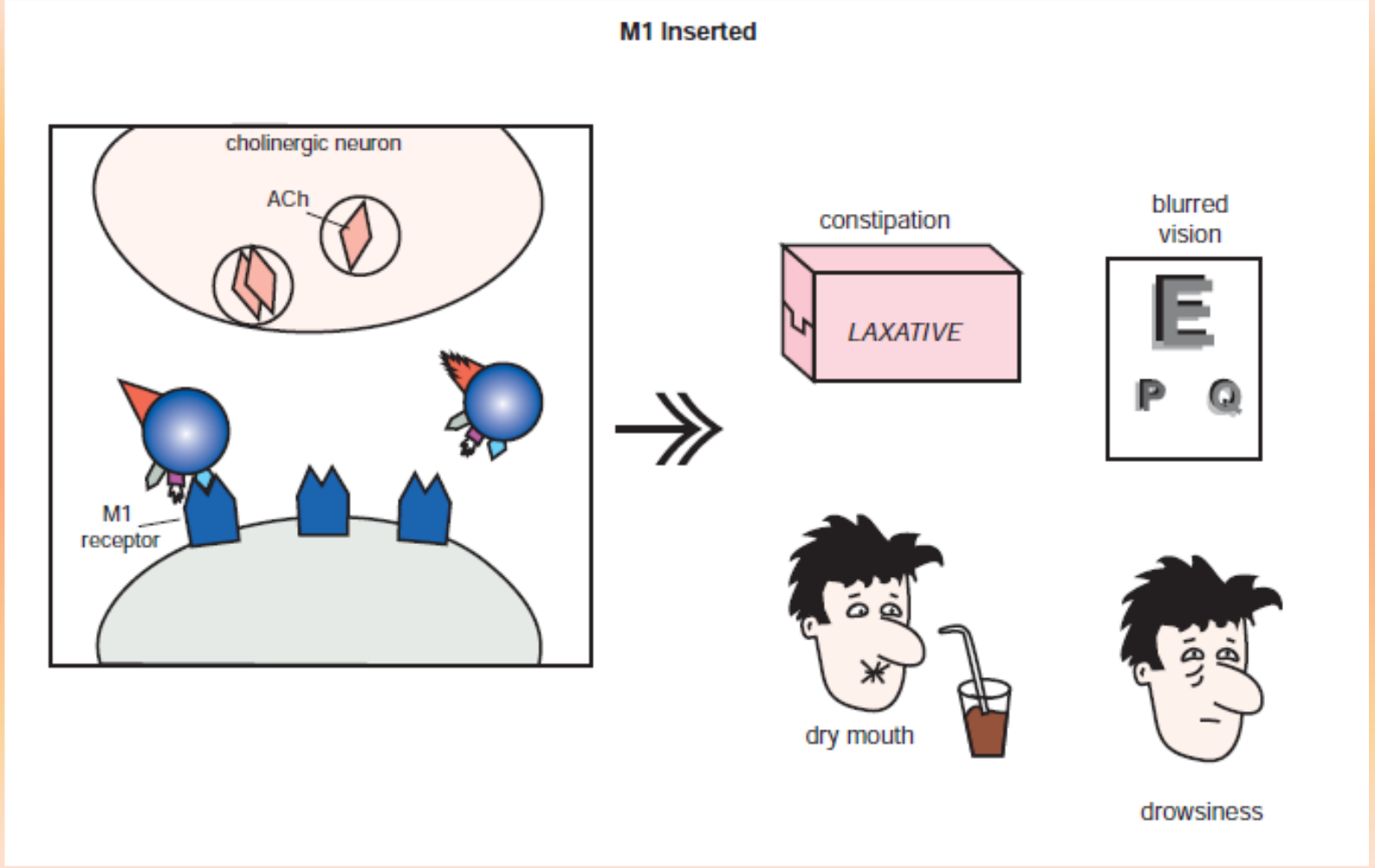
Hiperactividad colinérgica



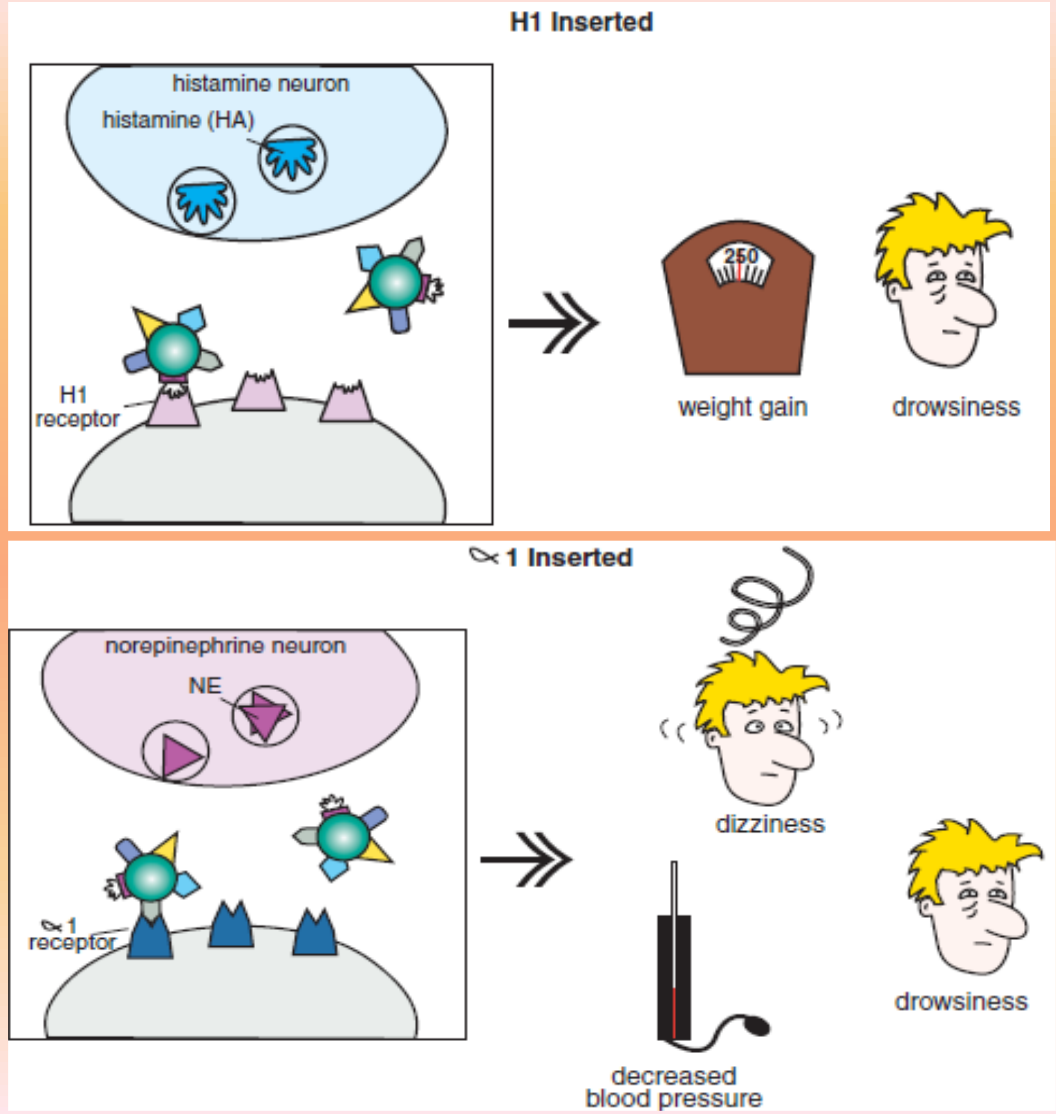
Antagonismo M1 mejora SEP



Efectos secundarios



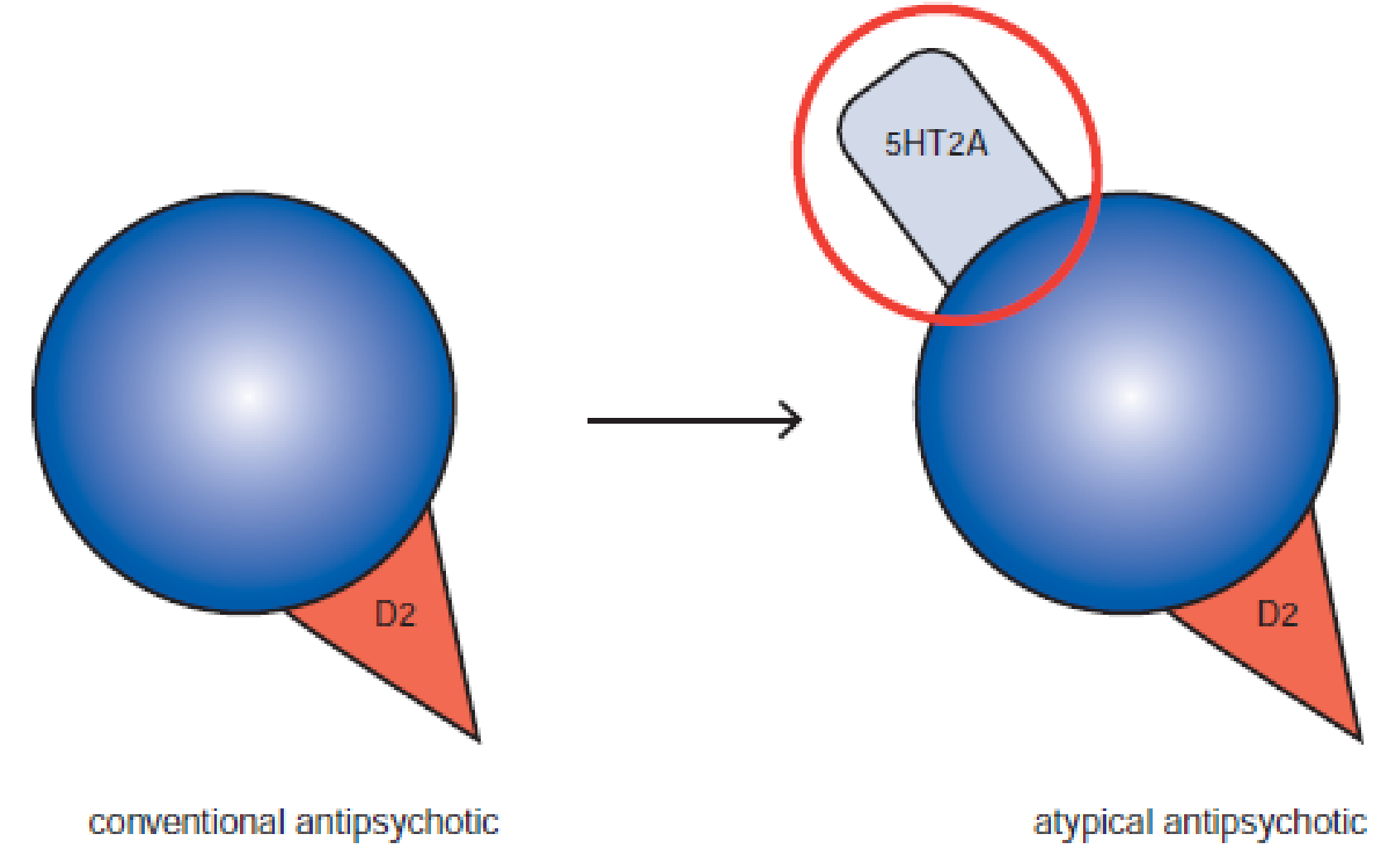
Efectos secundarios



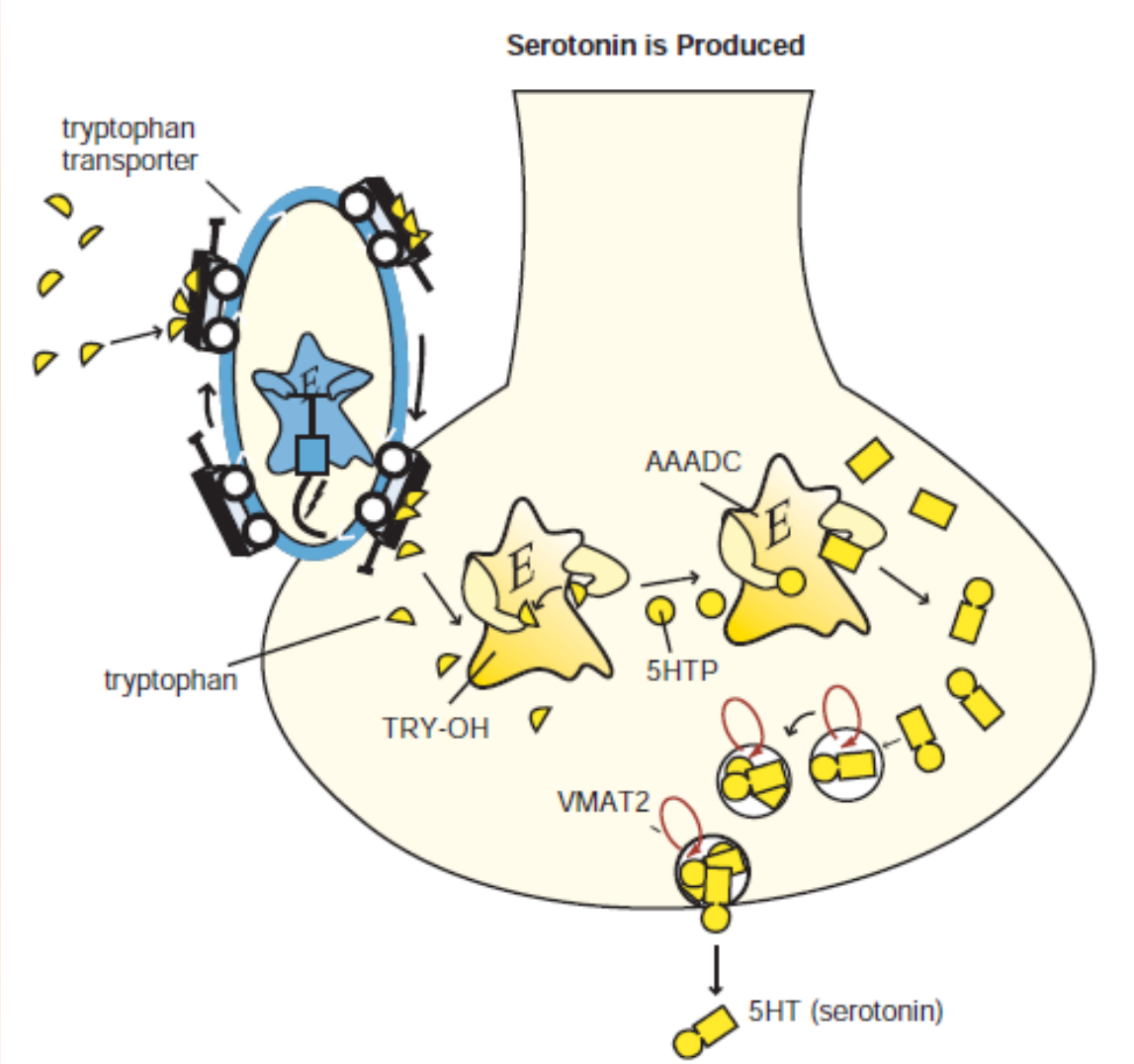
Antagonistas D2

- Clorpromacina: Sedación. Trata agitación
- Flufenacina: Más potente y menos sedante
- Haloperidol: Potente y menos sedante
- Sulpirida: Mejor tolerada
- Amisulpirida: + selec D2 mesolim q nigroest. Débil 5HT7 = antidep y ok sínt neg a dosis bajas

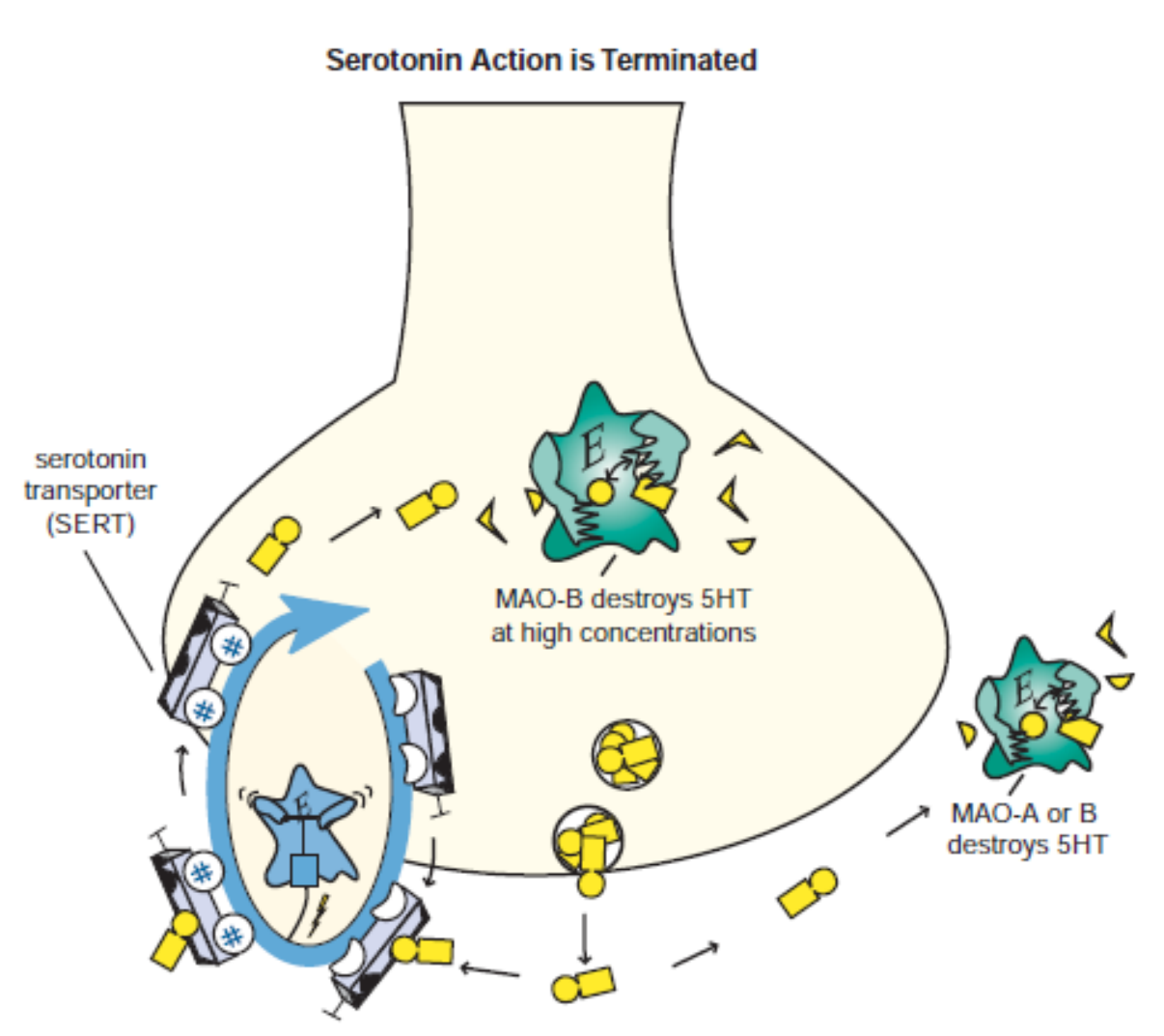
Antipsicóticos atípicos



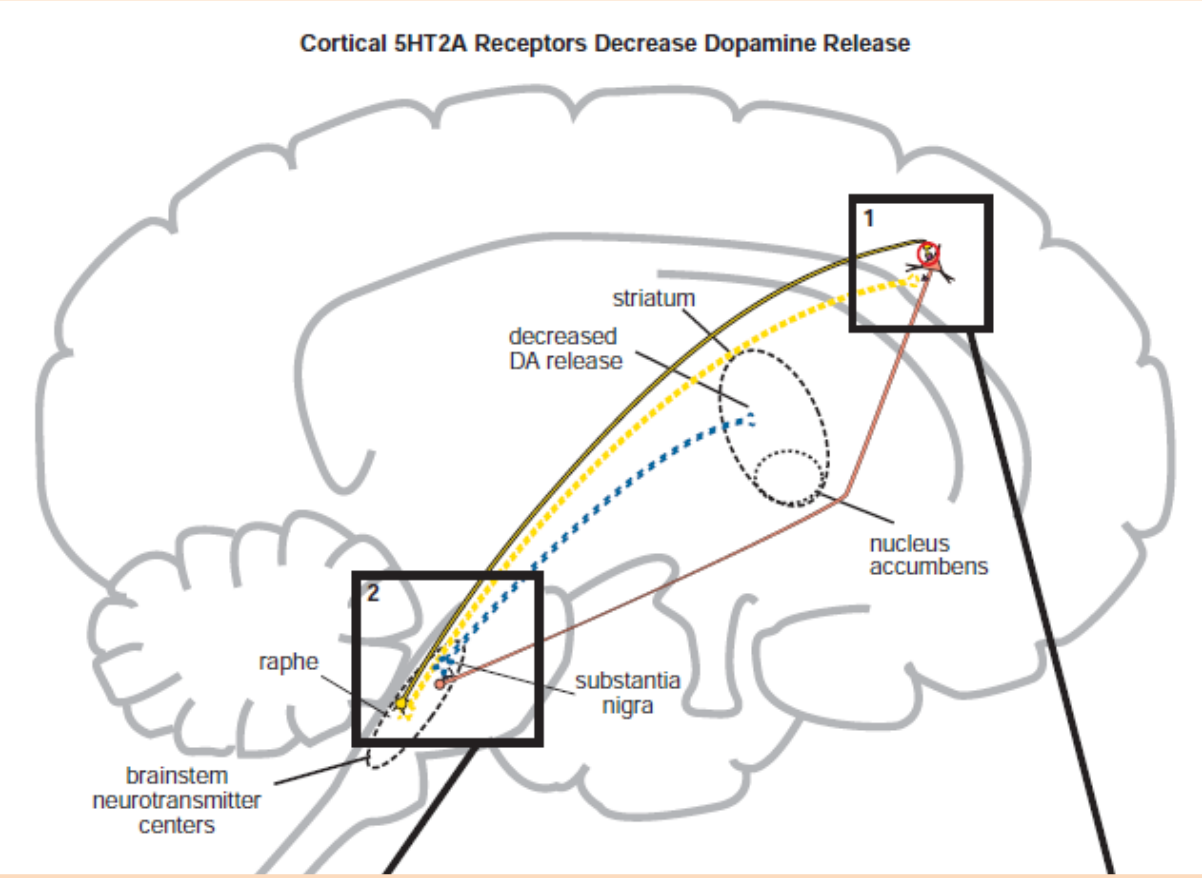
Síntesis de serotonina



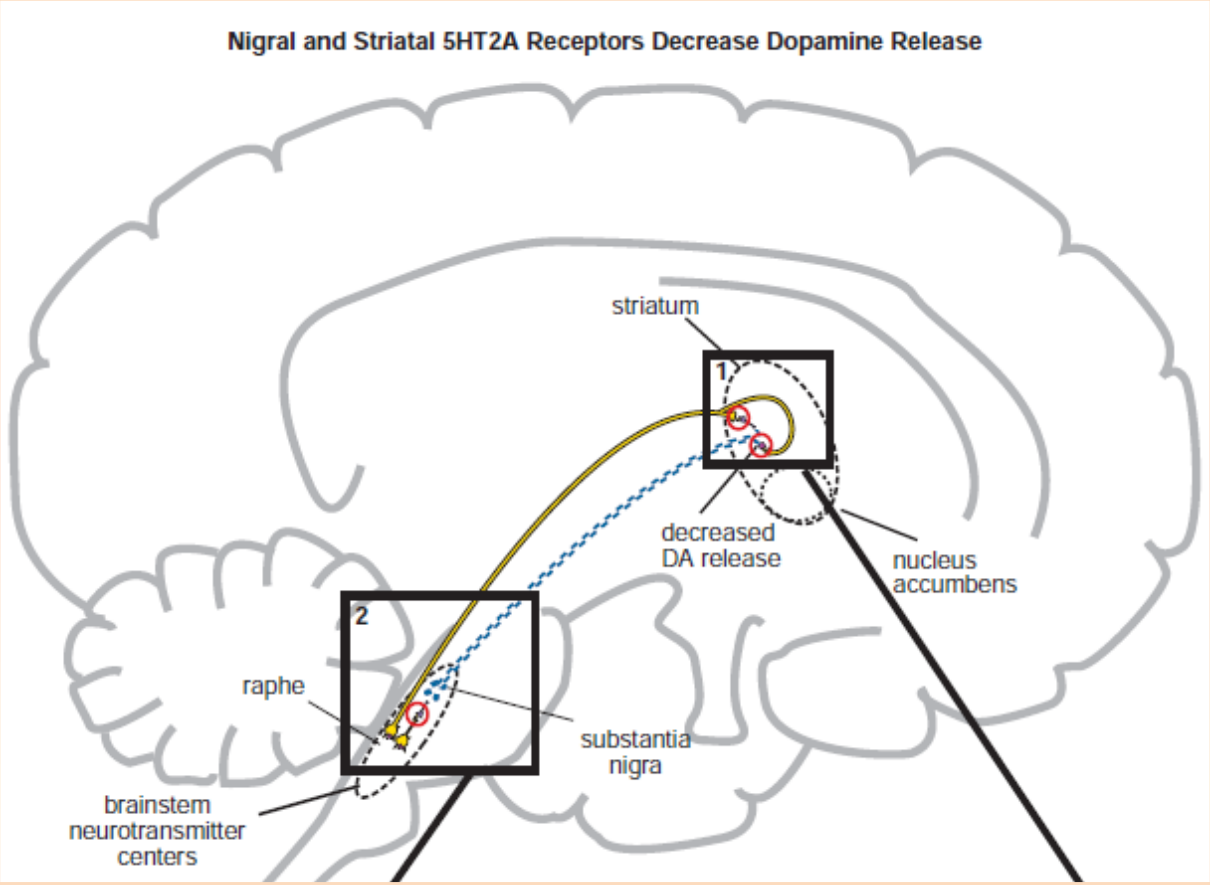
Degradación de serotonina



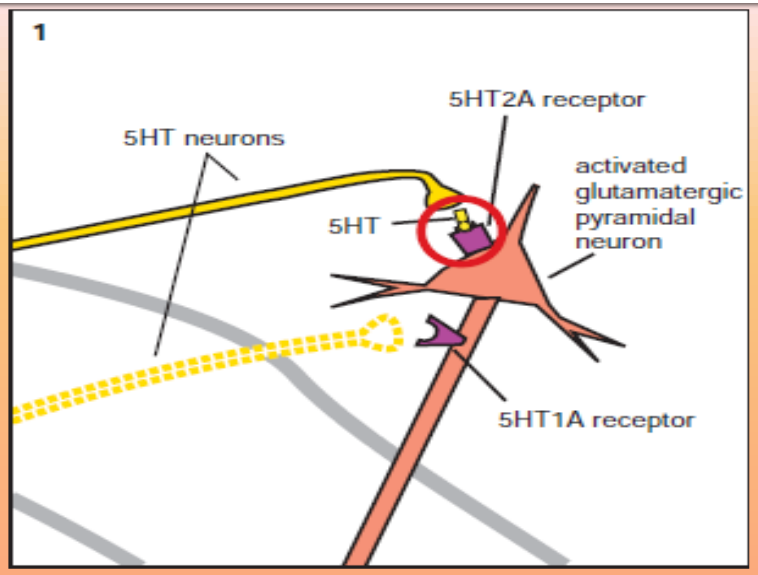
Influencia de la serotonina en la vía nigroestriada

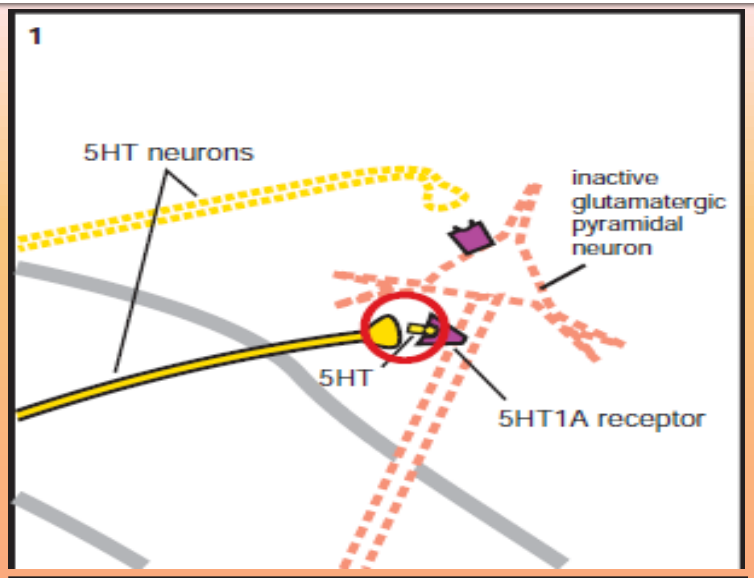


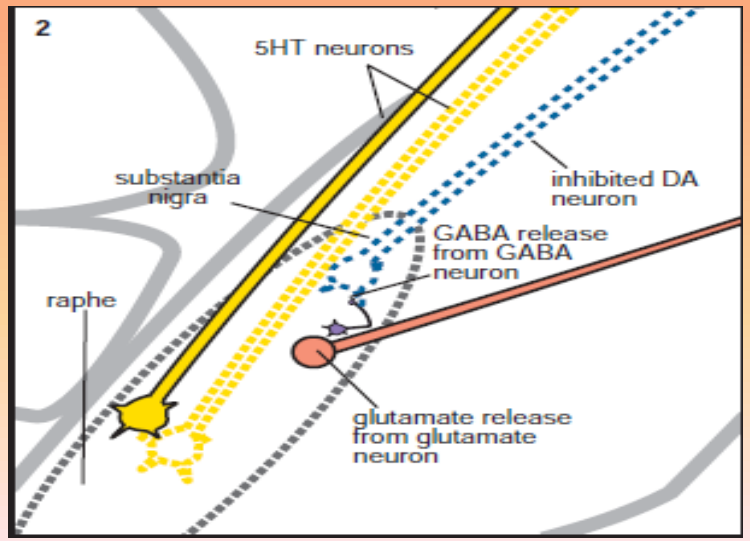
Influencia de la serotonina en la vía nigroestriada

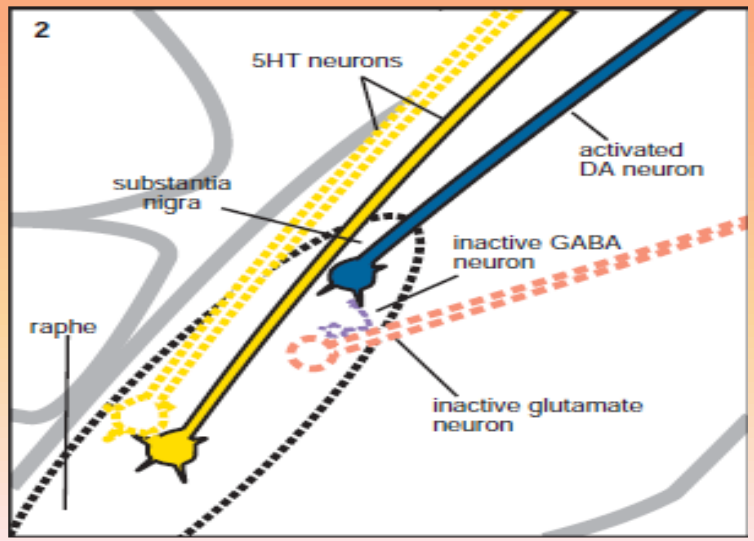


Receptores de serotonina en neuronas glutamatérgicas

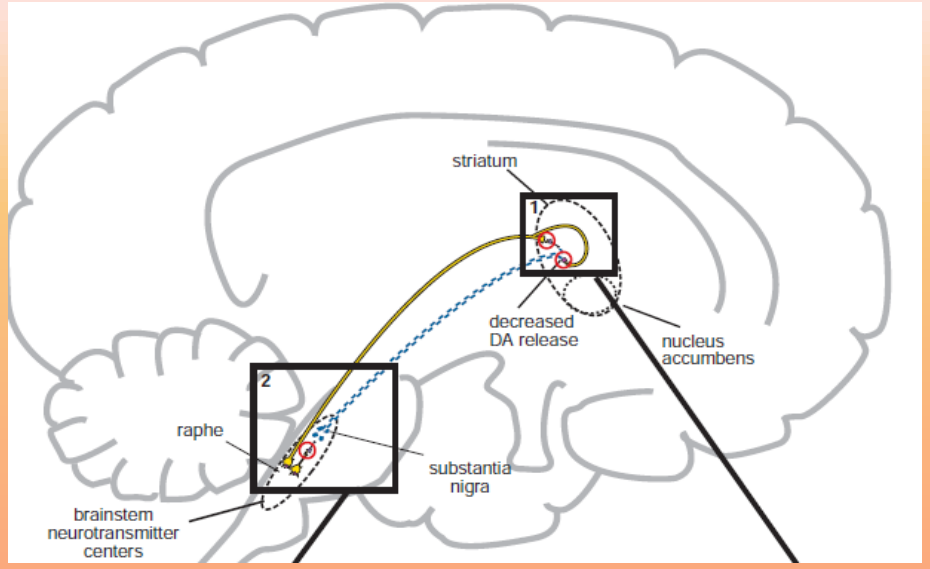


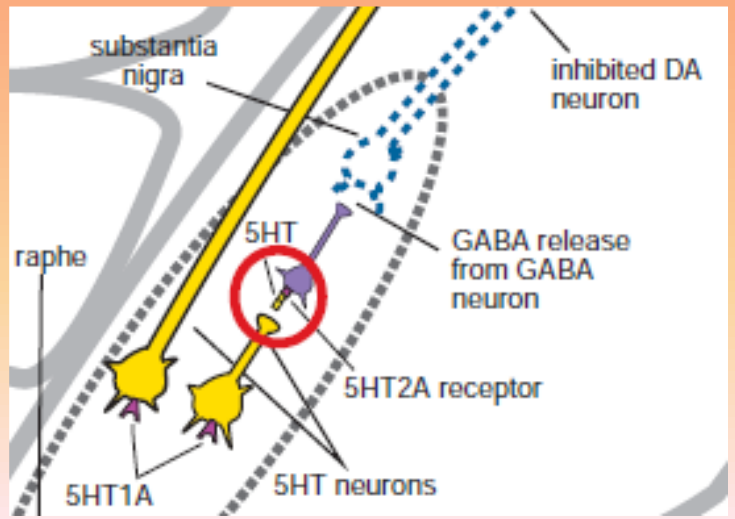


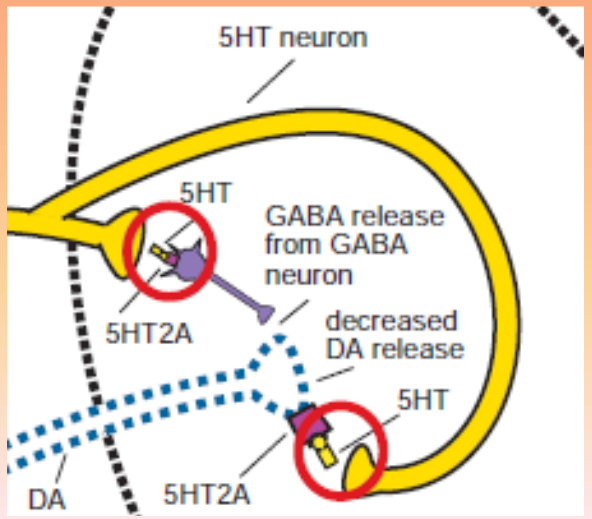




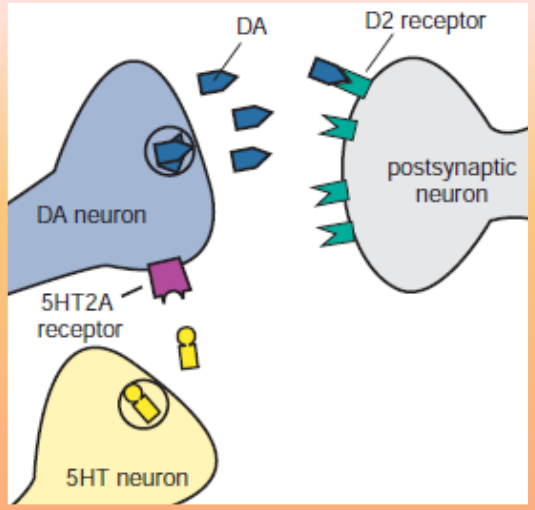
Receptores de serotonina en neuronas GABAérgicas, serotoninérgicas y dopaminérgicas

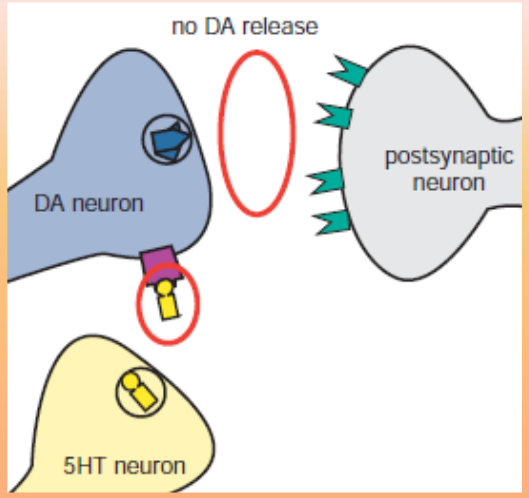


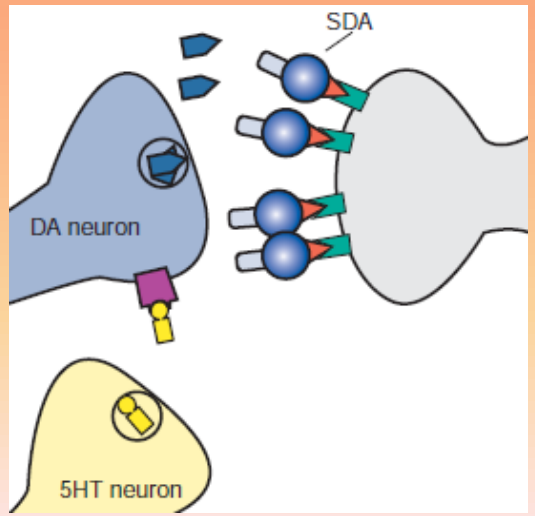


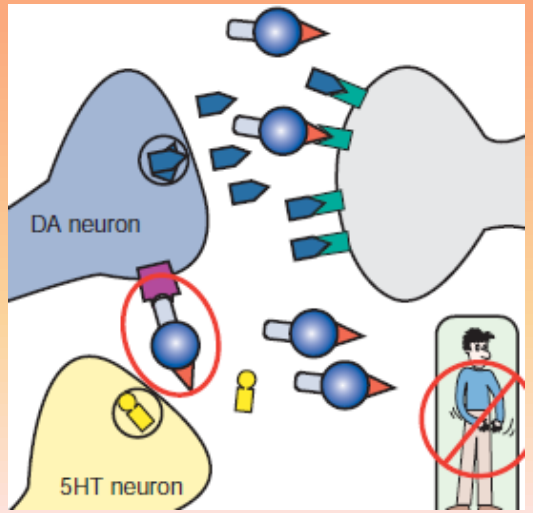


Efecto neto en la vía nigroestriada

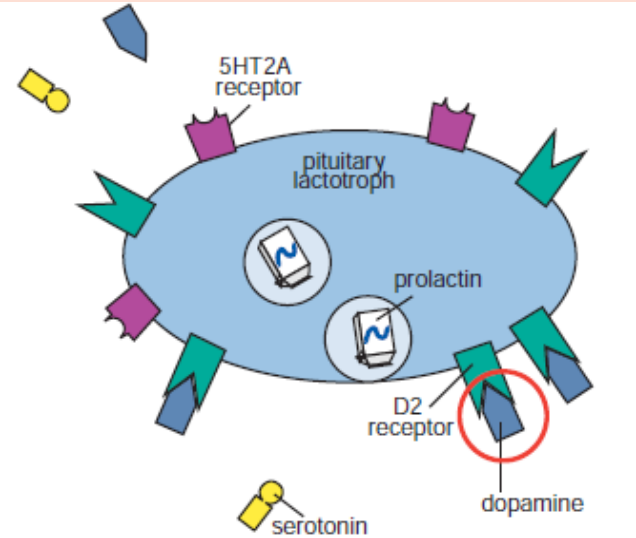


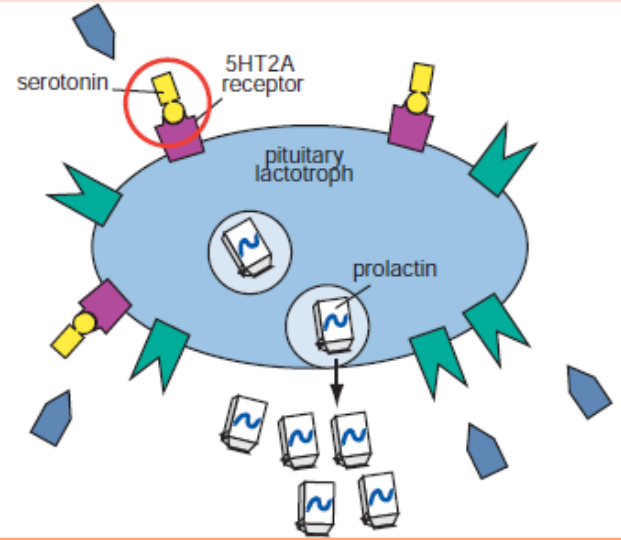


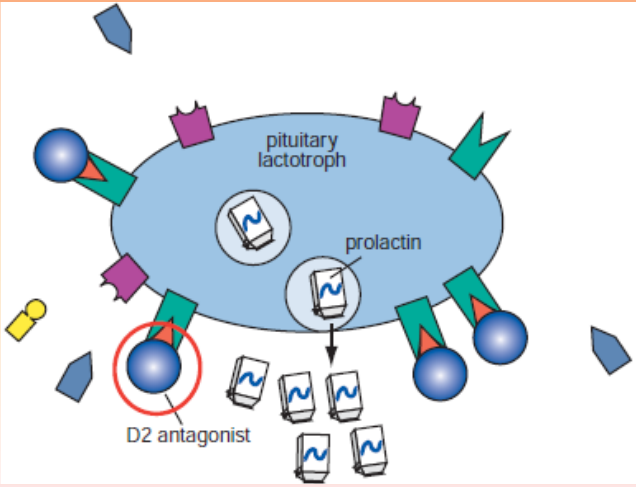


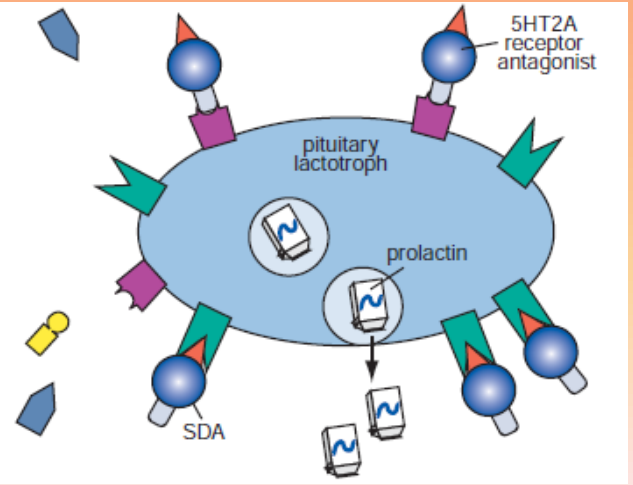


Efecto en células lactótropas

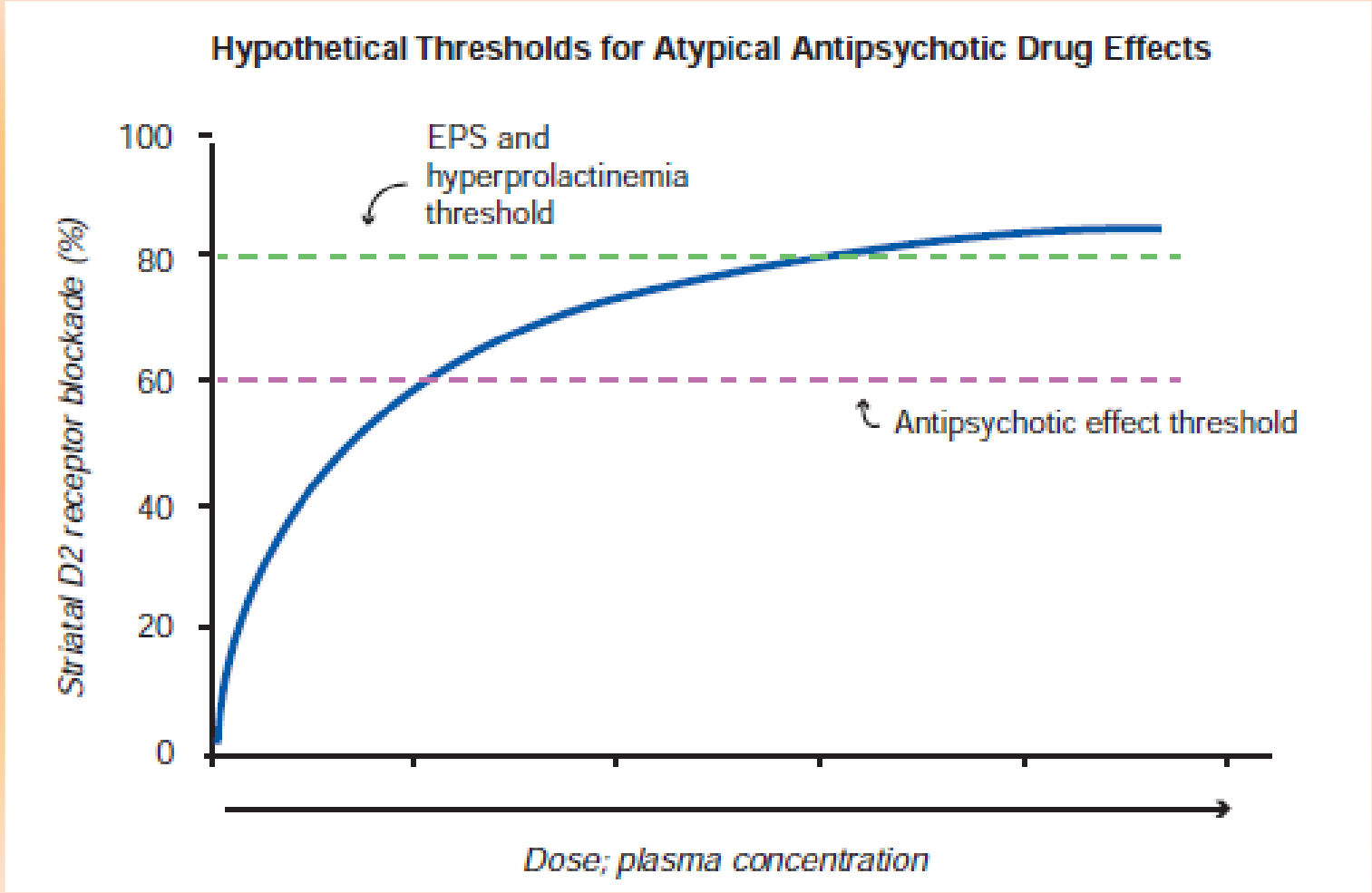




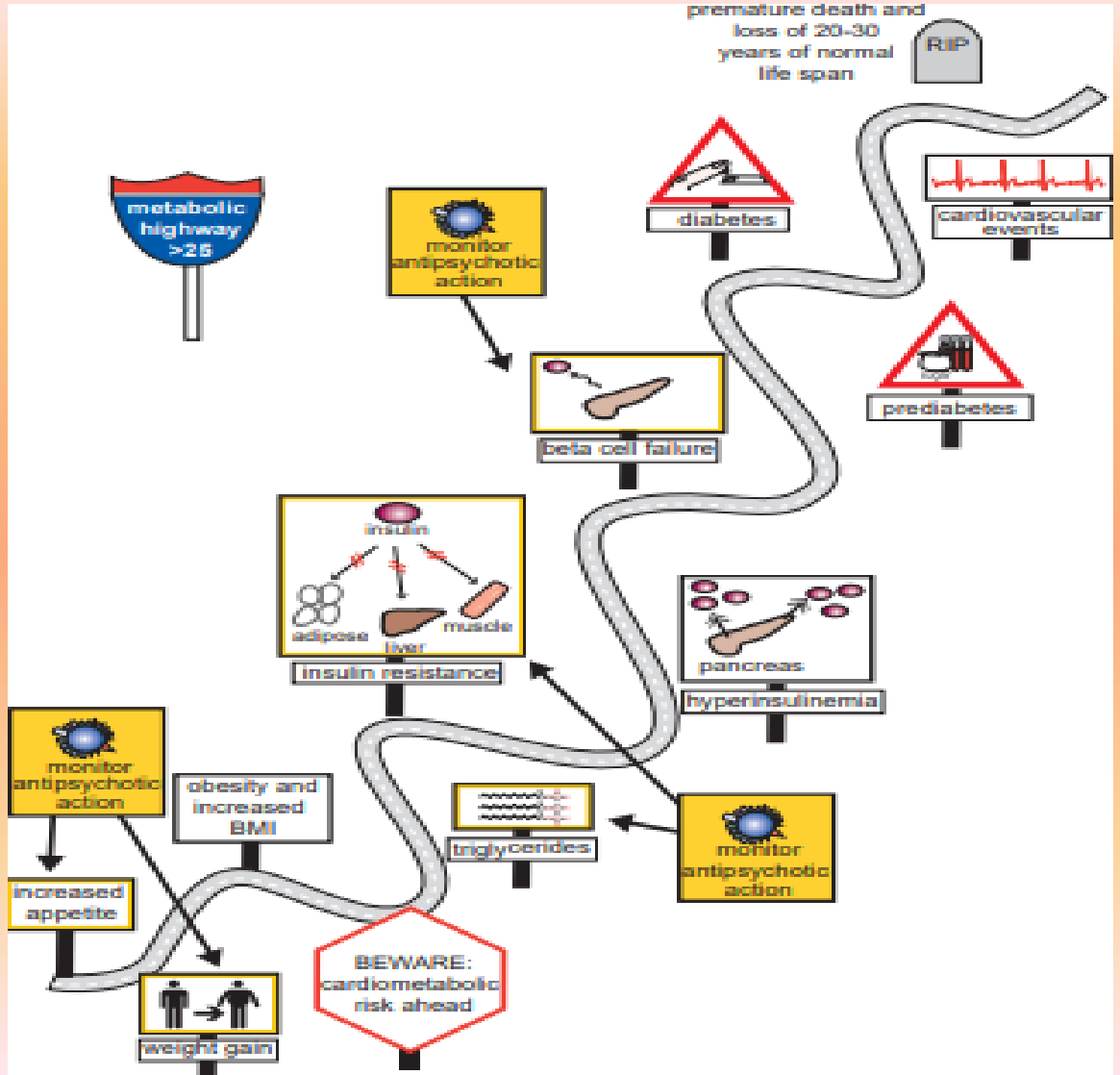




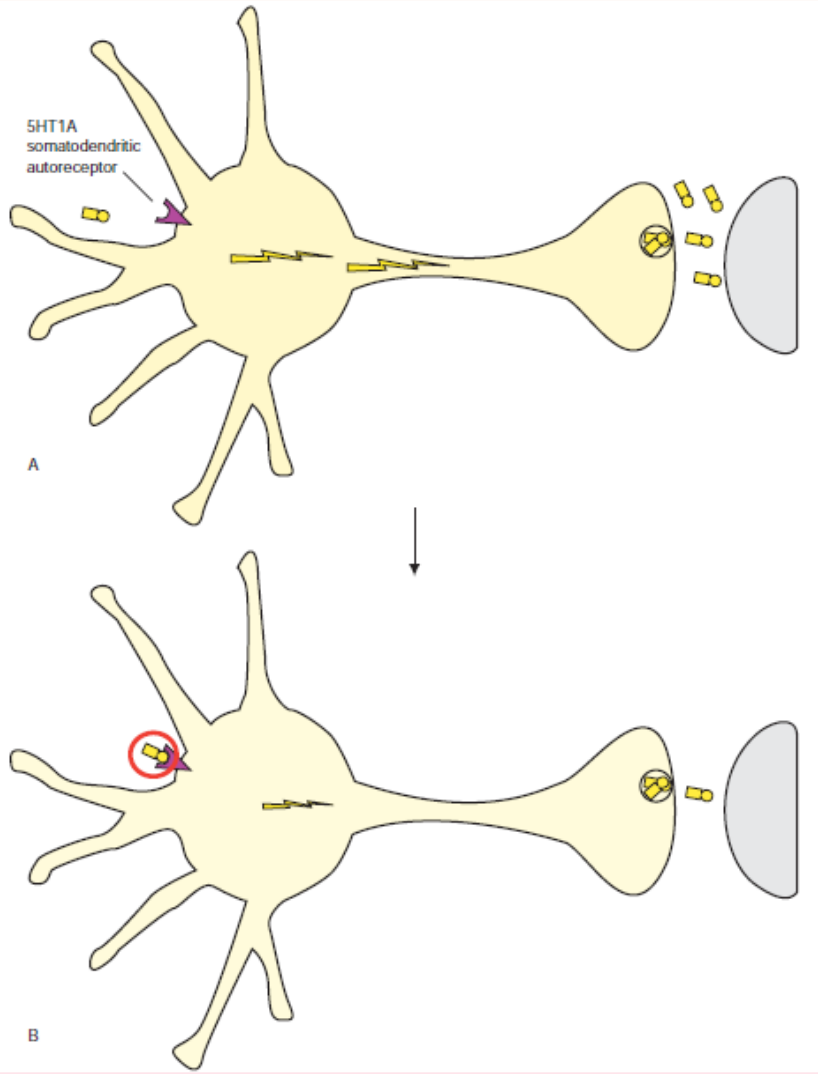
Ampliación de la ventana terapéutica

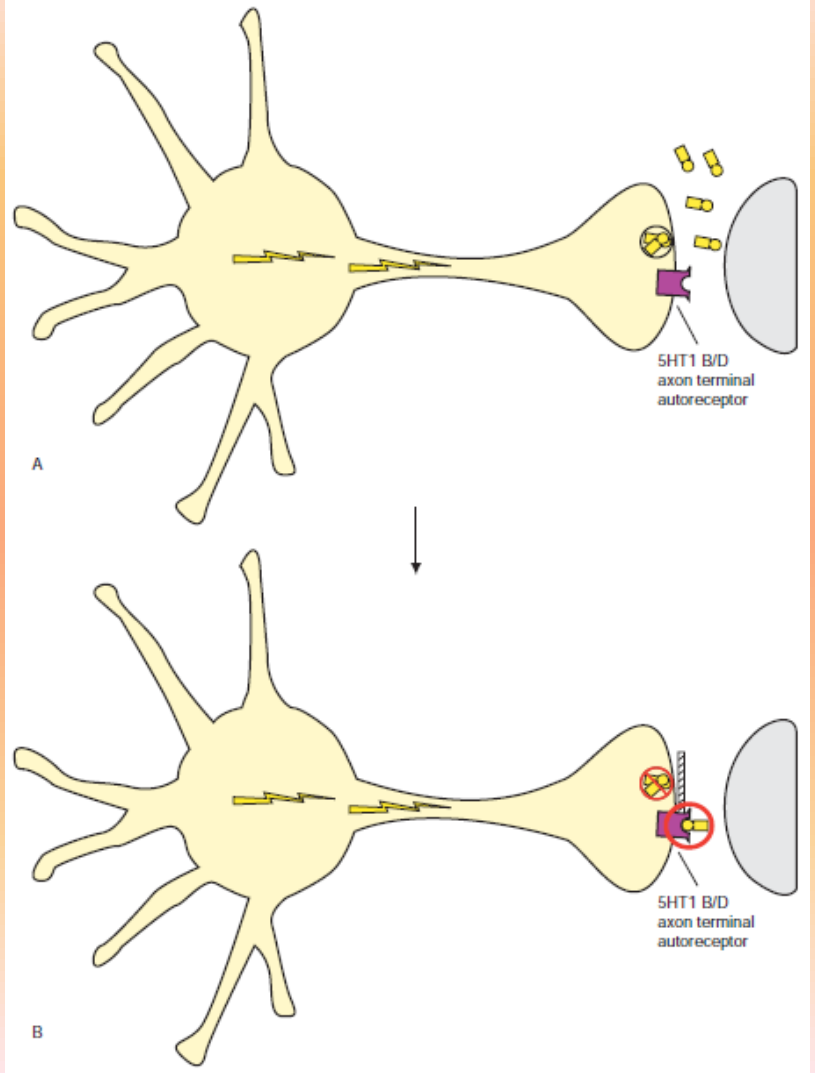


Autopista metabólica

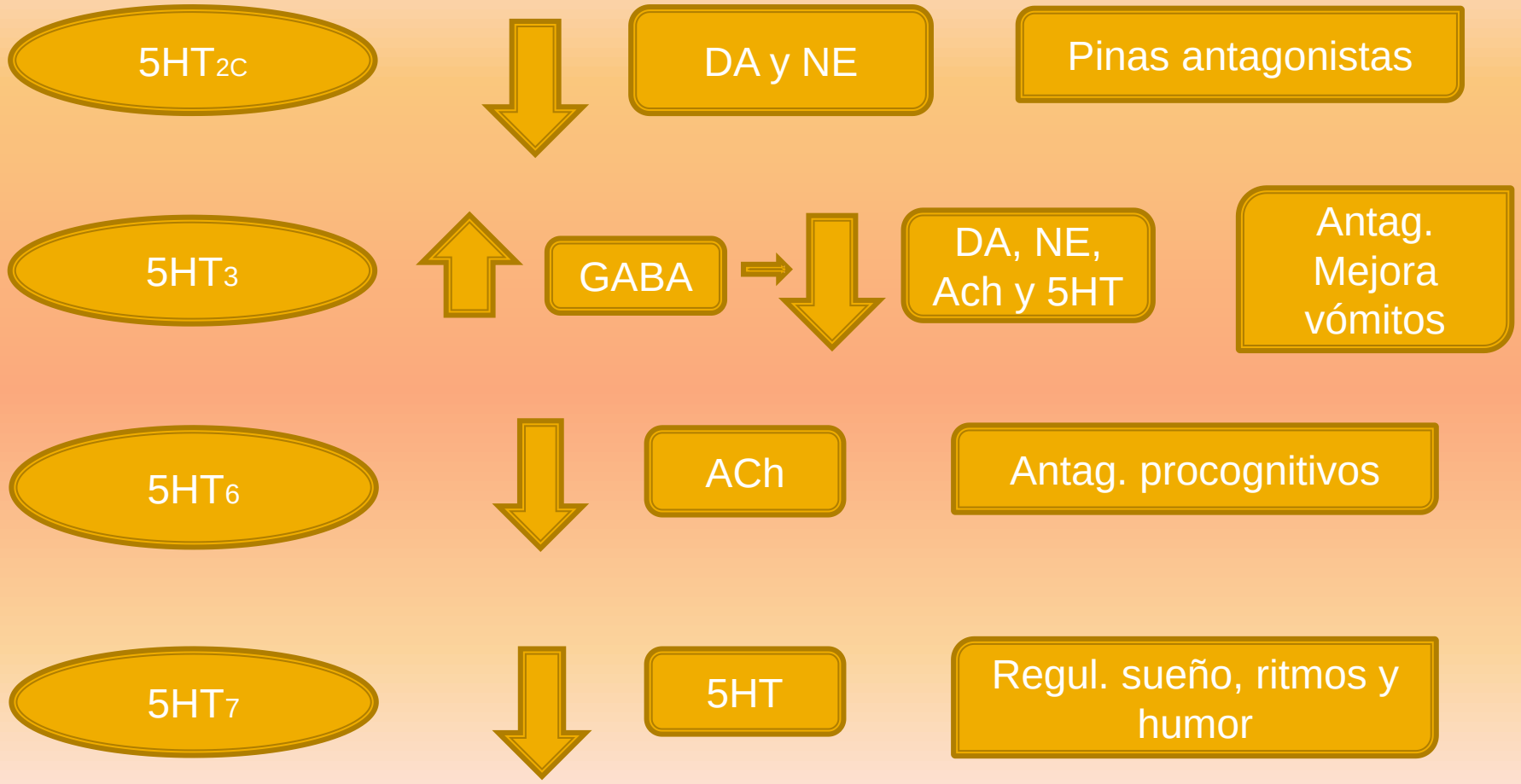


Autorreceptores serotoninérgicos

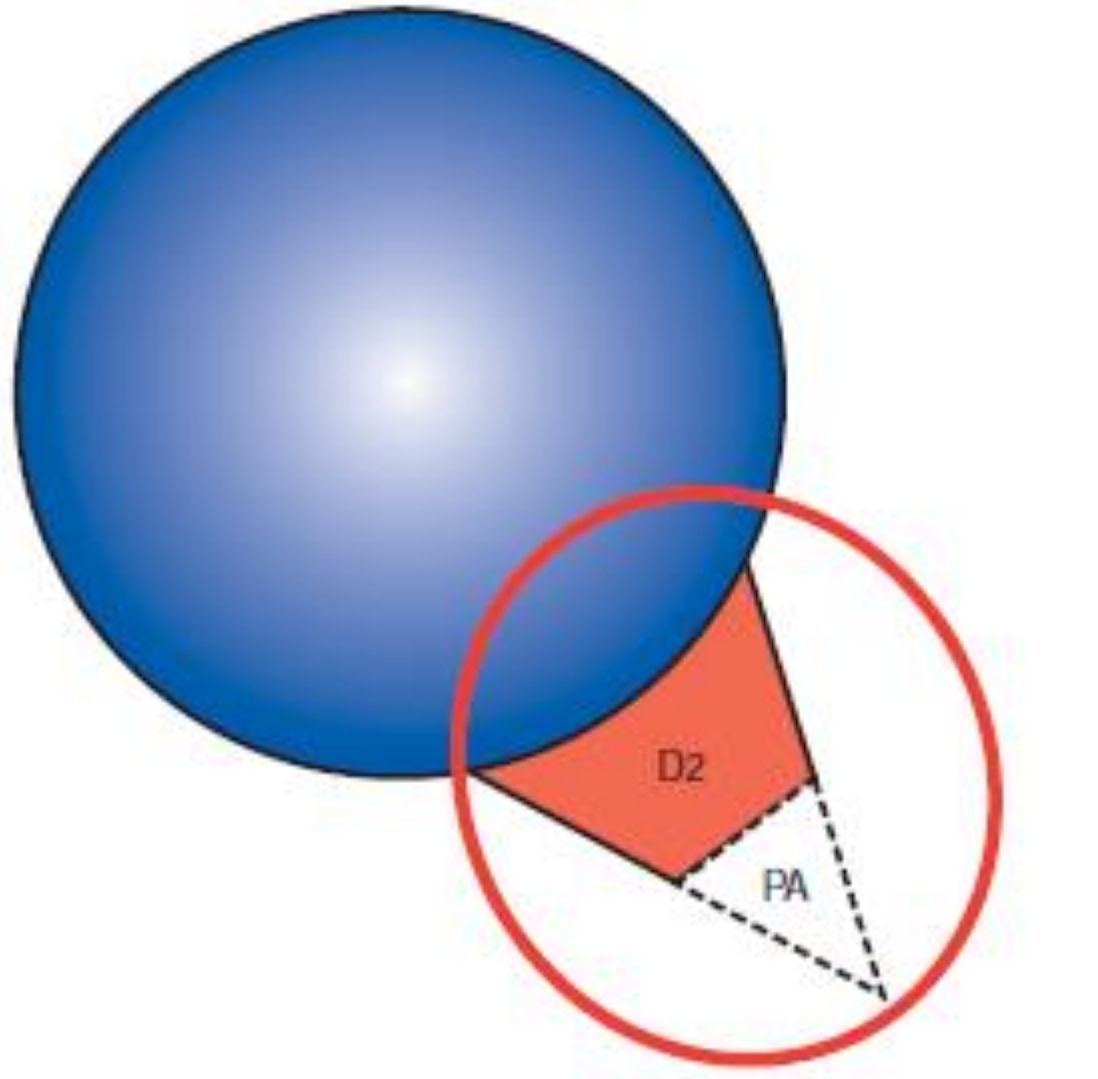




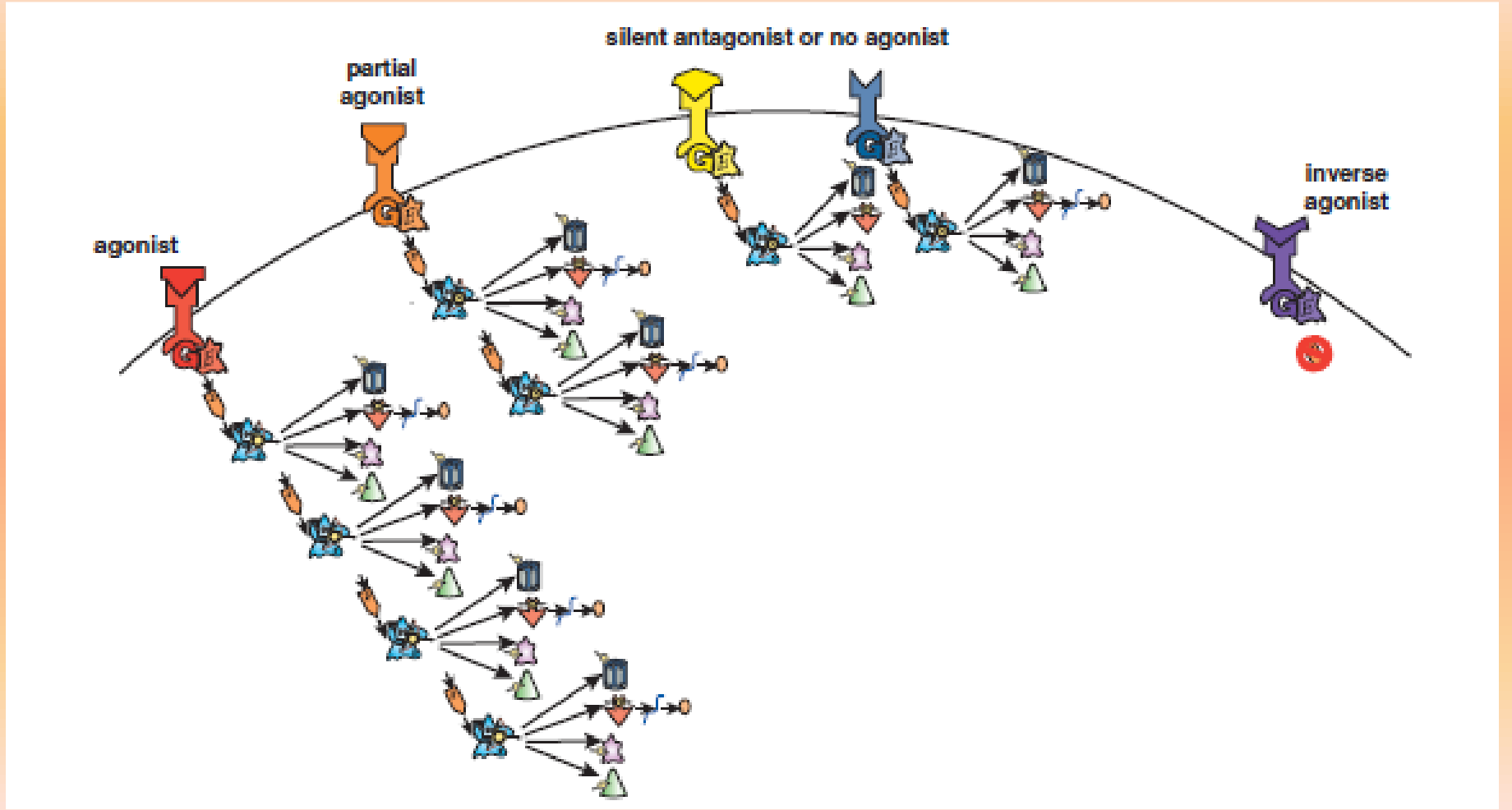
Otros receptores 5HT



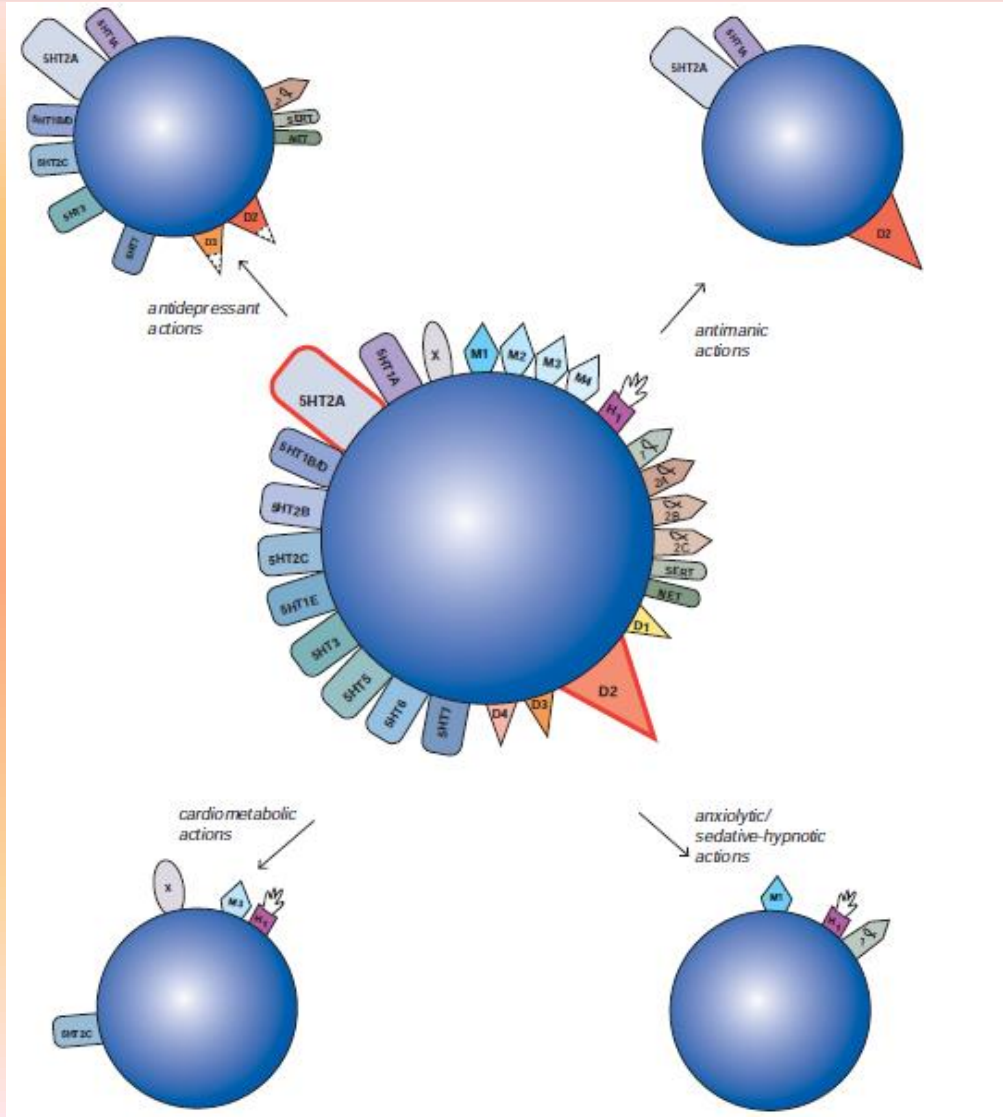
Otra posibilidad de antipsicótico atípico: agonista parcial D2



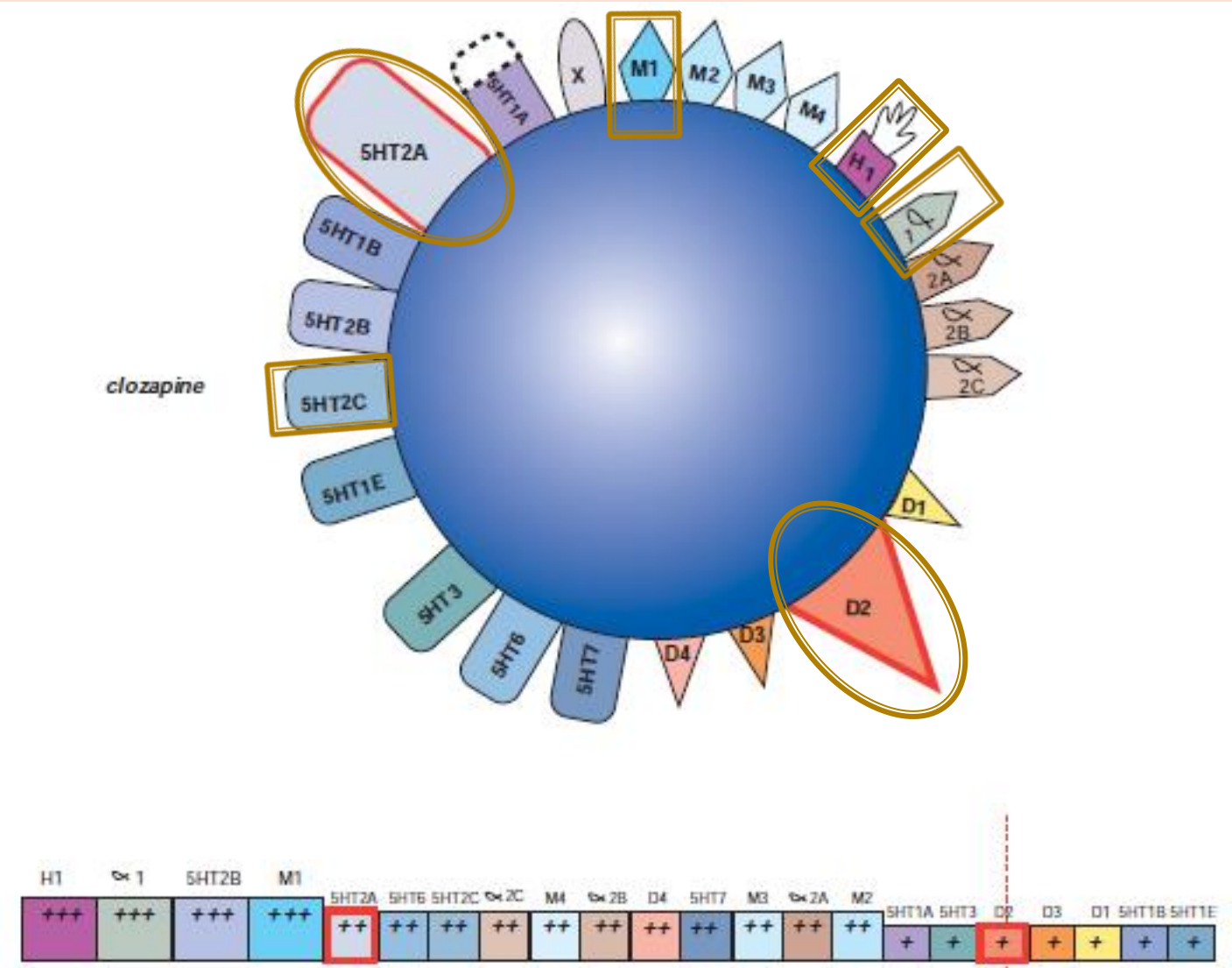
Espectro agonista



Acciones clínicas

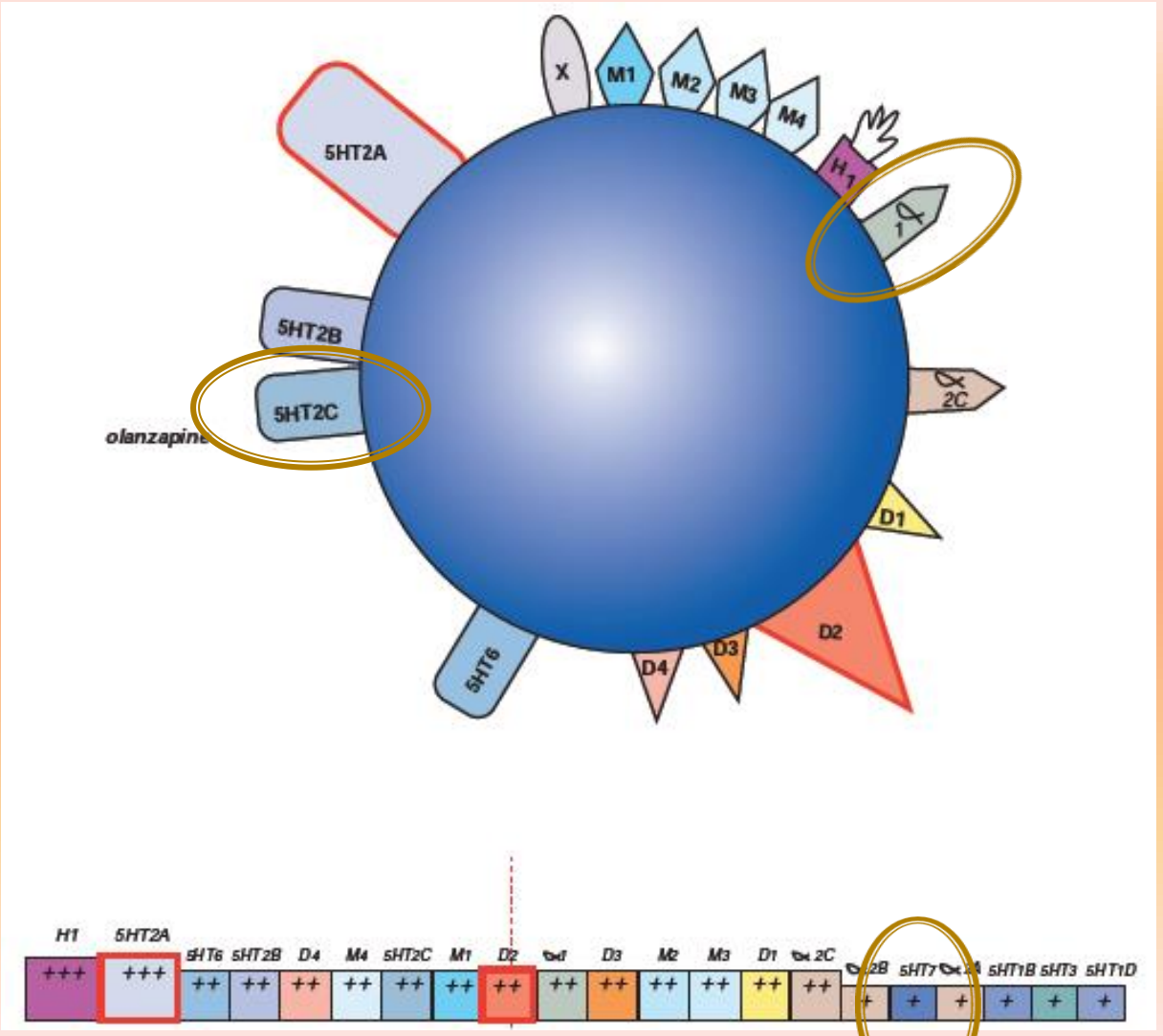


Antipsicóticos atípicos: las pinas

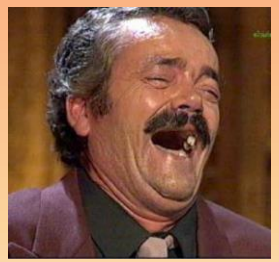


Agranulocitosis
convulsiones
exceso de saliva
miocarditis
ganancia peso
sedación

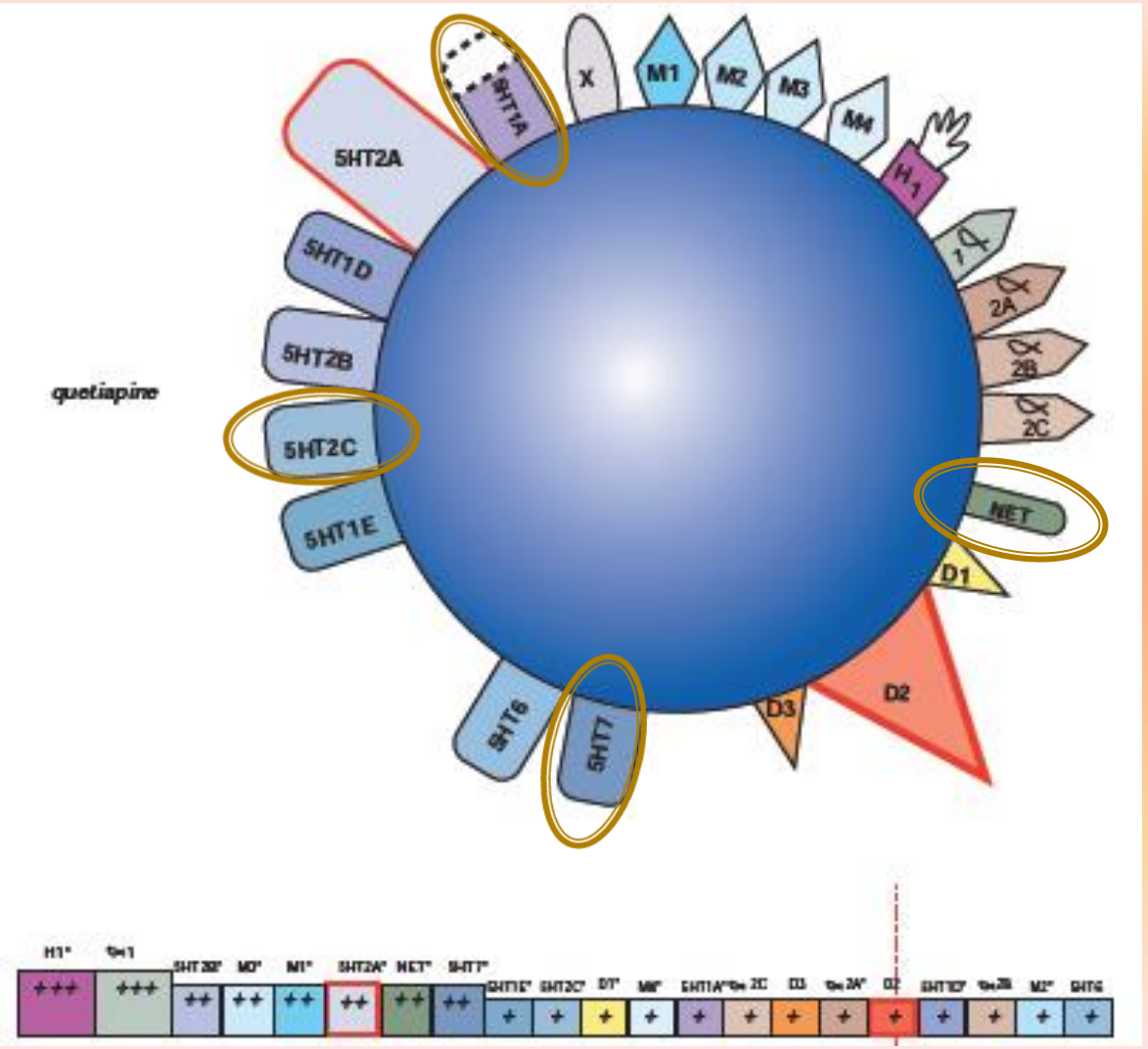
Antipsicóticos atípicos: las pinas



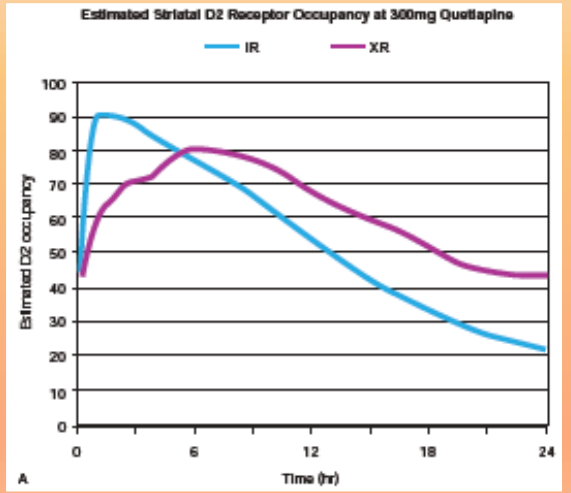
Sedación (- clo)
Ganancia de peso
Riesgo cardiometabólico

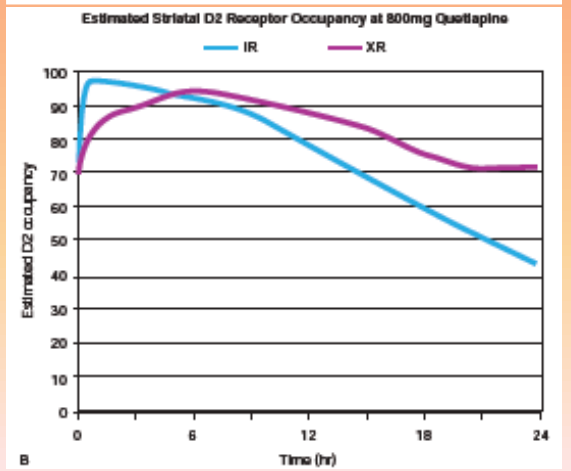


Antipsicóticos atípicos: las pinas



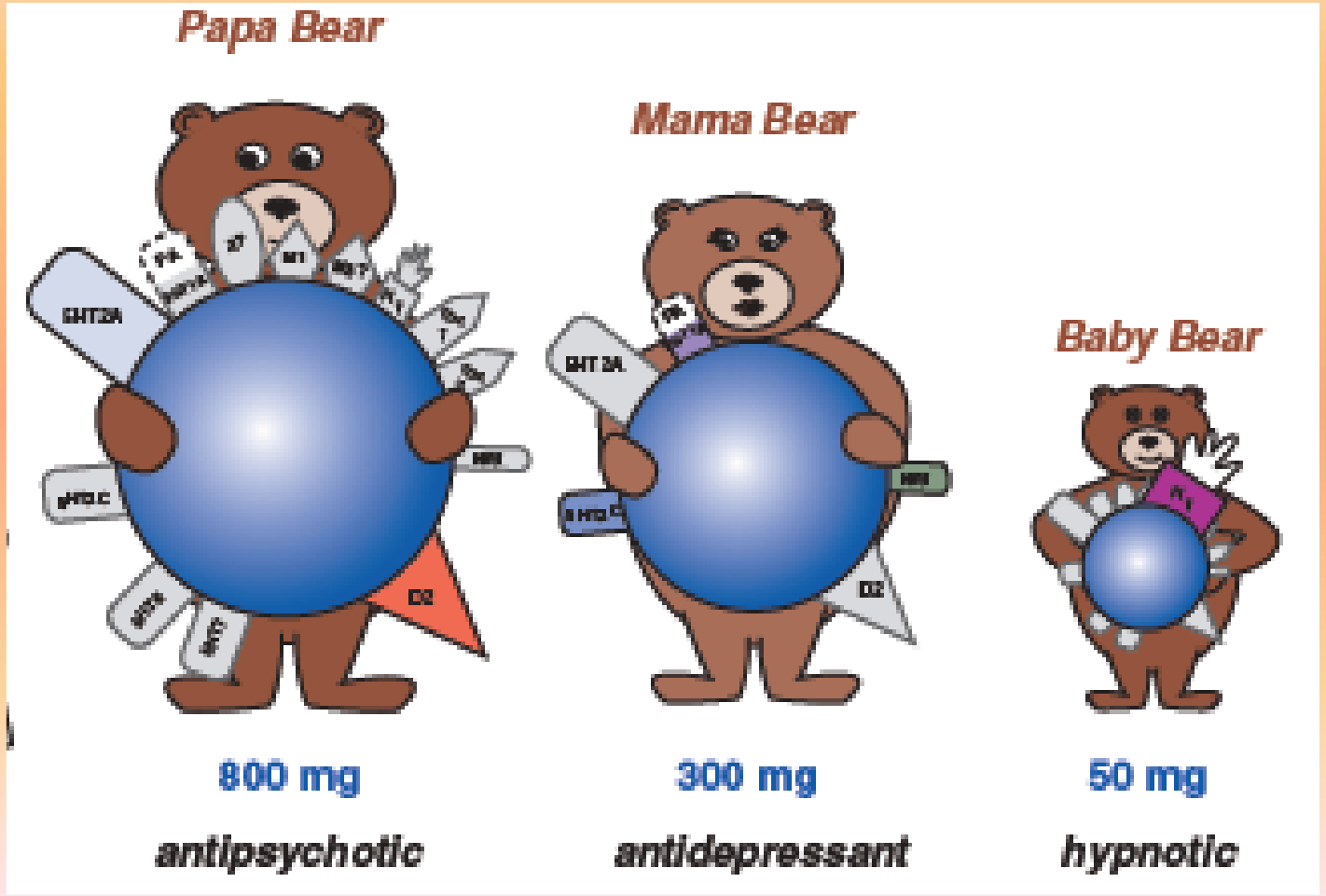
Metabolito norquetiapina



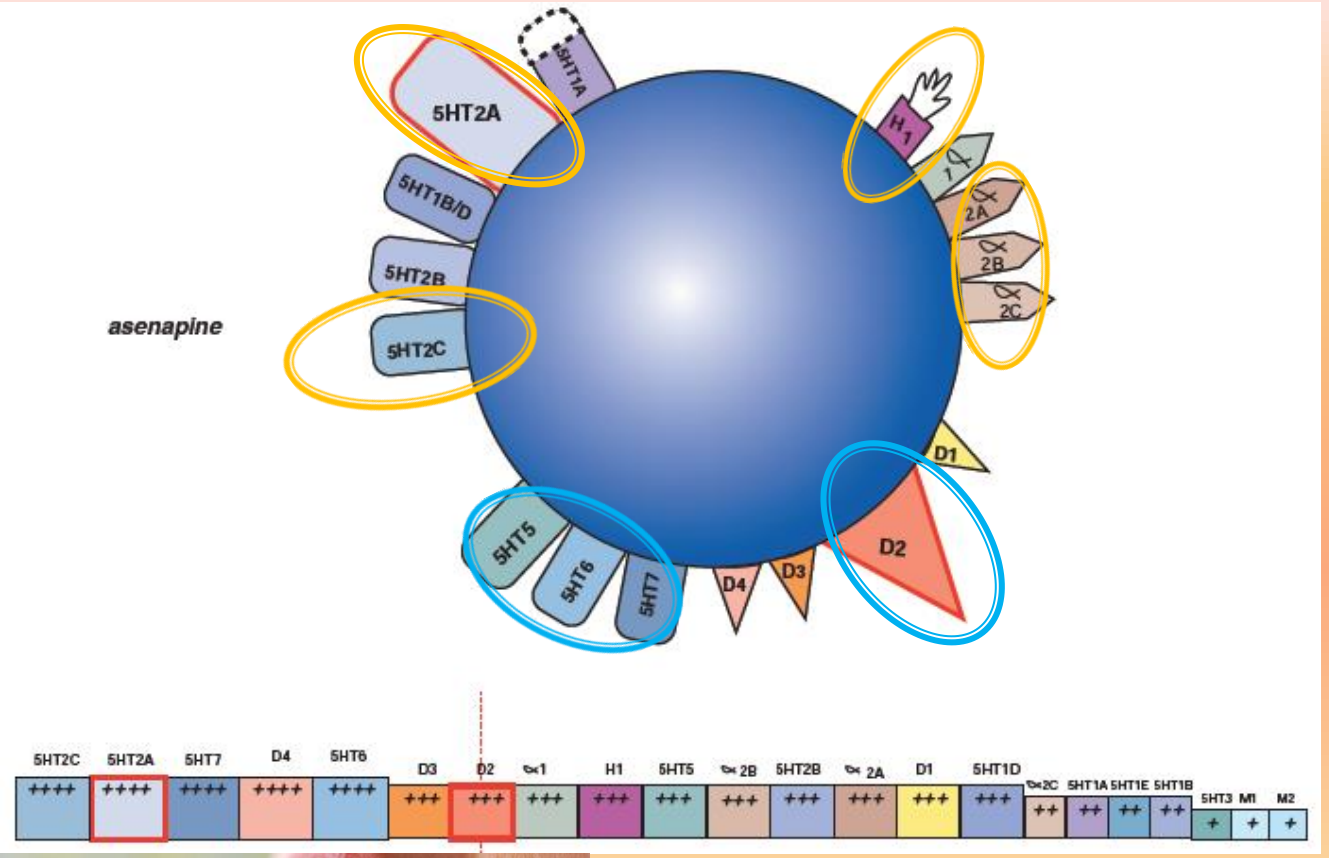


Antipsicóticos atípicos: las pinas

Quetiapina: 3 fármacos en uno



Antipsicóticos atípicos: las pinas



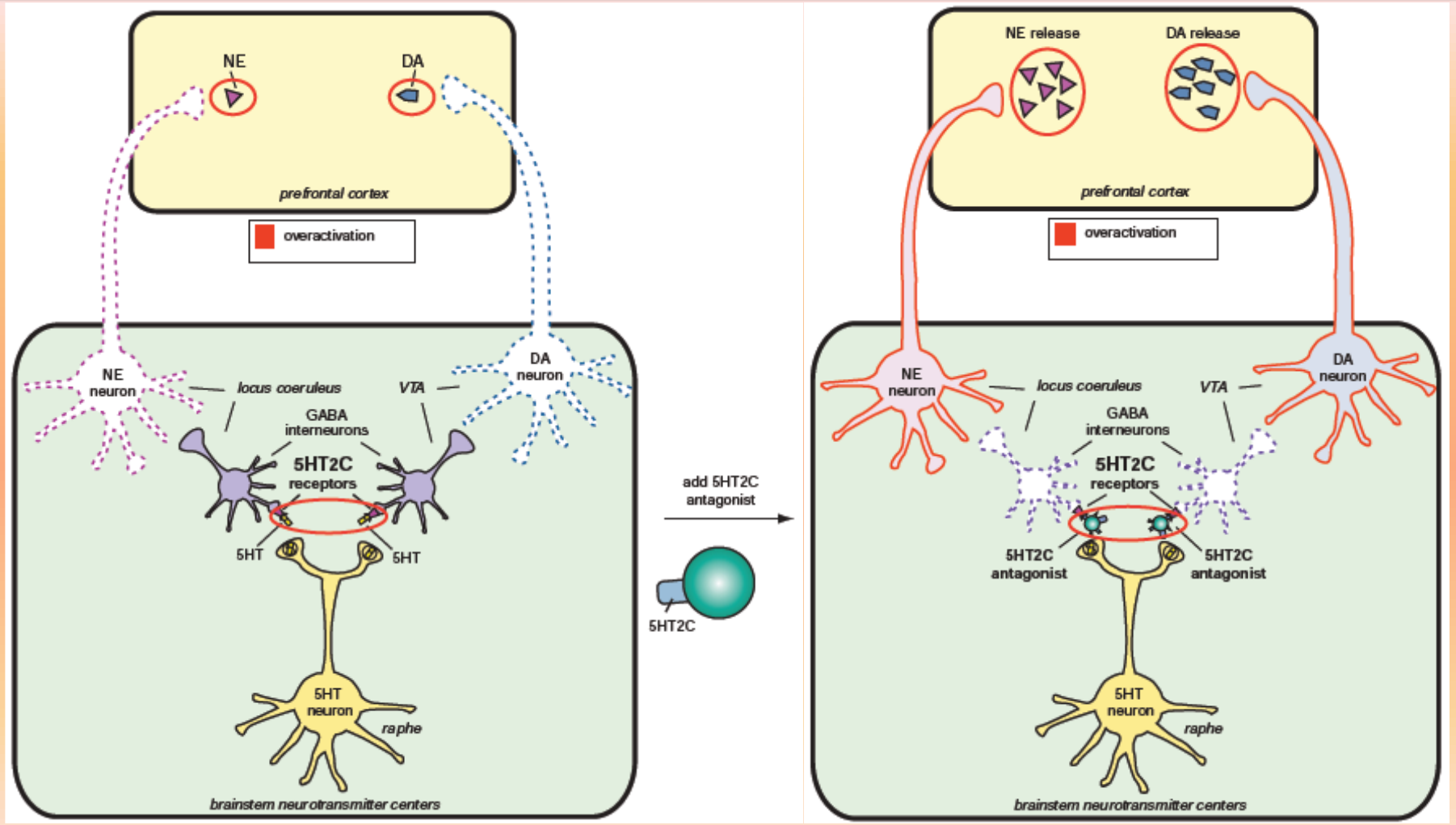
= Mirtazapina:

≠ Mirtazapina

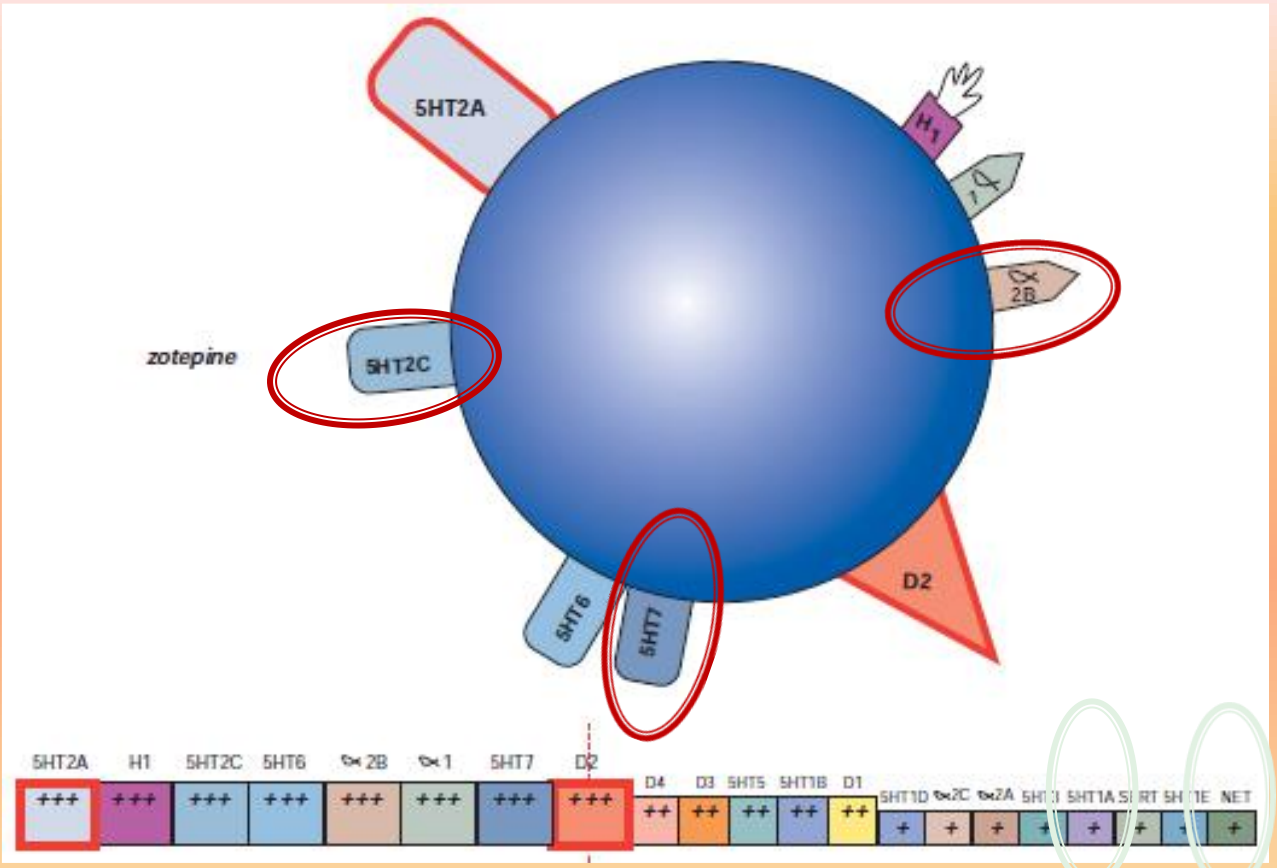
Teórico antipsicótico y antidepresivo

2 tomas diarias / uso antips. de acción rápida / hipoestesia oral / no comer ni beber hasta 10’ después

Efectos del antagonismo 5HT2C



Antipsicóticos atípicos: las pinas



Fuerte

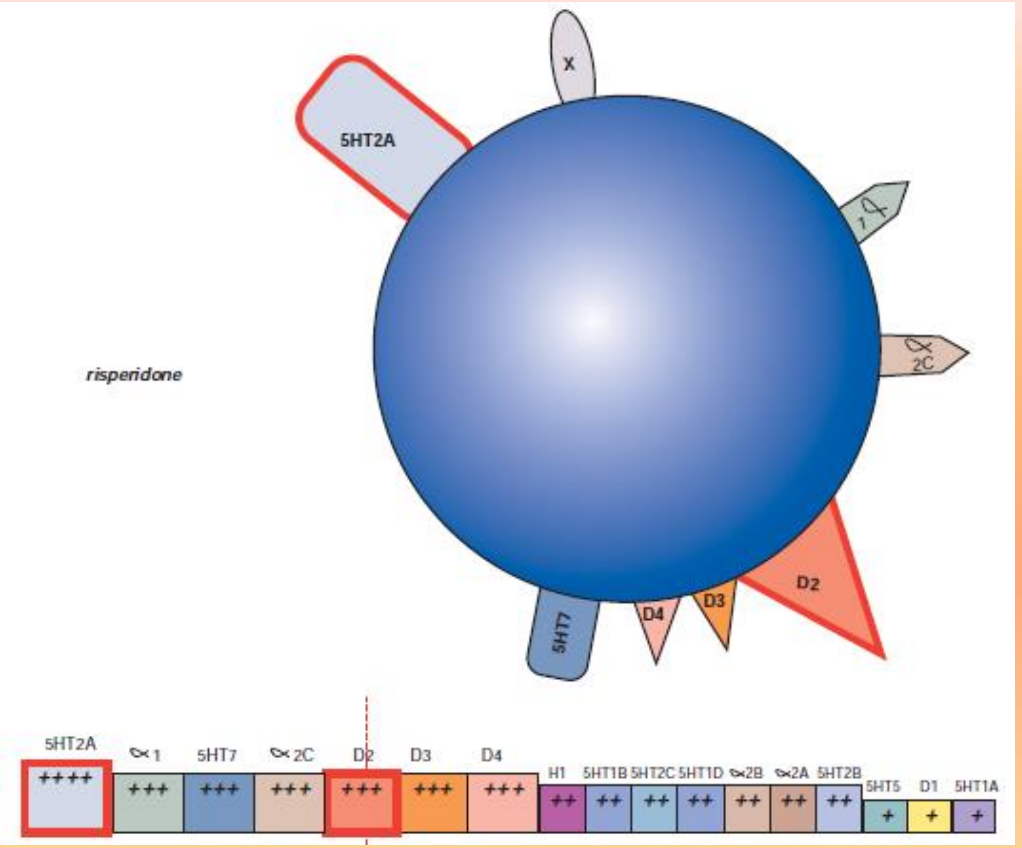
Débil

Sí en Japón y Europa

No en EE.UU.

Riesgo SEP / Elevación prolactina / Convulsiones / Aumento de peso y sedación

Antipsicóticos atípicos: las donas



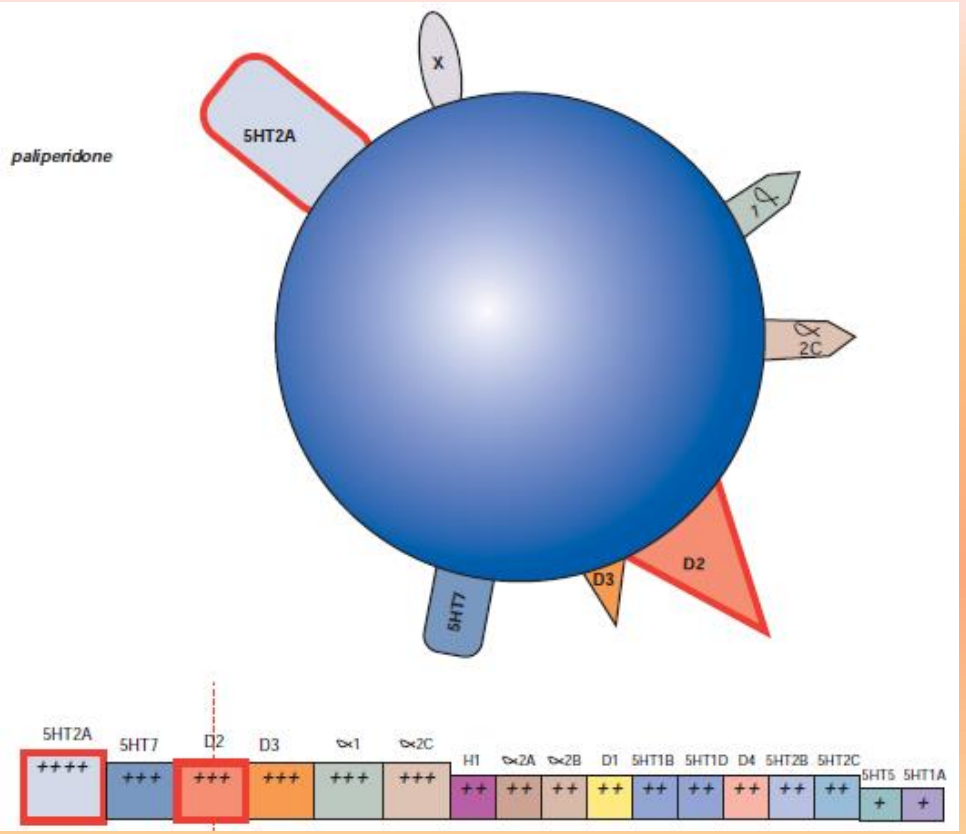
Atípico a dosis bajas
Convencional a dosis altas

Niños y adolescentes. Irritabilidad en autistas

Depot 15 días
Comprimidos
líquido

Aumento peso y prolac. Incluso a dosis bajas

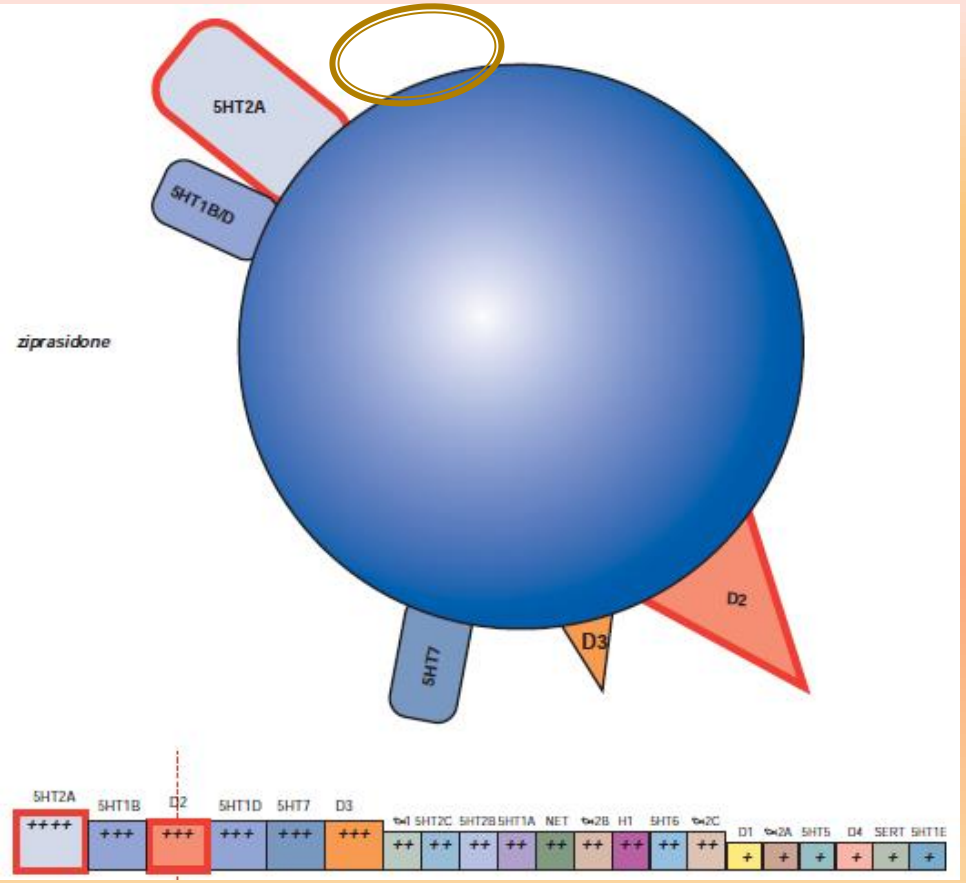
Antipsicóticos atípicos: las donas



Metabolito de Risperidona
Menos efectos secundarios
Mejor a dosis altas
Diferente farmacocinética
No metaboliza en el hígado

Oral de liberación prolongada -------- 1 dosis / día
Depot de 4 semanas --------- El depot preferido

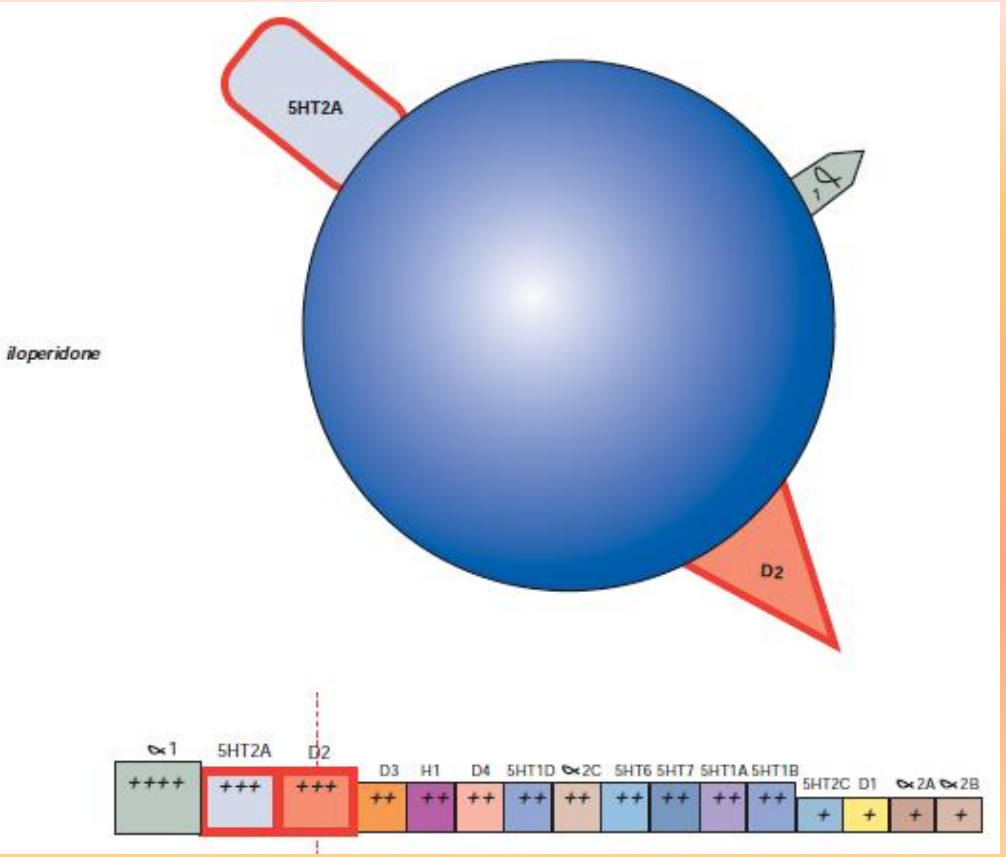
Antipsicóticos atípicos: las donas



NO GANANCIA DE PESO
No riesgo metabólico
No aumento intervalo Q-Tc

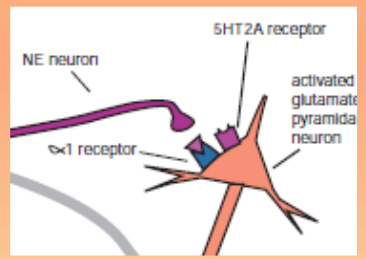
2 veces al día con comida 500 cal. / intramuscular de urgencia

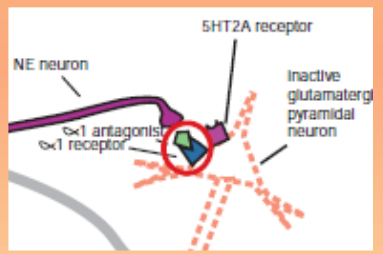
Antipsicóticos atípicos: las donas



Bajo SEP
Baja dislipidemia
Poco aumento de peso

Antagonismo α como cloza y + que queti

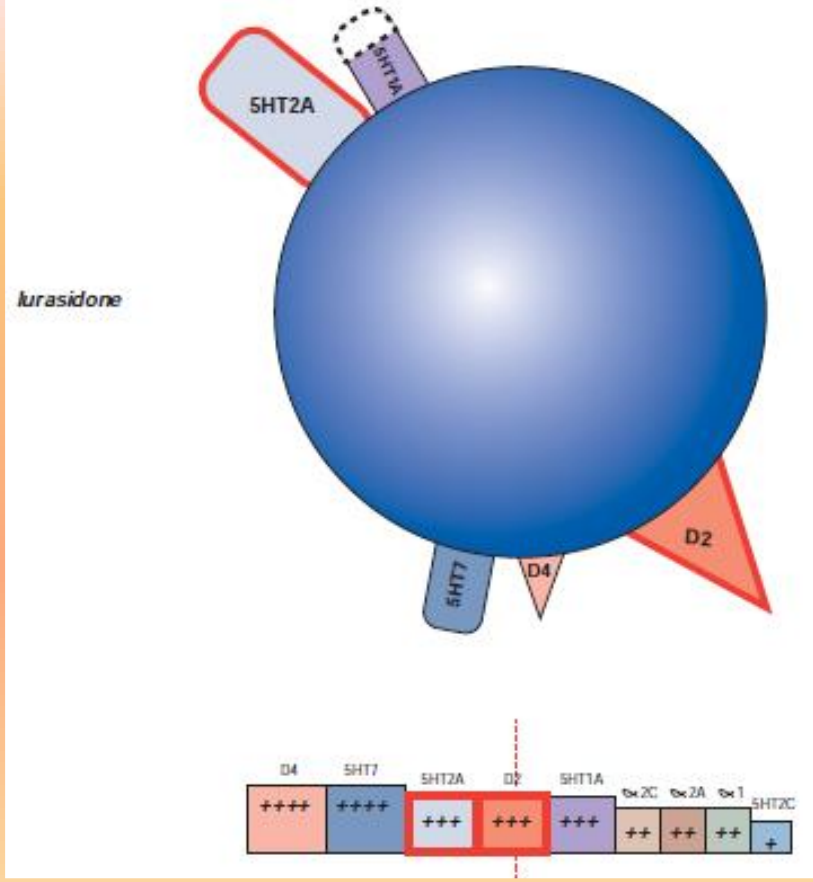




α

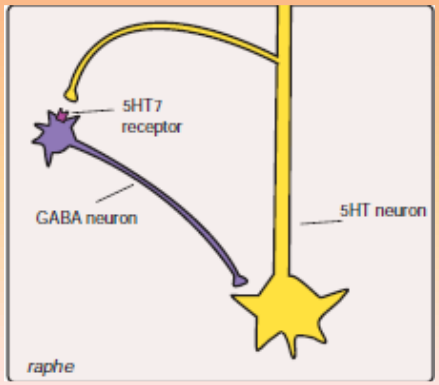
Desceso tensión → 2 dosis / día e ir ajustando → no sustituto rápido

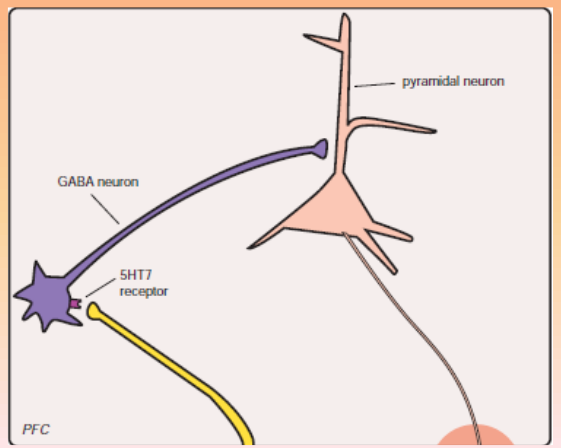
Antipsicóticos atípicos: las donas



No sedación / No peso / No dislipidemia

Mejor con comida 500 cal

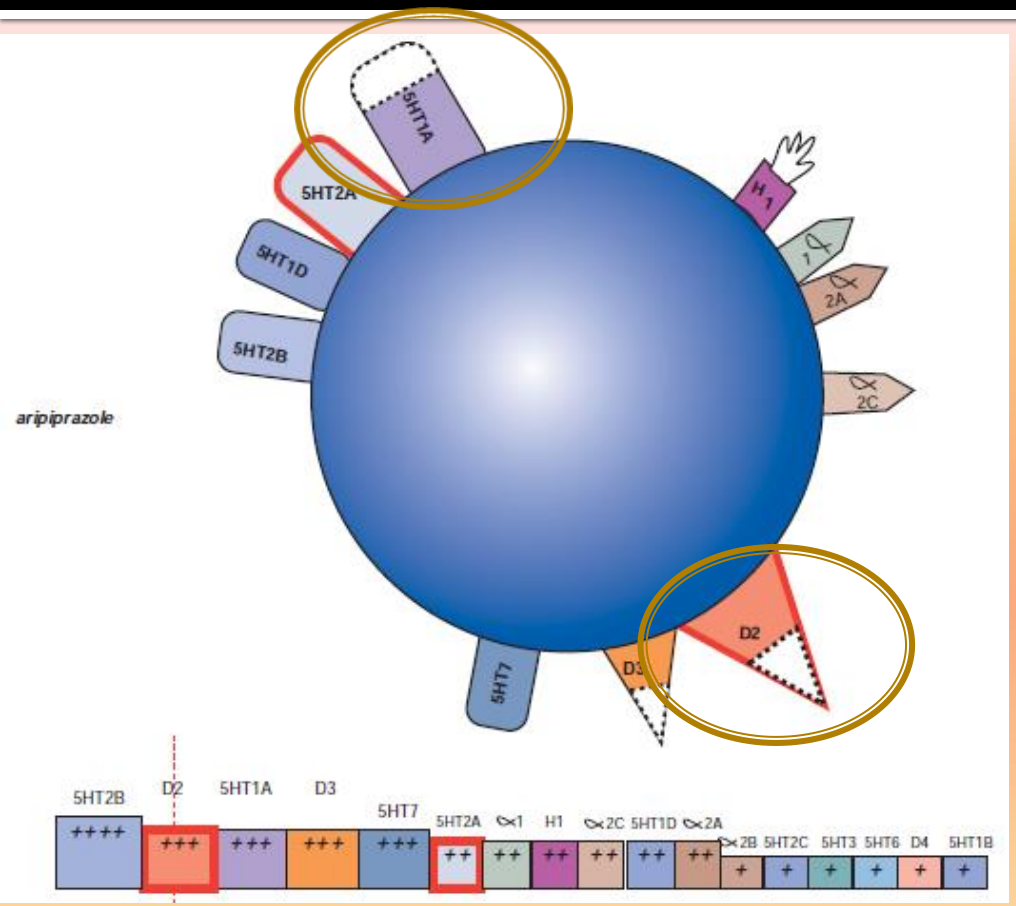




La rona

- Lumateperona
  - - A diferencia de donas, inhib recap 5HT
  - - Pruebas preclínicas indican que puede funcionar sobre D2 como agonista presináptico y como antagonista postsináptico

Antipsicóticos atípicos: 2 pips y 1 rip



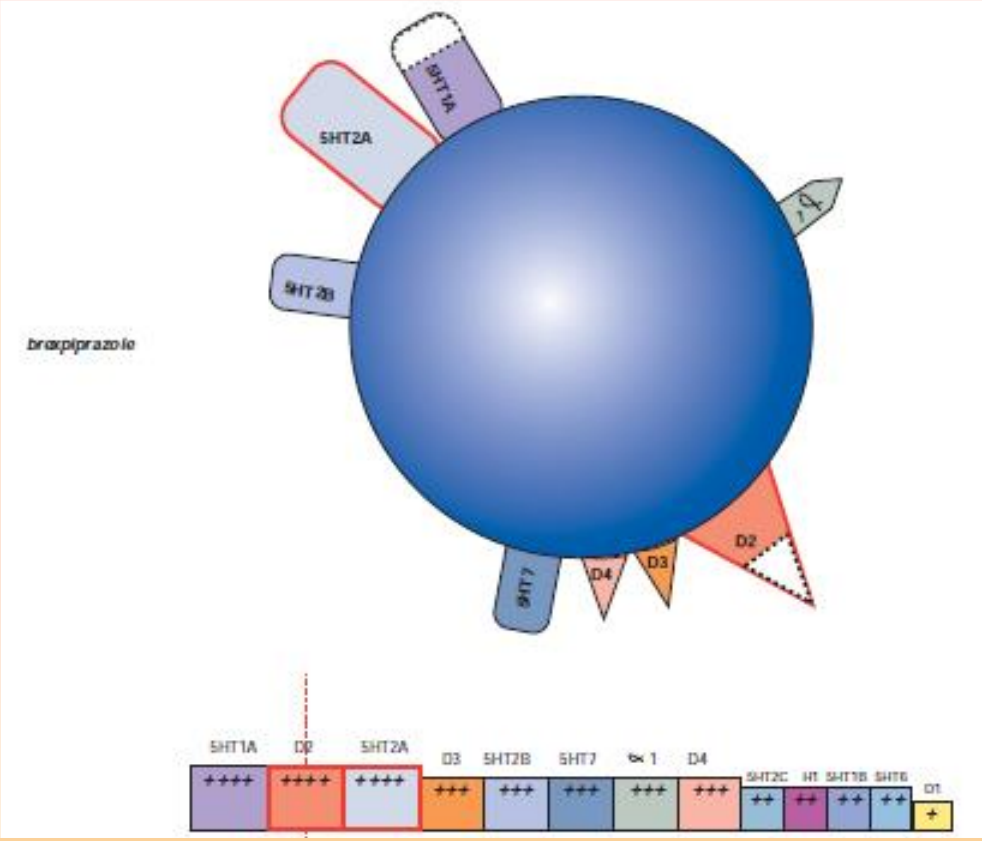
Eficaz en esquizofrenia y manía

Niños y adolescentes. Agitación en autistas

No aumento de peso ni dislipidemia

Antidepresivo a dosis bajas / más ago D2 a dosis bajas

Antipsicóticos atípicos: 2 pips y 1 rip

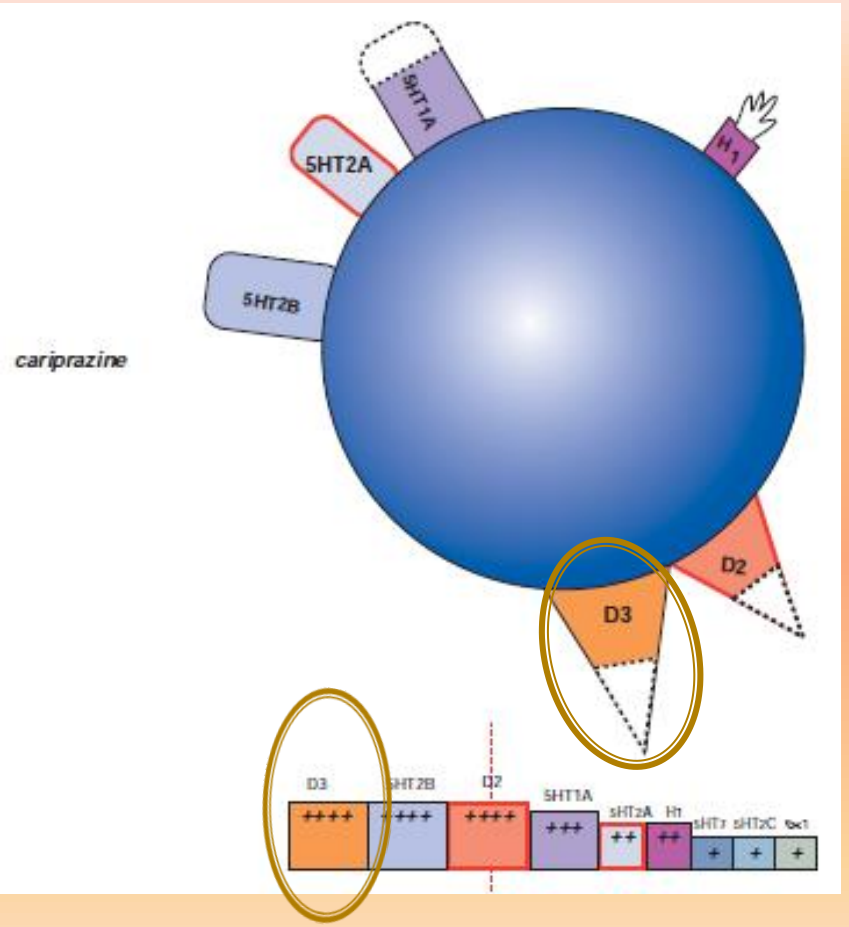


Respecto a Aripi:

- Más Ago Par 5HT1A
- Más Anta 5HT2A y $\alpha 1$

Potencialmente:
Antipsicótico más tolerable
Antidepresivo
Tratamiento para agitación y psicosis en demencia (Alfa 1)

Antipsicóticos atípicos: 2 pips y 1 rip



Potente ag/parc D3 = mejora sínt neg

Dosis altas → Manía y esquizofrenia

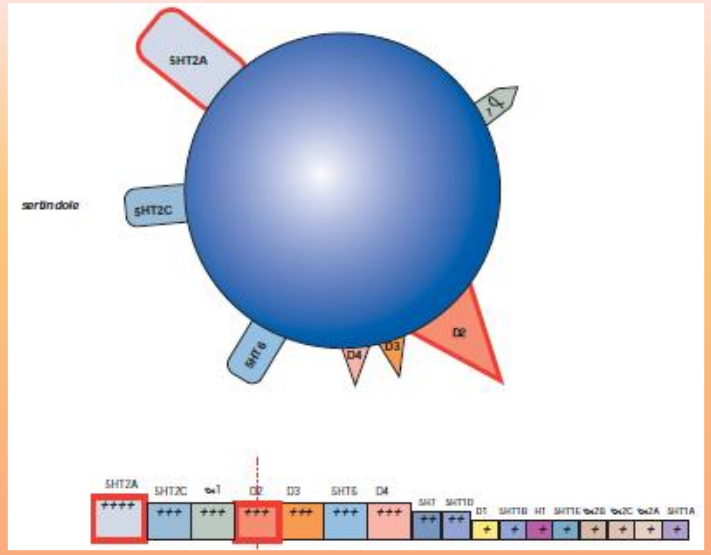
Dosis Bajas → Depresión

Dos metabolitos de muy alta duración → Posible **depot oral** hasta mensual

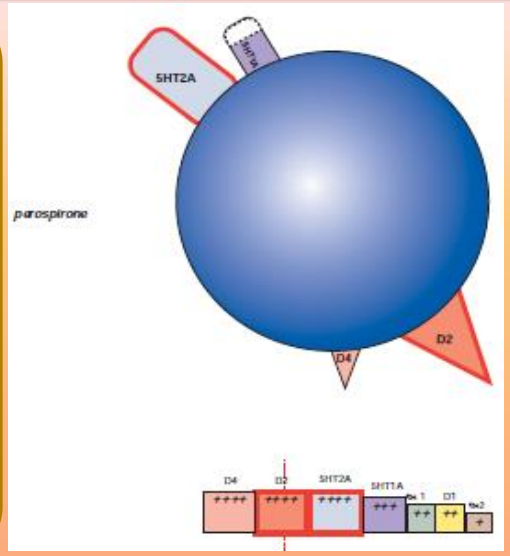
Antagonista selectivo 5HT2A

- Pimavanserina
  - - Único antipsicótico sin acción sobre D2
  - - Potente antag 5HT2A + antag 5HT2C
  - - Aprov para psicosis en Párkinson y última fase de ensayos para psicosis en demencia

Antipsicóticos atípicos: los otros



Anta
5HT2A-D2
Riesgo Q-Tc
Reintroduc.
2ª línea



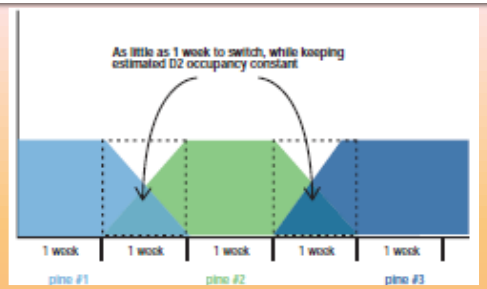
Anta
5HT2A-D2
Japón
Ago Par
5HT1A

Blonanserina

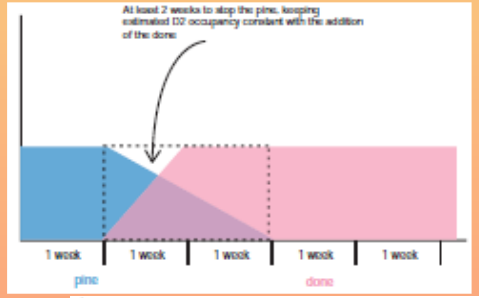
Anta 5HT2A-D2
Más afinidad x D3 que la DA
Posible mejora sínt neg y depre bipolar

Práctica clínica: A cambiar

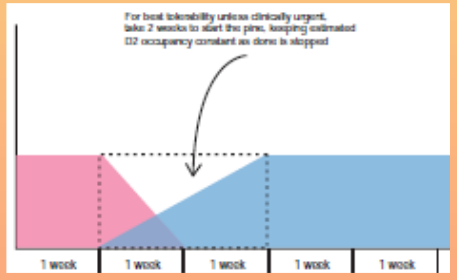
De = a =



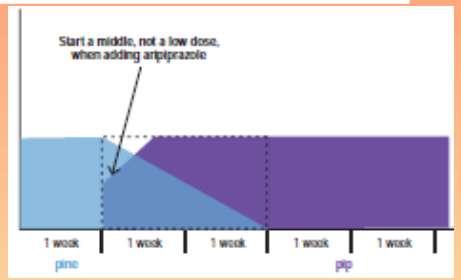
De P a D

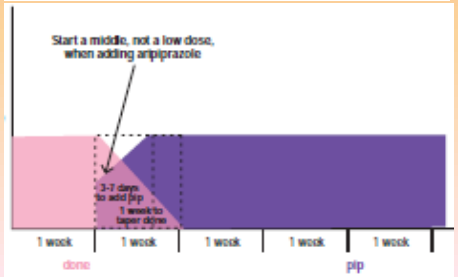


De D a P

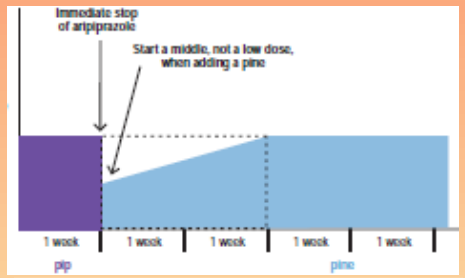


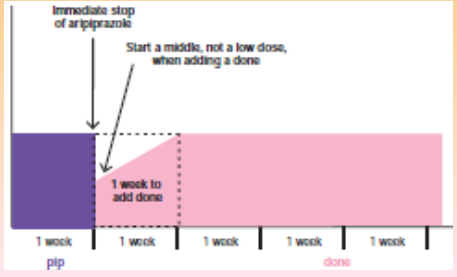
A Aripi



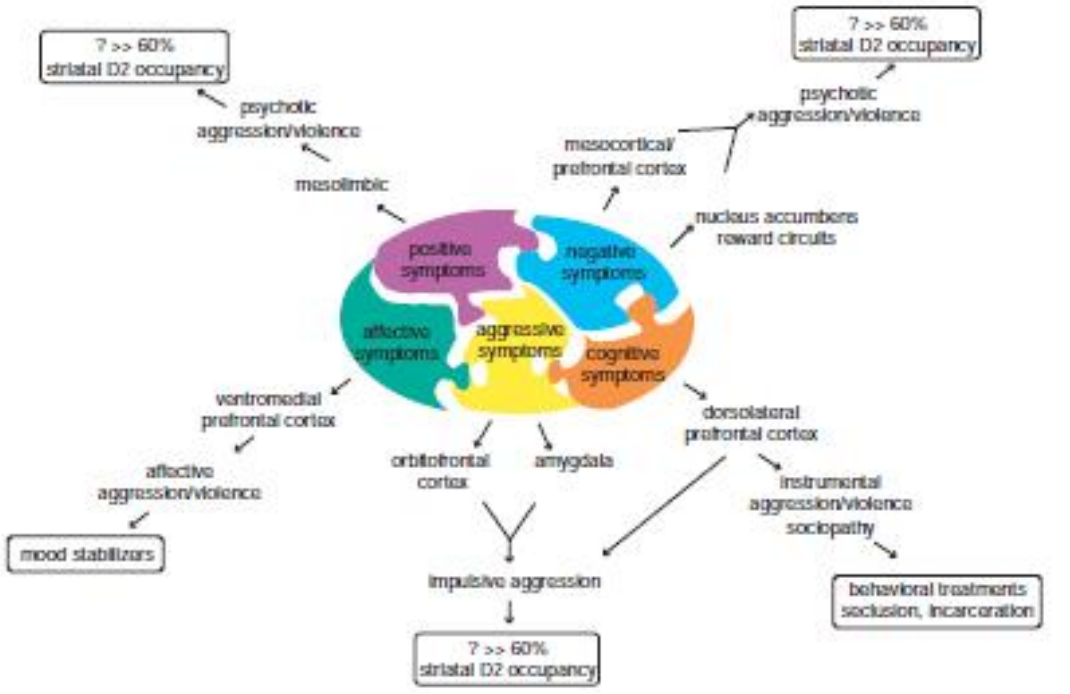


De Aripi





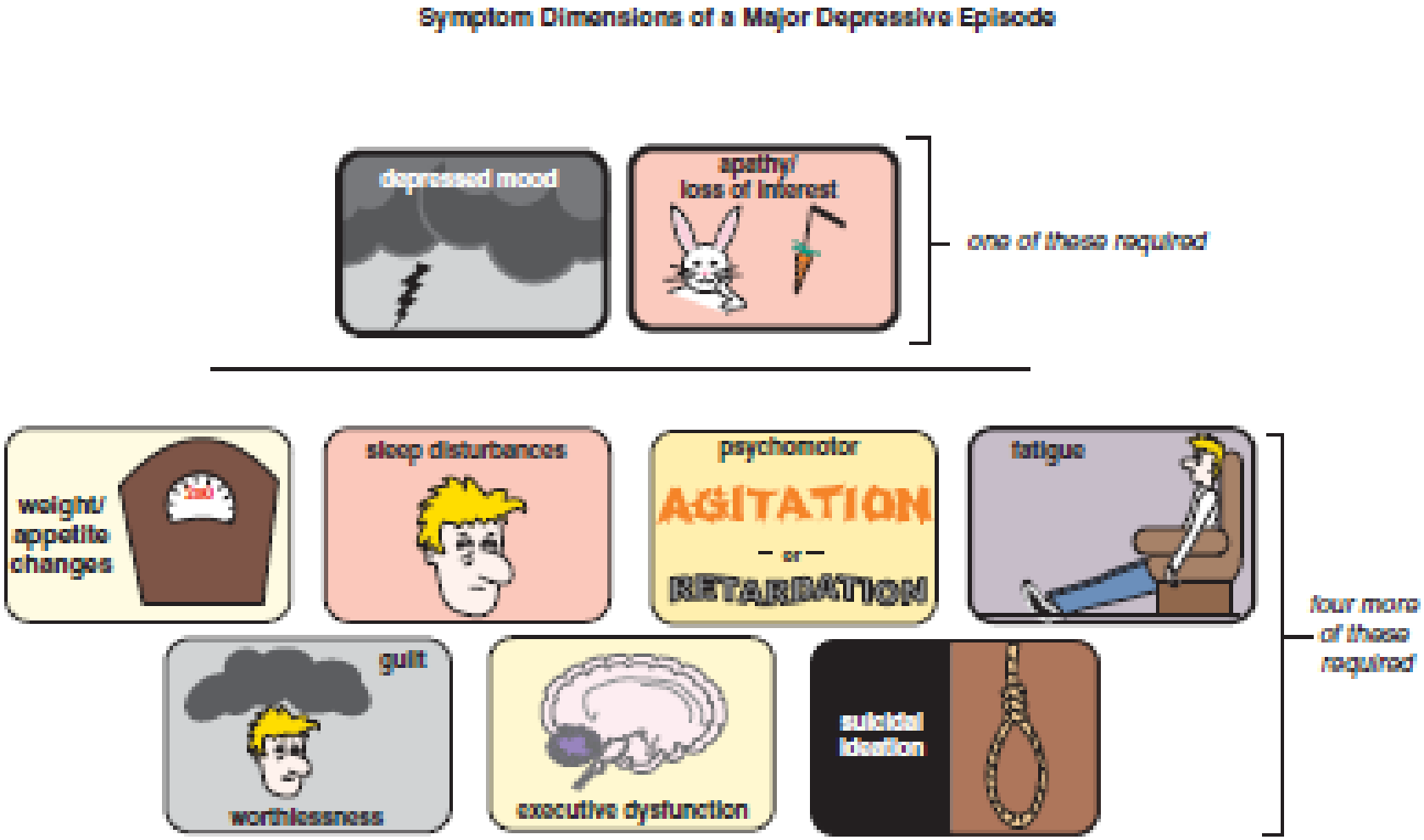
Práctica clínica: Violencia



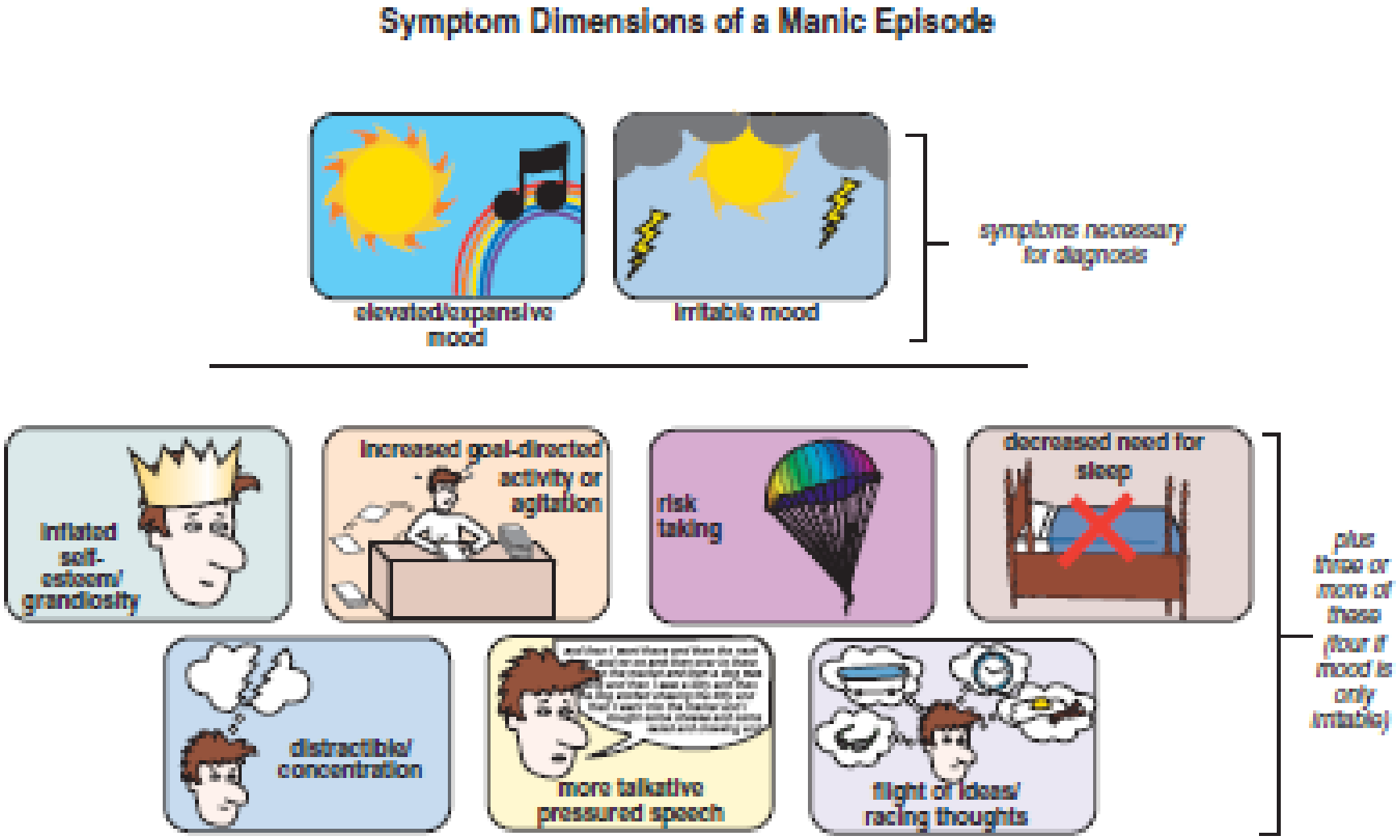
Fallo farmacoCINÉTICO

Fallo farmacoDINÁMICO

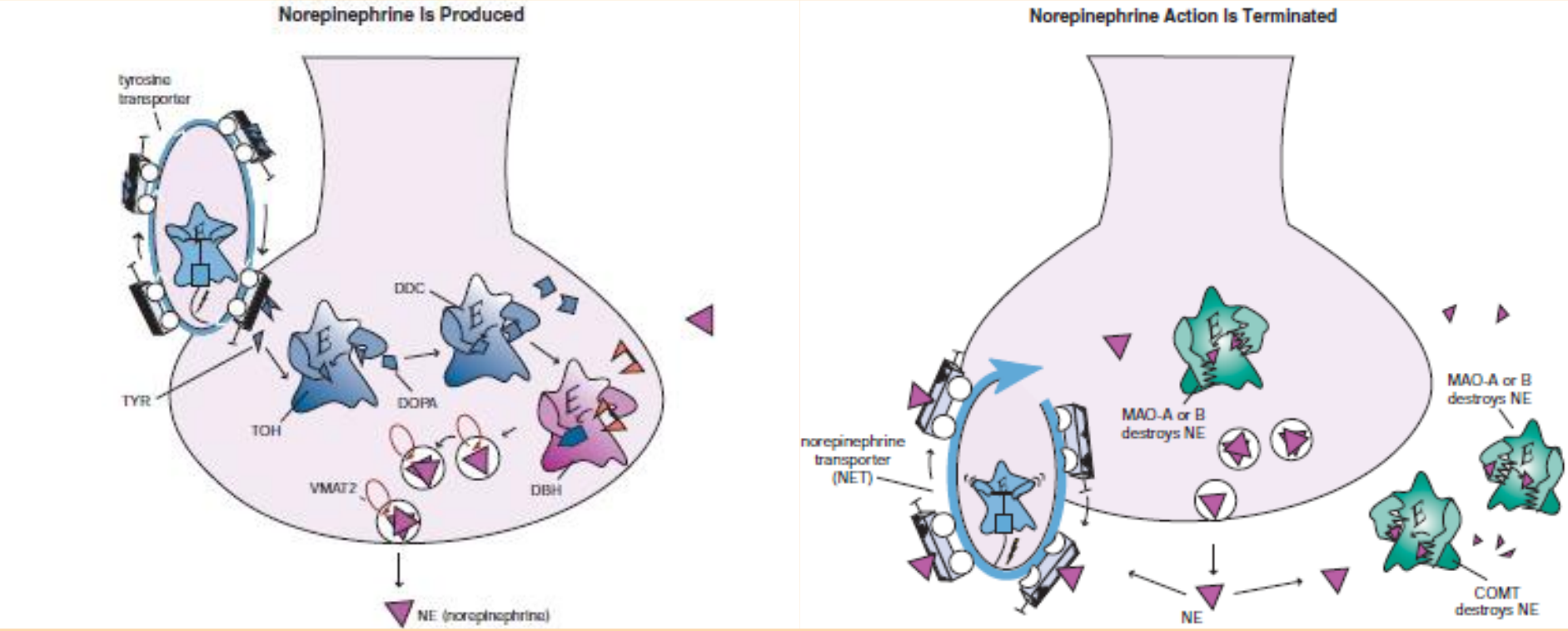
Trastornos del humor: Dimensiones sintomáticas



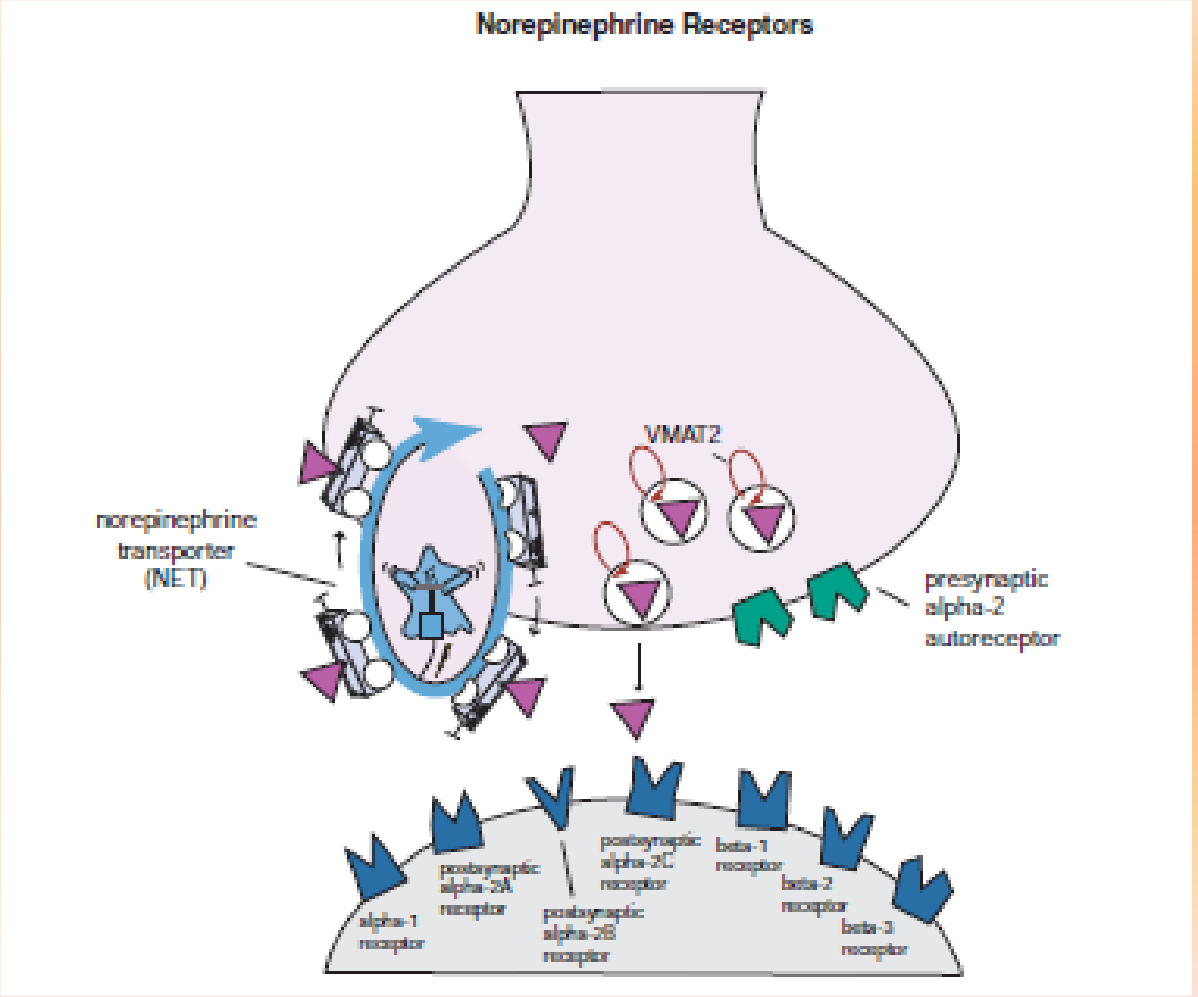
Trastornos del humor: Dimensiones sintomáticas



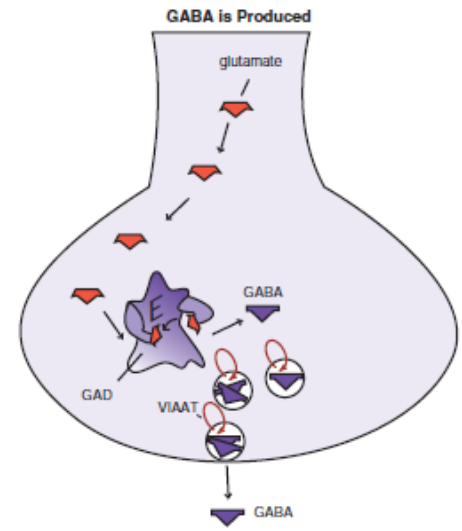
Trastornos del humor: La tercera monoamina

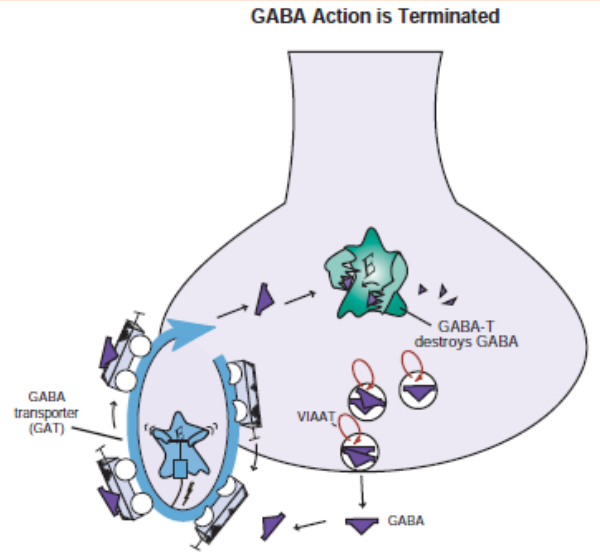


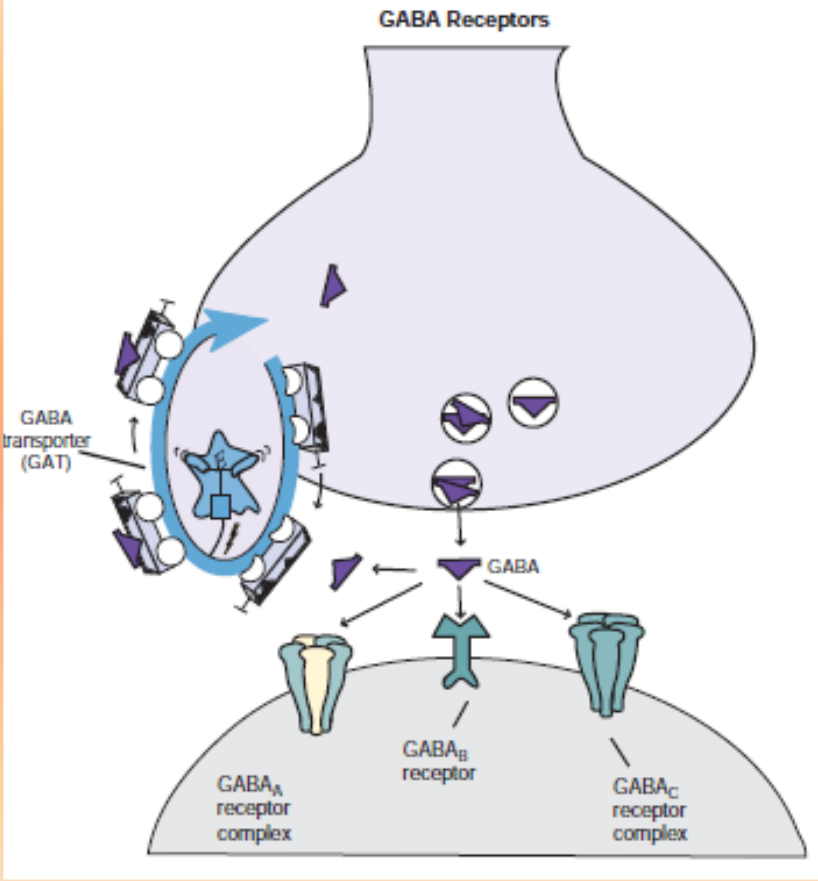
Trastornos del humor: La tercera monoamina



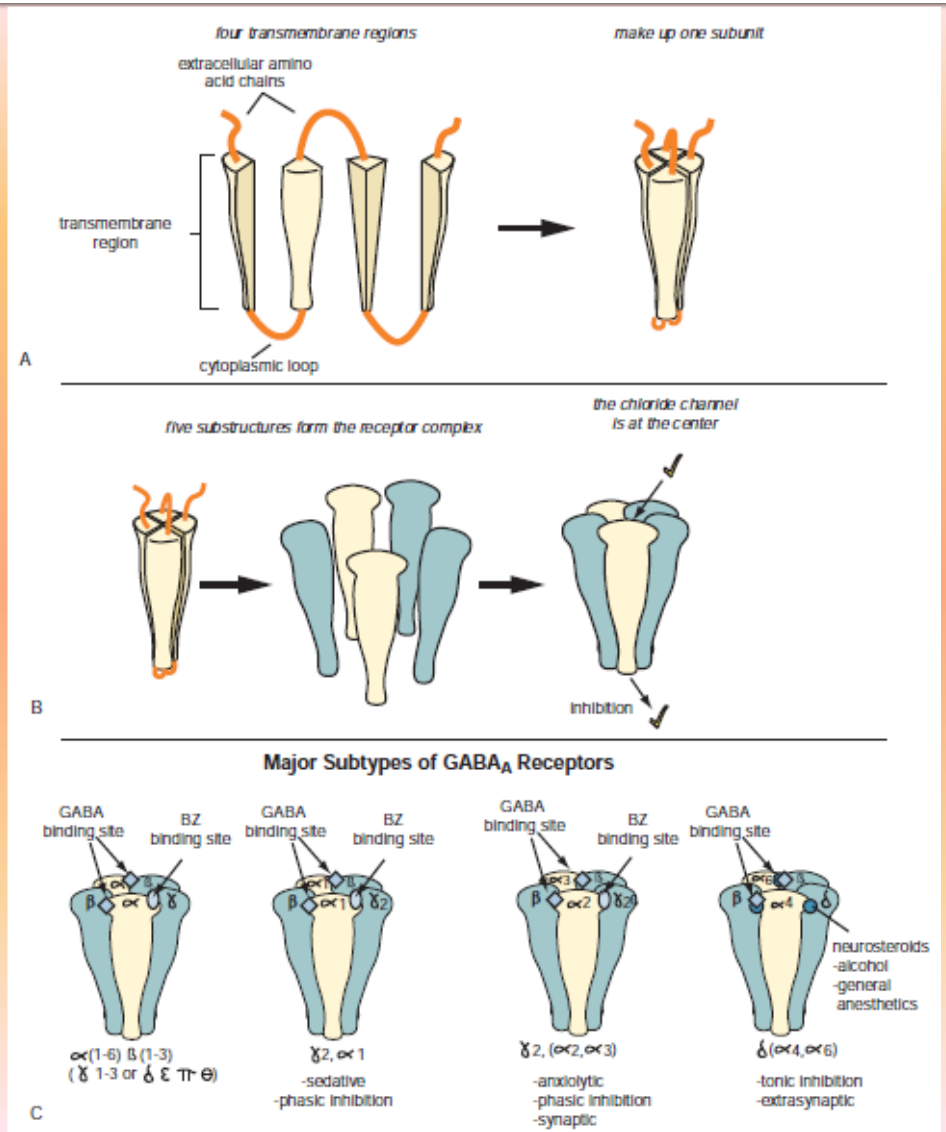
Neurotransmisión GABAérgica



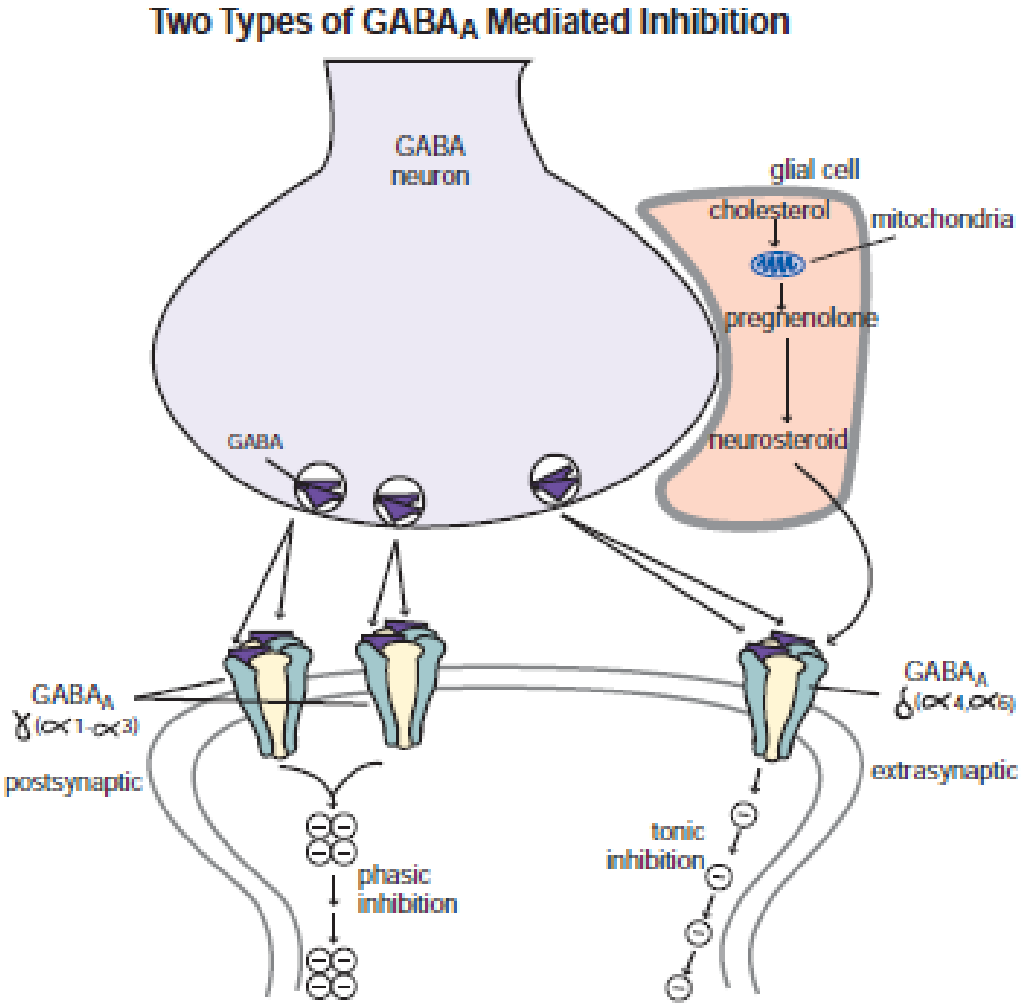




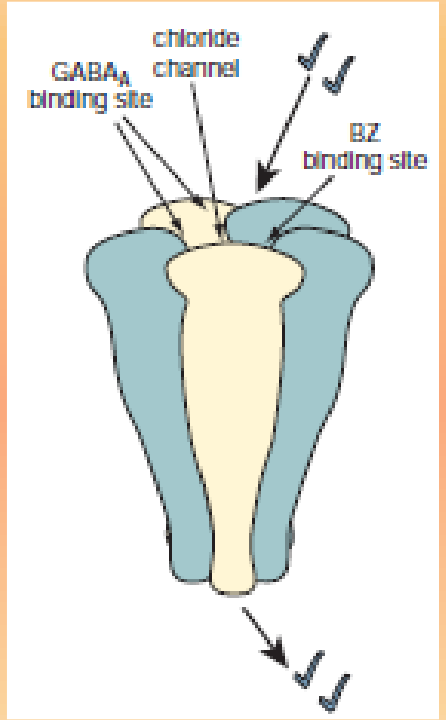
Estructura de receptores $GABA_A$

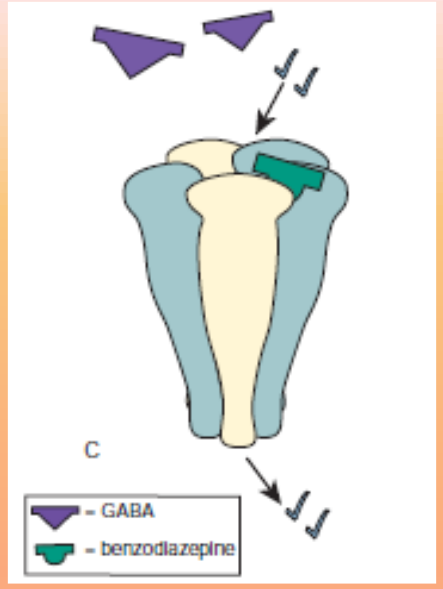


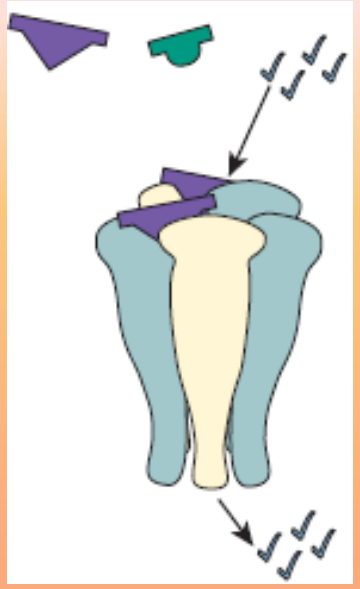
Inhibición GABAérgica



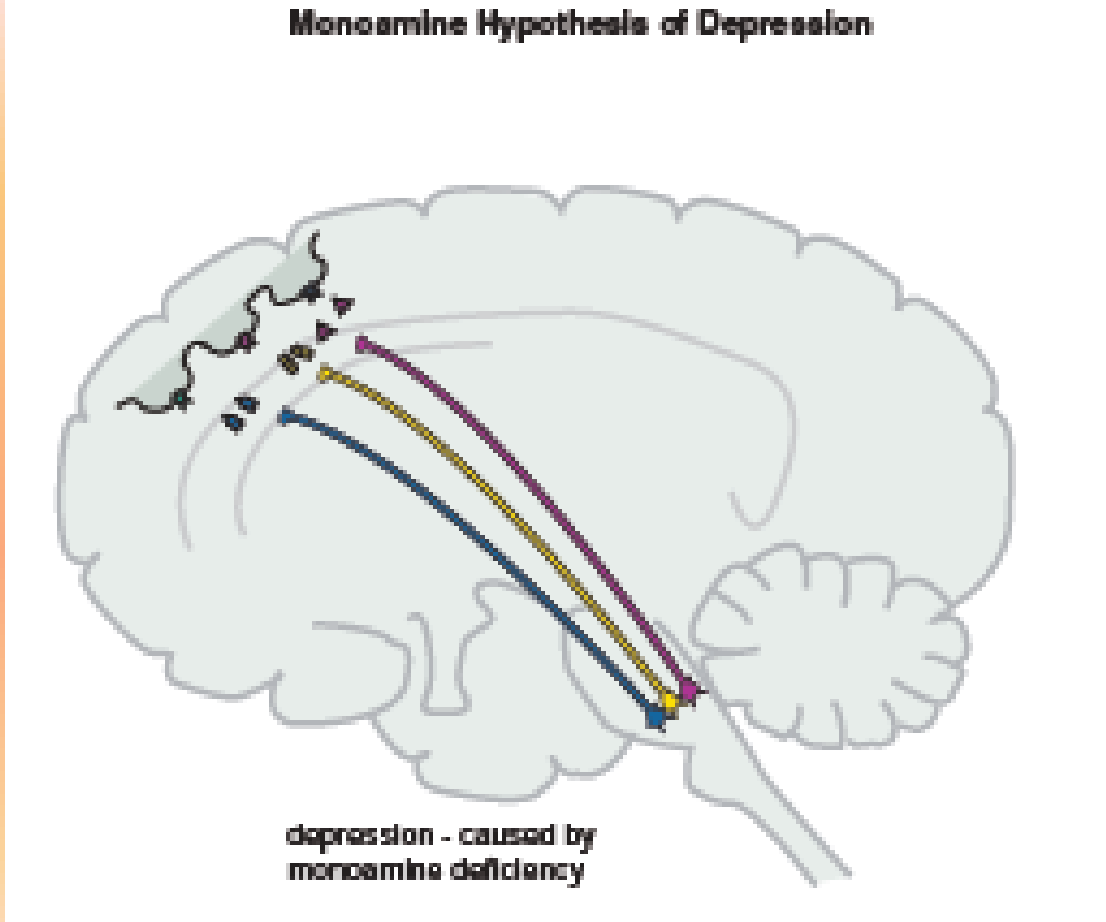
Inhibición GABAérgica





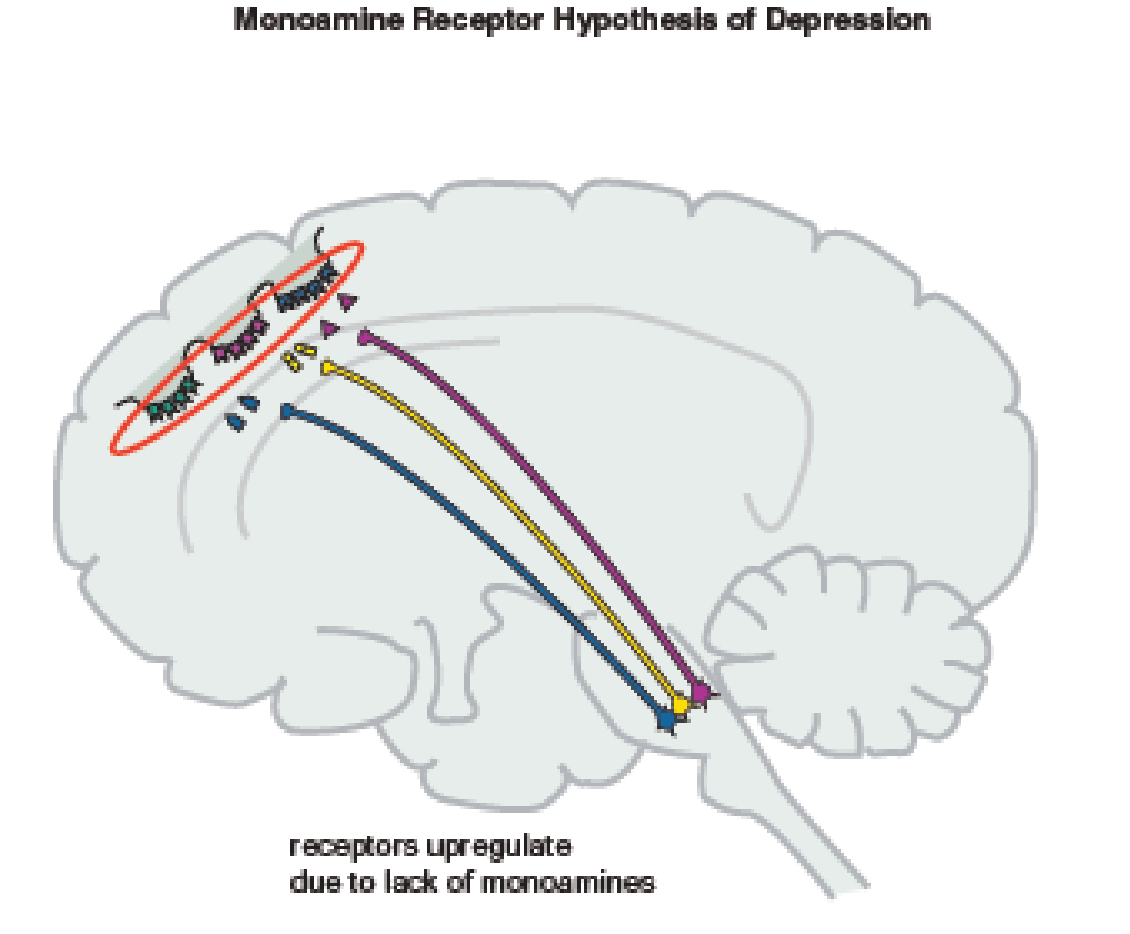


Trastornos del humor: Hipótesis monoaminérgica



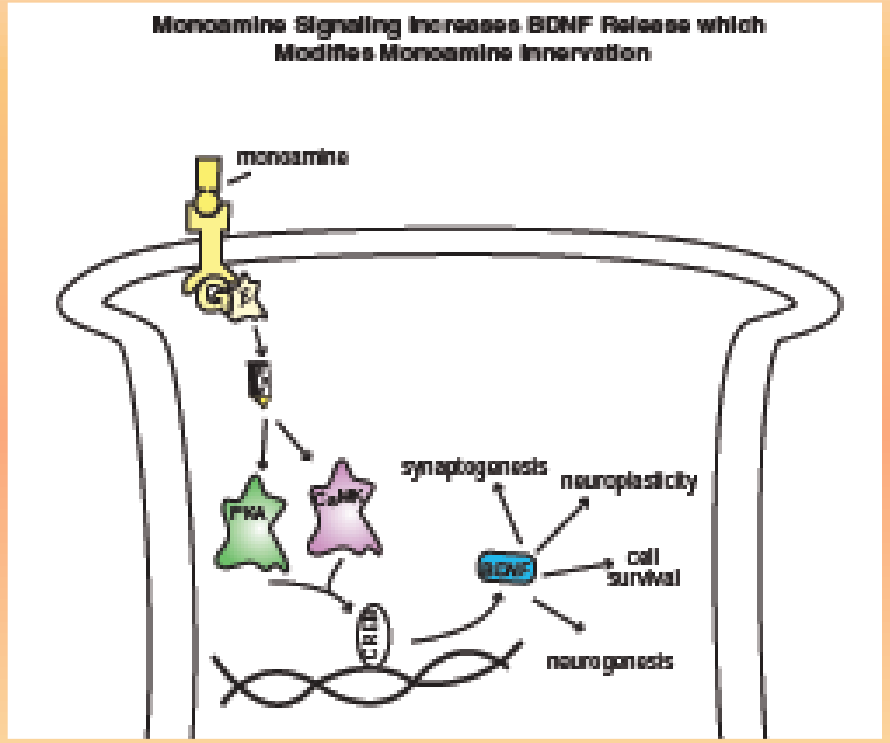
No hay evidencia suficiente

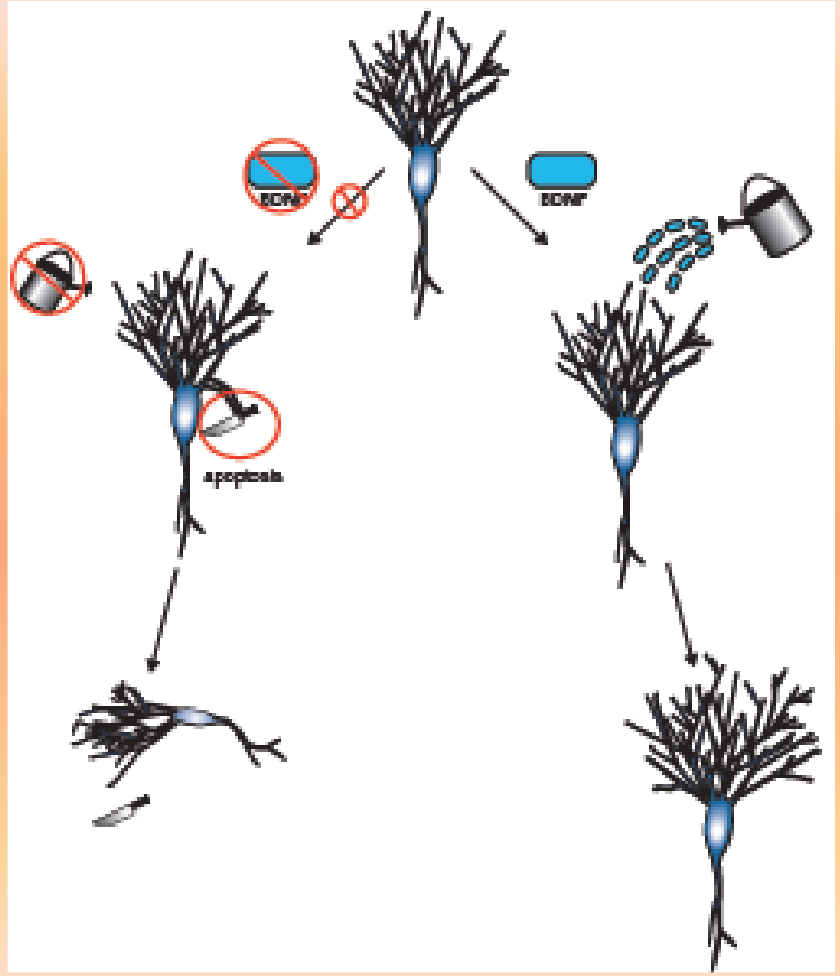
Trastornos del humor: Hipótesis receptor monoaminérgico



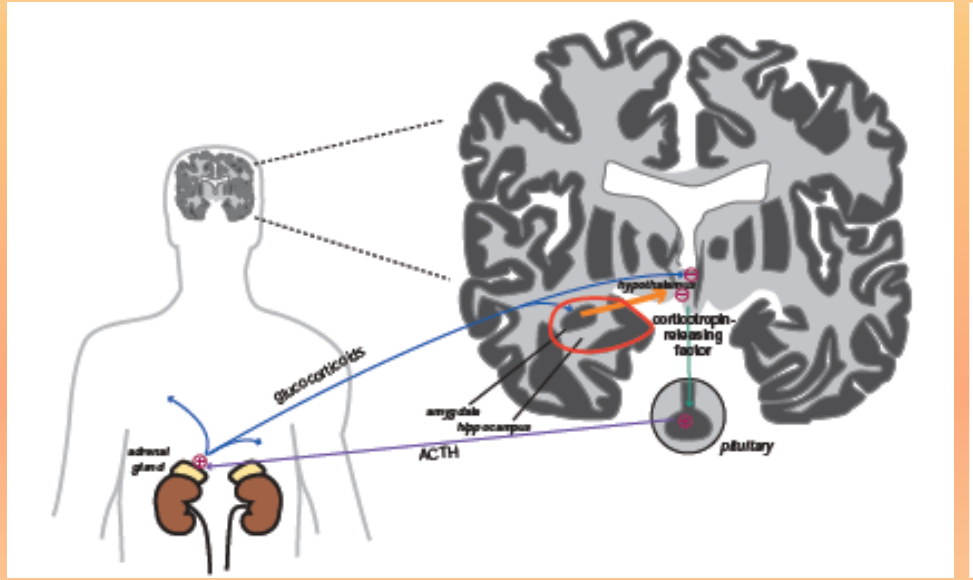
Tampoco suficiente evidencia

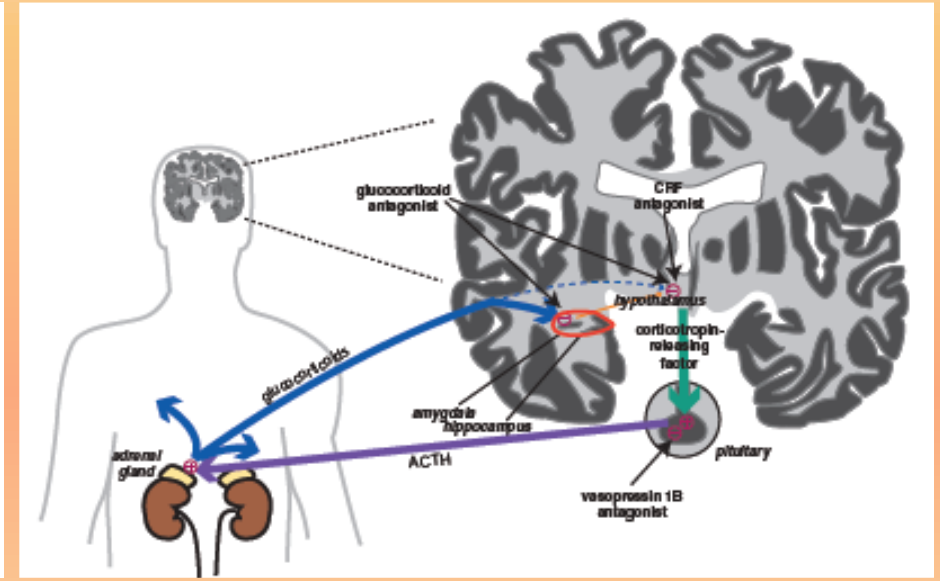
Trastornos del humor: Aguas abajo



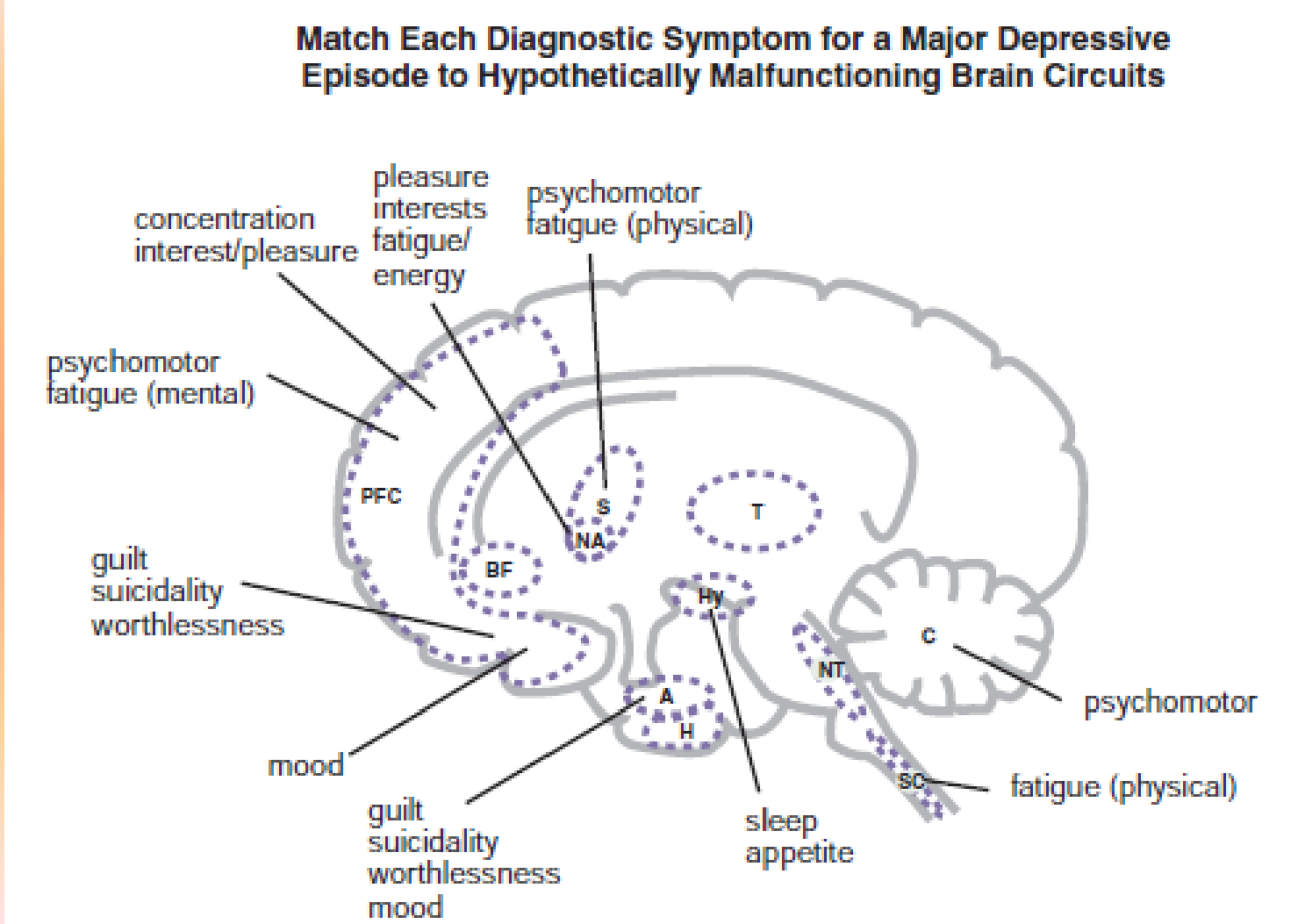


Trastornos del humor: Efectos del estrés crónico

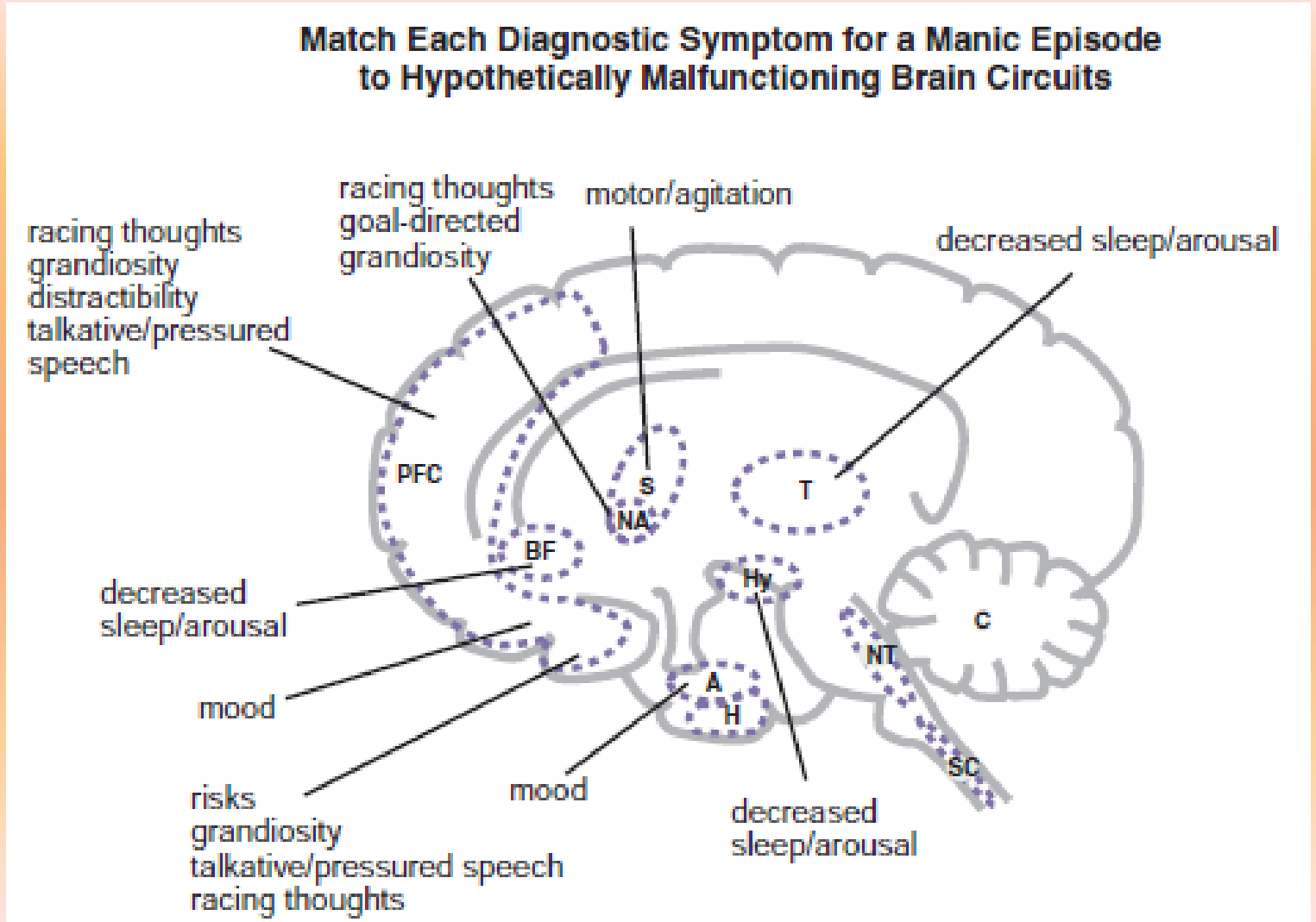




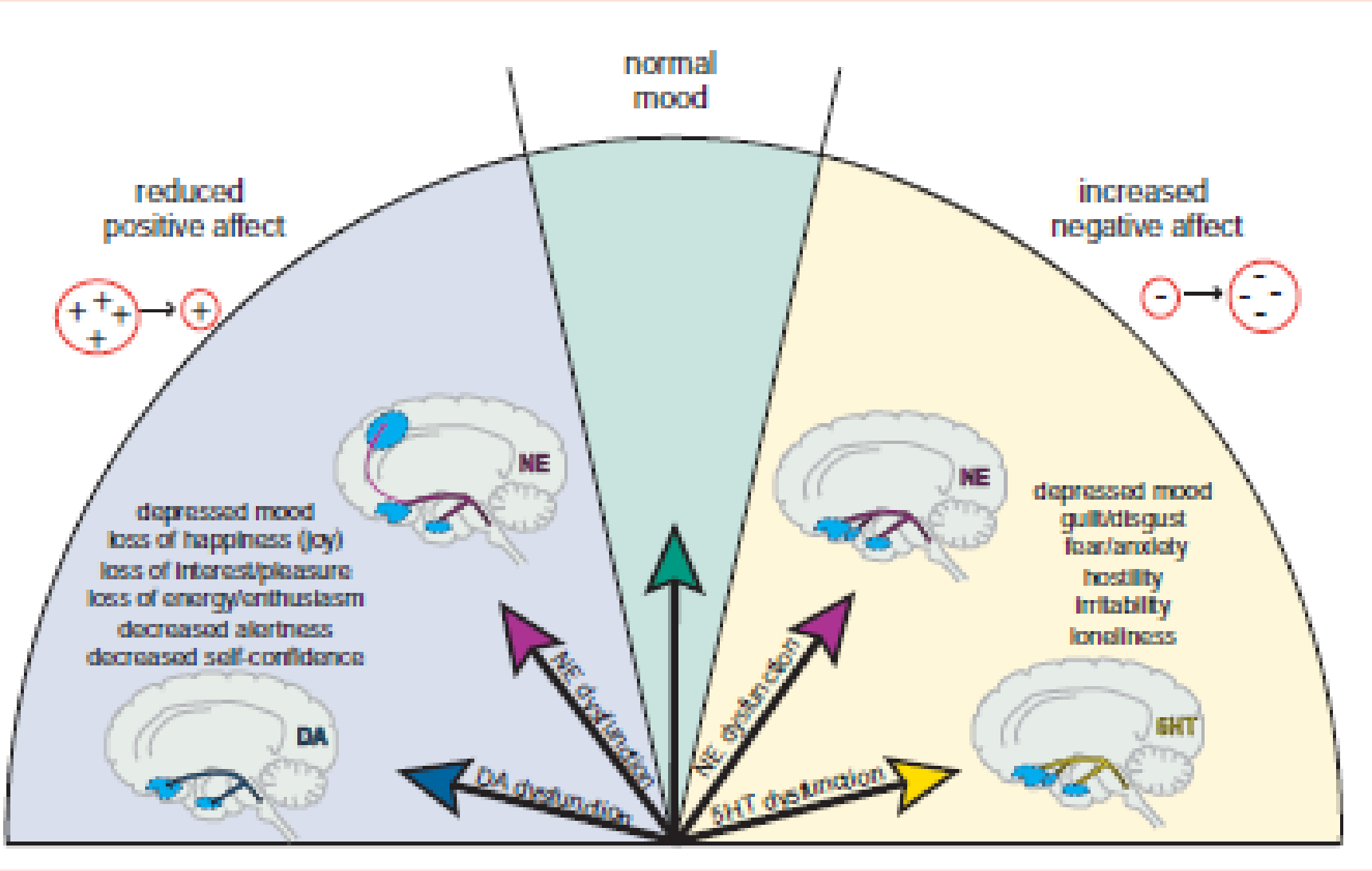
Trastornos del humor: Dimensiones sintomáticas



Trastornos del humor: Dimensiones sintomáticas



Trastornos del humor: Dimensiones sintomáticas



Antidepresivos

TSER

NAT

TDA

ISRS

Fluoxetina
Sertralina
Paroxetina
Fluvoxamina
Citalopram
Escitalopram

IRSN

Venlafaxina
Desvenlafaxina
Duloxetina
Milnacipran

IRND

Bupropion

APIRS

Vilazodona

AIRS

Trazodona
Vortioxetina

2ª Línea

Ag MT1 y 2

Agomelatina

Anta α2

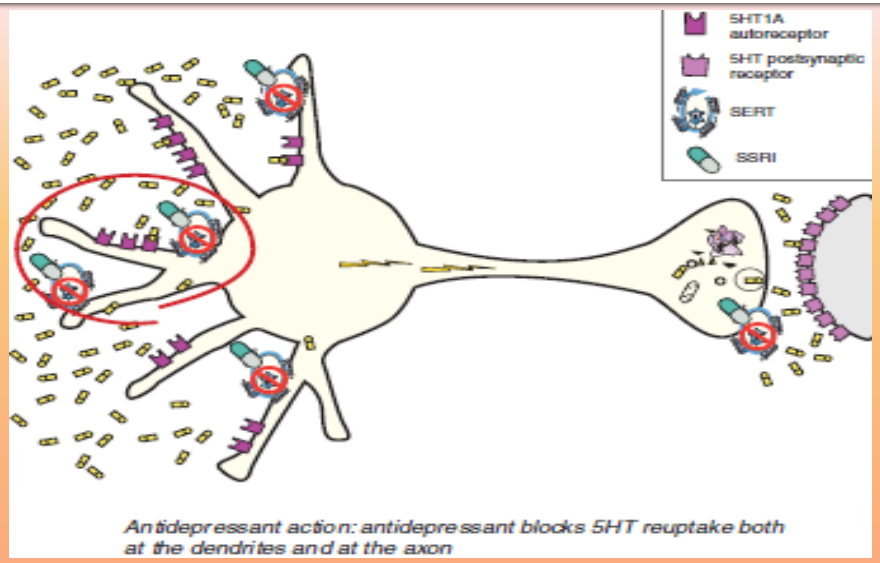
Mirtazapina

Esteroides neuroactivos

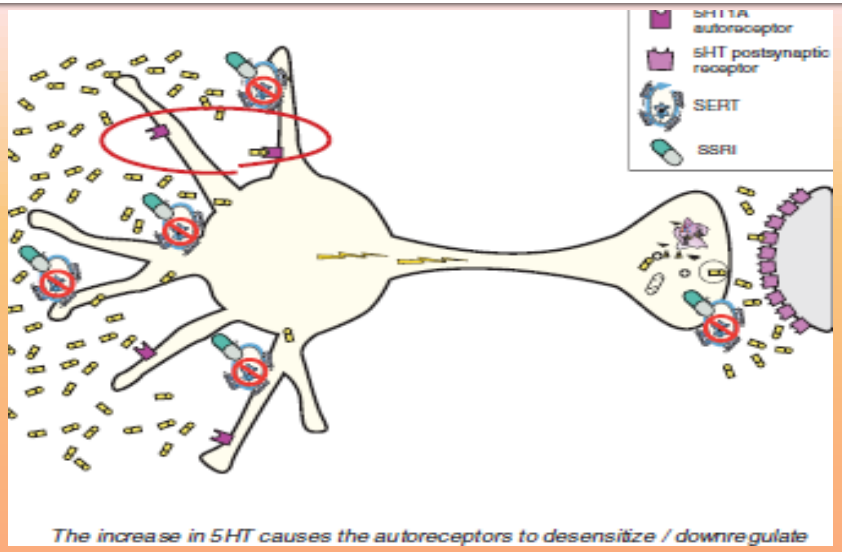
Tricíclicos

IMAOS

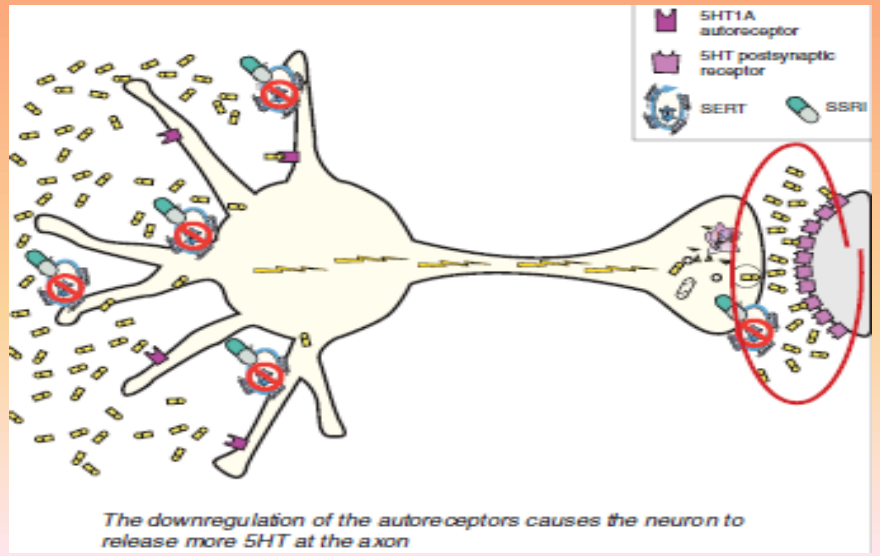
Antidepresivos: mecanismos



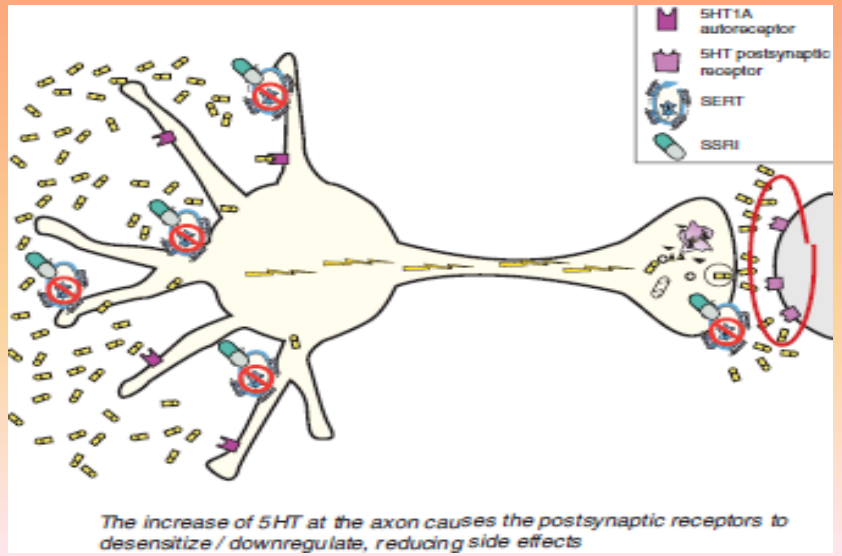
Antidepressant action: antidepressant blocks 5HT reuptake both at the dendrites and at the axon



The increase in 5HT causes the autoreceptors to desensitize / downregulate

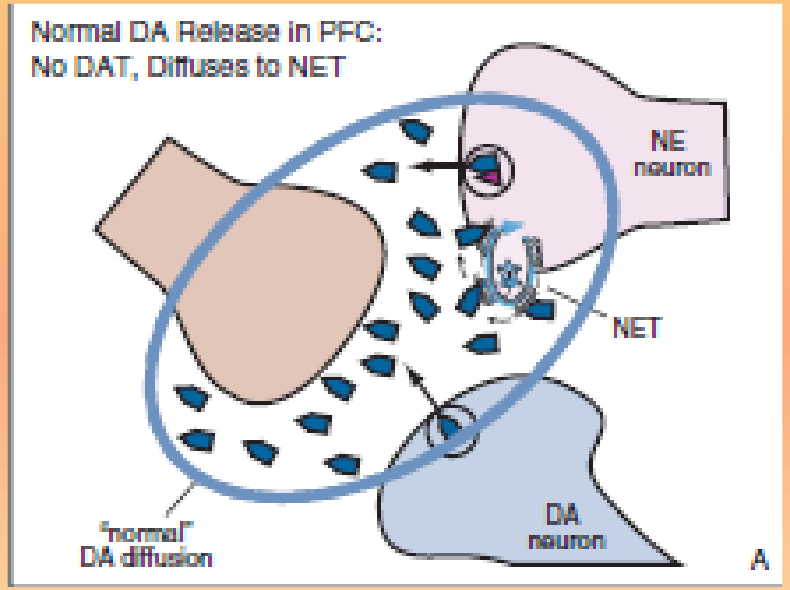


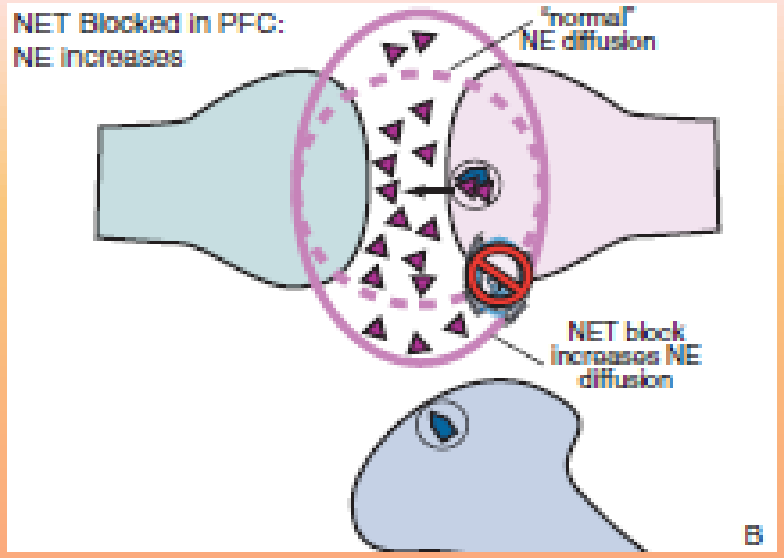
The downregulation of the autoreceptors causes the neuron to release more 5HT at the axon

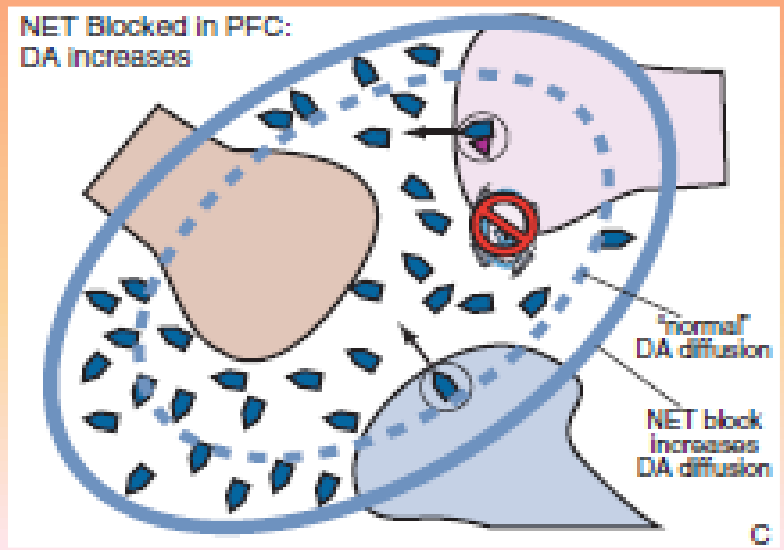


The increase of 5HT at the axon causes the postsynaptic receptors to desensitize / downregulate, reducing side effects

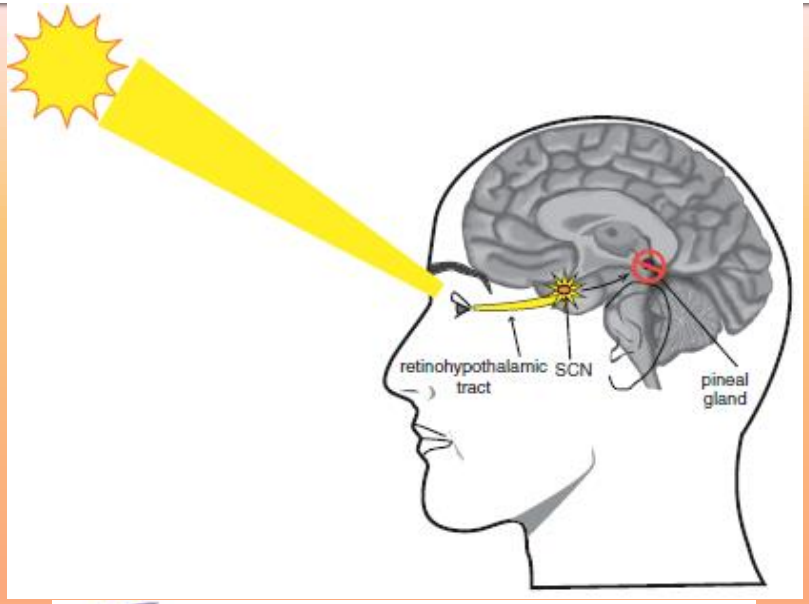
Antidepresivos: mecanismos

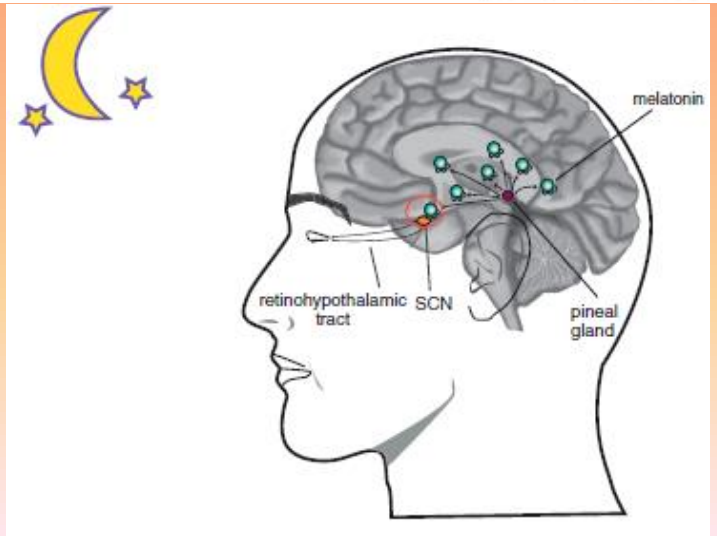


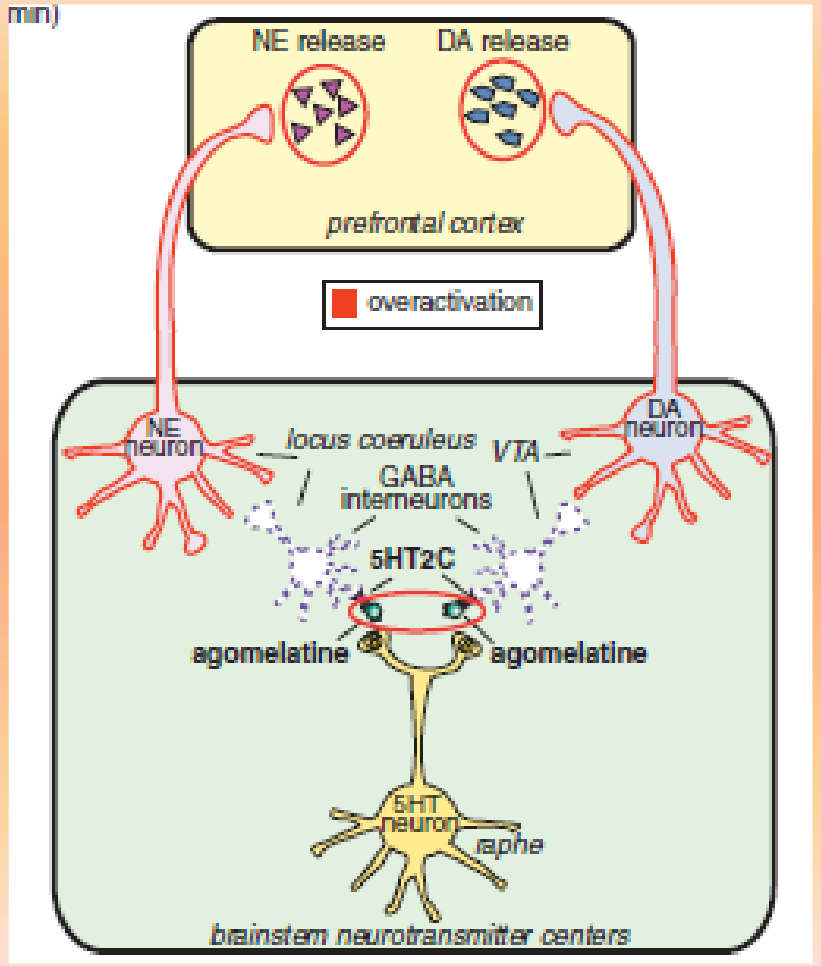




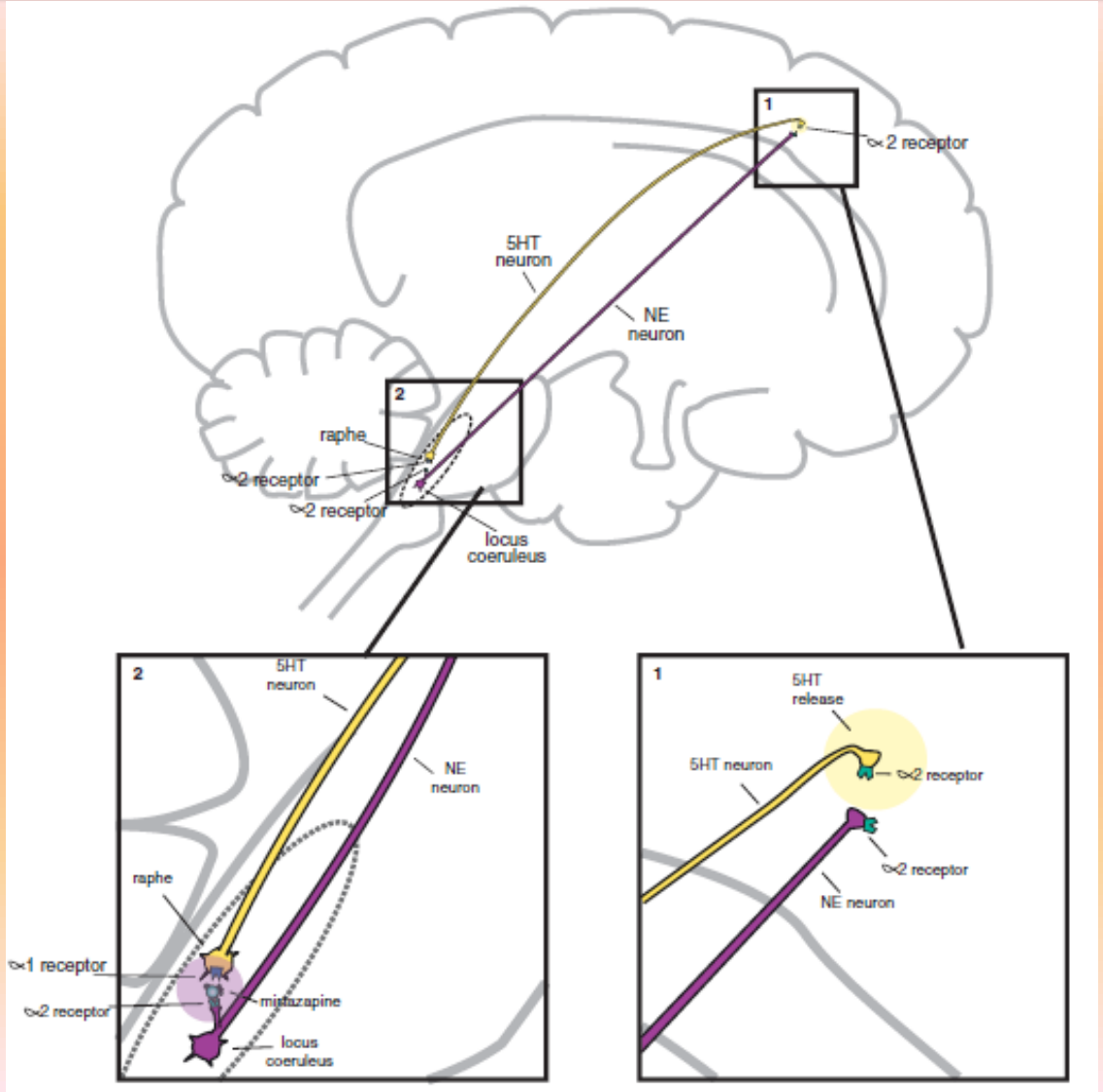
Antidepresivos: mecanismos



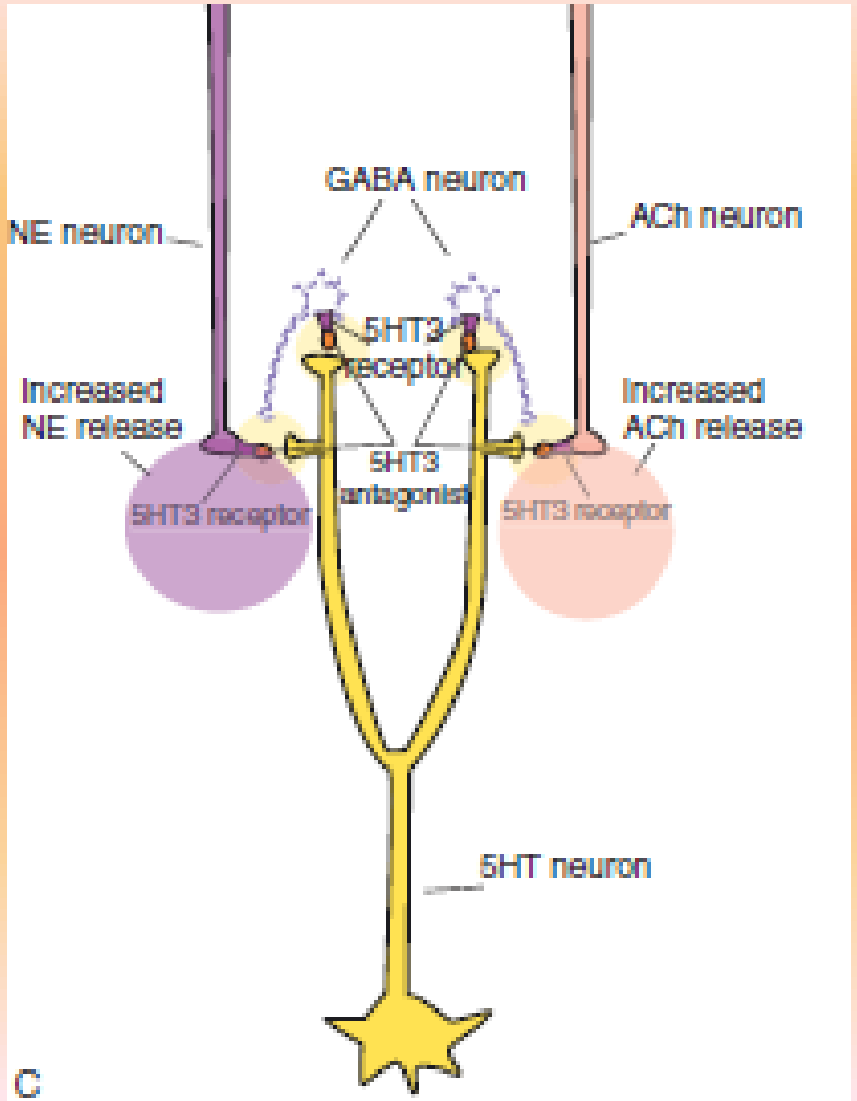




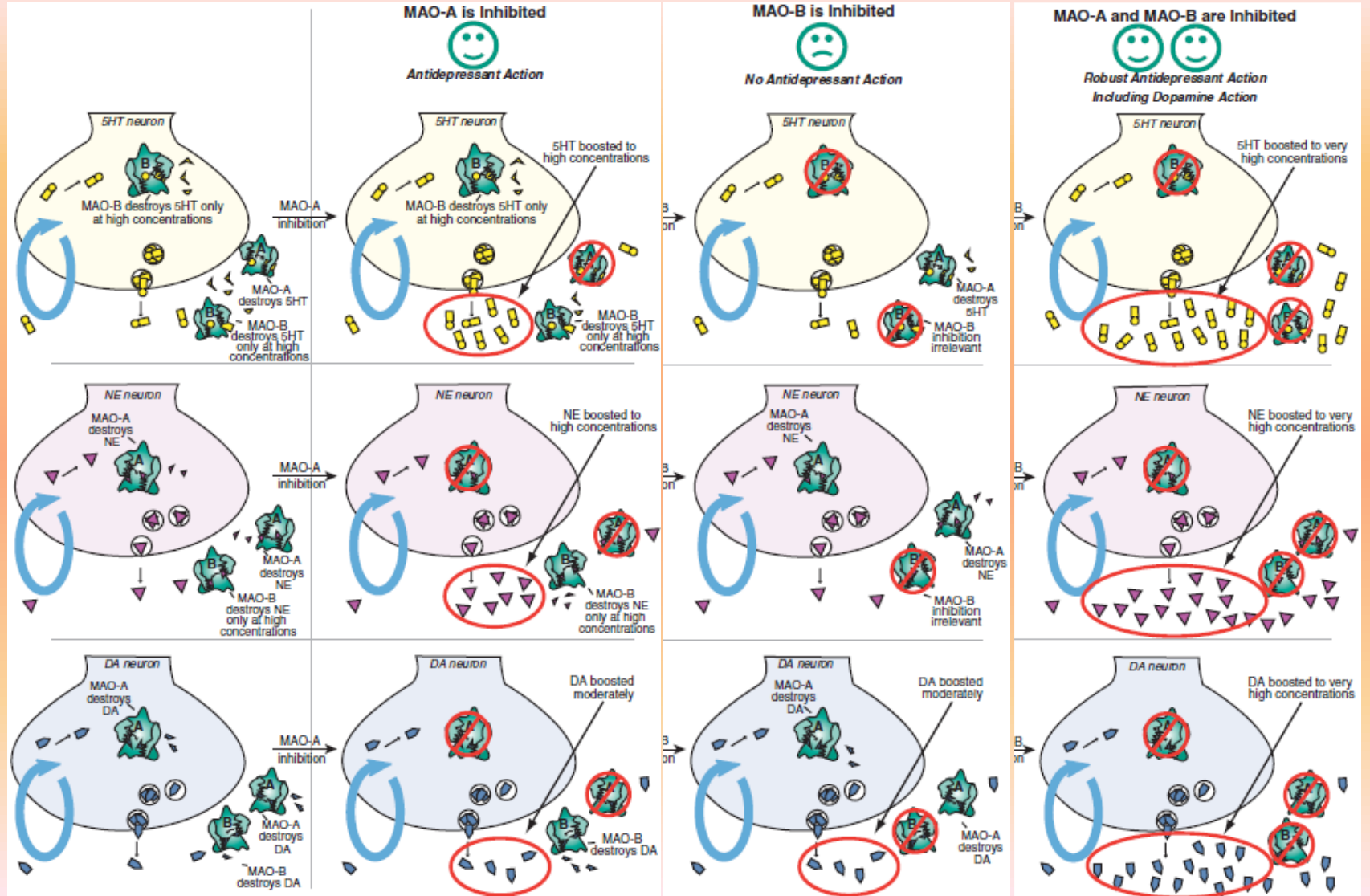
Antidepresivos: mecanismos



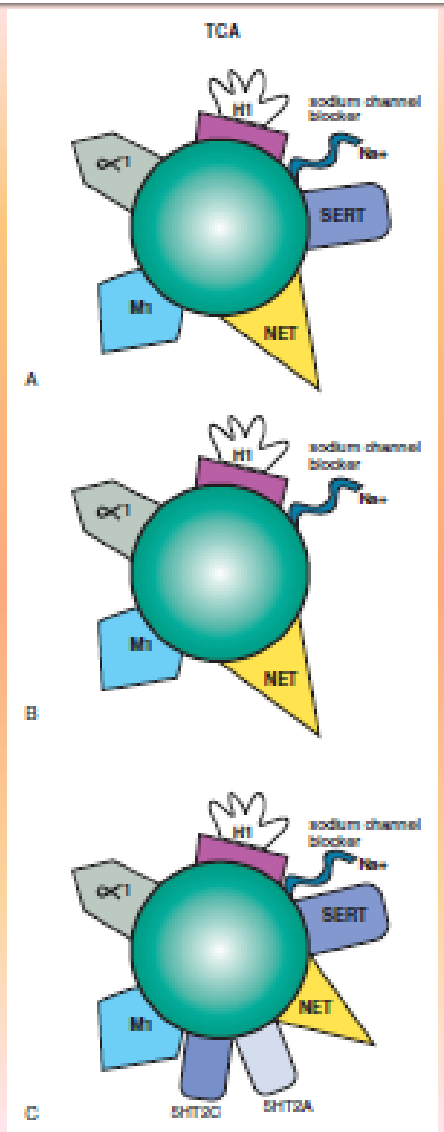
Antidepresivos: mecanismos

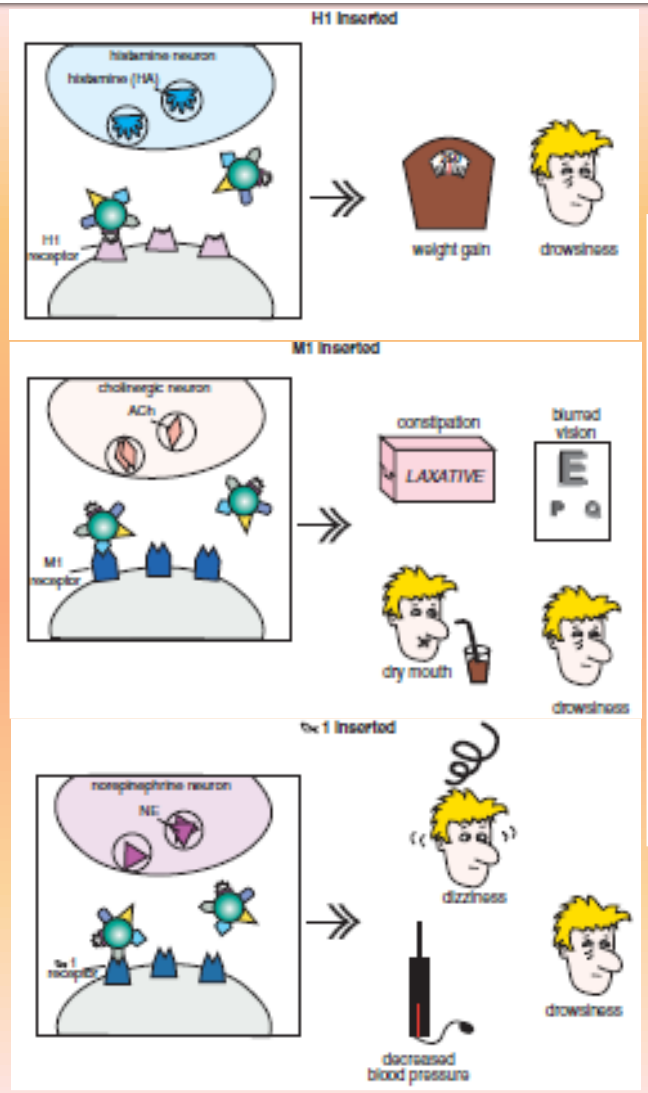


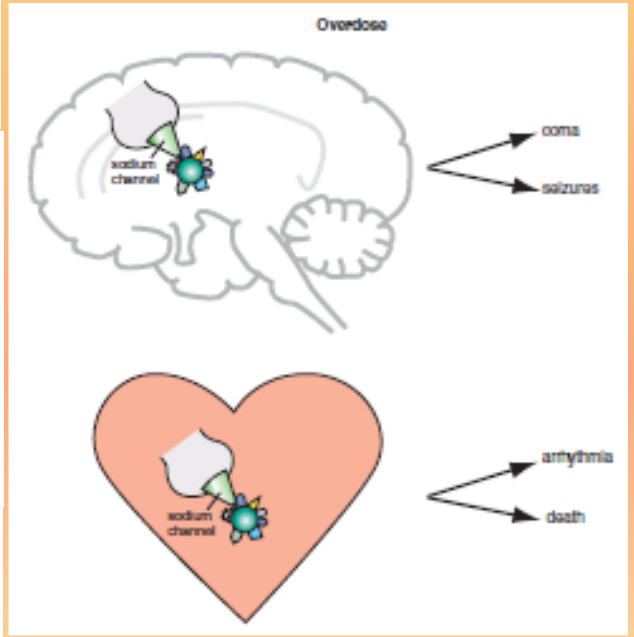
Antidepresivos: mecanismos



Antidepresivos: ATC







Resistencia al tratamiento

Antag/Agon 5HT/DA

Olanza + Fluoxet
Aripiprazol
Brexpiprazol
Caripracina

Ketamina y Esketamina

- Infusión intravenosa dosis subanestésica
- Mejoría casi inmediata
- Desaparece en pocos días

-Bloqueo NMDA → ⇧ Glu → →
→ ⇧ Sinaptog + Liberac BDNF y VEGF

En desuso

Litio
Buspirona
Horm Tiroideas

Combos

Triple acción: ISRS/IRSN + IRND
Combus Cohet Calif: IRSN + Mirtaza
Combos activadores: IRSN + inh TDA

Trastorno bipolar

Antag/Agon 5HT/DA (1ª línea)

Olanza + Fluoxet
Quetiapina
Lurasidona
Caripracina

Litio

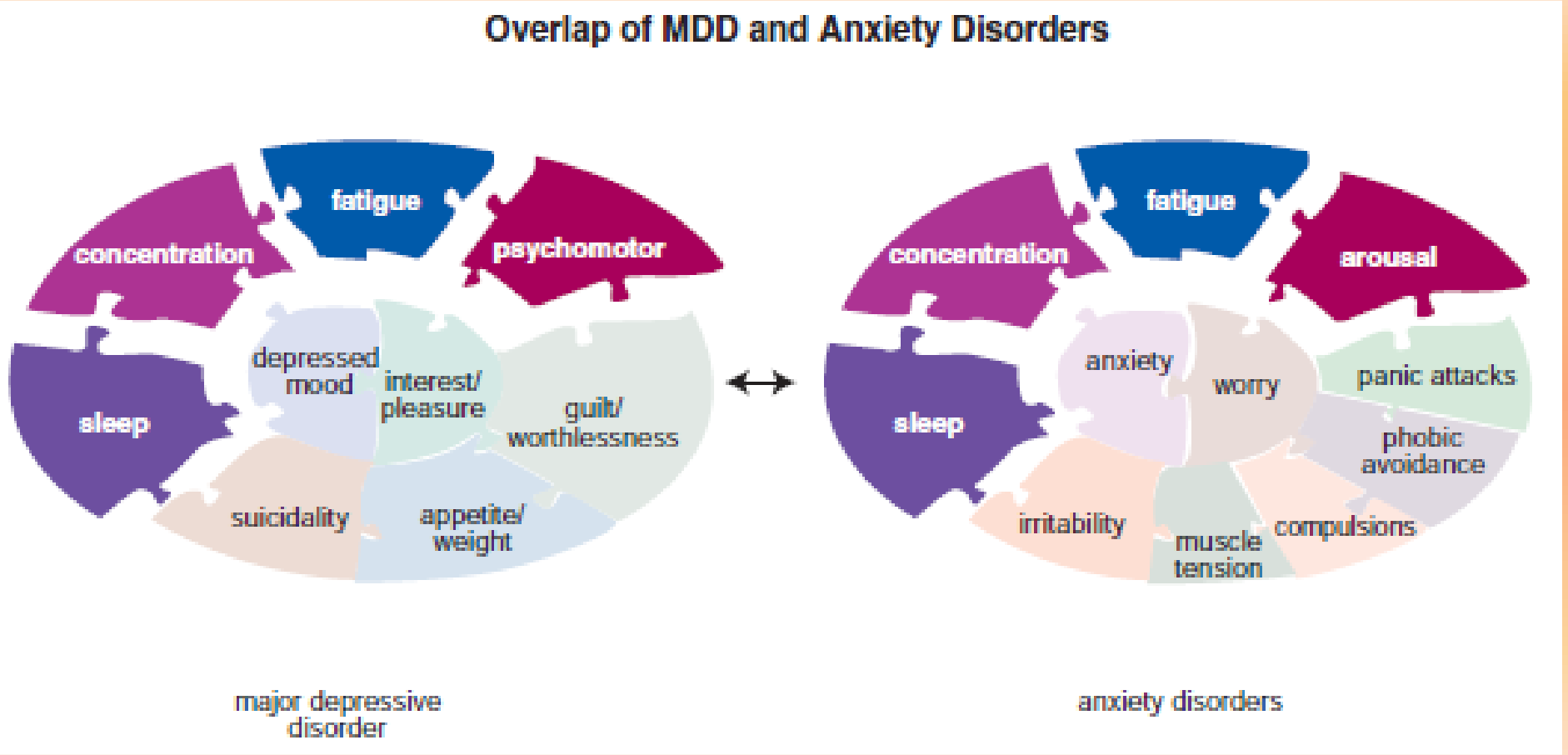
Anticonvulsivos

Ácido Valproico
Carbamazepina
Lamotrigina
(único desde abajo)

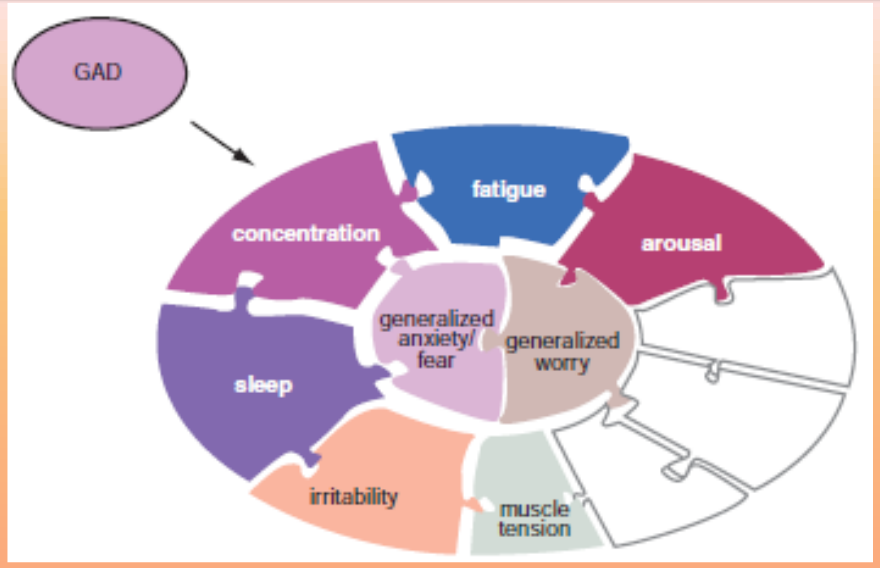
Anticonvulsivos de eficacia dudosa

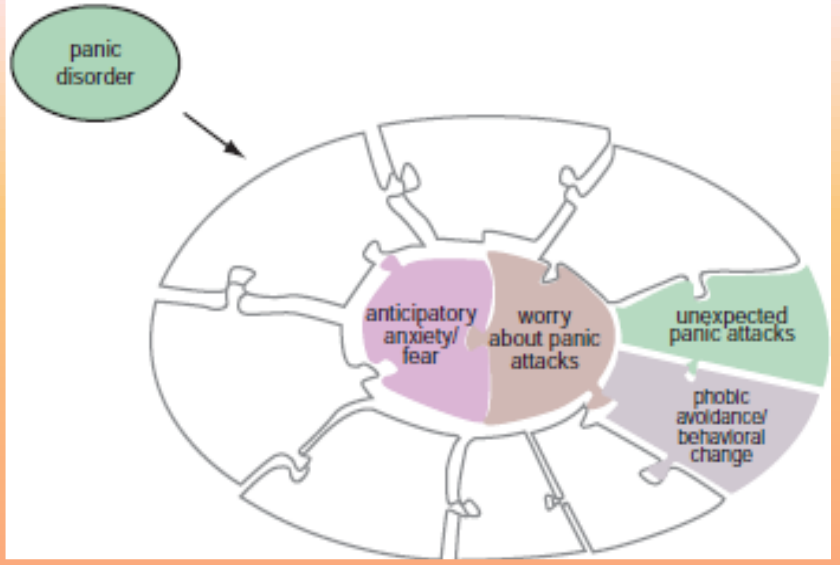
Oxcarbazepina/ eslicarbazepina
Topiramato
Gabapentina y pregabalina
Bloqueadores canal Ca tipo L
Riluzol

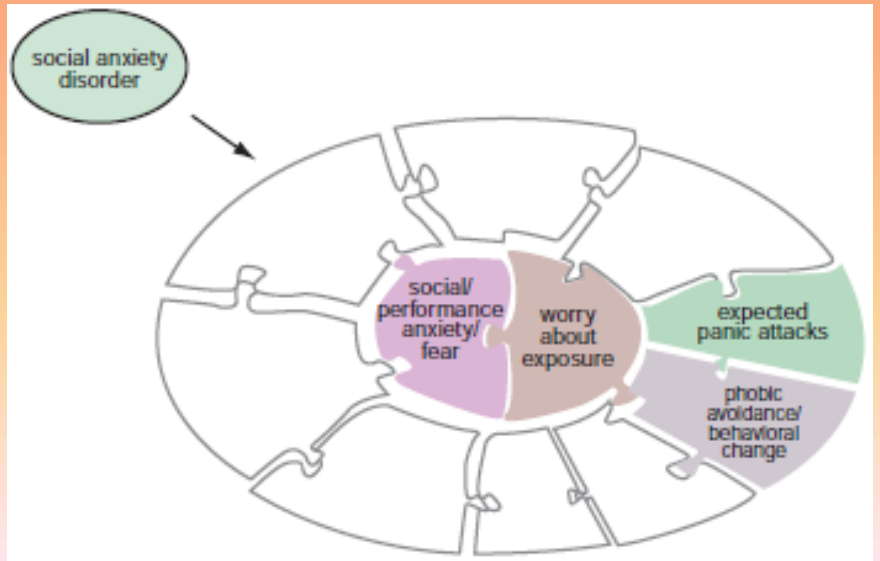
Trastornos de ansiedad

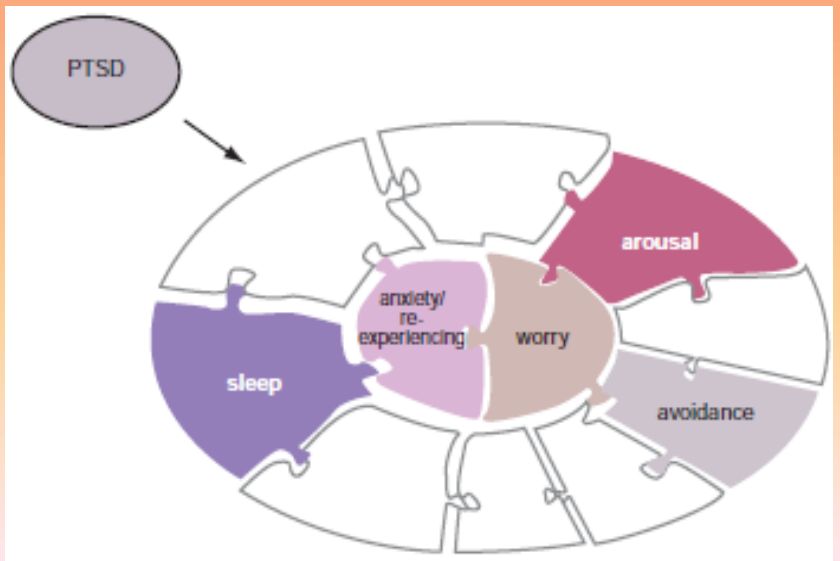


Trastornos de ansiedad

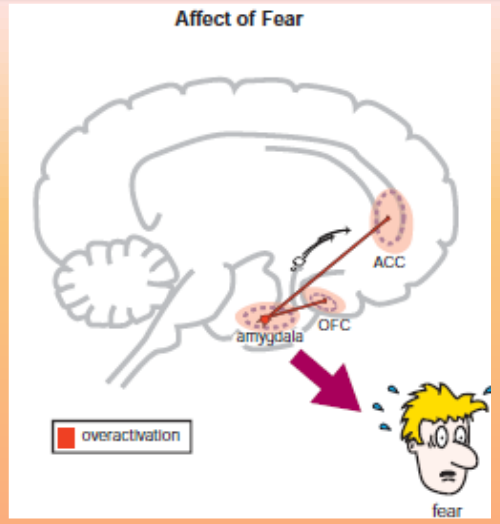


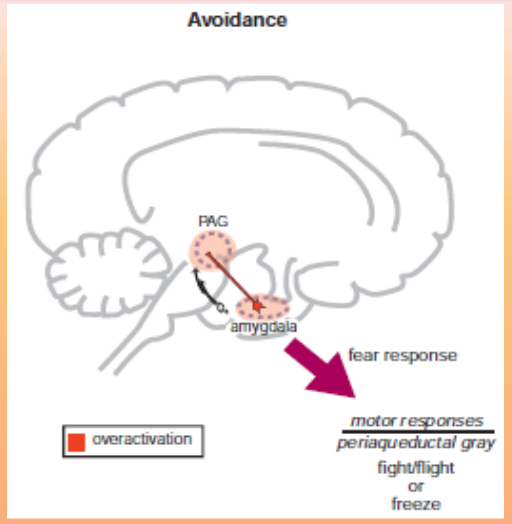


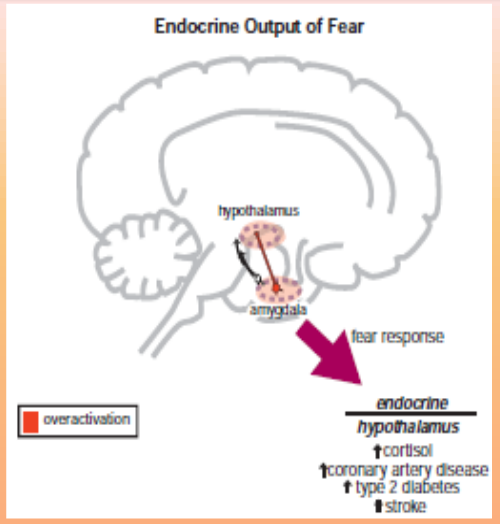


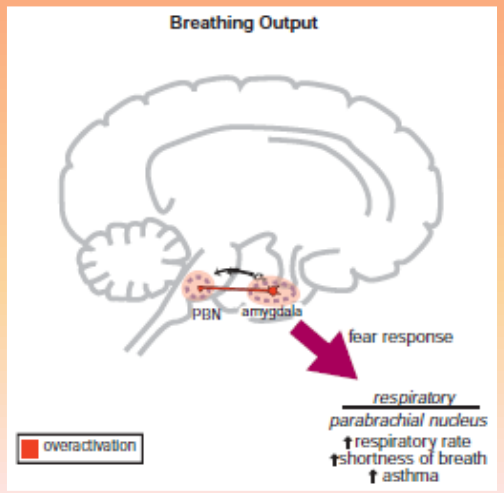


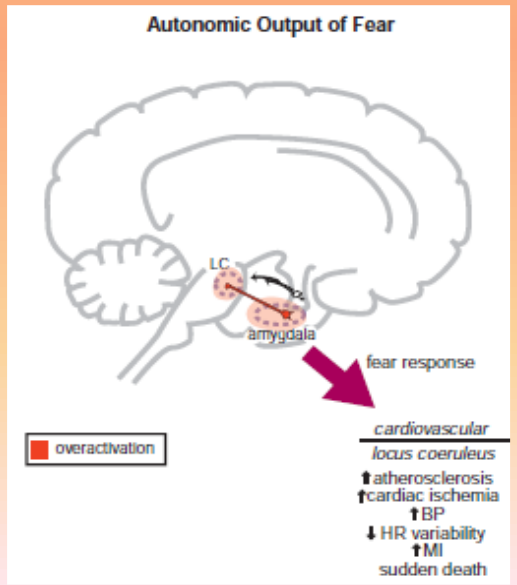
Amígdala y miedo

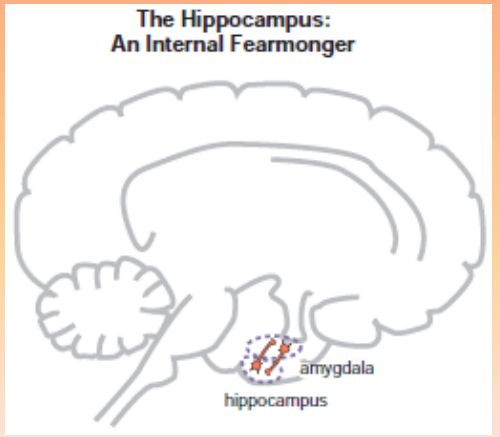




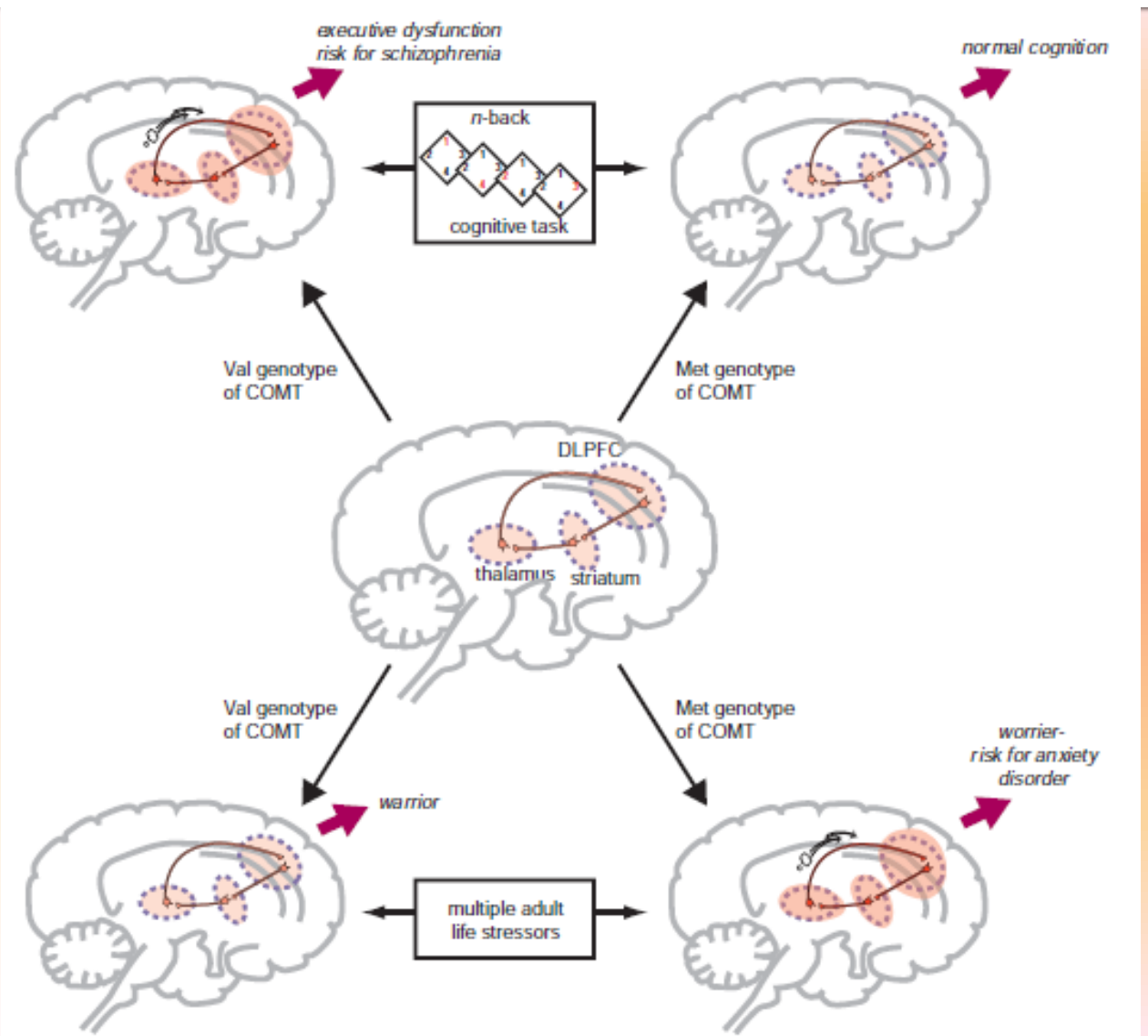




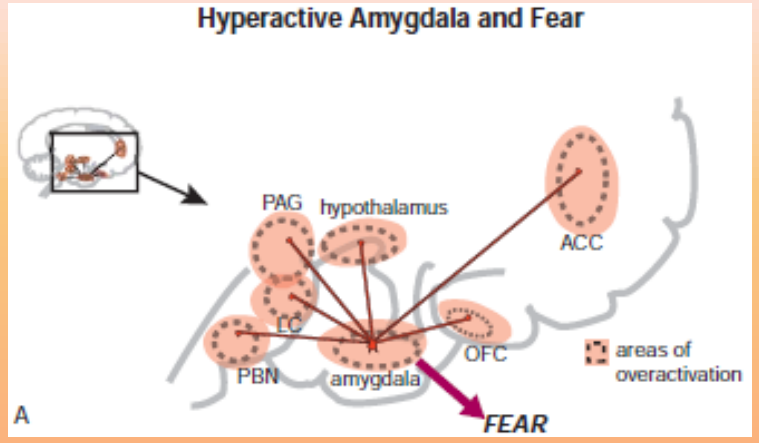


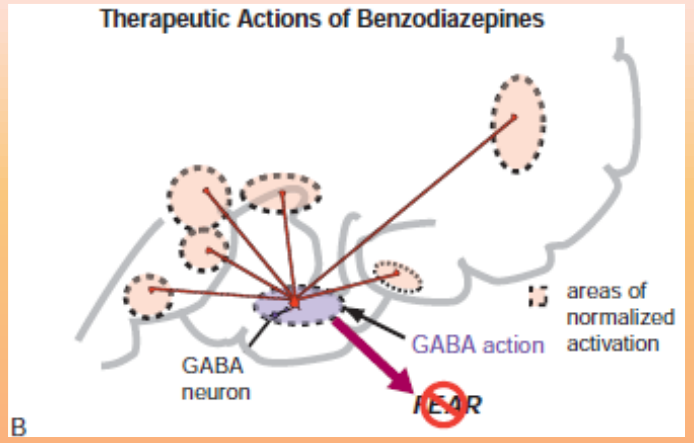


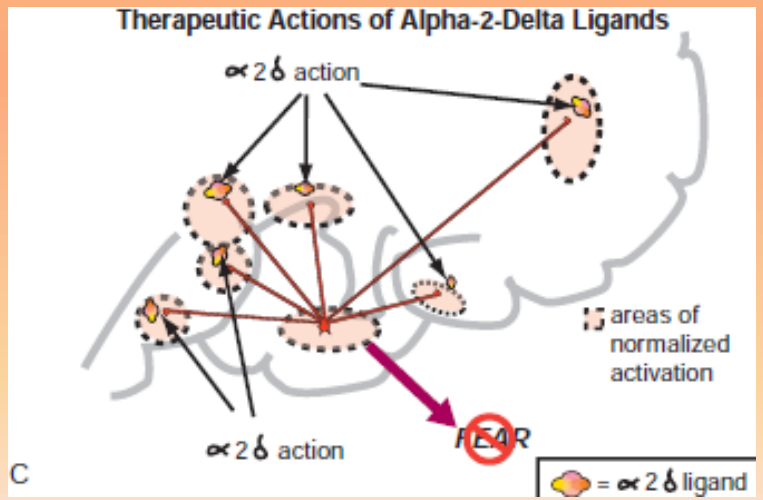
Circuito de preocupación

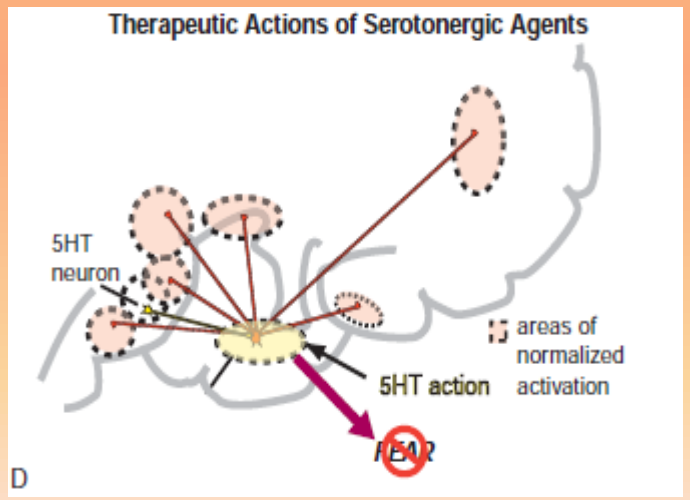


Miedo y ansiolisis



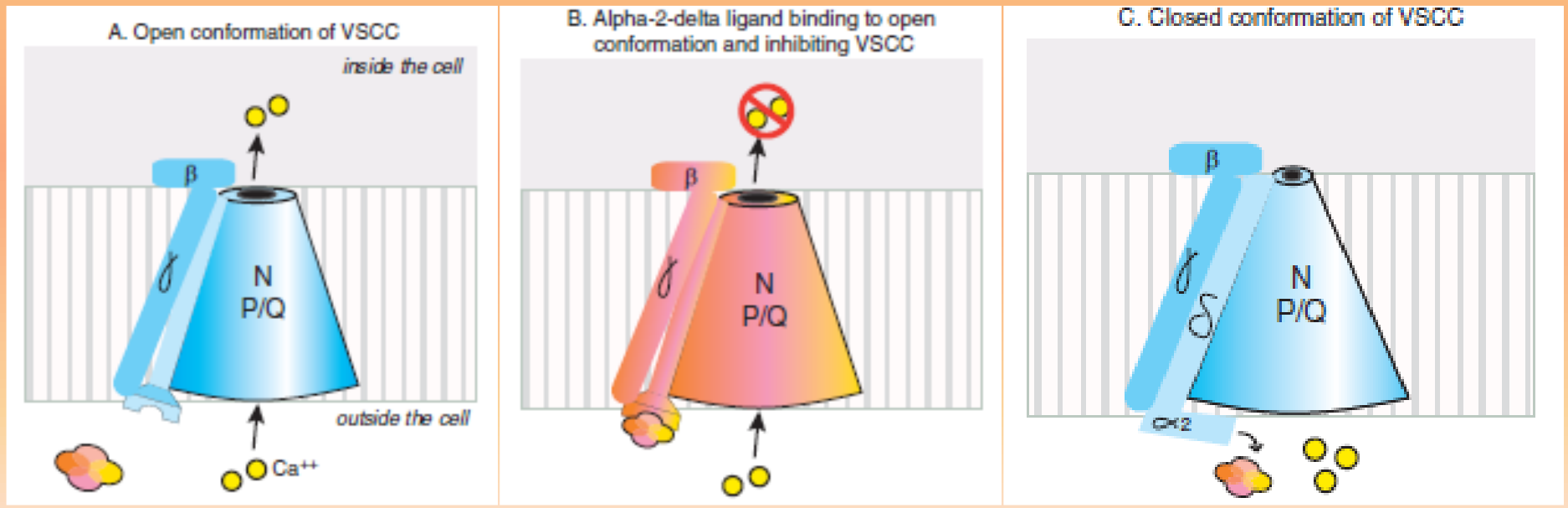




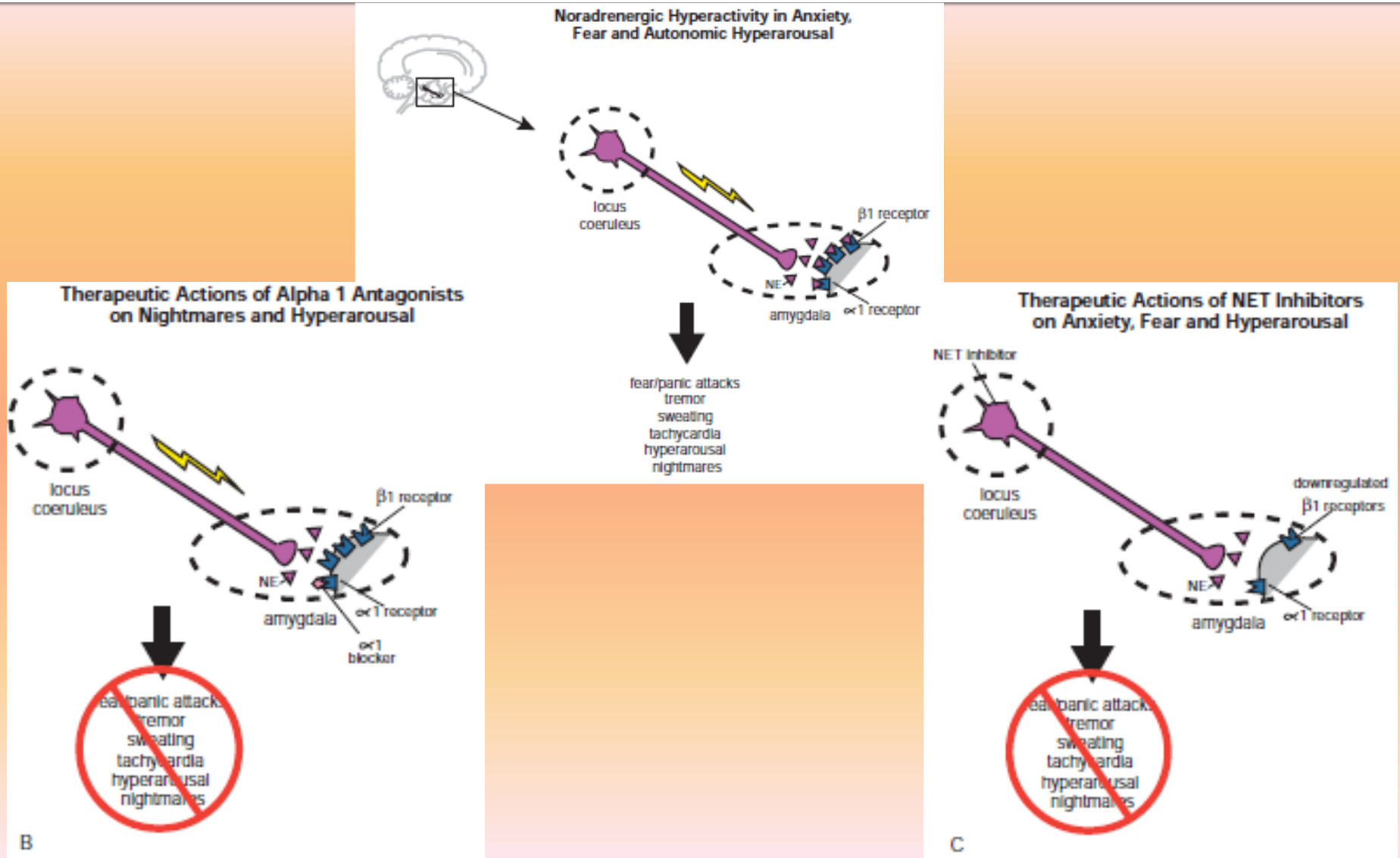


Miedo y ansiolisis

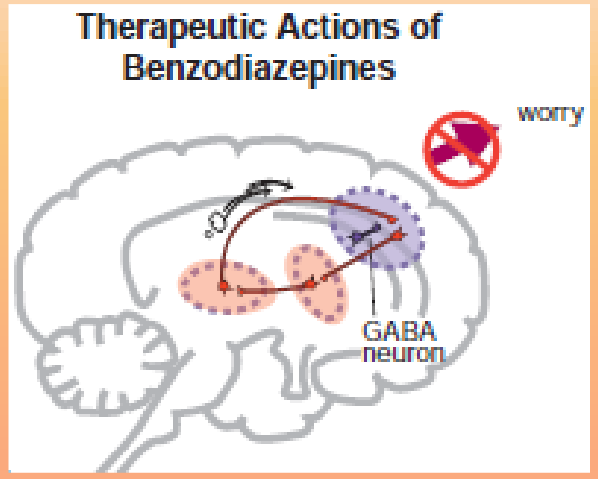
Funcionamiento de los ligandos Alfa-2-Delta

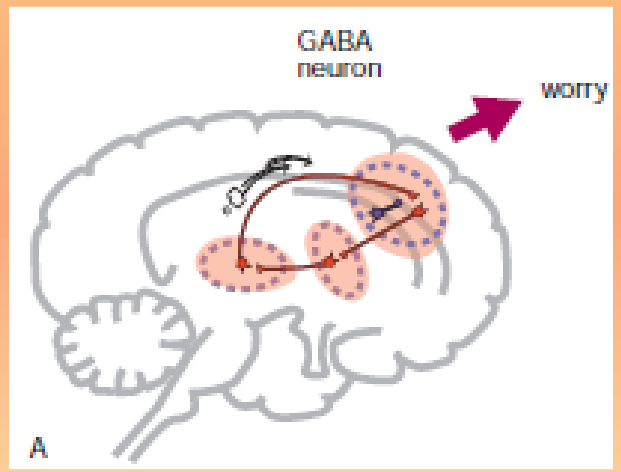


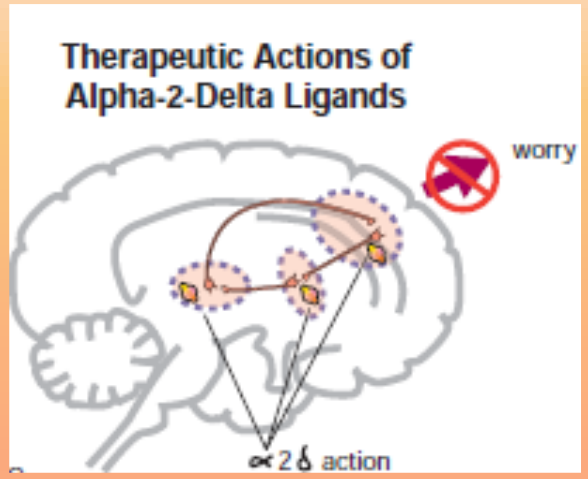
Miedo y ansiolisis

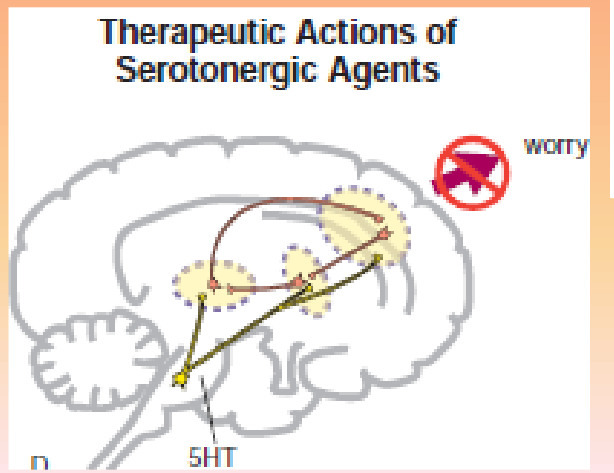


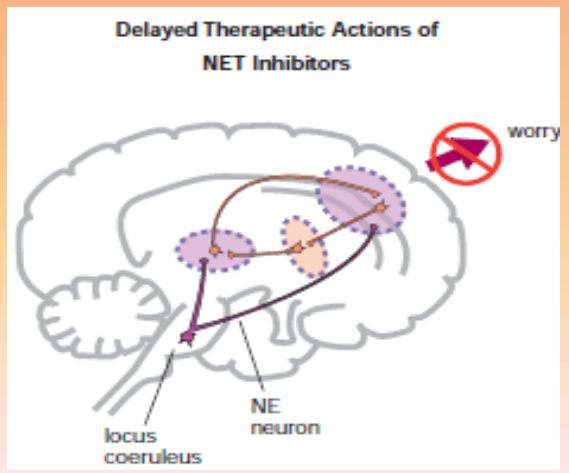
Preocupación y ansiolisis



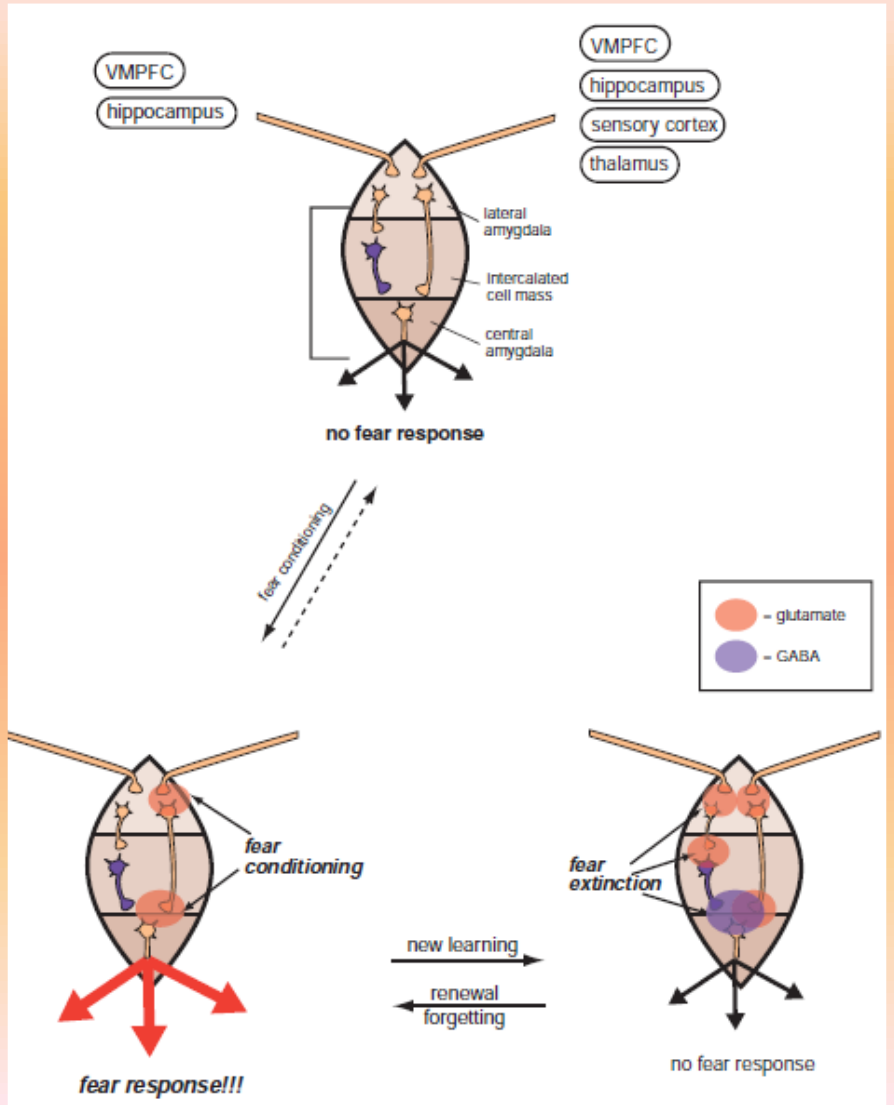


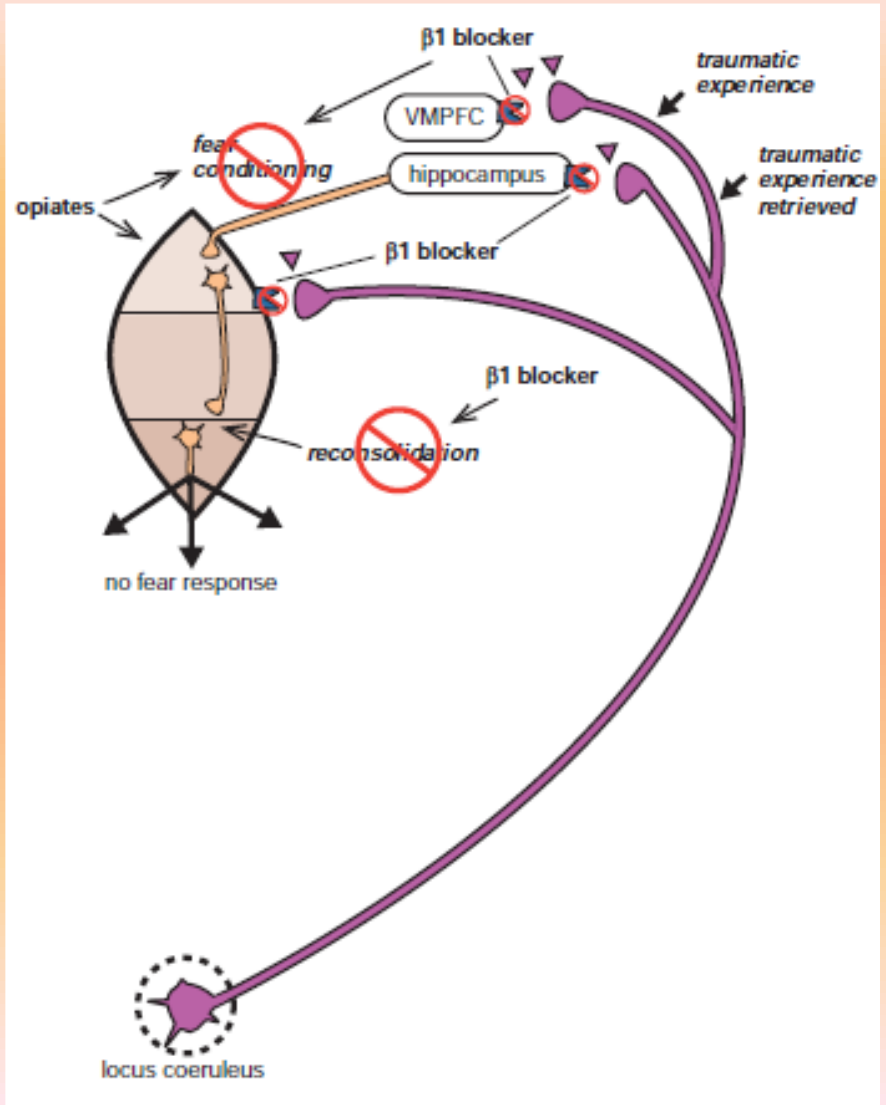




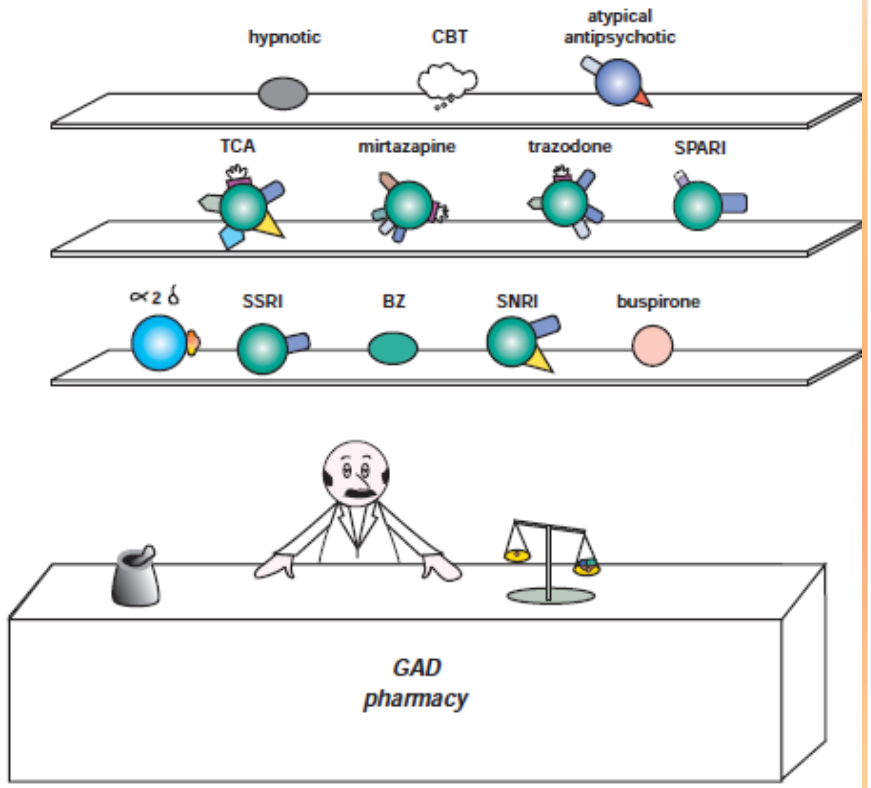


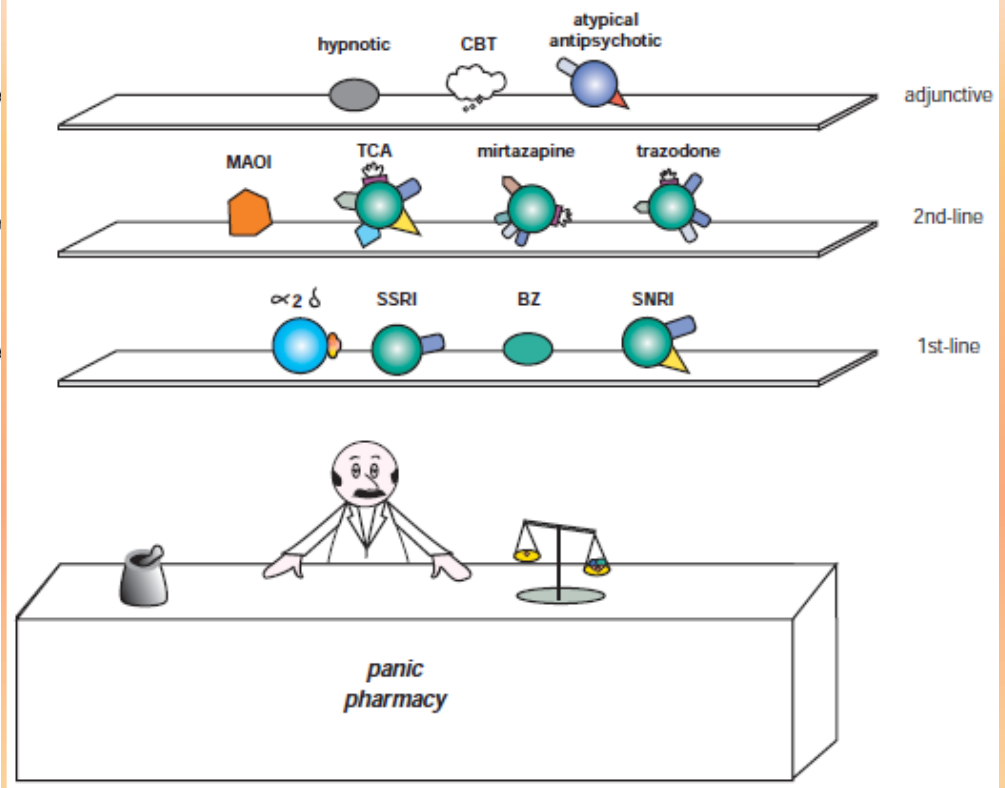
Condicionamiento, extinción y reconsolidación



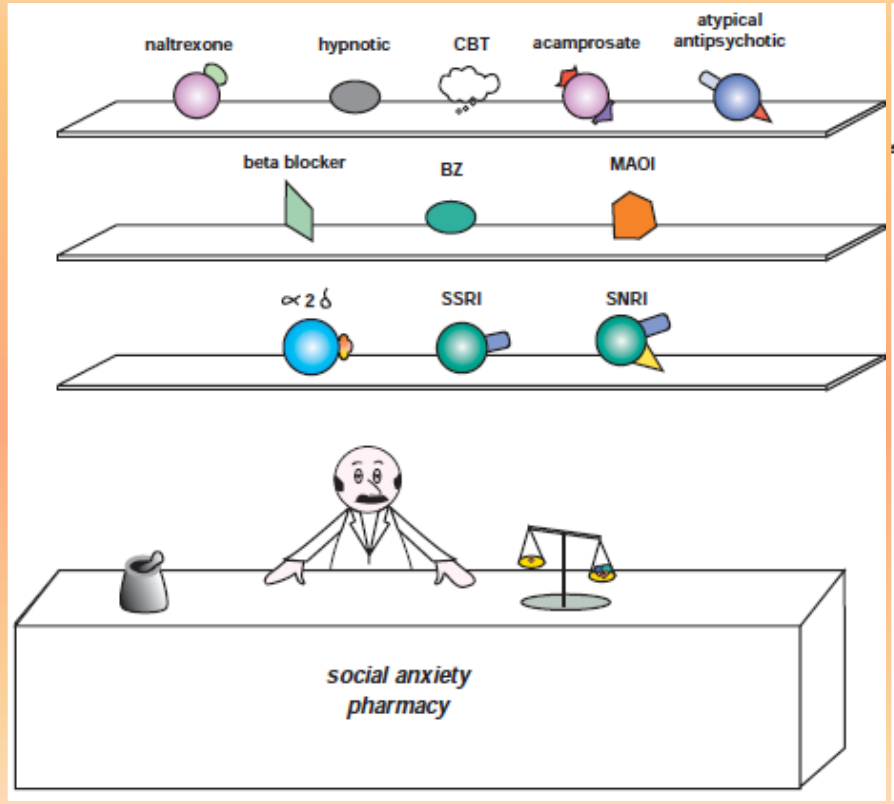


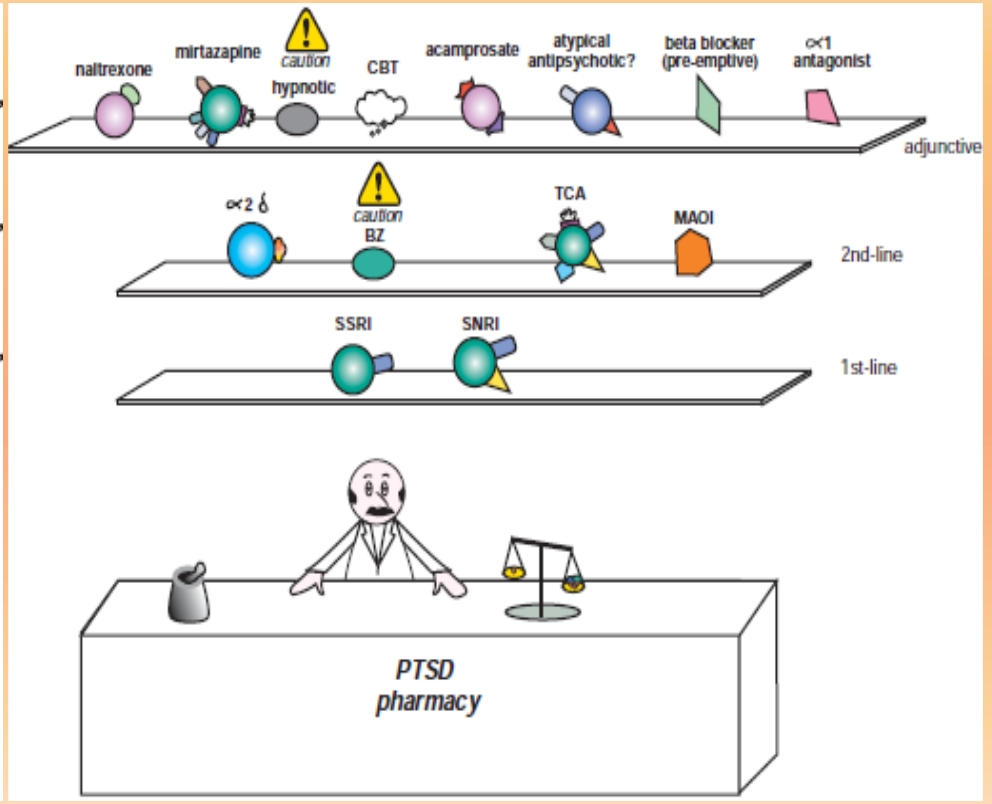
Farmacopea


hypnotic
CBT
atypical antipsychotic
TCA
mirtazapine
trazodone
SPARI
∝2 δ
SSRI
BZ
SNRI
buspirone
GAD pharmacy

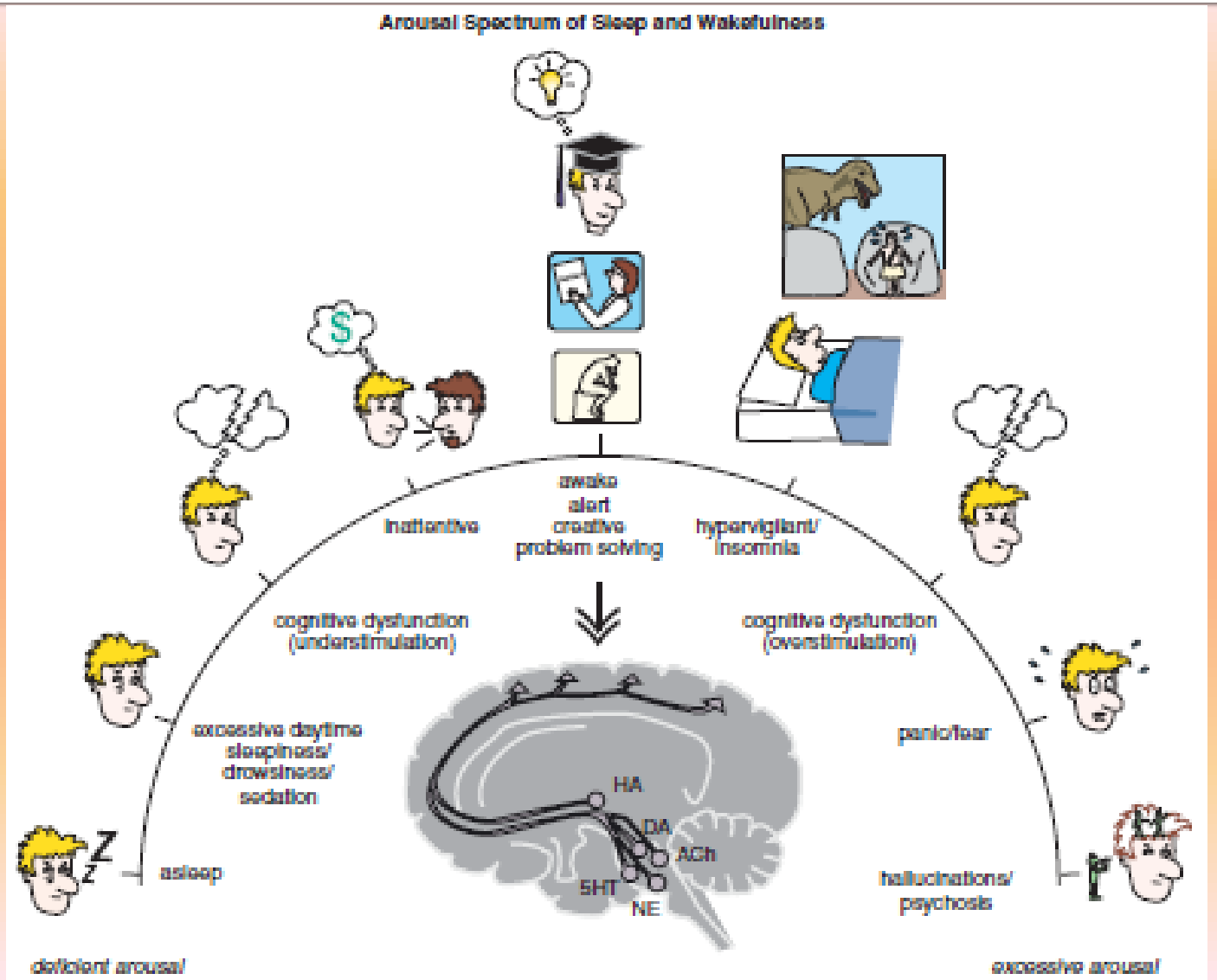

hypnotic
CBT
atypical antipsychotic
adjunctive
MAOI
TCA
mirtazapine
trazodone
2nd-line
∝2 δ
SSRI
BZ
SNRI
1st-line
panic pharmacy

Farmacopea

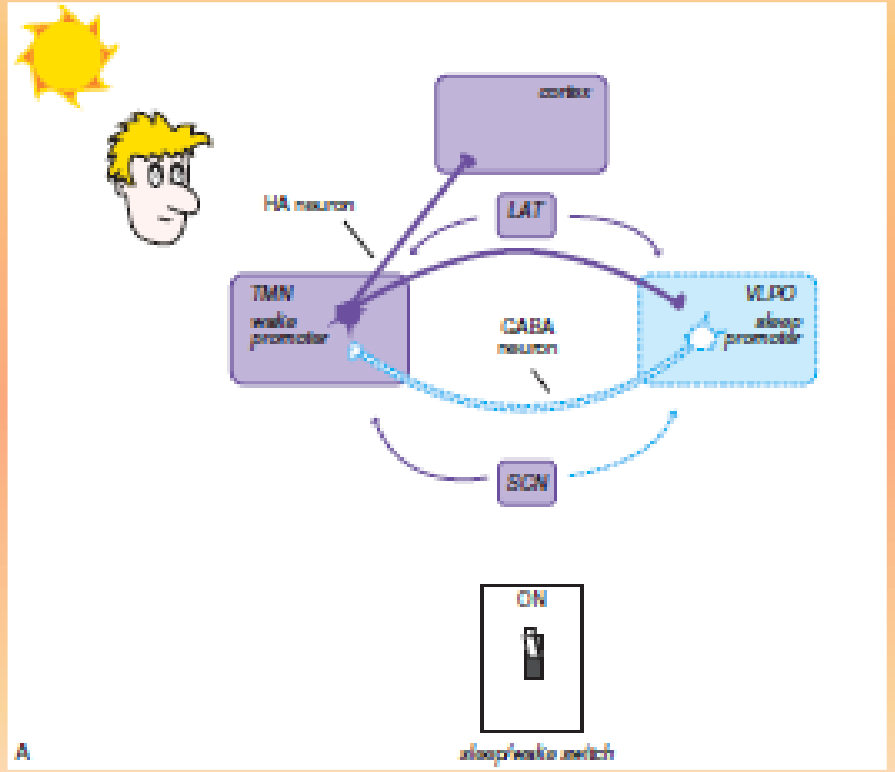

naltrexone
hypnotic
CBT
acamprosate
atypical antipsychotic
beta blocker
BZ
MAOI
∝2δ
SSRI
SNRI
social anxiety pharmacy

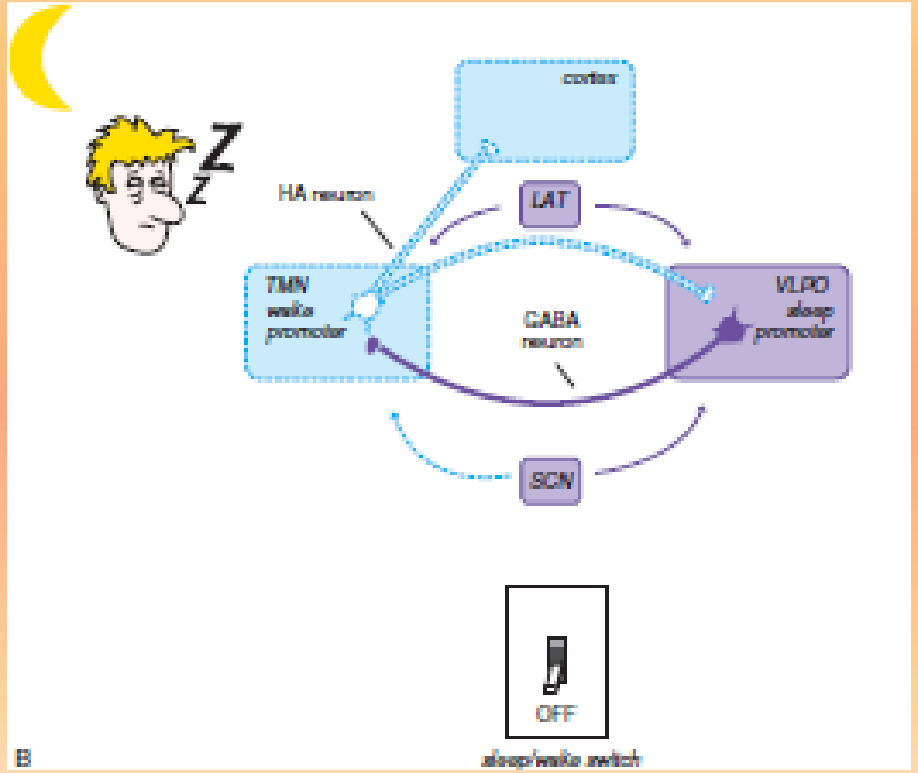

naltrexone
mirtazapine
caution
hypnotic
CBT
acamprosate
atypical antipsychotic?
beta blocker (pre-emptive)
∝1 antagonist
adjunctive
∝2δ
caution
BZ
TCA
MAOI
2nd-line
SSRI
SNRI
1st-line
PTSD pharmacy

Trastornos del sueño

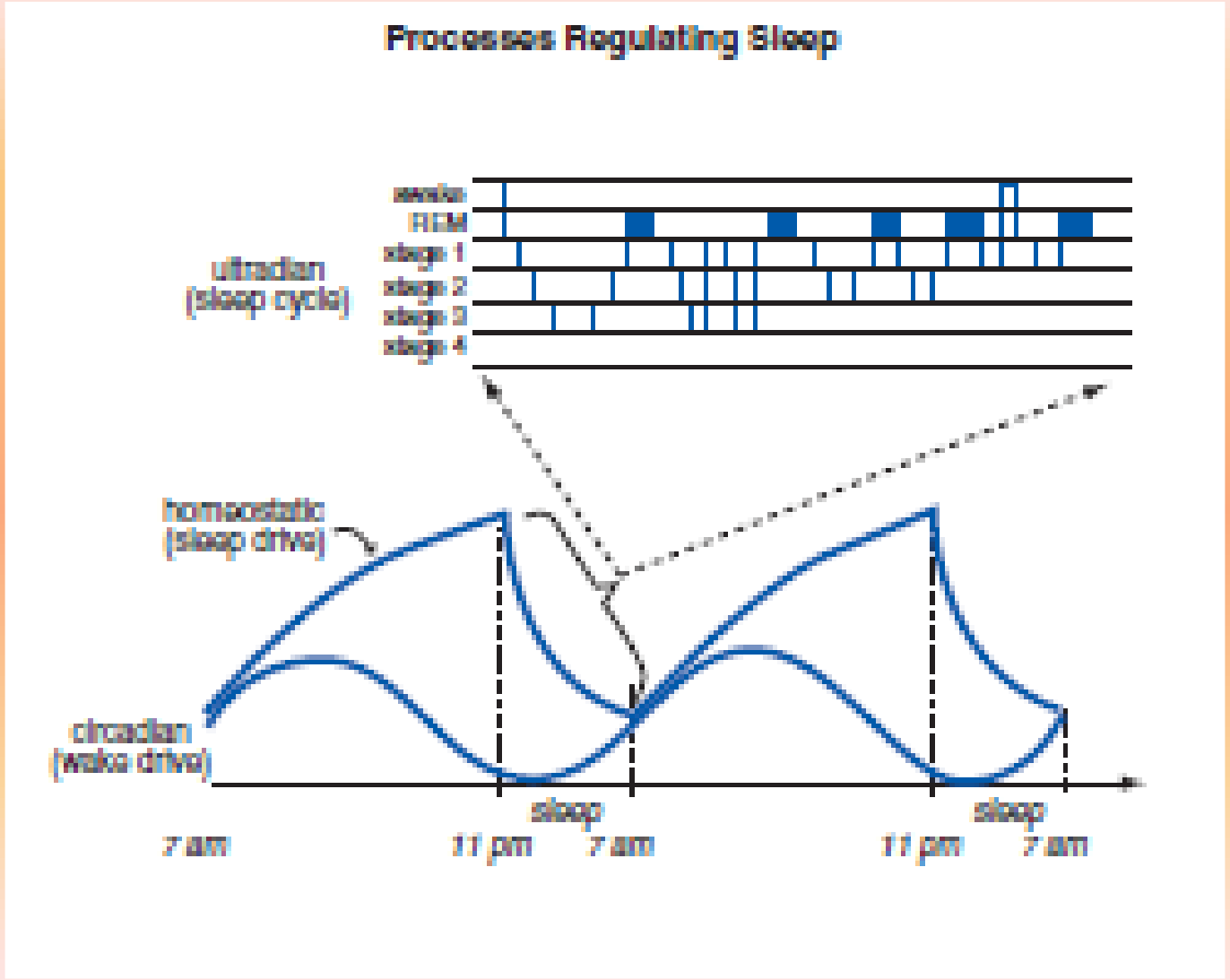


Trastornos del sueño

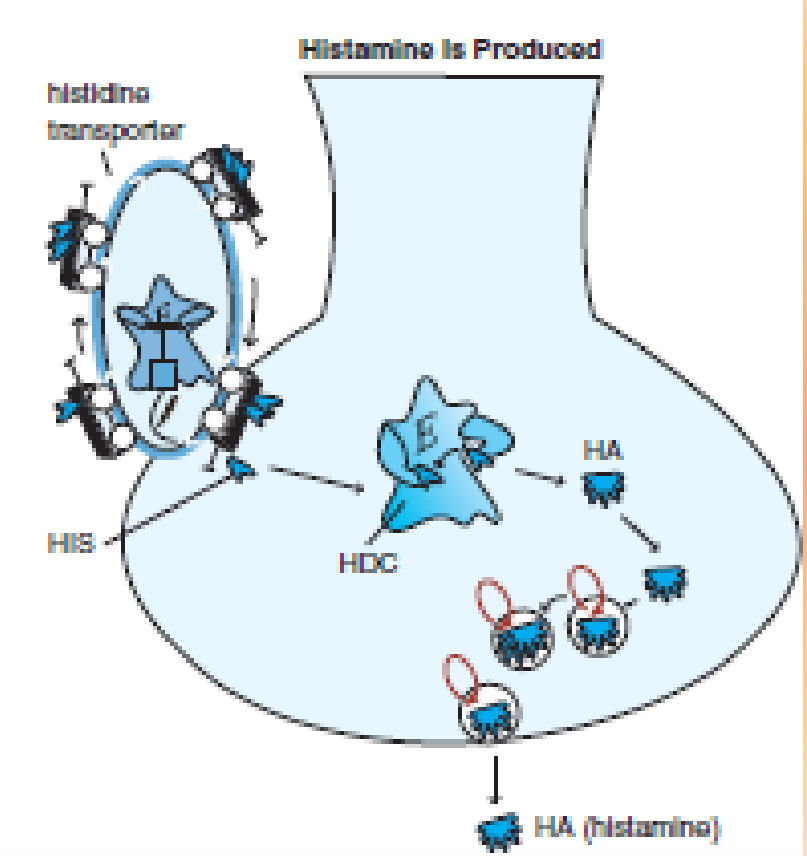


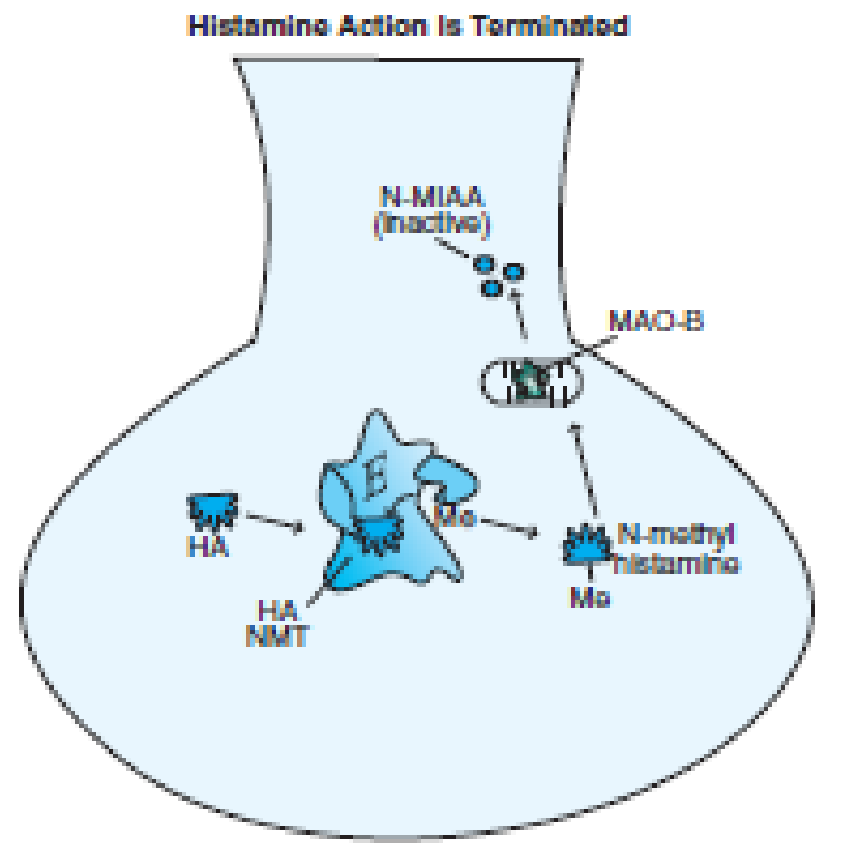


Sueño y ritmo circadiano

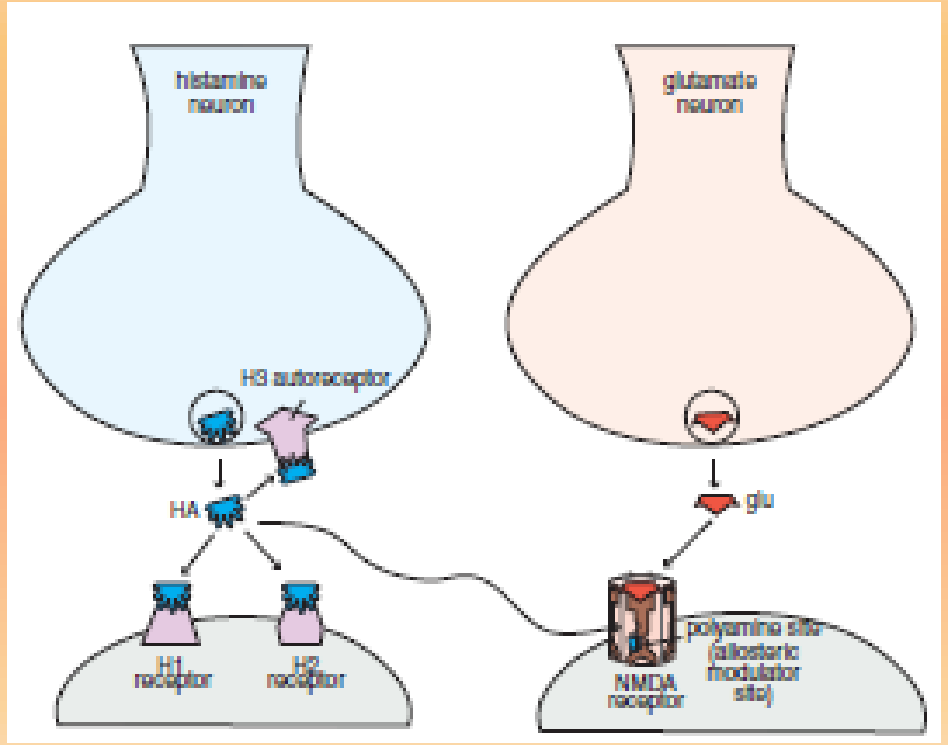


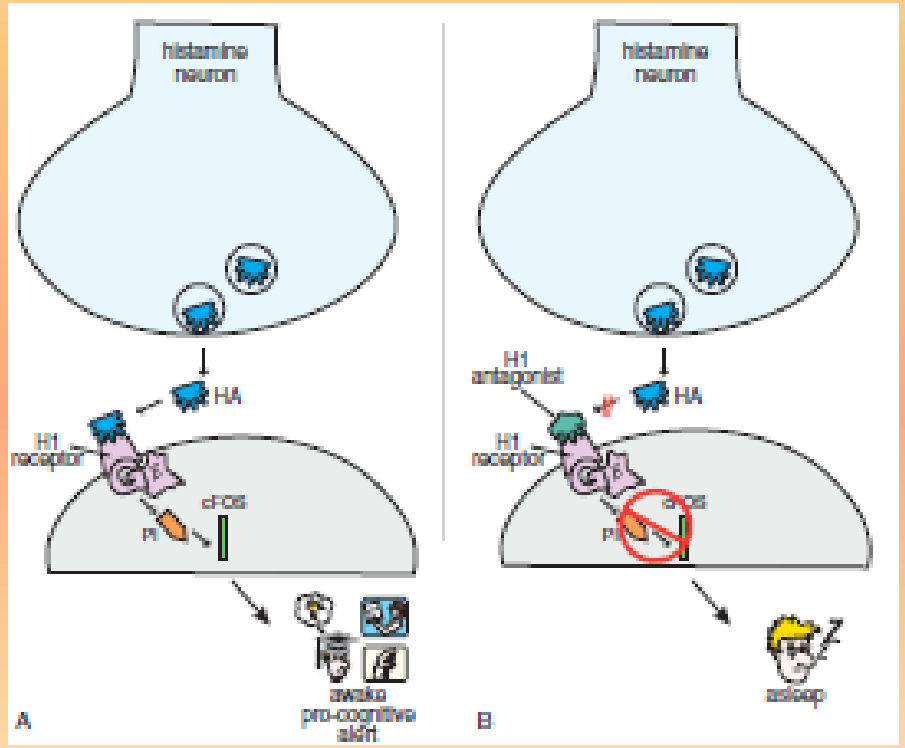
Histamina


Histamine Is Produced
histidine transporter
HIS
HDC
HA
HA (histamine)


Histamine Action Is Terminated
N-MIAA (inactive)
MAO-B
HA
HA NMT
Me
N-methyl histamine
Me

Receptores de histamina





Moduladores alostéricos GABAa