BHARATHIDASAN UNIVERSITY

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Programme: M.Sc., Biomedical Science

Course Title : Pharmacology and Toxicology
Course Code : BM35C7

Unit-2
Pharmacology of CNS - Part 4

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Anti-Anxiety Drugs

(fear of the known or unknown)

- Emotional state
- Unpleasant in nature
- Associated with uneasiness
- Discomfort and concern or fear
- About some defined or undefined future threat.
- Treatment - disproportionate and excessive.

- Cardiac neurosis

(unfounded fear of heart disease palpitation)

- GI neurosis

(fixation on bowel movement, distention, eructation)

- Social anxiety (fear of being observed)
- Obsessive-compulsive disorder (OCD),
- Post-traumatic stress disorder
- Phobias

- Some amount of anxiety

(fear of the known or unknown)

- Is a normal physiological response that assists the individual in solving various problems in life.
- Amygdala modulates fear and anxiety

Generalized Anxiety Disorder (GAD) Symptoms

Excessive anxiety and worry

Increased muscle aches or soreness

Impaired concentration

Fatigue

Irritability

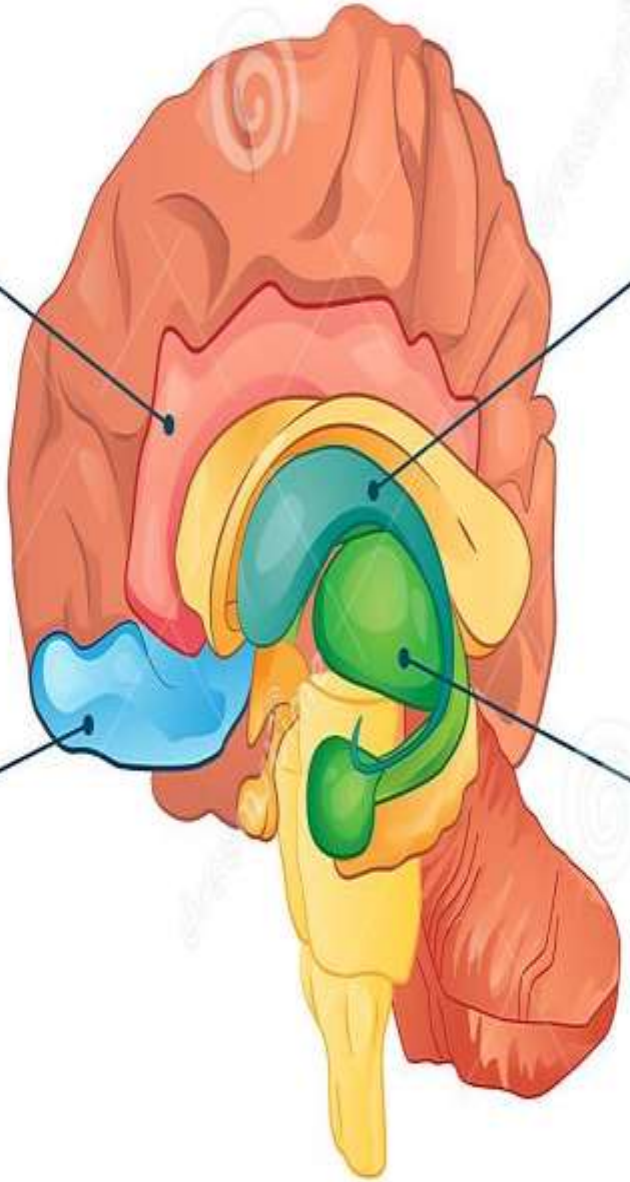
Restlessness

Difficulty sleeping

well


Social Anxiety Disorder Symptoms
Blushing and sweating
Racing heart
Shaking
Lump in throat
Nausea and dizziness
Muscle tension and pain
Escape
Avoidance
verywell

OCD Malfunctions in the Brain



CINGULATE GYRUS

NORMAL	OCD
Adds Emotional Response to Thoughts	Adds Emotions Like Disgust, Guilt to Anxious Thoughts

CAUDATE NUCLEUS

NORMAL	OCD
Processes and Filters Information, Removes Unwanted Thoughts	Fails to Filter Anxious Thoughts

ORBIFRONTAL CORTEX

NORMAL	OCD
Integrates Sensory Information, Makes Decisions, Anticipates Rewards and Punishment	Detects an Error Where there Isn't One, and Sends "Worry" Signals

BASAL GANGLIA

NORMAL	OCD
Controls Movements, Thinking and Judgment	Causes Reflexive or Repatative Behaviors

Subtypes of OCD

Contamination obsessions with cleaning compulsions

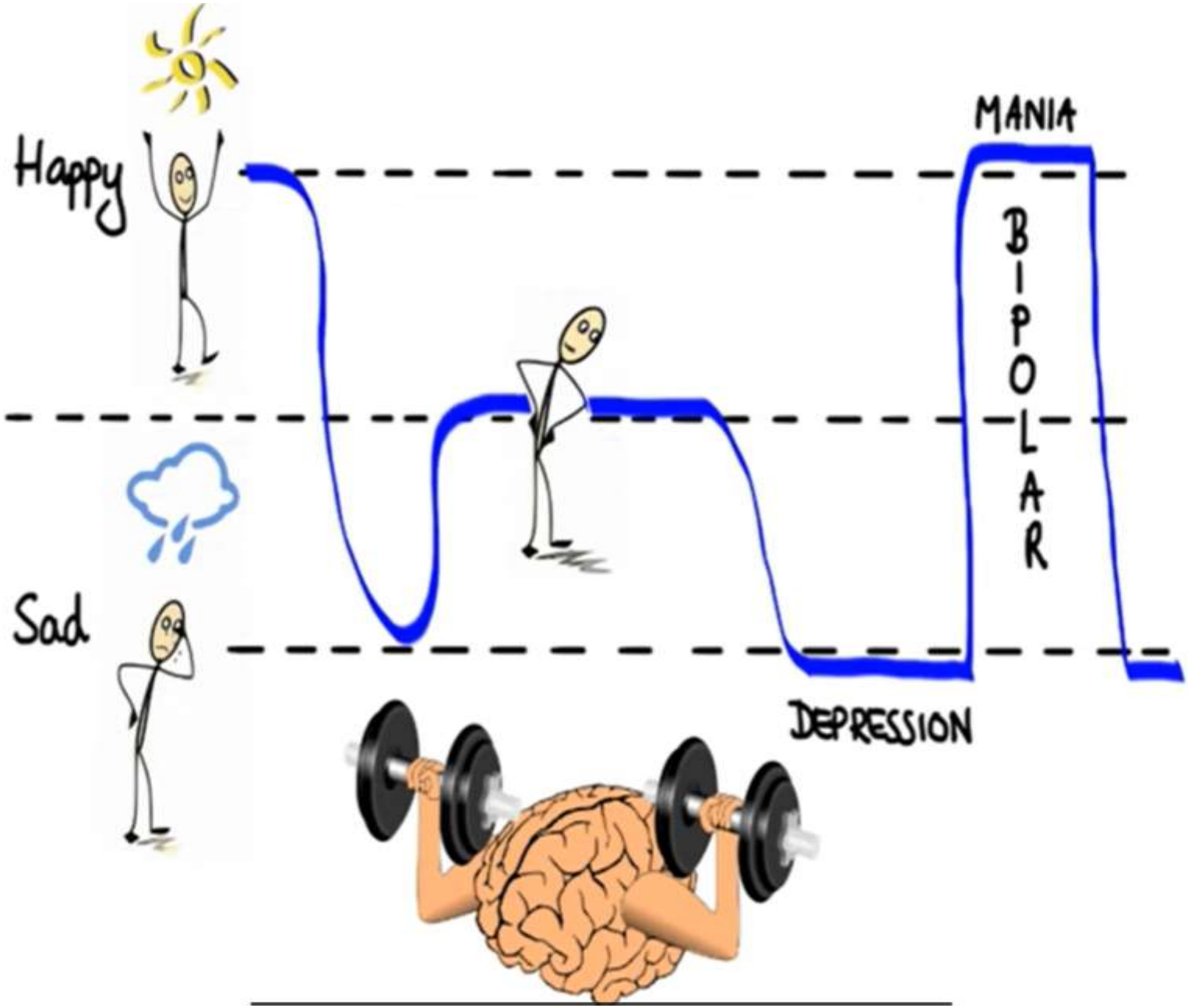
Hoarding

Symmetry obsessions with ordering compulsions

Obsessions without visible compulsions

Harm obsessions with checking compulsions

verywell


Happy
Sad
MANIA
BIPOLAR
DEPRESSION

CLASSIFICATION

1.	*Benzodiazepines*	Diazepam Chlordiazepoxide Oxazepam Lorazepam, Alprazolam
2.	*Azapirones*	Buspirone, Gepirone, Ispapirone
3.	*Sedative antihistaminic*	Hydroxyzine
4.	β *blocker*	Propranolol

In addition to the above drugs, antidepressants, especially the selective serotonin reuptake inhibitors (SSRIs) are effective in obsessive-compulsive disorder (OCD), phobias, panic and many types of severe generalized anxiety disorders.

Selective serotonin reuptake inhibitors (SSRIs)

Fluoxetine, Fluvoxamine, Paroxetine,
Sertraline, Citalopram, Escitalopram

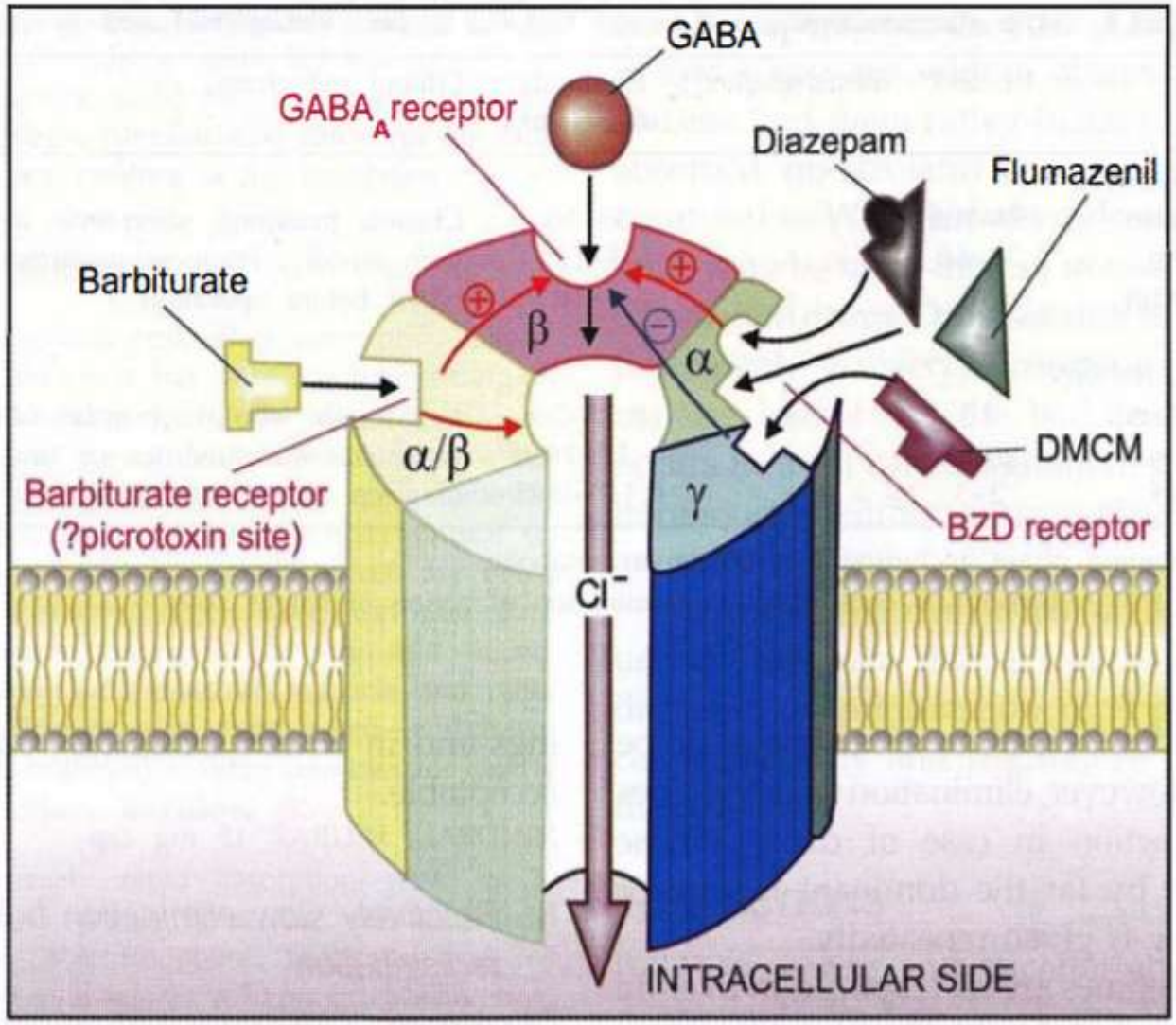


Fig. 29.3: Schematic depiction of $GABA_A$-benzodiazepine receptor-chloride channel complex

The chloride channel is gated by the primary ligand GABA acting on $GABA_A$ receptor located on the β subunit. The benzodiazepine (BZD) receptor located on the interface of α and γ subunits modulates $GABA_A$ receptor in either direction: agonists like diazepam facilitate, while inverse agonists like DMCM hinder GABA mediated Cl^- channel opening, and BZD antagonist flumazenil blocks the action of both. The barbiturate receptor, located either on α or β subunit also facilitates GABA and is capable of opening Cl^- channel directly as well. Bicuculline blocks $GABA_A$ receptor, while picrotoxine blocks the Cl^- channel directly

Buspirone

- Relieves mild-to-moderate GAD
- maximum benefit delayed up to 2 weeks.
- Mechanism of anxiolytic action is not clearly known,
- But has selective partial agonistic action on 5-HT1A receptors.
- By stimulating presynaptic 5-HT1A autoreceptors, it reduces the activity of dorsal raphe serotonergic neurones.
- After chronic treatment, adaptive reduction in cortical 5-HT2 receptors
- Buspirone has weak dopamine D2 blocking action.
- A mild mood elevating action has been noted occasionally-
- -Due to facilitation of central noradrenergic system.

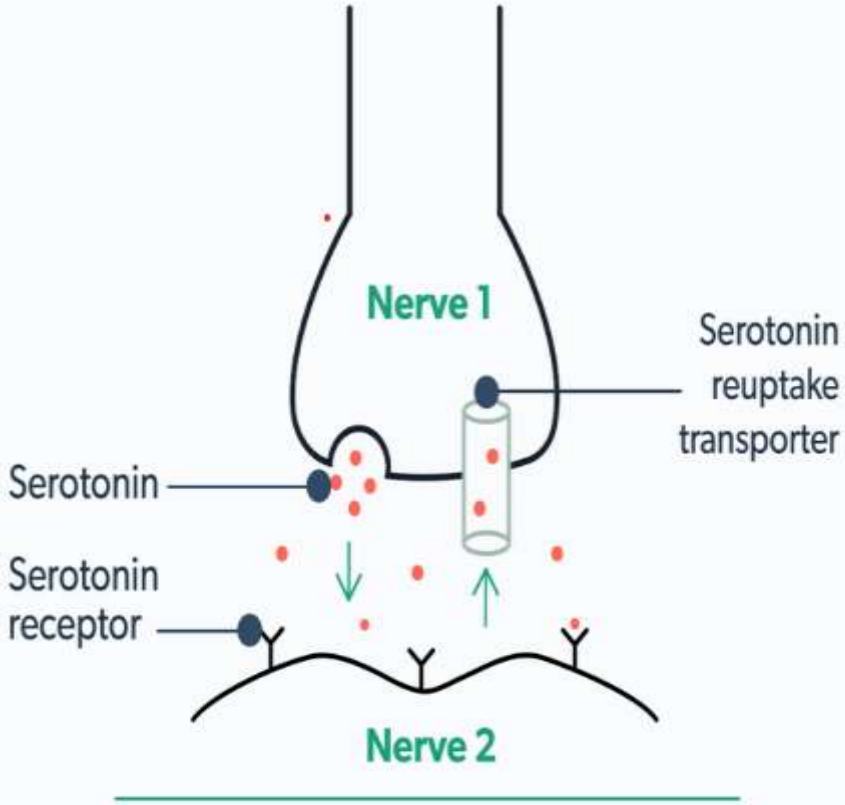
$5\text{-}HT_{1A}$

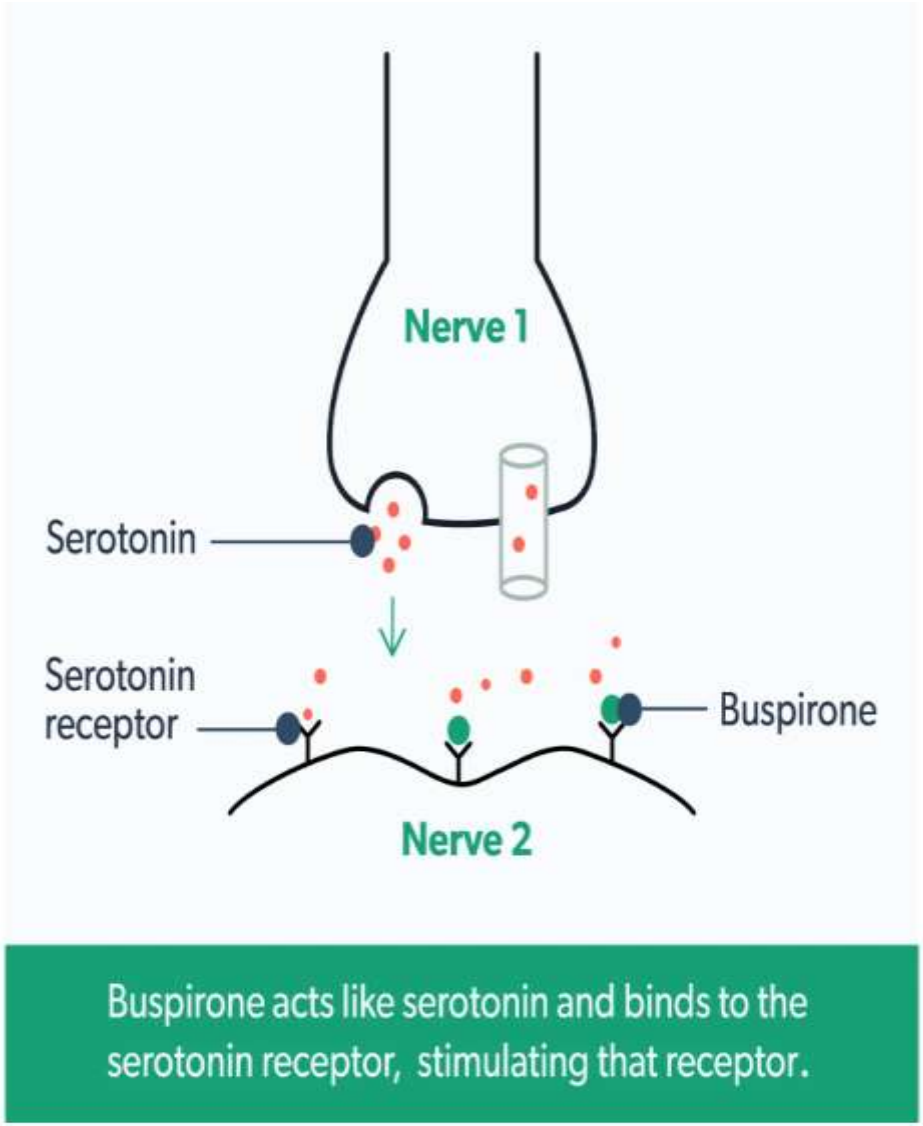
Autoreceptors

Raphe nuclei

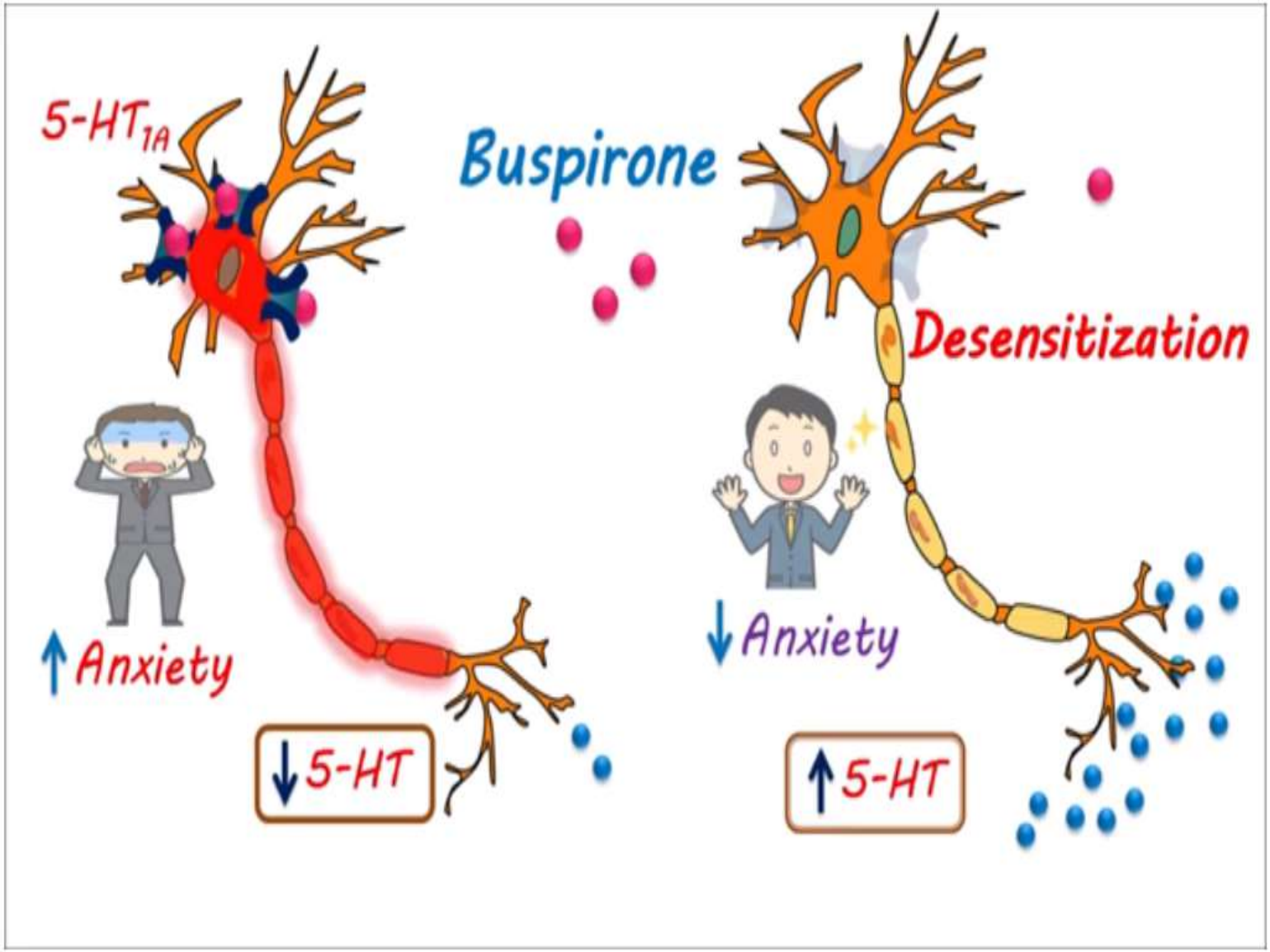
Heteroreceptors

How buspirone works





Buspirone acts like serotonin and binds to the serotonin receptor, stimulating that receptor.



Buspirone (Buspar) for anxiety

Buspirone

- Rapidly absorbed;
- First pass metabolism; Bioavailability <5%
- One metabolite is active
- Excretion occurs both in urine and faeces; t1/2 is 2-3.5 hrs.
- Side effects : Dizziness, Nausea, Headache,
- Remain alert, those operating machinery/motor vehicles- cautioned

Beta Blockers

Symptoms of Anxiety

(palpitation, rise in BP, shaking, tremor, GI hurrying)

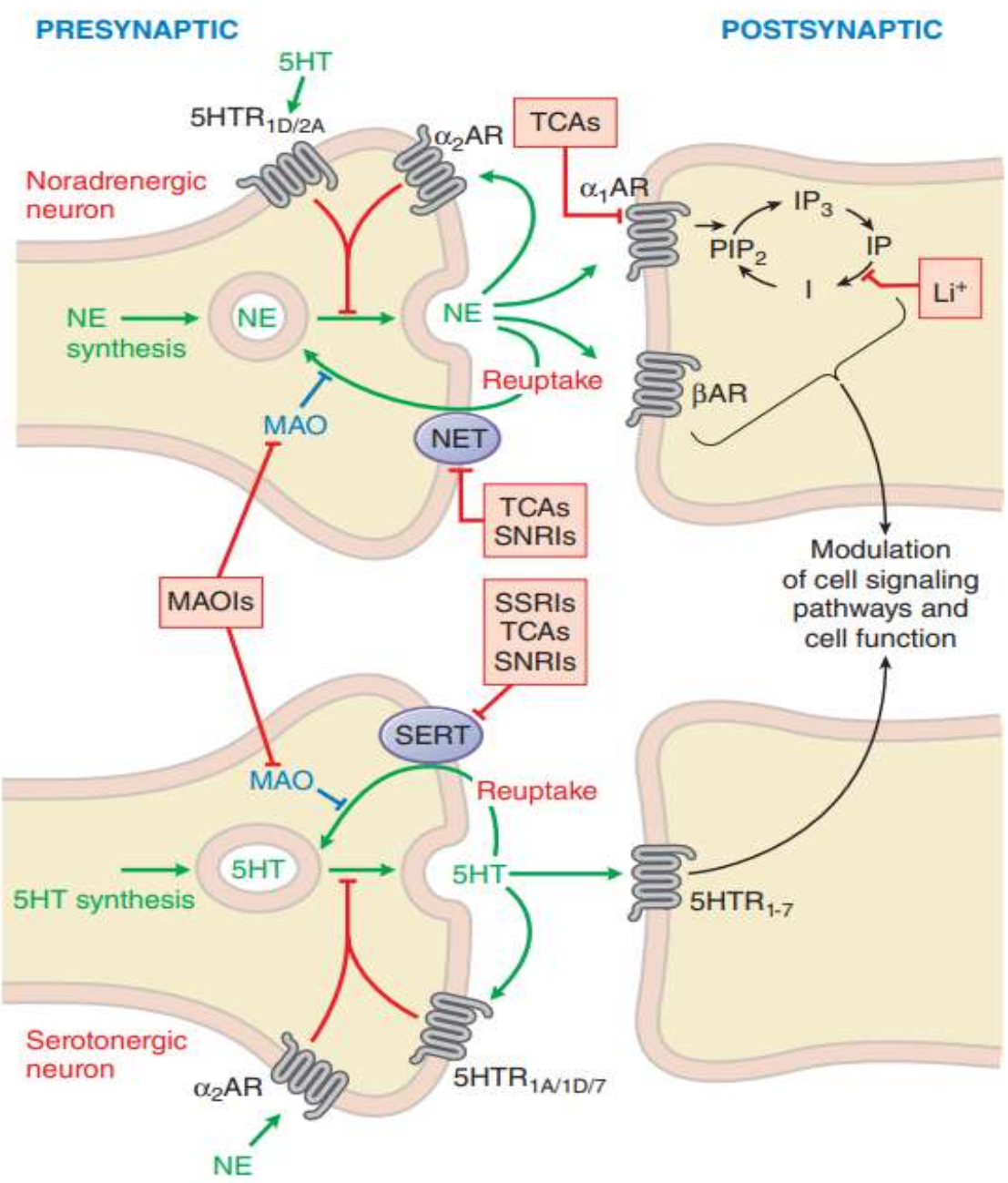
- Due to sympathetic overactivity, reinforce anxiety.
- Propranolol and other nonselective Beta blockers.
- They do not affect psychological symptoms(worry, tension & fear)
- Valuable stressful (exam fear, unaccustomed public appearance)
- Performance / situational anxiety or as adjuvant to BZDs.

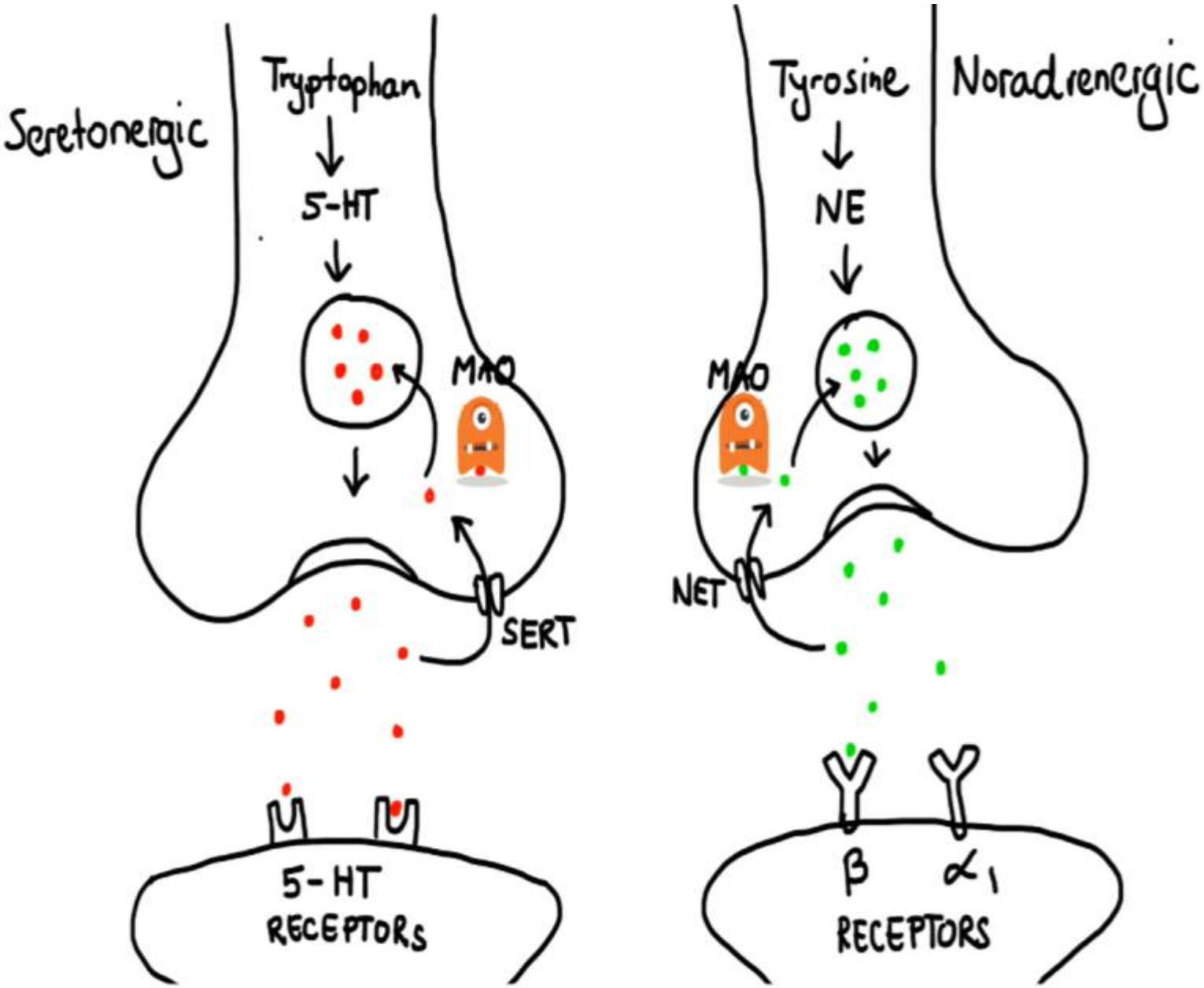
- Persist in a severe form, distress/suffering and impair performance.
- It should be treated with drugs only when excessive
- BZDs smallest dose- to be found out for each patient- by titration
- The drug should be withdrawn as soon as it is no longer required
- Longer periods-withdrawal should be gradual.
- ½ to 2/3 of the daily dose at bed time to ensure good nightly rest;
- the remaining is divided in 2-3 doses given at day time.
- Required to avoid high peaks.

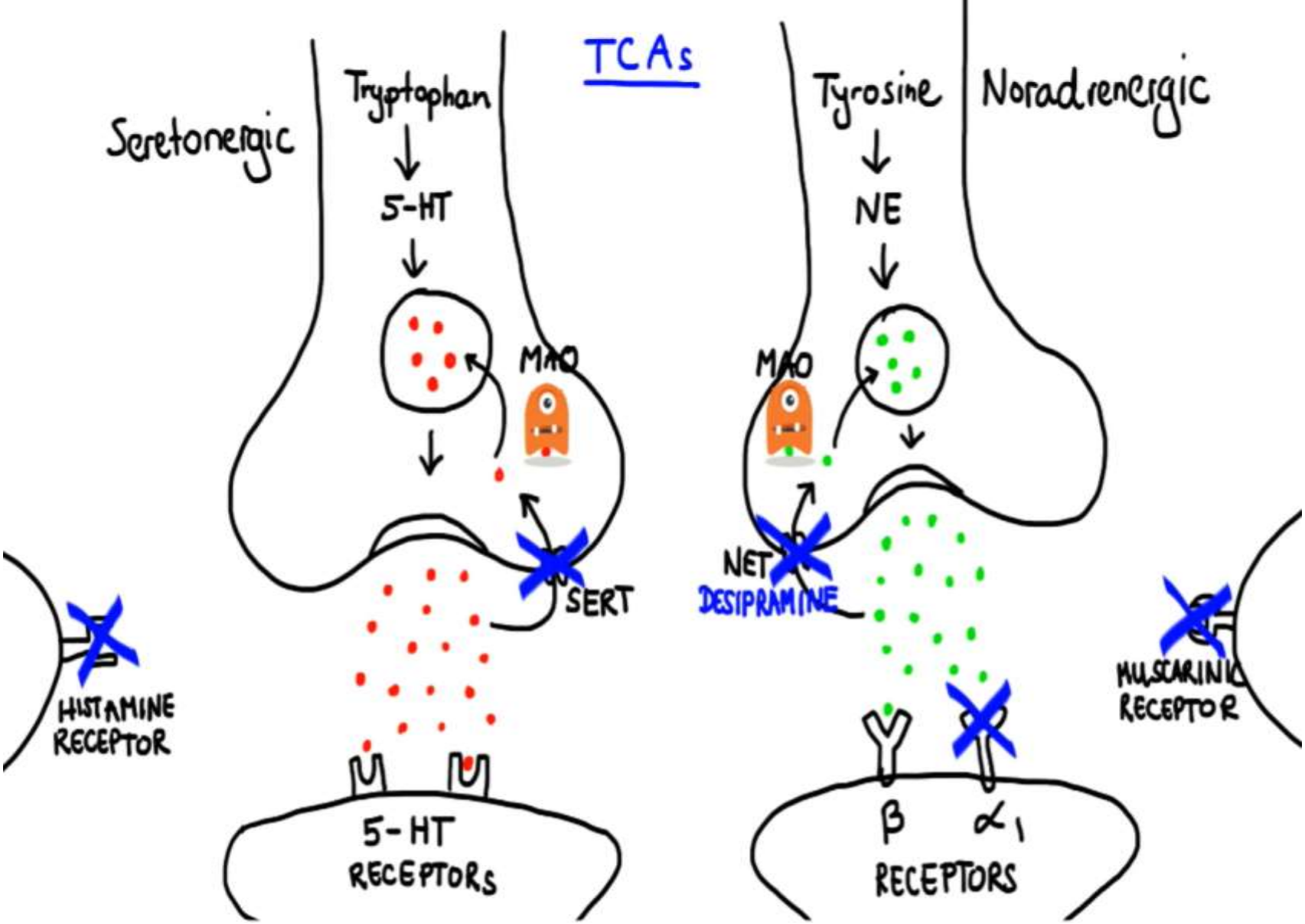
Selective serotonin (5-HT) reuptake inhibitors (SSRI)

- The relative safety and better acceptability of SSRIs
- 1st line drugs in depression and use in anxiety, phobias, OCD
- No sedation, do not interfere with cognitive and psychomotor function or produce anticholinergic side effects.

- Action: inhibit the reuptake of serotonin by tryptaminergic neurons.
- They bind to the serotonin transporter (SERT) at a site other than the binding site of 5-HT and inhibit the transporter.
- SSRI are well absorbed orally and have long half lives,
- which permits their once-a-day administration.
- All SSRI except Citalopram and Escitalopram inhibit one or more CYP450


PRESYNAPTIC
POSTSYNAPTIC
5HT
5HTR1D/2A
α2AR
TCAs
α1AR
Noradrenergic neuron
IP3
PIP2
IP
I
Li+
NE synthesis
NE
NE
Reuptake
βAR
MAO
NET
TCAs SNRIs
Modulation of cell signaling pathways and cell function
MAOIs
SSRIs TCAs SNRIs
SERT
MAO
Reuptake
5HT
5HT synthesis
5HT
5HTR1-7
Serotonergic neuron
α2AR
5HTR1A/1D/7
NE


Seretonergic
Tryptophan
5-HT
MAO
SERT
5-HT
RECEPTORS
Tyrosine
Noradrenergic
NE
MAO
NET
β
α1
RECEPTORS


TCAs
Seretonergic
Tryptophan
5-HT
MAO
SERT
HISTAMINE RECEPTOR
5-HT RECEPTORS
Noradrenergic
Tyrosine
NE
MAO
NET
DESIPRAMINE
MUSCARINIC RECEPTOR
β
α1
RECEPTORS

Fluoxetine

- A bicyclic compound, prototype of the SSRIs and the longest acting;
- Plasma half life 2 days
- Its active demethylated metabolite is 7-10 days.
- Children 7 years or older for depression and OCD
- Only when psychotherapy fails
- Produce little or no sedation,
- Do not interfere with cognitive and psychomotor

Acknowledgement

- The Presentation is being used for educational and non commercial Purposes
- Thanks are due to all the original contributors and entities whose pictures were used in the creation of this presentation.