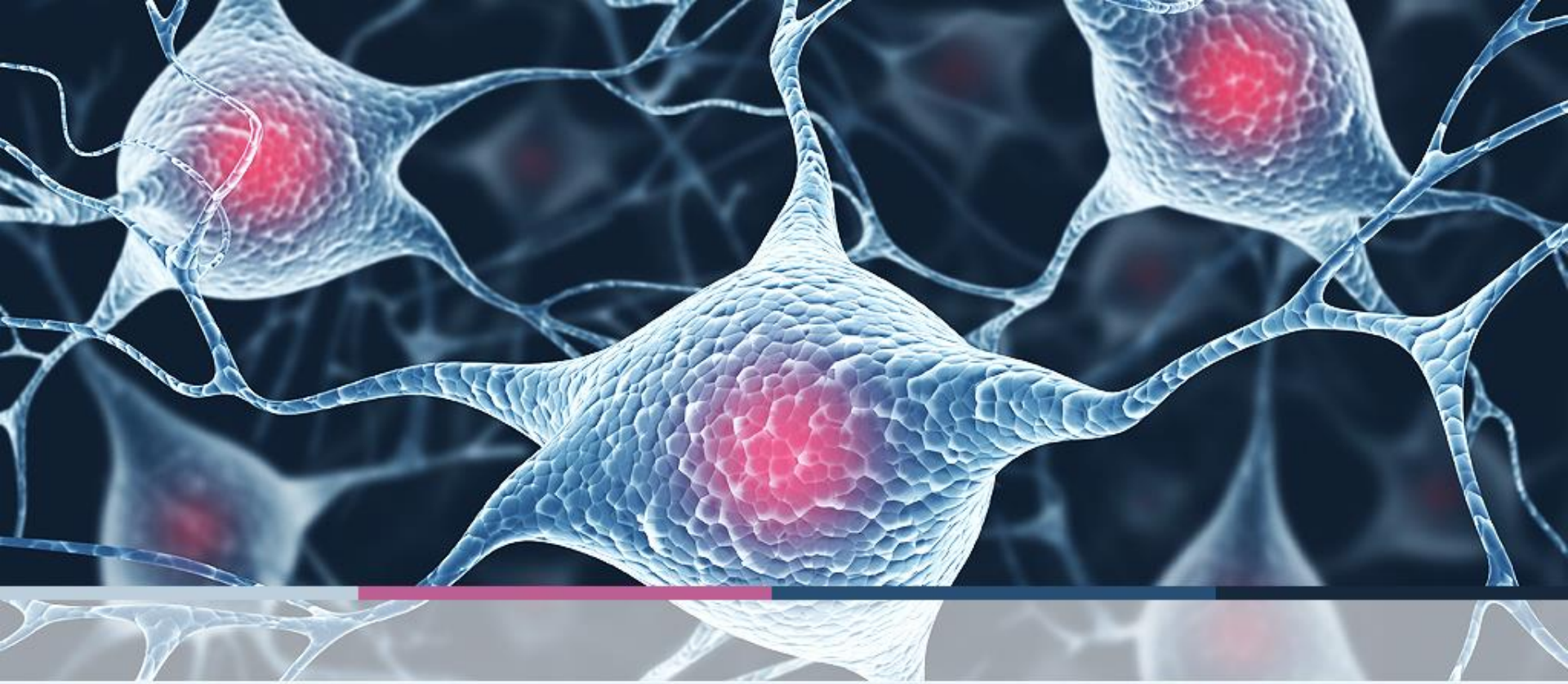
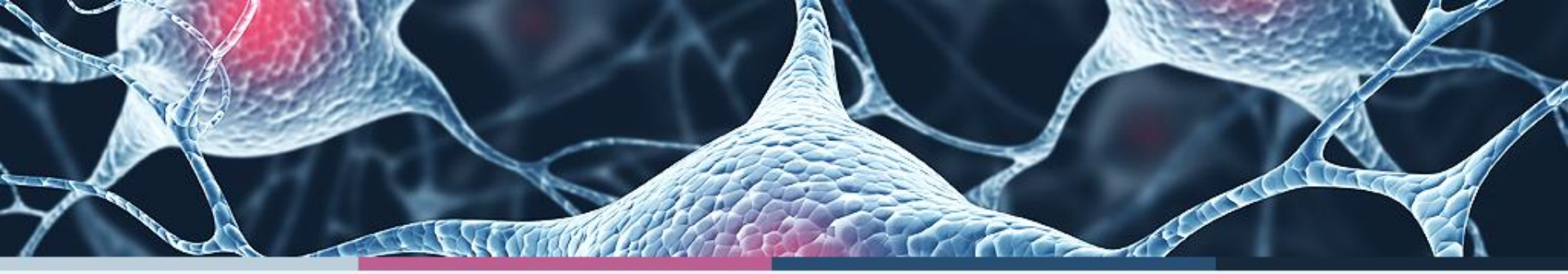
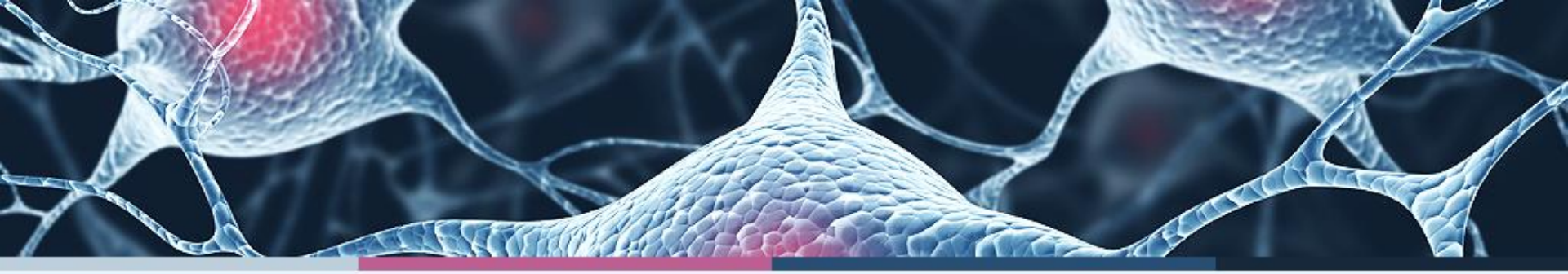


CLINICAL PHARMACOLOGY OF PSYCHOTROPIC DRUGS

Assoc. prof. L. Turcan



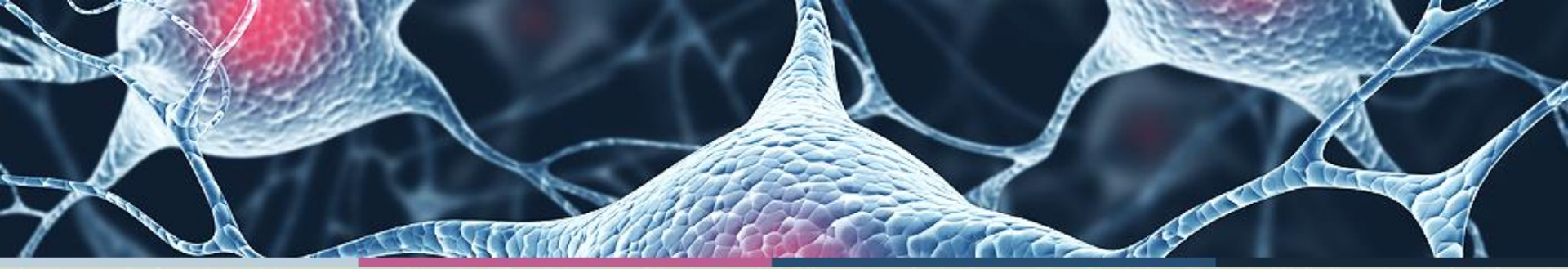
- ✓Antipsychotics
- ✓Anxiolytics
- ✓Antidepressants
- ✓Nootropics
- ✓Thymoisoleptics
- ✓Sedatives
- ✓Stimulants (psychostimulant drugs)



Antipsychotic drugs

Schizophrenia is a serious mental illness that affects how a person thinks, feels, and behaves. People with schizophrenia may seem like they have lost touch with reality, which can be distressing for them and for their family and friends. The symptoms of schizophrenia can make it difficult to participate in usual, everyday activities, but effective treatments are available. Many people who receive treatment can engage in school or work, achieve independence, and enjoy personal relationships.

(National Institute of Mental Health)

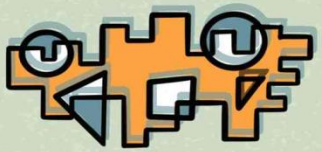


Signs & Symptoms of Schizophrenia

Positive Symptoms

Hallucinations

Delusions



Disorganized speech and thoughts

Negative Symptoms

Anhedonia

Avolition

Blunted affect

Cognitive Symptoms

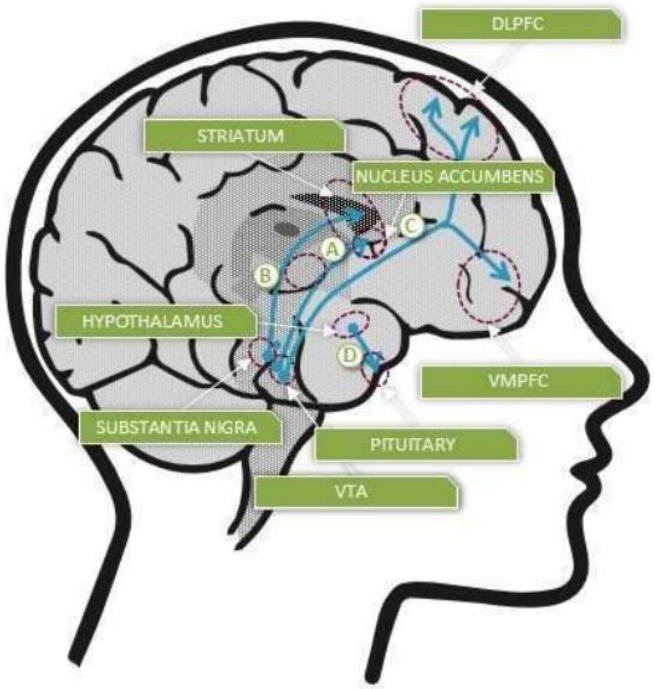
Memory issues

Inability to process social cues

Impaired sensory perception

psych scene
EXCELLENCE IN PSYCHIATRY

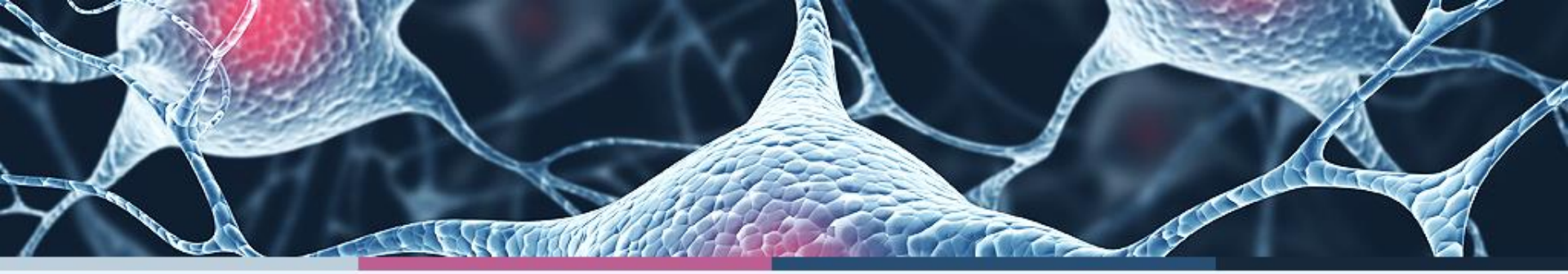
CONCEPTUALISATION OF SCHIZOPHRENIA



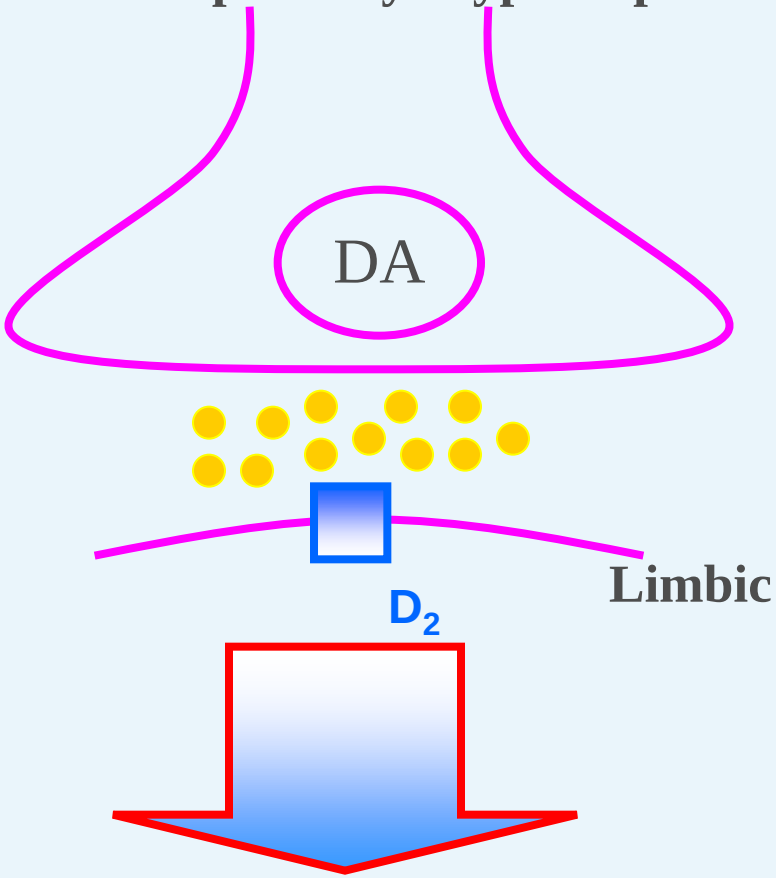
A	VTA	NA	Positive symptoms
B	Substantia Nigra	Striatum	EPSE
C	VTA	VMPFC	Affective
C	VTA	DLPFC	Cognition
D	Hypothalamus	Anterior pituitary	Elevated prolactin

METABOLIC SYNDROME

VTA – ventral tegmental area, DLPFC – dorsolateral prefrontal cortex, VMPFC – ventromedial prefrontal cortex, NA – nucleus accumbens

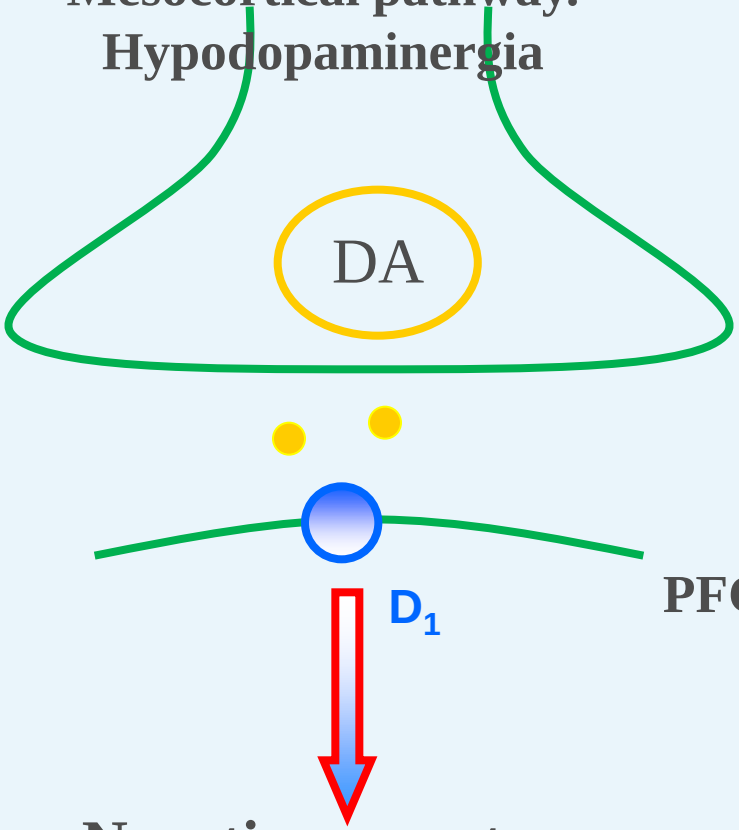


Mesolimbic pathway. Hyperdopaminergia

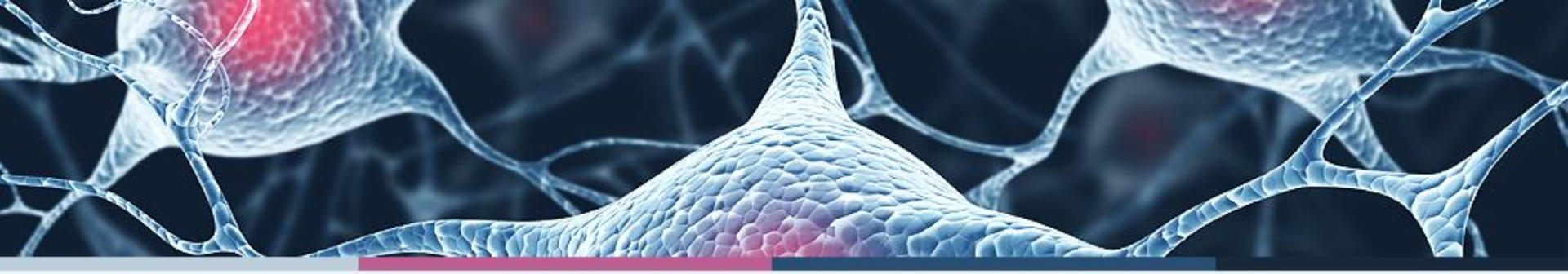


Positive symptoms

Mesocortical pathway.
Hypodopaminergia



Negative symptoms
Cognitive symptoms
Affective symptoms



Treatment Goal of Schizophrenia

Acute Phase Treatment

- Rapid symptom control

- Initiation of therapeutically effective dose
- No need for initial dose titration for tolerability

Stabilization Phase Treatment

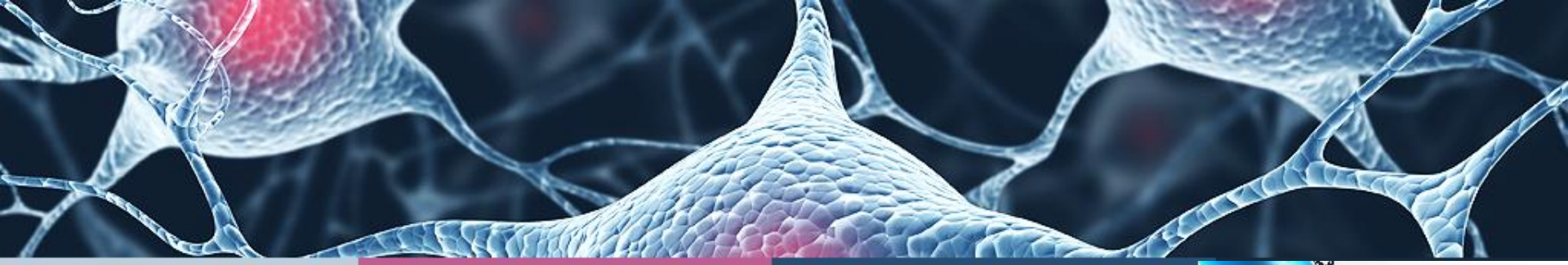
- Patient relationship
- Insight on medication

- Minimal drug-drug interaction
- Proven efficacy and safety

Maintenance Phase Treatment

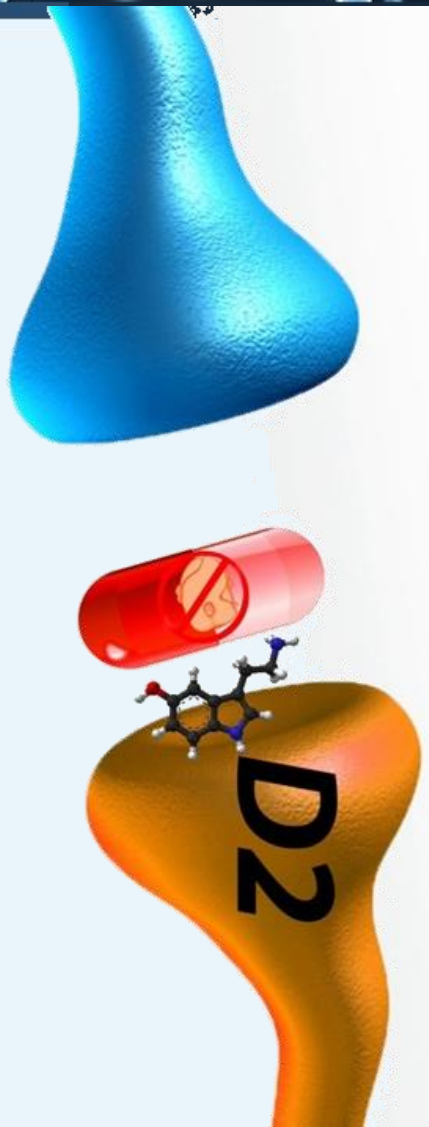
- Relapse/recurrence prevention
- Adherence
- Functional recovery

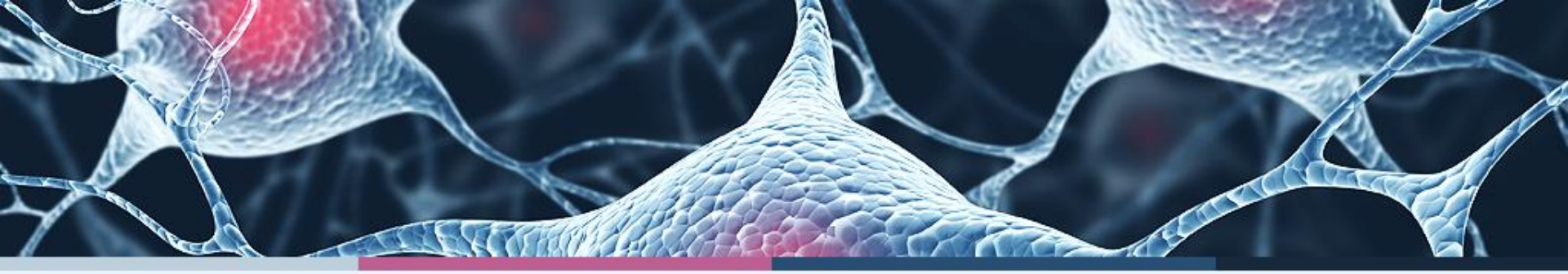
- Increased tolerance to occasional missed doses
- Proven relapse prevention effect
- Improved PSP



Classification of antipsychotic drugs

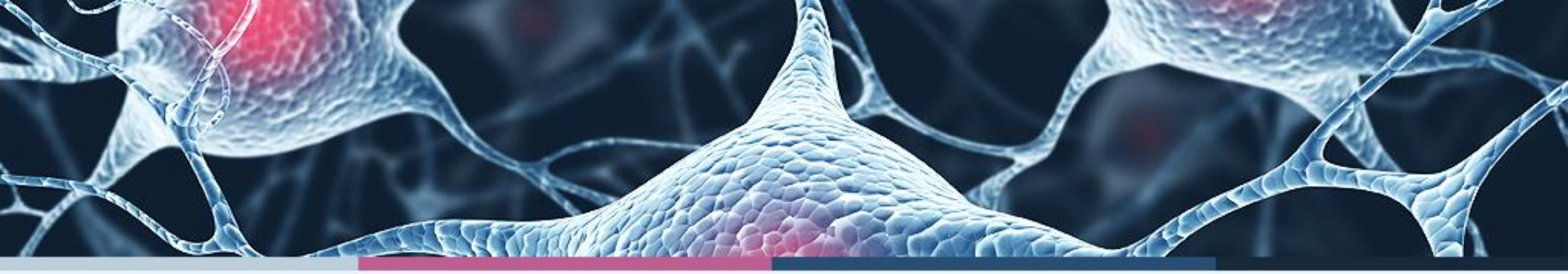
- Typical antipsychotics
  - **Phenothiazines**
    - e.g. chlorpromazine, fluphenazine, thioridazine
  - **Butyrophenones**
    - e.g. haloperidol, droperidol
  - **Thioxanthines**
    - e.g. chlorprotixen, thiothixene
- Atypical antipsychotics
  - **Benzamides**
    - remoxipride (investigational)
  - **Diphenylbutylpiperazines**
    - e.g. pimozide
  - **Dibenzodiazepines**





CLASSIFICATION ACCORDING TO THE CLINICAL SPECTRUM:

- **Sedative neuroleptics** - intense sedative and moderate antipsychotic effect, with marked neurovegetative phenomena: chlorpromazine, levomepromazine, chlorprothixene, clozapine, reserpine.
- **Medium (small) neuroleptics** - moderate sedative and antipsychotic effect, without marked side effects:- thioridazine, propazine, periciazin, alimemazine, tiapride, risperidone.
- **Polyvalent neuroleptics** - intense antipsychotic effect, with sedative action or disinhibitors and marked extrapyramidal disorders:- haloperidol, droperidol, trifluperidol, fluphenazine, thioproperazine, pipothiazine, fluspirilene, pimozide, penfluridol, olanzapine, flupentixol, zuclopenthixol, sultopride.

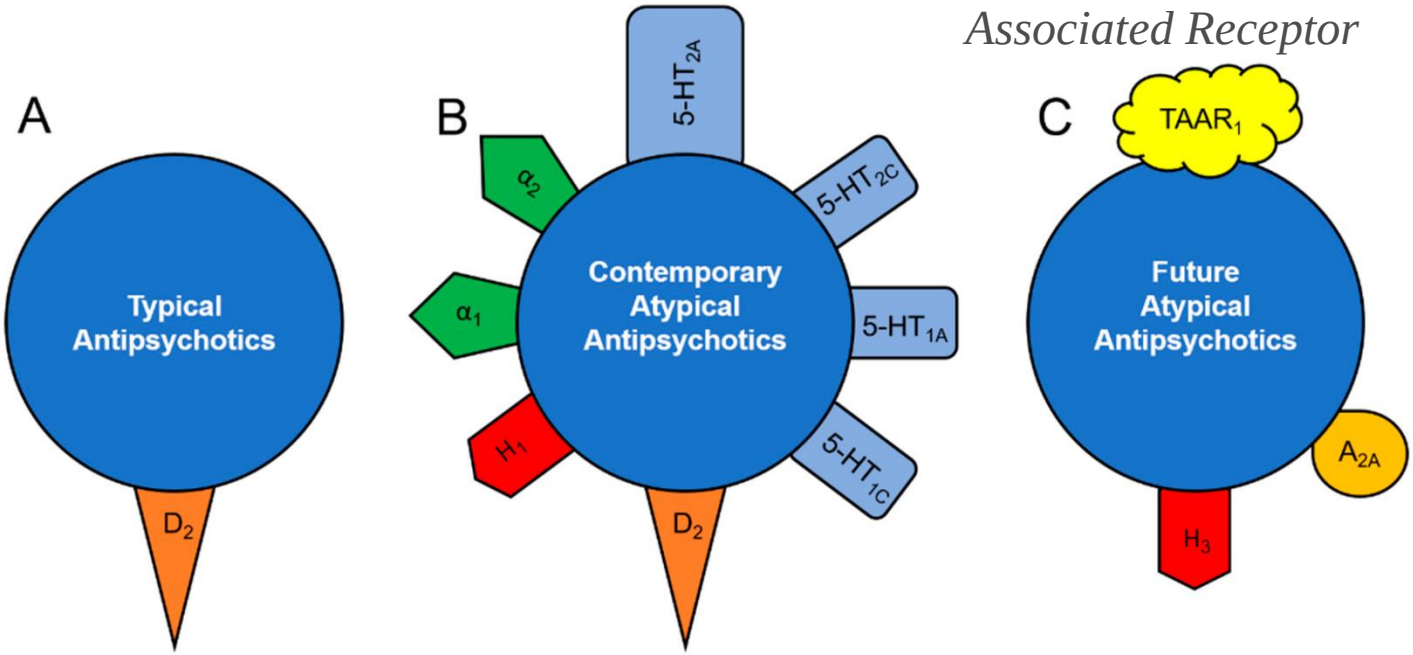


CLASSIFICATION ACCORDING TO THE CLINICAL SPECTRUM:

- **disinhibitory, "anti-deficit", "incisive" neuroleptics** (manifest moderate antipsychotic effect (in contrast to negative symptoms), weak or absent sedative action,moderate or marked extrapyramidal phenomena):- perphenazine, pipothiazine, trifluoperazine, sulpiride, amisulpiride, carbidin.
- **"antiproductive" or "reducing" neuroleptics** (active against positive symptoms or"florid" psychoses - hallucinations, delirium, agitation, stereotyped behavior):- chlorpromazine, fluphenazine, pipothiazine, haloperidol, penfluridol, thioproperazine.

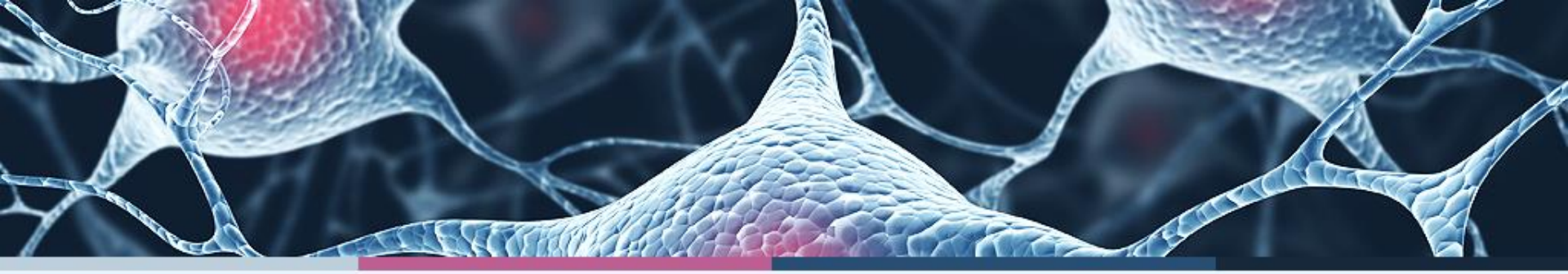
Antipsychotic drugs

TAAR1 – Trace Amine Associated Receptor



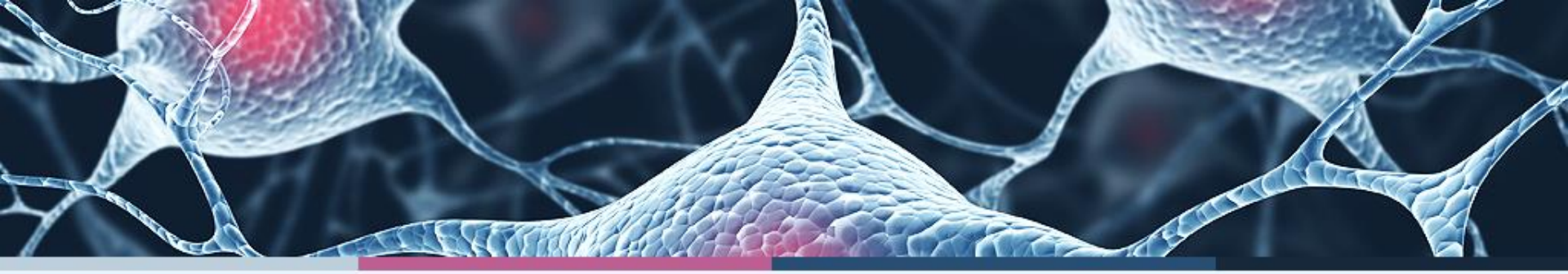
D2 – blocker effect ➔ EPDs

5HT2A blocker effect ➔ Metabolic syndrome



Differences among antipsychotic drugs – receptor affinity:

- ✓ Chlorpromazine: α1 = 5-HT2A > D2 > D1
- ✓ Haloperidol: D2 > α1 > D4 > 5-HT2A > D1 > H1
- ✓ Clozapine: D4 = α1 > 5-HT2A > D2 = D1
- ✓ Olanzapine: 5-HT2A > H1 > D4 > D2 > α1 > D1
- ✓ Aripiprazole: D2 = 5-HT2A > D4 > α1 = H1 >> D1
- ✓ Quetiapine: H1 > α1 > M1,3 > D2 > 5-HT2A



Higher potency

Higher EPS

Lower anticholinergic effect

Lower potency

Low EPS

Higher anticholinergic effect

Haloperidol

Fluphenazine

Trifluoperazine

Thioxanthine

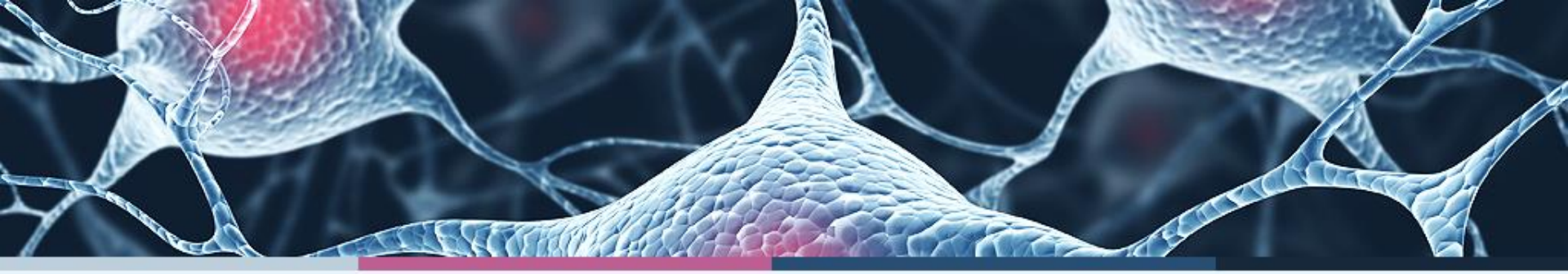
Perphenazine

Pimozide

Chlorpromazine

Thioridazine

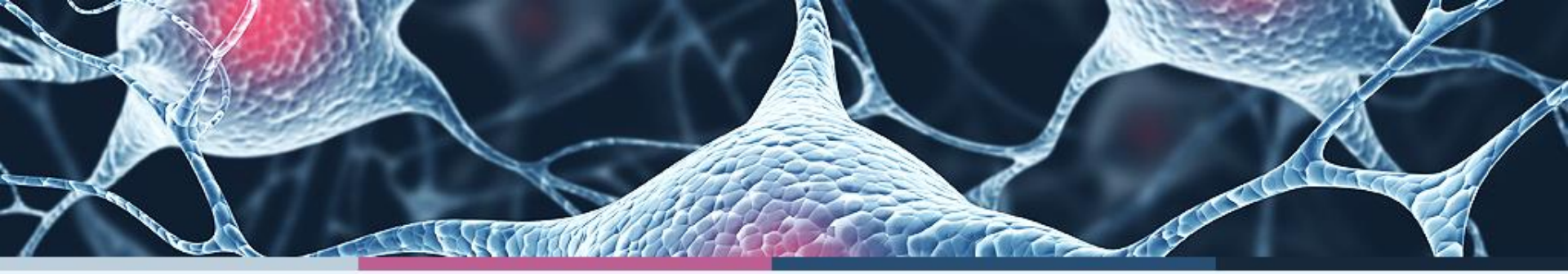
Mesoridazine



Effects of blockade of neuroreceptors:

Receptors	Effects of blockade
α_1	Postural hypotension, dizziness, syncope, nasal congestion
α_2	Antidepressive effect, increase alertness, increase blood pressure
H_1	Anxiolytic, sedation, weight gain, potentiate CNS depressant drug

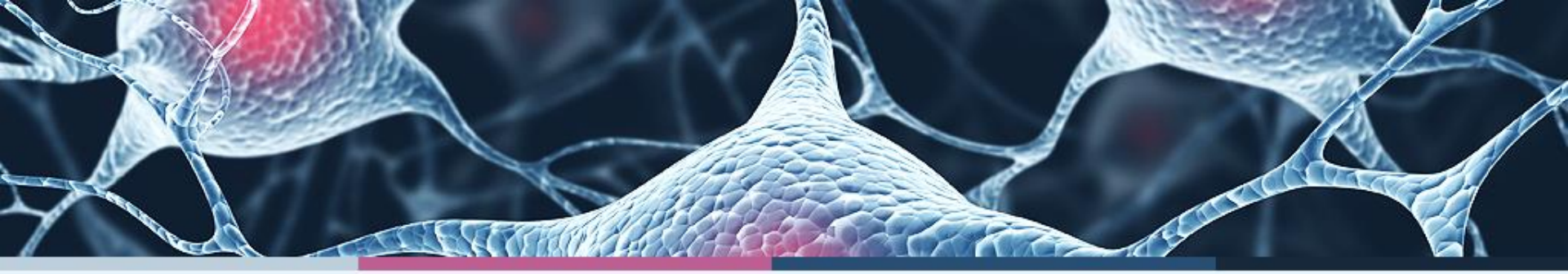
Modified from J Clin Psychiatry 2008;69[suppl4]:26-36.



Effects of blockade of neuroreceptors:

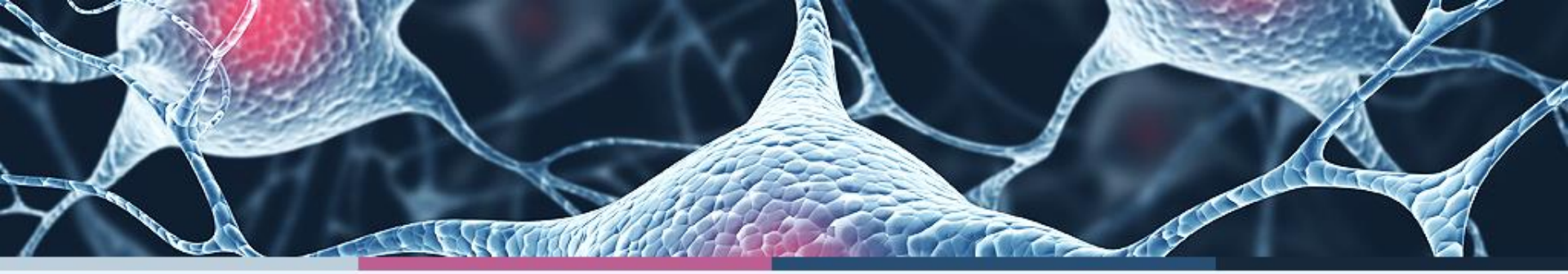
Receptors	Effects of blockade
M_1 (central)	Memory dysfunction, delirium, confusion, sedation, REM sleep disturbance
M_2, M_3 (peripheral)	Blurred vision, attack or exacerbation of narrow-angle glaucoma, dry mouth, sinus tachycardia, constipation, urinary retention, interfere pancreatic insulin release

Modified from J Clin Psychiatry 2008;69[suppl4]:26-36.



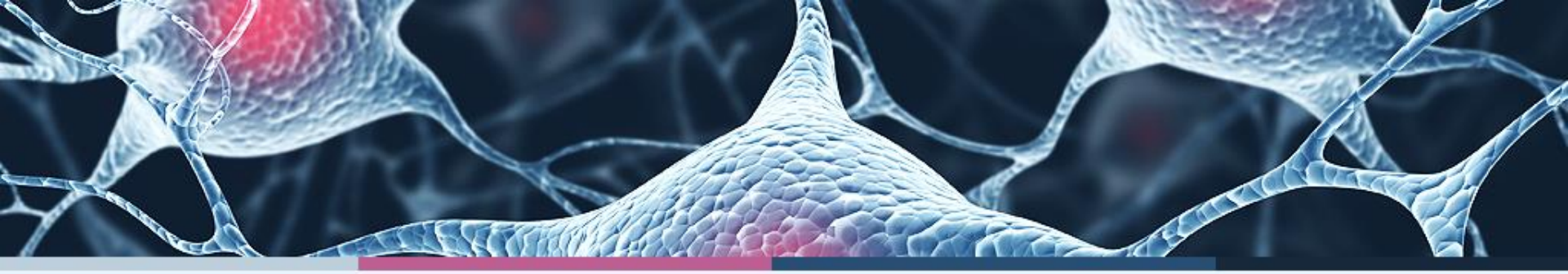
Pharmacodynamics:

Effect	Manifestations
Antipsychotic	**D-blocker / Ser – lytic** ✓ remove personality changes and behavioral disorders;- remove delirium, hallucinations, confusional states, autism, angers; ✓ reactivating effects, ➔ interest in the environment returns, initiative;
Psychosedative	**α-adrenoblocking action / M-cholinoblocker / H1-blockers.** ✓ drowsiness, weakness, decrease in nervous tension, agitation and aggressiveness, suppression of anxiety, apathy, mental and motor depression (inhibition); ✓ depression of initiative, will, interest in the environment; ✓ produce affective and emotional neutrality.
Antiemetic	**D-blocker / Ser – lytic of receptors from the trigger zone of the vomiting center.** The potency of the antiemetic action is manifested as follows: pimozide > droperidol > chlorpropazine > trifluperazine > fluphenazine > sulpiride> chlorpromazine.



Pharmacodynamics:

Muscle relaxant and anticonvulsive effect	**Muscle relaxant effect – decrease the tone of the striated muscles and the motor activity** **Anticonvulsant effect:- influence the convulsive threshold;- they are useful as symptomatic anticonvulsants for controlling convulsions and status epilepticus.**
Hypothermic effect	**α-adrenoblocking action / Ser – lytic** ✓ caused by the decrease in the activity of thermoregulatory centers ✓ vasodilatation and heat loss
Potentiation of action of analgesics, anesthetics, and other CNS depressant	**α-adrenoblocking action / M-cholinoblocker / H1-blockers.** ✓ amplify the effect and duration of action of the drugs with inhibitory action on CNS;- ✓ the negative action of these drugs is potentiate and on the vital centers (respiratory, etc.); ✓ droperidol is most frequently used in combination with fentanyl (thalamonal) for performing neuroleptanalgesia.

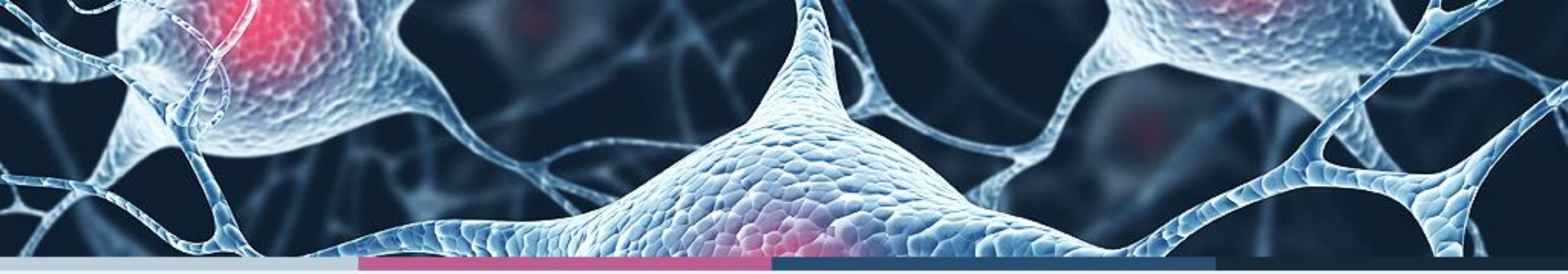


Indications. Psychiatry:

I. **Treatment of psychoses with hallucinations, delirium, mania,aggression, etc. in the:**
   - different forms of schizophrenia;
   - manic-depressive psychoses (manic phase);
   - mental disorders in organic brain disorders;
   - endogenous psychoses.

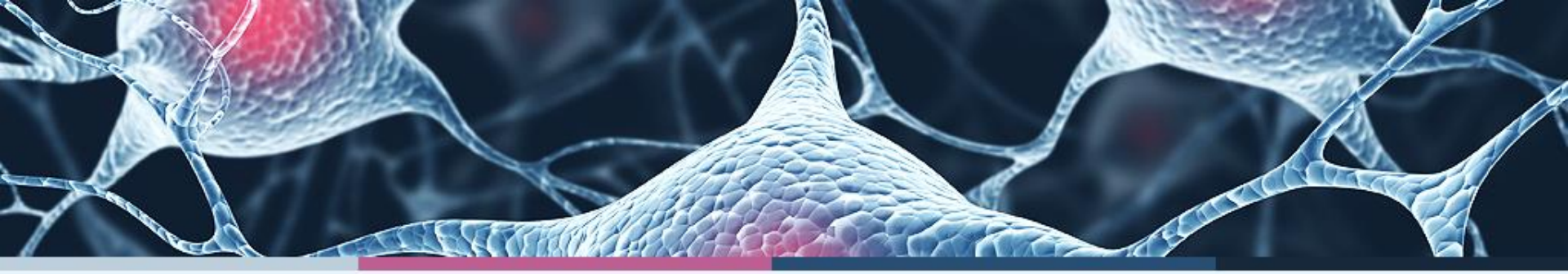
II. **Psychomotor excitement in:**
   - recurrence, exacerbation of mental illnesses;
   - trauma, infections, postoperative period;
   - psychotraumatic situations (calamities, catastrophes, etc.);
   - abstinence syndrome (alcoholism, drug addiction, etc.).

III. **Intermediate states like:**
   - psychoses,
   - exaggerated excitement,
   - aggressivity,
   - behavioral disorders in children and the elderly



Indications. Somatic diseases:

1) vegetoneurosis in ischemic heart disease, ulcerative disease, climacteric period, etc.;
2) nausea and vomiting: of central origin, postoperatory and postanesthetic, in radiation sickness, GIT diseases, produced by drugs (opioids, digoxin, estrogens, cytotoxic);
3) hypertensive emergencies;
4) complex treatment of traumatic shock, combustion (only after resolving the circulating blood volume deficit) to improve microcirculation;
5) for performing neuroleptanalgesia in case of surgical interventions;
6) potentiation of the effect of analgesics used in unoperable tumor, serious combustions, etc.;
7) spastic states of the striated muscles after stroke, brain trauma
8) critical febrile states or for induced hypothermia;
9) as an adjuvant in the suppression of different origin convulsions.



ANTIPSYCHOTICS. SIDE EFFECTS

- ✓ Sedation - initially considerable; tolerance usually develops after a few weeks of therapy; dysphoria
- ✓ Postural hypotension - results primarily from adrenergic blockade; tolerance can develop
- ✓ Anticholinergic effects - include blurred vision, dry mouth, constipation, urinary retention; results from muscarinic cholinergic blockade
- ✓ Endocrine effects - increased prolactin secretion can cause galactorhea; results from antidopamine effect
- ✓ Hypersensitivity reactions - jaundice, photosensitivity, rashes, agranulocytosis can occur
- ✓ Idiosyncratic reactions - malignant neuroleptic syndrome

Neurological Side Effects of antipsychotics

REACTION	FEATURES	TIME OF MAXIMAL RISK	PROPOSED MECHANISM	TREATMENT
Acute dystonia	Spasm of muscles of tongue, face, neck, back; may mimic seizures; not hysteria	1 to 5 days	Unknown	Antiparkinsonian agents are diagnostic and curative
Akathisia	Motor restlessness; not anxiety or "agitation"	5 to 60 days	Unknown	Reduce dose or change drug: antiparkinsonian agents,b benzodiazepines or propranolol may help
Parkinsonism	Bradykinesia, rigidity, variable tremor, mask facies, shuffling gait	5 to 30 days	Antagonism of dopamine	Antiparkinsonian agents helpful
Neuroleptic malignant syndrome	Catatonia, stupor, fever, unstable blood pressure, myoglobinemia; can be fatal	Weeks; can persist for days after stopping neuroleptic	Antagonism of dopamine may contribute	Stop neuroleptic immediately: dantrolene or bromocriptined may help: antiparkinsonian agents not effective
Perioral tremor ("rabbit" syndrome)	Perioral tremor (may be a late variant of parkinsonism)	After months or years of treatment	Unknown	Antiparkinsonian agents often help
Tardive dyskinesia	Oral-facial dyskinesia; widespread choreoathetosis or dystonia	After months or years of treatment (worse on withdrawal)	Excess function of dopamine hypothesized	Prevention crucial; treatment unsatisfactory

a. Many drugs have been claimed to be helpful for acute dystonia. Among the most commonly employed treatments are diphenhydramine hydrochloride, 25 or 50 mg intramuscularly, or benztropine mesylate, 1 or 2 mg intramuscularly or slowly intravenously, followed by oral medication with the same agent for a period of days to perhaps several weeks thereafter. b. For details regarding the use of oral antiparkinsonian agents, see the rest of slides c. Propranolol often is effective in relatively low doses (20-80 mg per day). Selective beta1-adrenergic receptor antagonists are less effective. d. Despite the response to dantrolene, there is no evidence of an abnormality of Ca2+ transport in skeletal muscle; with lingering neuroleptic effects, bromocriptine may be tolerated in large doses (10-40 mg per day).

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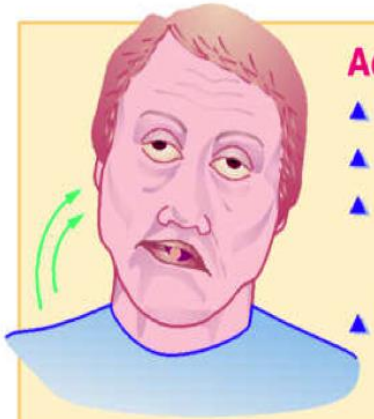
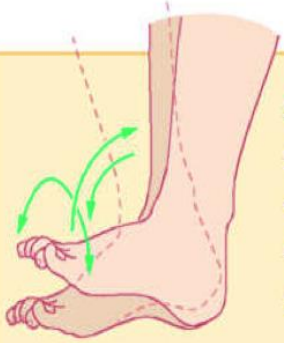
Pseudoparkinsonism

- Stooped posture
- Shuffling gait
- Rigidity
- Bradykinesia
- Tremors at rest
- Pill-rolling motion of the hand



Acute dystonia

- Facial grimacing
- Involuntary upward eye movement
- Muscle spasms of the tongue, face, neck and back (back muscle spasms cause trunk to arch forward)
- Laryngeal spasms

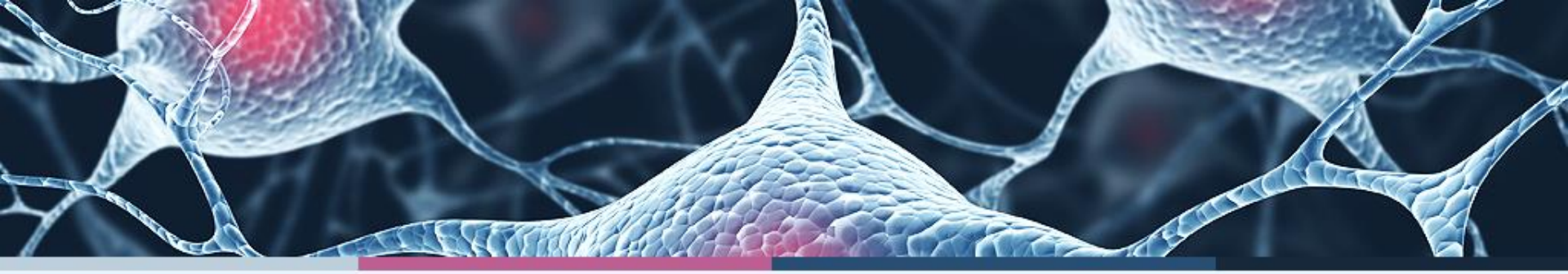


Akathisia

- Restless
- Trouble standing still
- Paces the floor
- Feet in constant motion, rocking back and forth

Tardive dyskinesia

- Protrusion and rolling of the tongue
- Sucking and smacking movements of the lips
- Chewing motion
- Facial dyskinesia
- Involuntary movements of the body and extremities



Antipsychotic Side Effect Profiles

Typical/Atypical

EPSE

less			more
cloz	arip	*chlo*	*halo*
olan	pali	lura	
quet	zipr	risp	

Wt gain

less		more
arip	pali	olan
halo	quet	cloz
lura	risp	*chlo*
zipr		

Inc PRL

less			more
arip	lura	*halo*	risp
chlor	olan		pali
cloz	zipr		
quet			

Sedation

less			more
arip	*halo*	ola	cloz
pali	lura	quet	*chlo*
	risp	zipr	

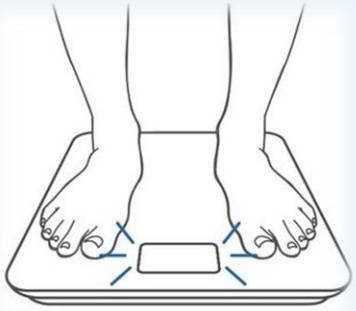
Key: aripiprazole, *chlorpromazine*, clozapine, *haloperidol*, lurasidone, olanzepine, paliperidone, quetiapine, risperidone, ziprasidone

O+C --? - 5HT2C --? hypergl, dislip

O, Q, C --H1 -- sedativ

R, C -- Alfa -- hipotensiv

!!!



Psychotropic Associated Cardiometabolic Adverse Effects

Weight gain

Antipsychotics
- Clozapine
- Olanzapine
- Quetiapine
- Risperidone

Mood stabilizers
- Valproic acid derivatives
- Lithium

Antidepressants
- Mirtazapine
- Tricyclic antidepressants
- Monoamine oxidase inhibitors
- Other antidepressants (except bupropion)

Dyslipidemia

Hypertriglyceridemia

Antipsychotics

Especially:
- Clozapine
- Olanzapine

Mood stabilizers
- Valproic acid derivatives
- Carbamazepine

Hypercholesterolemia

Antidepressants
- Mirtazapine
- SSRIs

Diabetes mellitus / insulin resistance

Antipsychotics
- Clozapine
- Olanzapine
- Other SGAs
- Low and mid-potency FGA
- High potency FGA

Mood stabilizers
- Valproic acid derivatives

Antidepressants
- Tricyclic antidepressants

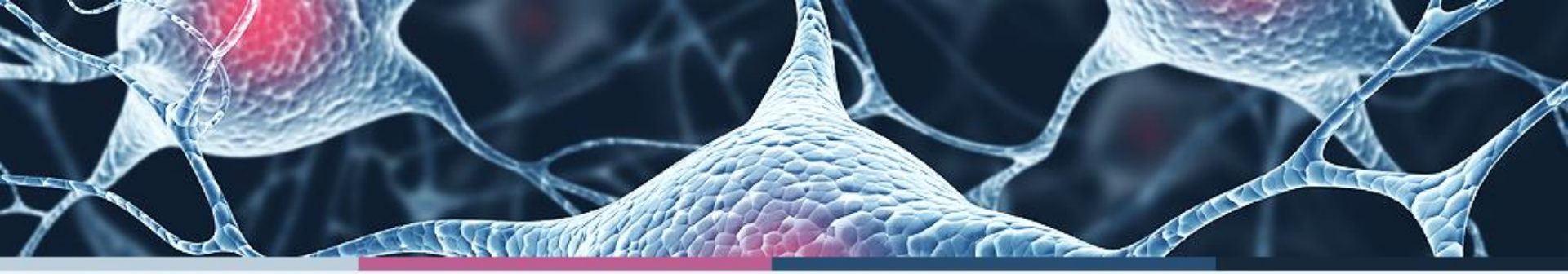
Hypertension

Psychostimulants
- Amphetamines
- Methylphenidate
- Other stimulants
- Atomoxetine

Antidepressants
- SNRIs
- Tricyclic antidepressants

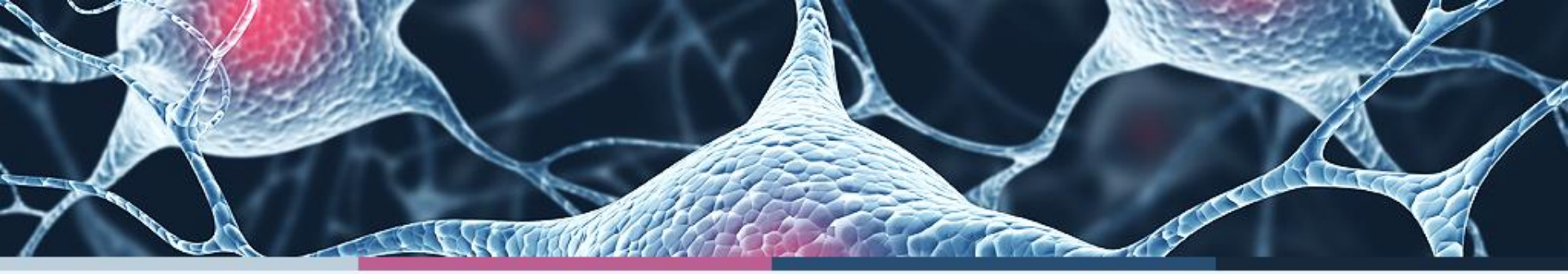
Antipsychotics
- Aripiprazole
- Clozapine
- Olanzapine
- Ziprasidone

Mood stabilizers
- Valproic acid derivatives



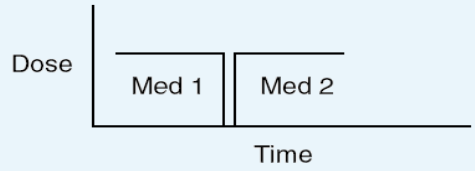
Antipsychotics switching

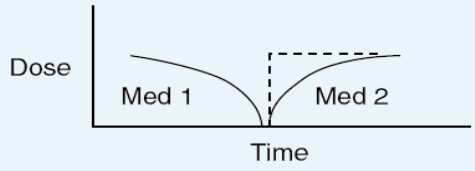
- Avoid if possible
- Consider in
  - **Not responing patient with adequate trial**
  - **Not able to tolerate**
  - **Non-compliance (switch to depot preparation)**
  - **Significant long term risk with current medication**
    - Obesity, TD, persistent cognitive deficit, CVS problems, DDI
  - **Patient/family member request**

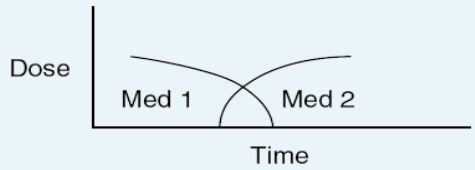


Switching techniques for anti psychotics

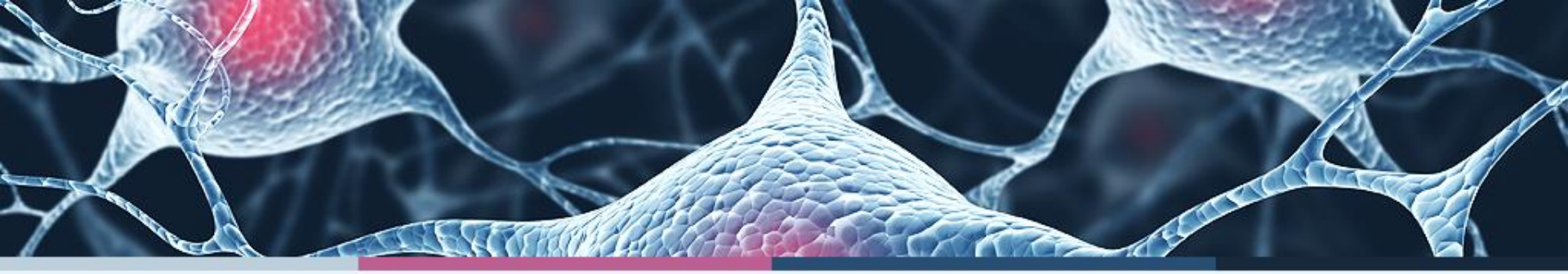
	Advantage	Disadvantage	Recommended for
Abrupt switching	Low risk of drug interactions	Withdrawal reactions	Patients with serious adverse event(s)
Gradual switching	Low risk of withdrawal reactions, hardly any drug interactions	Danger of symptom exacerbation	Patients with low risk of relapse
Cross-tapering	Safest to prevent relapse	Drug interactions complicated	Recently stabilised patients







CNS Drugs 2005; 19 (1): 27-42



Anxiolytic drugs

- ✓ a class of medications used to prevent or treat anxiety symptoms or disorders
- ✓ selectively remove states of fright, fear, emotional tension, adaptation problems to the environment
- ✓ are effective in neuroses and intermediate states.

Anxiolytic drugs. Classification according to the duration of action

Short duration – t ½ – 3 – 10 hours

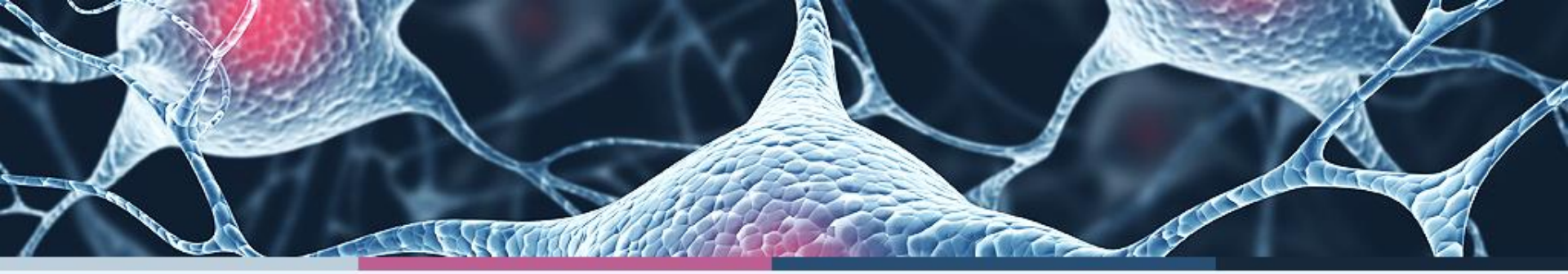
- ✓ Oxazepam
- ✓ Tofisopam
- ✓ Triazolam
- ✓ Clotiazepam

Medium duration – t ½ – 1 – 40 hours

- ✓ Alprazolam
- ✓ Bromazepam
- ✓ Lorazepam

Long duration – t ½ - 30 – 90 hours:

- ✓ Diazepam
- ✓ Fenazepam
- ✓ Medazepam
- ✓ Chlordiazepoxide
- ✓ Chlorazepat



Classification according to the clinical use:

As anxyolytics:

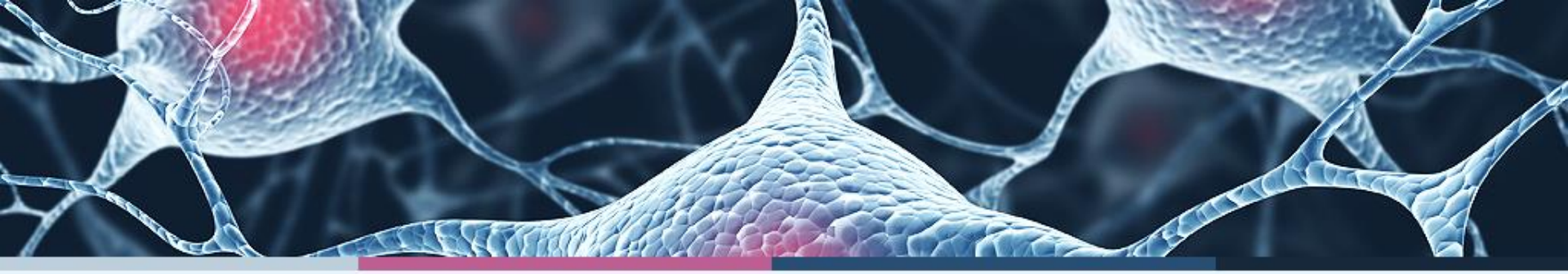
- ✓ Alprazolam
- ✓ Bromazepam
- ✓ Clobazam
- ✓ Clorazepate
- ✓ Lorazepam
- ✓ Medazepam
- ✓ Prozepam
- ✓ Chlordiazepoxide

As hypnotics:

- ✓ Flurazepam
- ✓ Flunitrazepam
- ✓ Nitrazepam
- ✓ Temazepam
- ✓ Triazolam
- ✓ Lormetazepam
- ✓ Midazolam
- ✓ Ketazolam

As central muscle relaxants:

- ✓ Diazepam
- ✓ Phenazepam
- ✓ Tetrazepam
- ✓ Bromazepam
- ✓ Ketazolam
- ✓ Temazepam



Classification according to the clinical use:

As anticonvulsants and antiepileptic:

- ✓ Clonazepam
- ✓ Diazepam
- ✓ Phenazepam
- ✓ Nitrazepam
- ✓ Flunitrazepam
- ✓ Bromazepam

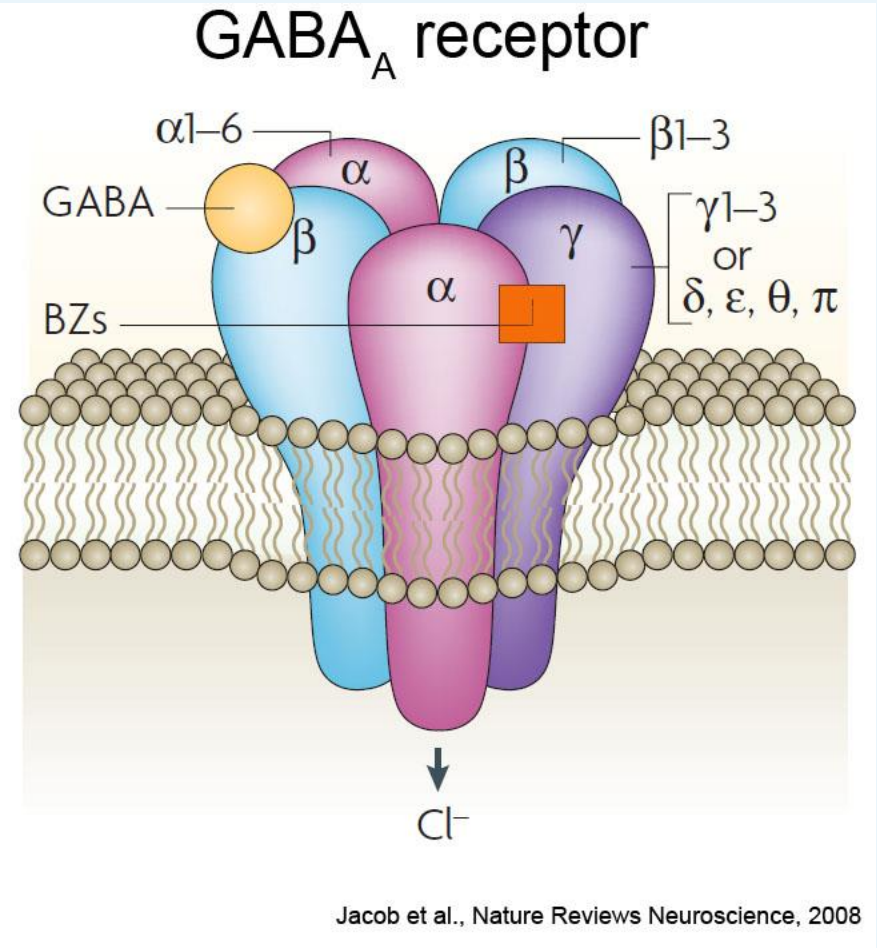
Antidepressant benzodiazepines:

- ✓ Alprazolam
- ✓ Opipramol

As general intravenous anesthetics:

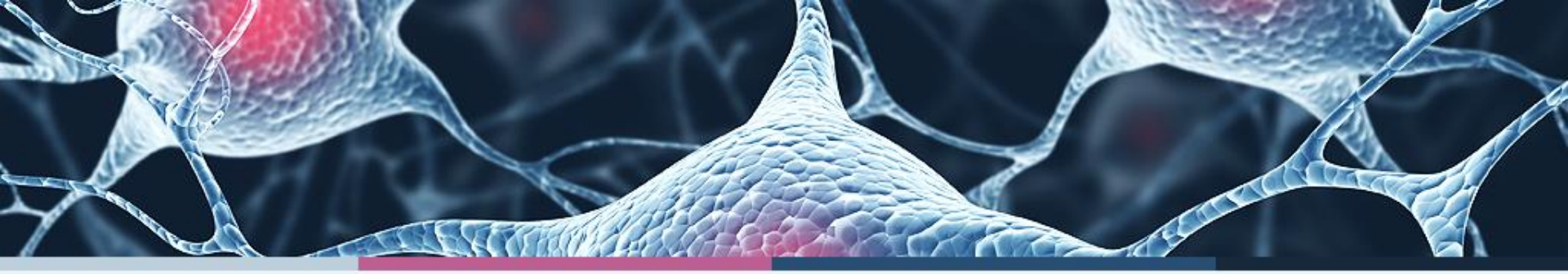
- ✓ Diazepam
- ✓ Midazolam

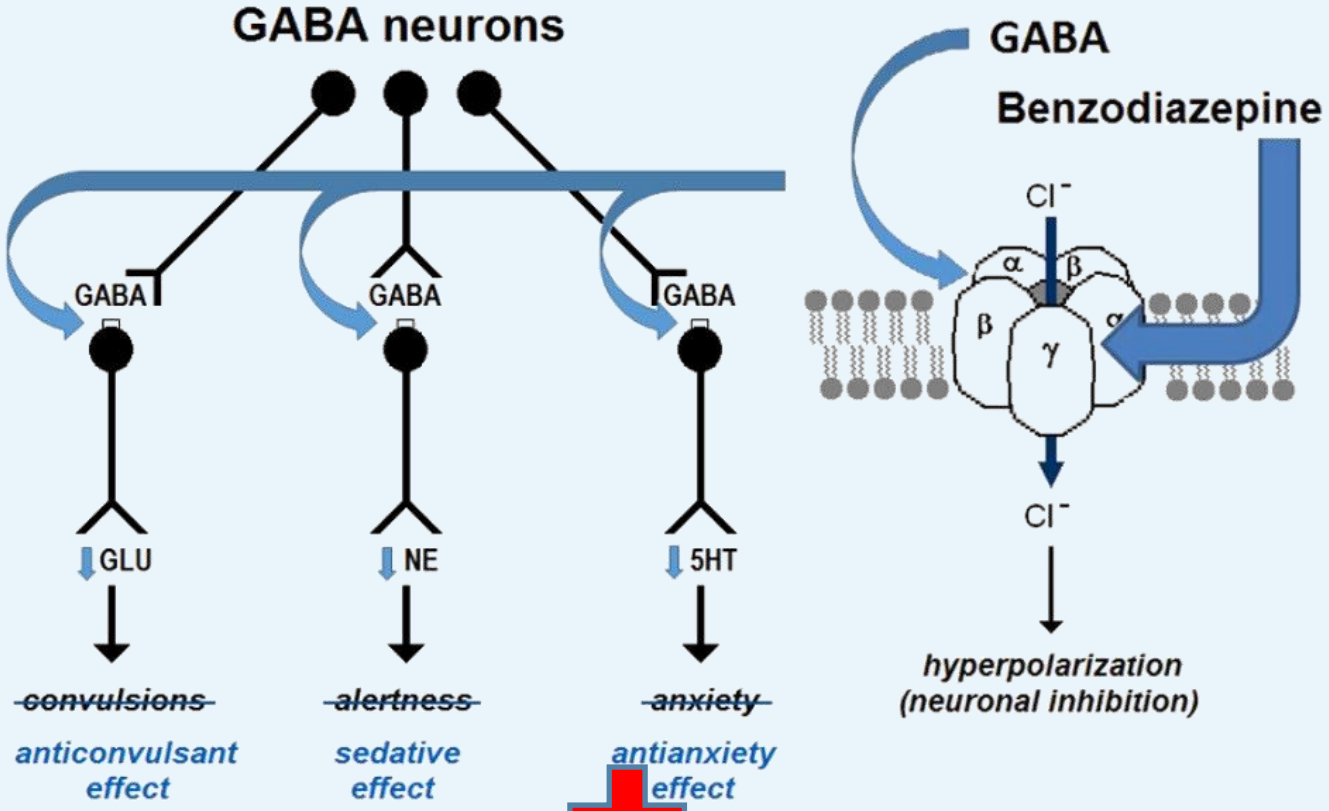
The anxiolytic effect



Jacob et al., Nature Reviews Neuroscience, 2008

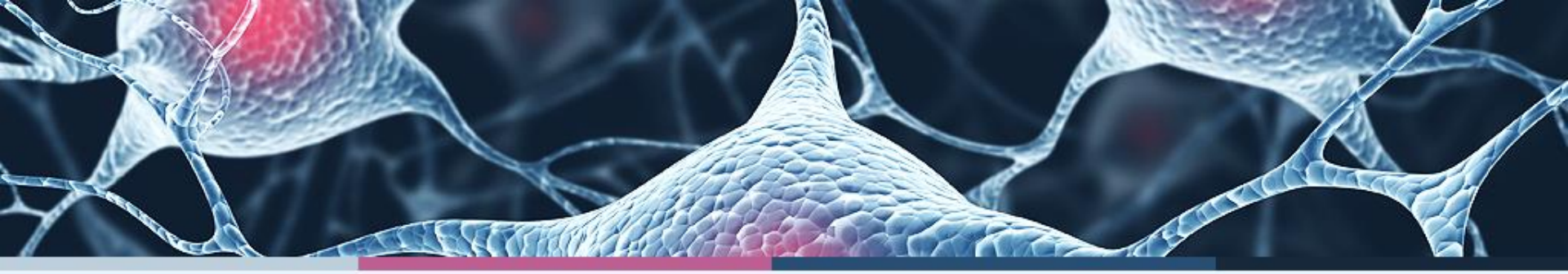
- ✓ reduce emotional lability;
- ✓ remove restlessness, fear, fear, mental tension;
- ✓ balance affective behavior;
- ✓ calm psychomotor excitement, vegetative and endocrine disorders;
- ✓ Improve asthenia, insomnia, functional disorders, palpitations, without influencing vigilance, intellectual capacities and sensory functions.





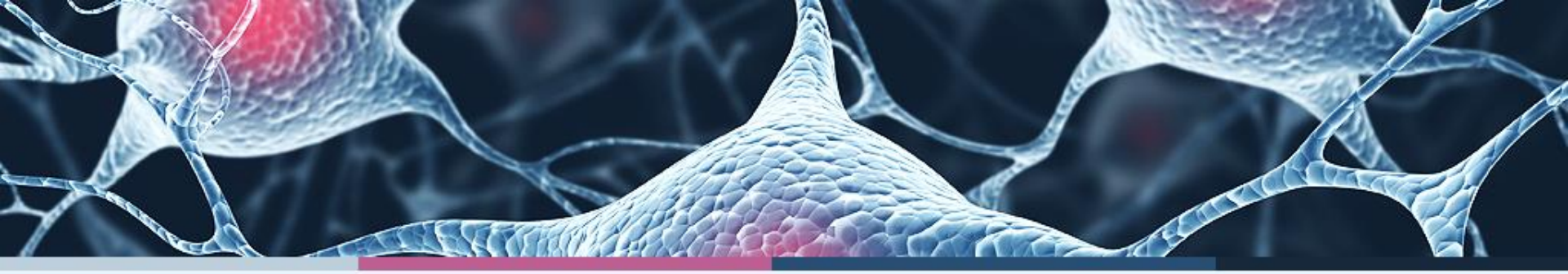
Activating effect
Hypnotic effect
Antiemetic effect

Miorelaxant effect
General anesthetic effect



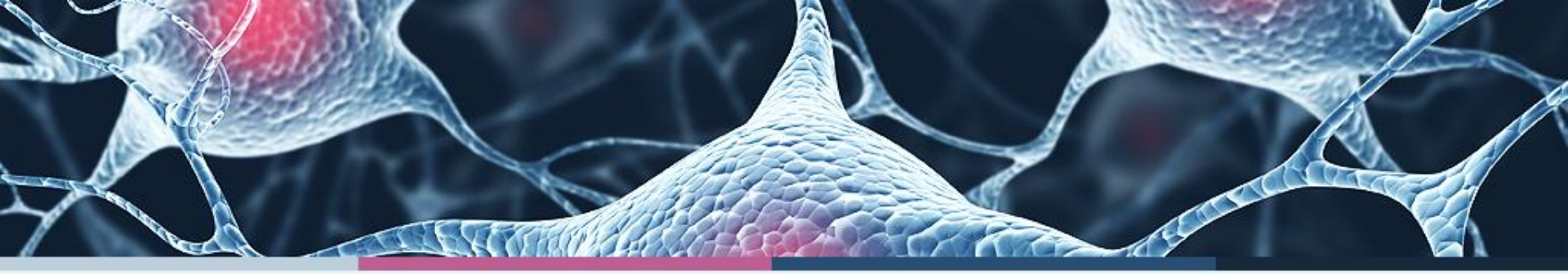
Indications:

- ✓ insomnia
- ✓ anxious, psycho-neurovegetative and neurotic syndrome,
- ✓ psychosomatic disorders
- ✓ ischemic heart disease, ulcer disease, IIS, bronchial asthma, premenstrual syndrome, etc.;
- ✓ preanesthetic and preoperatory preparation, as well as postoperatory care;
- ✓ in alcoholics, in combating acute psychotoxic manifestations - delirium tremens,confusional states, abstinence syndrome;
- ✓ states of neurosis when attending medical institutions, especially in children, preparing patients, more often children, for various curative manipulations and diagnostics;
- ✓ nocturnal enuresis;
- ✓ treatment of eczema, neurodermatitis.



Indications:

- ✓ convulsive states of different genesis – tetanus, convulsions in alcoholics, etc.;
- ✓ epilepsy treatment (major and akinetic seizures, status epilepticus);
- ✓ Anesthetic effect – induction, maintenance or completion of general anesthesia;
- ✓ Muscle relaxant effect – the treatment of spastic states of the striated muscles
- ✓ Antiemetic effect – prevention of nausea and vomiting;



Most common anxiety medication side effects in order of average percentage of occurrence

Cognitive disorder	28.9%
Memory impairment	20.8%
Weight gain	16.0%
Excessive drowsiness	15.5%
Increased appetite	15.1%
Abnormal coordination	14.4%
Weight loss	13.7%
Irritability	13.4%

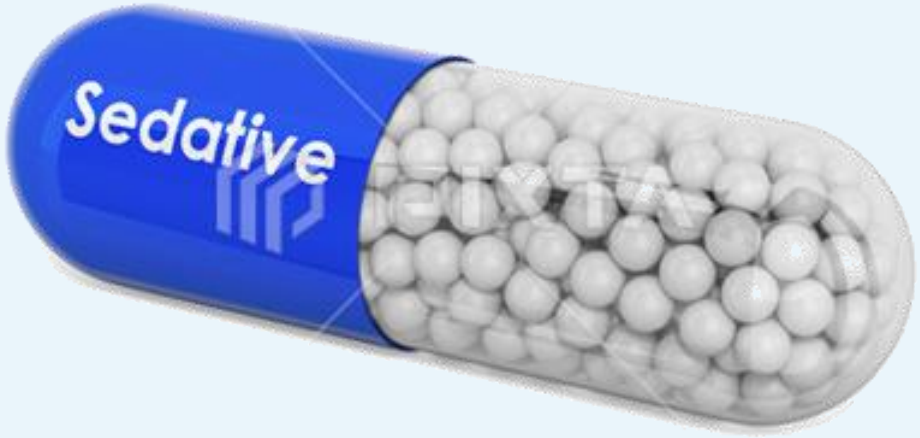
Hyperhidrosis	13.2%
Nasal congestion	12.4%
Decreased libido	11.5%
Fatigue	11.0%
Strangury (difficult urination)	10.9%
Increased body temperature	10.6%
Salivary hypersecretion	10.5%

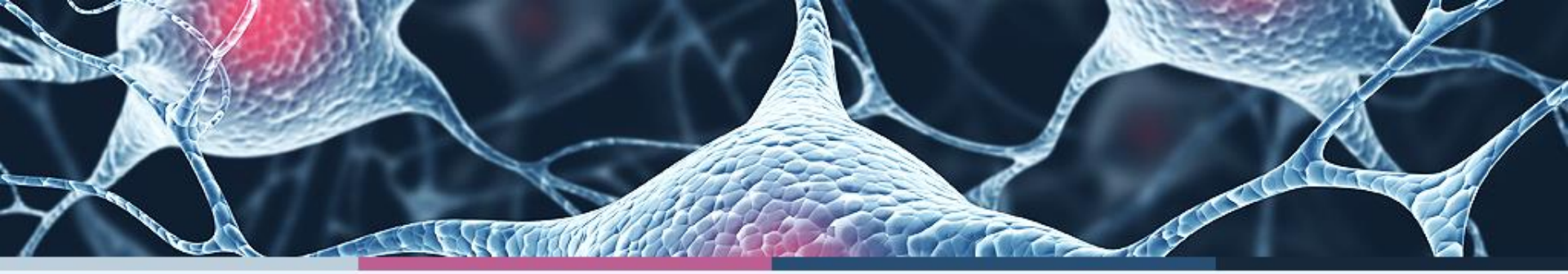
**Includes anxiolytics and benzodiazepines*

Source • SIDER Side Effect Resource, 2015

Sedative drugs

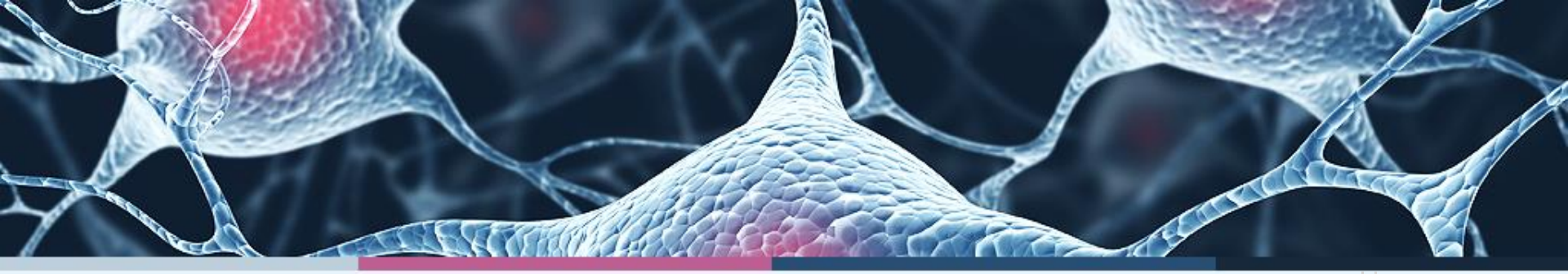
drugs from various pharmacological groups with non-specific calming action due to the reduction of CNS excitation and its reactivity to external agents





Classification:

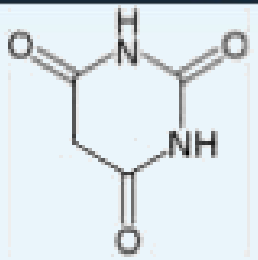
- ✓ Bromides – sodium bromide (Sodium bromide),potassium bromide (Kaliu bromide).
- ✓ Benzodiazepines (in small doses) – diazepam,chlordiazepoxide etc.
- ✓ Barbiturates (in small doses) – babital sodium, phenobarbital.
- ✓ H1 – antihistamines – diphenhydramine, promethazine,chloropyramine, clemastine.
- ✓ Vegetal agents – odolean (Valeriana), hawthorn (Crataequs), goose foot (Leonurus).
- ✓ Combined remedies – corvalol, valocordin, beloid, novo-pasit, corvaldin, persen, extraveral, sanosan, belataminal.



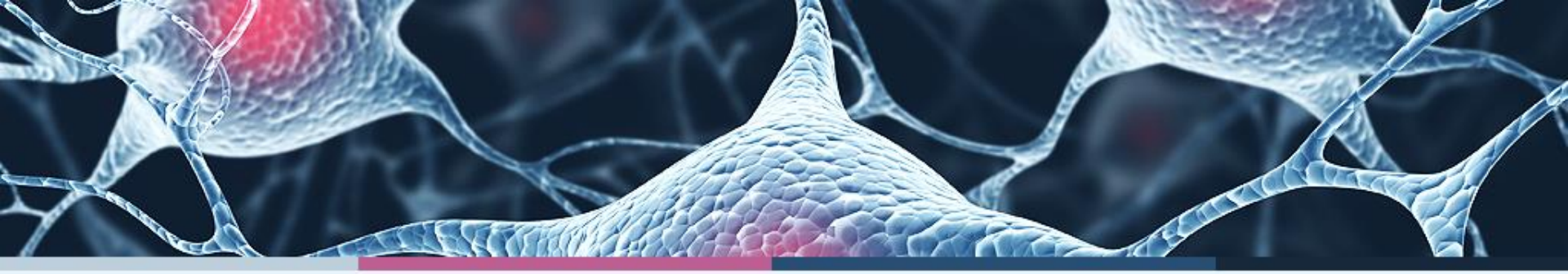
Bromides

- ✓ reduce the motor and emotional reaction to exogenous factors, contributes to the establishment and deepening of sleep.
- ✓ slow elimination, the half-life is 12 days, and traces of bromides are determined over a month or more.
- ✓ Accumulation ➔ chronic intoxication (bromism)

Barbiturates



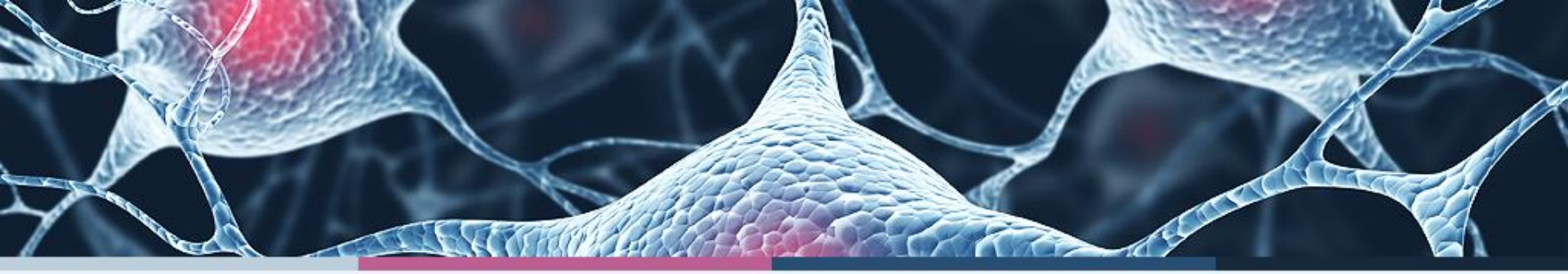
- All derivatives of Barbituric acid
- They are CNS depressants. They are effective as anxiolytics, hypnotics, anticonvulsants and analgesics.
- They have addiction potential, both physical and psychological.
- Thus Benzodiazipines have largely replaced them in term of sedative-hypnotic



Thimoisoleptics:

Drugs that are reducing circulatory disorders of the affective sphere (mood deviations), and on prophylactic use – to prevent development of depressive and manic symptoms.

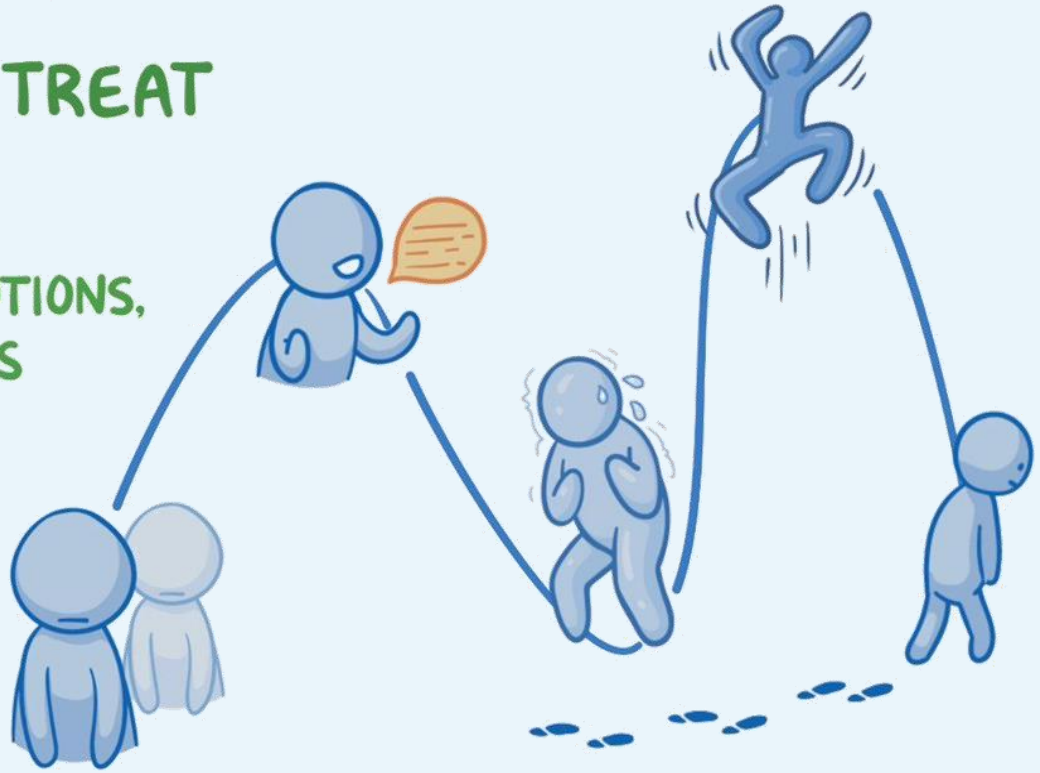
- ✓ Lithium salts – lithium carbonate, oxybate, chloride,gluconate
- ✓ Valproates – valproic acid, sodium valproate;
- ✓ Carbazepine derivatives - carbamazepine;
- ✓ Calcium channel blockers – verapamil,diltiazem, nifedipine.

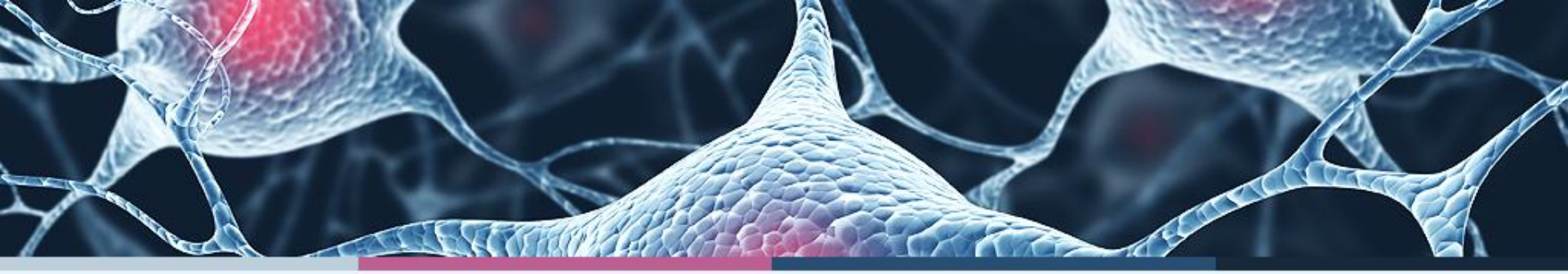


MOOD STABILIZERS

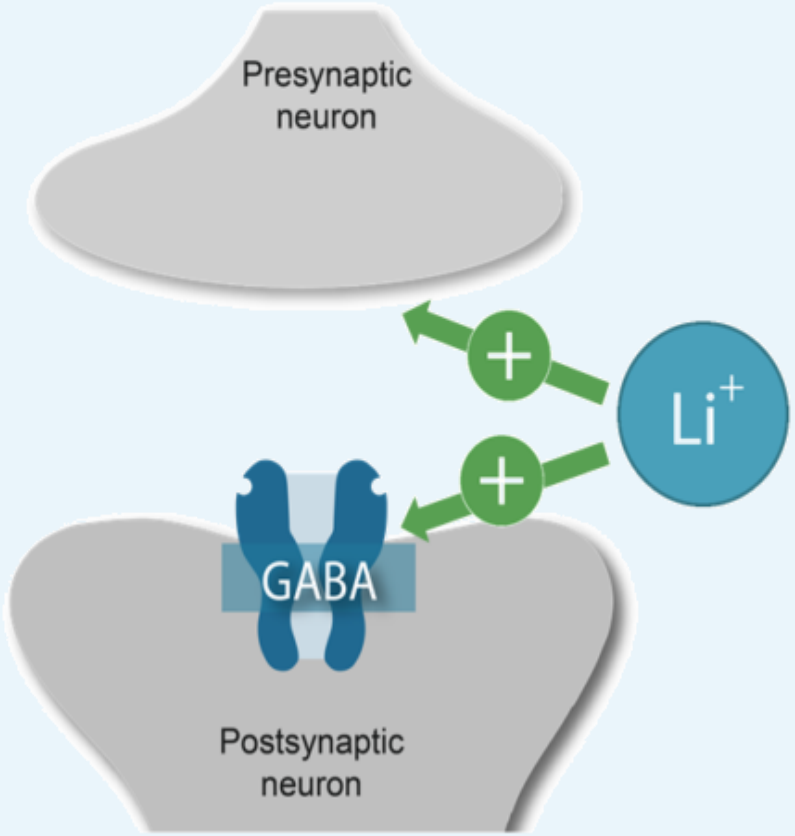
* MEDICATIONS used to TREAT BIPOLAR DISORDER

  ↳ DRAMATIC SHIFTS in EMOTIONS, MOOD, & ENERGY LEVELS



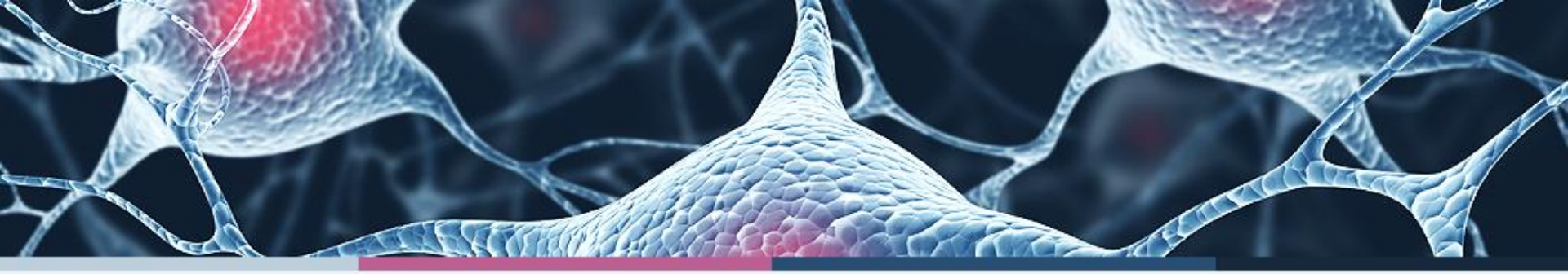


Lithium promotes GABAergic neurotransmission



- Lithium:
  - Increases GABA levels in CSF
  - Presynaptic: facilitates GABA release
  - Postsynaptic: upregulates $GABA_B$ receptors

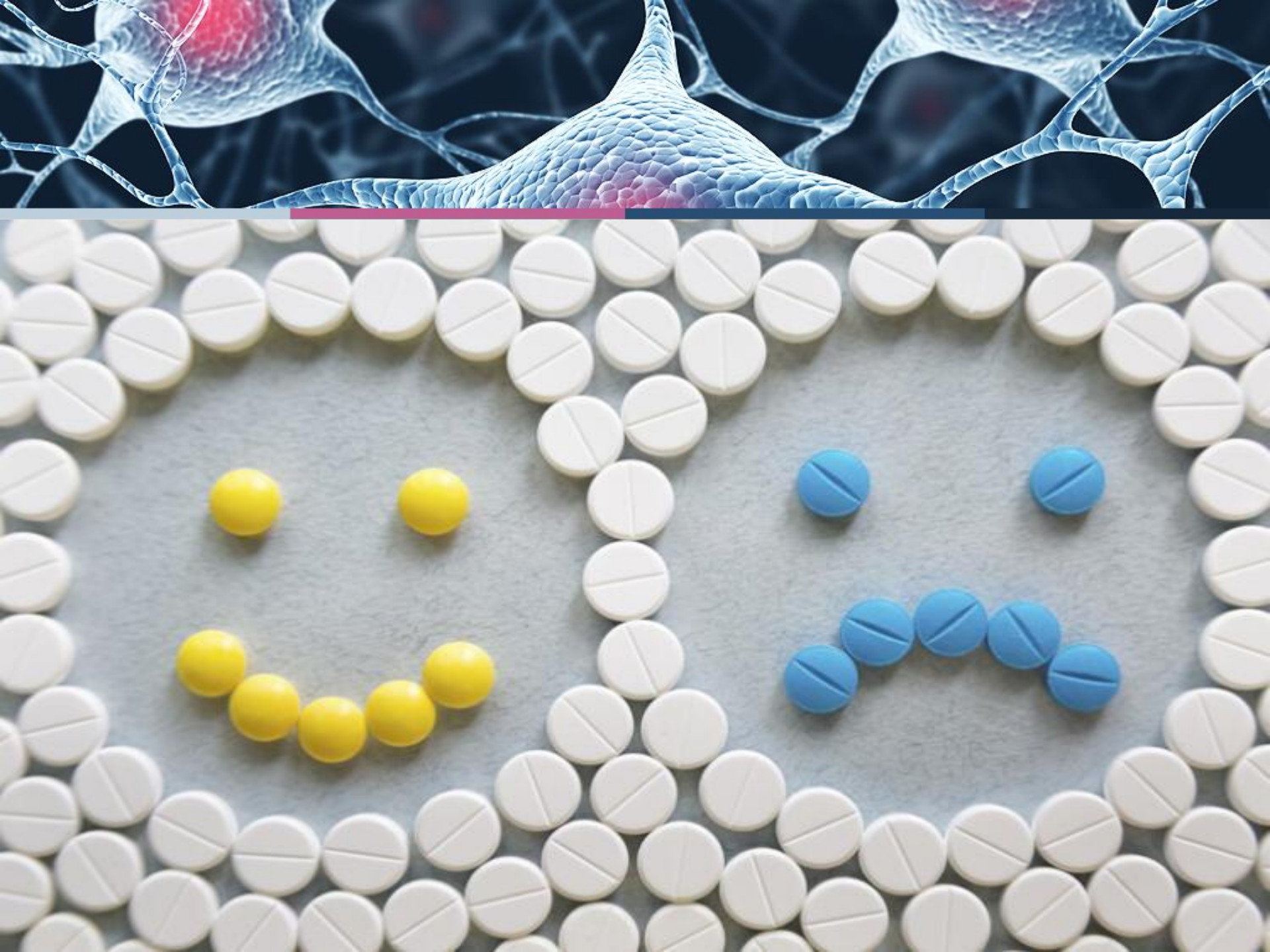
Malhi, G. S., Tanious, M., Das, P., Coulston, C. M., & Berk, M. (2013). Potential mechanisms of action of lithium in bipolar disorder. *CNS drugs*, *27*(2), 135-153.

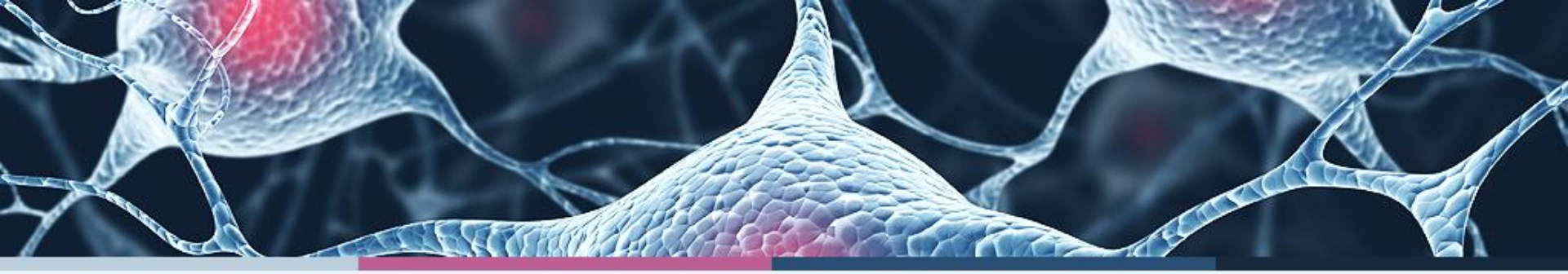


Common side effects of mood stabilizers

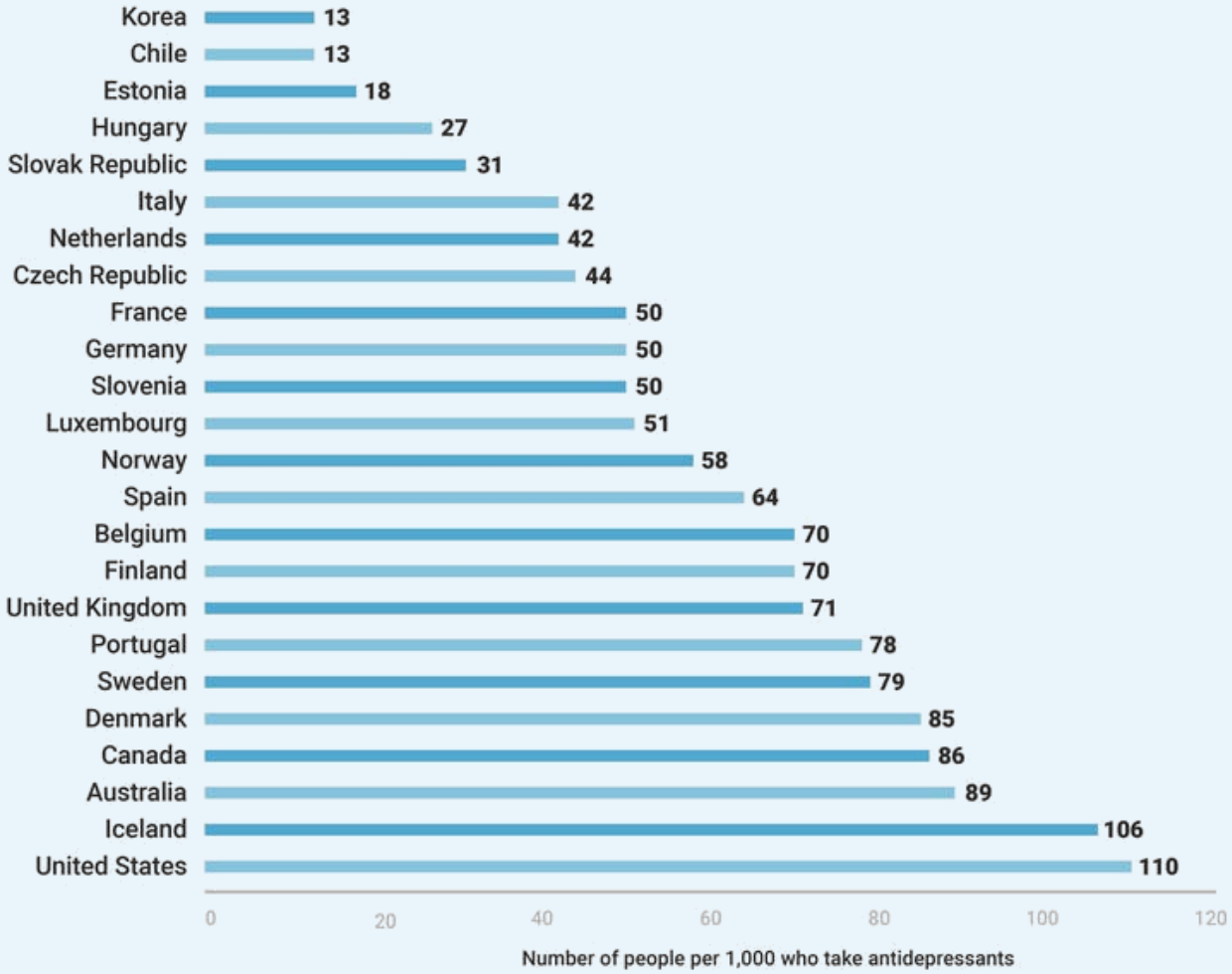
LITHIUM	VALPROATE	LAMOTRIGINE	CARBAMAZEPINE
Headaches	Headaches	Loss of balance or coordination	Dizziness
Nausea or vomiting	Bloating or swelling in the limbs	Blurred or double vision	Abnormal thinking
Dizziness or drowsiness	Bleeding gums	Diarrhea or constipation	Difficulty speaking
Tremors	Delusions	Missed or painful periods	Dry mouth
Increased thirst	Joint pain	Stomach, back, or joint pain	Constipation
Acne-like rash	Rapid weight loss or gain	Loss of appetite and weight loss	Uncontrollable shaking in certain body parts

Source: NAMI; Mayo clinic; Medline plus



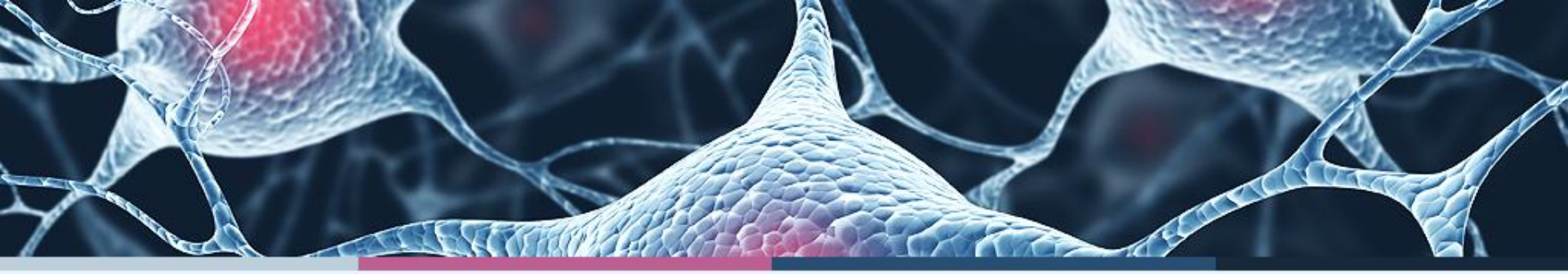


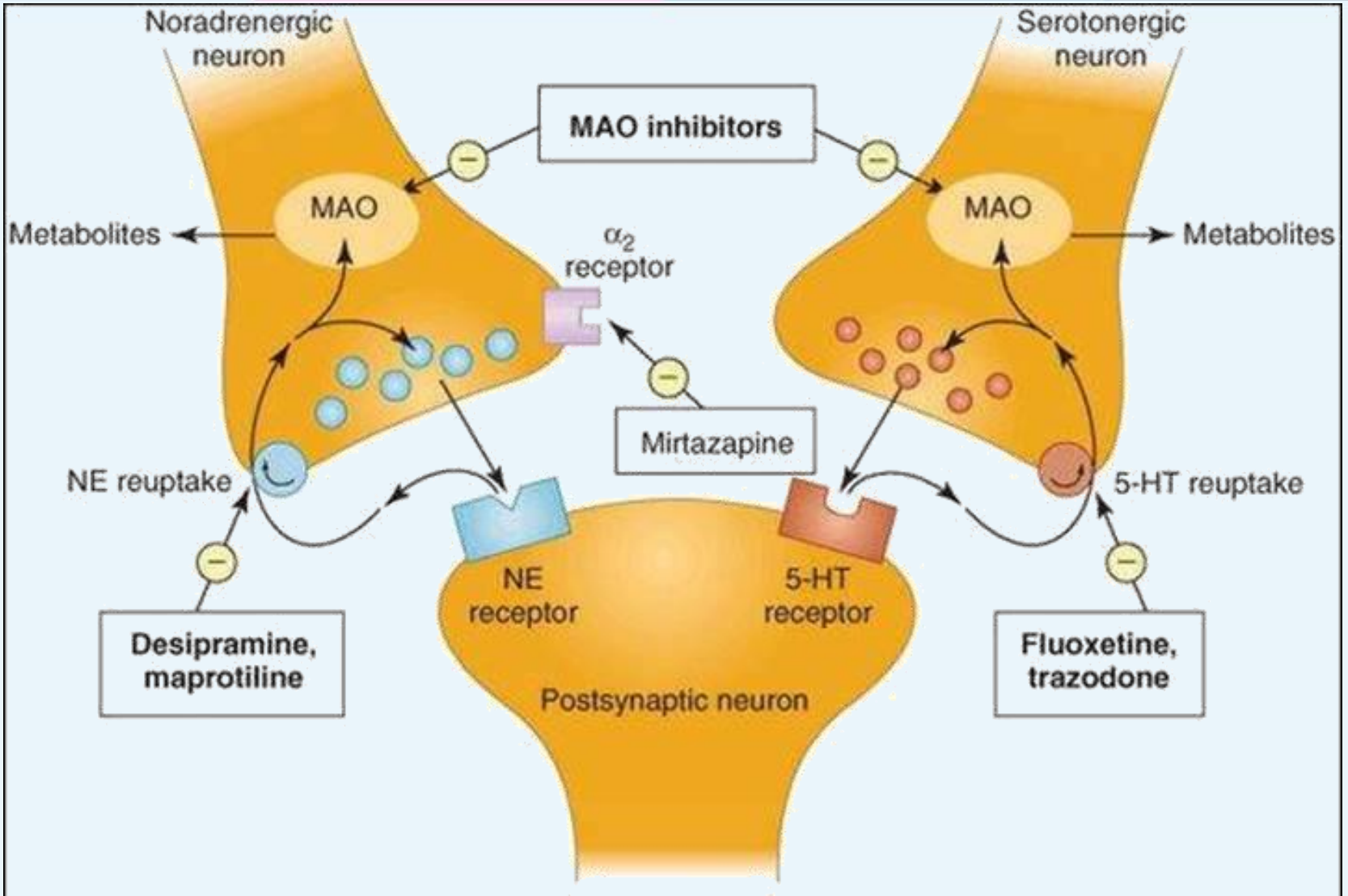
GLOBAL ANTIDEPRESSANT USERS PER 1,000 PEOPLE



SOURCES: OECD, CDC

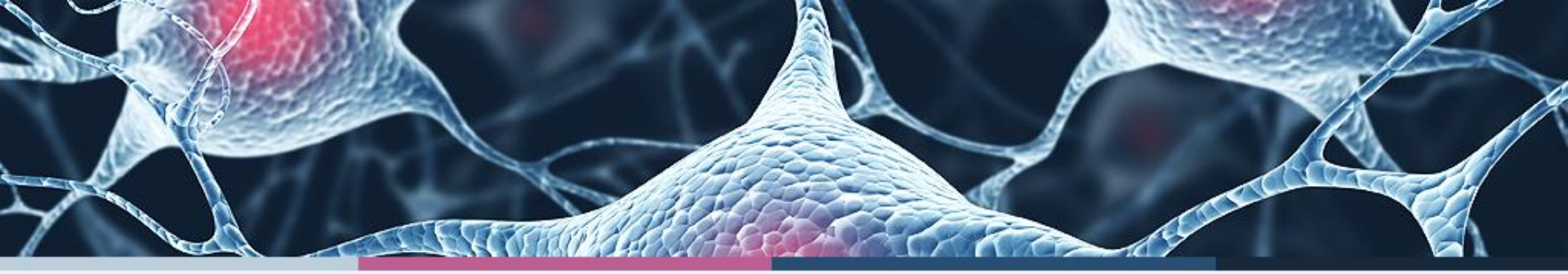
BUSINESS INSIDER




Noradrenergic neuron
Serotonergic neuron
MAO inhibitors
MAO
MAO
Metabolites
Metabolites
α_2 receptor
Mirtazapine
NE reuptake
5-HT reuptake
NE receptor
5-HT receptor
Desipramine, maprotiline
Fluoxetine, trazodone
Postsynaptic neuron

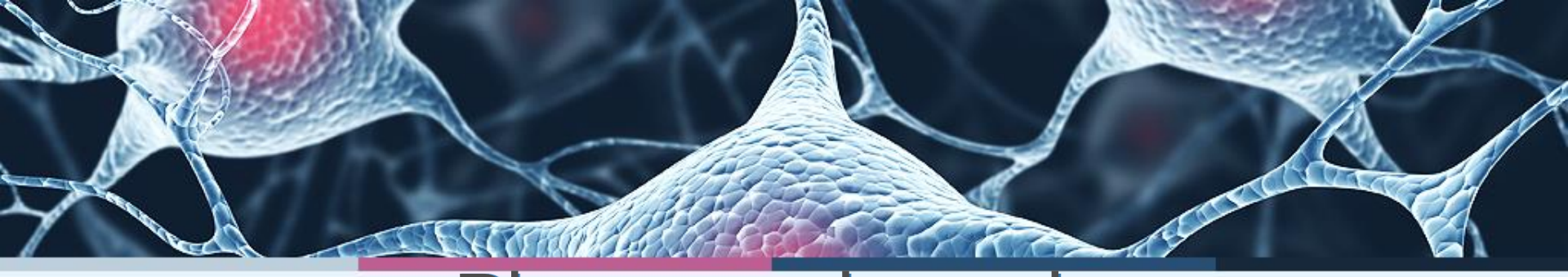
- **Thymoleptic antidepressants** (with sedative effect): amitriptyline, trimipramine, doxepin, amoxapine, mianserin,pipofesine, opipramol, fluvoxamine, fluorazizin, alprazolam, adinazolam, mirtazapine, trazodone,femoxetine buttriptyline, clovoxamine, nefazodone.

- **Thimeretic antidepressants** (with an activating effect): desipramine, imipramine, cephedrine, nortriptyline,tranylcypromine, viloxazine, fluoxetine, amineptine, moclobemide, nialamide, phenelzine, protriptyline,bupronion, citalopram, tomoxetine, metralindole, toloxatone, methyltryptamine, brofaromine, minaprine, etc.



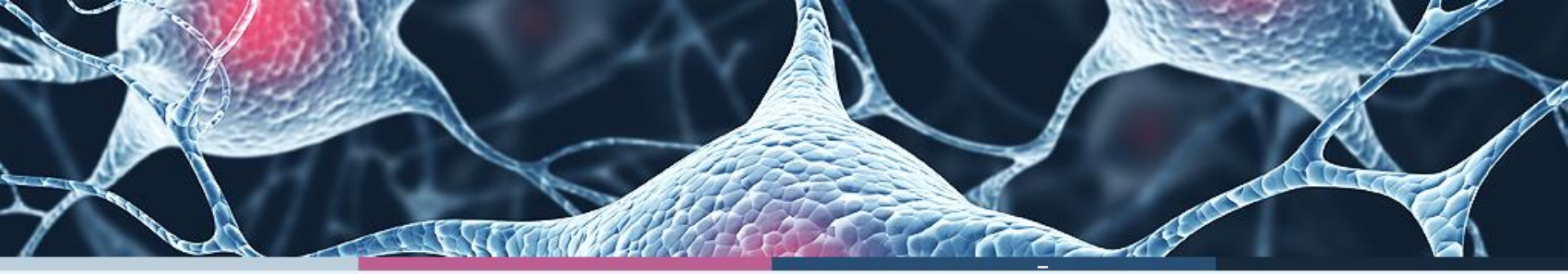
- ✓ Balancing antidepressants or psychomotor stabilizers: maprotiline, dosulepin, tianeptine,lofepramine, ritanserin, sertraline, paroxetine, pirlindole, clomipramine, minacipran, caroxazone, venlafaxine.

- ✓ Antidepressants with an anxiolytic effect: opipramol, alprazolam, adinazolam, fluvoxamine, sertraline, mianserin, clomipramine



Pharmacodynamics:

- ✓ **Antidepressant effect** – increases and re-establishes the mood, suicidal thoughts disappear.
- ✓ **Timoretic effect** (activator, stimulant effect) – restores motivation, initiative, improves the mood.
- ✓ **Sedative and anxiolytic effect** - sedation, removal of the negative emotions, fear, anxiety.
- ✓ **Analgesic effect** and the ability to potenciate the action of analgesics.
- ✓ **Orexigenic/anorexigenic effect**
- ✓ **H1 – blocker effect** - sedative action, orexigenic and hypotensive eff.
- ✓ **α-adrenoblocker effect** – vasodilation, decreases blood pressure, tachycardia
- ✓ **Serotoninolytic effect** - block. 5HT2 and 5HT3 - anxiolytic, antipsychotic, antiemetic, hypnotic.
- ✓ **Sympathomimetic effect** (MAOI) - especially effects cardiovascular ➔ increases BP, potentiates the action of sympathomimetics.



Indications:

Persistent feelings of sadness

Loss of interests In activities

Trouble sleeping or oversleeping

Appetite or weight changes

Fatigue or decreased energy

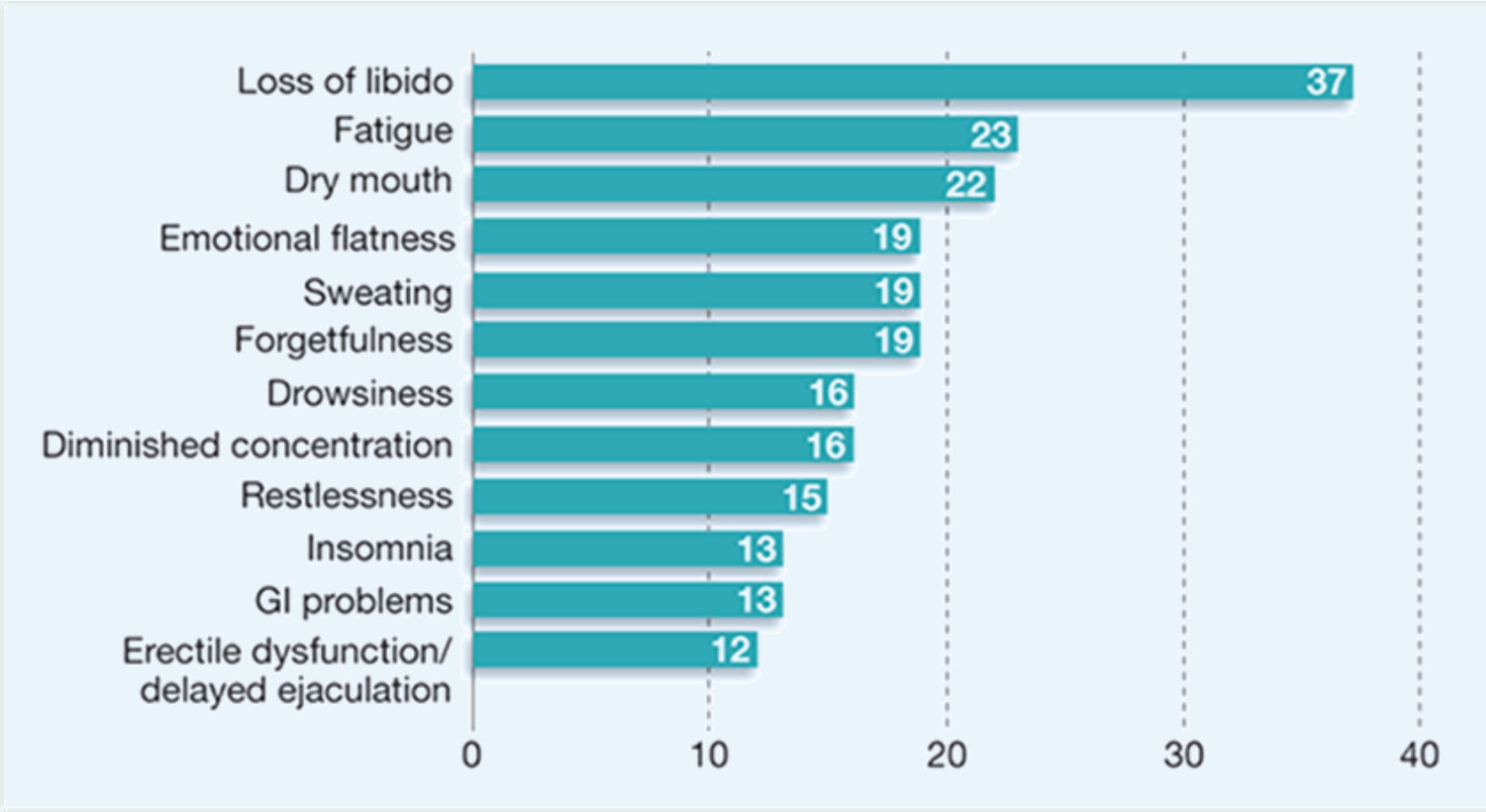
Difficulty thinking clearly or quickly

Irritability, frustration, or pessimism

Physical aches and pains

Recurrent thoughts of death or suicide

Most frequent adverse effects in primary care patients using different types of antidepressants



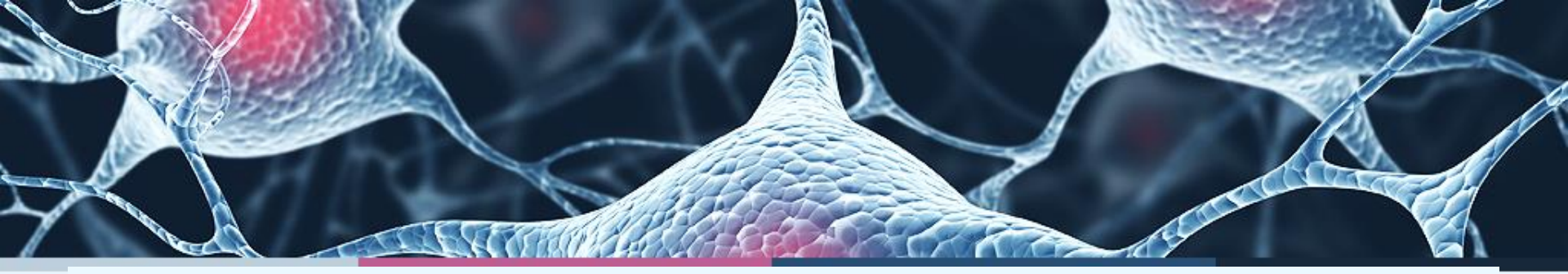
SSRI's

Adverse Effects "S-S-S"

- Stomach upset
- Sexual dysfunction
- Serotonin syndrome
  (with other serotonergic agents)

DRUGS "Effective For Sadness, Panic, & Compulsions"

Effective - Escitalopram
For - Fluoxetine, Fluvoxamine
Sadness, - Sertroline
Panic, - Paroxetine
& Compulsions - Citalopram



Pros and Cons of Antidepressants

Pros

Helps manage symptoms

Effective

Safe

Cons

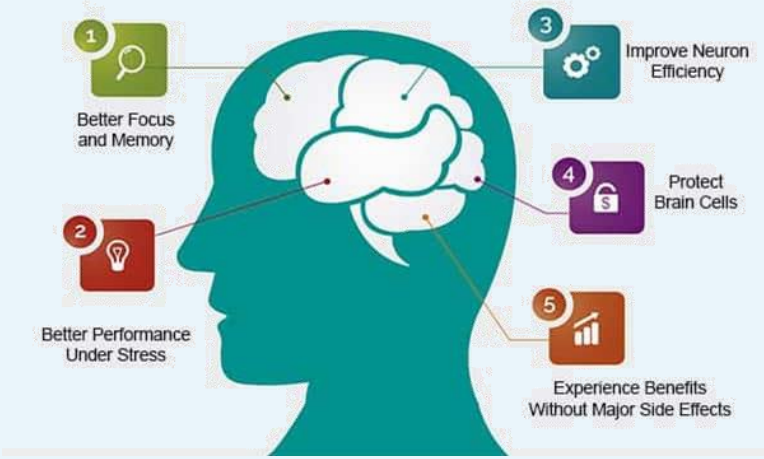
Can cause side effects

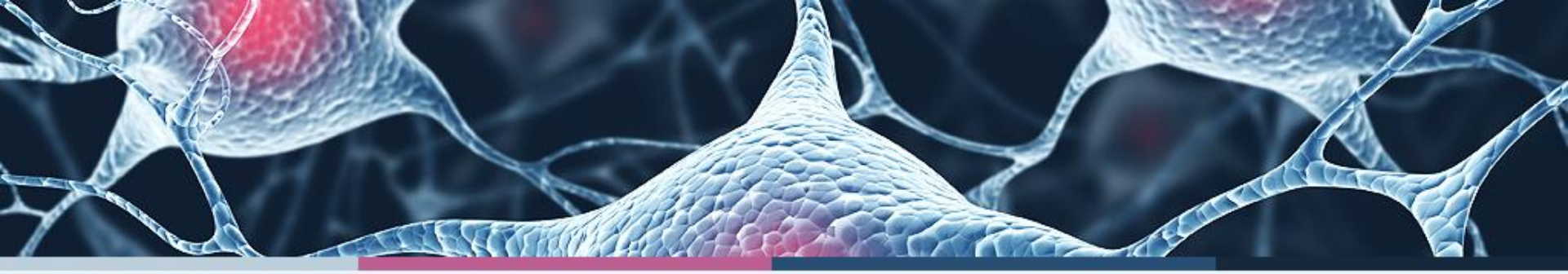
Takes time to see results

Some may not work

Nootropics

Drugs that activate or regulate brain metabolism and neuronal biochemical processes, especially when are affected in various brain pathologies, acute or chronic caused by hypoxia, intoxication or trauma.



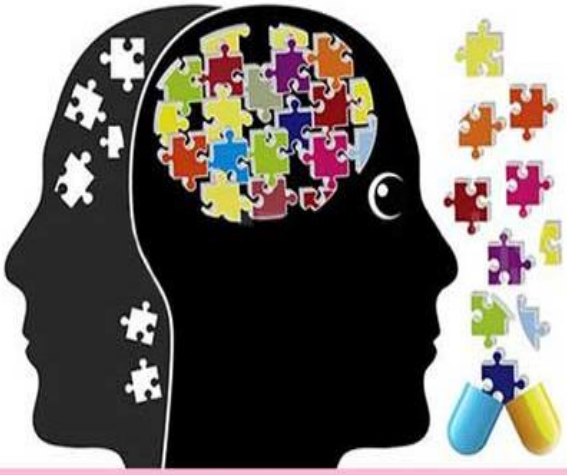


Classification:

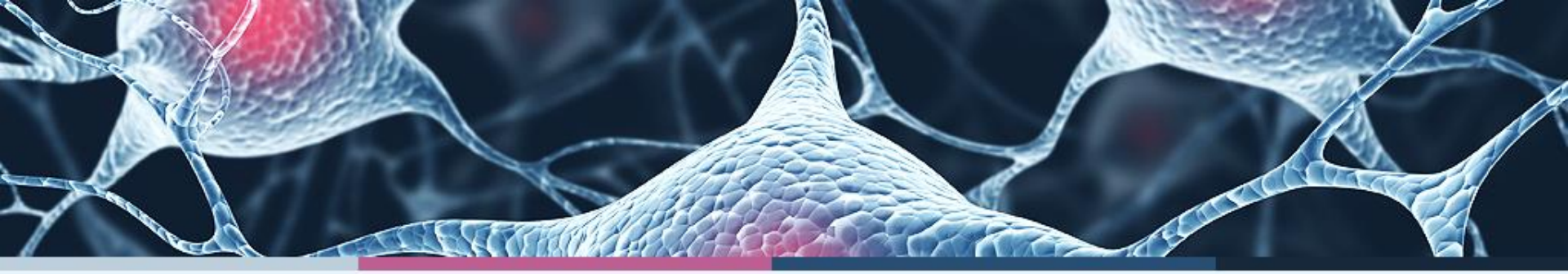
- ✓ Pyrrolidone derivatives - Piracetam (nootropil), Aniracetam, Dipracetam
- ✓ Vitamin derivatives – Pyritinol (pyridinol)
- ✓ GABA derivatives – Nicotinoyl gamma-aminobutyric acid(picamilon), Gamma-aminobutyric acid, Calcium homopantothemate, (pantogam)
- ✓ Dimethylaminoethanol derivatives – Meclofenoxat
- ✓ Cerebrovascular drugs – Ginkgo-Biloba extract, vinpocetine, cinnarizine, pentoxifylline, nicergoline.
- ✓ Combined drugs – Phezam (piracetam+cinnarizine), Vinotropil (piracetam+vinpocetine)

Nootropic drugs. Effects:

- ✓ Restores associative and superior integratives functions – attention, memory, ↓ number of mistakes long term memory
- ✓ Restores interest in the environment, optimism, self-confidence; general tone in the elderly
- ✓ Increases the resistance of the CNS and the body to different aggressions (hypoxia, hypo- or hyperthermia)
- ✓ Accelerates restoration processes and reparative after trauma,neuroinfections, intoxications, CVA.
- ✓ Antistress action
- ✓ Improvement of cerebral circulation.



- Improved focus and alertness
- Clarity of thoughts and reasoning
- Motivation
- Reduced anxiety
- Improved memory
- Enhanced concentration
- Improved wakefulness

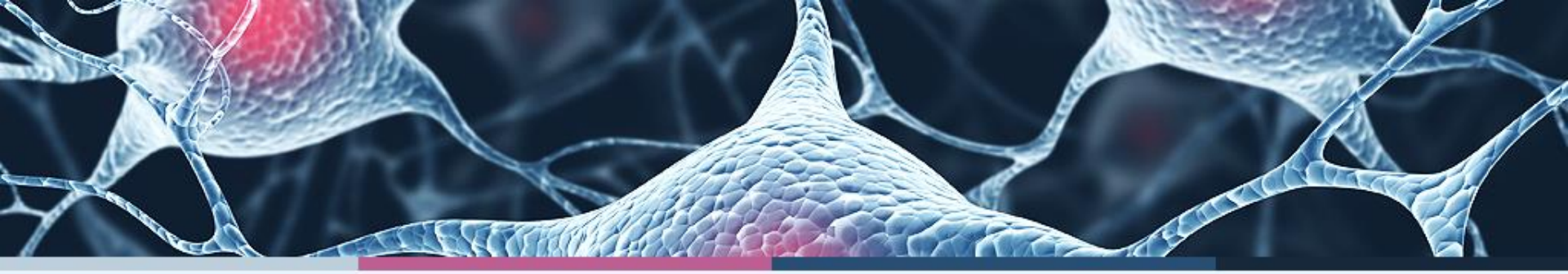


Nootropic drugs. Indications:

- ✓ Different states of cerebrovascular insufficiency
- ✓ Encephalopathies and cerebroasthenic states of different genesis (traumatic, vascular, toxic,etc.)
- ✓ Memory and attention defficiency
- ✓ In pediatrics - behavioral disorders anda daptation to the environment; retention in psychomotor developmen; nocturnal enuresis, mental retard
- ✓ Migraine, rebellious headache, dizziness,trigeminal neuralgia
- ✓ In some acute states: transient disturbances of cerebral circulation, ischemic stroke, trauma, meningitis.
- ✓ Traumatic and toxic coma, delirium tremens
- ✓ For prophylactic purposes in stressful situations.

Psychostimulants

- ✓ Phenylalkylamine derivatives – amphetamine, methamphetamine
- ✓ Sydnonimine derivatives – Mesocarb (sydnocarb)
- ✓ Piperidine derivatives - Methylphenidate (Meridil), Pyridrol (pipradol)
- ✓ Methylxanthines – Caffeine sodium benzoate
- ✓ Imidazole derivatives – ethimizole



Phenylalkylamine derivatives

- ✓ Psychomotor stimulant
- ✓ Increase mental and physical performance
- ✓ Stimulate the respiratory center
- ✓ Anorexigenic effect – inhibits the hunger center
- ✓ Remove fatigue and the requirement for sleep
- ✓ Cardiovascular (↑BP, tachycardia) and metabolic effects (↑ gl, trigl., free fatty acids, lactate).

Methylxanthine derivatives

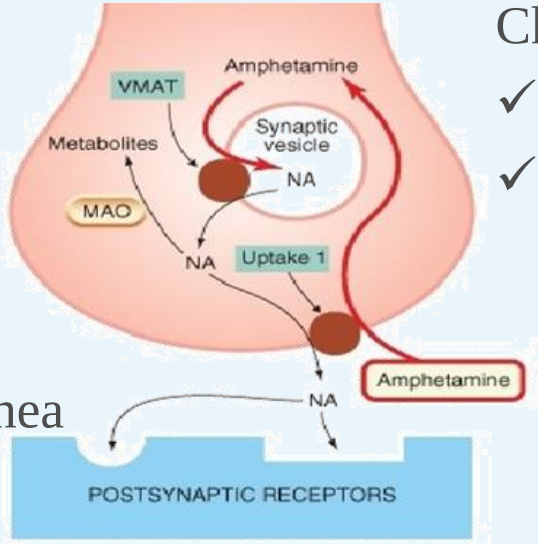
- ✓ Moderate psychomotor stimulatory effect.
- ✓ Stimulate the respiratory and the vasomotor center.
- ✓ Increase mental and less physical performance
- ✓ Removes the need for sleep and fatigue.
- ✓ Stimulate cardiac activity, peripheral vasodilator effect
- ✓ Moderate diuretic effect
- ✓ Stimulate gastric secretion
- ✓ Spasmolytic effect

Side effects

Phenylalkylamine derivatives

In regular doses for short time:

- ✓ Agitation
- ✓ Restlessness
- ✓ Insomnia
- ✓ Dizziness
- ✓ Headache
- ✓ Tremors
- ✓ Dry mouth,
- ✓ Nausea,
- ✓ Constipation or diarrhea



In high doses:

- ✓ Tachycardia
- ✓ Hypertension
- ✓ Arrhythmias
- ✓ Psychotic reactions

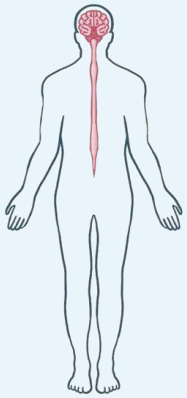
Chronic abuse:

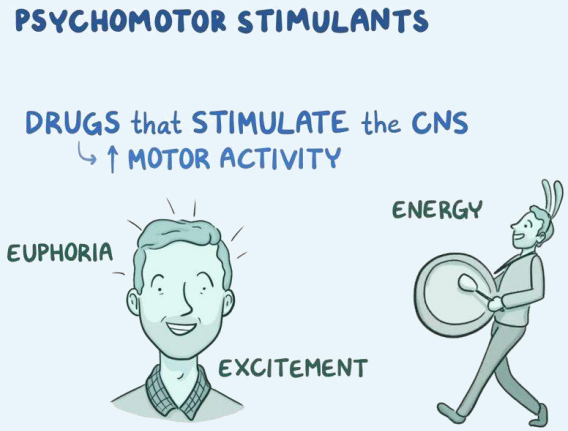
- ✓ Tolerance
- ✓ Mental drug addiction (the physical one is minor)

Side effects:

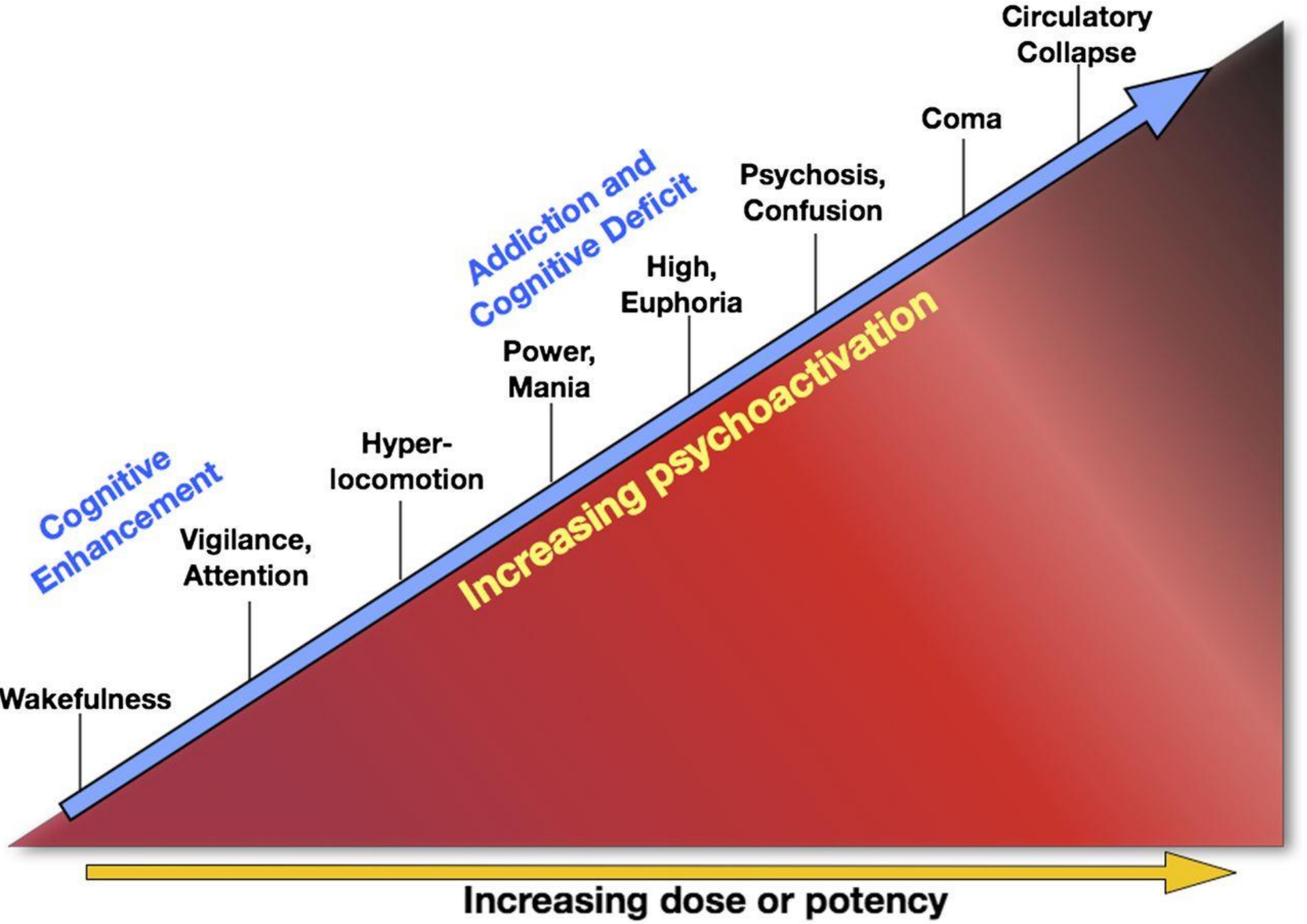
Methylxanthine derivatives:

- Restlessness, anxiety, confusion
- Insomnia
- Palpitation, tachycardia, arrhythmias
- Vertigo, headache
- Trembling of the extremities
- Vision and hearing disorders
- Epigastric discomfort and heartburn.





Continuum of Psychostimulant Activation



THANK YOU