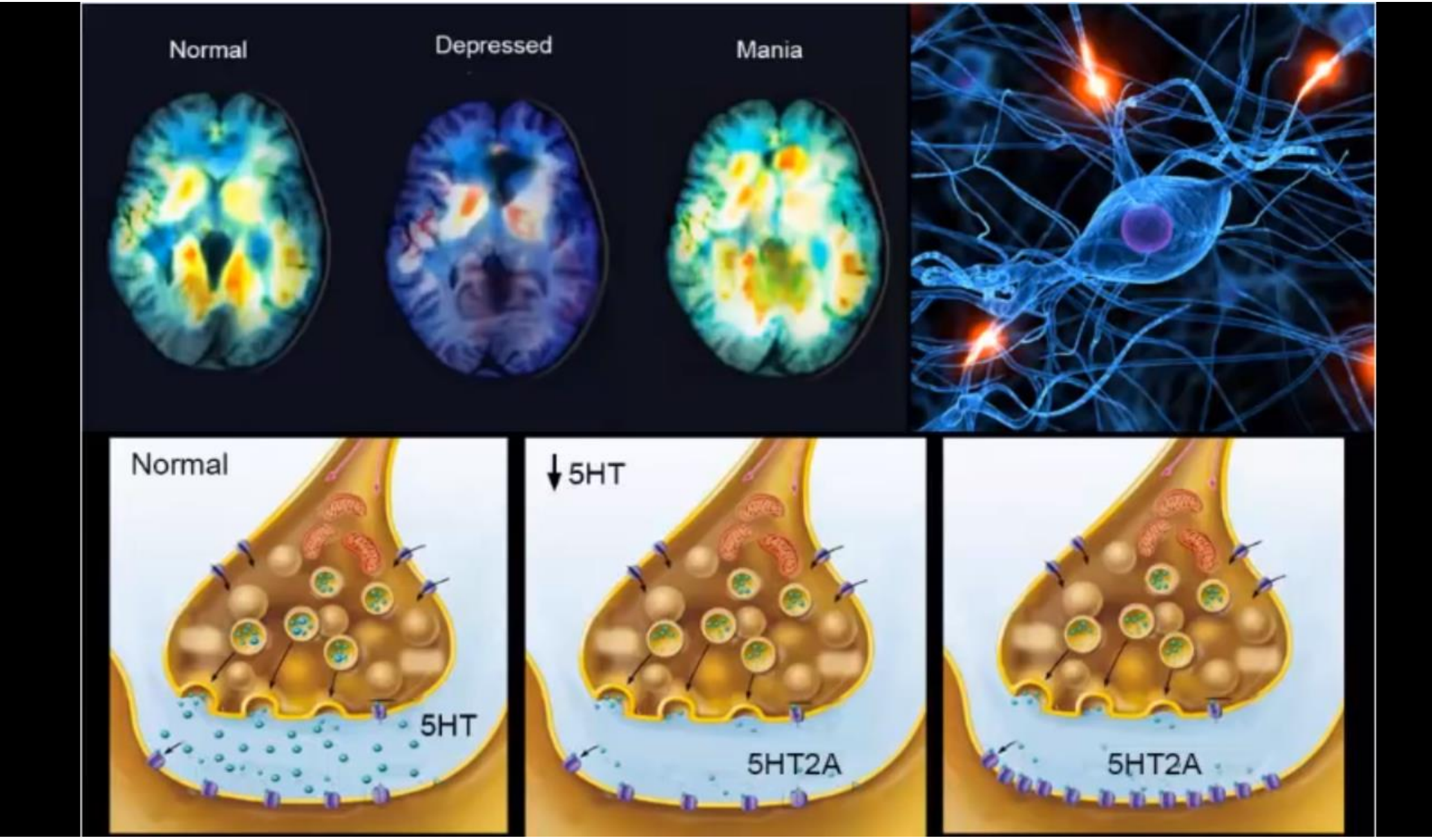
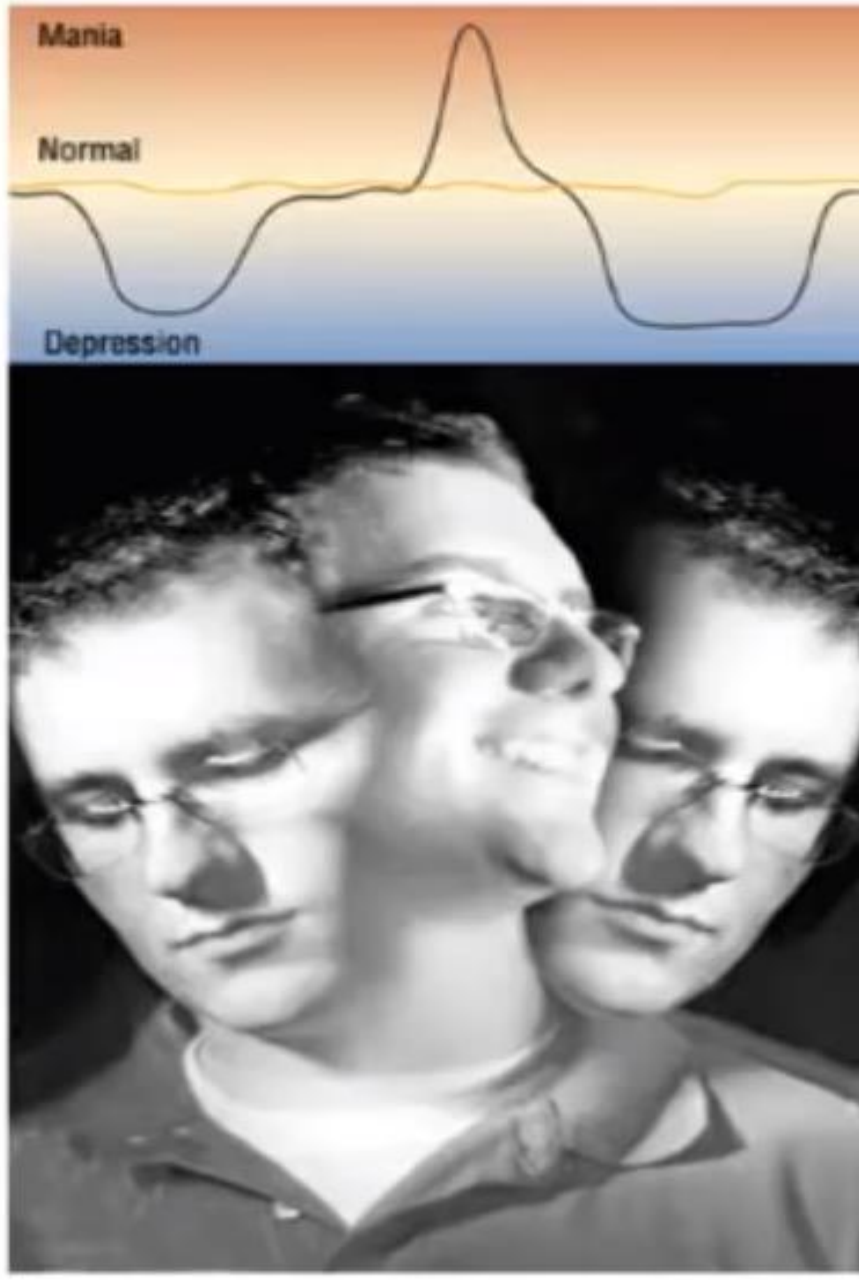
Antidepressant

Positro emission tamogram

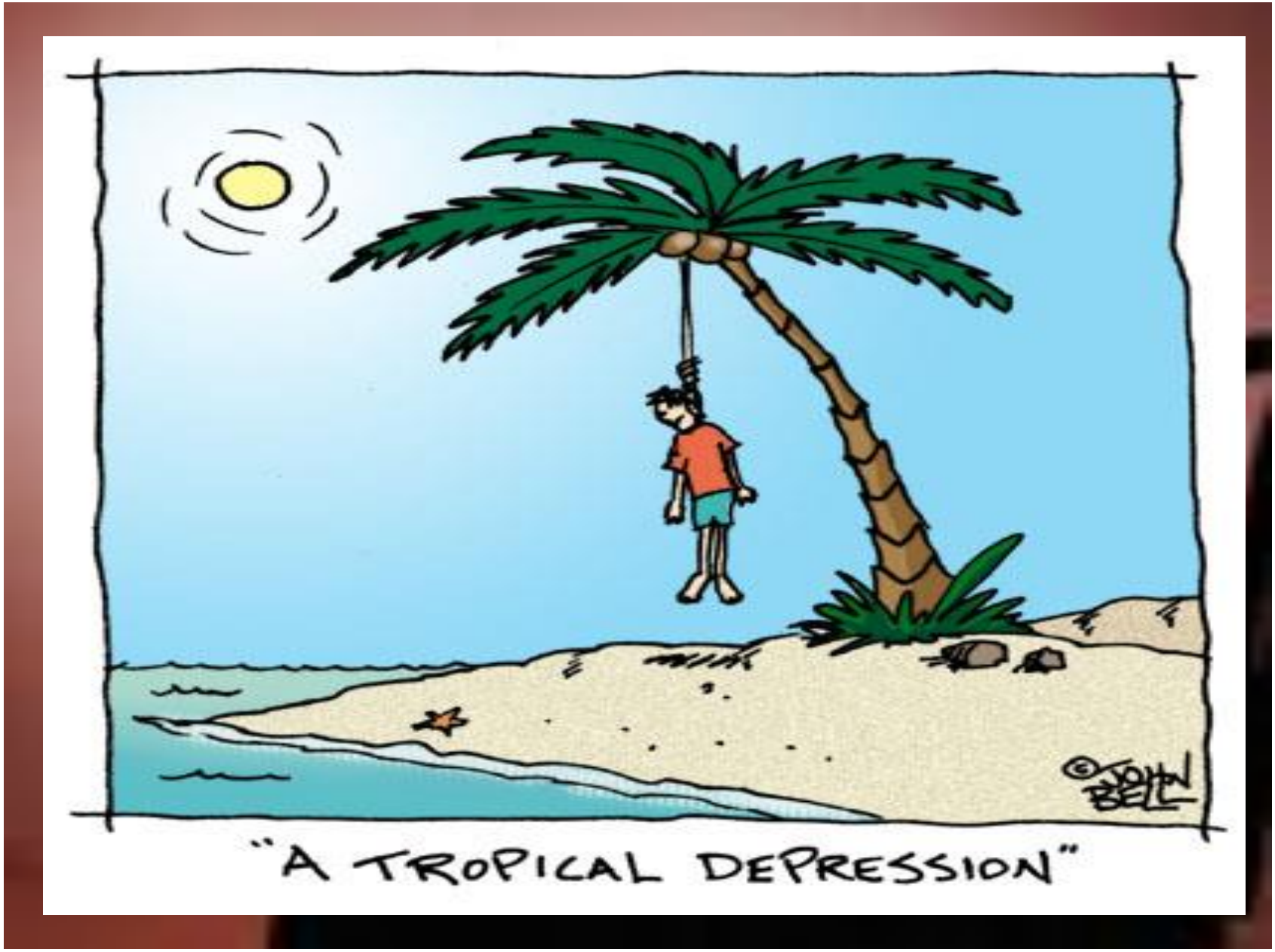


- Depression is a disorder of mood rather than disturbance of thought or cognition. It is postulated that depression is due to **deficiency** of **NA** and/or **5-HT** in the CNS while **mania** results from functional **excess**. Psychic depression is characterized by both ***emotional*** and ***biological*** symptoms.
- Recent studies suggest that overactivity of post-synaptic **5-HT$_2$A** receptors in some brain areas is involved in the pathogenesis of depression and psychosis.

The sad woman by Edith Wilkinson



- **Unipolar depression (major depressive disorder):** more common, may be ***reactive*** (70%) or ***endogenous*** (25%), characterized by low mood and loss of interest or pleasure in normally enjoyable activities.
- **Bipolar depression (manic-depressive disorder):** less common, characterized by oscillating periods of depression and mania. There is strong hereditary origin.


"A TROPICAL DEPRESSION"

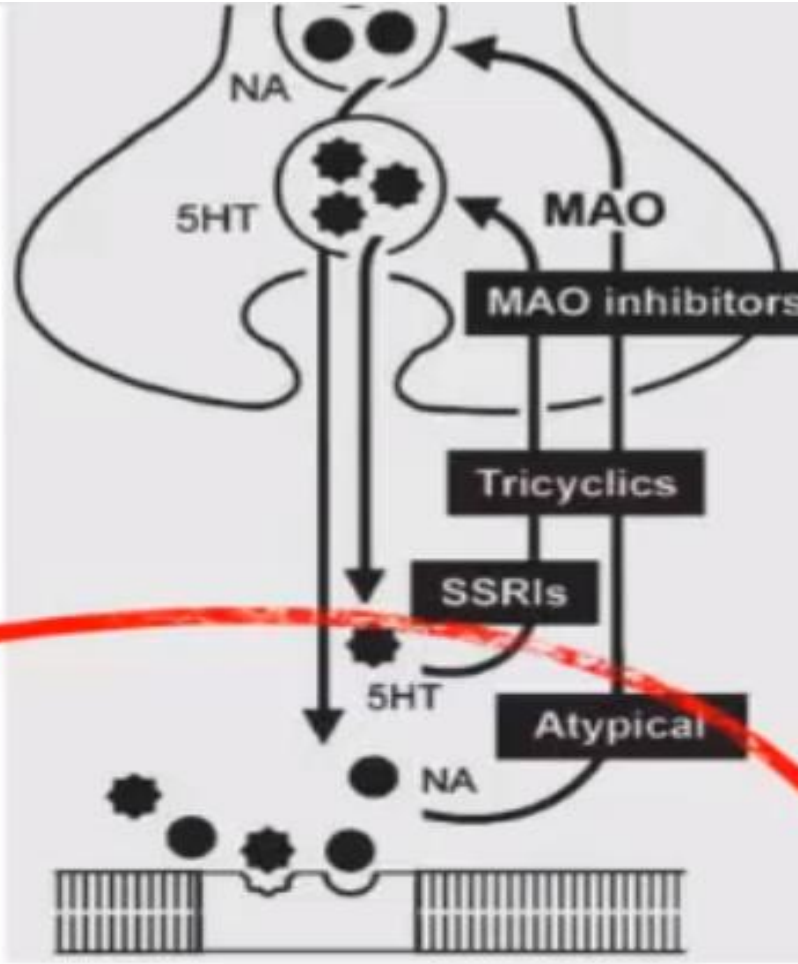
Therapeutic target

- ↑ 5-HT & NA in brain
  (typical antidepressant)

- other mechanisms Block 5-HT2A
  (Atypical antidepressant)

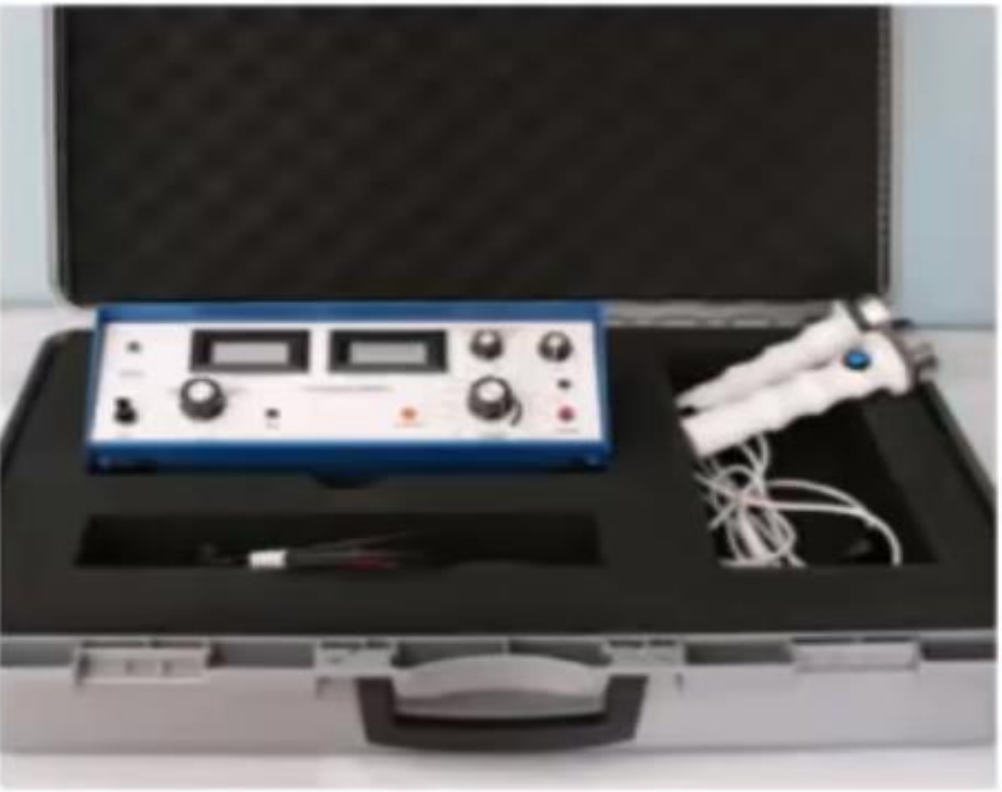
disorder): less common, characterized by oscillating periods of depression and mania. There is strong hereditary origin.

- The therapeutic effect occurs only after **2-3 weeks** of drug administration and is more closely associated with adaptive changes in neuronal receptors and brain neurotrophic factors.



Classification of antidepressant drugs:

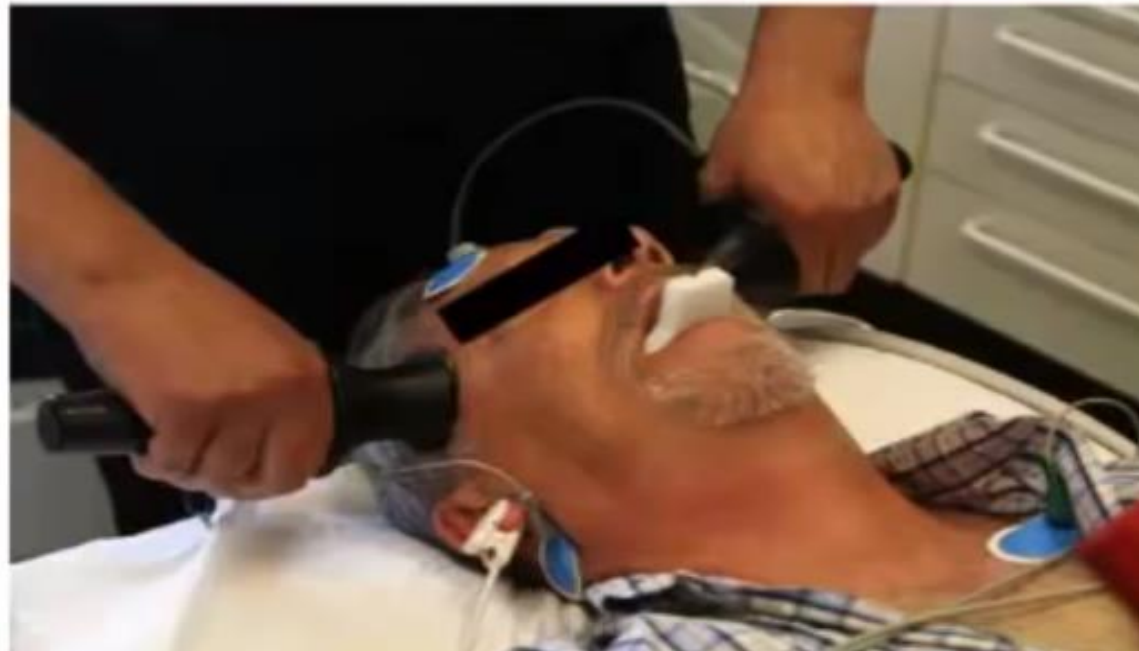
- **Tricyclic antidepressants (TCA)** e.g. imipramine, amitriptyline.
- **Selective serotonin reuptake inhibitors (SSRI):** e.g. fluoxetine, sertraline.
- **Atypical heterocyclic antidepressants:** e.g. maprotiline, trazodone.
- **Monoamine oxidase inhibitors (MAOI)** e.g. clorgyline, selegiline.



Electroconvulsive Therapy (ECT)

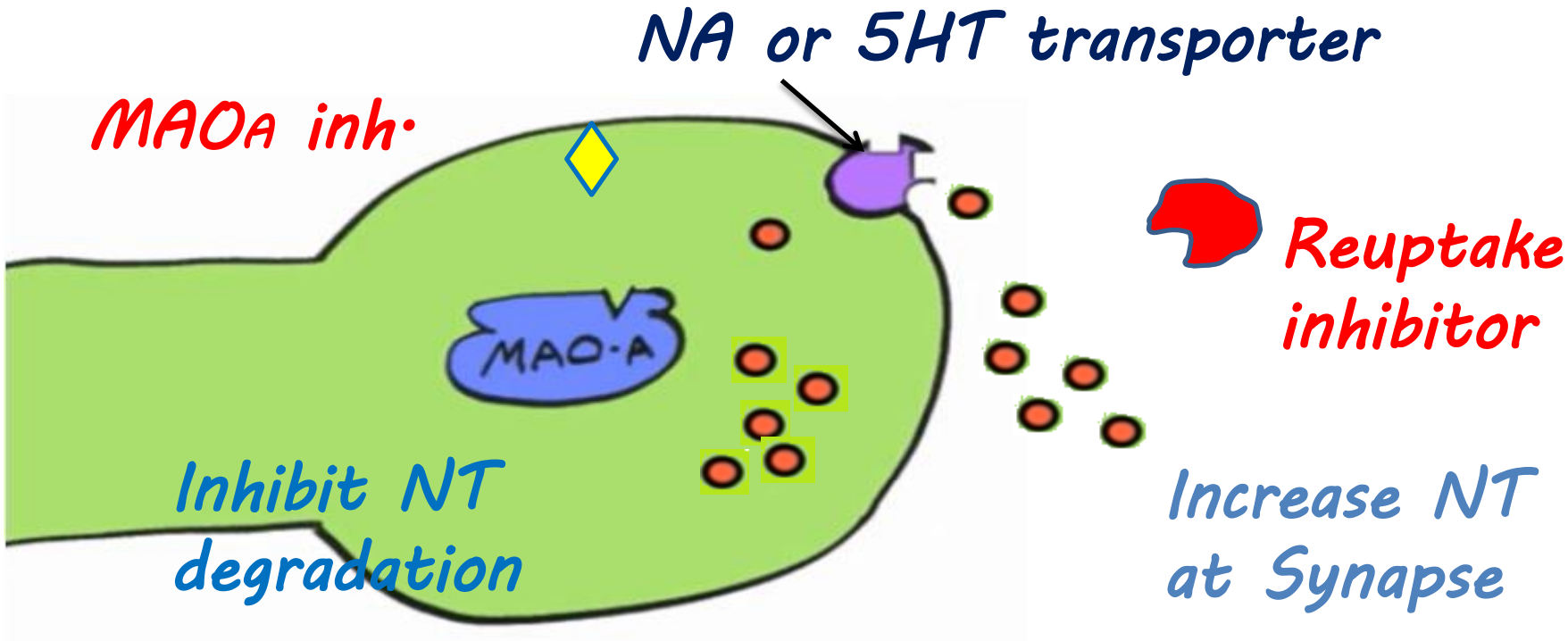
Rapid and effective method in cases of severe depression.

Done under general anaesthesia.



Typical Antidepressants

General MOA: ↑ NA & 5HT in CNS by either block (reuptake or degradation) of these NT.



1. Tricyclic antidepressants (TCA)

Imipramine, Desipramine, Clomipramine, Amitriptyline, Nortriptyline

Pharmacokinetics

- They are well absorbed after oral administration. They have **large Vd**.
- Most TCA have **long $t_{1/2}$** because they are metabolized into active metabolites and undergo enterohepatic cycling.

Mechanism of action: *(inhibition of the amine pump)*

- TCA inhibit neuronal reuptake of both 5-HT & NA leading to their accumulation in synaptic spaces and the brain tissue.
- It has been suggested that improvement of the **emotional** symptoms is related to enhancement of **5-HT** transmission while improvement of **biological** symptoms is related to enhancement of **NA** transmission.
- Elevation of mood in depressed patients occurs after 2-3 weeks

Indications of antidepressant

- D - Depression
- E - Enuresis (Imipramine)
- P - Phobia
- R - Recurrent panic attacks
- E - Eating disorders (Bulimia) click
- S - Smoking cessation (Bupropion)
- S - Stress disorder (Post traumatic)
- I - Impulse disorder (Kleptomania) click
- O - Obsessive compulsive disorder click
- N - Neuropathic pain

Adverse effects

- **Sedation** is common at the start of therapy but tolerance develops later. It may be due to antagonism with histamine H1 and/or muscarinic receptors.
- **CNS troubles:** memory dysfunction, agitation, seizures, and suicidal thoughts.
- **Atropine-like action:** very common - dry mouth, blurred vision, urine retention, etc.
- **Orthostatic (postural) hypotension**: due to peripheral α1 receptor blockade.
- Cardiac **arrhythmias:** tachycardia, widening of QRS, and ↑ QT interval.
- **Hepatotoxicity:** cholestatic hepatitis.
- Weight gain.

Drug interactions

- Toxic synergism with **MAOIs** and **SSRIs** (irritability and convulsions).
- TCA antagonize the antihypertensive effect of **clonidine** and **methyldopa**.
- TCA have additive **anticholinergic effect** with other drugs having anticholinergic activity.

TCA overdose

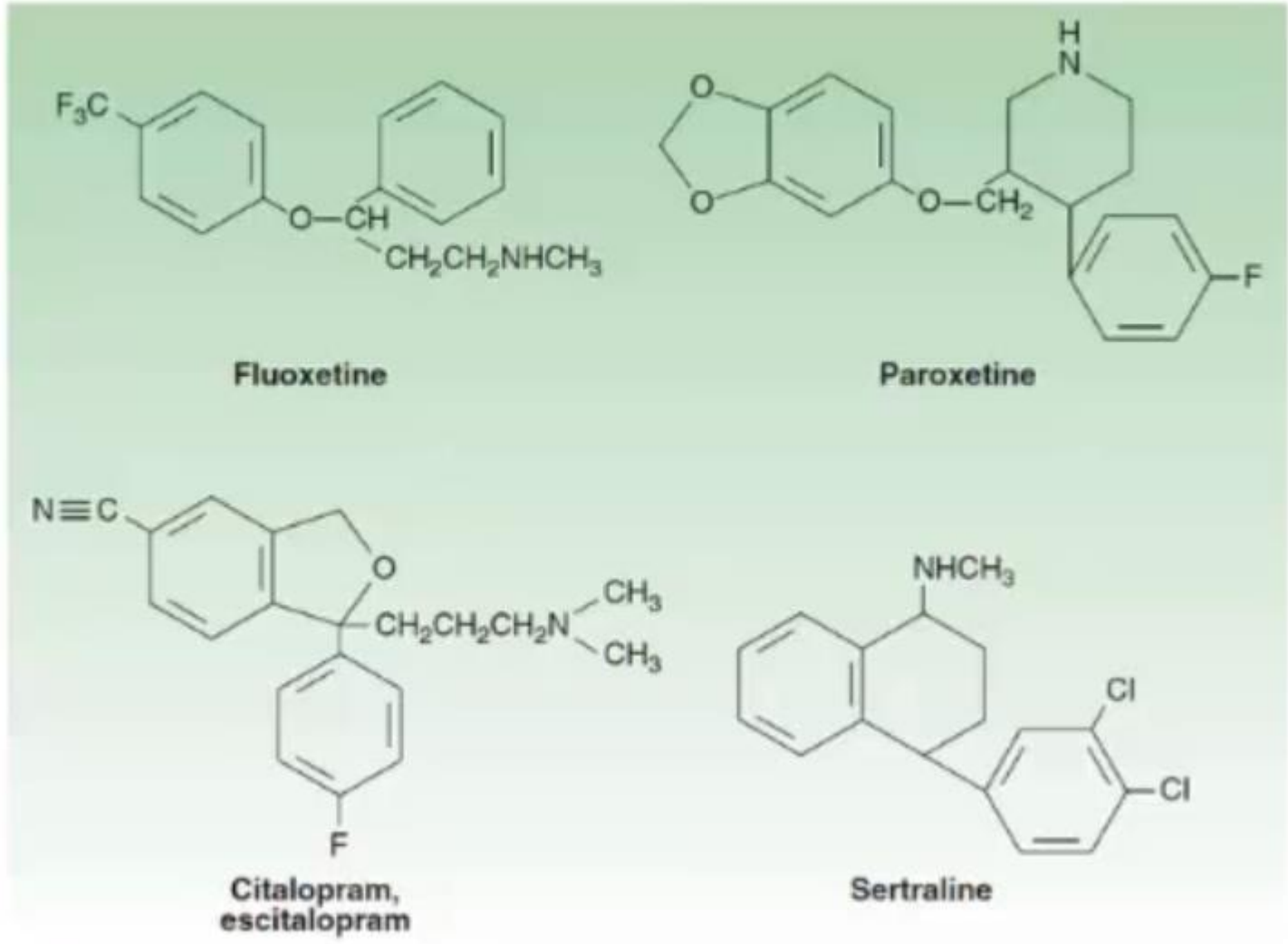
- Metabolic acidosis
- Atropine-like effects
- Cardiac arrhythmia

Management

- IV $NaHCO_3$ (1st step).
- IV lidocaine
- Dialysis is ineffective

2. Selective serotonin reuptake inhibitors (SSRIs)

Fluoxetine, Paroxetine, Sertraline, Citalopram, Escetalopram



2. Selective serotonin reuptake inhibitors (SSRIs)

Fluoxetine, Paroxetine, Sertraline, Citalopram, Escetalopram

- They are the most commonly prescribed antidepressants due to their limited toxicity. They are also used for some other psychiatric disorders.
- **Sertraline** is the preferred antidepressant following **myocardial infarction** as there is more evidence for its safe use in this situation than other antidepressants.
- When stopping an SSRI the dose sho period, this reduces the risk of relapse.

Mechanism of action

- They selectively block SHT reuptake leadi
- Their effect appears after 2-3 weeks like

Therapeutic uses

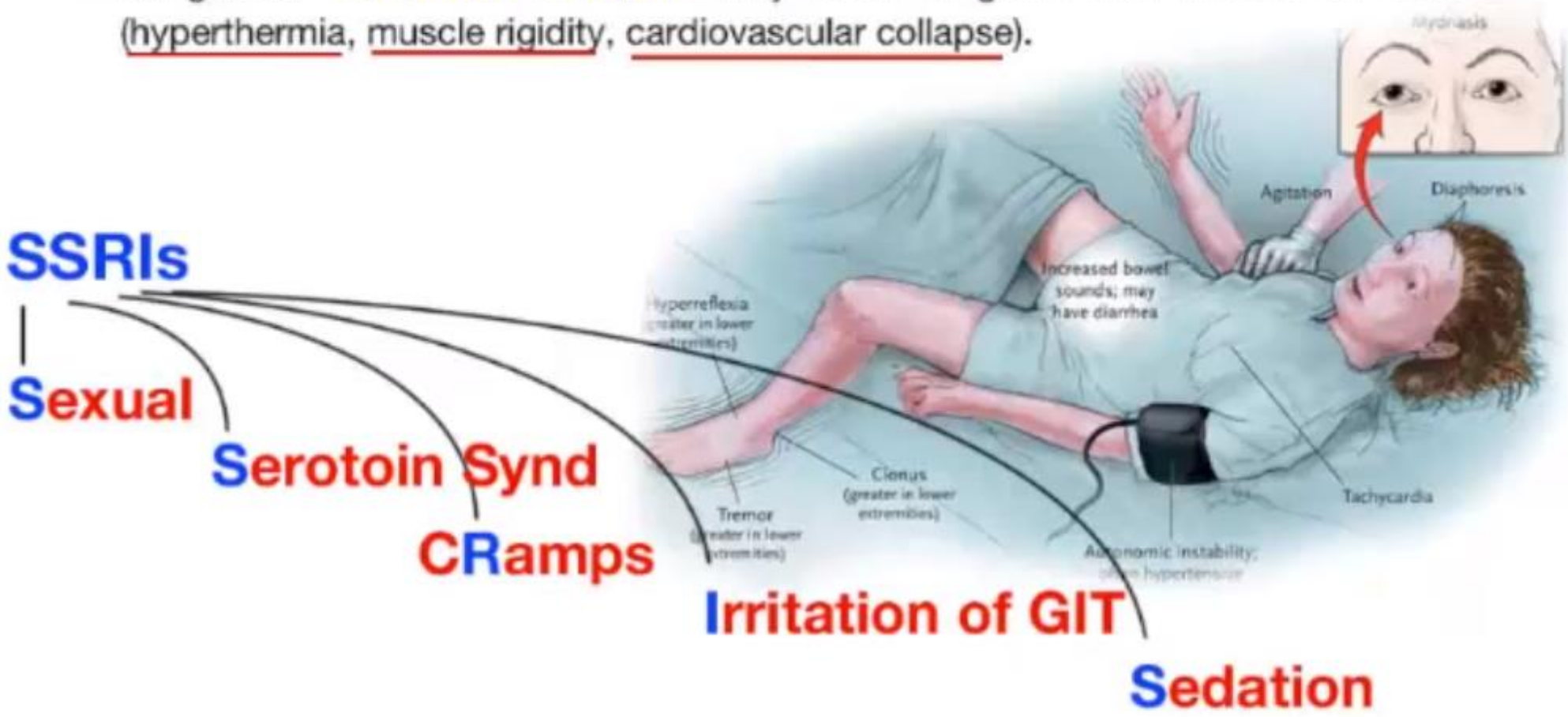
- Major depressive disorder.
- Obsessive-compulsive disorder (OCD).
- Anxiety disorders (generalized anxiety

Therapeutic uses

- Major depressive disorder.
- Obsessive-compulsive disorder (OCD).
- Anxiety disorders (generalized anxiety disorder, social phobia, panic disorder).

Adverse effects

- **GIT irritation** is the most common side effect. A **proton pump inhibitor** should be prescribed if a patient is also taking a NSAID to avoid GIT bleeding.
- **Sedation** or **insomnia** at the start of therapy but tolerance develops later.
- **Muscle cramps** and twitches.
- **Sexual dysfunction** in up to 40% of patients – the main cause of noncompliance.
- Dangerous **"serotonin reaction"** may occur if given with **MAOIs** or **TCA** (hyperthermia, muscle rigidity, cardiovascular collapse).



3- Monoamine oxidase inhibitor (MAO-I)

MAO inhibitors

MAO-A
metabolizes NA, 5-HT & DA in intestine, peripheral nerve endings and liver.

MAO-B
metabolizes DA in brain, platelets and liver.

- Non selective MAO inhibitor

Tranylcypromine, Phenelzine.

- Reversible Inhibitors of MAO-A

Moclebemide

- Selective MAO-B inhibitors.

Selegiline

MAO inhibitors

Non selective MAO inhibitor

Tranylcypromine, Phenelzine.

- Inhibits both isoforms of MAO irreversibly
- Their anti-depressant effect takes 3-4 weeks to develop.
- exhibit a large number of drug and food interactions

Reversible selective MAO -A inhibitor

Moclebemide

- inhibits MAO-A selectively and reversibly.
- It can be used as an alternative to TCAs for the treatment of depression.

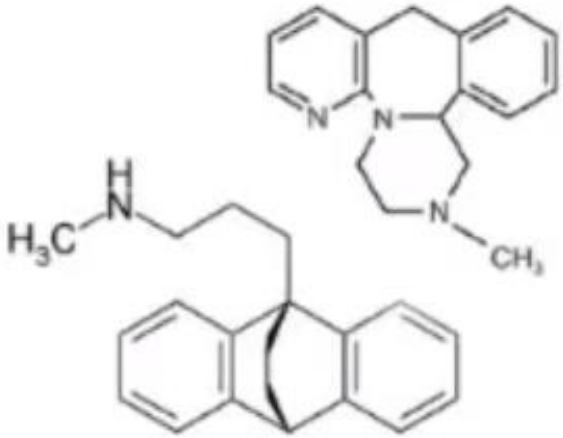
selective MAO -B inhibitor

Selegiline

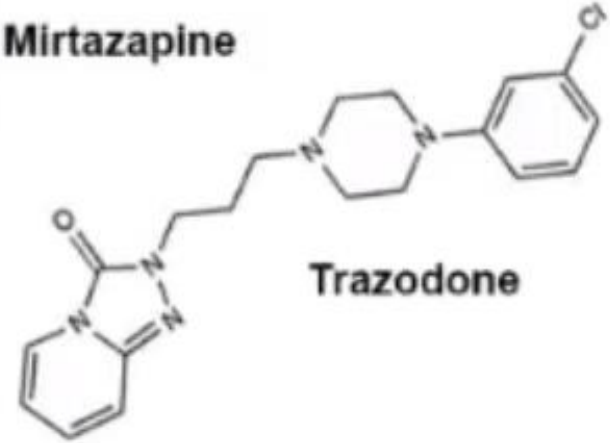
- inhibits MAO-B selectively .
- Useful in Parkinsonism. It is available as a transdermal patch for treatment of depression.

MAO inhibitors drug & food Interaction

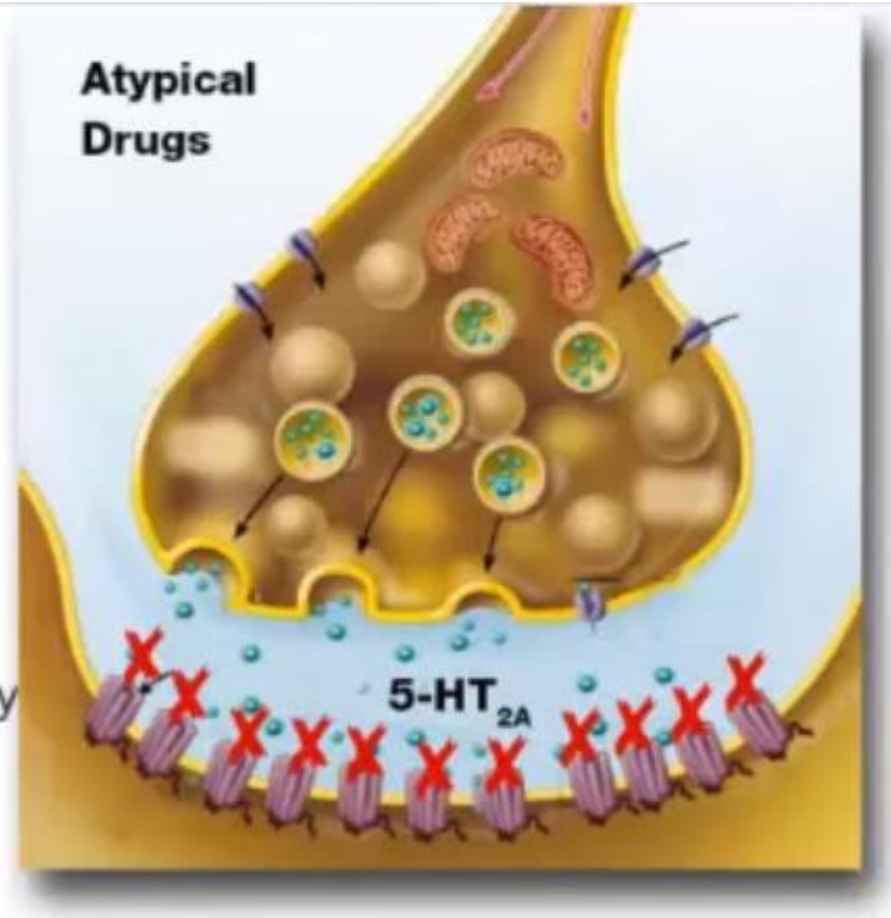
- **Cheese reaction** Cheese, beer contain tyramine (indirectly acting sympathomimetic). Normally it is metabolized by MAO-A in the intestine. taking non-selective MAO inhibitors, Tyramine escapes degradation and can lead to hypertensive crisis.
- Non-selective MAO inhibitors increase the risk of seizures if given along with **pethidine** due to enhanced generation of excitatory metabolite nor-meperidine.
- **Serotonin syndrome** (Too much 5HT in brain lead to headache, nausea, restlessness, high fever, seizure) If given along with **SSRIs** or just after discontinuation of MAO inhibitors,



Mirtazapine



Trazodone



3. Atypical antidepressants

The pharmacological properties of atypical heterocy
similar to those of TCAs.

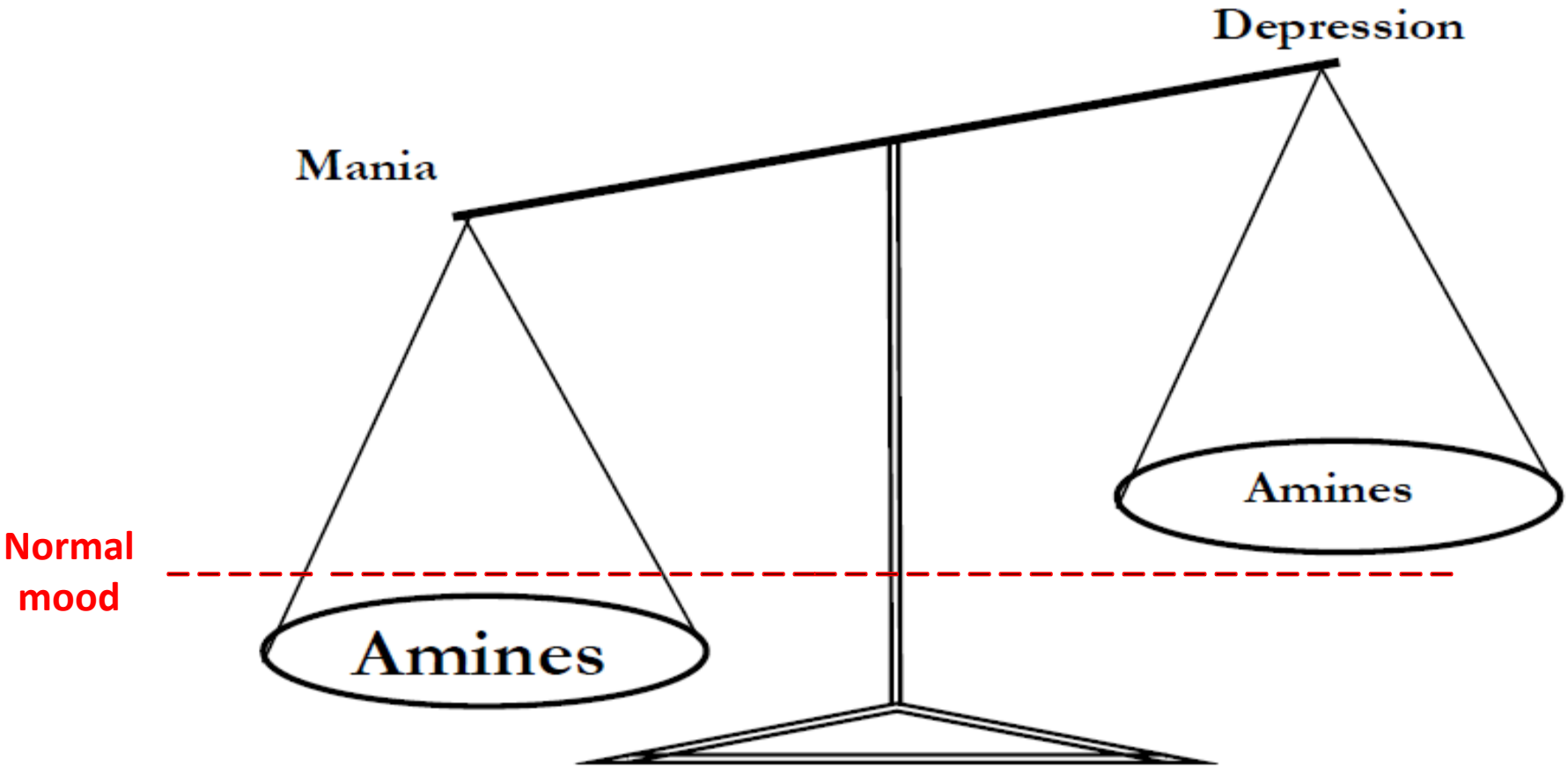
Mechanism of action

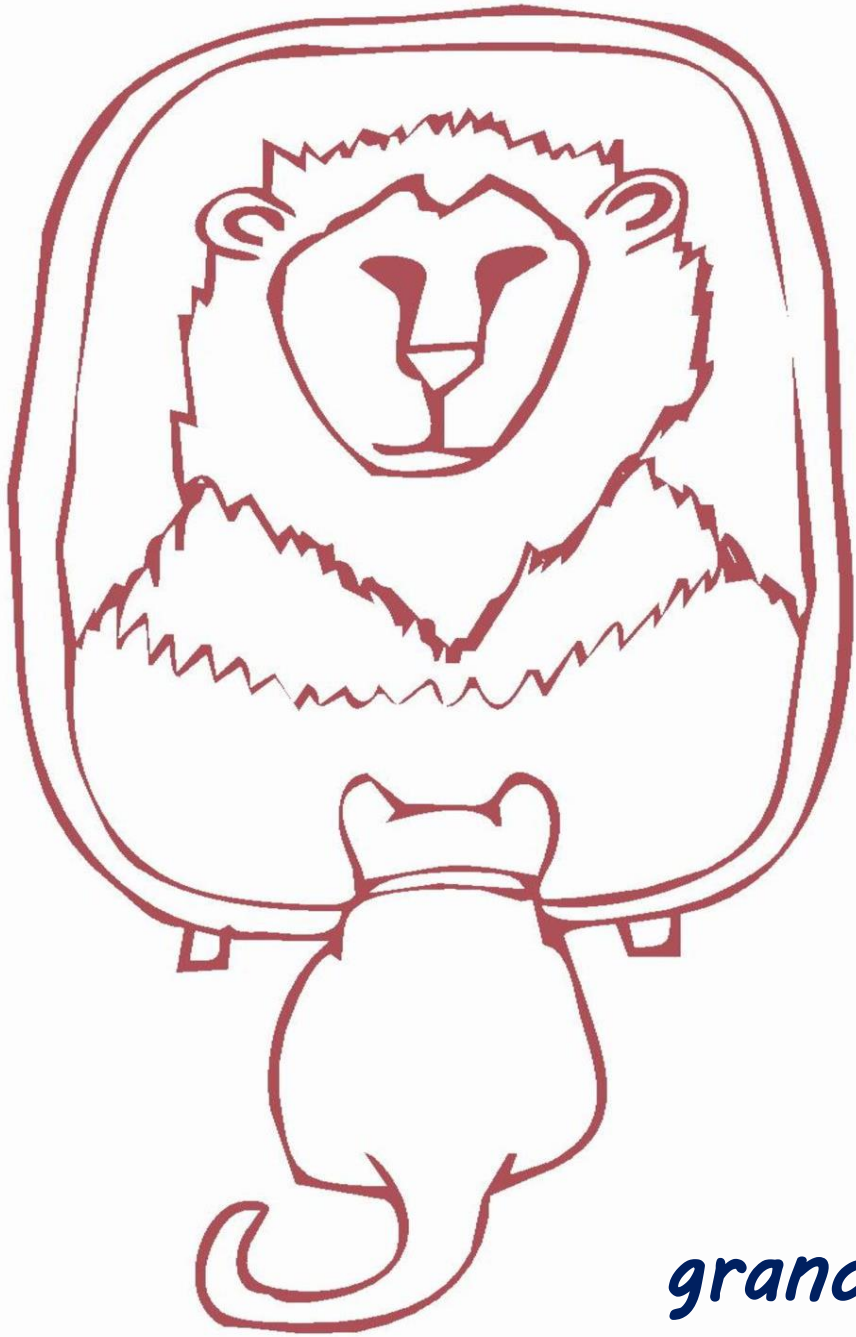
- **Trazodone:** blocks mainly **5HT$_2$A** receptors in addition to **H1**, and **α1** receptors. It is highly sedating and can cause postural hypotension.
- **Mertazapine:** blocks mainly **5HT$_2$A** receptors in addition to **H1**, and **α2** receptors. It causes weight gain.

Manic- depressive illness

Mania الاكتئاب الهوسي

severely elevated mood, irritability, hyper-sexuality, hyperactivity, talkativeness, and grandiose ideas and plans· التصرف بتهور

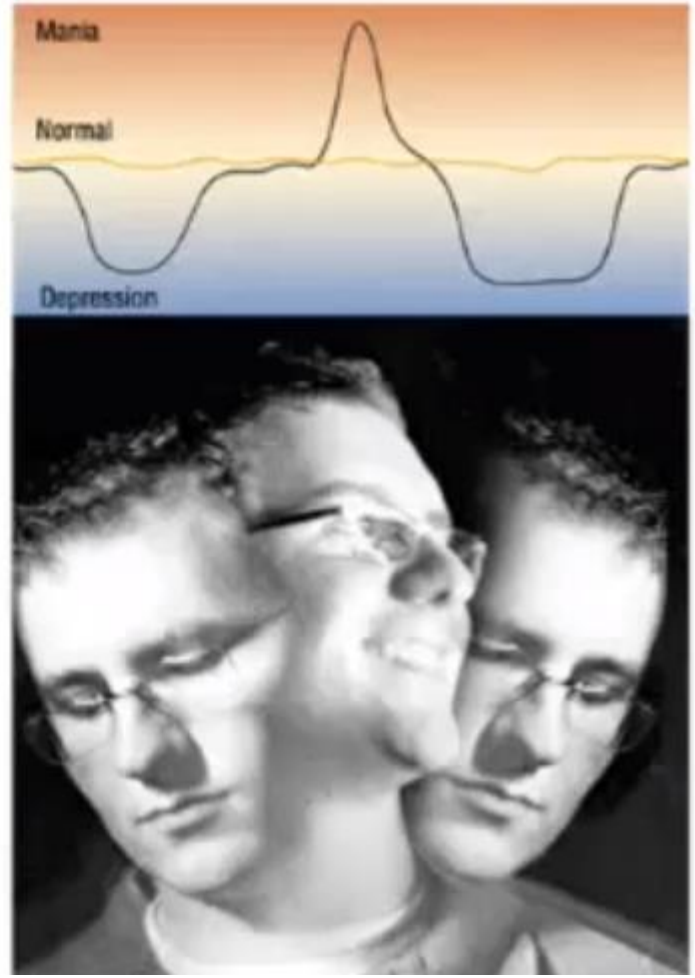




grandiose idea

Antimanic

- **Sodium valproate** is the only specific antimanic agent and is the treatment of choice in the **acute stages.**
- **Lithium** is the drug of choice for **long-term** treatment to prevent relapse.



Lithium carbonate

Mechanism of action

- It ↓ cAMP in neuronal cells and ↓ NA release → ↓ neuronal firing.
- It inhibits many metabolic processes in the nerve tissue.

Lithium Carbonate

- monovalent cation ; on prolonged use acts as a mood stabilizer.
- acts by inhibiting the regeneration of IP_3 and DAG by inhibit inositol monophosphatase enz

- narrow margin of safety, hemodialysis is indicated in toxicity
- It takes 1-2 weeks to exert its maximum effect. the drug of choice for prophylaxis of bipolar disorder.
- Thiazide which increase lithium renal tubular reabsorption leading to Lithium toxicity.

Lithium adverse effect

L- Leucocytes

I- Increased

T- Tremor

H- Hypothyroidism

I- Increased

U- Urine

} polyuria

M- avoided in expected mother