بسم الله الرحمن الرحيم

Antidepressant drugs

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INTRODUCTION

Types of depression:

1) Reactive (neurotic) depression:

➢Marked sadness due to anxious life events (e.g. illness, death of a family member, failure in business, etc.).

➢ It represents 60 % of the cases of depressions.

➢It may resolves by social support from relatives and friends.

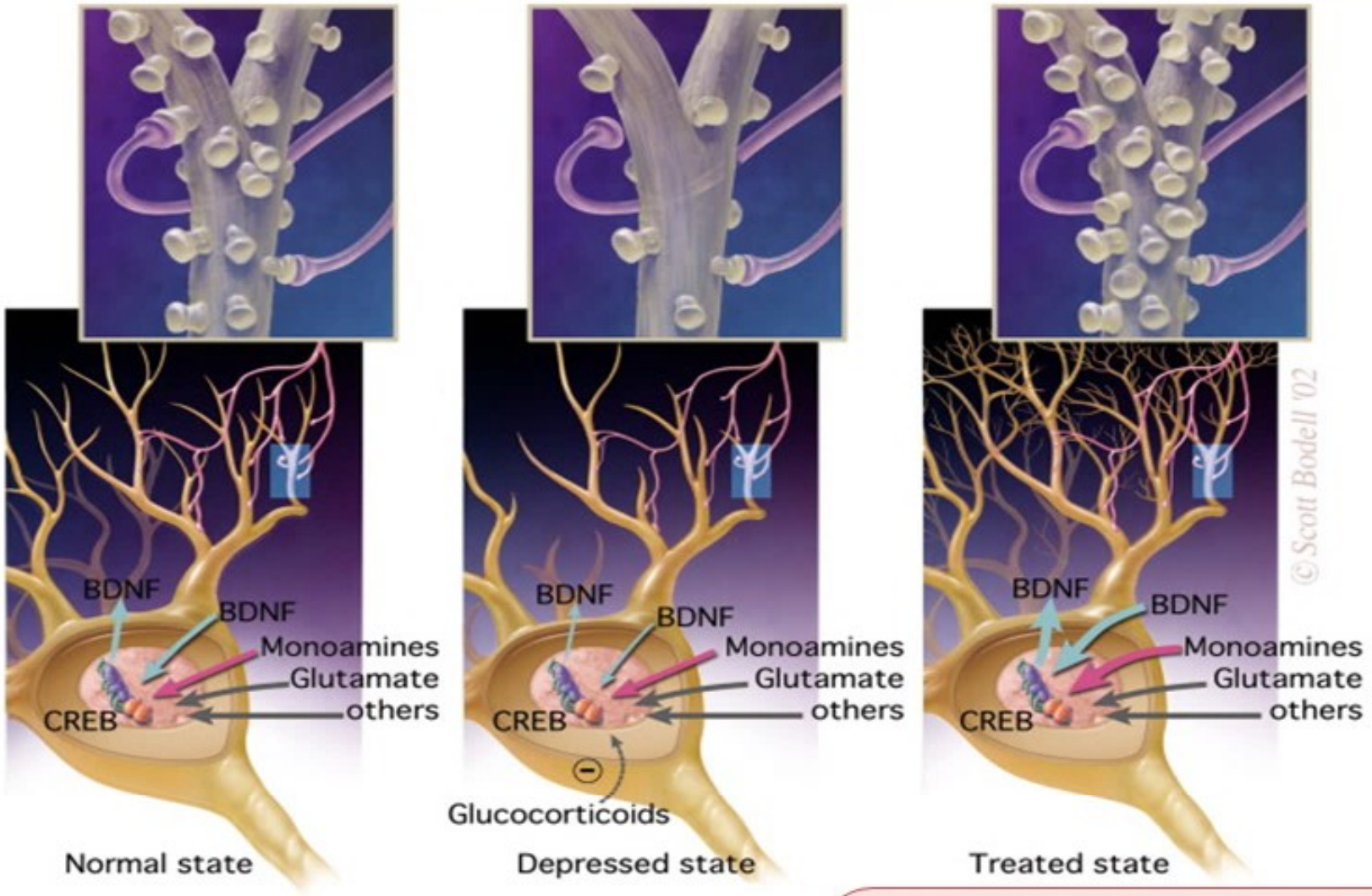
➢antidepressants are often effective If severe or persistent or suicidal intents exists.

2) Endogenous (*Major depressive disorder (MDD)*:

❑A **brain disease** causing feeling of sadness, guilt, disturbances in sleep and appetite, and deficits in cognition and energy, and suicidal attends.

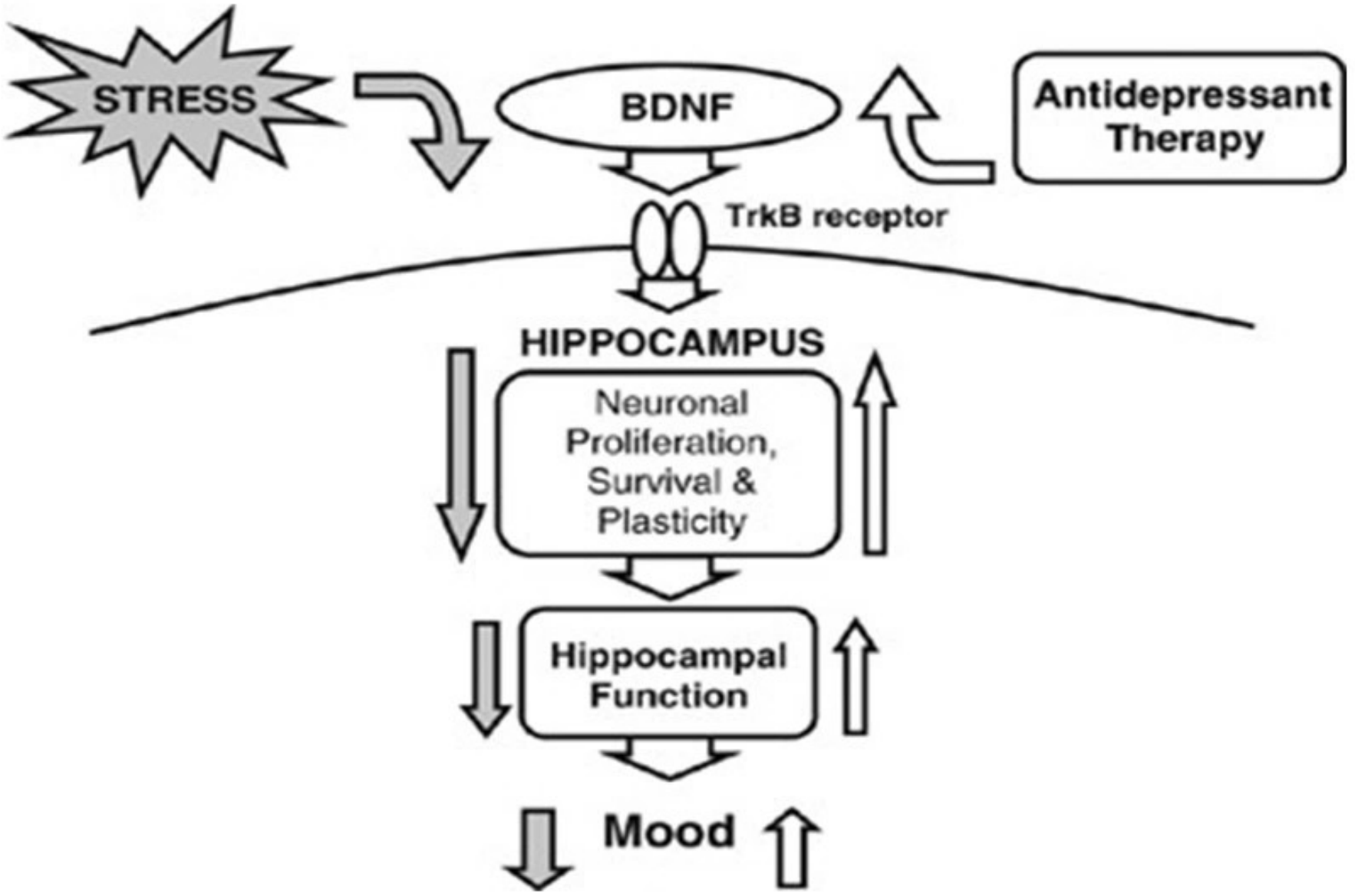
❑Coronary artery disease, diabetes, and stroke appear to be more common in depressed patients. Depression may worsen the prognosis for patients with a variety of co-morbid medical conditions.

Neurotrophic Hypothesis



Brain-derived neurotrophic factor (BDNF)

antidepressant therapies ↑neurogenesis & synaptic connectivity in cortical areas and hippocampus.


STRESS
BDNF
Antidepressant Therapy
TrkB receptor
HIPPOCAMPUS
Neuronal Proliferation, Survival & Plasticity
Hippocampal Function
Mood

- MDD represents 25 % of the cases of depressions.
- There is tendency for **recurrence** (unipolar depression).
- Respond to antidepressant drugs, electroconvulsive therapy (**ECT**), and psychological treatment.

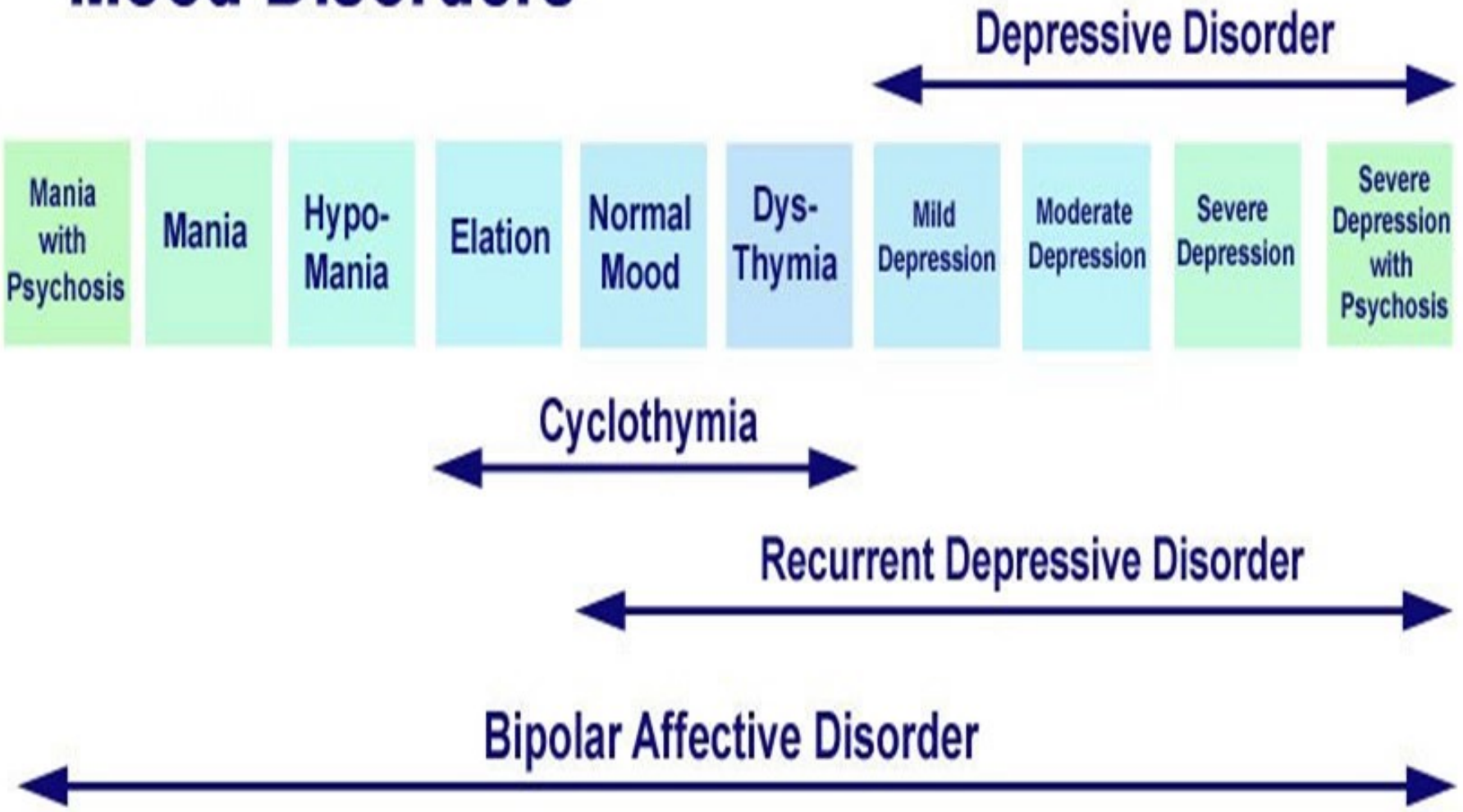
3) Bipolar affective (manic-depressive) disorder:

- Episodes of recurrent depression alternated with mania.
- **Mania** (unreasonable euphoria, hyperactivity, and delusions).
- It represents 10-15 % of cases of depressions
- Family history is positive.
- Treatment mainly by mood stabilizers like lithium.

4) Major depression with psychotic features

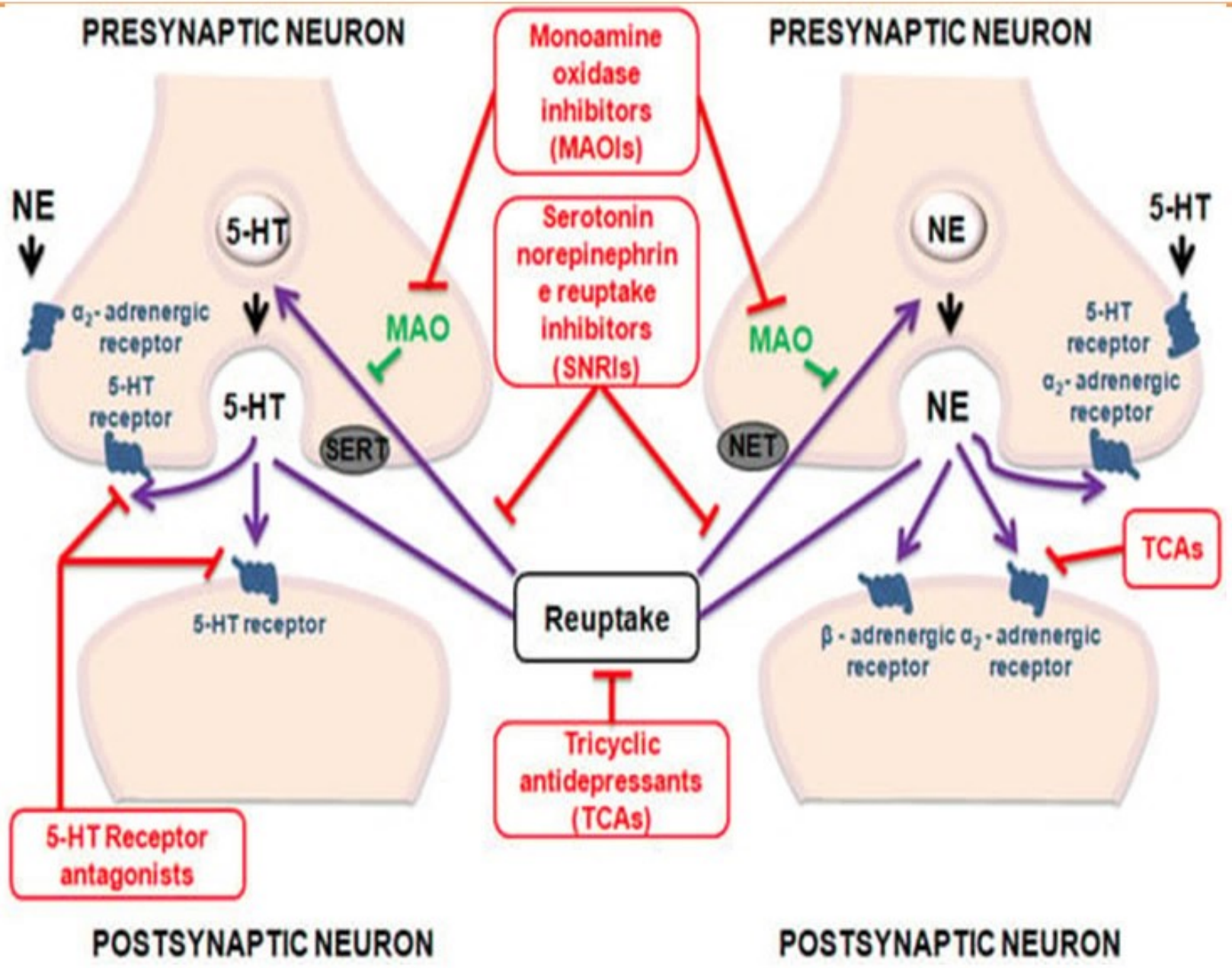
- It is a mental disorder in which a person has depression along with loss of touch with reality (psychosis).
- Combined antidepressant and antipsychotic medications are used.

Mood Disorders




MOOD
DISORDERS

Classical Antidepressant drugs tend to increase the synaptic levels of monoamines (Norepinephrine and serotonin), The elevated NE, 5-HT levels could increase the BDNF and increase synaptic connectivity in the brain



Selective serotonin reuptake inhibitors (SSRIs)

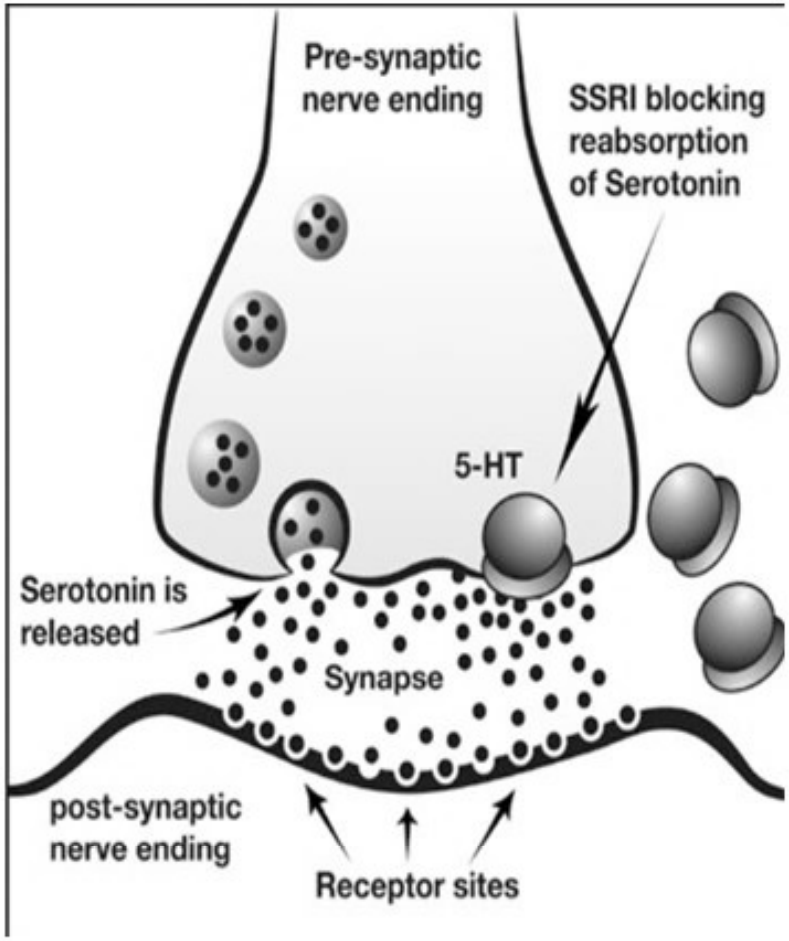
Fluoxetine, **paroxetine**, **citalopram**, **Escitalopram** and **sertraline**.

Mechanism:

Block serotonin reuptake transporter (↑serotonergic activity)

Advantages:

- ❑**Safer than other antidepressants (TCAs & MAO inhibitors).**
- ❑**SSRIs have faster onset of action.**
- ❑**No anticholinergic or CVS side effects**
- ❑**No sedation**.
- ❑**The toxic dose is very high**, so they have **high margin of safety** and there is much difficult to be used as a method for suicide.



Pharmacokinetics of SSRIs

- Metabolized extensively by hepatic CYP2D6 followed by conjugation.
- **Fluoxetine & paroxetine** are **potent inhibitors** of **CYP2D6** (eliminating tricyclic antidepressant, neuroleptics, and some antiarrhythmic drugs).
- SSRIs are excreted in urine, except paroxetine & sertraline (in feces)

Therapeutic uses:

1. **Major depression** (at least 2 weeks to manifest and maximum benefit may require up to 12 weeks or more).
2. **Generalized Anxiety** disorders
3. Panic disorder
4. Obsessive-compulsive disorder (OCD)
5. Post-traumatic stress disorder (PTSD)
6. Peri-menopausal vasomotor symptoms
7. Eating disorder (bulimia nervosa and anorexia nervosa)
8. Off-label treatment of **premature ejaculation**.

Side effects of SSRIs:

1. GIT disturbance as nausea and vomiting (due to ↑5-HT)
2. CNS stimulation: akathisia, tinnitus, headache, & insomnia.
3. Sexual dysfunction " impotence" (sildenafil could help), and delayed (or retrograde) ejaculation and orgasm.
4. SSRIs discontinuation syndrome on sudden withdrawal causing dizziness, paresthesias, and flu-like symptoms.
5. Weight gain, particularly with paroxetine.
6. Inhibition of cytochrome P_{450} by fluoxetine.
7. If fluoxetine is combined with MAO-inhibitors, there is marked increase in serotonin levels and causing **serotonin syndrome** (hyperthermia, convulsion, disturbance in mental state and vital signs and muscle **rigidity**). This reaction is self-limiting in cases of stoppage of the drug.

Serotonin-Norepinephrine Reuptake Inhibitors(SNRIs)

Venlafaxine, **desvenlafaxine** and **Duloxetine**.

Mechanism: blockade of NE & 5-HT reuptake (↑ both NE & 5-HT).

Therapeutic uses of SNRIs:

1. Major **depression**
2. Chronic pain disorders and **neuropathies**.
3. **Fibromyalgia**
4. Menopausal vasomotor symptoms
5. Urinary **stress incontinence** (**Duloxetine**)

Side effects:

1- Sympathomimetics effects:↑ Blood Pressure & ↑ heart rate.

2- CNS: **insomnia**, anxiety, and agitation.

3- **Cardiac toxicity** with **venlafaxine** overdose.

4-**Hepatic toxicity** with **duloxetine**.

5-A discontinuation syndrome resembling that seen with SSRIs.

6- Drug interactions: duloxetine, desvenlafaxine inhibit CYP2D6.

Tricyclic antidepressants (TCAs)

- **Imipramine** and Desipramine
- **Clomipramine**
-Amitriptyline and Nortriptyline
-**Doxepin**

Mechanisms of action:

❑Blockade of NE & 5-HT reuptake → acute ↑in serotonergic and adrenergic synaptic activity (Like SNRIS)

❑**Desipramine inhibits reuptake of NE only.**

❑Clomipiramine inhibits **reuptake of 5-HT** only **(resembling SSRIs)** and this explains its benefits in the treatment of **OCD**.

❑TCAs cause a significant blockade of muscarinic, and alpha receptors.

❑ **100 mg amitriptyline is equivalent to 5 mg atropine.**

❑**Doxepin** block Histamine receptors.

Therapeutic uses of TCAs:

1. Major depression not responsive to other drugs
2. Chronic **pain disorders and neuropathy.**
3. Urinary incontinence (due to anti-muscarinic effects)
4. Obsessive-compulsive disorder (**clomipramine**)
5. Doxepin is used as hypnotic and for treating pruritus (antihistamine).
6. **Desipramine**, had a beneficial short-term effect for children and adolescents with **ADHD**. However, TCAs also had unwanted cardiac effects, and sudden death limited their use in children.

Side effects of TCAs:

1-Anticholinergic effects (the most common)

Blurred vision, dry mouth, constipation, urinary retention & tachycardia.

2- Postural hypotension (α- blocking effect).

3- *Sedation* (early in therapy) and **weight gain (H1 blocking).**

4-Sexual dysfunction more with **clomipramine** (as delay orgasm).

5- **Prolong Q-T interval**, life-threatening **arrhythmias** occur in toxicity.

6- Hypersensitivity : rash, **obstructive jaundice** & **agranulocytosis.**

7- CNS stimulation:

➢ **Excitement** & even **mania** (precaution in bipolar disorder).

➢TCAs lower the **seizure** threshold (precaution in epileptic patients)

❑TCAs have narrow therapeutic index & overdose give acute toxicity which could be **fatal** (gives picture like atropine poisoning and treated with IV **physostigmine).**

➢Precaution with depressed patients with suicidal intents; such patients should be **given limited quantities of these drugs.**

8-Tolerance & Physical **dependence** and even **addiction** may occur.

❑Discontinuation syndrome characterized by cholinergic rebound and flu-like symptoms.

9- **Drug interactions**: SSRIs can inhibit the metabolism of TCAs leading to TCAs toxicity.

Atropine-like poisoning

Mad as hatter
Red as beet
Blind as bat
Dry as bone
Hot as oven
Rapid as rabbit

Atypical antidepressants
I-Serotonin (5-HT2) receptor modulators

- These drugs act away from the inhibition of (NE &/or 5-HT) reuptake.
- They may inhibit NE &/or 5-HT uptake (but this is not the main mechanism).

1-Trazodone block 5-HT_2A and Histamine-1 receptors.

2- Nefazodone: block 5-HT_2A receptors and inhibits 5-HT reuptake.

3- Vortioxetine (5-HT1, 3, 7 antagonist , 5-HT1B partial agonist & 5-HT1A agonist. It also inhibits the Uptake of 5-HT).

Uses:

1. **Major depression**.
2. **Trazodone** is used as **hypnotic** (unlabeled) , no tolerance or dependence.

Side effects:

1. **trazodone : Sedation** and **priapism** with **(never sexual dysfunction)**
2. Postural **hypotension** (α-blocking)
3. **Hepatotoxicity** with nefazodone
4. **Drug interaction** as Nefazodone inhibits CYP3A4
5. GIT side effects are rare.

II- Tetracyclic and unicyclic antidepressants

Mechanisms of action (NOT clear):

-Bupropion: ↑**release of NE** and ↑activity of NE & **dopamine** (but not 5-HT).

-Amoxapine resemble TCAs. rarely used

-Mirtazapine: Alpha 2 antagonist causing ↑ **release of NE & 5-HT**.

Mirtazapine **has a** Potent **H1, 5-HT2 and 5-HT3 receptors antagonist**.

Uses:

1. Major **depression** and Seasonal (winter) depression **(Bupropion).**
2. **Smoking cessation (Bupropion)**
3. **Anxiety** (mirtazapine), Antiemetic (mirtazapine blocks 5-HT3)
4. Off-label uses of **Bupropion** in (Attention Deficit Hyperactivity Disorder)

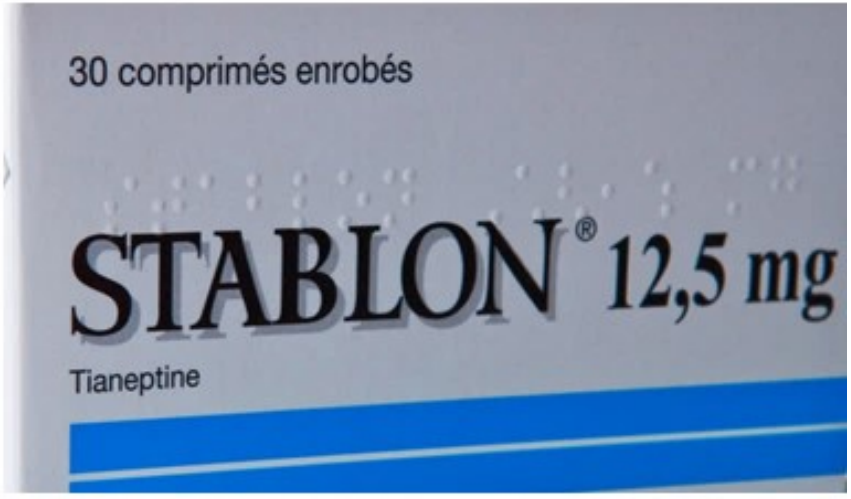
Side effects:

1. Amoxapine may cause Parkinsonism (D_2 -blocking action).
2. **Mirtazapine** has significant **sedative** effect and **weight gain**.
3. **Bupropion** occasionally causes agitation, **insomnia**, and **convulsions.**
4. Drug interactions as inhibition **of CYP2D6** by Bupropion

III- Agomelatine

- **Melatonin receptor agonist**
- 5-HT2C antagonist →increasing NE and **dopamine** release
- No hypnotic actions (because NE release increase arousal)
- ➢ It is hepatotoxic
- ➢ Used for treatment of depression.

VI-Tianapetine



- It blocks NMDA receptors & ↑ BDNF
- ↑ **dopamine** (opioid receptor mediated)
- ↑ 5-HT reuptake.
- Used for treating anxiety, depression and irritable bowel syndrome
- It may cause hepatotoxicity and **abuse**.
- The FDA has issued warnings (January 2024) about the dangers of recreational tianeptine use and the risks of dietary supplements containing undeclared tianeptine.

MAO-inhibitors

1-Non-selective (for MAO-A and B), irreversible inhibitors:

Phenelzine Tranylcypromine Isocarboxazide

2- Selective inhibitors to MAO-A, reversible: Moclobemide

N.B. ***Selegiline*** is a selective MAO-B inhibitor used for treating Parkinsonism.

Mechanism: inhibition of MAO, so blocking metabolism of biogenic amines leading to accumulation of NE and 5-HT (and may dopamine)

Pharmacokinetics:

They are well absorbed after oral use.

They are ***"hit and run"*** drugs i.e. their action persists for 2-3 weeks after therapy has been withdrawn.

Therapeutic uses:

Last line for treatment of **endogenous depression**, as they are less effective and have more toxic effects, so used only in patients **refractory to other drugs and refusing ECT.**

Side effects:

1. **Insomnia** and restlessness.
2. Phenelzine causes sedation
3. Postural **hypotension (**due to inhibition of central vasomotor control).
4. Hepato-cellular damage and **jaundice** (common with phenelzine).
5. Sexual dysfunction (as inhibition of ejaculation and anorgasmia).

Drug interactions:

➢**Hypertensive crisis** if MAO-inhibitors are used with tyramine rich foods (as aged cheeses, yeast, chicken liver, chocolate, beer, and wine) as tyramine will be absorbed orally and cause release of NE causing marked increase in BP ***(cheese reaction)*** which is treated by I.V. phentolamine.

➢Interaction with TCAs causing marked **CNS toxicity** (hyperthermia, convulsions, and coma), so tricyclic antidepressant must be given at least 3 weeks of cessation of MAO-inhibitors.

➢If used with fluoxetine (SSRI), ***serotonin syndrome*** is occurred due to marked increase in serotonin levels.

Novel antidepressant drugs
1- NMDA Receptor Antagonists

Esketamine

- Esketamine was approved for the treatment of major depression in **2019**.
- Esketamine is related ketamine (general anesthetic).
- **NMDA blocking is the major mechanism of action**.
- Ketamine was used OFF-label in **resistant depression** since 2006.

Disadvantages of ketamine included the short duration (5–7 days), IV route, dissociative symptoms, and risk of **abuse**.

- **Esketamine** was developed as **an intranasal preparation** for use in **treating -resistant depression**.
- It acts **rapidly to control depression**
- It may have somewhat **fewer dissociative effects** than ketamine.
- Esketamine has also been studied as **a rapid treatment for acute suicidal ideation.**

2- Neurosteroids (Allosteric Modulators of GABAA)

Allopregnanolone

- Allopregnanolone (**brexanolone**) facilitates GABA system.
- Allopregnanolone is a **derivative of progesterone.**
- Allopregnanolone had some anxiolytic and anticonvulsant properties.
- Used **IV** for treating **postpartum depression**
- Allopregnanolone is administered for continuous 60-hour IV infusion.
- It acts rapidly with evidence of response by 60 hours.
- Unlike ketamine and Esketamine, **the effects of** Allopregnanolone **persist for 30 days** after infusion and is **not associated with dissociative symptoms** or **risk of abuse.**

- Zuranolone is another **modulator of GABAA.**

It is an **oral** drug for treating depression & for postpartum depression.

3- Serotonin agonist (Gepirone)

- Gepirone was approved in 2023 for treating depression.
- Gepirone acts as a **serotonin (5-HT1A) receptor partial agonist.**
- Gepirone also targets the glutamate pathway, providing rapid relief of depression symptoms.
- Additionally, common adverse effects from other antidepressants such as weight gain and sexual dysfunction are **not listed** with gepirone.

Serious side effects of gepirone include

1- QT prolongation (increases the risk of a potentially life-threatening cardiac arrhythmia called torsade de pointes),

2- serotonin syndrome (especially in the presence of other serotonergic drugs)

3- activation of mania in people with bipolar disorder.

Mood stabilizers (Lithium)

Lithium carbonate is not sedative, euphoriant or depressant.

Mechanism of action: Exact mechanism is unknown

Pharmacokinetics:

- ❑ It is well absorbed after oral administration.
- ❑ The peak effect after 6-10 days.
- ❑ Slow transport across BBB, cross placenta and excreted in the milk.
- ❑ Excreted in urine, t ½ is 24 h.,
- ❑ No metabolism occurs, it does not bind to plasma proteins.
- ➢ Lithium is a drug with low therapeutic index (so it needs TDM).
- ➢ Loss of Na^+ and water (by diuretics, diarrhea, vomiting) can ↑ lithium Toxicity

Therapeutic uses:

1. Prophylaxis against recurrence of bipolar **manic-depressive illness**.
2. Treatment of **acute mania** (It is usually given with antipsychotic drug for immediate effect, then maintenance therapy is done by lithium alone).
3. Prophylaxis against recurrence of **unipolar endogenous** depression.
4. Help in treatment of **resistant cases of schizophrenia.**

Side effects of lithium:

1. GIT: nausea, vomiting and diarrhea.
2. CNS: tremors (treated by propranolol) chorea, convulsions & confusion.
3. Kidney: nephrogenic diabetes insipidius (treated by amiloride).
4. Thyroid dysfunction: thyroid enlargement (goiter) or hypothyroidism.
5. CVS: hypotension and cardiac arrhythmia.
6. Teratogenicity.

➢ N.B. The ("sick sinus") syndrome is a contraindication for using lithium.

➢N.B. Cardiac anomalies of the fetus (if lithium used in early pregnancy). However, more recent data suggest that lithium carries a relatively low risk of teratogenic effects.

➢**Excreted in milk** causing toxicity to the newborn in the form of lethargy, cyanosis, poor suck, and hepatomegaly.

➢Hemodialysis is highly effective in treatment of lithium overdose because lithium had a small volume of distribution.

Other mood stabilizers

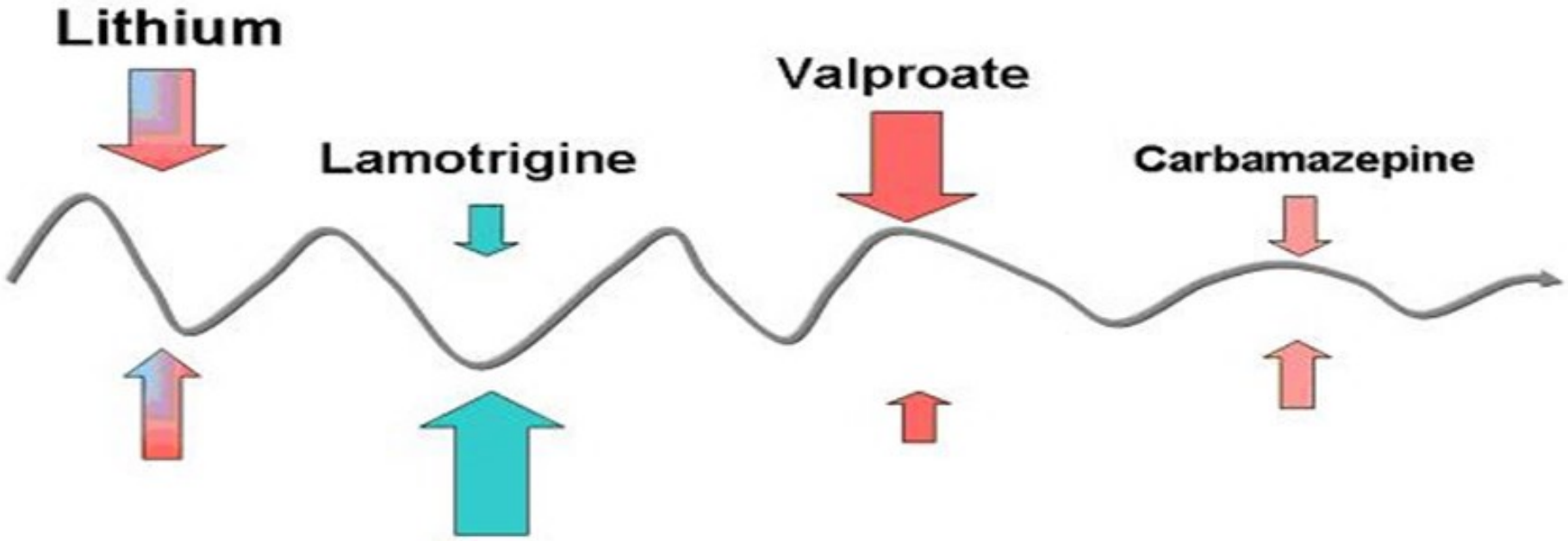
1- Valproic acid: it has broader margin of safety than lithium.

2- Carbamazepine: a mood stabilizer in rapid cyclers (4 or more episodes of mood swings per year), non-responders or intolerant to lithium.

3- Lamotrigine: can be used as a long term maintenance therapy in bipolar disorders.

4- Calcium channel blockers e.g. **verapamil.** It is indicated when patient is non-responsive to any of the mentioned mood stabilizing drugs.

Kinds of stabilizer effect of Mood Stabilizers



The thickness of the arrows indicate the intensity of the effect of each Mood Stabilizer.
Your address whether the therapeutic effects are predominantly exercised by a depressive prevention effect or a manic prevention effect


Thank You