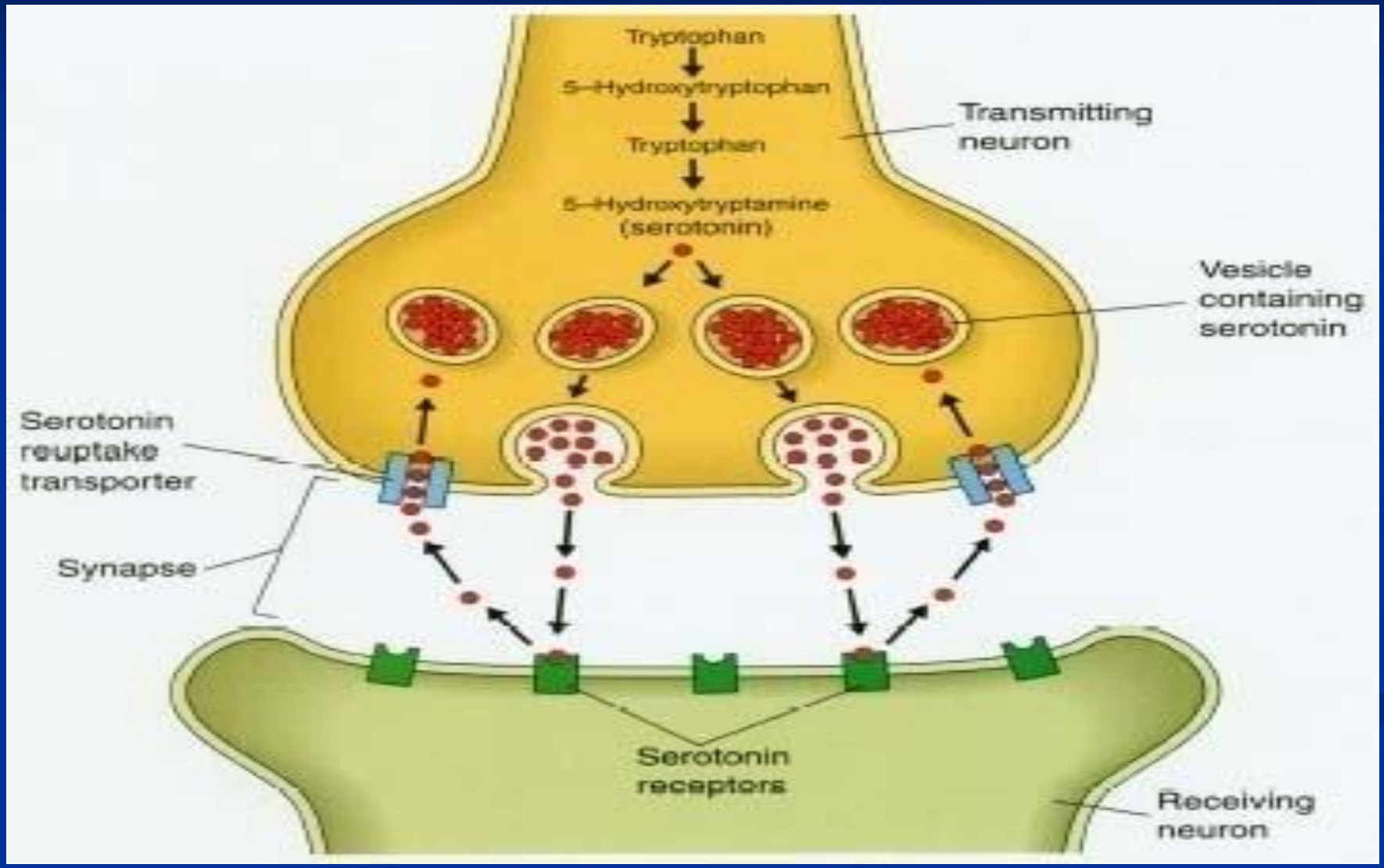
Drugs used in Depression- New groups

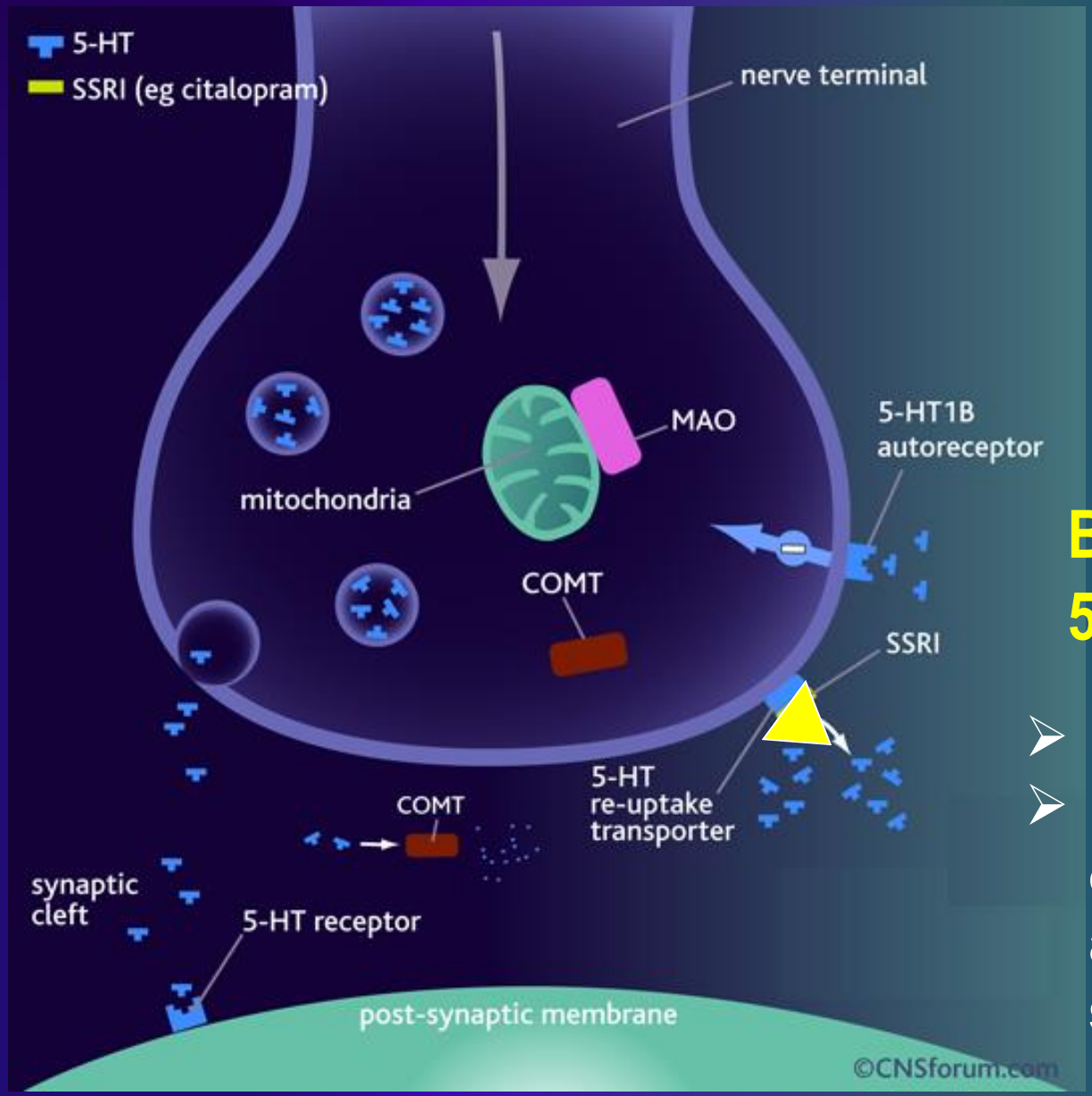
Prof. Yieldez Bassiouni

1. Selective Serotonin Reuptake Inhibitors (SSRIs)

- SSRIs are currently the most widely utilized class of antidepressants in clinical practice.
- They act within the brain to increase the level of serotonin (5-HT) in the synaptic gap by inhibiting its re-uptake.
- SSRIs are described as 'selective' because they affect only the reuptake pumps responsible for serotonin.

Mechanism of Action of SSRIs





Fluoxetine
Fluvoxamine
Citalopram
Escitalopram
Sertraline
Paroxetine

Binds to SERT → ↑ 5-HT levels in synapse

- No effect on NET
- No block to mAch, H, or α_1 Adrenoceptor → so no antimuscarinic nor sedative effects Except Paroxetine

- They are nearly of comparable efficacy but of preferential response in each individual

Advantages of SSRIS

- The Most commonly prescribed antidepressants

- Lacks cardiovascular and anticholinergic side effects compared to TCA

- In contrast to MAOI, they do not cause ‘cheese’ reaction

- Safer (low risk of overdose)

- Acute toxicity is less than that of MAOIs or TCAs

Pharmacokinetics

t1/2 :

➔Too long (3-11 days): Fluoxetine (Prozac)

➔ Moderate length (~24hr): Sertraline, Paroxetine, Citalopram.

Metabolism: P450 then conjugation

- **They are enzyme inhibitors**
- **➔ Weak inhibitors < Sertraline, Citalopram ➔↓ interaction**
- **➔ Strong inhibitors > Fluoxetine, Paroxetine ➔↓ metabolism of TCAs, neuroleptics, some antiarrhythmics, β-blockers.**

- **Fluoxetine** differs from others members of this class in:

  1- It has a longer $t_{1/2}$ (50hrs).

  2- Available ➔ as sustained release preparations

  ➔once weekly.

  3- Metabolite norfluoxetine = potent as parent drug $t_{1/2}$

  10 days.

Adverse effects of SSRIs:

- GIT symptoms: Nausea vomiting & diarrhea.
- Changes in appetite ---weight loss/ gain.
- Sleep disturbances: Drowsiness with Fluvoxamine.
- Anxiety & Tremors.
- **Sexual dysfunction:** Loss of libido , delayed ejaculation.

Discontinuation syndrome:

- Symptoms are headache ,malaise & flu-like symptoms, agitation , irritability & nervousness

Therapeutic Uses of SSRIs

Same as for TCA, in addition effective in the following conditions

- Depression.
- Anxiety Disorder.
- Eating disorders- bulimia nervosa (fluoxetine), Anorexia nervosa.
- Post traumatic stress disorder.
- Premenstrual dysphoric disorder.
- Attention Deficit Hyperkinetic Disorder.
- Treatment of premature ejaculation.

Drug interactions of SSRIs

- **SSRIs are potent inhibitors of liver microsomal enzymes. Therefore they should not be used in combination with TCAs because they can inhibit their metabolism increasing their toxicity.**

- **SSRIs should not be used in combination with MAOIs because of the risk of life-threatening "serotonin syndrome" (tremors, hyperthermia, cardiovascular collapse and death). Both drugs require a "*washout*" period of 6 weeks before the administration of the other.**

2. Noradrenergic and specific Serotonergic Antidepressant s (NaSSA)

Mirtazapine

- α2 receptor antagonist
- Increase NE and 5HT levels
- Blocks 5HT2A, 5HT3 and thus reduces side effects of anxiety, and sexual dysfunction
- Blocking 5HT2C, and H1 receptors cause side effects: sedation, and weight gain.

Mirtazapine

Preferred in cancer patients because:

1. Improves appetite
2- ↓nausea & vomiting (5-HT_3 blocking)
3- ↑ body weight
4- Sedation (potent antihistaminic)
5- Less sexual dysfunction (5-HT_2 blocking)
6- Has no anti-muscarinic effect .

3. Serotonin-2A Antagonist and Reuptake Inhibitors (SARI)

Trazodone, Nefazodone

- **Blocks 5HT uptake selectively but in a less potent manner than tricyclics. This reduces depression.**
- **However, they are powerful 5HT2A antagonists, blockade of 5HT2A receptors stimulates 5HT1A receptors, which may help reduce depression.**
- **5HT2A antagonism also reduces the risk of anxiety, sedation or sexual dysfunction which is normally associated with SSRIs.**
- **Nefazodone: Structurally related to trazodone but has less sedative effect and does not block α- adrenoceptors , however; it likes most SSRI inhibit P450 3A4 isoenzyme.**

4. Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs)

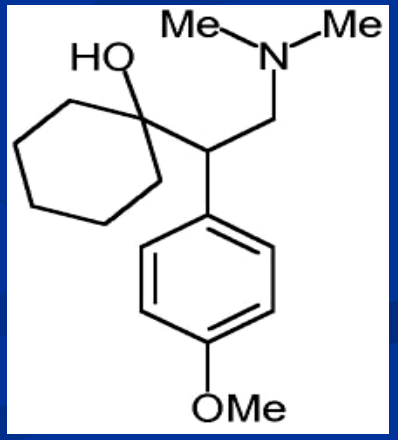
Venlafaxine (Effexor)

- It is used primarily for the treatment of depression, generalized anxiety disorder, and social anxiety disorder in adults. Venlafaxine is the first and most commonly used SNRI.

- Selective 5HT and NE uptake blockers combines the action of SSRI and NRI.

- But without α1, M1 cholinergic or H receptor blocking properties.

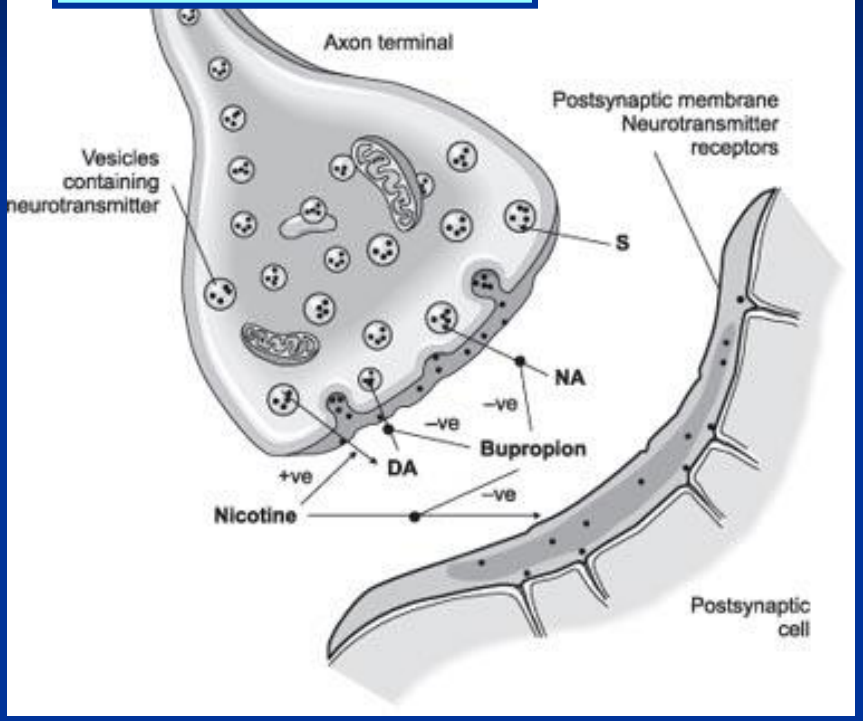
- Desvenlafaxine is a metabolite of Venlafaxine



Venlafaxine

5. Norepinephrine and Dopamine Reuptake Inhibitors (NDRI)

Bupropion



Is unique in possessing significant potency as NE and DA reuptake inhibitor, with no direct action on 5HT.

Therapeutic uses:

1- Treatment of major depression and bipolar depression.

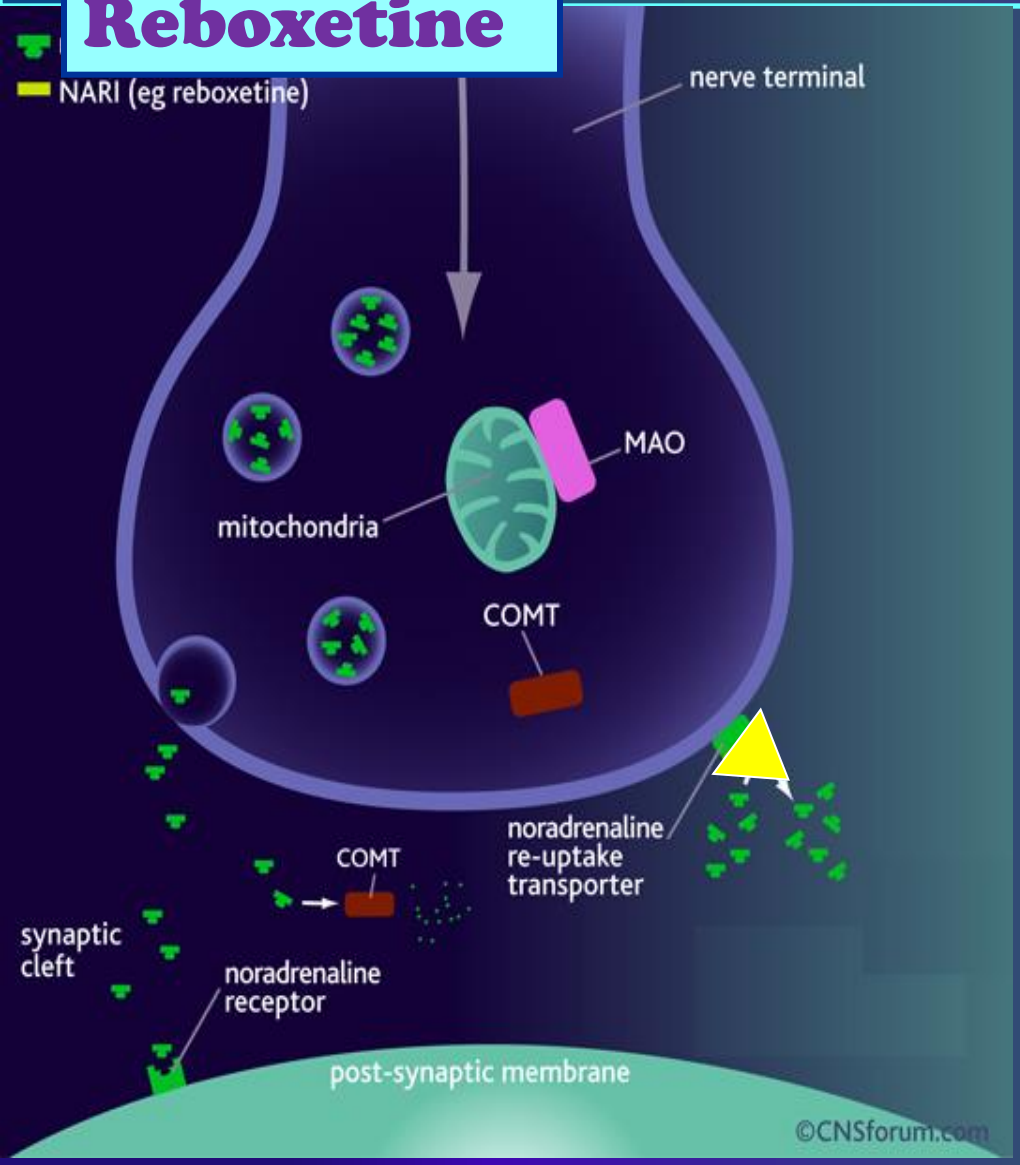
2- Can be used for smoking cessation. As it reduces the severity of nicotine craving & withdrawal symptoms

Advantages: No sexual dysfunction ➔given in young
No weight gain [No 5HT effect]
No orthostatic hypotension.

Side effects: Seizures; it ↓ threshold of neuronal firing

6. NE Selective Reuptake Inhibitors (NRIs)

Reboxetine



Block only NET

No affinity for 5HT, DA, ADR, H, mAch receptors

So, has positive effects on the concentration and motivation in particular.

Safe to combine with SSRIs

Minimal side effects only related to activation of ADR system as tremor, tachycardia, and urinary hesitancy

Side effects of atypical antidepressants

Drug	Toxicity	Sedation	Hypotension	Anticholinergic effects
Mirtazepine	-	++	-	+
Nefazodone	-	+	+	-
Trazodone	+	+++	+++	-
Venlafaxine	+	++	-	+

Clinical uses of Antidepressant Drugs.

A. Endogenous Depression (SSRIs (first Choice) New generation and Tricyclics can be used

B. Panic Disorders (Imipramine or SSRIs)

C. Obsessive Compulsive Disorders (SSRIs and Clomipramine) & Chronic pain (**Amitriptyline**)

D. Anorexia nervosa and Bulemia (SSRIs)

E. Schizo-Afective Disorders (Amoxapine or SSRI + Haloperidol)

F. Premature ejaculation (SSRI)

Clinical Uses of Antidepressants (Continue…)

G. Anxiety disorders (**Amitriptyline**)

H. Migraine and Anxiety & IBS (**Amitriptyline**)

I. Nocturnal Enuresis in children e.g. Imipramine

K. Neuropathic Pain (Dual NE and 5-HT reuptake Blockers)

Thank You