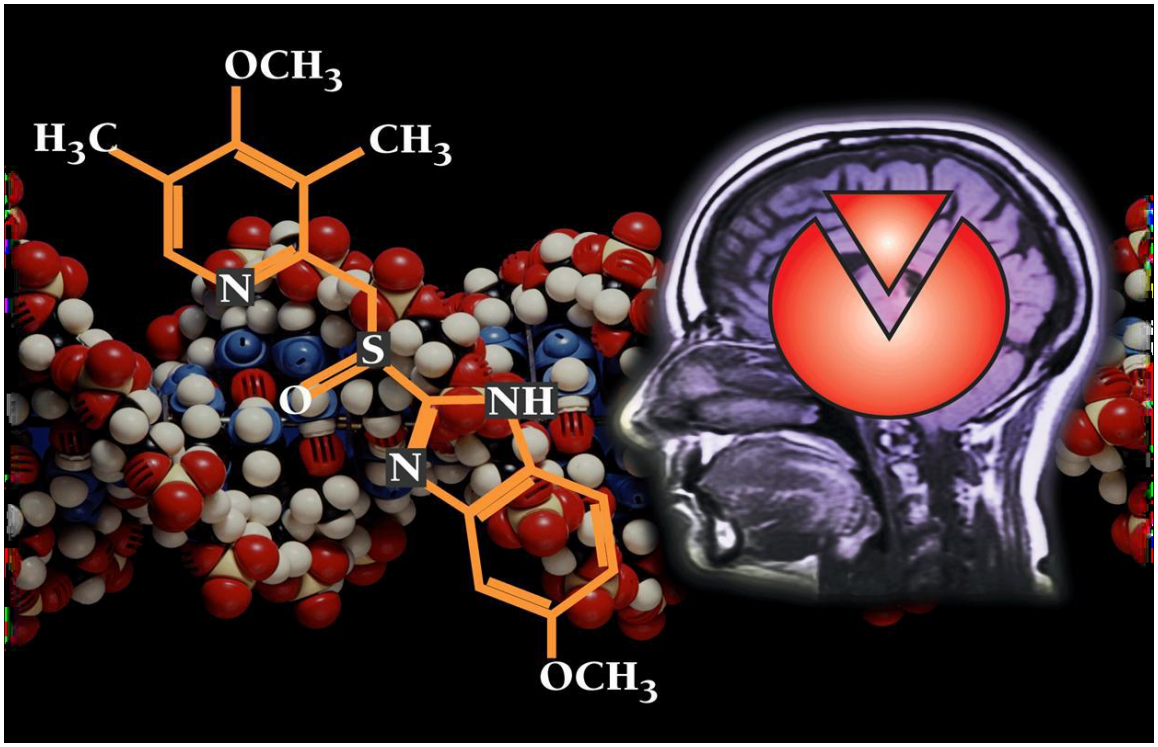
King Saud University
College Of Medicine
Pharmacology Team 430
CNS Block

New Antidepressants



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New antidepressant drugs:

- **Selective Serotonin Reuptake Inhibitors SSRIs**
  -Fluoxetine
  -Fluvoxamine
  -Citalopram
  - Sertraline
  -Paroxetine

- **Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) (it's derivatives of TCA)**
  -Venalafaxine

- **Norepinephrine Reuptake Inhibitors (NRIs)**
  -Reboxetine

- **Noradrenergic & Specific Serotonergic Antidepressants (NaSSAs)**
  -Mirtazapine

- **Norepinephrine Dopamine Reuptake Inhibitors (NDRIs)**
  -Bupropion

- **Serotonin Antagonists & Reuptake Inhibitors (SARIs)(DEREVITIVES OF TCI DRUGS)**
  -Trazodone
  -Nefazodone

1)Selective Serotonin Reuptake Inhibitors SSRIs

- ✓ **Fluoxetine**
- ✓ **Fluvoxamine**
- ✓ **Citalopram Sertraline**
- ✓ **Paroxetine**

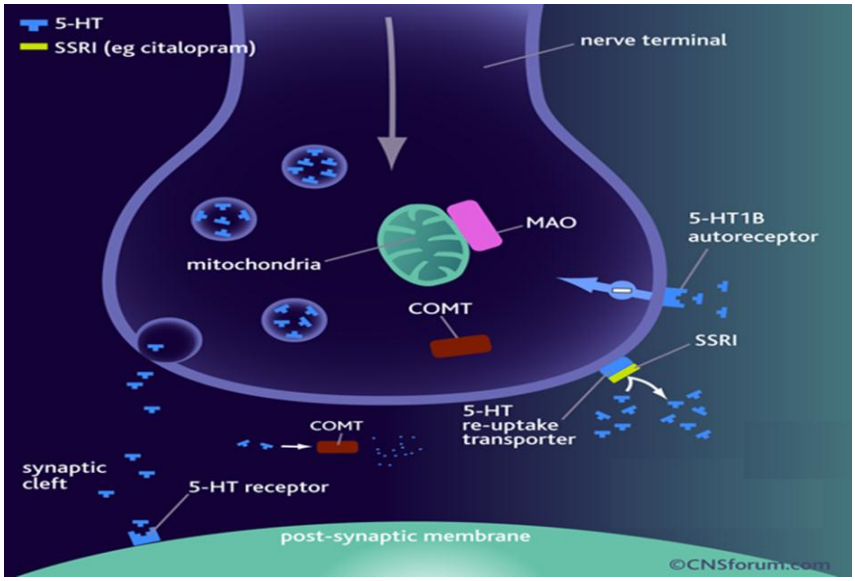
MOA:

Binds to SERT ➔ ↑ 5-HT levels in synapse (no other effect)

No effect on NET

No block to mAch, H, or a_1 Adrenoceptor ➔ so no antimuscarinic nor sedative effect (it has low side effects)

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



Pharmacokinetics :

- **$t_{1/2}$:**

  ➔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 TCA, neuroleptic, some antiarrhythmic, β-blockers.

- **Primarily excreted through kidney;** not paroxetine & sertraline → undergo partially fecal excretion.

- 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.

Clinical Indications:

* First choice for most depression. Comparable efficacy as TCAs but much safer < sedation & antimuscarinic side effects< toxicity in over doses

* Fluoxetine is approved in (all ages) children, adolescence, elderly males with prostatic hypertrophy & relatively safe in pregnancy.

Used in:

- Anxiety and panic disorders
- Obsessive-compulsive disorders
- Some eating disorders (bulimia)
- Pain associated with diabetic neuropathy
- Premature ejaculation (because of the impotence(delayed ejaculation effect of drug) effect of the drug)
- Premenstrual syndrome. (it controls affective responses to pain and stress associated with the menstrual period)
- Alcohol abuse. (it was noticed that this drug has good effect in reducing the psychological effect _craving _that occur in the addicted pt after stoppage alcohol)
- **Anorexia nervosa**.(it's severe depression causes loss of appetite –it differs from bulimia)
- **Generalized anxiety disorder** (GAD).

Bulimia nervosa is an eating disorder characterized by binge eating consuming a large amount of food in a short amount of time, followed by an attempt to rid oneself of the food consumed(forced vomiting)

ADR:

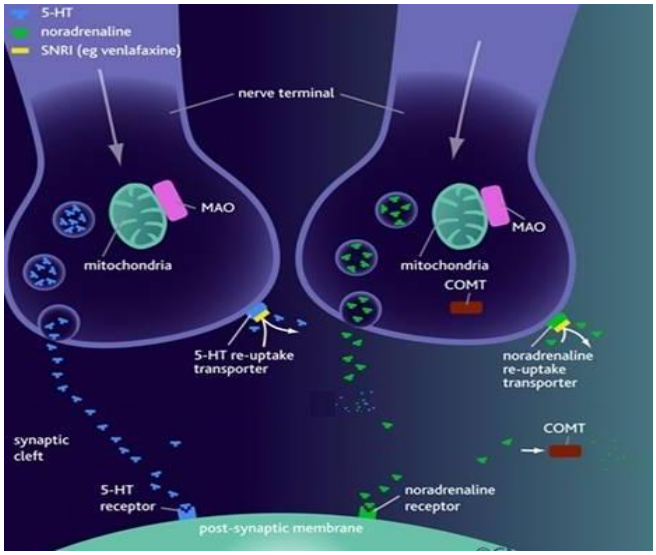
- Insomnia, anxiety, agitation, nervousness > fluoxetine > citalopram
  - ✓ useful in fatigued patients and it's better to give it the pt in the morning
- Sedation & lassitude > paroxetine, sertraline
  - ✓ Useful in patients with difficult sleep .
- GIT upset (nausea, vomiting, diarrhea) (indirect stimulation of 5-HT_3 receptors in the enteric nervous system)
- Anorexia & weight loss
- Impotence & sexual dysfunction; loss libido, delayed ejaculation (Indirect CNS stimulation of 5-HT_2)
  - ✓ Useful in patients who have premature ejaculation.
- Mild CV & minimal antimuscarinc side effects unlike TCAs
- Withdrawal manifestation < intensity than TCAs

INTERACTIONS:

- Serotonin Syndrome ➔if combined with MAOIs > other ADDs : [Autonomic instability (changes in BP, pulse, hyperthermia), muscle rigidity, respiratory depression, mental confusion, shivering, sweating and diarrhea]
- Enzyme inhibitors (fluoxtine & paroxetine)➔↓ metabolism = ↑ toxicity of TCA, neuroleptic, some antiarrhythmic, β-blockers.

2-Serotonin Norepinephrine Reuptake Inhibitors [SNRIs]

Venalafaxine



MOA:

Restore the levels of NE & 5HT in the synaptic cleft by binding to NET & SERT Has mild antimuscarinic effect (no antiadrenergic and antihistamine effect)

Pharmacokinetics :

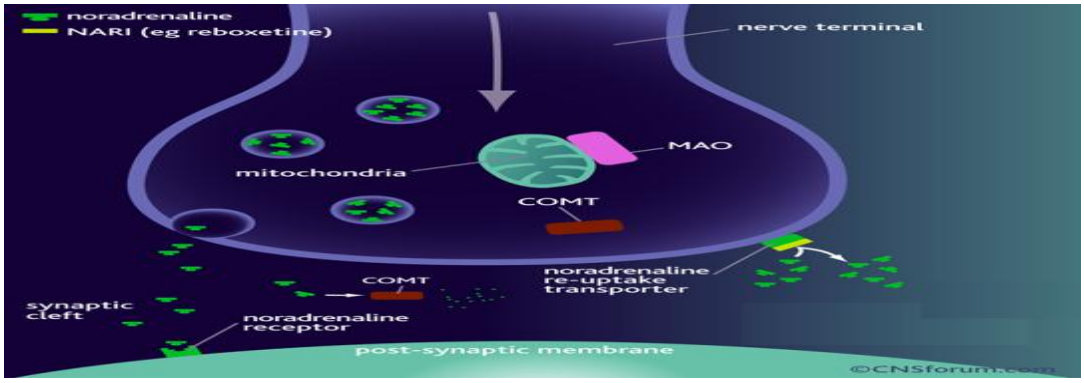
Short $t_{1/2}$ ➔↑HR & BP

Side effects :

similar to SSRI drugs but may be accompanied with withdrawal manifestations on discontinuation ➔ may need dosage tapering

3-Norepinephrine Reuptake Inhibitors [NRIs]

Reboxetine



MOA:

- Block only NET
- No affinity for 5HT, DA, ADR, H, mAch receptors
- So, has positive effects on the concentration and motivation in particular.

Pharmacokinetics:

Safe to combine with SSRIs

Side effects:

Minimal side effects only related to activation of ADR system as tremor, tachycardia, and urinary hesitancy (when NE level is high)

5HT1:

Inhibit the depression when is stimulated

5HT3:

Nausea +vomiting when stimulated

: 5HT2

Sexual dysfunction +loss of appetite when is stimulated

4-Noradrenergic & Specific Serotonergic Antidepressants[NaSSAs]

Mirtazapine

MOA: Blocks presynaptically :

1- a_2 adrenoceptors (it's autoregulatory receptor ,it inhibit the NE when it's reach certain level so when we inhibit it there will be an increase NE level)

2- **$5HT_3$ > $5HT_2$** receptors (just : 5HT1 is stimulated)

Preferred in cancer patients because:

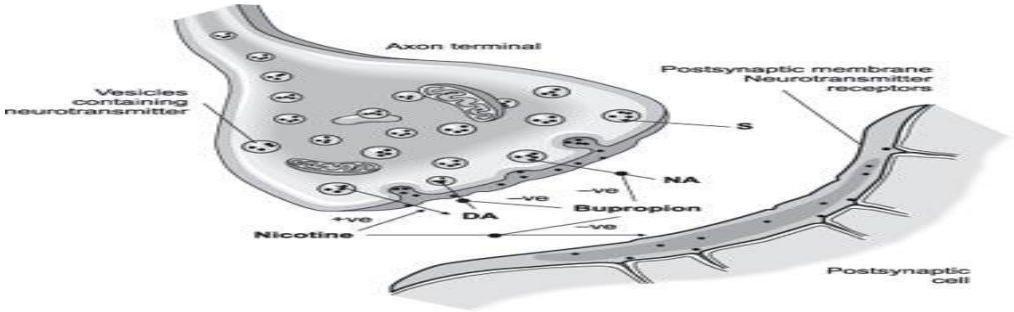
1. Improves appetite
2. ↓nausea & vomiting (5-HT_3 blocking)
3. ↑ body weight (↑appetite because of 5HT2 Blocking)
4. Sedation (potent antihistaminic)
5. Less sexual dysfunction (5-HT_2 blocking)
6. Has no anti-muscarinic effect .

Side effects:

Drowsiness, ↑appetite, and weight gain

5-Norepinephrine Dopamine Reuptake Inhibitors (NDRIs)

Bupropion



MOA:

- Is unique in possessing significant potency as NE and DA reuptake inhibitor, with no direct action on 5HT.
- Acts as a nAch antagonist (it's differs from peripheral ACH)

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:given in young because:

- No sexual dysfunction
- No weight gain [No 5HT effect]
- No orthostatic hypotension.

Side effects: Seizures; it ↓ threshold of neuronal firing (because of the release of nACh)

6-Serotonin Antagonists & Reuptake Inhibitors (SARIs)_Atypical TCI DRUGS_

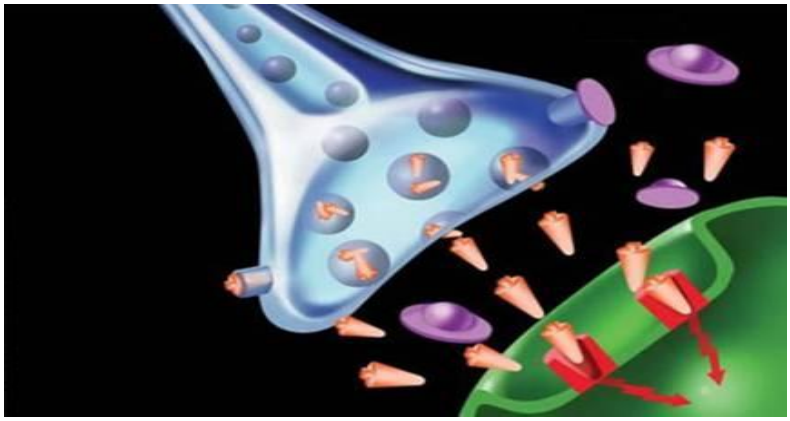
Trazodone	Nafazodone
Psychotropic drug (change behavior or perception.)	Trazodone is its precursor
Weak block of SERT > NET	Weak block of SERT > NET
Block 5-HT_2 (no sexual dysfunction or weight loss)	Block 5-HT2 (no sexual dysfunction or wight loss)
α- blocking effect (hypotension)	NO
Potent H_1- blocker(sedation)	NO
High protein bound	
Extensive hepatic metabolism	Inhibit Cyt450 (more interaction than trazodone)
Urine excretion	Urine excretion
Cause priapism (a antagonisim)	**Hepatic failure**
Arrythmogenic	NO A ANTAGONIST EFEECT

Note:

Priapism: It's occur in using TRAZODONE➔ Sustained eructation because of massive vasodilatation and congestion of the capillary (alpha antagonist effect) so we use it with awareness in male

Augmenter drugs:

Some antidepressants work better in some patients when used in combination with another drug.



This "augmenter" drugs include:

- Buspirone
- Antipsychotics; *typical or atypical*
- Lithium; is used to augment ADDs (antidepressant drugs) in resistant unipolar depression (manic state)

Trazadone, Nafazodone, Bupropion are sometimes included among augmenters but there use as such should be under strict clinical supervision (used in low dosage)

-Clinical uses of Antidepressant Drugs.

A. Endogenous Depression **(SSRIs (first Choice) New generation or Tricyclics.**

B. Panic Disorders **(Imipramine or SSRIs)**

C. Obsessive Compulsive Disorders (**SSRIs and Clomipramine**)

& Chronic pain, and (**Amitriptyline**)

D. Anorexia nervosa and Bulemia **(SSRIs)**

F. Premature ejaculation **(SSRI)**

G. Anxiety disorders

H. Migraine and Anxiety & IBS (irritable bowel syndrome).(**Amitriptyline**)

I. Nocturnal Enuresis in children e.g. **Imipramine**