Pharmacology Team 431

(CNS BLOCK)

Antidepressants NEW Group

Done by :

Alaa Al-anizy
Faisal Rashed
Ahmed Al Sanea

Mohammed Al Jibree

Selective Serotonin Reuptake Inhibitors SSRIs

Fluoxetine, Fluvoxamine, Citalopram, Sertraline, Paroxetine, Escitalopram

Mechanism	Pharmacokinetics	Clinical Indications	ADRs	Interactions
• Binds to SERT ➔ ↑ 5-HT levels in synapse • No effect on NET No block to mAch, H, or a_1 Adrenoceptor ➔ so no antimuscarinic nor sedative effects • They are nearly of comparable efficacy but of preferential response in each individual	$t_{1/2}$: ➔ 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.	• First choice for most depression. Comparable efficacy as TCAs but much safer < sedation & antimuscarinic side effects < toxicity in over doses • Fluoxetine is approved in 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 Premenstrual syndrome. Alcohol abuse. Anorexia nervosa. Generalized anxiety disorder (GAD).	Insomnia, anxiety, agitation, nervousness > fluoxetine > citalopram ➔ useful in fatigued patients Sedation & lassitude > paroxetine, sertraline ➔ useful in patients with difficult sleep (IMPORTANT). GIT upset (nausea, vomiting, diarrhea) (indirect stimulation of 5-HT3 receptors in the enteric nervous system) Anorexia & weight loss Impotence & sexual dysfunction; loss libido, delayed ejaculation (Indirect CNS stimulation of 5-HT2) ➔ useful in patients who have premature ejaculation. Mild CV & minimal antimuscarinc side effects unlike TCAs Withdrawal manifestation < intensity than TCAs	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 ➔ ↓ metabolism = ↑ toxicity of TCA, neuroleptic, some antiarrhythmic, β-blockers.

Once upon a time ,there is **a SSRI** company for helping depressive PPL , The company was hiring 5 employees, **Fluoxe ,Fluvox ,Citalo, Sertra ,Parox**.

Fluoxe and Parox have STRONG personality, so they haven't worked together. They worked as leaders to other WEAK employees. **Fluoxe** loves working with the WEAK **Citalo** to help Fatigued Lazy Pt , **Parox** loves working with WEAK **Sertra** to help pt with difficult Sleep. **Fluvox** doesn't have an obvious job. He assists other friends when it is necessary. The boss of the company noticed that **Fluoxe** is the best to help children and elderly males and pregnancy, but he had a LONG TIME to do his work.

Break time to link your information

Reuptake Inhibitors & Mixed Action Novel ADDs

Groups of Drug	Info
Serotonin Norepinephrine Reuptake Inhibitors [SNRIs] **Venalafaxine** Doesn't use it with patients suffer from hypertension.	**Restore the levels of NE & 5HT in the synaptic cleft by binding to NET & SERT Has mild antimuscarinic effect** **Short $t_{1/2}$ → ↑ HR & BP** **Side effects similar to SSRI drugs but may be withdrawal manifestations on discontinuation → may need dosage tapering**
Norepinephrine Reuptake Inhibitors [NRIs] **Reboxetine** Doesn't have any serotonin effect.	**Block only NET No affinity for 5HT, DA, ADR, H, mAch receptors** **So, has a positive effect on the concentration and motivation in particular.** **Safe to combine with SSRIs. (IMPORTANT!)** **Minimal side effects only related to activation of ADR system as tremor, tachycardia, and urinary hesitancy.**
Noradrenergic & Specific Serotonergic Antidepressants [NaSSAs] **Mirtazapine** Use it to treat the depression of cancer patients in terminal end of life. + Prevent some side effect of cancer therapies	**Blocks presynaptic a_2 adrenoceptors (work in the receptors)** **+ $5HT_3$ > $5HT_2$ receptors** ***Preferred in cancer patients (IMPORTANT!) 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 .** ***Side effects;*** **drowsiness, ↑ appetite, and weight gain.**

<table>
<tr><th>Groups of Drug</th><th colspan="2">Info</th></tr>
<tr><td>Norepinephrine Dopamine Reuptake Inhibitors (NDRIs)
Bupropion

Use it with young patients because they don’t cause obesity nor sexual dysfunction.</td><td colspan="2">Is unique in possessing significant potency as NE and DA reuptake inhibitor, with no direct action on 5HT. Acts as a nAch antagonist
Therapeutic uses:
1- Treatment of major depression and bipolar depression.
2- Can be used for smoking cessation. (IMPORTANT!)
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</td></tr>
<tr><td rowspan="5">Serotonin Antagonists & Reuptake Inhibitors (SARIs)</td><td>Trazodone</td><td>Nafazodone</td></tr>
<tr><td>Psychtropic drug
Weak block of SERT > NET
Block 5-HT$_2$</td><td>Trazodone is its precursor</td></tr>
<tr><td>α- blocking effect (hypotension)
Potent H$_1$- blocker(sedation)</td><td>No α- blocking effect
No Potent H$_1$- blocker</td></tr>
<tr><td>High protein bound
Extensive hepatic metab
Urine excretion</td><td>Inhibit Cyt450</td></tr>
<tr><td>Cause priapism (a antagonisim)
Arrythmogenic
labelling]</td><td>Hepatic failure [Black box labelling]</td></tr>
</table>

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 in resistant unipolar depression**
- ***Trazadone, Nafazodone, Bupropion are sometimes included among augmenters but there use as such should be under strict clinical supervision***

Dr Omnia said Don't memorize them

Summary :

1- Antidepressants when block other postsynaptic receptors can confer side effects. Such receptors include mainly histaminergic [H_1], muscarinic, [a_1]-adrenergic.

- Histaminergic antagonism has been associated with sedation and drowsiness. Can contribute to increased appetite & weight gain.
- Muscarinic-receptor antagonism is responsible for gastrointestinal disturbances; constipation, dry mouth, tachycardia, blurred vision, urine retention
- Block of the [a_1]-adrenergic receptor may be responsible for dizziness and orthostatic hypotension

---

2- Antidepressants increase variably the availability of 5HT & NE at synapes

- Increased NE transmission → tremors, insomnia.
- Increased 5HT transmission → sedation, and a decrease in sexual drive.

3- Antidepressants & sexual dysfunction?
Through acting on $5HT_2$ → sexual dysfunction (loss of sexual desire and impaired sexual response (ejaculatory delay, erectile dysfunction, anorgasmia)
ADDs with $5HT_2$ blocking action as mirtazipine, has minimal action on sexual dysfunction.
With > NE than 5HT as Bupropion , have minimal sexual side effects
Trazodone, nafazodone, With dual action are better than SSRIs with respect to sexual side effects

---

4- Antidepressants & Sedation

- Sedating ADDs are; Amitryptyline, Paroxiteine, Sertraline, Mirtazapine, Trazadone, So better given near bed time
- Less Sedating ADDs are; Bupropion, Venalafoxine , MOAIs, So can be given in the morning as some cause insomnia as side effect.

5- Antidepressants and appetite???
DA is responsible for eating. 5HT action on $5HT_2$ halts dopamine release so suppress appetite.
Depression is accompanied more by weight loss.
SSRIs by ↑ 5HT availability to act on $5HT_2$ → could suppress appetite. At least no weight gain with SSRIs.

Most TCAs have dual reuptake inhibition + sedation + antihistaminic effects ➔ ↑ weight gain
Mirtazepine blocks $5HT_2$ ➔ so cannot shut off dopamine signals ➔ ↑ weight gain
N.B. Antidepressants isn't always a direct cause to cause alteration in weight. Other contributing factors to weight gain during antidepressant therapy are for example: ↑ day time sleep, ↑ craving for food when mood alleviates,

Nausa & Vomiting by SSRIs ➔ ↑ 5HT availability ➔ act on 5HT3 ➔ nausea & vomiting

---

6- Antidepressants safe combinations;

- Bupropion + Desipramine
- SSRIs + Mertazepine, Reboxetine or any other NRIs / SNRIs/
- Antidepressant approved for use in children; fluoxetine
- Antidepressants good for elderly are SSRIs because they can be used at lower dosage giving least side effects in this age group
- SSRIs use is more than TCAs because they are better tolerated by patients
- Antidepressants dangerous combinations;
  - ➔ MAO Is + SSRIs ➔ Serotonin syndrome
  - ➔ Paroxetine / Fluoxetine / Nefazodone / + Desipramine, Nortryptiline ➔ severe sedation or > toxicity

---

7- Others:

Enuresis ➔ Imipramine
Chronic pain ➔ TCAs (Tertiary better than 2ndry amines) ➔ Duloxetine(SSRIs not effective)
Bulimia ➔ Fluoxetine
Obsessive convulsive disorder ➔SSRIs
Cancer associated depression ➔ Mirtazapine
Depression in Adolescence and young adults ➔Bupropion
Depressive phase of bipolar add? Lamotrigine (anticonvulsant) or lithium

Questions:

1) Which ONE of the following antidepressant Drug can be given in depressed patient having difficulty to sleep?
   a) Fluoxetine
   b) Fluvoxamine
   c) Citalopram
   d) Paroxetine

2) 73-year old Depressed Cachectic suffering from end-stage of cancer, which ONE of the following antidepressants can be prescribed in his condition?
   a) Fluoxetine
   b) Paroxetine
   c) Imipramine
   d) Mirtazapine

3) Which of the Following SSRIs has the longest half-life?
   a) Fluoxetine
   b) Fluvoxamine
   c) Citalopram
   d) Paroxetine

4) A 27 year old married male smoker suffers from major depression disorder, he also wants to quit smoking, Which ONE of the following Anti-depressants is the best for his case:
   a) Fluoxetine
   b) Buspirone
   c) Bupropion
   d) Amitriptyline

ANSWERS: D – D – A – C