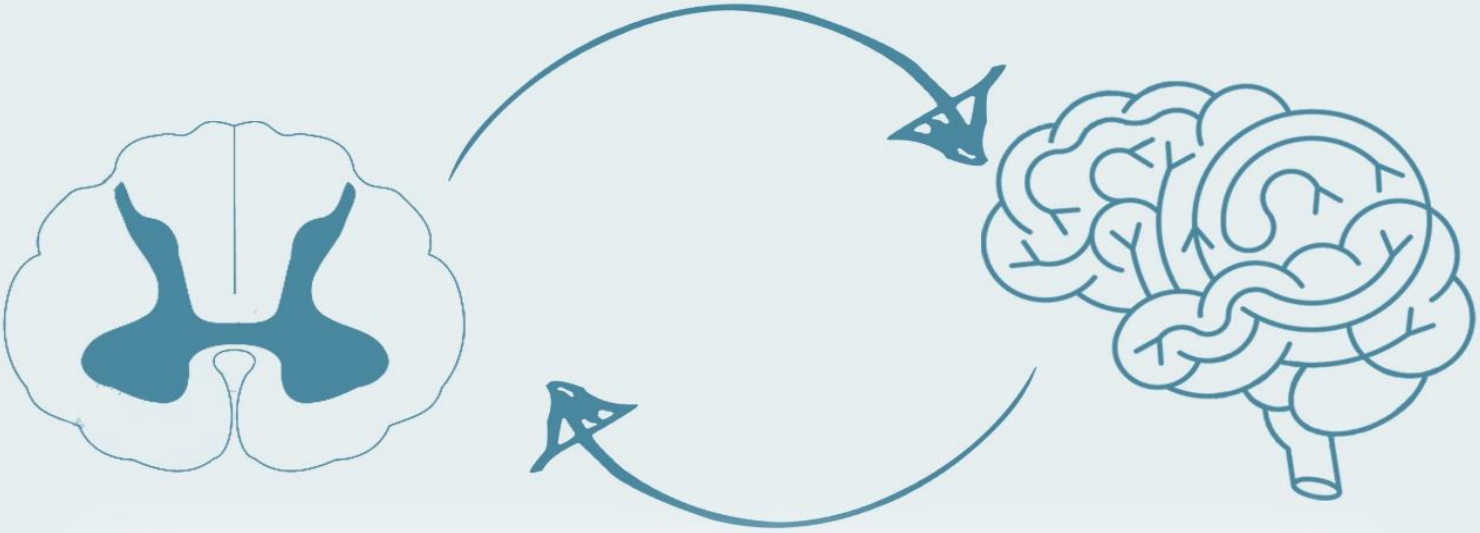


CNS

Anatomy

slides | sheets

number	10
Done by	Jumana Jihad
Correction	Dr. Munir
Doctor	Munir Gharaibeh

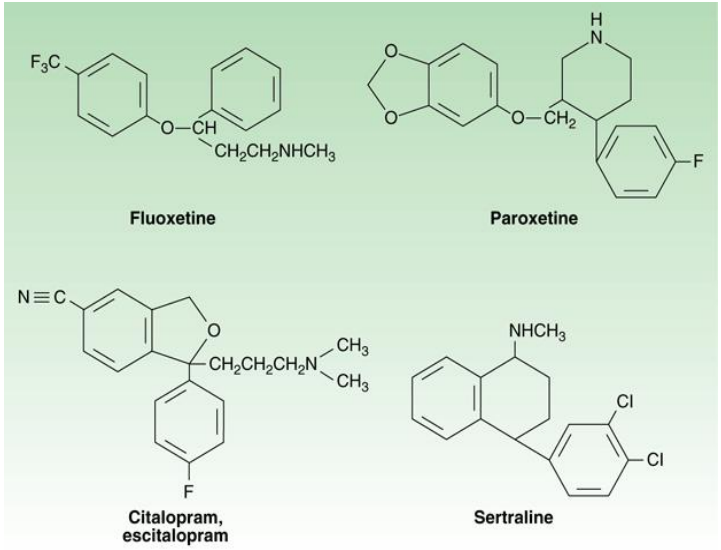
Today we will continue talking about **Antidepressant**
Starting with **Selective Serotonin Reuptake Inhibitors "SSR →came much later to the tricyclic maybe after 30 years of using tricyclic amines , which caused** serious side effects and delayed therapeutic activity.
The side effects appear much Sonner than the therapeutic action and the patient must wait at least 3 to 4 weeks, so it is hard to convince the patient and his family to continue taking the drug and stick to it.

Tachycardia, Blurring of vision, confusion, constipation, dry mouth, urinary retention, etc. all are Side Effects and Toxic Reactions of TCA.

Back to SSRI:
They are relatively safe drugs, they do not have sedative, anticholinergic or cardiovascular side effects like the tricyclic drugs.

Can cause stimulation rather than sedation, Nausea, Vomiting, and Diarrhea, (all could be "tolerable or acceptable" side effects)
But they can cause sexual dysfunction which is an unacceptable side effect especially in younger patients.

Some of the SSRI and their structures :
-Fluoxetine
-Paroxetine
-Sertraline



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 12th edition*: www.accessmedicine.com

Mechanism of action:
They inhibit the reuptake of serotonin →this will lead to the accumulation of serotonin

→consequently this will cause dawn regulation of the receptors (Desensitization**).**

Desensitization→ 5HT1A receptors leading to increased firing rate of serotonergic neurons)
While downregulation of 5HT1B receptors leads to increased 5HT release.
Consequently, the net result is enhancement of 5HT neurotransmission.

1- Fluoxetine:

-Prozace the trade name
-The first SSRI
-Greatly dropped the rates of suicidal attempts.
-The only problem with this drug is→ it Inhibits P450 enzymes. So, it will inhibit the metabolism of many drugs leading to increased levels of these drugs.

2-Paroxetine:

Increases weight, so should not be used in obese people, and it have more sedating effect

3-Sertraline.

4-Citalopram:

-Least effect on P450 enzymes so it is prescribed for patients taking other drugs metabolized by this enzyme

Monoamine Oxidase Inhibitors:

They inhibit the action of monoamine oxidase enzyme which breaks down monoamines like norepinephrine and you know that low levels of NE is associated with depression.

-They are old fashioned drugs
-Very effective
-Very toxic drugs

-Mostly cause CNS stimulation and hypertension
But why we will have hypertension????
Hypertension is due to dietary interactions → foods and beverages contain tyramine.
This compound has an effect on blood pressure and is regulated by the MAO enzyme
MAOIs work to restrict this enzyme, which can result in a reduction in symptoms of depression and anxiety.

However, when the MAO enzyme is inhibited (such as when taking a MAOI), tyramine can reach dangerously high levels. This can result in critically high blood pressure because tyramine will be converted to Noradrenaline. While taking a MAOI, it will be necessary to avoid foods and beverages high in tyramine to prevent potentially fatal blood pressure spikes like(cheese and nuts)

Drugs in this group:

1-Phenelzine

2-Isocarboxamide.

3-Tranycypromine:

Increases weight, so it is given to children to increase their weight. This is a side effect in adults and it's useful in children
Also, it has antihistamine activity.

4-Selegiline: No liver toxicity or dietary-induced hypertension.

MAOI drugs and tricyclics are only prescribed by psychiatrists and when it is strongly indicated, while with the SSRI the idea changed, and they can be freely prescribed by general practitioners very comfortably because they are very safe drugs.

Miscellaneous Agents

1-Venlafaxine:

-"Effexor".

-Decreases the reuptake of both 5HT& NE. And it Elevates BP.

2-Bupropion:

-Weak reuptake inhibitor.

-No impotence.

3-Mitrazepine:

Inhibits α2 receptors leading to enhancement of both NE and 5HT transmission but do not have an activity on MAO.

Electroconvulsive Therapy (ECT):

Highly indicated when depression is associated with suicidal attempt or thoughts.

Suicidal attempts are 2 types:

In depression the patients really want to kill themselves and they feel helpless and want to get rid of life.

In other people with anxiety state, they attempt suicide → seeks to draw attention.

It's very wrong to leave a patient with depression untreated.

Lithium Carbonate:

-Drug of choice for acute mania and bipolar depression.

-No actions in normal people.

Mania is associated with increased alertness, excitement, anxiety, and aggressiveness.

-**so we use it to Block manic behavior in combination with phenothiazines and anxiolytics**.

Mania is also associated with increased levels of NE so this drug Inhibits release and increases reuptake of NE, and does not interfere with 5HT

Remember: depression is associated with low levels of 5HT

-Competes with Mg on G-proteins.

-High Na lowers Li and vice versa. So the use of diuretics will lower Na and cause hyponatremia → leading to increased activity of Lithium carbonate

Toxic drugs we talked about:
1-Tricyclic
2- **Lithium Carbonate** → has a TI = 2-3, so should be monitored and you should not increase the dose what so ever.

Lithium carbonate has:
1-Mild toxicity:
2- **Severe toxicity:**
Impaired consciousness, confusion, rigidity, increased reflexes, tremor, seizures, coma and death.
3-Chronic toxicity:
Hypothyroidism (5%).
DI (diabetes mulitas).
Leukocytosis.
Renal toxicity**.**

Other Drugs:

-Lamotrigine, Carbamazepine and Valproic acid: have an antiepileptic effect but also used for maintenance and prophylaxis of bipolar affective disorders.
-Clonazepam and Lorazepam For acute mania.

More about the effect of some antidepressant drug on CYP450:
This system of enzymes participates in the degradation of many usable drugs.

And we have different isoforms for this enzyme,3A4 is the most common which metabolizes many clinically used drugs.

Antipsychotic Drugs

Mechanism of action:

A common mechanism to all antipsychotic drugs is dopamine receptor antagonism

-The therapeutic effects are mainly due to D2 antagonism.

- They have Different Potencies but the same efficacy

- Different Activities & Toxicities where many of these drugs also work to antagonize other receptors like $5HT_{2A}$

Different Responses of Patients→ some patients do not respond to some drugs so the doctor shifts from one drug to another.

- Each may have special benefits for selected patients

In some patients they can cause increase in the weight

And in others it will cause great sedative effect→ in these cases we must change the drug if the patient complains about these side effects.

- Older drugs have lower cost and can be given by depot IM injections.

One of them is chlorpromazine which is the prototype of this group

We classify these drugs into:

1- **Typical or Older Antipsychotic Drugs**:
   They work mainly on D2 (pure D2 antagonist)
   Lowe potency: Chlorpromazine
   High potency: Haloperidol

2- **Atypical or New Antipsychotic Drugs**
   Divided into:
   -Pure D2 and 5HT → Risperidone
   -Multireceptor antagonist (they block D4 in addition to D2 and 5HT)

Typical or Old Antipsychotic Drugs

- Chlorpromazine.
- Phlophenazine.
- Thiothixine.
- Haloperidol.

– These have high occupancy of D2 receptors, but inhibit 5HT2A receptors to a much lesser extent

– They also can inhibit α, muscarinic, and histamine receptors so they are non-selective and they have antihistaminic activity so we can use them as pre-anesthetic medications, and in the treatment of motion sickness.

Also, they have a role in reducing blood pressure so they were used as antihypertensive drugs in emergency situations.

All of this will contribute to their wide spread of side effects.

– This means increased antipsychotic activity is associated with high toxicity.

Atypical or New Antipsychotic Drugs:

These inhibit both D2 and 5HT with lower occupancy of D2 receptors

Note: 5HT has no relation to psychosis but it inhibits dopamine release at various sites.

So, these drugs will increase dopamine release in the nigrostriatal, mesocortical, and hypothalamic pathways, but not in the mesolimbic pathway→ which is the pathway involved in the pathogenesis of psychosis.

– This means increased antipsychotic activity and reduced extrapyramidal toxicity.

-**D2/5HT$_{A2}$ ratio** is a very important ratio in classifying the drug into typical or atypical
The typical have a high ratio → they are toxic
The atypical have low ratio→ very low extrapyramidal toxicity.

In general, these drugs are:

1. Incompletely absorbed because they have anticholinergic activity which decreases the motility → decrease absorption
2. Subjected to **first - pass metabolism,** so not all the dose will reach the systemic circulation.
3. High lipid soluble, so can cross the BBB.
4. Highly bound to proteins which causes drug-drug interaction.
5. Metabolized by oxidative by microsomal metabolism &Conjugation.
6. T½ 10 - 24h. But, have much longer clinical duration than would be estimated from their plasma half- lives.

The pharmacological actions:

Actions differ in psychotic patients compared to normal people:

In Psychotic Patients:

They will reduce psychotic signs and symptoms (reduce hallucinations, delusions…)
However these drugs will cause profound sedation (sedate a very aggressive patients), sleepiness and alleviation of psychosis, **together with improvement in performance.**

In Normal People:

Unpleasant subjective effects, sedation, restlessness, and autonomic effects create bad experiences, unlike those of sedatives and hypnotics. So will not result in addiction problems because they produce side effects.

They affect the EEG.

GOOD LUCK

إذا غامَرْتَ في شَرَفٍ مَرُومِ فَلا تَقنَعْ بما دونَ النّجومِ