YU - MEDICINE
PASSION ACADEMIC TEAM

Central Nervous System

Sheet# 2 - Pharmacology

Lec. Title : Antidepressants

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Antidepressants

CNS 1 Module 3rd Year MD

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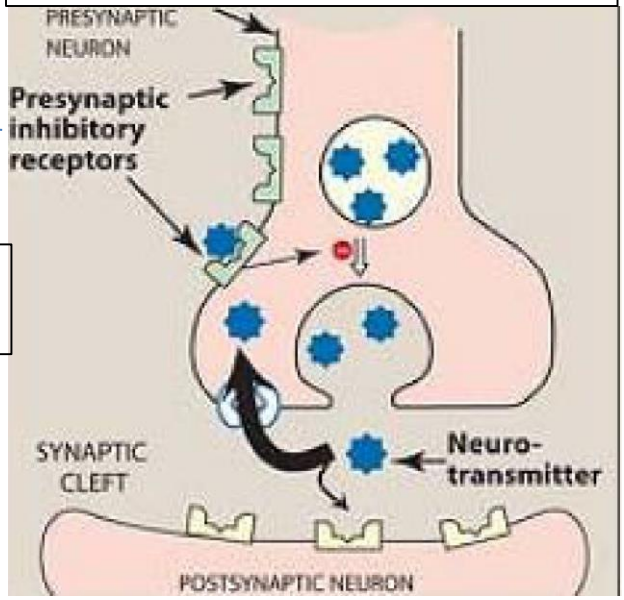
At first we need to know that in any nervous disease (like anxiety, fear, depression or stress) with an obvious cause, we shall treat the cause not the disease.
But if the cases were without any cause, we can use CNS drugs

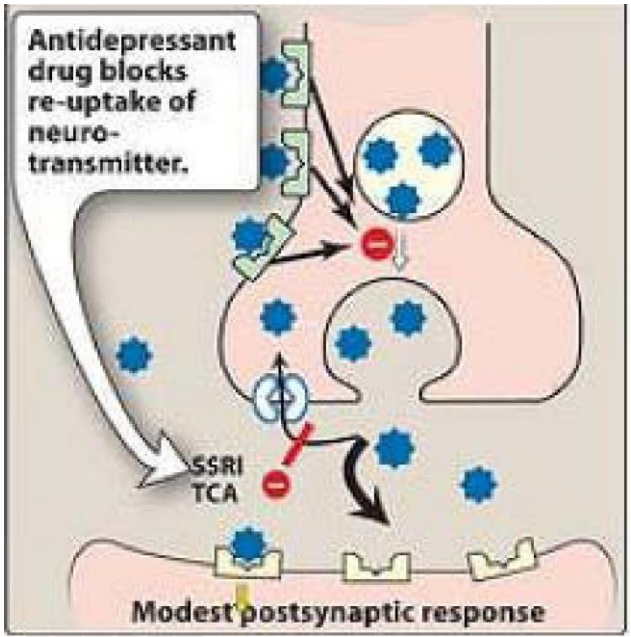
Remember: the part of brain responsible for emotions is the limbic system

A) Before treatment



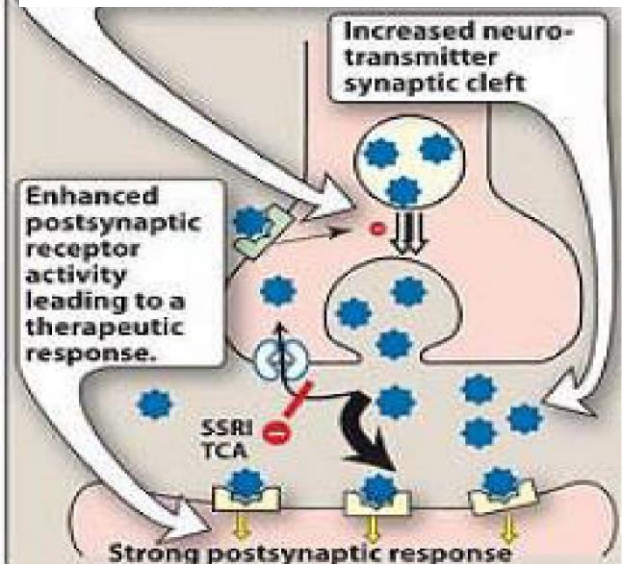
Alpha 2 receptors

B) Acute effect of the drug



C) Chronic effect of the drug

Down regulation of pre synaptic inhibitory receptors lead to increased release of neurotransmitters



Normally (as in picture A in the previous slide), neurons terminals have vesicles that contain the amines (Serotonin, Norepinephrine and Dopamine) which are secreted to act on the next neuron, then it will be reuptaked into their neurons but some of them will bind to the presynaptic inhibitory receptors to prevent further release.

Normal people have abundant amount of amine neurotransmitter. depressive patients have a low amount of serotonin and dopamine and high amount of presynaptic inhibitory receptors.

In acute cases when we want a fast effect we don't give any drugs to the patient but rather we give an electric impulses called ECT (Electro convulsive therapy) to activate neurons and stimulate secretions of amines.

After understanding the physiology of depression what kind of drugs shall we give to these patients ?

As we have a low amount of amines we need to prevent the reuptake of amines in order to make them accumulate in the neuronal synapsis, the solution is a “Reuptake Inhibitor” which are available in many forms: selective or non selective

After reducing the uptake we need to think what basically cause the reuptake
It is the presynaptic inhibitory receptors, so we need to down regulate these receptors which will also down regulate the reuptake of the amines

The enzyme responsible for amines break down is Monoamine oxidase (MAO Enzyme) and it exists in two forms
1- Non-Selective MAO “A”: breaks down all amines
2- Selective MAO “B” : only breaks dopamine

So MAO A inhibitors will increase the level of all of the amines and MAO B inhibitors will increase the level of Dopamine only which is useful in diseases like Parkinson and tremors

Selective Serotonin Reuptake Inhibitors

- SSRIs have greater selectivity for the Serotonin transporter as compared to the norepinephrine transporter.
- This contrasts with the ***tricyclic antidepressants*** that ***nonselectively*** inhibit the uptake of norepinephrine and serotonin
- SSRIs take ***at least 2 weeks*** to produce significant improvement in mood, and maximum benefit may require up to 12 weeks or more.
- **Note:** These drugs do not usually produce CNS stimulation or mood elevation in normal individual And cause variant degrees of headache

CNS stimulation differs from mood elevation

- SSRIs have *little blocking activity at* muscarinic, α1-adrenergic, and histaminic H1 receptors.

SSRIs "α1 blocking effect" can reduce blood pressure, and **SSRIs** "norepinephrine reuptake inhibition effect" can increase blood pressure
It is also responsible for 3 S's side effects: 1-Sleepness 2-Sedation 3-Sexual dysfunction

Pay attention: tricyclic antidepressants not SSRIs

- Therefore, ***common side effects*** associated with **tricyclic antidepressants**, such as orthostatic hypotension, sedation, dry mouth, and blurred vision, are not commonly seen with the SSRIs.

- So, largely replaced tricyclic antidepressants and monoamine oxidase inhibitors as the drugs of choice in treating depression.

Therapeutic uses

- Depression → الوسواس القهري
- Obsessive-compulsive disorder (the only approved indication for *fluvoxamine*),
- Panic disorder, → الهلع و الخوف المرضي
- Generalized anxiety disorder,
- Posttraumatic stress disorder,
- Social anxiety disorder, → social phobia
- Premenstrual dysphoric disorder, and
- Bulimia nervosa (only *fluoxetine* is approved for this).

a serious eating disorder, you eat large amounts of food and then purge to get rid of extra calories.

Sedation means confusion, drowsiness and lack of concentration
Depressive patients have sleep problems and weight changes and also depression drugs have the same effect
Obsessive-compulsive disorder can be treated by drugs other than fluvoxamine, but Bulimia nervosa cant be treated by drugs other than fluoxetine

- ***Fluoxetine* differs from the other members of the class in two respects;**

1. Has a much longer half-life (50 hours) and is available as a sustained-release preparation allowing ***once-weekly dosing***.
2. its metabolite (paroxetine) is as potent as the parent compound. The half-life of the metabolite is quite long, averaging 10 days.

- Fluoxetine and paroxetine are **potent inhibitors of a hepatic cytochrome P450 isoenzyme (CYP2D6)** responsible for the elimination of:

  1)Tricyclic antidepressant drugs
  2)Neuroleptic drugs
  3)Antiarrhythmic
  4)Anti psychosis and
  5)Beta blockers

CYP2D6 is an important cytochrome P450 isoenzyme in metabolism of many drugs, so I need to be carful about the patients medical situation and the drugs he is taking before prescribing these drugs to avoid drug-drug interaction

Note: Sertraline and escitalopram are two SSRIs that are not metabolized by the P 450 System

Adverse effects

- Headache,
- Sweating,
- Anxiety and agitation,
- Gastrointestinal effects (nausea, vomiting, diarrhea),
- Weakness and fatigue,
- Sexual dysfunction,
- Changes in weight,
- Sleep disturbances (insomnia and somnolence), and
- Drug-drug interactions
- **Discontinuation syndrome(or withdrawn manifestations);** *Fluoxetine* has the lowest risk *(headache, malaise and flu-like symptoms, agitation and irritability, nervousness, and changes in sleep pattern)*

the state of feeling drowsy, ready to fall asleep for unusually long periods

Has no addiction effect

Serotonin is the most related neurotransmitter for emotions, mood, appetite, and good sleep ;

So, as the disease it self involves serotonin changes, and its drugs have serotonin changes effect and the discontinuation of the drugs cause serotonin changes, all of the previous actions has bad impacts on the sleep cycle.

Serotonin-Norepinephrine Reuptake Inhibitors

- *Venlafaxine* and *duloxetine* selectively inhibit the re-uptake of both serotonin and norepinephrine.

- SNRIs may be effective in treating depression in patients in whom SSRIs are ineffective.

- Furthermore, depression is often accompanied by chronic painful symptoms, such as backache and muscle aches, against which SSRIs are also relatively ineffective.

SNRIs have a very unique analgesic feature for Neuropathic pains (pain of neuronal fibers due to a type of lesion involving neurons them self, not a pain because of an inflammation or a tumor in another part of the body), like **Trigeminal neuralgia** or **Diabetic peripheral neuropathy**

SNRIs and tricyclic antidepressants, with their dual actions of inhibiting both serotonin and norepinephrine reuptake are sometimes effective in relieving physical symptoms of neuropathic pain,

Neuropathic only patients can take these drugs normally

SNRIs unlike the tricyclic antidepressants, have little activity at adrenergic, muscarinic, or histamine receptors and, thus, have fewer of these receptor-mediated adverse effects than the tricyclic antidepressants.

May precipitate a discontinuation syndrome

Atypical Antidepressants

Bupropion

There will be a question on this drug in the exam for sure

- Acts as a weak dopamine and norepinephrine reuptake inhibitor, and has no effect on serotonin meaning they have a minor role in depression treatment

- Short half-life so, may require more than once-a-day dosing or the administration of an extended-release formulation
- A very low incidence of sexual dysfunction, and
- An increased risk for seizures at high doses. Also has a risk of convulsion

- It assists in decreasing the craving and attenuating the withdrawal symptoms for *nicotine* in tobacco users trying to quit smoking.

Other Members of the family:

1) **Mirtazapine**: It has an powerful antihistaminic effect and pre synaptic alpha 2 activity to reduce norepinephrine

2) Trazodone: it has a sedative effect

3) Maprotiline

TCAs

Prevent the reuptake of amines

1. *The tertiary amines;* (the prototype drug), *amitriptyline*, *clomipramine*, *doxepin* and *trimipramine.*

2. *The secondary amines; desipramine* and *nortriptyline*

- Patients who do not respond to one TCA may benefit from a different drug in this group.
- These drugs are a valuable alternative for patients who do not respond to SSRIs.

TCAs are:

Antimuscarinic, antihistaminic, alpha blocking

They have been replaced by SSRIs

They can't be used except if there is no benefit from using SSRIs

Therapeutic effects starts to appear after 3 weeks

TCAs

e.g. *imipramine, amitriptyline*

- **Inhibition of neurotransmitter reuptake:** TCAs are potent inhibitors of the neuronal reuptake of norepinephrine and serotonin into presynaptic nerve terminals

- **Blocking of receptors:** TCAs also block serotonergic, α-adrenergic, histaminic, and muscarinic receptors

Therapeutic uses of TCAs

- Moderate to severe major depression
- Panic disorder
- *Imipramine;* control bed-wetting in children (older than 6 years) *by causing contraction of the internal sphincter of the bladder. (used cautiously because of the inducement of cardiac arrhythmias and other serious cardiovascular problems).*

Because of its anti cholinergic effect (the atropine like effect), but it can increase norepinephrine and raise the blood pressure

- *Amitriptyline*, used to treat migraine headache and chronic pain syndromes (for example, neuropathic pain)

Due to its alpha blocking effect which vasodilate cerebral blood vessels, but take care Amitriptyline only used as prophylaxis not for acute attacks of migraine

Adverse effects of TCAs

- ***Blockade of muscarinic receptors;*** blurred vision, xerostomia (dry mouth), urinary retention, constipation, and aggravation of narrow-angle glaucoma.
- ***Block α1-adrenergic receptors;*** orthostatic hypotension (*Imipramine* is the most likely).
- ***Block histamine H1 receptors;*** Sedation, especially during the first several weeks of treatment.
- Weight gain
- Sexual dysfunction

Monoamine Oxidase Inhibitors

The last choice

- Three MAO inhibitors are currently available for treatment of depression:

1. *phenelzine*,
2. *tranylcypromine* and
3. *Selegiline;* the agent that was prior-approved for Parkinson's disease, but is now also approved for depression.

The non-selective type

Therapeutic uses

- Depressed patients who are unresponsive or allergic to TCAs or who experience strong anxiety.
- Patients with low psychomotor activity may benefit from the stimulant properties of the MAO inhibitors.
- Phobic states.
- Atypical depression

Note; Despite their efficacy in treating depression, because of their risk for drug-drug and drug-food interactions, the MAO inhibitors are considered to be last-line agents in many treatment venues.

In another words they are considered last choice because they inhibit liver enzymes, have drug-drug interactions and food-drug interactions

Adverse effects

- ***Cheese reaction;*** tyramine is contained in certain foods, such as aged cheeses and meats, chicken liver, pickled or smoked fish and red wines, is normally inactivated by MAO in the gut. Individuals receiving a MAO inhibitor are unable to degrade tyramine obtained from the diet. Tyramine causes the release of large amounts of stored catecholamines from nerve terminals, resulting in occipital headache, stiff neck, tachycardia, nausea, hypertension, cardiac arrhythmias, seizures, and possibly, stroke.

Maybe a case question in the exam

Remember: TCAs have alpha blocking activity, but MAO inhibitors have alpha 2 agonist activity preventing the release of norepinephrine which explains its Orthostatic hypotension

- Drowsiness,
- Orthostatic hypotension,
- Blurred vision, dry mouth, dysuria, and constipation.
- The MAO inhibitors and SSRIs should not be coadministered. Both types of drugs require washout periods of at least 2 weeks before the other type is administered, with the exception of *fluoxetine,* which should be discontinued at least 6 weeks before a MAO inhibitor is initiated.

To prevent over release of serotonin and serotonin syndrome subsequently

A case the will come in the exam as the doctor said:

A depressive patient with myocardial infarction

Drug of choice is: **Sertraline**… why?

-It has no effect on P450 system isoenzyme CYP2D6

-To avoid arrhythmias and tachycardia which could be possible in other antidepressant drugs

From this slide to the end of the lecture is for general knowledge

Antidepressants in depression

- Treatment response
  - Weeks 1-2
    - Physical responses
      - Improvement in appetite and sleep
  - Weeks 3-4
    - Energy and cognitive responses
      - Improvement in energy
      - Improvement in guilt, concentration
  - Weeks 5-6
    - Emotional responses
      - Improvement in mood

Drug treatment mild depression

- ‘Antidepressants are not recommended for the initial treatment of mild depression, because the risk-benefit ratio is so poor’
- Start CBT (**cognitive behavioral therapy)**
- Persistent symptoms – start SSRI
- Mild depressive episode in those with a history of moderate or severe depression – treat with SSRI

Treatment of moderate to severe depression

- ‘In moderate depression, offer antidepressant medication routinely, before psychological interventions’
- Delay in onset of effect
- Risk assessment – See those considered high risk of suicide and less than 30 years old one week post initiation, limit quantity prescribed

Treatment of moderate to severe depression

- If increased agitation develops early in treatment with an SSRI, provide appropriate information and, if the patient prefers, either change to a different antidepressant (Mirtazapine, Moclobemide)or consider a brief period of concomitant treatment with a **benzodiazepine** followed by a clinical review within 2 weeks.

Special patient characteristics

- Women – poorer toleration of **imipramine**
- **Sertraline** 1st choice in those with recent MI or unstable angina
- ECG and BP must be checked before starting a **TCA** in a patient at significant risk of CVD
- Venlafaxine and TCA contraindicated in those with recent MI or high risk serious cardiac arrhythmias