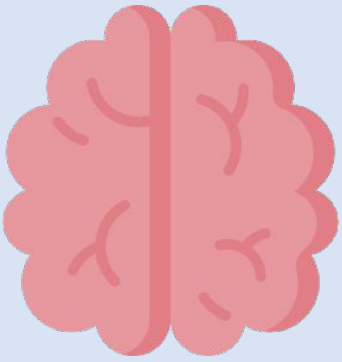

Revised & Approved

Abdullah Alsubaihi
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Pharmacology 439

MED439

Neuropsychiatry Block

Pharmacology Team 439

Helpful video

Color index:

Main Text

Important

Dr's Notes

Female Slides

Male Slides

Extra

Drugs Used in Depression -Old & New

Click here to watch a video explanation of this lecture by a student.

Objectives: (EXTRA)

1- Realize neurotransmitter defects in different types of depression
2- Elaborate on how antidepressants generally act.
3- Classify the existing antidepressant into elder (TCAs & MAO Is) and newer groups (SSRIs,SNRIs, NRIs, NAASs, NDRIs, SARIs).
4- Expand on pharmacology of each group; setting examples, discussing pharmacodynamics potentials, pharmacokinetic differences, varied indications, contraindications and side effects.
5- Enumerate augmenter drugs used in depression.

Editing file

Depression

- Depression is a very common psychiatric disorder that is related to the "mood" (Affective disorder).

Classification of Depression		
According to severity of symptoms	Mild depression	• Self-limiting
	Moderate depression	• Difficulties at home and work
	Severe depression	• Serious, associated with suicidal thoughts
According to type	Unipolar depression (Major depression)	• Mood swings are always in the same direction (depression) and It has two types: 1. About 75% of cases are **non-familial:** - Accompanied by symptoms of anxiety and agitation. - Associated with stressful life events. - Reactive depression 2. 25% **Familial:** - Unrelated to external stresses. - Endogenous depression.
	Bipolar depression (Manic depressive)	• In which depression alternates with **mania**. • It is mainly hereditary and appears in early adult life.
Other forms of depression	Psychotic depression	• is a subtype of major depression that occurs when a severe depressive illness includes some form of psychosis. The psychosis could be hallucinations (such as hearing a voice telling you that you are no good or worthless), delusions (such as, intense feelings of worthlessness, failure, or having committed a sin) or some other break with reality.
	Postpartum depression	• Postpartum means the period just after delivery . Postpartum refers to the **mother**. • Postpartum depression (PPD) is a complex mix of physical, emotional, and behavioral changes that happen in a woman after giving birth.
	Atypical depression	• Atypical depression is a subtype of major depression or dysthymic disorder that involves several specific symptoms, including increased appetite or weight gain, sleepiness or excessive sleep, marked fatigue or weakness.

Depression, cont.

Symptoms of	
Depression	Mania
• Symptoms of depressive illness are highly recognizable, both to those affected and to those closest to them, once they are told what to look for. • Here is a checklist of symptoms of Depressive illness. **1. Loss of energy and interest:** - Diminished ability to enjoy oneself. - Decreased or increased sleeping or appetite. - Difficulty in concentrating; indecisiveness; slowed or fuzzy thinking. - Exaggerated feelings of sadness, hopelessness, or anxiety. **2. Feelings of worthlessness:** - Recurring thoughts about death and <u>suicide</u>. - If most of these symptoms last for **two weeks** or more, the person probably has Depressive illness.	• Mania is a period of **extreme high energy** or **mood** associated with bipolar disorder. Everyone's moods and energy levels change throughout the day and overtime. But mania is a serious change from the way a person normally thinks or behaves, and it can last for weeks or even months. It makes sense that this could cause serious problems in a person's relationships, work, and school. • **Causes mood swings creating periods with the following symptoms:** 1. A high energy level with decreased need for sleep. 2. Unwarranted or exaggerated belief in one's own ability. 3. Extreme irritability. 4. Rapid, unpredictable emotional changes. 5. Impulsive, thoughtless activity, with a high risk of damaging consequences i.e., stock speculations, sudden love affairs, etc.

Biochemical Theory of Affective Disorders

Depression

- ↓NE
- Treated by: Drugs that ↑NE

Affective disorders leads to ↓**serotonin**

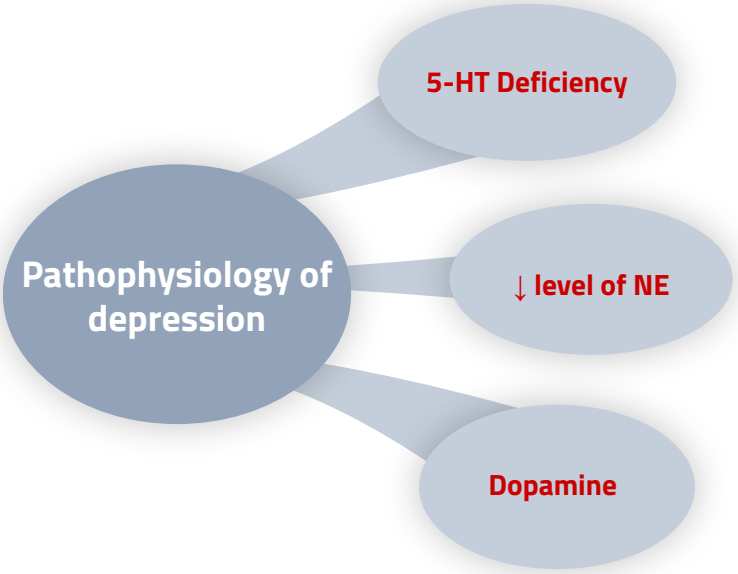
Mania

- ↑NE and sometimes dopamine
- Treated by: Drugs that ↓NE

What is the evidence to support this theory?

- ❖ Amphetamine causes mania (by inhibiting dopamine reuptake, thus ↑DA).
- ❖ While, **Reserpine** & **Methyldopa** (used as hypertensive drugs) produce depression (these drugs depletes NE and Dopamine storage).

Depression, cont.



May cause sleep problems, irritability, anxiety associated with depression and emotional disturbance.

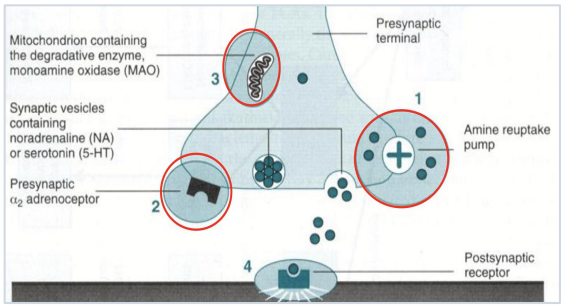
Disturbance in mood, alertness, arousal, appetite, reward & drives. May contribute to the fatigue and depressed mood of the illness and can cause chronic pain syndrome.

important for pleasure, sexual function & psychomotor activity.

What are the features of drugs that should be used for treatment of depression ?

- Simply to **increase the levels of these amines** (5-HT, NE and dopamine).

Site of Action for Antidepressants



Male DR explanation: α_2 receptors in depressed patients are upregulated "increased number of receptors" because the NE release is very low "if there's decrease in the agonist, our body will upregulate the receptors as a defense mechanism". This causes the NE release to decrease further because α_2 is being activated and that will inhibit the release of NE. Also, this mechanism decreases the effect of reuptake inhibitors because the increased number of NE will activate the upregulated α_2 receptors. **And it takes a few weeks until the receptors are downregulated.**

1. **Monoamine** (NE or/and 5-HT) reuptake pump inhibitors.
   - What is the MOA of Monoamine (NE and/or 5-HT) reuptake pump inhibitors? **block** the reuptake of **NE** and **5-HT** which will cause excessive release of the NTs in the synaptic cleft.
2. Blockade of **presynaptic α_2** receptors.
   - Why do we block presynaptic α_2 receptors? These presynaptic α_2 receptors is linked to negative feedback (inhibitory receptors). If it's stimulated it will decreases the release of NE and if we block this receptor it will increase the release of NE.
3. Inhibition of **MAO enzyme**.
   - What inhibit MAO "monoamine oxidase " enzyme? Drugs that **block** the **MAO enzyme** (MAOIs) in order to decrease the degradation of Monoamines and this will allow more Monoamines to be stored in the vesicles and released.

Classification of Antidepressants based on the site of action

Drugs that **block** the reuptake of **NE** and **5-HT**.	Drugs that **inhibit MonoAmine Oxidase (MAO)**	Drugs that **selectively block reuptake of 5-HT (SSRIs)**	Drugs that block **presynaptic α_2** adrenoceptors
e.g. Most **Tricyclics** (Old Antidepressants)	e.g. MAOIs : **Phenelzine**, **Tranylcypromine**, **Moclobemide** (Old Antidepressants)	e.g. **Fluoxetine**, **Paroxetine**, **Sertraline**, **Citalopram** (New Antidepressants)	e.g **Mirtazapine**, **Mianserin**

Antidepressants available in the market (Worldwide)

Classes	Drugs
1. Tricyclics (TCAs) and Tetracyclics Not to be mistaken with **Tetracycline** antibiotics	**Tetracyclics:** Amoxapine, Maprotiline **Tricyclics:** Imipramine, Nortriptyline, Clomipramine, Desipramine, Amitriptyline.
2. Monoamine Oxidase Inhibitors (MAOIs)	Tranylcypromine, Phenelzine, Moclobemide.
3. Selective Serotonin Reuptake Inhibitors (SSRIs)	Fluoxetine, Paroxetine, Fluvoxamine, Sertraline, Citalopram, Escitalopram.
4. Serotonin & Norepinephrine Reuptake Inhibitor (SNRI)	Venlafaxine, Duloxetine.
5. Serotonin-2 Antagonist & Reuptake Inhibitors (SARIs)	Nefazodone, Trazodone.
6. Norepinephrine & Dopamine Reuptake Inhibitor (NDRI)	Bupropion.
7. Noradrenergic and Specific Serotonergic Antidepressant (NaSSA)	Mirtazapine.
8. Noradrenaline Reuptake Inhibitor (NRI)	Reboxetine

Slow Onset of Action

- **Antidepressants do not act immediately** (show clinical effects after 3 weeks, and it is very important to **alert the patient** that the drug takes a minimum of 3 weeks, because the patient might stop using the drug thinking it doesn't work) indicating that secondary adaptive changes must occur before the benefit is gained.
- The most consistent adaptive change seen with antidepressant drugs is the downregulation of β-, α_2 and 5-HT_2 receptors. These receptor mediate negative feedback on monoamine release in the brain. Use of α_2 and 5-HT_2 Will decrease the delay in response to treatment but it will also increase the ADRs
- **Desensitization** (down-regulation) of β- adrenoceptors (↓c-AMP) is very important and is related to clinical response. The NE will not bind to β-adrenoceptor due to down regulation so it will not cause arrhythmia and hypertension (which it associated with stimulation of β-adrenoceptor)

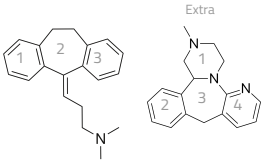
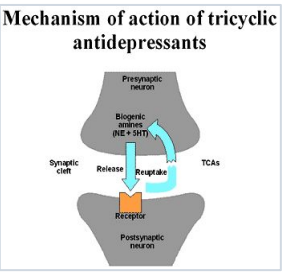
A) Old Antidepressants

1) **TCAs**

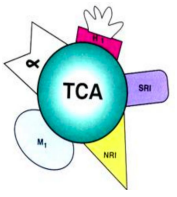
2) **MAOIs**

Abdel-Motaal Fouda - TCAs

1) TRICYCLIC ANTIDEPRESSANTS (TCAs)

Drug	Imi**pramine**, Desi**pramine**, Clomi**pramine**, Trimi**pramine**, Amit**riptyline**, Nor**triptyline**, Doxepin.
Overview	• TCAs are the oldest class of antidepressant drugs. • **Tri**cyclic (They have characteristic **three**-ring nucleus). • Keep in mind that **Tetra**cyclic Antidepressants (another type of Antidepressants) has a characteristic **four**-ring nucleus, which include : *Amoxapine*, *Maprotiline*. Extra 
★ **M.O.A** Male DR: what is MOA of Tricyclic? Inhibit reuptake of serotonin & NE	All tricyclics block reuptake pumps for BOTH **5-HT** and **NE** in nerve terminals by competing for binding site of the transport protein, so ↑ conc. of **NE** & **serotonin** in the synaptic cleft & at the receptor site. - Some have more potency for inhibition of **5-HT** uptake pump: ***C**lomipramine, **I**mipramine, **A**mitryptyline* Can I Apologize يعني عادي اعتذر لاني قفلت السيرتونين - Others have more potency for inhibition of **NE** uptake pump: ***D**esipramine, **N**ortriptyline* Male DR mnemonic: NE inhibition: Nortriptyline (ND) نسبة الى ند/هد 
P.k	• **Peak levels:** 2-6 hours post ingestion • TCAs are "lipophilic" in nature, therefore they are well absorbed from the GIT and readily cross the blood brain barrier to penetrate the CNS. • **Elimination:** hepatic oxidation • TCAs are metabolized in the liver by: - **Demethylation** (the chemical process resulting in the removal of a methyl group (CH3) from a molecule). *Imipramine* metabolized into *Desipramine*, *Amitriptyline* metabolized into *Nortriptyline* it's good because it increases t ½, but bad because it causes more ADRs - **Hydroxylation** into metabolites that retain the biological activity of the parent compounds.
P.D	The antidepressant effect may develop after several weeks of continued treatment (**2-3 weeks**) • Elevate mood • Improve mental alertness • Increase physical activity • **In non-depressed patients**: They cause sedation, confusion & motor incoordination, these effects show Immediately (**not after 3 weeks**) and are not affected by the downregulation of the receptors. So it is important to alert the patient of: 1) the delayed onset of action. 2) these ADRS which will show immediately.
Uses	• Endogenous (Major) Depression -moderate to severe. • Panic attack /acute episode of anxiety. • ***Imipramine*** is used for treatment of **nocturnal enuresis** (involuntary urination) in children & geriatric patients as it constricts internal urethral sphincter (antimuscarinic effect). **Very specific for imipramine**, but not approved • Generalized Anxiety Disorder (GAD). • Obsessive Compulsive Disorder (OCD). • Attention Deficit Hyperkinetic Disorder (ADHD) • Chronic neuropathic pains or unexplained body pains. (sedating properties, it can also treat migraine)
C.I	• Patients with Glaucoma or with enlarged prostate because of their **atropine-like action.** • TCAs (**given alone**) are C.I in manic-depressive illness aka Bipolar, because they tend to "switch" the depressed patient to the "manic" phase, therefore, they **should be combined with "lithium salts"** (a mood stabilizer). TCA's can trigger manic phases because they ↑NE and it's already high in bipolar. • Seizure disorders (TCAs increases NA level in brain)

Cont..

ADRs	To understand the ADRs we need to know that TCAs also block : - **M_1** cholinergic receptors (atropine-like) - **H_1** histamines receptors - **α_1** adrenergic receptors - **5-HT_2** receptors  ● **Anti-cholinergic:** Dry mouth, blurred vision, constipation & urine retention, aggravation of glaucoma. ● **Anti-histaminic:** Sedation, confusion. ● **Anti-adrenergic:** Postural hypotension, arrhythmias (widening of QRS complex), conduction defects. ● Serotonergic: Weight gain (may be due to regained appetite), sexual dysfunction (delayed ejaculation, beyond physiological limits) & impotence ● Lower seizure threshold (Due to ↑NE which is a CNS stimulant) ● **TCAs have narrow therapeutic index thus toxicity can develop:** excitement, delirium , convulsions, respiratory depression (may cause acidosis, thus arrhythmia), coma, atropine-like effects, cardiac arrhythmias, sudden death ● **TCAs** are highly protein bound and **have a large volume of distribution** therefore hemodialysis is NOT effective for treatment of TCAs toxicity. Take it into consideration if a patient overdose as a suicide attempt Later on in this lecture, there is a class of antidepressants that has similar MOA but without blocking these receptors hence less side effects
Drug interactions	● TCAs are strongly bound to plasma protein, therefore their effect can be potentiated by drugs that compete for their plasma protein binding site (***Aspirin*** and ***Phenylbutazone***). ● TCAs are metabolized by liver microsomal enzymes, therefore their effect can be: - **Reduced** by inducers of liver microsomal enzymes (***Barbiturates***), - or **potentiated** by inhibitors of liver microsomal enzymes (***Oral contraceptives***, ***Antipsychotics***, and ***SSRIs***). ● TCAs (inhibitors of monoamine reuptake) should not be given with ***MAOIs*** (inhibitors of monoamine degradation). Because it may lead to "**serotonergic & hypertensive crisis**" Serotonin syndrome is because of the increase in serotonin due to toxic synergistic action, and hypertensive crisis is because of the↑ in NE ● Additive to ***antipsychotics*** & ***anti-parkinsonisms*** → ***↑anti-cholinergic*** effects.

Abdel-Motaal Fouda - MAOI (skip to 33:00)

2) MonoAmine Oxidase Inhibitors (MAOIs)

Monoamine Oxidase (MAO) is a mitochondrial enzyme found in nearly all tissues

Monoamine oxidase (MAO) has two forms:

1. MAO-**A**

Responsible for :
- Catabolism of **NE**, **5-HT**
- Metabolizes **tyramine** of ingested food

Inhibitor used in depression

2. MAO-**B**

This type is more selective for **dopamine** metabolism

Inhibitor used in parkinson's

Monoamine Oxidase **Inhibitors** (MAO**I**s) can be divided according to their selectivity into:

1. **Non Selective Inhibitors**

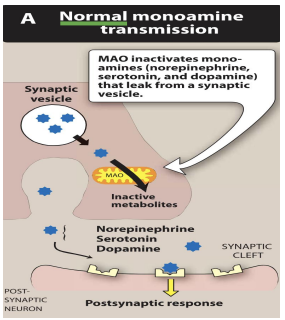
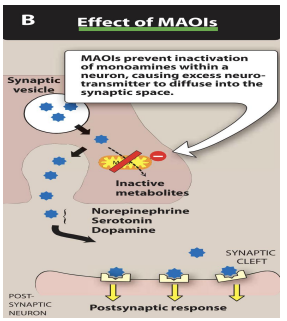
- **Ir**reversible "*Phenelzine*"
- **Ir**reversible "*Tranylcypromine*"

The effect of **irreversible** MAOIs persists for a period of 2-3 weeks after stopping treatment, time needed by the body to synthesize new enzyme.

2. **Selective Reversible Inhibitors**

- MAO-**A** selective "*Moclobemide*"
- MAO-**B** selective "*Selegiline*"

Drug / Action	Sedation action	Anticholinergic effects	Hypotension
Isocarboxazid	+	++	+
Phenelzine	+	++	+
Tranylcypromine	-	+	+
Moclobemide	-	-	-

Drug	Phenelzine, Isocarboxazid	Tranylcypromine	Moclobemide	Selegiline
selectivity	Non-Selective "MAO-A & MAO-B"		Selective "MAO-A"	Selective "MAO-B"
	Irreversible "Long acting"	Irreversible	Reversible "Short acting"	Reversible
M.O.A	- MAO normally degrades Monoamines transmitters by inactivating the Monoamines that leak from a synaptic vesicles. (Pic **A**) - MAOIs prevent inactivation of monoamines within a neuron, causing excess neurotransmitter to diffuse into the synaptic space. (Pic **B**)			
Uses	• **Only** used for refractory cases and in atypical depression where phobia and anxiety are prominent symptoms. • *Selegiline* used for Parkinsonism. • **Limited use now because:** - ADR. - Food & Drug Interactions. - Low antidepressant efficacy. - Low benefit/risk ratio. • Moclobemide (depression) and Selegiline (Parkinson's) are the ones used clinically			
ADRs	• Similar to TCA ADRs • Antimuscarinic effects. (M_1 cholinergic receptors) • Sedation, sleep disturbance. (H_1 histamines receptors) • Postural hypotension. (α_1 adrenergic receptors) • Weight gain. (Serotonergic) • Specific ADRs for ***Phenelzine*** : - Hepatotoxicity. - Sexual dysfunction			
Interaction with tyramine (**Cheese reaction**)	This occurs when **Tyramine** rich foods are taken with **MAOIs**. (food restrictions) • **Tyramine** rich foods include: Old cheese , Concentrated yeast products, Pickled or smoked fish, Red beans, Red Wine, Chicken liver, Sausages. • **Tyramine** (pressor amine) in food is normally degraded in the gut by **MAO-A**. Remember? • Since the enzyme is inhibited by **MAOIs**, **tyramine** from ingested food is absorbed, and then taken up into adrenergic neurons where it is converted into **octopamine** (a false transmitter) which causes massive release of **NE** and may result in **hypertensive crisis** (cheese like reaction); severe hypertension, severe headache (may be first sign) and fatal intracranial Haemorrhage (Tyramine → vasoconstriction → ↑BP) • **The special advantage** claimed for *Moclobemide* is that, No cheese reaction occurs with its use. Since the action of moclobemide on MAO-A is reversible, high concentrations of tyramine will displace the drug from the enzyme, further facilitating the degradation of tyramine.			
Drug interactions	• ***Pethidine***: MAOIs interact with the opioid receptor agonist (*pethidine*) which may cause: severe hyperpyrexia (very high fever), restlessness, coma, hypotension. The mechanism still unclear, but it is likely that an abnormal pethidine metabolite is produced because of inhibition of normal demethylation pathway. • ***Levodopa*** *(anti-parkinson's)*: Precursor of dopamine can interact with MAOIs leading to hypertensive crisis and mania. • ***Amphetamine & Ephedrine:*** Indirectly acting sympathomimetics can interact with MAOIs causing the liberation of accumulated monoamines in neuronal terminals leading to hypertensive crisis. Due to ↑NE levels • ***TCAs*** (inhibitors of monoamine reuptake): can interact with MAOIs (inhibitors of monoamine degradation) leading to Serotonergic & hypertensive crisis (Both of them ↑NE levels). (remember TCAs interactions?) • ***SSRIs***: Serotonin syndrome/Crisis (Both of them ↑5-HT levels). **Give 1-2 weeks gap before initiating SSRIs.**			

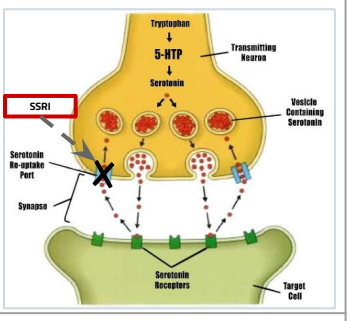
B) New Antidepressants

- **SSRI** — Selective Serotonin Reuptake Inhibitors
- **SNRI** — Serotonin and Noradrenaline Reuptake Inhibitors
  basically glorified TCAs with no ADRs
- **NaSSA** — Noradrenergic and specific Serotonergic Antidepressant
- **NDRI** — Norepinephrine and Dopamine Reuptake Inhibitors
- **SARI** — Serotonin-2A Antagonist and Reuptake Inhibitors
- **NRI** — Norepinephrine selective Reuptake Inhibitors

Abdel-Motaal Fouda - SSRI

1. Selective Serotonin Reuptake Inhibitors (SSRIs)

Drug	Fluo**xetine**	Paro**xetine**	Sertraline	Citalo**pram**	**Es**citalo**pram**	Fluvox**amine**
Overview	• The most widely utilized class of antidepressants in clinical practice. First line • They act within the brain to increase the level of serotonin (5-HT) in the synaptic gap by inhibiting its re-uptake. • Described as 'selective' because they affect **only** the reuptake pumps responsible for Serotonin.					
M.O.A	Bind to SERT (serotonin transporter) ⟶ **Block 5-HT transport ⟶ increase 5-HT levels in synapse** (synaptic cleft). - They have No effect on NET (norepinephrine transporter). - They don't block mAch, H, or α_1 Adrenoceptor unlike TCAs and MAOIs ➔ so no antimuscarinic nor sedative effect, Except ***Paroxetine*** " it will cause urinary retention, constipation, dry mouth... etc" - They are nearly of comparable efficacy but of preferential response in each individual.					
Advantages	• The most commonly prescribed antidepressants. • Lacks cardiovascular (indicated for depressed, MI patients) & anticholinergic side effects compared to ***TCAs***. • In contrast to MAOI, they do not cause 'cheese' reaction so there's no food restrictions. • Safer (low risk of overdose). • Acute toxicity is less than that of MAOIs or TCAs.					



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Drug		Fluo**xetine**	Paro**xetine**	Sertraline	Citalo**pram**	**Es**citalo**pram**	Fluvox**amine**
P.K	T ½	Too long (3-11 days) For a Long Time Dose is still daily	Moderate length (~24hr)			-	-
	Metabolism	P450 then conjugation. **They are enzyme inhibitors**					
		Strong inhibitors → ↓ metabolism of TCAs, neuroleptics, some antiarrhythmics, β-blockers	**Weak inhibitors →** ↓ interaction			-	-

Uses

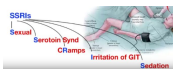
Same as for TCA, in addition effective in the following conditions:

- Anxiety Disorder.
- Eating disorders:
  - Bulimia nervosa ***(Fluoxetine)***. in which bouts of extreme overeating are followed by vomiting.
  - Anorexia nervosa (restricting eating). For your knowledge: (it's only used in severe cases according to AMBOSS)
- Post traumatic stress disorder (PTSD).
- Premenstrual dysphoric disorder.
- Attention Deficit Hyperkinetic Disorder (ADHD).
- Treatment of **premature ejaculation (**via stimulation of **5-HT$_{2A}$)**. There is no delay before the patient is improved unlike in psychiatric conditions

ADRs

Adverse effects of SSRIs:

- GIT symptoms: Nausea vomiting (due to **5-HT$_3$** stimulation) & diarrhea. Worse than TCA and MAOIs
- Changes in appetite: weight loss. (due to **5-HT$_3$** stimulation)
- Sleep disturbances: Drowsiness with ***Fluvoxamine***, Paroxetine "add it to your slides"



- Anxiety & Tremors.
- Sexual dysfunction: Loss of libido, delayed ejaculation (due to **5-HT$_{2A}$** stimulation). main cause of non-compliance

Drug	Cardiotoxicity	Nausea	Anticholinergic effects	Sedation
Fluoxetine	-	++	-	-
Paroxetine	-	++	+	+
Sertraline	-	++	-	-
Fluvoxamine	-	+++	-	+

Discontinuation syndrome: NEVER stop abruptly, but instead decrease the dose gradually (drug tapering) to avoid it and to reduce the risk of relapse

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

Drug Interactions

- 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"**: "HARM": Hyperthermia -Autonomic instability -Rigidity -Myoclonus. (tremors, hyperthermia, cardiovascular collapse and death).

Both drugs require a "washout" period of 6 weeks before the administration of the other.

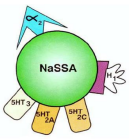
Drug: Fluoxetine (Prozac)

Differences

Fluoxetine It is a strong inhibitor and differs from other members of this class in:

1. It has a longer $T_{1/2}$ (50 hrs). Fluoxetine : For a Long Time
2. Available as sustained release preparations → once weekly.
3. Its metabolite norfluoxetine = potent as parent drug $T_{1/2}$: 10 days.
4. Indicated in bulimia nervosa.

2. Noradrenergic and specific Serotonergic Antidepressants (NaSSA)

Drug	**Mirtazapine** " مرتزة باين "
M.O.A	 - **α_2 receptors antagonist.** - Increase NE and 5-HT levels. - **Blocks 5-HT$_{2A}$, 5-HT$_3$** and thus reduces side effects of anxiety, & sexual dysfunction. Stimulation of **5-HT$_{2A}$** receptor it will cause sexual dysfunction so blocking this receptor will reduce the psychological symptoms and one of them is sexual dysfunction. - **Blocks 5-HT$_{2C}$** receptor ⟶ weight gain , and **Block H$_1$** receptor ⟶ sedation.
Uses	**Preferred in cancer patients because:** You can read about mirtazapine effect on cancer mice here. 1. Improves appetite. 2. ↓ **Nausea & vomiting** (5-HT$_3$ blocking). 3. ↑ Body weight (**5-HT$_{2C}$ blocking effect**) (may be due to improved appetite) 4. Sedation (potent **Antihistaminic**) MirtaZZZapine H$_1$ blocking 5. Less sexual dysfunction (5-HT$_2$ blocking). 6. Has no anti-muscarinic effect.
ADRs	Blocking 5-HT$_{2C}$, and H$_1$ receptors cause side effects: • Sedation (due to **H$_1$** blocking effect). • Weight gain. (due to **5-HT$_{2C}$** blocking effect). Cancer patients will also suffer from N&V, which may lead to weight loss. So if they take mirtazapine which blocks **5-HT$_3$** in the CTZ, **N&V** decreases and that allows them to gain the weight they lost back (advantage).

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

Drug	Nefa**zodone**	Tra**zodone**
M.O.A	واحد يتكلم عن العلاج: زودوني ترى نفع او ترى نفع زودوني Nefa Tra zodone • **Blocks 5-HT uptake selectively** but in a less potent manner than tricyclics. This reduces depression. • However, they are powerful **5-HT$_{2A}$ antagonists**, blockade of 5-HT$_{2A}$ receptors **stimulates 5-HT$_{1A}$ receptors**, which may help reduce depression. • **5-HT$_{2A}$** antagonism also reduces the risk of anxiety, sedation or **sexual dysfunction** which is normally associated with SSRIs. 5-HT$_{2A}$ Antagonism effect is thought to be the reason behind priapism side effect (abnormally prolonged erection) 5-HT$_{2A}$ is thought to be the "bad" serotonin receptor	
Differences	*Nefazodone* is structurally related to *trazodone* but: • Has less sedative effect. • Does not block α- adrenoceptors. However; it likes most SSRI inhibit P450 3A4 isoenzyme.	

4. Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs)

Drug	**Venlafaxine (Effexor)** "فين الـفـاكسين"
M.O.A	• *Venlafaxine* is the first and most commonly used SNRI. • Selective 5-HT and NE uptake blockers combines the action of SSRI and NRI, but without α_1, M_1 cholinergic or H receptor blocking properties. • ***Des**venlafaxine* is a metabolite of *Venlafaxine*
Uses	• Depression • Generalized anxiety disorder • Social anxiety disorder in adults.
Drug Interactions	Drug interactions and serotonin syndrome if combined with MAOIs and TCA, don't combine them because they work similar to SSRI but with less ADRs. They may also trigger Mania

5. Norepinephrine and Dopamine Reuptake Inhibitors (NDRI)

Drug	**Bupropion**
M.O.A	• Is unique in possessing significant potency as **NE (Norepinephrine)** and **DA (Dopamine)** reuptake inhibitor, with no direct action on 5-HT.
Uses	• Treatment of major depression and bipolar depression. • Used for **smoking cessation** → As it reduces the severity of nicotine craving & withdrawal symptoms Nicotine increases dopamine release so withdrawal of nicotine will cause a decrease in dopamine. This is where this drug comes in to help (Can help in a variety of addiction withdrawal situations not only smoking)
Advantages	• No sexual dysfunction → given in young. • No weight gain [No 5-HT effect]. • No orthostatic hypotension.
ADRs	• Seizures; it ↓threshold of neuronal firing (increases the stimulating NT) → Similar to TCAs. • Mania due to ↑NE levels.

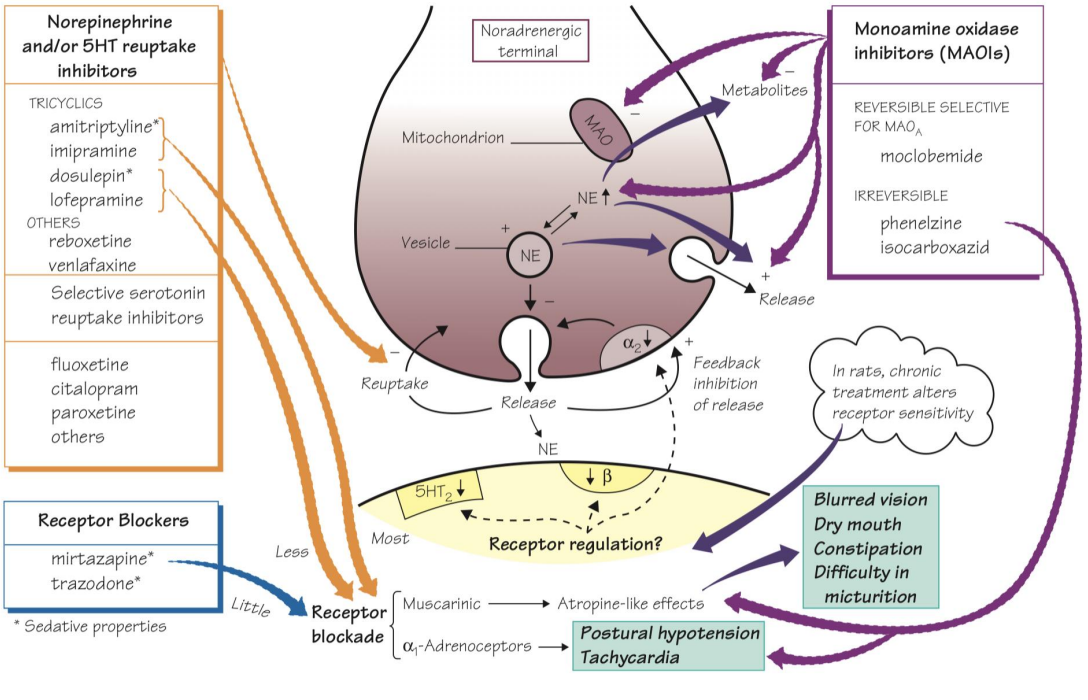
6. NE Selective Reuptake Inhibitors (NRIs)

Drug	**Reboxetine**
M.O.A	• **Block only NET** (norepinephrine transporter) • No affinity for 5-HT, DA, ADR (Adrenergic receptor), H, mAch receptors. So, has positive effects on the concentration and motivation in particular.
Advantages	• **Safe to combine with SSRIs.** Good choice for combination therapy
ADRs	• Minimal side effects only related to activation of ADR system as tremor, tachycardia, and urinary hesitancy. The adrenergic effect happens because of the effect on NE since its reuptake is inhibited which means NE levels will increase and activate the ADR system . The **RECEPTOR** is not affected by the drug itself, however the drug **INDIRECTLY** increases the effect on ADR system by ↑NE levels that will bind to them. • Mania due to ↑NE levels. • Seizures it ↓threshold of neuronal firing. (increases the stimulating NT) → Similar to TCAs.

Clinical uses of Antidepressant Drugs

Disorder	Drug
Endogenous Depression	• SSRIs (first Choice) • New generation • Tricyclics
Panic Disorders	• Imipramine • SSRIs
Obsessive Compulsive Disorders (OCD)	• SSRIs • Clomipramine
Chronic pain	• Amitriptyline (TCAs)
Anorexia nervosa & Bulimia	• SSRIs
Schizo-Affective Disorders	• Amoxapine or SSRI + Haloperidol
Premature ejaculation	• SSRI
Anxiety disorders	• Amitriptyline
Migraine & Anxiety & irritable bowel syndrome	• Amitriptyline (TCAs)
Nocturnal Enuresis in children	• Imipramine
Neuropathic Pain	• Dual NE+ 5-HT reuptake Blockers

EXTRA Summary



MCQs

Q1: A 55-year-old teacher was diagnosed with depression After 6 weeks of therapy with fluoxetine, his symptoms improved, but he complains of sexual dysfunction. Which of the following drugs might be useful for management of depression in this patient?			
A- Sertraline	B-Citalopram	C-Mirtazapine	D-Lithium
Q2: A 51-year-old woman with symptoms of major depression also has angle-closure glaucoma. Which antidepressant should be avoided in this patient?			
A- Amitriptyline	B-Bupropion	C-Mirtazapine	D-Fluvoxamine
Q3: A 36-year-old man presents with symptoms of compulsive behavior. He realizes that his behavior is interfering with his ability to accomplish his daily tasks, but cannot seem to stop himself. Which drug would be most helpful to this patient?			
A- Desipramine	B-Paroxetine	C-Amitriptyline	D-Selegiline
Q4: Which antidepressant agent has significant α_1 receptor antagonism and, thus, is a poor choice in an elderly female with depressive symptoms due to a higher risk of falls related to orthostatic hypotension?			
A- Venlafaxine	B-Bupropion	C-Escitalopram	D-Amitriptyline
Q5: The principal mechanism of action of antidepressant agents is:			
A- Stabilization of dopamine and β-adrenergic receptors	B- Inhibition of the storage of serotonin and epinephrine in the vesicles of presynaptic nerve endings	C-Blocking epinephrine or serotonin reuptake pumps	D-Stimulation of α_2-norepinephrine receptors
Q6: Which of the following drugs is least likely to be prescribed to patients with prostatic hypertrophy, glaucoma, coronary and cerebrovascular disease?			
A- Amitriptyline	B-Paroxetine	C- Bupropion	D-Fluoxetine
Q7: 65-year-old patient suffering from weight loss due to cancer treatment presents to you with moderate depression, which of these is the best choice of treatment?			
A- Nefazodone	B- Venlafaxine	C- Reboxetine	D- Mirtazapine
Q8: Which of the following drugs reduces nicotine craving and can be used for smoking cessation?			
A- Bupropion	B-Reboxetine	C-Selegiline	D-Amitriptyline
Q9: Which of the following is an advantage of Reboxetine?			
A- Safe to combine with SSRI	B- Affinity for 5-HT	C-No sexual dysfunction	D-No cheese reaction

1	2	3	4	5	6	7	8	9
C	A	B	D	C	A	D	A	A

SAQ

Q1) Patient with very severe depression. His uncle is an undergraduate medical student. He advised him to take Citalopram combined with Moclobemide.
a) mention the mechanism of action of each drug?
b) what will result in combining these 2 drugs?
c) What is the recommended time to switch these drugs?

Q2/Patient was suffering from depression. His doctor prescribed antidepressant (Tranylcypromine). After two days, patient came ER by an ambulance suffering from severe hypertension symptoms. After taking History patient mention attending cheese-wine tasting party.
a) Explain by which mechanism the drug work and it where it takes place?
b) Why do you think he developed hypertension in relation with patient history?
c) Which drug do you think would have been a better option for the patient, why?

Q3/A 53-year-old man comes to clinic for depression. He has had decreased interest and a depressed mood for the past 6 months. He also smokes half a pack of cigarettes a day and thinks that if he could quit, that would help his mood as well.
What is the most appropriate treatment for his depression and cessation of smoking?
What is the mechanism of action of the drug ?

Answers

A1.a) **Citalopram: SSRI. Moclobemide: MAOI**

b) **Serotonin syndrome. marked by: tremors, hyperthermia, cardiovascular collapse and death**

c) **Washout period of 6 weeks**

A2.a) **Tranylcypromine acts on blocking presynaptic MAO enzyme**

b) **Cheese and wine contain Tyramine normally, and it's degraded in the gut by MAO enzyme which was blocked by the Drug.**

c) **Moclobemide. It does not have "cheese reaction"**

A3) Bupropion, Norepinephrine and Dopamine Reuptake inhibitor (NDRI)

Feedback Form

Neuropsychiatry Block

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