MED437
KING SAUD UNIVERSITY

Pharmacology
435 team

Pharmacology
Team 437

Drugs used in depression Old & New

Color index:

- Drugs names
- Doctors notes
- Important
- Extra

Depression

Definition

Depression (major depressive disorder or clinical depression) is a common but serious mood affective disorder. It causes severe symptoms that affect how you feel, think, and handle daily activities, such as sleeping, eating, or working. To be diagnosed with depression, the symptoms must be present for at least two weeks.

Pathophysiology

- Neurotransmitter Imbalances & Dysregulation → creates a state of deficiency in monoamines → creates a state of deficiency in NTs (serotonin (5-HT), Dopamine, NE)

Changes in mood are associated with depression and/or mania.

Disorders of mood rather than disturbance in thought or cognition.

Incidence: Depression is a chronic and recurrent illness that can affect at least 20% of the population at some period in their lifetime.

An estimated 35-40 million Americans living today will suffer from major Depressive Illness during their lives.

Cost: 15-35 billions $ / year in USA only.

Classification of Depression

According to severity of symptoms:

1. **Mild depression** self-limiting
2. **Moderate depression** difficulties at home and work
3. **Severe depression** serious, associated with **suicidal** thoughts

According to type:

1- Unipolar depression (major depression):

-mood swings are always in the same direction (depression)

-About 75% of cases are non-familial

- accompanied by symptoms of anxiety and agitation
- Associated with stressful life events

-25% familial

- unrelated to external stresses.
- endogenous depression

2- Bipolar depression (manic-depression):

-In which depression alternates with **mania**

-It is mainly hereditary and appears in early adult life

Other forms of depression:

1. Psychotic depression
2. Postpartum depression
3. Atypical depression

Just read it !!

Symptoms of Depression

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.

Feelings of worthlessness.

Recurring thoughts about death and suicide.

If most of these symptoms last for two weeks or more, the person probably has Depressive illness

Symptoms of Mania

causes mood swings creating periods with the following symptoms:

A high energy level with decreased need for sleep.

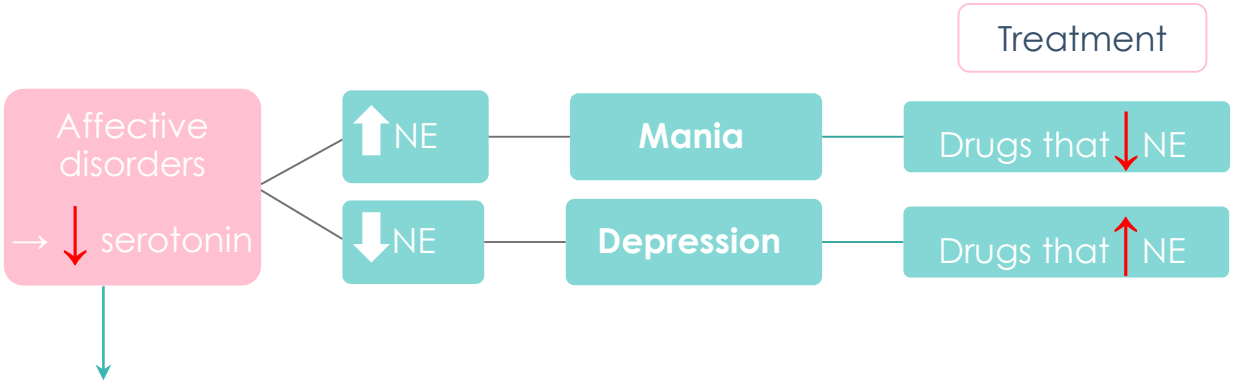
Unwarranted or exaggerated belief in one's own ability.

Extreme irritability.

Rapid, unpredictable emotional changes.

Impulsive, thoughtless activity, with a high risk of damaging consequences (i.e., stock speculations, sudden love affairs, etc.).

Biochemical Theory of Affective Disorders



the neurotransmitters (serotonin, dopamine,NE) are low they cause depression,so we need to increase the level of the neurotransmitters to treat it.

- What is the evidence to support this theory ?

Amphetamine make you alert it called"student drug" causes **mania** while **reserpine** antihypertensive it deplete NE storage in your body and **methyldopa** produce antihypertensive decrease NE depression (these drugs depletes NE and dopamine storage).

Reserpine: antihypertensive causes depression because it lowers the monoamines in the synaptic cleft.
Amphetamine: drugs of addiction, release amounts of monoamines so causes mania and psychosis.

5-HT deficiency — may cause the sleep problems (Insomnia), irritability and anxiety associated with depression

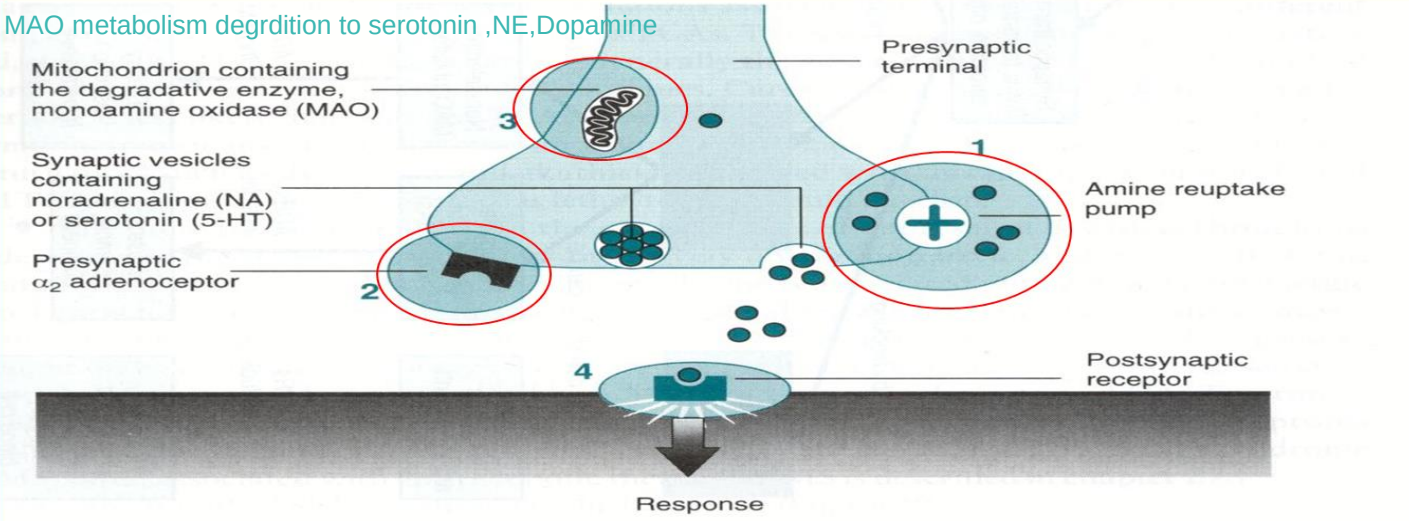
Decreased level of NE — which regulates mood. alertness, arousal, appetite, reward & drives, may contribute to the fatigue and depressed mood of the illness

However, **dopamine** is important for pleasure, sex & psychomotor activity.

What are the features of drugs that should be used for treatment of Depression?
→ Simply to **increase the levels of these amines**

Antidepressants

Sites of Action for Antidepressants:



1- **Monoamine** (**NE** or/and **5-HT**) **reuptake pump inhibitors**

2- **Blockade of <u>presynaptic</u> a_2 receptors**

3- **Inhibition of MAO enzyme**

Classification of antidepressants based on site of action

Drugs that **block** the **reuptake of NE and 5-HT**	e.g. Most **tricyclics** (**old Antidepressants**)
Drugs that **<u>selectively</u> block reuptake of 5-HT (SSRIs)** (most common)	**Fluoxetine; Paroxetine; Sertraline; Citalopram** (**New Antidepressants**)
Drugs that **Block Presynaptic a_2-** adrenoceptors	e.g.: **Mirtazapine** **Mianserin**
Drugs that Inhibit **MonoAmine Oxidase**	MAOIs, **Phenelzine, Tranylcypraine, Moclobemide** (**old Antidepressants**)

Antidepressants available in the market (worldwide)

Class	Drugs
Tricyclics (TCAs) and Tetracyclics	Imipramine, Amoxapine, Maprotiline, Nortriptyline, Trimipramine, Clomipramine, Protriptyline, Desipramine, Amitriptyline
Monoamine Oxidase Inhibitors (MAOIs)	Tranylcypramine not used clinically, Phenelzine use for research not clinically, Moclobemide
Selective Serotonin Reuptake Inhibitors (SSRIs)	Fluoxetine, Fluvoxamine, Citalopram, Sertraline, Paroxetine, Escitralopram
Serotonin and Norepinephrine Reuptake Inhibitor (SNRI)	Venlafaxine, Duloxetine
Serotonin Antagonist and Reuptake Inhibitors (SARIs)	Nefazodone, Trazodone,
Norepinephrine and Dopamine Reuptake Inhibitor (NDRI)	Bupropion
Noradrenaline Reuptake Inhibitor (NRI)	Reboxetine
Noradrenergic and Specific Serotonergic Antidepressant (NaSSA)	Mirtazapine

this table contain both old & new antidepressant drugs

Slow onset of action

Antidepressants do **not** act immediately (show clinical effects **after 3 weeks**) indicating that secondary adaptive changes must occur before the benefit is gained.

The most consistent adaptive change seen with antidepressant drugs is the **downregulation** (Number of receptors decreases) **of beta-, alpha-2 and 5-HT2 receptors** these receptor up-regulated in depressed patients .

Desensitization (down-regulation) of **β- adrenoceptors** (decrease c-AMP) is very important and is related to clinical response that's why antidepressants take 3 weeks to show effect .

Old Antidepressant

The oldest one

Tricyclic antidepressant

Tricyclic (They have characteristic three-ring nucleus:

- Imipramine
- Desipramine
- Clomipramine
- Amitriptyline
- Nortriptyline
- Doxepin
- Trimipramine

Both TCAs & tetracyclic have the same MOA

- Maprotiline
- Amoxapine

Tetracyclic

Monoamine Oxidase inhibitors

Note: depression also comes in mild forms that do not require treatment with antidepressants. Treatment is only required to suffer from severe forms of depression mentioned above.

Old Antidepressant

Drug

Tricyclics (TCAs)

Imipramine anticholinergic, **Amoxapine**, **Maprotiline**, **Nortriptyline**, **Trimipramine**, **Clomipramine**, **Protriptyline**, **Desipramine**, **Amitriptyline** common

Mechanism of action

- All tricyclics **block reuptake pumps for both 5HT (serotonin) and NE** (norepinephrine) 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.

- **Clomipramine**, **Imipramine**, **Amitriptyline** have **more potency for inhibition of 5HT uptake pump.**

- **Nortriptyline**, **Desipramine** have **more potency for inhibition of NE uptake pump.**

- TCAs also block serotonergic, alpha-adrenergic, histaminic, and muscarinic receptors.

pharmacological action

-Elevate mood
-Improve mental alertness
- Increase physical activity.

Note:

- The antidepressant effect may develop after several weeks of continued treatment (2-3 weeks).
- **In non-depressed patients: They cause sedation, confusion & motor incoordination.**

P.K

- **Peak levels**: 2-6 hours. They are **"lipophilic"** in nature well absorbed from the GIT and cross the blood brain barrier to penetrate CNS.

- **Elimination**: **hepatic oxidation**.

- **TCAs** are metabolized in the **liver** by **demethylation (Imipramine to Desipramine, Amitriptyline to Nortriptyline)** and by hydroxylation into metabolites that retain the biological activity of the parent compounds. → This affects the T1\2 by increasing it.

Indicatios

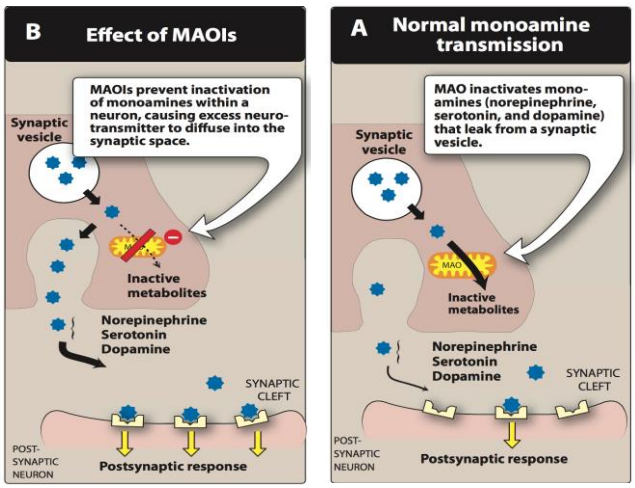
- Endogenous (Major) Depression → moderate to severe.
- Panic attack /**acute** episode of anxiety.
- **Imipramine** because it's anticholinergic **is used for treatment of nocturnal enuresis** (**bed wetting** التبول اللا إرادي) in children and geriatric patients →**(M.O.A)** it constricts internal urethral sphincter (anti-muscarinic effect).
- Generalized Anxiety Disorder (GAD).
- Obsessive Compulsive Disorder (OCD)
- Attention Deficit Hyperkinetic Disorder (ADHD - فرط الحركة).
- Chronic neuropathic pains or unexplained body pains. → e.g. pain involved in diabetic pts, or any pain affecting the nerves.

Drug	Tricyclics (TCAs) (cont.)
ADRS	**TCAs block:** - **α_1** adrenergic receptors - **H1** histamines receptors - **M1** cholinergic receptors - **5HT2** receptors - **Anti-cholinergic**: Dry mouth **blurred vision**, constipation & urine retention, aggravation of **glaucoma** ,(dental problem; **xerostomia**). - **Anti-histaminic**: **Sedation**, confusion. → H1 receptor effects. - **Anti-adrenergic**: Postural hypotension, arrhythmias, conduction defects. - **Weight gain, sexual dysfunction** & impotence. →the **old group causes sexual dysfunction while most of new group doesn't cause .** - **Lower seizure threshold**. - TCAs have narrow therapeutic index: toxicity can develop; excitement, **delirium** , convulsions, **respiratory depression**, coma, **atropine-like effects, cardiac arrhythmias, sudden death.** - TADs are **highly protein bound** and have a **large volume of distribution** → Therefore **hemodialysis** is **not** effective for treatment of TCA toxicity.
Drug Interaction	- TCA 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**). → increase their effect. - 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) → **cause hypertensive crisis** why?NA will cause vasoconstriction. - Additive to anti-psychotics and anti-parkinsonism (which have anti-cholinergic effect) → increase anti-cholinergic effects. - A helpful picture summarize there interactions.
C.I	- TCAs should not be used in patients with **Glaucoma** or with **enlarged prostate** because of their **atropine**-like action. - TCAs (given alone) are **contraindicated** in **manic-depressive illness (Bipolar disease)**, because they tend to "**switch**" the depressed patient to the "**manic**" phase, therefore, they should be combined with "**lithium salts**". لو الشخص عنده bipolar disease وأعطيته أدوية مضادة للاكتئاب فقط، بتطلع لي حالته الثانية mania، يعني في هذي الحالة أنا عالجت شيء وطلع لي شيء ثاني وكلهم ما أبيهم، في هذي الحالة لازم أعطي أدوية تضاد الاكتئاب، وأدوية تضاد ال (mania mood stabilizers) مع بعض - Seizure disorders. → b/c they decrease its threshold.

Monoamine oxidase

MAO is a mitochondrial enzyme found in nearly all tissues, and they exist in two forms:

- **MAO-A:** responsible for **NE**, **5-HT** catabolism. It also metabolizes tyramine of ingested food better for depression .
- **MAO-B:** is more selective for dopamine metabolism these better for parkinson, they have risk factor for mania



Monoamine Oxidase Inhibitors (MAOIs)

Better than non-selective

Non-Selective Irreversible

- **Phenelzine** (Irreversible) long acting
- **Tranylcypromine** (reversible)

→ 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.

Mnemonics:
phen elzine (as the cute phen) is in a long distance relationship (long acting) w/ someone called trany

Selective

- **Moclobemide (A)**
  The drug of choice for the depression, because it is selective & reversible
- **Selegiline (B)**

Mnemonics:
- Maclobemide: maco (no more) mid (this why you won't feel depressed but just for a short time bc the final is coming)
- Selegiline: seleg (سليقis a soft food therefore it's good for parkinsonism since they'll have difficulty in eating hard food)
- M letter is before S letter so M would be acting on (A) while S on (B)

Monoamine Oxidase Inhibitors (MAOIs)

Drug	Phenelzine	Tranylcypromine	Moclobemide	Selegiline
Type	**Non- selective** act on MAO A & B mostly in labs not for patients		**Selective & Reversible**	
	Irreversible long acting (2-3 weeks)	reversible	- Act on MAO-A - **Anti depressant action.** - **Short acting**	- Act on MAO-B - Used in the treatment of **Parkinsonism.**
Clinical Uses	Only used for refractory cases and in **atypical depression where phobia and anxiety are prominent symptoms.** -limited uses because: • ADRs • food and drug interactions • low antidepressant efficacy = Low benefit/risk ratio.			
ADRs	- Anti-muscarinic effects - Postural hypotension - Sedation - sleep disturbance - Weight gain. ▪ **Specific ADRs for(Phenelzine):** - **Sexual dysfunction** - **Hepatotoxicity**			
Drugs Interaction	**1- Pethidine**: MAOIs interact with the **opioid receptor agonist** (pethidine) which may cause **severe hyperpyrexia, 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. **2- Levodopa**: Precursor of dopamine can interact with MAOIs leading to **hypertensive crisis**. **3- Amphetamine and Ephedrine**: Indirectly acting **sympathomimetic** can interact with MAOIs causing the liberation of accumulated monoamines in neuronal terminals leading to **hypertensive crisis.** **4- TCAs**: (inhibitors of monoamine reuptake) can interact with MAOIs (inhibitors of monoamine degradation) leading to **hypertensive crisis.** 5- MAOIs & SSRIs: Serotonin syndrome. -When the doctor wants to switch drugs he has to stop the drug first and wait 2-3 weeks before switching to another drug (washout period)			

MAOIs interaction with tyramine

- This occurs when **Tyramine** are taken with MAOIs
-Tyramine rich foods include old cheese, concentrated yeast products, Pickled or smoked fish, Red beans, Red Wine, Chicken liver, Sausages).
-Tyramine in food is normally degraded in the in the gut by MAO-A.
-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**, severe hypertension, severe headache and fatal intracranial hemorrhage.

-Important Note: Moclobemide has No cheese reaction occurs with its use.

New Antidepressant

The **new** groups are **6** in number:

1. Selective Serotonin Reuptake Inhibitors (**SSRIs**)
2. Noradrenergic and specific Serotonergic Antidepressant s (**NaSSA**)
3. Serotonin-2A Antagonist and Reuptake Inhibitors (**SARI**)
4. Serotonin and Noradrenaline Reuptake Inhibitors (**SNRIs**)
5. Norepinephrine and Dopamine Reuptake Inhibitors (**NDRI**)
6. NE Selective Reuptake Inhibitors (**NRIs**)

New Antidepressant

1. Selective Serotonin Reuptake Inhibitors (SSRIs)

The **most widely utilized** class of antidepressants in **clinical practice**

How does this group act?

By increasing the level of **serotonin** (5-HT) in the synaptic gap by **inhibiting** its re-uptake within the brain.
→ **Block 5HT transport → ↑ 5-HT levels in synapse.**

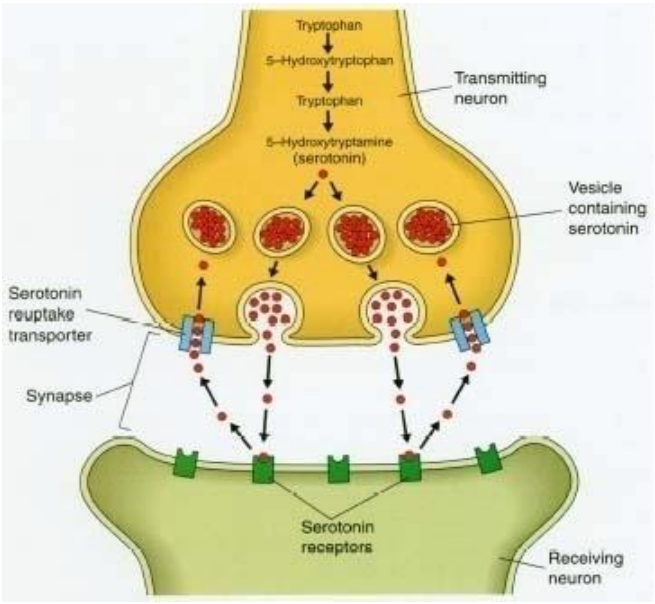
Why do we call them SELECTIVE?

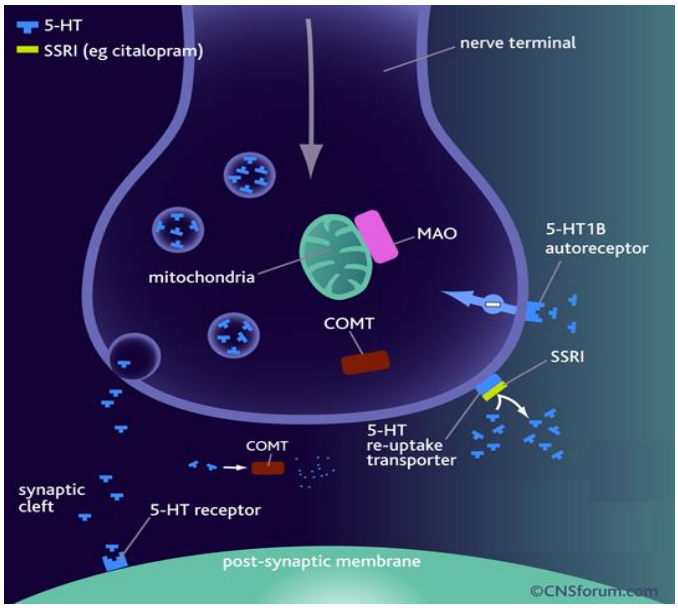
Because they affect only the reuptake pumps responsible for Serotonin only.

Examples:

Fluoxetine, **Paroxetine**, **Fluvoxamine**, **Sertraline**, **Citalopram**, **Escitalopram**

Mechanism of Action of SSRIs





Selective serotonin reuptake inhibitors **(SSRI):**
Binds to SERT→ Block 5HT transport➔ increase 5-HT levels in synapse.

They have **No effect on NET** (norepinephrine transporter) and they do **not block mAch**, **H**, or **α1** Adrenoceptor ➔ so **no antimuscarinic** nor **sedative** effects **Except Paroxetine** → has sedative & anti-muscarinic effects.

They are nearly of comparable efficacy but of preferential response in each individual (the response differ from one to another)

SSRIs (cont.)

Advantages

- The Most commonly prescribed antidepressants
- Lacks cardiovascular and anticholinergic side effects compared to **TCA** (tricyclic antidepressants)
- In contrast to **MAOI** (monoamine oxidase inhibitors), **they do not cause 'cheese' reaction**.
- **Safer** (low risk of overdose)
- **Acute toxicity is less than that of MAOIs or TCAs**

P.K

- **$T_{1/2}$**:
→ **Too long** (3-11 days)but the dose is for everyday: **Fluoxetine** (Prozac)
→ **Moderate length** (~24hr): **Sertraline**, **Paroxetine**, **Citalopram**.
- Metabolized by **P450** then **conjugation**.
  → They are **enzyme inhibitors**
  → Weak inhibitors → **Sertraline**, **Citalopram** → ↓ interaction
  → Strong inhibitors toxicity will increase → **Fluoxetine**, **Paroxetine** → ↓ metabolism of TCAs, neuroleptics, some antiarrhythmics, β-blockers.

Indications

- Same as for TCA, but it is effective in the following conditions
- Depression.
- Anxiety Disorder.
- **Eating disorders- bulimia nervosa** (الرغبة في الأكل بشراهة) (**fluoxetine**), **Anorexia nervosa** *(restricting eating).* (they are opposite but the drug is for the psychological causes).
- Post traumatic stress disorder.
- Premenstrual dysphoric disorder.
- Attention Deficit Hyperkinetic Disorder.
- **Treatment of premature ejaculation → by stimulation of 5-HT2A.**

ADRs

- GIT symptoms: Nausea, vomiting and **diarrhea** (due to 5-HT3 stimulation).
→ b/c of increased serotonergic activity in the gut.
- Changes in appetite weight loss/gain (5-HT3 stimulation).
- **Sleep disturbances**: Drowsiness with **Fluvoxamine**.
- Anxiety & Tremors (if combined with other antidepressants).
- **Sexual dysfunction**: Loss of libido (الرغبة) , **delayed ejaculation (5-HT2A stimulation)**
→ useful for treatment of premature ejaculation. (b/c of increased serotonergic tone at the level of the spinal cord and above)

Discontinuation syndrome

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

Drug interactions of SSRIs

Important

• 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** if you want to combine with tricyclic choose drug selective for NE , also if combined with non selective tricyclic it will cause serotonin syndrome.

• SSRIs should not be used in combination with **MAOIs** because of the risk of **life-threatening "serotonin syndrome" (tremors, hyperthermia, cardiovascular collapse and death)**. Both drugs require a "*washout*" period of **6 weeks** before the administration of the other.

Fluoxetine

It's different from others members of this class in:

1- It has a **longer $t_{1/2}$ (50 hrs)**.

2- Available → as **sustained release preparations** الشركات تصنع هالنوع تجلس الجرعة لأسبوع في البداية اول ماتاكلة يعطي مفعول قوي ثمن يخف المفعول شوي شوي → once weekly.

3- Its metabolite **norfluoxetine** = **potent** as parent drug $t_{1/2}$ =**10** days.

2. Noradrenergic and specific Serotonergic Antidepressants (NaSSA)

Mirtazapine

Pharmacodynamic

- **α_2** receptor antagonist
- Increase **NE** and **5HT** levels
- **Blocks $5HT_{2A}$, $5HT_3$ and thus reduces side effects of sexual dysfunction and anxiety.**
- Blocking **$5HT_{2C}$**, and **H_1** receptors cause **side effects**:
  - **Sedation** → (H1 blocking effect)
  - **weight gain** → (5-HT2C blocking effect)

Preferred in cancer patients because:

1- It improves appetite
2- ↓ nausea & vomiting (by 5-HT_3 blocking)
3- ↑ body weight(5-HT2C blocking effect)
4- Sedation (H1 blocking effect)
5- Less sexual dysfunction (by 5-HT_2 blocking)
6- Has **no** anti-muscarinic effect.

Other types of new antidepressant

3- Serotonin-2A Antagonist and Reuptake Inhibitors
- Selective **Blockage** of 5HT to Reduce Depression
- **Trazodone, Nefazodone**

4-Serotonin and NE Reuptake Inhibitors
- Selective Blockage of **5HT** and **NE**
- **Venlafaxine**

5- NE and Dopamine Reuptake Inhibitors
- NE and DA Reuptake Inhibitor, With No Direct Action on 5HT
- **Bupropion**

6-NE selective Reuptake Inhibitors
- Block only NET
- **Reboxetine**

New antidepressant

Drug	3. Serotonin-2A Antagonist and Reuptake Inhibitors (SARI) **Trazodone, Nefazodone** (Serotonin modulators)	4. Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs) **Venlafaxine** (effexor)
Mech. of Action	**1- Blocks 5HT uptake selectively** but in a **less potent** manner than **TCAs**. This reduces depression. **2-** However, they are powerful **5HT2A antagonists**, blockade of $5HT_{2A}$ receptors **stimulates 5HT1A receptors**, which may help reduce depression. **3- $5HT_{2A}$ antagonism** also reduces the **risk of anxiety**, **sedation** or **sexual dysfunction** which is normally associated with **SSRIs.** **4- Nefazodone**: Structurally related to **trazodone** but has **less sedative** effect and **does not** block a- adrenoceptors , however; it likes most SSRI inhibit **P450 3A4 isoenzyme**.	**1-** It is used primarily for the treatment of **depression**, generalized anxiety disorder, and social anxiety disorder in adults. **Venlafaxine** is the **first and most commonly used SNRI**. (it is more tolerable) **2-** Selective **5HT** and **NE uptake blockers** combines the action of **SSRI** and **NRI**, but without **a1, M1 cholinergic or H receptor** blocking properties. **3- Desvenlafaxine** is a metabolite of **Venlafaxine** - Similar to TCAs, but they have better tolerability.

Class of drugs

Drug	5. Norepinephrine and Dopamine Reuptake Inhibitors (NDRI) Bupropion	6. NE Selective Reuptake Inhibitors (NRIs) Reboxetine
Mech. of Action	**1-** Is **unique** in possessing significant potency as **NE and DA reuptake inhibitor**, with **no** direct action on 5HT.	**1- Block only NET** (norepinephrine transporter) → No affinity for **5HT**, **DA**, **ADR**, **H**, **mAch** receptors. So, has positive effects on the concentration and motivation in particular. → effects of NE.
Indications	Therapeutic uses: 1- Treatment of **major depression** and **bipolar depression**. 2- **Can be used for smoking cessation.** (because of DA release) → As it reduces the severity of nicotine craving & withdrawal symptoms.	---
Advantages	**1- No sexual dysfunction** → (b/c no 5-HT blocking effect) given in young. (combination with SSRIs to avoid **sexual dysfunction**) **2- No weight gain [No 5HT effect]** 3- No orthostatic hypotension.	**Safe to combine with SSRIs** → **Minimal side effects** only related to activation of ADR system as tremor, tachycardia, and urinary hesitancy.
ADRs	**Seizures** → **it ↓ threshold of neuronal firing**. (increases the stimulating NT) → Similar to TCAs. **-contraindicated in epileptic patient.**	---

Clinical uses of Antidepressant Drugs

1. Endogenous depression → **SSRIs** (**first choice**), new generation and **tricyclics** can be used
2. **Panic disorders** (**imipramine** or **SSRIs**)
3. Obsessive Compulsive Disorders (**SSRIs** and **Clomipramine**), & Chronic pain (**Amitriptyline**)
4. **Anorexia nervosa and Bulimia** (**SSRIs**)
5. **Schizo-Affective Disorders** (**Amoxapine** or SSRI + **Haloperidol**) → you have to give him Anti-depressant + Anti-psychosis.
6. Anxiety disorders (**Amitriptyline**)
7. Migraine and Anxiety & IBS (**Amitriptyline**)
8. **Nocturnal Enuresis in children** e.g. **Imipramine**
9. **Premature ejaculation** (**SSRI**)
10. Neuropathic Pain (Dual NE and 5-HT reuptake Blockers)

Prof.Yieldez notes:

- **Very important to know the <u>Mechanism Of Action</u> of each drug (antidepressant <u>Old&New</u>).**
- **Q: Which one do you prefer from the MAO inhibitors?**
  Moclobemide " The Best" Why?
  Selective,reversible , Also has:
  - No severe sedative effect
  - No anticholinergic effect
  - No alpha blocking effect
  هذا الدواء نبهت عليه بروف يلدز كثير واحتمال كبير يجي بال MCQs
- **Important to know drugs that works in reuptake transport , which are :**
  1- TCA→ work on both serotonin + NE.
  2-SSAI→ work on serotonin.
  3- venlafaxine→ work on serotonin + NE (more selective).
  4- Reboxetine→ work on NE.
  Bupropion→ work on dopamine .
- **Mirtazapine it's important.**

Summary of old antidepressants

Drug	TCA's	MAOI
Mechanism of Action	Inhibit reuptake of norepinephrine and serotonin = ↑ conc	Inhibits MAO which is responsible for NE, and 5-HT catabolism 1- Non Selective Inhibitors (MAO-A & MAO-B) Irreversible → **Phenelzine**, long acting Irreversible → **Tranylcypromine** 2- Selective Reversible Inhibitors → **Moclobemide**, (MAO-A) (antidepressant action, Short acting) □ **Selegiline**, (MAO-B) (used in the treatment of Parkinsonism)
P.K + Drug Interaction	- Lipophilic - Metabolized into metabolites that retain the biological activity - Strongly bound to plasma proteins Aspirin, and **Phenylbutazone** (compete for plasma protein binding site and increase potential)	Pethidine (severe hyperpyrexia, coma, hypotension) • Levodopa, amphetamines, Ephedrine, and TCAs(Hypertensive crisis) • SSRI (serotonin syndrome)
Indications	Used for major depression, chronic neuropathic pains or unexplained body pains. Imipramine is used for nocturnal enuresis in children and geriatric patients.	Refractory cases Atypical depression
ADRs	TCAs have narrow therapeutic index - Anti-cholinergic effects (M1), Anti-histaminic effects (H1) Anti-adrenergic effects (a1) - Narrow therapeutic index -> toxicity + haemodialysis is not effective. **Weight gain**, sexual dysfunction & impotence	Cheese reaction: (MAOI + food containing tyramine → false neurotransmitter → Hypertensive crisis)*except for **Moclobemide** Antimuscarinic effects, Postural hypotension, Sexual dysfunction (phenelzine.), Sedation, sleep disturbance. Weight gain, Hepatotoxicity (**phenelzine**).
C.I	- Glaucoma, Enlarged Prostate - Monotherapy in manic-depressive illness - Seizure disorders - **TCAs should not be given with MAOIs "hypertensive crisis".**	------

Summary of new antidepressants

Group	SSRI's	NaSSA	SARI
Drug	Fluoxetine, Paroxetine, Fluvoxamine, Sertraline, Citalopram, Escitalopram	Mirtazapine	Trazodone, Nefazodone
MOA	Inhibit reuptake of serotonin = ↑ conc	• Blocks presynaptic a2 • Blocks 5-HT3 & 5-HT2A	Blocks 5HT uptake 5HT2A antagonists
General Information	No antimuscarinic nor sedative effects Except Paroxetine. Shouldn't use with: TCA (increase toxicity) MAOI (Serotonin syndrome) They are enzyme inhibitors	Preferred in cancer patients because: 1. Improves appetite 2- nausea & vomiting (5-HT3 blocking) 3- body weight 4- Sedation (potent antihistaminic) 5- Less sexual dysfunction (5-HT2 blocking) 6- Has no anti-muscarinic effect .	---
Indications	Depression Eating disorders- bulimia nervosa (fluoxetine), Anorexia nervosa. Treatment of premature ejaculation (via stim of 5-HT2A).	Anti-depressant for cancer patients	---
ADRs	GIT symptoms (5-HT3 stimulation) Drowsiness (by fluvoxamine) Loss of libido, delayed ejaculation. (5-HT2A stimulation) Discontinuation syndrome	Blocking 5HT2C, and H1 receptors cause side effects: sedation, and weight gain.	---

Summary of new antidepressants (cont.)

Group	SNRIs	NDRI	NRIs
Drug	Venlafaxine	Bupropion	Reboxetine
MOA	Selective 5-HT and NE reuptake inhibitors But without a1, M1 cholinergic or H receptor blocking properties.	NE and DA reuptake inhibitor No action on 5HT	NE reuptake inhibitor
General Information	Venlafaxine is the first and most commonly used SNRI. Desvenlafaxine is a metabolite of Venlavaxine	No weight gain [No 5HT] No orthostatic hypotension	Safe to combine with SSRI
Indications	depression, generalized anxiety disorder, and social anxiety disorder in adults.	Treatment of major depression and bipolar depression. Can be used for smoking cessation. No sexual dysfunction -> given to young adults.	Limited to ADR system; Seizures, tachycardia, and urinary hesitancy.
ADRs	---	Seizures	

Questions (old antidepressants)

MCQs

Q1/ according to symptoms classification of depression, mild depression is ____.

A-self-limiting

B-lead to suicide thoughts sometimes

C-difficulty dealing with surrounding environment.

D-A and C.

Q2/ Type of depression associated with (mania).

A-Unipolar depression. B-Bipolar depression. C-psychotic depression. D-Atypical depression.

Q3/ Hypertensive patient is under treatment plan, she's taking reserpine. She came to psychiatry clinic complaining of depression.

Which of the follow effect is produced by this drug?

A-blocking of Alpha receptors B-Blocking beta receptors. C-inhibition of serotonin effect. D-depletion of serotonin and NE storage.

Q4/which of the following Drugs it's mechanism of action to inhibit reuptake of serotonin and NE? A-moclobemid. B-Amoxapine. C-Fluoxetine. D-venlafaxine.

Q5/ mechanism of action of TAC (tricyclic antidepressant)

A- ↓ reuptake of serotonin. B-↓ reuptake of dopamine. C-↓reuptake NE. D-A&C

Q6/ True statement

A-TAC are lipophilic, excreted by kidneys.

B-TAC are lipophilic, Eliminated by Hepatic oxidation.

C-TAC are not lipophilic, excreted by kidneys.

D-TAC are lipophilic, Eliminated by hepatic demethylation.

MCQs Answers:
1-A
2-B
3-D
4-D Why? because it's more selective
5-D
6-B

Questions (new antidepressants)

MCQs

Q1/ which of the following drugs is SSRI (serotonin selective reuptake inhibitor)?

A-mirtazapine.

B-Trazodone.

C-venlafaxine.

D-fluvoxamine

Q2/ which of the following SSRI (serotonin selective reuptake inhibitor) has sedation and anticholinergic side effects?

A-sertraline.

B-paroxetine.

C- fluvoxamine.

D- paroxetine and fluvoxamine.

Q3/ which of the following SSRI (serotonin selective reuptake inhibitor) used to treat OCD?

A-sertraline.

B-paroxetine.

C- fluvoxamine.

D-fluoxetine.

Q4/patient with premature ejaculation. What is the recommended treatment in this case?

A- drugs block 5HT2A receptor.

B-drugs block 5HT3 receptor.

C-drugs stimulate 5HT2A receptor.

D-drugs block D2 receptor.

Q5A patient recently had stroke. And now he is on warfarin (anticoagulant medications). After 3 hours patient showed in MRI, intra-abdominal bleeding.After taking history, patient is on antidepressant medication. What do you think the drug might be?

A-Trazodone.

B-Reboxetine.

C-Nefazodone.

D-venlafaxine.

Questions (new antidepressants)

MCQs

Q6/ which of the following is one of the therapeutic uses of Bupropion (NDRI)?

A-Anxiety.

B- OCD.

C-seizures preventions.

D-smoking cessation.

MCQs answer:

1. D
2. B
3. C
4. C
5. C
6. D

SAQ

Q1/ patient with very severe depression. His uncle is an undergraduate medical student. He advised him to take Citalopram combined with Moclobemide.

Q1.1/ mention the mechanism of action of each drug?

Citalopram: SSRI.

Moclobemide: MAOI

Q1.2/ what will result in combining these 2 drugs?

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

Q1.3/What is the recommended time to switch these drugs?

Washout period of 6 weeks

Q2/ patient was diagnosed with medulloblastoma recently. during chemotherapy she developed nausea, then vomited. Oncologist prescribed her Mirtazapine.

Q2.1/Which type this drug belongs to?

Antidepressants

Q2.2 What is the mechanism of action behind this drug+ targeted receptors?

NASSA (noradrenalin, specific serotonergic antidepressant).

-Alpha2 receptor -5HT2A receptor

-5HT3 receptor -5HT2C receptor -H1 receptor

Q2.3/ Give 3 reasons why it's preferable with Cancer patients?

1-improves appetite.

2-increase Body weight.

3-sedation due to anti-histamine effect.

Questions

SAQ

Q1/ types of medication (According to site of action) used in depression?

1-TAC: Blocking presynaptic monoamine reuptake channel.

2-MAOI:inhibiting MAO Enzyme within presynaptic Terminal.

3-Alpha 2 blockers: By blocking presynaptic Alpha 2 receptor.

Cases

Q1/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.

Explain by which mechanism the drug work and it where it takes place?

It acts on blocking presynaptic MAO enzyme.

Q1.2/Why do you think he developed hypertension in relation with patient history?

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

Q1.3/Which drug do you think would have been a better option for the patient, why?

Moclobemide. It does not have "cheese reaction"

Team leaders:

Ghaida Saad Alsanad
Omar Alsuhaibani

Team Members:

Adel Alsuhaibani
Sultan Alnasser
Dawood Ismail
Abdulrahman Alaujan
Rinad Alghoraiby
Munira Alhadlg
Razan Alhamidi
Alanoud Almansour
Saif Almeshari

References:

- Doctors' slides and notes.
- pharmacology Team 435.

Special thank for team 435❤

@Pharma4370

Pharm437@gmail.com