#8-10
Drugs used in depression Old & New

Objectives:

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

Color index:

- Drugs names
- Doctors notes
- Important
- Extra

قبل أن نبدأ المحاضرة، ندعوا للبروف **عبدالقادر الحيدر** بالرحمة؛
هو الذي عمل المحاضرة الأصلية التي استخدمناها كمرجع.
نسأل الله أن يغفر له ويرحمه ويجعل قبره روضة من رياض الجنة.

Depression

Definition

Depression (major depressive disorder or clinical depression) is a common but serious mood 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)

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

Forms 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
unrelated to external stresses
endogenous depression

2- Bipolar depression (manic-depressive):

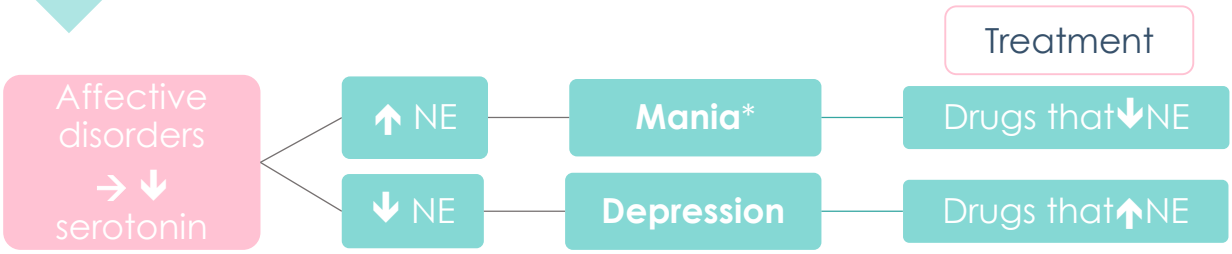
In which depression alternates with **mania**
It is mainly hereditary and appears in early adult life

Other forms of depression:

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

To Understand Better

1. One main cause of depression is the reduction in the concentration of certain neurotransmitters in the brain, such as serotonin and dopamine
2. Which leads to disturbed neuronal signal processing
3. which in a long run leads to alterations in the structure of the neuronal networks
4. These structural changes are believed to be one of the main reasons for depression.



- What is the evidence to support this theory ?
Amphetamine causes **mania** while **reserpine** and **methyldopa** produce depression (these drugs depletes NE and dopamine storage).

5-HT deficiency	may cause the sleep problems, 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**

To Understand Better

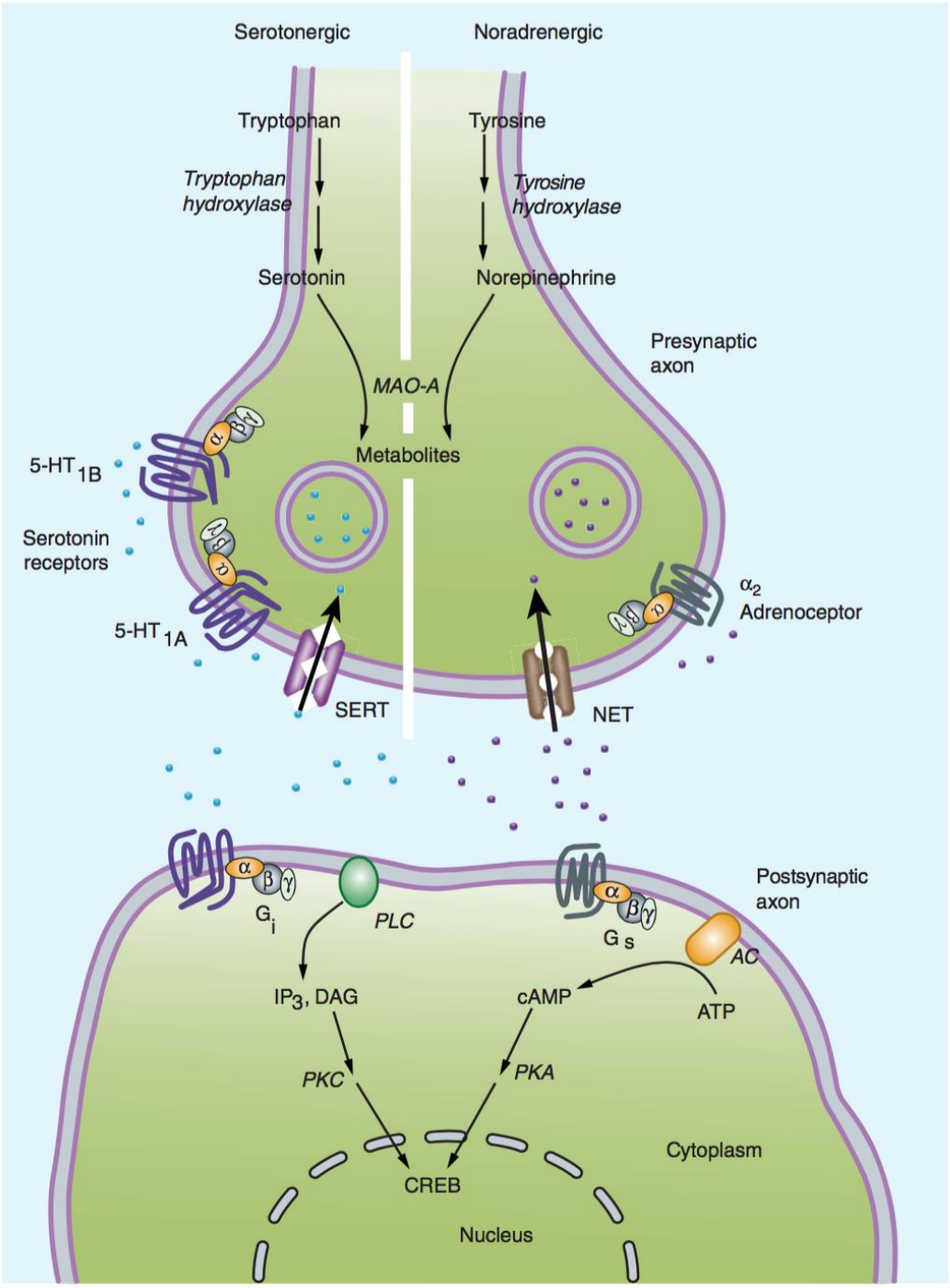


FIGURE 30–2 The amine hypothesis of major depression. Depression appears to be associated with changes in serotonin or norepinephrine signaling in the brain (or both) with significant downstream effects. Most antidepressants cause changes in amine signaling. AC, adenylyl cyclase; 5-HT, serotonin; CREB, cAMP response element-binding (protein); DAG, diacyl glycerol; IP_3, inositol trisphosphate; MAO, monoamine oxidase; NET, norepinephrine transporter; PKC, protein kinase C; PLC, phospholipase C; SERT, serotonin transporter. (Redrawn, with permission, from Belmaker R, Agam G: Major depressive disorder. N Engl J Med 2008;358:59.)

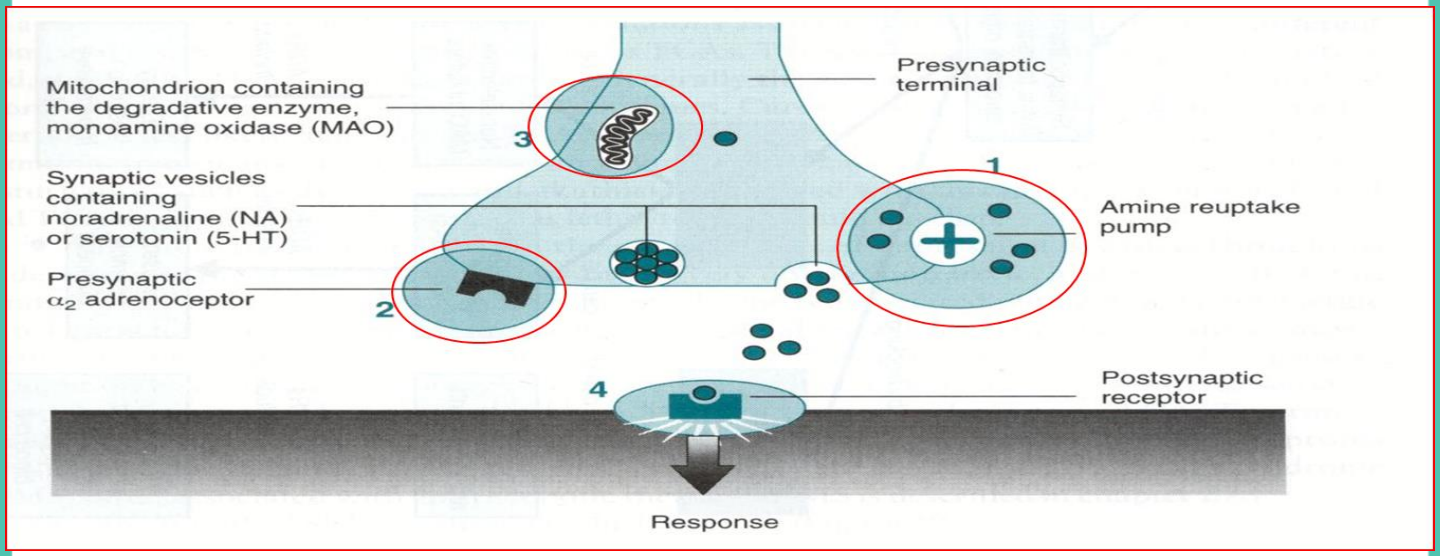
Antidepressants

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 of beta-, alpa-2 and 5-HT2 receptors**.

Desensitization (down-regulation) of **β- adrenoceptors** (decrease c-AMP) is very important and is related to clinical response.

Sites of Action for Antidepressants:



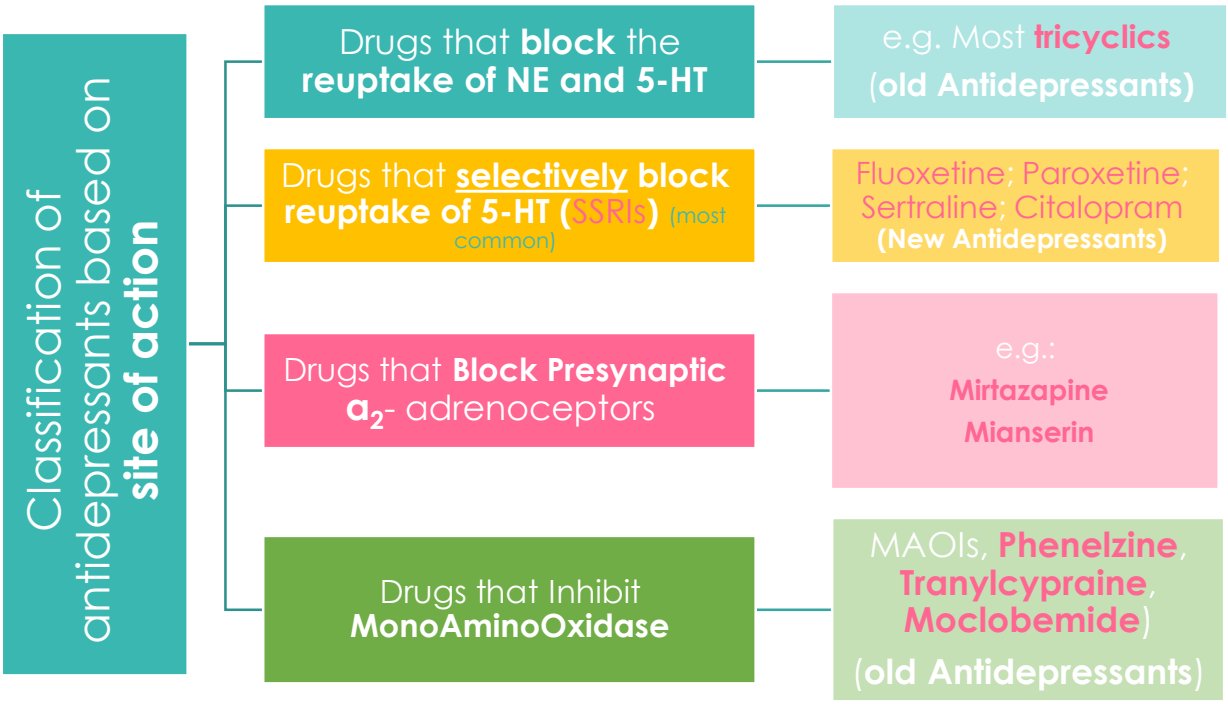
1- **Monoamine** (**NE** or/and **5-HT**) **re-uptake pump inhibitors**

2- **Blockade of pre-synaptic a_2 receptors**

3- **Inhibition of MAO enzyme**

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, Phenelzine, 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
Serotonin Reuptake Enhancer	Tianeptine
Noradrenergic and Specific Serotonergic Antidepressant (NaSSA)	Mirtazapine



Old Antidepressant

The oldest one

Tetracyclic antidepressant

Tricyclic:

- **Imipramine**
- **Desipramine**

Transforms to

- **Clomipramine**
- Amitriptyline
- Nortriptyline

Transforms to

- Doxepin
- Trimipramine

- **Maprotiline**
- **Amoxapine**

Tetracyclic

Monoamine Oxidase inhibitors

Only used for **refractory cases** and in atypical depression where **phobia** and **anxiety** are prominent symptoms.

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.

30:05 minutes

30:33 minutes

Old Antidepressant

Drug

Tricyclics (TCAs)

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

Mech. 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 actions

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.

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- **Peak levels**: 2-6 hours. They are "lipophilic" in nature (well absorbed from the GIT and cross the blood brain barrier).
- **Elimination**: **hepatic oxidation**. They 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.

Indications

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

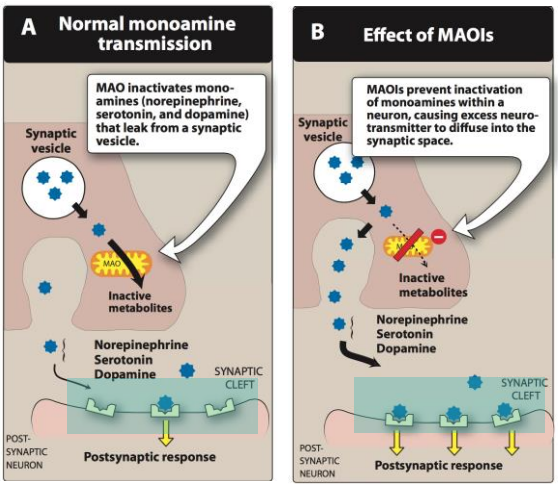
Drug	Tricyclics (TCAs) (cont.)
ADRs	**TCAs block: α_1** adrenergic receptors - **H1** histamines receptors - **M1** cholinergic receptors - **5HT2** receptors; - **Anti-cholinergic**: Dry mouth (dental problem; **xerostomia**), **blurred vision**, constipation & urine retention, aggravation of **glaucoma**. - **Anti-histaminic**: **Sedation**, confusion. → H1 receptor effects. - **Anti-adrenergic**: Postural hypotension, arrhythmias, conduction defects. - **Weight gain**, sexual dysfunction & impotence. → old group causing sexual dysfunction. - **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 (monoamine oxidase inhibitors, which are inhibitors of monoamine degradation) → cause **hypertensive crisis**. - **Additive to anti-psychotics and anti-parkinsonism** (which have anti-cholinergic effect) → increase anti-cholinergic effects. - A helpful picture summaries 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 عنه 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 الmania مع بعض (mood stabilizers) - Seizure disorders. → bc they decrease its threshold. - Cardiovascular (IHD (ischemic heart disease) & arrythmias)

Monoamine oxidase

What is it?

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.
- **MAO-B:** is more selective for dopamine metabolism



Monoamine Oxidase Inhibitors (MAOIs)

Non-Selective Irreversible

- **Phenelzine** (Irreversible)
- **Tranylcypromine** (Irreversible)

→ 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.

Selective

Better than non-selective

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

Type	Drug	Sedation	Anti-cholinergic	Hypotension
Non-selective Irreversible	Isocarboxazid	+	++	+
	Phenelzine	+	++	+
	Tranylcypromine	-	+	+
Selective Reversible	Moclobemide	-	-	-

Monoamine Oxidase Inhibitors (MAOIs)

Drug	Phenelzine	Tranylcypromine	Moclobemide	Selegiline
Type	**Non- selective** mostly in labs not for patients		**Selective**	
	Irreversible long acting (2-3 weeks) Non-selective = act on MAO A & B		- Act on MAO-A - Anti depressant action. - Short acting - Reversible.	- 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**		الأسئلة بتجي على drug interaction بهذي الصياغة: واحد يأخذ MOAI وبعدها راح للدكتور وأعطاه دواء خاص بحالة ثانية عنده، وبعدها تكونت عنده أعراض الدرق (المذكورة هنا).. إيش الدرق اللي وصفه له الطبيب؟	
Drugs Interaction	**1- Pethidine**: MAOIs interact with the **opioid receptor agonist** (pethidine) which may cause severe hyperpyrexia, restlessness, coma, hypotension. **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 (NE) in neuronal terminals leading to hypertensive crisis. **4-** TCAs: (inhibitors of monoamine reuptake) can interact with MAOIs (inhibitors of monoamine degradation) leading to accumulation of monoamines (NE) which will cause hypertensive crisis. **5- MAOIs & SSRIs: Serotonin syndrome**. (give 1-2 weeks gap before initiating SSRIs)			

❖ Cheese Reaction

This occurs when **Tyramine** rich foods (Old cheese, Concentrated yeast products, Pickled or smoked fish, Red beans, Red Wine, Chicken liver, Sausages) are taken with **MAOIs**.

- 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** → It can be displaced from MAO-A by tyramine, and this mitigates the risk of food interactions

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**)

1. Selective Serotonin Reuptake Inhibitors (SSRIs)

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

How do 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.**

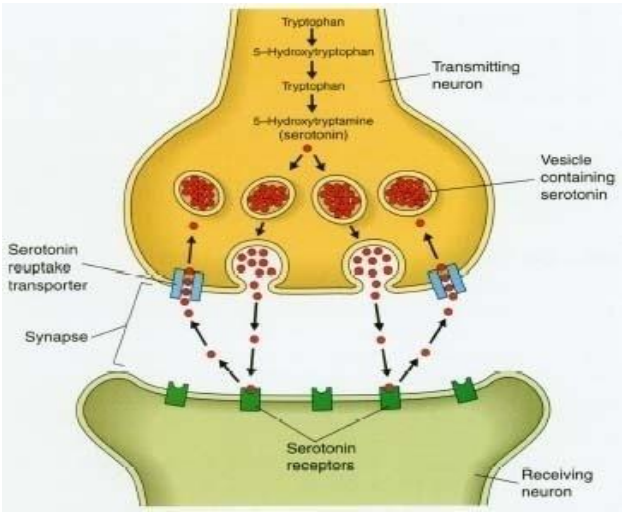
Why do we call them SELECTIVE?

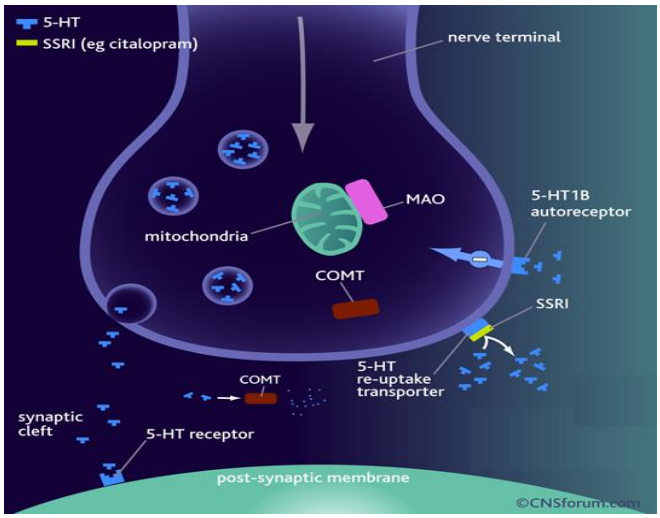
Because they affect only the reuptake pumps responsible for **Serotonin** only.

Examples:

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

Mechanism of Action of SSRIs





The serotonin transporter (SERT) is a monoamine transporter protein

This is a membrane protein that transports **serotonin** from **synaptic** spaces into **presynaptic** neurons.

Selective serotonin reuptake inhibitors (SSRI) and other antidepressants **block the SERT transporter**

The result is an increased availability of serotonin **(5-HT)** in the synaptic space

They have **No effect on NET** (norepinipherine transporter) and they do **not block mAch**, **H**, or **a1** 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 anther)**

For better understanding watch these videos

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**

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- $T_{1/2}$:
  - ➔ **Too long** (3-11 days): **Fluoxetine** (Prozac)
  - ➔ **Moderate length** (~24hr): **Sertraline**, **Paroxetine**, **Citalopram**.
- Metabolized by **P450** then **conjugation**.
  - ➔ They are **enzyme inhibitors**
  - ➔ Weak inhibitors → **Sertraline**, **Citalopram** ➔ ↓ interaction
  - ➔ Strong inhibitors → **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** (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 (due to 5-HT3 stimulation) and **diarrhea**. → bc of increased serotonergic activity in the gut.
- Changes in **appetite** weight loss (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. (bc 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

- 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**" (tremors, hyperthermia, cardiovascular collapse and death). Both drugs require a "***washout***" period of **6 weeks** before the administration of the other.

ADRs of SSRIs				
Drug	Cardiotoxicity	Nausea	Anti-cholinergic	Sedation
Citalopram	?	++	-	-
Fluoxetine	-	++	-	-
Fluvoxamine	-	+++	-	+
Paroxetine	-	++	+	+
Sertraline	-	++	-	-

REMEMBER

Fluoxetine differs from others members of this class in:

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

2- Available → as **sustained release preparations** → once weekly.

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

2. Noradrenergic and specific Serotonergic Antidepressants (NaSSA)

Mirtazapine

Pharmacodynamic

- **a_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 (appetite stimulant)**
4- Sedation (potent **antihistaminic**)
5- Less sexual dysfunction (by **5-HT_2 blocking**)
6- Has **no** anti-muscarinic effect.

Mirtazapine acts as an antagonist at central pre-synaptic alpha(2)-receptors, inhibiting negative feedback to the presynaptic nerve and causing an increase in NE release. Blockade of heteroreceptors, alpha(2)-receptors contained in serotenergic neurons, enhances the release of 5-HT, increasing the interactions between 5-HT and 5-HT_1 receptors and contributing to the anxiolytic effects of mirtazapine. Mirtazapine also acts as a weak antagonist at 5-HT_1 receptors and as a potent antagonist at 5-HT_2 (particularly subtypes 2A and 2C) and 5-HT_3 receptors. Blockade of these receptors may explain the lower incidence of adverse effects such as anxiety, insomnia, and nausea. Mirtazapine also exhibits significant antagonism at H1-receptors, resulting in sedation. Mirtazapine has no effects on the reuptake of either NE or 5-HT and has only minimal activity at dopaminergic and muscarinic receptors

Other types of new anti-depressant

4- Serotonin-2A Antagonist and Reuptake Inhibitors	5- Serotonin and NE Reuptake Inhibitors	6- NE and Dopamine Reuptake Inhibitors	7-NE selective Reuptake Inhibitors
Selective **Blockage** of 5HT to Reduce Depression	Selective Blockage of **5HT** and **NE**	NE and DA Reuptake Inhibitor, With No Direct Action on 5HT	Block only NET
Trazodone, Nefazodone	**Venlafaxine**	**Bupropion**	**Reboxetine**

▶ 11:09 minutes ▶ 16:18 minutes

New anti-depressant

Drug	3. Serotonin-2A Antagonist and Reuptake Inhibitors (SARI) **Trazodone, Nefazodone** (Serotonin modulators)	4. Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs) **1-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 α- 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 **α1, 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.
Advantages	1- **No sexual dysfunction** → (bc 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.	**1- Safe to combine with SSRIs** → **Minimal side effects** only related to activation of ADR system as tremor, tachycardia, and urinary hesitancy.
Indications	Therapeutic uses: 1- Treatment of **major depression** and **bipolar depression**. 2- Can be used for **smoking cessation**. (because of DArelease) → As it reduces the severity of nicotine craving & withdrawal symptoms.	Clinical depression
ADRs	**Seizures** → **it ↓ threshold of neuronal firing**. (increases the stimulating NT) → Similar to TCAs.	

Bupropion selectively inhibits the neuronal reuptake of dopamine, norepinephrine, and serotonin; actions on dopaminergic systems are more significant than imipramine or amitriptyline whereas the blockade of norepinephrine and serotonin reuptake at the neuronal membrane is weaker for bupropion than for tricyclic antidepressants. The increase in norepinephrine may attenuate nicotine withdrawal symptoms and the increase in dopamine at neuronal sites may reduce nicotine cravings and the urge to smoke. Bupropion exhibits moderate anticholinergic effects.

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 Bulemia (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)

Summary of old antidepressants

Drug	TCA's	MAOI
Mech. 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)
PKs + 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 α2 • Blocks 5-HT3 & 5-HT2A	Blocks 5HT uptake 5HT2A antagonists
General info	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
Mech. of action	Selective 5-HT and NE reuptake inhibitors But without α1, M1 cholinergic or H receptor blocking properties.	NE and DA reuptake inhibitor No action on 5HT	NE reuptake inhibitor
General info	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	

Side effects of antidepressant medications

Drug	Anticholinergic	Drowsiness	Insomnia/agitation	Orthostatic hypotension	QTc prolongation*	Gastrointestinal toxicity	Weight gain	Sexual dysfunction
Selective serotonin reuptake inhibitors (SSRIs)¶								
Citalopram	0	0	1+	1+	1+Δ	1+ (all SSRIs: see¶)	1+	3+
Escitalopram	0	0	1+	1+	1+	1+	1+	3+
Fluoxetine	0	0	2+	1+	1+	1+	1+	3+
Fluvoxamine	0	1+	1+	1+	0 to 1+	1+	1+	3+
Paroxetine	1+	1+	1+	2+	0 to 1+	1+	2+	4+
Sertraline	0	0	2+	1+	0 to 1+	2+◇	1+	3+
Atypical agents								
Agomelatine§ (not available in United States)	0	1+	1+	0	0	1+	0	0 to 1+
Bupropion	0	0	2+ (immediate release) 1+ (sustained release)	0	1+	1+	0	0
Mirtazapine	1+	4+	0	0	1+	0	4+	1+
Serotonin-norepinephrine reuptake inhibitors (SNRIs)¶								
Desvenlafaxine¥	0	1+	2+	0	0	2+ (initially)¶ 1+ (after 1 week)	0	3+
Duloxetine	0	0	2+	0	0	2+¶	0	3+
Milnacipran¥	1+	1+	0	0	0	2+¶	0	0
Venlafaxine¥	0	1+	2+	0	1+	2+ (immediate release)¶ 1+ (extended release)¶	0	3+
Serotonin modulators								
Trazodone	0	4+	0	1+ (hypnotic dose) 3+ (antidepressant dose)	1+ (hypnotic dose) 2+ (antidepressant dose)	1+ (hypnotic dose) 3+ (antidepressant dose)	0 (hypnotic dose) 1+ (antidepressant dose)	1+‡
Vilazodone	0	0	2+	0	0	4+†	0	2+
Nefazodone""	1+	2+	0	1+	0	2+	0	0
Tricyclic and tetracyclic antidepressants (TCAs)¶¶ جامع كل الADRs								
Amitriptyline	4+	4+	0	3+	3+	1+ (all TCAs see¶¶)	4+	3 to 4+
Amoxapine	2+	2+	2+	2+	2+	0	2+	ND
Clomipramine	4+	4+	1+	2+	2+	1+	4+	4+
Desipramine	1+	2+	1+	2+	3+	0	1+	ND
Doxepin	3+	3+	0	2+	3+	0	4+	3+
Imipramine	3+	3+	1+	4+	3+	1+	4+	3+
Maprotiline	2+	3+	0	2+	3+	0	2+	ND
Nortriptyline	2+	2+	0	1+	3+	0	1+	ND
Protriptyline	2+	1+	1+	2+	3+	1+	1+	3 to 4+
Trimipramine	4+	4+	1+	3+	1+	0	4+	ND
Monoamine oxidase inhibitors								
Isocarboxazid	1+	1+	2+	2+	0	1+	1+	4+
Phenelzine	1+	2+	1+	3+	0	1+	2+	4+
Selegiline	1+	0	1+	1+	0	0	0	0
Tranylcypromine	1+	1+	2+	2+	0	1+	1+	4+

Scale: 0 = none; 1+ = slight; 2+ = low; 3+ = moderate; 4+ = high; ND = inadequate data.

* Risk of QTc prolongation or torsades de pointes is also elevated with advanced age, female sex, heart disease, congenital long QT syndrome, hypokalemia or hypomagnesemia, elevated serum drug concentrations (eg, drug overdose, interacting drugs, organ failure) and combination of drugs with QTc prolonging effects. Refer to topic on acquired long QT syndrome.

¶ All SSRIs and SNRIs are associated with transient nausea and gastrointestinal discomfort upon initiation or dose increase.

Δ Based upon reports of dose related QTc prolongation and arrhythmia, the maximum recommended dose of citalopram is 20 mg for patients at increased risk of elevated citalopram serum concentrations.

◇ Sertraline is associated with higher rates of diarrhea.

§ Agomelatine may be hepatotoxic and is contraindicated with any degree of liver impairment. Transaminase monitoring is required.

¥ May cause persistent dose-related increases in blood pressure (primarily diastolic) and heart rate. Monitor blood pressure regularly.

‡ Trazodone is associated rarely with priapism, which is considered a medical emergency. Refer to UpToDate topic on Serotonin modulators.

† Vilazodone is associated with higher rates of nausea, vomiting, and diarrhea.

"" Caution: can cause liver failure. Not available in Europe, Canada, and several other countries.

¶¶ Gastrointestinal forms of anticholinergic side effects include: dry mouth, constipation, epigastric distress, decreased esophagogastric tone. Refer to "Anticholinergic" data for frequency rankings.

Created with data from:

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5. *Howland RH. A benefit-risk assessment of agomelatine in the treatment of major depression. Drug Saf 2011; 34:709.*

الدكتور كان أضافها في آخر سلايد عبارة عن مقارنة للآثار الجانبية للأدوية لو ذاكرتوها من الملف هذي مجرد تجميع لنفس المعلومات لتسهيل المقارنة د.بلدز: لو فيه أي زيادة في هذا الجدول فهي غير داخلة معنا.

SUMMARY Antidepressants

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)				
• Fluoxetine • Citalopram • Escitalopram • Paroxetine • Sertraline	Highly selective blockade of serotonin transporter (SERT) • little effect on norepinephrine transporter (NET)	Acute increase of serotonergic synaptic activity • slower changes in several signaling pathways and neurotrophic activity	Major depression, anxiety disorders • panic disorder • obsessive-compulsive disorder • post-traumatic stress disorder • perimenopausal vasomotor symptoms • eating disorder (bulimia)	Half-lives from 15–75 h • oral activity • *Toxicity:* Well tolerated but cause sexual dysfunction • risk of serotonin syndrome with MAOIs • *Interactions:* Some CYP inhibition (fluoxetine 2D6, 3A4; fluvoxamine 1A2; paroxetine 2D6)
• *Fluvoxamine: Similar to above but approved only for obsessive-compulsive behavior*				
SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs)				
• Duloxetine • Venlafaxine	Moderately selective blockade of NET and SERT	Acute increase in serotonergic and adrenergic synaptic activity • otherwise like SSRIs	Major depression, chronic pain disorders • fibromyalgia, perimenopausal symptoms	*Toxicity:* Anticholinergic, sedation, hypertension (venlafaxine) • *Interactions:* Some CYP2D6 inhibition (duloxetine, desvenlafaxine)
• *Desvenlafaxine: Desmethyl metabolite of venlafaxine, metabolism is by phase II rather than CYP phase I* • *Milnacipran: Significantly more selective for NET than SERT; little effect on DAT*				
TRICYCLIC ANTIDEPRESSANTS (TCAs)				
• Imipramine • Many others	Mixed and variable blockade of NET and SERT	Like SNRIs plus significant blockade of autonomic nervous system and histamine receptors	Major depression not responsive to other drugs • chronic pain disorders • incontinence • obsessive-compulsive disorder (clomipramine)	Long half-lives • CYP substrates • active metabolites • *Toxicity:* Anticholinergic, α-blocking effects, sedation, weight gain, arrhythmias, and seizures in overdose • *Interactions:* CYP inducers and inhibitors
5-HT_2 ANTAGONISTS				
• Nefazodone • Trazodone	Inhibition of 5-HT_{2A} receptor • nefazodone also blocks SERT weakly	Trazodone forms a metabolite (m-cpp) that blocks 5-$HT_{2A,2C}$ receptors	Major depression • sedation and hypnosis (trazodone)	Relatively short half-lives • active metabolites • *Toxicity:* Modest α- and H_1-receptor blockade (trazodone) • *Interactions:* Nefazodone inhibits CYP3A4
TETRACYCLICS, UNICYCLIC				
• Bupropion • Amoxapine • Maprotiline • Mirtazapine	Increased norepinephrine and dopamine activity (bupropion) • NET > SERT inhibition (amoxapine, maprotiline) • increased release of norepinephrine, 5-HT (mirtazapine)	Presynaptic release of catecholamines but no effect on 5-HT (bupropion) • amoxapine and maprotiline resemble TCAs	Major depression • smoking cessation (bupropion) • sedation (mirtazapine) • amoxapine and maprotiline rarely used	Extensive metabolism in liver • *Toxicity:* Lowers seizure threshold (amoxapine, bupropion); sedation and weight gain (mirtazepine) • *Interactions:* CYP2D6 inhibitor (bupropion)
MONOAMINE OXIDASE INHIBITORS (MAOIs)				
• Phenelzine • Tranylcypromine • Selegiline	Blockade of MAO-A and MAO-B (phenelzine, nonselective) • MAO-B irreversible selective MAO-B inhibition (low-dose selegiline)	Transdermal absorption of selegiline achieves levels that inhibit MAO-A	Major depression unresponsive to other drugs	Very slow elimination • *Toxicity:* Hypotension, insomnia • *Interactions:* Hypertensive crisis with tyramine, other indirect sympathomimetics • serotonin syndrome with serotonergic agents, meperidine

- Click on the picture to see it clearly

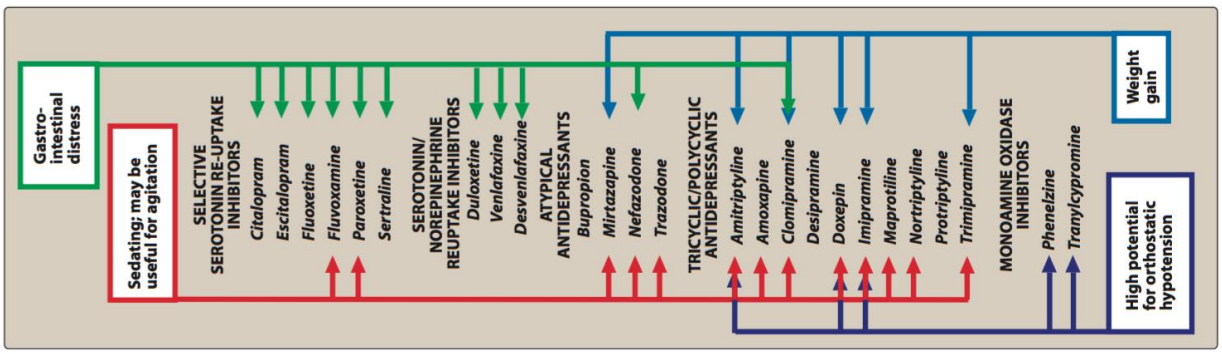

Figure 12.10
Side effects of some drugs used to treat depression.

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Sources:
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2-435's slides
3- Basic & Clinical Pharmacology by Katzung. 12th edition .
4- Pharmacology (Lippincotts Illustrated Reviews Series), 5th edition.