



Artery Academy

Done By Saja DW

اللهم إني أسألك فهم النبيين و حفظ المرسلين و الملائكة المقربين ..
اللهم اجعل ألسنتنا عامرة بذكرك و قلوبنا بخشيتك و أسرارنا بطاعتك انك على كل شيء قدير ..

Antidepressant Drugs

Pharmacology II
Dr. Heba Khader



Depression

أمراض الاكتئاب الشديد :

- The diagnosis of depression still rests primarily on the clinical interview.
- Major depressive disorder (MDD) is characterized by depressed mood most of the time for at least 2 weeks or loss of interest or pleasure in most activities, or both.
- In addition, depression is characterized by disturbances in sleep and appetite as well as deficits in cognition and energy.
- Thoughts of guilt, worthlessness, and suicide are common.

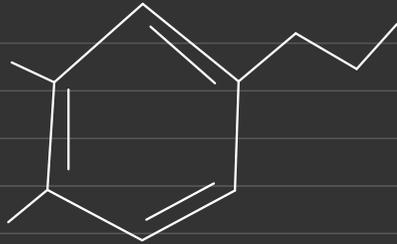
↓
الشعور بالذنب

↓
الشعور بانعدام بالذات

↓
أفكار بالانتحار

* Antidepressant

* these drug affected a class of neurotransmitters called **Monoamines**



Monoamines

* Several different researchers converged on an answer:

* the most effective antidepressants all seemed to act on **one Monoamine**.

Called **SEROTONIN**
Selective serotonin reuptake inhibitor or SSRI's

which **block** the reabsorption of Serotonin, leaving more available in the Brain.

↓
"Depressant" * بال
يكون عصب
نقص بال Monoamines
"Brain Synapses" بال

↓
عشان هيك الأدوية بتعمل
restore that balance
عند طريق ازيها تعمل

increasing the availability of Monoamines in Brain

* كبرى فرضيات =

① Monoamine Hypothesis

↓ 5HT / DA / NE → depression

Antidepressant → ↑ 5HT / DA / NE

② Neurotrophic Hypothesis

inflammatory factor in the Brain & over-excitation and over stimulation of neuronal activity

↓ neurogenesis

Stress → Cortisol released
irreversible

also decrease neurogenesis because of the increase circulating level of Cortisol

Antidepressant drug: reverse Cortisol effect

↑ BDNF : neurotrophic factor → stimulate dendritic factor sprouting & new neuron growth

↓
decrease Cortisol

TAKE IT EASY

Pathphysiology

✓

- **Neurotrophic Hypothesis**

- The evidence suggests that depression is associated with the loss of neurotrophic support (such as brain-derived neurotrophic factor (BDNF)) and that effective antidepressant therapies increase neurogenesis and synaptic connectivity in cortical areas such as the hippocampus.

②

①

✓

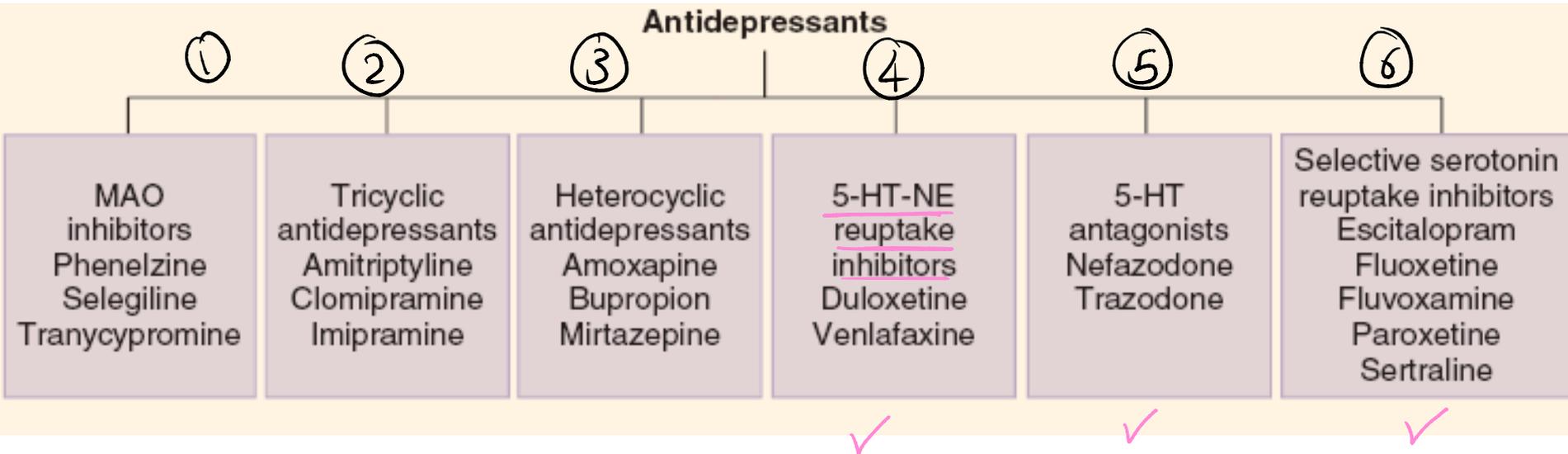
- **Monoamines Hypothesis**

- The monoamine hypothesis of depression suggests that depression is related to a deficiency in the amount or function of cortical and limbic:

1. Serotonin (5-HT)
2. Norepinephrine (NE)
3. Dopamine (DA)

Antidepressants

- The drugs used in major depressive disorder are of varied chemical structures; many have effects that enhance the CNS actions of norepinephrine, serotonin, or both.



① MAO inhibitor



prevent inactivation of
Monoamines within
a neuron

↑ Monoamines

② SSRIs



blocking reuptake
of Serotonin

↑ Serotonin in the
Brain

③ SNRIs & TCA



blocking reuptake of
norepinephrine & Serotonin

↑ norepinephrine
↑ Serotonin

④ 5-HT₂ antagonist



block of 5-HT₂

↑ Serotonin
↑ NE

Pharmacodynamics

- All currently available antidepressants enhance monoamine neurotransmission by one of several mechanisms:

- The most common mechanism is inhibition of the activity of serotonin transporter (SERT), norepinephrine transporter (NET), or both. Antidepressants that inhibit SERT, NET, or both include the **SSRIs** and **SNRIs**, and the **TCAs**.
- Another mechanism for increasing the availability of monoamines is inhibition of their enzymatic degradation (by the **MAOIs**).
- Additional strategies for enhancing monoamine tone include binding presynaptic autoreceptors (mirtazapine) or specific postsynaptic receptors (5-HT₂ antagonists and mirtazapine).

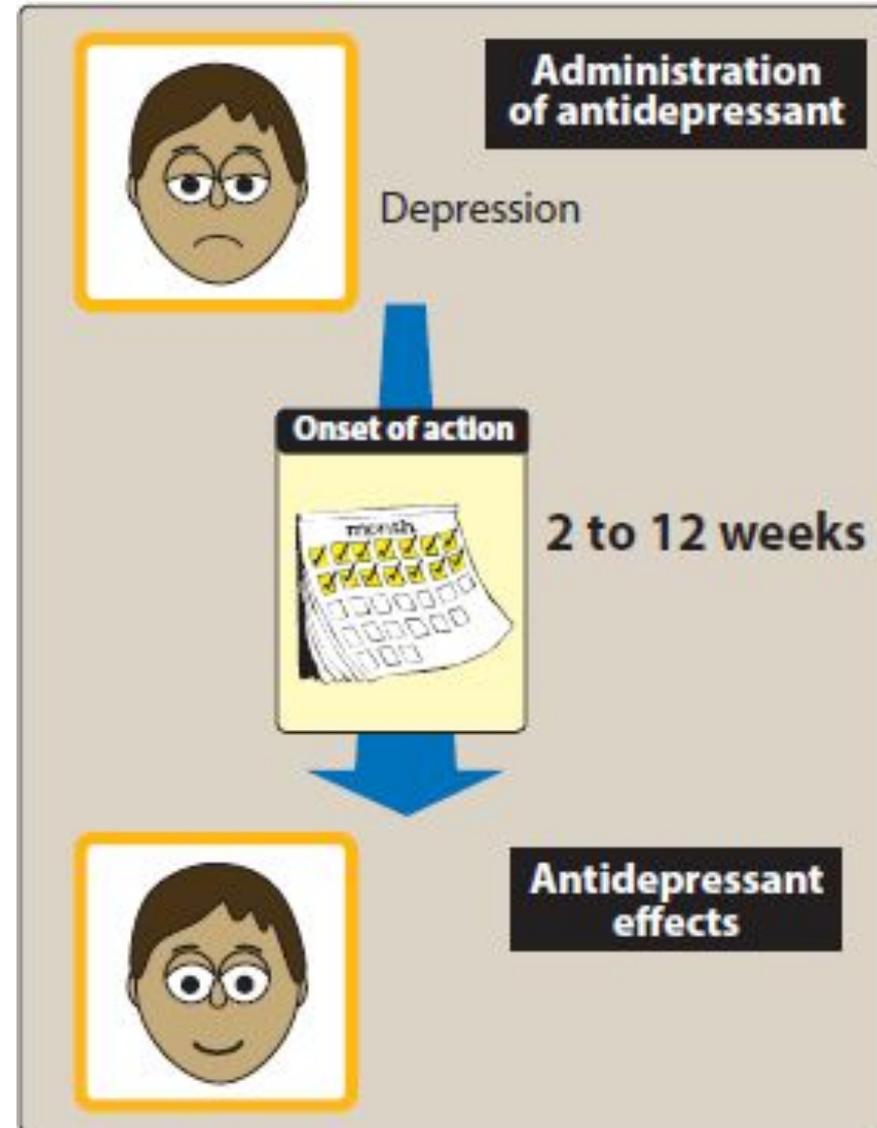
DRUG	UPTAKE INHIBITION	
	Nor-epinephrine	Serotonin
Selective serotonin reuptake inhibitor <i>Fluoxetine</i>	0	++++
Selective serotonin/norepinephrine reuptake inhibitors <i>Venlafaxine</i> <i>Duloxetine</i>	++* ++++	++++ ++++
Tricyclic antidepressant <i>Imipramine</i>	++++	+++

Handwritten annotations on the table:
 - An arrow labeled "5-HT₂ Serotonin II" points from the Venlafaxine row to the Serotonin column.
 - A double-headed arrow labeled "Same" connects the Duloxetine cells in the Nor-epinephrine and Serotonin columns.

Pharmacodynamics

- Antidepressants typically take at least 2 weeks to produce significant improvement in mood, and maximum benefit may require up to 12 weeks or more.

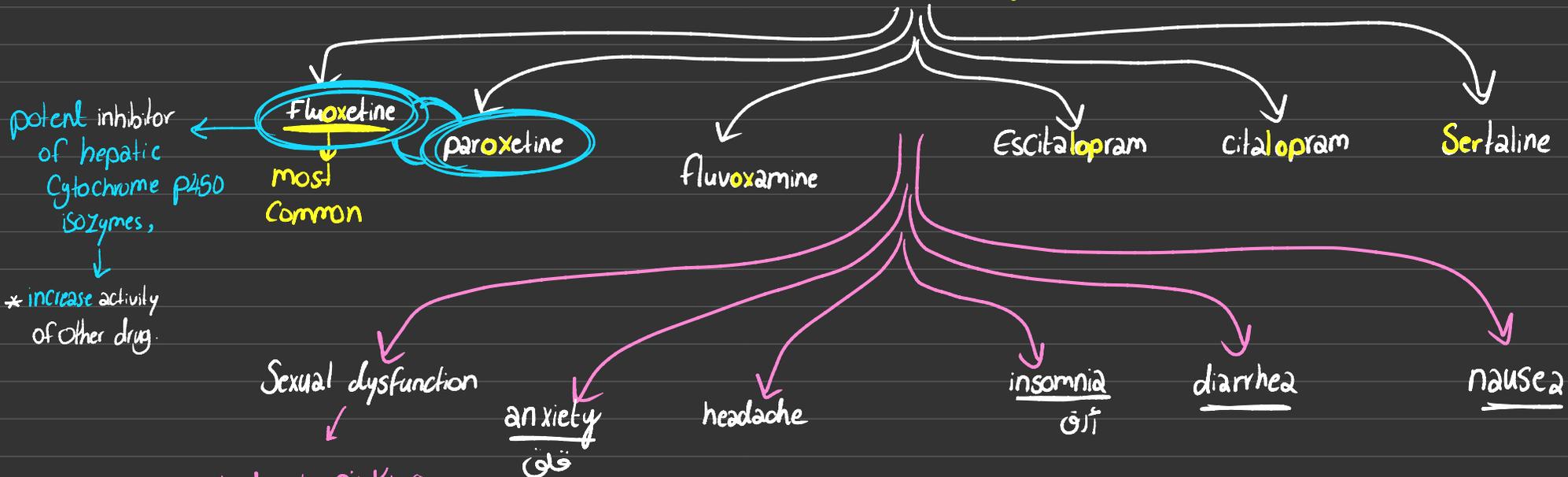
↑ Onset of action (2 - 12) w



1 Selective Serotonin Reuptake Inhibitors (SSRIs)

- There are currently six available SSRIs, and they are the most common antidepressants in clinical use. **Fluoxetine, paroxetine, fluvoxamine, sertraline, citalopram** and **Escitalopram**.
- **Fluoxetine** was introduced in the United States in 1988 and quickly became one of the most commonly prescribed medications in medical practice.
- The popularity of SSRIs stems largely from their ^① safety in overdose, ^② relative tolerability, ^③ cost (all are available as generic products), and ^④ broad spectrum of uses.

(SSRIs)



potent inhibitor of hepatic Cytochrome p450 isozymes,
 * increase activity of other drug.

① اكل انيس ادور على دوا
 آثاره الجانبية ال
 أقل مثل
 bupropion / Mirtazapine

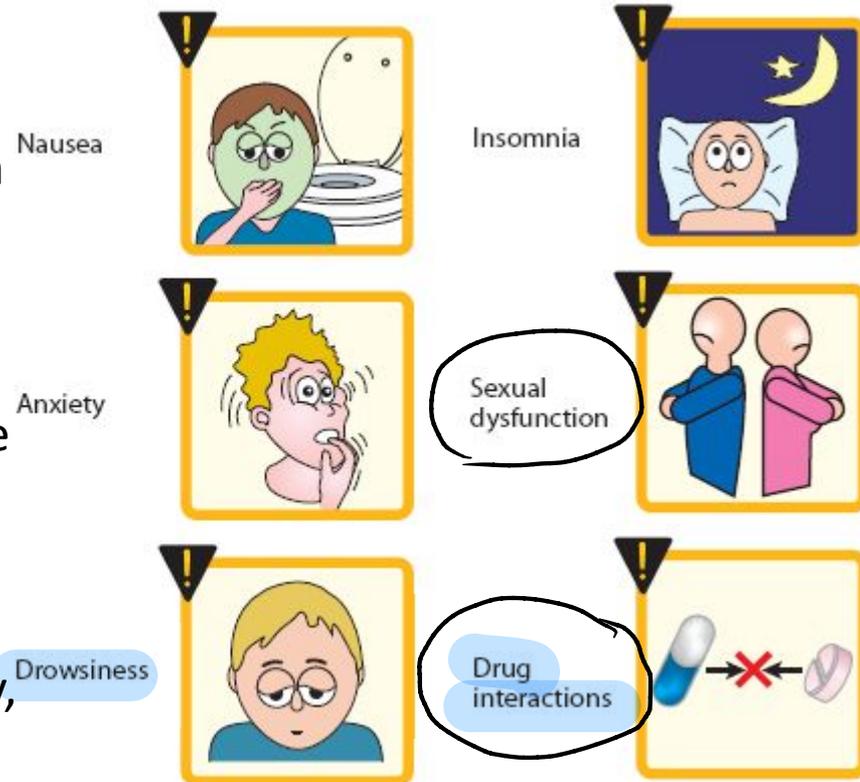
② أقل الجرعة (dose)

تقدر أخفف الأجراس عن طريق إنه يمش الدواء بجرعة أقل، أو عن طريق مساند "adjunctive" مثل ال "benzodiazepines"

Selective Serotonin Reuptake Inhibitors (SSRIs)

Side Effects:

- SSRIs may cause **nausea, diarrhea, anxiety, headache and insomnia** which can be alleviated by starting with low doses or by adjunctive use of benzodiazepines.
- Sexual dysfunction** is common with the SSRIs. One option for managing it is to change the antidepressant to one with fewer sexual side effects, such as *bupropion* or *mirtazapine*. Alternatively, the dose of the drug may be reduced.
- Fluoxetine** and **paroxetine** are potent **inhibitors** of hepatic cytochrome P450 isozymes, an action that has led to increased activity of other drugs.



Serotonin-Norepinephrine Reuptake Inhibitors

- Two classes of antidepressants act as combined serotonin and norepinephrine reuptake inhibitors:
 1. Selective serotonin-norepinephrine reuptake inhibitors (SNRIs)
 2. TCAs.

2 Tricyclic Antidepressants

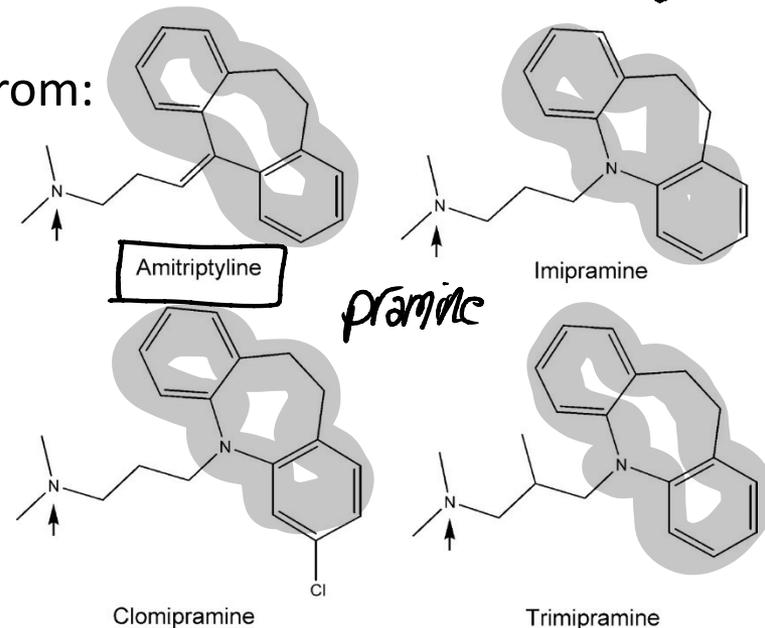
- eg, **imipramine, amitriptyline**
- The TCAs were the dominant class of antidepressants until the introduction of **SSRIs** in the 1980s and 1990s.
- They all have an iminodibenzyl (tricyclic) core.
- At the present time, the TCAs are used primarily in depression that is unresponsive to more commonly used antidepressants such as the SSRIs or SNRIs.
- Their loss of popularity stems in large part from:
 - relatively **poorer tolerability** compared with newer agents

سواء من فئة الثلاثية

- lethality in overdose.**

على نكس ال SNRIs

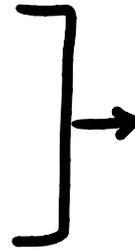
لأنه فقدت شعبيتها وصارت ال SNRIs أفضل منها



Tricyclic Antidepressants

- TCAs also block:

- α -adrenergic
- Histaminic receptors
- Muscarinic receptors



مو معروف إذا في أي فوائده
ال rec ، بس من المحتمل إنه
يكون همدود مسؤولة عن
عثير (Adverse effect) ل (TCAs).

- It is not known if any of these actions produce TCAs' therapeutic benefit. However, actions at these receptors are likely responsible for many of the adverse effects of the TCAs.

Tricyclic Antidepressants

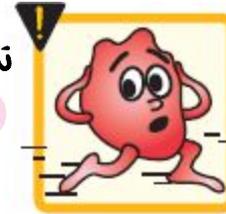
Side Effects:

The adverse effects of TCAs include:

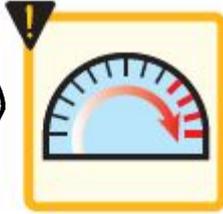
- 1) Excessive sedation, fatigue, and, occasionally, confusion.
 - ✓ 3) Atropine-like effects
 - 4) Orthostatic hypotension, electrocardiogram (ECG) abnormalities, and cardiomyopathies
 - 5) Tremor and paresthesias ^{تَمَل}
 - ✓ 6) Weight gain
- Overdosage with tricyclics is extremely hazardous, and the ingestion of as little as a 2-week supply has been lethal.

تسارع نبضان القلب

Tachycardia



Weight gain



Arrhythmias



Dry mouth



Nausea



Constipation



Drowsiness



Urinary retention



Blurred vision

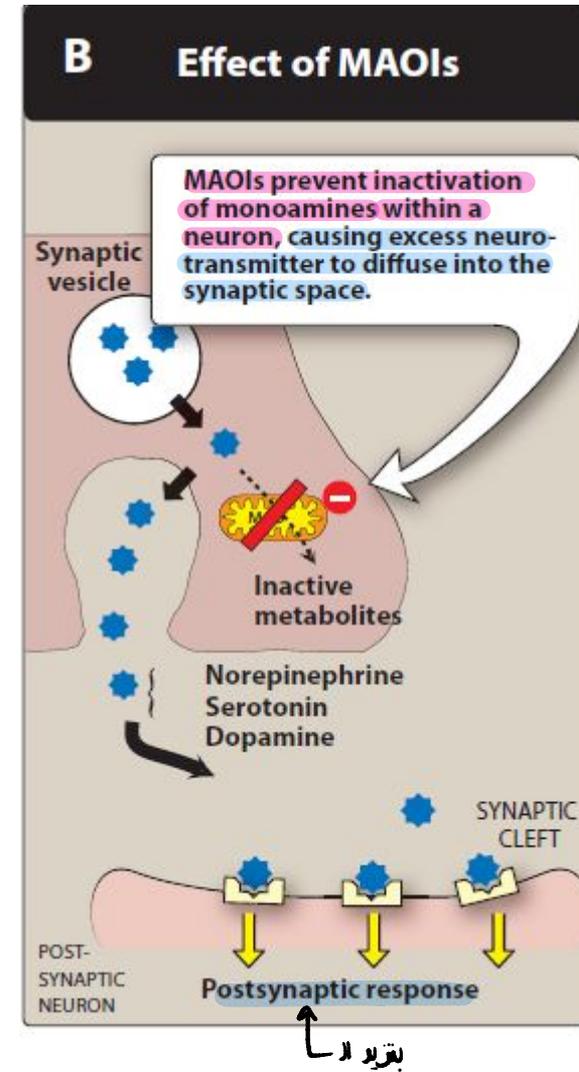


3 Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

- The SNRIs include **venlafaxine**, its metabolite **desvenlafaxine**, **duloxetine**, and **levomilnacipran**.
- ✓ • All SNRIs bind the serotonin (SERT) and norepinephrine (NET) transporters, as do the TCAs. However, unlike the TCAs, the SNRIs do not have much affinity for other receptors.
- SNRIs have many of the serotonergic adverse effects associated with SSRIs. In addition, SNRIs may also have noradrenergic effects, including increased blood pressure and heart rate, and CNS activation, such as insomnia, anxiety, and agitation.

4 Monoamine Oxidase Inhibitors

- Monoamine oxidase inhibitors (MAOIs) were introduced in the 1950s but are now rarely used in clinical practice because of toxicity and potentially lethal food (**tyramine effect**) and drug interactions (**Serotonin syndrome**).
- Their primary use now is in the treatment of depression unresponsive to other antidepressants.
- Current MAOIs include phenelzine, isocarboxazid, tranylcypromine and selegiline.
- **Selegiline**, is a selective MAO-B inhibitor at low doses and a non-selective MAO inhibitor at higher doses, was recently approved for treatment of depression.

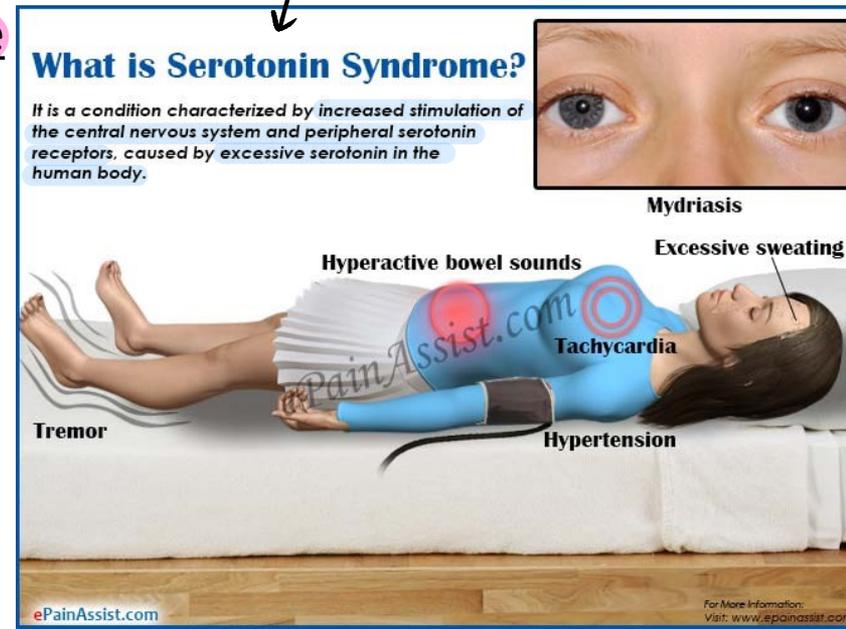


Monoamine Oxidase Inhibitors

- MAOIs with serotonergic agents including SSRIs, SNRIs, and most TCAs along with some analgesic agents such as meperidine result in a life-threatening serotonin syndrome.
- The serotonin syndrome is thought to be caused by overstimulation of 5-HT receptors in the central gray nuclei and the medulla.
- Symptoms range from mild to lethal and include a triad of cognitive (delirium, coma), autonomic (hypertension, tachycardia, diaphoresis), and somatic (myoclonus, hyperreflexia, tremor) effects.

تعرق

* لقاؤند MAOIs + Serotonergic agent



Monoamine Oxidase Inhibitors

- **Most serotonergic antidepressants** should be discontinued at least 2 weeks before starting an MAOI.
- **Fluoxetine**, because of its long half-life, should be **discontinued for 4–5 weeks** before an MAOI is initiated.
- Conversely, an **MAOI** must be discontinued for at least 2 weeks before starting a serotonergic agent.

SSRIs



trazodone

↓
لعلاج الاكتئاب

↓
من أعراضه أيضا يعمل لنوم

و (Sedation)



فصلا استخدام
هو ليس للاكتئاب
صلا علاج للنوم
مشاكل النوم ++

و النوم Insomnia
و تأخير



⑤ 5-HT₂ Receptor Modulators

- Two antidepressants are thought to act primarily as antagonists at the 5-HT₂ receptor: **trazodone** and **nefazodone**.
- **Trazodone** was among the most commonly prescribed antidepressants until it was supplanted by the SSRIs in the late 1980s. The most common use of trazodone in current practice is as an unlabeled hypnotic, since it is highly sedating and not associated with tolerance or dependence.
- The principle action of both nefazodone and trazodone appears to be blockade of the 5-HT_{2A} receptor.
- Inhibition of this receptor in both animal and human studies is associated with substantial antianxiety, antipsychotic, and antidepressant effects.
- The 5-HT receptor more directly linked with the antidepressant effects of SSRIs has been the 5-HT_{1A} receptor.

6 Tetracyclic and Unicyclic Antidepressants

- A number of antidepressants (do not fit neatly) into the other classes. Among these are bupropion, mirtazapine, amoxapine, vilazodone, and maprotiline.
less sexual dysfunc. 2 الی جنسی
- **Mirtazapine** has a complex pharmacology:
 1. It is an antagonist of the presynaptic α_2 autoreceptor and enhances the release of both norepinephrine and 5-HT. → Serotonin
 2. In addition, mirtazapine is an antagonist of 5-HT₂ and 5-HT₃ receptors.
 3. Finally, mirtazapine is a potent H₁ antagonist, which is associated with the drug's sedative effects.

Tetracyclic and Unicyclic Antidepressants

- **Bupropion**
- Bupropion is a weak dopamine and norepinephrine reuptake inhibitor that is used to alleviate the symptoms of depression. → * بس عشان يخفف أعراضه الاكتئاب *
- Bupropion is also useful for decreasing cravings and attenuating withdrawal symptoms of nicotine in patients trying to quit smoking.

Bupropion

↓

أخفف أعراضه الاكتئاب

↓

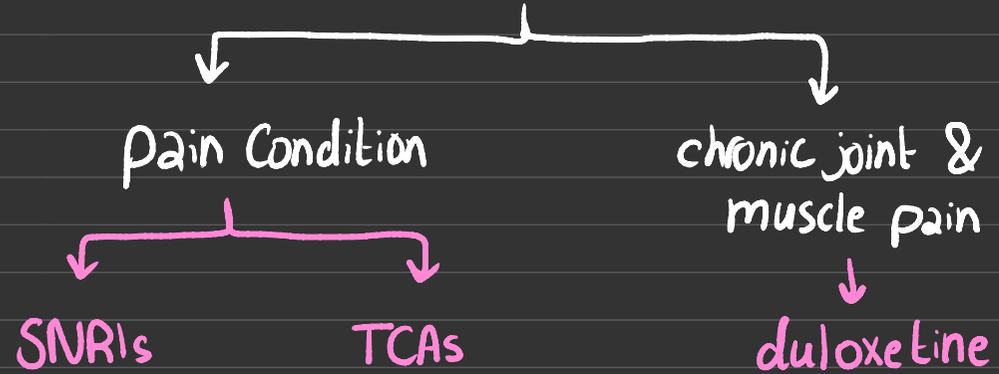
خففوا الأعراض
الناجمة عن محاولة
الإقلاع عن التدخين



① Depression



② pain disorder



③ pre Menstrual Dysphoric Disorder (PMDD)



④ Eating disorder



⑤ Smoking Cessation



Clinical Uses

مُختصر قبل

- **Depression**
- **Anxiety disorders**
 - A number of SSRIs and SNRIs have been approved for all chronic anxiety disorders.
- **Pain disorders**
 - TCAs and SNRIs appear to be useful in the treatment of pain conditions.
 - In 2010, duloxetine was approved for the treatment of chronic joint and muscle pain.
- **Smoking cessation**
 - Bupropion was approved in 1997 as a treatment for smoking cessation.
- **Premenstrual Dysphoric Disorder (PMDD)**
 - The SSRIs are known to be beneficial to many women with PMDD, and fluoxetine and sertraline are approved for this indication.
- **Eating disorders**
 - Antidepressants appear to be helpful in the treatment of bulimia but not anorexia. Fluoxetine was approved for the treatment of bulimia in 1996.

↳ a very severe form of
menstrual syndrome

الشرع عند الأكل

Pharmacokinetics

- The antidepressants share several pharmacokinetic features.
- Most have fairly rapid oral absorption, achieve peak plasma levels within 2–3 hours, are tightly bound to plasma proteins, undergo hepatic metabolism, and are renally cleared.
- However, even within classes, the pharmacokinetics of individual antidepressants varies considerably.

" Keep searching for the colours when everything turns gray." ♡♡

Saja Dwaikat || Artery academy

" اللهم اني استودعك ما قرأت و ما حفظت و تعلمت فرده عند حاجتي إليه انك على كل شيء قدير .. "

