**LEC. 3 Pharmacology Dr. Ihab Alkhalifa**

**Drugs for Depression & Mania**

**Anti-depressants : Drugs for Depression**

* **Depression :** are feelings of sadness and hopelessness, as well as the inability to experience pleasure in usual activities, changes in sleep patterns and appetite, loss of energy, and suicidal thoughts.

**Biogenic amine theory** proposes that depression is **due to a deficiency of monoamines, such as norepinephrine and serotonin, at certain key sites in the brain.**

* **Mania** : is characterized by the **opposite behavior**: enthusiasm, anger, rapid thought and speech patterns, extreme self-confidence, and impaired judgment.

Conversely, the **theory proposes that mania is caused by an overproduction of these neurotransmitters .**

**Antidepressant drugs classes**

* **Tricyclic antidepressants (TCAs)**
* **Mono amino oxidase Inhibitors ( MAOI)**
* **Selective Serotonin Reuptake Inhibitors ( SSRI)**
* **Serotonin/norepinephrine reuptake inhibitors (SNRIs)**



**الجدولللاطلاع حول تقسيم المجاميع**

**MECHANISM OF ANTIDEPRESSANT DRUGS**

**Most clinically useful antidepressant drugs (Figure 10.1) potentiate, either**

**directly or indirectly, the actions of norepinephrine and/or serotonin (5-HT)**

**in the brain**.

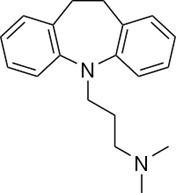
Although , the pharmacological effects of any of the antidepressant and anti-mania drugs on neurotransmission, which often occur immediately; however, **the time course for a therapeutic response occurs over several weeks.**

This suggests that decreased reuptake of neurotransmitters is only an initial effect of the drugs, which may not be directly responsible for the antidepressant effects.

* **TRICYCLIC ANTIDEPRESSANTS (TCAs)**

The TCAs elevate mood, improve mental alertness, increase physical activity of individuals with major depression by blocking norepinephrine and serotonin reuptake into the presynaptic neuron . these old drugs are not preferred today since show different adverse effects relative to other newer class of antidepressants ( SSRIs & SNRIs) .

**The TCAs include**

* **the Tertiary Amines:**

**Imipramine [ee-MIP-ra-meen] (the prototype drug)**

**Desipramine [dess-IP-ra-meen]**

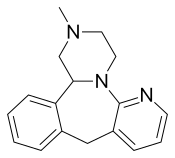
**Amitriptyline [amee- TRIP-ti-leen]**

**Clomipramine [kloe-MIP-ra-meen] Nortriptyline [nor-TRIP-ti-leen] IMMPRAMINE**

* **The secondary Amines (** These Antidepressants , Are related “**tetracyclic**” antidepressant agents and are commonly included in the general class of TCAs.

Patients who do not respond to one TCA may benefit from a different drug in this group .

Tetracyclic antidepressants (TeCAs) are a class of antidepressants that were first introduced starting in the 1970s. They are named after their tetracyclic chemical structure, containing four rings of atoms, and are closely related to the tricyclic antidepressants (TCAs), which contain three rings of atoms.

**Maprotiline**

**Mianserin**

**Mirtazapine**

**TRICYCLIC ANTIDEPRESSANTS (TCAs)**

**A-class :** Tricyclic antidepressants (TCAs) are a class of medications that are used primarily as antidepressants. TCAs were first discovered in the early 1950s and were marketed later . They are named after their chemical structure, which contains **three rings of atoms**.

**B- Mechanism of action :**

1. Inhibition of neurotransmitter reuptake: TCAs are potent inhibitors of the neuronal reuptake of norepinephrine and serotonin into presynaptic nerve terminals in the brain The TCAs are effective in treating moderate to severe depression. .
2. Blocking of receptors: TCAs also block serotonergic, α-adrenergic, histaminic, and muscarinic receptors. It is not known if any of these actions produce the therapeutic benefit of the TCAs. However, **actions at these receptors are likely responsible for many of their adverse effects.**

**C-** **Pharmacokinetics**

TCAs are well absorbed upon oral administration. Because of their lipophilic nature, they are widely distributed and readily penetrate into the CNS.

As a result of their variable first-pass metabolism in the liver, TCAs have low and inconsistent bioavailability.

These drugs are metabolized by the hepatic microsomal system (and, thus, may be sensitive to agents that induce or inhibit the CYP450 isoenzymes) and conjugated with glucuronic acid. Ultimately, the TCAs are excreted as inactive metabolites via the kidney.

**D. Therapeutic uses & Adverse effects**

The TCAs are effective in treating :

* moderate to severe depression.
* Some patients with panic disorder also respond to TCAs.
* Imipramine has been used to control bed-wetting in children older than 6 years of age; however, it has largely been replaced by desmopressin and non pharmacologic treatments (enuresis alarms).
* The TCAs, particularly amitriptyline, have been used to help prevent migraine headache and treat chronic pain syndromes (for example, neuropathic pain) in a number of conditions for which the cause of pain is unclear.
* Low doses of TCAs, especially doxepin, can be used to treat insomnia.

**Adverse effects**

**Blockade of muscarinic receptors leads to** Anticholinergic side effects :

* blurred vision, dry mouth
* urinary retention
* sinus tachycardia
* Constipation
* Aggravation of angle-closure glaucoma (Figure 10.7).
* **The TCAs also block α-adrenergic receptors**, causing orthostatic hypotension, dizziness, and reflex tachycardia.

Imipramine is the most likely, and nortriptyline the least likely, to cause orthostatic hypotension.

* Sedation may be prominent, especially during the first several weeks of treatment, and is related to the ability of these drugs to **block histamine H1 receptors.**
* **Weight gain** is a common adverse effect of the TCAs.
* **Sexual dysfunction** occurs in a minority of patients, and the incidence is lower than that associated with the SSRIs.
* These agents may precipitate **life-threatening arrhythmias** in an overdose situation.

**Q/ Precautions of TCAs ?**

A/ TCAs (like all antidepressants) should be used with caution in patients **with bipolar disorder**, even during their depressed state, because antidepressants may cause a switch to manic behavior.

The TCAs have a narrow therapeutic index (for example, five- to sixfold the maximal daily dose of imipramine can be lethal).

Depressed patients who are suicidal should be given only limited quantities of these drugs and be monitored closely.

Drug interactions with the TCAs are shown in Figure 10.8. The TCAs may exacerbate certain medical conditions, such as benign prostatic hyperplasia, epilepsy, and preexisting arrhythmias.

**Q/ Dosage of Antideprresent ?**

* The onset of the mood elevation is slow, requiring 2 weeks or longer (Figure 10.3). Patient response can be used to adjust dosage. After a therapeutic response, the dosage can be gradually reduced to improve tolerability, unless relapse occurs.
* Physical and psychological dependence have been rarely reported.
* This necessitates slow withdrawal to minimize discontinuation syndromes and cholinergic rebound effects.

**Q/ These old drugs ( TCAs) are not preferred today relative to other newer class of antidepressants ( SSRIs & SNRIs) ?**

A/ since show different adverse effects , due to TCAs also block serotonergic, α-adrenergic (block α-adrenergic receptors, causing orthostatic hypotension, dizziness, and reflex tachycardia) , histaminic, and muscarinic receptors ( causing Anticholinergic side )

* **MONOAMINE OXIDASE INHIBITORS ( MAO I)**

Monoamine oxidase (MAO) is a mitochondrial enzyme found in nerve and other tissues, such as the gut and liver.

**In the neuron, MAO** **functions** as a “safety valve” to oxidatively deaminate and inactivate any excess neurotransmitters (for example, norepinephrine, dopamine, and serotonin) that may leak out of synaptic vesicles when the neuron is at rest.

**The MAOIs** may irreversibly or reversibly inactivate the enzyme, permitting neurotransmitters to escape degradation and, therefore, to accumulate within the presynaptic neuron and leak into the synaptic space.

The MAOIs currently available for treatment of depression include :

* **Phenelzine [FEN-el-zeen],**
* **Tranylcypromine [tran-il-SIP-roe-meen],**
* **Selegiline [seh-LEDGE-ah-leen].**

**Mechanism of action**

Most MAOIs, such as *phenelzine,* form stable complexes with the enzyme, causing irreversible inactivation. This results in increased stores of norepinephrine, serotonin, and dopamine within the neuron and subsequent diffusion of excess neurotransmitter into the synaptic space (Figure 10.9).



**الشكل للحفظ مع ميكانيكية عمل الادوية**

**C. Pharmacokinetics**

These drugs are well absorbed after oral administration.

MAOIs are hepatically metabolized and excreted rapidly in urine.

**D- Therapeutic uses & Adverse effects**

The MAOIs are indicated for depressed patients who are unresponsive or allergic to TCAs and SSRIs or who experience strong anxiety.

A special subcategory of depression, called atypical depression, may respond preferentially to MAOIs. Because of their risk for drug– drug and drug–food interactions, the MAOIs are considered last-line agents in many treatment settings.

Although MAO is fully inhibited after several days of treatment, the antidepressant action of the MAOIs, like that of the SSRIs, SNRIs, and TCAs, is delayed several weeks.

**Adverse effects**

**Severe and often unpredictable side effects**, **due to**

* **Drug–food interactions**, For example, tyramine, which is contained in foods, such as aged cheeses and meats, chicken liver, pickled or smoked fish, and red wines, is normally inactivated by MAO in the gut. Individuals receiving a MAOI are unable to degrade tyramine obtained from the diet.

Tyramine causes the **release of large amounts of stored catecholamines from nerve terminals**, resulting in a **hypertensive crisis, headache, tachycardia, and cardiac arrhythmias. ( tyramine crises )**

Patients must, therefore, be educated to avoid tyramine-containing foods when use MAOI drugs .

Phentolamine and prazosin are helpful in the management of tyramine-induced hypertension.

* **Drug-drug interactions :** the use of MAOIs with other antidepressants is contraindicated. For example, SSRIs should not be co-administered with MAOIs. Both SSRIs and MAOIs require a washout period of (2-6) weeks before the other type is administered
* **Other possible side effects** of treatment with MAOIs include : **drowsiness, orthostatic hypotension, blurred vision, dry mouth, and constipation.**

**Q/ Use of MAOIs is limited due to the complicated dietary restrictions required while taking these agents.**

A/ These drugs inhibit not only MAO in the brain but also MAO in the liver and gut that catalyzes oxidative deamination of drugs and potentially toxic substances, such as tyramine, which is found in certain foods (such as aged cheeses and meats, chicken liver, fish, and red wines, is normally inactivated by MAO in the gut , . The MAOIs, therefore, show a high incidence of drug–drug and drug–food interactions. THERFORE , the MAOIs are considered last-line agents in many treatment settings.

**Selegiline**administered as the transdermal patch may produce less inhibition of gut and hepatic MAO at low doses because it avoids hepatic first-pass metabolism.

In addition, the MAOIs have many other critical drug interactions, and caution is required when administering these agents concurrently with other drugs. Figure 10.10 summarizes the side effects of the antidepressant drugs.

**Q / when switching antidepressant agents, a minimum of 2 weeks of delay must be allowed after termination of MAOI therapy and the initiation of another antidepressant from any other class ?**

A/ Since monoamino oxidase (MAO ) Enzyme regeneration, when irreversibly inactivated, by theses drugs varies, and is it usually occurs several weeks after termination of the drug. Thus, a minimum of 2 weeks of delay must be allowed after termination of MAOI therapy before starting a new therapy .

**SELECTIVE SEROTONIN REUPTAKE INHIBITORS**

**The SSRIs include :**

* **Fluoxetine [floo-OX-e-teen] drug),**
* **Citalopram [sye-TAL-oh-pram] & escitalopram [es-sye-TAL-ohpram],**
* **Paroxetine [pa-ROX-e-teen]**
* **Sertraline [SER-tra-leen]**

**المعلومات التالية تشمل الانواع اعلاه**

**A-Class** : The selective serotonin reuptake inhibitors (SSRIs) are a group of antidepressant drugs that **specifically inhibit serotonin reuptake**, having 300- to 3000-fold greater selectivity for the serotonin transporter, as compared to the norepinephrine transporter.

**B- MECHANISM OF ACTION**  : The SSRIs block the reuptake of serotonin, leading to increased concentrations of the neurotransmitter in the synaptic cleft available to bind to the postsynaptic receptor.

**C- Pharmacokinetics**

* All of the SSRIs are well absorbed after oral administration. **Peak levels are seen in approximately 2 to 8 hours on average.**
* Fluxetine Achieves maximum concentration in about 6-10 hours and reaches steady-state in 7-14 days.
* Mostly show hepatic metabolisim and act as **inhibitor of Hepatic CYP 450 with**  Less than 2% of an oral dose is excreted in urine unchanged. **therfore these drugs show wide D-D interactions**

**Food has little effect on absorption for which food increases its absorption, so it is prefered to be given after meal**

* The majority of SSRIs have plasma half-lives that range between 16 and 36 hours.
* Metabolism by cytochrome P450 (CYP450)–dependent enzymes and glucuronide or sulfate conjugation occur extensively.

**Fluoxetine differs** **from the other members of the class** by having a much longer half-life (50 hours), and the **half life of its active metabolite *S*-norfluoxetine is quite long**, averaging 10 days. It is available as a sustained-release preparation allowing once-weekly dosing.

* **Fluoxetine and paroxetine are potent inhibitors of a CYP450 isoenzyme** (CYP2D6) responsible for the elimination of TCAs, antipsychotic drugs, and some antiarrhythmic and β-adrenergic antagonist drugs.
* Other CYP450 isoenzymes (CYP2C9/19, CYP3A4, CYP1A2) are involved with SSRI metabolism and may also be inhibited to various degrees by the SSRIs.

**Therfore , Dosages of the SSRIs should be reduced in patients with hepatic impairment.**

**D- Therapeutic uses & adverse effects**

The primary indication for SSRIs is depression, for which they are as effective as the TCAs.

A number of other psychiatric disorders also respond favorably to SSRIs, including

* Obsessive–compulsive disorder
* Panic disorder,
* Generalized anxiety disorder,
* Posttraumatic stress disorder,
* Premenstrual dysphoric disorder
* Bulimia nervosa (only *fluoxetine* is approved for bulimia).

Note/ The SSRIs Antidepressants, typically take at least 2 weeks to produce significant improvement in mood, and maximum benefit may require up to 12 weeks or more (Figure 10.3).



**Adverse effects**

Although the SSRIs are considered to have fewer and less severe adverse effects than the TCAs and MAOIs, the SSRIs are not without adverse effects, such as :

* Headache
* Sweating
* Anxiety
* Agitation
* Gastrointestinal (GI) effects (nausea, vomiting, diarrhea)
* Sexual dysfunction which may include loss of libido, delayed ejaculation, is common with the SSRIs.
* Sleep disturbances : Insomnia and somnolence
* Somnolence (alternatively "sleepiness" or "drowsiness") is a state of strong desire for sleep . Somnolence is often viewed as a symptom rather than a disorder by itself.

**Paroxetine and fluvoxamine are generally more sedating ( less somnolence ) than fluoxetine**

* Drug–drug interactions since SSRI are potent CYP inhibitors , also show drug-drug interaction with some drugs as ( ethanol alcohol, adrenergic drugs & MAOI) IF GIVEN TOGETHER ). Additionally, SSRIs may interact in elderly using diuretics .

**Q/ What are options can be used for managing SSRI-induced sexual dysfunction ?**

A/ 1- is to change the antidepressant to one with fewer sexual side effects, such as bupropion or mirtazapine.

2- The dose of the drug may be reduced.

**Q/ Antidepressants should be used cautiously in children and teenagers ?**

A/ because about 1 out of 50 children report suicidal ideation as a result of SSRI treatment.

Fluoxetine, sertraline, fluvoxamine and citalopram are approved to treat childhood depression .

**Q/ Discontinuation syndrome ?**

A/ All of the SSRIs have the potential to cause a discontinuation syndrome after their abrupt withdrawal, Possible signs and symptoms of SSRI discontinuation syndrome include headache, malaise, and irritability, nervousness, and changes in sleep pattern.

Such symptoms more common with agents with shorter half-lives and inactive metabolites.

Fluoxetine has the lowest risk of causing an SSRI discontinuation syndrome due to its longer half-life and active metabolite.

**SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS (SNRI)**

* **Venlafaxine [VEN-la-fax-een]**
* **Duloxetine [doo-LOX-e-teen]**
* **Venlafaxine**

1. **Class :** SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS (SNRI) , Anti-depressants
2. **Mechanism of action** : inhibit the reuptake of both serotonin and norepinephrine (Figure 10.5).
3. **Pharmacokinetics** : Venlafaxine is well absorbed, with at least 92% of an oral dose being absorbed into systemic circulation. It is extensively metabolized in the liver via the CYP isoenzyme to active metabolite desvenlafaxine which is just as potent a SNRI as the parent compound, The primary route of excretion of venlafaxine and its metabolites is via the kidneys . The half-life of venlafaxine is relatively short.
4. **Therapeutic uses & Adverse effects** : These agents, termed SNRIs, may be effective in **treating depression** in patients in whom SSRIs are ineffective.

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

**This pain is, in part, modulated by serotonin and norepinephrine pathways in the central nervous system (CNS).**

**Both SNRIs and the TCAs, with their dual inhibition of both serotonin and norepinephrine reuptake, are sometimes effective in :**

* **Relieving pain** **associated with diabetic peripheral neuropathy**
* **Post herpetic neuralgia ( pain of herpes viral infection )**
* **Fibromyalgia ( muscle fiber pain )**
* **Low back pain.**
* **Adverse effects**  : The SNRIs, unlike the TCAs, **have little activity at α-adrenergic, muscarinic, or histamine receptors and, thus, have fewer of these receptor-mediated adverse effects than the TCAs. The most common side effects of *venlafaxine*** are nausea, headache, sexual dysfunction, dizziness, insomnia, sedation, and constipation.
* **At high doses, there may be an increase in blood pressure and heart rate.**
* The SNRIs may **precipitate a discontinuation syndrome** if treatment is abruptly stopped.
* Venlafaxine has minimal inhibition of the CYP450 isoenzymes and is a substrate of the CYP2D6 isoenzyme, show Drug-drug interaction with drugs metabolized by liver and not preferred in patients with liver disease.
* Desvenlafaxine is the active, demethylated metabolite of *venlafaxine.*

**The clinical activity and adverse effect profile of desvenlafaxine are similar to that of venlafaxine.**

* **Duloxetine** It is extensively metabolized in the liver to **inactive metabolites** and should be avoided in patients with liver dysfunction.
* **Duloxetine** is a moderate inhibitor of CYP2D6 isoenzymes and may increase concentrations of drugs metabolized by this pathway, such as antipsychotics.

****

**الرسم مطلوب لتوضيح ميكانيكية الادوية (SNRI)**

**SUMMARY OF ANTIDEPRESSENT THERAPY**

* Moreover, the SSRIs have little blocking activity at muscarinic, α-adrenergic, and histaminic H1 receptors. Therefore, common side effects associated with TCAs, such as orthostatic hypotension, sedation, dry mouth, and blurred vision, are not commonly seen with the SSRIs.
* Because they have different adverse effects and are relatively safe even in overdose, the SSRIs have largely replaced TCAs and monoamine oxidase inhibitors (MAOIs) as the drugs of choice in treating depression.
* Patients who do not respond to one antidepressant may respond to another, and approximately 80% or more will respond to at least one antidepressant drug.

**الجدول للاطلاع لملاحظة الادوية وتاثيراتها الجانبية**

**Treatment of Mania and Bipolar Disorder**

The treatment of bipolar disorder has increased in recent years, due to increased recognition of the disorder and also an increase in the number of available medications for the treatment of mania.

* **Lithium**

*Lithium salts* are used acutely and prophylactically for managing bipolar patients. *Lithium* is effective in treating 60% to 80% of patients exhibiting mania and hypomania.

Although many cellular processes are altered by treatment with *lithium salts*, the mode of action is unknown.

The therapeutic index of *lithium* is extremely low, and *lithium salts* can be toxic. Common adverse effects may include headache, dry mouth, polydipsia, polyuria, polyphagia, GI distress (give *lithium* with food), fine hand tremor, dizziness, fatigue, dermatologic reactions, and sedation.

Adverse effects due to higher plasma levels may indicate toxicity and include ataxia, slurred speech, coarse tremors, confusion, and convulsions.

Thyroid function may be decreased and should be monitored.

Unlike other mood stabilizers, *lithium* is renally eliminated, and though caution should be used when dosing this drug in renally impaired patients, it may be the best choice in patients with hepatic impairment.

* **Other drugs**
* **Several antiepileptic drugs**, including : c**arbamazepine, valproic acid, and lamotrigine,**have been approved as mood stabilizers for bipolar disorder. **ستشرح في محاضرات لاحقة**
* Other agents that may improve manic symptoms include the older (**chlorpromazine and haloperidol)** and newer antipsychotics. **ستشرح في محاضرات لاحقة**