Dr:3azzah

Week : 8

Anti depressant Drugs

❖Definition of depression:

- Depression is the most common of the affective disorsders of mood rather than disturbances of thoughts or behavior.
- Depression is the most common cause of disability and premature death.

❖Symptoms of depression:

❖Emotional symptoms:

- loss of energy and motivation.
- feeling of guilt.
- diminished ability to enjoy oneself.
- recurrent thoughts about death and sucide.

❖Biological symptoms:

- loss of libido.
- sleep disturbances.
- loss or increase appetite.

❖Classification of depression:

❶**uni polar:** *mood swings* in the same direction

❷**bipolar affective** disorder: depression *alternates* with mania

❶Unipolar depression:

- about 75% of cases.
- non familial ,associated with stressful life events and accompanied by symptoms of anexiety and agitation.
- this type is sometimes termed(reactive depression).
- other patients 25% have (endogenous depression) they show familial pattern unrelated to external stress.

❷bipolar:

- usually appears in early adult life.
- less commonly, the mood swings between *depression* and *mania* over a period of few weeks.
- maybe familial.

❖The mono-amine theory of Depression:

Depression caused by functional decrease in monoamine transmitters (NE and 5-HT)at certain sites in the brain while mania results from functional excess.

⍋NE = norepinephrine 5-HT= serotonin

Depression → Decrease in :

Amount or function of neurotransmitters

Mania → increase in :

Amount or function of neurotransmitters

❖ANTI Depressant Drugs:

- all drugs take weeks to manifest their clinical improvement, even though their pharmacological effects are produced immediately, indicating that secondary adaptive changes are important.
- treatment should continue for 6 months at a full therapeutic doses before withdrawal.
- withdrawal of drugs must be gradual.

➲must be:

- full therapeutic dose
- full therapeutic course
- gradual withdrawal

➲The pharmacological action of antidepressant drugs starts immediately whereas their therapeutic effect or clinical improvement of patient status takes weeks to occur.

➲The period between pharmacological action of the drug & clinical improvement are called secondary adaptive changes.

❖Classification of Anti depressant drugs according to the site of action:

1) drugs that block the re-uptake of NE and 5HT (TCA and Heterocyclic)
2) drugs that selectively block the re uptake of seretonine (SSRIs)
3) drugs that block presynaptic α2 adrenoceptors (mirtazapine)
4) drugs that inhibit MAO enzymes

➲ MAO enzyme is a major degradative pathway for the amine neurotransmitters, blocking it will permits more amine to accumulate in presynaptic stores & more to be released.

❖Secondary adaptive changes:

- Blocking neurotransmitters uptake is only an initial effects of drugs. after that a down regulation of *pre-synaptic inhibitory receptors* permits greater synthesis and release of neurotransmitters into synaptic clefts and enhanced signaling in the post synaptic neurons leading to *therapeutic effects*

➲The problem is that there are few neurotransmitters reaching the post synaptic neurons so, by administrating the drug it will lead to ↓ reuptake of neurotransmitters → ↑ synthesis & release due to down-regulation of presynaptic receptors.

❖***Pharmacological actions:***

- *TCA, heterocyclic, MAOIs* have:
  1) αadrenergic blocking effects. → postural hypotension.
  2) anti muscurinic.→ dry mouth, blurred vision, constipation, urine retention.
  3) CVS. → arrhythmia.
  4) Endocrinal. → sexual dysfunction & wt. gain.

- *SSRI:*
  1) CNS
  2) less anti muscurinic, cardiac and endocrinal effects

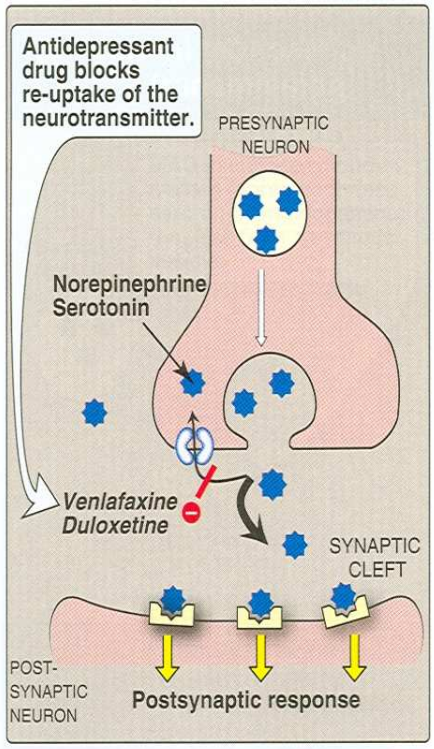

Figure 12.6
Proposed mechanism of action of selective serotonin/norepinephrine re-uptake inhibitors antidepressant drugs.

❖ ***Pharmacokinetic of*** TCA:

- **Imipramine** , **Amitriptyline**, **Desipramine**, **Doxepin**
- most TCA are incompletely absorbed and undergoes 1st pass metabolism
- highly bound to plasma protein → drug-drug interaction.
- most of them give active metabolites → giving them long T1/2
- imipramine gives desipramine
- amitriptyline gives nortriptyline
- given once daily
- excreted in urine

✹ ***Adverse effects of*** TCA:

1) Anti-muscarinic effects: dry mouth, blurred vision, constipation, urine retention (# in prostatic hypertrophy BPH)
2) CVS effects: postural hypotention (alfa-adrenergic blocking), arrhythmia as Torsad de-point (prolong Q-T interval), heart block (blocking of a particular type of cardiac K^+ channel)
3) Sedation (H1 blocking effect)
4) Sexual dysfunction & impotence
5) Lower seizure threshold (# in epilepsy)
6) Weight gain (increase appetite, that's why it is used for anorexia nervosa)

✹ ***Drug interaction of*** TCA:

1. They are strongly bound to plasma proteins, so their effect tend to be enhanced by competing drugs as: aspirin & phenylbutazone
2. They are primarily metabolized by hepatic microsomal enzymes, this may be inhibited by competing drugs as: anti-psychotic drugs
3. With MAOI (this include non-selective MAO and MAOAI coz they will increase NE but MAOBI will not) or SSRIs (coz it is enzyme inhibitor) or any sympathomimetic drugs causing hypertensive crisis (fatal hypertension)

❖***Pharmacokinetic of MAOI:***

1- Non selective (MAOA and MAOB)

- **hydrazide group** eg: **phenelzine**, long acting, its action persists for 2 weeks after discontinuation (irreversible inhibition to both forms of MAO enz.)
- **Non hydrazide groun** eg : **tranylcypromine** its effect continue for 7 days after discontinuation (reversible inhibition)

2- selective reversible (MAOAI) eg : **Moclobemide** (they are short acting drugs)**.**

- All of them are well absorbed ,metabolized in liver and excreted in urine.

➲MAO-A is the amine oxidase primarily responsible for NE,5HT & tyramine metabolism.

➲MAO-B is more selective for dopamine .

Do you remember **selegiline**?

It was in Parkinson's disease lecture because it's a MAO-B inhibitor so, it loses activity as antidepressant but it's useful in Rx. of Parkinsonism.

➲Phenelzine:

- Non selective.
- Irreversible MAOI.
- Long acting.

It's subjected to a very high risk of HTN reaction to tyramine ingested in food.

➲Tranylcypromine:

- Non selective.
- reversible MAOI.
- Long acting.

➲Moclobemide:

- Selective MAOAI.
- reversible MAOAI.
- Short acting.

Relatively free of cheese reaction.

➲ ***Adverse effects of*** MAOI***:***

- Antimuscarinic effects.
- Postural hypotension.
- <u>Sexual dysfunction mainly with phenelzine</u>.
- Sedation ,sleep disturbance.
- ↑ or ↓ appetite .
- <u>Hepatotoxicity (phenelzine)</u>.💣

➲ ***Drug interactions of*** MAOI ***:***

1- With indirect acting sympathomimtic drugs (phenelzine & tranylcypromine have a mild amphetamine like stimulant effect causing sever hypertension

2- With SSRI causing fatal serotonin syndrome (at least 6 weeks space between the 2 groups of drugs)

3- With TCA drugs .

4- With *opioid* analgesic drugs. **Imp** Especially with pethidine

(Fatal syndrome because it affect metabolism of opioid forming abnormal metabolites leading to hyperpyrexic coma , HTN).

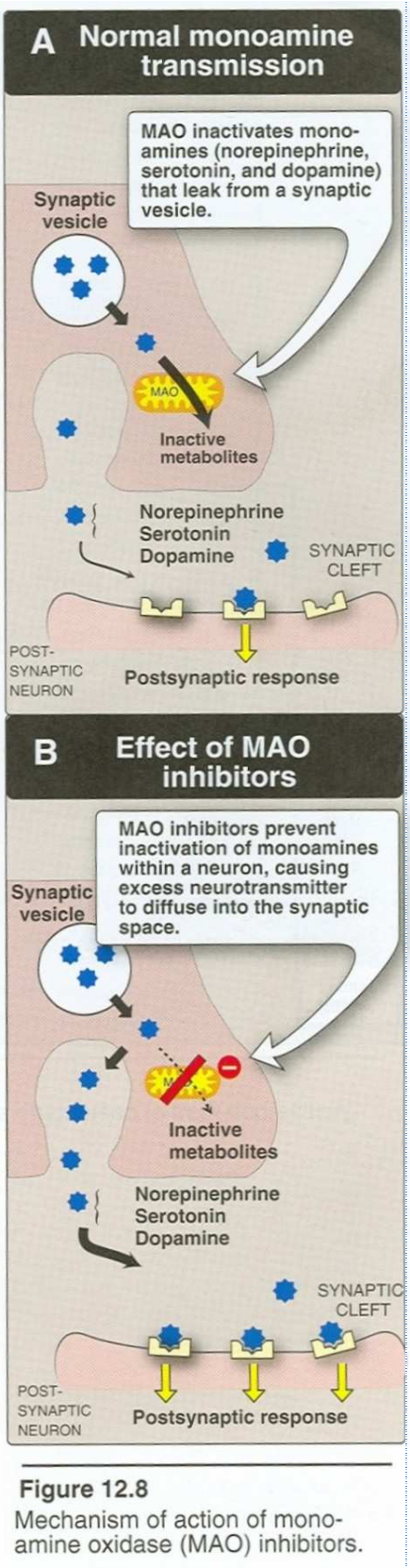

Figure 12.8
Mechanism of action of mono-amine oxidase (MAO) inhibitors.

➲ ***Food interaction of*** MAOI ***:***

- Food containing tyramine as aged cheeses, chicken liver, beer, red wine are normally inactivated by MAO in the gut.

MAOI causing accumulation of tyramine that release large amount of stored catecholamine from nerve terminal causing *headache ,tachycardia, hypertension, nausea.* → with non selective MAOI or MAOAI but not MAOB.

❖***Pharmacokinetic of SSRIs:***

- **fluoxetine , paroxetine,sertraline,citalopram**
- they have long plasma half life (16-36 hr)
- metabolized by P450 enzymes glucuroniod or sulfate conjucation
- most of them have inactive metabolites
- **Fluoxetine** differs from other members of this class in :
    - has longer half life (50hrs).
    - it is available as sustained release preparation given once weekly
    - the metabolite (norfluxetine) is as potent as the parent drug and its half life is long (10 days)
- **fluoxetine** and **paroxetine** are potent inhibitors of hepatic cytochrome p 450.
- Isoenzyme (cyp 2D6) responsible for the metabolism of TCA , neuroleptic drugs , some antiarrythmic, and ß adrenergic antagonist drugs.
- primarily excreted through kidney except **paroxetine** and **sertraline** undergo fecal excretion.

◎***Adverse effects of*** SSRIs:

1. Insomnia, anxiety, agitation, nervousness with fluoxetine & citalopram (give diazepam to prevent insomnia)
2. Sedation with paroxetine & fluvoxamine

this may be useful in patients who have difficulty in sleep, while patients who are fatigued may benefit from the activating drugs as fluoxetine

3. impotence & sexual dysfunction (loss of libido, delayed ejaculation → useful for premature ejaculation)
4. Weight loss→useful for bulimia
5. GI upset (nausea, vomiting, anorexia)
6. Mild effect on CVS as compared to TCA drugs
7. Mild anti-muscarinic effect as compared to TCA drugs, they are preferred in male patients with prostatic hypertrophy (BPH)

◎ ***Percaution of*** SSRIs:

- Pediatric patient should be observed for worsening depression & suicidal thinking whenever one of these drugs is started or their dose increase or decrease.

➲clinical reports that SSRIs usage ↑ suicidal ideation were not supported because the suicidal thoughts could be part of the depression.

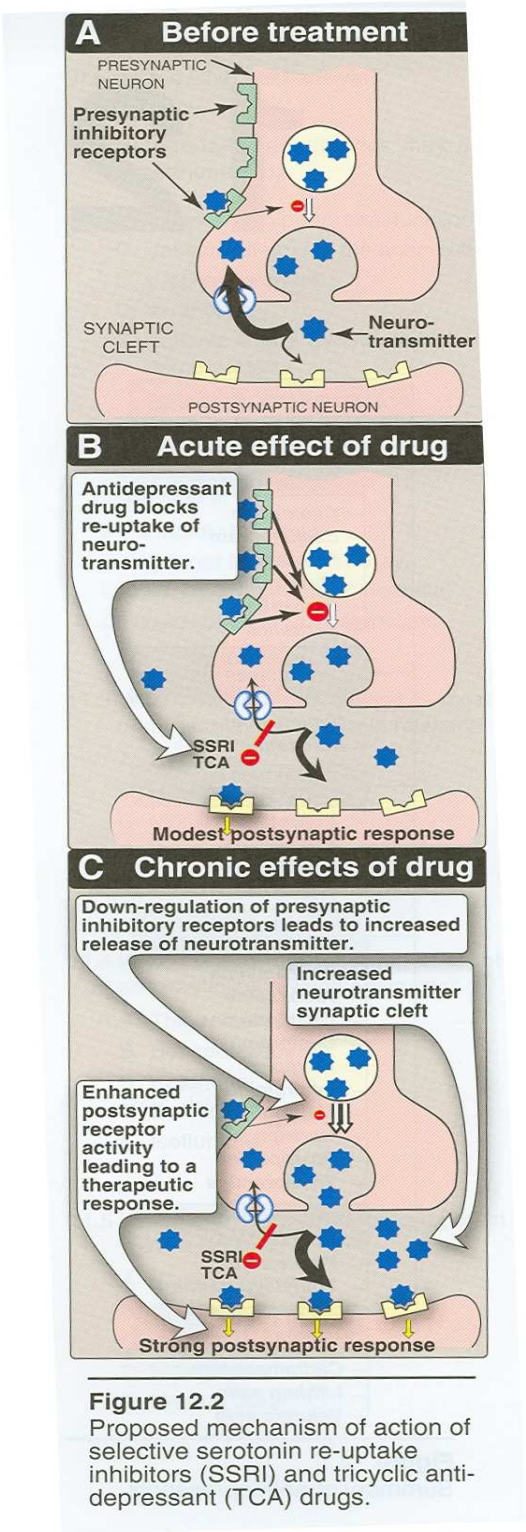

Figure 12.2
Proposed mechanism of action of selective serotonin re-uptake inhibitors (SSRI) and tricyclic anti-depressant (TCA) drugs.

◎ ***Drug interactions of*** SSRIs: V.imp ☺

1- Serotonin reaction or syndrome as a result of combination with MAOI drugs (hyperthermia, muscle rigidity, Cardiovascular collapse).→ absolute # with non selective MAOI or MAOAI but not MAOB.

➲This some times fatal syndrome results from marked ↑ of serotonin in the synapses due to combination of ↑ store of monoamine + inhibition of reuptake after release.

2- Enzyme inhibitor

❖***Pharmacokinetic of heterocyclic :***

- 2nd generation: **Amoxapine**, **maprotilline**, **trazodone**
- 3rd generation: **Nefazodone**, **venlafaxine**, **mirtazepine**
- they have similar PK as TCA

◆Heterocyclic Antidepressant Drugs:

❶Venlafaxine: (T&F) ☺

- Blocks 5-HT &NE uptake (potent inhibitor of 5-HT uptake).
- produce mild or moderate increase in HR &blood pressure.
- Mild anti-muscarinic effect.
- Side effects similar to SSRIs drugs.

❷ Amoxapine:

- Metabolite of antipsychotic drug Loxapine (dopamine antagonism).
- Suitable for depression in psychotic patient.→ schizo affective disorder
- Its dopamine antagonism causing parkinsonism, amenorrhea-galactorrhea syndrome, tardive dyskinesia.

➲Amoxapine is antidepressant drug carring its own father genes (antipsychotic action and dopamine receptor antagonism).

❸ Maprotiline:

- Has fewer sedation& antimuscarinic effects than older TCA.

➲ potent NE uptake inhibitor.

❹ Trazodone:

- Weak inhibitor of serotonin re-uptake.
- has a significant α-blocking effect (hypotension).
- potent H_1-blocker(sedation). → useful as hypnotic.

❺ Nefazodone:

- Related to trazodone, but has no sedation, no α-blocking effects.
- As SSRIs inhibit P450 3A4 isoenzyme.

❻ A2- adrenoceptors antagonism:

- **Mirtazapine**(commonly used).
- Mianserin.
- Increase realse of 5-HT &NE by blocking a2-presynaptic receptors.
- Mirtazapine is preffered in cancer patient because: imp ☺

1. Improve appetite.
2. decrease N&V (5-HT3 blocking).
3. increase body weigh.
4. sedation(potent antihistaminic).
5. less sexual dysfunction(5-HT2 blocking effect). imp
6. Has *no* antimuscarinic effect. Imp

➲ To say the truth, mirtazapine is a good drug *if & only if* patients can tolerate its sedative effect.

❖***Clinical uses of Anti depressants:***

1. endogenous depression(1st drug of choice is SSRI)
2. panic disorders
3. obsessive compulsive disorders (SSRIs)
4. Prophylaxis of migraine (TCA) coz of their slow onset of action.
5. chronic pain (TCA)
6. IBS (TCA and SSRI) and IBD esp. in UC as Rx. And prophylaxis.
7. generalized anexiety disorders (Amitriptyline)
8. Anorexia Nervosa (TCA) coz it ↑ appetite.
9. Bulimia (SSRIs)
10. Nocturnal enuresis (imipramine)
11. premature ejaculation (SSRIs) one of its AE is delayed ejaculation.
12. attention deficit hyperactivity disorder (ADHD) we could choose TCA
13. schizo affective disorder ➲scizoaffective = schizophrenia + depression
14. social phobia (SSRIs)

➲ What's between brackets is group of choice.

◆ Over Doses Of ADD: (not fatal):

- Mainly on CNS & CVS
- The initial effect of TCA is excitement, delirium, convulsion, respiratory depression , coma, atropine like effects, cardiac arrhythmia, sudden death.
- Treatment: haemodyalysis or peritoneal dialysis are *NOT* effective ,only symptomatic treatment.

N.B: (*all* of them are teratogenic)(Giving them to pregnant woman is the doctor choice)

Taking antidepressant in normal human brain will have no effect!

Done by :

نرمين ,حنان , دانة, أشجان , الدانة

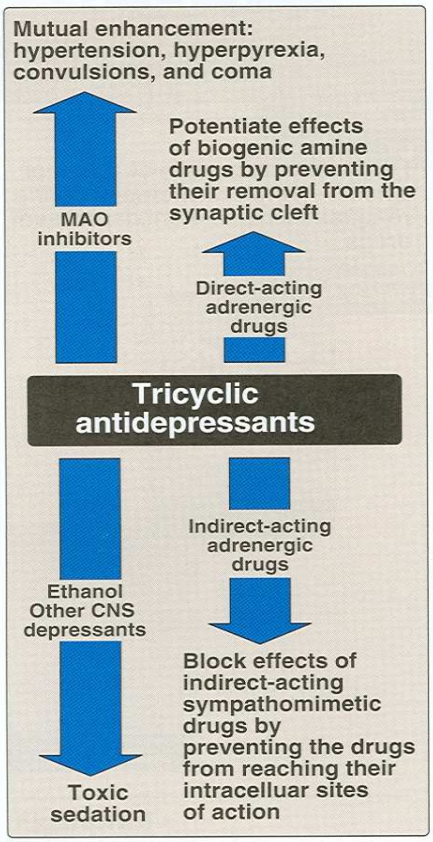

Figure 12.7
Drugs interacting with tricyclic antidepressants. CNS = central nervous system; MAO = mono-amine oxidase.

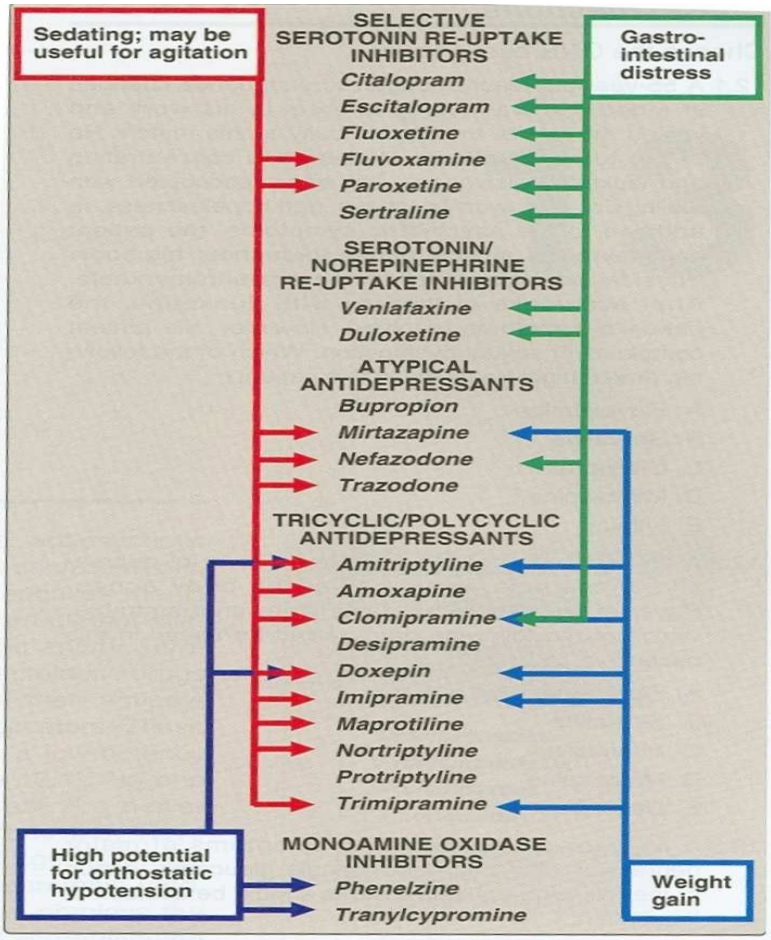

Figure 12.9
Side effects of some drugs used to treat depression.

DRUG	UPTAKE INHIBITION		RECEPTOR AFFINITIES		
	Norepinephrine	Serotonin	Muscarinic	Histaminergic	Adrenergic
Selective serotonin re-uptake inhibitor					
Fluoxetine	0	++++	0	0	0
Selective serotonin/ norepinephrine re-uptake inhibitors					
Venlafaxine	++*	++++	0	0	0
Duloxetine	++++	++++	0	0	0
Tricyclic antidepressant					
Imipramine	++++	+++	++	+	+

Figure 12.3
Relative receptor specificity of some antidepressant drugs. **Venlafaxine* inhibits norepinephrine re-uptake only at high doses. ++++ = very strong affinity; +++ = strong affinity; ++ = moderate affinity; + = weak affinity; 0 = little or no affinity.