Antidepressant Agents

Definition: An effective disorder. Disturbance in the state of mood rather than of thought or behavior. Depression tends to affect the way one feels about himself (emotional changes), the way the person eats or sleeps (biological changes), the way one thinks about things and the way he reacts (behavioral changes)

Classification of depression:

- **Unipolar depression:** Mood swings are always towards one condition (depression or mania). Unipolar depression is more common in elderly where it is associated with stressful life effects and/or symptoms of anxiety and agitation (reactive depression). Depressed patients are usually inert.

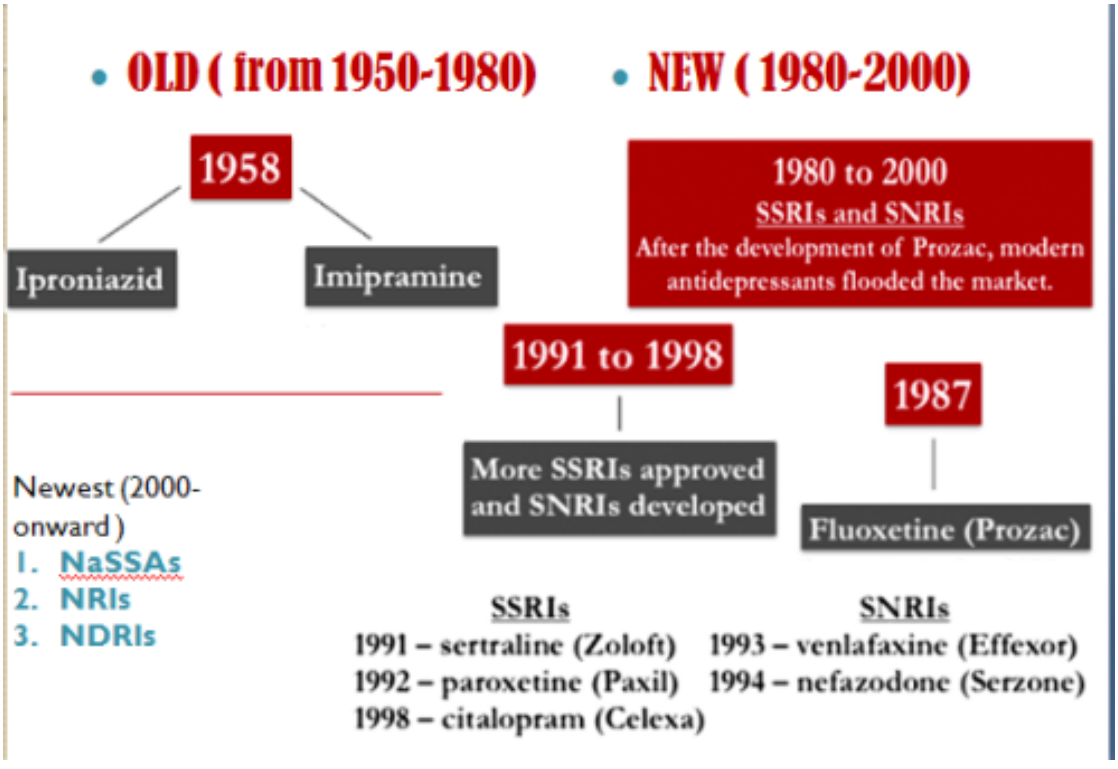
- **Bipolar depression:** Depression alternates with mania which mainly develops early in life. Bipolar depression runs in families (endogenous depression). Episodes can sometimes be provoked by stressful experiences or physical illnesses.

Pathophysiology:
A decrease in monoaminergic activity transmitters —> alteration in receptors density —> decreased brain-derived neurotrophic factor (BDNF) —> hippocampal atrophy and ↓ neurogenesis.

Imbalance and dysregulation of the following neurotransmitters creates a state of deficient monomines:

- **Dopamine:** in the mesocortical, mesolimbic, nigrostriatal, tuberoinfundibular pathways and motor system
- **Serotonin (5-HT):** dorsal (and rostral) raphe nucleus
- **Norepniephrine (NE):** in locus coeruleus and lateral tegmental field.

Antidepressants



SSRI: selective serotonin reuptake inhibitors.

SNRI: selective norepinephrine reuptake inhibitors

NRI: norepinephrine reuptake inhibitors

NaSSA: noradrenergic & specific sertonergic antidepressants.

NDRI: norepinephrine dopamine reuptake inhibitors

- The concept of action of all drugs relies on increasing extracellular biogenic amines in the brain indirectly by blocking their catabolism or directly by preventing their uptake.
- All drugs take weeks to manifest their clinical effect
- Treatment should continue for at least 6 months at full therapeutic doses before withdrawing or changing to another drug.
- Withdrawal of drugs must be very gradual otherwise withdrawal symptoms manifest

Goals of therapy:
- Relieve symptoms of depression
- Prevent suicide
- Restore optimal functioning
- Prevent recurrence

Monoamine oxidase (MAO) inhibitors

Monoamine oxidase is a mitochondrial enzyme presents in all tissues. Two forms of this enzyme exist:
1. MAO-A: which degrades NE, 5-HT, and Tyramine. It is important for the catabolism of monoamines ingested in food.
2. MAO-B: relates to dopamine metabolism

Types of MAO inhibitors:
1. Selective: moclobemide (MAO-A) and selegiline (MAO-B)
2. Non selective:
    I. Reversible: tranylcypromine (acts for 7 days)
    II. Irreversible: phenelzine (persists for 2 weeks)

Pharmacokinetics: readily absorbed from the GI tract

Mechanism of action:
- MAOIs decrease activity of MAO preventing monamine break down—> ↑availability indirectly
- Possess both a Adrenoceptor and muscarinic blocking effects

Indications:
- MAOIs are reserved for last line of defense in atypical depression and depression refractory to other lines of therapy
- In treatment of social anxiety (agrophobia)

Adverse effects:
- Antimuscarinic effects
- Postural hypotension
- Sexual dysfunction epically with phenelzine
- Sedation & sleep disturbance
- Weight gain
- Hepatoxicity (phenelzine)

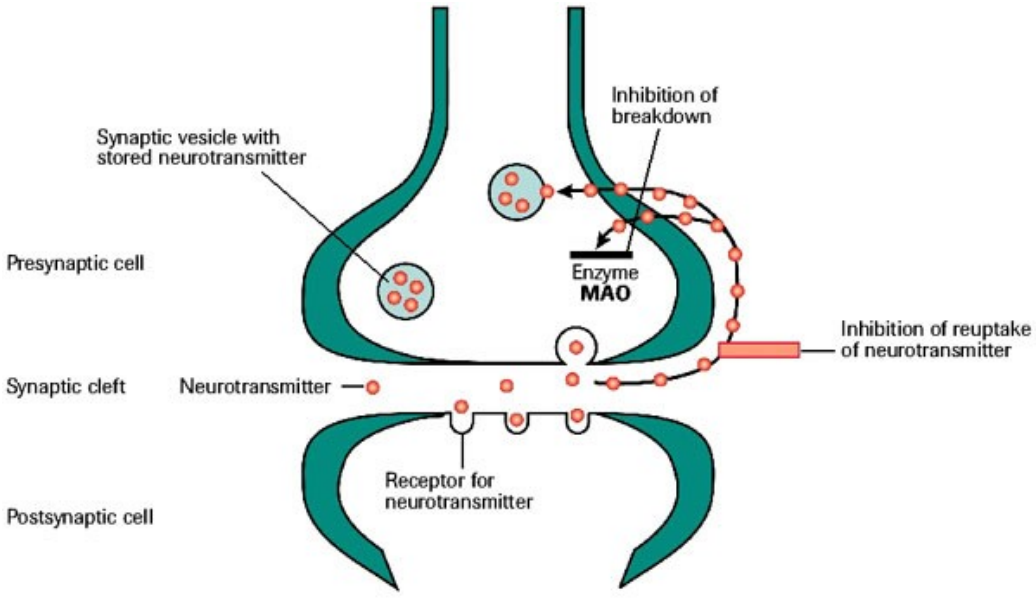
Food interactions:

I. Many foods containing tyramine are degraded by MAO-A
II. MAOIs inhibits this process leading to absorption of tyramine and to be converted into *octopamine*, a false transmitter which replaces NE in the vesicles and releases it into the synaptic vessicle which might lead to hypertensive crisis.
III. Thus it is advised to avoid eating food containing high levels of Tyramine e.g. aged cheese, liver, sausages, fish , and yeast extracts.
IV. Also, food containing levodopa e.g. broad beans, fava beans should also be avoided when taking MOA inhibitors.

Drug interactions:

I. With indirect acting symapthomimetic, flu medication, local anesthetics, and TCA, similar manifestation (hypertensive crisis) might occur.
II. Concomitant use with SSRIs augmenting free serotonin which might result in the fatal "serotonin syndrome" manifested as hyperthermia, muscle rigidity, changes in mental status, and cardiovascular collapse. Thus, at least 6 weeks of drug-free period between the two groups of drugs should be maintained in order to avoid this drastic complication.
III. With pethidine, as MAOIs inhibit its normal pharmacologic demethylation pathway increasing its levels leading to hyperpyrexia, irritability, hypotension, and coma.

Overdosage: it's unusual. Agitation, delirium, and neuromuscular excitability are followed by seizures, shock, and hyperthermia.



Tricyclic antidepressants (TCA)

Classification:

- Tertiary amines: blocks 5-HT and NE reuptake carrying more side effects:
  1. Imipramine (Tofranil)
  2. Amitriptyline (Elavil)
- Secondary amines: more selective for NE with less side effects:
  1. Desipramine (Norpramin)
  2. Nortriptyline (Pamelor)

Other actions:

- TCAs are also capable of blocking ADR (α_1), Histamine (H_1), and Ach (M_1) receptors.
- Receptors and postreceptors effects:
  - cAMP concentrations are decreased in postsynaptic neuron
  - Number of receptors are decreased.

Pharmacokinetics:

- TCAs are incompletely absorbed
- Undergoes first-pass metabolism
- Highly bound to plasma proteins and have high lipid solubility.
- Some of them are metabolized to active metabolites :
  - Imipramine—>Desipramine
  - Amitriptyline—>Nortriptyline

Clinical indications:

1. Treatment of depression:

- Used for long duration without loss of effectiveness [preferable to MAOIs] for:
  1. Mood enhancement
  2. Improve mental alertness
  3. Increase physical activity
- Depressed phase of bipolar depression in conjunction with lithium.
- Treatment of resistant depression refractory to other lines of therapy
- Together with antipsychotics in depressed psychotic patients

2. Other psychiatric disorders:

- Obsessive-compulsive disorders (OCD) when psychostimulants are ineffective or contraindicated
- Generalized anxiety disorders
- Anorexia nervosa
- Panic disorders
- Attention deficit hyperkinetic disorder

3. *Other disorders:*

- Control bed-wetting (enuresis) in children; Imipramine increases internal sphincter contraction of the bladder. Desmopressin is preferred
- Gradually withdrawn; treatment with TCAs should not exceed a period of 3 months.
- Prophylaxis of migraine/vertigo

- Neuropathic pain; better Tertiary amines which modulate endorphins Their pain relieving properties can typically be felt at lower doses than of those prescribed for depression.

Adverse effects:

- Anticholinergic, dry mouth, blurred vision, constipation and urine retention, aggravation of glaucoma.
- Antihistaminic, sedation, confusion. Stop sedatives 1-2 weeks before use
- Anti-adrenergic mainly on α receptors with subsequent postural hypotension, arrhythmias (prolonged QT interval - heart block).
- Weight gain, sexual dysfunction, and impotence
- Lower seizure threshold
- Aggravation of psychosis
- EARLY IN USE: During the 1st month, aggravate suicidal thoughts especially in young aged. Can happen less upon changing the dose.

DURING USE: narrow therapeutic index; toxicity can develop with slight increase in therapeutic doses

On stopping the medication: Withdrawal Symptoms; characterized by cholinergic rebound, flu-like symptoms

Drugs interaction:

- Being strongly bound to plasma proteins: toxicity enhanced by aspirin, phenylbutazone
- Being metabolized by hepatic microsomal enzymes: toxicity enhanced by enzyme inhibitors
- With MAOIs, SSRIs or any sympathomimetic drugs: cause hypertensive crisis
- Additive to sedatives or other CNS depressants: ↓respiration
- Additive to antipsychotics and antiparkinson drugs: increase in anticholinergic effects
- With alcohol —> impairment of driving ability

Contraindications: glaucoma, heart disease, liver disease, seizure disorder, thyroid disease, prostate hypertrophy, pheochromocytoma, chronic bronchitis

Tertiary and Secondary Amine Tricyclic Antidepressants			
Medications	**Initial/Max Dose**	**Comments**	**Adverse Effects**
Tertiary Amine TCAs			
Amitriptyline (Elavil)	25-75 mg/200 mg daily	5HT > NE	Orthostatic hypotension, drowsiness, weight gain, anticholinergic, QT prolongation (in overdose)
Amoxapine (Asendin)	50 mg bid/400 mg daily	5HT = NE, weak DA	
Clomipramine (Anafranil)	25 mg/250 mg daily	5HT > NE	
Doxepin (Sinequan)	50-75 mg/300 mg daily	5HT = NE; highly sedating	
Imipramine (Tofranil)	50-100 mg/200 mg daily	5HT = NE	
Secondary Amine TCAs			
Desipramine (Norpramin)	100-200 mg/300 mg daily	NE > 5HT; metabolite of imipramine	Same as above, but with more drowsiness, somnolence, and weight gain than tertiary
Maprotiline (Ludiomil)	25 mg tid/225 mg daily	NE > 5HT	
Nortriptyline (Pamelor)	25-50 mg/150 mg daily	NE > 5HT; metabolite of amitriptyline	

Selective serotonin reuptake inhibitors (SSRIs)

Examples: *Fluoxetine, Fluvoxamine, Citalopram, Sertraline*, and *Paroxetine*

Mechanism of action:

- Binds to SERT (serotonin trasnsporter) increasing the level of 5-HT in the synapse
  SSRIs have no effect on NET (NE transporter)
- No block to Ach, H1, or a_1 adrenoceptor, hence no antimuscarinic or sedative effects are apparent in clinical use of SSRIs
- They are nearly of comparable efficacy but of preferential response in each individual.

Pharmacokinetics:

- $T_{1/2}$: Very long (3-11 days): Fluoxetine (Prozac), Moderate length (~24hr): Sertraline, Paroxetine, Citalopram.
- Metabolism: Metabolism: P450 through glucuronide or sulfate conjugation
- They are enzyme inhibitors:
  - Weak inhibitors (sertaline & citalopram)
  - Strong inhibitors (fluoxetine & paroxetine) —> affect the metabolism of TCA, neuroleptics, some antiarrhythmic drugs, and β blockers
- pimarily excreted through kidney, except for paroxetine and sertraline which undergo partial fecal excretion.
- Fluoxetine has an active metabolite, norfluoxetine, which is as potent as fluoxetine, with $t_{1/2}$ of 10 days

Clinical indications:

- First choice for the majority cases of depression. Comparable efficacy of TCAs, but are much safer with less drug interactions and sedation.
- Fluoxetine is approved in children, adolescence, elderly males with prostatic hypertrophy, and is considered to be relatively safe in pregnancy.

- **Used in:**
    1. Anxiety and panic disorders
    2. Obsessive compulsive disorders (OCD)
    3. Eating disorders (bulimia)
    4. Pain associated with diabetic neuropathy
    5. Premature ejaculation
    6. Premenstrual syndrome
    7. Alcohol abuse
    8. Anorexia nervosa
    9. Generalized anxiety disorder

Adverse effects:

- Insomnia, anxiety, agitation, and nervousness which are relatvely more common to occur with fluoxetine than with citalopram. These adverse effects could be useful in fatigued patients.
- Sedation and lassitude with paroxetine, sertraline, and fluvoxamine. Sedation could be of advantage in patients with sleeping difficulty.
- GIT upset presenting as nausea, vomiting, and diarrhea which are the results of the indirect activation of 5-HT_3 receptors in the enteric nervous system.
- Anorexia and weight loss
- Impotence and sexual dysfunction; loss of libido delay ejaculation by indirect CNS stimulation of the 5-HT_2 receptor.
- Mild CVS and minimal antimuscarinic side effects unlike TCAs
- Withdrawal manifestation are milder than those seen with TCAs
- Paroxetine: has a muscarinic action and teratogenic potentiality

Drug interactions:

- Serotonin syndrome could happen if SSRIS are combines with MAOIs and other antidepressants.

Serotonin norepinephrine reuptake inhibitrs (SNRI)

Venlafaxine

Mechanism of action: Restore the levels of NE and 5-HT in the synaptic cleft by binding to NET (norepinephrine transporter) and SERT (serotonin transporter). They have mild antimuscarinic effect.

Pharmacokinetics: $t_{1/2}$ 4-10 hours

Adverse effects: same as SSRIs + hyper tension, increased heart rate, and withdrawal symptoms on abrupt discontinuation

Norepinephrine reuptake inhibitors (NRI)

Reboxetine

Mechanism of action:

- Only blocks NET No affinity for 5-HT, DA, ADR, H1, muscarinic receptors. Thus, have positive effects on concentration and motivation in particular.
- Safe to combine with SSRIs

Side effects: Minimal side effects only related to activation of ADR system as tremor, tachycardia, and urinary hesitancy.

Noradrenergic and specific serotonergic antidepressants (NESSA)

Mirtazapine

Mechanism of action: Blocks presynaptic α_2 adrenoceptors and $5HT_{3+2}$ receptors

Preferred in cancer patients because:

1. Improves appetite
2. ↓Nausea and vomiting (5-HT_3 blocking)
3. ↑Body weight
4. Sedation (antihistaminic)
5. Less sexual dysfunction (5-HT_2 blocking)
6. Has no anti-muscarinic effect .

Side effects: drowsiness, □appetite, and weight gain.

Norepinephrine dopamine reuptake inhibitors (NDRIs)

Bupropion

Mechanism of action:

- Is a unique in possessing significant potency as NE and DA reuptake inhibitor, with no direct action on 5-HT.
- Acts as muscarinic antagonist.

Therapeutic uses:

1- Treatment of major depression and bipolar depression.

2- Can be used for smoking cessation. As it reduces the severity of nicotine craving and withdrawal symptoms.

Advantages:

No sexual dysfunction —> given for young patients
No 5-HT effect —> No weight gain
No orthostatic hypotension

Side effects: Seizures; it decreases the threshold of neuronal firing, dizziness, dry mouth, sweating, and tremor

Serotonin antagonist and reuptake inhibitors (SARIs)

trazodone	nefazadone
Psychotropic drug Weak block of SERT Alpha (α) blocking effect Potent H_1 blocker	Trazodone is its precursor No effect on histamine or adrenergic receptors
High protein binding Extensive hepatic metabolism Urine excretion	Inhibit CYP 450
Causes priapism, arrhythmogenic	Causes hepatic failure

Augmentor drugs

Some antidepressants work better in some patients when used in combination with other drugs.

Augmentor drugs include

- Buspirone
- Antipsychotics: typical and atypical
- Lithium: augment in case of resistant unipolar depression

Trazadone, Nafazodone, Bupropion are sometimes included among augmenters but their use, as such, should be under strict clinical supervision.

"It's a new anti-depressant—instead of swallowing it, you throw it at anyone who appears to be having a good time."