Antidepressants

A. Definition: Depression is a psychiatric illness characterized by mental and physical symptoms, including depression mode , loss of interest in normal activities, feeling of guilt, inability to take decisions, loss of confidence, loss of appetite, difficulty in sleep and suicide ideas. Depression is of two types unipolar and bipolar (manic-depression)

B. Amine theory: Depression occurs due to disturbances in the catecholamines concentrations in the brain including the reduction in serotonin, and noradrenaline in certain sites in the brain. In support of this theory is the fact that most antidepressant drugs act mainly by increasing catecholamines centrally in the brain. Reserpine, a drug which depletes catecholamines centrally in the brain can cause depression as a side effect. However depression may be caused by more complex mechanisms including genetic factors

C. Drugs useful in the treatment of depression:

1. Tricyclic antidepressants: imipramine, amitriptyline, clomipramine.
2. Second generation: mianserine, maprotiline, amoxapen , trazodone, bupropion, nefazodone and venlafaxine
3. Monoamine-oxidase inhibitors:
    a. non-selective and irreversible: phenelzine, isocarboxazid, tranylcypromine
    b. selective and reversible (MAOI-A): meclobemide
4. Selective Serotonin reuptake inhibitors: Fluoxetine, citalopram, paroxetine, Sertraline
5. Lithium : useful in manic-depression

Tricyclic-antidepressants:

Imipramine, amitriptyline, nortriptyline and clomipramine

Called tricyclic due to their chemical structure which contain three cycles

Mechanism of action: all act by inhibiting the neuronal reuptake of catecholamine (noradrenaline and/ or serotonin) centrally in the brain and increasing the brain stores of these amines. They usually take two weeks for the full clinical benefit to occur. Amitriptyline has a sedative effect in addition to the anti-depressant action, so it is useful in agitated patients. Imipramine has less sedative effect.

Pharmacokinetics:

- Intestinal absorption is slow and incomplete specially in high doses due to anticholinergic effect
- Highly lipid soluble
- Extensive first pass metabolism
- Active metabolites
- High protein binding (85-90%)

Clinical uses:

1. Depression
2. Panic attacks and severe anxiety states

3. Nocturnal enuresis in children, due to anticholinergic effect and changing sleep pattern
4. Co-analgesics: administered with analgesic drugs especially in chronic pain as it improves pain control by inhibiting pain pathway and relieving associated depression

Adverse effects:

1. Anticholinergic: dry mouth, constipation, tachycardia, retention of urine
2. CNS: tremor, sedation, confusion, insomnia, convulsions
3. Cardiovascular : postural hypotension (alpha blockade) , tachycardia, ECG changes (flat T wave, ST depression and QT prolongation), AV block
4. Allergic reactions; skin rash, cholestatic jaundice and bone marrow depression

Drug interactions with tricyclic antidepressants

1. Potentiate other CNS depressants as benzodiazepines and barbiturates
2. Potentiate the effects of monoamine oxidase inhibitors
3. Potentiate the effect of anti-muscarinic drugs
4. Reduce the antihypertensive effect of guanithidine and clonidine by inhibiting their neuronal uptake
5. Potentiate the effects of sympathomimetic amines as noradrenaline and amphetamine

2. Second generation antidepressants:

Trazodone:

Acts by antagonism at serotonin receptors (5HT-$_{2A}$ or 5HT$_{2C}$) and blocking presynaptic (alpha2) adrenoceptors and increased catecholamine secretion. It lacks anticholinergic effects and causes less interactions with drugs and is relatively safe in overdose. But it may cause seizures especially in overdose

Maprotiline:

Is a tetracyclic compound similar in action to the tricyclic compounds, has a long half-life and can be given in a single daily dose

Amoxapen:

Causes less cardiac toxicity but may cause extra-pyramidal symptoms

Nefazodone

Also lacks anticholinergic effects, but may cause hypotension, it improves sleep.

3.Monoamine oxidase inhibitors:

Irreversible and non-selective: phenelzine, isocarboxazid, tranylcypromine

They act by irreversible inhibition of MAO enzymes and increase catecholamine centrally in the brain, some of them have prolonged action even after cessation of therapy. They are only used when there is no response to other drugs. Also they take 2 weeks for clinical response to occur.

Adverse effects:

1. Atropine like action as dry mouth, blurring of vision, retention of urine and constipation
   c. CNS : anxiety, acute confusion, tremor, hyper-reflexia
   d. Others, hepatocellular necrosis, skin rash and jaundice

Drug interactions:

1. Cause severe hypertension when given in combination with amines as Adrenaline, ephedrine and amphetamine. This may lead to sub- arachnoid hemorrhage
2. Also hypertensive reaction may occur following the ingestion of tyramine containing food as cheese and banana
3. MAOIs can also inhibit the metabolism of other drugs as barbiturates and hypoglycemic agents

<u>Reversible selective MAOIs (MAOI-A)</u>

<u>Meclobemide:</u>

Inhibits MAO-A in the brain, but has no effect on MAO-B which is widely distributed in the body including the GIT. Therefore meclobemide is less likely to cause hypertensive reactions. It has also a reversible action with loss of all the activity after 24 to 48 hours following cessation of treatment.

Adverse effects:

Nausea, vomiting, dizziness insomnia and agitation

Less interaction with food and less toxicity in overdose

3. Selective serotonin reuptake inhibitors (SSRIs):

Fluoxetine, paroxetine, sertraline

Selectively inhibit serotonin uptake, they have little effect on other catecholamine like dopamine and noradrenaline. They have no effects on muscarinic, adrenergic or histamine receptors.

They have fewer adverse effects and can be given in a single daily dose due to long half life

Adverse effects:

1. Nausea, vomiting and diarrhea
2. Headache, nervousness, agitation and insomnia
3. Fewer interactions with other drugs and free from cardiovascular side effects

Lithium

Is clinically used as lithium salts like lithium carbonate. Lithium is effective in the treatment of manic-depression. The mechanism of action includes ; as a mono-valent cation Li^+ can replace Na^+ ions which lead to altered neuronal function, it also interacts with second messengers (G-proteins) and causes inhibition of inositol phosphate

Pharmacokinetics:

- Lithium salts as lithium carbonate converted inside the body into lithium ions (Li^{+3})
- Not bound to plasma proteins
- Low therapeutic index so requires serum level monitoring during treatment
- Diuretics reduce renal clearance

Adverse effects:

1. CNS: drowsiness, dizziness, ataxia, tremor, dysarthria coma and convulsions
2. Cardiovascular: hypotension and cardiac dysrhythmias
3. Nephrogenic diabetes insipidus (antagonizes ADH hormone)
4. GIT: nausea, vomiting and diarrhea