**Depression**

**Etiology:**

Genetic, hormonal, biochemical, environmental and social factors all have some role in determining an individual's susceptibility to developing the disorder:

- ***Genetic causes;***

The incidence of affective disorder in first-degree relatives of someone with severe depression may be about 20%. Twins have found fairly strong evidence for a genetic factor.

- ***Environmental factors;***

Studies shows that employment, higher socio-economic status and the existence of a close and confiding relationship have been consistently noted to offer some protection against the development of an episode.

- ***Biochemical factors;***

Although many neurotransmitters may be implicated, the theory focuses on an involvement of the neurotransmitters ***noradrenaline*** (norepinephrine), ***serotonin*** (5-hydroxytryptamine) and ***dopamine***.

This theory emerged from the findings that both monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants appeared to increase neurotransmitter amines, particularly noradrenaline (norepinephrine), at important sites in the brain.

Some studies have found reduced activity in depressed patients, and an over activity has been postulated in mania.

***- Endocrine factors:***

People with depression have been found to have increased ***cortisol*** levels, which also supported the proposition that mood disorders may be linked to dysfunction within the hypothalamic-pituitary-adrenal (HPA) axis. This led to the development of a dexamethasone suppression test for depression in the 1970s.

Some endocrine disorders such as hypothyroidism and Cushing's syndrome have also been associated with changes in mood.

***Physical illness and side effects of medication:***

Disorders of mood, particularly depression, have been associated with several types of medication and a number of physical illnesses:

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| **Drugs** | **Physical illness** |
| Analgesics | Viral illness |
| Antidepressants | Carcinoma |
| Antihypertensives | Neurological disorders |
| Anticonvulsants | Diabetes |
| Opiate withdrawal | Multiple sclerosis |
| Amfetamine withdrawal | Thyroid disease |
| Antiparkinsonism agents | Addison's disease |
| Antipsychotics | Systemic lupus erythematosus |
| Benzodiazepines | Pernicious anemia |
| Oral contraceptives |  |
| Steroids |  |

**Clinical manifestations**

- Low mood is the central feature of depression.

- Loss of interest or pleasure in normally enjoyable activities.

- Thinking is pessimistic and in some cases suicidal.

- Have little or no energy.

- In severe cases, psychotic symptoms such as hallucination or delusion may be present.

- Anxiety or agitation.

- In contrast to agitation, psychomotor retardation may be a presenting feature.

- Biological features of sleep disturbances, weight loss and loss of appetite are often present.

- *In some cases*, the biological symptoms are reversed and excessive eating and sleeping may occur.

- Sexual drive is often reduced

**Investigations**

* Mainly depends on the clinical symptoms and the severity of the disorder; which can be assessed by rating scale, self-reporting scale or used by a health care professional.
* Dexamethasone suppression test; however, the relationship between cortisol and symptoms of depression is complex which severely limits the clinical utility of such a test.

**Treatment**

* The aim of treatment is to prevent harm and to relieve distress or to be prophylactic.
* In the treatment of depression, all the antidepressants currently available may be considered to be equally effective.
* There is increasing evidence that patients with more severe episodes of depression are more likely to respond to antidepressant drugs.
* The major difference between antidepressant agents is in their side effect profile and their toxicity in overdose.
* There are some generalizations which may help individualize the choice of antidepressant; tricyclic antidepressants are less well tolerated in females and more likely to be toxic in overdose than the selective serotonin reuptake inhibitors (SSRIs).
* Patients may prefer one drug over another based on their past experience of benefit or side effects.

***Non-pharmacological***

* Non-pharmacological therapies are effective and in mild depression they are considered preferable to drug treatment.
* Non-drug treatments and antidepressant medication are not mutually exclusive and in some cases it is preferable to use both in combination.
* They include cognitive behaviour therapy (CBT) and Electroconvulsive therapy (ECT).

***Drug treatment***

***Tricyclic antidepressants:***

* The primary effect of these drugs was related to their ability to block the reuptake of noradrenaline (norepinephrine) and/or 5HT following their release and action as neurotransmitters. This effect occurs some weeks before the antidepressant response.
* Clearly this is not the whole story; following chronic administration, further biochemical changes take place, particularly with pre- and postsynaptic receptor sensitivity. Reduction of presynaptic α2-inhibitory receptor sensitivity occurs, and this increases the production of noradrenaline (norepinephrine).
* Other effects which may be relevant include an increase in α1 and β1 receptor sensitivity; these receptor changes in the cerebral cortex and hippocampus may be more relevant to the antidepressant response than simple reuptake inhibition.
* There are a number of tricyclic antidepressants in current clinical use; all of them block the reuptake of noradrenaline (norepinephrine) and 5HT to a greater or lesser degree, and there are some differences in adverse effect profile between them.
* ***Imipramine*** the more common used, produce less sedating than other TCA, may trigger cardiovascular problems & significant anti-muscarinic effects.
* Females tend to tolerate imipramine less well than males.
* Starting with a lower dose of the drug and gradually increasing the dose over a week may develop tolerance to some unpleasant side effects.
* ***Amitriptyline*** has a similar poor side effect and toxicity profile to imipramine but is more sedative.
* ***Clomipramine*** one of the first antidepressants found to be a potent 5HT reuptake inhibitor, which may explain the benefit of this drug in the management of obsessive-compulsive disorder.
* ***Dosulepin***guidelines for the management of depression but advice to not be prescribed because of the risks associated with cardiac problems and toxicity in overdose compared to other available treatments.
* ***Doxepin***has similar effects and side effects to the traditional TCA. Limited evidence suggests that it may have fewer cardiac effects in patients with pre-existing cardiac disease.
* ***Lofepramine*** has favourable side effect profile and low toxicity in overdose, lofepramine may be considered as a reasonable option if an SSRI is ineffective or not tolerated.
* lofepramine is significantly safer in overdose than the traditional agents. This may be due to lofepramine antagonizing the cardiac effects of its metabolite (desipramine).
* ***Nortriptyline*** (major metabolite of amitriptyline) and ***Trimipramine*** present with few differences from the rest of the traditional tricyclics.

***Monoamine oxidase inhibitors:***

* Two types of MAOI are available: the traditional MAOIs, which are both non-selective and irreversible, and moclobemide, which is a selective reversible inhibitor of monoamine oxidase type A (RIMA).
* Due to the potential for drug and food interactions (with other drugs and tyramine-containing foods), MAOIs should be reserved for use in situations where a first-line SSRI antidepressant has failed.
* It is important that patients are made aware of the dietary restrictions and potential for serious drug interactions.
* MAOIs inhibit the enzymes responsible for the oxidation of noradrenaline (norepinephrine), 5HT and other biogenic amines. Two forms of monoamine oxidase have been found to exist, MAO-A and MAO-B. The traditional MAOIs are all non-selective and inhibit both forms of the enzyme.
* Tyramine is metabolised by both forms of the enzyme, if tyramine-containing foods are consumed, tyramine is metabolised by MAO-B enzymes as well as MAO-A (very large quantities of tyramine are ingested).
* Inhibition of MAO-A is thought to be responsible for the antidepressant effects. It is also responsible for metabolizing tyramine and producing the interaction.
* Moclobemide is an antidepressant that acts as a reversible inhibitor of MAO-A.
* This appears to prevent the typical hypertensive reaction seen with conventional MAOIs and tyramine-containing foods by using MAO-A selective inhibitor.
* **Traditional MAOIs** have little anticholinergic effect, hypertension which follows the interaction of tyramine-rich foods with the traditional MAOIs.
* *Tranylcypromine* has a significant stimulant effect (amfetamine-like alerting), and because of this could be more likely to give rise to problems around dependence. Unlike the other MAOIs, it does not irreversibly inhibit monoamine oxidase, which is said to recover some 5 days after withdrawal of the drug.
* *Phenelzine* has a hydrazine structure and because hydrazines have been associated with hepatocellular jaundice, it is recommended that phenelzine should be avoided in patients with hepatic impairment or abnormal liver function tests.
* **Reversible inhibitors of monoamine oxidase**, although moclobemide is an effective antidepressant, with less propensity for interactions with tyramine-rich foods, caution should still be exercised as other drug interactions do occur.
* It could be considered as an option if a first- or second-line SSRI is ineffective.

**Selective serotonin reuptake inhibitors (SSRIs)**

* The SSRIs are better tolerated by most patients and considerably less toxic in overdose; this means that they should be the *first-line choice for the pharmacological management of moderate or severe depression.*.
* They are equally effective & have a broadly similar range of side effects, but there are variations in the intensity or duration.
* ***Fluvoxamine:***  patients experience few antimuscarinic side effects, other problems related to serotonergic enhancement such as nausea, headache and nervousness.
* ***Fluoxetine****:* have the longer half-lives of both the parent drug and its primary active metabolite, desmethylfluoxetine.
* The long half-life of fluoxetine and its major metabolite is a problem if severe side effects develop, while this long half-life means that the risks of discontinuation syndrome are reduced.
* ***Paroxetine*** has been reported to cause extrapyramidal-type movements more than other SSRIs, particularly following abrupt discontinuation of high doses.
* ***Sertraline, Citalopram & Escitalopram*** have similar side effect profile to other SSRIs.

**Serotonin-noradrenaline reuptake inhibitors (SNRIs)**

* They have more efficacy over the standard agents, by prevent the reuptake of both serotonin and noradrenaline (norepinephrine)
* ***Venlafaxine***: the first in a new class of antidepressants, indicated for severe cases but without the anti-muscarinic, cardiac or toxic effects of the older drugs, but with poor tolerability.
* ***Duloxetine:***Like venlafaxine, is an SNRI. It weakly inhibits dopamine reuptake and may be less well tolerated than SSRIs.
* The drug is considered to be a second-line treatment option.
* ***Reboxetine***: is a specific noradrenergic (norepinephrinergic) reuptake inhibitor (NARI).
* Patients experiencing problems with serotonergic-related side effects may benefit from a switch to reboxetine.
* ***Mirtazapine:*** is a noradrenergic and specific serotonergic antidepressant (NaSSA).
* It enhances both noradrenergic (norepinephrinergic) and 5HT1 serotonergic transmission.
* Specific 5HT1 neurotransmission is achieved as the drug also acts as a 5HT2 and 5HT3 antagonist, that may explain some reduction in sexual dysfunction and nausea compared to other SSRIs.
* ***Agomelatine***: is structurally related to melatonin, it is thought to act as an agonist at melatonin MT1 and MT2 and antagonist at 5HT2c.
* ***Trazodone:*** has a mixed serotonin agonist/antagonist, but clinically it is thought to operate as a serotonin agonist.
* Trazodone is much safer than the TCA following overdose but causes pronounced sedative and hypotensive effects in some patients.
* Priapism has also been noted probably due to its potent α-receptor blocking properties.

**Choice of antidepressant**:

* The severity of the disorder, patient preference, cost and previous experience should also play a part.
* For most people with moderate-to-severe depression, unless otherwise contraindicated, the use of a generic SSRI (sertraline and escitalopram) as the first-line choice is appropriate.
* Previous response, tolerance and the likelihood of drug interactions should also be considered.

***Dr. Mohammed M. M.***

***PhD Clinical Pharmacy Good Luck***