**Antidepressants**

* As their name suggests, the antidepressants are used primarily to relieve symptoms of depression.
* In addition, these drugs can help patients with anxiety disorders.
* As a rule, antidepressants are not indicated for uncomplicated bereavement.
* The antidepressants fall into four major groups: tricyclic antidepressant, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, and atypical antidepressants.

**Major Depression: Clinical Features, Pathogenesis, and Treatment Modalities**.

* Depression is the most common psychiatric illness.
* In the United States, about 30% of the population will experience some form of depression during their lives.
* At any given time, about 5% of the adult population us depressed.
* The risk of suicide among depressed people is about 25%.
* Unfortunately, depression is underdiagnosed and undertreated: Only 30% of depressed individuals undergo treatment; the other 70% remain untreated.
* This is especially sad in that treatment can help between 85% and 90% of patients: About 70% respond to drugs and another 20% respond to electoconvulsive therapy (ECT).

**Pathogenesis**

* The etiology of major depression is undoubtedly complex and not yet known.
* Since depressive episodes can be triggered by stressful life events in some individuals but not in others, it would appear that, for some individuals, a predisposition to depression exists.
* Social, developmental, and biologic factors, including genetic heritage, may all contribute to that predisposition.
* Clinical observations made in the 1960s led to formulation of the monoamine hypothesis of depression, which asserts that depression is caused by a functional insufficiency of monoamine neurotransmitters (norepinephrine, serotonin, or both)
* Clinical observations made in the 1960s led to formulation of the monoamine hypothesis of depression, which asserts that depression is caused by a functional insufficiency of monoamine neurotransmitters (norepinephrine, serotonin, or both)
* Although these observations lend support to the monoamine hypothesis, it is now clear that the hypothesis is far too simplistic.
* However, despite its shortcomings, the monoamine hypothesis does provide a useful conceptual framework for understanding antidepressant drugs.

**Tricyclic Antidepressants**

* The TCAs are drugs of first choice for many patients with major depression. The first tricyclic agent -imipramine- was introduced to psychiatry in the late 1950s.
* Since then, the ability of TCAs to relieve depressive symptoms has been firmly established.
* The most common adverse effects of TCAs are sedation, orthostatic hypotension, and anticholinergic effects.
* The most hazardous effect is cardiac toxicity.
* Because all of the TCAs have similar properties, we will discuss these drugs as a group rather than focusing on a representative prototype,

**Mechanism of Action**

* TCAs block monoamine (NE and serotonin) reuptake.
* By blocking reuptake of these neurotransmitters, TCAs can intensify their effects.
* Such a mechanism would be consistent with the monoamine hypothesis of depression. That is, the monoamine hypothesis, which asserts that depression stems from a deficiency in monoamine-mediated neurotransmission, would predict that drugs capable of increasing the effects of monoamines would reduce symptomes of depression.
* This prediction is fulfilled by the tricyclic drugs.

**Therapeutic Uses**

Depression

Biopolar Disorder.

**Adverse effects**

* Orthostatic Hypotension
* Anticholinergic Effects
* Diaphoresis
* Sedation
* Cardiac Toxicity
* Seizures

**Drug Interactions**

* Monoamine Oxidase Inhibitors
* Direct-Acting Sympathomimetic Drugs
* Indirect-Acting Sympathomimetic Drugs
* Anticholinergic Agents
* CNS Depressants

**Selective Serotonin Reuptake Inhibitors**

* In recent years, drugs that produce selective blockade of serotonin reuptake have become available. These SSRIs are as effective as the TCAs, but do not cause hypotension, sedation, or anticholinergic effects.
* Moreover, overdose does not cause cardiotoxicity.
* Death by overdose is extremely rare.
* Characteristic side effects of the SSRIs are nausea, insomnia, and sexual dysfunction (especially anorgasmia).
* SSRIs can interact adversely with MAOIs, and hence the combination must be avoided.
* Fluoxetine, the most popular SSRI, will serve as our prototype for the group.

**Fluoxetine**

* Fluoxetine [Prozac] is the most widely prescribed antidepressant in the United States.
* The drug is as effective as the TCAs, cause fewer side effects, and is less dangerous when taken in overdose.
* Combined use with MAOIs can cause serious adverse effects, and therefore must be avoided.

**Mechanism of action**

* Fluoxetine produces selective inhibition of serotonin reuptake, and thereby intensifies transmission at serotonergic synapse.
* As with TCAs, blockade of transmitter uptake occurs quickly, whereas therapeutic effects develop slowly.
* Hence, we can conclude that adaptive cellular changes that take place in response to prolonged uptake blockade must be the actual basis of dopamine or NE. In contrast to the TCAs fluoxetine does not block cholinergic, histaminic, or alpha₁- adrenergic receptors. Furthermore, fluoxetine produces CNS excitation rather than sedation.

**Therapeutic Uses**

* Fluoxetine is used primarily to treat major depression.
* Antidepressant effects begin in 1 to 3 weeks and are equivalent to those produced by TCAs.
* Fluoxetine is also approved for obsessive-compulsive disorder and bulimia nervosa-and is a preferred drug (although not approved) for panic disorder and premenstrual syndrome. Investigational uses include alcoholism, attention-deficit/hyperactivity disorder, bipolar disorder, migrane, Tourette’s syndrome, and obesity

**Adverse Effects**

* Fluoxetine is safer and better tolerated than TCAs and MAOIs.
* Death from overdose with Fluoxetine alone has not been reported,
* In contrast to TCAs, Fluoxetine does not block receptors for histamine, NE, or acetylcholine, and hence does not cause sedation, orthostatic hypotension, and ticholinergic effects, or cardiotoxicity.
* The most common side effects are sexual dysfunction (70%), nausea (21%), headache (20%), and manifestations of CNS stimulation, including nervousness (15%), insomnia (14%), and anxiety (10%).
* Fluoxetine and other SSRIs appear safe for use during pregnancy.
* Sexual Dysfunction
* Weight gain
* Serotonin Syndrome
* Withdrawal Syndrome

**Drug interactions**

* Monoamine Oxidase Inhibitors
* Warfarin
* Tricyclic Antidepressants and Lithium.

**Atypical Antidepressants**

* Bupropion
* Trazodone
* Nefazodone
* Venlafaxine
* Mirtazepine
* Amoxapine
* Reboxetine

**Mirtazepine**

* Mirtazepine [Remeron] is the first representative of a new class of antidepressants.
* Therapeutic effects appear to result from increased release of serotonin and NE.
* Mirtazepine increases release by blocking presynaptic alpha₂-adrenergic receptors that serve to inhibit release. In addition to promoting release of serotonin and NE, Mirtazepine is a powerful blocker of two serotonin receptor subtypes: 5-HT₂ and 5-HT₃. The contribution of this effect is unclear.
* Mirtazepine is well absorbed following oral administration and reaches peak plasma levels in 2 hours.
* The drug undergoes extensive hepatic metabolism followed by excretion in the urine (75%) and feces (25%).

The elimination half-life is 20-40 hours.

* Mirtazepine is generaly well tolerated.
* Somnolence is the most prominent adverse effect, occuring in 54% of patients.
* Other side effects include increased appetite (17%), weight gain (8%), cholesterol elevation(15%) , and dizziness (7%).
* Reversible agranulocytosis and neuropenia occure rarely.
* Blockade of muscarinic receptors is moderate; hence, anticholinergic effects are relatively mild.
* Mirtazepine-induced somnolence can be exacerbated by alcohol, benzodiazepines, and other CNS depressants; hence, these agents should be avoided. Mirtazepine should not be combined with MAOIs.
* Mirtazepine is available in tablets (15, 30, and 45 mg) for oral administration. The initial dosage is 15mg once a day at bedtime. Dosage may be gradually increased to a maximum of 60mg/day.