Chapter 1

Introduction

As compare to other species, human allowing us to achieve the wonder of walking on the moon; and composing masterpieces of literature, art and music. Throughout recorded time, as compared to a telephone switchboard and a supercomputer the human brain a mass of fatty tissue, spongy weigh in three pound.

But the brain is much more complicated than any of these devices, a fact scientist confirm almost daily with each new discovery. The extent of the brain’s capabilities is unknown, but it is the most complex living structure known in the universe. The brain is an assembly of interrelated neural systems that regulates their own and each other's activity in a dynamic and complex fashion. Morphological properties of central neurons have been very useful for the description of the functional characteristics.

This single organ controls all body activities, ranging from heart rate and sexual function to emotion, learning and memory. The brain is even reflection to power to response to various disease of the immune system and to determine how well people respond to medical treatments. Ultimately, it shapes our thoughts, hopes, dreams and imagination. In short, the brain is what makes us human (Joseph et al., 2002).

Nervous system is one of the body’s principle control and integrating centre, which serves majorly sensory, motor and integrative functions. The nervous system is divided into two principal divisions, the central nervous system and the peripheral nervous system. The nervous system is unique to control actions it can perform and complexity of thought processes. Body gives responses to millions of bits of information from the different sensory nerves and sensory organs which receive from it. Evolution of brain over the past 500 years understanding the structure and function which permitting researchers to see the living, feeling, and thinking human brain at work with the tools such as neuroimaging and neurophysiology. Combination of the tools with cognitive neuroscience, imaging technologies make it increasingly possible to identify the specific parts of the brain used to different aspects like thinking and emotion.
The brain is an extremely complex organ which is responsible for molding genetic, molecular and biochemical information. The brain consists of two types of cells neurons and neuroglia. Neurons are accountable for sending and receiving nerve impulses or signals whereas Neuroglia provides nourishment, protection and structural support to neurons. Collectively, there are more than one hundred billion neurons in the brain, comprise thousands of distinct types. Each of these neurons communicates with other neurons by way of specialized structures called synapses. More than one hundred special brain chemicals, called neurotransmitters, communicate across these synapses. In aggregate, there are almost certainly more than 100 trillion synapses in the brain. Circuits, created by hundreds or thousands of neurons, give rise to complex mental and behavioral processes.

A specialized cell designed to transmit information to other nerve cells, muscle or gland cells, where the neuron is the basic working unit of the brain. The brain is nothing but it is because of the structural and functional properties of neurons. Efficient communication between these cells is critical to the normal functioning of the central and peripheral nervous systems (Tortora & Grabowski, 2003). The functions of nervous system are synchronized by different neurotransmitters viz. noradrenaline, dopamine, serotonin, acetylcholine, GABA, glutamate etc., which are concerned in the control of many of our mental states, sometimes acting on their own and other times acting together. These and other neurotransmitters are likely to play a essential role in pathological basis of various mental illnesses.

1.1 Neurotransmitters:

Neuropsychopharmacology continues to be well thought-out primarily according to the neurotransmitters that are utilized by various populations of neurons for synaptic transmission (Joseph et al., 2002). In 1921, an Austrian scientist named Otto Loewi revealed the first neurotransmitter.

Neurotransmitters are the chemicals which explanation for the transmission of signals from one neuron to the other across synapses. They are also found at the axon endings of motor neurons. Neurotransmitters are molecules that regulate brain functions. They are chemicals, which transmit message from nerve to nerve both within the brain and outside the brain. They are used all over the body to convey information and signal. They are synthesized
and used by neurons (nerve cell), actively elated along the axons and stored in synaptic vesicles and are released into synaptic clefts between the neurons by exocytosis. By means of actions, there are two types of neurotransmitters: excitatory and inhibitory neurotransmitters. Neurotransmitters act on specific receptor sites on the post synaptic membrane of the subsequently neuron at a neuronal synapse, neuromuscular junction and neuroglandular junction (Tortora & Grabowski, 2003). The simply direct action of a neurotransmitter is to activate a receptor. Therefore, the effects of a neurotransmitter system depend on the associates of the neurons that use the transmitter, and the chemical properties of the receptors that the transmitter binds to. Diseases may influence specific neurotransmitter systems. Drugs targeting the neurotransmitter affect the whole system; this fact explains the mode of action of many drugs acting on central nervous system (Blows, 2000).

1.1.1. Overview of Different Neurotransmitters Regulating Different Functions of the Central Nervous System:

More than 50 chemical substances have been proved or postulated to function as synaptic neurotransmitters, which provide two groups of synaptic transmitters. One group comprises small-molecule, rapidly acting transmitters and other is made up of a large number of neuropeptides of much larger molecular size that usually much more slowly acting.

The small-molecule, rapidly acting transmitters are the ones that cause most acute responses of the nervous system, viz. transmission of sensory signals to the brain and of motor signals back to the muscles. The neuropeptides, in contrast, more often than not cause more prolonged actions, such as long-term changes in numbers of neuronal receptors, opening or closure of certain ion channels, and possibly even changes in numbers of synapses. Neurotrophic factors have long been predictable for their role in neural growth and differentiation during development, and also important for regulating the survival and plasticity of adult neurons.

The structure of the neurotransmitter is sealed and accordingly its biological activity does not vary due to a strict structural–functional relationship. Neurotransmitters are either fast-acting substances, which open ligand-gated ion channels and elicit an immediate flow of current through the activated channel or they behave as slow-acting agents which induce long-lasting changes at the
postsynaptic site. The slow-acting neurotransmitters affect the membrane permeability indirectly through second-messenger systems. All neurotransmitters, with the exemption of histamine, are recaptured by highly specific transport systems. The transporters play a major role in the rapid inactivation of the released neurotransmitter, limiting its temporal and spatial action. Some neuropeptides operate like neurotransmitters. Neuropeptides with classic neurotransmitter effects are named putative neurotransmitters or co-transmitters. Additional classes of substances with neurotransmitter properties are gaseous molecules like nitric oxide (NO) or carbon monoxide (CO). These gaseous substances rally some criteria of neurotransmitters. Some essential neurotransmitter criteria, like receptor interaction, specific re-uptake; and degradation mechanisms, are not fulfilled by this group and thus they do not qualify as true neurotransmitters (Guyton & Hall, 2006; Halbach & Dermietzel, 2006).

### Table 1.1 Small-molecules, class of rapidly acting neurotransmitters

<table>
<thead>
<tr>
<th>Class</th>
<th>Neurotransmitter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Acetylcholine</td>
</tr>
<tr>
<td>Class II The Amines</td>
<td>Serotonin, Catecholamines (Norepinephrine, Epinephrine, Dopamine), Histamine</td>
</tr>
<tr>
<td>Class III Amino Acids</td>
<td>Gamma-aminobutyric acid (GABA), Glycine, Glutamine, Aspartate</td>
</tr>
<tr>
<td>Class IV</td>
<td>Nitric Oxide (NO)</td>
</tr>
<tr>
<td>Class V Purines</td>
<td>Adenosine (ATP, GTP and their derivatives)</td>
</tr>
</tbody>
</table>

### Table 1.2 Neuropeptide, slowly acting transmitters or growth factors (Large-molecules):

<table>
<thead>
<tr>
<th>Neuropeptide, slowly acting transmitters or growth factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nerve growth factor, Brain-derived neurotransmitter, Neurtensin, Vasoactive intestinal polypeptide (VIP), β-Endorphin, Hypothalamic-releasing hormones, Thyrotropin-releasing hormone, Luteinizing hormone-releasing hormone, Somatostatin (growth hormone inhibitory factor), Pituitary peptides, Melanocyte-stimulating hormone, Prolactin, Thyrrotropin, Growth hormone, Vasopressin, Oxytocin, Peptides that act on gut and brain, Leu-enkephalin, Met-enkephalin, Substance P, Angiotensin II, Bradykinin etc.</td>
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1.1.2 Mechanism of Neurotransmitter Release:

Communication of information between neurons is consummate by movement of chemicals across a small gap called the synapse. Neurotransmitters, a chemical are released from one neuron at the presynaptic nerve terminal followed by cross the synapse where they may be accepted by the subsequently neuron at a specialized site called a receptor which leads to activation of a receptor site resulted either depolarization (an excitatory postsynaptic potential) or hyperpolarization (an inhibitory postsynaptic potential).

The principal mechanism of transmitter release in both peripheral and central nervous system is exocytosis, whereby the transmitter is stored in intracellular vesicles, which fuse transiently with the cell membrane and discharge their contents in response to an increase in the intracellular calcium concentration.

In neurons, the process is initiated by the arrival of an action potential, which depolarizes the membrane, thereby opening the voltage activated calcium channels and causing calcium to enter the cell.

The synaptic vesicles, loaded with transmitter, attach to docking sites located inside the synaptic membrane facing the synaptic cleft. These sites are closely associated with the calcium channels, so the vesicles are optimally placed to respond by discharging their contents when the channel opens and calcium enters the nerve terminal. Having done so, the empty vesicle is captured by endocytosis and returns to the interior of the terminal, where it fuses with the large endosomal membrane. The endosome buds off new vesicles, which take up transmitter from the cytosol by means of specific transport proteins and are again docked on the presynaptic membrane (Tripathi, 2008).

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Figure 1.1 Differentiation of neurotransmitters based on their chemical structures
1.1.3 Termination of Transmitters Action:

Chemically transmitter synapses incorporate a mechanism for rapidly disposing of the released transmitter, so that its action remains brief and localized. At cholinergic synapses, the released acetylcholine is inactivated very rapidly in the synaptic cleft by acetylcholinesterase, but in most cases, transmitter action is terminated by active reuptake into the presynaptic nerve or into supporting cells such as ganglia (Tripathi, 2008).

**Figure 1.2 Synthesis, storage, release and metabolism of neurotransmitters**

1.1.4 Process involved in synthesis, storage and release of neurotransmitter:
1. Uptake of precursors
2. Synthesis of transmitter
3. Storage of transmitter in vesicles
4. Degradation of surplus transmitter
5. Depolarization by propagated action potential
6. Influx of Ca$^{2+}$ in response to depolarization
7. Release of transmitter by exocytosis
8. Diffusion to postsynaptic membrane
9. Inactivation with postsynaptic receptors
10. Inactivation of transmitter
11. Reuptake of transmitter or degradation products
12. Interaction with presynaptic receptors (Rang et al., 2003).

1.1.5 Acetylcholine:

The chemical compound acetylcholine (often abbreviated ACh) is neurotransmitters originate in the peripheral nervous system (PNS) and central nervous system (CNS), autonomic nervous system (ANS) and all autonomic ganglia in many organisms including humans. Acetylcholine is the only neurotransmitter used in the somatic nervous system.
Acetylcholine (ACh) was first identified by Henry Hallett Dale in 1914 for its actions on heart tissue. It was confirmed by Otto Loewi as a neurotransmitter who initially gave it the name vagusstoff because it was released from the vagus nerve. Acetylcholine was the first neurotransmitter discovered by scientists; it was isolated in the 1920s from one of the nerves that regulate heart function. The chemical formula \( \text{CH}_3\text{COOCH}_2\text{CH}_2\text{N}^+\text{(CH}_3)_3 \) is the ester of acetic acid and choline of Ach.

Acetylcholine is found at all nerve-muscle junctions, as well as many sites in the central nervous system. The actions of ACh are called cholinergic actions and those that are blocked are anticholinergic drugs.

**Synthesis, storage and release:**

ACh is synthesized locally in the cholinergic nerve endings from choline, which is taken up into the nerve terminal by the axonal membrane by a \( \text{Na}^+ \)-choline cotransporter. Choline is acetylated with the help of ATP and coenzyme-A by the enzyme acetyl choline transferase present in the axoplasm. ACh is produced throughout the neurons and is stored in tiny vessels (synaptic vesicles) at the tips of cholinergic axon terminals which are mainly accumulated at the nerve endings. On the receipt of a stimulus, they combine with membrane into synaptic cleft and discharge their content of ACh. After released, ACh acts on nerve or muscle fibers to broken down into choline and acetate by an enzyme called acetylcholinesterase. This breakdown helps to reabsorb choline and acetate back into the releasing neuron.

**ACh receptors:**

ACh has mainly excitatory effects, which are mediated by various subtypes of either muscarinic (G-protein coupled) or nicotinic (ionotropic) receptor. Some muscarinic receptors are inhibitory.

Nicotinic receptors are located at synapses between two neurons and skeletal muscle cells. Upon activation acts as a channel for the movement of ions into and out of the neuron which straight results in depolarization of the neuron. Muscarinic receptors, located at the synapses of nerves with smooth or cardiac muscle which activate a chain of chemical events referred to as signal transduction.

The muscarinic receptors in the brain are predominantly of the M class (M₁, M₃ and M₅ subtypes). The block and stimulation of these receptors leads to
Central actions of muscarinic antagonists and anticholinesterases respectively. The muscarinic receptors act presynaptically to inhibit ACh release from cholinergic neurons. Many of behavioral effects coupled with cholinergic pathways seem to be produced by acetylcholine acting on muscarinic receptors namely effects on arousal, learning and short term memory.

Nicotinic receptors are also widespread in the brain but are much sparer than muscarinic receptors. They are typical pentameric ionotropic receptors. Nicotinic receptors are mainly found in the cortex and hippocampus. For the most part, nicotinic acetylcholine receptors are situated presynaptically and act to facilitate the release of the other transmitters, such as glutamate and dopamine. They function postsynaptically to mediate fast excitatory transmission as in periphery in few situations.

**Cholinergic pathway in the CNS:**

![Figure 1.3 Acetylcholine pathways in the CNS](image)

Red areas show the location of cholinergic terminals. **Am**-amygdaloid; **C**-cerebellum; **Hip**-hippocampus; **Hyp**-hypothalamus; **Sep**-septum; **SN**-substantia nigra; **Str**-corpus striatum; **Th**-thalamus

Acetylcholine is very extensively distributed in the brain, occurring in all parts of the forebrain (including the cortex), midbrain and brainstem, though there is little in the cerebellum. Cholinergic neurons in the forebrain and brainstem send diffuse projections to many parts of the cortex and hippocampus. These neurons lie in a small area of the basal forebrain, forming the *magnocellular forebrain nuclei*. Degeneration of one of these, which mainly projects to the cortex, is associated with Alzheimer’s disease. Another cluster, the *septohippocampal nucleus*, provides the main cholinergic input to the hippocampus and is involved in the memory.
Functional aspects:

In the central nervous system, Ach has a variety of effects as a neuromodulator, e.g., plasticity and excitability. Other effects are arousal and reward.

Acetylcholine operates as a primary neurotransmitter in brain areas that handle dealing out of learning and memory, of states of attention and alertness. As such, it was no surprise that Alzheimer’s disease would be related to acetylcholine dysfunction. The damage to the cholinergic system in the brain has been recommended to play a role in the memory deficits associated with Alzheimer's disease. In this disease the region of the brain mainly responsible for the synthesis of acetylcholine undergoes degeneration (Rang et al., 2003; Tripathi, 2008; Barar, 2007; Brunton & Parker, 2008)

The main functions ascribed to cholinergic pathways are-

- Arousal
- Learning and memory
- Motor control

1.1.6 Serotonin:

Serotonin was first renowned as a powerful vasoconstrictor in blood serum. It was isolated in 1948 by Page and was later on set up to be associated with the central nervous system. Serotonin is one of the important neurotransmitter in CNS. The chemical name for serotonin is 5-hydroxytryptamine which is often abbreviated to 5-HT. Serotonin is an inhibitory neurotransmitter that has been found to be intimately concerned in emotion and mood. Too little serotonin has been exposed to lead to depression, problems with anger control, obsessive-compulsive disorder, and suicide. Too small also leads to an increased appetite for carbohydrates (starchy foods) and difficulty sleeping, which are also coupled with depression and other emotional disorders.

Synthesis, storage and release:

Tryptophan is the precursor for the synthesis of 5-HT. It is hydroxylated to 5-hydroxytryptophan by enzyme tryptophan hydroxylase and then decarboxylated by a non-specific amino acid decarboxylase to 5-HT. 5-HT is stored in secretory granules by a vesicle transporter and released by exocytosis. The greatest concentration of 5-HT (90%) is found in the enterochromaffin cells of the gastrointestinal tract. Most of the remainder of the body’s 5-HT is found
in platelets and the CNS. The amount of 5-HT in the CNS runs parallel to that of Noradrenaline i.e. highest in the hypothalamus and mesencephalon. Degradation of 5-HT occurs mainly by monoamine oxidase, forming 5-hydroxyindoleacetic acid (5-HIAA), which is excreted in the urine.

**5-HT receptors:**

There are different types of 5-HT receptors. Four families of 5-HT receptors (5-HT₁, 5-HT₂, 5-HT₃, 5-HT₄-7) comprising of 14 subtypes have been recognized. All are G-protein-coupled receptors except for 5-HT₃, which is ligand-gated cation channel. 5-HT₁ receptors are predominantly inhibitory in their effects. 5-HT₁A-receptors are expressed as autoreceptors by the 5-HT neurons in the *raphe nuclei*, hippocampus 5-HT₁b- and 5-HT₁D-receptors are found mainly as presynaptic inhibitory receptors in the basal ganglia and substantia nigra. 5-HT₂-receptors (mostly 5-HT₂A in the brain) gives an excitatory postsynaptic cause and are abundant in the cortex and limbic system. 5-HT₃-receptors are excitatory ionotropic receptors and are chiefly found in the *arena prosterma*. 5-HT₃ receptors are involved in the neuronal excitation, emesis and behavioral effects like anxiety. 5-HT₃ receptors mediate the inhibitory effects of 5-HT on acetylcholine release. 5-HT₄-receptors exert a presynaptic facilitatory effect.

**5-HT pathway in the CNS:**

![Figure 1.4 Serotonergic pathway in the CNS](image)

Red areas show the location of serotonergic terminals. Am-amgydaloïd; C-cerebellum; Hip-hippocampus; Hyp-hypothalamus; Sep-septum; SN-substantia nigra; Str-corpus striatum; Th-thalamus

The allotment of 5-HT containing neurons resembles that of noradrenergic neurons. The cell bodies are grouped in the pons and upper medulla, referred to as raphe nuclei. The rostrally positioned nuclei project, via the medial forebrain bundle, to many parts of the cortex, hippocampus, basal
ganglia, limbic system and hypothalamus. The caudally situated cells project to the cerebellum, medulla and spinal cord.

**Functional aspects:**

As a neurotransmitter, serotonin helps to relay messages from one area of the brain to another. Because of the extensive distribution of its cells, it is believed to affect a variety of psychological and other body functions. Of the approximately 40 million brain cells, most are influenced either directly or indirectly by serotonin. The role of this neurotransmitter, allowing numerous functions in the human body include the control of appetite, sleep, memory and learning, temperature regulation, mood, behavior, emesis, cardiovascular function, muscle contraction, endocrine regulation, gastrointestinal function, motor function, perception, sensory function, sexual desire, sleep, vascular function and depression. In terms of our body function, serotonin can also affect the functioning of our heart, muscles, and various elements in the endocrine system. Researchers have also found evidence that serotonin may play a role in regulating milk production in the breast. Subsequent to discovery of serotonin, it was commented that no physiological substance known possesses such diverse actions in the body as dose serotonin (Rang et al., 2003; Tripathi, 2008; Brunton & Parker, 2008; Blows, 2002).

**5-HT is important in**

- Various behavioral responses
- Feeding behavior
- Control of mood and emotions
- Control of sleep / wakefulness
- Control of sensory pathways, nociception, vomiting, body temperature etc.

5-HT has been implicated in almost every conceivable physiologic or behavioral function. Moreover, most drugs that are currently used for the treatment of psychiatric disorders (e.g., depression, mania, schizophrenia, autism, obsessive compulsive disorder, anxiety disorders) are attention to act, at least to some extent, through serotonergic mechanisms. How is it possible for 5-HT to be concerned in so many dissimilar processes? One answer lies in the anatomy of the serotonergic system, in which 5-HT cell bodies clustered in the brainstem raphe nuclei are positioned through their vast projections to influence all regions of the neuroaxis. Another answer lies in the molecular diversity and differential
cellular distribution of the many 5-HT receptor subtypes that are expressed in brain and other tissues. During the ancient times decade, molecular cloning techniques have confirmed that putative 5-HT receptor subtypes, predicted from radioligand binding and functional studies (e.g., 5-HT₁, 5-HT₂, 5-HT₃, 5-HT₄), stand for separate and different gene products. This knowledge has revolutionized contemporary research on the serotonergic system. Several classes of drugs aim the 5-HT system together with some antidepressants, antipsychotics, anxiolytics, antiemetics, and antimigraine as well as the psychedelic drugs (Bloom & Kupfer, 1999).

1.1.7 Noradrenaline:

Norepinephrine or noradrenaline (abbreviated NA) is a catecholamine with dual roles as a hormone and a neurotransmitter. The transmitter role of noradrenaline (NA) in the brain was suspected in the 1950s.

**Synthesis, storage and release:**

Catecholamines (CA) are synthesized from the amino acid L-phenylalanine, which is oxidized by phenylalanine hydroxylase to form L-tyrosine. Within the neuronal cytoplasm, L-tyrosine is hydroxylated to form L-DOPA by tyrosine hydroxylase. Further by the action of dopa decarboxylase, L-DOPA is converted to dopamine within the neural cytoplasm. Dopamine is further hydroxylated to form noradrenaline by dopamine β-hydroxylase within the granules. Synthesis of NA occurs in the adrenergic neuron, while that of adrenaline occurs only in adrenal medullary cells. Endogenous NA is stored in the synaptic vesicles as a complex with ATP and a soluble protein called chromogranin. The nerve impulse coupled release of catecholamine takes place by exocytosis.

**Adrenergic receptors:**

Norepinephrine performs its actions on the target cell by binding to and activating adrenergic receptors. Unlike epinephrine, which activates all adrenergic receptors (α₁, α₂, β₁, β₂) while norepinephrine activates all but not β₂ receptors. The target cell look of different types of receptors determines the definitive cellular effect, and thus norepinephrine has dissimilar actions on different cell types.
There are two distinct types of post synaptic receptors: α- and β-receptors. α-receptors are further subdivided into α₁ and α₂ receptors. α₁-receptors are found postsynaptically on vascular smooth muscles, gastrointestinal tract, urinary sphincters, eye, pancreas, spleen and certain glands. α₂-receptors are located presynaptically and control release of NA by negative feedback. β-receptors are further subdivided as β₁ and β₂-receptors. Stimulation of β-receptors produces inhibition in most of organs and tissues, except heart. β₁-receptors are located primarily in the heart, while β₂-receptors are located in the bronchial, gastrointestinal, uterine, and urinary smooth muscles etc.

**Noradrenergic pathway in the CNS:**

**Figure 1.5 Noradrenergic pathway in the CNS**

Red areas show the location of noradrenergic terminals. Am-amygadaloid; C-cerebellum; Le-locus ceruleus; Hip-hippocampus; Hyp-hypothalamus; MFB-median forebrain bundle; NTS-nucleus of the tractus solitarius; RF-brainstem reticular formation; Sep-septum; SN-substantia nigra; Str-corpus striatum; Th-thalamus.

Norepinephrine is released when host physiological changes are activated by a stressful event. In the brain, this is caused in part by activation of an area of the brain stem called the locus ceruleus (LC). The norepinephrine pathway arises from this nucleus in brain. Noradrenergic neurons project bilaterally (send signals to both sides of the brain) from the locus ceruleus along distinctive pathways too many locations, including the cerebral cortex, limbic system, and the spinal cord, forming a neurotransmitter system. The cell bodies of noradrenergic neurons occur in small clusters in the pons and medulla, and send extensively branching axons to many other parts of the brain and spinal cord. The most prominent cluster is the locus ceruleus, which is found in the gray matter of the pons. Millions of noradrenergic terminals run throughout the cortex, hippocampus and cerebellum. Other noradrenergic neurons lie close to the LC in the pons and medulla. Axons from these cells innervate the hypothalamus, hippocampus and
other parts of the forebrain, and also to cerebellum and spinal cord. Norepinephrine is too free from postganglionic neurons of the sympathetic nervous system, to convey the fight-or-flight response in every tissue respectively.

**Functional aspects:**

The neurotransmitter obtained from noradrenergic neurons in the brain when activated exerts effects on large areas of the brain. The effects are alertness, arousal, and influences on the reward system. Norepinephrine as a stress hormone, affects parts of the brain where awareness and responding actions are controlled. Combining epinephrine with norepinephrine also underlies the fight-or-flight response by directly increasing heart rate as well as increasing blood flow to skeletal muscle and triggering the release of glucose from energy stores (Rang et al., 2003; Tripathi, 2008; Brunton & Parker, 2008; Barar, 2007; Blows, 2000).

**Noradrenergic transmission is important in-**

- The arousal system controlling wakefulness and alertness
- Blood pressure regulation
- Control of mood (functional deficiency contributing to depression).

**1.1.8 Dopamine:**

Dopamine was first synthesized in 1910. It was named dopamine because it was a monoamine, and its synthetic precursor was 3, 4-dihydroxyphenylalanine (L-DOPA). Dopamine is not only a neurotransmitter but also a precursor of norepinephrine (noradrenaline) and epinephrine (adrenaline).

Dopamine (DA) is the major neurotransmitter in the mammalian central nervous system. Dopamine is particularly important in relation to neuropharmacology, since it is involved in several common disorders of brain function, notably Parkinson’s disease, schizophrenia and attention deficit disorders. Many of drugs used clinically to treat these conditions work by influencing dopamine transmission. The significance of this neurotransmitter system is helpful in the human disorders ranging from Parkinson’s disease to schizophrenia. It has resolute an intensive range of investigations oriented in the direction of increasing our thoughtful of this complex system in normal conditions as well as disease states.
Synthesis, storage and release:

The synthesis of DA follows the same route as that of noradrenaline, namely conversion of tyrosine to DOPA by enzyme tyrosine hydroxylase. This step is followed by decarboxylation to dopamine by DOPA decarboxylase. Dopaminergic neurons lack dopamine β-hydroxylase and, therefore do not produce noradrenaline.

Dopamine receptors:

Dopamine receptors are a class of metabotropic G protein-coupled receptors that are well-known in the vertebrate central nervous system. The dopamine as a neurotransmitter is the chief endogenous ligand for dopamine receptors.

Dopamine receptors have variety of important roles in many processes, which include the control of motivation, fine motor movement and learning as well as modulation of neuroendocrine signaling. Abnormal dopamine receptor signaling as well as dopaminergic nerve function is fretful in several neuropsychiatric disorders. Thus, dopamine receptors are widespread neurologic drug targets; antipsychotics are frequently dopamine receptor antagonists while psychostimulants are typically indirect agonists of dopamine receptors.

In the brain DA receptors are found on postsynaptic neurons which are DA-enriched. In the mid brain as well as on their terminals in the forebrain they reside presynaptically on DA neuronal cell bodies and dendrites. There are five subtypes of dopamine receptors, D₁, D₂, D₃, D₄, and D₅. D₁-like family has dopamine receptors viz. D₁ and D₅ receptors members, whereas D₂-like family has D₂, D₃ and D₄ receptors members. There is also some evidence of receptors viz. D₆ and D₇ existence is possible, but such receptors have not been conclusively identified. All belong to the family of G-protein coupled receptors. DA acts presynaptically as well as postsynaptically. When D₁-like family receptor activated it coupled to the G protein, which subsequently activates adenyl cyclase, increasing the intracellular concentration of the second messenger cyclic adenosine monophosphate (cAMP). Excitatory effect occurs when increased in cAMP in neurons and can induce an action potential by modulating the activity of ion channels. D₂-like activation is coupled to the G protein, which directly inhibits the formation of cAMP by inhibiting the enzyme adenylate cyclase.
Dopamine pathway in the CNS:

**Figure 1.6 Dopaminergic pathways in the CNS**

Red areas show the location of dopaminergic terminals. Am-amygdaloid; C-cerebellum; Hip-hippocampus; Hyp-hypothalamus; Sep-septum; SN-substantia nigra; Str-corpus striatum; Th-thalamus; P-pituitary gland; Ac-nucleus accumbens.

From DA cell bodies in the substantia nigra and ventral tegmental area in mid-brain regions Dopamine containing neurons arise. Dopaminergic neurons form three main systems

- The nigrostriatal pathway - involving neurons projecting from the substantia nigra pars compacta to corpus striatum. This is the major DA system in the brain as it account for about 75% of the total DA in the brain. The degeneration of this pathway makes a major contribution to the pathophysiology of Parkinson’s disease.

- The mesolimbic / mesocortical pathway - the cell bodies of these pathways occur in group in the midbrain and the fibers project, also via the medial forebrain bundle, to parts of the limbic system, especially the nucleus accumbens and the amygdaloid nucleus and to the frontal cortex.

- The tuberohypophyseal system- this group of short neurons runs from the ventral hypothalamus to the median eminence and pituitary gland, the secretions of which they regulate.

Functional aspects:

The differential distributions of the diverse dopaminergic systems indicate that dopamine influences a variety of brain functions. For instance, dopamine is involved in the modulation of arterial blood-flow, higher brain functions like cognition and learning and in anxiety-related behavior. Dopamine has significant roles in behavior, inhibition of prolactin production (involved in lactation), motor activity, mood, motivation and reward, sleep, attention, and learning (Rang et al., 2003; Tripathi, 2008; Brunton & Parker, 2008; Blows, 2000).
Dopamine is involved in-
- Motor control (nigrostriatal system)
- Behavioral effects (mesolimbic and mesocortical system)
- Endocrine control (tuberohypophyseal system).

1.1.9 Gamma-Aminobutyric Acid (GABA):

GABA is the most abundant inhibitory neurotransmitter in the central nervous system. In the brain it is particularly abundant in the nigrostriatal system and occurs at lower concentrations throughout the gray matter. In 1950, Eugene Roberts and J. Awapara discovered GABA, as an inhibitory neurotransmitter. GABA acts like a brake to the excitatory neurotransmitters that lead to anxiety. People with too little GABA tend to suffer from anxiety disorders, lots of other drugs influence GABA receptors, including alcohol and barbiturates. If GABA is lacking in some parts of the brain, epilepsy results.

Synthesis, storage and release:

GABA is formed from glutamate by the action of glutamic acid decarboxylase (GAD), an enzyme found only in the GABA-synthesizing neurons in the brain. It is worth noting that this process converts the principle excitatory neurotransmitter (glutamate) into the principal inhibitory one (GABA). GABA is destroyed by a transamination reaction to succinic semialdehyde and then succinic acid. The reaction is catalyzed by GABA transaminase. GABAergic neurons and astrocytes take up GABA via specific transporters.

GABA receptors:

There are two distinct types of GABA receptors, GABA<sub>A</sub>-receptor being a ligand-gated channel and GABA<sub>B</sub>-receptor being a G-protein-coupled receptor. GABA<sub>A</sub>-receptor, located postsynaptically, mediate fast postsynaptic inhibition, the channel being selectively permeable to Cl<sup>−</sup>. GABA<sub>B</sub>-receptor are located pre- and postsynaptically, and are G-protein-coupled receptor, linked to inhibition of cAMP formation. They cause pre- and postsynaptic inhibition by inhibiting calcium channel opening and increasing K<sup>+</sup> conductance. GABA<sub>C</sub>-receptor belongs to inotropic receptors that triggers opening of a Cl<sup>−</sup> ion-selective pore (Rang et al., 2003; Brunton & Parker, 2008).

Functional aspects:

GABA acts as Inhibitory transmitter at both pre- and post synaptic neuronal process.
1.1.10 Glutamate:

Glutamate is excitatory neurotransmitter in the mammalian nervous system most abundantly, widely and fairly uniformly distributed in the CNS. Glutamate is formed mainly from α-oxoglutarate, by the action of GABA aminotransferase. At synapses, glutamate is stored in vesicles triggering the nerve impulses glutamate release from the pre-synaptic cell and the glutamate action is terminated mainly by carrier-mediated reuptake into the nerve terminals and neighboring astrocytes.

**Glutamate receptors:**

On the basis of studies with selective agonists and antagonists, four types of receptors are distinguished as NMDA (N-methyl D-aspartate), AMPA (α-amino-3-hydroxy-5-hydroxy-5-methyl-4-isoxazolepropionate), Kainate and metabotropic receptors (Rang et al., 2003).

**Functional aspects:**

Glutamate is involved in-

- Synaptic plasticity
- Excitotoxicity
- Epileptic Seizures
- Learning And Memory

Table 1.3 A brief comparison of the major neurotransmitter systems

<table>
<thead>
<tr>
<th>Neurotransmitter systems</th>
<th>System</th>
<th>Origin</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noradrenaline system</td>
<td>Locus ceruleus</td>
<td>Arousal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lateral tegmental field</td>
<td>Reward</td>
<td></td>
</tr>
<tr>
<td>Dopamine system</td>
<td>Dopamine pathways:</td>
<td>Motor system, reward,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Mesocortical pathway</td>
<td>cognition, endocrine.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Mesolimbic pathway</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>• Nigrostriatal pathway</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Tuberoinfundibular</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>pathway</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serotonin system</td>
<td>Caudal dorsal raphe nucleus</td>
<td>Increase mood, anxiety,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rostral dorsal raphe nucleus</td>
<td>body temperature and sleep,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>while decreasing ociception.</td>
<td></td>
</tr>
<tr>
<td>Cholinergic system</td>
<td>Pontomesencephalo tegmental</td>
<td>• Learning</td>
<td></td>
</tr>
<tr>
<td></td>
<td>complex</td>
<td>• Short-term memory</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Basal optic nucleus of Meynert</td>
<td>• Arousal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medial septal nucleus</td>
<td>• Reward</td>
<td></td>
</tr>
</tbody>
</table>
1.2 Co-Transmission:

Several different neurotransmitters can be released from a single nerve terminal, including neuropeptides and small molecule neurotransmitters. In addition to acting as neurotransmitters in their own right, neuropeptides can act as co-transmitters. They can stimulate specific pre- or postsynaptic receptors to alter the responsiveness of the neuronal membrane to the action of ‘classical’ neurotransmitters viz. noradrenaline and serotonin. Serotonin, noradrenaline and dopamine are concerned in the control of many of our mental states, sometimes acting on their own and at other times acting together. These and other neurotransmitters are likely to play a essential role in the pathological basis of mental illness and diseases of the brain. Much of the evidence for this stems from the fact that most of the efficient antidepressant drugs are consideration to work by changing serotonin and/or noradrenaline metabolism or receptor sensitivity to these neurotransmitters.

Figure 1.7 Co-transmission of various neurotransmitters

Understanding the numerous neurotransmitters, their receptors, locations and interactions with one another has been central to the design of medicines for mental illness. This acquired knowledge has led to the development of successful products for many brain disorders including epilepsy, schizophrenia, Parkinson’s disease, depression, anxiety disorders and migraine.
1.3 Central Nervous System Disorders:

Central nervous system disorders or mental disorders or mental illnesses are the psychological or behavioral pattern that occurs in an individual and is thought to cause distress or disability that is not expected as part of normal development or culture. Central nervous system disorders are characterized by alterations in thinking; mood or behavior (or some combination thereof) coupled with significant distress and impaired functioning over an extended period of time. Condition that affect brain and result in intellectual, behavioral, and psychological dysfunction are referred to as "organic mental disorders". These disorders represent a broad group of disorders. The symptoms of mental illness vary from mild to severe depend upon on the type of mental illness like the individual, the family and the socio-economic environment. In the course of a lifetime, every individual experiences feelings of isolation, loneliness, emotional distress or disconnection at times. These are usually normal, short-term reactions to difficult situations, rather than symptoms of mental illness. The recognition and understanding of mental disorders has changed over time and across cultures. Categories of diagnoses in these schemes may include dissociative disorders, mood disorders, anxiety disorders, psychotic disorders, eating disorders, developmental disorders, personality disorders, and many other categories. In many cases there is no single accepted or consistent cause of mental disorders, although they are often explained in terms of a diathesis-stress model and biopsychosocial model. Mental disorders have been found to be common, in most countries reporting sufficient criteria at some point in their life. Mental health is as important as physical health to daily living. In fact, the two are intertwined. Individuals with physical health problems often experience anxiety or depression that affects their response to the physical illness. Individuals with mental illnesses can develop physical symptoms and illnesses, such as weight loss and blood biochemical imbalances. Feelings, attitudes and patterns of thought strongly influence people’s experience of physical health or illness, and may affect the course of illness and the effectiveness of treatment. Mental illnesses may occur together (Kessler & Ahangang, 1999; Aarli et al., 2006).

1.3.1 Impact of Mental Illnesses:

Mental health is as important as physical health to the overall well-being of individuals, societies and countries. Yet only a small minority of the 450
million people suffering from a mental or behavioral disorder is receiving treatment. Advances in neuroscience and behavioral medicine have shown that, like many physical illnesses, mental and behavioral disorders are the result of a complex interaction between biological, psychological and social factors. While there is still much to be learned, we already have the knowledge and power to reduce the burden of mental and behavioral disorders worldwide (Murray & Lopez, 1994).

Figure: 1.8 Interaction of biological, psychological and social factors in the development of mental disorders

Mental illnesses affect people in all occupations, educational and income levels and cultures. The distribution is not random or uniform; some mental illnesses are more prevalent in some population groups. However, no one is immune, and at some point in their lives, all people are likely to be affected by a mental illness.

1.3.2 Social Impact:

The onset of most mental illnesses occurs during adolescence and young adulthood. This affects educational achievement, occupational or career opportunities and successes, and the formation and nature of personal relationships. The effect extends throughout an individual's life. The greater the number of episodes of illness that an individual experiences; the greater the degree of lasting disability. Receiving and complying with effective treatment and having the security of strong social supports, adequate income, housing and educational opportunities are essential elements in minimizing the impact of mental illness. In developed countries, mental illnesses (major depression,
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bipolar disorder, schizophrenia, and obsessive-compulsive disorder) account for four of the 10 leading causes of disability.

Suicide is a significant risk for individuals with some mental illnesses, such as major depression, bipolar disorder, schizophrenia and borderline personality disorder. Mental illnesses have a significant impact on the family. To begin with, they may face difficult decisions about treatment, hospitalization, housing and contact with the family member with mental illness. The individuals and their families face the anxiety of an uncertain future and the stress of what can be a severe and limiting disability. The heavy demands of care may lead to burnout. Families sometimes fear that they caused the illness. The cost of medication, time off work, and extra support can create a severe financial burden for families. Both the care requirements and the stigma attached to mental illness often lead to isolation of family members from the community and their social support network and may even contribute to the suicide of a family member (WHO, 2001; Murray & Lopez, 1994; Lopez & Murray, 1998).

1.3.3 Economic Impact:

Mental illnesses also have a major impact on the economy in terms of productivity losses and health care costs. While estimates will vary widely depending on what costs are included, it is clear that the economic burden of mental illnesses is enormous.

1.3.4 Burden of Mental and Behavioral Disorders:

Mental and behavioral disorders are common, affecting more than 25% of all people at some time during their lives. They are also universal, affecting people of all countries and societies, individuals at all ages, women and men, the rich and the poor, from urban and rural environments. They have an economic impact on societies and on the quality of life of individuals and families. Mental and behavioral disorders are present at any point in time in about 10% of the adult population. Around 20% of all patients seen by primary health care professionals have one or more mental disorders. One in four families is likely to have at least one member with a behavioral or mental disorder. These families not only provide physical and emotional support, but also bear the negative impact of stigma and discrimination. It was estimated that, in 1990, mental and neurological disorders accounted for 10% of all diseases and injuries. This was 12% in 2000. By 2020, it is projected that the burden of these disorders will have
increased to 15%. Common disorders, which usually cause severe disability, include depressive disorders, substance use disorders, schizophrenia, epilepsy, Alzheimer’s disease, mental retardation, and disorders of childhood and adolescence. Factors associated with the prevalence, onset and course of mental and behavioral disorders include poverty, sex, age, conflicts and disasters, major physical diseases, and the family and social environment (Stephens & Joubert, 2001; Murray & Lopez, 1994; Lopez & Murray, 1998).

1.3.5 Causes of Mental illness:

Research suggests that mental illnesses are the result of a complex interaction of genetic, biological, personality and environmental factors; however, the brain is the final common pathway for the control of behavior, cognition, mood and anxiety. At this time, the links between specific brain dysfunction and specific mental illnesses are not fully understood. The causes of mental illness are the genetic endowment (e.g. inherited dysfunctions affecting brain chemistry) and the environment (e.g. external physical and psychosocial factors). It is important not to over-interpret the available evidence about the role of either genetic or environmental factors in causing mental illnesses as much more research is needed to fully understand the cause of mental illness.

Most mental illnesses are found to be more common in close family members of a person with a mental illness, suggesting a genetic basis to the disorders. In some instances there is research evidence suggesting that particular genetic factors affecting brain chemistry contribute to the onset and progression of mental illness. However, there is also increasing evidence that long-term changes in brain function can occur in response to factors in the environment such as stimulation, experiences of traumatic or chronic stress, or various kinds of deprivation. In other words, the interaction between brain biology and lived experience appears to work both ways. For reasons that may be biological, psychosocial, or both, age and sex affect rates of mental illness. Environmental factors such as family situation, workplace pressures and the socio-economic status of the individual can precipitate the onset or recurrence of a mental illness. Lifestyle choices (e.g. substance abuse) and learned patterns of thought and behavior can influence the onset, course and outcome of mental illness. Since a great deal remains unknown about the respective roles and interactions of
heredity and environment, brain dysfunction and lived experience, it is prudent to give them equal consideration (Schwartz, 1999).

1.3.6 Scenario of Central nervous disorders:

According to World Health report (WHO, 2001) approximately 450 million people currently suffer from mental or behavioral disorders, placing mental disorders among the leading causes of ill-health and disability worldwide. One in four people in the world will be affected by mental or neurological disorders at some point in their lives. This amount of 12.3% of the global burden of diseases and will rise to 15% by 2020. Anxiety disorders and depression are the most common. Approximately 2.5 million adults or over 10% of the population will have a depressive disorder. Mental disorders figure among the leading causes of disease and disability the world over. Depressive disorders are already the fourth-leading cause of the global disease burden; they are expected to rank second by 2020, behind ischaemic heart disease. Meta-analysis studies indicated high prevalence rate of mental disorders in the community. The extent of the burden of these disorders is largely ignored, and awareness of the existence of modern means of intervention is too often lacking (Reddy & Chandrashekar, 1998; Kumar, 2001; WHO, 2001).

Figure 1.9 Mental Disorders Lifetime prevalence

1.3.7 Disorders of the nervous system:

- **Vascular disorders**- such as stroke, transient ischemic attack (TIA), subarachnoid hemorrhage, subdural hemorrhage and hematoma, and extradural hemorrhage
- **Infections**- such as meningitis, encephalitis, polio, and epidural abscess
- **Structural disorders** - such as brain or spinal cord injury, Bell's palsy, cervical spondylosis, carpal tunnel syndrome, brain or spinal cord tumors, peripheral neuropathy, and Guillain-Barre syndrome
- **Functional disorders** - such as epilepsy, psychosis, mood disorders (depression and mania), anxiety, personality disorders, cognitive dysfunctions and neuralgia
- **Degenerative disorders** - such as Parkinson’s disease, Alzheimer’s disease, multiple sclerosis, amyotrophic lateral sclerosis (ALS) and Huntington’s chorea.

### 1.3.8 Signs and symptoms of nervous system disorders:

The most common general signs and symptoms of a nervous system disorders in each individual may experience symptoms differently like headache that changes or is different, loss of feeling or tingling, weakness or loss of muscle strength, sudden loss of sight, memory loss, impaired mental ability, lack of coordination, muscle rigidity, tremors and seizures, back pain which radiates to the feet, toes, or other parts of the body, dementia.

**Table 1.4 Brief overview of neurotransmitters and CNS disorders (Halbach & Dermietzel, 2006)**

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acetylcholine</strong> is a very widely distributed excitatory neurotransmitter that triggers muscle contraction In the central nervous system, it is involved in learning and memory, wakefulness, attentiveness, anger, aggression, sexuality, motor control and thirst.</td>
<td>Alzheimer’s disease is associated with a lack of acetylcholine in certain regions of the brain. Excess of acetylcholine is involved in Parkinson disease.</td>
</tr>
<tr>
<td><strong>Dopamine</strong> is an inhibitory neurotransmitter involved in controlling movement and posture. It also modulates mood and plays a central role in positive reinforcement and dependency</td>
<td>The loss of dopamine in certain parts of the brain causes the muscle rigidity typical of Parkinson’s disease. Excess of dopamine in certain parts of brain causes schizophrenia.</td>
</tr>
<tr>
<td><strong>Serotonin</strong> contributes to various functions, such as regulating body temperature, sleep, mood, appetite, and pain.</td>
<td>Depression, suicide, impulsive behavior, anxiety, mania and aggressiveness all appear to involve certain imbalances in serotonin.</td>
</tr>
<tr>
<td><strong>Norepinephrine</strong> is a neurotransmitter that is important for attentiveness, emotions, sleeping, dreaming, and learning. Norepinephrine is also released as a hormone into the blood, where it causes blood vessels to</td>
<td>Norepinephrine plays a role in mood disorders such as manic depression.</td>
</tr>
</tbody>
</table>
GABA (gamma-aminobutyric acid) is an inhibitory neurotransmitter that is very widely distributed in the neurons of the cortex. GABA contributes to motor control, vision, and many other cortical functions. It also regulates anxiety. Deficiency of GABA in brain leads to anxiety, insomnia and epilepsy. Some drugs that increase the level of GABA in the brain are used to treat epilepsy and to calm the trembling of people suffering from Huntington’s disease.

Glutamate is a major excitatory neurotransmitter that is associated with learning and memory, epileptic seizures, excitotoxicity, synaptic plasticity. Excess of glutamate is involved in epilepsy. It is also thought to be associated with Alzheimer’s disease, whose first symptoms include memory malfunctions.

1.3.9 CNS Market Trends:

The global market for drugs treating Central Nervous System (CNS) disorders has grown rapidly in recent years to reach US$55.5 billion in 2005, a year-on-year increase of 6.6%. Between 2003 and 2005, global CNS sales increased by 19% and accounted for 9.2% of total global pharmaceutical sales in 2005. The global CNS market is forecast to expand to US$63.9 billion in 2010. The global market for CNS-related pharmaceuticals was dominated by the antidepressant drug class with a market share of more than 30%. Particular attention is drawn to the drug classes like, Epilepsy, Depression, Psychosis, Anxiety, Alzheimer’s disease, Migraine, Parkinson’s disease etc.

1.4 Pharmacology and Pharmacotherapeutics of CNS Disorders:

A central promise of Neuropsychopharmacology as we enter a new century is to evaluate the vast arrays of various neurotransmitters as targets for entirely new families of pharmacotherapeutic agents. Modern neuroscience advanced our understanding of putative CNS disorders mechanisms, which led to improved therapeutics.

Drugs that act to influence brain function have long been essential to medical practice. Because of the importance of brain to normal physiologic and psychological functions, the actions of centrally acting drugs are diverse. Drugs acting on CNS induce anesthesia, relieve pain and fever, prevent or modify seizures, induce sleep, reduce anxiety and ameliorate symptoms of major mental illness (Bhattacharya & Muruganandam, 2003). An improved understanding of the predisposition factors, signs and symptoms, discoveries in the field of CNS disorders, valid and reliable biomarkers, and predictive preclinical models likely will unravel the various substances for central nervous system disorder, hopefully
leading us to better mechanism-based targets for prevention, and ultimately yielding drugs with optimal therapeutic ratios or indices.

### 1.4.1 Insomnia:

Insomnia is a symptom of sleeping disorder characterized by persistent difficulty falling asleep or staying asleep despite the opportunity. Insomnia is a symptom, not a stand-alone diagnosis or a disease. By definition, insomnia is difficulty in initiating or maintaining sleep or both and it may be due to inadequate quality or quantity of sleep. It is typically followed by functional impairment while awake. Insomniacs have been known to complain about being unable to close their eyes or "rest their mind" for more than a few minutes at a time. Both organic and non-organic insomnia constitute a sleep disorder.

According to the Department of Health and Human Services in year 2007, approximately 64 million people suffer from insomnia on a regular basis each year. Insomnia is 1.4 times more common in women than in men.

#### Types of Insomnia:

Although there are several different degrees of insomnia, three types of insomnia have been clearly identified: transient, acute, and chronic.

- **Transient insomnia** lasts from days to weeks. It can be caused by another disorder, by changes in the sleep environment, by the timing of sleep, severe depression, or by stress. Its consequences - loss of sleep and impaired psychomotor performance are similar to those of sleep deprivation.

- **Acute insomnia** is the inability to consistently sleep well for a period of between three weeks to six months.

- **Chronic insomnia** lasts for years at a time. It can be caused by another disorder, or it can be a primary disorder. Its effects can vary according to its causes. They might include loss of sleep, muscular fatigue, hallucinations, and/or mental fatigue; but people with chronic insomnia often show increased alertness (Thomas & Roehrs, 2004; Kripke et al., 2002).

#### Causes:

Insomnia can be caused by:

- Psychoactive drugs or stimulants, including certain medications, herbs, caffeine, cocaine, ephedrine, amphetamines, methylphenidate, methamphetamine.
• Fluoroquinolone antibiotic drugs e.g. Fluoroquinolone toxicity, associated with more severe and chronic types of insomnia.
• Hormone shifts such as those that precede menstruation and those during menopause.
• Life problems like fear, stress, anxiety, emotional or mental tension, work problems, financial stress.
• Mental disorders such as bipolar disorder, clinical depression, general anxiety disorder, post traumatic stress disorder, schizophrenia, or obsessive compulsive disorder.
• Disturbances of the circadian rhythm, such as shift work, can cause an inability to sleep at some times of the day and excessive sleepiness at other times of the day. The insomnia experienced by shift workers is also a circadian rhythm sleep disorder.
• Estrogen is considered to play a significant role in women’s mental health (including insomnia). The sudden estrogen withdrawal, fluctuating estrogen, and periods of sustained estrogen low levels correlated with significant mood lowering.
• Certain neurological disorders, brain lesions, or a history of traumatic brain injury.
• Medical conditions such as hyperthyroidism.
• Abuse of over-the-counter or prescription sleep aids can produce rebound insomnia.
• Poor sleep hygiene e.g., noise.
• Parasomnia, which includes a number of disruptive sleep events including nightmares, sleepwalking, violent behavior while sleeping, and REM behavior disorder, in which a person moves his/her physical body in response to events within his/her dreams.
• A rare genetic condition can cause a prion-based, permanent and eventually fatal form of insomnia called fatal familial insomnia.
• Parasites can cause intestinal disturbances while sleeping (Lawrence et al., 2006; Douma et al., 2005; Lasiuk & Hegadoren, 2007).

Treatment for insomnia:

In many cases, insomnia is caused by another disease, side effects from medications or a psychological problem. It is important to identify or rule out
medical and psychological problems before deciding on the treatment for the insomnia. Attention to sleep hygiene is an important first line treatment strategy and should be tried before any pharmacological approach is considered (Flamer, 1995; Kirkwood, 1999).

**Non-pharmacological strategies:**

Non-pharmacological strategies are superior to hypnotic medication for insomnia because tolerance develops to the hypnotic effects as well as dependence can develop with rebound withdrawal effects developing upon discontinuation. Non pharmacological strategies however, have long lasting improvements to insomnia and are recommended as a first line and long term strategy of managing insomnia. The strategies include attention to sleep hygiene, stimulus control, behavioral interventions, sleep-restriction therapy, patient education and relaxation therapy.

**Medications:**

**Benzodiazepines:** The most commonly used class of hypnotics prescribed for insomnia is the benzodiazepines. Benzodiazepines bind to the GABA<sub>A</sub> receptor. These include drugs such as temazepam, flunitrazepam, triazolam, flurazepam, midazolam, nitrazepam and quazepam. These drugs can lead to tolerance, physical dependence and the benzodiazepine withdrawal syndrome upon discontinuation, especially after consistent usage over long periods of time.

**Non-benzodiazepines:** Nonbenzodiazepine sedative-hypnotic drugs, such as zolpidem, zaleplon, zopiclone and eszopiclone, are a newer classification of hypnotic medications. They work on the benzodiazepine site on the GABA<sub>A</sub> receptor complex similarly to the benzodiazepine class of drugs. Some but not all of the nonbenzodiazepines are selective for the α<sub>1</sub> subunit on GABA<sub>A</sub> receptors which is responsible for inducing sleep and may therefore have a cleaner side effect profile than the older benzodiazepines. These drugs appear to cause both psychological dependence and physical dependence though less than traditional benzodiazepines and can also cause the same memory and cognitive disturbances along with morning sedation.

**Antidepressants:** Some antidepressants such as amitriptyline, doxepin, mirtazapine, and trazodone can often have a very strong sedative effect, and are prescribed off label to treat insomnia. The major drawback of these drugs is that they have antihistaminergic, anticholinergic and antiadrenergic properties which
can lead to many side effects. Some also alter sleep architecture. As with many benzodiazepines, the use of antidepressants in the treatment of insomnia can lead to physical dependence; withdrawal may induce rebound insomnia and actually further complicate matters in the long-term. Mirtazapine is known to decrease sleep latency, promoting sleep efficiency and increasing the total amount of sleeping time in patients suffering from both depression and insomnia.

**Melatonin and melatonin agonists:** The hormone and supplement melatonin is effective in several types of insomnia. Melatonin has demonstrated effectiveness in regulating the sleep/waking cycle. One particular benefit of melatonin is that it can treat insomnia without altering the sleep pattern which is altered by many prescription sleeping tablets. Another benefit is it does not impair performance related skills. Melatonin agonists, including ramelteon (Rozerem) and tasimelteon, seem to lack the potential for abuse and dependence. Natural substances such as L-Tryptophan have been said to fortify the serotonin-melatonin pathway and aid people with various sleep disorders including insomnia.

**Antihistamines:** The antihistamine diphenhydramine is widely used in nonprescription sleep aids. Cyproheptadine is a useful alternative to benzodiazepine hypnotics in the treatment of insomnia. Cyproheptadine may be superior to benzodiazepines in the treatment of insomnia because cyproheptadine enhances sleep quality and quantity whereas benzodiazepines tend to decrease sleep quality.

**Atypical antipsychotics:** Low doses of certain atypical antipsychotics such as quetiapine, olanzapine and risperidone are also prescribed for their sedative effect but the danger of neurological and cognitive side effects make these drugs a poor choice to treat insomnia. Over time, quetiapine may lose its effectiveness as a sedative. Eplivanserin is an investigational drug with a mechanism similar to these antipsychotics, but probably with fewer side effects.

**Other substances:** Some insomniacs use herbs such as valerian, chamomile, lavender, hops, and passion-flower. Valerian has undergone multiple studies and appears to be modestly effective. Cannabis has also been proven as an effective treatment for insomnia.
1.4.2 Anxiety:

Anxiety is a psychological and physiological state characterized by cognitive, somatic, emotional, and behavioral components. These components combine to create an unpleasant feeling that is typically associated with uneasiness, fear, or worry. Anxiety is a generalized mood state that occurs without an identifiable triggering stimulus. As such, it is distinguished from fear, which occurs in the presence of an external threat. Additionally, fear is related to the specific behaviors of escape and avoidance, whereas anxiety is the result of threats that are perceived to be uncontrollable or unavoidable. Anxiety is a normal reaction to stress. It may help a person to deal with a difficult situation, for example at work or at school, by prompting one to cope with it. When anxiety becomes excessive, it may fall under the classification of an anxiety disorder. Anxiety disorders affect 12% of the population, causing mild to severe impairment (Ohman, 2000).

Anxiety disorders as recognized clinically include:

- **Generalized anxiety disorder**- an ongoing state of excessive anxiety lacking any clear reason or focus.
- **Panic disorders**- attacks of overwhelming fear occurring in association with marked somatic symptoms, such as sweating, tachycardia, chest pain trembling etc.
- **Phobias**- strong fear of specific things or situations e.g. snakes, open space, social interaction.
- **Post-traumatic stress disorders**- anxiety triggered by insistent recall of past stressful experiences.

Social and Economic Impact:

Symptoms of anxiety disorders often develop during early adulthood. Although the majority of people have mild or no impairment, anxiety disorders can seriously restrict an individual's education, work, recreation and social activities because he/ she avoid situations that precipitate the symptoms. Individuals severely affected by anxiety disorders are also more likely to have either another type of anxiety disorder, major depression, alcohol or substance abuse, or a personality disorder. Because they are so common, anxiety disorders have a major economic impact. They contribute to lot of productivity due to both time away from work and unemployment.
Symptoms:
Anxiety can be accompanied by physical effects such as heart palpitations, fatigue, nausea, chest pain, shortness of breath, stomach aches, or headaches. Physically, the body prepares the organism to deal with a threat. Blood pressure and heart rate are increased, sweating is increased, blood flow to the major muscle groups is increased, and immune and digestive system functions are inhibited (the fight or flight response). External signs of anxiety may include pale skin, sweating, trembling, and pupillary dilation. Someone suffering from anxiety might also experience it as a sense of dread or panic. Although panic attacks are not experienced by every anxiety sufferer, they are a common symptom. Panic attacks usually come without warning, and although the fear is generally irrational, the perception of danger is very real. There are many emotional symptoms involved as well. Some of them include: Feelings of apprehension or dread, trouble concentrating, feeling tense or jumpy, anticipating the worst, irritability, restlessness, watching (and waiting) for signs or danger, and, feeling like your mind's gone blank. There are also, nightmares/bad dreams, obsessions about sensations, a trapped in your mind feeling, and feeling like everything is scary. One of the most common symptoms of anxiety is fear (Rosen & Schulkin, 1998).

Medication:
The main groups of drugs are:
1. Barbiturates are now largely obsolete.
2. Benzodiazepines, the most important class, are used for treating both anxiety states and insomnia.
3. 5-HT\textsubscript{1A}-receptor agonists - Buspirone have been recently introduced and show anxiolytic activity with little sedation.
4. The β-adrenoreceptors antagonists - Propanolol are used mainly to reduce physical symptoms of anxiety.

Anxiolytic drugs are among frequently prescribed substances, used regularly by upward of 10% of the population in most developed countries (Rang et al., 2003; Dadds et al., 1997).
1.4.3 Psychosis:

Psychosis (from the Greek "psyche", for mind or soul, and "osis", for abnormal condition), with adjective psychotic, literally means abnormal condition of the mind, and is a generic psychiatric term for a mental state often described as involving a "loss of contact with reality". Schizophrenia from the Greek roots *skhizein* ("to split") and *phren* ("mind") is a psychiatric diagnosis that describes a mental disorder characterized by abnormalities in the perception or expression of reality. It most commonly manifests as auditory hallucinations, paranoid or bizarre delusions, or disorganized speech and thinking with significant social or occupational dysfunction. Diagnosis is based on the patient's self-reported experiences and observed behavior (Tien, 1991; Beer, 1995).

The prevalence of schizophrenia in the general population is estimated to vary between 0.2% and 2%, depending upon the measures used. However, a prevalence rate of 1% is generally accepted as the best estimate. Schizophrenia is a brain disease and one of the most serious mental illnesses. Schizophrenia affects about 1% of the population. It is one of the most important forms of psychiatric illness, because it affects young people, is often chronic and usually highly disabling. Common symptoms are mixed-up thoughts, delusions (false or irrational beliefs), hallucinations (seeing or hearing things that do not exist) and bizarre behavior. People suffering from schizophrenia have difficulty in performing tasks that require abstract memory and sustained attention. All the signs and symptoms of schizophrenia vary greatly among individuals. There is a strong evidence of hereditary factor in its etiology and evidence suggestive of a fundamental biological disorder (WHO, 2001).

**Social and Economic Impact of Schizophrenia:**

The onset of schizophrenia typically occurs between the late teens and mid-30s. Onset before adolescence is rare. Men and women are affected equally by schizophrenia, but men usually develop the illness earlier than women. If the illness develops after the age of 45, it tends to appear among women more than men, and they tend to display mood symptoms more prominently. Schizophrenia places a substantial financial burden on individuals with the illness, the members of their family and the health care system. In 1996, the total direct cost of schizophrenia was estimated to be $2.35 billion. This includes health care costs, administrative costs of income assistance plans, value of lost productivity, and
incarceration costs attributable to schizophrenia. The indirect costs of schizophrenia are estimated to account for another $2 billion yearly. Globally, nearly 3% of the total burden of human disease is attributed to schizophrenia (WHO, 2001; Johns & Jim, 2001).

**The main clinical features are:**

**Positive symptoms**
Delusions and/or hallucinations, lack of motivation, thought disorders, abnormal behaviors such as stereotyped or aggressive behaviors.

**Negative symptoms**
Withdrawal from social contacts, flattening of emotional responses, lack of volition, poverty of thought, difficulty with abstract thinking and anhedonia

**Affective symptoms**
Unstable mood, depression, irritable, and mood elevation

**Cognitive impairments**
Impaired attention, impaired information processing, impaired verbal fluency.

**Aetiology and pathogenesis of Schizophrenia:**

Schizophrenia is a disease of the brain with unknown etiology in which patients suffer from a cluster of symptoms. However, it is easier to make this assertion than to document any actual deviations in brain physiology. Since the illness represents a disturbance in some, but not all, brain functions, it is reasonable to suppose that specific areas or neural circuits of the brain are involved and that the manifestations of schizophrenia must necessarily involve altered processing of physiological information; this altered processing would, in turn, be dependent on disturbances of cytoarchitectural, biochemical, or electrophysiological properties of the neural systems. Whereas the true causes underlying schizophrenia are still subject of debate, evidence has been accumulating over the last five decades that the symptoms of the disease may be the result of neurochemical and/or anatomical abnormalities in the central nervous system (CNS).

Psychosis has been traditionally linked to the neurotransmitter dopamine. In particular, the dopamine hypothesis of psychosis has been influential and states that psychosis results from an overactivity of dopamine function in the brain, particularly in the mesolimbic pathway. The two major sources of evidence given to support this theory are that dopamine-blocking drugs (i.e.
antipsychotics) tend to reduce the intensity of psychotic symptoms, and that drugs which boost dopamine activity (such as amphetamine and cocaine) can trigger psychosis in some people. The connection between dopamine and psychosis is generally believed to be complex. While antipsychotic drugs immediately block dopamine receptors, they usually take a week or two to reduce the symptoms of psychosis. Moreover, newer and equally effective antipsychotic drugs actually block slightly less dopamine in the brain than older drugs whilst also affecting serotonin function, suggesting the 'dopamine hypothesis' may be oversimplified.

While the pathophysiology of schizophrenia remains unclear, several neurotransmitter systems have been suggested to be implicated e.g. dopamine, serotonin, glutamate and Ach, among these, the dopamine and serotonin has received most attention.

It is widely accepted that the dopaminergic system plays a key role in schizophrenic illness. Affected individuals may exhibit a wide spectrum of behavioral and other symptoms, ranging from social withdrawal, catatonia and affective flattening of the personality (negative symptoms, thought to be associated with dopaminergic hyperactivity in the prefrontal cortex) to hallucinations, paranoia and disorganized behavior (positive symptoms, thought to be associated with hyperactive dopaminergic transmission in the mesolimbic region of the brain) (Tsuang et al., 2000; Kapur et al., 2005; Rang et al., 2003; Pantelis et al., 2003)

**Medication:**

**Anti-psychotics:** The first line psychiatric treatment for schizophrenia is antipsychotic medication. These can reduce the positive symptoms of psychosis. Currently available antipsychotics fail however to significantly ameliorate the negative symptoms, and the improvements on cognition may be attributed to the practice effect. Molecule of chlorpromazine, which is revolutionized treatment of schizophrenia in the 1950s. Although expensive, the newer atypical antipsychotic drugs are usually preferred for initial treatment over the older typical antipsychotic, although they are more likely to induce weight gain and obesity-related diseases. The two classes of antipsychotics are generally thought equally effective for the treatment of the positive symptoms. Some researchers have
suggested that the atypical offer additional benefit for the negative symptoms and cognitive deficits associated with schizophrenia, although the clinical significance of these effects has yet to be established (Livingstone, 2008; Rang et al., 2003; Jones & Pilowsky, 2002).

1.4.4 Epilepsy:

Epilepsy is the most common brain disorder in the general population. It is a chronic neurological disorder characterized by recurrent unprovoked seizures, which is often associated with convulsions but may occur in many other forms. These seizures are transient signs and/or symptoms of abnormal, excessive or synchronous neuronal activity and caused by outbursts of excessive electrical activity in part or the whole of the brain. The majority of individuals with epilepsy do not have any obvious or demonstrable abnormality in the brain, besides the electrical changes. However, a proportion of individuals with this disorder may have accompanying brain damage, which may cause other physical dysfunctions such as spasticity or mental retardation. Epilepsy affects 0.5-1% of the population. About 50 million people worldwide have epilepsy, with almost 90% of these people being in developing countries. Epilepsy is more likely to occur in young children or people over the age of 65 years; however it can occur at any time.

WHO estimates that about 37 million individuals globally suffer from primary epilepsy, Epilepsy is usually controlled, but not cured, with medication, although surgery may be considered in difficult cases. However, over 30% of people with epilepsy do not have seizure control even with the best available medications. Not all epilepsy syndromes are lifelong some forms are confined to particular stages of childhood. Epilepsy should not be understood as a single disorder, but rather as a group of syndromes with vastly divergent symptoms but all involving episodic abnormal electrical activity in the brain (WHO, 2001; Fisher et al., 2005).

Symptoms of Epilepsy:

Epileptic seizures vary greatly in frequency, from several a days to once every few months. The manifestation of epilepsy depends on the brain areas involved. Usually the individual undergoes sudden loss of consciousness and may experience spasmodic movements of the body. Injuries can result from a fall during the seizure.
The symptoms of epilepsy are:

- Brief episodes of loss of consciousness (seizures).
- With or without characteristic body movements (convulsions).
- Sensory or psychiatry phenomena.

Types of Epilepsy:

- **Generalized seizures**—Generalized seizures are divided according to the effect on the body but all involve loss of consciousness (Rang et al., 2003).
  - Generalized tonic-clonic seizures
  - Absence seizures
  - Atonic seizures
  - Myoclonic seizures
  - Infantile spasms

- **Partial seizures**—Partial seizures are further divided on the extent to which consciousness is affected.
  - Simple partial seizures
  - Complex partial seizures

**Epidemiology:**

Epilepsy is one of the most common of the serious neurological disorders. Genetic, congenital, and developmental conditions are mostly associated with it among younger patients; tumors are more likely over age 40; head trauma and central nervous system infections may occur at any age. The prevalence of active epilepsy is roughly in the range 5-10 per 1000 people. Up to 5% of people experience non febrile seizures at some point in life; epilepsy's lifetime prevalence is relatively high because most patients either stop having seizures or (less commonly) die of it. Epilepsy's approximate annual incidence rate is 40-70 per 100,000 in industrialized countries and 100-190 per 100,000 in resource-poor countries; socioeconomically deprived people are at higher risk. Beyond symptoms of the underlying diseases that can cause certain epilepsies, people with epilepsy are at risk for death from four main problems: status epilepticus (most often associated with anticonvulsant noncompliance), suicide associated with depression, trauma from seizures, and sudden unexpected death in epilepsy. Those at highest risk for epilepsy-related deaths usually have underlying
neurological impairment or poorly controlled seizures; those with more benign epilepsy syndromes have little risk for epilepsy-related death (Sander, 2003; Frucht et al., 2000).

**Aetiology and pathogenesis of Epilepsy:**

Most of the causes are primary (idiopathic), or some may be secondarily. Often there is no recognizable cause. The causes of epilepsy include genetic predisposition, brain damage caused by birth complications, surgery on head, infections and parasitic diseases, brain injuries, intoxication and tumors. Cysticercosis (tapeworm), schistosomiasis, toxoplasmosis, malaria, and tubercular and viral encephalitis are some of the common infectious causes of epilepsy in developing countries.

Neurochemical basis of the abnormal discharge is not well understood. It may be associated with enhanced excitatory amino acid transmission (Glutamate) or impaired inhibitory transmission (GABA) or abnormal electrical properties of the affected cells. The glutamate content in the areas surrounding an epileptic focus may be increased. Repeated epileptic discharge can cause neuronal death i.e. excitotoxicity (Rang et al., 2003).

**Social and Economic Impact:**

Epilepsy places a significant burden on communities, especially in developing countries where it may remain largely untreated. It is estimated that the aggregate burden due to epilepsy to be 0.5% of the total disease burden. In addition to physical and mental disability, epilepsy often results in serious psychosocial consequences for the individual and the family. The stigma attached to epilepsy prevents individuals with epilepsy from participating in normal activities, including education, work and sports (WHO, 2001).

**Medication:**

**Anticonvulsant**- The mainstay of treatment of epilepsy is anticonvulsant medications. Often, anticonvulsant medication treatment will lifelong and can have major effects on quality of life. The choice among anticonvulsants and their effectiveness differs by epilepsy syndrome. Mechanisms, effectiveness for particular epilepsy syndromes, and side effects, of course, differ among the individual anticonvulsant medications. Epilepsy is treated mainly with drugs, though brain surgery may be used for severe cases. Current antiepileptic drugs
are effective in controlling seizures in about 70-80% of patients, but their use is often limited by side effects (Rang et al., 2003; Cascino, 1994). Three main mechanisms appear to be important in the action of antiepileptic drugs.

1. **Enhancement of GABA action** - Phenobarbital, Benzodiazepines, Vigabatrin, Tiagabine, Gabapentin.

2. **Inhibition of sodium channel function** - Phenytoin, Carbamazepine, Valproate, Lomotrigine.

3. **Inhibition of calcium channel function** - Ethosuximide, Valproate, Gabapentine.

**1.4.5 Depression:**

Depression is the most common of the affective disorders (disorders of mood rather than disturbances of thought or cognition). The terms depression or depressed refer to sadness and other related emotions and behaviors. The Diagnostic and Statistical Manual of Mental Disorders (DSM) states that a depressed mood is often reported as feeling depressed, sad, helpless, and hopeless. In traditional colloquy, depressed is often synonymous with sad. It may range from a very mild condition, bordering on normality, to severe (psychotic) depression accompanied by hallucination and delusions. Worldwide, depression is a major cause of disability and premature death.

**Epidemiology:**

Depression is a major cause of morbidity worldwide. People are most likely to suffer their first depressive episode between the ages of 30 and 40, and there is a second, smaller peak of incidence between ages 50 and 60. The risk of major depression is increased with neurological conditions such as stroke, Parkinson's disease, or multiple sclerosis and during the first year after childbirth. It is also more common after cardiovascular illnesses. Major depression is currently the leading cause of disease burden in many countries, and the fourth-leading cause worldwide. In the year 2030, it is predicted to be the second-leading cause of disease burden worldwide after HIV, according to the World Health Organization. Major depression frequently co-occurs with other psychiatric problems. The 1990-92 National Comorbidity Survey (US) reports that 51% of those with major depression also suffer from lifetime anxiety. Anxiety symptoms can have a major impact on the course of a depressive illness,
with delayed recovery, increased risk of relapse, greater disability and increased suicide attempts (Rickards, 2005; Hirschfield, 2001).

**Symptoms of depression:**
The symptoms of depression include emotional and biological components.

- **Emotional symptoms** - misery, apathy and pessimism, low self-esteem, feeling of guilt, inadequacy and ugliness, indecisiveness, loss of motivation.
- **Biological symptoms** - retardation of thought and action, loss of libido, sleep disturbances and loss of appetite.

**Types of depression:**
There are two distinct types of depressive syndrome

- **Unipolar depression** - which the mood swings is always in the same direction. Unipolar depression is very common (about 75% of cases) non-familial, associated with stressful life-events and accompanied by symptoms of anxiety and agitation.

- **Bipolar affective disorder** - which depression alternates with mania. Bipolar depression usually appears in early adult life and less common (Rang et al., 2003).

**An etiology and pathogenesis of Depression: Monoamine hypothesis:**

The main biochemical theory of depression is the monoamine hypothesis. According to hypothesis, depression is caused by a functionally deficient monoaminergic (noradrenergic and/or serotonergic) transmission in the certain sites of brain, while mania results from a functional excess. The serotonergic system is known to modulate mood, emotion, sleep and appetite and thus is implicated in the control of numerous behavioral and physiological functions. Decreased serotonergic neurotransmission has been proposed to play a key role in the aetiology of depression. The concentration of synaptic serotonin is controlled directly by its reuptake into the pre-synaptic terminal and thus, drugs blocking serotonin transport have been successfully used for the treatment of depression. Most antidepressants increase synaptic levels of serotonin. Serotonin is hypothesized to help regulate other neurotransmitter systems; decreased serotonin activity may allow these systems to act in unusual and erratic ways. According to this "permissive hypothesis", depression arises when low serotonin
levels promote low levels of norepinephrine, another monoamine neurotransmitter. Some antidepressants enhance the levels of norepinephrine directly, whereas others raise the levels of dopamine, a third monoamine neurotransmitter. These observations gave rise to the monoamine hypothesis of depression. In its contemporary formulation, the monoamine hypothesis postulates that a deficiency of certain neurotransmitters is responsible for the corresponding features of depression: Norepinephrine may be related to alertness and energy as well as anxiety, attention, and interest in life; serotonin to anxiety, obsessions, and compulsions; and dopamine to attention, motivation, pleasure, and reward, as well as interest in life. The proponents of this theory recommend the choice of an antidepressant with mechanism of action that impacts the most prominent symptoms. Anxious and irritable patients should be treated with selective serotonin reuptake inhibitors or norepinephrine reuptake inhibitors, and those experiencing a loss of energy and enjoyment of life with norepinephrine and dopamine enhancing drugs (Nutt, 2008; Hirschfield, 2000; Delgado, 2000; Duman et al., 1997).

Medication:

Antidepressants are used for the treatment of clinical depression as well as often for anxiety and other disorders. There are a number of antidepressants beginning with the tricyclics, moving through a wide variety of drugs that modify various facets of the brain chemistry dealing with intercellular communication (Karasu et al., 2000; Tsapakis, 2008). Antidepressant drugs used are:

1. Inhibitors of monoamine uptake- Tricyclic antidepressants have more side effects than SSRIs and are usually reserved for the treatment of inpatients, for whom the tricyclic antidepressant amitriptyline, in particular, appears to be more effective e.g. imipramine, amitriptyline (non-selective inhibitors).

2. Selective 5-HT (serotonin) uptake inhibitors- Selective serotonin reuptake inhibitors (SSRIs) are the primary medications prescribed owing to their effectiveness, relatively mild side effects, and because they are less toxic in overdose than other antidepressants e.g. fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram.

3. Monoamine oxidase (MOA) inhibitors- Monoamine oxidase inhibitors, an older class of antidepressants, have been plagued by potentially life-
threatening dietary and drug interactions. They are still used only rarely, although newer and better tolerated agents of this class have been developed e.g. phenelzine, tranylcypromine, which are non-selective with respect to MAO-A and MAO-B.

4. **MAO-A selective**- Moclobemide.

5. **Miscellaneous**- Bupropion, trazodone, mirtazepine

### 1.4.6 Stress:

Stress is defined as a state of threatened homeostasis and is counteracted by a complex repertoire of physiologic and behavioral responses that reestablish homeostasis (adaptive stress response). Stress is a biological term which refers to the consequences of the failure of a human or animal body to respond appropriately to emotional or physical threats, whether actual or imagined. The stress response is subserved by a complex neuroendocrine, cellular and molecular infrastructure. The adaptive response of an individual to stress is determined by a multiplicity of genetic, environmental and developmental factors. Alterations of the ability to respond to stressors, as for example inadequate, excessive and/or prolonged reactions, may lead to disease. Moreover, excessive and/or chronically imposed stressors may have adverse impact on a variety of physiologic functions, such as growth, reproduction, metabolism and the immuno competence, as well as on personality development and behavior. Prenatal life, infancy, childhood and adolescence are critical periods characterized by increased vulnerability to stressors (Selye, 1956; Chrousos & Gold, 1992).

### Types of stress:

- **Acute stress**- Acute stress appears to have limited aversive effects since the body sets in motion an array of physiological, biochemical and endocrine responses to counter stress effects.
- **Chronic stress**- Chronicity and excessiveness of the stressor, and the inability of the organism to cope with the stress, appear to induce the syndromal state.

### Signs and Symptoms of Stress:

The specific signs and symptoms of stress vary widely from person to person but they generally fall into four categories.

- **Cognitive symptoms**- Memory problems, indecisiveness, inability to concentrate, poor judgment, seeing only the negative, fearful anticipation.
• **Physical symptoms**- Headache, nausea, dizziness, insomnia, chest pain, rapid heartbeat, weight gain or loss, loss of sex drive.

• **Emotional symptoms**- Moodiness, restlessness, short temper, irritability, impatience, sense of loneliness, depression.

• **Behavioral symptoms**- Isolating from others, neglecting responsibilities, addiction to drugs or alcohol.

**Causes of Stress:**
There are external and internal causes of stress.

**External stressors**
- **Physical environment**: Noise, shock, hot and cold temperature, immobilization in a confined space.
- **Chemical**: Various toxic agents, narcotics etc.
- **Social** (interaction with people): Rudeness, bossiness or aggressiveness on the part of someone else.
- **Major life events**: Death of a relative, lost job, promotion.
- **Daily hassles**: Commuting, misplacing keys, mechanical breakdowns.

**Internal stressors**
- **Psychological**: Responsibility, loss of job, boredom etc.
- **Lifestyle choices**: Insomnia, overloaded schedule etc.
- **Negative self-talk**: Pessimistic thinking, self-criticism, over-analyzing etc.

**Pathophysiology of Stress:**
Selye (1956) proposed the concept of general adaptation syndrome (GAS). General adaptation syndrome, or GAS, is a term used to describe the body's short-term and long-term reactions to stress which consists of three stages. It includes a state of alarm and adrenaline production, short-term resistance as a coping mechanism, and exhaustion. It refers to the inability of a human or animal body to respond

1. The alarm reaction.
2. The stage of resistance.
3. The stage of exhaustion.
Neurochemical alterations:

Various neurotransmitters are involved in pathophysiology of stress like serotonin, dopamine, noradrenaline, acetylcholine, GABA etc (Jorgensen et al., 1998; Dunn, 1988; Tsagarakis, 1969). The neurochemistry of the stress response is now believed to be well understood, although much remains to be discovered about how the components of this system interact with one another, in the brain and throughout the body. In response to a stressor, corticotropin-releasing hormone (CRH) and arginine-vasopressin (AVP) are secreted into the hypophyseal portal system and activate neurons of the paraventricular nuclei (PVN) of the hypothalamus. The locus ceruleus and other noradrenergic cell groups of the adrenal medulla and pons, collectively known as the LC/NE system, also become active and use brain epinephrine to execute autonomic and neuroendocrine responses, serving as a global alarm system. The autonomic nervous system provides the rapid response to stress commonly known as the fight-or-flight response, engaging the sympathetic nervous system and withdrawing the parasympathetic nervous system, thereby enacting cardiovascular, respiratory, gastrointestinal, renal, and endocrine changes. The hypothalamic-pituitary-adrenal axis (HPA), a major part of the neuroendocrine system involving the interactions of the hypothalamus, the pituitary gland, and the adrenal glands, is also activated by release of CRH and AVP. This results in...
release of adrenocorticotropic hormone (ACTH) from the pituitary into the general bloodstream, which results in secretion of cortisol and other glucocorticoids from the adrenal cortex. These corticoids involve the whole body in the organism's response to stress and ultimately contribute to the termination of the response via inhibitory feedback (Tsigos & Chrousos, 2002). Oxidative stress also plays a major role in stress. Free radicals are generated from the process of oxidation. Free radicals initiate the chemical reactions in the body that cause damage to cells and DNA (Maxwell, 1995; McCarty, 1989).

Medication:

1. **Benzodiazepine Anxiolytics**: Diazepam, oxazepam, lorazepam, chlordiazepoxide.

2. **Neuroleptic**: Chlorpromazine, Haloperidol, Clozapine (Tripathi, 2008).