2. Literature review
2. LITERATURE REVIEW

2.1 Introduction to the subject area of research

Neuropharmacology is the specialized branch of Pharmacology dealing with study of drugs that modify the functions of brain, spinal cord, and the nerves that communicate with all parts of the body. It is also concerned with the study of the neurochemical interactions of neuropeptides, neurohormones, neuromodulators, enzymes, secondary messenger systems of the central nervous system (CNS), co-transporters, ion channels, receptor proteins and much more.

Technical advances in recent years have allowed progress toward the understanding of the brain and how drugs can be made to affect it which led to its further refinement into many sub disciplines, two of which are Psychopharmacology and Neuropsychopharmacology.

- **Psychopharmacology**

  The term *Psychopharmacology*, is derived from greek words, psyche-meaning soul/mind, pharmacon-Drug and logos -meaning study. Therefore *Psychopharmacology* can be defined as "study of drug-induced changes in mood, thinking and behavior".

  The subject covers a wide range of substances with various types of psychoactive properties, though doesn't typically focus on psychedelic or recreational drugs; the majority of studies are conducted on medicinal psychoactives (http://en. Wikipedia.org).

- **Neuropsychopharmacology**

  Neuropsychopharmacology is an interdisciplinary science related to psychopharmacology and basic neuroscience. It covers research of mechanisms of neuropathology, drug action, psychiatric illness and states of consciousness.

  These studies involve neurotransmission/receptor activity, bio-chemical processes and neural circuitry. Developments in neuropsychopharmacology may directly influence the studies of anxiety disorders, affective disorders, psychotic disorders, degenerative disorders, eating behavior and sleep behavior.
2.2. Overview

An implicit premise in neuropsychopharmacology with regards to the psychological aspects is that all states of mind (normal and drug-induced altered states, and mental or cognitive dysfunction) have a neuro-chemical origin and at a higher level certain circuit pathways in the CNS. Thus the understanding of nerve cells or neurons in the brain is central to understanding the mind. It is reasoned that the mechanisms involved in these can be elucidated through,

1. Modern clinical and research methods such as genetic manipulation in animal subjects

2. Imaging techniques such as *functional magnetic resonance imaging* (fMRI), radiological imaging\(^1\) such as *positron emission tomography* (PET) and *single-photon emission computed tomography* (SPECT) are extremely sensitive and can image tiny molecular concentrations on the order of \(10^{-10}\) M such as found with extrastriatal D\(_1\) receptor for dopamine.

3. *In vitro* studies using selective binding agents on live tissue cultures which allow neural activity to be monitored and measured in response to a variety of test conditions (http://en.wikipedia.org/wiki/).

The ultimate goal thus is to devise and develop treatments for a variety of neuro-pathological conditions and psychiatric disorders.

A direct product of neuropsychopharmacological research is the knowledge base required to develop drugs which act on very specific receptors within a neurotransmitter system. These hyperselective-action drugs would allow the direct targeting of specific sites of relevant neural activity thereby maximizing the *efficacy* of the drug within the clinical target and minimizing *adverse effects*. 
2.3 Role of Neurotransmitters in behavior

The behavior is a result of coordinated interplay of neuronal inhibition and excitation (Roberts 1974) in the CNS which is in turn a function of a number of specific neurotransmitters.

Advanced and exhaustive research in the field of molecular biology, neurochemistry and neurophysiology has identified $\gamma$- Amino butyric acid (GABA) and glycine as major inhibitory neurotransmitters in brain and spinal cord respectively, while glutamate and aspartate as major excitatory neurotransmitters in CNS. As these neurotransmitters maintain normal physiological function, however also have been implicated to be involved in various CNS disorders such as epilepsy, Parkinson disease, Huntington's chorea, anxiety, depression, schizophrenia and Alzheimer disease (Mcldmnin Garlhwalte. 1990; Shlgetada. 1992). Modification of altered levels of neurotransmitters has been found to be useful in ameliorating various disease symptoms by drug therapy. For ex, elevated levels of GABA in the brain result in anticonvulsant activity and anxiolytic effects (Wood, Peesker. 1975). Likewise, abnormally low levels of glutamate can compromise normal levels of excitation and excessive levels induce seizures and other toxic effects (Farooqui. Horrockes, 1991).

However, there is a complex interregulation among different neurotransmitters and themselves in the brain posing a greatest challenge in understanding the role played by them in various physiological and pathological conditions.

2.3.1 Neurotransmission

Everything a person perceives feels, thinks, knows and does is a result of neurons firing and resetting. When a cell in the brain fires, small chemical and electrical swings called the action potential may affect the firing of as many as a thousand other neurons in a process called neurotransmission. In this way signals are generated and carried through
networks of neurons. The electrical effect of which can be measured directly on the scalp by a device called Electro Encephalo Graph (EEG).

Steps involved in neurotransmission are

- Synthesis of neurotransmitter
- Storage in synaptic vesicles
- Transport of synaptic vesicles
- Release of neurotransmitters into the synapse
- Receptor activation and cascade function
- Inactivation mechanisms (reuptake) and/or enzyme degradation

The critical changes affecting cell firing occur when the signalling neurotransmitters from one neuron, acting as ligands, bind to receptors of another neuron. Many neurotransmitter systems and receptors are well known, and research continues toward the identification and characterization of a large number of very specific sub-types of receptors.

Fig 2.1 Neurotransmission and synapse (adopted from http://www.ghettodriveby.com/n/)

In the figure above shown is the typical synapse between, two neurons or a neuron and target cell. Above shown is the dopaminergic nerve ending containing
synaptic vesicles which are filled with the dopaminergic neurotransmitter, which on stimulation releases the dopamine into the synapse, by a process called as exocytosis, to bind on the postsynaptic dopaminergic receptors.

2.3.2 Neural networks

The function of a neuron is to receive input information, process it and sends as output. This is the case in all neurons whether sensory, motor or an interneuron. Interneuron on the other hand receives input information from other neurons through synapses, processes and sends as output to other neurons through synapses. Consequently, an interneuron cannot fulfill its function if it is not connected to other neurons in a network.

A network of neurons (or neural network) is a group of neurons through which information flows from one neuron to another. The figure below represents a typical neural network. "Information" flows between the blue neurons through electrical synapses. Information flows from neuron A (yellow) to neuron B (blue) to neuron C (pink) via chemical synapses (http://en. Wikipedia.org/wiki).

The membrane of a neuron acts as a barrier to electrically charged ions. When the concentration of ions on the inside of the neuron changes, the electrical property of the membrane itself changes. When the electrical property of the membrane reaches a point of no return called a threshold (as a result of ions entering and leaving through ion channels in the membrane), a large electrical signal is generated. This is the action potential. This signal is then propagated along the axon until it reaches its axon terminals. It is at axon terminals where the neuron sends its output to other neurons. At electrical synapses, the output will be the electrical signal itself. At chemical synapses, the output will be neurotransmitter.
Fig 2.2 Neuronal circuits and neuronal communication (Adopted from http://www.mind.ilstu.edu/)
Fig 2.3 Overlap of Neurotransmission and metabolic activity

The above diagram shows overlap between neurotransmission and metabolic activity. Neurotransmitters bind to receptors which cause changes to ion channels (black, yellow), metabotropic receptors also affect DNA transcription (red), transcription is responsible for all cell proteins including enzymes which manufacture neurotransmitters (blue) (http://en.Wikipedia.org/wiki)
Fig 2.4 Transduction mechanism of different receptors (http://employees.csbsju.edu/hjakubowski/classes/ch331/signaltrans/neurotranskinase.gif).

1. Agonist → Na → Activation of conductance
2. Agonist → G-Protein Activation → Generation of Second Messenger → Activation of Cell Signaling
3. Agonist → Phosphorylation of Tyrosines on Key Signaling Molecules → Activation of Cell Signaling
4. Agonist → Transport to the Nucleus → Activation of transcription and translation

Fig 2.5 - Transduction mechanism of G Protein receptors

G protein activation of adenylate cyclase

hormone → receptor → adenylate cyclase → GDP → GTP → ATP → cAMP
2.3.3 Receptors and Transduction Mechanisms

Any cellular macromolecule that a drug binds to initiate its effects is called as receptor. Neurotransmitters act on receptors, which are transmembrane proteins that have an extracellular site that binds the neurotransmitter and undergoes some conformational change. If the receptor happens to be an ion channel, it is said to be a direct gating receptor, and binding the neurotransmitter will either cause it to open or close. There is a second type of receptor which is coupled to intracellular second messenger cascades, but eventually some part of the cascade will affect an ion channel, and thus its membrane potential. The sequence of events intracellularly which follows the binding of a ligand on the receptor is called as Transduction mechanism (See figs 2.6 and 2.7).

Types of receptors

1. Ion channels linked receptors
   a. Ligand gated
   b. Voltage gated
   c. Messenger regulated

2. G-Protein coupled receptors

3. Tyrosine kinase receptors

4. Nuclear receptors
2.3.4 Neurotransmitters

Neurotransmitters are small molecules that are liberated by a presynaptic neuron into the synaptic cleft and cause a change in the postsynaptic membrane potential. This change can be either a direct depolarization or hyperpolarization, or the activation of second messengers that eventually lead to changes in firing rate. There are other molecules that act on the neuron and change its firing characteristics, but act from a distance and are not involved in synaptic transmission, and these are called neuromodulators. The same kind of molecule can act as a neurotransmitter or a neuromodulator, depending if its action is synaptic or long range (http://www.ifisiol.unam.mx/Brain/neuron.htm).

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Neurotransmitters are synthesized in the cell body and are transported to the terminal synaptic buttons of the axon where they are encapsulated into vesicles and stay close to the synaptic region of the button. When an action potential occurs, an influx of calcium ions induces the vesicles to fuse with the presynaptic membrane and its contents are poured into the synaptic cleft.

The three major categories of substances that act as neurotransmitters are

(1) Amino acids (primarily glutamic acid, GABA, aspartic acid & glycine

(2) Peptides (vasopressin, somatostatin, neurotensin, etc.) and

(3) Monoamines (norepinephrine, dopamine & serotonin) plus acetylcholine.
Neurotransmitters can act as inhibitory or excitatory signals to the postsynaptic cell, by hyperpolarizing or depolarizing its membrane, although the same molecule can function as an inhibitor or an excitator. This happens because there are a small number of neurotransmitters but a great variety of their receptors on different types of cells. Acetylcholine, for instance can act as an excitator when it binds to one type of receptor, and as an inhibitor when bound on another kind, even if both types of receptors are present in the same cell. The following is a list of several known and well studied neurotransmitters although some others have been proposed along with bioactive peptides such as substance P and neuropeptide Y.

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Function</th>
<th>Synthesis by enzymes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine</td>
<td>mostly excitatory</td>
<td>Choline acetyltransferase</td>
</tr>
<tr>
<td><strong>Bioactive amines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine</td>
<td>Excitatory and inhibitory</td>
<td>Tyrosine hydroxilase</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>excitatory</td>
<td>Tyrosine hydroxilase and dopamin-b-hydroxilase</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>excitatory</td>
<td>Tyrosine hydroxilase and dopamin-b-hydroxilase</td>
</tr>
<tr>
<td>Serotonin</td>
<td>excitatory</td>
<td>Tryptophan hydroxilase</td>
</tr>
<tr>
<td><strong>Amino acids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glutamate</td>
<td>excitatory</td>
<td>Metabolic amino acid</td>
</tr>
<tr>
<td>Glycine</td>
<td>mostly inhibitory</td>
<td>Metabolic amino acid</td>
</tr>
<tr>
<td>g-Aminobutiric acid (GABA)</td>
<td>inhibitor</td>
<td>Glutamate descarboxylase</td>
</tr>
<tr>
<td><strong>Peptides</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vasopressin, somatostatin,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>neurotensin, etc.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Although there are many neurotransmitters in the CNS, the PNS has only two, acetylcholine and norepinephrine. Functions performed by brain neurotransmitters are not
as uniform as they might superficially appear. Some (like glutamate) are excitatory, whereas others (like GABA) are primarily inhibitory. In many cases (as with dopamine) it is the receptor which determines whether the transmitter is excitatory or inhibitory. Receptors can also determine whether a transmitter acts rapidly by direct action on an ion channel (eg, nicotinic ACh receptors) or slowly, by a second-messenger system that allows for synaptic plasticity (eg, muscarinic ACh receptors).
2.3.5 Major brain neurotransmitters

1. GLYCINE

Glycine is the simplest of amino acids, consisting of an amino group and a carboxyl (acidic) group attached to a carbon atom. Its function is to make post-synaptic membrane more permeable to Cl⁻ ion. This hyperpolarizes the membrane, making it less likely to depolarize. Thus glycine is an inhibitory neurotransmitter. It is de-activated in the synapse by a simple process of reabsorption by active transport back into the pre-synaptic membrane.

Glycine is a neurotransmitter only in vertebrate animals. The glycine receptor is primarily found in the ventral spinal cord. Strychnine is a glycine antagonist which can bind to the glycine receptor without opening the chloride ion-channel (i.e., it inhibits inhibition). The resultant spinal hyperexcitability which is the poisonous effect of strychnine.

2. ASPARTIC ACID (ASPARTATE)

Like glycine, aspartate is primarily localized to the ventral spinal cord. Like glycine, aspartate opens an ion-channel and is inactivated by reabsorption into the pre-synaptic membrane. Unlike glycine however aspartate is an excitatory neurotransmitter, which increases the likelihood of depolarization in the postsynaptic membrane. Aspartate & glycine form an excitatory/inhibitory pair in the ventral spinal cord comparable to the excitatory/inhibitory pair formed by glutamate & GABA in the brain.

3. GLUTAMIC ACID (GLUTAMATE)

Glutamate is the most common neurotransmitter in the brain. It is always excitatory, usually due to simple receptors that increase the flow of positive ions by opening ion-channels. Glutamate stimulation is terminated by a (chloride-independent) membrane transport system that is only used for re-absorbing glutamate & aspartate across the pre-synaptic membrane. Glutamate & aspartate re-enter the cell by a transporter driven by the high extracellular concentrations of Na⁺ and the high intracellular concentrations of...
K\(^+\). Sodium enters the cell along with the amino acids and potassium leaves the cell. Thus, glutamate/aspartate entry is indirectly powered by the ATP-driven Na\(^+\)-K\(^+\)-ase (sodium pump) which creates the high ion concentration gradients.

Possibly the most complicated of all neurotransmitter receptors is the NMDA glutamate receptor. N-Methyl-D-Aspartate is a synthetic chemical not naturally found in biological systems but it binds specifically to the NMDA glutamate receptor. The NMDA receptor is the only known receptor which is regulated both by a ligand (glutamate) and by voltage. There are at least 5 binding sites which regulate NMDA receptor activity i.e. sites for (1) glutamate (2) glycine (3) magnesium (4) zinc and (5) a site that binds the hallucinogenic substance phenecyclidine (PCP).

NMDA receptors have a capacity for an activity-dependent increase in synaptic efficiency known as LTP (Long-Term Potentiation), which may be crucial to some forms of learning & memory. Inhibition of NMDA activity (and LTP) is believed to be an important part of the way ethanol affects brain functions.

NMDA receptors are most densely concentrated in the cerebral cortex (hippocampus, particularly the CA1 region), amygdala, & basal ganglia.

Glutamate released into synapses is either reabsorbed directly into neurons by the ion-exchange transport system described above, or is soaked-up by astrocytes (glial cells) which convert the glutamate into glutamine (a molecule which cannot cause excitotoxicity). The glutamine can then be safely transported back to neurons for re-conversion into glutamate.

4. GAMMA AMINO BUTYRIC ACID (GABA)

GABA is the major inhibitory neurotransmitter of the brain, occurring in 30-40% of all synapses (second only to glutamate as a major brain neurotransmitter). It is most highly concentrated in the substantia nigra & globus pallidus nuclei of the basal ganglia, followed by the hypothalamus, the periaqueductal grey matter ("central grey") and the hippocampus.
Fig 2.6 Molecular structure of GABA along with binding sites for different ligands

5. ACETYLCHOLINE

Acetylcholine was the first neurotransmitter discovered and is the major neurotransmitter in the peripheral nervous system. Acetylcholine is usually (but not always) an excitatory neurotransmitter in contrast to the monoamine neurotransmitters, which are nearly always (with a few exceptions) inhibitory. Acetylcholine in the brain is produced from acetyl-CoA, resulting from glucose metabolism, and from choline, which is actively transported across the blood-brain barrier. Most dietary choline comes from phosphatidyl choline, the major phospholipid in the membranes of plants & animals (but not bacteria). The acetyl-CoA & choline are independently synthesized in the neuron cell...
body and independently transported along the axon to the synapse where they are conjugated into acetylcholine.

There are relatively few cholinergic neurons in the brain with their distribution being "spotty" in contrast to the monoamines which have distinct midbrain nuclei serving as the major sources of brain innervation. Most brain cholinergic receptors are muscarinic, which may make sense insofar as only second-messenger controlled receptors are capable of synaptic plasticity. The site of greatest acetylcholine synthesis in the brain is the interpeduncular nucleus (located near the substantia nigra in the midbrain). All of the interneurons in the striatum (caudate nucleus & putamen of the basal ganglia) and the nucleus accumbens are cholinergic. The septum provides cholinergic fibers to the septo-hippocampal tract. The primary cholinergic input to the cerebral cortex comes from the basal nucleus of Meynert, which is the most prominent structure in the substantia innominata (ventral to the anterior half of the globus pallidus, and adjacent to the hypothalamus). Meynert's nucleus also innervates the basolateral amygdala, the basal ganglia and the reticular nucleus of the thalamus. Cholinergic input from the basal nucleus to the cerebral cortex is active in both the waking state and in REM sleep, but is reduced in non-REM sleep.

6. Dopamine

Dopamine & epinephrine are primarily inhibitory neurotransmitters that produce arousal. This may sound paradoxical, but the most likely explanation for this effect is that the postsynaptic cells for catecholamines themselves are inhibitory. There are 3-4 times more dopaminergic cells in the CNS than adrenergic cells. Dopamine in the caudate nucleus facilitates posture, whereas dopamine in the nucleus accumbens is associated with an animal's speed (and pleasure).

There are two primary dopamine receptor-types: D₁ (stimulatory) and D₂ (inhibitory), both of which act through G-proteins. D₂ receptors often occur on the dopaminergic neurons partially for the purpose of providing negative feedback. These so-called autoreceptors can inhibit both dopamine synthesis and release.
The binding of dopamine to D₁-receptors stimulates the activity of Adenylyl Cyclase (AC), which converts ATP to cyclic AMP (cAMP), a second messenger which binds to Protein Kinase A (PKA). PKA then modulates the activity of various proteins by the addition of phosphate.

There are 4 main dopaminergic tracts in the brain:

1. **nigrostriatal tract** from the substantia nigra to the striatum which accounts for most of the brain's dopamine.

2. **tuberoinfundibular tract** from the arcuate nucleus of the hypothalamus to the pituitary stalk which has a controlling effect on the release of the hormones prolactin through tonic inhibition via D₂ receptors.

3. **mesolimbic tract** from the ventral tegmental area to many parts of the limbic system and

4. **mesocortical tract** from the ventral tegmental area to the neocortex, particularly the prefrontal area. Dopamine cells project topographically to the areas they innervate.

The darkly pigmented neurons in the **pars compacta** of the substantia nigra accounts for 80% of the dopamine in the brain. The dark pigment **neuromelanin** is a dopamine polymer that makes the substantia nigra appear black. Motor control in the striatum (caudate nucleus and putamen) is thought to involve a balance between inhibitory dopaminergic (D₂) and excitatory cholinergic neurons.

The mesolimbic & mesocortical dopaminergic systems are thought to play an important role in **motivation**, by attaching cognition of incentive significance to stimuli. In experiments on animals that are motivated to electrically self-stimulate themselves with electrodes implanted in their brains, dopamine is the mediating neurotransmitter for the locus ceruleus, lateral hypothalamus, ventral tegmental area and sulcal prefrontal cortex (but not the nucleus accumbens or substantia nigra).
7. NOREPINEPHRINE (NORADRENALINE)

Norepinephrine (along with acetylcholine) is one of the two neurotransmitters in the peripheral nervous system. Norepinephrine is synthesized from dopamine by means of the enzyme Dopamine Beta-Hydroxylase (DBH), with oxygen, copper and Vitamin C as co-factors. Dopamine is synthesized in the cytoplasm, but norepinephrine is synthesized in the neurotransmitter storage vesicles.

![Noradrenergic pathway and areas innervated by it](image)

The most prominent noradrenergic (ie, norepinephrine-containing) nucleus is the locus ceruleus in the pons, which account for over 40% of noradrenergic neurons in the rat brain. Most of the other noradrenergic neurons are clustered in a region described as the lateral tegmental area. The neocortex, hippocampus, and cerebellum receive noradrenergic stimulation exclusively from the locus ceruleus. Most of the dopaminergic innervation of the hypothalamus comes from the lateral tegmental nuclei.

Electrical stimulation of the locus ceruleus produces a state of heightened arousal. The noradrenergic system is most active in the awake state and it seems to be important
for focussed attention, in contrast to the motor arousal of dopamine. Although the locus ceruleus has been identified as a pleasure center, it also seems to contribute to anxiety. Increased neuronal activity of the locus ceruleus is responsible for the occurrence of unexpected sensory events. Brain norepinephrine turnover is increased in conditions of stress.

8. SEROTONIN (5-HYDROXYTRYPTAMINE, 5-HT)

Only 1-2% of the serotonin in the body is in the brain, insofar as serotonin is widely distributed in platelets, mast cells, etc. But there is no equilibration between body serotonin and brain serotonin. Serotonin in the brain is independently synthesized from tryptophan transported across the blood-brain barrier.

Fig—2.8 Serotonergic pathway and areas innervated by it
The richest concentration of serotonin in the body can be found in the pineal body, even though this gland does not use serotonin as a transmitter. Instead, serotonin is primarily used for synthesis of melatonin, so-called because it can darken the skin of amphibians ('melas' is Greek for 'black') -- although it has also been reported to induce pigment lightening in cells.

Serotonin neurotransmitter neurons are located in the raphe nuclei. The caudal (closer to the "tail") nucleus projects largely to the medulla and spinal cord for the regulation of pain perception. The rostral (closer to the "beak") nucleus projects extensively to the limbic structures and the cerebral cortex. In the limbic system, especially, the projections are co-localized with norepinephrine receptors and the two transmitters seem to work in conjunction in the regulation of arousal.

The Supra Chiasmatic Nucleus (SCN) of the hypothalamus regulates the mammalian circadian clock ("day-night cycles"), partially in response to light. Melatonin release is inhibited as a result of the response of the SCN to light. The SCN is richly innervated by serotonergic input from the dorsal raphe nucleus. Serotonin inhibits the responsiveness of the SCN (and thus the circadian rhythm) to light. Sleep deprivation increases serotonin release in the SCN. Depletion of serotonin is believed to be related to the disruption of the circadian rhythm associated with senescence.

Serotonin seems to have distinctive actions contributing to anxiety and impulsive behavior. Patients with evidence of low serotonin levels have attempted suicide. This may explain some of the therapeutic effects of fluoxetine, which selectively prevents the re-uptake of serotonin. Fluoxetine is also distinctive because it has a half-life of about four days. Fluoxetine has been used therapeutically for panic, obsessive-compulsive and eating disorders (such as bulimia). Unlike the tricyclic anti-depressants which often stimulate appetite, fluoxetine more often reduces appetite. Fluoxetine may even enhance learning.

9. PEPTIDES

Peptides are the most common neurotransmitters in the hypothalamus. Their complex structure can allow for high receptor specificity. They are all synthesized on
ribosomes and are all inactivated by hydrolysis at the synapse (rather than by re-uptake). Peptides are far more potent than other neurotransmitters, requiring only very small amounts to produce a profound effect. Even very minute amounts of somatostatin can inhibit growth hormone release.

**Opioid peptides** include the endorphins, enkephalins and dynorphins. Enkephalins are frequently found in presynaptic (axo-axonic) synapses. Opiates and enkephalins (or endorphins) inhibit the firing of locus ceruleus neurons. The highest concentration of opioid receptors are found in the sensory, limbic and hypothalamic regions of the brain -- and are particularly high in the amygdala & periaqueductal grey area. Opioids tend to be released as slower-acting co-transmitters which modulate the action of the associated neurotransmitter (such as glutamate) which is being released from the same synapse. Although opioids are generally inhibitory, they have an excitatory effect on hippocampal pyrimidal neurons mediated by inhibition of GABA release.

**Cholecystokinin (CCK)** seems to function in the production of satiety. Injection of small quantities of this peptide into the ventricles or the paraventricular nucleus can inhibit feeding. CCK is associated with dopamine synapses in some limbic areas, and appears to modulate dopamine release. Such peptide synergy with other transmitters is common. For example, GABA is often associated with somatostatin and serotonin with Substance P.

Low doses of the **peptide vasopressin** have been shown to enhance learning in laboratory animals. However, humans with vasopressin deficiency show no signs of memory impairment. Because vasopressin is potent in increasing blood pressure, its use by humans should be approached with caution. Safer analogues may yet be found.
2.4 INTRODUCTION TO ANXIETY

Anxiety is a universal feeling state that is a part of the everyday human life. Feelings of anxiety and fear are often unpleasant emotions commonly caused by the perception of potential danger that threatens the security of the individual, somatic and autonomic effects, restlessness and agitation, tachycardia, sweating, gastrointestinal disorders, sleep disturbance etc., interference with normal productive activities (Rang et al, 2005). However, the distinction between a pathological & normal state of anxiety is hard to draw.

2.4.1 DSM – IV classification of Anxiety disorders

1. Generalised Anxiety disorder
2. Panic Disorder
   a. With agoraphobia (An unexplained fear of open spaces)
   b. Without agoraphobia
3. Agoraphobia without a history of panic disorder
4. Phobic disorders
   a. Social Phobia
   b. Specific Phobia
5. Obsessive-compulsive disorder
6. Post-traumatic stress disorder
7. Acute stress disorder (Dipiro, et al.)

1. GENERALISED ANXIETY DISORDER

Generalised anxiety disorder (GAD) involves a broad presentation of anxiety. The pattern of symptoms will vary from patient to patient. But typical symptoms include restlessness, fatigue, difficulty in concentrating, irritability, muscle tension and sleep disturbances (Jack, et al.). GAD is characterized by excessive, exaggerated anxiety and worry about everyday life events. People with GAD tend to always expect disaster and can't stop worrying about health, money, family, work or school. In people with GAD, the worry often is unrealistic or out of proportion for the situation. Daily life becomes a constant state of worry, fear and dread. Eventually, the anxiety so dominates the person’s thinking that it interferes with daily functioning, including work, school, social activities and relationships.
2. PANIC ATTACKS

Can be associated in many anxiety disorders, typically lasting a few minutes with symptoms such as more forceful heart action, trembling, shortness of breath, chest pain, abdominal distress, dizziness and fear on the part of the patient that "He" or "She" is going crazy" or will die.

3. PHOBIC DISORDER

Specific phobia involves excessive fear that is used by specific stimulation, such as heights, enclosed places or other situations. The phobic individual may experience full panic attacks when exposed to such stimuli. Social Phobia is a marked & persistent fear of social situations.

4. OBSESSIVE – COMPULSIVE DISORDER

It is particularly important form of anxiety disorder. Obsessions include recurrent thoughts that may not be about real-life problems and which the person fails to ignore or suppress. Compulsions are repetitive behaviors that the person feels driven to perform in response to an obsession. The compulsive behaviors attempt to reduce the distress from the obsessions.

5. POST-TRAUMATIC STRESS DISORDER

Stems from which serious threat to oneself or another with response to fear or horror. Patients have persistent symptoms of increased arousal, including difficulty in sleeping, irritability, difficulty in concentrating, hyper vigilance etc. The disorder can continue for a sustained period of time with marked impairment in functioning.
2.4.2 PREVALENCE

About 4 million adult Americans suffer from GAD. It is more common in women than in men. Phobia is the most commonly seen anxiety disorder, and 49.5% of people reporting an unreasonably strong fear and 22.7% of those people meeting criteria for simple phobia. Social anxiety disorder is the next most common disorder of anxiety, with 13.3% of people reporting symptoms, which meet the DSM criteria. PTSD which is often unrecognized afflicts approximately 7.8% of the overall population and 12% of women, in whom it is significantly more common. Surprisingly, disorders that are more commonly recognized, such as GAD and PD, have lower lifetime prevalence rates of 4.1-6.6% and 1.5% respectively. Of the panic sufferers, 40% also meet criteria for agoraphobia. Another often under-diagnosed disorder, OCD, is found in 2.5% of the population.

2.4.3 PATHOPHYSIOLOGY

Definitive pathophysiological mechanisms have not yet been determined; anxiety symptoms and the resulting disorders are thought to be due to disrupted modulation within the central nervous system. Physical and emotional manifestations of this dysregulation are the result of heightened sympathetic arousal of varying degrees. Several neurotransmitter systems have been implicated to have a role in one or several of the modulatory steps involved. The most commonly considered are the serotonergic and noradrenergic neurotransmitter systems.

In very general terms, it is thought that an under activation of the serotonergic system and an over activation of the noradrenergic system are involved. These systems regulate and are regulated by other pathways and neuronal circuits in various regions of the brain, resulting in dysregulation of physiological arousal and the emotional experience of this arousal. Disruption of the γ-amino butyric acid (GABA) system has also been implicated because of the response of many of the anxiety spectrum disorders to treatment with benzodiazepines. More recently there has been some interest in the role of corticosteroid regulation and its relationship to symptoms of fear and anxiety. Corticosteroids may increase or decrease the activity of certain neural pathways, affecting
not only behavior under stress, but also the brain's processing of fear inducing stimuli. Many studies indicate that a genetic predisposition in developing an anxiety disorder is likely. However, environmental stressors clearly play a role, to varying degrees and all of the disorders are affected in some way by external causes (see also figs. 2.9, 2.10, 2.11). Adopted from American College of Neuropsychophiology, 5th generation).
Fig 2.9 Innervation of parasympathetic nervous system from limbic structures is thought to mediate visceral symptoms associated with anxiety.
Fig 2.10 Schematic diagram of the outputs of the basolateral amygdala to various target areas and how these connections may be involved in fear and anxiety.

Fig 2.11 Schematic diagram of the outputs of the central nucleus of the amygdala and the lateral division of the bed nucleus of the stria terminalis to various target areas and how these connections may be related to specific aspects of fear and anxiety.

BNST, bed nucleus of the stria terminalis; CER, conditioned emotional response; EEG, electroencephlographic; N, nucleus.
2.4.4 Signs and symptoms

GAD affects the way a person thinks, but the anxiety can lead to physical symptoms as well which include, excessive, ongoing worry and tension, an unrealistic view of problems, Restlessness or a feeling of being uneasy, irritability, muscle tension, headaches, sweating, difficulty in concentrating, nausea, incontinence, tiredness, Trouble falling or staying asleep. Trembling, Being easily startled.

In addition, people with GAD often have other anxiety disorders (such as PD, OCD and phobias), suffer from depression, and/or abuse drugs or alcohol.

A subjective experience of distress with accompanying disturbances of sleep, concentration, social and/or occupational functioning are common symptoms in many of the anxiety disorders. Despite their similarities these disorders often differ in presentation, course and treatment. Patients often present with complaints of poor physical health as their primary concern. This may temporarily distract from the underlying anxiety symptoms. This is particularly common in panic disorder, which is characterized by a short period of intense fear and a sense of impending doom, with accompanying physical symptoms, such as chest pain, dizziness and shortness of breath. Very often these patients will first present to an emergency department. When complicated by agoraphobia, the individual fears having a panic attack in a place that prevents escape. This results in the patient avoiding such situations, with subsequent disturbances in functioning.GAD rarely occurs without a co-morbid psychiatric disorder with the patient experiencing consistent worry over multiple areas of his or her life for at least 6months.

SAD describes fear and anxiety in social situations leading to avoidance of social interaction. Specific phobia is characterized by similar symptoms and behavior but is triggered by a specific object or situation such as a fear of certain animals or heights.

PTSD and acute stress disorder occur after a patient experiences a traumatic event with subsequent physiological arousal in the face of stimuli that trigger memories of the event, avoidance of such stimuli; and a sense of re-experiencing the event. The later occurs in the short term, while the former describe a more chronic version of the disorder.
Finally OCD is characterized by repeated behaviors (compulsions), which serve to reduce anxiety connected to unwanted and intrusive thoughts (obsessions). Commonly seen behaviors are cleaning or washing in response to concerns about contamination, or repeatedly checking to see if a stove is turned off in response to concerns over a fire starting. Some people repeatedly check work or seek excessive reassurance due to obsessive self-doubt.

2.5.5 Causes of Generalized Anxiety Disorder

The exact cause of GAD is not fully known, but a number of factors -- including genetics, brain chemistry and environmental stresses -- appear to contribute to its development.

Genetics

Family history plays a part in increasing the likelihood that a person will develop GAD. This means that the tendency to develop GAD may be passed on in families.

Brain chemistry

GAD has been associated with abnormal levels of certain neurotransmitters in the brain. If the neurotransmitters are out of balance, messages cannot get through the brain properly. This can alter the way the brain reacts in certain situations, leading to anxiety.

Environmental factors

Trauma and stressful events, such as abuse, the death of a loved one, divorce, changing jobs or schools, may lead to GAD. GAD also may become worse during periods of stress. The use of and withdrawal from addictive substances, including alcohol, caffeine and nicotine, can also worsen anxiety.
2.4.6 Diagnosis

In order for a patient with symptoms of anxiety to be diagnosed with one of the disorders, DSM-IV criteria should be met. Diagnosis is often complicated by frequent comorbidity with other psychiatric disorders.

➤ In GAD, 60% of sufferers have a co-morbid condition, with PD and major depressive disorder being the most common. Panic disorder (PD) is often co-morbid with alcohol abuse, with an increased risk for suicide. Agoraphobia is commonly connected to panic disorder with comorbidity rates approaching 40%. Many of these disorders have overlapping signs and symptoms, requiring the clinician to explore several lines of questioning to clarify the primary diagnosis.

➤ Important in the diagnosis of post traumatic stress disorder (PTSD) is identifying a history of trauma and being sure to ask questions related to avoidance, re-experiencing and physiological arousal in the face of triggering stimuli. The symptoms of PTSD may be misconstrued for depression, other anxiety disorders and/or dysfunctional personality traits. Patients may not be able to identify a connection between the symptoms and the history of trauma, requiring that the clinician be sensitive to the possibility that a trauma history exists. If the patient presents with complaints within 4 weeks of the trauma (with resolution within 4 weeks of symptom onset) then acute stress disorder should be the diagnosis.

➤ Patients with OCD are often secretive regarding their symptoms. These are secondary to feelings of shame and a sense of isolation. Many are not aware that others suffer from the same constellation of thoughts and behavior. Questions should explore whether certain routines are related to specific fears, thoughts and/or images. OCD is often co-morbid with major depressive disorder (in 2/3 of patients overlifetime) and panic attacks, with rates up to 60%. One must also distinguish between OCD and obsessive-compulsive personality disorder (OCPD). Although 25% of patients suffering from OCD also suffer from OCPD, the two can present very differently. Interestingly, if the source of compulsive behavior is kept secret, a patient with OCD can sometimes appear to be suffering from psychosis.
➤ The treatment strategy for psychosis differs markedly, making it very important to distinguish between the two when presented with bizarre behavior. Questions should differentiate between "voices" and intrusive thoughts.

➤ The patient suffering from OCD knows his or her thoughts and actions are irrational. The symptoms of SAD can also be confused with psychosis. One must distinguish between paranoia and the fear of being evaluated.

➤ Those suffering from SAD desire social interaction, but avoid it in order to reduce anxiety. When diagnosing specific phobia, the clinician should remember that the majority of patients who meet the criteria have more than one fear-inducing object or situation. Central to the diagnosis of any of the anxiety disorders is a good history, often requiring collateral from friends and family.

➤ One must also rule out any medical disorders, which may be causing the distress (eg, hyperthyroidism, pheochromocytoma), as well as substance abuse or dependence. It is important to note, however, that anxiety disorders are common and finding an underlying medical cause is unusual. Finally, the symptoms must result in a deficit in social and/or occupational functioning.
2.4.7 Prevention of Generalized Anxiety Disorder

Anxiety disorders cannot be prevented. However, there are some things that can be done to control or lessen symptoms, like

- Stopping or reducing consumption of products containing caffeine, such as coffee, tea, cola and chocolate.
- Consult the doctor or pharmacist before taking any over-the-counter medicines or herbal remedies. Many contain chemicals that can increase anxiety symptoms.
- Exercise daily and eat a healthy, balanced diet.
- Seek counseling and support after a traumatic or disturbing experience.

2.4.8 Flow chart for Assessment of Anxiety disorders
2.4.9 Biological basis of anxiety

The anxiety disorders are primarily biologic illnesses associated with underlying genetic vulnerability. Anxiety may not reflect an imbalance in single neurotransmitters including NE, GABA & 5HT.

2.4.9.1 NORADRENERGIC MODEL

The basic premise of the noradrenergic theory is that, the ANS of anxiety patients in hypersensitive clearly display symptoms of peripheral autonomic hyperactivity like hyperventilation, palpitation and tremulousness. The locus coeruleus (LC), a mid brain nucleus, may play a major role in regulating anxiety. The LC contains neurons that supply 50-70% of the brains NE with widespread projections to many brain areas. In response to anxiety or fearful situations the LC serves as an alarm centre activating NE release and stimulating the sympathetic nervous system. The presynaptic \( \alpha_2 \) adrenergic auto receptor plays a significant role in controlling the release of NE from the synapse. Chronic central noradrenergic over activity down regulates \( \alpha_2 \) auto receptor in GAD patients. This receptor may also be abnormal in some patients with panic disorders. Drugs with anxiolytic or antipanic effects (eg. Benzodiazepine, Antidepressants and clonidine) inhibit LC firing thereby decreasing noradrenergic activity and block the effects of anxiogenic drugs.

2.4.9.2 BENZODIAZEPINE RECEPTOR MODEL

The BZ receptor is functionally linked to the GABA type A (GABA\(_A\)) receptor and a chloride ion channel. This is referred to as the supra molecular receptor complex.

GABA is the major inhibitory neurotransmitter in the CNS. In addition, the GABA system has a strong regulatory or inhibitory effect on the 5HT & NE systems. When GABA binds to its receptor, the adjacent chloride ion channels open and permits the influx of negatively charged chloride ions. This results in hyper polarization of the cell membrane and causes a decrease in nerve cell excitability when BZs bind to their receptor. GABA’s inhibitory effects are potentiated via an increase in the frequency of chloride ion
channel openings. Benzodiazepines in the absence of GABA have little effect on the nerve cell excitability.

The therapeutic effects of Benzodiazepine (Anxiolytic, Anticonvulsant, Sedative and Muscle relaxant actions) are mediated through the GABA<sub>A</sub> receptor and also enhance GABA effects.

2.4.9.3 SEROTONIN MODEL

In general pharmacological manipulations that enhance serotonin also enhance anxiety, whereas reduced serotonin may also reduce anxiety. This is essentially the opposite of depression.

5HT is an inhibitory neurotransmitter, its origin is in the raphe nuclei of the brain stem and 5HT functions are regulated by eight different receptor sub types. Azapirone and Buspirone are selective 5HT<sub>1A</sub> partial agonists reduce serotonergic activity, 5HT reuptake inhibitors are effective in antipanic compounds.

**FIG 2.12** Modulation of excitatory and inhibitory transmission by multiple 5-hydroxytryptamine (5-HT) receptors in the cerebral cortex. (Adopted from American College of Neuropsychophiology, 5th generation).
5-HT$_{2A}$ receptors are depicted as enhancing glutamate release from a glutamatergic terminal onto a layer V pyramidal cell; the same terminal is seen to be negatively modulated by various Gi/Go-coupled receptors (e.g. μ-opiate, 5-HT$_{1B}$, and mGluR II/III). In addition, 5-HT$_{2A}$ receptors are shown to have a direct postsynaptic excitatory effect that is opposed by postsynaptic 5-HT$_{1A}$ receptors. Finally, 5-HT$_2$ and 5-HT$_3$ receptors are shown on anatomically distinct GABAergic inputs to the somatobasilar and apical regions, respectively, of the pyramidal cell.

**FIG 2.13** Schematic representation of local regulatory circuitry within the dorsal raphe nucleus (DRN).

In addition to somatodendritic 5-HT$_{1A}$ autoreceptors on the 5-HT neurons per se, local GABAergic and glutamatergic neurons in the DRN/ventral periaqueductal gray (PAG) region modulate the activity of serotonergic neurons (Reproduced from American college of Neuropsychopharmacology, 5th generation).

**Note**

The location of inhibitory opiate receptors on both categories of local neurons. Also depicted are excitatory 5-HT$_{2A/3C}$ and inhibitory 5-HT$_{1A}$ receptors on GABAergic neurons and excitatory NK1 (substance P) and NK3 (neurokinin B) receptors on glutamate neurons in the DRN/PAG.
2.4.10 CLASSIFICATION OF ANXIOLYTICS DRUGS BASED ON TYPES OF DSM-IV DISORDERS

Anxiolytic drugs are among the most frequently used by upwards 10% of the population in developed countries.

1. Generalised Anxiety Disorder (GAD) → Benzodiazepine, Tricyclic antidepressant, Buspirone, Trazdone. B-Blockers

2. Panic disorders (PD) → Tricyclic antidepressant, Selective serotonin reuptake Inhibitor, Monoamine oxidase inhibitor, Benzodiazepines.

3. Obsessive-Compulsive disorders (OCD) → Clomipramine or SSRI MAOI, Buspirone Clonazepam, Fenfluramine

4. Post-Traumatic Stress disorder (PSTD) → TCA, SSRI, Trazadone, MAOI (Phenelzine), Carbomazepine, Valproic acid, Alaprazolam, Clonidine, β - Blockers or Benzodiazepine.

5. Phobic Disorder → β - Blockers, Benzodiazepine. SSRI, Buspirone, MAOI, Herfindal, et al.,

2.4.10 THERAPY

An important part of any intervention with a patient with an anxiety disorder is education. The practice guidelines for PD recommend education of the family as well. Many people are confused by the symptoms and behavior and are reassured to know they are not alone and that there are effective interventions. The patient should receive appropriate medical work-up, such as a physical exam, and studies (e.g., EKG, TSH) when indicated. After ruling out a medical condition, developing a working alliance with the patient will provide a basis for ongoing management, and prevent further inappropriate utilization of the medical system. A combination of psychotherapy and medication management is recommended in all of the anxiety disorders.

Cognitive behavioral therapy (CBT) has the strongest support of all the psychotherapies, but requires commitment to treatment on the part of the patient. Its efficacy is also contingent on the ability of the therapist and the length of therapy, with a 78% response rate in PD patients who have committed to 12-15 weeks of therapy. While
therapy has the advantage of no physical side effects, some studies have found that CBT alone is inferior to medication alone, while others have shown that CBT alone has similar efficacy when compared to medication. The selective serotonin reuptake inhibitors (SSRIs) have been shown to be the best-tolerated medications, with response rates significantly higher than placebo for PD, OCD, PTSD, SAD and GAD. This class of medication includes fluoxetine, fluvoxamine, citalopram, paroxetine and sertraline. Some improvement should be noted within 3-4 weeks, with appropriate increase of the dose if no improvement is seen. In OCD, symptoms may take 8-12 weeks of treatment to respond. These patients often require doses at the higher end of the dosage range, so one should not be hesitant to make increases. It is also rare to achieve absolute resolution of symptoms in OCD, with partial reduction being the norm. In all of the anxiety disorders, SSRIs should be started at low doses and gradually titrated up to therapeutic levels, to avoid an initial exacerbation of anxiety.

Benzodiazepines, which have been used commonly in the past to treat anxiety disorders, continue to be useful in the short-term management of symptoms until an acceptable reduction of symptoms is achieved with an SSRI and/or CBT. The tolerability and lack of addiction potential make the SSRIs more desirable for long-term management, but the delay in response makes short-term symptom relief with abenzodiazepine desirable to those with the greatest impairment. Because of the risk for rebound anxiety on short half-life benzodiazepines, such as alprazolam (Xanax), many psychiatrists prefer the longer-acting benzodiazepines, such as clonazepam (Klonopin).

If a lack of response to the combination of CBT and medication occurs, a re-evaluation of symptoms may reveal a co-morbid disorder missed on the first exam. Many clinicians will try switching between SSRIs before considering the next step in treatment. Finally, a referral to a psychiatrist for further evaluation and management may be necessary if none of these strategies work. Treatment-refractory anxiety can be extremely frustrating for both patient and clinician. This can lead to increased dependence on benzodiazepines, and an escalation of doses required for the same effect.
In addition, relaxation techniques, such as deep breathing and biofeedback, may help to control the muscle tension that often accompanies GAD.

Complications of Treatment

Dependency on anti-anxiety medications (benzodiazepines) is a potential complication of treatment. Other side effects of medications include sleepiness and sexual problems.
2.5 INTRODUCTION TO DEPRESSION

Depression is considered as an affective disorder, characterised primarily by change of mood (depression and mania) rather than thought disturbances.

Depression is a common disorder associated with significant morbidity and morality. The prevalence of major depression in the general population is estimated at 5% (Blazer, et al., 1999). In medical patients, the prevalence ranges from 9% in ambulatory setting to as high as 30% in hospitalized patients (Katon and Sullivan, 1990). More specifically, major depression occurs in approximately 20% of patients with coronary artery disease (Schleifer, et al., 1989) and in 24% of patients after a stroke (Robinson, et al., 1984).

The most important point to be considered in depressed patient is suicidal tendencies. 20-40% of patients with an affective disorder exhibit non-fatal suicidal behaviors, including thoughts of suicide. Estimates associate 16000 suicides in the US annually depressive disorder. 15% of those hospitalized for major depressive disorder attempt suicide (Stahl, 1998).

2.5.1 Signs and symptoms

The symptoms of depression include emotional and biological components.

1. Emotional Symptoms:
   - Misery, apathy and pessimism.
   - Low esteem, feeling of guilt, inadequacy and ugliness.
   - Indecisiveness and loss of motivation.

2. Biological Symptoms:
   - Retardation of thought and action.
   - Loss of Libido.
   - Sleep disturbances and loss of appetite.

Mania in most aspects is exactly opposite, with excessive exuberance, enthusiasm and self-confidence, accompanied by impulsive action. These signs are often being combined with mania (Rang, et al., 1999).
2.5.2 Prevalence

Clinical depression affects about 7% - 18% of the population on at least one occasion in their lives, before the age of 40. In some countries, such as Australia, one in four women and one in six men will suffer from depression. The mean age of onset, from a number of studies, is in the late 20s. About twice as many females as males report or receive treatment for clinical depression, due to stress and adversity, though this imbalance is shrinking over the course of recent history; this difference seems to completely disappear after the age of 50-55.

According to the World Health Organization clinical depression is currently the leading cause of disability in North America as well as other countries, and is expected to become the second leading cause of disability worldwide (after heart disease) by the year 2020.

2.5.3 Types of depression

The diagnostic category major depressive disorder appears in the DSMM of the American Psychiatric Association. The term is generally not used in countries which instead use the ICD-10 system, but the diagnosis of depressive episode is very similar to an episode of major depression. Clinical depression also usually refers to acute or chronic depression severe enough to need treatment. Minor depression is a less-used term for a subclinical depression that does not meet criteria for major depression but where there are at least two symptoms present for two weeks.

Major clinical depression

Major Depression, or, more properly, Major Depressive Disorder (MDD), is characterized by a severely depressed mood that persists for at least two weeks. Major Depressive Disorder is specified as either "a single episode" or "recurrent"; periods of depression may occur as discrete events or recur over the lifespan. Episodes of major or clinical depression may be further divided into mild, major or severe. Where the patient has already had an episode of mania or markedly elevated mood, a diagnosis of bipolar...
Depression with Psychotic Features

Some people with Major Depressive or Manic episode may experience psychotic features. They may be presented with hallucinations or delusions that are either mood-congruent (content coincident with depressive themes) or non-mood-congruent (content not coincident with depressive themes). It is clinically more common to encounter a delusional system as an adjunct to depression than to encounter hallucinations, whether visual or auditory.

Other categories of depression

Dysthymia is a long-term, mild depression that lasts for a minimum of two years. There must be persistent depressed mood continuously for at least two years. By definition the symptoms are not as severe as with Major Depression, although those with Dysthymia are vulnerable to co-occurring episodes of Major Depression. This disorder often begins in adolescence and crosses the lifespan. People who are diagnosed with major depressive episodes and dysthymic disorder are diagnosed with double depression. Dysthymic disorder develops first and then one or more major depressive episodes happen later.

Bipolar I Disorder is an episodic illness in which moods may cycle between mania and depression. In the United States, Bipolar Disorder was previously called Manic Depression. This term is no longer favored by the medical community, however, even though depression plays a much stronger (in terms of disability and potential for suicide) role in the disorder. "Manic Depression" is still often used in the non-medical community. Bipolar II Disorder is an episodic illness that is defined primarily by depression but evidences episodes of hypomania.

Postpartum Depression or Post-Natal Depression is clinical depression that occurs within two years of childbirth. Owing to physical, mental and emotional exhaustion combined with sleep-deprivation, motherhood can "set women up", so to speak, for clinical depression."
Premenstrual dysphoria is a pattern of recurrent depressive symptoms tied to the menstrual cycle. The premenstrual decline in brain serotonin function is strongly correlated with the concomitant worsening of self-rated cardinal mood symptoms. Of considerable clinical importance, the recent understanding of premenstrual dysphoria as depression points directly to effective treatment with Selective serotonin reuptake inhibitor (SSRI) antidepressants. Previously, disrupting ovarian cyclicity had been the only recognized treatment. A recent review of studies of a number of SSRIs has revealed that they can effectively ameliorate symptoms of premenstrual dysphoria and may actually work best when taken only during the part of the menstrual cycle when dysphoric symptoms are evident.

2.5.4 Role of biological systems in Depression

2.5.4.1 Limbic System

Those who research clinical depression have been interested in a particular part of the brain called the limbic system. This is the area of the brain that regulates activities such as emotions, physical and sexual drives, and the stress response. There are various structures of the limbic system that are of particular importance. The hypothalamus is a small structure located at the base of the brain. It is responsible for many basic functions such as body temperature, sleep, appetite, sexual drive, stress reaction, and the regulation of other activities. The hypothalamus also controls the function of the pituitary gland which in turn regulates key hormones. Other structures within the limbic system that are associated with emotional reaction are the amygdala and hippocampus. The activities of the limbic are so important and complex that disturbances in any part of it, including how neurotransmitters function, could affect mood and behavior.

2.5.4.2 Hormones and the Endocrine System

This system works with the brain to control numerous activities within the body. The endocrine system is made up of small glands within the body, which create hormones and release them into the blood. The hormones that are released into the body by the glands regulate processes such as reaction to stress and sexual development. It has been
found that a great number of people who are depressed have abnormal levels of some hormones in their blood despite having healthy glands. It is believed that such hormonal irregularities may be related to some depressive symptoms such as problems with appetite and sleeping since they play a part in these activities. Further clues to the role of the endocrine system has to do with the fact that those who have particular endocrine disorders sometimes develop depression, and some individuals who are depressed develop endocrine problems despite having healthy glands.

The endocrine system usually keeps the hormonal levels from becoming excessive through an intricate process of feedback. When a specific hormone rises to particular level the gland stops producing and releasing the hormone. When an individual is depressed this feedback process may not function as it should.

Problems with hormone levels may be intertwined with the changes in brain chemistry that are seen in clinical depression. The endocrine system is connected with the brain at the hypothalamus which controls many bodily activities such as sleep, appetite, and sexual drive. The hypothalamus also regulates the pituitary gland that, in turn, controls the hormonal secretion of other glands. The hypothalamus uses some of the neurotransmitters that have been associated with depression as it manages the endocrine system. These neurotransmitters, serotonin, norepinephrine, and dopamine all have a role in the management of hormone function.

The development of clinical depression may be a symptom of a disorder present within organs that produce hormones. Such conditions include thyroid disorders, Cushing's syndrome, and Addison's disease.

Of those individuals who are clinically depressed, about one-half will have an excess of a hormone in their blood called cortisol. Cortisol is secreted by the adrenal glands. Located near the kidneys, the adrenal glands assist in reactions to stressful events. Cortisol may continue to be secreted even though a person already has high levels in his or her blood. This hormone is believed to be related to clinical depression since the high levels usually reduce to a normal level once the depression disappears.
The hypothalamus may be the culprit when it comes to excessive levels of cortisol in the blood. It is responsible for starting the process that leads to the secretion of cortisol by the adrenal glands. The hypothalamus first manufactures corticotrophic-releasing hormone (CRH) which stimulates pituitary gland to release adrenocorticotropic hormone (ACTH). This hormone then makes the adrenal glands secret cortisol in the blood. When the endocrine system is functioning properly, the hypothalamus monitors the level of cortisol that is in the blood. When the level rises, the hypothalamus slows down its influence on the pituitary gland in production of CRH. When cortisol levels become reduced, the hypothalamus causes the pituitary gland to produce more CRH. In a person who is depressed, the hypothalamus may continuously influence the pituitary to produce CRH without regard to the amount of cortisol that is in the blood.

Other research concerning cortisol has shown that the timing of the release of this hormone may be problematic in those who are depressed. People who are not depressed tend to have secretions of cortisol at certain times of the day. Cortisol levels are highest at approximately 8:00 a.m. and 4:00 p.m., and then lowest during the night. This normal cycling of cortisol levels does not occur in some people who are depressed. For instance, they might have a consistent level of cortisol all the time, or highest amounts in the middle of the night.

Cortisol levels can be tested using something called a dexamethasone suppression test (DST). This is not a test for depression since some people who are depressed may not be identified by the results of the test, but it can be used to confirm a diagnosis of depression in some people. This test involves giving a dose of dexamethasone, a synthetic cortisol, to an individual before he or she goes to sleep at night. At 8:00 a.m. the next morning, the person's blood is tested for cortisol. It is tested again at 4:00 p.m. In healthy individuals cortisol levels drop at first, but then return to normal as the hypothalamus compensates for the dexamethasone in the blood. In those who are severely depressed, approximately one-half will have abnormal results. Cortisol secretion may not be reduced by the hypothalamus, or there may be no change at all after receiving the synthetic cortisol.
2.5.4.3 The role of anxiety in depression

The different types of Depression and Anxiety are classified separately by the DSM-IV-TR, with the exception of hypomania, which is included in the bipolar disorder category. Despite the different categories, depression and anxiety can indeed be co-occurring (occurring together, independently, and without mood congruence), or comorbid (occurring together, with overlapping symptoms, and with mood congruence). Although there is no specific diagnostic category for the comorbidity of depression and anxiety in the DSM or ICD, the National Comorbidity Survey (US) reports that 58 percent of those with major depression also suffer from lifetime anxiety. Supporting this finding, two widely accepted clinical colloquialisms include

- agitated depression - a state of depression that presents as anxiety and includes akathisia, suicide, insomnia (not early morning wakefulness), nonclinical (meaning "doesn't meet the standard for formal diagnosis") and nonspecific panic, and a general sense of dread.

- akathitic depression - a state of depression that presents as anxiety or suicidality and includes akathisia but does not include symptoms of panic.

It is also clear that even mild anxiety symptoms can have a major impact on the course of a depressive illness, and the comingling of any anxiety symptoms with the primary depression is important to consider.

2.5.5 Causes of clinical depression

The theories regarding the causes of clinical depression can be broadly classified into two categories

Organic and

Sociopsychologicl causes
Organic causes

Heredity

The tendency to develop depression may be inherited; there is some evidence that this disorder may run in families, though biological and environmental factors may both be responsible. A 2004 press release from the National Institute of Mental Health declares "major depression is thought to be 40–70 percent inheritable, but likely involves an interaction of several genes with environmental events".

Neurotransmitters allow electrical signals to move from the axon of one nerve cell to the neuron of another. A shortage of neurotransmitters impairs brain communication.

Physiology

Many modern antidepressant drugs change levels of certain neurotransmitters, such as serotonin, which stimulates neurogenesis (the production of nerves), and norepinephrine (noradrenaline). However, the relationship between serotonin, SSRIs, and depression usually is typically greatly oversimplified when presented to the public, and is not supported by the evidence, but may instead involve changes in neural plasticity. Recent research has suggested that there may be a link between depression and neurogenesis of the hippocampus. This horse shoe-shaped structure is a center for both mood and memory. Loss of neurons in the hippocampus is found in depression and correlates with impaired memory and dysthemic mood. That is why treatment usually results in the increase levels of serotonin in the brain which would in turn stimulate neurogenesis and therefore increase the total mass of the Hippocampus and restores mood and memory, therefore assisting in the fight against the mood disorder.

Seasonal affective disorder

- Seasonal affective disorder (SAD) is a type of depressive disorder that occurs in the winter when daylight hours are short. It is believed that the body's production of melatonin, which is produced at higher levels in the dark, plays a major part in the onset of
SAD and that many sufferers respond well to bright light therapy, also known as phototherapy.

**Medical conditions**

Certain illnesses, including cardiovascular disease, hepatitis, mononucleosis, hypothyroidism, and organic brain damage caused by degenerative conditions such as Parkinson disease, Multiple Sclerosis or by traumatic blunt force injury may contribute to depression, as may certain prescription drugs such as hormonal contraception methods and steroids. Gender dysphoria can also cause depression.

**Diet**

The increase in depression in industrialised societies has been linked to diet, particularly to reduced levels of omega-3 fatty acids in intensively farmed food and processed foods. This link has been at least partly validated by studies using dietary supplements in schools and by a double-blind test in a prison. An excess of omega-6 fatty acids in the diet was shown to cause depression in rats.

**Alcohol and other drugs**

Alcohol can have a negative effect on mood, and misuse of alcohol, benzodiazepine-based tranquilizers, and sleeping medications can all play a major role in the length and severity of depression.

**Sociopsychological causes**

**Psychological factors**

Low self-esteem and self-defeating or distorted thinking are connected with depression. Although it is not clear which is the cause and which is the effect, it is known that depressed persons who are able to make corrections in their thinking patterns can show improved mood and self-esteem (Cognitive Behavioral Therapy). Psychological
factors related to depression include the complex development of one's personality and how one has learned to cope with external environmental factors such as stress.

*Early experiences*

Events such as the death of a parent, abandonment or rejection, neglect, chronic illness, and physical, psychological, or sexual abuse can also increase the likelihood of depression later in life. Post-traumatic stress disorder (PTSD) includes depression as one of its major symptoms.

*Life experiences*

Job loss, poverty, financial difficulties, gambling addiction, long periods of unemployment, the loss of a spouse or other family member, rape, divorce or the end of a committed relationship, involuntary celibacy, inability to have proper sex or premature ejaculation or other traumatic events may trigger depression. Long-term stress at home, work, or school can also be involved.

2.5.6 DIAGNOSIS

It is hard for people who have not experienced clinical depression, either personally or by regular exposure to people suffering it, to understand its emotional impact and severity, interpreting it instead as being similar to "having the blues" or "feeling down." As the list of symptoms below indicates, clinical depression is a serious, potentially lethal systemic disorder characterized by the psychiatric profession as interlocking physical, affective, and cognitive symptoms that have consequences for function and survival well beyond sad or painful feelings.

**DSM-IV-TR criteria for diagnosis**

According to the DSM-IV-TR criteria for diagnosing a major depressive disorder (cautionary statement) one of the following two elements must be present for a period of at least two weeks:
• Depressed mood, or
• Anhedonia

It is sufficient to have either of these symptoms in conjunction with five of a list of other symptoms over a two-week period. These include:

• Feelings of overwhelming sadness and/or fear, or the seeming inability to feel emotion (emptiness).
• A decrease in the amount of interest or pleasure in all, or almost all, daily activities.
• Changing appetite and marked weight gain or loss.
• Disturbed sleep patterns, such as insomnia, loss of REM sleep, or excessive sleep (hypersomnia).
• Psychomotor agitation or retardation nearly every day.
• Fatigue, mental or physical, also loss of energy.
• Intense feelings of guilt, nervousness, helplessness, hopelessness, worthlessness, isolation/loneliness and/or anxiety.
• Trouble concentrating, keeping focus or making decisions or a generalized slowing and obtunding of cognition, including memory.
• Recurrent thoughts of death (not just fear of dying), desire to just "lie down and die" or "stop breathing", recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
• Feeling and/or fear of being abandoned by those close to one.

Mnemonics commonly used to remember the DSM-IV criteria are SIGECAPS (sleep, interest (anhedonia), guilt, energy, concentration, appetite, psychomotor, suicidality) and DEAD SWAMP (depressed mood, energy, anhedonia, death (thoughts of), sleep, worthlessness/guilt, appetite, mentation, psychomotor).

Other symptoms

Other symptoms often reported but not usually taken into account in diagnosis include.
• Self-loathing.
• A decrease in self-esteem.
• Inattention to personal hygiene.
• Sensitivity to noise.
• Physical aches and pains, and the belief these may be signs of serious illness.
• Fear of 'going mad'.
• Change in perception of time.
• Periods of sobbing.
• Possible behavioral changes, such as aggression and/or irritability.

An additional indicator could be the excessive use of drugs or alcohol. Depressed adolescents are at particular risk of further destructive behaviours, such as eating disorders and self-harm.

Depression in children is not as obvious as it is in adults. Children may show symptoms such as:

• Loss of appetite.
• Irritability.
• Sleep problems, such as recurrent nightmares.
• Learning or memory problems where none existed before.
• Significant behavioral changes; such as withdrawal, social isolation, and aggression.

### 2.5.7 Patient Health Questionnaire

The Patient Health Questionnaire (PHQ2) is a faster, two question questionnaire that may be as sensitive as the DSM-IV[27]. “During the past month, have you often been bothered by:

1. Little interest or pleasure in doing things?
2. Feeling down, depressed, or hopeless?
If either question is positive, then the SALSA questionnaire should be used for more certainty. A positive test is one of the above answers positive and two of the answers below positive:

1. Sleep disturbance nearly every day for the last 2 weeks?
2. Have you experienced little interest or pleasure in doing things nearly every day for the last 2 weeks (Anhedonia)?
3. Have you experienced Low Self esteem nearly every day for the last 2 weeks?
4. Have you experienced decreased Appetite nearly every day for the last 2 weeks?

2.5.8 Treatment

Treatment of depression varies broadly among individuals and the levels, types, and methods of intervention around the globe varies dramatically. Various types and combinations of treatments may have to be tried. There are two primary modes of treatment, typically used in conjunction: medication and psychotherapy. A third treatment, electroconvulsive therapy (ECT), may be used when chemical treatment fails.

Although treatment is generally effective, in some cases the condition does not respond. Treatment-resistant depression warrants a full assessment, which may lead to the addition of psychotherapy, higher medication dosages, changes of medication or combination therapy, a trial of ECT/electroshock, or even a change in the diagnosis, with subsequent treatment changes. Although this process helps many, some people's symptoms continue unabated.

In emergencies, psychiatric hospitalization is used simply to keep suicidal people safe until they cease to be dangers to themselves. Another treatment program is partial hospitalization, in which the patient sleeps at home but spends the day, either five or seven days a week, in a psychiatric hospital setting in intense treatment. This treatment usually involves group therapy, individual therapy, psychopharmacology, and academics (in child and adolescent programs).
Medication

Typical first-line therapy for depression is the use of an selective serotonin reuptake inhibitor, such as citalopram, fluoxetine, paroxetine, and sertraline. Under some circumstances, medication and psychotherapy may be more effective than either treatment separately.

Pharmacology of antidepressants

MAOIs and TCAs were introduced during the late 1950s. Early MAOIs appeared to be limited in efficacy at the doses used and presented both toxic risks and potentially dangerous interactions with other agents, thus limiting their acceptance in favour of the TCAs. TCAs are also associated with CVS side effects, which hinder their compliance.

After decades of limited progress, a series of SSRIIs like Citalopram, Fluoxetine, Flavoxamine, Paroxetine, Sertraline and Venlafaxine emerged. Others including Bupropion, Nefazodone and Mirtazapine-have less well-defined neuropharmacology and can be considered as “Atypical”, whereas the efficacy of the newer agents is not superior to that of older agents. Their relative safety and collateral tolerability has lead to their rapid acceptance as the most commonly prescribed antidepressants (Goodman and Gilman, 2001.)

<table>
<thead>
<tr>
<th>Function</th>
<th>Antidepressants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoamine oxidase inhibitor</td>
<td>Isocarboxazid, Phenelzine</td>
</tr>
<tr>
<td></td>
<td>Tranylcypromine, Meclobamide</td>
</tr>
<tr>
<td>Norepinephrine transport blocker</td>
<td>Amoxapine, Desipramine</td>
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<tr>
<td></td>
<td>Doxepin, Maprotiline, Protriptyline</td>
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<tr>
<td></td>
<td>Nortriptyline, Reboxetine</td>
</tr>
<tr>
<td>Serotonin transport blocker</td>
<td>Amitriptyline, Citloproam</td>
</tr>
<tr>
<td></td>
<td>Clomipramine, Fluoxetine</td>
</tr>
<tr>
<td></td>
<td>Fluvoxamine, Imipramine</td>
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<tr>
<td></td>
<td>Paroxetine, Sertraline</td>
</tr>
<tr>
<td></td>
<td>Trimipramine, Venlafaxine (SNRI)</td>
</tr>
</tbody>
</table>
Dopamine transport blocker | Bupropion
---|---
Serotonin 5-HT\textsubscript{2A} receptor blocker | Mirtazapine, Nefazodone, Trazodone

Selective serotonin reuptake inhibitors (SSRIs)

Selective serotonin reuptake inhibitors (SSRIs) are a family of antidepressant considered to be the current standard of drug treatment. It is thought that one cause of depression is an inadequate amount of serotonin, a chemical used in the brain to transmit signals between neurons. SSRIs are said to work by preventing the reuptake of serotonin by the presynaptic nerve, thus maintaining higher levels of 5-HT in the synapse. Recent research indicates that these drugs may interact with transcription factors known as "clock genes", which may be important for the addictive properties of drugs of abuse and possibly in obesity. Drugs belonging to this category are fluoxetine, paroxetine, escitalopram, citalopram, and sertraline. These antidepressants typically have fewer adverse side effects than the tricyclics or the MAOIs, although such effects as drowsiness, dry mouth, nervousness, anxiety, insomnia, decreased appetite, and decreased ability to function sexually may occur. Some side effects may decrease as a person adjusts to the drug, but other side effects may be persistent. Though safer than first generation antidepressants, SSRIs may not work as often, suggesting the role of norepinephrine. However, it should be noted that all psycho-active medications extend the reaction time, thus increasing the likelihood of falls and road crashes.

Serotonin-norepinephrine reuptake inhibitors (SNRIs)

Serotonin-norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine (Effexor) and duloxetine (Cymbalta) are a newer form of antidepressant that works on both norepinephrine and 5-HT. They typically have similar side effects to the SSRIs, although there may be a withdrawal syndrome on discontinuation that may necessitate dosage tapering.
Noradrenergic and specific serotonergic antidepressants (NASSAs)

Noradrenergic and specific serotonergic antidepressants (NASSAs) form a newer class of antidepressants which purportedly work to increase norepinephrine (noradrenaline) and serotonin neurotransmission by blocking presynaptic alpha-2 adrenergic receptors while at the same time minimizing serotonin related side-effects by blocking certain serotonin receptors. The only example of this class in clinical use is mirtazapine (Avanza, Zispin, Remeron).

Norepinephrine (noradrenaline) reuptake inhibitors (NRIs)

Norepinephrine (noradrenaline) reuptake inhibitors (NRIs) such as reboxetine (Edronax) act via norepinephrine (also known as noradrenaline). NRIs are thought to have a positive effect on concentration and motivation in particular, though they have been known to increase aggression.

Norepinephrine-dopamine reuptake inhibitors

Norepinephrine-dopamine reuptake inhibitors such as bupropion (Wellbutrin, Zyban) inhibit the neuronal reuptake of dopamine and norepinephrine (noradrenaline).

Tricyclic antidepressants (TCAs)

Tricyclic antidepressants are the oldest and include such medications as amitriptyline and desipramine. Tricyclics block the reuptake of certain neurotransmitters such as norepinephrine (noradrenaline) and serotonin. They are used less commonly now due to the development of more selective and safer drugs. Several side effects include increased heart rate, drowsiness, dry mouth, constipation, urinary retention, blurred vision, dizziness, confusion, and sexual dysfunction. Toxicity occurs at approximately ten times normal dosages. However, tricyclic antidepressants are still used because of their high potency, especially in severe cases of clinical depression.
Monoamine oxidase inhibitor (MAOIs)

*Monoamine oxidase inhibitors* (MAOIs) such as phenelzine (Nardil) may be used if other antidepressant medications are ineffective. Because there are potentially fatal interactions between this class of medication and certain foods and drugs, they are rarely prescribed anymore. MAOIs are used to block the enzyme monoamine oxidase which breaks down neurotransmitters such as dopamine, 5-HT, and norepinephrine (noradrenaline). MAOIs are as effective as tricyclics, though tend to have more dangerous/fatal side effects as a result of inhibition of cytochrome P450 in the liver. A new MAOI has recently been introduced. Moclobemide (Manerix), known as a reversible inhibitor of monoamine oxidase A (RIMA), follows a very specific chemical pathway and does not require a special diet.

**Dietary supplements**

5-**HTP** supplements are claimed to provide more raw material to the body's natural serotonin production process. There is a reasonable indication that 5-**HTP** may not be effective for those who haven't already responded well to an SSRI because of their similar function: SSRIs allow the brain to use its serotonin more effectively, while 5-**HTP** induces production of more serotonin.

*S-adenosyl methionine* (SAM-e) is a derivative of the amino acid methionine that is found throughout the human body, where it acts as a methyl donor and participates in other biochemical reactions. It is available as a prescription antidepressant in Europe and an over-the-counter dietary supplement in the United States. Clinical trials have shown SAM-e to be as effective as standard antidepressant medication, with fewer side effects; however, some studies have reported an increased incidence of mania resulting from SAM-e use compared to other antidepressants. Its mode of action is unknown.

*Omega-3 fatty acids* (found naturally in oily fish, flax seeds, hemp seeds, walnuts, and canola oil) have also been found to be effective when used as a dietary supplement (although only fish-based omega-3 fatty acids have shown antidepressant efficacy.)
Dehydroepiandrosterone (DHEA), available as a supplement in the U.S., has been shown to be effective in small trials.

Magnesium supplementation has gathered some attention as a possible treatment for depression. Some case reports demonstrate rapid recovery from major depression using magnesium treatment. "The possibility that magnesium deficiency is the cause of most major depression and related mental health problems including IQ loss and addiction is enormously important to public health and is recommended for immediate further study.

St John's Wort Except under medical supervision, St. John's Wort should not be used with SSRIs or MAOIs due to the risk of serotonin syndrome.

Ginkgo Biloba Effective natural antidepressant said to stabilise cell membranes, inhibiting lipid breakdown and aiding cell use of oxygen and glucose - so subsequently a mental and vascular stimulant that improves neurotransmitter production. Also popular for treating mental concentration (such as for Alzheimer's and stroke patients).

Siberian Ginseng [Eleutherococcus senticosus] Although not a true panax ginseng it is a mood enhancement supplement against stress. Also popular for treating depression, insomnia, moodiness, fatigue, poor memory, lack of focus, mental tension and endurance.

Zinc has had an antidepressant effect in an experiment.

Biotin: a deficiency has caused a severe depression. The patient's symptoms improved after the deficiency was corrected.

Vitamin B-12: Symptoms of a vitamin B-12 deficiency can include depression and other psychiatric disorders.

Cannabis has also been shown to reduce the symptoms of depression.

Lithium remains the standard treatment for bipolar disorder and is often used in conjunction with other medications, depending on whether mania or depression is being treated. Lithium's potential side effects include thirst, tremors, light-headedness, and
nausea or diarrhea. Some of the anticonvulsants, such as carbamazepine, sodium valproate, and lamotrigine, are also used as mood stabilizers, particularly in bipolar disorder.

**Psychotherapy**

In psychotherapy, or counseling, one receives assistance in understanding and resolving habits or problems that may be contributing to or the cause of the depression. This may be done individually or with a group and is conducted by mental health professionals such as psychiatrists, psychologists, clinical social workers, or psychiatric nurses.

Effective psychotherapy may result in different habitual thinking and action which leads to a lower relapse rate than antidepressant drugs alone. Medication, however, may yield quicker results and be strongly indicated in a crisis. Medication and psychotherapy are generally complementary, and both may be used at the same time.

It is important to ask about potential therapists' training and approach; a very close bond often forms between practitioner and client, and it is important that the client feel understood by the clinician. Moreover, some approaches have been convincingly demonstrated to be much more effective in treating depression.

Counselors can help a person make changes in thinking patterns, deal with relationship problems, detect and deal with relapses, and understand the factors that contribute to depression.

There are many counseling approaches, but all are aimed at improving one's personal and interpersonal functioning. Cognitive behavioral therapy has been demonstrated in carefully controlled studies to be among the foremost of the recent wave of methods which achieve more rapid and lasting results than traditional "talk therapy" analysis. Cognitive therapy, often combined with behavioral therapy, focuses on how people think about themselves and their relationships. It helps depressed people learn to replace negative depressive thoughts with realistic ones, as well as develop more effective
coping behaviors and skills. Therapy can be used to help a person develop or improve *interpersonal skills* in order to allow him or her to communicate more effectively and reduce stress. Interpersonal psychotherapy focuses on the social and interpersonal triggers that cause their depression. *Narrative therapy* gives attention to each person's "dominant story" by means of therapeutic conversations, which also may involve exploring unhelpful ideas and how they came to prominence. Possible social and cultural influences may be explored if the client deems it helpful. *Behavioral therapy* is based on the assumption that behaviors are learned. This type of therapy attempts to teach people more helpful types of behaviors. *Supportive therapy* encourages people to discuss their problems and provides them with emotional support. The focus is on sharing information, ideas, and strategies for coping with daily life. *Family therapy* helps people live together more harmoniously and undo patterns of destructive behavior.

**Transcranial magnetic stimulation**

Repetitive transcranial magnetic stimulation (rTMS) is under study as a possible treatment for depression. Initially designed as a tool for physiological studies of the brain, this technique shows promise as a means of alleviating depression. In this therapy, a powerful magnetic field is used to stimulate the left prefrontal cortex, an area of the brain that typically shows abnormal activity in depressed people.

**Vagus nerve stimulation**

Vagus nerve stimulation therapy is a treatment used since 1997 to control seizures in epileptic patients and has recently been approved for treating resistant cases of treatment-resistant depression (TRD). The VNS Therapy device is implanted in a patient's chest with wires that connect it to the vagus nerve, which it stimulates to reach a region of the brain associated with moods. The device delivers controlled electrical currents to the vagus nerve at regular intervals.
Electroconvulsive therapy

Electroconvulsive therapy (ECT), also known as electroshock or electroshock treatment, uses short bursts of a controlled current of electricity (typically fixed at 0.9 ampere) into the brain to induce a brief, artificial seizure while the patient is under general anesthesia.

In contrast to direct electroshock of years ago, most countries now allow ECT to be administered only under anaesthesia. In a typical regimen of treatment, a patient receives three treatments per week over three or four weeks. Repeat sessions may be needed. Short-term memory loss, disorientation, and headache are very common side effects. Detailed neuropsychological testing in clinical studies has not been able to prove permanent effects on memory. ECT offers the benefit of a very fast response; however, this response has been shown not to last unless maintenance electroshock or maintenance medication is used. Whereas antidepressants usually take around a month to take effect, the results of ECT have been shown to be much faster. For this reason, it is the treatment of choice in emergencies (e.g., in catatonic depression in which the patient has ceased oral intake of fluid or nutrients).

There remains much controversy over electroshock. Advocacy groups and scientific critics, such as Dr Peter Breggin,\(^{[51]}\) call for restrictions on its use or complete abolition. Like all forms of psychiatric treatment, electroshock can be given without a patient's consent, but this is subject to legal conditions dependent on the jurisdiction. In Oregon patient consent is necessary by statute.

Other methods of treatment

Light therapy

Bright light (both sunlight and artificial light) is shown to be effective in seasonal affective disorder, and sometimes may be effective in other types of depression, especially atypical depression or depression with "seasonal phenotype" (overeating, oversleeping, weight gain, apathy).
Exercise

It is widely believed that physical activity and exercise help depressed patients and promote quicker and better relief from depression. They are also thought to help antidepressants and psychotherapy work better and faster. It can be difficult to find the motivation to exercise if the depression is severe, but sufferers should be encouraged to take part in some form of regularly scheduled physical activity. A workout need not be strenuous; many find walking, for example, to be of great help. Exercise produces higher levels of chemicals in the brain, notably dopamine, serotonin, and norepinephrine. In general this leads to improvements in mood, which is effective in countering depression.

Meditation

Meditation is increasingly seen as a useful treatment for some cases of depression. The current professional opinion on meditation is that it represents at least a complementary method of treating depression, a view that has been endorsed by the Mayo Clinic. Since the late 1990s, much research has been carried out to determine how meditation affects the brain. Although the effects on the mind are complex, they are often quite positive, encouraging a calm, reflective, and rational state of mind that can be of great help against depression. Although many religions include meditative practice, it is not necessary to be a member of any faith to meditate. But in some cases meditation may make the sufferer worse.

Archaic methods

Insulin shock therapy is an old and largely abandoned treatment of severe depressions, psychoses, catatonic states, and other mental disorders. It consists of induction of hypoglycemic coma by intravenous infusion of insulin.

Atropinic shock therapy, also known as atropinic coma therapy, is an old and rarely used method. It consists of induction of atropinic coma by rapid intravenous infusion of atropine.
Atropinic shock treatment is considered safe, but it entails prolonged coma (4-5 hours), with careful monitoring and preparation, and it has many unpleasant side effects, such as blurred vision.

Relapse

Relapse is more likely if treatment has not resulted in full remission of symptoms. In fact, current guidelines for antidepressant use recommend 4 to 6 months of continuing treatment after symptom resolution to prevent relapse.

Combined evidence from many randomized controlled trials indicates that continuing antidepressant medications after recovery substantially reduces (halves) the chances of relapse. This preventive effect probably lasts for at least the first 36 months of use. Anecdotal evidence suggests that chronic disease is accompanied by relapses after prolonged treatment with antidepressants (tachyphylaxis). Psychiatric texts suggest that physicians respond to relapses by increasing dosage, complementing the medication with a different class, or changing the medication class entirely. The reason for relapse in these cases is as poorly understood as the change in brain physiology induced by the medications themselves. Possible reasons may include aging of the brain or worsening of the condition. Most SSRI psychiatric medications were developed for short-term use (a year or less) but are widely prescribed for indefinite periods.
2.5.9 Biological basis of depression

2.5.9.1 Monoamine hypothesis

This theory hypothesize that depression is due to a deficiency of monoamine Neurotransmitters, notably NE and 5HT. Evidence for this is rather simplistic. Certain drugs that deplete these neurotransmitters could induce depression and the known antidepressants (TCAs and MAOIs) could increase neurotransmitter.

2.5.9.2 Neurotransmitter receptor hypothesis

This theory points that something is wrong with the receptor for the key monoamine neurotransmitters. According to this theory, an abnormality in the functioning of receptors for monoamine neurotransmitters leads to depression. Such a disturbance in neurotransmitter receptors may itself be caused by depletion of monoamine neurotransmitters.

2.5.9.3 Blue genes and the monoamine hypothesis

This theory links with the genetic and environmental risk factors for depression. It proposes, “Stress, possibly acting through monoaminergic neurotransmission, can cause depression by down regulating critical genes (Figure 1), so that their key gene products are not produced.”

One candidate mechanism that has been proposed as a specific site of one of the hypothetical flows in signal transduction from monoamine receptors is the target gene for Brain-Derived Neurotropic Factor (BDNF). Normally, BDNF sustains the validity of brain neurons under stress, however the gene for BDNF is repressed to atrophy and possible apoptosis of vulnerable neurons in the hippocampus when their neurotropic factor is cut off (see figure 2), these events in turn leads to depression and consequences of repeated depressive episodes.
2.6 ANIMAL MODELS IN DEFINING ANXIOLYTIC ACTIVITY

2.6.1 CLASSIFICATION

A. Exploratory Behaviour
   1. Elevated Plus Maze Test
   2. Zero Maze Test
   3. Open Field Test
   4. Stair Case Test
   5. Hole Board Test
   6. Light-dark exploration

B. Social Interaction Test.

C. Conflict Tests.
   1. Geller Seifter Test
   2. Vogel Test
   3. Four Plate Test

D. Miscellaneous Tests
   a. Novelty induced suppression of feeding & drinking
   b. Defensive burying test.
   c. Cork gnawing test.
   d. Foot Shock induced freeze test.
   E. Anti aggression test.
   f. Antistress test.
   g. Drug withdrawal induced anxiety.
2.6.2 ANIMAL MODELS IN DEFINING ANXIOLYTIC ACTIVITY & THEIR VALIDITY

1. Elevated plusmaze

- The test has been proposed for selective identification of anxiolytic and anxiogenic drugs, anxiolytic compounds by decreasing anxiety, increase the open arm exploration time; anxiogenic compounds have the opposite effect (Vogel, et al., 1997).

- The primary measures are the proportion of entries into the open arms & the time spent on the open are expressed as a percentage of the total time spent on both open and closed arms.

- Factor analysis of data from undrugged animals tested in the hole board and elevated plus maze yielded three orthogonal factors interpreted as assessing anxiety, directed exploration and locomotion. (Richar G.Lister, 1987).

- To measure anxiety levels in mice, the authors studied their behaviour in an 'elevated plus maze' mice generally prefer to be in a 'safe' environment, such as in the closed arm's of the maze, but their natural curiosity causes them to explore more aversive environments such as open arms of the maze. Their level of anxiety is determined by the amount of time that they spend exploring the aversive compartment of the apparatus; the more adventurous the mouse, the less anxious it is perceived to be (Gross, et al., 2002).

- The elevated plus maze is now widely accepted as an animal model of 'anxiety' It features technical simplicity together with a high throughout, thus allowing rapid pharmacological evaluation of drug effects of anxiety. The model is based on the observation of spontaneous activity of rodents placed in an aversive environment produced by height and open spaces (Michel Reibund. et al., 1993).

- The unstable elevated exposed plus maze has been proposed as a novel model of anxiety which elicits unconditioned escape related behaviour in rats thought to mimic the persistent fight/flight state exhibited by patients suffering from extreme anxiety disorders. This tests investigate the predictive validity of the UEPPM by examining the behaviour of rats exposed to the test following administration of drugs known to induce panic and anxiety in panic disorder and post-traumatic stress disorder patients, namely in m-Chlorophenyl piperazine (m.CPP). Caffeine and . The sensitivity of UEPPM to two
further anxiogenic agents, the benzodiazepine partial agonist FG71H2 and Paentylenetetrazol (PTZ) was also assessed. (Nicholas Jones, et al., 2002).

- The elevated plus maze is claimed to be an 'ethologically valid' animal model of anxiety because it uses 'Natural Stimuli' that can induce anxiety in humans it is assumed that the open arms of the maze combine the fear of a novel, brightly lit open space and the fear of balancing on a relatively narrow, raised platform, the used arms have high walls forming a narrow alley that affords good protection from potential predators (Gerald R.Dawson, et al., 1995).
2.7 ANIMAL MODELS IN DEFINING ANTIDEPRESSANT ACTIVITY AND CRITERIA OF VALIDATION

Animal models form an interface between psychiatry and basic research in behavioral neuroscience. On the other hand, they are the major channels through which developments at the basic level are brought into clinical perspective; on the other, they provide a particularly informative means of investigating the psychobiological foundations or psychopathology (Willner, 1991).

2.7.1 Validation criteria for psychological models:

1. Psychological models must satisfy at least the four validation criteria defined by McKinney (1977)
   a. Similarity of inducing conditions
   b. Similarity of the behavioral state induced
   c. Similarity of the underlying mechanisms
   d. Similarity of clinically effective treatment techniques

2. According to Prossolt, et al., the most important criterion is to show a maximum sensitivity to different kinds of antidepressant drugs (absence of false negatives) while at the same time showing maximum of selectivity (absence of false positive).

Validation criteria for psychopharmacological models:

Unlike psychological models, pharmacological models do not require any assumed similarities with depressive illness. They simply have to show the effectiveness of known drugs. Other requirements of pharmacological modes are simplicity, rapidity and reliability.

Key words in validation criteria of animal models (Willner, 1984; Prossolt, et al., 1991)

Face validity

Assessed by whether antidepressant effects are only present on or potentiated by chronic administration and model resembles depression in a number of aspects.

In Anxiety: The behavioral state some similarity with clinical anxiety.

Predictive validity

Assessed by whether a model correctly identifies antidepressant treatments of pharmacologically diverse type, without making errors of omission or commission.
In Anxiety: The inducing conditions (fear, conflicts etc.) should be similar.

*Constructive Validity*

Assessed by whether both behavior in the model and the features of depression being modeled can be unambiguously interpreted and are homologous and whether the feature being modeled stands in an empirical and theoretical relationship to depression.

In Anxiety: The anxiety model should have similar underlying neurobiological mechanisms.

*Pharmacological validity*

Clinically effective anxiolytic agents should be effective in the model as well.

*False negative*

Some models may fail to show positive response to certain antidepressants. This is known as false negative. ‘Absence of false negative’ is an indication of showing maximum sensitivity to different kinds of antidepressant drug (Prosolt, *et al.*, 1991)

*False positive*

Some models may fail to distinguish true antidepressant from other psychotropic/any drugs (i.e. they give positive response to drugs other than antidepressants). Absence of false positive’ is an indication of showing maximum selectivity to antidepressants (Prosolt, *et al.*, 1991).
2.7.2 ANIMAL MODELS AND THEIR VALIDITY

1. Psychological (Induced behavioral) Models

FORCED SWIM TEST
- It has "predictive and face validity" (Willner, 1984).
- Sensitive to a large number of typical antidepressants otherwise inactive in more classical drugs.
- It is simple and can be performed rapidly.
- Results are highly reproducible.
- Model is purely behavioral without presuppositions concerning the mechanism of action of potential antidepressant (Porsolt, et al., 1991).

LEARNED HELPNESS
- It has predictive, face and constructive validity
- It shows clear sensitivity to a wide range of antidepressants
- Highly sensitive but more time-consuming ((Willner, 1984; Porsolt, et al., 1991)

THE CHRONIC MILD STRESS MODEL
- It has predictive, face and constructs validity (Willner, 1984).
- It is the most validated animal model of depression, implicating stress as the etiological cause of depression (Bourin, et al., 2001).
- It has much simulation with the clinical depression.
- But this model exhibits poor reliability (Bourin, et al., 2001).

TAIL SUSPENSION TEST
- Tail suspension is simple and rapid but appears to be less sensitive; nevertheless 5-HT uptake inhibitors are active.
- Tail suspension test in authorized form provides a rapid and reliable behavioral screening test for antidepressants and other classes of psychotropics (Porsolt, et al., 1991).

INTRA CRANIAL SELF-STIMULATION (ICSS)
- It has predictive face and also constructs validity (Willner, 1984).

SEPARATION MODEL
- It has predictive face and constructs validity (Willner, 1984).
II. PHARMACOLOGICAL MODELS

1. RESERPINE REVERSAL

As per Willner (Willner, 1984), it has poor predictive, face and construct validity. It is sensitive to molecule having no antidepressant action.

But in animal model of depression, this method is most frequently used to evaluate antidepressant action and remains as choice because of largely justified by the fact that all Imipramine-like antidepressants or MAOI as well as almost of the new antidepressants are active in this test (Bourin, et al., 1983).

This test is divided into 3 observations (Bourin, 1990)

1. Antagonism of hypothermia
   To indicate substances (most often antidepressants) having direct or indirect B-mimetic activity.

2. Antagonism of ptosis
   To indicate substance having alpha-adrenergic activity (thus not antidepressants) or serotonergic activity (possibly antidepressants).

3. Antagonism of alkinesia
   To indicate direct or indirect dopaminergic activity found in antidepressant having an added psycho stimulant action.

2. YOHIMBINE TOXICITY ENHANCEMENT

   Enhancement of yohimbine toxicity is indicative of beta adrenergic activity (Bourin, et al., 1988). According to Willner, 1984, this test is has predictive validity.

   The effects of Yohimbine in man or in animals though not clearly related to depression or mania. Yohimbine potentiation particularly in mice appears to represent a simple and rapid test for detecting the antidepressant activity of a wide range of compounds and greatest sensitivity (Proso1t, et al., 1991).

3. NOREPINEPHRINE (NE) TOXICITY ENHANCEMENT

   This test is only a measure of the norepinephrine-uptake inhibition (Vogel and Vogel, 1997).

4. 5-HYDROXY Tryptophan POTENTIATION IN MICE AND RATS

   - This model is extremely weak in both predictive and faces validity. In fact, this model was explicitly developed as a behavioral system with in which to test the
effects of drugs on 5-HT neurotransmission, in this role, it serves a useful function (Willner, 1984).

- This test is considered to be additional evidence for antidepressant activity based on uptake inhibition.

5. TRYPHTAMINE SEIZURE POTENTIATION IN RATS:

- This method can be used to evaluate the in vivo MAO inhibiting properties of compounds (Vogel and Vogel, 1997).

6. POTENTIATION OF L-DOPA INDUCED BEHAVIOUR:

- The behavioral excitation induced by L-DOPA is positively correlated with the increase in brain DA level and its potentiation has been regarded as an in vivo index of MAO inhibition. This test does not discriminate between MAO-A and B subtypes well (Kato, et al., 1998).

7. ANTAGONISM OF APOMORPHINE INDUCED HYPOTHERMIA:

- Pucnch, et al., (1981) have shown hypothermia induced by high doses of Apomorphine (16mg/kg) is antagonized by antidepressants, where as low doses (1mg/kg) are antagonized by narcoleptic.

- Apomorphine-induced hypothermia is usually considered to be related to stimulation of dopaminergic receptors but also involves beta adrenergic nervous system (Bourin,1990)
2.8 INTRODUCTION TO INVESTIGATIONAL DRUG, TRANS-01

2.8.1 Traditional systems of medicine

Basic aim of the entire healthcare system of medical practices is to provide people with proper medical and other healthcare services. Different healthcare services differ in their philosophy and concept as to the causes of disease, their approach to healing, methods of treatment, and composition and preparation of medicinal products. For convenience, they can be broadly classified into (i) Traditional and (ii) Modern system of medicine.

Traditional system

It is an art of healing based on traditional use of plants, animals, and other natural substances, and cultural habits, social practices, religious beliefs, and in many cases, superstitions of the present and previous generations of people (Ghani 1990). The forms of traditional medicine practiced today vary from highly organised and long established Ayurvedic, Unani, Chinese systems etc to various folk medical practices, such as herbalism, spiritualism and religious medical practices.

Ayurvedic system

Ayurveda is one of the oldest systems of medicine which has been practiced in Indian subcontinent for over 3,000 years. Ayurveda, meaning the science of life, is rooted to the social, cultural and philosophical principles that prevailed in India during the period 600 BC to 700 AD.

Ayurveda considers the human being as a miniature universe. The properties found in the universe are believed to be present in the human body, which like the universe, consists of five gross elements: earth, water, fire, air and the ethereal parts of the sky. These body constitutions are taken into consideration while treating a patient under this system. It aims to integrate the body, mind and spirit to prevent and treat disease. It makes extensive use of plant-derived compound formulations, massage and yoga for the treatment of various ailments after a careful study into the nature of the disease (Lad, 1984; Sharma and Dash, 1998; Khanand Balick, 2001).
Plants are complex mixtures of compounds and no single compound can provide
the desired activity. Some compounds potentiate a desired therapeutic action, others
reinforce this action, and yet others interact to neutralize and counteract any possible side
effects that may exist. Therefore, several plants with common desired activities, but
different undesirable activities, are selected so that the final formulation will have a
concentrated desired activity and the undesired activities will be diluted or absent
altogether (Kulkarni, 1997). Further, according to the Ayurvedic system of medicine, the
body is composed of tridosha or three humors: vata, translated as wind, corresponds to the
mind and nervous system; pitta, translated as bile, is responsible for all metabolic
transformations, including digestion and assimilation of food; and kapha, translated as
water or mucus, is responsible for the anabolic functions, such as development of muscle
and bone tissues (Sharma and Dash, 1998; Khan and Balick, 2001). In the Ayurvedic
system of medicine, the treatment of an ailment is such that the effect is felt by all the
three humors and the functional potency is brought out both quantitatively and
qualitatively (Sivaranjan and Balachandra, 1996).

The medicinal preparations employed in this system are mainly derived from plant
materials and are presented in the form of powders, semi-solid preparations, decoctions,
elixirs and distillates. Many of them also contain inorganic chemical substances, minerals
and animal products. Alcoholic extracts and alcoholic solutions of the ingredients,
tinctures and elixirs are also frequently used in Ayurvedic medicine. The materia medica
of Ayurvedic medicine contains some 8,000 published recipes. Many more are held as
secret information among certain families practicing the Ayurveda system.

Unani system

Unani system was originated in Greece and was named after the name of Unan province,
which is regarded as the original place of development and practice of this system. Hakim
Iskalibus of Greece was the first person to propagate the Unani system of medicine.
However, this system flourished only when Arabian and Persian Muslim intellectuals like
Al-Razi, Ibn-Sina, Al-Rashid, and others enriched it with newer scientific knowledge and
discoveries in the 7th century. Because of the significant contributions of Arabian
physicians to the development of this system, the Unani system is also known as the Greeko-Arab system.

According to the Unani system, the basic factors composing the human physique are four elements (fire, air, water and earth), four types of temperament (hot and dry, hot and wet, cold and dry, and cold and wet), four humours (blood, phlegm, yellow bile and black bile) organs, vital spirit, powers and functions. Whole plants or their powders or pastes or products and their extracts, infusions, decoctions and distillates are major constituents of Unani medicine. Minerals, inorganic chemicals and animal products are also frequently used in preparing these medicines.

**Traditional Chinese Medicine (TCM)**

TCM is a complete system of healing that dates back to 200 B.C. in written form. Korea, Japan, and Vietnam have all developed their own unique versions of TCM originating in China. In the TCM view, the body is a delicate balance of two opposing and inseparable forces: yin and yang. The concept of two opposing yet complementary forces described in traditional Chinese medicine. *Yin* represents cold, slow, or passive aspects of the person, while *yang* represents hot, excited, or active aspects. A major theory is that health is achieved through balancing yin and yang and disease is caused by an imbalance leading to a blockage in the flow of *qi* (or vital energy).

In traditional Chinese medicine, the vital energy or life force proposed to regulate a person's spiritual, emotional, mental, and physical health and to be influenced by the opposing forces of yin and yang and of blood along pathways known as meridians. TCM practitioners typically use herbs, acupuncture (http://nccam.nih.gov/health/backgrounds/wholemed.htm)

**Homeopathic system**

Homeopathic system was developed in Europe by a German allopathic physician named Samuel Hahnemann (1755-1843) in the early 19th century from the allopathic system. In this system drugs are applied in very small and diluted doses. It is believed that the strength or curative power of a drug increases mathematically with the increasing degree of its dilution. There are about 1200 medicines in homeopathy, of which more than
500 are obtained from medicinal plants, a few from animals, and the rest from pure chemicals. Plant derived medicines in this system are used as mother tinctures. No excipient (preservative, colour, sweetener, flavour, etc) is used in preparing homeopathic medicine. Homeopathy seeks to stimulate the body's ability to heal itself by giving very small doses of highly diluted substances that in larger doses would produce illness or symptoms (an approach called "like cures like").

Naturopathy

Naturopathy originated in Europe and aims to support the body's ability to heal itself through the use of dietary and lifestyle changes together with therapies such as herbs, massage and joint manipulation.

Modern system

This is the highly advanced system of health management. This system does not limit itself to only curative treatment of the patient but also endeavours to extend its services to the prevention of diseases by immunization and improving the personal and environmental hygiene of the patient and the community. Well-educated and professionally trained experts practice this system of medical treatment. Technologically advanced highly sophisticated equipment and methods are used in this system to attain precise diagnosis and treatment of diseases. Highly efficacious medicinal preparations prepared from purified synthetic or natural chemical substances are used in this system. It has developed sophisticated and precise method and technology of surgical operations and performs critical operations like open-heart surgery, heart transplant, and transplantation of other vital organs of human body with high degree of precision and safety (WHO, 1990).

2.8.2 Herbal drugs and polyherbal preparations

Herbal drugs have been used by mankind since time immemorial to treat various disorders and offer an alternative to the synthetic compounds, as they have been considered either non-toxic or less toxic. The mechanism of action of herbal drugs and their extract
preparations differ in many respects from that of the synthetic drugs or single substances (Wagner, 1999).

It can be characterized as a polyvalent action and interpreted as additive or, in some cases, potentiating. Further, it has also been observed that in such formulations, certain other compounds may be of help in enhancing the potency of the active compounds resulting in an additive or synergistic positive effect, which in its final total gives immense benefit to the patient (Kulkarni, 1997; Ganesh Chandra, 2004).

Some of the widely used herbal formulations for various indications are Chyavanprasha, triphala, geriforte, septilin, Panvita, InFex, LIPON, LIV-52, Tentex forte, Menlat, etc. The investigational drug Trans-01 is such a polyherbal formulation, with the following composition, Valeriana wallichii (45%), Convolvus microphyllus (30%), Plumbago zylanica (7.5 %), Boswellia serrata (15 %) and Acorus calamus (3.5 %). The aqueous extract of the formulation was used in the study.
2.8.1 Valeriana wallichii

(Youngken HW, 1950; Bisset NG, 1994; Bruneton J, 1995; Hänsel R and Schultz J, 1982)

**Family Valerianaceae**

**Other names**

- English: Indian valerian
- Hindi: tagar
- Sanskrit: Tagurah

**Parts used:** Rhizomes and roots

**Description**

It is a small perennial herb, stem many, radical leaves cordate, ovate, heart shaped, cauline leaves entire, small and few. Flowers, white or pink, clusters on top of the leaf less stem. Sepals 5, petals funnel shaped with 5 lobed, stamens 3, fruit crowned with a persistent pappus like calyx.

**Habitat**

Valeriana Wallichii is found in Bultora Glaciers, Nagar 3,800 metres along Minapin Glacier 3,200 metres. Rama forest Astore small quantity, Kamari forest considerable quantity. Grow abundantly and most luxuriantly in the shady moist places of Kalapani forest.

**Medicinal uses**

It is useful in hysteria, insomnia, habitual constipation, neurosis, cholera and in scorpion sting and also used for perfumery. Locally the dry roots are used to remove foul odour of mouth caused by tooth trouble.

**Geographical distribution**

Valeriana wallichii is an extremely polymorphous complex of sub-species with natural populations dispersed throughout temperate and sub-polar Eurasian zones. The species is common in damp woods, ditches, and along streams in Europe, and is cultivated as a medicinal plant, especially in Belgium, England, Eastern Europe, France, Germany, India, the Netherlands, the Russian Federation, and the United States of America.
Chemical constituents


Medicinal uses

Anodyne, antispasmodic, aromatic, calmative, carminative, diuretic, expectorant, nerveine (an agent that has a calming or soothing effect on the nerves, any agent that acts on the nervous system to restore the nerves to their natural state), relaxant, sedative, stimulant, tranquilizer. Used in Anxiety, breathlessness, epilepsy, giddiness and fainting fits, has a remarkable influence on the cerebro-spinal system, hypochondriasis (abnormal concern about one's health), hysteria, insomnia, migraines, nervous unrest and nervous tension, neuralgia, neurasthenia, muscle spasms, pain etc.

Pharmacological activities

➤ Valerian was shown to inhibit the binding of [3H] flunitrazepam to central benzodiazepine receptor. Suggesting the involvement of BZD Rs in inducing its and sedative and anxiolytics effects (Lee et al., 2003).

➤ Valeriana was reported to have anxiolytic, tranquilizing, and sleep inducing effects (Leuschner J, et al., 1993; Leathwood PD and Chauffard F., 1985; Balderer G and Borbely AA, 1985; Lindahl O, Lindwall L, 1989).

➤ In in vitro binding studies to GABA receptors, Valerian was found to displace the agonist, muscimol, suggesting its binding to these receptors (Cavadas C., et al; 1995).

➤ Valerian extract was also found to contain GABA and other amino acids. The GABA content of valerian extract could also be responsible for the stimulated release and reuptake of GABA. This could be an indirect mechanism of GABA agonistic activity of valerian extract (Santos MS et al., 1994a; Santos MS et al., 1994b).
2.8.2 Convolvus microphyllus

(Bruneton J, 1995; Hänsel R and Schultz J, 1982)

Family Convolvulaceae

Other names

English: Aloe weed
Hindi: Shankaphuli
Sanskrit: Shankapushpi

Distribution

West tropical Africa to India, plant is very common in lawns on ridges along waysides and in unused lands.

Parts used Whole plant

Chemical constituents:

The plant contains alkaloids, convolvine, convulamine, phyllabine, convolodine, confolcinf, subhirsine, convosine and convolvidine along with scopoline and sitosterol.

Medicinal uses

Shankapushpi is quoted in Charaka to be the single greatest herb for enhancing all three aspects of mind power, learning (Dhi), memory (Driti), and recall (Smriti). Thus it is called the greatest Medhya Rasayana (that which enhances the mind). It helps the quality of sleep by improving mind-body coordination.

Used to promote intellect promoting tonic, brain tonic. Also used in insomnia, epilepsy and other mental disorders.

Pharmacological activities

It was found to have Anxiolytic, antiaggressive and antidepressant effects. It potentiates cognitive process and enhances learning process.
50% ethanolic extract has been found to reduce total serum cholesterol, triglycerides, phospholipids and non esterified fatty acids following treatment for 30 days in hyperlipidemic rats.

Shankhapushpi is used to treat various disorders related to nervous weakness, problems like insomnia, mental as well as physical fatigue, loss of memory etc. Primarily Shankhapushpi is used as a brain tonic. Shankhapushpi is one of the best and prominent natural medicine which helps in improving memory. From ancient times in India, people of all age groups (especially students, teachers, philosophers, etc.) always have tried Shankhapushpi. Natural chemical composition in the Shankhapushpi helps brain to calm down and relieves the tension, which is why Shankhapushpi is also used as tranquilizer for those who suffer from insomnia. Shankhapushpi is also used as one of the most important ingredient in treatment of disorders/syndromes such as hypertension, hypotension, anxiety neurosis, stresses etc 'Kumar V., 2006).
2.8.3 Plumbago zeylanica

(Alpana Ram, 1996; holisticonline.com/herb_home.htm; www.himalayahealthcare.com, updated on sept, 2007)

Family Plumbaginaceae

Other names

English: White eadwort
Hindi: Chitak
Sanskrit: Chitra

Parts Used: Root, root bark, seeds

Description:

This herb is found throughout India. It grows wild as a garden plant in East, North and Southern India and Ceylon. Plumbago zeylanica is an allied species and is considered to be a cultivated variety of Plumbago rosea

 Constituents

Root contains an acid crystalline principle called 'Plumbagin.' Plumbagin is present in all the varieties of plumbago to a maximum of about 0.91%.

Reported activities

50% v/v ethanolic extract of Plumbago zeylanica (root) alone and combined with vitamin E (an antioxidant) was studied in experimentally induced hyperlipidaemic rabbits and was found to have significant antioxidant effect (Alpana Ram, 1996).

P. zeylanica was reported to have antioxidant effects. Plumbagin, chemical constituent of P. zeylanica was found to stimulate CNS in small doses, while with larger doses produces paralysis (Tilak JC et al., 2004).
2.8.4 Boswellia serrata

(holisticonline.com/herb_home.htm; www.himalayahealthcare.com, updated on sept, 2007)

Family BRUSERACEAE

Other names

English: White leadwort, Indian frankincense
Hindi: LUBAN

Common Name:
Indian olibanum tree, olibunum, gond.

Part Used

Bark, Gum Resin

Description

Boswellia (the resin is also known as Indian frankincense) is a moderate to large branching tree found in the dry, hilly areas of India. When the tree trunk is tapped, a gummy oleoresin is exuded. A purified extract of this resin is used in modern herbal preparations.

Active Compounds:

The gum oleoresin consists of essential oils, gum and terpenoids. The terpenoid portion contains the boswellic acids that have been shown to be the active constituents in boswellia. Extracts are typically standardized to contain 37.5-65% boswellic acids.

History

In the ancient Ayurvedic medical texts of India, the gummy exudate from boswellia is grouped with other gum resins, which are referred to collectively as guggals. Historically, the guggals were recommended for a variety of conditions, including arthritis, diarrhea, dysentery, pulmonary disease and ringworm.

Uses

The bark is sweet, cooling and tonic. It is good in vitiated conditions of Pitta, cough, asthma. It is useful in fevers, urethrorrhea, diaphoresis, convulsions, chronic laryngitis, jaundice and arthritis. Bursitis, Osteoarthritis, Rheumatoid arthritis
Reported activities

In patients suffering from ulcerative colitis grade II and III was reported have beneficial effects, this effect was contributed to the boswellic acids, the biologically active ingredients of the Boswellia serrata, which are inhibitors of 5-lipoxygenase, the key enzyme of leukotriene biosynthesis (Gupta I, 1997).

In a double-blind, placebo-controlled study, patients with bronchial asthma, treated with a preparation of gum resin of 300 mg thrice daily for a period of 6 weeks showed improvement of disease (Gupta I, 1998).
2.8.5 Acorus calamus

(holisticonline.com/herb_home.htm; www.himalayahealthcare.com, updated on sept, 2007)

*Family Acoraceae*

*Other names*
Flag root, muskrat root, sweet calomel, sweet flag, sweet sedge

*Parts used* Leaves and rhizome

*Description*

It is a semi aquatic, perennial aromatic herb with creeping rhizomes. Branched and aromatic root or rhizome (underground horizontal stem of a plant that produces roots) from which rise its long crect leaves. The roots have a sweet fragrance and the leaves smell similar to lemon.

The sword-like leaves of the plant resemble those of other similar plants so much, that before the Acorus calamus is in flower, it is difficult to recognize it simply by the appearance of its leaves.

In late spring, green flowers appear in 2 to 4 long spadices (plural form of spadix) below the leaf tips. The flowers eventually give way to small berries.

*Habitat*

Calamus is found in both temperate and sub-temperate areas of the globe. The sheathing leaves of this perennial are from 2 to 6 feet in height and about 1 inch in width. They are sharp pointed and have a ridged midrib running their entire length.
Chemical constituents

Hydrocarbon, Acorin Trimethylamine Asarone, acorenone, beta-asarone, calamendiol, a-seinene, a-calacorene, calamusenone, camphone and shyohunone.

Medicinal Uses

Both the leaves and rhizome are apparently psychoactive, with the rhizome being more potent. In lesser amounts it can have a stimulating or sedative effect on the user. The plant is an aphrodisiac. In Ayurvedic medicine calamus is an important herb, and is valued as a rejuvenator for the brain and nervous system, and as a remedy for digestive disorders, used as an anesthetic for toothache and headaches.

In Western herbal medicine the herb is chiefly employed for digestive problems such as gas, bloating, colic, and poor digestive function.

Acorus calamus extract is anti-rheumatic and analgesic. The extract is used in the form of powder and balms and it is very much useful in case of asthma, bronchitis and cough.

The essential oil is anticonvulsant, antiveratrine and antiarrhythmic. It is also taken as an infusion, tincture or fluid extract. The essence, which contains asarone, has a tranquilizing action.

The rhizome alcoholic extract has sedative and analgesic properties and causes depression in blood pressure and respiration. Extracts are used to treat intestinal cholis, anorexia, gastritis and gastric ulcers.

Reported activities

*A. calamus* has been shown to cause direct potentiation of pentobarbitone, barbiturate and ethanol induced hypnosis. It was also found to reduce aggressive behaviour in isolated mice and anticonvulsant action against metrazol-induced seizure (Panchal et al., 1989; Vohora et al., 1990).