



**A REVIEW ON DEPRESSION**

**P. Kanchana\*, S. K. Ammaji<sup>1</sup> and M. Lakshmisantha<sup>2</sup>**

\*Department of Pharmacology, Assistant Professor, NRI College of Pharmacy, Agiripalli Mandal, Krishna District, Affiliated to JNTUK, A.P, India.

<sup>1</sup>Department of Pharmaceutical Chemistry, Assistant Professor, NRI College of Pharmacy, Agiripalli Mandal, Krishna District, Affiliated to JNTUK, A.P, India.

<sup>2</sup>Department of Pharmacology, Assistant Professor, ASN Pharmacy College, Burrepalem Road, Tenali, Guntur(Dt), A.P, India.

**\*Corresponding Author: P. Kanchana**

Department of Pharmacology, Assistant Professor, NRI College of Pharmacy, Agiripalli Mandal, Krishna District, Affiliated to JNTUK, A.P, India.

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**ABSTRACT**

Depression is a debilitating illness and has become a leading cause of morbidity globally. Major depression is a mood disorder characterized by a sense of inadequacy, despondency, decreased activity, pessimism, anhedonia and sadness where these symptoms severely disrupt and adversely affect the person's life, sometimes to such an extent that suicide is attempted or results. The search for an extended understanding of the causes of depression, and for the development of additional effective treatments is highly significant. Clinical and pre-clinical studies suggest stress is a key mediator in the pathophysiology of depression.

**KEYWORDS:** Depression, neurotransmitters, stress, treatment, anti depressants.

**INTRODUCTION**

Depression is the most common affective disorder (defined as disorders of mood rather than disturbances of thought or cognition); it may range from a very mild condition, bordering on normality, to severe (psychology) depression accompanied by hallucinations and delusions.

It is a common mental disorder, characterized by sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, low energy and poor concentration (WHO, 2011). Depression has a worldwide prevalence in various forms, of 12-20%. The World Health Organization (WHO) has ranked depression fourth in a list of the most urgent health problems worldwide. Depression is the leading cause of disability as measured by Years Lived with Disability (YLDs) and the 4<sup>th</sup> leading contributor to the global burden of disease as measured by Disability Adjusted Life Years (DALYs) in 2000. It will become the second leading cause of premature death or disability worldwide by the year 2020. At its worst, it can lead to suicide, a tragic fatality associated with the loss of about 8,50,000 lives every year globally. In India the prevalence of depression is 31.2 / 1000 population (Madhav SM; 2001).

**HISTORY**

The history of depression is as old as mankind. The term *depression* was derived from the Latin verb *deprimere* "to press down". From the 14<sup>th</sup> century, "to depress" meant to subjugate or to bring down in spirits. What is known

today as depression or major depressive disorder was described by Hippocrates as melancholia. He described melancholia as "black bile", a state of "aversion to food, despondency, sleeplessness, irritability and restlessness". The illness was thought to arise from the substrate of the serious melancholic temperament, which, under the influence of the planet Saturn, made the spleen secrete black bile, ultimately leading to mood darkening through its influence on the brain (Akiskal SH; 2005). In the seventeenth century many important ideas about mental functioning were developed by philosophers and literary figures (Zax M, Cowen EL ; 1976). Robert Burton's *Anatomy of melancholy* appeared for the first time in 1621. He described in detail the psychological and social causes (such as poverty, fear and solitude) that were associated with melancholia and seemed to cause it (Ackerknecht EH; 1959).

In the mid-20<sup>th</sup> century, researchers theorized that depression was caused by a chemical imbalance in neurotransmitters in the brain, a theory based on observations made in the 1950s of the effects of reserpine and isoniazid in altering monoamine neurotransmitter levels and affecting depressive symptoms (Schildkraut, JJ; 1965). During the 1960s and 70s, manic-depression came which refer to just one type of mood disorder (now most commonly known as bipolar disorder), which was distinguished from (unipolar) depression. The terms unipolar and bipolar had been coined by German psychiatrist Karl Kleist (Davison, K; 2006). The term

*Major depressive disorder* was introduced by a group of US clinicians in the mid-1970s as part of proposals for diagnostic criteria based on patterns of symptoms (called the Research Diagnostic Criteria, building on earlier Feighner Criteria), and was incorporated in to the DSM-III in 1980 (Spitzer RL; 1975).

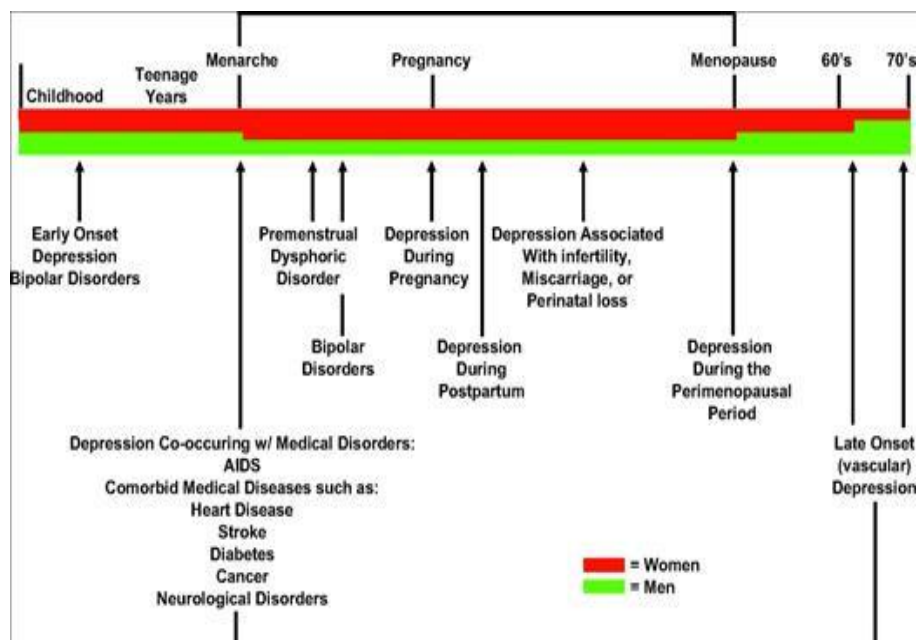
## EPIDEMIOLOGY

The true prevalence of depressive disorders in the United States is unknown. The National Comorbidity Survey Replication found that 16.2% of the population studied had a history of major depressive disorder in their lifetime, and more than 6.6% had an episode with in the past 12 months (Kessler RC; 2003). Women are at increased risk of depression from early adolescence until their mid-50s, with a lifetime rate that is 1.7 to 2.7 times greater than for men (Burt VK; 2002). Although depression can occur at any age, adults 18 to 29 years of age experience the highest rates of major depression during any given year. The estimated lifetime prevalence of major depression in individuals aged 65 to 80 years recently was reported to be 20.4% in women and 9.6% in men (Steffens DC; 2000). Depressive disorders are common during adolescence, with comorbid substance abuse, suicide attempts, and deaths occurring frequently in these young patients (Kessler RC; 1998, Larsson B; 1998). Depressive disorders and suicidality tend to occur within families. For example, approximately 8% to 18%

of patients with major depression have at least one first-degree relative (father, mother, brother, or sister) with a history of depression, compared with 5.6% of the first-degree relatives of those without depression (Weissman MM; 1984). Further-more, first-degree relatives of patients with depression are 1.5 to 3 times more likely to develop depression than normal controls (Warner V; 1999). A recent meta-analysis found that the heritability of liability for major depression was 37%, whereas there remaining 63% of the variance in liability was caused by individual specific environment (Sullivan PF; 2000). Therefore major depressive disorder is relatively common, occurs more frequently in women than men, and prevalence is influenced by both genetic and environmental factors.

## PREVALENCE

Depression is a major cause of morbidity worldwide (WHO; 2001). As per WHO statistics prevalence of Depressive disorder in elderly population in India varies from 13% to 25% with a determined rate of 21.7 % (Ankur; 2010). Lifetime prevalence varies widely, from 3% in Japan to 17% in the US. In most countries the number of people who would suffer from depression during their lives falls within an 8–12% range (Andrade L; 2003). It is twice common in women than in men, although it is unclear.



## Mood Disorders across the Life Cycle

In North America the probability of having a major depressive episode within a year long period is 3–5% for males and 8–10% for females (Murphy JM; 2000). The relative increase in occurrence is related to pubertal development between the ages of 15 and 18, and appears associated with psychosocial more than hormonal factors.

People are most likely to suffer their first depressive

episode between the ages of 30 and 40, and there is a second, smaller peak of incidence between ages 50 and 60 (Eaton WW; 1997). The risk of major depression is increased with neurological conditions such as stroke, Parkinson's disease, or multiple sclerosis and during the first year after childbirth (Rickards H; 2005). It is most common in urban than in rural population and the prevalence is in groups with higher socioeconomic factors (Gelder M; 2005).

## TYPES AND SYMPTOMS OF DEPRESSION:

(<http://www.depression-help-resource.com>)

There are several different types of depression. Often they are distinguished by their prevalent features, duration and severity of symptoms. According to Diagnostic and Statistical Manual of Mental Disorders (DSM) different types depressions are as follows:

### Major Depressive Disorder (also known as Major Depression, Clinical Depression or unipolar disorder)

A major depressive episode occurs with symptoms that last for most of the day nearly every day for at least two weeks. A symptom must either be;

- 1) Depressed mood or
- 2) A noticeable decrease in interest or pleasure in all or most activities.

At least four (or more) additional symptoms are present:

1. Significant weight loss / weight gain or decrease / increase in appetite
2. Difficulty in sleeping or increase in sleeping
3. Fatigue or loss of energy
4. Feeling worthless or excessive guilt
5. Difficulty in thinking, concentrating or making decisions
6. Repeatedly thinking about death or suicide, trying to attempt suicide or having a specific plan to commit suicide.

### Dysthymic Disorder (or also referred to as Dysthymia)

Nearly constant depressed mood for at least 2 years accompanied by at least two (or more) of the following symptoms:

1. Decrease or increase in eating
2. Difficulty in sleeping or increased duration of sleep.
3. Low energy or fatigue
4. Low self-esteem
5. Difficulty in concentrating or making decisions.
6. Feeling hopeless

Symptoms do not occur for more than two months at a time. Generally, this type of depression is described as having persistent but less severe depressive symptoms than Major Depression.

### Manic Depression (known as Bipolar Disorder)

This kind of depression includes periods of mania and depression. Cycling between these two states can be rapid or only mania can be present without any depressive episodes. A manic episode consists of a persistent elevated or irritable mood that is extreme, which lasts for at least one week. At least three (four if only irritable mood) other features are also present:

1. Inflated self-esteem or self-importance.
2. Decreased need for sleep
3. More talkative than usual or compelled to keep talking
4. Experiencing racing thoughts or ideas
5. Easily distracted
6. Increase in goal-oriented activity (social, work, school, sexual) or excessive movement
7. Excessive involvement in potentially risky pleasurable

behavior (e.g. overspending, careless sexual activity, unwise business investments).

Symptoms can be severe enough to warrant hospitalization to prevent harm to self or others or include psychotic features (e.g. hallucinations, delusions).

### Post Partum Depression

It is a Major depressive episode that occurs after having a baby. Depressive symptoms usually begin within four weeks of giving birth and can vary in intensity and duration.

### Seasonal Affective Disorder (SAD)

It is a type of depressive disorder which is characterized by episodes of major depression which reoccur at a specific time of the year (e.g. fall, winter).

### Atypical Depression (Sub-type of Major Depression or Dysthymia)

Characterized by a temporary improvement in mood in reaction to positive events and two (or more) of the following:

1. Significant weight gain or increase in appetite
2. Over sleeping
3. Heavy feeling in arms or legs.
4. Long standing pattern of sensitivity to rejection.

### Chronic Depression

It is a Major depressive episode that lasts for at least two years.

### Psychotic Depression

It is a Major depressive episode with psychotic symptoms such as hallucinations (e.g. hearing voices) and delusions (false beliefs).

### Double Depression

Someone who has Dysthymia (chronic mild depression) also experience a major depressive episode (more severe depressive symptoms lasting at least two weeks).

### Endogenous Depression

Endogenous means from within the body. This type of depression is defined as feeling depressed for no apparent reason.

### Situational Depression or Reactive Depression (also known as Adjustment Disorder with Depressed Mood)

Depressive symptoms developing in response to a specific stressful situation or event (e.g. job loss, relationship ending). These symptoms occur within 3 months of the stressor and lasts no longer than 6 months after the stressor (or its consequences) has ended. Depression symptoms cause significant distress or impairs usual functioning (e.g. relationships, work, school) and do not meet the criteria for major depressive disorder.

### Agitated Depression

It is a Kind of major depressive disorder which is

characterized by agitation such as physical and emotional restlessness, irritability and insomnia.

#### **Melancholic Depression** (Sub-type of Major Depressive Disorder)

Main features of this kind of depression include either a loss of pleasure in virtually all activities or mood does not temporarily improve in response to a positive event. Also, three (or more) of the following are present:

1. Depressed mood that has a distinct quality (e.g. different from feeling depressed when grieving).
2. Depression is consistently worse in the morning
3. Waking up earlier than usual (at least 2 hours).
4. Noticeable excessive movement or slowing down.
5. Significant decrease in appetite or weight loss.
6. Feeling excessive or inappropriate guilt.

#### **Catatonic Depression** (Sub-type of Major Depressive Disorder)

This type of depression is characterized by at least two of the following:

1. Loss of voluntary movement and inability to react to one's environment.
2. Excessive movement (purposeless and not in response to one's environment).
3. Extreme resistance to instructions/suggestions or unable/unwilling to speak.
4. Odd or inappropriate voluntary movements or postures (e.g. repetitive movements, bizarre mannerisms or facial expressions).
5. Involuntarily repeating someone's words or movements in a meaningless way.

#### **Illnesses Co- Exist with Depression**

Depression often co-exists with other illnesses. Such illnesses may precede the depression, cause it, and/or be a consequence of it. Anxiety disorders, such as post-traumatic stress disorder (PTSD), obsessive-compulsive disorder, panic disorder, social phobia and generalized anxiety disorder, often accompany depression. Alcohol and other substance abuse or dependence may also co-occur with depression. Depression also often co-exists with other serious medical illnesses such as heart disease, stroke, cancer, HIV/AIDS, diabetes, and Parkinson's disease. Studies have shown that people who have depression in addition to another serious medical illness tend to have more severe symptoms of both depression and the medical illness (National Institute of Mental Health).

#### **Etiology of Depression**

The etiology of depression remains uncertain and will clearly prove multi factorial. Several theories of biogenic amine abnormalities in major depressive disorders exist, but convincing evidence is lacking. There is no single known cause of depression. Rather, it likely results from a combination of genetic, biochemical, environmental, and psychological factors. Research indicates that depressive illnesses are disorders of the brain. Brain-imaging (MRI), have shown that the brains of people

who have depression look different than those without depression. The parts of the brain responsible for regulating mood, thinking, sleep, appetite and behavior appear to function abnormally.

Some people may be depressed because of one factor while others develop depression due to a mixture of factors. Usually the causes cannot be truly determined but experts say that risk factors such as heredity, brain chemicals, personality traits, medications taken, medical conditions, vitamin deficiencies, type of diets, etc. cause depression in people.

The causes of clinical depression are likely to be different for different people. Sometimes a depressive episode can appear to come out of nowhere at a time when everything seems to be going fine. Other times, depression may be directly related to a significant event in person's lives such as losing a loved one, experiencing trauma, any stressful situation or battling a chronic illness (<http://www.allaboutdepression.com>).

In addition, important neurotransmitters that brain cells use to communicate appear to be out of balance. But these images do not reveal why the depression has occurred. Some types of depression tend to run in families, and the risk is associated with the influence of multiple genes acting together with environmental or other factors (Tsuang MT; 2004). However, it can occur in people without family histories of depression as well (Tsuang MT, Faraone SV; 1990).

The researchers concluded that variation among the serotonin transporter (5-HTT) gene affects the people with very stressful life events who experience depression i.e 40% of women and 30% of men (Schuckit MA; 1997). A substance-induced mood disorder is linked to long-term drug use or withdrawal from certain sedative and hypnotic drugs (Ashton PH; 2002, Bennett P N).

#### **Genetic Factors**

In depression, one theory suggests that a variant of the gene responsible for encoding the serotonin transporter protein could account for early childhood experiences being translated into an increased risk of depression through stress sensitivity in adulthood. In bipolar disorder some genetic linkage has been found with chromosomal region 6q16-q21.

The incidence of affective disorder in first-degree relatives of someone with severe depression may be about 20%, which is almost three times the risk for relatives in control groups. Comparison of the risk of affective disorder in the children of both parents with an affective disorder show a four times greater risk, and the risk is doubled in children with one parent with an affective disorder. Studies looking at twins have found fairly strong evidence for a genetic factor.

Evidence of a genetic link has also been found in studies



of children from parents with affective disorder who were adopted by healthy parents. A higher incidence of affective disorder was found in the biological parents of adopted child with affective disorder than in the adoptive parents.

### **Biochemical Factors**

In its simplistic form the biochemical theory of depression postulates a deficiency of neurotransmitter amines in certain areas of the brain. This theory has been developed to suggest that receptor sensitivity changes may be important. Alternative propositions suggest a central role of acetylcholine arising from dysregulation of the cholinergic and nor-adrenergic neurotransmitter systems.

Although many neurotransmitters may be implicated, the theory focuses on an involvement of the neurotransmitters nor-adrenaline, serotonin and dopamine. This theory emerged from the finding that both monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants appeared to increase neurotransmitter amines, particularly nor-adrenaline, at important sites in the brain. When it was found that reserpine, previously used as an antihypertensive, caused both a depletion of neurotransmitter and also induced depression. This was taken as an apparent confirmation of the theory. Although less attention has been paid to dopaminergic activity, some studies have found reduced activity in depressed patients and an over activity has been postulated in mania.

### **Insomnia and Sleep Disorders**

Studies estimate that 20% of people with insomnia suffer from major depression and 90% of people with depression have insomnia. Although stress and depression are major causes of insomnia, insomnia may also increase the activity of the hormones and pathways in the brain that can produce emotional problems. Even modest alterations in waking and sleeping patterns can have significant effects on a person's mood. Persistent insomnia may actually be a symptom of later emotional disorders in some cases (<http://www.mydepressionconnection.com>)

### **Environmental factors**

Although environmental stresses can often be identified prior to an episode of mania or depression, a causal relationship between a major event in someone's life and the development of an affective disorder has not been firmly established. It may be that life events described as threatening are more likely to be associated with depression.

### **Endocrine factors**

The endocrine system, particularly the hypothalamic-pituitary-adrenal (HPA) axis and the hypothalamic-pituitary-thyroid (HPT) axis, is felt to be implicated in the development of thyroidism and Cushing's syndrome has also been associated with changes in mood. People with depression are more commonly found to have increased

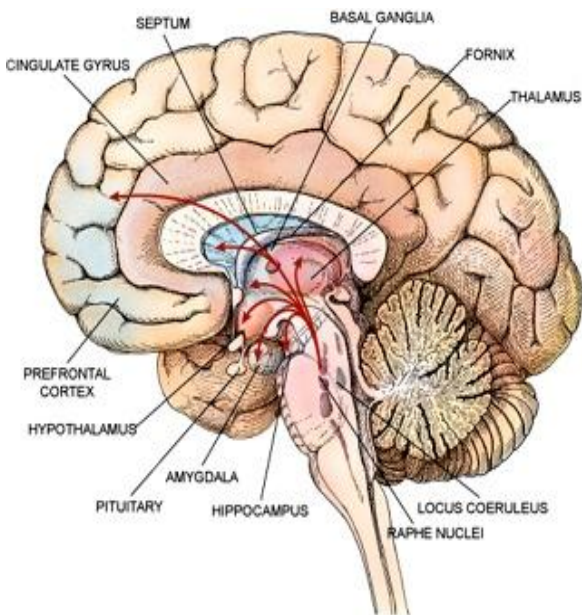
cortisol levels, which also supports the proposition that mood disorders may be linked to dysfunction within the hypothalamic-pituitary-adrenal axis (Roger walker, Shah PJ; 2002).

### **The Neuroanatomy of Depression**

Neurotransmitters and receptors interact with each other within pathways or circuits to regulate various functions of the brain. Theoretically, dysfunction of certain distinct circuits can result in the symptoms of various psychiatric disorders (Cook SC; 2004). Although there is little doubt that various neurotransmitter systems are pathologically involved in the etiology of depression, no single neurotransmitter systems appears to be solely responsible. This is not surprising when one considers the panoply of symptoms that comprise the depressive syndrome including depressed mood, loss of interest in usual activities, inability to experience pleasure, impaired concentration, disturbed sleep, decreased appetite, and suicidality (Zaidi SM ; 2005). A more recent conceptual approach to the biology of depression is to consider it a systems-level disorder involving several critical brain regions and pathways involving these regions. Advances in brain imaging have allowed for rapid advances in these research areas (Drevets W; 2011). Structural brain imaging using magnetic resonance imaging (MRI) has generated a number of reports of altered volumes of several brain regions in patients with depression, most notably a reduction in hippocampal and caudate nucleus size and an increase in pituitary volume (Ressler, KJ; 2007). Positron emission tomography (PET) imaging studies have revealed multiple abnormalities of regional cerebral blood flow (CBF) and glucose metabolism in limbic and prefrontal cortical (PFC) structures in mood disorders.

Brain imaging has identified numerous regions of altered structure or activity in the brain during major depression suggesting disordered neuro circuitry in a variety of structures, such as the anterior & posterior cingulate cortex; the ventral, medial, and dorsolateral prefrontal cortex; the insula; the ventral striatum; the hippocampus; the medial thalamus; the amygdala; and the brain stem (Drevets, W.C; 2000). These brain areas regulate emotional, cognitive, autonomic, sleep, and stress-response behaviors that are impaired in mood disorders. Several brain regions and circuits regulate emotion, reward and executive function, and dysfunctional changes within these highly interconnected limbic regions have been implicated in depression and antidepressant action. A large body of post-mortem and neuro imaging studies of depressed patients have reported reductions in grey-matter volume and glial density in the prefrontal cortex and the hippocampus, regions thought to mediate the cognitive aspects of depression, such as feelings of worthlessness and guilt. These abnormalities implicate limbic-thalamic cortical and limbic cortical striatal pallidum thalamic circuits, involving the amygdala, orbital and medial PFC, and anatomically related parts of the striatum and thalamus in the pathophysiology of

depression.



Parts of the brain responsible of depression

### Neurotransmitter Systems

The catecholamines, adrenaline, noradrenaline and dopamine form the adrenergic systems within the central nervous system (CNS). Some of these adrenergic neurons radiate from the ancient limbic system (emotional centres) and discharge catecholamines into the frontal cortex. The catecholaminergic pathways are thus responsible for alertness, mood and stress (fight or flight) responses. Serotonin is the primary neurotransmitter modulating the excitatory catecholamine systems of the CNS.

**Noradrenaline** - responsible for the control of

- Alertness
- Concentration
- Energy
- Anxiety
- Attention
- Motor activity
- Interest in life

The NA neurons found in pons, medulla & thalamus and important neurons found in locus coeruleus (found in dorsal pons), the axon of NA neurons found in thalamus, hypothalamus, hippocampus, amygdala. (Drummond PD May 15, 2013)

**Serotonin** - responsible for the control of

- Memory
- Mood
- Sexuality
- Anger
- Aggression
- Sleep
- Compulsion and Appetite (Stahl S.M; 2000).

The neurons found in raphe nucleus (midbrain, pons, & medulla) and projects throughout the cortex.

**Dopamine** is mainly related to

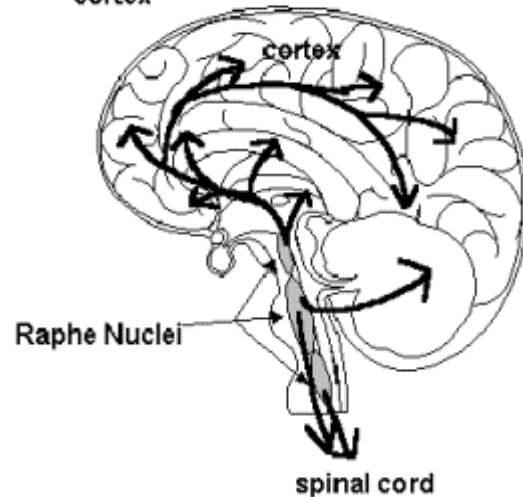
- Attention
- Motivation
- Pleasure
- Reward
- Planning & Problem solving

The DA neurons responsible for depression are found in Mesolimbic system which be gains at ventral tegmental area and extend to Amygdala & Hippocampus.

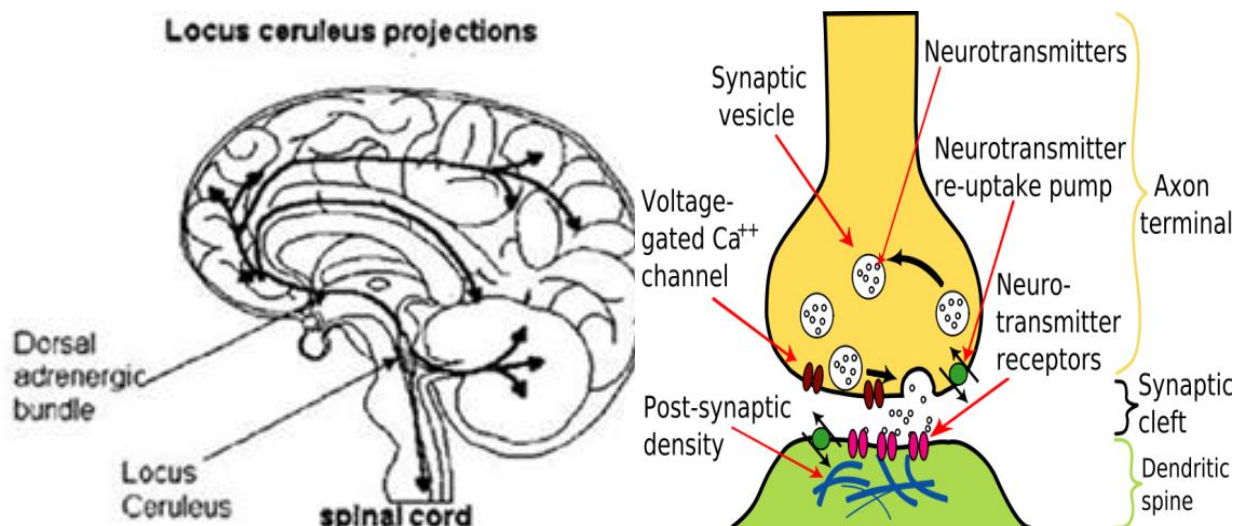
The serotonin and noradrenaline systems have their most important cell bodies in small areas of the brain stem that serve as headquarters for sending axonal projections throughout the brain in specific pathways that mediate specific functions (See Figure 1.1 for an illustration of the serotonin projections and Figure 1.2 for an illustration of the noradrenergic projections). Multiple serotonergic and noradrenergic pathways may be dysfunctional in depression, generating many different symptoms (Stahl S.M. 2000).

### Serotonin projections

Raphe Projects throughout the cortex



The projections of the serotonin system ([www.cellscience.com/CCA.htm](http://www.cellscience.com/CCA.htm))



### The projection of the noradrenaline system ([www.cellscience.com/CCA.htm](http://www.cellscience.com/CCA.htm))

The projections of the serotonin system arise from the nuclei of the dorsal raphe and the raphe magnus. The serotonin receptors (5-HT) have been identified into various sub-types with the 5-HT<sub>1</sub> and 5-HT<sub>2</sub> sub-types being of greater interest in psychiatry. The most important of the 5-HT<sub>1</sub> subclass is 5-HT<sub>1A</sub> which is concentrated in the raphe and hippocampus. This receptor is implicated as an auto receptor that modulates 5-HT release from the presynaptic neurons. The 5-HT<sub>2</sub> receptors occur in high concentrations in the frontal cortex and nucleus accumbens (Van Oekelen D. *et al.* 2003).

### PHYSIOLOGICAL PROCESSES

- The initial step of synthesis of neurotransmitters are the facilitated transport of amino acids from blood to the brain, where precursors are converted via enzymatic reactions into transmitters, which are stored in synaptic vesicles, and finally released into the synaptic cleft by a Ca<sup>2+</sup>-dependent process.
- Amines in the synaptic cleft bind to postsynaptic receptors to produce a post synaptic response.
- The synaptic effects of neurotransmitters are terminated by binding of the transmitters to specific transporter proteins and reuptake into the presynapse, where they are metabolized by enzymes, for example, monoamine oxidase (MAO), or stored once again in the vesicles (Jean PM; 2002). This would inturn leads to a decreased level of transmitters at certain sites in the brain, which causes depression.

### Pathophysiological features of depression

Recent findings have substantially increased our understanding of the pathophysiology of depression (Richard C, Shelton ; 2007). There has been a correspondingly significant increase in our understanding of the efficacy and tolerability of currently available treatments (Nemeroff CB; 2005). The latter database has convincingly demonstrated a large unmet need for the more than one half of depressed patients who fail to achieve remission after adequate trial of antidepressant monotherapy. Despite our increased understanding of both its pathophysiology and treatment, depression remains highly prevalent, accounting for more disability than any other disorder worldwide (Wong MA, Licinio J; 2001). Despite its prevalence and social impact, its prognosis and management are often poor, not only due to the heterogeneity of this ailment, but also our lack of knowledge of the pathophysiology underlying depression. Various areas of brain like forebrain, hippocampus, amygdale, limbic system and medial prefrontal cortex appear to be implicated in depression (Ansorge MS; 2005, Vyas A; 2002). A number of neuromodulators have been reported to be involved in the pathophysiology of depression (Graybiel AM; 1990).

### Decreased Monoaminergic Neurotransmission

The main biochemical theory of depression is the **monoamine hypothesis**, which states that depression is caused by a functional deficit of monoamines (norepinephrine, serotonin and dopamine) at certain sites in brain (Nutt DJ; 2002). There are both clinical and experimental evidences to suggest that increased central cholinergic activity can precipitate depression and reduced the noradrenergic activity (Millan MJ ; 2004, Goldman LS; 1999). Most of the serotonergic, noradrenergic and dopaminergic neurons are located in midbrain and brainstem nuclei and project to large areas of the entire brain. This anatomy suggests that monoaminergic systems are involved in the regulation of a broad range of brain functions, including mood, attention reward processing, sleep, appetite, and cognition. Many of these functions have been



demonstrated to be impaired in patients with depression (Dunlop BW ; 2007). Almost every compound that inhibits monoamine reuptake, leading to an increased concentration of monoamines in the synaptic cleft, has been proven to be a clinically effective antidepressant. Inhibiting the enzyme monoamine oxidase, which induces an increased availability of monoamines in presynaptic neurons, also has antidepressant effects. The emerging new tools of molecular neurobiology and functional brain imaging have provided additional support for the involvement of these three systems (Owens MJ; 1994). Reduced monoamine metabolite levels have been found in the cerebrospinal fluid of depressed individuals; likewise, serotonin (5-HT), norepinephrine (NE) or dopamine depletion exerts pro-depressive effects (Charney DS; 1998). These monoamine transporters are most likely localized presynaptically in corresponding neurons, remove neurotransmitters from outside cells and recycle it back into the releasing and/or neighboring terminals. Hence it represents established targets of many psycho stimulants and antidepressants, which exert their post-psychotropic action via interference with transporter function resulting in a rise in extracellular levels of monoamines. The clinically effective antidepressants increase monoaminergic signaling and there is compelling evidence that monoamines play a role in developmental processes involved in depression (Ressler KJ; 2001).

Low levels of NE (Norepinephrine) metabolites are found in the urine and CSF of depressed patients (Millan MJ; 2004). Increased density of adrenergic receptors is found in post-mortem brain tissue in the cortex of depressed suicide victims. Stress, which precipitates depression in vulnerable individuals, increases activity of the NE circuits in the brain. MAO is enzyme protein responsible for metabolizing monoamines like NE, DA & 5-HT. MAO-A has substrate preference for serotonin and is the main target for the antidepressant monoamine oxidase inhibitors (MAOIs). MAO-B has substrate preference for phenyl ethyl amine. Both enzymes act on nor- adrenaline and dopamine. In case of depression the level monoamine oxidase enzyme in brain is increased which turn reduce the levels of monoamines. Increased MAO-A activity is found in the CNS of depressed patients. Depletion of NE in depressed patients in remission treated with a NE reuptake inhibitor precipitates a relapse in depressive symptoms. Alterations in noradrenergic circuits may play a preeminent role in patients with treatment-resistant depression (John F; 2001) of the major catecholamine systems, NE-containing circuits have long been considered to be pathologically involved in the etiology of mood disorders. Moreover, neurochemical and neuroendocrine studies in depressed patients and post-mortem findings support a role for NE dysfunction in depression.

Low concentrations of the major metabolite of 5HT (5-hydroxyl indole acetic acid) are found in the CSF of patients in depression (Caspi A; 2003). Increased density

of 5HT<sub>2</sub> receptors has been reported in both blood platelets and brain postmortem tissue of patients with depression. Decreased 5HT transporter (SERT) binding site density is seen in the midbrain and blood platelets of patients with depression. Decreased plasma concentrations of L-tryptophan, the precursor to 5HT, are found in patients with depression (Owens MJ; 2004). Depletion of 5HT in depressed patients in remission provokes a rapid relapse depressive symptoms. The role for central nervous system (CNS) DA circuits with many investigators suggesting that the now well-documented suboptimal therapeutic responses to SSRIs and selective serotonin-nor epinephrine reuptake inhibitors (SNRIs) may be due, in part, to their relative lack of effect on brain DA circuits. As regards CNS 5HT systems, even more evidence has accrued to support a preeminent role for their involvement in depression. In addition to the very impressive evidence of reduced activity of serotonergic neurons in depression as assessed in postmortem, CSF, and neuroendocrine studies, there are new data from both postmortem and positron emission tomography (PET) imaging studies demonstrating a reduction in the number of serotonin transporter (SERT) binding sites (the site of action of SSRIs) in the midbrain and amygdale of drug-free depressed patients, as well as a reduction in both presynaptic (in the midbrain) and postsynaptic (in the mesiotemporal cortex) 5HT<sub>1A</sub> receptor density (Pariente CM; 2008). The effects of serotonin are mediated through 5-HT receptors. In patients with depression, an increased density of postsynaptic 5-HT<sub>2</sub> receptor binding sites has repeatedly been reported in both frontal cortex and platelets (Charney DS; 1998). Dysfunction in the serotonergic system is a well-established theory explaining the pathophysiology of depression.

Dopaminergic neurons therefore innervate brain areas associated with behavioral and physiological functions that are altered in depression (e.g., the cortex, limbic structures and pituitary gland Dopamine (DA) is the major neurotransmitter that mediates the ability to experience pleasure. Anhedonia is the inability to experience pleasure, a cardinal feature of depression. A high rate of depression is seen in patients with Parkinson's disease, a disorder characterized by DA neuron degeneration. Brain imaging and postmortem studies have revealed decreased dopamine transporter binding and increased postsynaptic D<sub>2</sub>/D<sub>3</sub> receptor binding, all indicative of reduced DA neurotransmission. Reductions in the major metabolites of DA have been reported in the CSF of depressed patients (Dunlop BW; 2007). Increased MAO-A activity is found in the CNS system of depressed patients. Drugs that increase DA neurotransmission such as MAOIs, DA reuptake blockers, and DA receptor agonists possess antidepressant properties. This emergence of a DA hypothesis of depression is not surprising in view of the fact that the inability to experience pleasure, anhedonia, is considered by many to be the most important pathognomonic symptom of depression.



There is some evidence for the involvement of glutamate, g- aminobutyric acid, substance P, brain derived neurotrophic factor (BDNF), thyrotropin-releasing hormone, somatostatin, leptin, and acetylcholine containing neurons in the pathogenesis of depression (Merali Z; 2004, Maeng S; 2007, Gold PW, Drevets WC; 2002). Clinical evidence supports the fundamental roles of serotonin and norepinephrine, as well as the interactions between these systems in the etiology of depression. In addition, corticotropin-releasing factor, dopamine, GABA, Somatostatin, substance P and thyroid-related hormones have been implicated in the pathophysiology of depression (Brouwer J P. et al; 2005)

### **Stress Hormones and Cytokines**

Any form of stressful life event is considered as the very initial sign of depression, there by depression is often thought as a stress related disorder. The human stress experience contributes to the pathogenesis of depression, and may also play a role in the severity and recurrence of this debilitating illness. The nature of association between stress and depression has been an area of intense debts. The hypothalamic-pituitary-adrenal (HPA) axis is known to be activated in many patients with depression and there is considerable evidence that this is driven by hyperactivity of hypothalamic and extra hypothalamic corticotropin-releasing factor (CRF) pathways. Neurons of the para-ventricular nuclei of the hypothalamus project to the median eminence where they secrete CRF into the hypothalamo-hypophyseal portal system. CRF is then transported in this specialized vascular system to the anterior pituitary where it acts on corticotrophs to increase ACTH secretion, thereby controlling HPA axis activity. Some nonpeptidic-CRF1 receptor antagonists (e.g. antalarmin) may possess antidepressant-like activity and therefore, represent a promising novel pharmacotherapeutic strategy in the treatment of depression. Corticotropin-releasing hormone (CRH) is released from the hypothalamus in response to the perception of psychological stress by cortical brain regions. There is convergent evidence for CRH to play a major role in the pathogenesis of certain types of depression. Levels of CRH in the cerebrospinal fluid are elevated in some depressed subjects (McEwen, B. S;2007).

### **Inflammatory Cytokines and Depression**

Increasing amount of data suggest that inflammatory responses have an important role in pathophysiology of depression (Dantzer R; 2008). Depressed patients have been found to have higher levels of pro-inflammatory cytokines, acute phase proteins, chemokines and cellular adhesion molecules. Moreover, pro-inflammatory cytokines have been found to interact with many of the pathophysiological domains that characterize depression, including neurotransmitter metabolism, neuro-endocrine function, synaptic plasticity and behavior. These findings suggest that targeting pro- inflammatory cytokines and their signaling pathways might represent a novel strategy to treat depression. There are clinical evidences showing

that there are increased levels of prostaglandin E2 (PGE2) in the plasma of depressed patients. Antidepressants like tricyclics and MAO-inhibitors normalized the central neurotransmission by reducing the brain concentration of both cytokines and PGE2. Depressed patients have been found to have higher levels of pro- inflammatory cytokines, acute phase proteins, chemokines & cellular adhesion molecules (Agren H; 1984).

### **Hypothalamic-pituitary-thyroid (HPT) axis and depression**

The overlap in symptoms between patients with hypothyroidism and those with major depression has led to number of studies on HPT axis in patients with mood disorders. Thyrotropin releasing hormone (TRH) is released from the hypothalamus and stimulates TRH receptors in the pituitary to release thyroid stimulating hormone (TSH) which in turn stimulates specific receptors in the pituitary to release tri-iodothyronine (T3) and thyroxin (T4) hormones. Thyroid hormones provide feedback to both the hypothalamus and pituitary to regulate the axis. CSF TRH was increased in two small studies of depressed patients as compared to control. In one study, depressed patients with high normal thyroid levels were also reported to demonstrate exaggerated TSH responses to TRH (Sajdyk, T. J. et al; 2008)

### **The Neurotrophic Hypothesis of Depression**

Risk factors for depressive episodes change during the course of the illness. The first depressive episode is usually reactive, i.e., triggered by important psychosocial stressors, while subsequent episodes become increasingly endogenous, i.e., triggered by minor stressors or occurring spontaneously. There is consistent evidence that the volume loss of the hippocampus and other brain regions is related to the duration of depression, suggesting that untreated depression leads to hippocampal volume loss, possibly resulting in increased stress sensitivity and increased risk of recurrence (Pezawas, L. et al; 2008). Glucocorticoid neurotoxicity, glutamatergic toxicity, decreased neurotrophic factors, and decreased neurogenesis have been proposed as possible mechanisms explaining brain volume loss in depression. There is no solid evidence on any of these mechanisms, since there are no imaging tools to directly examine neurotoxic and neurotrophic processes in vivo. Brain derived neurotrophic factor (BDNF) has attracted considerable interest. Specifically, preclinical studies have shown correlations between stress-induced depressive-like behaviors and decreases in hippocampal BDNF levels, as well as enhanced expression of BDNF following antidepressant treatment. There are interesting evidences for the involvement of the BDNF in both the pathophysiology of depression and the mechanisms of action of antidepressants. Several classes of antidepressants increased BDNF expression in rat brain as well as in depressed patients. BDNF is found in blood, where it mostly accumulates in platelets. Interestingly, several studies have found decreased blood levels of BDNF in depressed patients.

### Human Growth Hormone and Depression

Growth hormone (GH) is synthesized in anterior pituitary. Two hypothalamic hormones, growth hormone releasing factors (GHRF) and somatostatin (growth hormone inhibiting factor) modulate its release from the pituitary (John F; 2010). The major neurotransmitters involved in mood regulation (e.g. nor-adrenaline, serotonin and dopamine) affect GH release. CSF levels of somatostatin (which inhibits GH, CRH and ACTH release) are reduced in depression.

### Malondialdehyde and Depression

In case of stress and oxidative damage of the cells, malondialdehyde (MDA) is generated. The levels of brain MDA were more in stressed mice as compared to normal mice (Pal R, Gulati K; 2006).

### Altered Glutamatergic and GABAergic Neurotransmission

A series of magnetic resonance spectroscopy studies consistently showed reductions in total gamma-aminobutyric acid (GABA) concentrations in the prefrontal and occipital cortex in acute depression. This may reflect acute stress effects, since psychological stress seems to induce presynaptic down-regulation of prefrontal GABAergic neurotransmission (Pelty F; 1992). Alternatively, low total GABA concentration may reflect reduction in the density and size of GABAergic interneurons. In addition, chronic stress may reduce GABA-A receptor function, possibly through changes in neuroactive steroid synthesis. Contradictory evidence of the GABA hypothesis of depression includes the lack of effects of GABAergic drugs on core depressive symptoms and normal prefrontal GABA concentration in subjects with remitted Depression. Several lines of evidence suggest a dysfunction of the glutamate neurotransmitter system in MDD: a single dose of the glutamate N-methyl-D-aspartate (NMDA) receptor antagonist ketamine produced rapid and large antidepressant effects in patients with treatment-resistant Depression; inhibitors of glutamate release (e.g., lamotrigine, riluzole) demonstrated antidepressant properties; abnormal glutamate levels were found in depressed subjects as determined by magnetic resonance spectroscopy; and there is evidence for abnormal NMDA signaling in post-mortem tissue preparations. Since glutamate is the major excitatory neurotransmitter involved in almost every brain activity, the characterization of the specific role of glutamate in depression deserves further investigation.

GABA is a major inhibitory neurotransmitter in brain and regulates seizure threshold as well as nor-adrenaline and dopamine turnover. Dysfunction of the gamma amino butyric acid (GABA)-ergic system has been purported to play a role in psychiatric disorders, including anxiety and major depression. There are two types of GABA receptors clear link between GABA<sub>A</sub> receptors and anxiety has long been established. However, despite the GABA system being the prominent inhibitory

neurotransmitter in the brain, a role in depression has been less well validated.

### Management of Depression

Patients who have symptoms of depression should be evaluated with a history, physical examination and limited laboratory testing (if indicated) to rule out secondary medical causes. Unipolar depression must be distinguished from bipolar depression since their treatment differs. Assessment for the presence of suicidal ideation is of paramount importance in all depressed patients. Evaluation in an emergency department and/or hospitalization should be considered for patients at a significant risk of suicide. Regardless of the modality of treatment selected for initial therapy, the goal of treatment should be symptom remission. The treatment strategy consists of three phases, acute, continuation and maintenance. The initial treatment objectives are symptom remission (which may be accomplished in the acute phase) and restoration of psychosocial functioning (which may be accomplished in the acute or continuation phases). The prevention of a symptomatic relapse is also an objective of continuation phase treatment. Finally, prevention of new depressive episodes (i.e. recurrences) is the aim of maintenance phase treatment. Various strategic choices in the management of depression are as follows.

#### A. Psychotherapy (Ebert MH; 2008)

Psychotherapy alone or in combination with antidepressant medication, is an option for patients with mild to moderate degree of major depression. The psychosocial interventions that have fared well in controlled trials relative to antidepressants include interpersonal psychotherapy, cognitive-behavioral therapy and some of the marital and family interventions. Beyond pure psychotherapeutic management, the therapeutic relationship contains other important factors. These include observing emerging destructive impulses toward self or others; providing ongoing education, knowledge and feedback about the patient's illness, its prognosis, and treatment; discouraging the patient from making major life changes while he or she is depressed; setting realistic, attainable and tangible goals; and enlisting the support of others in the patient's social network.

#### B. Electro convulsive therapy

ECT has shown efficacy in all types of major depressive disorder. It appears to be most effective in the most severely depressed patients. Recent evidence suggests that it is less useful in patients whose depressive episodes occur in the context of a concurrent mental or medical disease (i.e., secondary depression) or in the treatment of depression that has been refractory to medications during the present episode. ECT is used as primary treatment when:

- An urgent need (either psychiatrically or medically) for a rapid response exists, since response of antidepressant drugs take 2-3 weeks to appear.

- Patient history of better response to ECT.
- Patient has responded poorly to pharmacotherapy or deteriorated.

### C. Deep brain stimulation

Clinical trials are focused on the use of DBS for epilepsy and depression but the FDA has not approved this use. It requires brain surgery by a neurosurgeon to drill a hole in the skull and insert an electrode into the patient's tissue and it is therefore the most invasive form of brain stimulation in the treatment of depression.

### D. Physical exercise

Physical exercise is recommended by U.K. health authorities for management of mild depression<sup>111</sup>, but it has only a moderate effect on major depressive disorder.

### E. Other somatic treatments

Repetitive transcranial magnetic stimulation (rTMS) applies powerful magnetic fields to the brain from outside the head. Multiple controlled studies support the use of this method in treatment-resistant depression; it has been approved for this indication in Europe, Canada, Australia, and the US.

### F. Pharmacotherapy

Antidepressant drugs which can elevate mood in depressive illness, practically all antidepressants affect monoaminergic transmission in the brain in one way or the other and many of them have other associated properties. Particularly over the past two decades, a large number of antidepressants with an assortment of effects on reuptake/metabolism of biogenic amines and on pre/post junctional aminergic or cholinergic receptors have become available so that a cogent classification is difficult.

The currently used antidepressant drugs are classified as follows:

#### I. MAO Inhibitors

- a. Non-Selective (MAO-A & MAO- B inhibitors).  
*Tranylcypromine.*
- b. Selective MAO-A inhibitors.  
*Moclobemide.*

#### II. Reuptake Inhibitors

##### 1. Serotonin and Norepinephrine reuptake inhibitors Older agents (TCAs)

Amitriptyline, Doxepin, Clomipramine, Imipramine

##### Newer agents (non-TCAs)

Venlafaxine, Milnacipran, Bupropion, Duloxetine

##### 2. Nonselective norepinephrine-reuptake inhibitors

Desipramine, Nortriptyline, Maprotiline

##### 3. Selective serotonin-reuptake inhibitors (SSRIs)

Fluoxetine, Paroxetine, Sertraline, Fluvoxamine, Citalopram, Escitalopram

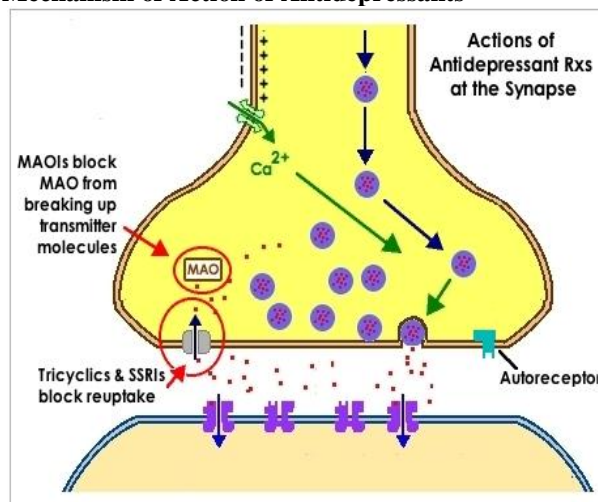
##### 4. Selective norepinephrine-reuptake inhibitors (NRIs)

Reboxetine

### III. Mixed-action newer agents or Atypical Antidepressants.

Mirtazapine, Mianserin, Nefazodone, Trazodone, Venlafaxine

### Mechanism of Action of Antidepressants



It is generally thought that the tricyclics act by increasing the availability of noradrenalin and serotonin as central neurotransmitters by blocking their neuronal re-uptake (Barar FSK; 1999). The monoamine oxidase [MAOs] comprise two structurally related flavin-containing enzymes, designated MAO-A and MAO-B; Inhibition of this enzyme system by MAO inhibitors causes a reduction in metabolism and a subsequent increase in the concentrations of biogenic amines. Of the two major molecular species of MAO, MAO-A preferentially deaminates epinephrine, norepinephrine, and serotonin, and is selectively inhibited by clorgyline. MAO-B metabolizes phenethylamine and is inhibited by selegiline. Dopamine and tyramine are metabolized by both MAO enzymes and both types are inhibited by phenelzine, tranylcypromine, and isocarboxazid (Dr. Bodhankar SL; 2007). The selective serotonin reuptake inhibitors [SSRIs] block neuronal re-uptake of serotonin into the serotonergic nerve ending. Hence they enhance serotonin levels in the synapses (Udaykumar P).

### Therapeutic Applications Of Antidepressants:

(Sweetman SC; 2009)

#### Psychiatric uses

SSRIs, tricyclic and tetracyclic antidepressants are used:

1. Primarily in depression particularly in major depression or endogenous depression as well as in episodes of bipolar depression. They may also be useful in reactive or secondary depression.
2. Panic disorders, generalized anxiety disorders and phobic states particularly agoraphobia- SSRIs and tricyclic antidepressants that inhibit serotonin reuptake, such as clomipramine and imipramine, have been given in the management of anxiety disorders including post traumatic stress disorder and trichotillomania, though SSRIs are drug of choice

due to better patient acceptability. Tricyclic antidepressants and the SSRIs have also been used in bulimia nervosa and kleptomania.

3. Obsessive compulsive disorder-SSRIs are the drugs of choice, though TCAs like imipramine and clomipramine are also used.

#### Non psychiatric uses

1. Chronic neuropathic pain: Tricyclic antidepressant, usually amitriptyline, is useful in alleviating some types of pain. Chronic neuropathic pain as seen in cancer, central post-stroke pain, diabetic neuropathy, phantom limb pain and post herpetic neuralgia responds to therapy with tricyclics. Tricyclics are also often of benefit in the treatment of idiopathic or of facial pain and may be of value for patients with complex regional pain syndrome. Pain and sleep quality may be improved by tricyclics in patients with fibromyalgia, a condition that responds poorly to analgesics and anti-inflammatory drugs. Patients with migraine or chronic tension type headache may also benefit from tricyclics.

2. Attention deficit hyperactivity disorder: Tricyclic antidepressants such as imipramine or desipramine are reserved for patients who fail to respond to or who are intolerant of stimulants.

3. Childhood enuresis: Tricyclic antidepressants like imipramine, amitriptyline, nortriptyline and clomipramine are among the drugs used as an alternative or adjunct to non-pharmacological methods for the treatment of nocturnal enuresis in children in whom organic pathology has been excluded. Tricyclic antidepressants are also sometimes used in the management of urinary incontinence in elderly patients.

4. Pruritis: Doxepin in particular has a very potent antihistaminic activity. It has been shown to be an effective oral alternative to conventional antihistamines in the treatment of chronic urticaria and an effective oral treatment for idiopathic cold urticaria.

#### Drug Interactions with Various Antidepressants: (Baldessarini RJ; 2006)

The drug interactions are common with most antidepressants. The metabolism of most antidepressants is mainly dependent on the activity of hepatic cytochrome P-450 isoenzymes. Some antidepressants are not only substrates for metabolism by CYPs but also can inhibit metabolic clearance of other drugs, producing clinically significant drug-drug interactions as follows.

Phenytoin, aspirin, aminopyrine, scopolamine and phenothiazines reduce the binding of tricyclic antidepressants to plasma albumin and can increase their toxicity. Barbiturates and many anticonvulsant agents (particularly carbamazepine), as well as cigarette smoking, can increase the hepatic metabolism of antidepressants by inducing CYPs. Several serotonin reuptake inhibitors are potent inhibitors of human hepatic CYPs. During the use of combinations of SSRIs with tricyclic antidepressants serum concentrations of the tricyclic drug may rise to toxic levels. Drug interactions

with SSRIs include potentiation of agents metabolized prominently by CYP1A2 (e.g., beta adrenergic receptor antagonists, caffeine, several antipsychotic agents and most tricyclic antidepressants); CYP2C9 (carbamazepine); CYP2C19 (barbiturates, imipramine, propranolol and phenytoin); CYP2D6 (Beta adrenergic antagonists, some antipsychotics and many antidepressants); and CYP3A3/4 (benzodiazepines, carbamazepine, many antidepressants and several antibiotics). Antidepressants potentiate the effects of CNS depressants like alcohol and antihistaminics. TCAs abolish the antihypertensive effect of guanethidine and clonidine by blocking their transport to adrenergic neurons. Tricyclic antidepressants potentiate the action of directly acting sympathomimetic amines and inhibit the action of indirectly acting sympathomimetics like ephedrine and tyramine. TCAs delay gastric emptying by their anticholinergic property and retard their own as well as other drugs metabolism; as well they increase the absorption of some drugs like digoxin and tetracyclines. SSRIs can interact with MAO inhibitors to cause serotonergic syndrome. MAO inhibitors cause dangerous hypertensive crisis.

#### Choice of antidepressants

As no antidepressant has been found to be more effective than any other, the choice will be determined by other factors. In some areas, cost has become a major factor in choice. In general the SSRI drugs appear to have a better side effect profile and are less toxic following overdose. For most people with moderate-to-severe depression, the use of a SSRI as the first-line choice is appropriate. If an SSRI is not appropriate then alternative agents include lofepramine. As long as there are no contraindications, then previous response and tolerance to a particular drug or patient preference should also be considered. The quantities of medication supplied to these patients should be carefully monitored (Roger walker)

#### Diagnosis of Depression

The diagnosis of mental disorders is often believed to be more difficult than diagnosis of somatic or general medical, disorders, since there is no definitive lesion, laboratory test, or abnormality in brain tissue that can identify the illness. A diagnosis of depression is confirmed when the patient meets established criteria which target the symptoms typically associated with depression. To meet the established criteria, a patient must exhibit either depressed mood or diminished interest or pleasure in usual activities and must have at least five symptoms from the following:

1. Significant weight loss or weight gain, or decrease or increase in appetite.
2. Insomnia or hypersomnia.
3. Psychomotor agitation or retardation as observed by others.
4. Fatigue or loss of energy.
5. Feelings of worthlessness, or inappropriate guilt.
6. Diminished ability to think or to concentrate.
7. Recurrent thoughts of death, suicidal ideation, suicide



attempt or a specific plan for suicide.

Various rating scales have been developed that may help to demonstrate the severity of depressive disorder distinguish a predominantly anxious patient from a depressed patient. Biochemical tests are generally not particularly helpful in determining the treatment plan or management of affective disorders. The dexamethasone suppression test is still used by some clinicians as an aid to diagnosis, but it must be considered as having limited value in practice. Within the UK, mental and behavioural disorders are commonly classified using the *international classification of diseases*, ICD 10 (WHO 1992). The American Psychiatric Association (1994) has developed a precise system of diagnosis, based on the description of symptoms in the *diagnostic and statistical manual of mental disorders* (DSM).

Bipolar disorder is frequently misdiagnosed, and consequently patients are often inappropriately treated. Several problems contribute to the misdiagnosis of bipolar disorder. Patients often consider their manic symptoms to be normal and fail to realise that they might require treatment. Secondly, symptoms are highly variable, ranging from impulsive behaviour or substance abuse, to fluctuations in energy levels, and are often attributed to disorders other than bipolar disorder (Hirschfeld RMA; 2004)

The identification of target symptoms may be useful in evaluating the response to treatment. In routine clinical practice, antidepressant medication should not generally be used to treat patients with mild depression. Non pharmacological strategies are preferable in this group.

### Rating Scales

Various rating scales can be used to assist with the assessment of the severity of the disorder. Two of the more commonly used rating scales are the Beck Depression Inventory and the Hamilton Depression Rating Scale.

#### 1. Beck Depression Inventory

This is a self-reporting scale looking at 21 depressive symptoms. The subject is asked to read a series of statements and mark on a scale of 1-4 how severe symptoms are. The higher the score, the more severely depressed a person may be.

#### 2. Hamilton Depression Rating Scale

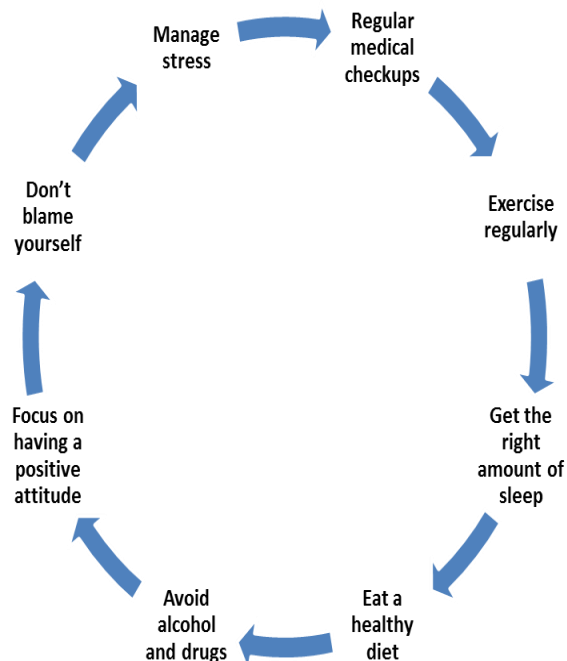
This rating scale is used by a healthcare professional at the end of an interview to rate the severity of the depression.

**Dexamethasone Suppression Test:** (Zoltan Rihmer ES; 1983, Kuhs H; 1985)

This test involves the administration of 1 mg of dexamethasone at 11 p.m., which is said to coincide with the low point of cortisol secretion. It would be expected that normally dexamethasone would suppress the

secretion of cortisol for about 24 hours. Blood samples are taken following day, at 8 a.m., 4 p.m. and 11 p.m. If it is found that serum cortisol levels are elevated between 9 and 24 hours after the administration of dexamethasone and then this is taken as a positive result, i.e. dexamethasone has failed to suppress normal cortisol secretion. It is important to note that this test is not specific to depression and other disorders may account for an apparent positive result. Similarly, there may be a high proportion of depressed people who show a negative result with this test.

### Prevention of Depression



### Current status of antidepressants

The pharmacological therapies in the treatment of depression bring acute and sustained remission only in a minority of patients (Rush AJ; 2006) For example recent effectiveness trials have shown that only one out of the three depressed out-patients receiving first step treatment of SSRI achieved remission from depressive symptoms (Barton F; 2008) Other large multicenter trials in chronically depressed out-patients confirm the modest remission rates (Keller MB; 1998, Keller MB, McCullough JP; 2000). A recent meta-analytic study of randomized controlled trial (RCT) data by Kirsch et al. effectively concluded that the new antidepressant drugs are either no better than placebos or only as effective as placebos (Kirsch I; 2008). In 2008 Turner et al. published In 2008 Turner et al. published literature on antidepressants was biased towards "favourable" results (Turner EH; 2008). There is a need for developing new effective drugs for the treatment of depression.

Neutraceuticals have started gaining much attention in today's world. Many natural products are believed to have role in treating diseases and promotion of health.

The role of nutraceuticals in the treatment of depression is also being evaluated (Targum SD; 2009). The small amount of controlled clinical research that has been done is encouraging with regard to the efficacy of some nutraceuticals that have shown benign side effect profiles and limited toxicity. In fact, the most commonly used nutraceuticals appear to be better tolerated than the more standard, conventionally used antidepressants, such as SSRIs. Some of these nutritional supplements can be used in patients who have achieved only partial treatment response to standard antidepressant medications and may offer additional clinical benefit without increasing the side effect burden. Studies have shown the efficacy of S-adenosylmethionine (SAME) (Delle Chiaie R; 2002) St. John's Wort (Kasper S; 2006) and omega-3 fatty acids (Jazayeri S; 2008) in the treatment of depression.

The plants like Glycine max and Annona squamosa are cultivated in almost every part of the world and has the potential to be utilized for human consumption. Experimental studies have a correlation with clinical applications found in the literature on the traditional medicine of many countries.

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