MOOD DISORDERS

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Keywords: Mood, Depression, Mania, Bipolar disorder, Psychopharmacological drug

ABSTRACT

Mood disorders are one of the most common psychiatric illnesses in the present world. They compromise mainly depression, mania and bipolar disorder. Depression is characterized by low mood whereas mania is characterized by elated mood and bipolar disorder characterized by cyclic change of mood from depression to mania intermittently. Mood disorders add up to significant morbidity leading to increased health care costs and decreased productivity. There are many hypotheses for etiology of mood disorders and also many psychopharmacological drugs are discovered for their treatment. Though there are many psychopharmacological drugs, none of them are effective in treating the mood disorders completely. The present review article gives an overview of different kinds of mood disorders, etiological factors, and psychopharmacological drugs available presently for their treatment and future prospective for improving their treatment.
INTRODUCTION
Mood disorders groups together a number of clinical conditions, the common feature being disturbance of mood accompanied by related cognitive, psychomotor, psychosocial and interpersonal difficulties.1 Affect is a short lived emotional response to an idea or an event, whereas mood is a sustained and pervasive emotional response which colors the whole psychic life.2 Alternatively affect and mood refers to the feeling tone of an individual. Affect sustaining over a period of time is called as mood. Affect and mood can be compared to “climate” and “weather” where the affect refers to actual weather and the mood to the prevailing climate.3 Mood disorders have been mentioned from the ancient period. Old testament describes king Saul was suffering from depressive disorder and used to respond to David’s soothing music. Hippocrates coined the term mania and melancholia to describe the mental disturbances in 400 BC. Later in 30AD Rome physician Aulus Cornelius described melancholia as depression and is caused by black bile. Jules Falretin 1854 described a condition called foliecirculaire, in which patients experience alternating moods of depression and mania. Karl Ludwig kahlbaum in 1882 made similar observation and stated that mania and melancholia were the different stages of the same disease and coined the term cyclothymia. Emil Keplin in 1921 made similar observation in mood disorders and concluded that all mood disorders are identical in certain ways and called underlying illness as manic depressive illness. Sigmund freud conceptualized two types of depression. He classified depression as endogenous depression which was biologically determined whereas exogenous depression was precipitated by loss. Psychotherapy was advocated for treatment of exogenous depression whereas medication and electroconvulsive therapy were advocated for endogenous depression treatment. In 1950 Leonhard divided the manic depressive illness into separate bipolar (alternating with mania and depression) and unipolar (recurrent depression or recurrent psychoses).4 WHO health report 2001 has identified unipolar depression as the 4th cause of disability adjusted life years (DALYs) in all ages and second cause in the age group of 14-15 years. Unipolar depression is also the first cause of years of life lived with disability (YLD) in all age groups. International classification of diseases 10th version (ICD-10) by WHO categorizes the mood disorders into i) Manic Episode ii) Depressive Episode iii) Bipolar Mood Disorder iv) Recurrent Depressive Disorder v) Persistent Mood Disorder
(cyclothymia and dysthymia) vi) Other Mood Disorders (mixed affective episode and recurrent brief depressive disorder).  
Mood disorder is a common mental health problem affecting 154 million people around the world.  
The prevalence of mood disorder does not differ among races. Major depression is one of the most prevalent mental disorders in the United States and Europe. Lifetime prevalence of major depression in America is 16.2% and 6.6% among women and men when compared to 16.5% and 8.9% among women and men in Europe. Major depressive disorder has two fold greater prevalence in women than in men. Greater prevalence of major depressive disorder in women may be due to hormonal differences, effects of childbirth and differing psychosocial stress for women. The mean age of onset for major depressive disorder is about 40 years with 50% of all patients having onset between the age of 20 and 50 years. Epidemiological data suggest that the incidence of major depressive disorder is increasing among people younger than 20 years of age due to the increased alcohol and drugs abuse. Major depressive disorder also occurs most often in persons with poor interpersonal relationships and in those who are divorced or separated. Prevalence of unipolar mood disorders ranges from 1.1% to 65.3% mainly because of different defining criteria used by different researchers. The one year prevalence rate for dysthymia worldwide ranges between 4.5% and 10.5%, whereas for cyclothymia is less than 1%. Bipolar disorder has an equal prevalence among men and women. In bipolar disorder men are prone for mania whereas females are prone for depression. The onset of bipolar disorder is earlier than that of major depressive disorder ranging from the age of 5 to 50 years or even older in rare instances. The mean age for occurrence of bipolar disorder is around 30 years. Mood disorders may also be accompanied with comorbid conditions among which the most frequent are alcohol abuse, alcohol dependence, panic disorder, obsessive compulsive disorder and social anxiety disorder. 
Major depressive disorder is characterized by one or more episodes of depressed mood or loss of interest in usual activities for minimum duration of two weeks accompanied by at least four additional symptoms of depression. The symptoms of depression are feeling of worthlessness, helplessness, hopelessness, loss of interest, inability to experience pleasure, change in appetite, sleep disturbances, decreased energy, fatigue, poor concentration and difficulty in making decisions.
In Manic disorder clinical features are generally opposite to those seen in depression. Manic individuals will have elevated mood, rush of ideas, psychomotor acceleration, grandiosity, unreasonable optimism, poor judgment, racing thoughts, decreased sleep, extremely short attention span and rapid shifts of mood from rage to sadness. Dysthmic disorder and cyclothymic disorder are characterized by the presence of symptoms that are less severe than major depressive disorder and bipolar disorder respectively. Dysthmic disorders are characterized by at least 2 years of depressed mood that is not sufficiently severe to fit into the diagnosis of major depressive episode. Cyclothymic disorder is characterized by at least 2 years of frequently occurring hypomanic symptoms that cannot fit into the diagnosis of manic episode and depressive symptoms that cannot fit into the diagnosis of major depressive disorder. Recurrent depressive disorders are characterized by recurrent episodes of mild, moderate or severe depressive episodes without any history of independent episodes of mood elevation or overactivity fulfilling the criteria of mania. Recurrent depressive disorders requires at least two episodes of depression, each lasting for a minimum of two weeks and separated by several months without significant mood disturbance.\(^\text{10}\)

**Etiology for Mood Disorders:**

**Mood Disorders**

- **Biological Factors**
- **Genetic factors**
- **Psychosocial Factors**

1) **Biological Factors**

In 1921 *Emil Kraepelin* speculated that the mood disorders are due to biological factors and considered psychological factors to be coincidental. He hypothesized that some inner control mechanism was accelerated or decelerated in mania and depression respectively. Since then nature of biological contribution has been examined by use of techniques of neurochemistry, psychopharmacology, neuroendocrinology and neurophysiology.
Biogenic Amines:

Norepinephrine (NA)  Serotonin (5HT)  Dopamine (DA)  Acetylcholine (Ach)  Gama amino buturic acid (GABA)  Glutamate & Glycine

Nor Epinephrine:
The cell bodies of the norepinephrine neurons occur in small clusters in the pons and medulla. They send extensive branching axons running in a discrete medial forebrain bundle giving rise to millions of nerve terminals throughout the cortex, hippocampus, thalamus, hypothalamus and cerebellum. Adrenergic receptors are expressed in the central nervous system except the β3 receptors. The α1 receptors are widely distributed and located both on the post synaptic neurons and the glial cells which may be involved in the motor control, cognition and fear. The α2 receptors are located on the presynaptic as well as post synaptic neurons involved in the blood pressure control, sedation and analgesia. The β1 receptors are found in the cortex, striatum and hippocampus whereas β2 receptors are found in the cerebellum. These β receptors have been implicated in the long term effect of the antidepressants treatment. Low level of the norepinephrine has been found in the unipolar depression whereas higher levels are found in bipolar depression patients. Low levels of norepinephrine have been associated with cognitive dysfunction, dysphoria, fatigue and apathy.11

There are several factors to prove norepinephrine involvement in the depression. Reserpinetreatment leading to depletion of monoamines is associated with depression. Patients responding to noradrenergic antidepressants such as desipramine are less likely to relapse if they are supplemented tryptophan free diet. Administration of norepinephrine
synthesis inhibitor is also associated with a rapid return of depressive symptoms in patients who respond to noradrenergic antidepressants. Activation of presynaptic β2 receptors results in a decrease of the amount of norepinephrine released. Presynaptic β2 receptors are also located on serotonergic neurons and regulate the amount of serotonin release. The correlation between the down regulations or decreased sensitivity of β2 adrenergic receptors and clinical antidepressant response indicate direct role of noradrenergic system in depression.12

**Serotonin:**
The cell bodies of serotonergic neurons are grouped in the pons and upper medulla, close to midline and often referred to as raphe nuclei. The axons from the nuclei pass through the median forebrain bundle to terminate on many parts of cortex, hippocampus, basal ganglia, limbic system and hypothalamus. 5HT1A receptors predominantly inhibit in their action and are expressed as auto receptors by serotonergic neurons in the raphenuclei. Their auto inhibitory effects tend to limit the rate of firing of these cells. The 5HT2 receptors are found in abundance in cortex and limbic system were they act as excitatory or inhibitory by releasing neurotransmitters glutamate or GABA. The 5HT3 receptors are found in the area postrema and in the gastrointestinal tract having role in emetic action. The 5HT4 receptors are expressed in the limbic system, basal ganglia, hippocampus and substantia nigra. They are present on both presynaptic and post synaptic neurons where they have facilitator effect on acetylcholine which enhances the cognitive function. Mood disorders are associated with the functional decrease in the serotonin transmission. This may be due to excessive reuptake of the serotonin or decreased release of the serotonin. Alteration in the serotonin levels is also implicated in suicidal tendency.11

There are many factors to prove the serotonin hypothesis of depression. Autopsy of the suicidal persons has showed decreased level of serotonin in CSF. Depressed patients responding to serotonergic antidepressants such as fluoxetine rapidly suffer relapse when given tryptophan free diet. Success of selective serotonin reuptake inhibitors in the treatment of depression indicates the role of serotonin in depression.12

**Dopamine:**
Three dopaminergic pathways present in the brain regulate the movements and cognitive function. Thenigrostriatal pathway in which the fibers arise from the substantia nigra and
terminates in the basal ganglia regulates the selection and execution of the motor activities. The mesolimbic pathway arising from the ventral tegmental area and projecting to limbic system is involved in the regulation of emotion and reward response. The mesocortical pathway arising from the ventral tegmental area terminates in the prefrontal cortex which regulates the social behavior and problem solving capacity. Dopamine released in the ventral striatum results in the experience of pleasure, which provides reinforcement for the individual to carry out day to day activities, such as eating and procuring. During depressive episode there is decreased concentration of the dopamine in the mesolimbic pathway leading to loss of motivation, loss of interest, physical slowing and inability to experience pleasure.\textsuperscript{13} Drug like reserpine decreasing the dopamine concentration leads to depression whereas drugs like tyrosine, amphetamine and bupropion increasing the concentration of dopamine decreases the symptoms of depression, which proves the dopamine hypothesis.\textsuperscript{14}

**Acetylcholine:**

Acetylcholine is the neurotransmitter of the cholinergic system. The cholinergic fibers are projected from the basal forebrain nucleus to almost all the portion of cortex. Acetylcholine produces multiple functions on the neuronal and cognitive function. In particular acetylcholine has role in the motor movements, memory and cognitive behavior. There occurs abnormalities in this neurotransmitter in patients with mood disorder, although further research is needed.\textsuperscript{15}

**Gama Aminobutyric Acid:**

It has an inhibitory effect on ascending monoamine pathways, particularly the mesocortical and mesolimbic systems. Reduction of GABA was observed in plasma, CSF, and brain levels in depression. Animal studies have also found that chronic stress can reduce and eventually can deplete GABA levels. By contrast, GABA receptors are up regulated by antidepressants and some GABAergic medications have weak antidepressant effects.\textsuperscript{16}

**Glutamate and Glycine:**

Glutamate and glycine are the major excitatory and inhibitory neurotransmitters in the CNS. Glutamate and glycine bind to N-methyl-D-aspartate (NMDA) receptor. Glutaminergic activity in conjunction with hypercortisolemia may mediate the deleterious neurocognitive effects of severe recurrent depression. Emerging evidences have suggested that drugs that antagonize NMDA receptors have antidepressant effects.\textsuperscript{17}
Brain Derived Neurotrophic Factor:
Growth factors such as Brain Derived Neurotrophic Factor (BDNF) are critical in the regulation of neural plasticity, resilience, and neurogenesis. Depression is associated with the loss of neurotrophic support. BDNF is thought to exert its influence on neuronal survival and growth effects by activating the tyrosine kinase B receptor in both neurons and glia. Animal and human studies indicate that stress and pain are associated with a drop in BDNF levels and this loss of neurotrophics support contributes to structural changes in the hippocampus, medial frontal cortex and anterior cingulate which are important in contextual memory and regulation of the hypothalamic pituitary-adrenal (HPA) axis. Similarly the anterior cingulate plays a role in the integration of emotional stimuli and attention functions, whereas the medial orbital frontal cortex plays a role in memory, learning and emotion. Structural imaging studies suggest that major depression is associated with 5–10% loss of volume in the hippocampus. Depression and chronic stress have been associated with a substantial loss of volume in the anterior cingulate and medial orbital frontal cortex. Loss of volume in hippocampus increases as duration of illness and the amount of time that the depression remains untreated. Administration of antidepressants increases BDNF levels in clinical trials which may be associated with an increase in hippocampus volume in patients.18

Secondary Messengers and Intracellular Cascades:
The binding of a neurotransmitter to the postsynaptic receptor triggers a cascade of membrane bound and intracellular processes which are mediated by second messengers. Receptors on cell membranes interact with the intracellular environment through guanine nucleotide-binding proteins (G proteins). The G proteins in turn connect to various intracellular enzymes e.g. adenylatecyclase, phospholipase C, and phosphodiesterase that regulate utilization of energy and formation of second messengers, such as cyclic nucleotides (cAMP&cGMP), phosphatidylinositols (inositol triphosphate &diacylglycerol) and calcium calmodulin. Secondary messengers regulate the function of neuronal membrane ion channels. Increasing evidence also indicates that mood stabilizing drugs act on G proteins or other second messengers.19

Hormonal Deregulations:
Hypothalamus Pituitary Axis: Studies in depressed humans indicate that a history of stress is associated with increased HPA activity accompanied by structural changes like atrophy or
decreased volume in the cerebral cortex. Elevated HPA activity is a hallmark of mammalian stress responses and links between depression and the biology of chronic stress. Elevated HPA activity in depression has been documented via:

- Excretion of urinary-free cortisol.
- 24-hour intravenous collections of plasma cortisol levels.
- Salivary cortisol levels.

**Thyroid Axis**

Approximately 5 to 10% of people with depression have previously undetected thyroid dysfunction which is reflected by an elevated basal TSH level or an increased TSH response to a 500 mg hypothalamic TRH. If the impairment of the thyroid is not corrected by hormone replacement, it may compromise the antidepressant therapy. An even larger subgroup of depressed patients (e.g., 20 to 30%) shows a blunted TSH response to TRH challenge. The major therapeutic implication of a blunted TSH response is evidence of an increased risk of relapse despite preventive antidepressant therapy.

**Growth Hormone**

Growth hormone (GH) is secreted from the anterior pituitary after stimulation by NE and Dopamine. Secretion is inhibited by somatostatin, a hypothalamic neuropeptide and CRH. Decreased CSF somatostatin levels are reported in depression, and increased levels are observed in mania.

**Prolactin**

Prolactin is released from the pituitary by serotonin stimulation and inhibited by DA. Most studies have not found significant abnormalities of basal or circadian prolactin secretion in depression, although a blunted prolactin response to various serotonin agonists has been described. This response is uncommon among premenopausal women, suggesting that estrogen has a moderating effect.²⁰

**Alterations of Sleep Neurophysiology**

Depression is associated with a premature loss of deep (slow wave) sleep and an increase in nocturnal arousal.

Depression is reflected by four types of sleep disturbance:

- An increase in nocturnal awakenings.
• A reduction in total sleep time.
• Increased phasic rapid eye movement (REM) sleep.
• Increased core body temperature.

The combination of increased REM drive and decreased slow wave sleep results in a significant reduction in the first period of non-REM (NREM) sleep, a phenomenon referred to as reduced REM latency. Reduced REM latency and deficits of slow wave sleep typically persist after recovery of a depressive episode. The combination of reduced REM latency, increased REM density, and decreased sleep maintenance identifies approximately 40% of depressed outpatients and 80% of depressed inpatients. Patients manifesting with abnormal sleep profile are less responsive to psychotherapy and have a greater risk of relapse or recurrence and may benefit preferentially from pharmacotherapy.\textsuperscript{21}

**Neuroanatomy:**
Modern affective neuroscience focuses on the importance of four brain regions in the regulation of normal emotions:
1. Prefrontal cortex (PFC).
2. Anterior cingulate.
3. Hippocampus.
4. Amygdala

**Prefrontal cortex (PFC):**
Area that holds representations of goals and appropriate responses to obtain these goals. Such activities are particularly important when multiple, conflicting behavioral responses are possible or when it is necessary to override affective arousal.

Evidence indicates some hemispherical specialization in PFC function:
• Left PFC is more involved in goal-directed or appetitive behaviors,
• Right PFC is implicated in avoidance behaviors and inhibition of appetitive pursuits.
• Subregions in the PFC localize representations of behaviors related to reward and punishment.

**The anterior cingulate cortex (ACC):**
Serve as the point of integration of attention and emotional inputs. Two subdivisions have been identified:
1. An affective subdivision in the rostral and ventral regions of the ACC.
2. A cognitive subdivision involving the dorsal ACC.

The former subdivision shares extensive connections with other limbic regions, and the latter interacts more with the PFC and other cortical regions. Activation of the ACC facilitates control of emotional arousal.\textsuperscript{22}

**The hippocampus**

Hippocampus is clearly involved in various forms of learning and memory, including fear conditioning, as well as inhibitory regulation of the HPA axis activity. Emotional or contextual learning appears to involve a direct connection between the hippocampus and the amygdala.

**The amygdala**

A crucial way station for processing novel stimuli of emotional significance and coordinating cortical responses. Located just above the hippocampi bilaterally, the amygdala has long been viewed as the heart of the limbic system.\textsuperscript{23}

**Genetic Factors**

Numerous family, adoption, and twin studies have documented the heritability of mood disorders.

**Family Studies:**

If one parent have mood disorder, child will have a risk of between 10 and 25% for mood disorder. If both parents are affected risk roughly doubles. The more members of the family affected, the greater the risk of child developing mood disorder. The risk is greater if the affected family members are first degree relatives. A family history of bipolar disorder conveys a greater risk for mood disorders and specifically for bipolar disorder. Unipolar disorder is typically the most common form of mood disorder infamilies of bipolar probands. This familial overlap suggests some degree of common genetic inheritance between these two forms of mood disorder.

**Adoption Studies:**

Adoption studies provide an alternative approach to separating genetic and environmental factors in familial transmission. Studies have found a threefold increase in the rate of bipolar disorder and a twofold increase in unipolar disorder in the biological relatives of bipolar probands. In a Danish sample, a threefold increase in the rate of unipolar disorder and a sixfold increase in the
rate of completed suicide in the biological relatives of affectively ill probands were reported. However, other studies have found no difference in the rates of mood disorders.

**Twin Studies:**

Twin studies provide the most powerful approach to separate genetic factors from environmental factors. Twin studies data provide compelling evidence that genes explain only 50 to 70% of the etiology of mood disorders while environment and other non-heritable factors explain the remainder 30%. These studies find a concordance rate for mood disorder unipolar and bipolar in the monozygotic (MZ) twins of 70 to 90% compared with the same sex dizygotic (DZ) twins of 16 to 35%.

**DNA Linkage Studies:**

DNA markers are segments of DNA of known chromosomal location which are highly variable among individuals. They are used to track the segregation of specific chromosomal regions within families affected with a mood disorder. When a marker is identified with disease in families then the disease is said to be genetically linked. Chromosomes 18q and 22q are the two regions with strongest evidence for linkage to bipolar disorder. Studies of unipolar depression have found strong evidence of linkage to the locus for cAMP. Eighteen other genomic regions were found to be linked; some of these displayed interactions with the CREB1 locus. Another study has reported evidence for a gene environment interaction in the development of major depression. Subjects undergoing adverse life events were at an increased risk for depression.25

**Psychological Factors:**

**Life Events and Environmental Stress:**

Stressful life events more often precede first rather than subsequent episodes of mood disorders. This is reported for both patients with major depressive disorder and bipolar disorder. The stress accompanying the first episode results in long lasting changes in the brain's biology. These changes may alter the functional states of various neurotransmitter and intra neuronal signaling systems like loss of neurons and an excessive reduction in synaptic contacts. As a result person has a high risk of undergoing subsequent episodes of a mood disorder even without an external stress. The environmental stressor most often associated with the onset of an episode of depression is the loss of a spouse, unemployment, persons out of work are more likely to report symptoms of an episode of major depression.26
Pharmacotherapy:
In 1957 the antidepressant property of isoniazid was discovered coincidentally and thisha\'s led the pharmacological research to develop drugs which inhibit monoamine oxidase and drugs which block the reuptake of noradrenaline. This resulted in the development of various monoamine oxidase inhibitors (MAOI) and tricyclic antidepressants (TCA) which dominated the treatment of depression for over 30 years, predominantly TCA\’s. In the 1990\’s selective serotonin reuptake inhibitors (SSRI) were introduced and quickly they became the first line of treatment for depression. Over the last decade the research was focused to enhance the efficacy, accelerate the onset of action and reduce the side effects. In this regard, many newer agents were introduced with different mechanisms of action and proved very helpful in many aspects. They include noradrenaline reuptake inhibitors (NARI), serotonin and noradrenaline reuptake inhibitors (SNRI), noradrenergic and specific serotonergic antidepressant (NaSSA) and more recently agomelatine.

Monoamine Oxidase Inhibitors:
Traditional MAOIs increase the levels of neurotransmitters by irreversibly blocking monoamine oxidase enzymes in the synapse and the enzyme blockade lasts for two weeks even after stopping MAOI. They block both MAO-A and MAO-B enzymes. Inhibition is not only in the nervous system but also in the gut. As a result, they have a dangerous interaction with tyramine containing foods and sympathomimetic drugs causing a hypertensive crisis. This restricts patients from consuming tyramine containing foods and certain other medications such as cold remedies and cough suppressants. MAOIs are now used as third line drug in the treatment of depression due to these limitations. They are very useful in patients who do not respond to SSRI and TCA. It is also useful in atypical depression and phobic anxiety disorders. A recent review concluded that MAOI, Phenelzineremains as the gold standard treatment for atypical depression.

The new generation MAOIs are more selective in their action blocking only MAO-A but not MAO-B enzymes. The inhibition is reversible and it doesn\’t require the lengthy wash out periods after stopping them. The efficacy of Moclobemide, the only drug currently available in this group, is similar to other MAOIs but with a much reduced possibility of hypertensive crisis. It has shown to produce rapid and significant improvement in both social functioning and quality of life.
Selective Serotonin Reuptake Inhibitors (SSRI)
The discovery of SSRIs in 1989 was a turning point in the treatment of depression. It switched the emphasis from noradrenergic to serotonergic system and stimulated research on serotonin receptors. SSRIs are more selective in inhibiting serotonin reuptake and have no action on histamine, adrenaline and cholinergic receptors. Their tolerability is much better compared to TCAs or MAOIs. They have similar efficacy as older drugs better tolerability, safety in overdoses and are the first line of treatment for depression over the last two decades. The drugs in this group are fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram and escitalopram. These six medications differ in their chemical structure and pharmacokinetic. There are no major differences in their efficacy or side effect profile. The common side effects include gastrointestinal problems, dry mouth, sweating, headache, asthenia and sexual dysfunction such as ejaculatory delay/failure. SSRIs have fewer drug interactions compared to older drugs and the most important one is with MAOI when concurrent administration may cause serotonin syndrome. Therefore MAOIs and RIMA are contraindicated in combination with SSRIs and there should be a washout period before swapping them. The safety profile of these drugs was found to be similar and they do not cause physical dependence but abrupt withdrawal or marked reduction in the dose of SSRI may lead to the development of discontinuation symptoms. The common discontinuation symptoms are dizziness, paraesthesia, tremors, anxiety, nausea and increased heart rate which may last for up to 10 days. Paroxetine causes discontinuation symptoms more often (5.1%) when compared to other SSRIs (0.06-0.9%).

Escitalopram the active isomer of citalopram is a highly selective SSRI and has shown better efficacy in the treatment of severe depression. In a recent multiple treatment metaanalysis, escitalopram and sertraline have shown the best profile of acceptability.

Serotonin Antagonist and Reuptake Inhibitors (SARI):
Trazodone and nefazodone belong to this group and chemically they are phenylpiperazines. They have dual action on the serotonergic system. They are potent 5HT2 receptor antagonists and weak reuptake inhibitors. This combination of actions enhances 5HT1A mediated neurotransmission and is thus effective in the treatment of depression. Trazodone has been available since 1998 but it is used infrequently as antidepressant because of its sedating property. Rather it is been prescribed in lower doses as hypnotic in addition to SSRIs. Sexual side effects
are less frequent but it can cause priapism in some patients. A recent review showed that trazodone has efficacy comparable to SSRIs and nefazodone. It is also relatively safe in overdose.\textsuperscript{33}

Nefazodone is a derivative of trazodone and is chemically related. It is found to be as effective as TCAs and superior to placebo in daily doses of 200-600mg. Sexual dysfunction was less reported with nefazodone compared with other antidepressants and there were no reports of priapism and also less sedating than trazodone. It has high hepatotoxicity because of which the drug has been withdrawn from many countries.\textsuperscript{34}

**Noradrenaline Reuptake Inhibitors (NARI)**

Reboxetine is similar in structure to fluoxetine but it is a relatively selective noradrenaline reuptake inhibitor. Its therapeutic effect is mainly through increasing noradrenaline neurotransmission and it has no interaction with other receptors such as histaminergic, muscarinic or \( \alpha_1 \) receptors. Therefore, reboxetine is useful for patients who could not tolerate tricyclic antidepressants or who have been treatment-resistant to SSRIs. Reboxetine is equally effective as TCAs in both hospital inpatients, outpatients and has better efficacy than fluoxetine. It also helps in alleviating anxiety symptoms associated with depression. It has moderately alerting effect and improves the motivation of the patients. The main side effects are linked to sympathetic overstimulation and include dry mouth, insomnia, sweating, tachycardia, vertigo, urinary hesitancy and impotence.\textsuperscript{35}

**Selective Serotonin and Noradrenaline Reuptake Inhibitors (SNRI)**

SNRIs have dual action and inhibit both serotonin and noradrenaline reuptake. They do not act on muscarinic, histaminic or adrenergic receptors. As a result they have more benefits and less side-effects compared to other antidepressants. Venlafaxine, duloxetine and milnacipran belong to this group.\textsuperscript{36}

Venlafaxine, a phenylethylamine, inhibits the reuptake of 5HT and NA and at higher doses inhibits the reuptake of dopamine. It has a rapid onset of action and improvement may be noticed within the first week of treatment. This is because of the fast down-regulation of \( \beta \) receptors induced by venlafaxine, which usually occurs only during long term treatment with other antidepressants. Venlafaxine is as effective as imipramine or fluoxetine. It is better tolerated compared to TCAs and safer in overdoses. It has less sedative and proconvulsant effects and
shows minimal drug interactions. Venlafaxine is also effective in the therapy of treatment resistant depression. Desvenlafaxine, a synthetic metabolite of venlafaxine, is a new SNRI available since 2008. Studies have reported that it has short-term efficacy in major depression and could improve the social functioning of the patients.

Duloxetine, another SNRI, is considered as the most potent in this group. It blocks both neurotransmitters equally, whereas venlafaxine has a stronger tendency towards serotonergic system and milnacipran towards noradrenergic system. A latest review reported that duloxetine is safe and effective in the acute phase treatment of depression. However, it appears to be less effective compared to venlafaxine in both remission and response rates.

Milnacipran, is reported to be as effective as TCAs with a 65% response rate and has slightly superior efficacy to SSRIs. A recent meta-analysis suggested that milnacipran has equal efficacy and tolerability compared to other antidepressants but can be slightly more favourable to TCAs in terms of adverse effects. Dysuria and headache are the common side-effects.

9. Noradrenergic and Specific Serotonergic Antidepressant (NaSSA)
Mirtazapine and Mianserin belong to this group. Mianserin is not used in most countries because of its hepatotoxicity and the risk of neutropenia. Thus mirtazapine is the only agent available in this group. Mirtazapine has unique pharmacological properties. It increases the release of serotonin and noradrenaline by blocking central α2auto and heteroreceptors. It has a marginal affinity for α1 receptor and a low affinity for 5HT1A receptor but good affinity for 5HT2 and 5HT3 receptors. The antidepressant effect appears to be a result of increased serotonin and noradrenaline neurotransmission. Due to its antihistaminergic action, it acts as a relatively sedative antidepressant although this effect is diminished at higher doses. It also blocks 5HT2 and 5HT3 receptors; therefore the sexual side-effects and nausea are less common compared to SSRIs. Mirtazapine has a more rapid onset of action and is equally effective as SSRIs. It also showed higher remission rates compared to SSRIs. Its side effects are relatively mild and transient.

Dopamine and Noradrenaline Reuptake Inhibitors (DNRI)
Bupropion is another dual acting drug which inhibits reuptake of dopamine and noradrenaline.
It is been used as antidepressant in some countries and in smoking cessation clinics. Its metabolite hydroxybupropion is a potent reuptake inhibitor and it has low receptor blocking effects. It is useful in the treatment of bipolar depression, depression with psychomotor retardation and atypical depression because of its dopamine related activating properties. The main side effects are caused by dopamine over stimulation and include nausea, insomnia, agitation, dry mouth, weight loss and psychosis. It also lowers the seizure threshold and seizures can occur in 0.5% of patients. In overdoses it leads to hallucinations, tachycardia, seizures and rarely death .Bupropion was found to be as equally effective and tolerable as SSRIs .It may be beneficial for patients with symptoms of sleepiness, fatigue, low energy, anhedonia and loss of interest.41

**Serotonin Reuptake Inhibitor And 5HT_{1A} Receptor Partial Agonists**

Vilazodone is a relatively new antidepressant which has been available for a year in the United States. It has dual action of inhibiting serotonin reuptake and partial agonist at 5HT_{1A} receptors. It does not cause weight gain and claimed not to cause any sexual sideeffects. Nevertheless, compared to other antidepressants, the data regarding its efficacy are limited and more research is required.

**Melatonin based therapy – Agomelatine**

In the last decade, advances in the understanding of the pathophysiology of depression including genetic, neurobiological and neuroimaging studies shifted the focus of research from the monoamines to different theories of depression. One of them assumes that disturbances in the circadian rhythms may play a significant role in the pathogenesis of depression. The links between circadian disturbances and symptoms of depression such as delay in sleep onset, early morning wakening, fatigue during the day, blunting of normal peaks in subjective energy, mood and alertness are very strong. Circadian disturbances affect the secretory rhythms of various neuroendocrine hormones such as melatonin, cortisol and noradrenaline. There are also changes in the diurnal variations of core body temperature and plasma cortisol levels. If this internal system desynchronises, the timing of various circadian rhythms is out of phase resulting in depressed mood, sleep changes and impaired neurocognition. Therefore any treatments of depression focusing on circadian rhythm not only restore the sleep-
wake cycle but also will have substantial improvements in mood, cognition and day-time fatigue. Melatonin is a hormone naturally secreted by the pineal gland in the body. Its secretion is usually high at night time in normal individuals. It has an important role in the regulation of circadian timing systems by binding to melatonin receptors (MT1 and MT2) in the brain. Based on this idea, melatonin based therapies have been developed recently for the treatment of depression.

Agomelatine, is a new antidepressant with a unique mechanism of action. It is a selective agonist at MT1 and MT2 receptors and an antagonist at 5HT2b and 5HT2c receptors. It has a rapid absorption rate and peak plasma levels are achieved between 45 and 90 min after a single oral dose of 25-50mgs. It has clinically significant antidepressant and anxiolytic effects. The clinical benefits occur from the combined effects of melatonin and monoamine actions as well as non-circadian processes such as increased production of brain-derived neurotrophic factors. Agomelatine has similar efficacy to SSRIs and venlafaxine. The common side-effects include nausea, dizziness and headache.42

**Combination treatments for treatment resistant depression**

Although the newer antidepressants have better efficacy in the treatment of depression nearly one third of patients fail to achieve remission. Moreover complete remission is not always possible and partially treated patients are at higher risk of relapse, experience more personal and socioeconomic problems and have poor quality of life. A patient is considered to suffer treatment resistant depression (TRD) if they fail to achieve remission with adequate trials of two different classes of antidepressants. There are few strategies available to tackle treatment resistance including both pharmacological and non-pharmacological therapies.

** Combination of two different antidepressants: ** to treat resistant depression has become a common practice. A recent systematic review showed that antidepressant combination was more effective than a single antidepressant in achieving remission. The superior combination was mirtazapine with SSRI. The other effective combinations are mirtazapine and SNRI, SSRI with bupropion, TCA with SSRI and bupropion with venlafaxine or mirtazapine. Combination of an antidepressant with an antipsychotic: is another useful strategy in treating resistant depression. 5HT2A/ 5HT2C antagonist effect of atypical antipsychotics potentiatethe efficacy of antidepressants and at times
counteract the side-effects of SSRIs. The mostuseful combination appears to be an SSRI with an atypical antipsychotic. Weight gain and sedation are the common adverse effects.

Augmentation: augmentation of an antidepressant with lithium, triiodothyronine and omega-3 fatty acids have also been beneficial in some patients.43

**Bipolar Disorder Treatment:**

Lithium carbonate is the mainstay of treatment in bipolar disorder. The response rate to lithium carbonate is 70 to 80% in acute mania, with beneficial effects appearing in 1 to 2 weeks. Lithium also has a prophylactic effect in prevention of recurrent mania and also in prevention of recurrent depression. A simple cation, lithium is rapidly absorbed from the gastrointestinal tract and remains unbound to plasma or tissue proteins. The mechanism by which lithium acts is i) inhibition of phospholipase C synthesis with resultant decrease in brain inositol triphosphate and diacyl glycerol concentration which reduces sensitivity of neurons to various neurotransmitter. ii) modification of GABA concentration in brain. iii) Decrease in the synthesis of DA and NA in brain and facilitation of their neuronal uptake. iv) Decrease in the function of brain kinase leading to alterations in the release of neurotransmitters and hormones.

Some 95% of a given dose is excreted unchanged through the kidneys within 24 h. Serious side effects from lithium administration are rare, but minor complaints such as gastrointestinal discomfort, nausea, diarrhea, polyuria, weight gain, skin eruptions, alopecia, and edema are common.

Chronic lithium administration may lead to decreased urine concentrating ability, but significant nephrotoxicity does not occur. Lithium exerts an antithyroideffect by interfering with the synthesis and release of thyroid hormones. More serious side effects include tremor, poor concentration and memory, ataxia, dysarthria, and incoordination. lithium is teratogenic inducing cardiac malformations if it is taken in first trimester.

The treatment of acute mania with lithium is initiated at 300 mg bid or tid, and the dose is then increased by 300 mg every 2 to 3 days to achieve blood levels of 0.8 to 1.2 meq/L. therapeutic effect of lithium may not appear until after 7 to 10 days of treatment, adjunctive usage of lorazepam (1 to 2 mg every 4 h) or clonazepam (0.5 to 1 mg every 4 h) may be beneficial to control agitation. Antipsychotics are indicated in patients with severe agitation who respond only
partially to benzodiazepines. Patients using lithium should be monitored closely, since the blood levels required to achieve a therapeutic benefit are close to those associated with toxicity. Valproic acid can be used as an alternative in patients who do not tolerate lithium or respond poorly to lithium. Valproic acid may be better than lithium for patients who experience rapid cycling (i.e., more than four episodes a year) or who present with a mixed or dysphoric mania. Tremor and weight gain are the most common side effects; hepatotoxicity and pancreatitis are rare toxicities.

Carbamazepine and oxcarbazepine, not formally approved by the U.S. Food and Drug Administration (FDA) for bipolar disorder, have clinical efficacy in the treatment of acute mania. Other anticonvulsant agents such as levetiracetam, zonisamide, and topiramate may possess some therapeutic benefit.

The recurrent nature of bipolar mood disorder necessitates maintenance treatment with blood lithium levels of at least 0.8 mEq/L. Antidepressant medications are sometimes required for the treatment of severe breakthrough depressions, but their use should generally be avoided during maintenance treatment because of the risk of precipitating mania or accelerating the cycle frequency. Loss of efficacy over time may be observed with any of the mood stabilizing agents. In such situations, an alternative agent or combination therapy is usually helpful.

**Future prospective in psychopharmacological drugs:**

The delayed onset of response to the earlier antidepressants and increased resistance among depressed has led to the development of newer drugs which are more efficacious and tolerable. The agents in development include multimodal serotonergic agents, triple uptake inhibitors, neurokinin (NK1) antagonists, glutamate antagonists, dopamine agonists and antiglucocorticoid agents. Multimodal serotonergic agents are simply an extension of SSRIs and SNRIs. They have both serotonin reuptake inhibition and either blocks 5HT2A receptor and/or act as partial agonist at 5HT1a receptor. Vilazodone, the first agent of this group, is already available in clinical practice and there are few other drugs in development. Triple uptake inhibitors combine the inhibition of serotonin, noradrenaline and dopamine transporters. Their development is based on the assumption that targeting dopamine neurotransmission would enhance overall efficacy and diminish certain symptoms such as anhedonia, apathy, sleepiness and fatigue as well as
counteract sexual side-effects induced by SSRI. Sibutramine is the only available drug with triple uptake inhibition and it is currently used in weight loss therapy. One of the limitations associated with this mechanism might be the risk of abuse linked with increased dopamine neurotransmission.

Neurokinin receptors (NK1 and NK2) and their endogenous ligand Substance P are found in brain areas known to be involved in the regulation of mood, stress and anxiety responses. However NK1 antagonist aprepitant failed to show greater efficacy to placebo. Currently studies focusing on NK2 antagonists are underway. Glutamate modulating agents such as ketamine (NMDA antagonist) generated significant interest in the field when rapid and sustained antidepressant effects were seen after injections of ketamine. Another NMDA antagonist and dopaminergic drug amantadine showed efficacy in depressed imipramine non-responders. It may be useful in depressed patients with prominent cognitive dysfunction. The main limiting factor in using these agents is the risk of inducing psychotic symptoms due to their hallucinogenic properties. Dopamine agonists, similar to DNRI bupropion, seem to be promising in the treatment of depression. A review showed that dopamine agonists had anxiolytic, anti-depressive and antianhedoniceffects, which were related to its action on dopamine D2 and D3 receptors. Two agents ropinirole and pramipexole proved efficacy as additional treatment to mood stabiliser in bipolar depression but further research is required to prove their efficacy and usefulness as antidepressants. Biological studies of depression have shown that the secretion of hypothalamic neuropeptides such as corticotrophin releasing hormone (CRH) and vasopressin is elevated in depressed patients. CRH acting through CRH1 receptor may cause symptoms of depression. Depressed patients also have increased cortisol levels which might be responsible for psychotic symptoms of depression. A review of the hypothesis that CRH1 receptor antagonists and anti-glucocorticoid agents may be useful in the treatment of depression supports this direction in the development of future antidepressants.45

CONCLUSION

Mood disorders are complex psychiatric conditions, with multiple etiological factors. As major depressive disorder and Bipolar disorder are the most common mood disorders, further extensive research is needed for the causative factor so that appropriate drug can be discovered which as faster onset of action, minimum side effects and completely treat the mood disorders.
REFERENCES