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Review Article

A REVIEW ON PATHOPHYSIOLOGY, CLASSIFICATION AND LONG TERM COURSE OF DEPRESSION

Arya Ashwani* and Verma Preeti
School of Pharmaceutical Education and Research, B.P.S. Women University, South Campus, Bhianswal Kalan, Sonepat, Haryana, India

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*E-mail: ashwaniarya5@rediffmail.com

ABSTRACT
Depression is an etiologically heterogeneous group of brain disorders characterized by a wide range of symptoms that reflect alterations in cognitive, psychomotor and emotional processes. Depression is a common problem affecting about 121 million people world-wide. It occurs in persons of all genders, ages, and back- grounds. 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. 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, amygdala, limbic system and medial prefrontal cortex appear to be implicated in depression. The two most well accepted international systems are the Diagnostic & Statistical Manual (DSM-IV) of the American Psychiatric Association and the International Classification of Disease and Related Health Problems (ICD-10) of the World Health Organization (WHO). Depression refers to a wide range of mental health problems which is characterized by Depressed mood most of the day, anhedonia, large increase or decrease in appetite, insomnia, psychomotor agitation (evident by, for example, hand wringing) or slowness of movement, fatigue or loss of energy, Indecisiveness or diminished ability to think or concentrate, Feelings of worthlessness or excessive or inappropriate guilt, Recurrent thoughts of death or suicide. Despite our increased understanding of both its pathophysiology and treatment, depression remains highly prevalent, accounting for more disability than any other disorder world wide.
KEY WORDS: Depression, Cognition, Monoamine, HPA, CRF, Serotonin.

INTRODUCTION

Depression is a state of low mood and aversion to activity that can affect a person's thoughts, behaviour, feelings and physical well-being. Depression is an etiologically heterogeneous group of brain disorders characterized by a wide range of symptoms that reflect alterations in cognitive, psychomotor and emotional processes[1]. Affected individuals differ remarkably regarding the profile of clinical features, severity and course of illness as well as their response to drug treatment and reintegration efforts. Genetic epidemiology has assembled convincing evidence that mood disorders including depression are substantially influenced by genetic factors and that the genetic component is highly complex, polygenic and epistatic. Because the mode of inheritance of depression is complex, it has been concluded that multiple genes of modest effect, in interaction with each other and in conjunction with environmental events, produce vulnerability to the disorder. Investigation of gene–environment interactions in humans and nonhuman primates, as well as gene inactivation studies in mice, have further advanced the identification of genes that are essential for the development and plasticity of brain systems related to depression[2]. Depression is a group of brain disorders with varied origins, complex genetics and obscure neurobiology[1,2].

Depression is a common chronic, and potentially debilitating form of psychiatric disorders. Although unhappiness is usually a normal human experience, it differs from clinical depression in both duration and severity. It occurs in persons of all genders, ages, and back-grounds[1]. Depression is almost twice as common in females as males. Any form of stressful life event is considered as the very initial sign of depression, thereby depression is often thought as a stress related disorder[4]. 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[5]. Mental depression represents a major public health problem worldwide. According to WHO estimation, 121 million people world wide suffer from clinical depression[6]. The high prevalence of suicide in depressed patients (up to 15%) coupled with complications arising from stress and its effects on the cardiovascular system have suggested that it will be the second leading cause of death by the year 2020. Depression is associated with a serious impairment of social, marital, and occupational functioning, as well as prominent personal and interpersonal distress[7].

Classification Systems Of Depression

International classification of depression is based on the mono- and bipolar dichotomy, a system of classification that separates those patients with depressive symptoms only from those that fluctuate between depression and mania (manic depression) or have only manic symptoms. The unipolar depression (in which mood swings are always in the same direction), is of two types- reactive and endogenous. The reactive depression is more common (about 75% cases), nonfamilial, clearly associated with stressful life events and accompanied by symptoms of anxiety and agitation. On the other hand, patients of endogenous depression (about 25% of cases) show a familial pattern, unrelated to external stresses, and with a somewhat different symptomatology. Bipolar depression, which usually appears in early adult life, is less common and results in oscillating depression and mania over a period of few weeks[8]. Different classification systems of depression exist and have changed over the years. The two most well accepted international systems are the Diagnostic and Statistical Manual (DSM-IV) of the American Psychiatric Association1 and the International Classification of Disease and Related Health Problems (ICD-10) of the World Health Organization (WHO). Both are systems that have well-defined operational criteria (See table-1) [9,10] .

Clinical Signs And Symptoms

Depression refers to a wide range of mental health problems which is characterized by[9, 12]:

- Depressed mood most of the day (in children and adolescents, irritability might signify a depressed mood).
- Anhedonia (Markedly diminished interest or pleasure in all or most activities most of the day)
- Large increase or decrease in appetite
- Insomnia or excessive sleeping
- Psychomotor agitation (evident by, for example, hand wringing) or slowness of movement
- Fatigue or loss of energy.
- Indecisiveness or diminished ability to think or concentrate.
- Feelings of worthlessness or excessive or inappropriate guilt.
- Recurrent thoughts of death or suicide.

Recent Understanding Of The Aetiology Of Depression

Although mental disorders are common and involve signs and symptoms that cluster recognisably as syndromes, the aetiology of the majority of mental disorders is multifactorial[7,16]. In particular, depression is often predisposed by genetic influences, developmental problems such as low self-esteem, chronic sociopsychological adversity, and lack of a social and family support network[2,15]. Frequently, the onset of depression is preceded by significant life events. There follows a chain of neurobiological changes, which include disturbed sleep, hormonal changes, the reduced release of neurotransmitters (particularly monoamines), and altered gene expression[2, 14]. A clinical syndrome of depression with mood, cognitive, somatic, and behavioural changes thus results. The established modes of treatment of depression consist of antidepressants, electroconvulsive therapy, formal psychotherapy, and—depending on the availability of resources and factors pertaining to help seeking a combination of these treatments. Less common methods include bright-light therapy for seasonal affective disorder, or sleep deprivation for resistant cases of depression[1,16]. Of all the available methods, the mainstay treatment is antidepressant therapy. While electroconvulsive therapy is a very effective treatment, it is usually reserved for patients with severe depression who refuse food or who are actively suicidal and hence require rapid treatment. Social and family support is very important in predicting the outcome and recovery of depressive patients. The most established psychotherapies that are thought to be useful in treating depressed patients are cognitive and interpersonal psychotherapy. Although the role of psychotherapy alone in the management of recurrent depression seems to be less promising than antidepressants alone its role as adjunct therapy to medication treatment in dealing with marital, familial, social, and occupational problems that often[1, 17].

Pathophysiological Features Of Depression

Recent findings have substantially increased our understanding of the pathophysiology of depression[17]. There has been a correspondingly significant increase in our understanding of the efficacy and tolerability of currently available treatments[1]. 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 an adequate trial of antidepressant monotherapy[1]. Despite our increased understanding of both its pathophysiology and treatment, depression remains highly prevalent, accounting for more disability than any other disorder worldwide[1, 12]. 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[7]. Various areas of brain like forebrain, hippocampus, amygdale, limbic system and medial prefrontal cortex appear to be implicated in depression[3,5]. A number of neuromodulators have been reported to be involved in the pathophysiology of deprerssion[14].

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[19]. There are both clinical and experimental evidences to suggest that increased central cholinergic activity can precipitate depression and reduced the noradrenergic activity[18,20]. Most of the serotonergic, noradrenergic and dopaminergic neurons are located in midbrain and brainstem nuclei and project to large areas of the entire brain[17]. 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[14,29]. 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[17]. 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[27]. 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[29,30]. 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 neighbouring terminals. Hence it represents established targets of many psychostimulants 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[24,29].

Noradrenergic cell bodies in the brainstem (lateral tegmental area & locus coeruleus) give rise to diverse projections to a variety of brain structures. The NE released following activation of noradrenergic neurons mediates effects through interaction with alpha and beta adrenoceptors[18]. Low levels of NE (Norepinephrine) metabolites are found in the urine and CSF of depressed patients[18,19]. Increased density of α - 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) [24]. MAO-B has substrate preference for phenylethyl amine. Both enzymes act on nor-

adrenaline and dopamine. In case of depression the level of monoamine oxidase enzyme in brain is increased which in turn reduce the levels of monoamines[18]. Increased MAO-A activity is found in the CNS of depressed patients[24]. Depletion of NE in depressed patients in remission treated with a NE reuptake inhibitor precipitates a relapse in depressive symptoms. A blunted growth hormone response to the D2 adrenergic agonist clonidine is found in depressed patients[14,18]. NE reuptake inhibitors are effective antidepressants (desipramine, reboxetine, and maprotiline). Alterations in noradrenergic circuits may play a preeminent role in patients with treatment-resistant depression[16]. Of the major catecholamine systems, NE-containing circuits have long been considered to be pathologically involved in the etiology of mood disorders[1,3]. Moreover, neurochemical and neuroendocrine studies in depressed patients and post-mortem findings support a role for NE dysfunction in depression[7, 18].

Low concentrations of the major metabolite of 5HT (5-hydroxyindole acetic acid) are found in the CSF of patients in depression[26]. Increased density of 5HT2 receptors has been reported in both blood platelets and brain postmortem tissue of patients with depression[27]. Decreased 5HT transporter (SERT) binding site density is seen in the midbrain and in blood platelets of patients with depression. Decreased plasma concentrations of L-tryptophan, the precursor to 5HT, are found in patients with depression[3,27]. Depletion of 5HT in depressed patients in remission provokes a rapid relapse in depressive symptoms. Polymorphisms in the SERT gene mediate the depressogenic effects of child abuse and neglect. Increased MAO-A activity is found in the CNS of depressed patients[26,27]. 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-norepinephrine reuptake inhibitors (SNRIs) may be due, in part, to their relative lack of effect on brain DA circuits[8, 25]. As regards CNS 5HT systems, even more evidence has accrued to support a preeminent role for their involvement in depression[29]. 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) 5HT1A receptor density[28]. The effects of serotonin are mediated through 5-HT receptors. In patients with depression, an increased density of postsynaptic 5-HT2 receptor binding sites has repeatedly been reported in both frontal cortex and platelets[30]. Dysfunction in the serotonergic system is a well-established theory explaining the pathophysiology of depression[28].

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[14,29]. Dopamine (DA) is the major neurotransmitter that mediates the ability to experience pleasure[29]. Anhedonia is the inability to experience pleasure, a cardinal feature of depression[12]. A high rate of depression is seen in patients with Parkinson's disease, a disorder characterized by DA neuron degeneration[8]. Brain imaging and postmortem studies have revealed decreased dopamine transporter binding and increased postsynaptic D2/D3 receptor binding, all indicative of reduced DA neurotransmission[12,14,29]. Reductions in the major metabolites of DA have been reported in the CSF of depressed patients[29]. 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, and pleasure, whether associated with eating, social, or sexual behavior, is well documented to be primarily mediated by DA neurons[17,29]. The burgeoning evidence for a role for altered dopaminergic circuits in depression[29]. The postmortem tissue and PET imaging studies have revealed reduced DA transporter binding sites and increased postsynaptic DA D2/D3 receptor density, indicative of a reduction in the synaptic availability of DA in depression[12, 29]. These findings suggest that treatments that enhance DA neurotransmission such as monoamine oxidase inhibitors (MAOIs), DA receptor agonists, or triple (5HT, NE, and DA) reuptake inhibitors (currently under development) may represent a novel approach to SSRI nonresponders[29].

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 [21, 31-35]. 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[21,29,33].

Stress Hormones and Cytokines

Any form of stressful life event is considered as the very initial sign of depression, thereby depression is often thought as a stress related disorder[4,8]. 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 debte[38].

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 extrahypothalamic corticotropin-releasing factor (CRF) pathways[35]. Neurons of the paraventricular 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[20]. 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[40].

Corticotropin-releasing hormone (CRH) is released from the hypothalamus in response to the perception of psychological stress by cortical brain regions[28]. 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[28,37]. Post-mortem studies reported an increased number of CRH secreting neurons in limbic brain regions in depression, likely reflecting a compensatory response to increased CRH concentrations[32]. In addition, CRH produces a number of physiological and behavioral alterations that resemble the symptoms of major depression, including decreased appetite, disrupted sleep, decreased libido, and psychomotor alterations[38]. CRF is a hypothalamic hypophycotropic factor that controls the release of corticotropin from the anterior pituitary gland. In turn, corticotropin stimulates the adrenal cortex to release hormones essential for the organism's response to stress (glucocorticoids & mineralocorticoids)[34, 35]. In addition to this neuroendocrine role, CRF plays a central role in coordinating the behavioral, autonomic, and immune responses to stress[4, 35]. Indeed, CRF is present in a variety of extrahypothalamic brain regions (the locus coeruleus & amygdala, which suggests a role for CRF in mood disorders[28]. People with depression also exhibit elevated basal levels of both cortisol and CRF[35]. CSF TRH was increased in two small studies of depressed patients[41]. Thus, excess secretion of cortisol and other hormones of the hypothalamic-pituitaryadrenal (HPA) axis have been posited to play a significant role in the etiology of depression[34,35].

Inflammatory Cytokines and Depression

Increasing amount of data suggest that inflammatory responses have an important role in pathophysiology of depression[40]. 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[51]. 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[41].

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[36]. 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 feed back to both the hypothalamus and pituitary to regulate the axis[33]. 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[33, 36].

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[28]. 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[44]. Glucocorticoid neurotoxicity, glutamatergic toxicity, decreased neurotrophic factors, and decreased neurogenesis have been proposed as possible mechanisms explaining brain volume loss in depression[39]. 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. The clinician should be aware of the potentially brain-damaging effect of depression and treat depressed patients as early and effectively as possible[45]. 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[44, 45]. BDNF is found in blood, where it mostly accumulates in platelets. Interestingly, several studies have found decreased blood levels of BDNF in depressed patients[44].

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[41, 48]. The major neurotransmitters involved in mood regulation (e.g. nor-adernaline, serotonin and dopamine) affect GH release. CSF levels of somatostatin (which inhibits GH, CRH and ACTH release) are reduced in depression[41] .

Malondiadehyde 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[49] .

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[47]. This may reflect acute stress effects, since psychological stress seems to induce presynaptic down-regulation of prefrontal GABAergic neurotransmission[47]. 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[48]. 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[48].

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[47]. There are two types of GAB-A receptors[47]. A clear link between $GABA_A$ 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. GABA-A receptors have been studied in anxiolysis because of these are coupled to Ca+2 channels. In rats, antidepressants and mood stabilizers appear to up- regulate frontal-cortical GABAB but not GABA-A receptors. GABA-B agonists may enhance C-AMP responses to nor-adrenaline and β-adrenergic down-regulation in response to tricyclic antidepressants suggesting a facilitative role for GABA-B. GABA levels have been reported to be decreased in the CSF of depressed patients in some studies[48]. Plasma GABA levels have also been reported to be lower in unipolar depressives and this may not normalise with treatment[47, 48] .

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.[52] 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[52,53]. 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 plea- sure, impaired concentration, disturbed sleep, decreased appetite, and suicidality[51]. 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[53]. 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[25]. 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[53].

Brain imaging has identified numerous regions of altered structure or activity in the brain during major depression, suggesting disordered neurocircuitry 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[53, 55]. These brain areas regulate emotional, cognitive, autonomic, sleep, and stress-response behaviors that are impaired in mood disorders[53, 55]. 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 anti depressant 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[55]. These abnormalities implicate limbic-thalamic–cortical and limbic–cortical–striatal–pallidal–thalamic circuits, involving the amygdala, orbital and medial PFC, and anatomically related parts of the striatum and thalamus in the pathophysiology of depression. These circuits have also been implicated more generally in emotional behavior by the results of electrophysiological lesion analysis and brain-mapping studies of humans and experimental animals[55].

THE LONG-TERM COURSE OF DEPRESSION

As long-term antidepressant therapy is often an essential component of treatment for individuals with severe depression, the drive to develop drugs with improved safety profiles has intensified. Although the newer antidepressant drugs have clinically important differences in efficacy and tolerability most drug development remains focused on the moderation of the same monoamine targets[20]. Recently, there have been major advances in our understanding of the biology of the circadian system, the clinical significance of disrupted daily cycles, the adverse effects of many antidepressant drugs on circadian cycles and sleep architecture, and the mechanism by which lithium has profound effects on circadian biology[56]. To the present knowledge, antidepressant drugs used in the treatment of major depressive disorders are believed to act on the central monoaminergic systems mainly 5-HT and NA synaptic neurotransmissions[1,16,20]. SSRIs (paroxetine, fluoxetine, citalopram, escitalopram, fluvoxamine, sertraline) and NRIs: (reboxetine, desipramine) are the most common prescribed antidepressant drugs[18, 20]. Although these are effective in treating most depressive episodes, a significant proportion of depressed patients do not display signs of mood improvement until 2–3 weeks after the start of the treatment. Furthermore, about one third of these patients show only partial or no response to the treatment[12] In addition, some side effects like sedation, anticholinergic effects (dried mouth, blurred vision, constipation, urinary retention etc.), postural hypotension, seizures, impotence, agitation, insomnia, dizziness, anxiety, cardiac dysrhythmias, anorgasmia, weight gain and cheese reaction (in case of MAOIs) are very common with chronic treatment of antidepressants[16, 20]. Although second generation antidepressants (e.g. maprotiline, lofepramine, mianserin etc) have eliminated some of the side effects associated with their predecessors, there have been few novel therapeutic targets like corticotrophin releasing factor 1 (CRF1) receptors, neurokinin 1 (NK1) receptors, CREB expression and neurotrophic factors that could significantly improve the management of mood disorders[22] In spite of the availability of antidepressant drugs like tricyclic antidepressants, selective reversible inhibitors of MAO-A, SSRIs, and SNRIs, depression continue to be a major medical problem[20, 23]

Recent studies of the long-term outcome of depressive illness reveal that the disorder is a chronic and highly recurrent one. Despite its prominent clinical, psychosocial, and economic burdens, depression has been under recognised and under treated. Only a small proportion of depressed subjects (<10%) receive appropriate treatment or drug treatment of a

sufficient dosage and duration.Reasons may include inadequate access to care, under diagnosis, under treatment, poor patient compliance, fear of stigmatisation, and preference for alternative psychosocial therapy[34,56]. Of considerable concern is the relatively recent realization stemming from several large-scale treatment studies, both of efficacy and effectiveness, that currently available antidepressants and psychotherapy, in particular cognitive behavior therapy (CBT), although clearly more effective than placebo, are as monotherapies associated with response (a 50% or more improvement in depressive symptoms) and remission (return to premorbid state) rates that are clearly unacceptably low. Combination or augmentation therapies comprised, respectively, of more than one antidepressant medication or an antidepressant and a second non antidepressant drug to enhance the effects of the antidepressant, and combination pharmacotherapy/ psychotherapy, although understudied, appear to be associated with better therapeutic responses than monotherapy. However, the increased side effects often, but not always, associated with coprescribing two medications, and the increased cost of treatment with combination psychotherapy and pharmacotherapy or two medications are major obstacles that prevent their wholesale clinical adoption[57,58].

CONCLUSION

Depression is a chronic and disabling illness that is associated with a significant social and economic burden. In addition to being highly prevalent, depression has high rates of psychiatric comorbidity and impairment. Depression is a group of brain disorders with varied origins, complex genetics and obscure neurobiology. Many new findings and research directions that require immediate follow-up because one or more presage rapid changes in clinical practice have recently emerged in diagnostics, the choice of currently available treatments, and novel treatment development itself. Depression is a common disorder that affects quality of life, productivity, and healthcare outcomes.

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Table:1 Major Type Of Depression

S.No	Depression	CHARACTERISTICS
1	Major Depressive disorder	Recurrent episodes of major depression, which is a common and serious illness, are called major depressive disorder. Major depressive disorder accounts for 4.4 percent of the total overall global disease burden[7, 11]. Major depression can be mild, moderate, or severe in intensity. An individual with major depression has a persistent low mood; anhedonia; negative cognition; and disturbances in sleep, appetite, and general activity for more than 2 weeks[11].
2	Dysthymia (Minor depression)	It is a chronic, milder mood disturbance in which a person reports a low mood almost daily over a span of at least two years. The symptoms are not as severe as those for major depression, although people with dysthymia are vulnerable to secondary episodes of major depression[12]. Dysthymia is a low-grade persistent depression that has lasted for 2 years or longer[12].
3	Bipolar Depression	It's previously known as manic-depressive disorder, is a condition in which depressive phases alternate with periods of mania or hypomania. Although depression is currently categorized as a separate disorder, there is ongoing debate because individuals diagnosed with major depression often experience some hypomanic symptoms, indicating a mood disorder continuum[13,12]. Cyclothymia: It is a mild form of bipolar disorder, characterized by recurring episodes of hypomania and depression[12].
4	Melancholic Depression	:It is characterized by a loss of pleasure in most or all activities, a failure of reactivity to pleasurable stimuli, a quality of depressed mood more pronounced than that of grief or loss, a worsening of symptoms in the morning hours, early morning waking, psychomotor retardation, excessive weight loss or excessive guilt[13].
5	Atypical Depression	: It is associated with labile mood, hypersomnia, increased appetite and weight gain, hypersomnia, leaden paralysis (a sensation of heaviness in limbs), and significant social impairment as a consequence of hypersensitivity to perceived interpersonal rejection[13] .
6	Catatonic Depression	:It is a rare and severe form of major depression involving disturbances of motor behaviour and other symptoms. Here the person is mute and almost stuporose, and either remains immobile or exhibits purposeless or even bizarre movements[13]. If the individual has only depression without mania, the diagnosis is unipolar depression. If manic or hypomanic episodes are present, the diagnosis is bipolar affective disorder[12].

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