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Depression: A Review

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ABSTRACT

Depression is one among the most rampant form of psychiatric disorders and a leading cause for morbidity and mortality. Depression should be recognized as a clinical syndrome that is characterised by a cluster of emotional, behavioural, and cognitive features. Depression also poses a significant economic burden to society as it leads to reduced productivity, treatment costs and loss of human life by suicide. Depression is a common problem affecting about 121 million people worldwide. It occurs in persons of all genders, ages, and back- grounds. Depression is almost twice as common in females as males. Depression refers to a wide range of mental health problems which is characterized by enduring sadness, anhedonia, guilt, low self esteem, disturbed sleep, poor appetite, low energy, suicidal thoughts, a lack of libido, fatigue, poor concentration and reduced attention, pessimistic and suicidal tendencies, food intake dysregulation. 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, substance P, corticotropin-releasing factor, dopamine, g-aminobutyric acid (GABA), somatostatin, and thyroid-related hormones have been implicated in the pathophysiology of Depression. Many brain regions have been implicated in regulating emotions; we still have a very rudimentary under standing of the neural circuitry underlying normal mood and the abnormalities in mood that are the hallmark of Depression. Depression is associated with a serious impairment of social, marital, and occupational functioning, as well as prominent personal and interpersonal distress.

Key words: Depression, Noreinephrine, Mood Disorder, Monoamines, Stress.

INTRODUCTION

Depression is one among the most rampant form of psychiatric disorders and a leading cause for morbidity and mortality. Misconceptions towards mental disorders and the prevailing stigmatizing attitude among both, the general public and health professionals constitute major barriers in the recovery of mentally ill patients. According to WHO, depression is projected to

reach second place of disease by the year 2020 [22]. Depression should be recognized as a clinical syndrome that is characterised by a cluster of emotional, behavioural, and cognitive features. Depression is a common problem affecting about 121 million people world-wide [42]. It occurs in persons of all genders, ages, and back- grounds. Depression is almost twice as common in females as males. Depression also poses a significant economic burden to society as it leads to reduced productivity, treatment costs and loss of human life by suicide. More than half of the economic burden will be accounted for by reduced productivity. Lifetime prevalence rates for depression range from 7% to 12% in men and 20% to 25% in women. Depression negatively affects patients' perception of health [22]. An estimated 40-50% of risk for depression is genetically determined [24]. However, no single vulnerability gene has been indentified yet, indicating a far more complex interplay of genetic and environmental factor underlying the causative etiology of this disorder [19]. Depression is associated with a serious impairment of social, marital, and occupational functioning, as well as prominent personal and interpersonal distress [22].

CLINICAL SIGNS AND SYMPTOMS

Depression refers to a wide range of mental health problems which is characterized by enduring sadness, anhedonia, guilt, low self esteem, disturbed sleep, poor appetite, low energy, suicidal thoughts, a lack of libido, fatigue, poor concentration and reduced attention, pessimistic and suicidal tendencies, food intake dysregulation. As defined by American Psychiatric Association, depression is a heterogeneous disorder often manifested with symptoms at psychological, behavioural and physiological [3].

Symptoms of Depression

Depressed mood most of the day (in children & adolescents, irritability might signify a depressed mood), Anhedonia (Loss of interest or pleasure in almost all activity), Irritability, Low self esteem, Feelings of worthlessness or excessive or inappropriate guilt, Decreased ability to concentrate and think, Decreased or increased in appetite, Weight loss or weight gain, Insomnia or Hypersomnia, Low energy, fatigue, Psychomotor agitation (evident by, example hand wringing) or slowness of movement, Recurrent thoughts of death and suicide [3].

Genetic and Environmental Causes of Depression

The specific cause of major depressive disorder is not known. As with most psychiatric disorders, depression appears to be multifactorial in its origin. Epidemiologic studies show that roughly 40% to 50% of the risk for depression is genetic. This makes depression a highly, heritable disorder, at least as heritable as several common complex medical conditions (type II diabetes, hypertension, asthma, certain cancers), which are often as genetic. Yet, the search for specific genes that confer this risk has been frustrating, with no genetic abnormality being identified to date with certainty. Depression is a complex phenomenon with many genes possibly involved. Thus, any single gene might produce a relatively small effect and would there- fore be difficult to detect experimentally. It is also possible that variants in different genes may contribute to depression in each family, which further complicates of the search for depression genes. In addition, vulnerability to depression is only partly genetic, with non genetic factors also being important. Nongenetic factors as diverse as stress and emotional trauma, viral infections (e.g., Borna virus), and even stowith (or random) processes during brain development have been implicated in the etiology of depression [14]. The role of stress warrants particular comment. Depression is often described as a stress-related disorder, and there is good evidence that episodes of depression- often occur in the context of some form of stress [31,5]. Depression in most people is caused by interactions between a genetic predisposition and some

environmental factors, which makes the mechanisms of such interactions an important focus of investigation [19].

DIAGNOSIS OF A MAJOR DEPRESSIVE EPISODE

Despite its prominent clinical, psychosocial, and economic burdens, depression has been under recognised and undertreated. Only a small proportion of depressed subjects (<10%) receive appropriate treatment or drug treatment of a sufficient dosage and duration [17]. Reasons may include inadequate access to care, under diagnosis, under treatment, poor patient compliance, fear of stigmatisation, and preference for alternative psychosocial therapy. Diagnosis of major depression is based on standardized clinical criteria published by the American Psychiatric Association in Diagnostic and Statistical Manual of Mental Disorders [10]. The criteria for the diagnosis of an episode include at least minimum two weeks of depressed mood or anhedonia plus four of seven other features that are sufficient to cause clinically important psychological or physical distress or functional impairment. These features include a weight change of 5 percent or more in one month or a persistent change in appetite, insomnia or hypersomnia on most days, changes in psychomotor state, fatigue, feelings of guilt and worthlessness, diminished concentration and decisiveness, and suicidal ideation or a suicide attempt. Conversely, major depression may be missed when patients present to primary care physicians with predominantly somatic symptoms, including pain. Typically, symptoms such as anorexia, weight loss, constipation, disturbed sleep, energies, loss of libido, vague aches and pains, and deficiencies in memory and concentration may result in a missed diagnosis, particularly if the patient does not spontaneously report low mood or other psychological symptoms, such as guilt, hopelessness, anxiety, suicidal ideation, or prior suicide attempts. Delusions of guilt and somatic illness complicate up to 14 percent of major depressive episodes, especially postpartum depression [16]. Depressive episodes in bipolar disorder may be similar to those in major depressive disorder or may present as part of a mixed state characterized by distressing combinations of depression and mania or hypomania (irritability, racing thoughts, anxiety, suicidal thoughts, and aggressive impulses). Patients with bipolar disorder who present with a depressive episode may be misdiagnosed as having major depressive disorder because they may often underreport hypomanic and manic symptoms, perceiving such features to be closer to wellbeing than illness. A family history of bipolar disorder can assist in making the correct diagnosis. Since the 1960s, Depression has been diagnosed as “major depression’’ based on symptomatic criteria set forth in the Diagnostic and Statically Manual. Depression should not be viewed as a single disease, but a heterogeneous syndrome comprised of numerous diseases of distinct causes and pathophysiologies [10].

TYPES OF DEPRESSION

Depression is a common, chronic, and potentially debilitating illness that has tempered the human condition since the beginning of recorded history. The annual incidence of mood disorders is estimated to range from 7% to 12% of the population [22,16]. 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 [4,17]**.**

Major Depressive Episode
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 [22,14].

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 [7,41].

Bipolar Disorder
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 [6,17,10].

Cyclothymia
It is a mild form of bipolar disorder, characterized by recurring episodes of hypomania and depression [41].

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 [10,18].

Atypical Depression
It is associated with labile mood, hypersomnia, increased appetite & weight gain, hypersomnia, leaden paralysis (a sensation of heaviness in limbs), and significant social impairment as a consequence of hypersensitivity to perceived interpersonal rejection [10].

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 [10,28].

PATHOPHYSIOLOGICAL FEATURES OF DEPRESSION

The majority of subsequent hypotheses suggest that depression arises from the deregulation of one or more neurotransmitters or neuroregulators in areas of the brain involved in mood regulation, e.g., the cerebral cortex and limbic system [2]. The heritability of depression suggests that, in some patients, there is a genetic predisposition to the development of this altered neurobiology. Particularly strong evidence exists for a preeminent role of the monoamine neurotransmitters serotonin (5-HT), norepinephrine (NE), possibly dopamine (DA), and the neuropeptide corticotropin-releasing factor in pathophysiology of Depression [9,27,37]. Some evidence also exists for a role of substance P in depressive disorders [23]. Consonant with such hypotheses, a host of deficiencies in serotonin, norepinephrine, dopamine, g-aminobutyric acid (GABA), brain-derived neurotrophic factor, somatostatin, and thyroid-related hormones — have been proposed as contributing to depression. Furthermore, over activity in still other neurotransmitter systems involving acetylcholine, corticotropin-releasing factor, and substance P are thought to be implicated in depression [20]. Furthermore, recent research has suggested that

the neurobiology of depression may involve adaptation of a variety of neural systems. The function of intracellular cascades initiated by the actions of neurotransmitters may therefore be altered in depression, leading to downstream changes in neural function. 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 [35].

- **Monoamines:** 5-HT, NE, and DA, are widely distributed neurotransmitter systems in the mammalian central nervous system, regulating a considerable array of behaviors including mood, appetite, cognition, libido, anxiety, and aggression, just to name a few. All three monoamines (5-HT, NE, and DA) are important in the regulation of mood, emotion, and cognitive function. Many of these functions have been demonstrated to be impaired in patients with depression [9]. The implication that dysfunction of monoamine systems may be involved in the etiology of depression has been the subject of considerable research [37]. MAO occurs bound to the surface membrane of mitochondria within cells. It is abundant in nor-adrenergic nerve terminals but is also present in many other places, such as liver and intestinal epithelium. MAO converts catecholamine into their corresponding aldehydes, which in periphery, are rapidly metabolized by aldehyde dehydrogenase to corresponding carboxylic acid. In case of nor-adrenaline, this yields dehydroxy-mandelic acid. MAO can also oxidize other monoamines like dopamine (DA) and serotonin. MAO is enzyme protein responsible for metabolizing monoamines like NE, DA and 5-HT. MAO is found in nearly all tissues. MAO exists in two similar molecular forms coded by separate genes. 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 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 [13].

- **Norepinephrine:** Noradrenergic cell bodies in the brainstem (lateral tegmental area and locus coeruleus) give rise to diverse projections to a variety of brain structures. The latter structure in the pons gives rise to 70% of the NE innervating the forebrain. The noradrenergic system is intimately involved in the mediation of stress responses. The locus coeruleus is sensitive to both external environmental stimuli and internal changes in homeostasis, and receives inputs from numerous other neurotransmitter systems, including 5-HT, opioid, alpha-aminobutyric acid (GABA), corticotropin-releasing factor (CRF), DA, and glutamate, which feed back information on the state of internal homeostasis [2]. The NE released following activation of noradrenergic neurons mediates effects through interaction with alpha and beta adrenoceptors, which may be present both pre- and postsynaptically [35]. Although there is more controversy surrounding a putative role for NE system dysfunction than for 5-HT circuits in the neurobiology of depression, a number of studies have suggested that a dysfunction of NE neurons and/or changes in adrenergic receptor sensitivity may be important in the etiology of depression [2].

- **Serotonin Transporter Function and Depressive Behaviour:** Serotonin mediates inhibitory and excitatory neurotransmission throughout the central nervous system [35]. From cell bodies concentrated in the dorsal and caudal raphe nuclei, widespread serotonergic projections extend to a considerable variety of brain areas believed to be associated with the symptoms of depression, including the hypothalamus, amygdala, cortex, hippocampus, basal ganglia, and brainstem. The serotonergic system is therefore anatomically well situated to mediate the signs and symptoms of depression, because these are so diverse that they could not possibly be mediated by just one brain region. The effects of serotonin are mediated through 5-HT receptors, of which at least 13 molecular subtypes are present, including three major receptor

families (5-HT1A, 5-HT2A/C, and 5-HT3) [2]. Receptors are present at pre- and postsynaptic sites, in addition to their location on serotonergic nerve-cell bodies. Dysfunction in the serotonergic system is a well-established theory explaining the pathophysiology of depression [37]. There is overwhelming evidence indicating a relative deficiency of 5-HT in most or all forms of depression. This evidence has been obtained from neuroendocrine studies, demonstrating blunted hormonal responses to serotonergic stimuli, from studies of the levels of 5-HT metabolites in postmortem tissue and cerebrospinal fluid (CSF), selective depletion studies of 5-HT in depressed patients, alterations in the 5-HT transporter and receptors in functional brain imaging studies and post-mortem tissue studies, and through study of the mechanism of action of antidepressant agents [35].

- **Dopamine:** The DA system in the brain, in contrast to the 5-HT and NE circuits, comprises point-to-point topographical projections from particular cell groups to particular terminal regions. Dopaminergic neurons are organized in three main pathways: the mesolimbic-mesocortical pathway linking midbrain DA cell groups with limbic and cortical regions; the nigrostriatal pathway; and the tuberoinfundibular pathway, which comprises an intrinsic hypothalamic DA pathway that modulates the anterior pituitary gland. 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) [9,35,37].

- **Selective Depletion of Serotonin and Norepinephrine:** Further evidence indicating that reduced levels of 5-HT is related to the development of depression is provided by the observation that depletion of 5-HT levels is associated with precipitation of symptoms of depression. Thus, these symptoms result from the depletion of all monoamine stores, including 5-HT, by administration of reserpine or the reduction of central 5-HT levels by the tryptophan hydroxylase inhibitor parachlorophenylalanine. Furthermore, depletion of tryptophan (the biosynthetic precursor of 5-HT) by use of a special diet causes a rapid clinical relapse in patients in remission from depression. Many effects of 5-HT, such as the regulation of mood, anxiety, and body temperature, and control of sexual function, sleep, obsessive-compulsive behavior, eating behavior, hallucinations, psychosis, and panic attack, are thought to be mediated by an interaction of 5-HT with postsynaptic 5-HT2 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 [9,39].

- **GABA (Gamma amino butyric acid):** GABA is a major inhibitory neurotransmitter in brain and regulates seizure threshold as well as nor-adrenaline and dopamine turnover. There are two types of GAB-A receptors. 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 cAMP 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 [36]. Plasma GABA levels have also been reported to be lower in unipolar depressives and this may not normalize with treatment [29].

- **Hypothalamic–pituitary–adrenocortical (HPA) axis and Depression:** 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 [9]. 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. HPA system receives and integrates various inputs indicative of stress, converging in paraventricular nucleus (PVN) of the hypothalamus. Neurons of PVN synthesize cortocotropin releasing hormone (CRH), which is released to the hypophyseal portal blood and reaches the anterior pituitary. Thus, CRH regulate the transcription of the proopiomalenocortin gene, a common precursor for synthesis of adrenocorticotropic hormone (ACTH) and related peptides, and stimulates the release of ACTH into the blood stream. Then, ACTH stimulates the biosynthesis and release of glucocorticoids, particularly cortisol, by cells of the adrenal cortex. In response to stress, glucocorticoids exert widespread metabolic effects, particularly involved in the mobilization of energetic resources aimed at coping with the stressful situation. These steroid hormones bind to minralocorticoid receptors and glucocorticoid receptors which belong to the family of transacting factors, structurally organized in different domains. Upon cortisol binding, these receptors undergo conformational changes to facilitate their subsequent binding to DNA. Therefore, the hormone receptor complex may regulate the expression of various target genes, either through activation and deactivation. In order to maintain glucocorticoids within physiological range, the HPA axis is controlled by multiple negative feedback loops mediated mainly by the steroids themselves. Therefore, the endocrine system is closely regulated by the CNS through HPA axis, and the reciprocal interplay between both systems provides a way through which thoughts and emotions may regulate hormone secretion. However under chronic stress, the HPA system is dysregulated resulting in pathophysiological changes, which may develop into various types of disorders such as major depression. In this regard, a significant association between stress and depression is now well documented, where for both syndromes hypercortisolism represents one of the most consistent biological markers [38].

- **Corticotropin-Releasing Factor:** 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. 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 and mineralocorticoids). In addition to this neuroendocrine role, CRF plays a central role in coordinating the behavioral, autonomic, and immune responses to stress. Indeed, CRF is present in a variety of extrahypothalamic brain regions (the locus coeruleus and amygdala, which suggests a role for CRF in mood disorders [32]. An abnormality in glutamate function has been implicated in the neural substrate of depression [25]. People with depression also exhibit elevated basal levels of both cortisol and CRF [15].

- **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 feed back 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.

- **BDNF and Depression:** In humans, brain BDNF (Brain derived neurotrophic factor) levels have been found to be reduced in postmortem samples from 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 [21]. The BDNF gene has a

complex genetic structure with seven upstream exons and one coding exon that give rise to multiple splice variants, each controlled by distinct promoters. Various polymorphisms are present in the human BDNF gene such as the functional val66met polymorphism that changes a valine to a methionine in the BDNF peptide [12]. The study implies that loss-of-function mutations in BDNF might predispose an individual to depression via dysregulation of the HPA system [26].

- **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. 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 [1].

- **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.

- **Inflammatory Cytokines and Depression:** Increasing amount of data suggest that inflammatory responses have an important role in pathophysiology of depression [8]. 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 [34].

NEURAL CIRCUITRY OF DEPRESSION

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 and 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 [33]. These brain areas regulate emotional, cognitive, autonomic, sleep, and stress-response behaviors that are impaired in mood disorders. Studies with the use of positron-emission tomography indicate a decrease in serotonin transporters as well as altered postsynaptic serotonin-receptor binding in many of the same brain regions, suggesting altered circuitry congruent with serotonin-system abnormalities. Mood, emotions and cognitive functions are regulated by NE, serotonin and dopamine [11]. 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. Neurotrophins and neurogenesis Volumetric decreases observed in the hippocampus and other forebrain regions in subsets of depressed patients [40]. Neocortex and hippocampus may mediate cognitive aspects of depression, such as memory impairments and feelings of worthlessness, hopelessness, guilt, doom, and suicidality. The striatum (particularly the ventral striatum or nucleus accumbens [NAc]) and amygdala, and related brain arfailed are important in emotional memory, and could as a result mediate the anhedonia (decreased drive and reward for pleasurable activities), anxiety, and reduced motivation that predominate in many patients. Of course, these various brain regions operate in a series of highly interacting parallel circuits, which perhaps begins to formulate a neural circuitry involved in depression [11,30,37].

CONCLUSION

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 highly prevalent and disabling condition associated with significant morbidity and mortality. Depression is a condition with a complex biologic pattern of etiology. 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. Depression is associated with a serious impairment of social, marital, and occupational functioning, as well as prominent personal and interpersonal distress. Depression is a common disorder that affects quality of life, productivity, and healthcare outcomes.

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