

## DEPRESSION: A REVIEW ON CAUSES, TYPES AND PATHOPHYSIOLOGY OF DEPRESSION

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### ABSTRACT

Depression is a mood disorder that causes a persistent feeling of sadness and loss of interest. Depression is a common illness worldwide, with an estimated 3.8% of the population affected, including 5.0% among adults and 5.7% among adults older than 60 years. Depression results from a complex interaction of social, psychological, and biological factors. At its worst, depression can lead to suicide. Over 700 000 people die due to suicide every year. Suicide is the fourth leading cause of death in 15-29-year-olds. In this review I have included types, causes, pathophysiology of depression.

**Keywords:** Depression, pathophysiology, major depressive disorder.

### INTRODUCTION

Major depressive disorder (MDD) is a severe major mental disorder. The lifetime prevalence of major depressive disorder is high, around 16.9% in the United States. In addition to potential suicidal risk, depression leads to functional impairment which causes burden of patients, their families, and the society. In WHO report, depressive disorder is the ninth leading cause of functional disability-adjusted life years and the first leading cause in years lost due to disability in 2012<sup>1</sup>.

In view of the morbidity, depression as a disorder has always been a focus of attention of researchers in India. Various authors have tried to study its prevalence and psychosocial risk factors including life events, symptoms in the cultural context, co morbidity, psycho neurobiology, treatment, outcome, prevention, disability and burden. Some of the studies have also tried to address various issues in children and elderly<sup>2</sup>. Major depressive disorder (MDD) is the most common psychiatric disease and a worldwide leading cause of years lived with disability<sup>3</sup>. Symptoms of major depression include complete loss of pleasure, lack of reactivity, psychomotor retardation, significant weight loss, excessive guilt, or distinct quality of depressed mood<sup>4</sup>.

### VARIOUS FORM OF DEPRESSION

Depression is still seen as a single clinical entity, especially in primary care. However, the sub typing of depression is fundamental for its correct treatment

#### Major Depressive Disorder

Major depressive disorder (MDD) has been ranked as the third cause of the burden of disease worldwide in 2008 by WHO, which has projected that this disease will rank first by 2030.<sup>[1]</sup> It is diagnosed when an individual has a persistently low or depressed mood, decreased interest in pleasurable activities, feelings of guilt or worthlessness, lack of energy, poor concentration, appetite changes, psychomotor retardation or agitation, sleep disturbances, or suicidal thoughts. The etiology of Major depressive disorder is believed to be multifactorial, including biological, genetic, environmental, and psychosocial factors. MDD was earlier considered to be mainly due to abnormalities in neurotransmitters, especially serotonin, norepinephrine, and dopamine. This has been evidenced by the use of different antidepressants such as selective serotonin receptor inhibitors, serotonin-norepinephrine receptor inhibitors, dopamine-norepinephrine receptor inhibitors in the treatment of depression. People with suicidal ideations have been found to have low levels of serotonin metabolites. However, recent theories indicate that it is associated primarily with more complex neuroregulatory systems and neural circuits, causing secondary disturbances of neurotransmitter systems.<sup>5</sup>

### **Atypical Depression**

A major depressive episode with the atypical features (atypical depression) can be present in almost all mood disorders. Distinguishing features of atypical depression are the following: (i) it is more likely to be present in bipolar disorders (especially bipolar II disorder); (ii) it is more likely to be present in seasonal depression; (iii) it is more likely to be present in younger than in older individuals; (iv) it has a lower age at onset compared with nonatypical depression; (v) it is more common in females; (vi) it has higher axis I co morbidity compared with non atypical depression; and (vii) it has more bipolar family history versus non atypical depression<sup>6</sup>.

### **Recurrent Brief Depressive Disorder**

Recurrent brief depressive disorder research criteria require meeting major depressive episode criteria, apart from the duration, which should be between at least 2 days but less than 2 weeks. It should occur at least once a month for 12 consecutive months. It must not meet criteria for major depressive episode, dysthymic disorder, mania, hypomania, or cyclothymic disorder<sup>7</sup>.

### **Seasonal Affective Disorder**

The criteria for depression with a seasonal pattern include having depression that begins and ends during a specific season every year (with full remittance during other seasons) for at least two years and having more seasons of depression than seasons without depression over a lifetime. Seasonal pattern disorders occur most frequently in winter although they can also occur in summer<sup>8</sup>.

### **Bipolar Disorder**

Bipolar disorder (BD) is a chronic illness associated with severely debilitating symptoms that can have profound effects on both patients and their caregivers. BD typically begins in adolescence or early adulthood and can have life-long adverse effects on the patient's mental and physical health, educational and occupational functioning, and interpersonal relationships<sup>9</sup>.

### **Postpartum Depression**

Postpartum depression is a debilitating mental disorder with a prevalence between 5% and 60.8% worldwide.

Previous history of depression and anxiety is among the factors that are associated with a higher risk of postpartum depression. The disease manifests as sleep disorders, mood swings, changes in appetite, fear of injury, serious concerns about the baby, much sadness and crying, sense of doubt, difficulty in concentrating, lack of interest in daily activities, thoughts of death and suicide. Feelings of hopelessness in severe cases of illness can threaten life and lead to suicide; it is a factor that causes 20% of maternal deaths in the course after giving birth<sup>10</sup>.

## **CAUSES**

### **Genetic Causes of Depression**

Family and twin studies have provided strong evidence for the contribution of genetic factors to the risk of depression. For instance, a meta-analysis of twin research data shows that the heritability rate for depression is 37% (95% CI: 31%–42%), and data from family studies show a two- to threefold increase in the risk of depression in first-degree offspring of patients with depression. Heritability has also been shown to be especially influential in severe forms of depression. The illness severity depends on whether DDs are inherited maternally or paternally<sup>11</sup>.

### **Environmental Causes of Depression**

Environmental causes of depression include events such as stress, traumatic events and childhood difficulties.

**Stress:** Most researchers believe that for some people there is a direct relationship between a stressful event and the development of depression. What is interesting to note is that this stress can be negative or positive. Examples of negative stress are loss of a loved one, loss of a job, loss of a relationship and divorce. Examples of positive stress are planning for a wedding, preparing for a new job, and moving to a new city.

**Traumatic Events:** It is a fact that many people have experienced a traumatic event prior to developing depression. Traumatic events in the lives of people include loss of a loved one, a serious medical illness, the end of a marriage or significant financial loss.

**Childhood Difficulties:** The most common childhood difficulties include sexual, emotional, or physical abuse, dysfunctional upbringing, parental separation, and mental illness in one or both of the parents<sup>12</sup>.

Childhood trauma is associated with sensitization of the neuroendocrine and autonomic stress response, glucocorticoid resistance, increased central corticotropin-releasing factor (CRF) activity, immune activation, and reduced hippocampal volume. A major focus of investigation in this area has been the role of the hypothalamic-pituitary-adrenal (HPA) axis, both as a marker of the stress response and as a mediator of additional downstream pathophysiologic changes. The HPA axis functions in close concert with the Locus Coeruleus-Norepinephrine (LC-NE) system, which is involved in extensive reciprocal innervation of regions throughout the central nervous system<sup>13</sup>.

The repeated recollection of traumatic memories is a central component of the phenomenological response to traumatic events.<sup>14</sup>

## **PATHOPHYSIOLOGY OF DEPRESSION**

### **MONOAMINE Hypothesis**

The first major hypothesis of depression was formulated about 30 years ago and proposed that the main symptoms of depression are due to a functional deficiency of the brain monoaminergic transmitters norepinephrine (NE), 5-HT, and/or dopamine (DA), whereas mania is caused by functional excess of monoamines at critical synapses in the brain. Evidence for this hypothesis came from clinical observations and animal experiments, which showed that the antihypertensive drug reserpine, which causes a depletion of presynaptic stores of NE, 5-HT, and DA, induced a syndrome resembling depression. In contrast to the effects obtained with reserpine, euphoria and hyperactive behavior were observed in some patients being treated with iproniazid, a compound synthesized for the treatment of tuberculosis, which increased brain concentrations of NE and 5-HT by inhibiting the metabolic enzyme MAO<sup>15</sup>.

### **Genetic Factors and Depression**

Family, twin, and adoption studies provide very solid and consistent evidence that MDD is a familial disorder and that this familiarity is mostly or entirely due to genetic factors. This important finding suggests that parental social behavior and other familial environmental risk factors are not as important in the pathogenesis of MDD as previously assumed and should not be the major focus of the treatment of the disorder.

The above-mentioned studies consistently show that the influence of genetic factors is around 30-40%. Non-genetic factors, explaining the remaining 60-70% of the variance in susceptibility to MDD, are individual-specific environmental effects (including measurement error effects and gene-environment interactions). These effects are mostly adverse events in childhood and ongoing or recent stress due to interpersonal adversities, including childhood sexual abuse, other lifetime trauma, low social support, marital problems, and divorce.

These results suggest that there is a huge potential in the prevention of MDD by means of psychosocial interventions (e.g., in schools, at workplace). In addition, these results mirror the clinical practice of empirically validated psychotherapies to treat depression, including interpersonal, psychodynamic and cognitive behavioral psychotherapies and cognitive behavioural analysis system of psychotherapy, which all focus directly or indirectly on interpersonal difficulties and skills. This does not exclude the fact that unidentified non-genetic, non-psychosocial risk factors may also play important roles in some patients (e.g., climatic change, medical conditions)<sup>16</sup>.

The physiologic response to stress consists of a rapid component and a slower one, acting in a coordinated temporal manner to reestablish homeostasis<sup>17</sup>. The rapid response is the activation of the sympathetic nervous system, which increases the levels of circulating norepinephrine and epinephrine and elevates the levels of norepinephrine in the brain. This is referred to as the "sympathetic-adrenomedullary system." The slower, longer-lasting response is activation of the HPA axis that begins with the release of CRF into the circulation from the paraventricular nucleus of the hypothalamus, which then stimulates the pituitary to release ACTH into the bloodstream. The released ACTH accelerates the discharge of glucocorticoids from the adrenal cortex<sup>18</sup>.

## CONCLUSION

Depression is a mood disorder that causes a persistent feeling of sadness and loss of interest. Depression is still seen as a single clinical entity, especially in primary care. However, the sub typing of depression is fundamental for its correct treatment. The various types of depression include major depressive disorder, recurrent brief depressive disorder, seasonal affective disorder, bipolar disorder, postpartum depression. The monoamine hypothesis states that insufficient activity of monoamines is the primary reason for the depression.

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