

## A review on Depression

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### Abstract

Depression is the leading cause of disability with a prevalence of more than 20% worldwide. It is associated with change in mood, loss of pleasure, inability to concentrate, lack of energy, sleep disturbance, guilty and suicidal tendency. The exact mechanism of depression is not known till now, but many hypothesis were implicated in the pathogenesis of depression which includes monoamino, GABAergic, glucocorticoid, neurotrophic, inflammatory hypothesis. The present review emphasized on different hypothesis for better understanding the pathogenesis of depression and identifying potential targets for screening of drugs for antidepressant activity.

**Keywords:** Depression, etiological factors, pathogenesis, treatment.

### 1. Introduction

Depression is a significant contributor to the global burden of disease and affects people in all communities across the world. The World Mental Health Survey conducted in 17 countries found that on average, about 1 in 20 people reported having an episode of depression [1]. According to World Health Organization, Depression is a common mental disorder that presents with depressed mood, loss of interest or pleasure, decreased energy, feelings of guilt or low self-worth, disturbed sleep or appetite, feelings of tiredness and poor concentration [2].

### 2. History

The history of depressive disorders is described in detail by Jackson. The experience of depression has plagued humans since the earliest documentation of human experience. Ancient Greek descriptions of depression referred to a syndrome of melancholia, which translated from the Greek means black bile. In humoral theory, black bile was considered an etiologic factor in melancholia[3]. During the late 19th and early 20th centuries, phenomenologists increasingly used the term depression or mental depression to refer to the clinical syndrome of melancholia[4].

### 3. Epidemiology

The National Comorbidity Survey Replication found that 16.2% of the population had a history of major depressive disorder in their lifetime, and more than 6.6% had an episode within the past 12 months. The estimated lifetime prevalence of major depression in individuals aged 65 to 80 years was reported to be 20.4% in women and 9.6% in men. Depressive disorders are common during adolescence, with comorbid substance abuse, suicide attempts, and deaths occurring frequently in young patients [5-7].

### 4. Etiology

Each type of depression is associated with different combination of causes. Research indicates that ongoing difficulties, such as long term unemployment, alcohol problems, chronic illness, or living in an abusive or uncaring relationship, are more likely to cause depression than recent stressful situations [8]. These include:

#### 4.1 Genetic factors

There is strong evidence that genetic factors play a significant role in a person's predisposition towards developing depression, especially melancholic depression, psychotic depression and bipolar disorder.

## 4.2 Biochemical factors

In depression neurotransmitters (Serotonin, Norepinephrine and Dopamine) function is disrupted. In normal brain function, neurotransmitters interact with a series of nerve cells. However, in people who are depressed, mood regulating neurotransmitters fail to function normally, so that the signal is either depleted or disrupted before communication to adjacent nerve cell.

## 4.3. Stress

Stress is an important etiological factor that affects every individual. Events like, Death or loss of someone close, breaking up with a partner, losing a job[9].

## 5. Signs and Symptoms

Feeling bad about oneself, reduced pain tolerance, decreased tolerance for minor aches and pains, not able to enjoy life, feelings of sadness or unhappiness, irritability or frustration even over small matters, loss of interest or pleasure in normal activities, reduced sex drive, insomnia or excessive sleeping, changes in appetite, agitation or restlessness, slowed thinking, speaking or body movements, indecisiveness, distractibility and decreased concentration, fatigue, tiredness and loss of energy, feelings of worthlessness or guilt, fixating on past failures, frequent thoughts of death, dying or suicide, crying spells for no apparent reason[10,11].

## 6. Types of Depression

Depression is a mood disorder in different forms like heart diseases and diabetes. The most common types of depressive disorders are discussed below.

### 6.1. Major depression

Major depression is characterized by sad and/or irritable mood that interfere with the ability to work, sleep, eat, and enjoy once pleasurable activities.

### 6.2. Dysthymia

Dysthymia is a less severe but usually more long-lasting type of depression compared to major depression. It involves long-term (chronic) symptoms and prevents the affected person from functioning. Sometimes, people with dysthymia also experience episodes of major depression.

### 6.3. Bipolar disorder (manic depression)

It encompasses a group of mood disorders that were formerly called manic-depressive illness or manic depression. These conditions show a particular pattern of inheritance. It involve cycles of mood that include at least one episode of mania or hypomania and episodes of depression as well. Mania often affects thinking, judgment, and social behavior cause serious problems and embarrassment [10].

## 7. Pathophysiology

The exact mechanism of depression is not known till now. The possible mechanism of depression has been proposed in the form of hypothesis such as:

- ✓ Monoamine hypothesis of depression
- ✓ Stress and the glucocorticoid hypothesis of depression
- ✓ Neurotrophic hypothesis of depression
- ✓ GABAergic hypothesis of depression
- ✓ Inflammatory hypothesis of depression

### 7.1. Monoamine hypothesis of depression

The vast majority of antidepressant medications operate on serotonin, norepinephrine or dopamine neurotransmitter systems. The initial evidence from the 1950's for neurotransmitter involvement in depression occurred in unrelated studies, when reserpine (which increases transport of several monoamines into the presynaptic cell) was found to increase depressive symptoms. The monoamine hypothesis became more entrenched in the 1960's as researchers continued to pursue a pharmacologically driven search for the roots of depression and found that the tricyclic antidepressant drug imipramine prevented norepinephrine (NE) reuptake. In tracking down the exact mechanism of imipramine, researchers found it also inhibited serotonin reuptake, leading to the first selective serotonin reuptake inhibitors (SSRI's). A more recent addition to the monoamine depression theories is that dopamine-mediated effects are a component of observed depression symptoms. The clinical basis for this hypothesis is observation of high levels of depression in pre-Parkinsonian patients and the pro-hedonic effect of some Parkinson's drugs [12,13].

### 7.2. Stress and the glucocorticoid hypothesis of depression

A classic definition of stress is "the non-specific response of the body to any demand for change". Glucocorticoid signaling is a major transducer of physiological/emotional stress. Brain structures respond to stress through a feed-forward activation of the paraventricular nucleus of the hypothalamus, anterior pituitary and adrenal glands (HPA axis) mediated by corticotropin releasing hormone (CRH), adrenal cortical releasing hormone (ACTH) and cortisol, which all feedback on the brain through CRH receptors and glucocorticoid and mineralocorticoid receptors[14]. Since glucocorticoids activate transcription factors that lead to transcription of hundreds of genes, their downstream effects are vast, activating dozens of major intracellular signaling pathways, including effects on ionotropic and metabotropic receptors, growth factors, enzymes, neurotransmitters, and cell morphology[15,16].

### 7.3. Neurotrophic hypothesis of depression

Synaptic plasticity and neurogenesis may play a role in depression pathology and antidepressant mechanisms of action. Neurogenesis in the subgranular zone of the hippocampus is often necessary for behavioral reversal of induced depression in mice. Brain derived neurotrophic factor (BDNF), which acts through TrkB receptors to inhibit MAPK and AKT mediated cell-death, is commonly used as a marker for neurotrophic effects [17]. Electroconvulsive shock therapy, the most effective therapy for treatment-resistant depression, also increases neurogenesis along with levels of BDNF. Several monoamine antidepressants increase levels of BDNF, increasing TrkB receptor activity alone has an antidepressant effect, and antidepressants have lower efficacy in the BDNF inducible mouse. Thus, there is strong evidence for the role of neuro/synaptogenesis in antidepressant mechanisms [18].

### 7.4 GABAergic hypothesis of depression

Gamma-aminobutyric acid (GABA) expressing cells are found in all depression-affected brain regions, including the hippocampus, frontal cortex and amygdala and modulate release of serotonin, norepinephrine and dopamine. Both ionotropic GABA-A and metabotropic GABA-B receptors can have depressive-related behavioral effects; however, GABA-B receptor knockouts a simultaneous increase in depressive and anxiety behaviors[19].

GABAergic deficits have been suspected in MDD for the last 30 years on the basis of blood and cerebrospinal fluid. This was long-standing support for GABA involvement because depression has extensive comorbidity with anxiety, which is highly responsive to benzodiazepines and are often adjunctive therapy for depression. Several microarray studies show GABA deficits in occipital, cingulate and pre-frontal cortex, in an approximate match for consensus dysregulated brain regions in MDD, but the results are highly region- and receptor subtype specific. A series of MRS (magnetic resonance spectroscopy) studies show evidence for lower GABA levels in brain regions including various segments of frontal cortex and anterior cingulate cortex and that patients most resistant to depression had the lowest GABA levels in these areas. Thus, it appears that one or more types of GABA deficits are associated with depression pathology [20].

### 7.5 Inflammatory hypothesis of depression

Inflammatory activation and modulation are entwined with the etiology of major depression as risk factors, secondary effectors and bridges between other theories of depression. The initial proposal of the inflammatory hypothesis lacked causal evidence, but rather noted the high comorbidity of inflammation-driven

processes such as coronary heart disease with depression, and also the similarity of depressive symptoms with behaviors of humans with immune response to viral infections. Now there is direct evidence of pro-depressive action of beyond these associations, as multiple SSRI's decrease pro-inflammatory cytokines. Reciprocally, level of TNF- $\alpha$  is associated with, and predictive of, SSRI response patients with high level of TNF- $\alpha$  is unlikely to show improvement [21].

Inflammatory modulators also feedback on serotonin levels by affecting the conversion of tryptophan to serotonin. Control over serotonin levels is likely the mechanism behind the association of interferon- $\alpha$ , and major depression. Studies of patients with hepatitis-C, which is treated with interferon- $\alpha$  have found that about half of all patients will develop depression during the course of their treatment. This is one of the few reliable pharmacological means to induce depression in subjects with no history of depression. The main accepted mechanism for immune induced depression is the action of TNF- $\alpha$  on several enzymes that control conversion of tryptophan to serotonin. While this induced depression is responsive to SSRI's, the serotonin-inflammation link is not critically indicated in this form of depression because the somatic complaints of patients remain, even while the "psychological" factors remit. Other depressive mechanisms besides serotonin levels may be recruited by inflammation; IL-6 and TNF- $\alpha$  have been shown to act as breaks on neurogenesis in the hippocampus, probably due to their interaction with STAT and MAPK. The depressive effects of interferon could be triggered by buildup of other metabolites associated with tryptophan conversion that activate NMDA receptor which further casts doubt on a pure serotonin mechanism behind inflammatory depression[22,23].

## 8. Diagnosis

The diagnostic possibility of depressive disorders can be approached based on observational factors, such as deterioration of personal appearance and look, low tone of voice, sad faces, easy or spontaneous weeping, and decreased attention.

### General diagnostic criteria of depressive episode according to ICD-10 guidelines

#### A. General criteria for depressive episode:

- The depressive episode should last for at least two weeks
- The episode is not attributable to psychoactive substance use or to any organic mental Disorder

#### B. Presence of at least two of the following symptoms:

- Depressed mood to a degree that is definitely abnormal for the individual, present for most of the day and almost every day, largely uninfluenced by env

environmental Circumstances and sustained for at least two weeks.

- Marked loss of interest or ability to enjoy activities that were previously pleasurable.
- Decreased energy or increase fatigability

**C. An additional symptom or symptoms from the following list should be present, to give a total of at least four:**

- Loss of confidence and self-esteem and feelings of inferiority
- Unreasonable feelings of self-reproaches or excessive and inappropriate guilt
- Recurrent thoughts of death or suicide or any suicidal behaviour
- Complaints or evidence of diminished ability to concentrate or think, accompanied by indecisiveness or vacillation
- Change in psychomotor activity, with agitation or inhibition
- Sleep disturbance of any type
- Changes in appetite (decrease or increase), with corresponding weight change

**D. There may or may not be the somatic syndrome:**

**Mild depressive episode:**

Two or three of the symptoms of criteria B are present. A person with a mild episode is probably capable of continuing with the majority of their activities.

**Moderate depressive episode:**

At least two of the symptoms of criteria B are present; in addition to symptoms of criteria C until there is a minimum total of 6 symptoms. A person with a moderate episode will probably have difficulties continuing with their ordinary activities.

**Severe depressive episode:**

There must be 3 symptoms of criteria B in addition to symptoms of criteria C until there is a minimum of 8 symptoms. People with this type of depression have symptoms that are marked, distressing, mainly the loss of self esteem and feelings of guilt or worthlessness. Suicidal thoughts and acts are common, and a number of somatic symptoms are present. Psychotic symptoms can appear, such as hallucinations, delusions, psychomotor retardation or severe stupor.

## 9. Treatment

### 9.1. Antidepressants

The drugs which can elevate mood in depressive illness are broadly categorised into selective serotonin reuptake inhibitors (Fluoxetine, Fluvoxamine, Paroxetine), tricyclic antidepressants (Imipramine, Desipramine, Amitriptyline, Nortriptyline), norepinephrine reuptake

inhibitors (Venlafaxine, Duloxetine), monoamine oxidase inhibitors (Phenelzine, Selegiline, Tancycipromine).

### 9.2. Psychological therapy

Although there are some studies comparing psychological therapies for depression, the majority of studies involve comparisons of psychological therapies with prescribed antidepressant medication treatment, waiting list control or care as usual. The evidence base was insufficient to support detailed recommendations on the number of therapy sessions required for efficacy, maintenance of effect or prevention of relapse. Behavioral therapy, counselling, family therapy, exercise some of the psychological therapy's.

### 9.3. Herbal remedies and nutritional supplements

This section considers herbal remedies and nutritional supplements which have been subjected to RCT (Randomized controlled trial) investigation to evaluate their efficacy in the treatment of depression. Folate, Hypericum extract (St John's Wort), Inositol, S-adenosyl-L-methionine is some of the herbal medicines used in depression.

## 10. Choosing of Anti Depressants

Most people benefit from taking antidepressants to some degree, but research suggest antidepressants may not be as effective as previously thought in cases of mild depression. However, they are the most effective treatment in relieving symptoms quickly, particularly in cases of severe depression. There is estimation that 50-65% of people treated with an antidepressant for depression will see an improvement, compared to 25-30% of those taking inactive "dummy" pills (placebo). This means that most people do benefit from antidepressants, even if it's sometimes a result of the placebo effect.

SSRIs (Selective serotonin reuptake inhibitors) are the most widely prescribed type of antidepressants. They are usually preferred over other antidepressants, as they cause fewer side effects when compare to other antidepressants. An overdose is also less likely to be serious. Fluoxetine is probably the best known SSRI sold under the Brand name Prozac.

## 11. Conclusion

Depression is mental disorder which contributes worldwide burden. WHO reported that on an average of one in twenty people are experiencing the depression especially teens. Depressed mood, loss of interest, decreased energy, guiltiness, disturbed sleep; changes in behaviour are determinants of depression. Besides the behavioural changes, neurochemical changes (especially in neuro transmitters) also involved in the pathogenesis of depression. Along with allopathic treatment, following

complementary and alternative medicine as an adjuvant will show better improvement in the treatment of depression.

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