IJPSR (2023), Volume 14, Issue 4 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 13 July 2022; received in revised form, 11 September 2022; accepted, 20 October 2022; published 01 April 2023

DEPRESSION: UNDERSTANDING THE PATHOPHYSIOLOGY AND TREATMENT MODALITIES

Anuradha Pannu and Abhilasha Ahlawat *

Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak - 124001, Haryana, India.

Keywords:

Depression, Monoamine Theory, Nor-Epinephrine, Serotonin, Dopamine

Correspondence to Author:
Abhilasha Ahlawat

Assistant Professor,
Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak - 124001, Haryana, India.

E-mail: abhilasha.rp.pharma@gmail.com

ABSTRACT: Depression is accepted as a condition of misery and is treated as a disorder that includes mental and emotional disorders. Depression is a deadly disease that affects about 5% of the general population. In addition, depression is a heavy burden on patients and families. Furthermore, many epidemiological studies have shown that the occurrence of depressive disorders in the general population is increasing at an alarming rate. Depression is the most common form of emotional disorder, from a very mild condition to severe depression associated with hallucinations and delusions. In addition, altered levels of serotonin and other biogenic amines have also been shown to contribute to neuromodulatory disturbance in the etiology of depression. According to monoamine theory in depressive disorder, patients with major depression have shown biochemical symptoms which may change monoamine neurotransmitters, specifically nor-epinephrine and serotonin. Clinical data suggested that dopamine is also involved in the pathophysiology and treatment of depression.

INTRODUCTION: Depression is commonly considered as mental disarray associated with a miserable attitude. Feelings of guilt or low self-esteem, trouble in sleep or loss of appetite, lack of energy, and difficulty concentrating can also accompany depression. Depression can be defined as mood, a condition without inspiration, a feeling of hopelessness, and an absence of physical energy. Many aspects of our life can trigger an emotional state. Any type of traumatic incident in life is considered the first sign of depression; thus depression is often considered a depressive disorder [1-7].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.14(4).1611-21

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.14(4).1611-21

Approximately 264 million patients worldwide are affected by major depressive disorder (MDD), making it the second leading cause of global morbidity [8]. Around 8 Lac suicides are reported annually by the World Health Organization (WHO) [9], suggesting MDD is a major community health challenge. Depression is not an analogous disorder, but this disorder has different subtypes as well as more than one etiology. Symptoms can differentiate subtypes of depression from mild to severe with or without psychotic features [8].

Therefore, this disorder is commonly considered an infirming disease that disturbs a person's daily routine like sleeping, eating, professional life, and overall health and ability to enjoy life [10]. A growing experimental and clinical research has shown that functions of serotonin and noradrenaline neurotransmitters' neuronal activity in the central nervous system (CNS) are altered in patients with depression [11, 12].

Brain-derived neurotrophic factor (BDNF) may also play an important role in depression [13]. Hyperactivity of Hypothalamic–pituitary–adrenal (HPA) axis is a common finding in psychoneuroendocrinology in diagnosing major depression [14]. In the mechanisms of depression, inflammatory cytokines and endogenous metabolites [15] and the gut microbiome play a critical role in depression by influencing the gut-brain axis [16]. Currently, in depression, monoamine re-uptake inhibitors are the utmost frequently recommended class of antidepressants [17] though there is a big problem with these class of drugs due to a long time between the effect of the first therapeutic effect on monoamine neurotransmitter function and the reduction in the severity of clinical symptoms. Conventionally, only half of the patients experience a significant minimization in symptoms after antidepressant drug therapy. Also, about 33% of patients show resistance to the treatment due to more than one drug therapy proven inefficient [18, 19]. Therefore, selecting and developing new, fast-acting, and more active antidepressant therapeutic agents is necessary. Presently, there are various antidepressants exist, but the side effects of these drugs make them less efficient.

Biomarkers of Depression: Investigators continuously search for biological or diagnostic makers for the evaluation and treatment of depressed patients. Despite all these facts, no biological marker has been discovered yet. In the case of major depression, around 45-60% of patients show the symptoms of hyposecretion of cortisol or hypersecretion of cortisol, or an irregular thyroid-stimulating hormone response is found. Whenever a patient has revealed an indication of depression, it is essential to consider the possibility of medical, psychiatric, and/or drug causes [20]. More than 25% of patients with chronic medical disorders like diabetes mellitus, obesity, cancer, and cardiovascular diseases develop major depression during the medical condition. Moreover, the diagnosis of depression is generally not accurate in the case of aged subjects. All depression patients should be examined for physical and psychological parameters along with complete blood analysis and other biochemical parameters like liver function tests, thyroid function tests, and electrolyte determinations to diagnose any possible medical complications [21].

Suicide and Risk Management: In the United States, suicide is the eighth prime reason for death, and depression was found to be the most significant causative factor at the time of death for most suicidal patients [22]. Generally, people who attempt suicide are crazy, and suicide is the outcome of emotional outbursts. Aspects that raise the risk for suicide include aging due to a life partner's death, living alone, being jobless, a part of a previous psychiatric problem, any drug abuse, depression, a family history of suicide, the existence of a chronic medical problem and absence of a public support system [23].

Although women have 2-3 times more tendency to attempt suicide, the success rate is 2-3 times more in the case of men. Moreover, the rate of suicide is almost double in elderly people as compared to the rate in the general population [24].

Occurrence of Depression Worldwide and in Indian Population: Depression is a worldwide phenomenon and contributes as a significant factor to the universal burden of disease affecting people of all communities and races worldwide. The present estimation shows that 350 million people are affected by depression. A survey conducted by World Mental Health in 17 countries revealed that 1 in 20 people reported having an episode of depression in 2011. Moreover, it is estimated in 2030 unipolar major depression can be the second prime reason for disability [25].

Epidemiological studies also stated that major depression has an annual prevalence of 1- 6% globally, and over time, it is becoming more prevalent in the younger population [26]. In the USA, approximately 6.7% of U.S adults experience a depressive disorder.

In terms of gender, women are more susceptible compared to men to experience depression during their lifetime *i.e.*, 70 % more women are likely to have depression than men. The incidences of depressive disorders are very common during adolescent years accompanied by comorbid substance abuse and suicidal tendencies, resulting in increased chances of death in these adolescent patients. Depressive disorders and suicide tend to have a family lineage, and the chances of depression are 1.5 to 3 times higher in first-degree

relatives of patients with depression as compared to normal controls [27]. In India, the prevalence of serious mental disorders is about 10-20 per 1000 of the population. Depression has always been a center of attention for researchers in India. Many studies have been conducted to discover its prevalence and associated factors of depression, like psychological stress and life events responsible for stress, co-morbidities, psycho-neurobiology, treatment options available for depression, the outcome of treatment, disability, and burden linked with depression. Several studies also included pediatric and geriatric populations [28].

Etiology of Depression: Depression is considered a multifactorial disorder **Fig. 1** in which several factors ranging from mild to severe, combined with vulnerability, leads to a predisposition to depression.

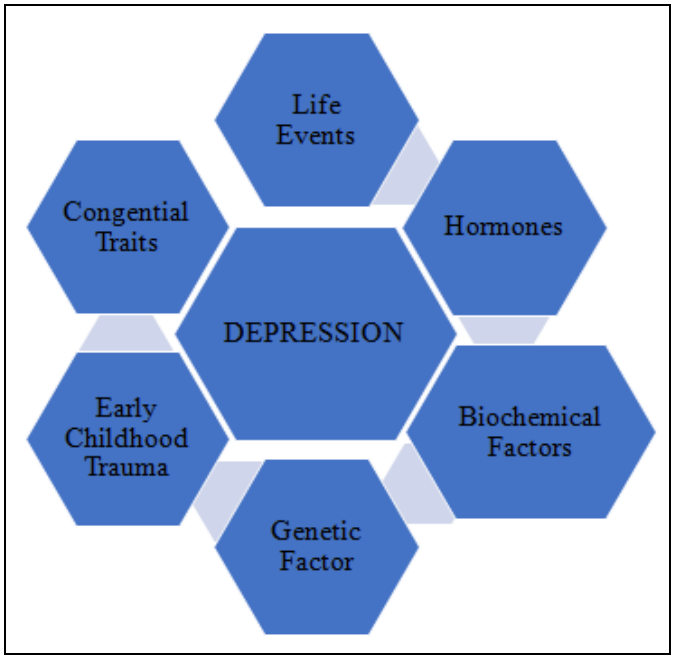

FIG. 1: ETIOLOGY OF DEPRESSION

Genetic Factors: Genetic factors have an important role in the person's predisposition towards developing depression, specifically psychotic depression, and bipolar disorder. Any modification on the serotonin transporter gene (SLC6A4) modulates anxiety-related personality traits [29] whereas it was partially replicated in subsequent studies [11, 23]. Moreover, further research confirmed that s-allele (s = short), which is a carrier of 5-HTTLPR-promotor polymorphism, is responsible for the improved neural activity in the amygdala to encounter negative emotional stimuli as compared to L-allele carriers.[30] Another gene that was found to affect emotion-related activity in the amygdala is monoamine oxidase-A (MAOA) which is responsible for the degradation of 5-HT and nor-epinephrine [31].

Biochemical Factors: Nerve cells communicate with each other *via* specific chemicals known as neurotransmitters responsible for the transfer of signals from one neuron to the next. Neurotransmitters like serotonin, GABA, glutamate, nor-epinephrine, and several others play a significant role in MDD [32]. Amongst all, serotonin is most likely one of the most significant neurotransmitters in the mechanism of depression *i.e.* alteration in the functioning of serotonin (*i.e.* the density of serotonergic receptors, metabolism of serotonin as well as the reactivity of the receptors) is associated in MDD [33]. It has been observed that in depression, the activity of one or more of these neurotransmitters is reduced and affects different areas of the brain responsible for the vital function of the body like sleep, appetite, mood, and sexual activity. Decreased level of these neurotransmitters leads to reduced communication between nerve cells and explain the typical signs of depression [34].

Hormones: Hormone is a significant part of the pathogenesis of depression. Variations in hormones

level may also activate depression. Hormone changes can be caused by thyroid problems, menopause, or many other conditions [35].

Congenital Traits: People whose biological family members also have a history of depression are more likely to develop depression. The research is being carried out to identify the genes involved in the pathogenesis of depression [36].

Life Events: Life events that affect the person's emotional status like sudden death or loss or separation from the loved one, financial issues, and high stress levels are considered some of the major triggering points for precipitation depression in some people [37].

Early Childhood Trauma: Stressful or unbearable events in childhood, for example, abuse or loss of a parent, can have a permanent impact on the brain making them more prone to depression [38].

Pathogenesis of Depression: Neurotransmitters are believed to play an important role in the etiology of depression [39]. The biogenic amine hypothesis or monoamine hypothesis came into focus as a result of numerous interpretations carried out in the early 1950 [40].

Monoaminergic Neurotransmission: Diminished signaling of monoamines has been considered to underlie the mechanism of depressive disorders. For example, in depressive patients, the levels of monoamine metabolite were found to be reduced in the cerebrospinal fluid. Moreover, serotonin, nor-epinephrine (NE), or dopamine depletion were also responsible for pro-depressive effects [41]. Monoamines are mostly presynaptically localized and neurotransmitters are removed from other cells and recycled back into the adjacent terminals. Therefore, these neurotransmitters are considered as recognized aim of several psychostimulants and antidepressant drugs which produce their mechanism via modulation of monoamines levels in the neurons. These findings are consistent with the observation that clinically effective antidepressants increased levels of monoamine concentration as well as monoaminergic signaling. It has been proved that these monoamines, especially serotonin, play an important role in the developmental mechanism and pathogenesis of depression vulnerability [42, 43].

Monoamine Oxidase (MAO): MAO is the class of enzymes responsible for the metabolism of monoamines such as serotonin, nor-epinephrine and dopamine. MAO is found in almost all types of tissues. Based on the molecular coding, MAO is present in two homogenous molecular types:

MAO-A: It has a very pronounced affinity for the 5HT. It is also considered the major target for depression treatment therapy.

MAO-B: Phenylethyl amine is the main preference for MAO-B.

Monoamine oxidase enzymes act on Nor-adrenaline, dopamine, and serotonin [43]. Classical hypotheses for the biological origin of depression have emphasized majorly the role of NE and 5-HT. Whereas, several pieces of evidence associated biogenic amine hypothesis could not provide enough indications between the distinguished role of NE and DA in the pathogenesis of depression [44]. In the brain, DA is a precursor to epinephrine and NE, and primarily a transmitter that controls behavior [45]. Many studies in humans and animals have shown that depression and DA transmission in the central nervous system are closely linked [46, 47]. Moreover, the patients suffering from depression have an increased level of DA transport, making presynaptic neurons more efficient at DA re-uptake [48].

GABA (Gamma Amino Butyric Acid) Neurotransmitter: In the brain, GABA is the most important neurotransmitter for inhibitory activity. Broadly, GABA receptors are classified into two types *i.e.,* $GABA_A$ and $GABA_B$. $GABA_A$ receptor muscimol is an agonist; however, bicuculline, picrotoxin and SR 95531 are antagonists. $GABA_A$ receptors have also been found to play an important role in the treatment of anxiety disorders due to their coupling to Ca^{+2} channels. Whereas in rats, several antidepressants and mood stabilizers were found to produce their action by upregulation of frontal cortical $GABA_B$ receptors not through $GABA_A$ receptors [49, 50]. $GABA_{-B}$ receptors are those for which baclofen is the typical agonist. $GABA_B$ agonists are responsible for enhanced cAMP responses due to the action of noradrenaline and down-regulation of β- adrenergic in response to tricyclic antidepressants indicating the important

role of $GABA_B$ in the management of depression. The level of GABA was also reported to be decreased in CSF of depressed patients [51]. In unipolar depression, GABA levels have also been reported to be decreased in plasma, which may not normalize with treatment [52].

Serotonin Transporter: 5-HT is broadly disbursed all over the nervous systems and its deficiency can precede to depression, phobias, anxiety and other psychological health disorders in humans [53]. Over the last few years, the 5-HT hypothesis has stimulated research into the etiology of depression. It has been reported that depressed patients have low 5-HT levels in the brain and may exhibit altered 5-HT receptors, such as elevated 5-HT2 and reduced 5-HT1A receptors [54]. Three potential mechanisms are responsible for the impairment of 5-HT1A activity in depression: civil solitude decreasing 5-HT1 neurotransmission, 5- HT2 receptors hindering 5-HT1 neurotransmission and hypercortisolaemia hindering 5-HT1 neurotransmission [27]. Neuronal proteins in an adult's brain like BDNF and neurotrophin-3, are correlated with the growth and activity of 5-HT neurons [55].

Hypothalamic Pituitary Adrenocortical (HPA) Axis System: Stress and emotional state are the key factors that stimulate the outbreak of MDD [56]. It has long been recognized that the HPA axis plays an important role in the mammalian stress response. Thus, alteration in the HPA axis in distress may detect the occurrence of depression symptoms. Stress triggers the release of corticotropin-releasing hormone (CRH) from the hypothalamus. It then stimulates the production of adrenocorticotrophic hormone (ACTH) in the pituitary, increasing glucocorticoid release from the adrenal cortex [57]. In several target tissues, glucocorticoids bind to their receptors like the HPA axis and inhibit the release of both productions of ACTH in the pituitary corticotropes and CRH in the hypothalamus. In patients with MDD, the HPA axis are excessively active under stressful situations, resulting in complications such as hypercortisolemia, reduced rhythmicity, and elated cortisol range [58, 59]. The stress associated with depression causes disturbances of the HPA axis and, as a result, there is increased production of cortisol and inadequate blockage of glucocorticoid receptor regulatory response [60, 61]. Also, high cortisol concentrations are associated with depression severity, especially when the condition of melancholic depression [62, 63].

Furthermore, patients with depression could not regularize their HPA axis after the treatment; subsequently, they had a poor clinical outcome [64, 65]. Anyhow, prior studies have exhibited that HPA axis-regulating treatments such as glucocorticoid receptor antagonists fail to relieve the indications of depression [66, 67]. 2 Several factors may be responsible for the induction of stress for example, sudden or drastic changes in body temperature, abrupt decrease or increases in blood pressure, decreased food intake for a long duration, chronic illness or infection, and pain. HPA stress axis is generally considered a slower backup resistance for the stress. Moreover, the HPA stress axis also plays a vital role in the cognitive evaluation of traumatic conditions along with the modulation of behavior and endocrinal status to adapt to the stress. Moreover, the HPA axis of stress also provides the substrates for energy, supporting the sympathetic responses [68].

In the case of experimental animal, various factors like nature of stress, duration, and mode of stress predict the pattern of HPA mal/adaptation. mRNA expression of corticotropic hormone is found to be elevated only in that stress associated with conserved HPA responses [69]. However, in maximum depressive patients shows dysfunction of HPA axis regulation whereas normalization of dysfunctional HPA axis was found to be preceded in successful antidepressant treatment of depression [70, 71, 72].

Hypothalamic Pituitary Thyroid (HPT) Axis System: Numerous studies have indicated the overlapping of symptoms is linked with patients with hypothyroidism and depression. TRH receptors in the pituitary gland are stimulated by Thyrotropin-releasing hormone (TRH) is released by the hypothalamus leading to the flow of stimulating thyroid hormone (TSH) and further TSH stimulates specific receptors triiodothyronine (T3) and thyroxin (T4). These thyroid hormones are responsible for providing feedback to the hypothalamus as well as the pituitary, which further regulate the HPT axis. TRH was found to be

increased in cerebral spinal fluid in depressive patients in two small studies when compared with control patients [73]. Moreover, one study also demonstrated exaggerated TSH responses in high normal thyroid levels in depressed patients [74].

BDNF (Brain-Derived Neurotrophic Factor): In the postmortem samples obtained from patients with a mental disorder, it has been found that the level of brain BDNF was reduced, and during the treatment of depression, BDNF level reached the normal range [75, 76]. BDNF is present in blood, and it gets accumulates in platelets. The BDNF gene has a complicated genetic organization with seven upstream exons and one coding exon that is responsible for the multiple splice variants controlled by different promoters. In the human BDNF gene, various polymorphisms are available *i.e.,* val66met polymorphism in which valine changes to methionine in the BDNF peptide [77]. These studies have concluded that loss of function due to mutations in BDNF may be responsible for depression through dysregulation of an individual's HPA system. Mutations in BDNF are responsible for reduced hippocampal volume, fear of learning, anxiety and a lack of response to chronic depression treatment [78].

Human Growth Hormone: The release and storage of growth hormone (GH) occur in the anterior pituitary gland. Growth hormone release is under the regulation of two hormones Growth hormone releasing factors (GHRF) and somatostatin (growth hormone inhibiting factor) which is secreted by the hypothalamus and these two hormones modulate the release of human growth hormone from the pituitary. The neurotransmitters *i.e.,* noradrenaline, serotonin, and dopamine have a major role in mood regulation and affect GH release. In depression, the level of somatostatin is decreased in CSF [79].

Inflammatory Cytokines: In depressed patients, the level of pro-inflammatory cytokines like chemokines and cellular adhesion molecules was found to be elevated. Moreover, administration of the cytokine, interferon–α resulted in the development of depression in approximately 50% of patients. Moreover, pro-inflammatory cytokines were found to have interaction and positive correlation with several pathophysiological factors which describe depression, like neuroendocrine function, synaptic plasticity, and behavior. Based on the role and involvement of these proinflammatory cytokines and their signaling pathway, a new approach can be designed by targeting these proinflammatory markers in the treatment of depression [80].

Oxidative Stress: Stress and oxidative stress are linked positively. Due to stress, the oxidative damage of cells is increased, leading to the generation of malonialdehyde (MDA). In stressed mice, the level of MDA was found to be in more concentration as compared to normal mice [81].

Treatment for Depression: It has been more than 40 years since tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs) were launched. These drugs have been found to be very harmful in managing depression. The side effects of these drugs lead to the development of selective serotonin re-uptake inhibitors (SSRIs) and selective noradrenaline re-uptake inhibitors (SNRIs). It is reliable in use [82].

Tricyclic Antidepressants: In the late 1950s, for the treatment of depression and associated disorders, imipramine was found to be effective. As a result of this discovery, several chemical analogs of imipramine were synthesized and evaluated for antidepressant activity. Collectively these compounds were called TCAs. However presently for the treatment of depression, TCAs are not considered first-line drugs. These drugs were found to be associated with significant side effects as well as life-threatening adverse effects. Moreover, in the case of TCAs uses in depression, there is a requirement for continuous monitoring of the blood level of the drug to avoid toxicity [83].

TCAs are categorized into different categories like tertiary or secondary amines. Desipramine, nortriptyline, and protriptyline are secondary amines whereas imipramine, amitriptyline, trimipramine, and doxepin are tertiary amines. Clomipramine is also considered a member of this tricyclic family due to its comparable pharmacological action and efficacy in the treatment of depressants. Maprotiline and amoxapine are heterocyclic antidepressant agents, they are not members of this tricyclic family but

because of their similar pharmacological action to the tricyclic amines, these drugs are included along with TCAs class of antidepressant. In the second generation of antidepressants, duloxetine was found to have a significant risk for the development of hepatotoxicity. In the category of TCAs, clomipramine and amitriptyline were also found to have higher incidences of hepatotoxicity than SSRIs. Pharmacovigilance studies conducted in Europe also revealed comparable results indicating the highest risk of hepatotoxicity with agomelatine [84].

Selective Serotonin Reuptake Inhibitors: For the treatment of major depression in 1987, fluoxetine was approved by the FDA. Fluoxetine is a selective serotonin re-uptake inhibitor (SSRIs). The other drugs in this class include citalopram sertraline, fluvoxamine, and paroxetine. SSRIs were found to be safer, and the tolerability of antidepressants increased significantly with the beginning of the SSRIs. These agents were found to be safer and devoid of cardiac side effects.

Moreover, these agents did not have any affinity toward cholinergic, β-adrenergic, or histamine receptors. These agents were found to be safe and tolerable in elderly patients and in cardiac patients [85]. The SSRIs are highly selective for the uptake of serotonin at the nerve terminals of synapse. This activity provides ample support to the hypothesis of the re-uptake of monoamines at the nerve terminals and reveals the mechanism of action of these drugs. These agents produce their therapeutic action by modulating serotonin neurotransmission in the brain [86].

The increased 5- HT levels further activate 5-HT1A autoreceptors and decrease neuronal firing. Whereas, desensitization of 5-HT1A autoreceptors increases serotonin release, terminal 5-HT1B autoreceptors also become desensitized. These receptors are responsible for the inhibition of the release of serotonin. All these events result from inhibiting serotonin re-uptake in the nerve terminal, which ultimately potentiates serotonin neurotransmission at central synaptic sites. The time-lapse in the development of these synaptic events is responsible for the delayed response of therapeutic activity of antidepressant drugs while treating depression [87]. Patients who have adverse reactions to one of the SSRI drugs may be identified, and it will be helpful to replace another drug from that class. SSRIs are more reliable than MAOIs and TCAs, have hardly any side effects, and reduce the affinity for acetylcholine and amine receptors, making overdose deaths less likely [88]. Nevertheless, various side effects, such as nausea, insomnia, and sexual dysfunction, are caused by SSRIs [89].

Monoamine Oxidase Inhibitors: Monoamine oxidase (MAO) is a mitochondrial enzyme and is widely distributed throughout the body but with high concentrations found in gastrointestinal, hepatic, and neuronal tissues. The enzyme plays an important role in the metabolism and oxidative deamination of several endogenous and exogenous monoamines and neurotransmitters. Moreover, monoamine oxidase is also responsible for detoxifying endogenous and exogenous amines. Two molecular forms of monoamine oxidase exist in the human body commonly called type A and type B and the substrates and inhibitors are also selective for this isozyme.

Neurotransmitter amines, like nor-epinephrine and 5HT, are specifically substrate to be metabolized by MAO-A in the brain, whereas dopamine is the preferential substrate to be catabolized by MAO-B. Iproniazid, which has anti-tubercular activity, was also found to exhibit mood-elevating properties in clinical trials in patients of tuberculosis with depression. Due to toxicity associated with monoamine oxidase inhibitors in treating depression, the use of drugs is limited. Hepatotoxicity is found to be associated with the administration of isocarboxazid or phenelzine. These hydrazine compounds have significant potential to damage the hepatic parenchymal cells, especially in patients who are slow acetylators of hydrazine compounds [90]. Today MAOIs are rarely prescribed or are the last antidepressants used because of drug-induced hypertensive crisis and potentially fatal food and drug interactions [88].

Reversible Inhibitors of MAO-A: The selective, reversible inhibitors of MAO-A (RIMAs) were synthesized in the 1980s in worldwide labs (RIMAs) [91]. This theory was tested in numerous clinical trials by using tyramine challenges in patients [92, 93]. Currently, moclobemide is the only

RIMA that is available for clinical use. Another RIMA is methylene blue [94, 95] which has several pharmacological actions like nitric oxidase synthase (NOS) and guanylate cyclase inhibition [96].

5-HT and NE Reuptake Inhibitors: Even though TCAs are very efficient in the treatment of major types of depression, their practice in the management of depression has decreased because of the accessibility of similarly active therapeutic options and greater safety, efficacy and tolerability. TCAs produce their mechanism of action by potentiating the action of nor-epinephrine and serotonin by hindering the re-uptake at the neural site. However, the potency and selectivity of Venlafaxine, a structurally novel antidepressant, is an effective inhibitor of 5-HT and NE re-uptake and a weak inhibitor of dopamine re-uptake. Venlafaxine has almost no affinity for muscarinic, histaminergic and α1-adrenergic receptors [97]. Both maprotiline and amoxapine are inhibitors of NE re-uptake, with fewer effects on 5-HT re-uptake. As compared to imipramine or amitriptyline the risk of seizures is higher in maprotiline [98].

NE and 5-HT Selective Antidepressants: The newly discovered antidepressant agent mirtazapine produces its mechanism by affecting 5HT and NE level CNS. Moreover, it is also devoid of cholinergic and cardiovascular effects. Mirtazapine has an exceptional mechanism of action and enhances noradrenergic and 5-HT_{1A}–mediated serotonergic neurotransmission which is responsible for the antidepressant activity of mirtazapine [83]. Moreover, mirtazapine does not, inhibits NE re-uptake and α_2-heteroreceptors in serotonergic nerve terminals leading to an increase in the concentration of neurotransmitters [99]. The use of mirtazapine for acute and chronic duration leads to weight gain [100]. SARIs have correlative potency and a minimal rate of induced sexual dysfunction correlated to other classes of antidepressants for the management of MD [8].

CONCLUSION: Disorders of the central nervous system are highly prevalent, accounting for approximately 15% of the global burden of diseases. Among these, 8–12% are affected by depression at least once in their life. Moreover, the prevalence distribution is drastically changed if epidemiological factors like age and sex are focussed. While disorders of the central nervous system pose a greater burden on the quality of life than any other single disease, psychotherapy still is not lacking a place in terms of research and funding. Various factors like lack of consensus surrounding classification, diagnosis, and treatment are some of the major factors responsible for the incomplete understanding of the mechanism and course of mental health disorders. Specifically, in mood disorders, the incomplete understanding of the nature and cause of disease makes mood disorders a tough challenge for the pharmacotherapy of mood disorders.

These mood disorders are the category that comprises the single largest burden in mental health. Major depressive disorder (MDD), is the most prevalent mood disorder of complex and heterogeneous illness, where 60% of patients experience resistance to treatment that prolongs and worsens episodes. Major depression is an ordinary which sometimes can be fatal also, 25% of psychiatric disorders in the general population worldwide are responsible for disability worldwide.

It is a highly prevalent and disabling condition associated with significant morbidity and mortality. A lot of evidence suggests a positive correlation between chronic stress and the development of depression. Despite advancements in Pharmacotherapy, psychiatry still depends majorly on 19th-Century diagnostic categories, and this criterion is based on the assemblage of symptoms rather than biological markers. Moreover, the treatment of these disorders was carried out with drugs discovered serendipitously several decades ago. Although depression has generally been explained with monoamine theory, it is far more multifactorial, and therapies that address the disease's pathway have not been developed.

Several studies have shown that oxidative stress may play an essential role in the pathophysiology of neuropsychiatric disorders. The mechanism of the development of depression and the involvement of stress has been widely investigated in animals for decades. For example, animal models established with maternal deprivation and chronic unpredictable stress exposure are commonly used models which depict the early life stress experience and adulthood of humans, respectively.

ACKNOWLEDGEMENTS: Nil

Funding: No funding has been received from any funding agency.

CONFLICTS OF INTEREST: There is no conflict of interest.

REFERENCES:

1. Abe-Higuchi N, Uchida S and Yamagata H: "Hippocampal sirtuin 1 signaling mediates depression-like behavior. Biological Psychiatry 2016; 80(11): 815–826.
2. Moloney P: The Therapy Industry: The Irresistible Rise of the Talking Cure, and Why It Doesn't Work. London: Pluto Press 2013.
3. Sophie M: Depression 101: Getting to the bottom of it. My depression ebook.com. 2008 1-6.
4. Krishnan V and Nestler EJ: The molecular neurobiology of depression. Nature 2008; 455: 894–902.
5. Hindmarch. Beyond the monoamine hypothesis: mechanisms, molecules and methods. Eur Psychiatr 2008; 17(3): 294–299.
6. Kulkarni SK, Bhutani MK and Bishnoi M: Antidepressant activity of curcumin: involvement of serotonin and dopamine system. Psychopharmaco 2008; 1(3): 435–442.
7. Nielsen DM, Carey GH and Gold LH: Antidepressant like activity of corticotropin releasing factor type -1 receptor antagonist in mice. Eur J Pharmacol 2004; 499: 135-146.
8. Tian H, Hu Z, Xu J and Wang C: The molecular pathophysiology of depression and the new therapeutics. MedComm 2022; 3: 156. https://doi.org/10.1002/mco2.15
9. Ruderfer DM, Walsh CG and Aguirre MW: Significant shared heritability underlies suicide attempt and clinically predicted probability of attempting suicide. Mol Psychiatry 2020; 25(10): 2422-2430.
10. Bondy B: Pathophysiology of depression and mechanisms of treatment. Dialogues in Clin Neurosc 2002; 4(1): 7-20.
11. Nemeroff CB: Recent advances in the neurobiology of depression. Psychopharmacol Bull 2002; 36(2): 6-23.
12. Wang J, Hodes GE and Zhang H: Epigenetic modulation of inflammation and synaptic plasticity promotes resilience against stress in mice. Nat Commun 2018; 9(1): 477.
13. Gonul AS, Akdeniz F, Taneli F, Donat O, Eker C and Vahip S: Effect of treatment on serum brain-derived neurotrophic factor levels in depressed patients. Eur Arch Psychiatry Clin Neurosci 2005; 255(6): 381-386.
14. Heim C, Newport DJ, Mletzko T, Miller AH and Nemeroff CB: The link between childhood trauma and depression: insights from HPA axis studies in humans. Psychoneuroendocrinology 2008; 33(6): 693-710.
15. Felger JC and Lotrich FE: Inflammatory cytokines in depression: neurobiological mechanisms and therapeutic implications. Neuroscience 2013; 246: 199-229.
16. Li Y, Hao Y, Fan F and Zhang B: The role of microbiome in insomnia, circadian disturbance and depression. Front Psychiatry 2018; 9: 669.
17. Miyazaki K, Miyazaki KW, Yamanaka A, Tokuda T, Tanaka KF and Doya K: Reward probability and timing uncertainty alter the effect of dorsal raphe serotonin neurons on patience. Nat Commun 2018; 9(1): 2048.
18. Liu B, Liu J, Wang M, Zhang Y and Li L: From serotonin to neuroplasticity: evolvement of theories for major depressive disorder. Front Cell Neurosci 2017; 11: 305.
19. Aleksandrova LR, Phillips AG and Wang YT: Antidepressant effects of ketamine and the roles of AMPA glutamate receptors and other mechanisms beyond NMDA receptor antagonism. J Psychiatry Neurosci 2017; 42(4): 222-229.
20. Katon W and Sullivan MD: Depression and chronic medical illness. Journal of Clinical Psychiatry 1990; 51(l): 3-11.
21. Hirschfeld RM: History and evolution of the monoamine hypothesis of depression. Journal of Clinical Psychiatry 2000; 6: 4-6.
22. Oquendo MA, Ellis SP and Greenwald S: Ethnic and sex differences in suicide rates relative to major depression in the United States. American Journal of Psychiatry 2001; 158: 1652–1658.
23. Malone KM, Oquendo MA and Haas GL: Protective factors against suicidal acts in major depression; Reasons for living. American Journal of Psychiatry 2000; 157: 1084–1088.
24. Alexopoulois GS, Bruce HL and Hull J: Clinical determinant of suicidal ideation and behavior in geriatric depression. Archives of General Psychiatry 1999; 56: 1048–1053.
25. Marina MM, Taghi Y and Mark VO: Depression: A Global Public Health Concern WHO 2012; 6-8.
26. Weissman MM, Bland RC and Canino GJ: Cross-national epidemiology of major depression and bipolar disorder. JAMA 1996; 276(4): 293–299.
27. Burcusa SL and Iacono WG: Risk of reoccurrence of depression. Clinical Psychology Reviews 2007; (8): 959-985.
28. Grover S, Dutt A and Avasthi A: An overview of Indian research in depression. Indian Journal of Psychiatry 2010; 52(1): 178–188.
29. Canli T and Lesch KP: Long story short: the serotonin transporter in emotion regulation and social cognition. Nature Neuroscience 2007; 10: 1103-1109.
30. Hariri AR, Mattay VS and Tessitore A: Serotonin transporter genetic variation and the response of the human amygdala. Science 2002; 297: 400-403.
31. Domschke K and Dannlowski U: Imaging genetics of anxiety disorders. Neuroimage 2010; 53: 822-831.
32. Wang J, Hodes GE, Zhang H: Epigenetic modulation of inflammation and synaptic plasticity promotes resilience against stress in mice. Nat Commun 2018; 9(1): 477.
33. Alcaro A, Panksepp J and Witczak J: Is subcortical-cortical midline activity in depression mediated by glutamate and GABA? A cross-species translational approach. Neuroscience and Biobehavioral Reviews 2011; 34: 592-605.
34. Savitz J, Lucki I and Drevets WC: 5-HT (1A) receptor function in major depressive disorder. Progress in Neurobiology 2009; 88: 17-31.
35. Berry J: What are neurotransmitters? https://www.medicalnewstoday.com. 2022.
36. Hage MP and Azar ST: The link between thyroid function and depression. J of Thyroid Research 2012; 590648: 1-8.
37. Shadrina M, Bondarenko EA and Slominsky PA: Genetic factor in major depression disease. Ncbi.com 2020.
38. Keyes MK, Pratt C and Galea S: The Burden of Loss: Unexpected death of a loved one and psychiatric disorders across the life course in a national study. American Journal of Psychiatry 2014; 171(8): 864–871.
39. Eisendrath SJ: Psychiatric disorders McPhee S.J. Current Medical Diagnosis & Treatment. New York, TheMcGraw-Hill Companies. Ed 1st 2011; 5.
40. Li Z, Ruan M, Chen J and Fang Y: Major depressive disorder: advances in neuroscience research and

translational applications. Neurosc Bull 2021; 37(6): 863-880.
41. Brown RE, Basheer R and Mckenna JT: Control of sleep and wakefulness. Physiolo Reviews 2012; 92(3): 1087-87.
42. Gennaro L, Leonardi N and Esposito C: Flavonoid and carbohydrate contents in Tropea red onions: Effects of homelike peeling and storage. Journal of Agricultural and Food Chemistry 2002; 50: 1904–1910.
43. Blakely RD, De Felice LJ and Hartzell HC: Molecular physiology of nor epinephrine and serotonin transporter. Journal of Experimental Biology 1994; 196: 263-281.
44. Reith MEA, Xu C and Chen NH: Pharmacology and regulation of the neuronal dopamine transporter. European Journal of Pharmacology 1997; 324: 1-10.
45. Willner P: Dopaminergic mechanisms in depression and mania. In: Bloom FE, Kupfer DJ, eds. Psychopharmacology: The Fourth Generation of Progress. New York, Raven 1995; 921-931.
46. Babaev O, Cruces Solis H and Arban R: Dopamine modulating agents alter individual subdomains of motivation-related behavior assessed by touchscreen procedures. Neuropharmacology 2022; 109056.
47. Salamone JD, Ecevitoglu A and Carratala-Ros C: Complexities and paradoxes in understanding the role of dopamine in incentive motivation and instrumental action: Exertion of effort *vs.* anhedonia. Brain Res Bull 2022; 182: 57-66. 31.
48. Mercuri NB, Federici M and Rizzo FR: Long-term depression of striatal DA release induced by mGluRs via sustained hyperactivity of local cholinergic interneurons. Front Cell Neurosci 2021; 15: 798464.
49. Duval F, Mokrani MC, Erb A, Gonzalez Lopera F, Danila V and Tomsa M: Neuroendocrine assessment of dopaminergicc function during antidepressant treatment in major depressed patients. Brain Sci 2021;11(4):425
50. Kimber JR, Cross JA and Horton RW: Benzodiazepines and GABAb receptors in rat brain followingchronic antidepressant drug administration. Biochemical Pharmacology 1987; 36(23): 4173 -4175.
51. Lioyd KG, Thuret F and Pile A: Upregulation of gammaaminobutyricacld (GABA) B binding sites in ratfrontal cortex. Journal of Pharmacology and Experimental Therapeutics 1985; 235(1): 191-199.
52. Roy A, Dejong J and Ferraro T: CSF GABA in depressed patients and normal controls. Psychological Medicine 1991; 21(3): 613-618.
53. Pelty F, Kramer GL and Gullion CM: Low plasma GABA levels in male patients with depression. Biological Psychiatry 1992; 32: 354 -363.
54. De-Miguel FF and Trueta C: Synaptic and extrasynaptic secretion of serotonin. Cell Mol Neurobiol 2005; 25(2): 297-312.
55. Maes M, Yirmyia R and Noraberg J: The inflammatory & neurodegenerative (I&ND) hypothesis of depression: leads for future research and new drug developments in depression. Metab Brain Dis 2009; 24(1): 27-53.
56. Xue Y, Liang H, Yang R, Deng K, Tang M and Zhang M: The role of pro- and mature neurotrophins in the depression. Behav Brain Res 2021; 404: 113162.
57. Tan X, Zhang L and Wang D: Influence of early life stress on depression: from the perspective of neuroendocrine to the participation of gut microbiota. Aging (Albany NY) 2021; 13(23): 25588-25601.
58. Sukhareva EV: The role of the corticotropin-releasing hormone and its receptors in the regulation of stress response. Vavilovskii Zhurnal Genet Selektsii 2021; 25(2): 216-223.
59. Murphy BE: Steroids and depression. J Steroid Biochem Mol Biol 1991; 38(5): 537-359.
60. Pariante CM and Lightman SL: The HPA axis in major depression: classical theories and new developments. Trends Neurosci 2008; 31(9): 464-468.
61. Keller J, Gomez R and Williams G: HPA axis in major depression: cortisol, clinical symptomatology and genetic variation predict cognition. Mol Psychiatry 2017; 22(4): 527-536.
62. Gomez RG, Fleming SH and Keller J: The neuropsychological profile of psychotic major depression and its relation to cortisol. Biol Psychiatry 2006; 60(5): 472-478.
63. Owashi T, Otsubo T, Oshima A, Nakagome K, Higuchi T and Kamijima K: Longitudinal neuroendocrine changes assessed by dexamethasone/CRH and growth hormone releasing hormone tests in psychotic depression. Psychoneuroendocrinology 2008; 33(2): 152-161.
64. Mickey BJ, Ginsburg Y and Sitzmann AF: Cortisol trajectory, melancholia, and response to electroconvulsive therapy. J Psychiatr Res 2018; 103: 46-53.
65. Lamers F, Vogelzangs N, Merikangas KR, de Jonge P, Beekman AT and Penninx BW: Evidence for a differential role of HPA-axis function, inflammation and metabolic syndrome in melancholic versus atypical depression. Mol Psychiatry 2013; 18(6): 692-699.
66. Nandam LS, Brazel M, Zhou M and Jhaveri DJ: Cortisol and Major depressive disorder-translating findings from humans to animal models and back. Front Psychiatry 2019; 10: 974.
67. Stetler C and Miller GE: Depression and hypothalamic-pituitaryadrenal activation: a quantitative summary of four decades of research. Psychosom Med 2011; 73(2): 114-26.
68. Aubry JM: CRF system and mood disorders. J Chem Neuroanat 2013; 54: 20-24.
69. Sapolsky RM: Glucorticoids a Berretinind hippocampal atropy in neuropsychiatric disorders. Archives of General Psychiatry 2000; 57: 925-935.
70. Brown RE, Basheer R and Mckenna JT: Control of sleep and wakefulness. Physio Rev 2012; 92(3): 1087-1187.
71. Aguilera G: Regulation of pituitary ACTH secretion during chronic stress. Frontiers in Neuroendocrinology 1994; 15: 321-50.
72. Pepin MC, Beaulieu S and Barden N: Antidepressants regulate glucocorticoid receptor messenger RNA concentrations in primary neuronal cultures. Molecular Brain Research 1989; 6: 77-83.
73. Reul JMHM, Stec I and Soder M: Chronic treatment of rats with the antidepressant amitriptyline attenuates the activity of the hypothalamic-pituitary-adrenocortical system. Endocrinology 1993; 133: 312-20.
74. Barden N, Reul JMHM and Holsboer F: Do antidepressants stabilize mood through actions on the hypothalamic-pituitary-adrenocortical system. Trends in Neurosciences 1995; 18: 6-11.
75. Banki CM, Bicsette G and Arato M: Elevation of immunoreactive CSF and TRH in depressed patients. Americal Journal of Psychiatry 1998; 145: 1526-1531.
76. Kraus RP, Phoenix E and Edmonds MW: Exaggerated TSH responses TRH in depressed patients with normal baseline. J of Clinical Psychiatry 1997; 58(6): 266-70.
77. Castren E: Neurotrophic effect of antidepressant drugs. Current Opinion in Pharmacology 2004; 4: 58-64.
78. Chen B, Dowlatshahi D and Macqueen GM: Increased hippocampal BDNF immune reactivity in subjects treated with antidepressant medication. Biological Psychiatry 2001; 50: 260-265.

79. Karege F, Bondolfi G and Gervasoni N: Low BDNF levels in serum of depressed patients probably results from lowered platelet BDNF release unrelated to platelet reactivity. Biological Psychiatry 2005; 57: 1068-1072.
80. Egan MF, Kojima M and Callicott JH: The BDNF val 66met polymorphism affects activity dependent secretion of BDNF and human memory and hippocampal function. Cell 2003; 112: 257-269.
81. Chen ZY, Jing D and Bath KG: Genetic variant BDNF (val 66met) polymorphism alters anxiety related behaviour. Science 2006; 314: 140-143.
82. Agren H and Lundquist G: Low levels of somatostatin in human CSF mark depressive episodes. Psychoendcrinology 1984; 9: 233-248.
83. Raison C, Capuron L and Miller AH: Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends in Immunology 2006; 27(1): 24-31.
84. Pal R, Gulati K and Chakraborti A: Role of free radicals in stress induced neurobehavioural changes in rats. Indian Journal of Experimental Biology 2006; 44: 816-820.
85. Kasper S, Praschak-Riedel N and Tauscher J: A risk-benefit assessment of mirtazapine in the treatment of depression. Drug Safety 1997; 17: 251–264.
86. Montastruc F, Scotto S and Vaz IR: Hepatotoxicity related to agomelatine and other new antidepressants: a case/noncase approach with information from the Portuguese, French, Spanish and Italian Pharma-covigilance systems. J of Clin Psychopharma 2014; 34: 327-30.
87. Nezafati P, Shomali A and Nezafati MH: A simple modified Bentall technique for surgical reconstruction of the aortic root – Short and long term outcomes. Journal of Cardiothoracic Surgery 2015; 10: 132.
88. Soomro GM: Selective serotonin re-uptake inhibitors (SSRIs) versus placebo for obsessive compulsive disorder (OCD). Cochrane Database Systemic Reviews 2008; (1): CD001765.
89. De Montigny C and Aghajanian GK: Tricyclic antidepressants: long term treatment increases responsivity of rat forebrain neurons to serotonin. Science 1998; 202: 1301-1306.
90. Sabella D: Antidepressant Medications. Am J Nurs 2018; 118(9): 52-59.
91. Kern DM, Cepeda MS, Castilla-Puentes RC, Savitz A and Etropolski M: Characteristics of patients with major depressive disorder switching SSRI/SNRI therapy compared with those augmenting with an atypical antipsychotic in a real-world setting. Curr Med Res Opin 2021; 37(8): 1377-1384.
92. De Colibus, L, Li M and Binda C: Three-dimensional structure of human monoamine oxidase A (MAO A): relation to the structures of rat MAO A and human MAO B. Proceedings of the National Academy of Sciences 2005; 102: 12684-12689.
93. Tipton KF, Dostert P and Strolin BM: Monoamine Oxidase and Disease. London: Academic Press 1984.
94. Finberg JP and Gillman PK: Selective inhibitors of monoamine oxidase type b and the cheese effect. In International Review of Neurobiology, eds M. B. Youdim and P. Riederer, (Burlington, VT: Academic Press) 2011; 169-190.
95. Finberg, JP: Update on the pharmacology of selective inhibitors of MAOA and MAO-B: focus on modulation of CNS monoamine neurotransmitter release. Pharmacology & amp; Therapeutics 2014; 143: 133–152.
96. Ramsay RR, Dunford C and Gillman PK: Methylene blue and serotonin toxicity: inhibition of monoamine oxidase A (MAO A) confirms a theoretical prediction. British Journal of Pharmacology 2007; 152: 946-951.
97. Naylor GJ, Smith AH and Connelly P: A controlled trial of methylene blue in severe depressive illness. Biological Psychiatry 1987; 22: 657-659.
98. Harvey BH, Duvenhage I and Viljoen F: Role of monoamine oxidase, nitric oxide synthase and regional brain monoamines in the antidepressant-like effects of methylene blue and selected structural analogues. Biochemical Pharmacology 2010; 80: 1580–1591.
99. Ballenger JC: Clinical evaluation of venlafaxine. Journal of Clinical Psychopharmacology 1996; 16(2): 29-35.
100. Bryant SG and Brown CS: Current concepts in clinical therapeutics: Major Affective Sisorders Part 1 Clinical Pharmacy 1986; 5: 304–318.
101. De Boer T: The pharmacological profile of mirtazapine. Journal of Clinical Psychiatry 1996; 57(4): 19–25.
102. Fava M: Diagnosis and definition of treatment-resistant depression. Biological Psychiatry 2003; 53(8): 649–659.

How to cite this article:
Pannu A and Ahlawat A: Depression: understanding the pathophysiology and treatment modalities. Int J Pharm Sci & Res 2023; 14(4): 1611-21. doi: 10.13040/IJPSR.0975-8232.14(4).1611-21.