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A Comprehensive Review of the Pathophysiology of Depression

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ABSTRACT

Depression is a common serious mood disorder, which spreads all over the world and is the leading cause of disability. It is mainly characterized by a loss of interest and hope in life. Despite decades of research, the pathophysiology of depression remains incompletely understood. So understanding the pathophysiology of depression is crucial to developing effective treatment strategies, which helps in the improvement of the patient's quality of life and prevents the recurrence. In this review, different mechanisms contributing to the onset, progression, and persistence of depressive symptoms are explained; such as neurotransmitter imbalances, particularly serotonin, norepinephrine, and dopamine as well as neuroinflammation, endocrine disturbances, genetic predisposition, neurostructural changes, Glutamatergic and GABAergic alterations, and finally circadian rhythm disturbances. All these mechanisms were found to be involved in the pathophysiology of depression but unfortunately, it varies between patients, so further studies are required to know much more about the intricate mechanisms and thus develop novel treatments that can make a breakthrough in the treatment and prevention of depression.

Keywords: *Monoamines; Inflammatory Cytokines; HPA Axis; BDNF; Circadian rhythm.*

1. Introduction

Depression is a mental illness that significantly impacts an individual's quality of life and is characterized by persistent feelings of sadness, fatigue, and disinterest in everyday tasks [1]. It is considered a common but serious health condition, affecting millions of individuals all over the world. According to the World Health Organization (WHO), nearly 300 million people worldwide have depression [2]. The onset of depression commonly occurs in the mid-20s, and women have nearly twice the chance of experiencing depression compared to men [3].

Depression stands as the primary contributor to suicide, a prominent global cause of mortality, particularly among teenagers, young adults, and older people [2]. Moreover, depression is the leading cause of disability worldwide [1]. Depression can manifest in various forms, each with its unique clinical features and underlying pathogenic mechanisms. Understanding these differences is essential for tailoring treatment approaches to individual patients [1]. This article aims to review the current understanding of the pathophysiology of depression, explore the underlying mechanisms associated with different types of depression, and outline conventional

therapies and new treatments for depression.

2. Types of Depression

According to the American Psychiatric Association's Diagnostic Statistical Manual of Mental Disorders, fifth edition (DSM-5), depression can be classified into various types, including major depressive disorder, persistent depressive disorder, disruptive mood dysregulation disorder, premenstrual dysphoric disorder, and depressive disorder due to another medical condition [3].

2.1. Major Depressive Disorder (MDD)

MDD is the most common type of depression and is characterized by persistent feelings of sadness, hopelessness, and loss of interest or pleasure [1]. The pathogenesis of MDD involves a complex interplay of genetic vulnerability, environmental stressors, and neurobiological abnormalities, including alterations in neurotransmitter function, neuroplasticity, and stress response systems [4, 5].

2.2. Persistent Depressive Disorder (PDD)

PDD, formerly known as dysthymia, is characterized by chronic, low-grade depressive symptoms lasting for at least two years [3]. The pathophysiology of PDD shares similarities with MDD but may involve more stable neurobiological abnormalities and a greater emphasis on early-life stressors and developmental factors [1].

2.3. Disruptive Mood Dysregulation Disorder (DMDD)

Primarily diagnosed in children and adolescents, DMDD is characterized by severe temper outbursts that are grossly out of proportion in intensity or duration to the situation, occurring frequently, and inconsistent with the developmental level of the individual [3]. The mood between temper outbursts is persistently irritable or angry most of the day, nearly every day. The pathogenesis may involve abnormalities in emotional regulation circuits in the brain and disruptions in neurotransmitter systems [6].

2.4. Premenstrual Dysphoric Disorder (PMDD)

PMDD involves the presence of significant mood symptoms such as sadness, irritability, and anxiety along with premenstrual syndrome symptoms like bloating and breast tenderness that occur in the week before menstruation and improve within a few days after the onset of menstruation [3]. PMDD is influenced by hormonal changes, particularly fluctuations in estrogen and progesterone, as well as psychosocial factors and genetic vulnerability [7].

2.5. Depressive Disorder due to another medical condition

Several medical conditions such as hypothyroidism, cancer, and heart disease can be associated with depression [3]. These conditions produce biological changes in patients leading to depression. The developed depression usually improves by treating the underlying medical condition [3].

These classifications provide a framework for diagnosing and understanding different presentations of depressive disorders based on specific symptom criteria outlined in the DSM-5. Understanding the underlying pathogenesis of each type of depression helps in diagnosing and treating patients effectively, often through a combination of pharmacological, psychotherapeutic, and psychosocial interventions tailored to the specific needs of the individual.

3. Pathophysiology of Depression

Depression involves dysregulation in various biological, psychological, and environmental

factors **[5]**. Neurotransmitter imbalances, alterations in neuroplasticity, inflammation, genetic predisposition, and stress-related changes in the hypothalamic-pituitary-adrenal (HPA) axis are among the key contributors to the pathophysiology of depression **[1, 5]**. The following is a detailed explanation of these contributors.

3.1. Genetic Influences

Genetic factors have a great impact on depression. According to family, twin, and adoption studies, around 30-40% of the risk for developing depression is attributed to genetic factors **[4]**. Moreover, these studies have shown a higher risk of depression among family members who are first-degree relatives of depressed patients compared to the general population **[3]**, indicating that depression is a familial disorder primarily influenced by genetic factors. However, the remaining 60-70% of the risk is explained by individual-specific environmental effects, such as stress, trauma, and adverse life events **[5]**. Gene-environment interactions play a crucial role in shaping individual vulnerability to depression, although identifying these specific interactions has proven challenging due to methodological limitations and the complexity of gene-environment interplay **[5]**.

It's important to note that while genetic and psychosocial risk factors play a significant role in the development of depression, other factors beyond these influences can also contribute to its onset and progression **[5]**.

3.2. Monoamine Hypothesis

One of the cornerstones of depression pathophysiology is the monoamine hypothesis, which suggests that levels of the brain's serotonin (5-HT), norepinephrine (NE), and/or dopamine (DA) are deficient **[5]**. Researchers reached this hypothesis through observation of three key events. Firstly, during the treatment of tuberculosis with iproniazide, an improvement in the mood of depressed tuberculosis patients was noted **[1, 8]**. Secondly, during the development of imipramine as an antipsychotic drug, which was structurally related to chlorpromazine, an antidepressant effect was observed **[1, 8]**. Lastly, during the development of antihypertensive drug reserpine, it was noticed that depressive symptoms among patients appeared more clearly and were antagonized by imipramine **[8]**. Initially, it was proposed that certain types of depression were linked to decreased levels of noradrenaline and dopamine in the synaptic cleft, known as the catecholaminergic hypothesis of depression, as these drugs elevate catecholamine levels **[9]**. However, the role of serotonin in depression and its antidepressant effects gained prominence shortly afterward, leading to the widely accepted monoaminergic theory of depression. This theory spurred the development of new antidepressant drugs aimed at enhancing the bioavailability of these monoamines **[1]**.

Several mechanisms have been proposed to cause this central deficiency of monoamines. One mechanism may involve disturbances in the synthesis of these neurotransmitters **[5]**. This could occur due to nutritional deficiencies (e.g. inadequate intake of precursor molecules required for neurotransmitter synthesis) or genetic factors affecting enzyme activity responsible for neurotransmitter synthesis or dysfunction in the synthesis process **[8]**. Another assumed mechanism involves the increased degradation of these monoamines, where the enzyme monoamine oxidase (MAO) is responsible for breaking down these neurotransmitters. An increase in the activity of this enzyme leads to deficiency of central monoamines by increasing their degradation **[8]**. Furthermore, monoamine deficiency may occur through disturbances in the brain's transporters responsible for neurotransmitter reuptake leading to the rapid removal of neurotransmitters from

synaptic cleft and decreasing their availability for signaling between neurons [8]. Additionally, changes in receptor function, either through changes in coupling between transmitters and receptors or changes in the downstream signal transduction cascade, can lead to disturbances in the neurotransmitter system and a subsequent decrease in monoamine levels in the brain [8].

These suggested mechanisms led to the development of the first generation of antidepressant drugs, which are monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants [10]. These drugs work by increasing monoamine levels in the synaptic cleft through either inhibiting monoamine oxidase activity by MAOIs or inhibiting neurotransmitter reuptake transporters by tricyclic antidepressants [10]. However, their severe side effects resulting from the blockage of certain postsynaptic receptors led to the development of more specific and safer antidepressant drugs. Thus, the second generation of antidepressants emerged, which includes selective serotonin reuptake inhibitors (SSRIs), selective noradrenaline reuptake inhibitors (SNRIs), and dual serotonin and noradrenaline reuptake inhibitors [10]. However, SSRIs have become the first line of treatment for depression. Fortunately, these drugs have a good safety profile and are relatively well tolerated, but they may be associated with some drug-related side effects like nausea, insomnia, or sexual dysfunction [10].

However, not all depressed patients respond to drugs targeting monoamines, suggesting that other factors may contribute to the pathophysiology of depression.

3.3. Inflammation Hypothesis

Even with the progress in treating severe depression, approximately one-third of individuals suffering from depression do not experience positive outcomes from treatment with traditional antidepressant drugs [11]. An assumed hypothesis explaining this treatment resistance for depression was that of inflammation. Recent studies show a strong correlation between inflammation and depression, where inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) are elevated in depression [1]. Additionally, the majority of autoimmune diseases are associated with depression, suggesting a relationship between inflammatory cytokines and the pathogenesis of depression [12].

One suggested mechanism is that inflammatory cytokines like TNF-α could potentially elevate the expression and activity of serotonin, norepinephrine, and dopamine reuptake transporters. This effect might occur through the activation of signaling pathways such as the p38 mitogen-activated protein kinase (p38 MAPK) pathway [13]. Also, through the STAT-3 signaling pathway, inflammatory cytokines such as Interleukin-6 can activate the expression and activity of serotonin transporter, depleting serotonin from the synaptic cleft and terminating its effect [14]. In addition, inflammatory cytokines can activate the indoleamine 2,3-dioxygenase enzyme, which breaks down tryptophan, the main amino acid precursor for serotonin, into kynurenine, thereby decreasing the concentration of serotonin in the brain [15]. Moreover, inflammation can decrease the concentration of tetrahydrobiopterin cofactor, essential for the activities of tryptophan and tyrosine hydroxylase enzymes responsible for the synthesis of serotonin, norepinephrine, and dopamine [11]. Furthermore, inflammatory cytokines activate nuclear factor κB, inhibiting neurogenesis, a crucial process in the creation of new neurons, thus counteracting the beneficial effects of traditional antidepressants [11].

Another assumption for the relation between

inflammation and depression is that an increase in pro-inflammatory cytokines can lead to oxidative stress. This means an increase in free radical formation owing to the activation of phagocytic cells and an increase in the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) [16]. This oxidative stress results in disturbances in the neurotransmitter system, where ROS decreases the synthesis and availability of neurotransmitters such as serotonin [16].

Moreover, it is worth mentioning that inflammation and oxidative stress mechanisms serve as common biological pathways for depression and neurodegenerative processes [1]. The relationship between depression and neurodegeneration is complex and bidirectional. While depression can be a symptom of certain neurodegenerative disorders, such as Alzheimer's disease and Parkinson's disease, it can also contribute to or exacerbate neurodegenerative processes [17]. Neurodegeneration affects brain regions involved in mood regulation, leading to depressive symptoms. For example, in Alzheimer's disease, there is degeneration in areas such as the hippocampus and frontal cortex, which are implicated in mood regulation [17]. On the other hand, chronic or severe depression may contribute to neurodegenerative processes through inflammation and oxidative stress, which are processes implicated in neurodegenerative diseases [1]. Chronic inflammation, for example, has been linked to the pathogenesis of Alzheimer's disease and other neurodegenerative disorders [17].

3.4. Endocrine Hypothesis

The endocrine system plays a crucial role in depression, where it has been found that cortisol levels are highly elevated [1, 5]. High levels of cortisol (stress hormone) can lead to serotonin deficiency by decreasing the availability of tryptophan, the substrate for 5-HT production [5].

The elevation of cortisol can be explained by dysregulation in the hypothalamic-pituitary-adrenal (HPA) axis [1, 5]. The HPA axis is mainly involved in stress response; upon stimulus, the hypothalamus releases corticotropin-releasing hormone (CRH), which stimulates the anterior pituitary gland to release adrenocorticotropic hormone (ACTH), which in turn activates the adrenal cortex to produce glucocorticoids, primarily cortisol. Then, cortisol exerts negative feedback on the hypothalamus and pituitary gland, inhibiting further release of CRH and ACTH, thus regulating the stress response and maintaining homeostasis, as shown in **Fig. 1. [5]**.
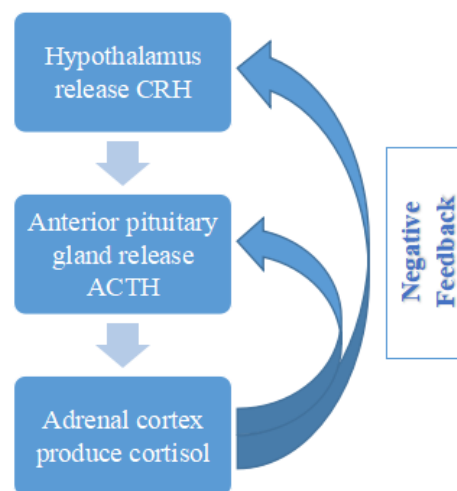

Fig.1. Schematic of the HPA axis [CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone].

Several mechanisms contribute to this dysregulation, either through hyperactivity of the HPA axis or through impairment in the negative feedback. Individuals with depression often exhibit hyperactivity of the HPA axis and subsequent elevation of CRH, ACTH, and cortisol levels, even in the absence of acute stressors [18]. This leads to prolonged exposure to high levels of cortisol. Also, dysfunction in the negative feedback of the HPA axis is commonly observed in depression, which may be due to reduced sensitivity of glucocorticoid receptors or

alterations in the regulation of CRH and ACTH release, resulting in prolonged secretion of cortisol [18].

Another finding was that when the HPA axis is dysregulated, it can suppress the transcription of the brain-derived neurotrophic factor (BDNF) gene [18]. BDNF is a protein belonging to the nerve growth factor family. Prolonged exposure to cortisol results in decreased synthesis and secretion of BDNF, leading to neurodegenerative changes primarily observed in brain structures like the hippocampus [18].

Another influence of hormones on depression was shown through thyroid-stimulating hormone (TSH) disturbances; either hypo or hyperthyroidism can contribute to mood disturbances and depression [19]. Thyroid hormones play a crucial role in regulating metabolism and brain function, so imbalanced levels affect neurotransmitter activity and mood regulation. Additionally, symptoms of thyroid disorders, such as fatigue, weight changes, and sleep disturbances, can mimic or exacerbate depressive symptoms. Treating thyroid dysfunction through the administration of triiodothyronine may improve depressive symptoms, although depression can also occur independently of thyroid issues [19]. Thyroid hormones affect neurotransmitters, maybe by increasing cortical serotonin release, or may act as a co-transmitter to NE in the adrenergic nervous system [19]. However, the exact mechanism of this interaction is not well known, especially with the finding that depressed individuals without hypothalamus-pituitary-thyroid axis abnormalities have reduced 5-HT function as well [19].

While the endocrine hypothesis of depression suggests that imbalances in hormone levels contribute to depressive symptoms, it was found that not all patients with endocrine disorders exhibit depressive symptoms, indicating that the relationship between hormones and depression is not straightforward.

3.5. Glutamatergic and GABAergic Alterations

Glutamergic and GABAergic alterations have been reported in depression, reflecting dysregulation in the balance between excitatory and inhibitory neurotransmission within the brain [20].

Glutamate is the primary excitatory neurotransmitter in the brain, and alterations in glutamatergic signaling have been associated with depression [20]. It was observed that there is an upregulation of N-methyl-D-aspartate (NMDA) receptors in certain brain regions of depressed patients, leading to an increase in excitatory activity and neuronal damage, thus contributing to depressive symptoms [5]. Another suggested mechanism involves a reduction in glutamate transporters, leading to alterations in glutamate clearance and an increase in extracellular glutamate levels, resulting in depression [5]. Additionally, glutamatergic dysfunction may disrupt synaptic plasticity mechanisms, which refers to the brain's ability to adapt and reorganize its neural connections in response to experiences, leading to depression [5].

GABA (gamma-aminobutyric acid) is the main inhibitory neurotransmitter in the brain, and disruptions in GABAergic neurotransmission have been implicated in depression [20]. Studies have reported reductions in GABA levels, alterations in GABA receptor subunit expression, and dysfunction in GABAergic interneurons in individuals with depression. These alterations suggest a reduction in inhibitory control over neural circuits involved in mood regulation, thus contributing to depression [5].

Overall, the imbalance between glutamatergic excitation and GABAergic

inhibition is thought to play a role in the pathophysiology of depression. Targeting this neurotransmitter system may be a breakthrough in the treatment of depression, although further research is needed to fully understand the precise mechanisms of glutamatergic and GABAergic alterations and their involvement in depression.

3.6. Neurotrophic Hypothesis

Recent studies show structural alterations in the brains of individuals with depression, revealing a decrease in the volume of the hippocampus and other brain regions in untreated depressed people, possibly resulting in increased stress sensitivity and an increased risk of recurrence [1]. It has been proposed that this loss of volume may be due to glucocorticoid neurotoxicity, glutamatergic toxicity, decreased neurotrophic factors, and decreased neurogenesis [5]. Unfortunately, these mechanisms couldn't be confirmed since there are no imagining tools to directly examine neurotoxic and neurotrophic processes *in vivo* [5].

The neurotrophic hypothesis of depression proposes that disruptions in neurotrophic factors, particularly brain-derived neurotrophic factor (BDNF), and its signaling pathways play a significant role in the pathophysiology of depression [1, 21]. BDNF is a protein that supports the growth, survival, and function of neurons in the brain. It plays a crucial role in neuroplasticity and promotes the formation of new synapses, enhancing neurotransmitter release, and protecting neurons from damage and death [1, 21].

According to the neurotrophic hypothesis, reduced levels of BDNF and impaired BDNF signaling may contribute to the development and persistence of depression. Preclinical studies have shown that chronic stress, a major risk factor for depression, can downregulate BDNF expression and impair neuroplasticity in key

brain regions involved in mood regulation, such as the hippocampus and prefrontal cortex [22].

Moreover, genetic and epigenetic factors that influence BDNF expression and function have been implicated in the vulnerability to depression. For example, variations in the BDNF gene and alterations in DNA methylation patterns that regulate BDNF expression have been associated with an increased risk of depression [22].

Conversely, antidepressant treatments, such as selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants, have been found to upregulate BDNF expression and enhance neuroplasticity [1]. These findings suggest that the therapeutic effects of antidepressants may, in part, be mediated by their ability to restore BDNF levels and normalize neurotrophic signaling pathways [1]. Overall, the neurotrophic hypothesis of depression highlights the importance of neuroplasticity and BDNF signaling in the pathogenesis of depression and suggests that targeting these pathways may represent a promising approach for the development of novel antidepressant treatments.

3.7. Circadian Rhythms Hypothesis

The Circadian rhythms hypothesis of depression suggests that disturbances in the body's internal biological clock, which regulates sleep-wake cycles and other physiological processes, may influence the development of depression [5]. According to this hypothesis, abnormalities in circadian rhythms, such as irregular sleep-wake patterns or changes in the timing of hormonal secretion, increase the risk of developing depression due to disruption in mood-regulating mechanisms [5]. It has been noticed that individuals who have insomnia or irregular sleep schedules may experience dysregulation of neurotransmitters involved in mood regulation,

such as serotonin, and are more susceptible to developing depression. Moreover, studies have suggested that depressive symptoms could occur due to dysregulation in circadian genes and clock genes, which are important in regulating circadian rhythms and mood [23].

On the other hand, depression itself can disrupt circadian rhythms, leading to sleep disturbances and exacerbating mood symptoms. For example, individuals with depression often exhibit alteration in the diurnal rhythm of cortisol, such as blunted cortisol awakening response (CAR) and elevated evening cortisol levels [5]. These abnormalities in cortisol secretion can cause depressive symptoms. Therefore, the relationship between depression and circadian rhythms is bidirectional, where both influence and trigger each other.

Researches supporting the circadian rhythms hypothesis depend on the improvement of depressed patients after stabilizing circadian rhythm as an adjunct therapy to antidepressant drugs by maintaining a regular sleep-wake schedule, exposure to sunlight, and time administration of drugs [23].

Overall, the circadian rhythms hypothesis provides valuable insights into the complex interplay between biological processes and mood regulation, emphasizing the importance of maintaining healthy sleep patterns and circadian rhythms for the treatment and prevention of depression.

4. Treatment of Depression

While conventional therapies such as antidepressant medications and psychotherapy remain cornerstone treatments for depression, new and emerging treatments offer promise for improved outcomes, especially for individuals with treatment-resistant depression or those seeking alternatives to traditional approaches. Continued research and innovation in the field of

depression treatment are essential for addressing the diverse needs of individuals living with this challenging condition.

4.1. Conventional Therapy

4.1.1. Antidepressant Medications: Selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and other classes of antidepressants are commonly prescribed to alleviate symptoms of depression [1, 3, 4]. These medications work by increasing the availability of neurotransmitters such as serotonin and norepinephrine in the brain, helping to regulate mood [1].

4.1.2. Psychotherapy: Cognitive-behavioral therapy (CBT), interpersonal therapy (IPT), and other forms of psychotherapy are widely used to treat depression [3]. These therapies aim to identify and modify negative thought patterns and behaviors, improve coping skills, and enhance interpersonal relationships, leading to symptom relief and improved functioning [3].

4.1.3. Electroconvulsive Therapy (ECT): ECT is a procedure in which electrical currents are passed through the brain to induce a controlled seizure [1]. While its precise mechanism of action is not fully understood, ECT is known to produce rapid and often effective relief of severe depression, particularly in cases where other treatments have been ineffective [1].

4.2. New Treatments

4.2.1. Ketamine and Esketamine: Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has shown rapid and robust antidepressant effects, even in treatment-resistant depression [4]. Esketamine, a nasal spray formulation of ketamine, has been approved by regulatory agencies for use in certain cases of treatment-resistant depression [4].

4.2.2. Transcranial Magnetic Stimulation (TMS): TMS involves the non-invasive delivery of magnetic pulses to specific regions of the brain implicated in depression, such as the dorsolateral prefrontal cortex **[1]**. This therapy has demonstrated efficacy in reducing depressive symptoms and is generally well-tolerated **[1]**.

4.2.3. Novel Pharmacological Approaches: Researchers are exploring novel pharmacological targets and mechanisms of action for treating depression **[24]**. These include drugs targeting the glutamatergic system, inflammatory pathways, and neurotrophic factors, to develop medications that are faster-acting, more effective, and better tolerated than current options **[24]**.

4.2.4. Digital Therapeutics: With the rise of digital health technologies, there is growing interest in digital therapeutics for depression **[25]**. These include smartphone apps, web-based programs, and virtual reality interventions designed to deliver evidence-based psychotherapy, mindfulness exercises, and other interventions remotely, increasing access to care and providing additional treatment options **[25]**.

Conclusion

In conclusion, the pathophysiology of depression is a complex interplay of neurobiological, genetic, and environmental factors, presenting a significant challenge in fully understanding this disorder. While the monoamine hypothesis has contributed to our understanding and guided treatment, it is clear that depression involves a multifaceted network of neurobiological processes beyond just monoamine dysfunction. Further studies are necessary to elucidate the exact mechanisms involved, leading to the development of more effective and personalized strategies. These efforts aim to help individuals affected by depression improve their quality of life and well-being.

Declarations

Consent to publish

All authors have read and agreed to the published version of the manuscript

Ethics approval and consent to participate

Not applicable.

Availability of data and material

All data generated or analyzed during this study are included in this published article in the main manuscript.

Conflict of Interest

The authors assert that there are no conflicts of interest.

Authors Contribution

The manuscript was drafted and written by Mariam Ahmed Fouad. All authors have read and approved the final -manuscript.

5. References

1. Fekadu N, Shibeshil W, Engidawork E. Major Depressive Disorder: Pathophysiology and Clinical Management. J Depress Anxiety 2016; 6(1), 255. [DOI: 10.4172/2167-1044.1000255]

2. Martins R, Almeida J, Henriques P, Novais P. Identifying Depression Clues using Emotions and AI. ICAART 2021; (2), 1137-1143. [DOI: 10.5220/0010332811371143]

3. Chand SP, Arif H. Depression. StatPearls 2023.

4. Haihua T, Zhenyu H, Jia X, Chuang W. The molecular pathophysiology of depression and the new therapeutics. MedComm 2022; 3(3), e156. [DOI: 10.1002/mco2.156]

5. Hasler, G. Pathophysiology of Depression: Do We Have Any Solid Evidence of Interest to Clinicians? World Psychiatry 2010; 9(3), 155-161. [DOI: 10.1002/j.2051-5545.2010.tb00298.x]

6. Perlman SB, Jones BM, Wakschlag LS, Axelson D, Birmaher B, Phillips ML. Neural substrates of child irritability in typically developing and psychiatric populations. Developmental Cognitive Neuroscience 2015; 14, 71-80 [DOI: 10.1016/j.dcn.2015.07.003]

7. Mishra S, Elliott H, Marwaha R. Premenstrual Dysphoric Disorder. StatPearls 2023.

8. Perez-Caballero L, Torres-Sanchez S, Romero-López-Alberca C, González-Saiz F, Mico JA, Berrocoso E. Monoaminergic system and depression. Cell and tissue research. 2019 Jul 5;377:107-13.

9. Montoya A, Bruins R, Katzman MA, Blier P. The noradrenergic paradox: implications in the management of depression and anxiety. Neuropsychiatric disease and treatment. 2016; 1:541-57.

10. Francisco L, Cecilio A. Monoaminergic neurotransmission: the history of the discovery of antidepressants from the 1950s until today. Current pharmaceutical design 2009; 15(14), 1563-1586. [DOI: 10.2174/138161209788168001]

11. Charles L. Raison, Robin E. Rutherford, Bobbi J. Woolwine. A Randomized Controlled Trial of the Tumor Necrosis Factor Antagonist Infliximab for Treatment-Resistant Depression. JAMA Psychiatry 2013; 70(1), 31-41. [DOI:10.1001/2013.jamapsychiatry.4]

12. Gianluca S, Alessandra C, Andrea A, Andrea Amerio, Alice T, Andrea E, et al. The Role of Inflammation in the Pathophysiology of Depression and Suicidal Behavior: Implications for Treatment. Medical Clinics of North America 2023; 107(1), 1-29. [DOI:10.1016/j.mcna.2022.09.001]

13. Andrew HM, Ebrahim H, Charles LR, Jennifer CF. Cytokine targets in the brain: impact on neurotransmitters and neurocircuits. Depress Anxiety 2013; 30(4), 297-306. [DOI: 10.1002/da.22084]

14. Kong E, Sucic S, Monje FJ, Reisinger SN, Savalli G, Diao W, Khan D, Ronovsky M, Cabatic M, Koban F, Freissmuth M. STAT3 controls IL6-dependent regulation of serotonin transporter function and depression-like behavior. Scientific reports. 2015 Mar 11;5(1):9009.

15. Kyu-Man H, Byung-Joo H. How Inflammation Affects the Brain in Depression: A Review of Functional and Structural MRI Studies. Journal of Clinical Neurology 2021; 17(4), 503-515. [DOI: 10.3988/jcn.2021.17.4.503]

16. Ibrahim E, Mustafa N, Arif D. Protective Effects of Lamotrigine, Aripiprazole, and Escitalopram on Depression-induced Oxidative Stress in Rat Brain. Neurochemical Research 2007;32: 1188-1195.

17. Ciaran PC. Galts, Luis EBB, David CJ, Charles CY, Patricia SB, Ana LSR, Jonathan ST, Joana G. Depression in neurodegenerative diseases: Common mechanisms and current treatment options. Neuroscience and Biobehavioral Reviews

2019; 102, 56-84. [DOI: 10.1016/j.neubiorev.2019.04.002]

18. Ewelina D, Marek W. Cortisol as a Biomarker of Mental Disorder Severity. Journal of Clinical Medicine 2021; 10(21), 5204. [DOI:10.3390/jcm10215204]

19. Bondy B. Pathophysiology of depression and mechanisms of treatment, Dialogues in Clinical Neuroscience 2002; 4(1), 7-20. [DOI: 10.31887/DCNS.2002.4.1/bbondy]

20. Sarawagi A, Soni ND, Patel AB. Glutamate and GABA homeostasis and neurometabolism in major depressive disorder. Frontiers in psychiatry. 2021 Apr 27;12:637863.
[DOI: 10.3389/fpsyt.2021.637863]

21. Minal J, Sashaina EF, Shreya G, Ronald S, Vidita AV. The Neurotrophic Hypothesis of Depression Revisited: New Insights and Therapeutic Implications. Neurobiology of Depression 2019;1: 43-62. [DOI:10.1016/B978-0-12-813333-0.00006-8]

22. Ronald SD, Lisa MM. A neurotrophic model for stress-related mood disorders. Biol Psychiatry 2006; 59(12), 1116-27. [DOI: 10.1016/j.biopsych.2006.02.013]

23. Peeraporn V, Ingrid YL. Molecular basis for the association between depression and circadian rhythm. Tzu Chi Medical Journal 2019; 31(2), 67-72.
[DOI: 10.4103/tcmj.tcmj_181_18]

24. Elias E, Zhang AY, Manners MT. Novel Pharmacological Approaches to the Treatment of Depression. Life 2022; 12(2), 196. [DOI:10.3390/life12020196]

25. Yongho L, Vinh P, Jieming Z, Tai-Myoung C. A Digital Therapeutics System for the Diagnosis and Management of Depression: Work in Progress. CCIS 2023.