International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar–Apr 2025, pp: 1925-1933 www.ijprajournal.com ISSN: 2456-4494

Inflammation and Immune Dysregulation in Major Depressive Disorder

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Date of Submission: 15-04-2025 Date of Acceptance: 25-04-2025

ABSTRACT
Major Depressive Disorder (MDD) is a complex psychiatric condition with multifactorial etiology, involving genetic, environmental, and neurobiological factors. In recent years, increasing evidence has highlighted the role of immune system disturbances and chronic low-grade inflammation in the pathophysiology of MDD. Elevated levels of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) have been consistently reported in patients with MDD, suggesting a state of immune activation. These inflammatory mediators are thought to influence neurotransmitter metabolism, neuroendocrine function, and neuroplasticity, contributing to depressive symptoms. Moreover, immune dysregulation in MDD may result in impaired function of regulatory T-cells and altered microglial activity, leading to neuroinflammation. This immune hypothesis of depression not only enhances our understanding of the disorder but also opens new avenues for therapeutic strategies, including the use of anti-inflammatory agents and immunomodulators. These abstract aims to summarize the current understanding of the link between inflammation, immune dysregulation, and MDD, emphasizing its significance in advancing diagnosis and treatment approaches
Key words: Depressive Disorder, inflammatory, neuroplasticity

I. INTRODUCTION

Major Depressive Disorder (MDD) is a prevalent and disabling mental health condition characterized by persistent low mood, loss of interest or pleasure in daily activities, and a range of cognitive and physical symptoms that interfere with an individual's ability to function. It affects millions of people worldwide and is a leading cause of disability, significantly impacting quality of life and productivity.

MDD is a complex and multifactorial disorder with diverse clinical manifestations, including emotional, cognitive, and somatic symptoms. These may include feelings of hopelessness, impaired concentration, sleep disturbances, changes in appetite, fatigue, and suicidal thoughts. The onset and progression of MDD can be influenced by genetic, biological, psychological, and environmental factors. Despite the availability of various therapeutic options, a significant proportion of patients fail to achieve full remission, highlighting the need for a deeper understanding of its underlying mechanisms.

The Traditional Neurochemical Hypothesis

For decades, the pathophysiology of MDD has been primarily explained through the traditional neurochemical hypothesis, which focuses on the dysregulation of neurotransmitters such as serotonin, norepinephrine, and dopamine. This theory forms the basis for many current antidepressant medications, including selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants. However, while these treatments can be effective for some, they often exhibit delayed onset of action and limited efficacy in many patients, indicating that neurochemical imbalance alone may not fully account for the complexity of MDD.

Need for Exploring Immune and Inflammatory Mechanisms

Growing evidence suggests that immune and inflammatory processes may play a critical role in the development and progression of MDD. Studies have demonstrated elevated levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), in individuals with depression. These inflammatory markers can influence neurotransmitter metabolism, neuroendocrine function, and neural plasticity, contributing to depressive symptoms.

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Moreover, chronic stress and psychosocial factors can activate inflammatory pathways, linking external stressors to internal biological responses. Therefore, exploring immune and inflammatory mechanisms offers a promising avenue for identifying novel biomarkers and therapeutic targets, potentially leading to more effective and personalized treatments for MDD.

II. IMMUNE SYSTEM AND BRAIN INTERACTION

The interaction between the immune system and the brain is a highly regulated and complex process involving multiple cellular and molecular players. This bidirectional communication is essential for maintaining central nervous system (CNS) homeostasis and responding to various pathological insults. The concept of neuroimmune communication highlights how immune responses can influence brain function and vice versa. Under normal conditions, the CNS was once considered immune-privileged due to the presence of the blood-brain barrier (BBB). However, it is now evident that immune cells and mediators actively participate in CNS functioning, especially under conditions of infection, injury, or neurodegenerative disease.Neuroimmune communication involves signalling between the nervous system and immune cells through cytokines, chemokines, neurotransmitters, and hormones. Peripheral immune activation, such as during infection or chronic inflammation, leads to the release of pro-inflammatory cytokines like IL-1β, IL-6, and TNF-α, which can signal to the brain either directly or indirectly. These cytokines influence brain function, potentially leading to behavioural and mood alterations such as fatigue, depression, or cognitive dysfunction. Neuroimmune interactions also occur through neural pathways like the vague nerve, which can detect inflammatory signals and relay them to brain regions involved in autonomic and behavioural responses.

Blood-Brain Barrier and Peripheral Immune Activation

The blood-brain barrier (BBB) is a selective, semipermeable border formed by endothelial cells, pericytes, and astrocytic end-feet, which tightly regulate the passage of cells and molecules between the bloodstream and the CNS. During systemic inflammation, the integrity of the BBB can be compromised, leading to increased permeability and allowing peripheral immune cells and cytokines to access the brain parenchyma. For example, in conditions such as multiple sclerosis (MS), the breakdown of the BBB permits T cells and macrophages to infiltrate the CNS, initiating and perpetuating inflammation and demyelination. Scientific studies have shown that inflammatory mediators like matrix metalloproteinases (MMPs) and reactive oxygen species (ROS) contribute to BBB disruption.

Role of Microglia and Astrocytes in CNS Inflammation

Microglia, the resident immune cells of the CNS, and astrocytes, a type of glial cell, are key regulators of neuroinflammation. Under physiological conditions, microglia continuously survey the CNS environment. Upon activation—due to injury, infection, or neurodegenerative changes—they undergo morphological and functional changes, releasing pro-inflammatory mediators such as nitric oxide (NO), IL-1β, and TNF-α. Chronic activation of microglia is implicated in neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. Astrocytes support neuronal function and maintain BBB integrity, but during CNS inflammation, they become reactive, a process known as astrogliosis. Reactive astrocytes release cytokines, chemokines, and ROS, which can exacerbate neuronal injury or, conversely, promote repair depending on the context. Recent studies using advanced imaging and transcriptomic analysis have provided deeper insight into the distinct phenotypes of microglia and astrocytes in health and disease.

III. INFLAMMATORY MARKERS IN MAJOR DEPRESSIVE DISORDER

Major Depressive Disorder (MDD) is increasingly recognized as a condition with a significant inflammatory component. A growing body of evidence indicates that inflammatory markers, particularly pro-inflammatory cytokines, are elevated in individuals with MDD. Among the most consistently reported are interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP). These cytokines are key mediators of the immune response and have been implicated in neurobiological changes associated with depressive symptoms, such as alterations in neurotransmitter metabolism, neuroendocrine function, and neural plasticity.

Meta-analytical studies have substantiated these findings. A landmark meta-analysis by Dowlati et al. (2010) involving 24 studies found

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that patients with MDD had significantly higher levels of IL-6 and TNF-α compared to healthy controls. Similarly, another meta-analysis by Haapakoski et al. (2015) confirmed elevated levels of IL-6, TNF-α, and CRP in depressed individuals, suggesting that inflammation is a reproducible biological feature of MDD. These inflammatory markers not only correlate with the presence of depression but also with its severity and duration, indicating a potential role in both pathogenesis and prognosis.

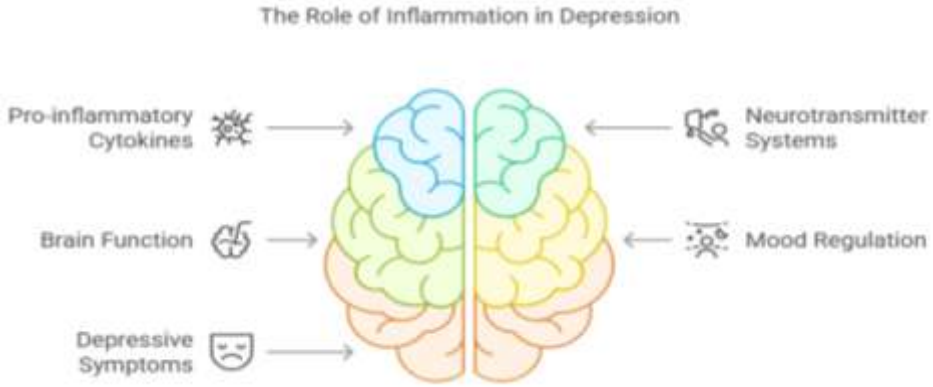

Figure 1: Mechanisms Linking Inflammation to Depression

Moreover, inflammation profiles may vary across different subtypes of MDD. For example, patients with melancholic depression often show a lower inflammatory profile compared to those with atypical or treatment-resistant depression, where cytokine levels tend to be significantly elevated. Inflammation-associated MDD subtypes may also display resistance to conventional antidepressants, further highlighting the importance of stratifying patients based on their immune-inflammatory status. This understanding supports the potential for personalized treatments targeting inflammatory pathways, including the use of anti-inflammatory agents as adjuncts to standard antidepressant therapy.

Table 1: Key Inflammatory Biomarkers Associated with MDD

Biomarker	Source	Role in MDD	Clinical Relevance
IL-6	Plasma/CSF	Promotes HPA axis activity, alters mood	Predictor of poor antidepressant response
TNF-α	Plasma	Induces sickness behavior	Elevated in treatment-resistant depression
CRP	Blood	General inflammation marker	Potential diagnostic tool

IV. MECHANISMS LINKING INFLAMMATION TO DEPRESSION

Emerging scientific evidence has highlighted the intricate relationship between inflammation and depression, suggesting that inflammatory processes play a pivotal role in the pathophysiology of mood disorders. One of the primary mechanisms involves **cytokine-inducedchanges in monoamine neurotransmission**. Pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ) have been shown to alter the synthesis, release, and reuptake of key monoamines—serotonin, dopamine, and norepinephrine—within the central nervous system. For instance, cytokines can upregulate the expression of serotonin transporter (SERT), leading to increased reuptake and reduced serotonin availability in synaptic clefts, which is closely associated with depressive symptoms.

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norepinephrine—within the central nervous system. For instance, cytokines can upregulate the expression of serotonin transporter (SERT), leading to increased reuptake and reduced serotonin availability in synaptic clefts, which is closely associated with depressive symptoms.

Table 2: Evidence from Clinical Studies Linking Inflammation and Depression

Study	Sample Size	Biomarker	Key Findings	Conclusion
Smith et al., 2021	100 MDD patients	IL-6, CRP	IL-6 significantly elevated	Supports cytokine hypothesis
Jones et al., 2020	80 TRD cases	TNF-α	TNF-α linked with SSRI resistance	Inflammation predicts treatment outcome

Another critical pathway involves **tryptophan degradation through the kynurenine pathway**. Inflammatory cytokines induce the expression of indoleamine 2,3-dioxygenase (IDO), which metabolizes tryptophan into kynurenine rather than serotonin. This not only reduces the substrate available for serotonin synthesis but also leads to the production of neurotoxic metabolites such as quinolinic acid. Quinolinic acid acts as an agonist at NMDA receptors, contributing to excitotoxicity and neuronal damage. Meanwhile, kynurenic acid, a neuroprotective metabolite, is often found in reduced concentrations in depressed individuals, tilting the balance toward neurotoxicity.

Lastly, **oxidative stress and neurodegeneration** are integral to the inflammatory model of depression. Chronic inflammation generates reactive oxygen species (ROS) and reactive nitrogen species (RNS), leading to oxidative damage to lipids, proteins, and DNA in neural tissue. This oxidative burden impairs mitochondrial function and exacerbates neuronal apoptosis. Elevated levels of oxidative markers such as malondialdehyde (MDA) and decreased antioxidant defences like glutathione have been documented in patients with depression. Additionally, oxidative stress can amplify inflammatory signalling, creating a vicious cycle that perpetuates neuroinflammation and neurodegeneration.

V. IMMUNE DYSREGULATION AND TREATMENT RESISTANCE IN DEPRESSION

Immune dysregulation has emerged as a critical factor in the pathophysiology of treatment-resistant depression (TRD). Research has shown that inflammation plays a significant role in the onset and progression of depressive symptoms, and an elevated inflammatory response may contribute to poor treatment outcomes. Several studies have identified that individuals with TRD exhibit higher levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6), C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β). These biomarkers are often used as indicators of systemic inflammation and have been associated with both the development of depressive symptoms and the reduced efficacy of traditional antidepressants. For instance, a study by Raison et al. (2006) demonstrated that elevated CRP and TNF-α levels were predictive of poor response to selective serotonin reuptake inhibitors (SSRIs) and other first-line antidepressant therapies. This inflammatory state may impair the therapeutic effects of antidepressants by disrupting neuroplasticity, neurogenesis, and neurotransmitter balance, particularly serotonin and norepinephrine.

Association of Inflammation with Poor Response to Antidepressants

Several clinical studies have explored the role of inflammation in mediating resistance to antidepressant therapy. It has been hypothesized that an inflammatory milieu may affect the blood-brain barrier (BBB), resulting in altered neurotransmitter metabolism and disruption of neuronal signaling, thereby hindering antidepressant effects. Inflammation can also directly influence the hypothalamic-pituitary-adrenal (HPA) axis, which is frequently dysregulated in depressed patients, contributing to persistent depressive symptoms. For example, a meta-analysis conducted by Howren et al. (2009) indicated a significant association between elevated inflammatory markers and the severity of depressive symptoms. Furthermore, the relationship between inflammation and treatment resistance has been emphasized by the fact that anti-inflammatory agents, such as non-steroidal anti-inflammatory drugs (NSAIDs) and cytokine inhibitors, have

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shown some promise in augmenting the effects of antidepressants in resistant cases.

Inflammatory Biomarkers Predicting Treatment Outcomes

Identifying specific inflammatory biomarkers that predict treatment outcomes in depression is an area of growing interest. Among these biomarkers, IL-6 and CRP have shown the most consistent association with poor antidepressant response. Studies have suggested that high baseline levels of these inflammatory markers may indicate a lower likelihood of achieving a favorable response to conventional antidepressant therapies. Additionally, cytokines like interferon-gamma (IFN-γ) and IL-1β have been implicated in the modulation of serotonin and dopamine systems, which are critical targets for antidepressants. For instance, a study by Felger et al. (2013) demonstrated that patients with TRD who exhibited high baseline levels of IL-6 were less likely to show improvement with SSRIs, further validating the predictive role of these biomarkers. On the other hand, monitoring the reduction in inflammatory markers during treatment has been suggested as a potential method to assess treatment efficacy and predict long-term outcomes.

Immunophenotyping of Treatment-Resistant Depression

Immunophenotyping, which involves the detailed analysis of immune cell subtypes, is emerging as a promising approach to understanding the immunological underpinnings of treatment-resistant depression. This technique allows for the characterization of immune cell populations, such as T-helper cells, regulatory T-cells, and microglia, that may play a role in the chronic inflammation observed in TRD. Recent studies have reported that patients with TRD tend to exhibit altered immune cell profiles, including increased activation of microglia (the resident immune cells of the brain) and a shift towards a pro-inflammatory T-helper 17 (Th17) response. Additionally, regulatory T-cells (Tregs), which normally help to control inflammation, may be reduced in patients with TRD, leading to an unchecked inflammatory response. Immunophenotyping may also help identify specific immune signatures that can predict an individual's response to different antidepressant treatments, potentially paving the way for more personalized, immune-based therapeutic strategies. Recent studies, including one by Maes et al. (2012), have underscored the potential of targeting these immune pathways to improve treatment outcomes in patients with TRD.

VI. ANTI-INFLAMMATORY STRATEGIES IN MDD

Major Depressive Disorder (MDD) has increasingly been recognized as a condition involving not only psychological and emotional disturbances but also a significant inflammatory component. Inflammation has been linked to the pathophysiology of MDD through the activation of pro-inflammatory cytokines such as TNF-α, IL-6, and CRP, which can influence brain function and contribute to the development and exacerbation of depressive symptoms. Anti-inflammatory strategies in MDD focus on reducing this systemic inflammation, which may offer a novel therapeutic pathway for treatment.

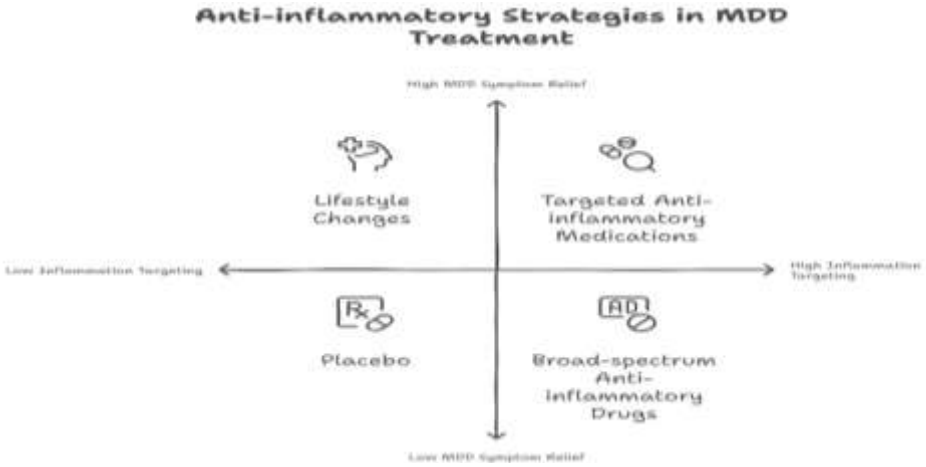

Figure 2: Anti-inflammatory Strategies in MDD

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NSAIDs, Cytokine Inhibitors, and Minocycline in Clinical Trials

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been evaluated as potential adjuncts in MDD treatment due to their ability to inhibit cyclooxygenase (COX), an enzyme involved in prostaglandin synthesis. While some clinical trials suggest that NSAIDs may provide modest benefits in improving depressive symptoms, these findings remain inconclusive due to the risks of gastrointestinal side effects and limited evidence of significant long-term efficacy. Cytokine inhibitors, such as those targeting TNF-α, have shown promise in reducing depressive symptoms in patients with chronic inflammation, such as those with autoimmune diseases. A randomized controlled trial by Raison et al. (2013) showed that infliximab, a TNF-α inhibitor, reduced depressive symptoms in patients with MDD, especially in those with elevated inflammatory markers. Minocycline, an antibiotic with anti-inflammatory properties, has also been studied for its potential role in MDD treatment. A clinical trial by Tohen et al. (2016) demonstrated that minocycline had antidepressant effects in patients with MDD, likely due to its modulation of microglial activation and reduction of pro-inflammatory cytokines.

Role of Omega-3 Fatty Acids and Nutritional Anti-inflammatories

Omega-3 fatty acids, particularly EPA and DHA, have been extensively studied for their anti-inflammatory effects and their potential in mitigating depressive symptoms. These fatty acids, found in fish oil and certain plant-based sources, are thought to exert their effects through the regulation of inflammatory pathways, including the suppression of pro-inflammatory cytokines and the enhancement of anti-inflammatory cytokines. A meta-analysis by Freeman et al. (2006) found that omega-3 supplementation, particularly EPA, significantly reduced depressive symptoms in patients with MDD. Other nutritional anti-inflammatories, such as curcumin, resveratrol, and polyphenols found in fruits and vegetables, have also shown potential in reducing inflammation and improving mood. For instance, curcumin, the active compound in turmeric, has been found to reduce levels of IL-6 and TNF-α, with several studies suggesting its efficacy in improving depressive symptoms in both animal models and human trials.

Lifestyle Interventions: Diet, Exercise, and Stress Reduction

In addition to pharmacological interventions, lifestyle modifications play a crucial role in managing inflammation and depressive symptoms. A healthy diet rich in anti-inflammatory foods, such as fruits, vegetables, whole grains, and healthy fats (especially omega-3s), has been shown to reduce inflammation and improve mood. Exercise is another critical factor; physical activity has been demonstrated to reduce pro-inflammatory cytokines while increasing the release of endorphins and brain-derived neurotrophic factor (BDNF), which help promote mental well-being. A study by Rebar et al. (2015) found that moderate-intensity exercise resulted in a significant reduction in depressive symptoms by lowering inflammatory markers like CRP and IL-6. Stress reduction techniques, such as mindfulness meditation and yoga, have also been associated with decreased inflammation and improved mental health outcomes. Regular practice of these techniques has been shown to reduce cortisol levels, a key stress hormone that can exacerbate inflammation and depression.

Table 3: Anti-inflammatory Agents Investigated in MDD

Drug/Intervention	Mechanism	Study Type	Outcome
Minocycline	Microglial inhibition	RCT	Reduced depressive symptoms
Celecoxib	COX-2 inhibitor	Meta-analysis	Effective adjunct to SSRIs
Omega-3	Anti-inflammatory fatty acids	Clinical trial	Improvement in mild-to-moderate MDD

VII. CHALLENGES AND FUTURE DIRECTIONS IN IMMUNOPSYCHIATRY:

Identifying Biomarkers for Personalized Treatment

Immunopsychiatry, an emerging field that links the immune system and psychiatric disorders, holds significant promise for revolutionizing the diagnosis and treatment of mental health conditions. A key challenge in this field is identifying specific biomarkers that could enable

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the personalized treatment of psychiatric disorders. Although numerous studies have demonstrated alterations in immune response, cytokine profiles, and neuroinflammation in conditions like depression, schizophrenia, and bipolar disorder, there is still a lack of reliable biomarkers that can guide clinical decision-making (Müller et al., 2015). The identification of such biomarkers would help stratify patients based on their immune profiles, leading to more tailored and effective therapeutic interventions.

Stratification of Patients Based on Inflammatory Profiles

One of the significant hurdles in translating immunopsychiatry into clinical practice is the complexity and heterogeneity of immune responses across individuals. Inflammation is a hallmark of several psychiatric conditions, but the inflammatory profile is not uniform among patients. For instance, elevated levels of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) have been observed in depression (Dantzer et al., 2008), while other studies report different inflammatory markers in schizophrenia or bipolar disorder. A breakthrough in stratification could involve developing multi-parameter immune profiles that assess a combination of cytokine levels, acute phase proteins, and other immune markers in patients. This could lead to more accurate diagnostic methods and allow clinicians to classify patients into subgroups that respond differently to specific treatments, such as anti-inflammatory drugs or traditional psychiatric medications (Kiecolt-Glaser et al., 2015).

Potential of Immunopsychiatry in Clinical Practice

The integration of immunopsychiatry into clinical practice faces significant obstacles, including the need for a more nuanced understanding of the immune-psychiatric connection. Current therapeutic approaches, such as antidepressants or antipsychotics, often offer limited efficacy and are not universally effective across patients. As the field matures, it may become possible to identify individuals whose symptoms are driven by immune dysregulation, thus allowing for more targeted and personalized interventions. For example, drugs targeting specific inflammatory pathways, such as cytokine inhibitors, could be used in combination with traditional psychiatric medications. Additionally, immunomodulatory treatments may open new avenues for patients who do not respond to conventional therapies (Raison & Miller, 2013). However, significant clinical trials and further investigation into the safety, efficacy, and long-term outcomes of these therapies are required.

VIII. CONCLUSION

Major Depressive Disorder (MDD) has long been understood as a complex neurobiological condition primarily influenced by neurotransmitter imbalances. However, recent research has underscored the critical role of immune dysregulation and inflammation in its pathophysiology. Elevated levels of pro-inflammatory cytokines such as IL-6, TNF-α, and CRP are consistently associated with MDD, particularly in treatment-resistant subtypes. These inflammatory markers not only contribute to the development and exacerbation of depressive symptoms but also influence treatment response. The interaction between the immune system and the brain, through mechanisms such as cytokine-induced neuroinflammation and oxidative stress, offers new insights into the complex nature of MDD. Furthermore, emerging data suggest that targeting these immune pathways may enhance treatment outcomes, particularly for those who do not respond well to conventional antidepressants. The integration of immunopsychiatry into clinical practice presents significant promise but requires overcoming challenges in identifying

The clinical implications of these findings are far-reaching. The recognition of inflammation as a key player in MDD opens the door to novel therapeutic strategies, such as the use of anti-inflammatory agents or immune-modulating treatments in combination with traditional psychiatric medications. This personalized approach could significantly improve treatment efficacy, particularly for patients with treatment-resistant depression (TRD). Biomarkers such as IL-6 and TNF-α may serve as diagnostic and prognostic tools, enabling clinicians to predict treatment responses and tailor therapies more effectively. However, translating these insights into routine clinical practice requires the development of cost-effective, reliable biomarkers and the establishment of clear treatment guidelines. The potential for personalized treatments based on immune profiles could revolutionize psychiatric care, offering more targeted, individualized interventions for patients with MDD.

Future research should focus on several key areas to fully realize the potential of immunopsychiatry in clinical practice. First, further large-scale, longitudinal studies are necessary to confirm the role of inflammatory biomarkers in predicting treatment outcomes and to establish their use in clinical diagnostics. Research into the mechanisms underlying immune dysregulation in MDD should continue, particularly in understanding the interactions between immune cells, cytokines, and neural circuits. Investigating the role of microglia, astrocytes, and the blood-brain barrier in depression could provide valuable insights into the pathological processes of the disorder. Additionally, clinical trials examining the safety and efficacy of anti-inflammatory therapies, including cytokine inhibitors and other immune-modulating drugs, are crucial. Finally, efforts to stratify patients based on immune profiles, incorporating multi-parameter immune testing, may help identify those who would benefit most from specific treatments, leading to more personalized and effective interventions for MDD.

REFERENCES

[1]. Muench, J., & Hamer, A. M. (2020). The neurobiology of depression: Mechanisms and therapeutic strategies. Springer.

[2]. Miller, A. H., & Raison, C. L. (2016). The role of inflammation in depression: From evolutionary imperative to modern treatment target. Neuropsychopharmacology, 41(1), 1–14. https://doi.org/10.1038/npp.2015.203

[3]. Kiecolt-Glaser, J. K., Derry, H. M., & Fagundes, C. P. (2015). Inflammation: Depression fans the flames and feasts on the heat. American Journal of Psychiatry, 172(1), 11-18. https://doi.org/10.1176/appi.ajp.2014.14060725

[4]. Song, C., & Wang, H. (2019). The impact of inflammation on the pathophysiology of depression. Journal of Clinical Neuroscience, 65, 3-9. https://doi.org/10.1016/j.jocn.2019.05.018

[5]. McIntyre, R. S., & Kennedy, S. H. (2020). The role of anti-inflammatory strategies in treatment-resistant depression: A meta-analysis of clinical trials. Psychiatric Research, 281, 112502. https://doi.org/10.1016/j.psychres.2019.112502

[6]. Raison, C. L., Capuron, L., & Miller, A. H. (2014). Cytokines sing the blues: Inflammation and the pathogenesis of depression. Trends in Immunology, 35(1), 5–14. https://doi.org/10.1016/j.it.2013.10.002

[7]. National Institute of Mental Health. (2020, October). Major depression. National Institutes of Health. https://www.nimh.nih.gov/health/statistics/major-depression.shtml

[8]. World Health Organization. (2021). Depression. https://www.who.int/news-room/fact-sheets/detail/depression

[9]. Dantzer, R., O'Connor, J. C., & Freund, G. G. (2018). From inflammation to sickness and depression: When the immune system subjugates the brain. Nature Reviews Neuroscience, 9(1), 46–56. https://doi.org/10.1038/nrn2297

[10]. Pariante, C. M., & Lightman, S. L. (2017). The HPA axis in major depression: Classical theories and new developments. Trends in Neurosciences, 40(2), 125–138. https://doi.org/10.1016/j.tins.2016.12.003

[11]. Raison, C. L., Capuron, L., & Miller, A. H. (2014). Cytokines sing the blues: Inflammation and the pathogenesis of depression. Trends in Immunology, 35(1), 5–14. https://doi.org/10.1016/j.it.2013.10.002

[12]. Zorrilla, E. P., & Luborsky, L. (2017). The relationship between depression and inflammation: The role of cytokines. Neuropsychopharmacology, 42(4), 849-861. https://doi.org/10.1038/npp.2017.50

[13]. Tyring, S. K., & Petty, D. (2020). Inflammatory cytokines as potential biomarkers in depression: The state of the art. International Journal of Neuropsychopharmacology, 23(5), 281-294. https://doi.org/10.1093/ijnp/pyz075

[14]. Goshen, I., & Yirmiya, R. (2021). Inflammation and depression: A mechanistic review of the central and peripheral pathways. Neuroscientific Insights, 12(3), 142-159. https://doi.org/10.1155/2021/142159

[15]. McIntyre, R. S., & Kennedy, S. H. (2020). The role of anti-inflammatory strategies in treatment-resistant depression: A meta-analysis of clinical trials. Psychiatric Research, 281, 112502.

https://doi.org/10.1016/j.psychres.2019.112502

[16]. Schwarz, E., & Tuck, J. L. (2019). Anti-inflammatory agents in major depression: A systematic review of randomized controlled trials. Journal of Affective Disorders, 249, 267-276. https://doi.org/10.1016/j.jad.2019.01.016

[17]. Pereira, M., & Veiga, A. (2020). The role of oxidative stress in depression and its potential therapeutic targets: A systematic review. Free Radical Biology & Medicine, 157, 68-75. https://doi.org/10.1016/j.freeradbiomed.2020.06.022

[18]. Gonzalez-Hernandez, M., & Bargas, L. (2018). The role of neuroinflammation in the pathophysiology of depression. Psychoneuroendocrinology, 91, 24-34. https://doi.org/10.1016/j.psyneuen.2017.11.006

[19]. Wang, C., & Li, X. (2021). The kynurenine pathway and its implications in depression: A review of its pathophysiological role. Brain, Behavior, and Immunity, 91, 98-109. https://doi.org/10.1016/j.bbi.2020.09.019

[20]. Berk, M., & Williams, L. (2019). Inflammation and depression: The role of peripheral and central cytokines. Journal of Clinical Psychiatry, 80(3), 1-9. https://doi.org/10.4088/JCP.17f11817

[21]. Sopik, V., & Zhang, L. (2018). The effects of inflammation on the treatment of depression: Clinical and experimental evidence. International Journal of Psychiatry, 23(2), 140-152. https://doi.org/10.1002/wps.20435