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CURRENT TOPIC

Emerging Trends in Pharmacological Strategies for Targeting Neuroinflammation in Depression

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Abstract

The article discusses evolving pharmacological strategies for addressing the neuroinflammation in depression, highlighting its role in major depressive disorder. Neuroinflammation is linked to neurotransmitter imbalances, hypothalamic-pituitary-adrenal axis dysregulation and impaired neurogenesis. Key treatments explored include anti-inflammatory agents such as N-acetylcysteine, toll-like receptor (TLR) inhibitors and cytokine blockers like anti-interleukin-6 and tumour necrosis factor alpha (TNF-α) agents. Glutamate modulation, antioxidants and omega-3 fatty acids are also examined for their therapeutic efficacy. The article emphasises the need for combination therapies and novel approaches like ketamine and microbiome-targeted treatments to combat inflammation-related depression. Despite significant progress, further research is needed to fully understand the mechanisms and optimise therapeutic strategies.

Key words: Neuroinflammatory diseases; Depression; Depressive disorder, major; Anti-inflammatory agents; Acetylcysteine; Toll-like receptors; Cytokines; Glutamates; Microbiota; Ketamine.

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Introduction

Depression is characterised by a persistent sense of emptiness, melancholy, or an inability to experience pleasure, often without an apparent cause.[1] According to the World Health Organization (WHO) estimates, depression affects one in five women and twelve men worldwide, making it the second most common condition in terms of morbidity by the next ten years. Not only can adults experience depression, but two percent of school-age children and five percent of teenagers do as well, with the majority of cases being unreported.[2]

Prevalence and impact on health

Major depression was identified by the WHO in 2008 as the third most common cause of disease burden worldwide and by 2030, it was expected to overtake all other causes. Given its wide range of manifestations, erratic course and prognosis and inconsistent response to treatment, it can be difficult for medical practitioners to recognise, diagnose and treat in practice. Over 264 million individuals of all ages have been impacted by the approximately 50 % rise in incident occurrences that has occurred globally over the past 30 years. As stated by the American Psychological Association (2000), Gotlib et al, Solomon et al and other groups, recurrences throughout the life course following an initial depressive episode are especially problematic, with estimates ranging as high as 75–90 %.[3]

Role of neuroinflammation in depression

Neuroinflammation plays a significant role in major depressive disorder (MDD) by interacting with the dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis, serotonin depletion and disruption in adult-generated neuron growth in the hippocampus dentate gyrus.[4] Studies show that anxiety and depression are linked to functional brain networks, particularly involving the medial prefrontal cortex (mPFC) and hyperconnectivity between default network seeds and hippocampus areas. Peripheral cytokine levels are correlated with brain function, wellbeing and cognition, affecting neurons, microglia and astrocytes. Therapeutic cytokines and autoimmune diseases may contribute to depression.[5] Higher levels of interleukin 6 (IL-6) in childhood increase the risk of depression later in life and post-mortem analysis shows microglial activation and neuroinflammation in depression patients' brains. This research has led to the investigation of using non-steroidal anti-inflammatory drugs for treating severe depression.[6]

Biomarkers involved in depression

Biomarkers are essential tools for predicting responses to interventions in psychiatric disorders, with potential markers including those related to inflammation, neuroendocrine, neurotrophic, neurotransmitter and metabolic systems. However, inconsistency in findings across these systems highlights the need for a comprehensive understanding through an "omics" approach. Neuroimaging and protein assays offer valuable insights, while technologies like metabolomics and transcriptomics continue to expand marker identification capabilities. Biomarkers associated with psychiatric disorders include changes in brain anatomy, circadian disruptions, hormonal imbalances, neurotransmitter alterations and genetic variations.[7] Inflammation, in particular, has been linked to MDD, with clinical research showing higher levels of inflammatory markers in MDD patients. Inhibition of pro-inflammatory cytokines has been found to enhance the effects of antidepressant medication, suggesting the importance of considering inflammatory pathways in treatment strategies. Further focused research is necessary to establish the clinical utility of these biomarkers (Figure 1).[8]

Mechanism involved neuroinflammation in depression

MDD aetiology involves the innate immune system determining the involvement of Th1 or Th2 cells and affecting the adaptive immune response. Macrophages initiate a Th1 response with proinflammatory cytokines during infections or tissue damage. Toll-like receptors (TLRs) in macrophages have not been definitively linked

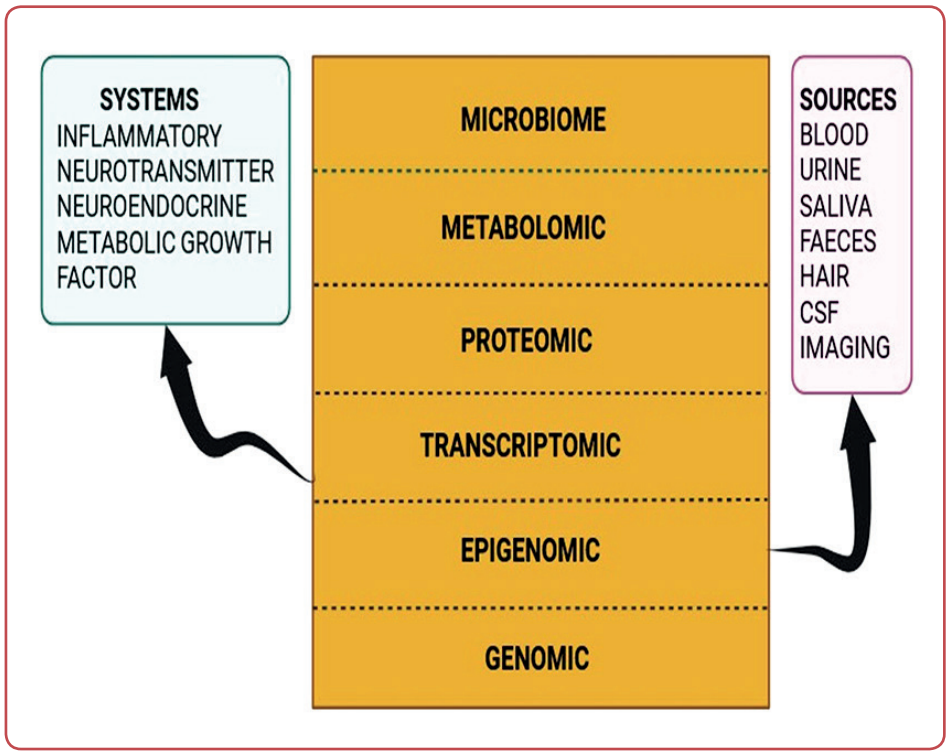

Figure 1: Possible depression biomarkers: biological systems, levels and sources

to MDD. Depressive symptoms can be triggered by lipopolysaccharides and endotoxins activating the peripheral immune system. Chronic physical ailments can lead to chronic inflammation and MDD through persistent microglia activation. Cytokines can cross the blood-brain barrier (BBB) actively or through leaky regions, potentially worsening MDD if the BBB is damaged. This information sheds light on the complex relationship between the immune system and MDD.[9]

Pharmacological targets for neuroinflammation in depression: emerging strategies

(A) Anti- inflammatory agents

1. N- acetylcysteine (NAC)

Due to its anti-inflammatory characteristics, NAC may play a therapeutic function in mental health issues. Research has shown that individuals with depression have dysregulated inflammatory pathways, which may impact neurotransmitter production and exacerbate the disorder's pathology.[10] NAC treatment shows promising results in alleviating symptoms of MDD by targeting various underlying mechanisms such as dysregulation of neurotransmitters, oxidative stress and inflammation. Compared to traditional antidepressants, NAC is associated with fewer side effects and better treatment adherence. Common minor side effects of oral NAC include gastrointestinal discomfort and musculoskeletal issues, but they are generally less severe than those of prescription antidepressants.[11]

2. TLR4 inhibitors

TLR4 is a crucial part of the immune system, recognising pathogens and initiating inflammatory responses. In the hippocampus, it binds to high mobility group box 1 protein (HMGB1), leading to neuroinflammation and depression symptoms.[12] E5564 and TAK-242 target TLR4 signalling to reduce inflammation and alleviate depressive symptoms. Asperosaponin VI extracted from *Radix Dipsaci* in traditional Chinese medicine ameliorates LPS-induced depression-like behaviour in rats by inhibiting the TLR4/NFκB signalling pathway. Flavonoids like apigenin and hesperidin also show antidepressant benefits through blocking TLR signalling (Figure 2).[13]

(B) Cytokine inhibitors

1. Anti-TNF-α agent

New approach studies link between inflammation and depression through medication suppressing TNF-α.[14] Etanercept cannot cross the blood-brain barrier, so peripheral injection only reduces peripheral TNF levels. Central TNF expression is

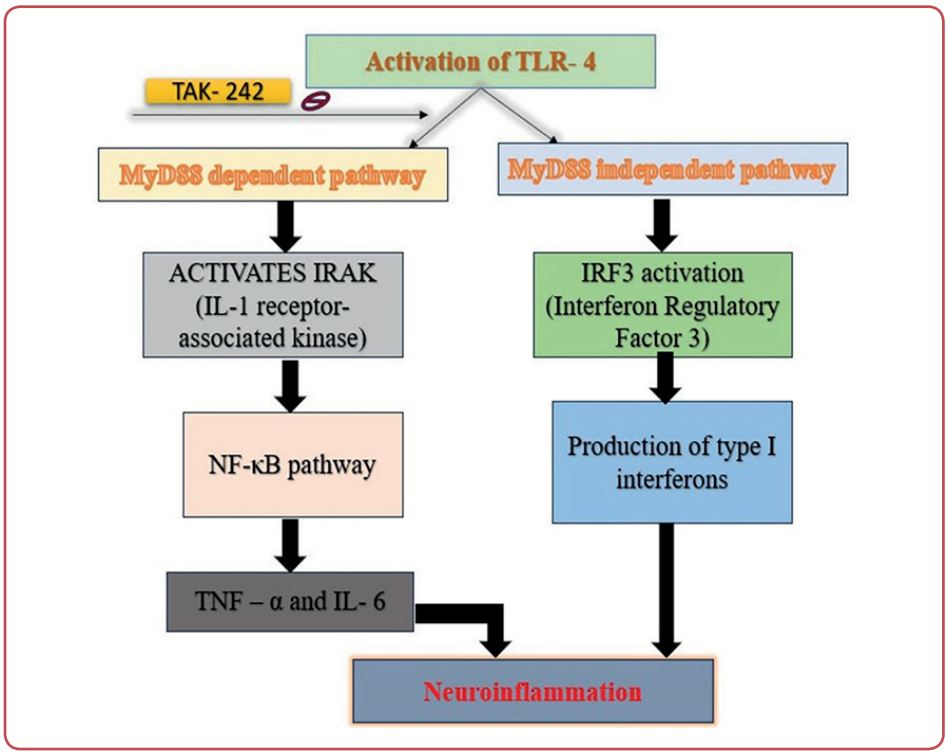

Figure 2: Representation of toll-like receptor 4 (TLR4) inhibitors mechanism

indirectly affected. TNF itself can enter the brain through a receptor-mediated process, leading to increased central inflammation by stimulating microglial cell.[15]

2. Anti-IL-6 agents

In patients with MDD, inflammatory markers like IL-6 are elevated. Differences in cell type expression of IL-6 receptor and gp130 signal transducer contribute to complex inflammatory signalling pathways.[16] Recent research suggests that individuals with MDD may benefit from using cytokine antagonists like tocilizumab to inhibit inflammatory signalling pathways.[17]

3. Anti-IL-1β agents

One important cytokine implicated with depression in the elderly is IL-1β, which is controlled by the P2X7 receptor, a purinergic ATP-gated cation channel of the P2X family.[18] Blocking IL-1β shows promise in treating mood disorders like depression and reducing inflammation in autoimmune diseases. Canakinumab, an anti-IL-1β antibody, is FDA-approved to treat conditions like TNF receptor-associated periodic syndrome and systemic juvenile idiopathic arthritis by neutralising IL-1β.[19]

4. Anti-IL-17 agents

Astrocytes, neurons and microglia in the central nervous system produce IL-17 during disease. It can cause inflammation and damage but also stimulate neurite outgrowth and enhance synaptic function.[20] Secukinumab (*Cosentyx*), an IL-17A antibody, is used for psoriasis and ankylosing spondylitis but may help treat inflammation-related depression. Brodalumab (*Siliq*), an IL-17 receptor antagonist, approved for psoriasis, might also address mood disorders linked to inflammation. Ixekizumab (*Taltz*), another IL-17A inhibitor, shows potential for similar uses, though research is limited.[21]

(C) Glutamate modulation

The potential of modulating glutamate to treat depression, especially in cases of treatment resistance, is supported by research on N-methyl-D-aspartate (NMDA)-receptor antagonists and gamma-aminobutyric acid (GABA) function. The imbalance between excitatory and inhibitory neurotransmitters due to stress and depression further suggests a role for glutamatergic dysfunction in depression.[22] If an adult has been diagnosed with MDD, did not improve after taking at least two antidepressants and is experiencing a moderate to severe major depressive episode, esketamine nasal spray is advised.[23]

1. Emerging pharmacological treatments for glutamate modulation

Anti-inflammatory agents, including neuropeptide Y and drugs like minocycline and celecoxib, have shown promise in treating MDD and other psychiatric conditions by regulating inflammation. AGN-241751, a new NMDA receptor positive allosteric modulator, is being studied as a potential antidepressant, but more research is needed to understand its mechanism of action.[24]

Dextromethorphan-bupropion (Auvelity®): Approved in 2022, this oral combination targets NMDA receptors and modulates glutamate signalling.

Rapastinel (GLYX-13): An investigational drug that functions as a partial agonist at the NMDA receptor's glycine site, showing rapid antidepressant effects in clinical trials.[2]

Apimostinel (NRX-1074): Another NMDA receptor modulator, similar to rapastinel, currently under investigation for its rapid antidepressant effects.

Esmethadone (REL-1017): This drug is an NMDA receptor antagonist being studied for its potential rapid antidepressant effects.[25]

Basimglurant: a metabotropic glutamate receptor 5 (mGluR5) antagonists, which has shown promise in early clinical trial for depression.[26]

2. N-acetylcysteine (NAC)

NAC, derived from cysteine, acts as an antioxidant and precursor to glutathione in cells. It can penetrate the blood-brain barrier, increasing brain GSH levels and impacting brain function.[27] It can restore mitochondrial function, important for mood disorders. The specific pathways for its therapeutic effects are still unclear (Figure 3).[28]

(D) Omega-3 fatty acids

Research suggests that omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), can help alleviate symptoms of depression. However, they have not been proven to be a standalone treatment for MDD.

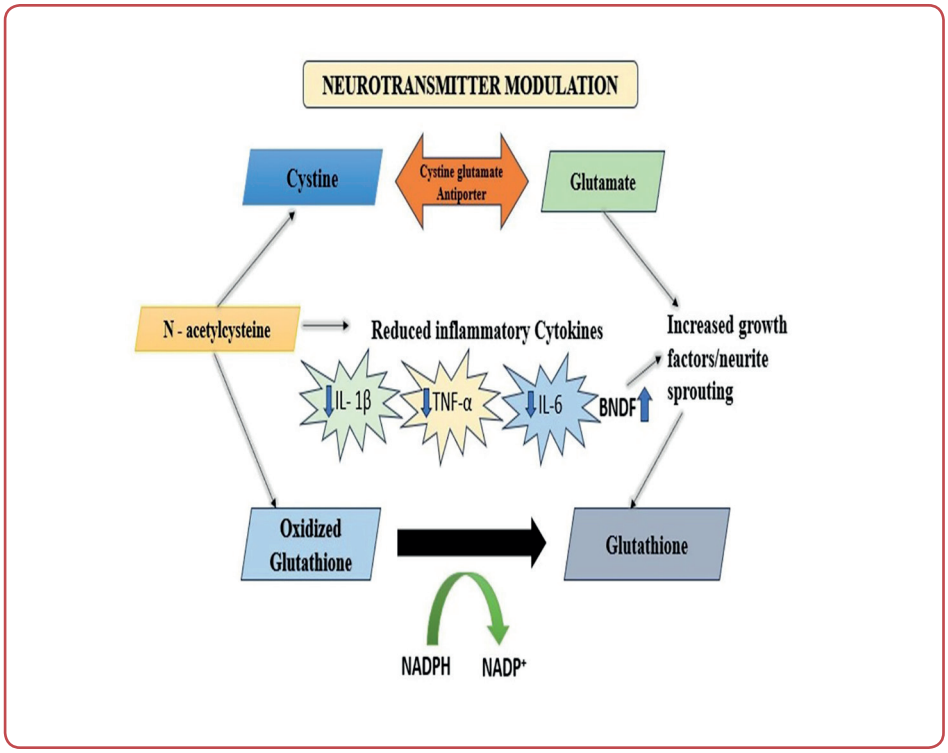

Figure 3: Mechanism of action of N-acetylcysteine

Lower dietary intake of omega-3 fish oil has been linked to increased depressive symptoms, while studies have shown that individuals with depression often have reduced levels of essential fatty acids in their blood.[29]

The biological mechanisms behind the antidepressant effects of omega-3 polyunsaturated fatty acids (PUFAs) remain largely unexplored, several potential explanations are outlined:

a) Neurotransmitter regulations: Long-term deficiency in omega-3 fatty acids can lead to changes in serotonin and dopamine receptors in the brain, potentially contributing to depression. Omega-3 PUFAs have been shown to increase levels of somatotrophin and CSF 5-HIAA, which may help alleviate symptoms of depression.

b) Anti-inflammation and anti-oxidation effects: The study discusses the role of inflammation in depression and the potential benefits of omega-3 PUFAs in treating depression and other illnesses linked to inflammation. The experiment shows omega-3 PUFAs may decrease inflammation in overweight, inactive middle-aged and older individuals.

c) Neuroplasticity effects: Chronic antidepressant treatments boost adult hippocampal neurogenesis, improving neuroplasticity and brain function. EPA supplementation can raise N-acetyl aspartate levels in the cortex, aiding in neuronal integrity. Omega-3 PUFAs stimulate hippocampal neurogenesis and influence neurotrophins, potentially promoting antidepressant effects. A diet rich in EPA and DHA also offers protection against medical conditions linked to antioxidant pathway defects.[30]

(E) Anti-oxidants

1. L-theanine

L-theanine and magnesium play important roles in improving sleep quality through their effects on neurotransmitters. Research suggests that L- theanine can increase relaxation by boosting GABA situations and dopamine and serotonin expression in the brain. also, L- theanine has neuroprotective parcels. A new compound, magnesium L-theanine, has the potential to enhance sleep regulation by combining the benefits of magnesium and L-theanine, although more research is needed to fully understand its effects on sleep and brain activity.[31]

2. B vitamins

B vitamins play a key role in regulating immune functions and are essential for brain health and mood. Scarcities in B12 and folate have been linked to an increased threat of depression. Fur-

ther research is needed to understand how B vitamin supplementation can prevent depressive symptoms.[32]

3. Vitamin D

Calcitriol, also known as neurosteroid hormone, has immunomodulatory and neurotrophic properties. It activates gene expression of tyrosine hydroxylase, involved in synthesising neurotransmitters like serotonin and dopamine. Vitamin D helps regulate calcium and GABA levels, affecting depression onset. It modifies the HPA axis and protects dopamine-releasing neurons when plasma levels surpass a threshold.[33]

4. Polyphenols

Recent research has highlighted the antidepressant properties of plant polyphenols, including tea polyphenols and apigenin flavonoids. These compounds interact with neurotransmitter pathways such as NMDA and GABA to produce sedative and neuroprotective effects. Icariin also shows promise in impacting the serotonergic system to alleviate depression. Additionally, red ginseng saponins, lemon essential oil, pectin and other substances have been linked to reducing depression through their effects on the brain's neurotransmitter systems. Lemon essential oil, for example, modulates dopamine and serotonin levels in specific brain regions to produce antidepressant-like effects.[34]

5. Polysaccharides

Factory polysaccharides can alter neurotransmitters in the brain, modulate synaptic transmission and reduce damage to neurons. They increase situations of serotonin (5-HT), dopamine (DA) and noradrenaline (NE), with antidepressant goods. Polysaccharides can help hyperactivity in the HPA axis, lowering corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and cortisol situations. They also reduce hippocampal neuronal damage. For illustration, *Polygonatum Sibiricum* polysaccharide (PSP) and *Lycium barbarum* polysaccharide (LBP) have shown promising results in regulating HPA axis exertion and dwindling depressive actions.[35]

6. Astaxanthin

Astaxanthin, an antioxidant and carotenoid pigment found in various organisms, has anti-inflammatory and neuroprotective properties. Recent studies suggest it may be beneficial in treating pain by targeting the p38 pathway. Earlier research shows it reduces inflammation through the Nrf2/HO-1 and MAPK pathways and may alleviate fibromyalgia symptoms by blocking NLRP3.[36]

8. Resveratrol

Research indicates that resveratrol can increase ATP levels in the hippocampus, boost mitochondrial DNA and enhance SIRT1 and PGC-1α expression, while lowering Na^+-K^+-ATPase and pyruvate levels. It also raises dopamine and serotonin levels in the prefrontal cortex and boosts NPY expression, suggesting it could be effective in treating depression.[37]

(F) Hormonal modulation

1. Thyroid hormone

Research suggests a connection between thyroid function and bipolar disorder, particularly rapid cycling bipolar disorder, indicating that thyroid hormones may influence affective illness.[38] Subclinical hypothyroidism, with high thyroid-stimulating hormone (TSH) levels but normal T3 and T4 levels, is common in treatment-resistant depression. Research is looking into using T3, T4, thyrotropin-releasing hormone (TRH) and TSH as potential treatments for severe depression, with T3 showing promise in accelerating response to antidepressants. T4 has shown some success in rapid-cycling bipolar disorder, but its effectiveness in treating depression is still uncertain. Early studies suggest combining T3 with TCAs may lead to quicker antidepressant response. Limited evidence exists for using T4 as an augmentation agent in MDD.[39]

2. Cortisol modulation (HPA axis)

The pathophysiology of major depression was initially associated with the hyperactivity of the HPA axis and impaired sensitivity to negative feedback regulation. However, recent research suggests a more complex relationship, with chronic hypersecretion from CRH neurons leading to aberrant glucocorticoid receptor (GR) signalling in MDD. Subclinical hypothyroidism, characterized by high TSH levels but normal T3 and T4 levels, is common in treatment-resistant depression. T3 has shown promise in accelerating response to antidepressants, while T4's effectiveness in treating depression is still uncertain. Combining T3 with TCAs may lead to quicker antidepressant response, but limited evidence supports using T4 as an augmentation agent in MDD. Antidepressants like selective serotonin reuptake inhibitors

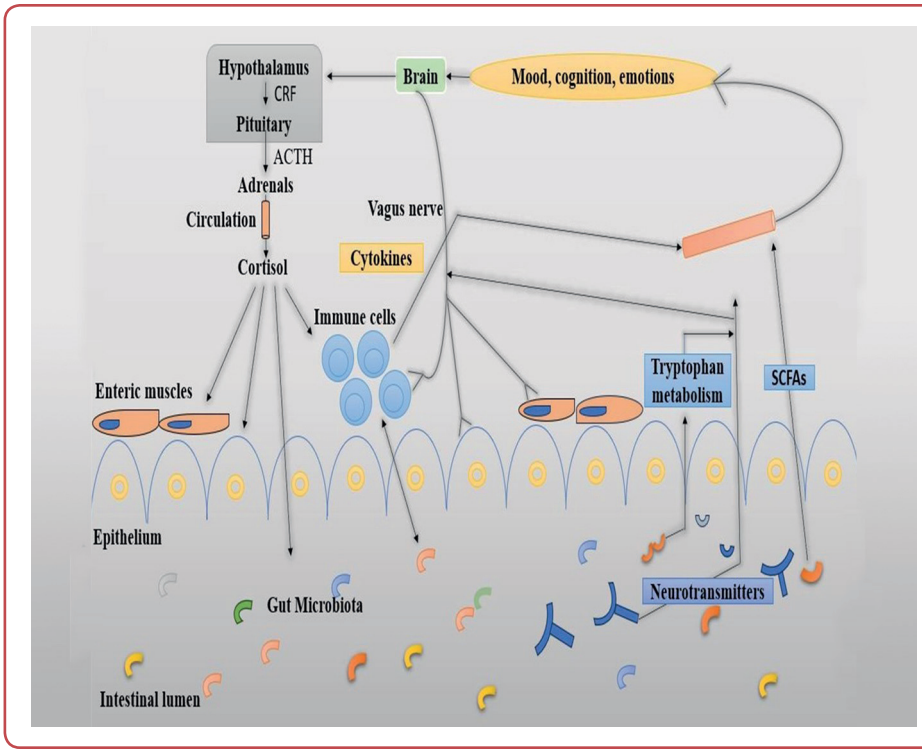

Figure 4: Pathways that facilitate communication in both directions between the brain and the gut bacteria

(SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) can increase cortisol levels, while mirtazapine may decrease cortisol levels by inhibiting CRH release. Cortisol levels tend to normalize with long-term antidepressant treatment, but their decrease doesn't always correlate with therapeutic response.[40]

3. Microbiome based therapies

Chronic stress in adults has been found to significantly impact the composition of the gut microbiota. Individuals exposed to prolonged psychosocial stress show a decrease in *Bacteroides spp* and an increase in *Clostridium spp* levels in the caecum. This stress also leads to higher levels of CCL2 and IL-6 in the blood, signalling immune activation. Certain bacterial genera, such as *Dorea spp, Pseudobutyri vibrio spp* and *Coprococcus spp*, have been linked to these stress-induced changes. Additionally, chronic stress can lead to a leaky intestinal barrier, increasing levels of immunomodulatory bacterial components in the bloodstream. Probiotics have been shown to counteract these effects, particularly by preventing HPA axis activation and inhibiting barrier leakiness. Research supports the importance of the gut-brain axis in regulating the stress response.[41] Recent research has emphasised the importance of gut microbiota in the management of MDD. Investigating the impact of alterations in gut microbiota on the gut-brain axis can provide valuable insights into the efficacy of SSRIs in treating depression. Serotonin, influenced by gut microbiota, plays a crucial role in the onset and management of depression.

4. Lactobacillus benefits to the digestive tract

Manipulating gut flora can be an effective treatment for depression, as *Lactobacillus bacteria* found in the gut microbiota have been found to positively impact MDD patients by influencing serotonin synthesis and reducing inflammation. Research on the synergistic effects of probiotics and SSRIs could lead to improved treatment plans for MDD (Figure 4).

5. The gut-brain axis

The vagal nerve connects the brain to the digestive system, impacting mood, serotonin levels and brain-derived neurotrophic factor (BDNF) levels in the hippocampus. Disruptions in vagal nerve communication can affect BDNF levels, which are crucial for neuron development. Gut bacteria may also play a role in controlling BDNF levels. Further research on this topic is needed to understand its impact on brain function and cognition.[42]

Other potential compounds

Lysergic acid diethylamide (LSD)

LSD, a highly addictive psychedelic, has poten-

tial medical benefits. High dosages of psychedelic drugs like psilocybin or LSD could be used to treat anxiety and mood disorders. Regular use of low doses of LSD may improve mood, wellbeing and cognitive function. However, the long-term benefits of low-dose LSD are not yet fully understood. LSD is globally prohibited and its addictive nature is debated. Some countries allow its medicinal use and for scientific research. The primary medium of LSD involves the activation of anterior cortical glutamate transmission through the stimulation of 5- HT2A receptors. LSD binds more strongly to 5-HT2A receptors compared to other hallucinogens and also affects 5-HT1 receptors, potentially enhancing the effects of other drugs. Further research is needed to understand the specific effects of LSD on humans compared to other hallucinogens.[43]

3,4-methylenedioxymethamphetamine (MDMA)

MDMA functions differently from traditional antidepressants by primarily acting as a monoamine release and reuptake inhibitor. It increases serotonin levels at the synaptic cleft, with lesser effects on norepinephrine and dopamine. MDMA-assisted therapy is being explored as a new approach in treating mental illnesses, including depression.[44]

Therapeutic process in MDMA involves an eight-hour remedy session, during which individualities wear an eye mask and headphones while lying down. A therapist provides support as the individual experiences a range of emotions, from euphoria to anxiety. MDMA is used to help access difficult emotions and memories, enhancing communication and promoting discovery of unexpressed thoughts and feelings. The therapist helps the individual integrate their experience and develop coping strategies. Further research is needed to understand the full potential of this therapy.[45]

N,N-dimethyltryptamine (DMT)

This study examines the impact of DMT on neuroplasticity, suggesting that DMT could aid in creating new neural connections, improving learning and memory and assisting in brain injury recovery. DMT and psilocybin partake a common medium of action on 5- HT2A receptors.[46]

Combination therapies

Combination therapies with multiple antidepressants are effective for treating acute depression. Bupropion (*Auvelity*) is now FDA-approved for severe depressive disorder in adults. A new fast-acting oral therapy option is the dextromethorphan-bupropion combination pill, but the short half-life of dextromethorphan limits its effectiveness. Bupropion competitively inhibits metabolism, extending dextromethorphan's half-life for sustained action on NMDA receptors.[47]

Current approaches to treating MDD and associated challenges

Treatment for MDD typically involves a combination of psychological therapies and pharmacological interventions. SSRIs and monoamine oxidase inhibitors are commonly used antidepressants, with remission rates ranging from 36 % to 67 %. However, some patients do not respond well to medication and experience adverse effects. Non-pharmacological options like cognitive behavioural therapy (CBT), exercise, yoga and acupuncture have shown promise in reducing depressive symptoms by improving emotional regulation, reducing oxidative stress and regulating neurotransmitters.[48]

Future directions for monoamine systems research

Future research in depression will examine the role of monoamines within a genetic-neurochemical-environmental framework. Interactions between serotonin, dopamine and norepinephrine are crucial in depressive pathology, involving brain regions like the hippocampus. Gene-environment studies will explore genetic variations in susceptibility to depression. Research will also look into developing "triple" reuptake inhibitors targeting all three monoamines, as well as investigating interactions with other neurochemical systems through functional imaging and genetic investigations, leading to more personalised therapeutic approaches for depression.[49]

Approved and investigational drugs

The examination of authorised medications shows the rise of pharmacological groups like NMDA antagonists and GABA modulators. Brexanolone and zuranolone are FDA-approved GABA modulators for postpartum depression treatment, while esketamine and dextrometho-

rphan/bupropion are used for MDD and its treatment-resistant variants. New combinations of medications like naloxone and samidorphan with buprenorphine are being tested, but are only moderately effective. GABA modulators represent a departure from the traditional serotonin-norepinephrine-dopamine depression theory, offering unique pharmacological activity. Ganaxolone and zuranolone are being studied for MDD, with positive remission rates, while esketamine has shown promising results in treating treatment-resistant depression. The majority of depression treatments are still experimental, highlighting the need for further clinical trials beyond conventional options.[50]

Conclusion

Evolving approaches in pharmacological methods to address neuroinflammation in depression show an increasing comprehension of intricate pathogenesis of MDD. Neuroinflammation is important in depression as it interacts with key neurobiological systems such as depletion of neurotransmitters, dysregulation of HPA axis and variations in neurogenesis. The advancement of anti-inflammatory drugs, such as NAC, blockers of cytokines and regulators of immune pathways like TLR4 and IL6, shows potential in treating depression. Furthermore, the potential for alleviating depressive symptoms has been demonstrated through various mechanisms, including glutamate modulation and the utilisation of antioxidants, omega-3 fatty acids and polyphenols.

The therapy options for MDD are constantly changing along with the development of new drugs such as ketamine, esketamine and MDMA, providing quick relief for symptoms, especially for those who do not respond well to other treatments. Additionally, the connection between the gut - brain, as well as therapies focused on the microbiome, show the promise of addressing inflammation and gut issues related to stress.

In general, although these new methods show promise for better management of depression, especially for cases that are resistant to treatment, more research is necessary to fully understand how they work and enhance their use in clinical settings. Further investigation into combining therapies, identifying biomarkers and tailoring treatment plans based on individual needs will improve the efficacy of depression treatments, possibly leading to better outcomes and patient's quality of life.

Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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References

1. Depression (major depressive disorder) [Internet]. Mayo Clinic. [Cited: 1-Jan-2025]. Available at: https://www.mayoclinic.org/diseases-conditions/depression/symptoms-causes/syc-20356007.
2. Iyer K, Khan Z. Depression – a review. Res J Recent Sci. 2012;1(4):79-87.
3. Monroe SM, Harkness KL. Major depression and its recurrences: life course matters. Annu Rev Clin Psychol. 2022;18:329–57. doi: 10.1146/annurev-clinpsy-072220-021440.
4. Troubat R, Barone P, Leman S, Desmidt T, Cressant A, Atanasova B, et al. Neuroinflammation and depression: A review. Eur J Neurosci. 2021 Jan;53(1):151-71. doi: 10.1111/ejn.14720.
5. Guo B, Zhang M, Hao W, Wang Y, Zhang T, Liu C. Neuroinflammation mechanisms of neuromodulation therapies for anxiety and depression. Transl Psychiatry. 2023 Jan 9;13(1):5. doi: 10.1038/s41398-022-02297-y.
6. Malhi GS, Mann JJ. Depression. Lancet. 2018 Nov 24;392(10161):2299-312. doi: 10.1016/S0140-6736(18)31948-2.
7. Strawbridge R, Young AH, Cleare AJ. Biomarkers for depression: recent insights, current challenges and future prospects. Neuropsychiatr Dis Treat. 2017 May 10;13:1245-62. doi: 10.2147/NDT.S114542.
8. Schmidt HD, Shelton RC, Duman RS. Functional biomarkers of depression: diagnosis, treatment, and pathophysiology. Neuropsychopharmacology. 2011 Nov;36(12):2375-94. doi: 10.1038/npp.2011.151.
9. Patel A. Review: the role of inflammation in depression. Psychiatr Danub. 2013 Sep;25 Suppl 2:S216-23. PMID: 23995180.
10. Hans D, Rengel A, Hans J, Bassett D, Hood S. N-Acetylcysteine as a novel rapidly acting anti-suicidal agent: A pilot naturalistic study in the emergency setting. PLoS One. 2022 Jan 28;17(1):e0263149. doi: 10.1371/journal.pone.0263149.
11. Russell SE, Skvarc DR, Mohebbi M, Camfield D, Byrne LK, Turner A, et al. The impact of N-acetylcysteine on major depression: qualitative observation and mixed methods analysis of participant change during a 12-week randomised controlled trial. Clin Psychopharmacol Neurosci. 2023 May 30;21(2):320-31. doi: 10.9758/cpn.2023.21.2.320.
12. Wei J, Zhang Y, Li H, Wang F, Yao S. Toll-like receptor 4: A potential therapeutic target for multiple human diseases. Biomed Pharmacother. 2023 Oct;166:115338. doi: 10.1016/j.biopha.2023.115338.
13. Souza-Junior FJC, Cunha LC, Lisboa SF. Toll-like receptor 4 in the interface between neuroimmune response and behavioral alterations caused by stress. Explor Neuroprotective Ther 2022;182–209. doi: 10.37349/ent.2022.00028.
14. Argolo FC, Cavalcanti-Ribeiro P, Netto LR, Quarantini LC. Prevention of posttraumatic stress disorder with propranolol: A meta-analytic review. J Psychosom Res. 2015 Aug;79(2):89-93. doi: 10.1016/j.jpsychores.2015.04.006.
15. Brymer KJ, Romay-Tallon R, Allen J, Caruncho HJ, Kalynchuk LE. Exploring the potential antidepressant mechanisms of TNFα antagonists. Front Neurosci. 2019 Feb 11;13:98. doi: 10.3389/fnins.2019.00098.
16. Hodes GE, Ménard C, Russo SJ. Integrating Interleukin-6 into depression diagnosis and treatment. Neurobiol Stress. 2016;4:15–22. doi: 10.1016/j.ynstr.2016.03.003.
17. Knight JM, Costanzo ES, Singh S, Yin Z, Szabo A, Pawar DS, et al. The IL-6 antagonist tocilizumab is associated with worse depression and related symptoms in the medically ill. Transl Psychiatry. 2021 Jan 18;11(1):58. doi: 10.1038/s41398-020-01164-y.
18. Farooq RK, Asghar K, Kanwal S, Zulqernain A. Role of inflammatory cytokines in depression: Focus on interleukin-1β. Biomed Rep. 2017 Jan;6(1):15-20. doi: 10.3892/br.2016.807.
19. Sardar M, Zia K, Ashraf S, Malik HN, Jabeen A, Khan KM, et al. Interface inhibitory action on Interleukin-1β using selected anti-inflammatory compounds to mitigate the depression: A computational investigation. Comput Biol Chem. 2022 Dec;101:107774. doi: 10.1016/j.compbiolchem.2022.107774.
20. Bliźniewska-Kowalska K, Halaris A, Gałecki P, Gałecka M. Role of interleukin 17 (IL-17) in the inflammatory hypothesis of depression. J Affect Disord Rep. 2023;14:100610. doi: 10.1016/j.jadr.2023.100610.
21. Mutoh T, Kudo M, Tsukada A. Ixekizumab for brodalumab-induced articular involvement in psoriatic arthritis: beyond IL-17A inhibition. Rheumatol Int. 2023;43:1559–61. doi: 10.1007/s00296-023-05329-y.
22. McIntyre RS, Jain R. Glutamatergic modulators for major depression from theory to clinical use. CNS Drugs. 2024;38:869–90. doi: 10.1007/s40263-024-01114-y.
23. Vasiliu O. Esketamine for treatment-resistant depression: A review of clinical evidence (Review). Exp Ther Med. 2023;25:111. doi: 10.3892/etm.2023.11810.
24. Njenga C, Ramanuj PP, de Magalhães FJC, Pincus HA. New and emerging treatments for major depressive disorder. BMJ. 2024 Jul 8;386:e073823. doi: 10.1136/bmj-2022-073823.
25. Vasiliu O. Investigational drugs for the treatment of depression (part 2): glutamatergic, cholinergic, sestrin modulators, and other agents. Front Pharmacol. 2022 Jun 17;13:884155. doi: 10.3389/fphar.2022.884155.
26. Henter ID, Park LT, Zarate CA. Novel glutamatergic modulators for the treatment of mood disorders: current status. CNS Drugs. 2021;35:527–43. doi: 10.1007/s40263-021-00816-x.
27. Sabrina K. Bradbury-Segal PD. Is N-Acetylcysteine (NAC) effective as psychiatric and neurological treatment? Where does the evidence lie? NEI's Master Psychopharmacol Progr. [Cited: 1-Jan-2025]. Available at: https://cdn.neiglobal.com/content/mpp/articles/at-art-20-04/at-art-20-04.pdf.
28. Hasebe K, Gray L, Bortolasci C, Panizzutti B, Mohebbi M, Kidnapillai S, et al. Adjunctive N-acetylcysteine in depression: exploration of interleukin-6, C-reactive protein and brain-derived neurotrophic factor. Acta Neuropsychiatr. 2017 Dec;29(6):337-46. doi: 10.1017/neu.2017.2.

29. Kim J, Park J-S, Bang O-S. Ethanol extract of Kilkyung-baek-san, a traditional herbal formula, induces G0/G1 cell cycle arrest in human lung cancer cell lines. Integr Med Res. 2015;4:178–84. doi: 10.1016/j.imr.2015.07.002.
30. Su K-P, Wang S-M, Pae C-U. Omega-3 polyunsaturated fatty acids for major depressive disorder. Expert Opin Investig Drugs. 2013;22:1519–34. doi: 10.1517/13543784.2013.836487.
31. Dasdelen MF, Er S, Kaplan B, Celik S, Beker MC, Orhan C, et al. A novel theanine complex, mg-l-theanine improves sleep quality via regulating brain electrochemical activity. Front Nutr. 2022 Apr 5;9:874254. doi: 10.3389/fnut.2022.874254.
32. Jahan-Mihan A, Stevens P, Medero-Alfonso S, Brace G, Overby LK, Berg K, et al. The role of water-soluble vitamins and vitamin D in prevention and treatment of depression and seasonal affective disorder in adults. Nutrients. 2024 Jun 17;16(12):1902. doi: 10.3390/nu16121902.
33. Akpınar Ş, Karadağ MG. Is Vitamin D important in anxiety or depression? What is the truth? Curr Nutr Rep. 2022;11;675–81. doi: 10.1007/s13668-022-00441-0.
34. Huang Q, Liu H, Suzuki K, Ma S, Liu C. Linking what we eat to our mood: a review of diet, dietary antioxidants, and depression. Antioxidants (Basel). 2019 Sep 5;8(9):376. doi: 10.3390/antiox8090376.
35. Yang YH, Li CX, Zhang RB, Shen Y, Xu XJ, Yu QM. A review of the pharmacological action and mechanism of natural plant polysaccharides in depression. Front Pharmacol. 2024 Feb 8;15:1348019. doi: 10.3389/fphar.2024.1348019.
36. Zhao L, Tao X, Wang K, Song Y, Zhang B, Yang L, et al. Astaxanthin alleviates fibromyalgia pain and depression via NLRP3 inflammasome inhibition. Biomed Pharmacother. 2024 Jul;176:116856. doi: 10.1016/j.biopha.2024.116856.
37. Shayganfard M. Molecular and biological functions of resveratrol in psychiatric disorders: a review of recent evidence. Cell Biosci. 2020;10:128.doi: 10.1186/s13578-020-00491-3.
38. Bauer M, Whybrow PC. Role of thyroid hormone therapy in depressive disorders. J Endocrinol Invest. 2021;44:2341–7. doi: 10.1007/s40618-021-01600-w.
39. Dwyer JB, Aftab A, Radhakrishnan R, Widge A, et al; APA Council of Research Task Force on Novel Biomarkers and Treatments. Hormonal treatments for major depressive disorder: state of the Art. Am J Psychiatry. 2020 Aug 1;177(8):686-705. doi: 10.1176/appi.ajp.2020.19080848.
40. Nandam LS, Brazel M, Zhou M, Jhaveri DJ. Cortisol and major depressive disorder-translating findings from humans to animal models and back. Front Psychiatry. 2020 Jan 22;10:974. doi: 10.3389/fpsyt.2019.00974.
41. Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nat Rev Neurosci. 2012;13:701–12. doi: 10.1038/nrn3346.
42. Irum N, Afzal T, Faraz MH, Aslam Z, Rasheed F. The role of gut microbiota in depression: an analysis of the gut-brain axis. Front Behav Neurosci. 2023 Jun 2;17:1185522. doi: 10.3389/fnbeh.2023.1185522.
43. Okumuş B, Metin A, Kariper İA. Understanding the effects of lysergic acid diethylamide and the importance of its prevention. Heal Sci Rev. 2023;8:100107. doi: 10.1016/j.hsr.2023.100107.
44. Kvam TM, Goksøyr IW, Stewart LH, Repantis D, Røssberg JI, Andreassen OA. Study protocol for "MDMA-assisted therapy as a treatment for major depressive disorder: A proof of principle study". Front Psychiatry. 2022 Oct 26;13:954388. doi: 10.3389/fpsyt.2022.954388.
45. The use of MDMA for the treatment of depression. [Internet]. Thrive. [Cited: 1-Jan-2025]. Available at: https://thriveketamine.com/the-use-of-mdma-for-the-treatment-of-depression/.
46. Colosimo FA, Borsellino P, Krider RI, Marquez RE, Vida TA. The clinical potential of dimethyltryptamine: breakthroughs into the other side of mental illness, neurodegeneration, and consciousness. Psychoactives. 2024;3(1):93–122. doi: 10.3390/psychoactives3010007.
47. McCarthy B, Bunn H, Santalucia M, Wilmouth C, Muzyk A, Smith CM. Dextromethorphan-bupropion (Auvelity) for the Treatment of Major Depressive Disorder. Clin Psychopharmacol Neurosci. 2023 Nov 30;21(4):609-16. doi: 10.9758/cpn.23.1081.
48. Riveros ME, Ávila A, Schruers K, Ezquer F. Antioxidant biomolecules and their potential for the treatment of difficult-to-treat depression and conventional treatment-resistant depression. Antioxidants (Basel). 2022 Mar 11;11(3):540. doi: 10.3390/antiox11030540.
49. Holtzheimer PE 3rd, Nemeroff CB. Future prospects in depression research. Dialogues Clin Neurosci. 2006;8(2):175-89. doi: 10.31887/DCNS.2006.8.2/pholtzheimer.
50. Namiot ED, Smirnovová D, Sokolov AV, Chubarev VN, Tarasov VV, Schiöth HB. Depression clinical trials worldwide: a systematic analysis of the ICTRP and comparison with ClinicalTrials.gov. Transl Psychiatry. 2024 Jul 31;14(1):315. doi: 10.1038/s41398-024-03031-6.