Decoding Major Depressive Disorder: A Comprehensive Review of Neurobiological Pathways, Biomarker Signatures, and Therapeutic Advances

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DOI: https://doi.org/10.51244/IJRSI.2026.1305000231

Received: 13 May 2026; Accepted: 18 May 2026; Published: 11 June 2026

ABSTRACT

Major depressive disorder (MDD) is a common and serious mental health disorder that arises from a complex combination of biological factors. Despite extensive scientific progress, the exact mechanisms responsible for its development are not entirely understood. Several interrelated processes—including imbalances in monoamine neurotransmitters, dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis, impaired neurogenesis and neuroplasticity, mitochondrial abnormalities, chronic neuroinflammation, and genetic as well as epigenetic influences—play important roles in the onset and continuation of depressive symptoms. Additionally, disturbances in glutamate and GABA signalling, alterations within the gut-brain axis, disruption of circadian rhythms, and defects in synaptic communication further contribute to the disorder's complexity. Recognition of these mechanisms has guided the advancement of treatment strategies. While conventional therapies such as pharmacological antidepressants and psychotherapy continue to be widely used, innovative options—including ketamine-based treatments, neuromodulation techniques, anti-inflammatory agents, and therapies targeting the microbiome—are emerging as promising alternatives. This review summarizes the key biological pathways implicated in depression and examines both established and evolving therapeutic approaches designed to improve outcomes and support long-term patient recovery.

Keywords: Major depressive disorder, Types of Depression Etiologies, Pathophysiology, Biomarkers, Neuroinflammation

INTRODUCTION

Depression is a prevalent affective disorder worldwide. Major depressive disorder (MDD) is one of the most common mood disorders, affecting nearly 350 million people globally and accounting for approximately 4.4% of the world population (World Health Organization, 2017). It ranks among the leading causes of global disease burden and is projected to become the second most prevalent disorder by 2030, thereby imposing a substantial socioeconomic burden on healthcare systems and society (Malhi and Mann, 2018). Furthermore, studies have predicted a marked rise in the prevalence of depressive disorders following the COVID-19 pandemic (Santomauro et al., 2021).

Depression is a psychiatric disorder characterized by psychological, behavioural, and physiological symptoms, including persistent low mood, diminished interest or pleasure in activities, impaired concentration, disturbances in appetite and sleep, cognitive dysfunction, feelings of worthlessness or excessive guilt, and suicidal ideation (Knol et al., 2006). These symptoms severely impair quality of life and contribute to MDD being recognized as one of the leading causes of disability worldwide (World Health Organization, 2023). The public health consequences of depression are extensive and include increased healthcare utilization, absenteeism, reduced productivity, and a heightened risk of suicide, particularly among young adults (Siu et al., 2016).

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), a diagnosis of major depressive disorder (MDD) requires the presence of depressed mood and/or a marked loss of interest or pleasure for at least two weeks, accompanied by additional symptoms such as disturbances in sleep, appetite,

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XIII Issue V May 2026

and energy levels (American Psychiatric Association, 2013). Antidepressant therapy is commonly prescribed; however, nearly half of affected individuals fail to achieve remission following first-line pharmacological treatment, emphasizing the urgent need for more effective and targeted therapeutic approaches (Caldiroli et al., 2021).

Recent advances in neuroimaging research have identified significant structural and functional abnormalities in the brains of individuals with MDD. These include reductions in cortical and subcortical brain volumes, particularly within the hippocampus and amygdala, along with widespread gray matter loss and enlargement of the lateral ventricles (Zhuo et al., 2019; Nolan et al., 2020). Microstructural white matter abnormalities suggesting impaired myelin integrity have also been consistently reported (Hellewell et al., 2019; Schmaal et al., 2020). Furthermore, postmortem studies have demonstrated alterations in neuronal and glial cell density and morphology across several brain regions associated with emotional regulation (Stockmeier and Rajkowska, 2004). Changes in the expression of genes related to synaptic transmission and glutamatergic signaling have also been observed, further supporting the involvement of synaptic dysfunction in the pathophysiology of depression (Duric et al., 2013; Li et al., 2021).

TYPES OF DEPRESSION

Table 1: Subtypes of Depression with Core Features, Treatments, Outcomes, and Clinical Limitations

Subtype	Core Features	Common Treatments	Therapeutic Outcomes	Clinical Limitations	References
Recurrent Depression	Involves multiple depressive episodes with a high chance of returning over time	MBCT, CBT	MBCT lowers relapse rates and enhances overall well-being	May not be very effective during severe or acute depressive phases	(Moriarty et al., 2022;) (Kuyken et al., 2008).
Treatment-Resistant Depression	Shows minimal improvement with standard antidepressant medications	Deep brain stimulation (DBS), IV ketone therapy	DBS benefits some patients; ketone therapy offers rapid symptom relief	Expensive, risk of adverse effects, and ketone benefits are short-lived	(Gadot et al., 2022)
Atypical Depression	Marked by excessive sleep, weight gain, and heightened sensitivity to negative experiences	SSRIs, CBT	Both treatments help improve mood patterns and daily functioning	Long-term medication use may produce undesirable side effects	(Gadot et al., 2022),(Guideline Development Panel for the Treatment of Depressive Disorders, 2022).
Seasonal Affective Disorder (SAD)	Symptoms usually appear during autumn and winter months	SSRIs, Light therapy	Generally safe and effective for seasonal mood disturbances	Limited response in individuals without seasonal patterns; may need combination therapy	(Pjrek et al., 2019)
Bipolar Depression	Depressive episodes alternating with	Mood stabilizers (e.g.,	Helps regulate mood and reduce shifts between	Requires ongoing monitoring; potential for significant side	(Riedinger et al., 2023;

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	manic or hypomanic phases	lithium), Clozapine	mania and depression	effects and medical complications	),(Straszek et al., 2022)
Adolescent Depression	Occurs mainly during teenage years; associated with emotional instability and behavioral changes	CBT, Family-based therapy	CBT improves emotional regulation; family therapy strengthens social and interpersonal functioning	Adolescents may show poor treatment adherence; progress influenced by developmental and environmental factors	(Hazell, 2021)
Late-Life (Senile) Depression	Often coexists with chronic physical illnesses, isolation, and has a high rate of recurrence	SSRIs, CBT, Psychotherapy	Notable improvement in mood and daily functioning; CBT particularly beneficial	Older adults may have lower adherence and experience more side effects	(Alexopoulos, 2019;)(Jayasekara et al., 2014)

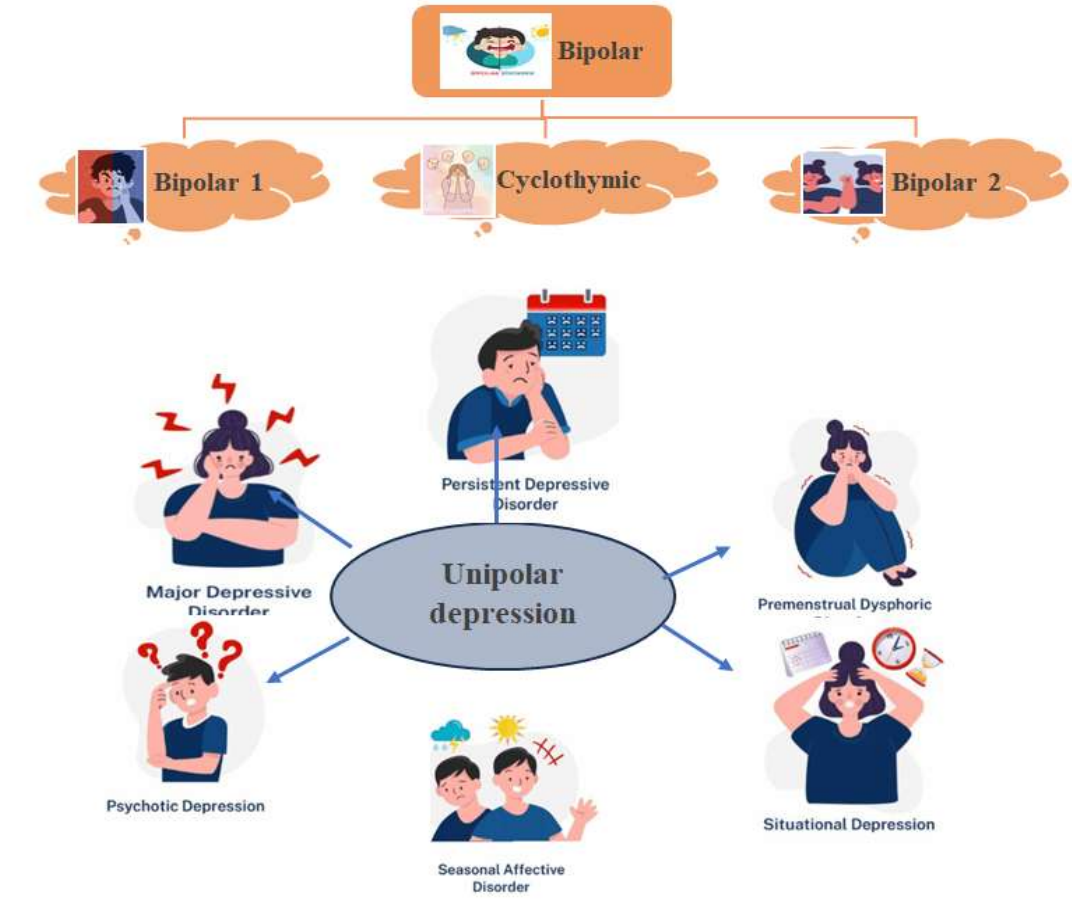

Fig 1- Types Of Depression

Potential Etiologies and Molecular Basis of Depression

The exact cause of Major Depressive Disorder (MDD) has not yet been fully determined; however, current evidence suggests that its development results from the interaction of several pathogenic influences. Beyond psychological elements, MDD has been linked to genetic predisposition, exposure to social and environmental stressors, and the presence of chronic medical conditions. Consequently, the origin of MDD cannot be explained by a single mechanism, but rather through a multifactorial framework.

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Genetic Factors

Most genetic association studies on mood disorders have focused on functional polymorphisms, which are DNA sequence variations capable of influencing gene expression or modifying the biological activity of gene products. These investigations mainly target genes involved in monoaminergic neurotransmission, including the serotonin transporter gene (SLC6A4), serotonin 2A receptor (5-HTR2A), tyrosine hydroxylase (TH), tryptophan hydroxylase 1 (TPH1), and catechol-O-methyltransferase (COMT), all of which play essential roles in serotonin and dopamine synthesis, signaling, and metabolism (Hare et al., 2005).

Depressive disorders have long been recognized to cluster within families, although earlier uncertainty remained regarding whether this pattern resulted from genetic inheritance or shared environmental influences. Current evidence supports the presence of a heritable component in depression. However, individuals do not inherit depression directly; rather, they inherit a genetic susceptibility that increases vulnerability to developing the disorder. Consequently, having a close relative with clinical depression elevates the likelihood of experiencing depression, although environmental stressors and life events remain critical contributing factors (Wells et al., 2002; Williams et al., 2008).

Stress

Stress, particularly during early stages of life, is considered one of the strongest risk factors for major depressive disorder (MDD) (Holsboer and Ising, 2010). Chronic stress contributes to numerous depressive symptoms and can induce both structural and functional alterations in neuronal circuits involved in emotional regulation (McEwen et al., 2016). The hypothalamic–pituitary–adrenal (HPA) axis plays a central role in the physiological stress response and is normally regulated through glucocorticoid-mediated negative feedback acting on glucocorticoid receptors (GRs). Long-term glucocorticoid exposure influences gene expression through nuclear GRs and may induce epigenetic modifications associated with chronic or early-life stress. Moreover, glucocorticoid receptors themselves are subject to epigenetic regulation (Daskalakis et al., 2022).

Many individuals with depression exhibit elevated cortisol levels, HPA axis hyperactivity, and impaired feedback inhibition (Keller et al., 2017). These findings have encouraged the development of stress-targeted therapeutic strategies, including corticosteroid synthesis inhibitors, glucocorticoid receptor antagonists, corticotropin-releasing hormone receptor blockers, tryptophan 2,3-dioxygenase (TDO) inhibitors, and FKBP51 antagonists. Since HPA axis dysfunction is not present in all patients with depression, baseline neuroendocrine assessments may help identify individuals most likely to benefit from such therapies (Menke, 2019). The glucocorticoid receptor antagonist mifepristone has also demonstrated promising therapeutic effects in patients with psychotic depression (Block et al.).

Comorbidity Factors

The presence of multiple physical and psychological comorbidities in individuals with depression highlights the close relationship between mental and physical health, thereby contributing to a broader understanding of major depressive disorder (MDD). Depression is associated with an increased risk of several medical conditions, including neurodegenerative disorders such as dementia, Alzheimer's disease, and Parkinson's disease, cardiovascular diseases including ischemic heart disease and myocardial infarction, metabolic and endocrine disorders such as obesity and diabetes mellitus, as well as autoimmune diseases (Depression and cardiovascular disease, 2014; Dunbar et al., 2008). The relationship between MDD and these medical conditions is complex and often bidirectional, with each disorder capable of influencing the progression and severity of the other (Fries et al., 2023).

Comorbid conditions substantially increase the social and economic burden associated with depression. A large proportion of healthcare expenditures related to MDD are attributed to the management of associated comorbidities rather than depression alone (Keller et al., 2017; Dong et al., 2015). Furthermore, individuals with MDD generally exhibit reduced life expectancy compared with the general population, and worsening comorbid medical conditions may contribute significantly to this increased mortality risk (Xia et al., 2020; De-Miguel and Trueta, 2005).

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Monoamine Hypothesis

Neurotransmitters are believed to play a fundamental role in the pathophysiology of depression. Serotonin (5-hydroxytryptamine, 5-HT), which is widely distributed throughout the central nervous system, is essential for emotional regulation, and its deficiency has been associated with depression, anxiety, phobias, and other psychiatric disorders (Maes et al., 2009). For several decades, the serotonin hypothesis has guided depression research, with studies demonstrating reduced brain serotonin levels and alterations in receptor activity among affected individuals, including increased 5-HT_2 receptor activity and decreased 5-HT_1A receptor function (Deakin and Graeff, 1991). Multiple mechanisms may contribute to impaired serotonergic signaling, including social isolation, increased cortisol levels, and inhibitory effects mediated through 5-HT_2 receptors. Neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and neurotrophin-3 are also involved in maintaining the survival and functional integrity of serotonergic neurons (Xue et al., 2021).

Dopamine (DA), another important neurotransmitter involved in motivation, reward processing, and behavioural regulation, has also been implicated in depression (Babaev et al., 2022). Experimental and clinical studies demonstrate a strong association between depressive symptoms and impaired dopaminergic neurotransmission (Mercuri et al., 2021). Individuals with depression frequently exhibit increased dopamine transporter activity, resulting in enhanced dopamine reuptake into presynaptic neurons and reduced synaptic dopamine availability (Zaghmi et al., 2022).

Glutamate, the principal excitatory neurotransmitter in the brain, plays a critical role in learning, memory, emotional regulation, and synaptic plasticity. Increasing evidence suggests significant dysregulation of the glutamatergic system in depression, including elevated glutamate concentrations in blood, cerebrospinal fluid, and brain tissue, as well as abnormalities in N-methyl-D-aspartate receptor (NMDAR) subunits (Tomasetti et al., 2019). Inhibition of NMDAR activity has been shown to produce antidepressant effects and protect hippocampal neurons from stress-induced structural damage (Musazzi et al., 2013). Ketamine, a well-known NMDAR antagonist, produces rapid antidepressant effects and may enhance α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) signaling through increased AMPAR subunit expression in hippocampal neurons (Kadriu et al., 2019; Beurel et al., 2016). Conventional antidepressants may also exert part of their therapeutic action through modulation of AMPAR-mediated pathways (Gould et al., 2008).

In contrast to glutamate, γ-aminobutyric acid (GABA) serves as the primary inhibitory neurotransmitter in the central nervous system. Although GABAergic neurons are fewer in number compared with glutamatergic neurons, inhibitory neurotransmission is essential for maintaining excitatory–inhibitory balance within the brain. GABAergic pathways are involved in anxiety regulation, motivation, reward processing, and emotional stability. Numerous studies have demonstrated abnormalities in GABAergic signaling among patients with major depressive disorder. Meta-analyses have shown that brain GABA levels are generally reduced in depressed individuals compared with healthy controls, although these levels may normalize following remission (Schur et al., 2016). Additional investigations have reported decreased GABA concentrations in cerebrospinal fluid and reduced expression of GABA-related enzymes, including glutamic acid decarboxylase, within the prefrontal cortex of individuals with depression. Overall, current evidence suggests that depression may arise from disturbances in the balance between glutamatergic and GABAergic neurotransmission, while activation of $GABA_a$ receptor subunits, particularly α_2 and α_3, may produce antidepressant effects. Experimental animal models further support the role of altered GABAergic signaling in the development of depression-like behaviours (Ren et al., 2016).

Hypothalamic–Pituitary–Adrenal Axis

In this section, we provide a concise and simplified overview of the intricate regulation of the hypothalamic–pituitary–adrenal (HPA) axis. As its name suggests, the HPA axis operates through a feedback circuit involving the hypothalamus, pituitary gland, and adrenal glands (Figure 1). Beyond these core components, several brain regions—including the hippocampus, amygdala, bed nucleus of the stria terminalis (BNST), and paraventricular nucleus (PVN)—play key modulatory roles in controlling HPA axis activity.

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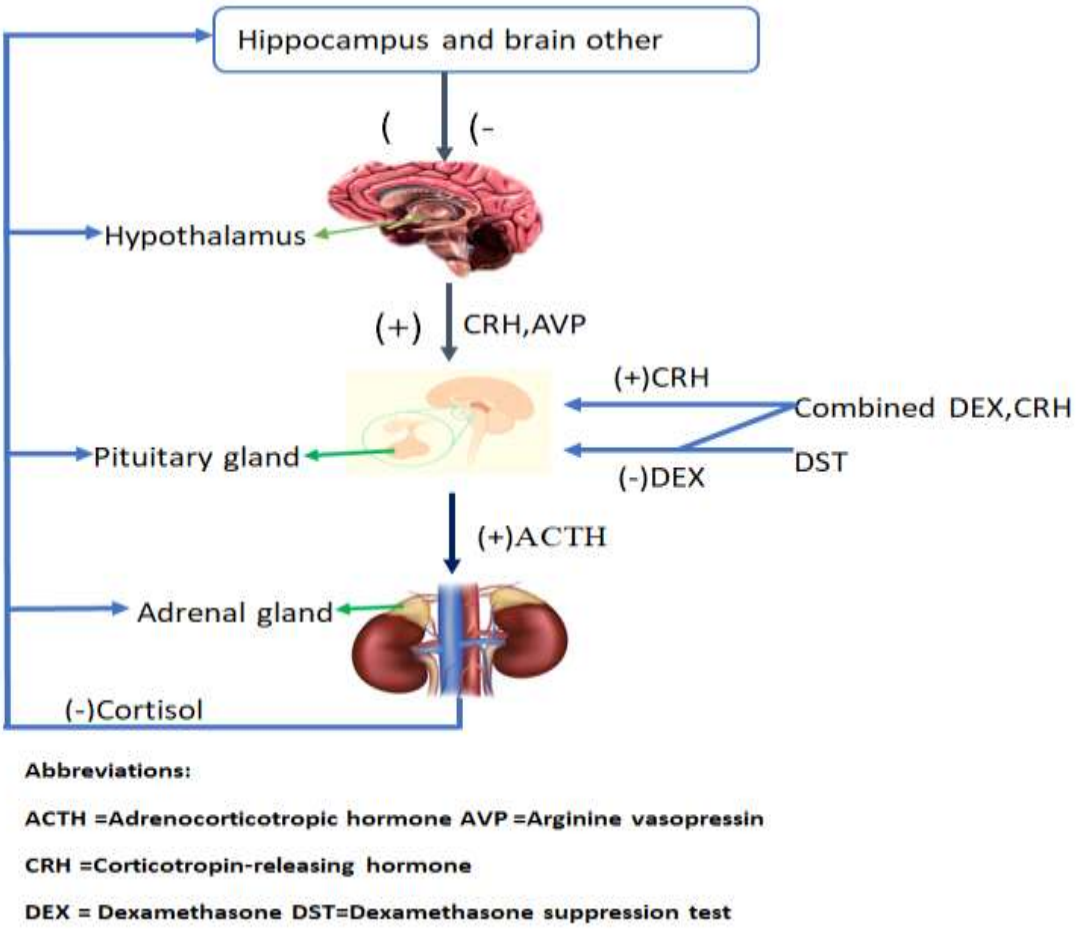

FIG 2 -Schematic Representation of the Hypothalamic–Pituitary–Adrenal (HPA) Axis in Major Depressive Disorder

When an individual experiences physical or psychological stress, the hypothalamic–pituitary–adrenal (HPA) axis becomes activated. In response, the hypothalamus releases corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), which stimulate the pituitary gland to secrete adrenocorticotropic hormone (ACTH). CRH, also referred to as corticotropin-releasing factor (CRF), is a 41–amino-acid peptide widely distributed throughout the central nervous system and serves as a major mediator of the mammalian stress response. After binding to receptors in the pituitary gland, CRH promotes ACTH release. (Coplan et al., 1996)

Once released into the bloodstream, ACTH travels to the adrenal cortex, where it stimulates the synthesis and secretion of cortisol. Cortisol is the primary glucocorticoid hormone in humans and other primates, whereas corticosterone predominates in rodents such as rats. In circulation, most cortisol remains bound to corticosteroid-binding globulin, while only the free fraction can interact with intracellular receptors.

Cortisol acts through two principal receptor types. Type I receptors, also known as mineralocorticoid receptors, possess a high affinity for cortisol and are saturated before activation of type II or glucocorticoid receptors occurs. This receptor-binding pattern differs from several synthetic glucocorticoids, including prednisone and dexamethasone, which preferentially bind glucocorticoid receptors. (de Kloet et al., 1990; de Kloet, 1995)

The HPA axis is regulated through negative feedback mechanisms in which cortisol suppresses further hormone release from both the pituitary gland and hypothalamus. Two major forms of feedback regulation have been described. The first is concentration-dependent feedback at the pituitary level, while the second is rapid or “fast” feedback mediated through receptor actions in the hypothalamus and hippocampus. (Dallman and Yates, 1969; Young et al., 1991)

HPA axis function is commonly assessed using neuroendocrine challenge tests. The dexamethasone suppression test (DST) is one of the most widely used methods. In this test, dexamethasone is administered in the evening,

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and cortisol levels are measured the following day. Under normal conditions, dexamethasone suppresses cortisol secretion through negative feedback. Failure to suppress cortisol secretion, commonly termed "DST non-suppression," has frequently been associated with hypercortisolemia and depressive disorders. The combined dexamethasone/CRH test, which simultaneously suppresses and stimulates the HPA axis, has also become an important research tool in depression studies. (Young et al., 1991)

Neuroinflammation

Accumulating evidence over the past two decades suggests that inflammation plays a critical role in the pathophysiology of major depressive disorder (MDD). Depression occurs more frequently in individuals with autoimmune and infectious diseases compared with the general population. Moreover, cytokine exposure can induce depressive symptoms even in individuals without a prior history of depression, and these symptoms may improve following antidepressant therapy. (Jeon and Kim, 2017; Miller and Raison, 2016)

Patients with MDD exhibit elevated levels of inflammatory mediators, including proinflammatory cytokines, chemokines, soluble adhesion molecules, and related receptors in both peripheral blood and cerebrospinal fluid. Peripheral inflammatory signals can influence central nervous system immune activity and behavioral responses and may also serve as biomarkers for antidepressant response. Increased tumor necrosis factor-alpha (TNF-α) levels have been observed in untreated MDD patients, with significant reductions following venlafaxine treatment, particularly among treatment responders. (Miller et al., 2002; Mao et al., 2018; Li et al., 2013)

Antidepressant therapies have additionally been shown to reduce circulating levels of IL-6, TNF-α, IL-10, and CCL2, supporting the hypothesis that antidepressants possess anti-inflammatory properties. Untreated patients generally demonstrate elevated inflammatory markers, whereas treatment responders show increased anti-inflammatory cytokine activity compared with nonresponders. Cytokine inhibitors, including monoclonal antibodies, have therefore been proposed as potential antidepressant therapies. (Kohler et al., 2018; Syed et al., 2018; Bavaresco et al., 2020)

Microglia play a central role in neuronal plasticity and the development of depressive pathology. Experimental studies have demonstrated that lipopolysaccharide-induced neuroinflammation increases microglial activation and promotes depressive-like behaviors in mice, accompanied by elevated expression of IL-1, IL-6, and TNF-α within the prefrontal cortex. Selective serotonin reuptake inhibitors have been shown to attenuate these inflammatory changes. Astrocytes are also involved in stress- and inflammation-associated depressive pathology. Sustained activation of microglia and excessive release of proinflammatory mediators may ultimately contribute to depression-like behavior. (Innes et al., 2019; Weng et al., 2019; Virmani et al., 2021; Sochocka et al., 2017)

Neurotrophic Hypothesis of Depression

The determinants of depressive episodes appear to evolve as the disorder progresses. Initial depressive episodes are often associated with significant psychosocial stressors and are considered more reactive in nature, whereas recurrent episodes may arise with minimal external stress and display a more endogenous pattern. (Kessing et al., 2004)

Several studies have demonstrated that reductions in hippocampal volume and structural alterations in other brain regions correlate with the duration and severity of depressive illness. These findings suggest that prolonged or inadequately treated depression may lead to progressive structural brain changes, thereby increasing vulnerability to stress and recurrence of depressive episodes. (Sheline et al., 2003; Hasler et al., 2007; Frodl et al., 2008)

Multiple mechanisms have been proposed to explain brain volume loss in depression, including glucocorticoid-mediated neurotoxicity, glutamate-induced excitotoxicity, impaired neurogenesis, and reduced neurotrophic support. Among these mechanisms, brain-derived neurotrophic factor (BDNF) has received considerable attention. Experimental studies indicate that stress-induced depressive-like behaviors are associated with reduced hippocampal BDNF expression, whereas antidepressant treatment enhances BDNF levels. These

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findings support the neurotrophic hypothesis of depression and highlight the importance of early and effective therapeutic intervention. (Martinowich et al., 2007)

Biomarkers Reflect Alterations Across Multiple Biological Systems and Sources.

Biomarkers reflect alterations across multiple biological systems and sources. Biomarkers represent a rapidly growing field in psychiatric research, offering important insights into the varied biological mechanisms underlying depression. Evidence accumulated to date suggests that biomarkers reflecting the activity of inflammatory, neurotransmitter, neurotrophic, neuroendocrine, and metabolic systems may hold predictive value for both mental and physical health outcomes in individuals with depression; however, substantial heterogeneity and inconsistency across studies limit definitive conclusions (Strawbridge et al., 2017; Jani et al., 2015). Previously published studies highlight the necessity for advanced and integrative research approaches to clarify the role of inflammation in major depressive disorder (MDD) (Paganin and Signorini, 2024). Advances in neuroimaging techniques, genetic profiling, and biochemical analyses have substantially enhanced understanding of the molecular underpinnings of depression (Licinio and Wong, 2020; Coleman et al., 2020), uncovering intricate interactions among neurotransmitter dysregulation, neuroendocrine disturbances, and immune system activation (Taub, 2008).

A range of genetic and epigenetic biomarkers has been linked to depression severity, treatment response, and disease prognosis. Notably, changes in neurotrophic factors such as brain-derived neurotrophic factor (BDNF), along with inflammatory cytokines, have been repeatedly associated with depressive symptomatology (Felger and Lotrich, 2013). These biomarkers not only support improved diagnostic accuracy but also provide opportunities for personalized therapeutic strategies aimed at maximizing treatment efficacy while minimizing adverse effects.

The clinical integration of such biomarkers holds the potential to transform depression management by facilitating early diagnosis, informing treatment selection, and enabling effective monitoring of disease progression. Nevertheless, successful translation into routine clinical practice requires robust validation through large-scale, longitudinal investigations to confirm consistency, reliability, and applicability across diverse populations.

Biomarkers Benefits

In addition to their relative simplicity and lower analytical cost, biomarkers can be assessed repeatedly within shorter timeframes. The development of composite biomarker panels capable of simultaneously detecting multiple proteomic markers, metabolic indicators, growth factors, cytokines, and hormonal signals represents a practical alternative to single-biomarker approaches. Several studies have reported measurable improvements in biomarker profiles among patients with major depressive disorder (MDD) compared with healthy control subjects (Hiles et al., 2010).

Nevertheless, a key limitation in the collection of depression-related biomarkers is the absence of well-defined associations between MDD and co-occurring depressive conditions. Recent evidence suggests that emerging MDD biomarkers may enable reliable identification of growth factors, hormones, cytokines, and proteomic markers within plasma samples. Correspondingly, biomarker platforms can concurrently quantify hormones, growth regulators, and other protein-based indicators, allowing for a more comprehensive assessment that enhances the differentiation of disease states and symptom profiles.

Biomarkers Types

Molecular biomarkers show considerable potential for routine use in clinical psychiatry. Among mental health disorders, major depressive disorder (MDD) has received heightened attention owing to its increasing prevalence and significant contribution to disease burden (Galvão et al., 2021). Despite this interest, MDD remains a biologically diverse condition for which dependable biomarkers to evaluate disease severity, subtype classification, or treatment responsiveness are still lacking. Accumulating evidence indicates that changes in peripheral growth factors, inflammatory cytokines, endocrine signals, and metabolic markers not only mirror the

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underlying pathophysiology of MDD but may also serve as predictors of therapeutic response, highlighting the importance of developing integrated biomarker panels to facilitate diagnosis and individualized treatment strategies (Schmidt et al., 2011).

Depression is a complex, multifactorial disorder resulting from the interaction between genetic susceptibility (nature) and environmental influences (nurture), both of which contribute to biomarker variability. Environmental exposures—including stress, dietary habits, trauma, and lifestyle factors—can induce epigenetic modifications such as DNA methylation, histone alterations, and changes in non-coding RNA expression, thereby regulating gene activity without modifying the DNA sequence itself. In parallel, genetic factors establish an underlying vulnerability by shaping neural function, neurotransmitter systems, and stress-related pathways. Biomarkers thus often capture the dynamic interaction between genetic predisposition and epigenetic regulation, wherein inherited risk is modulated by environmental factors to influence disease onset and progression. Elucidating these interactions is essential for advancing biomarker-based diagnostic and therapeutic approaches in depression.

Growth Factor–Neurogenic Biomarkers

Growth factors are essential for neuronal growth, differentiation, and survival. Although they are not direct genetic or epigenetic markers, their expression is influenced by both processes, particularly through exposure to environmental stress. Thus, alterations in growth factor levels may indicate underlying changes in gene regulation associated with depression.

Brain-derived neurotrophic factor (BDNF) is the most widely studied neurogenic biomarker. Circulating BDNF reflects central levels and is typically reduced in individuals with depression, with greater reductions seen in more severe cases (Autry and Monteggia, 2012). Antidepressant therapy gradually increases BDNF levels, even when symptomatic improvement is not evident. In contrast, pro-BDNF concentrations are elevated in depression and decrease following treatment. Lower BDNF levels have also been reported in diabetes and smoking, both of which are independent risk factors for depression.

Nerve growth factor (NGF) levels are consistently decreased in depressive disorders, correlate with symptom severity, and generally do not change in response to treatment. Similar patterns have been observed for glial-derived neurotrophic factors. Conversely, vascular endothelial growth factor (VEGF) is increased in depression, particularly in treatment-resistant patients, possibly due to inflammatory mechanisms and altered blood–brain barrier integrity. Insulin-like growth factor-1 (IGF-1) and fibroblast growth factor-2 (FGF-2) are also reported to be elevated and tend to decline with treatment, although this finding differs from our results (Duarte et al., 2017).

Neurotransmitters as Biomarkers

The hypothalamic–pituitary–adrenal (HPA) axis is central to the stress response and, although genetically regulated, is strongly influenced by epigenetic changes induced by chronic stress. Therefore, HPA axis biomarkers reflect both genetic susceptibility and environmental exposure.

Depression is commonly associated with HPA axis dysfunction, characterized by elevated basal cortisol, reduced dexamethasone suppression, and increased corticotropin-releasing hormone. Glucocorticoids affect hippocampal neurogenesis, while thyroid and sex hormones also contribute to depressive pathology (Zajkowska et al., 2022).

Cortisol is the most widely studied HPA axis biomarker and can be measured in blood, urine, saliva, or hair. Elevated cortisol levels are consistently observed in depression, including in our initial findings. Hair cortisol reflects long-term stress and may help distinguish depression from other psychiatric disorders, while awakening salivary cortisol shows diagnostic value in adolescents (Fischer et al., 2017).

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Higher cortisol levels predict poorer response to treatment. In contrast, individuals with childhood trauma may show blunted cortisol responses, and atypical depression is associated with reduced cortisol levels, aiding differentiation from melancholic depression.

Immunological Biomarkers

Several immunological biomarkers have been associated with depression, including C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-1β (IL-1β), tumor necrosis factor-α (TNFα), soluble urokinase plasminogen activator receptor (suPAR), 3-nitrotyrosine, and heat-shock protein 70 (HSP70), which are typically measured in blood or serum (Chocano-Bedoya et al., 2014).

One study reported that CRP significantly predicted a shorter time to the onset or relapse/recurrence of depression based on hazard ratio analysis. In contrast, three studies found that TNFα did not significantly predict depression outcomes. The inflammatory marker suPAR was shown to predict a reduced time to the development of major depressive disorder (MDD). Additionally, baseline levels of 3-nitrotyrosine and HSP70 were higher in individuals who later developed MDD compared with those who did not (Pasquali et al., 2017).

Gastrointestinal Biomarkers

Only one study has examined gastrointestinal biomarkers, reporting that children who experienced abdominal symptoms such as nausea or vomiting following tryptophan (L-5HTP) infusion had a higher risk of developing major depressive disorder (MDD) compared with children who did not report these symptoms (Campo et al., 2003).

Metabolic biomarkers

Key biomarkers associated with the metabolic alterations observed in MDD include ghrelin, leptin, high-density lipoprotein (HDL), adiponectin, insulin, albumin, triglycerides, and creatine. The relationship between these metabolic markers and depression has been explored in several previous studies. Compared with healthy controls, patients with depression generally exhibit lower levels of leptin and ghrelin, with antidepressant treatment often contributing to normalization of these levels alongside clinical recovery. Insulin resistance may also be present in depression, although typically to a milder degree (Pg et al., 2011).

Alterations in lipid profiles, particularly fluctuations in HDL cholesterol, have been observed in individuals with poor physical health and in some cases of depression. Additionally, hyperglycaemia and hypoalbuminemia have been reported in depressive disorders. In clinical settings, molecular metabolomics panels can be used to identify biochemical signatures associated with common metabolic diseases. Elevated glucose and lipid-related metabolite patterns have been shown to reliably predict MDD diagnoses, consistent with earlier findings, particularly when analysed using artificial intelligence–based models (Carvalho et al., 2014).

Oxidative stress has also been implicated in the pathophysiology of depression, with evidence suggesting that impaired antioxidant defences contribute to disease mechanisms. Recent studies indicate that individuals with recurrent depression exhibit higher malondialdehyde levels than those experiencing a single depressive episode. Superoxide dismutase (SOD) activity is another marker of oxidative stress under investigation in MDD, with findings showing decreased serum SOD levels or increased erythrocyte SOD activity in depressed patients.

Gut Flora Markers

The concept of gut microbiota as a biomarker for depression has gained increasing support in recent research. Multiple studies have demonstrated distinct alterations in the gut microbial composition of patients with depression compared to healthy individuals (Pennisi, 2019; Naseribafrouei et al., 2014). These alterations include shifts in the relative abundance of specific bacterial taxa and changes in microbiota-derived metabolites associated with depressive symptoms. For instance, patients with major depressive disorder (MDD) show an increased abundance of the genus Bacteroides, while the genera Blautia and Eubacterium are reduced (Yang et al., 2020). At the phylum level, higher proportions of Anaplasma, Aspergillus, and Actinobacteria have been

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reported, alongside a reduction in thick-walled bacterial phyla (Liu et al., 2022). Additional studies have linked gut microbiota alterations with clinical characteristics, inflammatory markers, metabolic parameters, and treatment response in depression (Huang et al., 2019; Trzeciak and Herbet, 2021; Johnson et al., 2021).

Intestinal dysbiosis is considered a key contributor to systemic inflammation. Altered gut microbiota composition reduces the production of short-chain fatty acids, which normally exert anti-inflammatory effects. Furthermore, increased intestinal permeability permits microbial components to translocate into the bloodstream, thereby amplifying systemic inflammatory responses (Suda and Matsuda, 2022).

Despite consistent findings of microbiota alterations, it remains unclear whether these changes are a cause, consequence, or parallel feature of depression. Confounding variables such as diet and medication use, particularly antidepressants, have not been adequately controlled, making causal inference and identification of core pathogenic species challenging.

A major advantage of gut microbiota analysis is its non-invasive nature, which offers promise for diagnostic and prognostic applications. Microbiota-based interventions, including probiotics, prebiotics, and dietary modification, represent an appealing translational strategy. However, the complexity of host–microbiota interactions, high interindividual variability, lack of standardized analytical methods, and unresolved causal relationships remain significant barriers to clinical implementation.

The pathophysiology of depression is increasingly understood as the outcome of dynamic interactions across multiple biological pathways, with evidence converging on three principal axes. Along the gene–environment–epigenetic axis, early-life stressors such as childhood trauma induce abnormal DNA methylation of key genes, including NR3C1, resulting in impaired glucocorticoid receptor function and persistent activation of the hypothalamic–pituitary–adrenal (HPA) axis. Genetic susceptibility factors, such as the 5-HTTLPR risk genotype, further intensify the impact of environmental stress on epigenetic regulation, collectively shaping vulnerability to depression.

Within the neuroendocrine–immune–microbiota axis, chronic HPA axis hyperactivation elevates cortisol levels, which increase intestinal epithelial permeability and facilitate the entry of microbial products, such as lipopolysaccharides, into systemic circulation. This process triggers systemic inflammation, characterized by elevated pro-inflammatory cytokines including IL-6 and TNF-α. These inflammatory mediators subsequently suppress brain-derived neurotrophic factor expression in the hippocampus, impairing neuroplasticity and accelerating structural damage, thereby exacerbating emotional and cognitive dysfunction.

Along the microbiota–metabolism–neuroaxis, gut microbiota imbalance—such as reduced abundance of the Blautia genus—leads to diminished short-chain fatty acid production, weakening immune regulation and indirectly intensifying neuroinflammation. Concurrently, disturbances in peripheral tryptophan metabolism, marked by significantly reduced plasma levels, limit central serotonin synthesis. The degree of tryptophan reduction shows a strong negative correlation with the severity of depressive symptoms.

Neuroendocrine Markers

Neuroendocrine markers play a significant role in depression research. Brain-derived neurotrophic factor (BDNF), which is essential for neuronal growth, differentiation, and survival, is consistently reduced in depressed patients and is linked to impaired neuroplasticity and cognitive dysfunction (Jiang and Salton, 2013). Alterations in plasma amino acid profiles have also been reported in major depressive disorder (MDD). Patients with MDD show reduced levels of Asp, Gly, and GABA and increased nitric oxide, changes that persist despite antidepressant treatment (Lu et al., 2014). Higher dietary intake of branched-chain amino acids is associated with a lower risk of depression, possibly due to their influence on neurotransmitter synthesis via competition at the blood–brain barrier (Koochakpoor et al., 2021). Disturbances in tryptophan, phenylalanine, and tyrosine metabolism may further contribute to MDD pathophysiology. Reduced serum amino acids and antioxidant vitamins have also been observed in unmedicated MDD patients, suggesting their potential as biomarkers (Islam et al., 2020).

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XIII Issue V May 2026

Elevated serum copper levels are associated with depression and may disrupt neurotransmitter regulation. Depressed patients also show reduced antioxidant enzyme activity alongside increased oxidative stress markers, as well as abnormalities in lipid metabolism and cholesterol levels. Serotonin concentrations correlate with disease severity and treatment outcomes in depression (Choi et al., 2022). Dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis leads to abnormal cortisol levels, with childhood trauma, sex differences, and stress responsiveness influencing symptom severity (Sendi et al., 2023). Attenuated dopamine signalling, abnormal thyroid function, and altered thyroid hormone levels are also frequently reported in depression (Mi, 2014).

Although biomarkers such as serum BDNF, cortisol rhythms, and amino acid profiles are relatively easy to measure and show promise for diagnostic or stratification purposes, their clinical utility remains limited by low specificity and high monitoring costs. Inflammatory markers like CRP are accessible but lack diagnostic precision.

LIMITATIONS AND FUTURE DIRECTIONS IN DEPRESSION BIOMARKER RESEARCH

Major Depressive Disorder (MDD) is a multifactorial condition influenced by genetic vulnerability and adverse environmental exposures. Its heterogeneous clinical manifestations and incomplete understanding of underlying biological mechanisms complicate accurate diagnosis and effective treatment. Research in this field is further challenged by the lack of suitable animal models, marked biological and clinical heterogeneity, and the existence of multiple depressive subtypes.

Single biomarkers are generally insufficient for diagnosing MDD due to minimal differences between depressed and healthy populations (Pitsillou et al., 2020). Supporting this, Professor Eun Young Kim reported that a combined panel of six biomarkers achieved only 68% diagnostic accuracy, highlighting the necessity of multi-biomarker approaches (Lee et al., 2016). The high heterogeneity of depressive symptoms and causes presents substantial obstacles for clinical management. For instance, Zhao's longitudinal neuroimaging study identified three distinct depression subtypes with unique clinical features and genetic expression profiles (Chen et al., 2023).

Genome-wide association studies indicate that MDD has a complex polygenic architecture, with numerous variants contributing modest risk, likely reflecting the disorder's diverse symptomatology and etiology. Increasing ancestral and global diversity in genetic research is essential for identifying key risk genes and improving the generalizability of findings (Zhao et al., 2023). Such diversity must be considered when applying biomarkers for diagnosis and treatment planning.

The Research Domain Criteria (RDoC) initiative introduced by the National Institute of Mental Health aims to move beyond symptom-based classification by integrating behavioral and neurobiological dimensions. This framework emphasizes identifying neural mechanisms that enable earlier diagnosis and prediction of treatment response (Carpenter, 2016). Compared with DSM-5 classifications, RDoC offers a more biologically grounded understanding of complex disorders like depression (Patrick and Hajcak, 2016; Auerbach, 2022).

FUTURE PERSPECTIVES

Future research in major depressive disorder (MDD) should focus on integrating neurobiological, genetic, inflammatory, metabolic, and microbiome-based findings to develop a more precise and personalized understanding of depression. Although significant advances have been made in identifying molecular and neurochemical mechanisms, the heterogeneity of MDD continues to limit accurate diagnosis and treatment selection. Future studies should therefore prioritize the development of multi-biomarker panels that combine neuroendocrine, inflammatory, neurotrophic, metabolic, and gut microbiota markers to improve diagnostic accuracy, predict treatment response, and identify disease subtypes.

Advances in genomics, epigenetics, proteomics, metabolomics, and artificial intelligence-based analytical models may enable early detection of depression and facilitate individualized therapeutic strategies. Longitudinal and large-scale multicenter studies across diverse populations are essential to validate biomarker reliability and

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XIII Issue V May 2026

establish clinically applicable standards. In addition, further exploration of the gut–brain axis, neuroimmune signaling, circadian rhythm disturbances, and synaptic plasticity mechanisms may reveal novel therapeutic targets for treatment-resistant depression.

Emerging therapies such as ketamine and other glutamatergic modulators, anti-inflammatory agents, neuromodulation techniques, microbiota-targeted interventions, stem cell–based therapies, and precision psychiatry approaches hold considerable promise for improving long-term outcomes. Integration of the Research Domain Criteria (RDoC) framework with neuroimaging and biomarker profiling may further refine depression classification beyond symptom-based diagnosis, enabling more mechanism-based and patient-centered treatment approaches.

Future research should also emphasize preventive psychiatry by identifying individuals at high risk through genetic, epigenetic, and environmental markers before the onset of clinical symptoms. Such advances could support earlier intervention, reduce disease burden, and improve overall quality of life for patients with MDD.

CONCLUSION

Major depressive disorder is a complex and multifactorial psychiatric illness involving intricate interactions among neurotransmitter dysregulation, neuroendocrine dysfunction, neuroinflammation, impaired neuroplasticity, oxidative stress, metabolic abnormalities, and gut microbiota disturbances. Increasing evidence demonstrates that depression cannot be explained by a single biological pathway; rather, it arises from the convergence of genetic susceptibility, environmental stressors, epigenetic modifications, and systemic physiological alterations.

The growing understanding of neurobiological mechanisms underlying MDD has significantly expanded the scope of potential diagnostic and therapeutic strategies. Biomarkers related to inflammatory cytokines, neurotrophic factors, HPA axis activity, neurotransmitter systems, and metabolic changes offer promising opportunities for early diagnosis, disease stratification, and prediction of treatment response. However, the substantial heterogeneity of depression and the absence of universally reliable biomarkers remain major challenges for clinical translation.

Conventional antidepressants and psychotherapy continue to form the foundation of MDD management, yet many patients fail to achieve complete remission. Consequently, emerging approaches—including ketamine-based therapies, neuromodulation, anti-inflammatory treatments, and microbiome-targeted interventions—represent important advancements in addressing treatment-resistant and biologically diverse forms of depression.

Overall, a deeper understanding of the molecular and neurobiological basis of depression is essential for advancing precision psychiatry and improving patient outcomes. Continued interdisciplinary research integrating neuroscience, immunology, genetics, and biomarker science will be critical for developing more effective, personalized, and mechanism-driven interventions for major depressive disorder.

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