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REVIEW ARTICLE

Emerging biomarkers in major depressive disorder: Diagnostic, prognostic, and therapeutic implications

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Abstract

Recent advancements in biomarker research for the diagnosis, prognosis, and treatment strategies of major depressive disorder (MDD) have yielded significant findings that warrant documentation. The clinical demand for biomarkers persists due to the limited accuracy and efficiency of subjective diagnostic approaches. This review scrutinized research papers related to MDD biomarkers published between January 2011 and till July 2024, focusing exclusively on human studies with statistically significant results. The compiled biomarkers encompass cellular membrane receptors, cytoplasmic organelles, and genomic and epigenomic intranuclear markers. Cell surface molecular receptors implicated in MDD pathogenesis include brain-derived neurotrophic factor (BDNF) receptors, N-methyl D-aspartate receptors (NMDAR), and interleukin (IL) receptors. Endogenous compounds with diagnostic and prognostic potential, such as L-carnitine and alpha-L-carnitine, have also been identified. Transcriptomic biomarkers, including mRNA expression levels of the BDNF, IL-1β, macrophage migration inhibitory factor, and tumor necrosis factor-alpha (TNF-α), have demonstrated utility in MDD management. MicroRNAs (miRNAs), the endogenous molecules that alter the structure of mRNA, show potential for diagnosis and treatment outcome prediction, with miR-221-3p, miR-129-5p, miR-134, and miR-184 emerging as key candidates for MDD monitoring. Long non-coding RNAs (lncRNAs), such as GSK3βAS1, GSK3βAS2, and GSK3βAS3 have been investigated for the evaluation of disease severity and treatment response. Most recently, the pathological role of circular (circRNA) and DNA methylation in MDD has also been documented. The rs155979 polymorphism in the lncRNA NOTHSAT102891 was significantly associated with depression and risk of suicide. The data compiled in this review aim to guide further research in the quest for biomarkers that will improve the management of MDD.

Keywords: Biomarkers; Cell signaling markers; Intranuclear markers; Major depressive disorder

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1. Introduction

Major depressive disorder (MDD), also known as clinical depression, is characterized by a persistent feeling of sadness and a loss of interest in daily activities, significantly impairing social and physical functioning. It is associated with an increased risk of self-harm and substance abuse.[1] It has a remitting and relapsing course and each episode lasts longer than 2 weeks. Due to poor treatment response, the majority of patients progress to chronic or treatment-resistant depression (TRD).[2] Worldwide, approximately 300 million people suffer from this debilitating disease accounting for 3.4% of the global population, with prevalence rates varying from across countries.[3] In our part of the world specifically in South Asia, this percentage is relatively low (3.0%) which may be attributed to insufficient reporting, lack of awareness about mental health disorders, and hesitancy in seeking medical care due to social barriers.[4] According to global health metric data, the years lived with disability due to depressive disorders increased by 47% during the last three decades for all ages and both sexes and marked MDD as the third leading cause of disability globally.[5] Mental health disorders impose an alarming burden on national and international health budgets but even then MDD has not received as much research attention as much as other diseases, e.g., cardiovascular disease and cerebrovascular accidents.[6] Despite extensive research, scientists could not reveal much about MDD pathophysiology which led to a rise in its prevalence and chronicity.

A biomarker is a computable biological measure that directly correlates with the detection or absence of a specific disease process, its severity, and/or its risk of evolving. Biomarkers are the essential guide and presently the keystone of disease management.[7] Biomarkers can serve as trait markers when they define disease pathogenesis or as state markers when they define the clinical progression of a disease. Due to the lack of differentiating markers that distinguish MDD from other disorders of this category, such as bipolar disorder and generalized anxiety disorder, diagnosis often takes months or even years and still relies on decades-old patient-centered and clinician-centered assessment interviews. Efficient disease management demands biomarkers for screening purposes, prediction, diagnosis, prognosis, and treatment response. However, presently there is no officially approved biomarker for highly prevalent MDD. Recently, various research projects explored valid and reliable biomarkers for predicting and diagnosing various forms of MDD, including early-onset MDD, late-onset MDD, and TRD. In parallel, scientists have probed biomarkers for predicting treatment responses to various antidepressants, aiming to personalized treatment and prevent TRD. Biomarker discovery has the potential to save time and money while benefiting both patients and physicians. Here, we have compiled potential biomarkers for MDD authenticated by published literature.

1.1. Pathophysiology of MDD

MDD is believed to arise from complex interactions between genetic, environmental, and biological factors. The pathophysiology of MDD is multifaceted, involving dysregulation in neurotransmitter systems, inflammation, and neuroplasticity changes, collectively contributing to the manifestation of depressive symptoms. It has been reported that genetic predisposition plays a significant role in the development of MDD. Family and twin studies have consistently shown that MDD is heritable, with heritability estimates ranging from 30% to 40%.[8] Several genetic variants have been implicated in MDD, including those affecting the serotonin transporter gene (5-HTT) and the brain-derived neurotrophic factor (BDNF) gene. Polymorphisms in these genes can influence neurotransmitter function and neuroplasticity, thereby increasing the risk of developing MDD.[9] Apart from genetic variations, environmental stressors are also critical in triggering depressive episodes, particularly in individuals with a genetic predisposition. Adverse life events such as childhood trauma, loss of a loved one, or chronic stress can precipitate the onset of MDD. These stressors can activate the hypothalamic-pituitary-adrenal (HPA) axis, leading to increased production of cortisol, a stress hormone that has been associated with depression.[10] Chronic stress can also result in epigenetic changes, altering gene expression and further contributing to the risk of MDD.[11]

The monoamine hypothesis of depression posits that dysregulation of neurotransmitters, such as serotonin, norepinephrine, and dopamine, is central to the pathophysiology of MDD. Reduced levels of these neurotransmitters in the synaptic cleft can lead to depressive symptoms. Antidepressant medications, which increase the availability of these neurotransmitters, provide indirect support for this hypothesis.[11,12] The single most potent neurotransmitter of the brain is glutamate as it plays a major role in learning, cognition, and mood stabilization by enhancing synaptogenesis and neuronal plasticity. Stress induces neurons to secrete glutamate at synaptic junctions, which strongly binds to the N-methyl D-aspartate receptor (NMDAR), initiating downstream signaling pathways. Blocking NMDAR or reducing glutamate levels exerts a profound antidepressant effect, as classically observed with ketamine administration in patients with suicidal thoughts.[13]

Inflammation is increasingly recognized as a critical component in the pathophysiology of MDD. Elevated levels of pro-inflammatory cytokines, such as interleukin-6

(IL-6) and tumor necrosis factor-alpha (TNF-α), have been observed in individuals with MDD.[11,13] These cytokines can influence brain function by altering neurotransmitter metabolism, reducing neurogenesis, and disrupting neuroplasticity. Inflammatory markers have also been linked to treatment-resistant depression, highlighting their potential role in MDD pathology.[14]

Neuroplasticity, the brain's ability to reorganize and form new neural connections, is impaired in MDD. Reduced neuroplasticity in regions, such as the hippocampus and prefrontal cortex, is associated with depressive symptoms. The neurotrophic hypothesis suggests that decreased levels of BDNF contribute to impaired neuroplasticity and neurogenesis in MDD.[15] Antidepressant treatments have been shown to increase BDNF levels and enhance neuroplasticity, further supporting this hypothesis.[16] The HPA axis, which regulates the body's response to stress, is often dysregulated in individuals with MDD. Hyperactivity of the HPA axis leads to elevated cortisol levels, which can have deleterious effects on the brain, including hippocampal atrophy and impaired neurogenesis.[17] These changes can contribute to the cognitive and emotional symptoms of MDD. Normalizing HPA axis function is a target of some antidepressant therapies, with the aim of reducing cortisol levels and mitigating their negative impact on the brain. The pathophysiology of MDD is not attributable to a single factor but rather to the integration of various biological systems. Dysregulation in neurotransmitter systems, inflammation, and impaired neuroplasticity interact in a complex manner to produce the symptoms of MDD. Understanding these interactions is crucial for developing more effective treatments. For example, combining anti-inflammatory agents with traditional antidepressants may enhance treatment efficacy for some patients.[18] Figure 1 demonstrates the overall pathology of MDD.

2. Material and methods

2.1. Selection criteria

Research articles published from January 2011 till July 2024 were selected according to the following criteria: (a) Studies in the English language, (b) studies in adult humans diagnosed with MDD and compared with age-matched healthy controls, (c) studies that applied valid statistical tools to explore association, (d) Studies with a sample size not <10, (e) all animal studies were excluded, and (f) all randomized controlled trials and clinical trials were selected.

2.2. Search strategy

Research papers were identified by searching PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Cochrane Library (https://www.cochranelibrary.com) using the following mesh words: Major depression, diagnostic biomarkers, prognostic biomarkers, and genetic biomarkers. After

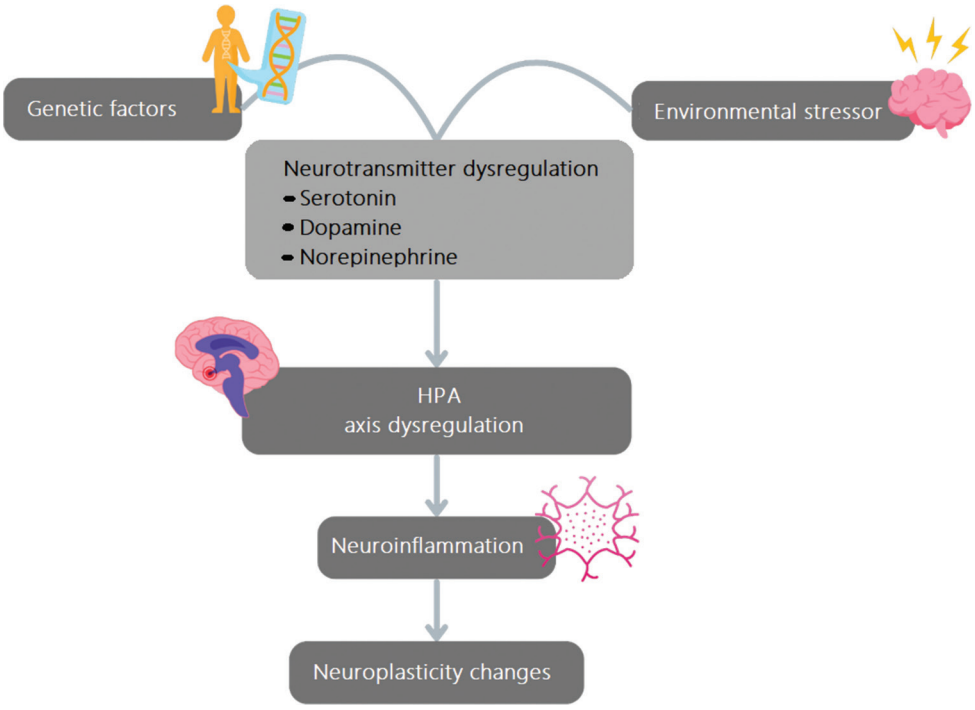


Figure 1. Pathophysiology of MDD. Figure created by the authors.
Abbreviations: HPA: Hypothalamic-pituitary-adrenal; MDD: Major depressive disorder.

removing duplicates, 568 articles in English were acquired. Based on the title and abstract, only 80 articles met the selection criteria. The search strategy is summarized in Figure 2.

3. Findings and discussion

3.1. Cell surface signaling biomarkers

MDD has been linked to various pathological processes activated by abnormal cellular signaling such as inflammation and immune mediation. These signaling pathways play a pivotal role in MDD pathogenesis and their components may provide clues for diagnosing MDD, predicting treatment response, or understanding treatment resistance. Toll-like interacting protein and vascular endothelial growth factor a (VEGFa) interact with numerous signaling components through their receptors. Both factors may serve as biomarkers for distinguishing patients with MDD, especially those who suffered from early childhood abuse.[19] Homocysteine acts as an agonist over the N-methyl D-aspartate (NMDA) subtype of glutamate receptor. Homocysteine can be a potential biomarker for registering MDD among patients with acute coronary syndrome.[20] Dehydroepiandrosterone sulfate (DHEAS) is a well-known neurosteroid and is vital for neuronal function through multiple cellular pathways. Its plasma concentration has been declared as a biomarker for treatment response.[21] With an animal model of depression, Blugeot *et al.* demonstrated that decreased serum BDNF levels along with normal corticosterone concentration may serve as a predictive biomarker for MDD vulnerability.[22] They also showed that the agonist of tropomyosin kinase B (TrkB), a BDNF receptor, will lead to the alleviation of MDD symptoms. Through multiplex bead-based assay analysis, TNF-α levels significantly differentiated cases of high-risk TRD.[23] In the genome-based therapeutic drugs for depression (GENDEP) study, participants were divided into two groups to determine drug response in relation to the baseline C reactive protein (CRP) levels, which proved its role as a biomarker for treatment response.[24] *Druzhkova et al.* pointed out the significant role of IL-6 and ciliary neurotrophic factor in the diagnosis of MDD and observed an acute stress-induced rise in TNF-α and glucose levels, suggesting the involvement of inflammatory and metabolic pathways.[25] Tolahunase *et al.* utilized elevated serum BDNF levels to validate MDD treatment response and demonstrated that elevated sirtuin 1 levels and decreased cortisol levels may also serve the same purpose.[21] Gadad *et al.* declared inflammatory proteins, i.e., interferon-gamma and eotaxin/CCL1, as predictors of treatment response in MDD patients.[26]

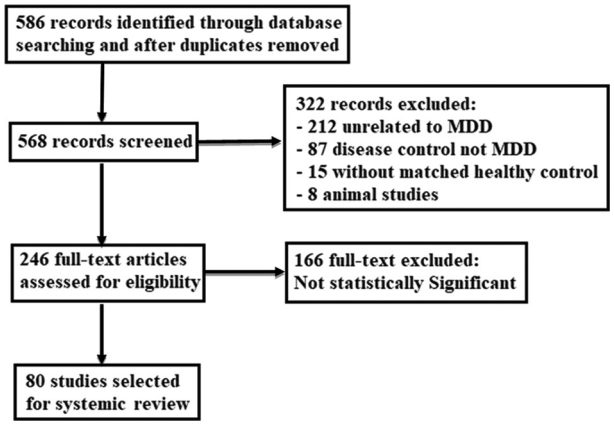


Figure 2. Flow chart for article selection
Abbreviation: MDD: Major depressive disorder.

Bot *et al.* worked on signal transduction, cell communication, and immune pathways to explore biomarkers for active MDD and declared pancreatic polypeptide, macrophage migration inhibitory factor (MIF), ENRAGE, IL-1 receptor antagonist, tenascin-C growth regulated alpha protein and von Willebrand factor as useful biomarkers.[27] On the other hand, Ramsey *et al.* worked on inflammatory pathway profile and declared CRP, trefoil factor 3, cystatin C, fetuin-A, β2-microglobulin, CD5L, FASLG receptor, and TNF receptor 2 with sufficient sensitivity and specificity (area under the curve [AUC] =0.63) for male gender.[28] Carboni *et al.* worked on treatment response predictors and established baseline cutoff values with significant accuracy and specificity for IL-6, IL-10, and TNF-α when using paroxetine, and for CRP when using venlafaxine as an antidepressant.[29] Most recently, Park *et al.* and Han *et al.* explored the role of a novel brain-specific chemokine, family with sequence similarity 19 member A5 (FAM19A5), as a biomarker for the pathogenesis of MDD. The researcher guaranteed authenticity with a significant area under the curve (AUC = 0.785), 60% sensitivity, and 100% specificity.[30,31] Yang *et al.* showed an excitatory relationship between proBDNF/p75 neurotropic receptors (p75NTR) signaling and inflammatory cytokines (IL-1β and IL-10) in the peripheral blood mononuclear cells of subjects diagnosed with MDD.[32] A summary of the cell surface signaling biomarkers in MDD is shown in Table 1.

3.2. Organelle-based or cytoplasmic biomarkers

L-carnitine and alpha L-carnitine are endogenous compounds that promote the β-oxidation of long-chain fatty acids in the mitochondria. Li- Juan *et al.* and Nasca *et al.* utilized human samples and established these compounds for diagnosing MDD, grading severity, and assessing treatment response, with acceptable sensitivity and specificity (AUC = 0.694 to 0.849).[33,34] Du *et al.* demonstrated that glucocorticoid (GC) toxicity results in

Table 1. Summary of cell surface signaling biomarkers in MDD

Biomarker	Source/Type	Role in MDD	Key findings	References
TOLLIP	Immune cells	Inflammation	May distinguish MDD patients with childhood abuse	19
VEGF	Blood	Neurogenesis	Potential diagnostic marker for MDD	30
Homocysteine	Blood	NMDAR agonist	Potential biomarker for MDD in acute coronary syndrome patients	20
DHEAS	Blood	Neurosteroid	Treatment response biomarker	21
BDNF	Serum	Neuroplasticity	Predictive biomarker for MDD vulnerability	22

Abbreviations: BDNF: Brain-derived neurotrophic factor; DHEAS: Dehydroepiandrosterone sulfate; MDD: Major depressive disorder; NMDAR: N-methyl D-aspartate receptors; TOLLIP: Toll-like interacting protein; VEGF: Vascular endothelial growth factor.

depression by stimulating the opening of mitochondrial permeability transition pores through transcriptional upregulation of cyclophilin D.[35] Cyclophilin D inhibition using a mitochondria-targeted compound, mito-apocynin, and a GC receptor antagonist, mifepristone, protects against mitochondrial dysfunction, synaptic loss, and behavioral deficits induced by GC.[35]

4. Intranuclear biomarkers

Intranuclear biomarkers (Figure 3) are the product of genetic machinery that plays a crucial cellular role including neurogenesis, neuro-inflammation, receptor toxicity, synaptogenesis, aging apoptosis, and mitochondrial respiratory chain.[36] The various intranuclear biomarkers and their clinical relevance are shown in below Table 2.

4.1. Transcriptional biomarkers for MDD

Transcriptional biomarkers are the members of the transcriptome family produced by DNA. They are broadly classified into the transcriptome, encompassing protein-coding RNAs (messenger RNAs; mRNAs) involved in protein synthesis, and the epitranscriptome, encompassing non-coding RNAs, such as microRNAs (miRs), long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs), involved in the regulation of protein synthesis. Recent advances in medical science have pointed out the fundamental role of these genomic and epigenomic components in the pathogenesis of highly intractable diseases, especially cancers and neurological disorders.[42,43]

4.1.1. mRNA expression as biomarkers for MDD

The dissociation between "predictors" and "targets" of antidepressant responders was first reported by Cattaneo *et al.* who extensively explored mRNA-based biomarkers for MDD management. MDD non-responders had higher baseline mRNA levels of IL-1β, MIF, and TNF-α. Antidepressants reduced these levels significantly but there was no effect on disease severity. MDD remission was associated with a significant rise in mRNA levels of BDNF and vascular growth factor (VGF) and a decrease in mRNA levels of IL-6 and GC receptor function-related

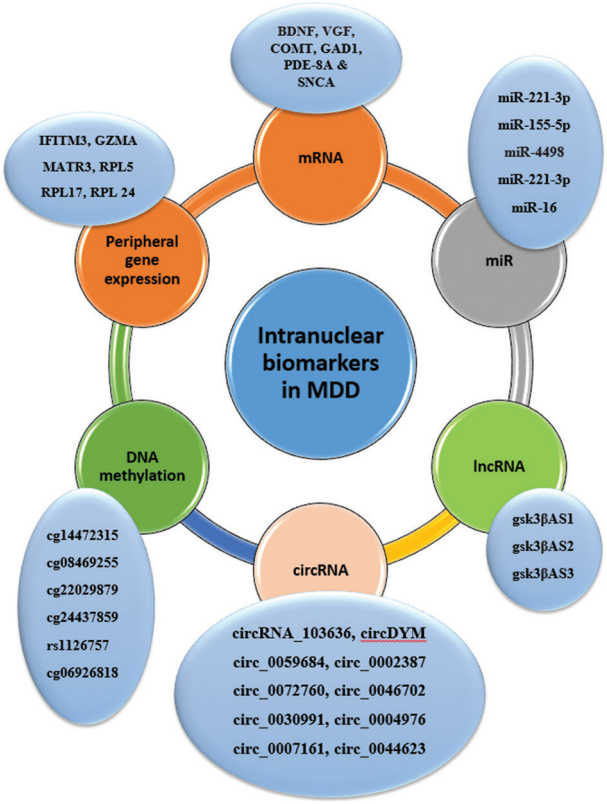


Figure 3. Intranuclear biomarkers associated with MDD. Figure created by the authors.
Abbreviations: BDNF: Brain-derived neurotrophic factor; circRNA: Circular RNA; lncRNA: Long non-coding RNAs; MDD: Major depressive disorder; mRNA: Messenger RNA; miR: microRNA; PDE-8A: phosphodiesterase 8A; SNCA: Alpha-synuclein.

FKBP-5.[44] Cattaneo *et al.* determined highly specific cutoff values for MIF and IL-1β mRNA levels from peripheral leukocytes that predict treatment response among MDD patients from a registered cohort as well as an independent cohort.[37] Lin *et at.* demonstrated a significant role of the mRNA expression levels of NMDAR genes (SRR, PSAT1, GCAT, GAD1, NRG1, and COMT) in white blood cells by plotting receiver operating characteristics curve for the accurate diagnosis of drug naïve MDD patients.[45] Most recently, significant differences in the phosphodiesterase

Table 2. Intranuclear biomarkers and their clinical relevance in MDD

Biomarker	Type	Role in MDD	Clinical utility	References
mRNA of IL-1β	Transcriptomic	Inflammation	Predicts treatment response	37
miR-221-3p	Epitranscriptomic	Post-transcriptional modification	Diagnostic and prognostic marker	38
gsk3βAS1 lncRNA	Epitranscriptomic	Synaptic plasticity	Diagnostic and therapeutic marker	39
circRNA_103636	Epitranscriptomic	Development stage-specific expression	Diagnostic marker with 73% sensitivity and 65% specificity	40
DNA methylation of GSK3β gene	Epigenetic	Gene regulation	Diagnostic marker with 100% sensitivity and specificity	41

Abbreviations: circRNA: Circular RNA; IL: Interleukin; lncRNA: Long non-coding RNAs; MDD: Major depressive disorder; mRNA: Messenger RNA; miR: microRNA.

8A (PDE-8A) mRNA editing profile have been observed in brain areas, including the dorsolateral prefrontal cortex and anterior cingulate gyrus, between depressed suicidal victims and healthy controls. They further suggested that suicidal ideation results from immune response-mediated brain damage due to the involvement of PDE-8A, and that in the future, this may act as a predictive biomarker for suicide.[46] In the same year, Salvetat *et al.* invented an application for estimating the mRNA editing profile of PDE8A from blood, saliva, and urine samples, demonstrating its potential for identifying mood disorders, including suicidal behavior.[47] Rotter *et al.* discovered a positive correlation between the RNA expression level of alpha-synuclein (SNCA) and the severity of MDD – characterized by the Hamilton Depression Rating Scale (HAM-D 17) and Beck's Depression Inventory (BDI-II) score.[48] The study showed that mRNA expression levels of SNCA, a presynaptic membrane protein, could serve as a potential biomarker for both diagnosis and grading MDD.[48] Most recently, it has been documented that mRNA expression of serotonin transporter (SERT) on the surface of peripheral blood mononuclear cells (PBMCs) is significantly reduced in subjects with MDD.[49]

4.1.2. miRs expression as biomarkers for MDD

miRs are small endogenous molecules consisting of approximately 20 nucleotides that play a role in post-transcriptional modification of mRNA. Several neurobiological processes including neurogenesis, neuronal proliferation, and synaptic plasticity have been linked to this epitranscriptome. As miR expression in the peripheral circulating cells changes both during MDD progression and remission, their levels could serve as potential biomarkers and may facilitate the management of intricate MDD.[50] Differential expression (DE) of miR can be determined through tissues (e.g., brain), cells (e.g., lymphocytes and monocytes), and body fluid exosomes (e.g., blood, urine, and saliva).[51,52] A summary of significant miR expression patterns for MDD diagnosis and treatment response is given in Table 3 and Table 4.

Torres-Berrio *et al.* documented that miR-218 expression in the prefrontal cortex significantly correlates with susceptibility to depression and its expression can be detected in the blood as well.[68] Feng *et al.* identified miR-221-3p expression in human serum and suggested that it can predict depressed mood.[38] Their work revealed that IFN-α-induced activation of nuclear factor kappa B (NF-κB) in astrocytes, mediated by miR-221-3p targeting of IRF2, may be one of the potential mechanisms underlying MDD.

4.1.3. lncRNA expression as biomarkers for MDD

Non-coding RNAs are pivotal for many cellular functions, such as splicing, gene regulation, chromosome structure regulation, and hormone-like activity. lncRNAs, which range from 200 to several hundred nucleotides, have recently been explored as genetic biomarkers for various diseases. While protein and DNA constitute the majority of chromatin, an increasing number of studies have revealed that lncRNAs occupy a large portion of chromatin and act as regulators of nuclear architecture and the expression of nuclear chromatin as coding RNA (genomic role) or non-coding RNA (epigenomic role).[69]

Liu *et al.* were the first to link co-expression of lncRNA and mRNA with MDD pathogenesis. Chromosomal regions chr10:874695-874794, chr10:75873456-75873642, and chr3:47048304-47048512 were identified as major sites co-expressions associated with MDD. Gene ontology (GO) and pathway analyses revealed metabolic pathway and neurodevelopment disease (Alzheimer's disease and Parkinson's disease) pathways.[70] Two studies examined the DE of lncRNAs in PBMCs among patients of schizophrenia (SZ), MDD, and generalized anxiety disorder (GAD).[71,72] After cross-validation, six downregulated lncRNAs (TCONS_00019174, ENST00000566208,

Table 3. miR expression for MDD diagnosis

Tissue	miR Expression	Associated signaling pathways	References
PBMCs (human)	Upregulated miR-26b, miR-4743, miR-4498, miR-4485 and miR-1972	GO, KEGG, and BioCarta	53
PBMCs (human)	Upregulated miR-26b, miR-1972, miR-4485, miR-4498, and miR-4743 Downregulated miR-338	Wnt/VEGF/mTOR/ErbB pathways	51
CSF (human)	Upregulated miR-125a-5p, miR-30a-5p, let-7d-3p, miR-34a-5p, miR-221-3p, miR-29b-3p, miR-10a-5p, miR-375, miR-155-5p, miR-33a-5p, miR-139-5p. Downregulated miR-185-5p, miR-590-5p miR-106b-5p, miR-15Bb-5p, miR-451a	Serine protein kinases 5HT/CRH/Glu/Wnt/VEGF/mTOR/ ErbB/LTD pathways	54
Serum (human)	Upregulated miR-221-3p, miR-34a-5p, let-7d-3p Downregulated miR-451		
CSF and serum (human and rat)	Downregulated miR-16	Serotonin pathway	55
PBMCs	Upregulated miR-199a-5p, miR-24-3p and miR-425-3p Downregulated miR-1915-3p, let-7a-5p, let-7d-5p and let-7f-5p	Wnt/mTOR/ErbB/insulin/Jak-STAT pathway	56
Blood (human)	Upregulated pmiR-chr11, miR-3158-3p, miR-433, miR-3944-5p Downregulated miR-1275, miR-4516, miR-30e-3p, miR-148b-3p	BRPF1 (required for mouse hippocampus development)	57
Hippocampus (mouse)	Downregulated miR-124	NO and cytokines inflammatory pathway	58
PBMCs, monocytes (human)	Downregulated PBMC: let-7e, miR-146a, and miR-155 Monocytes: miR-146a and miR-155 (Both upregulated after treatment)	TLR4 signaling pathway	59
Plasma (human)	Downregulated miR-184		60
PBMCs (human)	Upregulated ENSG00000238243.3_1, ENSG00000126353.3_2 ENSG00000198034.10_1, ENSG00000254996.5_2 ENSG00000184613.10_2, ENSG00000139193.3_2 ENSG00000101224.17_1, ENSG00000197153.4_2 ENSG00000103064.13_2, ENSG00000256235.1_1 Downregulated ENSG00000150991.14_2, ENSG00000172057.9_2	CC chemokine receptor activity, T cell receptor pathways.	47
Plasma (human) Hippocampus, PFC (rat)	Upregulated miR-134	Microglial activation pathway	61
Extracellular vesicles	Downregulated miR-92a-3p miR-129-5p	Microglial activation pathway	62
PFC	miR-194-5p, miR-25-3p, miR-125-5p	Th17 differentiation in the immune system	63

Abbreviations: BRPF1: Bromodomain and PHD finger-containing protein 1; CSF: Cerebrospinal fluid; CRH: Corticotropin releasing hormone; Glu: Glutamate; lncRNA: Long non-coding RNAs; LTD: Long-term depression; MDD: Major depressive disorder; miR: microRNA; mTOR: Mammalian target of rapamycin; NO: Nitric oxide; PBMC: Peripheral blood mononuclear cells; PFC: Prefrontal cortex; VEGF: Vascular endothelial growth factor; 5HT: 5 – hydroxyl tryptan.

Table 4. MiR expression for MDD treatment response

Tissue/Sample	miR Expression	Associated signaling pathways	References
PBMCs (Human)	Upregulated miR-4743, miR-4498, miR-4485 and miR-1972 Downregulated miR-4485	GO, KEGG and BioCarta	53
Plasma and PFC (human) Plasma (mouse)	Downregulated miR-146a-5p, miR-146b-5p, miR-24-3p and miR-425-3p	MAPK/Wnt	52
Plasma, exosome EDP, PNBCs	Upregulated miR-26a (in EDP – exosomes depleted plasma) miR-494 (in exosomes and EDP) Among MDD-treated patients	MAPK and Wnt	64
Plasma (human)	Upregulated miR-16-5p, miR-146a-5p and miR-21-5p	Morphogenesis, COPII vesicle coating, IP3 metabolic process, apoptotic process, cytoplasmic stress granule, NO metabolic process, NO synthase, and virion assembly	65
PBMCs (human)	Upregulated miR-27a-3p, miR-197-3p, miR-22-5p, miR-221-3p, miR-126-3p, miR-128-1-5p, miR-30b-5p, miR-339-3p, miR-301a-3p, miR-345-5p, miR-505-3p, miR-1249, miR-132-3p, miR-550a-5p, miR-589-5p, miR-769-5p, miR-10b-5p, miR-210-3p, miR-628-3p, let-7d-3p, miR-148a-5p, miR-155-5p, miR-140-3p, miR-150-3p, miR-181a-5p, miR-24-3p, miR-629-5p, let-7a-3p, miR-194-5p, miR-28-3p, miR-378a-3p, miR-6852-5p, miR-7706	Prion diseases (TGFβ) and morphine addiction signaling pathways	66
Plasma (human)	Upregulated miR-135a-5p (the higher the miR-135a-5p expression, the faster the remission.)	MAPK and Wnt	67

Abbreviations: EDP: Exosomes depleted plasma; lncRNA: Long non-coding RNAs; MDD: Major depressive disorder; miR: microRNA; MAPK: Mitogen-activated protein kinase; NO: Nitric oxide; PBMC: Peripheral blood mononuclear cells; PFC: Prefrontal cortex; PNBC: Peripheral nucleated blood cells; TGFβ: Transforming growth factor beta.

NONHSAG045500, ENST00000517573, NONHSAT034045, and NONHSAT142707) were found highly sensitive and specific for the diagnosis of MDD (AUC = 0.719). Seki *et al.* discovered RMRP, a nuclear DNA-encoded lncRNA and a component of nuclear RNase mitochondrial RNA processing (MRP) complex, as a potential biomarker for the diagnosis and severity assessment of MDD in both human and animal research models.[73] Most recently, Liu *et al.* conducted *in vitro* and *in vivo* studies on regulatory antisense lncRNAs of GSK3β, a serine-threonine kinase involved in synaptic plasticity, neurogenesis, and resilience to neuronal injury.[39] The study identified gsk3βAS1 [ENST00000482027], gsk3βAS2 [ENST00000491262], and gsk3βAS3 [BC035247] as novel diagnostic and therapeutic biomarkers for MDD. A summary of lncRNAs that play a significant role in the diagnosis and treatment response of MDD is presented in Table 5.

4.1.4. circRNA expression as biomarkers for MDD

Previously considered just a byproduct of genetic malfunctioning, circRNAs have now been assigned multiple regulatory roles in physiological and pathological processes at the nuclear and cellular levels. The mysterious circRNAs are formed from pre-mRNA through back-splicing of introns, exons, or both, while the canonical splicing of the same pre-mRNA results in the formation of protein-coding mRNA.[74,75]

Cui *et al.* were the first to recommend the expression of circRNAs (circRNA_103636) in PBMCs as a biomarker for MDD diagnosis and treatment response, with 73% sensitivity and 65% specificity as determined by receiver operating characteristic (ROC) curve analysis.[40] Zhang *et al.* conducted experiments to validate the ameliorative effects of circRNA DYM (circDYM) expression in depressive-like mice models. *In vitro* studies on BV-2 cells revealed that circDYM inhibits miR-9 which increases target-HECT domain E3 ubiquitin protein ligase 1 (HECTD1) and depresses microglial activation.[61] Following Zhang *et al.*, Song *et al.* sorted out the correlation between downregulated plasma circDYM and MDD up to 94% sensitivity.[55]

Table 5. Significant lncRNA related to MDD

Expression	Utility	Signaling pathway	References
Downregulated gsk3βAS1	Diagnostic marker (upregulated post-treatment)	Synaptic plasticity	39
Downregulated TCONS_00019174 ENST00000566208 NONHSAG045500 ENST00000517573 NONHSAT034045 NONHSAT142707	Diagnosis and treatment response	Ribosome activities, Alzheimer's disease, RNA degradation, pancreatic cancer, Parkinson's disease, cell cycle, DNA replication, prostate cancer, Huntington's disease and long-term depression	71
Upregulated Y5, MER11C, PCAT1, PCAT29	Diagnosis and severity	Gene regulation	73
Downregulated gsk3βAS1 [ENST00000482027], gsk3βAS2 [ENST00000491262] gsk3βAS3 [BC035247]	Diagnosis, severity, and treatment response (upregulated post-treatment)	Wnt signaling pathway	39
Downregulated RMRP	Diagnostic and severity assessment	Gene regulation	73
Downregulated TCONS_00019174	Diagnosis	Cellular pathways	71
Upregulated ENSG00000229807.1_2 ENSG00000234449.2_1 ENSG00000205663.5_1 ENSG00000271964.1_2 ENSG00000279995.1_2 ENSG00000271109.1_1 ENSG00000205662.2_1 ENSG00000244620.1_1 ENSG00000204282.4_2 ENSG00000225938.1_1 Downregulated ENSG00000273295.1_1 ENSG00000218537.1_1 ENSG00000271869.1_1	Diagnosis	CC chemokine receptor activity and cytokine-cytokine receptor interactions and T cell receptor	47

Abbreviation: MDD: Major depressive disorder.

An *et al*. investigated DE of circRNAs among patients of MDD and type II diabetes and reported that the following circRNAs were exclusively and significantly expressed in MDD, summarized in Table 6.[76] Yu *et al.* documented that circHIPK2 expression was significantly enhanced (AUC = 0.796) in MDD individuals and it is highly specific for diagnosing and predicting MDD l.[77]

4.1.5. DNA methylation in MDD

Numata *et al.* explored the role of DNA methylation in diagnosing MDD using blood samples.[41] A multiplex DNA methylation profile, predominantly from gene promoter regions within CpG islands, demonstrated 100% sensitivity and specificity as a diagnostic biomarker for MDD. Among 313 differentially methylated CpG sites in the CGIs in the gene promoter regions, several genes, such as DGKH (cg00109274), GSK3B (cg14472315), and SGK1 (cg06642177), have been implicated in MDD. DGKH and SGK1 are specific for bipolar disorder whereas the GSK3B is specific for MDD.[41] Clive *et al.* worked on validating their previously identified biomarker – spindle and kinetochore-associated protein (SKA2) – which predicts suicide risk and post-traumatic stress disorder (PTSD).[78] DNA methylation of SKA2 revealed three probes (cg08469255, cg22029879, and cg24437859) that were significantly correlated with the biosignature for DNA methylation-based suicidal behavior prediction. Powel *et al.* investigated IL-11 gene-related DNA methylation across the CpG island and its role in predicting MDD treatment response in the GENDEP clinical trial.[79] In the same clinical trial, the role of IL-11 transcriptional differences and the associated single nucleotide polymorphism (SNP), rs1126757, in predicting MDD treatment response was also determined. DNA methylation in the IL-11 gene has thus proved to

Table 6. circRNA expressed in MDD

Upregulated		Downregulated	
circRNA ID	**Gene name**	**circRNA ID**	**Gene name**
circ_0046702	YES1	circ_0009024	TXLNG2P
circ_0059684	ZNF337-AS1	circ_0008297	DDX3Y
circ_0002387	TNIK	circ_0001953	ZFY
chr5:162909647-162911251	HMMR	chr5:178043882-178044435	CLK4
circ_0072760	CCNB1	circ_0006660	CHPT1
chr3:195781950-195782172	TFRC	chr19:11759172-11759299	ZNF833P
circ_0030991	CUL4A	circ_0003068	SYNE1
circ_0004976	ASXL2	chr11:66372959-66373063	CCS
circ_0007161	YAF2	circ_0028904	RNF10
circ_0044623	LUC7L3	chr1:41474465-41474562	CTPS1 9

Abbreviations: YES1: YES Proto-Oncogene 1, Src Family Tyrosine Kinase), ZNF337-AS1: ZNF337 Antisense RNA 1, TNIK: TRAF2 and NCK-Interacting Protein Kinase, HMMR: Hyaluronan Mediated Motility Receptor, CCNB1: Cyclin B1, TFRC: Transferrin Receptor, CUL4A: Cullin 4A, ASXL-2: ASXL Transcriptional Regulator 2, YAF2: YY1 Associated Factor 2, LUC7L3: LUC7 Like 3 Pre-MRNA Splicing Factor, TXLNG2P: Taxilin Gamma Y-Linked, DDX3Y: DEAD-Box Helicase 3 Y-Linked, ZFY: Zinc Finger Protein Y-Linked, CLK4 - CDC Like Kinase 4, CHPT1: Choline Phosphotransferase 1, ZNF833P: Zinc Finger Protein 833, Pseudogene, SYNE1: Spectrin Repeat Containing Nuclear Envelope Protein 1, CCS: Copper Chaperone For Superoxide Dismutase, RNF10: Ring Finger Protein 10, CTPS19: CTP Synthase 1.

Table 7. Genes involved in MDD remission

Drug	Clinical variable	Genetic variable
Escitalopram	Appetite, sleep change, somatic symptoms, and interest activity	rs1392611, rs10812099, rs1891943, rs151139256, rs11002001, rs62182022, rs28373080, rs7757702, rs76557116, rs9557363, rs2704022
Nortriptyline	Not applicable	rs6794400, rs79693177, rs12874087, rs2345113, rs17091959, rs10792321, rs199561596, rs144829540, rs149619279, rs34319049, rs151132095, rs37596, rs8053632, rs111685823, rs4279984, rs17057129, rs5889536, rs34841556, rs4773117, rs8082631

Abbreviation: MDD: Major depressive disorder.

be an authentic biomarker for predicting MDD treatment response and may guide the selection of best-suited treatment in the future.[79] Kang *et al.* worked on the DNA methylation profile of the BDNF gene and revealed it could precisely predict suicidal ideation status and also the treatment outcome.[80] Ju *et al.* identified differentially methylated positions (DMP) in peripheral DNA samples for predicting MDD treatment response.[81] After validations, DMP in the CHN2 gene (cg06926818) was successfully replicated, demonstrating 100% specificity and sensitivity.[81]

4.1.6. Peripheral gene expression in MDD

Guilloux *et al.* identified and validated a set of six peripheral genes with 76% accuracy and 86% sensitivity for the prediction of MDD drug responses. These double-validated genes include IFITM3 (INF-induced transmembrane protein 3), GZMA (granzyme A), MATR3 (matrin 3), and ribosomal proteins RPL5, RPL17, and RPL24.[82] Iniesta *et al.* documented a validated set of genes for drug-specific treatment response among MDD subjects. For escitalopram response, both genetic and clinical variables predict remission with high accuracy, while for nortriptyline response, only genetic variables serve as predictors (AUC = 0.77) (summarized in Table 7).[83]

Pajer *et al.* worked for authenticated genetic peripheral markers for diagnosing MDD at earlier onset.[84] A set of 11 candidate transcriptomic genes (ATP11C, CD59, IGSF4/CADM1, MAF, RAPH1, AMFR, CAT, CDR2, CMAS, PSME1, and PTP4A3) could differentiate MDD cases from healthy subjects with sufficient accuracy. Similarly, Redei *et al.* explored diagnostic genetic markers from peripheral blood samples and reported that RAPH1, KIAA1539, and DGKA gene expression demonstrated the highest specificity and sensitivity for differentiating MDD cases, regardless of treatment status, as determined by ROC curve analysis.[85] Most recently, Wang *et al.* documented differentially expressed hub genes, including MRPS2, MRPS7, MRPS11, MRPS18, MRPL2, MRPL9, MRPL15, MRPL16, MRPL27, MRPL36, RPS3, RPS19, RPS19, RPL6, RPL11, RPL19, RPL26L1, RPL29, NAS2, NHP2, and RPP38, which were highly specific and sensitive for MDD diagnosis (ROC AUC >0.8).[86] Furthermore, Liang *et al.*

and Li *et al.* have recently conducted case–control studies in a Chinese cohort and established that the rs155979 polymorphism in the lncRNA NONHSAT102891 was significantly associated with depression susceptibility and risk of suicide.[87,88]

5. Conclusion

This review highlights the progress made in identifying cellular and nuclear biomarkers for MDD. These biomarkers hold promise for enhancing diagnostic accuracy, predicting treatment response, and personalizing therapeutic approaches. However, further research is required to validate these biomarkers in clinical settings and to explore their application in routine clinical practice. Despite extensive and advanced research, the cure for MDD is partial and inadequate. Major challenges persist in screening, diagnosis, effective treatment, and prognosis. Identifying specific genetic factors could enable personalized treatment strategies, potentially improving outcomes.

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Conflict of interest

The authors declare they have no competing interests.

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