The Open Biomarkers Journal
DOI: 10.2174/0118753183381834250617133639, 2025, 15, e18753183394103
ISSN: 1875-3183

REVIEW ARTICLE **OPEN ACCESS**

The Role of Brain-Derived Neurotrophic Factor (BDNF) in Depression: A Narrative Review

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Abstract:
Depression is a psychological illness defined by persistent sadness, loss of interest or pleasure in daily activities (anhedonia), hopelessness, and a range of cognitive and physical symptoms. Untreated depression can have serious implications, such as a deteriorating mental and physical state and an increased risk of suicidal behaviour. Early diagnosis and treatment can help to prevent these adverse outcomes. Traditional diagnostic approaches primarily rely on self-reported symptoms, clinical evaluations, and questionnaire-based assessments, which, although significant, may vary and depend on perspective, necessitating the exploration of biological markers. This narrative review is based on the existing literature regarding the role of Brain-Derived Neurotrophic Factor (BDNF) in the neurobiological function and evaluates its potential as a biomarker for the diagnosis, treatment, and monitoring of disease progression. The Brain-Derived Neurotrophic Factor (BDNF) is the most common neurotrophin abundantly present in the central nervous system and peripheral tissues, and it is found in both serum and plasma. In the context of depression, BDNF has a fundamental function in the serotonergic, noradrenergic, and dopaminergic pathways, which are linked to the progression of clinical depression and are implicated in mood regulation. An extensive quantity of research on BDNF supports the neurotrophic theory of depression. According to this theory, low BDNF levels cause neuroplastic alterations such as neuronal atrophy, impaired hippocampus neurogenesis, and synaptic plasticity, contributing to its inception and progression. Several clinical findings consistently established that people with depression show lower levels of BDNF, with these levels generally increasing after successful antidepressant therapy, further supporting this hypothesis. This article provides an overview of BDNF's effect on the aetiology of depression, highlighting its significance as a possible marker.

Keywords: Depression, Brain-derived neurotrophic factor, Biomarkers, Neuroinflammation, Neurogenesis, Neuroplasticity, Antidepressant therapy.

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Cite as: Varghese T, Singh R, Chand S. The Role of Brain-Derived Neurotrophic Factor (BDNF) in Depression: A Narrative Review. Open Biomark J, 2025; 15: e18753183394103. http://dx.doi.org/10.2174/0118753183381834250617133639

Received: February 18, 2025
Revised: April 25, 2025
Accepted: May 06, 2025
Published: June 25, 2025

1.. INTRODUCTION

Untreated psychological disorders account for 13% of the worldwide disease toll. It is estimated that by 2030, mental health illnesses, especially depressive disorders, will become the primary cause of death and disability worldwide [1]. Depression is a common psychological disorder that impairs mental, emotional, and physical health. Depression differs from occasional mood swings and discouraging feelings related to daily life [2, 3]. Globally, an estimated 5% of adults, making over 280 million people, suffer from depressive symptoms. As per

the World Health Organization's (WHO) most recent report, 56 million people, *i.e.*, 4.5% of Indians, are experiencing depression [4]. Depressive symptoms are approximately 50% more frequent in women compared to men. More than 10% of prenatal and postnatal women suffer from depression worldwide. People with depressive symptoms are at increased risk of suicide. Each year, over 700,000 people die by suicide [5]. India's National Mental Health Survey analysed that more than 15% of the adult population in India requires an active care plan for mental health concerns, including signs of depressive symptoms [6].

Depression can be difficult to diagnose due to its complexity and wide range of symptoms. Its diagnosis is further complicated by its frequent link with other mental health issues, such as anxiety disorders [7]. Conditions other than mental disorders can be detected by identifying specific biomarker concentrations in body fluids [8]. Biomarkers are the biological indicators that detect the presence, severity, and treatment response to a disease [9]. However, psychological diseases are mainly diagnosed through self-reported symptoms, clinical interviews, and questionnaire-based procedures like the Hamilton Depression Rating Scale (HAMD), Diagnostic and Statistical Manual of Mental Diseases (DSM), Patient Health Questionnaire (PHQ-9), and International Classification of Diseases (ICD). This is one of the reasons why depressive symptoms are always undiagnosed and untreated [10]. While these standard tools are valuable and relevant in clinical practice, they are fundamentally based on personal perception, may vary depending on the healthcare professional's interpretation, and do not always capture the biological underpinnings of the disease. Without timely intervention, depression can negatively impact an individual’s quality of life and is linked with increased morbidity and mortality due to suicide and comorbid physical health conditions [11]. Therefore, research into objective and trustworthy biological indicators that can aid in early diagnosis, track treatment results, and forecast relapse is urgently needed. One such promising biomarker is the Brain-Derived Neurotrophic Factor (BDNF), which is a kind of neurotrophic factor that encourages neuron differentiation, maturation, and endurance in the nervous system. These neurotrophic factors are indispensable for the growth, development, survival, and plasticity of neurons, and their dysregulation has been linked to depressive disorders. It also protects neurons from advert situations such as ischemia, hypoglycaemia, glutamatergic stimulation, and neurotoxicity [12]. Studies consistently showed that serum BDNF levels are considerably lower in people with Major Depressive Disorder (MDD) than in healthy controls. Serum BDNF levels in untreated depressive patients usually decrease below 10–12 ng/mL, but those in non-depressed people frequently exceed 20 ng/mL, according to a meta-analysis by Sen *et al.* [13]. (2008) and later verified by Molendijk *et al.* (2014) [14]. These variations provide credence to the usefulness of BDNF as a state biomarker, reflecting the severity of depression and present mood state. This narrative review aimed to summarize current evidence on the role of BDNF in the neurobiology of depression, examine its potential role as a diagnostic and prognostic biomarker, expose limitations, and suggest future research avenues. This review provides an overview of the involvement of BDNF in the inception, progression, and prevention of depression. It will examine the roles of BDNF in health and disease and whether this mediator could act as a prognostic biomarker to diagnose depressive symptoms.

2.. METHODOLOGY

The literature search was conducted using databases such as PubMed, Scopus, and Google Scholar. The key terms “Depression,” “Brain-Derived Neurotrophic Factor,” “Biomarkers,” “Neuroinflammation,” “Neurogenesis,” “Neuroplasticity,” and “Antidepressant Therapy” were employed to obtain the results along with Boolean operators (AND, OR). English-language articles, original research articles, reviews, systematic reviews, and meta-analyses regarding depression and BDNF were included. Case reports, editorials, abstracts from conferences, and articles without full-text access were not included. Titles and abstracts were screened, while the data extraction was carried out manually.

2.1. BDNF: The Brain Growth Factor

2.1.1. Biosynthesis and Degradation of BDNF

The process of synthesizing BDNF in neurons is a series of stages that eventually result in its production and release. It is synthesized by a number of stages that comprise transcription, different splices, translation, post-translational modulation, intracellular transferring, and release. BDNF production starts with the transcription of a responsible gene positioned on chromosome 11 in humans and is made up of several exons and introns [15]. Transcription factors like cAMP Response Element-Binding protein (CREB) control the activity of this gene in response to a variety of physiological signals such as neuronal activity, stress, and synaptic input. When activated, these transcription factors link to specific DNA sequences inside the BDNF gene promoter region, thereby starting the transcription process. BDNF degradation is a multi-step process [16]. The primary step is enzymatic degradation, in which proteases break down BDNF into smaller fragments. Additionally, BDNF can be internalized and then degraded within cells *via* lysosomal pathways [17]. Ultimately, BDNF can be replaced from the extracellular space through absorption by adjacent cells or diffusion away from the point of release. These processes of degradation play a major role in regulating BDNF levels and activity in the brain, which influences neuronal function and plasticity.

2.1.2. Biological Characteristics of BDNF

It is a protein that is biologically related to and classified within the same group of Nerve Growth Factor (NGF). These are extensively expressed in the CNS. It is predominantly seen in the hippocampus, amygdala, cortex,

and striatum. Its expression in the brain depends on both BDNF protein translation and BDNF mRNA transcription [18]. It is also produced and secreted by endothelial cells and can be seen in the gut. BDNF's numerous roles in the CNS contribute to its involvement in several neurological and psychiatric illnesses. In the human brain, BDNF exists in two forms: proBDNF (precursor form) and mBDNF (mature form) [19]. Precursor form, mainly warehoused in axons and dendrites, is produced as pre-proBDNF in the Endoplasmic Reticulum (ER) and then removed from the signal peptide in the Golgi bodies to create its percussor form. ProBDNF is transformed into mature BDNF (mBDNF) through intracellular or extracellular cleavage, resulting in the loss of the prodomain. It contains 119 amino acids and has a distinct β-trefoil structure [20]. The ratio of the two kinds of BDNF varies throughout brain development. ProBDNF levels peak in the early postnatal period, while mature BDNF dominates at the time of maturity. BDNF acts by binding to two receptors, TrkB (tyrosine kinase receptor B) and p75 (pan-neurotrophin receptor or p75NTR). BDNF expression and secretion are controlled by a number of internal and extrinsic variables, including neuronal activity, neurotransmitters, neurotrophic factors, hormones, and environmental stimuli [21].

2.1.3. Physiological Functions of BDNF

BDNF develops in the hippocampus, the basal forebrain, and the cortex, which support the progress, maturation, and growth of CNS, the distinction of nerve cells, and various brain functions, including synaptic transmission and neuroplastic changes. Therefore, it is necessary for learning, memory, higher thinking, and cognitive abilities [22]. As a result, BDNF exerts a broad influence on mood, sleeping, and eating habits. It helps to preserve existing nerve cells while also fostering the formation of new nerve cells and synapses [23]. ProBDNF binds to the p75 NTR receptor, facilitating LTD (Long-Term depression) and inducing programmed cell death.

In contrast, mature BDNF is mostly linked to Tyrosine Kinase Receptors (TrkB), which improves cell survival, facilitates LTP (Long-Term Potentiation), and increases spine complexity [24]. LTD and LTP are synaptic plasticity (formation of new nerve cells) mechanisms that describe long-term changes in the degree of strength of interactions between neurons. LTD typically involves a decline in synaptic strength, whereas LTP involves an increase, and both mechanisms are essential for the development of memories and learning in the brain [25]. Maintaining brain plasticity promotes good cognitive performance as people age. BDNF functions as a neuroprotective factor, protecting neurons from a variety of insults and injuries, including oxidative damage, excitotoxicity, and inflammation [26]. It enhances the survival of neurons and repair processes in response to damage or disease, hence improving overall brain function and its development. BDNF can also be found in the kidneys, prostate gland, retinal cells, GI system, lungs, salivary glands, and the female reproductive system, especially in the uterus muscles [27]. It helps regulate glucose metabolism by increasing glucose absorption by muscles and protecting the pancreas' sensitive insulin-producing beta cells as it is present in the pancreas. Dysregulation of BDNF signalling is linked to metabolic disorders like obesity and hyperglycaemia. BDNF regulates the Cardiovascular (CVS) system by promoting the circulation of endothelial Nitric Oxide Synthase (eNOS), an enzyme that relaxes smooth muscle cells in artery walls [28]. Hence, it helps in the regulation of normal blood pressure, heart rate, and vascular tone. BDNF modulates immune cell function and cytokine production. It also influences neuroinflammation. Alteration in BDNF concentrations in peripheral blood and the CNS, as well as imbalances in the formation of matured BDNF *via* its percussor, is linked to depression [29].

2.2. BDNF and Depression: Unravelling the Neurobiological Link

2.2.1. The Role of BDNF in Neurogenesis

The formation of neurons predominantly takes place in the hippocampus and subventricular region. The Dentate gyrus present in this region signifies a main involvement in the carrying out of brain functions, especially regulation of mood, memory, and learning skills [30]. BDNF, including other factors, is crucial for neurogenesis, growth, neurite outgrowth (the extension of neuronal processes), and the proper functioning of neurons. BDNF carries out the critical function of neurogenesis and synaptic plasticity, both essential for brain function and mood regulation. BDNF receptors are widely expressed in the hippocampus and are required for the proliferation and differentiation of brain progenitor cells [31, 32]. The improper regulation of neurotrophic factor signalling has been connected to different neurological and psychiatric conditions, including neurodegenerative conditions, mood disorders, and depression. Reduced concentrations of BDNF have been reported in people suffering from depression due to impaired neurogenesis and synaptic plasticity. The altered BDNF level modulates the mechanism of the Hypothalamic-Pituitary-Adrenal axis (HPA), monoaminergic systems, and inflammatory pathways, entirely of which are often dysregulated in depression [33]. Clinical investigations have shown that antidepressant medications such as SSRIs, electroconvulsive therapy, and physical exercise raise BDNF levels, encouraging neurogenesis and enhancing synaptic plasticity, which helps reduce depressed symptoms. Clinical studies have proven that antidepressant treatments, including SSRIs, electroconvulsive therapy, and physical exercise, increase BDNF levels, thereby promoting neurogenesis and improving synaptic plasticity, which helps alleviate depressive symptoms [34].

2.2.2. BDNF and its Impact on Neuroplasticity and Impulse Transmission

Neuroplasticity, the foremost function of CNS, can be defined as the ability to adapt and rearrange in accordance with experiences and changes in the

environment. This includes synaptic plasticity, the ability to reinforce or deteriorate synaptic connections in retort to action levels [35]. This plasticity is critical to learning, memory, and overall mental functioning. BDNF promotes synaptic plasticity by enhancing the format growth and distinction of novel synapses and improves the strength and efficiency of prevailing synaptic connections. It enhances the growth and strength of synapses and promotes the generation of new synaptic connections [36]. It does so *via* a variety of signalling channels, including the activation of TrkB receptors, which initiate intracellular cascades that promote neuronal survival, growth, and synaptic regulation. In depressive patients, decreased transmission of impulses reduces BDNF expression and release, affecting synaptic plasticity [37].

2.2.3. Neuroinflammation and BDNF Levels

Neuroinflammation is the inflammation that occurs inside the brain or spinal cord, as indicated by microglial activation and the generation of cytokines and Reactive Oxygen Species (RoS). Recent preclinical and clinical research established the plausible linkage between neuroinflammation and depressive disorders and probably associated with the decreased level of neurotransmitters like serotonin, dysregulation of the HPA axis, and changes in the continuous production of neurons [38]. Activation of the hypothalamus-pituitary-adrenal axis system causes an increase in glucocorticoid resistance and influences the production of serotonin and metabolism, neuronal apoptosis and neurogenesis, and neuroplasticity leads to brain dysfunction. Microglia, the brain's immuno-competent resident cells, safeguard the brain from environmental stressors but can also stimulate the development of pathogenic neuroinflammatory processes by generating proinflammatory cytokines (*e.g.*, IL-1β, IL-6, TNF-α), can lower BDNF levels thereby contribute to neurotoxicity [39]. Activated microglia produce inflammatory cytokines, which are involved in the development of depression and can impair BDNF synthesis and signalling, leading to neurodegenerative processes and mood disorders. Inflammation over time may cause a sustained drop in BDNF levels, impairing brain function [40].

2.2.4. The Effect of Stress Response on BDNF and Depression

The neurotrophic hypothesis theory of depression proposes that changes in neurotrophic factor signalling and neuroplasticity contribute to the onset and progression of depression [41]. This theory emphasizes that stress can diminish the expression of neurotrophic factors in brain areas. This concept is based on the physical and physiological changes in the brain, like a diminished synthesis of neurons, dendritic atrophy, and synaptic loss, which are linked to depression [42]. Current data suggests that poor neuroplasticity caused by abnormalities in neurotrophic growth factors and related signalling pathways may contribute to the pathogenesis of depressive disorders [43]. Preclinical studies reported persistent stress, a key risk factor for depression, decreases neurogenesis and alters synaptic plasticity in the hippocampus. These structural changes are hypothesized to reduce synaptic plasticity. Chronic stress can modify neurotrophic factor expression and synaptic connections in mood-regulating brain areas, which contributes to the development of depression [44]. Clinical studies indicate that individuals suffering from depression may have a lower resilience to stress, as evidenced by increased HPA axis activity, impaired negative feedback control, and altered immunological responses. Chronic stress may additionally interrupt the Hypothalamic-Pituitary-Adrenal (HPA) axis, reducing BDNF signalling [45]. Stress-induced declines in BDNF levels can be relatable to the onset and persistence of depression symptoms. The literature identifies that Individuals suffering from depression have consistently low levels of BDNF. This decline is thought to lead to neuron shrinkage and malfunction, reducing neuroplasticity and stress resilience, both of which are important contributors to this condition. Several preclinical and clinical research have shown that prolonged exposure to stress or inflammation reduces BDNF levels, limiting synaptic plasticity and eventually leading to diminished function and neuronal death [46, 47].

2.3. Assessment of BDNF Levels in the Blood and Methods of Measurement

Serum BDNF levels contain BDNF generated from platelets during clotting. They are typically thought to be more stable and indicative of the total circulating BDNF, even though both serum and plasma BDNF can be analyzed. In contrast, the lack of this platelet-derived release results in lower and more fluctuating plasma BDNF levels [48, 49]. Consequently, serum BDNF is used as a more accurate and trustworthy biomarker in the majority of studies examining BDNF in depression. Healthy adults normally have blood BDNF concentrations between 8 and 30 ng/mL. However this can vary significantly according to the assay equipment, sample processing methods, and population demographics. BDNF levels in plasma are significantly lower, often falling between 0.5 and 2 ng/mL [50]. In serum, plasma, or whole blood samples, BDNF concentrations are frequently assessed using Enzyme-Linked Immunosorbent Assay (ELISA) methods. Due to its sensitivity, specificity, and repeatability in measuring BDNF levels, ELISA is regarded as the gold standard. After centrifuging blood samples to extract serum or plasma, certain antibodies are used to detect BDNF. In research contexts, more sophisticated techniques like western blot, multiplex immunoassays, or Luminex tests are also employed for high-throughput or comparative analysis [51].

2.3.1. Effects of Antidepressant Drugs on BDNF

Antidepressants are medications that help to reduce the symptoms of depression and other mood disorders. They usually influence neurotransmitter systems, especially serotonin, norepinephrine, and dopamine. Literature suggests that Selective Serotonin Reuptake

Inhibitors (SSRIs) and Tricyclic Antidepressants (TCAs) are known to have significant impacts on BDNF levels [52]. This impact is thought to be mediated by increased serotonin and norepinephrine levels, which stimulate BDNF expression. BDNF has a high affinity for the Tropomyosin Receptor Kinase B (TrkB), a tyrosine kinase receptor that is expressed both pre- and post-synaptically. The upregulation of BDNF by these antidepressant medications enhances synaptic plasticity and neurogenesis, which improves mood and cognitive performance while reducing depression symptoms [53]. Several clinical studies confirm that patients with major depression typically have reduced amounts of BDNF in their blood and brain. Effective antidepressant therapy is usually associated with an increase in BDNF levels. Antidepressant medicines such as SSRIs, SNRIs, TCAs, and MAOIs can elevate BDNF levels for at least four weeks to eight weeks, which aids in their therapeutic effects by increasing neuroplasticity, neuronal maturation synaptogenesis, and neurogenesis. This method emphasizes the relevance of BDNF in the pathogenesis of depression, as well as the possibility of using BDNF-related tactics to generate novel antidepressants. For example, BDNF levels significantly increased after SSRI treatment in patients with moderate to severe depression, according to research by Lee and Kim (2010) [54]. There are several studies carried out to assess the implication of BDNF in patients diagnosed with depression, as summarized in Table **1**.

Table 1. Summary of clinical studies that evaluate the role of BDNF in depressed patients.

Authors	Aim	Sample	Findings
Yousef, A.M. *et al.* 2021 [61]	To assess the serum BDNF and suicidal ideation among drug-naïve and drug-treated MDD patients attending university hospitals and comparing them to healthy control.	Blood samples were collected to measure plasma BDNF levels.	The MDD group had lower BDNF than the control group. Within the MDD group, drug-naïve patients had significantly lower BDNF than drug-treated patients.
Lee Y *et al.* [62]., 2021	To measure the concentration level of BDNF in women with postpartum depression	A total of 104 pregnant women were selected for the study, and 60 non-pregnant women were selected as normal controls. The pregnant participants were separated into three groups: perinatal non-depressed controls (n = 61), postpartum depression-recovery (n = 18), and postpartum depression (n = 25).	BDNF level was higher in the pregnant group and lower in the postpartum depression group (6 weeks after delivery) than in the perinatal non-depressed group. In the postpartum depression-recovery group, the BDNF concentration increased at 6 weeks after delivery compared to that at 24 weeks of gestation. This study clearly indicates significant changes in plasma levels of BDNF concentration in depressed pregnant women.
Emon *et al.* [63]., 2020	To evaluate the serum Brain-Derived Neurotrophic Factor (BDNF) levels in depressed patients with or without antidepressant therapy compared to healthy controls.	MDD patients without antidepressant therapy (n = 41), drug-treated MDD patients (n = 44), and age- and sex-matched HCs (n = 82).	Statistically Significant inverse correlations between serum BDNF levels and Hamilton Depression rating (Ham-D) scores were observed in MDD patients without antidepressant therapy (n = 41) and drug-treated MDD patients.
Knorr U *et al.* [64]., 2017	To understand the relation between BDNF levels in the plasma of healthy volunteers with and without a family history of depression.	healthy participants with a family history of depression (n = 76) compared to healthy people without (n = 39) family history of depression,	BDNF levels were considerably higher in healthy persons with a family history of depression (n = 76) compared to healthy people without (n = 39) family history of depression, and this effect was maintained after controlling for age and gender differences. A family history of depression may trigger elevated BDNF levels.
Varambally S *et al.* [65]., 2013	To measure serum BDNF levels in depressive patients without antidepressant therapy and relate this to the severity of depression.	43 (19 females) patients with depression (outpatients) and 24 (13 females) healthy volunteers	Significant reductions in BDNF levels were observed in depressed patients than in healthy volunteers. There was a significant negative correlation between the level of BDNF and total scores (HDRS), indicating that depressed patients had lower BDNF values and higher HDRS scores.
Guilloux *et al.* [66]., 2012.,	To investigate large-scale gene expression in the post-mortem brain of depressed patients.	Post-mortem brain of MDD subjects paired with matched controls (n=21 pairs).	The study's findings revealed that low RNA/protein (direct) and low BDNF-dependent gene pattern (indirect) were indicators of reduced BDNF function in the amygdala of female depressive patients. The study reported that the expression of BDNF and its receptor TrkB was reduced in postmortem brain samples of female patients diagnosed with depression.
Gonul AS *et al.* [67]., 2007	To investigate the level of serum BDNF in depressed patients before and after antidepressant therapy.	Depressed patients' (n=28) sBDNF levels were compared before and after 8 weeks of antidepressant therapy to those of healthy controls (n=18).	Patients' baseline serum BDNF levels were considerably lower than those of controls, and they linked negatively with HAM-D ratings. After 8 weeks of treatment, patients' sBDNF levels had increased substantially and were no longer different from those of controls.

(Table 1) contd.....

Authors	Aim	Sample	Findings
Shimizu E *et al*. [68]., 2003	To investigate the levels of BDNF in antidepressant-naive patients with MDD, antidepressant-treated patients with MDD, and normal control subjects.	Normal control subjects (*n* = 50), antidepressant-naive patients with MDD (*n* = 16), and antidepressant-treated patients with MDD (*n* = 17).	Study results showed that serum BDNF was significantly lower in the antidepressant-naive group than in the treated or in the control group. There was a significant negative correlation between serum BDNF and HAM-D scores in all patients.
Karege *et al*. [69]., 2002	To assess how BDNF levels vary in depressed patients and healthy controls	30 depressed patients (15 females and 15 males) and 30 healthy controls (15 females and 15 males).	The study found that BDNF levels were considerably lower in depressed patients than in healthy controls. These findings confirmed that major depressive disorder is associated with low serum BDNF levels, supporting the relationship of the role played by neurotrophic factors in affective disorders.

Abbreviations: BDNF: Brain-Derived Neurotrophic Factor, MDD: Major Depressive Disorder. HDRS: Hamilton Depression Rating Scale.

2.3.2. Exercise

Increased BDNF levels have been repeatedly associated with regular aerobic exercise. Acute and long-term exercise promotes the release of BDNF, especially in the hippocampus, which improves cognitive function and synaptic plasticity. One non-pharmacological way to support antidepressant treatment and avoid relapse is through exercise. Exercise has a moderate impact on raising peripheral BDNF levels in both clinical and healthy individuals, according to a study by Szuhany *et al.* (2015) [55].

2.3.3. Electroconvulsive Therapy (ECT)

For patients with severe, treatment-resistant depression (TRD) and other mental illnesses like bipolar disorder and schizophrenia, electroconvulsive therapy (ECT) is a tried-and-true and very successful treatment. It requires the administration of a brief electrical current to the brain, which induces a controlled seizure [56]. To guarantee the patient's comfort and safety, this treatment is usually carried out under general anaesthesia and muscle relaxants. The effect of ECT on levels of Brain-Derived Neurotrophic Factor (BDNF) is one of the strongest hypotheses for its therapeutic benefits. A neurotrophin that promotes neuron survival, development, and differentiation, BDNF is essential for neuroplasticity, or the brain's capacity to change and rearrange itself. It has been demonstrated that BDNF is markedly decreased in Major Depressive Disorder (MDD) patients, which leads to poor neuroplasticity, neuronal atrophy, and altered hippocampus neurogenesis.

Studies have demonstrated that ECT quickly raises BDNF levels in depressive patients' brains and serum, indicating that improved hippocampus and neuroplasticity may be two ways ECT elevates mood. Research has repeatedly shown that following a course of ECT treatments, BDNF levels increase, frequently in tandem with a clinical improvement in depressive symptoms [57]. According to Bocchio-Chiavetto *et al*. (2006), patients who received ECT experienced a significant increase in serum BDNF levels, which were associated with improvements in mood and depressive symptoms. Another preclinical study carried out by Nishi *et al*. (2011) discovered that ECT administration in rats increased BDNF expression in the hippocampus [58, 59]. The neurotrophic hypothesis of depression is supported by the rise in BDNF after ECT treatment, indicating that enhancing neuroplasticity may be essential for establishing long-lasting remission in depression. Clinical professionals may be able to identify which patients would benefit from this intervention with the help of more studies into BDNF as a biomarker for ECT response [60].

CONCLUSION

BDNF has emerged as a significant molecule in understanding the mechanism of depression, supporting the neurotrophic theory and providing insight into the disease mechanism. Improving neurotrophic factors signalling holds great potential for treating depression. BDNF regulates neuroplasticity, neurogenesis, neuronal survival, synaptic modulation, and synaptic plasticity. It plays an integral part in the pathways underlying depressive illnesses and has been proposed by two mechanisms as a potential biomarker for depression. The Trk signalling pathway, which is triggered by neurotrophins, may be crucial for the screening of new antidepressant medications. Several studies have repeatedly demonstrated that people with depression had lower levels of BDNF than controls may negatively correlate with the symptoms of depression severity, with these levels significantly improving after successful antidepressant treatment. This link shows that BDNF could be a useful marker for predicting depressed symptoms or antidepressant response. Despite its potential, various limitations must be addressed before BDNF may be utilized as a biomarker. However, its clinical application faces substantial challenges, such as variability, standardization, and the peripheral-central BDNF link. By resolving these issues through rigorous study, BDNF has the potential to become a helpful tool in the early detection and treatment of depression, ultimately improving outcomes for people at higher risk. The combination of BDNF measures with other biological and clinical indications may pave the way for a more comprehensive and precise approach to predicting and treating depression.

AUTHORS' CONTRIBUTIONS

The authors confirm their contribution to the paper as follows: T.P.V.: Study conception and design; R.S.: Analysis and interpretation of results; S.C.: Draft manuscript. All authors reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

BDNF	=	Brain-Derived Neurotrophic Factor
WHO	=	World Health Organization's
ICD	=	International Classification of Diseases
MDD	=	Major Depressive Disorder
NGF	=	Nerve Growth Factor
ER	=	Endoplasmic Reticulum
eNOS	=	endothelial Nitric Oxide Synthase

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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