Proceedings of ICBioMed 2026 Symposium: Biomedical Engineering and Public Health: Real-Time Wearables for Disease Detection
DOI: 10.54254/2753-8818/2026.ES38447

Targeting BDNF to Overcome Treatment Resistance in Depression: Research Progress from Mechanism to Clinic

Yige Wang

School of Medicine, Qinghai University, Xining, China
3123433463@qq.com

Abstract. Depression ranks among the top causes of disability worldwide. About 40%-50% of the patients have insufficient response to conventional antidepressants, and treatment resistance has become a core clinical bottleneck. BDNF, as a key regulatory molecule of neuroplasticity, is regarded as the common final pathway of antidepressant action. This article systematically reviews the biological basis of the BDNF/TrkB signaling pathway and its differential mechanisms in treatment sensitivity and resistance. In the sensitive state, antidepressants up-regulate BDNF in the hippocampal dentate gyrus and TrkB signaling in the dorsal raphe nucleus through epigenetic modification, and promote neurogenesis and synaptic remodeling; in the resistant state, the high methylation of the BDNF promoter, the imbalance of pro-BDNF/mBDNF conversion, the disorder of TrkB conduction and the impairment of neurogenesis together constitute the molecular basis. In addition, this article sorts out the regulatory effects of genetic polymorphism, environmental stress, inflammation and the gut microbiota-gut-brain axis on the BDNF treatment response, and discusses the BDNF-based treatment stratification strategy, and holds that targeting the BDNF system is expected to provide a new strategy for the precise treatment of treatment-resistant depression.

Keywords: Brain-derived neurotrophic factor, Depression, Treatment resistance, TrkB receptor, Epigenetic regulation

1. Introduction

Depression, as one of the mental diseases with the highest disability rate in the world, takes persistent low mood, loss of interest and the impairment of cognitive and somatic function as the core features, and has become the second largest cause of the global burden of disability [1, 2]. Although the disease burden is heavy, the expenditure on depression treatment in high-income countries is 25 times that in middle- and low-income countries, and the gap in treatment accessibility is significant [2]. At present, the pathogenesis of depression has not been fully clarified, and it mainly involves theories such as the monoaminergic neurotransmitter hypothesis and the functional abnormality of the hypothalamic-pituitary-adrenal axis [3]. However, the limitations of the monoamine hypothesis have become increasingly prominent. A large number of antidepressants do not act directly on monoamine reuptake, but exert their effects by regulating the glutamatergic N-methyl-D-aspartate receptor receptor, the γ-aminobutyric acidergic signaling, opioid receptors and

© 2026 The Authors. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (https://creativecommons.org/licenses/by/4.0/).

DOI: 10.54254/2753-8818/2026.ES38447

other pathways, suggesting that different antidepressant mechanisms may have a common final pathway [4].

The neuroplasticity hypothesis holds that the key molecule of this pathway is brain-derived neurotrophic factor BDNF and its receptor tropomyosin receptor kinase B [5]. BDNF is widely distributed in the cerebral cortex and the hippocampus, and has an important regulatory effect on the growth, differentiation, survival and synaptic plasticity of neurons. Antidepressant drugs and physical therapy usually exert their efficacy by increasing BDNF expression and promoting neuron regeneration [6, 7]. Both animal models and autopsy studies of patients with depression show that stress exposure or the depressive state is related to the decrease of BDNF levels in the hippocampus and the cortex [8]. However, about 40%-50% of the patients with depression have insufficient response to conventional antidepressants, and those who still cannot achieve remission after two or more adequate courses of treatment are defined as treatment-resistant depression (Treatment-resistant depression, TRD) [9]. The continuous activation of the κ opioid receptor can lead to the epigenetic silencing of Bdnf transcripts II and IV in the prefrontal cortex by up-regulating HDAC5, and the NTRK2 gene polymorphism can also increase the risk of treatment resistance by affecting the hippocampal volume, suggesting the core position of the BDNF-TrkB signaling pathway in antidepressant efficacy [10, 11]. New drugs such as ketamine provide new options for TRD, and also further support the potential of BDNF as a biomarker of antidepressant efficacy [12]. This article systematically summarizes the mechanism of action and the clinical research progress of BDNF in depression, in order to provide a scientific basis for the treatment of TRD.

2. BDNF signaling pathway and the antidepressant mechanism of action

BDNF is a member of the neurotrophic factor family. Its gene is located on human chromosome 11 (11q13) and encodes a precursor protein of about 70 kb. Its biologically active form is a homodimer, and the mature mBDNF is generated from pro-BDNF through proteolytic cleavage. This process can be mediated by intracellular proconvertase cleavage or the extracellular tPA/plasmin system, and the latter participates in the regulation of long-term hippocampal synaptic plasticity [13, 14]. BDNF is mainly distributed in the cerebral cortex and the hippocampus. After it binds to the TrkB receptor, it activates downstream signaling pathways and promotes neuron survival, the maintenance of dendritic spine morphology and hippocampal neurogenesis [13, 15-17]. On the contrary, the binding of pro-BDNF to the p75NTR receptor can induce cell apoptosis and long-term depression, forming a functional antagonism [18]. The down-regulation of BDNF system expression or the imbalance of TrkB/p75 signaling has been confirmed to participate in the pathological process of a variety of neuropsychiatric diseases such as Alzheimer's disease, schizophrenia and depression [19-21]. In addition, BDNF is also distributed in the peripheral nervous system and the gut, and participates in the regulation of intestinal motility and the maintenance of metabolic homeostasis, but its regulatory effect on neuroplasticity in the central nervous system is the core basis of its antidepressant effect [22-24].

Classical antidepressants need 1-2 weeks of continuous administration before they can significantly up-regulate the expression of hippocampal BDNF and TrkB, and then activate downstream signaling pathways and relieve the inhibition of chronic stress on BDNF expression [25-27]. Different classes of antidepressants (SSRI, SNRI, tricyclics, MAOIs) and electroconvulsive therapy can all up-regulate BDNF expression [28, 29]. In addition, studies have shown that the virus-targeted knockout of BDNF in the hippocampal dentate gyrus of mice significantly weakens the effect of antidepressants [30]. The rapid-acting antidepressant ketamine also depends on BDNF/TrkB signaling to exert its efficacy, and its antidepressant effect is weakened in conditional

DOI: 10.54254/2753-8818/2026.ES38447

BDNF or TrkB knockout mice [5]. Both typical and rapid-acting antidepressants can directly bind to the TrkB receptor and enhance BDNF signal transduction through allosteric effects [31]. The existence of this common pathway explains why drugs with different mechanisms can finally improve depressive symptoms.

3. The role of BDNF in treatment sensitivity in depression

Whether peripheral BDNF can predict the response to antidepressant treatment is still inconsistent in the current research results. Some systematic reviews and light therapy studies have found that a higher baseline BDNF level or the increase of BDNF after treatment is related to better efficacy, suggesting that BDNF changes may serve as a candidate marker for efficacy prediction [32, 33]. However, the detection method may affect its predictive efficacy. For example, serum BDNF mainly comes from the release of platelet α granules during coagulation, while whole blood BDNF needs to be measured after cell lysis. Studies have shown that the whole blood BDNF of patients with depression is about 14% lower than that of healthy controls, but the baseline level can neither predict the efficacy of escitalopram nor change with the improvement of symptoms, suggesting that whole blood BDNF is more suitable as a diagnostic marker than as a prognostic marker [34]. In addition to the protein level, the methylation of CpG sites in the promoter region of the BDNF gene also shows the potential of efficacy prediction. Among them, the methylation of the BDNF exon IV promoter has been confirmed by a number of studies to be related to the response to antidepressant treatment, and a German multicenter clinical trial is verifying whether BDNF -87 methylation can guide treatment decisions [35, 36]. The conditional knockout of BDNF in the hippocampal dentate gyrus can significantly weaken the behavioral effects of antidepressants, which establishes the core position of BDNF in mediating antidepressant efficacy [30]. However, this effect has obvious brain region specificity. The knockout of BDNF in the dentate gyrus is enough to weaken the drug efficacy, while the knockout in the CA1 region has no effect, indicating that BDNF in the dentate gyrus is necessary for the efficacy [30, 37]. In addition, the selective knockout of the TrkB receptor in the dorsal raphe nucleus also weakens the antidepressant response, suggesting that BDNF-TrkB signaling needs the coordinated participation of multiple brain regions [38]. At the mechanistic level, antidepressants can promote the transcription of specific exons by up-regulating the H3K18 acetylation level in the BDNF promoter region, and enhance BDNF expression and neuronal plasticity [39].

The Bdnf gene contains nine non-coding exons driven by independent promoters, and can be transcribed to produce nine different Bdnf transcripts, which show differential expression patterns in different brain regions and developmental stages [40]. Different classes of antidepressants regulate the expression of BDNF exons in specific ways, and the regulatory mechanism has no unified rule. This regulation also shows obvious brain region specificity. For example, the chronic administration of the tricyclic antidepressant imipramine can up-regulate the transcription level of specific BDNF exons through epigenetic modifications such as histone acetylation [41, 42]. The antidepressant effect of the BDNF-TrkB pathway depends on the complete receptor-ligand system and the coordinated integration of multiple brain regions such as the hippocampus and the dorsal raphe nucleus [38]. The selective knockout of TrkB in the dorsal raphe nucleus can significantly weaken the behavioral effects of classical antidepressants, suggesting that the activation of TrkB in this nucleus is a necessary link of antidepressant efficacy. After antidepressants enhance the serotonergic tone, they may activate the TrkB receptors in the dorsal raphe nucleus by up-regulating the release of BDNF in the hippocampal dentate gyrus, forming a positive feedback loop. Future studies need to further verify this hypothesis and clarify the downstream intracellular signaling pathways that

DOI: 10.54254/2753-8818/2026.ES38447

participate in the antidepressant response mediated by BDNF-TrkB in the dorsal raphe nucleus [38]. After BDNF-TrkB signaling is activated, multiple intracellular cascade reactions can be initiated. The core effect is to promote neuronal plasticity and synaptic remodeling, to regulate the occurrence, maturation and stability of dendritic spines, to increase the dendritic complexity of hippocampal neurons, to repair the synaptic damage caused by chronic stress, and the recovery of the hippocampal BDNF expression level is positively correlated with the improvement of depression-like behavior [43, 44].

4. The role of BDNF in treatment resistance in depression

BDNF has been studied as a potential biomarker in the pathophysiological process of TRD (Table 1). Similar to ordinary MDD, the BDNF level of TRD patients also changes under the influence of continuous antidepressant treatment [45]. A number of studies have shown that the baseline serum BDNF level of TRD patients is decreased, and the low level of BDNF is closely related to the poor response to conventional antidepressant treatment and the refractoriness of the disease [46, 47]. The relevant evidence of electroconvulsive therapy suggests that BDNF may play an important role in the clinical efficacy of TRD patients, and it is speculated that the patients may need a higher mBDNF level before remission can be achieved [48]. However, the existing clinical research evidence is still controversial. Some clinical studies on ketamine and repetitive transcranial magnetic stimulation did not observe a significant increase in the BDNF level of the treatment group of MDD patients. In addition, studies have confirmed that BDNF-TrkB signaling has a key mediating role and potential predictive value in the treatment of TRD patients with low-dose ketamine infusion [49]. The abnormality of the BDNF signaling pathway is closely related to treatment resistance. The knockdown of BDNF in the hippocampal dentate gyrus can block the behavioral effects of desipramine and citalopram; mice that over-express the truncated TrkB receptor have no response to imipramine and fluoxetine. The basal level of BDNF in the brain of DRL rats is down-regulated, traditional antidepressants are ineffective, and the depression-like behavior can be reversed after brain stimulation up-regulates BDNF, and the insufficient BDNF signaling in the medial prefrontal cortex also leads to the failure of the antidepressant effect of ketamine [50, 51].

The down-regulation of BDNF expression in the treatment-resistant state involves a variety of molecular abnormalities. In TRD patients, the BDNF promoter region is highly methylated, accompanied by the increased activity of DNA methyltransferase (DNA methyltransferase, DNMT). Among them, DNMT1 is responsible for the maintenance of the methylation pattern, while DNMT3A and DNMT3B have the activity of catalyzing DNA methyl transfer [52, 53]. In the nucleus accumbens (NAc) that regulates reward behavior, in the postmortem brain tissue of depressed patients and in animal models of depression, the up-regulation of the DNMT3A level has been detected [54]. In addition, the expression and activity of histone deacetylases HDAC2 and HDAC5 are enhanced, which catalyze the deacetylation of histones H3 and H4, leading to the compression of the chromatin structure and hindering the binding of transcription factors such as CREB to the BDNF promoter region, thereby inhibiting gene transcription [42]. At the same time, the inhibitory effect of MeCP2 on BDNF transcription is also enhanced [55]. The biological activity of BDNF depends on the conversion efficiency of its precursor pro-BDNF to the mature form mBDNF, and the blocking or reversal of this process can lead to treatment resistance. After BDNF is synthesized, it needs to be cleaved by proteases such as prohormone convertase or extracellular plasminogen activator before mBDNF with biological activity can be generated [56]. In the treatment-resistant state, this cleavage process is inhibited, pro-BDNF accumulates abnormally in

DOI: 10.54254/2753-8818/2026.ES38447

the synaptic cleft, and the mBDNF level decreases significantly. In addition, matrix metalloproteinase-9, as the key enzyme that regulates the conversion of pro-BDNF to mBDNF, has abnormal expression or activity under pathological conditions and cannot accurately complete the cleavage, thus breaking the dynamic balance of pro-BDNF/mBDNF [57].

The down-regulation and disorder of the BDNF/TrkB system have been fully confirmed to participate in the pathogenesis of depression and a variety of nervous system diseases. After the TrkB receptor binds to BDNF, it can activate a number of downstream signaling pathways such as PI3K/Akt and MAPK-ERK, and plays an important supporting role in the survival of central neurons [58]. In the treatment-resistant state, the ratio of pro-BDNF to mBDNF is unbalanced. pro-BDNF mainly binds to the p75NTR receptor and induces cell apoptosis, neuron death and long-term depression, forming a functional antagonism with the neuroprotective effect mediated by BDNF/TrkB [18]. In addition, long-term pathological stress can lead to the reduction of the number of functional TrkB receptors on the cell membrane surface, further weakening the conduction efficiency of downstream signals. Traditional antidepressants mainly up-regulate the expression level of BDNF, but cannot effectively improve the functional defect of the TrkB receptor. Even if the expression of BDNF protein increases, the downstream neuroprotective signal is still difficult to be transmitted effectively, the synaptic damage persists, and finally leads to poor drug response. The serum and plasma BDNF levels of TRD patients are significantly lower than those of healthy controls and treatment-sensitive patients, and a number of studies have shown that the increase of BDNF in TRD patients after antidepressant treatment is significantly smaller than that in treatment-sensitive patients, suggesting that the insufficient response of the BDNF system may constitute an important marker of treatment resistance [59, 60]. At the level of cerebrospinal fluid, the BDNF level is more closely correlated with the expression of hippocampal BDNF. The cerebrospinal fluid BDNF level of TRD patients is lower than that of treatment-sensitive patients, and is negatively correlated with the severity of depression. The longer the clinical course and the more the number of previous treatment failures, the lower the BDNF level. At the same time, early-onset and late-onset TRD may also differ in the abnormal pattern of the BDNF system. Neuroimaging studies have provided objective evidence for the involvement of BDNF system abnormality in TRD. Imaging techniques such as PET and fMRI show that the hippocampal volume of TRD patients is reduced and the activity of the prefrontal cortex is decreased, and the above changes are related to the decrease of the BDNF level [61]. The hippocampal gray matter volume of BDNF Val66Met polymorphism carriers is smaller. Among them, the left hippocampal volume of Val66 homozygous patients is significantly negatively correlated with the number of days of symptom remission. Such patients have a worse response to treatment and are more likely to develop treatment resistance [62].

Table 1. Comparison of the differential mechanisms of BDNF in treatment sensitivity and resistance in depression

Dimension	Treatment-sensitive state	Treatment-resistant state
BDNF expression level	Antidepressants up-regulate BDNF expression in the hippocampus and the prefrontal cortex	The BDNF promoter region (P1/P4) is highly methylated, DNMT activity is increased, and BDNF transcription is inhibited
proBDNF/mBDNF balance	proBDNF is normally cleaved into mBDNF by the tPA/plasmin system	Cleavage is blocked, proBDNF accumulates abnormally, and mBDNF decreases

DOI: 10.54254/2753-8818/2026.ES38447

Table 1. (continued)

TrkB signal transduction	TrkB receptor function is intact, and the downstream PI3K/Akt and MAPK-ERK pathways are activated	Long-term stress reduces TrkB receptors, and the signal transduction efficiency decreases
Key brain regions	BDNF in the hippocampal dentate gyrus and TrkB in the dorsal raphe nucleus participate synergistically	Insufficient BDNF in the medial prefrontal cortex causes the rapid effect of ketamine to fail
Epigenetic regulation	H3K18 acetylation promotes the transcription of BDNF exons	HDAC2/HDAC5 are up-regulated, chromatin is compressed, and CREB binding is blocked
Neurogenesis and synaptic plasticity	The generation of dendritic spines increases, and synaptic remodeling is enhanced	Neurogenesis is impaired, and the hippocampal volume is reduced
Intervention strategy	SSRI, SNRI, ketamine, etc. are effective	It is necessary to combine TrkB agonists, demethylating drugs or cleavage-promoting strategies

5. Regulatory factors influencing the response of BDNF in the treatment of depression

5.1. Genetic and environmental factors

Current studies suggest that TRD may be jointly driven by genetic and epigenetic mechanisms. The two interact by regulating synaptic plasticity, neurotransmitter function and the immune-neurobiological pathway, and participate in the occurrence and development of the disease [63]. Among the BDNF gene polymorphisms, the Val66Met locus has the closest correlation with the response to antidepressant treatment, and can partially predict the efficacy of SSRI drugs in patients with major depressive disorder. Among them, the treatment response of patients with the Val/Val genotype is better than that of Val/Met carriers [64, 65]. In addition, some studies have also shown that the Met/Met genotype is closely related to the severity of depression [66]. Further studies have found that the BDNF Val66Met polymorphism can predict the treatment response to escitalopram, and a more significant improvement of efficacy was observed in Met allele carriers [67]. At the epigenetic level, a variety of miRNAs, including miR-30a, miR-133b, miR-16, miR-1202 and the let-7 family, are continuously abnormally expressed in TRD and tend to be normalized after successful treatment, suggesting that miRNA participates in the regulatory process of antidepressant efficacy [63].

In addition to genetic factors, environmental stress also plays an important role in epigenetic modification and may induce or aggravate depressive symptoms. Both negative life events and traumatic experiences can increase the risk of depression [68]. Chronic stress is a key exogenous factor that induces the down-regulation of BDNF expression and promotes depression-like behavior. The changes of Bdnf mRNA expression induced by antidepressant treatment are regulated by epigenetic mechanisms, involving processes such as DNA methylation and histone modification. However, preclinical studies have found that exposure to unpredictable chronic mild stress can lead to the impairment of the DNA demethylation mechanism that targets Bdnf transcripts [37], and

DOI: 10.54254/2753-8818/2026.ES38447

chronic stress can interfere with BDNF-TrkB signal transduction and damage the structural and functional integrity of synapses [69]. On the contrary, regular aerobic exercise can significantly increase the BDNF level and exert an antidepressant effect, suggesting that exercise can be used as a non-drug intervention, or be applied in synergy with antidepressant treatment, to improve the cognitive and emotional symptoms of patients with major depressive disorder [70].

5.2. Inflammatory and metabolic factors

The inflammatory response and the metabolic state of the body jointly participate in the pathological process of depression. The levels of pro-inflammatory cytokines in the serum of patients with depression are increased, including tumor necrosis factor α, interleukin-6 and IL-1β [71]. Clinical studies have also shown that after patients with psoriasis received the TNF-α antagonist etanercept, the symptoms of major depression were alleviated, while depression-related adverse reactions are common during the treatment with IFN-α and IL-2, further suggesting the important role of inflammatory signaling pathways in the pathogenesis of depression [72]. One of the core mechanisms of TRD involves pro-inflammatory cytokines interfering with the synthesis and release of monoamine neurotransmitters, leading to the decrease of the 5-HT level and the up-regulation of the inhibitory 5-HT2C receptor, thereby inducing or aggravating depressive symptoms [9]. In addition, the aggravation of peripheral and central inflammatory responses is also closely related to the appearance of depressive symptoms, suggesting that anti-inflammatory strategies may have potential therapeutic value for patients with depression [73]. At the metabolic level, diabetes is one of the most common metabolic diseases. Its insulin resistance in the central nervous system can damage synaptic plasticity, interfere with the neurotransmitter systems related to emotion regulation, and is closely related to the increase of antidepressant prescriptions, treatment non-response, the enhancement of drug resistance and the prolongation of the disease course [74].

5.3. Gut microbiota-gut-brain axis

The imbalance of the gut microbiota-gut-brain axis has been confirmed to participate in the pathogenesis of depression. This axis regulates the response to antidepressant treatment through the vagus nerve, the immune system and the hypothalamic-pituitary-adrenal axis. Gut microbiota dysbiosis can reduce the production of short-chain fatty acids, destroy the intestinal barrier and induce neuroinflammation, and then significantly inhibit BDNF expression. At the same time, the disturbance of the microbiota can interfere with tryptophan metabolism and over-activate the hypothalamic-pituitary-adrenal axis, further down-regulating the BDNF level and damaging neuroplasticity [75]. Studies have shown that specific pathogen-free mice treated with oral antibacterial drugs have increased hippocampal BDNF levels after a transient disturbance of the gut microbiota, and show a preventive effect on depression-like behavior [76, 77]. Other studies have confirmed that there are significant differences in the composition of the gut microbiota between patients with depression and healthy controls, among which the changes of the Bacteroidaceae flora are particularly prominent [77, 78]. Randomized controlled trials have shown that after patients with depression continuously supplemented probiotics for 8 weeks, the serum BDNF level increased significantly and the depression score decreased [79]. In addition, gut microbiota dysbiosis can drive the progression of depression through neuroimmune and metabolic pathways, and the depressive state itself can also reversely change the intestinal microenvironment and reshape the structure of the microbiota, and the two form a vicious circle of mutual promotion [75].

DOI: 10.54254/2753-8818/2026.ES38447

6. Conclusion and outlook

The BDNF/TrkB pathway plays a core role in the pathogenesis and treatment of depression. This article systematically sorts out the differential mechanisms of BDNF in treatment sensitivity and resistance, and reveals multi-level molecular obstacles such as epigenetic silencing, pro-BDNF/mBDNF imbalance, TrkB signaling disorder and impaired neurogenesis. Based on the above analysis, this article puts forward a core view, that is, treatment resistance does not originate from the insufficient total amount of BDNF, but is caused by the specific obstacles of this signaling pathway at the three levels of epigenetics, cleavage processing and receptor conduction. Therefore, the key to overcoming TRD lies in the precise repair of the specific damaged link of the pathway, rather than the general increase of BDNF. Under this framework, this article puts forward the following hypothesis: the combination of a TrkB allosteric agonist and an epigenetic regulator (such as a DNMT or HDAC inhibitor) can synergistically restore the function of BDNF signaling, thereby reversing antidepressant treatment resistance. In terms of clinical translation, the potential of BDNF as a marker for efficacy prediction has been recognized, but the inconsistency of detection methods, the heterogeneity of studies and the overlapping expression of diseases still restrict its standardized application. In the future, it is necessary to establish standardized norms for BDNF detection and combine multi-index models to improve the ability to predict TRD, to deeply clarify the abnormal mechanism of the cleavage enzyme system under pathological conditions, to clarify the differential functions and the integration mechanism of BDNF/TrkB signaling in different brain regions, and to verify the guiding value of genetic and epigenetic markers in individualized treatment through large-scale longitudinal studies.

References

[1] Xu, F. N., Liu, Q. Z., & Zhang, L. D. (2024). Research progress on the correlation between brain-derived neurotrophic factor and depression treatment. *Journal of Medical Research and Combat Trauma Care, 37*(2), 219–24.

[2] Zhang, Z., Chen, X., Wu, S., et al. Global, regional and national burden of anxiety and depression disorders from 1990 to 2021, and forecasts up to 2040. *J Affect Disord, 393*(Pt A), 120299.

[3] Wen, Y. L., Ning, L. C., Bi, Y. M., et al. (2018). Study on the changes of BDNF expression in patients with depression and its relationship with disease severity. *Journal of Guangzhou Medical University, 46*(3), 31–4.

[4] Chávez-Castillo, M., Núñez, V., Nava, M., et al. Depression as a neuroendocrine disorder: Emerging neuropsychopharmacological approaches beyond monoamines. *Adv Pharmacol Sci, 2019*, 7943481.

[5] Björkholm, C., Monteggia, L. M. BDNF - a key transducer of antidepressant effects. *Neuropharmacology, 102*, 72–9.

[6] Dong, P., Lyu, S. M., Bi, D. Z., et al. (2024). Discussion on the mechanism of acupuncture intervention in depression based on the brain-derived neurotrophic factor signaling pathway. *World Chinese Medicine, 19*(10), 1505–9.

[7] Zhou, H. T., & Huang, M. L. (2019). Related research on duloxetine in the treatment of depression based on the BDNF hypothesis. *China Modern Doctor, 57*(25), 166-8.

[8] Chakrapani, S., Eskander, N., De Los Santos, L. A., et al. (2020). Neuroplasticity and the biological role of brain derived neurotrophic factor in the pathophysiology and management of depression. *Cureus, 12*(11), e11396.

[9] Kajumba, M. M., Kakooza-Mwesige, A., Nakasujja, N., et al. (2024). Treatment-resistant depression: Molecular mechanisms and management. *Mol Biomed, 5*(1), 43.

[10] Paolini, M., Fortaner-Uyà, L., Lorenzi, C., et al. (2023). Association between NTRK2 polymorphisms, hippocampal volumes and treatment resistance in major depressive disorder. *Genes (Basel), 14*(11).

[11] Yadav, A., Dogra, S., Boda, A. K., et al. (2024). Kappa opioid receptor activation induces epigenetic silencing of brain-derived neurotropic factor via HDAC5 in depression. *ACS Chem Neurosci, 15*(18), 3286-97.

[12] Medeiros, G. C., Gould, T. D., Prueitt, W. L., et al. (2022). Blood-based biomarkers of antidepressant response to ketamine and esketamine: A systematic review and meta-analysis. *Mol Psychiatry, 27*(9), 3658-69.

DOI: 10.54254/2753-8818/2026.ES38447

[13] Hempstead, B. L. (2015). Brain-derived neurotrophic factor: Three ligands, many actions. *Trans Am Clin Climatol Assoc, 126*, 9–19.
[14] Pang, P. T., Teng, H. K., Zaitsev, E., et al. (2004). Cleavage of proBDNF by tPA/plasmin is essential for long-term hippocampal plasticity. *Science, 306*(5695), 487–491.
[15] Colucci-D'Amato, L., Speranza, L., & Volpicelli, F. (2020). Neurotrophic factor BDNF, physiological functions and therapeutic potential in depression, neurodegeneration and brain cancer. *Int J Mol Sci, 21*(20).
[16] Iu, E. C. Y., & Chan, C. B. (2022). Is brain-derived neurotrophic factor a metabolic hormone in peripheral tissues? *Biology (Basel), 11*(7).
[17] Kowiański, P., Lietzau, G., Czuba, E., et al. (2018). BDNF: A key factor with multipotent impact on brain signaling and synaptic plasticity. *Cell Mol Neurobiol, 38*(3), 579–593.
[18] Yang, M., Wu, S., Luo, R., et al. (2025). The role and mechanism of brain-derived neurotrophic factor in chronic pain. *Journal of Medical Research, 54*(10), 128–132+76.
[19] Li, H. J., & Han, B. (2014). The role of brain-derived neurotrophic factor in Alzheimer's disease. *Chinese Journal of Clinicians (Electronic Edition), 8*(21), 3888-91.
[20] Lin, X. F. (2022). The relationship between BDNF and pathological pain. *Fujian Light and Textile*, (2), 28-32+7.
[21] Sun, M. M., & Liu, L. F. (2011). Research progress on the association between brain-derived neurotrophic factor BDNF and schizophrenia. *Journal of Psychiatry, 24*(5), 392-4.
[22] Yan, F., Liao, H. J., Xue, Z. L., et al. (2025). Effects of oxygen-glucose deprivation on the expression levels of euchromatic histone lysine methyltransferase 2 and brain-derived neurotrophic factor in rat cardiomyocytes. *Journal of Xinxiang Medical University, 42*(5), 345-50.
[23] Zhao, J. M., Fang, Y. F., & Liang, C. (2025). Research progress on the detection value and mechanism of action of brain-derived neurotrophic factor in intestinal dysfunction. *Laboratory Testing, 3*(23), 193-5.
[24] Lei, M., Liu, Q., Nie, J., et al. (2024). Impact and mechanisms of action of BDNF on neurological disorders, cancer, and cardiovascular diseases. *CNS Neurosci Ther, 30*(12), e70138.
[25] Ma, T., Zhang, J. H., Wang, R., et al. (2025). Effects of Lactobacillus reuteri CCTCC M 2016546 on the behavior of depressed rats and the related mechanism. *Acta Microbiologica Sinica, 65*(11), 5008–5021.
[26] Harmer, C. J., Duman, R. S., & Cowen, P. J. (2017). How do antidepressants work? New perspectives for refining future treatment approaches. *Lancet Psychiatry, 4*(5), 409–418.
[27] Hillhouse, T. M., & Porter, J. H. (2015). A brief history of the development of antidepressant drugs: From monoamines to glutamate. *Exp Clin Psychopharmacol, 23*(1), 1–21.
[28] Balu, D. T., Hoshaw, B. A., Malberg, J. E., et al. (2008). Differential regulation of central BDNF protein levels by antidepressant and non-antidepressant drug treatments. *Brain Res, 1211*, 37–43.
[29] Duman, R. S., Deyama, S., & Fogaça, M. V. (2021). Role of BDNF in the pathophysiology and treatment of depression: Activity-dependent effects distinguish rapid-acting antidepressants. *Eur J Neurosci, 53*(1), 126–139.
[30] Adachi, M., Barrot, M., Autry, A. E., et al. (2008). Selective loss of brain-derived neurotrophic factor in the dentate gyrus attenuates antidepressant efficacy. *Biol Psychiatry, 63*(7), 642–649.
[31] Casarotto, P., Umemori, J., & Castrén, E. (2022). BDNF receptor TrkB as the mediator of the antidepressant drug action. *Front Mol Neurosci, 15*: 1032224.
[32] Kosanovic Rajacic, B., Sagud, M., Begic, D., et al. (2023). Plasma brain-derived neurotrophic factor levels in first-episode and recurrent major depression and before and after bright light therapy in treatment-resistant depression. *Biomolecules, 13*(9).
[33] Mikoteit, T., Beck, J., Eckert, A., et al. (2014). High baseline BDNF serum levels and early psychopathological improvement are predictive of treatment outcome in major depression. *Psychopharmacology (Berl), 231*(15): 2955-65.
[34] Navarro, M. L., Breum, A. W., Ozenne, B., et al. (2025). Whole blood BDNF is lower in patients with depression and unchanged by escitalopram in patients and healthy controls. *Prog Neuropsychopharmacol Biol Psychiatry, 141*: 111470.
[35] Lieb, K., Dreimüller, N., Wagner, S., et al. (2018). BDNF plasma levels and BDNF exon IV promoter methylation as predictors for antidepressant treatment response. *Front Psychiatry, 9*: 511.
[36] Maier, H. B., Neyazi, A., Bundies, G. L., et al. (2024). Validation of the predictive value of BDNF -87 methylation for antidepressant treatment success in severely depressed patients-a randomized rater-blinded trial. *Trials, 25*(1): 247.
[37] Cubillos, S., Engmann, O., & Brancato, A. (2022). BDNF as a mediator of antidepressant response: Recent advances and lifestyle interactions. *International Journal of Molecular Sciences, 23*(22).
[38] Adachi, M., Autry, A. E., Mahgoub, M., et al. (2017). TrkB signaling in dorsal raphe nucleus is essential for antidepressant efficacy and normal aggression behavior. *Neuropsychopharmacology, 42*(4), 886–94.

DOI: 10.54254/2753-8818/2026.ES38447

[39] Wang, F., Li, Z., Li, B., et al. (2025). Xiaochaihutang ameliorates depression-like behaviors induced via chronic social defeat stress by regulating exon-specific Bdnf transcription through H3K18 acetylation in the hippocampus of mice. *Phytomedicine, 140*, 156567.
[40] You, H., & Lu, B. (2023). Diverse functions of multiple Bdnf transcripts driven by distinct Bdnf promoters. *Biomolecules, 13*(4).
[41] Dwivedi, Y., Rizavi, H. S., & Pandey, G. N. (2006). Antidepressants reverse corticosterone-mediated decrease in brain-derived neurotrophic factor expression: Differential regulation of specific exons by antidepressants and corticosterone. *Neuroscience, 139*(3), 1017–29.
[42] Tsankova, N. M., Berton, O., Renthal, W., et al. (2006). Sustained hippocampal chromatin regulation in a mouse model of depression and antidepressant action. *Nature Neuroscience, 9*(4), 519–25.
[43] Yang, T., Nie, Z., Shu, H., et al. (2020). The role of BDNF on neural plasticity in depression. *Front Cell Neurosci, 14*, 82.
[44] Zagrebsky, M., Tacke, C., & Korte, M. (2020). BDNF signaling during the lifetime of dendritic spines. *Cell Tissue Res, 382*(1), 185–99.
[45] Mancuso, E., Sampogna, G., Boiano, A., et al. (2023). Biological correlates of treatment resistant depression: A review of peripheral biomarkers. *Front Psychiatry, 14*, 1291176.
[46] Kurita, M., Nishino, S., Kato, M., et al. (2012). Plasma brain-derived neurotrophic factor levels predict the clinical outcome of depression treatment in a naturalistic study. *PLoS One, 7*(6), e39212.
[47] Wolkowitz, O. M., Wolf, J., Shelly, W., et al. (2011). Serum BDNF levels before treatment predict SSRI response in depression. *Prog Neuropsychopharmacol Biol Psychiatry, 35*(7), 1623–30.
[48] Psomiades, M., Mondino, M., Galvão, F., et al. (2022). Serum mature BDNF level is associated with remission following ECT in treatment-resistant depression. *Brain Sci, 12*(2).
[49] Chen, M. H., Kao, C. F., Tsai, S. J., et al. (2021). Treatment response to low-dose ketamine infusion for treatment-resistant depression: A gene-based genome-wide association study. *Genomics, 113*(2), 507–14.
[50] Deyama, S., & Duman, R. S. (2020). Neurotrophic mechanisms underlying the rapid and sustained antidepressant actions of ketamine. *Pharmacol Biochem Behav, 188*, 172837.
[51] Moshe, H., Gal, R., Barnea-Ygael, N., et al. (2016). Prelimbic stimulation ameliorates depressive-like behaviors and increases regional BDNF expression in a novel drug-resistant animal model of depression. *Brain Stimul, 9*(2), 243–50.
[52] Duan, Z., & Lu, J. (2020). DNA methyltransferases in depression: An update. *Front Psychiatry, 11*, 538683.
[53] Kleimann, A., Kotsiari, A., Sperling, W., et al. (2015). BDNF serum levels and promoter methylation of BDNF exon I, IV and VI in depressed patients receiving electroconvulsive therapy. *J Neural Transm (Vienna), 122*(6), 925–8.
[54] Park, H. S., Kim, J., Ahn, S. H., et al. (2021). Epigenetic targeting of histone deacetylases in diagnostics and treatment of depression. *Int J Mol Sci, 22*(10).
[55] Chen, W. G., Chang, Q., Lin, Y., et al. (2003). Derepression of BDNF transcription involves calcium-dependent phosphorylation of MeCP2. *Science, 302*(5646), 885–9.
[56] Zhang, F., Luo, J., & Zhu, X. (2018). Ketamine ameliorates depressive-like behaviors by tPA-mediated conversion of proBDNF to mBDNF in the hippocampus of stressed rats. *Psychiatry Res, 269*, 646–51.
[57] Yang, B. Y., Hu, Y. L., Yu, L. J., et al. (2026). MMP-9 participates in the pathogenesis of vascular cognitive impairment based on synaptic plasticity. *Journal of Clinical and Pathology, 46*(5), 779–89.
[58] Numakawa, T., & Kajihara, R. (2025). The role of brain-derived neurotrophic factor as an essential mediator in neuronal functions and the therapeutic potential of its mimetics for neuroprotection in neurologic and psychiatric disorders. *Molecules, 30*(4).
[59] Yoshimura, R., Okamoto, N., Chibaatar, E., et al. (2023). The serum brain-derived neurotrophic factor increases in serotonin reuptake inhibitor responders patients with first-episode, drug-naïve major depression. *Biomedicines, 11*(2).
[60] Zheng, W., Jiang, M. L., He, H. B., et al. (2020). Serum BDNF levels are not associated with the antidepressant effects of nonconvulsive electrotherapy. *Neuropsychiatr Dis Treat, 16*, 1555–60.
[61] Miola, A., Meda, N., Perini, G., et al. (2023). Structural and functional features of treatment-resistant depression: A systematic review and exploratory coordinate-based meta-analysis of neuroimaging studies. *Psychiatry Clin Neurosci, 77*(5), 252-63.
[62] Cardoner, N., Soria, V., Gratacòs, M., et al. (2013). Val66Met BDNF genotypes in melancholic depression: Effects on brain structure and treatment outcome. *Depress Anxiety, 30*(3), 225-33.
[63] Sulić, P., Ražić Pavličić, A., Đapić Ivančić, B., et al. (2025). Role of genetic and epigenetic biomarkers in treatment-resistant depression: A literature review. *Genes (Basel), 16*(12).

DOI: 10.54254/2753-8818/2026.ES38447

[64] Kishi, T., Yoshimura, R., Ikuta, T., et al. (2017). Brain-derived neurotrophic factor and major depressive disorder: Evidence from meta-analyses. *Front Psychiatry, 8*: 308.
[65] Zelada, M. I., Garrido, V., Liberona, A., et al. (2023). Brain-derived neurotrophic factor (BDNF) as a predictor of treatment response in major depressive disorder (MDD): A systematic review. *Int J Mol Sci, 24*(19).
[66] Wu, H., Zhou, J. J., Chen, X. Y., et al. (2025). BDNF gene polymorphism and antidepressant response in Han Chinese patients with first-episode late-life depression. *Alpha Psychiatry, 26*(2): 39955.
[67] El-Hage, W., Vourc'h, P., Gaillard, P., et al. (2015). The BDNF Val(66)Met polymorphism is associated with escitalopram response in depressed patients. *Psychopharmacology (Berl), 232*(3), 575–81.
[68] Krishnan, V., & Nestler, E. J. (2008). The molecular neurobiology of depression. *Nature, 455*(7215), 894–902.
[69] Takahashi, M., & Shelton, R. C. (2025). From trauma to depression: Structural, synaptic, epigenetic, and molecular pathways linking early stress to lifelong vulnerability. *Front Psychiatry, 16*, 1666599.
[70] Guerrera, C. S., Furneri, G., Grasso, M., et al. (2020). Antidepressant drugs and physical activity: A possible synergism in the treatment of major depression? *Front Psychol, 11*, 857.
[71] Hannestad, J., DellaGioia, N., & Bloch, M. (2011). The effect of antidepressant medication treatment on serum levels of inflammatory cytokines: A meta-analysis. *Neuropsychopharmacology, 36*(12), 2452–9.
[72] Kovacs, D., Gonda, X., Petschner, P., et al. (2014). Antidepressant treatment response is modulated by genetic and environmental factors and their interactions. *Ann Gen Psychiatry, 13*, 17.
[73] Zhang, J. C., Yao, W., & Hashimoto, K. (2016). Brain-derived neurotrophic factor (BDNF)-TrkB signaling in inflammation-related depression and potential therapeutic targets. *Current Neuropharmacology, 14*(7), 721-31.
[74] Fanelli, G., Bralten, J., Franke, B., et al. (2026). Insulin resistance and poorer treatment outcomes in depression: Evidence from UK Biobank primary care data. *British Journal of Psychiatry, 229*(1), 26-35.
[75] Su, Y., & Xia, Y. (2026). Gut microbiota dysbiosis and depression: Bidirectional interactions, mediating pathways, and microecological therapeutics. *Current Research in Food Science, 12*, 101372.
[76] Bercik, P., Denou, E., Collins, J., et al. (2011). The intestinal microbiota affect central levels of brain-derived neurotropic factor and behavior in mice. *Gastroenterology, 141*(2), 599-609, .e1-3.
[77] Liaqat, H., Parveen, A., & Kim, S. Y. (2022). Antidepressive effect of natural products and their derivatives targeting BDNF-TrkB in gut-brain axis. *International Journal of Molecular Sciences, 23*(23).
[78] Zheng, P., Yang, J., Li, Y., et al. (2020). Gut microbial signatures can discriminate unipolar from bipolar depression. *Advanced Science (Weinh), 7*(7), 1902862.
[79] Heidarzadeh-Rad, N., Gökmen-Özel, H., Kazemi, A., et al. (2020). Effects of a psychobiotic supplement on serum brain-derived neurotrophic factor levels in depressive patients: A post hoc analysis of a randomized clinical trial. *Journal of Neurogastroenterology and Motility, 26*(4), 486–95.