Effects of Antidepressant Medication on Brain-derived Neurotrophic Factor Concentration and Neuroplasticity in Depression: A Review of Preclinical and Clinical Studies

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Abstract
Depression is the most prevalent and debilitating disease with great impact on societies. Evidence suggests Brain-Derived Neurotrophic Factor (BDNF) plays an important role in pathophysiology of depression. Depression is associated with altered synaptic plasticity and neurogenesis. BDNF is the main regulatory protein that affects neuronal plasticity in the hippocampus. A wealth of evidence shows decreased levels of BDNF in depressed patients. Important literature demonstrated that BDNF-TrkB signaling plays a key role in therapeutic action of antidepressants. Numerous studies have reported antidepressant effects on serum/plasma levels of BDNF and neuroplasticity which may be related to improvement of depressive symptoms. Most of the evidence suggested increased levels of BDNF after antidepressant treatment. This review will summarize recent findings on the association between BDNF, neuroplasticity, and antidepressant response in depression. Also, we will review recent studies that evaluate the association between postpartum depression as a subtype of depression and BDNF levels in postpartum women.

Keywords: Antidepressant medication, Brain-derived neurotrophic factor, Depression, Neuroplasticity


Introduction
Major Depressive Disorder (MDD) is the most common disease in the world, as well as the leading cause of disability and the fourth leading contributor to the global burden of disease and has great impact on society 1,2. MDD is described by a depressed mood or feeling of sadness and loss of interest in daily activities 1. MDD is the third cause behind disease burden in 2008. The World Health Organization predicts depression will rank first among diseases by 2030 3. The global point prevalence rate of elevated self-reported depressive symptoms from 2001 to 2020 was 34% (95% CI: 0.30-0.38) and the point prevalence for MDD was 8% (95% CI: 0.02-0.13) 4. Several hypotheses including neurotransmission, neuroinflammation, clock gene machinery pathways, oxidative stress, role of neurotrophins, Hypothalamus-Pituitary-Adrenal (HPA) axis dysfunction, stress response pathway dysfunction, and inflammatory markers could be involved in pathophysiology of MDD 5,6. Many studies indicate that BDNF plays an important role in pathophysiology of psychiatric and neurological disorders and antidepressant pharmacotherapy 7. Brain-Derived Neurotrophic Factor (BDNF) belongs to the neurotrophic family that is involved in neuronal survival, cell proliferation, migration, and differentiation during nervous system development 10-12. The human BDNF gene spans over 70 kbs and has a complex gene structure with 11 exons and nine functional promoters that are expressed in non-neuronal tissues and brain regions 13. BDNF has two different receptors with the tropomyosin receptor kinase B (TrkB) having a higher affinity and the p75 neurotrophin receptor (p75NTR) having a lower affinity 9. BDNF gene expression is significantly lower in depressed patient's lymphocytes 10. A recent study revealed that BDNF and NTRK2 genes were significantly associated with risk of geriatric depression 14. Hung et al found that levels of TrkB protein were significantly higher in depressed patients (p=0.047) but they did not find any significant differences in BDNF levels between MDD patients and control groups (p=0.701) 15. Serotonin and BDNF regulate neurogenesis and synaptic plasticity. Also, 5-HT stimulates expression of

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BDNF. BDNF signaling is related to changes in the 5-HT system. Changes in synaptic plasticity and neurogenesis are related to levels of synaptic serotonin and its receptors. This review explored evidence that indicated an association between BDNF and antidepressant response in depression in preclinical studies and clinical trials.

**BDNF and inflammation**

Chronic neuroinflammatory biomarkers contribute to circuitry dysregulation in depression. BDNF-TrkB signaling plays a key role in pathophysiology of depression and therapeutic action of antidepressants. Neuroinflammation also inhibits neurogenesis. Moreover, increased levels of inflammatory cytokines are involved in development of depression. Systemic immune activation induced by Lipopolysaccharide (LPS) can disturb neuronal plasticity and BDNF levels in the hippocampus. BDNF levels were significantly lower in postmortem brains of suicide victims than in non-psychiatric healthy control individuals. Reduced levels of mature BDNF were detected in serum, plasma, and platelets from depressed patients. Reduced BDNF receptor (TRKB) expression was found in postmortem MDD patients. Systemic administration of LPS can induce expression of pro-inflammatory cytokines in the brain. Zhang et al. evaluated effects of TrkB agonist, 7,8-dihydroxy-flavone (7,8-DHF), and TrkB antagonist, ANA12, on depressive-like behavior after intraperitoneal administration of LPS in mice. Results emphasized that LPS reduced BDNF concentration in CA3 (p=0.020), dentate gyrus (p=0.033) of the hippocampus and Prefrontal Cortex (PFC) (p=0.010) and increased BDNF levels in nucleus accumbens (p=0.036). Moreover, both TrkB agonists and antagonists showed antidepressant effects on depressive-like behaviors in LPS-treated mice. Fluoxetine inhibits production of LPS-induced inflammatory mediators in microglia. Administration of systemic LPS or interleukin-1β (IL-1β) downregulates BDNF expression in the rat hippocampus. Similarly, Guan et al. reported decreased levels of BDNF after injection of LPS.

**BDNF and synaptic plasticity**

Neuroplasticity is the nervous system’s reaction to intrinsic or extrinsic stimulation by reorganizing its function, structure, and connections. Results of a meta-analysis on neuroimaging studies revealed that MDD is associated with reduced basal ganglia and hippocampal volume. BDNF is the central regulator of neuronal plasticity within the postnatal hippocampus. Multiple studies evaluated the effects of BDNF on plasticity. Lin et al. showed that presynaptic BDNF and postsynaptic TrkB are involved in hippocampal Long-Term Potentiation (LTP). Deletion of BDNF in CA3 or CA1 revealed that presynaptic (CA3) BDNF contributes to induction of LTP while postsynaptic (CA1) BDNF is involved in LTP maintenance, and BDNF modulates basal neurotransmission in both presynaptic and postsynaptic terminals. Nikoletopoulou et al. indicated that BDNF signaling downregulates transcription of autophagic machinery components and suppresses autophagy in the forebrain of adult mice. Moreover, increased autophagy mediates synaptic defects due to BDNF deficiency. BDNF can increase dendritic outgrowth and spine density. Altered synaptic serotonin levels are associated with altered synaptic plasticity and neurogenesis. Evidence suggests that antidepressant drugs increase neural plasticity by activating BDNF. Dendritic remodeling and synaptic contacts in the hippocampus and prefrontal cortex have been considered the basis of antidepressant actions in mood disorders. Chronic administration of fluoxetine increased BDNF expression in the visual cortex and restores neuronal plasticity in the visual system of adult amnioblyic rats. Findings of a recent study showed that administration of venlafaxine did not significantly change cortical inhibition, facilitation, and plasticity after 1 and 12 weeks of treatment in late-life depressed patients. However, this study did not assess other cortical areas associated with depression and results were specific to the motor cortex. Results of a double-blind, placebo-controlled trial of an imaging study revealed that administration of escitalopram did not influence white matter microstructures during relearning intervention. Molly et al. reported a negative correlation between plasma escitalopram levels and altered psycho-physiological interaction connectivity. In addition, higher levels of escitalopram are associated with greater reduction in thalamo-cortico connectivity. Similarly, another clinical trial showed that plasma levels of escitalopram had a negative correlation with premotor cortex response. Infusion of ketamine in 31 healthy individuals had a significant effect on hippocampal subfield volume compared to placebo (p=0.009) that indicated short-term effects of ketamine on hippocampal volume. McDonnell et al. tested the effects of a single dose of fluoxetine on practice-dependent plasticity and no significant change was observed in the fluoxetine group compared to the placebo. Therefore, long-term treatment with Selective Serotonin Reuptake Inhibitors (SSRIs) was needed to increase motor performance and plasticity.

**BDNF in postpartum depression**

Postpartum Depression (PPD) has diagnostic criteria similar to MDD that begins within 4 weeks after delivery. The placental BDNF/TrkB system may exert an important role in the fetoplacental unit development. The gene encoding BDNF has a polymorphism (Val66Met) that regulates protein secretion. It seems that BDNF gene has a role in PPD symptom development. Findings of a case-control study, including 275 women from a cohort in Sweden, revealed a significant association with BDNF Met66 carrier status and development of PPD symptoms at 6 weeks postpartum.
However, results of another study did not show any association with BDNF polymorphisms and PPD \(^{52}\). Lower BDNF methylation and BDNF protein expression were observed in pregnant women compared to men \(^{52}\). Significant changes in plasma levels of BDNF are associated with hormonal changes \(^{54,55}\). Impaired synaptic transmission and neuroplasticity, considered as a functional role of BDNF, are associated with mood disorders and suicidal behavior. A marked decrease in serum BDNF concentration occurs both before and after delivery \(^{56}\). Lower levels of serum BDNF were related to suicidal risk among women with PPD \(^{57}\). Lee \textit{et al} reported lower levels of BDNF in postpartum depressed patients than in the non-depressed group 6 weeks after delivery \(^{58}\). It appears that lower BDNF levels correlated with maternal depressive symptoms at 3 months postpartum. Gao \textit{et al} followed 340 women who gave birth in a three-month period. Findings of this study demonstrated that serum BDNF levels after delivery were significantly lower in PPD patients than in women without PPD. Moreover, they mentioned that serum BDNF concentration at admission could be a potential biomarker to predict risk of developing PPD three months after delivery \(^{59}\). In addition, a cross-sectional study indicated that there was a relationship between lower serum BDNF levels in early pregnancy and antepartum depression. Moreover, they suggested that BDNF could be evaluated as a potential biomarker for monitoring response to treatment for antepartum depression \(^{60}\).

Allopregnanolone, as a neurosteroid, has been approved recently for treatment of postpartum depression \(^{61}\). Treatment with allopregnanolone after chronic stress restores BDNF levels to normal and prevents HPA dysfunction \(^{62}\). It seems SSRIs upregulate allopregnanolone and reduce depressive-like behaviors in the Forced Swimming Task (FST) \(^{63,64}\).

**BDNF and conventional antidepressant effects in animal studies**

Considerable evidence implicates involvement of BDNF in the efficacy of antidepressant treatments in rodent models. In an animal study, eight-week-old male rats were divided into 4 groups (n=16 rats/group). They administered anti-anxiety/anti-depressive drugs, agomelatine and venlafaxine, or voluntary wheel running. After 4 weeks of pharmacological treatment or exercise intervention, rats were subjected to 4-week restraint stress induction. Findings revealed that pharmacological treatments have significant effects in prevention of depressive-like behavior in stressed rats. Moreover, both running and pharmacological treatments effectively prevented anxiety-like behaviors and improved memory in stressed rats. In addition, results showed that venlafaxine and running exercise upregulated BDNF expression in the hippocampus \(^{64}\). Another preclinical study was conducted to evaluate the effects of administration of SSRIs in different environments. They treated adult male rats with fluoxetine and exposed them to enriched or stressful environments. Results showed a significant increase in BDNF levels in mice that were exposed to enriched environments after a period of stress compared to controls. By contrast, worsening of the depressive-like phenotypes and lower brain BDNF levels were observed in mice who were exposed to stressful conditions. Therefore, different effects of SSRIs in clinical studies may be due to different clinical conditions \(^{65}\). Studies suggest that combination of SSRI and BDNF have synergistic effects on antidepressant activity \(^{66}\). In an animal study by Deltheil \textit{et al}, 100 mg intrahippocampal BDNF was locally perfused 60 minutes after paroxetine administration or during citalopram perfusion in young adult male mice. Data showed that BDNF injection has synergistic effects on 5-HT levels in the ventral hippocampus (vHi) \(^{66}\).

**BDNF and antidepressant effects of ketamine in animal studies**

In recent years, there is growing body of evidence that evaluated ketamine, a glutamate NMDA (N-methyl-D-aspartate) receptor antagonist, as a novel antidepressant \(^{67,68}\). BDNF-TrkB signaling is one of mechanisms involved in ketamine’s rapid antidepressant effects in depression \(^{69,71}\). Ardalan \textit{et al} injected intraperitoneal dose of S-ketamine (15 mg/kg) or saline to male or female rats. They demonstrated that serum BDNF levels significantly increased in female rats one hr after ketamine injection (p=0.004) \(^{72}\). Combination of imipramine and NMDA receptor antagonist ketamine would produce synergistic anti-depressive-like effects in the FST and increased BDNF protein levels in the rat hippocampus and amygdala \(^{73}\). In contrast, Lindholm \textit{et al} emphasized that ketamine does not increase BDNF levels in hippocampus or TrkB phosphorylation but produced antidepressant-like effects in the forced swim test (FST) in heterozygous heterozygous BDNF knockout (bdnf\(^{-/-}\)) mice at 45 min after a single injection \(^{74}\). A recent study suggests that ketamine did not have any effect on rapid antidepressant-like behaviors and pro-BDNF synthesis in the PFC of the vesicular glutamate transporter 1 (VGLUT1) \(^{+/−}\) model. It seems PFC VGLUT1 levels can modulate depressive-like behaviors and rapid-antidepressant action of ketamine \(^{75}\).

**BDNF and conventional antidepressant effects in clinical trials**

In recent years, multiple studies were conducted to evaluate the effects of conventional antidepressants including SSRIs \(^{76-78}\) and Serotonin norepinephrine reuptake inhibitors (SNRI) \(^{79,80}\) on BDNF levels. Antidepressant efficacy in depressed patients may be associated with BDNF Val66Met polymorphism. A 6-month prospective study on 345 Caucasian depressed patients determined that patients with the Val66 allele had higher response rate after treatment with SSRI than carriers of the Met allele (p=0.04). On the other hand, a lower remission rate was observed in Val66 allele pa-
tients who were treated with SNRI or TCA than in Met allele carriers (p=0.02) 81. In a randomized controlled trial, patients with moderate to severe MDD were prescribed fluoxetine or desvenlafaxine for 12 weeks. Results showed that BDNF levels significantly increased at the end of the trial (p<0.05) in both groups. 82. In a study by Yoshimura et al, forty-two patients were administered paroxetine or milnacipran for 8 weeks. They indicated a negative correlation between serum BDNF levels and baseline17-item Hamilton Depression Rating Scale (HDRS-17) score. In addition, BDNF levels were significantly increased after treatment with paroxetine or milnacipran in responders. 83. Shimizu et al demonstrated that BDNF levels were significantly lower in the antidepressant-naive patients in the MDD group than in the antidepressant-treated or normal control group. 84. In a meta-analysis by Sen et al, higher levels of BDNF were reported after antidepressant treatment (p=0.003) 85. Pre- and post-treatment BDNF levels were measured in MDD patients who were treated with fluoxetine or agomelatine as a melanorenergic drug for 12 weeks. BDNF levels were 2.44±0.38 ng/ml at baseline which significantly changed to 2.87±0.44 ng/ml (p<0.05) at week 12 in the agomelatine group. Similarly, BDNF levels at start of treatment were 2.54±0.37 ng/ml that significantly changed to 3.07±0.33 ng/ml (p<0.05) at the end of the study in the fluoxetine group. 86. In a clinical trial study that was conducted in 2011, twenty-five MDD patients were treated with escitalopram or sertraline for 8 weeks and serum BDNF levels were assessed at baseline and end of the trial. The results of this study showed that BDNF levels were lower in the treatment groups than in the control group (p=0.001). Baseline BDNF levels were not associated with improvement in depression. They did not find any significant correlation between change in BDNF levels and change in depression severity according to the HDRS scores. Moreover, they indicated that serum BDNF levels in the treatment groups were significantly higher than the control groups (p=0.005). 87. In a study by Umene-Nakano et al, fifty-nine depressed patients were treated with sertraline and clinical improvement was assessed using the HDRS-17. Results showed that BDNF levels slightly increased in responders (at least a 50% decrease in the Ham-D score) (p=0.058) 86. Another clinical trial was conducted to evaluate BDNF concentration in MDD patients who received vortioxetine for 8 weeks. Results showed that BDNF levels were significantly higher in post-treatment than in pre-treatment (p<0.0001) 87. In a longitudinal study by Sagud et al, 44 depressed patients were administered 5–15 mg daily vortioxetine and were followed up for 4 weeks. Platelet 5-HT and plasma BDNF concentrations were measured in the depressed and control group before and after treatment. At baseline, platelet 5-HT concentrations had no significant difference between the two groups but plasma BDNF levels were lower (p=0.011) in depressed patients than in the control groups. Moreover, vortioxetine treatment significantly (p=0.0001) decreased platelet 5-HT concentration and significantly (p=0.004) increased plasma BDNF concentration in depressed patients compared to their baseline levels. 88. In another study, pre-and post-treatment BDNF levels from 21 MDD studies (n=735) were meta-analyzed. The result showed that serum and plasma BDNF were decreased in acute MDD. Serum BDNF levels significantly increased in responders and remitters than in non-responders. 89. It seems, measurement of BDNF levels in serum is more reliable than in plasma. 90. Zhou et al conducted a systematic analysis to evaluate the effects of antidepressant medications on BDNF levels in MDD. Results of analysis of 20 trials revealed that antidepressant treatment has a significant effect on increased BDNF levels (SMD=0.62, 95%CI=0.31–0.94, Z=3.92, p<0.0001). In addition, sertraline demonstrated statistically significant effect on BDNF levels after a short duration of antidepressants treatment (SMD=0.53, 95%CI=0.13–0.93, Z=2.62, p=0.009), while no significant effect for paroxetine, sertraline and escitalopram in pre and post-treatment BDNF levels were observed. 90.

Described studies confirmed that levels of BDNF increased after treatment with antidepressants. However, some studies in our review are inconsistent with the hypothesis that antidepressants exert their therapeutic effects through changes in BDNF levels.

Several studies indicated that different antidepressant medications have variable effects on BDNF levels. 91,92. A clinical trial was conducted to evaluate desvenlafaxine in treatment of MDD patients. They reported that there is no significant correlation between changes in BDNF levels and changes in HDRS scores. However, significantly reduced HDRS scores were observed in the treatment group compared with the placebo group at the end of the trial (p=0.006). 91. In a 6-week, double-blind, randomized controlled trial, 73 patients with MDD were randomized to active/sham (Transcranial direct current stimulation) tDCS and sertraline/placebo groups (four groups) and BDNF plasma levels were measured at baseline and the end of the trial. BDNF plasma levels did not significantly increase in treatment with sertraline (39 and 38 participants in the real and placebo arm, respectively, F1,153=0.78, p=0.36) and tDCS (40 and 37 patients in the active and sham arm, respectively, F1,153=0.33, p=0.58) at the endpoint of trial, regardless of clinical improvement. Baseline levels of BDNF were not associated with depression improvement. Moreover, they have mentioned that improvement in depression is not associated with increased levels of BDNF and it was impossible to disengage antidepressant treatment effects from time effects and drug effects in platelets that store BDNF in the blood. 94. In another clinical trial, 25 MDD patients were prescribed duloxetine, and changes in serum BDNF and Hamilton Depression Rating score were
assessed for 6 weeks. BDNF levels increased significantly and continuously from baseline to week 2. However, serum BDNF levels at baseline and week 6 did not differ significantly. 79 They mentioned that these conflicting results should be associated with small sample size and lack of a control group. 79 Chiou et al evaluated serum BDNF levels in patients with first-episode drug-naive MDD compared with sex-matched healthy controls during a 6-year period. Results demonstrated that depressive patients had significantly lower BDNF levels than healthy controls (F= 5.859, p=0.017). Among 71 MDD patients, 41 patients received antidepressant treatment including fluoxetine, escitalopram, paroxetine, venlafaxine, and mirtazapine for 4 weeks and serum BDNF levels were not significantly elevated after treatment with antidepressants (10.7±6.9 ng/ml vs. 12.9±11.9 ng/ml; p=0.126). They provided some reasons for these conflicting findings including antidepressant metabolic polymorphisms, differences in duration of antidepressant intake, different clinical profiles, sample size, and tested materials (serum or plasma). 95

**BDNF and antidepressant effects of ketamine in clinical trials**

In recent years, a growing body of evidence suggested ketamine as a novel antidepressant. 68,96-98 Several clinical trials evaluated antidepressant effect of ketamine on BDNF concentrations. In a clinical trial, ninety-four patients aged 18 to 62 years with unipolar or bipolar depression received six intravenous infusions of ketamine (0.5 mg/kg) and pBDNF concentrations were measured at baseline, 13 days, and 26 days after treatment. Findings showed a significant effect in Montgomery-Asberg Depression Rating Scale (MADRS) scores and pBDNF concentrations after treatment with six ketamine infusions compared to baseline (p<0.05). 99 In a randomized controlled trial, breast cancer patients with post-operative mild to moderate depression were randomly divided into 3 groups (racemic ketamine group, S-ketamine group, and control group). Results showed significantly lower HDRS scores and significantly higher serum BDNF and 5-HT levels in the S-ketamine group at three days, one week, and one month after surgery. 100 Chen et al emphasized that ketamine infusion in patients with Treatment-Resistant Depression (TRD) have rapid and sustained antidepressant effects in both affective (p=0.014) and cognitive (p=0.005) depression symptom according to the Beck Depression Inventory-II (BDI-II). Also, response to low-dose ketamine infusion was observed in TRD patients with the Val allele at the BDNF rs6265 polymorphism (p=0.011). 101 Findings of a randomized placebo-controlled study showed higher levels of BDNF after ketamine infusion are related to altered Resting-State Functional Connectivity (RSFC) of the dorsomedial prefrontal cortex (dmPFC) that increased synaptic plasticity: this may have a key role in ketamine antidepressant action. 102 In a clinical trial study by Wang et al, significantly higher serum BDNF and 5-HT levels were observed in the high dose S-ketamine group than in the control group (p<0.05) at 1 day and 3 days after surgery in cervical carcinoma patients with mild to moderate depression according to the HDRS score who underwent modified radical hysterectomy. 103

However, some studies reported that BDNF is not a suitable biomarker for determining the antidepressant effects of ketamine. Zheng et al reported that there was no significant correlation between serum BDNF levels and antidepressant effects of Electroconvulsive Therapy (ECT) with ketamine anesthesia (p>0.05). 104 Another preliminary study suggested that ECT with ketofol anesthesia did not change serum BDNF levels in TRD patients despite its decreasing depressive symptoms. 105

**Conclusion**

All of the aforementioned evidence discussed in this review demonstrate that BDNF plays a key role in pathophysiology of depression. Serotonin can stimulate expression of BDNF. BDNF has regulatory effect on neurogenesis and synaptic plasticity in the hippocampus and prefrontal cortex. Higher levels of the TrkB protein were observed in depressed patients and BDNF-TrkB signaling is involved in therapeutic actions of antidepressants. 106,107 In our review, most studies are in line with this hypothesis that antidepressant response is related to altered BDNF levels. Accumulating evidence suggests that levels of BDNF concentration increased in response to antidepressant drugs. On the other hand, TrkB agonists and antagonists showed antidepressant effects on depressive-like behaviors in mice. Therefore, BDNF may be a potential marker to predict response to antidepressant medications. Further research is needed to evaluate underlying mechanisms of BDNF action as a possible target for new drugs in treatment of depression. 108 In particular, these studies in children (or comorbidities) will be interesting for researchers. 109-112

**Conflict of Interest**

The authors declare no conflict of interest.

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