



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

To cite this article: Esalatmanesh S, Kashani L, Akhondzadeh Sh. Effects of Antidepressant Medication on Brain-derived Neurotrophic Factor Concentration and Neuroplasticity in Depression: A Review of Preclinical and Clinical Studies. *Avicenna J Med Biotech* 2023;15(3):129-138.

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Received: 10 Mar 2023

Accepted: 30 Mar 2023

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 activities¹. MDD is the third cause behind disease burden in 2008. The World Health Organization predicts depression will rank first among diseases by 2030³. 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 MDD⁵⁻⁸. Many studies indicate that BDNF plays an important role in pathophysiology of psychiatric and neurological disorders and antidepres-

sant pharmacotherapy⁹. Brain-Derived Neurotrophic Factor (BDNF) belongs to the neurotrophic family that is involved in neuronal survival, cell proliferation, migration, and differentiation during nervous system development¹⁰⁻¹². 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 regions¹³. 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 affinity⁹. *BDNF* gene expression is significantly lower in depressed patient's lymphocytes¹⁰. A recent study revealed that *BDNF* and *NTRK2* genes were significantly associated with risk of geriatric depression¹⁴. 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

BDNF¹⁶. BDNF signaling is related to changes in the 5-HT system¹⁷. Changes in synaptic plasticity and neurogenesis are related to levels of synaptic serotonin and its receptors^{16,18}. 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 depression⁸. BDNF-TrkB signaling plays a key role in pathophysiology of depression and therapeutic action of antidepressants¹⁹. Neuroinflammation also inhibits neurogenesis²⁰. Moreover, increased levels of inflammatory cytokines are involved in development of depression²¹. Systemic immune activation induced by Lipopolysaccharide (LPS) can disturb neuronal plasticity and BDNF levels in the hippocampus²². BDNF levels were significantly lower in postmortem brains of suicide victims than in non-psychiatric healthy control individuals ($p < 0.001$)²³. Reduced levels of mature BDNF were detected in serum, plasma, and platelets from depressed patients²⁴. Reduced BDNF receptor (TRKB) expression was found in postmortem MDD patients²⁵. Systemic administration of LPS can induce expression of pro-inflammatory cytokines in the brain²⁶. 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 mice²⁷. 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 mice²⁷. Fluoxetine inhibits production of LPS-induced inflammatory mediators in microglia²⁸. Administration of systemic LPS or interleukin-1 β (IL-1 β) downregulates BDNF expression in the rat hippocampus²⁹. Similarly, Guan *et al* reported decreased levels of BDNF after injection of LPS²².

BDNF and synaptic plasticity

Neuroplasticity is the nervous system's reaction to intrinsic or extrinsic stimulation by reorganizing its function, structure, and connections³⁰. Results of a meta-analysis on neuroimaging studies revealed that MDD is associated with reduced basal ganglia and hippocampal volume^{31,32}. BDNF is the central regulator of neuronal plasticity within the postnatal hippocampus³³. 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 terminals³⁴. Nikolettou *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 deficiency³⁵. BDNF can increase dendritic outgrowth and spine density³⁶. Altered synaptic serotonin levels are associated with altered synaptic plasticity and neurogenesis^{32,37}. Evidence suggests that antidepressant drugs increase neural plasticity by activating BDNF^{32,38}. Dendritic remodeling and synaptic contacts in the hippocampus and prefrontal cortex have been considered the basis of antidepressant actions in mood disorders^{39,40}. Chronic administration of fluoxetine increased BDNF expression in the visual cortex and restores neuronal plasticity in the visual system of adult amblyopic rats⁴¹. 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 cortex⁴². 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 intervention⁴³. 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 connectivity⁴⁴. Similarly, another clinical trial showed that plasma levels of escitalopram had a negative correlation with premotor cortex response⁴⁵. Infusion of S-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 volume⁴⁶. 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 plasticity⁴⁷.

BDNF in postpartum depression

Postpartum Depression (PPD) has diagnostic criteria similar to MDD that begins within 4 weeks after delivery⁴⁸. The placental BDNF/TrkB system may exert an important role in the fetoplacental unit development^{49,50}. 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 postpartum⁵¹.

However, results of another study did not show any association with BDNF polymorphisms and PPD⁵². Lower BDNF methylation and BDNF protein expression were observed in pregnant women compared to men⁵³. 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 delivery⁵⁶. Lower levels of serum BDNF were related to suicidal risk among women with PPD⁵⁷. Lee *et al* reported lower levels of BDNF in postpartum depressed patients than in the non-depressed group 6 weeks after delivery⁵⁸. It appears that lower BDNF levels correlated with maternal depressive symptoms at 3 months postpartum. Gao *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 delivery⁵⁹. 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 depression⁶⁰.

Allopregnanolone, as a neurosteroid, has been approved recently for treatment of postpartum depression⁶¹. Treatment with allopregnanolone after chronic stress restores BDNF levels to normal and prevents HPA dysfunction⁶². It seems SSRIs upregulate allopregnanolone and reduce depressive-like behaviors in the Forced Swimming Task (FST)^{61,63}.

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 hippocampus⁶⁴. Another preclinical study was conducted to evaluate the effects of administration of SSRIs in different environments. They treated adult male rats with fluoxetine and ex-

posed 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 conditions⁶⁵. Studies suggest that combination of SSRI and BDNF have synergistic effects on antidepressant activity⁶⁶. In an animal study by Deltheil *et al*, 100 ng 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 depression⁶⁹⁻⁷¹. Ardalan *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 amygdala⁷³. In contrast, Lindholm *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 injection⁷⁴. 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 ketamine⁷⁵.

BDNF and conventional antidepressant effects in clinical trials

In recent years, multiple studies were conducted to evaluate the effects of conventional antidepressants including SSRIs⁷⁶⁻⁷⁸ 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 groups⁸². 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 baseline 17-item Hamilton Depression Rating Scale (HDRS-17) score. In addition, BDNF levels were significantly increased after treatment with paroxetine or milnacipran in responders⁸³. Shimizu *et al* demonstrated that BDNF levels were significantly lower in the antidepressant-naïve patients in the MDD group than in the antidepressant-treated or normal control group⁸⁴. 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 melatonergic 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 group⁸. 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 ($p=0.005$)⁷⁷. 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 pa-

tients 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 levels⁸⁸. 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-responders⁸⁹. It seems, measurement of BDNF levels in serum is more reliable than in plasma^{89,90}. 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 observed⁹⁰.

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 ($p=0.006$)⁹³. 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, $F_{1,153}=0.78$, $p=0.36$) and tDCS (40 and 37 patients in the active and sham arm, respectively, $F_{1,153}=0.33$, $p=0.58$) 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 blood⁹⁴. 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 significantly⁷⁹. They mentioned that these conflicting results should be associated with small sample size and lack of a control group⁷⁹. Chiou *et al* evaluated serum BDNF levels in patients with first-episode drug-naïve 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 surgery¹⁰⁰. 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 action¹⁰². 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 hysterectomy¹⁰³.

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 symptoms¹⁰⁵.

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 depression¹⁰⁸. In particular, these studies in children (or comorbidities) will be interesting for researchers¹⁰⁹⁻¹¹².

Conflict of Interest

The authors declare no conflict of interest.

References

1. Abdoli N, Salari N, Darvishi N, Jafarpour S, Solaymani M, Mohammadi M, et al. The global prevalence of major depressive disorder (MDD) among the elderly: A systematic review and meta-analysis. *Neurosci Biobehav Rev* 2022;132:1067-73.
2. Reddy MS. Depression: the disorder and the burden. *Indian J Psychol Med* 2010;32(1):1-2.
3. Mathers C. The global burden of disease: 2004 update: World Health Organization; 2008.
4. Shorey S, Ng ED, Wong CHJ. Global prevalence of depression and elevated depressive symptoms among

- adolescents: A systematic review and meta-analysis. *Br J Clin Psychol* 2022;61(2):287-305.
5. Pitsillou E, Bresnehan SM, Kagarakis EA, Wijoyo SJ, Liang J, Hung A, et al. The cellular and molecular basis of major depressive disorder: towards a unified model for understanding clinical depression. *Mol Biol Rep* 2020; 47(1):753-70.
 6. Worthen RJ, Beurel E. Inflammatory and neurodegenerative pathophysiology implicated in postpartum depression. *Neurobiol Dis* 2022;165:105646.
 7. Tang AC, Reeb-Sutherland BC, Romeo RD, McEwen BS. On the causes of early life experience effects: evaluating the role of mom. *Front Neuroendocrinol* 2014; 35(2):245-51.
 8. Gupta K, Gupta R, Bhatia MS, Tripathi AK, Gupta LK. Effect of agomelatine and fluoxetine on HAM-D score, serum brain-derived neurotrophic factor, and tumor necrosis factor- α level in patients with major depressive disorder with severe depression. *J Clin Pharmacol* 2017; 57(12):1519-26.
 9. Zhao XP, Li H, Dai RP. Neuroimmune crosstalk through brain-derived neurotrophic factor and its precursor pro-BDNF: New insights into mood disorders. *World J Psychiatry* 2022;12(3):379-92.
 10. Pandey GN, Dwivedi Y, Rizavi HS, Ren X, Zhang H, Pavuluri MN. Brain-derived neurotrophic factor gene and protein expression in pediatric and adult depressed subjects. *Prog Neuropsychopharmacol Biol Psychiatry* 2010;34(4):645-51.
 11. Mitre M, Mariga A, Chao MV. Neurotrophin signalling: novel insights into mechanisms and pathophysiology. *Clin Sci (Lond)* 2017;131(1):13-23.
 12. Piccinni A, Marazziti D, Del Debbio A, Bianchi C, Roncaglia I, Mannari C, et al. Diurnal variation of plasma brain-derived neurotrophic factor (BDNF) in humans: an analysis of sex differences. *Chronobiol Int* 2008;25(5):819-26.
 13. Pruunsild P, Kazantseva A, Aid T, Palm K, Timmusk T. Dissecting the human BDNF locus: bidirectional transcription, complex splicing, and multiple promoters. *Genomics* 2007;90(3):397-406.
 14. Lin E, Hong CJ, Hwang JP, Liou YJ, Yang CH, Cheng D, et al. Gene-gene interactions of the brain-derived neurotrophic-factor and neurotrophic tyrosine kinase receptor 2 genes in geriatric depression. *Rejuvenation Res* 2009;12(6):387-93.
 15. Hung YY, Lin CJ, Huang TL. Higher serum tropomyosin-related kinase B protein level in major depression. *Prog Neuropsychopharmacol Biol Psychiatry* 2010;34(4):610-2.
 16. Mattson MP, Maudsley S, Martin B. BDNF and 5-HT: a dynamic duo in age-related neuronal plasticity and neurodegenerative disorders. *Trends Neurosci* 2004;27(10):589-94.
 17. Roy M, Tapadia MG, Joshi S, Koch B. Molecular and genetic basis of depression. *J Genet* 2014;93(3):879-92.
 18. Kraus C, Castrén E, Kasper S, Lanzenberger R. Serotonin and neuroplasticity-Links between molecular, functional and structural pathophysiology in depression. *Neurosci Biobehav Rev* 2017;77:317-26.
 19. Zhang JC, Yao W, Hashimoto K. Brain-derived neurotrophic factor (BDNF)-TrkB signaling in inflammation-related depression and potential therapeutic targets. *Curr Neuropharmacol* 2016;14(7): 721-31.
 20. Monje ML, Toda H, Palmer TD. Inflammatory blockade restores adult hippocampal neurogenesis. *Science* 2003; 302(5651):1760-5.
 21. Dunn AJ, Swiergiel AH, de Beaurepaire R. Cytokines as mediators of depression: what can we learn from animal studies? *Neurosci Biobehav Rev* 2005;29(4-5):891-909.
 22. Guan Z, Fang J. Peripheral immune activation by lipopolysaccharide decreases neurotrophins in the cortex and hippocampus in rats. *Brain Behav Immun* 2006;20(1):64-71.
 23. Banerjee R, Ghosh AK, Ghosh B, Bhattacharyya S, Mondal AC. Decreased mRNA and protein expression of BDNF, NGF, and their receptors in the hippocampus from suicide: An analysis in human postmortem brain. *Clin Med Insights Pathol* 2013;6:1-11.
 24. Jiang C, Salton SR. The role of neurotrophins in major depressive disorder. *Transl Neurosci* 2013;4(1):46-58.
 25. Tripp A, Oh H, Guilloux JP, Martinowich K, Lewis DA, Sibille E. Brain-derived neurotrophic factor signaling and subgenual anterior cingulate cortex dysfunction in major depressive disorder. *Am J Psychiatry* 2012;169(11): 1194-202.
 26. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci* 2008;9(1):46-56.
 27. Zhang JC, Wu J, Fujita Y, Yao W, Ren Q, Yang C, et al. Antidepressant effects of TrkB ligands on depression-like behavior and dendritic changes in mice after inflammation. *Int J Neuropsychopharmacol* 2014;18(4).
 28. Liu D, Wang Z, Liu S, Wang F, Zhao S, Hao A. Anti-inflammatory effects of fluoxetine in lipopolysaccharide (LPS)-stimulated microglial cells. *Neuropharmacology* 2011;61(4):592-99.
 29. Lapchak PA, Araujo DM, Hefti F. Systemic interleukin-1 β decreases brain-derived neurotrophic factor messenger RNA expression in the rat hippocampal formation. *Neuroscience* 1993;53(2):297-301.
 30. Cramer SC, Sur M, Dobkin BH, O'Brien C, Sanger TD, Trojanowski JQ, et al. Harnessing neuroplasticity for clinical applications. *Brain* 2011;134(6):1591-609.
 31. Kempton MJ, Salvador Z, Munafò MR, Geddes JR, Simmons A, Frangou S, et al. Structural neuroimaging studies in major depressive disorder. Meta-analysis and comparison with bipolar disorder. *Arch Gen Psychiatry* 2011;68(7):675-90.
 32. Castrén E, Rantamäki T. The role of BDNF and its receptors in depression and antidepressant drug action: Reactivation of developmental plasticity. *Dev Neurobiol* 2010;70(5):289-97.
 33. von Bohlen und Halbach O, von Bohlen und Halbach V. BDNF effects on dendritic spine morphology and hippo-

- campal function. *Cell Tissue Res* 2018;373(3):729-41.
34. Lin P-Y, Kavalali ET, Monteggia LM. Genetic dissection of presynaptic and postsynaptic BDNF-TrkB signaling in synaptic efficacy of CA3-CA1 Synapses. *Cell Rep* 2018;24(6):1550-61.
 35. Nikolettou V, Sidiropoulou K, Kallergi E, Dalezios Y, Tavernarakis N. Modulation of autophagy by BDNF underlies synaptic plasticity. *Cell Metab* 2017;26(1):230-42.e5.
 36. Park SW, Nhu LH, Cho HY, Seo MK, Lee CH, Ly NN, et al. p11 mediates the BDNF-protective effects in dendritic outgrowth and spine formation in B27-deprived primary hippocampal cells. *J Affect Disord* 2016;196:1-10.
 37. Crispino M, Volpicelli F, Perrone-Capano C. Role of the serotonin receptor 7 in brain plasticity: From development to disease. *Int J Mol Sci* 2020;21(2):505.
 38. Kozisek ME, Middlemas D, Bylund DB. Brain-derived neurotrophic factor and its receptor tropomyosin-related kinase B in the mechanism of action of antidepressant therapies. *Pharmacol Ther* 2008;117(1):30-51.
 39. Hajszan T, MacLusky NJ, Leranath C. Short-term treatment with the antidepressant fluoxetine triggers pyramidal dendritic spine synapse formation in rat hippocampus. *Eur J Neurosci* 2005;21(5):1299-303.
 40. Bessa JM, Ferreira D, Melo I, Marques F, Cerqueira JJ, Palha JA, et al. The mood-improving actions of antidepressants do not depend on neurogenesis but are associated with neuronal remodeling. *Mol Psychiatry* 2009;14(8):764-73.
 41. Maya Vetencourt JF, Sale A, Viegi A, Baroncelli L, De Pasquale R, O'Leary OF, et al. The antidepressant fluoxetine restores plasticity in the adult visual cortex. *Science* 2008;320(5874):385-8.
 42. Lissemore JI, Mulsant BH, Rajji TK, Karp JF, Reynolds CF, Lenze EJ, et al. Cortical inhibition, facilitation and plasticity in late-life depression: effects of venlafaxine pharmacotherapy. *J Psychiatry Neurosci* 2021;46(1):E88-e96.
 43. Vanicek T, Reed MB, Unterholzner J, Klöbl M, Godbersen GM, Handschuh PA, et al. Escitalopram administration, relearning, and neuroplastic effects: A diffusion tensor imaging study in healthy individuals. *J Affect Disord* 2022;301:426-32.
 44. Molloy EN, Zsido RG, Piecha FA, Beinhözl N, Scharrer U, Zheleva G, et al. Decreased thalamo-cortico connectivity during an implicit sequence motor learning task and 7 days escitalopram intake. *Sci Rep* 2021;11(1): 15060.
 45. Molloy EN, Mueller K, Beinhözl N, Blöchl M, Piecha FA, Pampel A, et al. Modulation of premotor cortex response to sequence motor learning during escitalopram intake. *J Cereb Blood Flow Metab* 2021;41(6):1449-62.
 46. Höflich A, Kraus C, Pfeiffer RM, Seiger R, Rujescu D, Zarate CA, Jr., et al. Translating the immediate effects of S-Ketamine using hippocampal subfield analysis in healthy subjects—results of a randomized controlled trial. *Transl Psychiatry* 2021;11(1):200.
 47. McDonnell MN, Zipser C, Darmani G, Ziemann U, Müller-Dahlhaus F. The effects of a single dose of fluoxetine on practice-dependent plasticity. *Clin Neurophysiol* 2018;129(7):1349-56.
 48. American Psychiatric Association A, Association AP. Diagnostic and statistical manual of mental disorders: DSM-5. Fifth ed: Washington, DC: American psychiatric association; 2013.
 49. Mayeur S, Silhol M, Moitrot E, Barbaux S, Breton C, Gabory A, et al. Placental BDNF/TrkB signaling system is modulated by fetal growth disturbances in rat and human. *Placenta* 2010;31(9):785-91.
 50. Kawamura K, Kawamura N, Fukuda J, Kumagai J, Hsueh AJW, Tanaka T. Regulation of preimplantation embryo development by brain-derived neurotrophic factor. *Dev Biol* 2007;311(1):147-58.
 51. Comasco E, Sylvén SM, Papadopoulos FC, Oreland L, Sundström-Poromaa I, Skalkidou A. Postpartum depressive symptoms and the BDNF Val66Met functional polymorphism: effect of season of delivery. *Arch Womens Ment Health* 2011;14(6):453-63.
 52. Figueira P, Malloy-Diniz L, Campos SB, Miranda DM, Romano-Silva MA, De Marco L, et al. An association study between the Val66Met polymorphism of the BDNF gene and postpartum depression. *Arch Womens Ment Health* 2010;13(3):285-9.
 53. Kittel-Schneider S, Davidova P, Kalok M, Essel C, Ahmed FB, Kingeter Y, et al. A pilot study of multilevel analysis of BDNF in paternal and maternal perinatal depression. *Arch Womens Ment Health* 2022;25(1):237-49.
 54. Begliumini S, Casarosa E, Pluchino N, Lenzi E, Centofanti M, Freschi L, et al. Influence of endogenous and exogenous sex hormones on plasma brain-derived neurotrophic factor. *Hum Reprod* 2007;22(4):995-1002.
 55. Cubeddu A, Bucci F, Giannini A, Russo M, Daino D, Russo N, et al. Brain-derived neurotrophic factor plasma variation during the different phases of the menstrual cycle in women with premenstrual syndrome. *Psychoneuroendocrinology* 2011;36(4):523-30.
 56. Lommatzsch M, Hornych K, Zingler C, Schuff-Werner P, Höppner J, Virchow JC. Maternal serum concentrations of BDNF and depression in the perinatal period. *Psychoneuroendocrinology* 2006;31(3):388-94.
 57. Pinheiro RT, Pinheiro KAT, da Cunha Coelho FM, de Ávila Quevedo L, Gazal M, da Silva RA, et al. Brain-derived neurotrophic factor levels in women with postpartum affective disorder and suicidality. *Neurochem Res* 2012;37(10):2229-34.
 58. Lee Y, Kim K-H, Lee B-H, Kim Y-K. Plasma level of brain-derived neurotrophic factor (BDNF) in patients with postpartum depression. *Prog Neuropsychopharmacol Biol Psychiatry* 2021;109:110245.
 59. Gao X, Wang J, Yao H, Cai Y, Cheng R. Serum BDNF concentration after delivery is associated with development of postpartum depression: A 3-month follow up study. *J Affect Disord* 2016;200:25-30.
 60. Fung J, Gelaye B, Zhong Q-Y, Rondon MB, Sanchez SE,

- Barrios YV, et al. Association of decreased serum brain-derived neurotrophic factor (BDNF) concentrations in early pregnancy with antepartum depression. *BMC Psychiatry* 2015;15(1):1-8.
61. Almeida FB, Nin MS, Barros HMT. The role of allopregnanolone in depressive-like behaviors: Focus on neurotrophic proteins. *Neurobiol Stress* 2020;12:100218.
 62. Evans J, Sun Y, McGregor A, Connor B. Allopregnanolone regulates neurogenesis and depressive/anxiety-like behaviour in a social isolation rodent model of chronic stress. *Neuropharmacology* 2012;63(8):1315-26.
 63. Molina-Hernández M, Tellez-Alcántara NP, Pérez García J, Olivera Lopez JI, Teresa Jaramillo M. Antidepressant-like actions of intra-accumbens infusions of allopregnanolone in ovariectomized Wistar rats. *Pharmacol Biochem Behav* 2005;80(3):401-09.
 64. Lapmanee S, Charoenphandhu J, Teerapornpantakit J, Krishnamra N, Charoenphandhu N. Agomelatine, venlafaxine, and running exercise effectively prevent anxiety- and depression-like behaviors and memory impairment in restraint stressed rats. *PLoS One* 2017;12(11):e0187671.
 65. Branchi I, Santarelli S, Capoccia S, Poggini S, D'Andrea I, Cirulli F, et al. Antidepressant treatment outcome depends on the quality of the living environment: a pre-clinical investigation in mice. *PLoS One* 2013;8(4):e62226.
 66. Deltheil T, Tanaka K, Reperant C, Hen R, David DJ, Gardier AM. Synergistic neurochemical and behavioural effects of acute intrahippocampal injection of brain-derived neurotrophic factor and antidepressants in adult mice. *Int J Neuropsychopharmacol* 2009;12(7):905-15.
 67. Garcia LS, Comim CM, Valvassori SS, Réus GZ, Barbosa LM, Andreazza AC, et al. Acute administration of ketamine induces antidepressant-like effects in the forced swimming test and increases BDNF levels in the rat hippocampus. *Prog Neuropsychopharmacol Biol Psychiatry* 2008;32(1):140-4.
 68. Zanos P, Gould TD. Mechanisms of ketamine action as an antidepressant. *Mol Psychiatry* 2018;23(4):801-11.
 69. Kang MJY, Hawken E, Vazquez GH. The mechanisms behind rapid antidepressant effects of ketamine: A systematic review with a focus on molecular neuroplasticity. *Front Psychiatry* 2022;13:860882.
 70. Tan Y, Fujita Y, Qu Y, Chang L, Pu Y, Wang S, et al. Phencyclidine-induced cognitive deficits in mice are ameliorated by subsequent repeated intermittent administration of (R)-ketamine, but not (S)-ketamine: Role of BDNF-TrkB signaling. *Pharmacol Biochem Behav* 2020;188:172839.
 71. Asim M, Hao B, Yang YH, Fan BF, Xue L, Shi YW, et al. Ketamine alleviates fear generalization through GluN2B-BDNF signaling in mice. *Neurosci Bull* 2020;36(2):153-64.
 72. Ardalan M, Elfving B, Rafati AH, Mansouri M, Zarate CA, Jr., Mathe AA, et al. Rapid effects of S-ketamine on the morphology of hippocampal astrocytes and BDNF serum levels in a sex-dependent manner. *Eur Neuropharmacol* 2020;32:94-103.
 73. Réus GZ, Stringari RB, Ribeiro KF, Ferraro AK, Vitto MF, Cesconetto P, et al. Ketamine plus imipramine treatment induces antidepressant-like behavior and increases CREB and BDNF protein levels and PKA and PKC phosphorylation in rat brain. *Behav Brain Res* 2011;221(1):166-71.
 74. Lindholm JS, Autio H, Vesa L, Antila H, Lindemann L, Hoener MC, et al. The antidepressant-like effects of glutamatergic drugs ketamine and AMPA receptor potentiator LY 451646 are preserved in *bdnf*^{-/-} heterozygous null mice. *Neuropharmacology* 2012;62(1):391-7.
 75. Belloch FB, Cortés-Erice M, Herzog E, Zhang XM, Díaz-Perdigón T, Puerta E, et al. Fast antidepressant action of ketamine in mouse models requires normal VGLUT1 levels from prefrontal cortex neurons. *Prog Neuropsychopharmacol Biol Psychiatry* 2023;121:110640.
 76. Gonul AS, Akdeniz F, Taneli F, Donat O, Eker Ç, Vahip S. Effect of treatment on serum brain-derived neurotrophic factor levels in depressed patients. *Eur Arch Psychiatry Clin Neurosci* 2005;255(6):381-86.
 77. Wolkowitz OM, Wolf J, Shelly W, Rosser R, Burke HM, Lerner GK, et al. Serum BDNF levels before treatment predict SSRI response in depression. *Prog Neuropsychopharmacol Biol Psychiatry* 2011;35(7):1623-30.
 78. Aydemir C, Yalcin ES, Aksaray S, Kisa C, Yildirim SG, Uzbay T, et al. Brain-derived neurotrophic factor (BDNF) changes in the serum of depressed women. *Prog Neuropsychopharmacol Biol Psychiatry* 2006;30(7):1256-60.
 79. Mikoteit T, Beck J, Eckert A, Hemmeter U, Brand S, Bischof R, et al. High baseline BDNF serum levels and early psychopathological improvement are predictive of treatment outcome in major depression. *Psychopharmacology* 2014;231(15):2955-65.
 80. Katsuki A, Yoshimura R, Kishi T, Hori H, Umene-Nakano W, Ikenouchi-Sugita A, et al. Serum levels of brain-derived neurotrophic factor (BDNF), BDNF gene Val66Met polymorphism, or plasma catecholamine metabolites, and response to mirtazapine in Japanese patients with major depressive disorder (MDD). *CNS Spectr* 2012;17(3):155-63.
 81. Colle R, Gressier F, Verstuyft C, Deflesselle E, Lépine JP, Ferreri F, et al. Brain-derived neurotrophic factor Val66Met polymorphism and 6-month antidepressant remission in depressed Caucasian patients. *J Affect Disord* 2015;175:233-40.
 82. Ghosh R, Gupta R, Bhatia MS, Tripathi AK, Gupta LK. Comparison of efficacy, safety and brain derived neurotrophic factor (BDNF) levels in patients of major depressive disorder, treated with fluoxetine and desvenlafaxine. *Asian J Psychiatr* 2015;18:37-41.
 83. Yoshimura R, Mitoma M, Sugita A, Hori H, Okamoto T, Umene W, et al. Effects of paroxetine or milnacipran on serum brain-derived neurotrophic factor in depressed patients. *Prog Neuropsychopharmacol Biol Psychiatry* 2007;31(5):1034-37.
 84. Shimizu E, Hashimoto K, Okamura N, Koike K,

- Komatsu N, Kumakiri C, et al. Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. *Biol Psychiatry* 2003;54(1):70-75.
85. Sen S, Duman R, Sanacora G. Serum brain-derived neurotrophic factor, depression, and antidepressant medications: meta-analyses and implications. *Biol Psychiatry* 2008;64(6):527-32.
 86. Umene-Nakano W, Yoshimura R, Ueda N, Suzuki A, Ikenouchi-Sugita A, Hori H, et al. Predictive factors for responding to sertraline treatment: views from plasma catecholamine metabolites and serotonin transporter polymorphism. *J Psychopharmacol* 2010;24(12):1764-71.
 87. Troyan AS, Levada OA. The diagnostic value of the combination of serum brain-derived neurotrophic factor and insulin-like growth factor-1 for major depressive disorder diagnosis and treatment efficacy. *Front Psychiatry* 2020;11:800.
 88. Sagud M, Nikolac Perkovic M, Vuksan-Cusa B, Maravic A, Svob Strac D, Mihaljevic Peles A, et al. A prospective, longitudinal study of platelet serotonin and plasma brain-derived neurotrophic factor concentrations in major depression: effects of vortioxetine treatment. *Psychopharmacology* 2016;233(17):3259-67.
 89. Polyakova M, Stuke K, Schuemberg K, Mueller K, Schoenknecht P, Schroeter ML. BDNF as a biomarker for successful treatment of mood disorders: a systematic & quantitative meta-analysis. *J Affect Disord* 2015;174:432-40.
 90. Zhou C, Zhong J, Zou B, Fang L, Chen J, Deng X, et al. Meta-analyses of comparative efficacy of antidepressant medications on peripheral BDNF concentration in patients with depression. *PLoS One* 2017;12(2):e0172270.
 91. Bařterzi AD, Yazici K, Aslan E, Delialiođlu N, Tařdelen B, Tot Acar S, et al. Effects of fluoxetine and venlafaxine on serum brain derived neurotrophic factor levels in depressed patients. *Prog Neuropsychopharmacol Biol Psychiatry* 2009;33(2):281-5.
 92. Matrisciano F, Bonaccorso S, Ricciardi A, Scaccianoce S, Panaccione I, Wang L, et al. Changes in BDNF serum levels in patients with major depression disorder (MDD) after 6 months treatment with sertraline, escitalopram, or venlafaxine. *J Psychiatr Res* 2009;43(3):247-54.
 93. Ninan PT, Shelton RC, Bao W, Guico-Pabia CJ. BDNF, interleukin-6, and salivary cortisol levels in depressed patients treated with desvenlafaxine. *Prog Neuropsychopharmacol Biol Psychiatry* 2014;48:86-91.
 94. Brunoni AR, Machado-Vieira R, Zarate CA, Vieira ELM, Vanderhasselt M-A, Nitsche MA, et al. BDNF plasma levels after antidepressant treatment with sertraline and transcranial direct current stimulation: Results from a factorial, randomized, sham-controlled trial. *Eur Neuropsychopharmacol* 2014;24(7):1144-51.
 95. Chiou Y-J, Huang T-L. Serum brain-derived neurotrophic factors in Taiwanese patients with drug-naïve first-episode major depressive disorder: effects of antidepressants. *Int J Neuropsychopharmacol* 2016;20(3):213-18.
 96. Derakhshanian S, Zhou M, Rath A, Barlow R, Bertrand S, DeGraw C, et al. Role of ketamine in the treatment of psychiatric disorders. *Health Psychol Res* 2021;9(1):25091.
 97. Caddy C, Giaroli G, White TP, Shergill SS, Tracy DK. Ketamine as the prototype glutamatergic antidepressant: pharmacodynamic actions, and a systematic review and meta-analysis of efficacy. *Ther Adv Psychopharmacol* 2014;4(2):75-99.
 98. Duman RS. Pathophysiology of depression and innovative treatments: remodeling glutamatergic synaptic connections. *Dialogues Clin Neurosci* 2014;16(1):11-27.
 99. Zheng W, Zhou YL, Wang CY, Lan XF, Zhang B, Zhou SM, et al. Plasma BDNF concentrations and the antidepressant effects of six ketamine infusions in unipolar and bipolar depression. *PeerJ* 2021;9:e10989.
 100. Liu P, Li P, Li Q, Yan H, Shi X, Liu C, et al. Effect of pretreatment of S-ketamine on postoperative depression for breast cancer patients. *J Invest Surg* 2021;34(8):883-88.
 101. Chen MH, Wu HJ, Li CT, Lin WC, Tsai SJ, Hong CJ, et al. Low-dose ketamine infusion for treating subjective cognitive, somatic, and affective depression symptoms of treatment-resistant depression. *Asian J Psychiatr* 2021;66:102869.
 102. Woelfer M, Li M, Colic L, Liebe T, Di X, Biswal B, et al. Ketamine-induced changes in plasma brain-derived neurotrophic factor (BDNF) levels are associated with the resting-state functional connectivity of the prefrontal cortex. *World J Biol Psychiatry* 2020;21(9):696-710.
 103. Wang J, Wang Y, Xu X, Peng S, Xu F, Liu P. Use of various doses of S-ketamine in treatment of depression and pain in cervical carcinoma patients with mild/moderate depression after laparoscopic total hysterectomy. *Med Sci Monit* 2020;26:e922028.
 104. Zheng W, Cen Q, Nie S, Li M, Zeng R, Zhou S, et al. Serum BDNF levels and the antidepressant effects of electroconvulsive therapy with ketamine anaesthesia: a preliminary study. *PeerJ* 2021;9:e10699.
 105. Huang XB, Huang X, He HB, Mei F, Sun B, Zhou SM, et al. BDNF and the antidepressant effects of ketamine and propofol in electroconvulsive therapy: A preliminary study. *Neuropsychiatr Dis Treat* 2020;16:901-08.
 106. Jafarinia M, Afarideh M, Tafakhori A, Arbabi M, Ghajar A, Noorbala AA, et al. Efficacy and safety of oral ketamine versus diclofenac to alleviate mild to moderate depression in chronic pain patients: A double-blind, randomized, controlled trial. *J Affect Disord* 2016;204:1-8.
 107. Yekhtaz H, Farokhnia M, Akhondzadeh S. Cardiovascular considerations in antidepressant therapy: an evidence-based review. *J Tehran Heart Cent* 2013;8(4):169-76.
 108. Rabbani B, Nakaoka H, Akhondzadeh S, Tekin M, Mahdih N. Next generation sequencing: implications in personalized medicine and pharmacogenomics. *Mol Biosyst* 2016;12(6):1818-30.
 109. Kahbazi M, Ghoreishi A, Rahiminejad F, Mohammadi MR, Kamalipour A, Akhondzadeh S. A randomized,

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double-blind and placebo-controlled trial of modafinil in children and adolescents with attention deficit and hyperactivity disorder. *Psychiatry Res* 2009;168(3):234-7.

110. Jafari P, Ghanizadeh A, Akhondzadeh S, Mohammadi MR. Health-related quality of life of Iranian children with attention deficit/hyperactivity disorder. *Qual Life Res* 2011;20(1):31-6.
111. Arabzadeh S, Ameli N, Zeinoddini A, Rezaei F, Farokhnia M, Mohammadinejad P, et al. Celecoxib ad-

junctional therapy for acute bipolar mania: a randomized, double-blind, placebo-controlled trial. *Bipolar Disord* 2015;17(6):606-14.

112. Abbasi SH, Behpourmia H, Ghoshchi A, Salehi B, Raznahan M, Rezazadeh SA, et al. The effect of mirtazapine add on therapy to risperidone in the treatment of schizophrenia: a double-blind randomized placebo-controlled trial. *Schizophr Res* 2010;116(2-3):101-6.