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Source / Izvornik: **Expert Review of Molecular Diagnostics, 2023, 23, 283 - 296**

Journal article, Accepted version
Rad u časopisu, Završna verzija rukopisa prihvaćena za objavljivanje (postprint)

https://doi.org/10.1080/14737159.2023.2200937

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:105:267765

The association of BDNF with diagnosis and treatment response in depression

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Abstract

Introduction: Recent evidence from the studies evaluating the association between brain derived neurotrophic factor (BDNF) concentration/levels, BDNF Val66Met (rs6265) polymorphism and major depressive disorders, referred as depression, and the association between BDNF levels and/or BDNF Val66Met with the treatment response in depression, is presented.

Areas covered: This mini review focuses on the changes in the peripheral BDNF levels in blood (serum, plasma, platelets) in patients with depression before or after treatment with antidepressant drugs or different therapeutic strategies. In addition, this review describes the recent data on the possible association between different antidepressants/therapeutic strategies and the particular BDNF Val66Met genotypes, evaluating the risk alleles associated with the response in patients with depression.

Expert opinion: BDNF has an important role in the pathophysiology and treatment response in depression. Most data reveal that peripheral BDNF levels are lower before than after antidepressant treatment and might be used as potential biomarkers of therapeutic response. Novel therapeutic strategies should target restoring/increasing BDNF levels.

Key words: brain derived neurotrophic factor, depression; BDNF Val66Met; treatment response

Highlights

- Peripheral BDNF levels are mostly decreased in depression
- Reduced BDNF levels are increased after antidepressant therapy
- Met allele might be a risk factor for depression
- Val allele carriers of the BDNF Val66Met often show better treatment response

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewers disclosure

Peer reviewers on this manuscript have no relevant financial relationships or otherwise to disclose.

Availability of supporting data

All data needed to evaluate the conclusions in the paper are present in the paper.

Funding

Part of the funding was received from the project BM126 “The influence of religiosity on the treatment outcome of depression: clinical and biochemical markers", PI Marina Sagud, University of Zagreb.

Abbreviations: 5-HTT=serotonin transporter; APOE=apolipoprotein E; BBB=blood-brain barrier; BDNF=brain derived neurotrophic factor; COMT= catechol-O-methyltransferase; ECT=electroconvulsive therapy; ELECT-TDCS=Electrical Current Therapy for Treating Depression Clinical Study; ERK=extracellular signal-regulated kinase; HTR2A=5-hydroxytryptamine receptor 2A; Hsp70=heat shock protein family A member 1A; HF-rTMS=high frequency repetitive transcranial magnetic stimulation; JNK=c-Jun N-terminal kinase; mBDNF=mature BDNF; LTD=long-term depression; LTP=long-term potentiation; MDD=major depressive disorder; Met=methionine; mRNA=messenger RNA; $p75^{NTR}$=pan-neurotrophin receptor; proBDNF=precursor protein; PI3K=phosphatidylinositol 3-kinase; PLCγ=phospholipase C gamma; tDCS=transcranial direct current stimulation; rTMS=repetitive transcranial magnetic stimulation; TrkB=tropomyosin receptor kinase B; SLC6A=solute carrier family 6 member 4 or serotonin transporter; 4SNRIs=serotonin and norepinephrine reuptake inhibitors; SSRIs=selective serotonin reuptake inhibitors (SSRIs); TRD= treatment-resistant depression; Val=valine.

1. Introduction

This article explores recent evidence (starting from 2013) from the studies evaluating the association between brain derived neurotrophic factor (BDNF) concentration/levels, BDNF Val66Met (rs6265) polymorphism with depression, and the association between BDNF levels and/or BDNF Val66Met in the treatment response in depression. In this text major depressive disorder (MDD) was referred as depression. Studies for this review were identified by searching PubMed/Google database for articles published in English language as research articles or reviews in the last 10 years with the search terms: “brain-derived neurotrophic factor” OR “BDNF” OR “BDNF polymorphism” OR “BDNF Val66Met” OR “BDNF rs6265” AND “antidepressant” OR “treatment response” OR “therapeutic response” AND “major depression” OR “major depressive disorder” OR “MDD” OR “depressive episode” OR “depression”. The limitation for the databases and the 10-year period was done due to the limited number of the citations (N=100) allowed in this review. Due to this limitation, and to keep the focus and length of this review within limits, we included only original research/review articles conducted with human subjects; and involved patients with diagnosis of MDD, referred in this text as depression. We excluded animal/in vitro studies.

1.1. Brain-derived neurotrophic factor (BDNF)

Brain-derived neurotrophic factor (BDNF) is a member of neurotrophin family that plays a key role in the regulation of neuronal survival, development and function, and in modulating neuroplasticity, long-term potentiation and synaptic transmission [1]. The gene coding for this neurotrophin is located on the chromosome 11, it contains 11 exons and 9 different promoters [Gao et al., 2022]. All *BDNF* transcripts give the same product, a precursor protein preproBDNF [Gao et al., 2022]. Following the cleavage of the signal peptide, preproBDNF is converted to proBDNF and, after the cleavage of the prodomain, into mature mBDNF [2]. The transport of BDNF in dendrites and its synaptic localization depend on the prodomain of this protein. It is known that the single nucleotide polymorphism (SNP) rs6265 (Val66Met), which is located in the prodomain region of the *BDNF* gene, results in the replacement of the amino acid valine (Val) with the amino acid methionine (Met) and affects the transport of BDNF in dendrites [Gao et al., 2022]. For the regulated secretion of the BDNF protein, its interaction with the receptor sortilin in the secretory granules is very important, and the prodomain of the BDNF protein plays a key role in this

interaction [Gao et al., 2022]. The proBDNF with the amino acid Met at codon 66 has a poorer secretion because of the weakened interaction with sortilin [Gao et al., 2022].

Proneurotrophins, such as proBDNF, promote apoptosis via the pan-neurotrophin receptor p75 ($p75^{NTR}$). This action is opposite to the action of mature neurotrophins [3]. By binding to the tropomyosin receptor kinase B (TrkB) receptor, mBDNF stimulates its dimerization and autophosphorylation. TrkB receptor signaling activates multiple downstream signaling pathways including the extracellular signal-regulated kinase (ERK) pathway, the phosphatidylinositol 3-kinase (PI3K) pathway, and the phospholipase C gamma (PLCγ) signaling pathway [3]. Activated ERK can phosphorylate other kinases, thereby activating cyclic AMP responsive element binding protein (CREB), the most studied transcription factor related to depression and antidepressant-like effects [Esvald et al., 2020]. Immature protein (proBDNF) binds to the $p75^{NTR}$ receptor and activates several signaling molecules, including the transcription factor NF-κB, c-Jun N-terminal kinase (JNK) and RhoA (protein that binds guanosine-triphosphate). BDNF is important in the process of long-term increase in the strength of signal transmission between two neurons, i.e. the long-term potentiation (LTP) [4], which is also considered the cellular equivalent of learning and memory. BDNF regulates besides LTP, also a long-term depression (LTD), a mechanism for reducing synaptic strength, and it occurs as a result of weaker use of certain synaptic connections over a longer period of time.

Novel findings relate BDNF to pathological changes linked to depression thus supporting the neurotrophic hypothesis of depression [4]. The decrease in neurotrophin BDNF concentration leads to the reduction of hippocampal neurogenesis, and loss of neurons and glial cells [5]. The neurotrophic hypothesis of depression is supported by findings suggesting decreased levels of BDNF messenger RNA and protein in postmortem brain samples of depressed patients [Castrén and Monteggia, 2021]. Studies suggested altered brain expression of both mBDNF and proBDNF in depression [Yang et al., 2017; Castrén and Monteggia, 2021] and hippocampal reduction in $p75^{NTR}$ [Xiong et al., 2022]. Reduced expression of BDNF and TrkB has also been repeatedly detected in prefrontal cortex and hippocampus of suicide victims [Castrén and Monteggia, 2021]. The neurotrophic hypothesis of depression is also supported by the ability of antidepressant treatment to restore neuronal atrophy and cell loss through neurotrophic actions [4,5]. However, the association of antidepressant treatment with BDNF signaling derives mostly from research on rodents [He et al., 2022]. Antidepressants increase the release of BDNF and it signaling through TrkB [Castrén and Monteggia, 2021]. The treatment promotes the activation of PLCγ and ERK signaling pathways [Castrén and Monteggia, 2021; Lepack et al., 2016]. Antidepressants are now known to indirectly regulate cell-survival pathways, including ERK/cyclic AMP responsive element binding protein (CREB)/BDNF pathway, which partially explains their delayed, long-term beneficial effects in depressed patients [Castrén and Monteggia, 2021]. The effect of typical and fast-acting antidepressants on BDNF and TrkB signaling was for a long time considered to be mediated by serotonin and N-methyl-D-aspartate receptors, however, recently, evidence of direct binding of antidepressants to TrkB have emerged [Casarotto et al., 2021]. Fast-acting antidepressants, such as (R,S)-ketamine, bind to TrkB in a stereoselective manner and promote synaptic plasticity through BDNF/TrkB signaling [Casarotto et al., 2021; Lin et al., 2021]. However, the precise mechanisms of action of (R,S)-ketamine is still unclear. From animal studies, we know that (R)-ketamine has greater potency and longer-lasting effects than (S)-ketamine, which could be associated with the nuclear receptor-binding protein 1 (NRBP1) [Yao et al., 2022]. Recently, it was suggested that (R)-ketamine increases the expression of BDNF in microglia through ERK-NRBP1-CREB signaling [Yao et al., 2022].

Even though studies motivated by the neurotrophic hypothesis of depression have yielded contradictory results, there is still a lot of experimental and clinical evidence that points to both BDNF plasma/serum concentration and BDNF genetic variations as potential players in the pathophysiology of depression and response to antidepressant treatment.

1.2. Depression

Major depressive disorder (referred in this text as depression) is a prevalent and disabling condition, associated with decreased quality of life, increased risk of suicidal behavior, worsening of physical health, high rates of hospital admissions, workload loss and considerable adverse impact on society. In 2019., depression was a leading cause of global disease burden among mental disorders worldwide, across the lifespan after the age of 14 [6]. Moreover, in 2020, additional 53.2 million cases of depression were recorded, which represents an increase of 27.6% after the emergence of the COVID-19 pandemic [7]. The Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) criteria [8] for major depressive disorder include depressed mood and/or loss of interest/pleasure, accompanied by weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, feeling worthless or excessive/inappropriate guilt, decreased concentration and thoughts of death/suicide, and patients must have at least 5 such symptoms, during the same 2-week period.

Etiology of depression is highly complex, representing the final result of the interplay between genetic vulnerability and stressful environment [9]. Epidemiological risk factors include low education and socioeconomic status, neuroticism, family history of severe depression, as well as childhood and adulthood trauma [10]. Biological underpinnings of depression are related to hypothalamic-pituitary-adrenal axis dysregulation, low-grade inflammation, neurotransmitter dysfunction, impaired neurotropic systems and neuroplasticity, as well as altered metabolic pathways and metabolites [11]. Despite extensive research, the underlying pathophysiology is still inconclusive compared to many other disorders.

Antidepressants are first-line of treatment, although no single antidepressant is superior to others in treating patients with depression [12]. The choice on antidepressants relies on trial and error practice, given that no predictors of clinical response are available. Many attempts have been made to generate reliable, easy-to-obtain blood-derived candidate biomarkers based on the current models of disease pathogenesis [13]. The identification of such biomarkers would help to establish early diagnosis and choose the most effective treatment [9,11]. One of the most investigated candidates is BDNF, which has been implicated both in the pathophysiology and treatment of depression.

1.3. Peripheral BDNF concentration in depression

Many studies examined circulatory BDNF levels in depression because of: 1) the potential to study BDNF levels in easily accessible samples (plasma, serum and less frequently platelets or whole blood) [11]; 2) the hypothesis of “peripheral as a window to the brain” as a proxy for its expression in the brain [14]; 3) their low values in depression; 4) their sensitivity to change during treatment [15,16]; and 5) stability, at least of serum BDNF, in healthy, untreated individuals [17].

In general, age and gender did not influence the heterogeneity of results [14,18], but the subgroup analyses have shown decreased BDNF levels in patients with no alcohol consumption and/or history of depression compared to healthy controls [14]. Notwithstanding the differences across studies, there is compelling evidence on the decreased peripheral BDNF levels, particularly in serum of patients with depression, as a marker of depression.

Meta-analyses of peripheral BDNF levels in patients with depression and control groups, mostly healthy individuals, published within last ten years, are provided in Table 1.

Please insert Table 1 here

The reason for the reduced blood BDNF levels in depression is difficult to explain with the present knowledge. Namely our understanding of BDNF's activity outside the brain is still rudimentary [23], but these decreased peripheral BDNF levels in depression may be related to: 1) decreased BDNF gene expression; 2) increased platelet activation; 3) altered mature and proBDNF ratio; 4) reduced physical activity in depression; or 5) the reflection of decreased brain BDNF activity. For example, hypermethylation of the *BDNF* gene is consistently reported in depression, at least in Asian population, and in leukocytes [24]. This may downregulate BDNF gene expression, such as in response to adverse environmental factors, particularly early life stress [25]. Likewise, mRNA expression levels of *BDNF*/*TrkB* related genes in leukocytes are negatively associated with depression severity in patients with unipolar and bipolar depression, whereby changes in BDNF mRNA expression are highly correlated with alterations in DNA methylation for multiple CpG sites [26]. Another explanation may be that decreased serum BDNF levels in depression result from depletion of platelet BDNF content [13], due to platelet pre-activation [13,27]. However, the relationship between platelet activation and the peripheral BDNF levels, as well as the origin of BDNF in platelets, are incompletely understood. Platelets are the major peripheral reservoir of BDNF, but it is unclear whether BDNF in platelets is inherited from megakaryocytes, or internalized from the circulating plasma. According to some authors, megakaryocytes represent the only significant source of BDNF in serum and platelets [28]. Others propose that serum BDNF is likely derived, in addition to megakaryocytes, from a number of tissue sources, such as brain, skeletal muscles, vascular endothelium, lymphocytes, monocytes, and interstitial fluid from different peripheral tissues [23].

While it was well-established that exercise increases *BDNF* expression and decreases *BDNF* methylation [25], lower daily physical activity has been correlated with both presence and severity of depression [29]. Therefore, symptoms of depression, particularly fatigue and psychomotor retardation, induce physical inactivity, which than contributes to low peripheral BDNF levels in patients.

Another debate continues whether low circulatory BDNF levels in depression mirror the changes in the brain. While it is not possible to measure BDNF in the living human brain, there is a meta-analytic evidence on the decreased BDNF concentration in the cerebrospinal fluid of depressed patients compared to healthy controls [30]. Importantly, the pattern of mRNA transcripts in human megakaryocytes is similar to neurons [28], suggesting that in depression, lower BDNF production may occur in both structures. Moreover, despite some controversies, both megakaryocytes and platelets exert TrkB receptors, although at low levels of expression [31]. In human postmortem study, BDNF brain tissue levels correlated with CSF and plasma levels, with plasma/brain ratio of

35.9 [32], while other authors reported negative results, given the lack of correlation for BDNF between the hippocampus and serum or leukocytes in epileptic patients who underwent brain surgery [33]. Certainly, BDNF has distinct roles in neurons and in the bloodstream. Whereas in brain, BDNF is implicated in neuronal growth and survival, in the circulation it induces platelet aggregation and stimulates platelet release of inflammatory and angiogenic cytokines [31]. The depletion of platelet BDNF content may adversely impact endothelial function and thrombus growing, and likely represents one of the links between depression and cardiovascular disease [27].

Some of the discrepancies within the results might arise from the fact that some commercial kits do not distinguish between proBDNF from mBDNF. As reported before (Polacchini et al. 2015), only two commercial kits (Aviscera-Bioscience and R&D System-Quantikine®) showed a remarkable preferential specificity for the mature form of BDNF, while other four kits were not specific, explaining the poor reproducibility of BDNF measures due to the differences in methods used for sample collection and BDNF analysis. Both molecules have important, but opposing roles in the maintenance of neurons. While there is no meta-analysis on their levels in depression, serum tissue plasminogen activator and the ratio of BDNF/proBDNF were lower in the patients with depression than in controls [34]. Mature BDNF is mainly stored in the α-granules in platelets [35] and megakaryocytes [31], and proBDNF is predominantly localized in the intracellular compartment. Platelets release only mature BDNF suggesting that plasma proBDNF does not come from platelets [35]. Since ethnic differences were found in the concentration of proBDNF and mature BDNF in sera from Japanese, Swedish and Jewish subjects, it was suggested to compare levels of both BDNF forms in human subjects to confirm or discard BDNF levels as reliable biomarkers for mood disorders (Hashimoto, 2016)

Future studies should take multiple confounders into account, and measure mBDNF and proBDNF separately rather than BDNF as a whole. Given the potential changes [15,16], and even normalization [36] of the peripheral BDNF levels during treatment of depression, blood BDNF concentration was proposed as a state, but not a trait marker. Decreased peripheral BDNF levels are well-established in depression, but similar alterations in peripheral BDNF levels were observed in a variety of disorders, such as Parkinson's disease [22], schizophrenia [20], and in depressed and manic phases of bipolar disorder [21].

Those findings implicate the shared BDNF system dysfunction across neurodegenerative and psychiatric disorders and emphasize the role of improving BDNF functioning in their treatment.

Several proposed mechanisms leading to decreased peripheral BDNF levels in depression are summarized in Figure 1.

Please insert Figure 1 here

1.4. BDNF concentration and the treatment response in depression

The search for the biomarkers of the treatment response in depression is an unmet need in psychiatry, since biomarkers might help to achieve a quicker response to antidepressant therapy and offer a personalized treatment [11]. The response to different antidepressants is studied, but most frequently effects of treatment with the selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs). Due to its therapeutic potential in

depression, BDNF is considered as a biomarker of the treatment response to antidepressant medication [5]. However, there are inconsistent findings regarding BDNF concentration in the blood of patients with depression treated with different antidepressant drugs [37]. A systematic meta-analysis reported that patients with depression have lower serum BDNF levels compared to controls, which were increased (i.e. normalized) after short term (8 weeks) of treatment with SNRIs and SSRIs, but within SSRIs only sertraline (in contrast to venlafaxine, paroxetine, and escitalopram) significantly increased BDNF levels [38]. In agreement, we have recently detected a significantly higher plasma BDNF concentration compared to baseline data in depressed patients treated for 4 weeks with vortioxetine but not escitalopram [39]. In line with these findings, baseline serum BDNF levels were significantly higher after than before vortioxetine treatment and were significantly inversely associated with depression status and severity of depression [40]. Consistent with these findings, plasma BDNF levels were significantly and negatively correlated with depressive symptoms, suggesting the association of higher plasma BDNF with lower severity after antidepressant treatment with different medication [41]. In patients with severe depression, 12 weeks of treatment with mirtazapine increased significantly serum BDNF levels compared to pretreatment BDNF data [42]. Although treatment response to 6-weeks of duloxetine was associated with a higher pretreatment serum BDNF levels, early response after 1-2 weeks of duloxetine treatment was also associated with elevated BDNF levels, suggesting that early increase of BDNF predicts improved depression [43]. After 12 weeks of treatment with paroxetine or fluoxetine, plasma BDNF concentration was significantly increased compared to baseline data [44] in depressed patients who attempted suicide.

However, there are also opposite findings regarding the usefulness of BDNF in predicting treatment response. Namely, baseline plasma BDNF concentration was not a good predictor of vortioxetine or escitalopram treatment response, since patients subdivided into responders and non-responders had similar plasma BDNF concentration [39]. A randomized, multi-center, double-blind, parallel-group, placebo- and active-controlled, flexible-dose study, that included longer period, 10-weeks of treatment with paroxetine and venlafaxine, could not find any significant effects of these two medications on plasma BDNF levels [45]. In the systematic review and meta-analysis that included 154 subjects with depression, treatment with different antidepressants from 5-12 weeks did not significantly affect serum BDNF levels [46]. In the drug-naïve first-episode patients, 4 weeks of treatment with escitalopram, fluoxetine, mirtazapine, paroxetine or venlafaxine was not associated with alterations in serum BDNF levels, although these subjects had lower serum BDNF levels compared to healthy controls [47]. There were no significant differences in plasma, platelet and platelet rich plasma BDNF levels before or after several weeks of treatment with escitalopram, sertraline, paroxetine, fluoxetine, or mirtazapine, venlafaxine, trazodone or agomelatine [41]. In agreement, baseline serum BDNF levels were not associated with reduction of depressive symptoms or treatment response, while serum BDNF levels were decreased after 8 and 12 weeks of treatment with nortriptyline or escitalopram [48], and baseline plasma BDNF was not correlated with reduction in depressive symptoms after 12 weeks of treatment with paroxetine or fluoxetine [44].

These discrepancies might be explained by the different length of the antidepressant treatment. Namely, a study reported [49] significantly decreased serum BDNF levels with the reduced clinical symptoms in patients with depression treated for 4-8 weeks with escitalopram, citalopram, fluoxetine, paroxetine, mirtazapine, paroxetine, venlafaxine, and others over the time course. In that study serum BDNF did not differ between baseline and 4 weeks of treatment, but was significantly lower after 6-8 weeks of treatment, and significantly decreased BDNF was found in responders and remitters compared to non-responders and non-remitters [49]. Different literature

findings might be explained also by the fact that blood BDNF concentration is affected also by age, sex, smoking status, and body mass index or weight [35].

The possible effects of the potential novel antidepressive drug riluzole, that acts as the glutamate release inhibitor, on serum and plasma BDNF levels was studied in a randomized controlled, adjunctive, sequential parallel comparison design trial, but due to the small number of subjects and low percent of riluzole responders, there were only marginal, nonsignificant decreases in serum and plasma BDNF levels in riluzole responders vs. non-responders [50]. No significant differences in plasma BDNF levels were also found after 10 weeks of treatment with escitalopram vs. Electrical Current Therapy for Treating Depression Clinical Study (ELECT-TDCS), and these data suggested that BDNF did not predict treatment improvement [51]. In adult patients with depression, baseline serum BDNF levels were not associated with outcome to cognitive behavioral therapy or interpersonal psychotherapy; however, decreased depressive symptoms after psychotherapy were related to increased pretreatment serum BDNF [52]. As a novel antidepressant strategy, the effects of 6-weeks of the low-field magnetic stimulation on serum BDNF levels were studied, and patients received rhythmic alpha stimulation or rhythmic delta stimulation [53]. Serum BDNF levels were increased after rhythmic alpha stimulation treatment, and this increase was stronger in responders vs. non-responders who had lower pretreatment BDNF levels compared to non-responders [53].

In patients with treatment-resistant depression (TRD), a meta-analysis revealed that pretreatment serum BDNF levels were increased following electroconvulsive therapy (ECT), ketamine, repetitive transcranial magnetic stimulation (rTMS) and treatment with atypical antipsychotics, but were not related to improvement in depressive symptoms [54]. These results suggested that peripheral BDNF could not be used to predict treatment response in TRD patients [54]. In line with these data, pretreatment serum BDNF levels could not distinguish patients with TRD treated with ECT subdivided into responders and non-responders, or remitters and non-remitters, or into sustained responders/non-responders and sustained remitters/non-remitters after 1 month of ECT [55]. This finding confirmed that pretreatment BDNF could not predict ECT response in TRD patients [55]. In contrast to ECT, plasma BDNF concentration was increased after six ketamine infusions compared to baseline values in depressed patients, and higher BDNF was associated with clinical improvement and with response and remission [56]. This finding was confirmed in a recent meta-analysis and a systemic review of biomarkers of antidepressant response in depression, that included 11 studies [57]. This study did not find overall significant differences in BDNF levels between responders and non-responders to ketamine. However, out of 332 patients with depression and bipolar disorder, 105 reported higher BDNF levels associated with greater improvement in depression scores measured 1-4 weeks after treatment with ketamine infusion [57]. In this review, one study, including 94 patients with depression and bipolar disorder, reported that responders, in contrast to non-responders, had increased levels of BDNF after 2-4 weeks after infusion of ketamine, compared to baseline levels [56]. This meta-analysis suggested that BDNF levels might present a potential dynamic biomarker of ketamine's antidepressant effects [57].

There are divergent results from the literature about the BDNF as a potential marker of the treatment response; however, since antidepressant medication increases BDNF mRNA and BDNF protein levels in the cerebral cortex and hippocampus [4], and most of the data reveal that different antidepressant drugs elevate serum/plasma BDNF levels that are reduced in patients with

depression, these findings suggest that BDNF might connect antidepressant effects and neuroplastic changes leading to improvement of depressive symptoms [5].

Most of the monoaminergic antidepressants downregulate serotonergic receptors leading to the weakening of the TrkB receptor inhibition, and elicit intracellular events such as promotion of BDNF transmission triggered by direct TrkB modulation [4]. These processes might explain the delay in the clinical response to antidepressants. It is proposed that BDNF mediates antidepressant response, since changes in BDNF signaling, either upstream or downstream, achieved via binding to TrkB receptors, integrate different environmental influences and therapeutic response [4,5].

The effects of different antidepressant medication and treatment strategies on serum or plasma BDNF concentrations are summarized in Table 2.

Please insert Table 2 here

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1.5. BDNF genetic variants and depression

Most of the studies discussing the association between *BDNF* genetic variants and depression are focused on *BDNF* Val66Met (rs6265) polymorphism, a single nucleotide polymorphism (SNP) that results in the substitution of 66th amino acid in the protein sequence, from valine (Val) to methionine (Met). Many studies have attempted to clarify the role of *BDNF* genetic variations, with emphasis on *BDNF* Val66Met, in depression. However, the results from the literature are conflicting due to inadequate sample sizes, ethnic heterogeneity, and non-inclusion of different confounding factors.

Given that Met substitution in the prodomain of BDNF has been shown to cause trafficking defects, different studies have assumed that subjects with one or two Met alleles would have an increased risk for depression. The association of *BDNF* Val66Met polymorphism and two other genetic variants, rs1048218, and rs1048220, was assessed in Malaysian patients with depression [57]. Using logistic regression, the authors demonstrated that Met allele increases the risk of developing depression. Another study reported a significant association between depression severity and *BDNF* Vall66Met polymorphism with more severe symptoms associated with the number of Met alleles [58]. The *BDNF* Met allele was also associated with the prevalence and persistence, but not the incidence, of depression among patients with acute coronary syndrome [59]. The association between *BDNF* Met allele and increased the risk for developing depression was confirmed [59]. There was no significant interaction between *BDNF* Val66Met polymorphism and suicide and/or early life adversity [59]. A meta-analysis by Zhao and colleagues suggested that *BDNF* Val66Met Met allele plays a role in moderating the relationship between stress and depression [60]. The *BDNF* Val66Met was also associated with cortical thickness alterations in the left rostral anterior cingulate of subjects with depression, and with *BDNF* Met allele as a vulnerability factor [61]. Opposed to these results, we have recently found that BDNF Val66Met was not significantly associated with depression in Caucasian subjects of the Croatian origin, but these results might be explained with a smaller number of depressed patients included in our research study [62] compared to a meta-analysis 60The relationship between the person's resilience towards acute stress and trauma, assessed with specific resilience scale, and *BDNF* Val66Met polymorphism was studied [63]. The

results showed higher baseline resilience scores in Met allele carriers diagnosed with depression then in patients who were Val/Val homozygotes [63]. The same study also demonstrated that cognitive therapy increased resilience and decreased depressive symptoms which is influenced by Val66Met and sex interaction [63].

Many studies reported no association between BDNF genetic variations and depression pathogenesis. No significant association was detected between the *BDNF* Val66Met polymorphism and susceptibility to depression in Romanian population [64]. Since BDNF is affected by diet, the association between depression, dietary quality, BDNF serum levels and *BDNF* Val66Met was investigated [65]. The logistic regression model suggested that lower dietary quality and higher BDNF serum concentration were associated with increased depression risk [65]. However, there was no interaction of Val66Met with BDNF levels, dietary quality, and depression [65]. In patients with depression who attempted suicide, no associations between *BDNF* Val66Met polymorphism, suicide ideation and treatment response were detected [44]. A mini review of meta-analyses focused on *BDNF* Val66Met role in depression found no evidence to confirm that *BDNF* Val66Met is a risk factor for depression [66]. However, according to this review [66], the literature data support the importance of this BDNF polymorphism in predicting the responses to treatment with antidepressants and BDNF peripheral levels as a marker for the state of depression [66]. The association between *BDNF* Val66Met and BDNF peripheral levels was also suggested [67]. Namely, a significant association for the *BDNF* Met allele and higher BDNF serum levels, and a correlation between Met allele and lower TNF-α serum concentration [67] was found.

The potential relationship of 7 polymorphisms in genes coding for apolipoprotein E (*APOE*), heat shock protein family A (Hsp70) member 1A (*HSPA1A*), solute carrier family 6 member 4 or serotonin transporter (*SLC6A4* or *5-HTT*), 5-hydroxytryptamine receptor 2A (*HTR2A*), and *BDNF*, with the risk of developing depression or Alzheimer's disease was studied [68]. The results of the study indicated significant interaction between analyzed polymorphisms and depression, confirming a synergistic effect of genes involved in inflammation, serotonergic and neurotrophic pathways on depression and Alzheimer's disease pathogenesis [68]. Another study [69] also assessed a possible synergistic effect of polymorphisms in *HTR2A*, *BDNF* and *APOE* genes on development of depression. The results suggested a possible interaction between serotonergic neurotransmission (*SLC6A4* and *HTR2A* genes), neurogenesis (*BDNF* and *APOE* genes), and the depression pathogenesis [69]. Increased risk for depression was associated with *BDNF* Met allele, in combination with other risk alleles (serotonin transporter intron 2 variable number of tandem repeats (*5-HTT-VNTR*) 10 allele, serotonin-transporter-linked promoter region (*5-HTTLPR*) S allele, *HTR2A* rs6313 C allele, *APOE3*) [69]. The interaction between two polymorphisms, *5-HTTLPR* and *BDNF* Val66Met, and neurostructural changes of emotion-processing regions was investigated in subjects with depression [70]. The results showed decreased cortical volume in the right anterior mid-cingulate gyrus for *5-HTTLPR* L allele carriers and a significant joint effect of depression and *BDNF* Val66Met polymorphism on the fractional anisotropy values of the right uncinate fasciculus [70]. A significant association of *5-HTTLPR* with a higher risk for development of depression was found, but with no evidence of association between *BDNF* Val66Met and depression [71]. The study results confirmed the interaction between these two polymorphisms in relation to depression, since the combination of *5-HTTLPR* LS genotype and *BDNF* Val homozygous genotype increased the odds of depression almost three times [71].

Several studies have investigated the effect of *BDNF* Val66Met on brain structure, with the emphasis on the brain regions which are linked with emotions. *BDNF* Val66Met Met allele was

associated with decreased fractional anisotropy values in the uncinate fasciculus of patients with depression [70,72]. The opposite findings were detected in healthy individuals where Met allele carriers had significantly higher fractional anisotropy measures [70,72]. In addition, reduced fractional anisotropy measures were reported in subjects who were both BDNF Met allele carriers and *HTTLPR* LS heterozygotes, and these results were later confirmed [70]. Both *BDNF* Val66Met and *5-HTTLPR* mediated the interaction between higher fractional anisotropy values in the left uncinate fasciculus and improvement in depression severity after antidepressant treatment [73]. The effect of *5-HTTLPR* and *BDNF* Val66Met on cortical thickness and brain volume in limbic and paralimbic regions of subjects diagnosed with depression was assessed [74], and this study found no significant effect of *BDNF* Val66Met, but the association of *5-HTTLPR* polymorphism with morphometric changes in investigated brain regions [74]. The cumulative effect of specific *5-HTTLPR*, *BDNF* Val66Met and catechol-O-methyltransferase *COMT* Val108/158Met functional polymorphisms on brain structure in subjects with depression was studied [75]. Patients with depression were found to be more frequently *BDNF* Val/Val homozygotes, *5-HTTLPR* L allele carriers and *COMT* Met allele carriers, compared to healthy individuals [75]. These results confirmed the expected cumulative effect of *5-HTTLPR*, *BDNF* and *COMT* functional polymorphisms on brain morphological features in both patients with depression and control subjects [75].

All these studies, regardless of the conflicting results and remaining unknowns, point out to the important role of BDNF and its genetic variations, in combination with other genetic variants related to serotonin and COMT, in the alterations in the brain structures and function associated with pathological changes of depression.

1.6. BDNF polymorphism and treatment response in depression

Genetic polymorphisms are important contributors to the individual differences in disease risks and drug responses, with SNP being the most frequent type of genetic polymorphisms [76]. Polymorphisms within the *BDNF* gene are often associated with changes in BDNF expression levels leading to interruption of cell signaling and are often studied as potentially having a role in the etiology of depression [77]. However, beside defining the etiology of depression, it would be more than useful to be able to predict antidepressant efficacy. Moreover, BDNF could be considered as a biomarker for the state of depression and response to depression appropriate treatment rather than as a risk factor for depression [66]. The genetic background of depression and antidepressant treatment response is very complex and hard to explore since genetic risk factors usually don't have individually large and easy observable effects. Nevertheless, there are different types of studies dealing with the role of BDNF polymorphisms in antidepressant efficacy. Most studied BDNF polymorphism is rs6265 (Val66Met), a SNP that affects intracellular trafficking and activity-dependent secretion of BDNF. In general, the literature data are inconsistent and often focused on different types of antidepressant therapy.

A network meta-analysis encompassing BDNF, but also several serotonergic genes, reported no significant difference in predictive value of BDNF Val66Met on the efficacy of antidepressants in depression [78]. Additionally, no association between BDNF Val66Met with transcranial direct current stimulation (tDCS) or escitalopram efficacy in depression was reported [79]. Similarly, although depressed patients who were Met carriers had higher plasma BDNF levels than Val carriers, BDNF Val66Met polymorphism was not found to be related to their clinical response to electroconvulsive therapy [80]. When the effect of BDNF Val66Met, but also three other BDNF SNPs

(rs925946, rs7124442, rs908867) on treatment response was tested in depressed patients treated with venlafaxine for six weeks, again no significant associations were reported [81].

On the other hand, there are also studies indicating that BDNF polymorphisms contribute to the treatment response. Namely, after three weeks of escitalopram treatment, significantly better response was noticed in patients with depression who were carriers of Met allele, while Val homozygotes had greater antidepressant resistance [82]. These results suggest that a significant effect of BDNF Val66Met on antidepressant efficacy is achieved since the Met allele is associated with better treatment response. However, antidepressant effect of a high frequency repetitive transcranial magnetic stimulation (HF-rTMS) approach that can induce changes in synaptic plasticity was reported to be associated with BDNF Val66Met polymorphism in patients with depression, in a way that previously medication-resistant Val homozygotes had significantly better treatment response than Met carriers [83]. Another study examined the interactions between the BDNF Val66Met and antidepressant drug classes in order to explain the treatment response and remission in depressed patients treated with either selective serotonin reuptake inhibitor (SSRI) or serotonin and noradrenalin reuptake inhibitor (SNRI)/tricyclic antidepressant (TCA) [84]. The results showed that Val homozygotes had higher response rate after three months of SSRI treatment and lower remission rate after six months of SNRI/TCA treatment [84]. Tatham et al. [73] assessed whether indices of white matter integrity and BDNF Val66Met polymorphism could predict how symptoms of depression will change following antidepressant treatment. They used fractional anisotropy as an indicator of white matter integrity assessed in the uncinate fasciculus and superior longitudinal fasciculus in patients with depression after eight weeks of treatment with citalopram or quetiapine XR [73]. Higher fractional anisotropy values were associated with better improvement of depressive symptoms after the obtained antidepressant treatment, with Val homozygotes exhibiting higher fractional anisotropy in the left uncinate fasciculus when compared to the Met allele carriers [73].

Although most of the published data is about the functional BDNF Val66Met polymorphism, there are also some studies focused on other BDNF polymorphisms. A review described published scientific papers dealing with BDNF and its receptors TrkB and $p75^{NTR}$ polymorphisms and their associations with the antidepressant efficacy in depressed patients [85]. The study included 5 genome-wide association and 30 association studies, out of which 27 studies focused on the functional, Val66Met polymorphism, whose Met allele was associated with a higher antidepressant efficacy in Asian patients [85]. Seven other BDNF polymorphisms (rs7103411, rs7124442, rs908867, rs2049046, rs61888800, rs10501087, rs1491850) and 5 haplotypes (rs7103411–rs6265–rs7124442, rs10501087–rs6265–rs1491850, rs1030094–rs11602246, r6265–rs11030109–rs10835211–rs2049046–rs4923468–rs12273363, rs12273363–rs908867–rs1491850) were also reported to be associated with antidepressant efficacy but no replications were available for those results [85]. Another study investigated the effects of two BDNF SNPs on response to two-and four-weeks long antidepressant treatment [86]. During the first 2 weeks of treatment no associations between symptom improvement and studied SNPs were found [86]. After four weeks of treatment, BDNF Val66Met was still not associated with the treatment response, but T homozygotes according to BDNF rs7124442 polymorphism had significantly better antidepressant response than the respective C homozygotes [86]. Other BDNF SNPs might be involved in the antidepressant mechanisms of low-dose ketamine infusion in patients with treatment-resistant depression [87]. Patients were genotyped for 684,616 SNPs and among the twelve selected ketamine-related genes was also BDNF rs2049048, for which an association with the rapid and persistent antidepressant effect of low-dose ketamine infusion was found [85].

Recent article questioned the utility of using peripheral BDNF concentration and BDNF Val66Met polymorphism as biomarkers related to pathophysiology of depression and treatment response to antidepressant medication [88]. They summarized that both animal and human studies indicate that altered (reduced in depression and higher after antidepressant treatment) blood BDNF levels (serum or plasma) and altered expression of the BDNF affected by the presence of the Met or Val allele of the BDNF Val66Met polymorphism, might be connected to depression and treatment response, but because of the high heterogeneity, lack of statistical power and inadequate sample sizes, the translational evidence is still not strong or solid [88]. There are numerous confounders that need to be considered.

Due to the mainly inconsistent results across studies, pharmacogenetic studies of BDNF in depression have yet not offered results that could be applicable in clinical practice. However, such a large number of different independent studies can offer useful recommendations, guidelines and strategies for further studies. Besides, since allele frequency and linkage disequilibrium (LD) differences are often ethnic related, differences in population genetic structure between patient samples should also be considered. Namely, it is quite possible that within the same population some members are not representative of others and it is even more possible that a single population does not reflect variation in other populations. With Met allele frequency ranging from 0 to 72 % BDNF across populations (as discussed in Yeebo (2015), Luo et al (2019) and González-Castro (2017), Val66Met polymorphism is just the right example of this phenomenon. Of course, not only ethnic related differences in polymorphisms, but ethnic differences in the serum levels of proBDNF and mature BDNF between Japanese, Swedish and Jewish subjects were reported (Hashimoto, 2016). Doubtless, this type of studies requires very detailed, exact and uniform diagnosing of depression, but it is also important to consider that not all antidepressants could be affected equally by different genetic factors. In order to increase the chances to confirm or reject the association between BDNF SNPs and antidepressant treatment response, it could be very useful to combine genetic analyses with pathway analysis and endophenotypes, which are more specific observable characteristics. Additionally, methodological improvement requires the integration of the GWAS with candidate gene approach. It is not wrong to conclude that a lot of knowledge about the genetics of BDNF in antidepressant treatment was already gained, but further studies are needed to clarify the clinical utility of BDNF genetic variants in the treatment selection and treatment response.

2. Conclusion

The discrepant finding regarding the role of BDNF and its genetic variants of the BDNF Val66Met in depression and treatment response in depression may be explained with many different factors such as stages of depression, medication free status or different medication and doses used, different time of treatment, various environmental factors, exercise, differences in the ethnicity, age, sex, BMI, nutrition, diet, life style, the use of serum or plasma samples, different methods for BDNF determination and synergistic effect of genes involved in serotonergic and neurotrophic pathways. Still, large proportion of the cited data suggest that reduced BDNF levels in patients with depression, and elevated (i.e. normalized) BDNF levels after antidepressant therapy, with the Val allele carriers of the BDNF Val66Met showing mostly better response to antidepressant treatment.

Nevertheless, as BDNF has an important role in long-term potentiation, modulation of dopaminergic, serotonergic and cholinergic neurotransmission, neuro-regeneration and survival of

neurons, and affects synaptic function and neuronal and synaptic plasticity, most of the findings confirm its role in the etiology and treatment response in depression.

3. Expert Opinion

1. The advances in the research using the brain derived neurotrophic factor (BDNF) concentration and genetic variants, that were presented here, might impact real world outcomes (primarily treatment guidelines and prediction of the treatment response, using pretreatment baseline peripheral BDNF levels) in depression. However, these results should be controlled for the possible confounders such as age, sex, ethnicity, medication status, determination of BDNF in plasma or serum or platelets, exercise, physical activity, stage and time course of depression, medication free status or different medication and doses used, the length of treatment, various environmental factors, differences in nutrition, diet, life style, different methods for BDNF assessment and synergistic effect of genes involved in serotonergic and neurotrophic pathways that might show cumulative effects. Some other factors might prevent implementation in the clinical/research practice (i.e. the costs of BDNF assessment). Genetic variants of the BDNF, especially BDNF Val66Met polymorphism, and other polymorphisms on the *BDNF* gene, and their association with depression and/or treatment response might be implemented in the clinical practice to reveal risk genotypes or haplotypes, but the limitation of this particular pharmacogenetic approach is that for the meaningful results, genetic analyses need to include a large number of samples.

2. The key area are that BDNF has an important role in the etiology and treatment of depression. Some current problems associated with the development or the search for the diagnostic, prognostic and theranostic biomarkers of depression/treatment response, in order to facilitate diagnosis, therapy monitoring, and prediction of treatment outcome and focus on the personal medicine approach, are discussed in this review, that involve technical, technological, or methodical limitations that prevent research from advancing into clinical practice.

3. This research holds a great potential for the future, given that either resistance to treatment (TRD) or non-response in depression is frequent and therefore strategies to improve BDNF function should be utilized and applied (such as exercise, physical activity, Mediterranean diet, and particular medication) for patients with depression. Novel therapeutic strategies, that are the urgent and unmet need in depression research, should be developed to target restoring and/or increasing BDNF levels.

4. This research has a bright future. For the genetic variants of the BDNF gene, more promising areas in the field are to evaluate interactions and cumulative effects of different genotypes and haplotypes related to BDNF, COMT and 5HTT genes; and to combine genetic analyses or GWAS with pathway analysis and endophenotypes, which are more specific observable characteristics of depression.

5. This field should evolve in the future, since remission is an unmet need to reach in the treatment of depression, and biomarkers, such as blood-based biomarkers, are useful tools that might help to achieve this goal in finding the best possible treatment for the individual patients, and reach the goal of personalized medicine. The research should include as a standard to assess plasma/serum BDNF levels before and after antidepressant treatment and genotyping of the individual genes with

GWAS to be able to determine all possible risk alleles/genotypes or haplotypes associated with depression or treatment response in depression.

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Table 1. Meta-analyses of peripheral BDNF levels in patients with depression and control groups

Population	**Type of peripheral BDNF samples**	**Number of studies**	**Number of patients**	**Results**	**Reference**
Patients with or without depression in the early stage of stroke	Serum	6	268 patients with poststroke depression, 425 Patients after stroke, without depression	Patients with poststroke depression had decreased serum BDNF levels compared to stroke patients without depression	Zhang et al. [18]
Drug-free or drug-naive patients with depression compared to nondepressed healthy controls	Serum or plasma, not separately analyzed, but majority of studies assessed serum levels	24	1130 patients with depression and 1378 healthy controls	Peripheral BDNF levels decreased in depressed relative to levels in nondepressed healthy controls	Tiwari et al. [14]
Patients with type 2 diabetes mellitus with or without depression, only one of the three studies excluded antidepressant use	two studies measured serum BDNF, while the third measured plasma BDNF, not separately analyzed	3	358 depression, 1512 T2DM without depression	Lower BDNF concentrations in people with T2DM and depression compared to patients with T2DM who did not have depression	Nguyen et al. [19]
Patients with depression	Serum or plasma, not separately analyzed	97	14,192 participants (7117 MDD patients and 7075 healthy controls), some patients were not drug-free	serum and plasma levels of BDNF were lower in depressed patients	Shi et al. [16]
Drug-naïve first-episode patients with depression	Serum	10	373 patients, 456 controls	Trend of decrease in BDNF levels	Çakici et al. [20]
Patients with depression	Serum	20	2384 antidepressant-free patients, 2982 healthy controls 1249, antidepressant-	low serum BDNF concentrations in antidepressant-free patients relative to healthy controls and to	Molendijk et al. [15]

			treated patients	antidepressant-treated depressed patients	
Patients with acute depression	Serum (32 studies) and plasma (6 studies)	38	2447 patients and 2147 controls	Decrease in overall BDNF, significant decrease in serum, nonsignificant in plasma	Polyakova et al. [21]
Patients with Parkinson disease with or without depression	Serum	8	101 patients with Parkinson disease and depression, 127 without depression, 192 healthy controls	No differences between depressed and nondepressed patients, but both groups had lower BDNF levels than controls	Rahmani et al. [22]

BDNF=brain derived neurotrophic factor; T2DM=type 2 diabetes

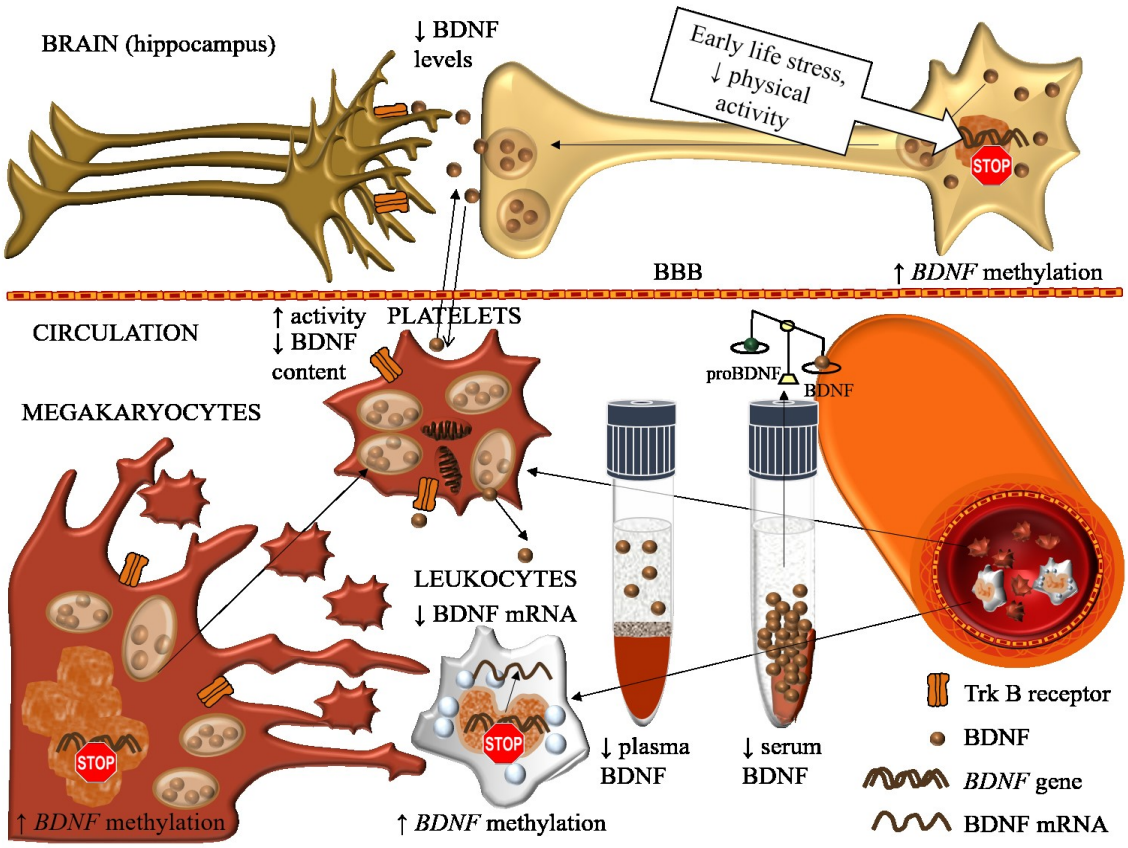
Table 2. Changes in BDNF concentration before or after antidepressant treatments

Population	**Type of BDNF samples**	**Number of patients; length of treatment**	**Results**	**Ref.**
Meta-analysis: patients with depression	serum/ plasma	SNRIs and SSRIs; 8 weeks	decreased BDNF s were increased (i.e. normalized) after 8 weeks of treatment with SNRIs and SSRIs; within SSRIs only sertraline had a significant effect; significantly higher serum than plasma after treatment; e venlafaxine, paroxetine, and escitalopram did not show significant effects	Zhou et al. [38]
Patients with depression	plasma	120: 60 treated with escitalopram and 60 treated with vortioxetine; 4 weeks treatment	significantly increased BDNF concentration vs. pretreatment levels in vortioxetine but not escitalopram treated patients	Dvojkovic et al. [39]
Patients with depression	serum	73 participants; 8 weeks of treatment with vortioxetine	pre-treatment BDNF levels were significantly higher after treatment with vortioxetine, and were inversely related to depression status	Troyan et al. [40]
Patients with depression and with AD with comorbid depression	plasma, platelet-rich plasma or platelets	85 AD patients (36 with comorbid depressive symptoms), 65 depressed patients, 96 healthy controls; different medication.	BDNF was associated with severity of depression in drug-naïve depressive patients.	Pláteník et al. [41]
Patients with depression	serum	30 patients; Mirtazapine; 12 weeks	Increased BDNF post-treatment levels in responders compared to baseline data	Gupta et al. [42]
Patients with depression	serum	25 patients; duloxetine; 6 weeks;	High baseline BDNF serum levels; but increased early serum BDNF associated with decreased depressive scores 1-2 weeks after treatment; but after 6 weeks this association was lost	Mikoteit et al. [43]
Patients with depression	plasma	125 patients and 91 healthy controls; fluoxetine or paroxetine, or SSRIs with low dose	Increased BDNF levels after treatment; significant association between the baseline BDNF concentrations with depression ratings	Ai et al. [44]

		olanzapine; 4, 8, and 12 weeks		
Patients with depression vs. healthy controls	plasma	106 with paroxetine and 108 with venlafaxine; 10 weeks	NS in BDNF after treatment vs. basal levels	Carboni et al. [45]
Meta-analysis; patients with depression	Plasma/ serum	154 subjects; 5-12 weeks	Post-tretment BDNF level increased significantly after antidepressant treatment, and changes in BDNF were significantly correlated with depression scores.	Arumu-gam et al. [46]
First-episode drug-naïve major depressive disorder patients;	serum	first-episode drug-naïve depression vs. healthy controls; 4-weeks; monotherapy	No correlation between BDNF and depression rating scores; no changes in BDNF after treatment with escitalopram, fluoxetine, mirtazapine, paroxetine or venlafaxine	Chiou et al. [47]
Patients with depression	plasma	138 patients; Escitalopram vs. Electrical Current Therapy for Treating Depression Clinical Study; 10 weeks	NS in post-treatment BDNF vs. basal levels	Brunoni et al. 2018. [51]
Adult patients with depression	serum	358 depression, cognitive behavioral therapy or interpersonal psychotherapy	increased BDNF at baseline associated with less depressive symptoms after psychotherapy in the presence of high working memory capacity	Bruijniks et al. [52]
Patients with treatment-resistant depression (TRD)	serum	Electroconvulsive therapy (ECT), ketamine, repetitive transcranial magnetic stimulation (rTMS)	serum BDNF were increased in studies after treatment with ECT, ketamine, rTMS and atypical antipsychotics; but no association with depressive symptoms	Meshkat et al. [54]
Meta-analysis: Patients with depression or bipolar depression	Plasma/ serum	332 subjects; 1-4 weeks after infusion of ketamine	higher BDNF at baseline was correlated with greater improvement in depression scores after treatment	Medeiros et al. [57]

AD=Alzheimer's disease; BDNF=brain derived neurotrophic factor; ECT=Electroconvulsive therapy; NS=no significant difference; rTMS=repetitive transcranial magnetic stimulation; SNRIs= Serotonin and norepinephrine reuptake inhibitors; SSRIs= Selective serotonin reuptake inhibitors.

Figure 1. Schematic representation of the potential causes of the low peripheral BDNF levels in depression



BBB=blood-brain barrier; BDNF=brain-derived neurotrophic factor; mRNA=messenger RNA; TrkB= Tropomyosin receptor kinase B;