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BDNF Dynamics During Early Antidepressant Treatment in Unipolar Depression

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Abstract: *Major depressive disorder frequently presents with prominent anxiety symptoms, reflecting overlapping disturbances in affective regulatory systems. Brain-derived neurotrophic factor (BDNF), a key mediator of synaptic plasticity, has been implicated in the neurobiological mechanisms underlying stress-related psychopathology. This longitudinal study examined whether changes in plasma BDNF concentrations during the first four weeks of antidepressant treatment were associated with improvements in depressive and anxiety symptom severity in patients with unipolar major depressive disorder. Twenty-six medication-free patients were evaluated at baseline and after four weeks using the Hamilton Depression and Hamilton Anxiety Rating Scales, and plasma BDNF levels were quantified by ELISA. Clinical improvement was accompanied by an increase in plasma BDNF concentrations. Greater reductions in depressive symptom severity were associated with larger BDNF increases, whereas no significant association was observed between anxiety symptom change and BDNF modulation. These findings suggest that BDNF dynamics may primarily reflect early neuroplastic adaptations related to depressive symptom improvement.*

Keywords: *major depressive disorder; anxiety; BDNF; biomarkers.*

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1. Introduction

Major depressive disorder (MDD) is one of the leading contributors to disability worldwide and remains a major public health concern, particularly because many patients receive delayed, inadequate, or no treatment (World Health Organization, 2025, August 29). Anxiety disorders are also highly prevalent and contribute substantially to disease burden, yet a large treatment gap persists globally (World Health Organization, 2025, September 8). Clinically, depression and anxiety are tightly intertwined: anxiety symptoms occur in a large proportion of patients with MDD and are associated with greater overall symptom burden and a less favourable course, supporting the view that depressive and anxiety dimensions often reflect overlapping disturbances in affect regulatory systems rather than fully separate processes (Hopwood, 2023; Ionescu et al., 2013; Kraus et al., 2019).

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR), anxiety disorders include separation anxiety disorder, selective mutism, specific phobia, social anxiety disorder, panic disorder, agoraphobia, generalised anxiety disorder, substance/medication-induced anxiety disorder, and anxiety disorder due to another medical condition (American Psychiatric Association, 2022). Although each disorder has distinct diagnostic criteria, they share characteristic features of excessive fear, anticipatory anxiety, hypervigilance, cognitive distortions, and avoidance behaviours, frequently accompanied by prominent somatic symptoms such as palpitations, dyspnoea, chest discomfort, tremor, dizziness, gastrointestinal symptoms, and muscular tension (Chand & Marwaha, 2023). Importantly, these anxiety-related symptoms and behaviours commonly overlap with symptom dimensions seen during major depressive episodes, and comorbidity between MDD and anxiety disorders is common and clinically meaningful (Hirschfeld, 2001).

The aetiology of both depressive and anxiety disorders is multifactorial, involving interactions between genetic vulnerability, psychosocial stressors, and biological alterations in stress-response systems and emotional processing networks. Beyond monoaminergic and inhibitory neurotransmission, dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis and stress-hormone signalling has been implicated across stress-related psychopathology (Adwas, Almokhtar, & Azab, 2019). Neuropeptidergic systems, including oxytocin, vasopressin, neuropeptide Y, and corticotropin-releasing factor, further contribute to the modulation of fear- and stress- neural circuitry (Martin et al., 2009). Within this broader biological context, identifying biomarkers that reflect core pathophysiological processes shared across depressive and anxiety symptom dimensions remains an important goal.

Brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family, has emerged as a key biomarker candidate because it is centrally involved in neuronal survival, synaptic plasticity, dendritic remodelling, and activity-dependent synaptic modulation (Bathina & Das, 2015). Elevated BDNF levels have been reported in limbic and cortical regions involved in emotion regulation, including the hippocampus, amygdala, and prefrontal cortex (Miranda et al., 2019). BDNF expression is responsive to environmental stress, physical activity, antidepressant treatment, and endocrine factors such as glucocorticoids and sex steroids (Miranda et al., 2019; Suliman, Hemmings, & Seedat, 2013). In models of stress-related mood pathology, chronic stress exposure has been associated with reduced hippocampal BDNF expression, whereas antidepressant interventions can upregulate BDNF signalling and reverse stress-related neuroplastic changes (Duman & Monteggia, 2006; Murakami et al., 2005). Moreover, recent evidence shows that BDNF, similar to oxytocin, regulates social and maternal behaviour, eating behaviour as well as obesity, impacting mood and anxiety. A series of animal studies found that oxytocin influences the expression of BDNF in rat mothers, where oxytocin antagonists in the ventral hippocampus significantly reduced BDNF gene expression, which could have a significant impact on maternal behavior and resilience to the stress of reproduction (Florea et al., 2022).

Although BDNF has been studied most extensively in the context of depression, evidence also implicates BDNF signalling in anxiety-related phenotypes, and experimental studies suggest

that BDNF-mediated plasticity in limbic–prefrontal circuits may influence both anxious and depressive behaviours (Duman & Monteggia, 2006). Consistent with this, studies examining peripheral BDNF in anxiety disorders have produced mixed results, some reporting lower BDNF levels in samples with anxiety-disordered and others finding no robust association with symptom severity (Ball et al., 2013; Shen et al., 2019). Differences between studies may be explained by variations in research methods, differences in patient characteristics, and the frequent overlap between anxiety and depression, suggesting that anxiety symptoms may reflect a broader internalising vulnerability rather than a disorder-specific biological mechanism (Ionescu et al., 2013; Hirschfeld, 2001).

Genetic variability may further modulate BDNF signalling. The Val66Met polymorphism, a common single-nucleotide variant in the BDNF gene resulting in a valine-to-methionine substitution at codon 66, affects intracellular trafficking and activity-dependent secretion of BDNF (Miranda et al., 2019). Associations between Val66Met and vulnerability to anxiety disorders have been reported, although the evidence remains inconsistent and requires further clarification (Moreira et al., 2015). Taken together, the literature supports a role for BDNF in stress-related affective pathology, but the relationship between peripheral BDNF levels and the co-occurring depressive and anxiety symptomatology remains insufficiently defined. Given the prognostic relevance of anxiety symptoms within MDD, examining BDNF dynamics in relation to both depressive and anxiety severity may help clarify whether BDNF modulation reflects a depression-specific signal or a broader marker of affective system recovery (Kraus et al., 2019; Hopwood, 2023). We hypothesised that increases in plasma BDNF would be associated with reductions in both depressive and anxiety symptoms.

2. Materials and Methods

Twenty-six patients were recruited from the Socola Institute of Psychiatry, Iași, Romania, between January and June 2025. All participants were diagnosed with unipolar major depressive disorder according to ICD-10 criteria following a comprehensive psychiatric evaluation by a board-certified psychiatrist. The present analysis was conducted on a prospectively followed clinical cohort, with the present investigation specifically focusing on levels of plasma BDNF in relation to depressive and anxiety symptom severity. Eligible participants were between 18 and 65 years of age and had not received psychotropic medication for at least two weeks before baseline assessment. Exclusion criteria included a history of bipolar disorder, psychotic disorders, substance use disorders, neurocognitive disorders, pregnancy, and clinically significant medical conditions that could affect inflammatory or neuroendocrine parameters. These included autoimmune diseases, active infectious conditions, endocrine disorders, chronic inflammatory diseases, malignancies, and systemic corticosteroid or immunomodulatory therapy. Prior to enrollment, all patients underwent a standardised physical examination and routine laboratory investigations to exclude relevant medical comorbidities. Written informed consent was obtained from all participants after a full explanation of the study procedures. The research protocol was reviewed and approved by the Ethics Committee of the Grigore T. Popa University of Medicine and Pharmacy Iași, and the Ethics Committee of the Socola Institute of Psychiatry.

Symptom severity was assessed at both baseline and week four using clinician-administered rating scales. Depressive symptoms were quantified using the 17-item Hamilton Depression Rating Scale (HAMD-17), and anxiety symptoms were evaluated using the Hamilton Anxiety Rating Scale (HAM-A). All assessments were performed by trained clinical psychiatrists. Change scores were calculated as baseline minus week-four values for each clinical scale, such that larger positive change scores reflected greater symptomatic improvement over the treatment interval. Antidepressant therapy was initiated immediately after baseline evaluation in accordance with routine clinical practice. The choice of antidepressant and subsequent dosage adjustments were determined by the treating psychiatrist based on clinical judgment. No participant received concomitant anxiolytic medication during the four-week observation period.

This present study reports a secondary analysis of a prospectively followed clinical cohort, examining the relationship between longitudinal changes in plasma BDNF concentrations and changes in depressive and anxiety symptom severity. Peripheral venous blood samples were obtained at both time points between 08:00 and 09:00 following an overnight fast of at least eight hours to reduce circadian and metabolic variability. Blood was collected into EDTA-containing tubes and processed promptly. Samples underwent a two-step centrifugation procedure to obtain platelet-poor plasma. The plasma supernatant was carefully separated, aliquoted into polypropylene tubes to avoid repeated handling, and stored at −80 °C until batch analysis. Repeated freeze–thaw cycles were avoided. Paired baseline and follow-up samples from the same participant were analysed within the same assay run to minimise inter-assay variability.

Plasma BDNF concentrations were determined using a commercially available human BDNF enzyme-linked immunosorbent assay (ELISA) kit (IBL International GmbH, Hamburg, Germany; Tecan Group Ltd.; catalogue number RB59041) based on the sandwich immunoassay principle. All samples were analysed in duplicate according to the manufacturer's instructions. Calibration standards were used to generate a standard curve, and concentrations were calculated using a four-parameter logistic(4PL) regression model. Measured values were corrected for sample dilution. Laboratory personnel were blinded to clinical data during the analytical procedure.

Statistical analyses were conducted to evaluate longitudinal changes in plasma BDNF concentrations and clinical symptom severity, as well as associations between biological and clinical variation during the four-week treatment period. All statistical analyses were performed using IBM SPSS v.31. Continuous variables are presented as mean ± standard deviation or median with interquartile range, depending on distribution, while categorical variables are expressed as frequencies and percentages. The distribution of baseline and change variables was assessed using the Shapiro–Wilk test. As several variables deviated from the normal distribution, non-parametric methods were applied. Within-subject comparisons between baseline and week four were performed using the Wilcoxon signed-rank test. Associations between changes in plasma BDNF concentrations and changes in HAMD-17 and HAM-A scores were evaluated using Spearman's rank-order correlation coefficient. Secondary exploratory analyses examined baseline associations between plasma BDNF levels and symptom severity. All statistical tests were two-tailed, and statistical significance was defined as $p < 0.05$.

3. Results

A total of 26 patients diagnosed with unipolar major depressive disorder were included in the analysis. The mean age of participants was 44.81 ± 10.23 years (range 24–63 years), and the majority of participants were female (76.9%) (see Table 1).

Table. The group of patients

Variable	Category	Value
Age	24-63 years	44.81 ± 10.23
Gender	F	20 (76.9%)
	M	6 (23.1%)
Living area	Rural	15 (57.7%)
	Urban	11 (42.3%)
Education	Middle school	2 (7.7%)
	Secondary education (10 years completed)	14 (53.8%)
	High school diploma	9 (34.6%)
	University degree	1 (3.8%)
Occupational status	Welfare benefits	4 (15.4%)
	Unemployed	10 (38.5%)
	Employed	12 (46.2%)
Marital status	Married	17 (65.4%)
	Unmarried	9 (34.6%)

Assessment of the distribution for change variables using the Shapiro–Wilk test indicated deviations from normality in several measures; therefore, non-parametric statistical methods were applied for inferential analyses.

After four weeks of antidepressant treatment, depressive symptom severity assessed with the HAMD-17 demonstrated a statistically significant reduction compared to baseline values (Wilcoxon signed-rank test, $p < 0.05$), indicating substantial clinical improvement during the acute treatment phase. Anxiety symptom severity measured using the HAM-A also showed a statistically significant reduction over the same period (Wilcoxon signed-rank test, $p < 0.05$), reflecting parallel improvement in anxiety symptoms. Graphical representations illustrate the magnitude of change in HAMD-17 (Fig. 1) and HAM-A (Fig. 2) scores between baseline and week four.

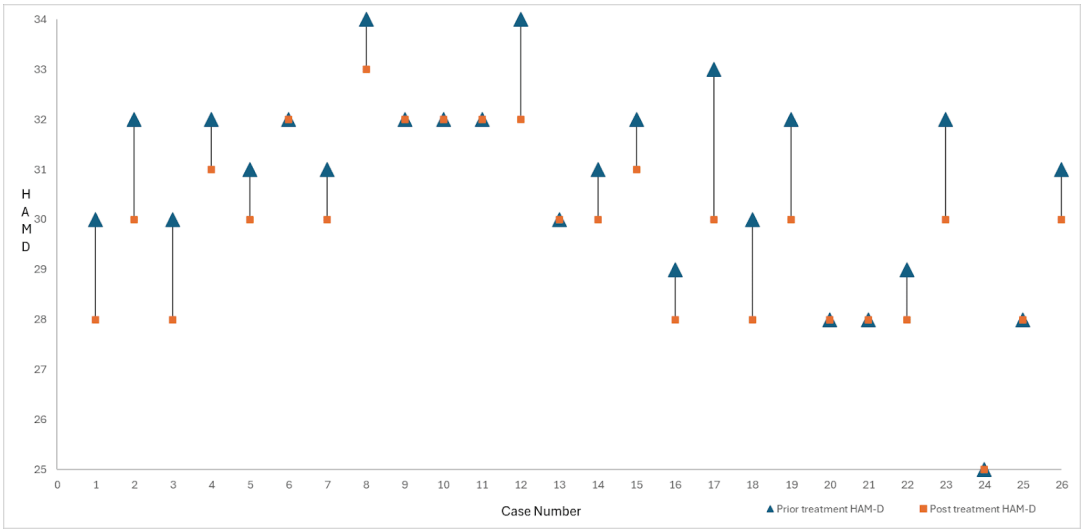

Figure 1. Changes in HAMD-17 before and after treatment

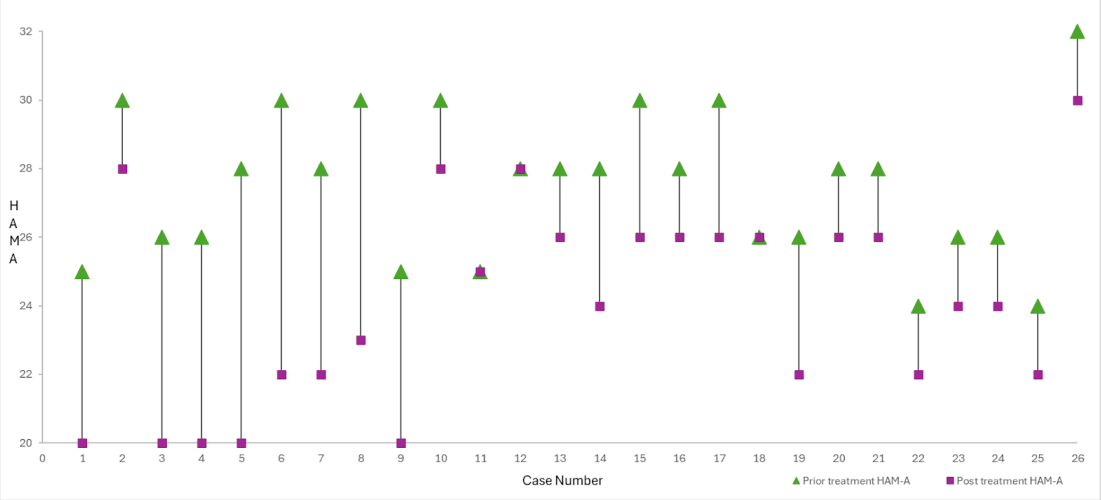

Figure 2. Changes in HAM-A before and after treatment

Plasma BDNF concentrations changed significantly over the four-week interval (Wilcoxon signed-rank test, $p < 0.05$), with an overall increase observed at week four relative to baseline (Fig. 3).

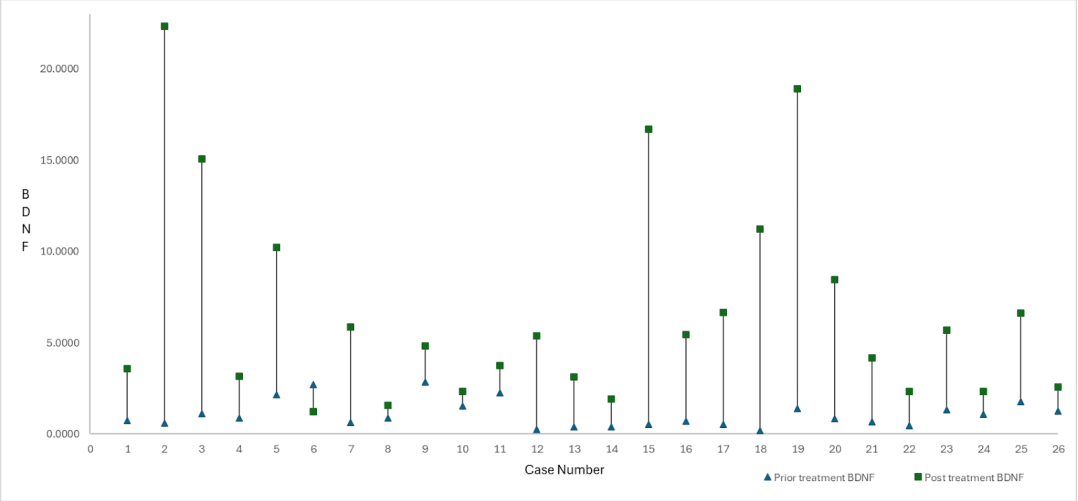

Figure 3. Changes in BDNF before and after treatment

Correlation analyses in the entire cohort revealed a statistically significant moderate negative association between changes in HAMD-17 scores and changes in plasma BDNF concentrations (Spearman's $\rho = -0.554$, $p = 0.003$; $N = 26$), indicating that greater reductions in depressive symptom severity were associated with larger increases in plasma BDNF levels.

In contrast, no statistically significant association was observed between changes in HAM-A scores and changes in plasma BDNF concentrations (Spearman's $\rho = 0.040$, $p = 0.848$; $N = 26$). The correlation coefficient indicated a very weak positive relationship, which did not reach statistical significance.

Overall, the four-week treatment period was characterised by significant clinical improvement in both depressive and anxiety domains, accompanied by significant modulation of plasma BDNF concentrations. The most robust biological–clinical association was observed between reductions in depressive symptom severity and increases in BDNF levels, whereas the relationship between anxiety change and BDNF modulation did not reach statistical significance.

4. Discussion

The main finding of the present longitudinal study is that improvement in depressive symptoms was associated with increases in plasma BDNF concentrations, supporting the interpretation of BDNF as a state-sensitive biological correlate of early treatment response.

This association is consistent with the neurotrophic hypothesis of depression, which proposes that stress-related reductions in neuroplasticity contribute to depressive symptoms and that antidepressant interventions partially reverse these effects through restoration of BDNF-TrkB signalling (Duman & Monteggia, 2006; Sen, Duman, & Sanacora, 2008). Meta-analytic evidence indicates that peripheral BDNF concentrations are reduced during acute depressive episodes and increased following effective treatment (Polyakova et al., 2015; Zhou et al., 2017). Within this framework, the present findings reinforce the interpretation of BDNF as a dynamic correlate of symptomatic improvement rather than a static vulnerability marker.

Although anxiety symptoms also decreased during the treatment interval, the correlation between changes in HAM-A scores and changes in plasma BDNF concentrations did not reach statistical significance. This suggests that, within the present sample, BDNF modulation more closely tracked changes in depressive symptoms than changes in anxiety symptoms during early pharmacological treatment. Several considerations may account for the absence of a significant association between anxiety change and BDNF modulation. Anxiety symptoms in major depressive disorder frequently reflect overlapping internalising dimensions rather than discrete neurobiological processes, and their temporal dynamics during early treatment may not be identical to those of core

depressive symptoms. In addition, the modest sample size may have limited statistical power to detect more modest associations.

Experimental models indicate that BDNF signalling within hippocampal–amygdalar circuits regulates both stress responsiveness and anxiety-related behaviours (Bath, Schilit, & Lee, 2013). Clinical research has similarly reported reduced peripheral BDNF levels in anxiety disorders and stress-related conditions, suggesting shared neuroplastic mechanisms across various aspects of psychopathology (Fernandes et al., 2011; Green et al., 2011; Molendijk et al., 2012; Monteleone et al., 2005). In anxiety disorders specifically, data suggest an overall decrease in peripheral BDNF levels, although findings remain heterogeneous (Suliman, Hemmings, & Seedat, 2013; Molendijk et al., 2012). In the present study, however, early BDNF increases were more clearly associated with improvement in depressive symptom domains than with anxiety symptom fluctuations.

BDNF appears to function as a common downstream mediator through which different classes of antidepressants exert neuroplastic effects. Despite pharmacodynamic differences between antidepressant classes, convergent enhancement of BDNF expression and TrkB activation has been observed in both preclinical and clinical contexts (Shirayama et al., 2002; Lee & Kim, 2010). Such convergence may explain why BDNF increases were associated with symptomatic improvement across depressive domains. These findings are consistent with the idea that recovery involves changes in synaptic connectivity within limbic–prefrontal circuits involved in mood regulation and cognitive-affective integration.

Interpretation of peripheral BDNF measurements requires careful attention to platelet biology. The majority of circulating BDNF is stored within platelets and released upon activation, with plasma concentrations substantially lower than serum levels. Platelets bind and internalise BDNF through high-affinity mechanisms, and only a proportion of stored BDNF is releasable during activation (Fujimura et al., 2002). Consequently, plasma BDNF values reflect not only systemic neurotrophic signalling but also pre-analytical handling and platelet activation status. The use of a standardised double-centrifugation protocol to obtain platelet-poor plasma in the present study aimed to reduce variability attributable to platelet contamination and enhance biological interpretability.

Beyond total BDNF concentrations, emerging evidence suggests that differential processing of proBDNF to mature BDNF may have important functional implications. Mature BDNF promotes synaptic strengthening via TrkB activation, whereas proBDNF preferentially engages p75NTR-mediated pathways linked to synaptic weakening and stress-related plasticity (Lu, Pang, & Woo, 2005; Zhao et al., 2017). The ratio of mature and precursor forms has been proposed as a potentially more sensitive indicator of neurotrophic balance in mood disorders (Zhao et al., 2017). Although only total BDNF levels were measured, it remains plausible that isoform-specific shifts could differentially influence depressive and anxiety symptom dimensions. Future studies incorporating molecular differentiation may help clarify these relationships.

Peripheral BDNF cannot be assumed to directly mirror central nervous system concentrations, as transport mechanisms and peripheral sequestration introduce uncertainty (Klein et al., 2011). Furthermore, variability in assay methodology, biological matrix selection, and pre-analytical processing contributes substantially to heterogeneity across studies (Polyakova et al., 2015). The modest sample size may also limit the stability of correlation estimates and preclude firm conclusions regarding predictive utility.

Several limitations should be acknowledged. The relatively modest sample size limits statistical power and may affect the stability of correlation estimates. With a sample of 26 participants, the study may have been underpowered to detect weaker biological–clinical associations, and the absence of a statistically significant correlation between changes in HAM-A scores and plasma BDNF concentrations should therefore be interpreted with caution.. Additionally, hormonal and metabolic factors that may influence peripheral BDNF expression, such as glucocorticoid levels, sex steroid fluctuations, or menstrual cycle phase, were not systematically assessed, potentially contributing to biological variability in the present sample. The absence of a

healthy control group prevents the determination of whether BDNF levels approached normative ranges following treatment. Only total plasma BDNF was measured, precluding analysis of mature-to-proBDNF ratios, which may offer greater specificity. The four-week follow-up period captures early treatment response but does not permit evaluation of longer-term neurotrophic trajectories or determination of whether early BDNF changes persist, stabilise, or predict longer-term clinical remission. Also, differences in antidepressant class were not controlled and may have influenced BDNF dynamics.

Nevertheless, because each participant was assessed at two time points, this longitudinal within-subject design allows a clearer interpretation of how changes in symptoms over time were linked to changes in BDNF levels. The observation that BDNF increases accompanied improvements in depressive symptoms supports its potential role as a peripheral correlate of early antidepressant response in major depressive disorder. Future investigations incorporating larger samples, longer follow-up intervals, and isoform differentiation will be necessary to clarify whether BDNF trajectories differentially track depressive versus anxiety symptom dimensions or reflect broader internalising vulnerability processes.

5. Conclusions

The present study provides additional evidence that increases in plasma BDNF concentrations accompany early clinical improvement in unipolar major depressive disorder. In this cohort, BDNF modulation was significantly associated with reductions in depressive symptom severity, supporting its role as a dynamic peripheral correlate of early antidepressant response.

Although anxiety symptoms also improved during the four-week treatment interval, changes in BDNF were not significantly correlated with changes in anxiety symptoms. This pattern suggests that, at least in the early phase of pharmacological treatment, peripheral BDNF dynamics may more closely reflect shifts in core depressive pathology than fluctuations in anxiety symptomatology within unipolar depression.

These results contribute to ongoing efforts to identify biologically informed markers of treatment-related neuroplastic adaptation. While peripheral BDNF cannot serve as a direct proxy for central synaptic remodelling, longitudinal changes in plasma levels may provide a clinically accessible indicator of biological engagement during antidepressant therapy.

Further research using larger samples, extended follow-up intervals, and more refined molecular differentiation of BDNF isoforms will be necessary to determine the extent to which BDNF trajectories can inform prognosis, stratify treatment response, or contribute to personalised therapeutic strategies in affective disorders.

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