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Peripheral Brain-Derived Neurotrophic Factor and Oxytocin Dynamics During Early Antidepressant Treatment in Unipolar Major Depressive Disorder

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Abstract: ***Background:*** *Brain-derived neurotrophic factor (BDNF) and oxytocin (OXT) have been independently implicated in the pathophysiology of major depressive disorder (MDD), yet few longitudinal studies have examined their concurrent modulation during early antidepressant treatment. This study investigated changes in plasma BDNF and oxytocin concentrations over the first four weeks of pharmacological treatment in patients with unipolar MDD and explored their association with changes in depressive symptom severity.* ***Methods:*** *Twenty-six medication-free patients with unipolar major depressive disorder were assessed at baseline, before antidepressant initiation, and after four weeks of treatment. Depressive severity was measured using the 17-item Hamilton Depression Rating Scale (HAMD-17). Plasma BDNF and oxytocin concentrations were quantified using enzyme-linked immunosorbent assay kits (ELISA). Within-subject changes were analysed using the Wilcoxon signed-rank test, and associations between changes in clinical severity and biomarker levels were examined using Spearman's rank correlation coefficients.*
Results: *Depressive symptom severity significantly decreased after four weeks of treatment. Plasma BDNF and oxytocin levels also demonstrated significant changes over the same period. A moderate negative correlation was observed between reductions in HAMD-17 scores and the change in BDNF concentrations ($\rho = -0.554$, $p = 0.003$), indicating that greater clinical improvement was associated with greater increases in plasma BDNF levels. A moderate positive correlation was found between changes in depressive severity and changes in oxytocin concentrations ($\rho = 0.414$, $p = 0.035$). No statistically significant differences in biomarker changes were observed across antidepressant classes; however, these subgroup analyses should be interpreted cautiously given the limited sample sizes in each treatment subgroup.*
Conclusions: *Early antidepressant treatment in unipolar MDD is accompanied by modulation of peripheral neurotrophic and neuropeptidergic markers. The association between symptom improvement and BDNF dynamics supports the relevance of neuroplasticity-related mechanisms during early treatment, while oxytocin alterations may reflect parallel adaptation within stress-regulatory systems. Larger longitudinal studies are required to clarify the predictive and mechanistic significance of these findings.*

Keywords: *major depressive disorder; BDNF; oxytocin; antidepressant treatment; biomarkers; neuroplasticity.*

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1. Introduction

Major depressive disorder (MDD) is a highly prevalent and complex psychiatric disorder that has a substantial impact on global functioning and quality of life. MDD is one of the leading causes of disability worldwide, affecting approximately 332 million people (about 4% of the global population), and it is about 1.5 times more common among women than among men (World Health Organization, 2025). The clinical presentation of MDD consists of persistent low or depressed mood, anhedonia, reduced energy, diminished concentration and attention, reduced self-esteem and self-confidence, feelings of guilt or worthlessness, pessimistic perspective of the future, thoughts or acts of self-harm or suicide, and sleep and appetite disturbances (Bains & Abdijadid, 2023).

Studies have shown that individuals with MDD usually have comorbid psychiatric or physical disorders that have a strong negative impact on treatment compliance and outcome, and on the general recovery possibilities. Patients with MDD frequently suffer from coexisting mental disorders such as substance use disorders, panic disorder, social anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder, psychotic disorders and personality disorders (Bains & Abdijadid, 2023; Thaipisuttikul et al., 2014). In addition, suicidality is common in patients with MDD, and the risk of suicide in individuals with MDD is higher than in individuals without MDD (Cai et al., 2021). While about two-thirds of individuals with MDD have suicidal thoughts, about 10-15% commit suicide (Bains & Abdijadid, 2023).

Moreover, the relationship between MDD and a large variety of physical diseases has been studied. MDD often occurs in patients with cancer and cardiovascular and metabolic disorders, such as heart failure, myocardial infarction, hypertension, diabetes mellitus, stroke, neurological disorders such as cognitive impairment, Alzheimer's disease, vascular dementia, Parkinson's disease, multiple sclerosis, epilepsy, amyotrophic lateral sclerosis, immune-related disorders such as rheumatoid arthritis, inflammatory bowel disease, and psoriasis. Other physical diseases associated with MDD are chronic obstructive pulmonary disease, fibromyalgia, irritable bowel syndrome, cranial and cervical dystonia and several eye and bone-related disorders (Berk et al., 2023).

The aetiology of MDD is complex and involves biological, genetic, environmental, and psychological factors. Although there is a wide variety of pharmacological and non-pharmacological treatment options, a significant number of patients show an incomplete response to treatment or therapeutic resistance. This further supports the complex nature of the pathophysiological mechanisms of MDD and the intricate interactions between multiple risk factors. Several theories regarding the pathogenesis of MDD have been proposed over time. The first was the monoamine hypothesis, which posits that the main depressive symptoms are a consequence of the malfunctioning of serotonergic, noradrenergic, and dopaminergic systems (Brigitta, 2002). Other potential mechanisms that have been studied include abnormalities in neurotransmitter receptors, endocrine imbalances and the role of pro-inflammatory cytokines (Brigitta, 2002; Kamran et al., 2022).

Given that the mechanisms of MDD are still not fully elucidated, recent studies have focused on finding additional correlations between various biomarkers and the pathogenesis of MDD. Contemporary evidence has revealed that brain-derived neurotrophic factor (BDNF) might play a key role in the context of MDD. BDNF belongs to the neurotrophin family of growth factors, which includes nerve growth factor (NGF), neurotrophin-3 (NT-3), NT-4/5, and NT-6. BDNF has essential functions as it facilitates neuronal differentiation and maturation, synaptic plasticity, and also exhibits a neuroprotective role (Bathina & Das, 2015).

Researchers have outlined the role of BDNF in the pathophysiology of several psychiatric disorders. BDNF is considered to be a key factor that mediates the relationship between cortisol and stress and diminished neurogenesis. While cortisol is normally released in response to different stressors, chronically elevated cortisol leads to reduced BDNF levels and reduced neurogenesis, consequently. Antidepressants and electroconvulsive therapy (ECT) prevent or reverse the negative consequences that high cortisol has on neurogenesis (Kamran et al., 2022).

Low levels of BDNF in the hippocampus and prefrontal cortex of the brain were noted in patients with MDD and also in individuals who died by suicide, compared to healthy individuals. Additionally, reduced mRNA and protein expression of BDNF in the hippocampus of post-mortem brains was observed (Mondal & Fatima, 2018). Antidepressants, as well as non-pharmacological treatments such as ECT and repetitive transcranial magnetic stimulation (rTMS), have been associated with an increase in BDNF (Mondal & Fatima, 2018; Carniel & da Rocha, 2021).

In addition to research that focused on BDNF, recent studies have analysed oxytocin (OXT) in the context of psychiatric disorders, including MDD. Oxytocin is a peptide hormone produced in the supraoptic and paraventricular nuclei of the hypothalamus, and it is also secreted into the bloodstream through the posterior pituitary gland to reach peripheral targets. Oxytocin is a significant modulator of emotional regulation and stress responsivity, as it was observed that in healthy individuals, it lowers cortisol release and regulates fear and anxiety reactions (Cochran et al., 2013). A potential correspondence between MDD and plasma oxytocin levels has been studied, but the results varied significantly. Thus, while some researchers have found that patients with MDD had lower plasma oxytocin levels compared to healthy individuals, other studies did not reveal such an association (Slattery & Neumann, 2010). This emphasises the fact that even if oxytocin could be a promising biomarker for MDD, it is not specific for the diagnosis of MDD, and its value should be considered alongside other variables.

Given the limited and inconsistent evidence regarding the interaction between neurotrophic and neuropeptidergic systems in MDD, the present study aimed to investigate the longitudinal relationship between plasma BDNF and oxytocin concentrations in patients with unipolar major depressive disorder before and four weeks after initiation of antidepressant treatment, and to examine their association with depressive symptom severity.

2. Materials and Methods

2.1. Study Design

This study employed a prospective, longitudinal, within-subject design. Plasma brain-derived neurotrophic factor and oxytocin levels were measured in patients with unipolar major depressive disorder at two time points: baseline (T0), immediately prior to initiation of antidepressant treatment and any other psychotropic medication, and follow-up (T1), four weeks after treatment initiation.

2.2. Participants

Twenty-six patients (6 males, 20 females; mean age ± SD: 44.8 ± 10.2 years) were recruited from the Socola Institute of Psychiatry, Iași, Romania, between January and June 2025. Inclusion criteria were age between 18 and 65 years and a primary diagnosis of unipolar major depressive disorder established according to ICD-10 criteria by a specialist psychiatrist. Participants had not received any psychiatric medication during the two weeks preceding enrolment. Exclusion criteria included bipolar disorder, psychotic disorders, organic mental disorders, substance use disorders, pregnancy, and any clinically diagnosed acute or chronic medical condition known to alter inflammatory markers or neuroendocrine function, including but not limited to autoimmune diseases, active infections, endocrine disorders (e.g., thyroid dysfunction, diabetes mellitus), chronic inflammatory diseases, malignant neoplasms, or current systemic corticosteroid or immunomodulatory treatment. All participants underwent a physical examination and routine laboratory investigations prior to inclusion to exclude relevant medical conditions. Treatment was conducted according to routine clinical protocols, and the prescribed treatment remained unchanged during the four-week follow-up period. All subjects provided written informed consent prior to enrolment. The study protocol was approved by the Ethics Committee of the Grigore T. Popa University of Medicine and Pharmacy Iași, Romania, and of the Socola Institute of Psychiatry, Iași, Romania.

2.3. Clinical Assessment

Depressive symptom severity was assessed at T0 and T1 using the 17-item Hamilton Depression Rating Scale (HAMD-17). Sociodemographic and clinical variables, including age, sex, body mass index (BMI), smoking status, antidepressant class and dose, were recorded. The interval between baseline and follow-up sampling was four weeks for all participants.

2.4. Blood Collection and Plasma Preparation

Venous blood samples were collected at T0 and T1 during morning hours, between 8 AM and 9 AM, after an overnight fast of at least 8 hours, to minimise circadian variability. Blood was drawn into EDTA anticoagulant tubes and processed within 30 minutes of collection.

Samples underwent a two-step centrifugation protocol to obtain platelet-poor plasma. For BDNF determination, plasma was collected on ice and prepared by centrifugation at 1000 × g for 15 minutes at 2–8 °C within 30 minutes of collection, followed by an additional centrifugation step of the separated plasma at 10,000 × g for 10 minutes at 2–8 °C to ensure complete platelet removal, according to the manufacturer's instructions (R&D Systems. (n.d.). The resulting supernatant plasma was carefully transferred into polypropylene tubes and stored at −80 °C until batch analysis. Repeated freeze–thaw cycles were avoided. Whenever feasible, both time-point samples from the same participant were analysed within the same assay run to minimise inter-assay variability.

For oxytocin analysis, EDTA tubes were supplemented with high-purity grade aprotinin to limit peptide degradation during sample handling, and plasma samples were further purified by solid-phase extraction using HyperSep C18 SPE cartridges (100 mg/1 mL) prior to analysis, in accordance with the validated analytical method (Bienboire-Frosini et al., 2017).

2.5. BDNF Quantification

Plasma BDNF concentrations were measured using a commercially available human BDNF ELISA kit (IBL International GmbH, Hamburg, Germany; Tecan Group Ltd.; catalogue number RB59041), based on the sandwich ELISA principle. Standards were prepared according to the manufacturer's instructions to construct a calibration curve. Plasma samples were diluted using the recommended assay diluent. All standards and samples were analysed in duplicate.

Following incubation with standards and samples, plates were washed and incubated sequentially with a biotinylated detection antibody and HRP-conjugated streptavidin. After substrate development, the reaction was terminated, and optical density was measured at 450 nm using a calibrated microplate reader. Concentrations were calculated from the standard curve and corrected for dilution factors. The manufacturer-reported minimum detectable concentration is 80 pg/mL.

2.6. Oxytocin Quantification

Plasma oxytocin levels were measured using a commercially available OT (Oxytocin) ELISA kit (Elabscience, Texas, USA; catalogue number E-EL-0029). Standards were reconstituted and serially diluted to generate a standard curve ranging from 0 to 1000 pg/mL. Fifty microliters of standards or plasma samples were added to each well, followed immediately by 50 µL of biotinylated detection antibody working solution. Plates were incubated for 45 minutes at 37 °C. After washing three times, 100 µL of HRP-conjugate working solution was added and incubated for 30 minutes at 37 °C. Following five wash cycles, 90 µL of substrate reagent was added and incubated for 15 minutes at 37 °C, protected from light. The reaction was stopped with 50 µL stop reagent, and the optical density was immediately measured at 450 nm. Concentrations were calculated using a four-parameter logistic (4PL) standard curve and adjusted for dilution factors.

The assay sensitivity was 9.38 pg/mL, with a detection range of 15.63–1000 pg/mL and an intra-assay coefficient of variation <10%.

2.7. Statistical Analysis

Statistical analyses were conducted to characterise clinical evolution over the four-week treatment period and to examine associations between changes in depressive severity and peripheral biomarker concentrations. All statistical analyses were performed using IBM SPSS v.31. Continuous variables were presented as mean ± standard deviation (SD), and categorical variables as frequencies and percentages. Normality of change variables was assessed using the Shapiro–Wilk test. As several variables deviated from the normal distribution ($p < 0.05$), non-parametric statistical methods were applied. Within-subject comparisons between baseline and week 4 were performed using the Wilcoxon signed-rank test. Between-group comparisons across antidepressant classes, namely selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and serotonin modulators and stimulators (SMSs), were performed using the Kruskal–Wallis test. Because of the relatively small subgroup sizes, these analyses were considered exploratory. Associations between changes in depressive severity and corresponding changes in plasma BDNF and oxytocin concentrations were evaluated using Spearman's rank correlation coefficient (ρ). All tests were two-tailed, with statistical significance set at $p < 0.05$.

3. Results

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

Table 1. Demographic characteristics of the sample

Variable	Category	Value
Age, years	24-63	44.81 ± 10.23
Gender	Female	20 (76.9%)
	Male	6 (23.1%)
	Total	26
Living area	Rural	15 (57.7%)
	Urban	11 (42.3%)
Education	Middle school	2 (7.7%)
	Secondary education (10 years)	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%)

After four weeks of antidepressant treatment, depressive symptom severity assessed using the HAMD-17 decreased from a median of 31.0 (IQR 30.0–32.0) at baseline (T0) to 30.0 (IQR 28.0–31.0) at week 4 (T1), and this reduction was statistically significant (Wilcoxon signed-rank test, $p < 0.05$). Over the same period, plasma BDNF concentrations increased from 0.873 (IQR 0.556–1.376) at T0 to 5.106 (IQR 2.722–7.997) at T1, with a statistically significant difference ($p < 0.05$). Plasma oxytocin concentrations also increased from 645.0 (IQR 450.0–912.5) at T0 to 1625.0 (IQR 1425.0–2068.8) at T1, and this change was statistically significant ($p <0.05$). These pre–post differences are illustrated in Figure 1.

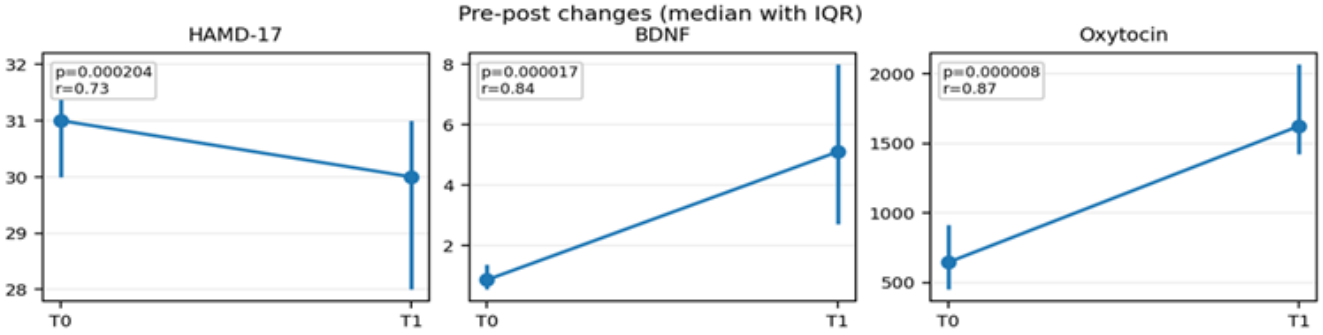

Figure 1. Changes in the 17-item Hamilton Depression Rating Scale (HAMD-17), brain-derived neurotrophic factor (BDNF), and oxytocin from baseline (T0) to week 4 (T1)

Correlation analysis performed in the entire cohort revealed a statistically significant moderate negative association between reductions in HAMD-17 scores and the change in BDNF concentrations (Spearman's $\rho = -0.554$, $p = 0.003$), indicating that greater clinical improvement was associated with greater increases in plasma BDNF levels. In contrast, a statistically significant moderate positive correlation was observed between the change in HAMD-17 scores and the change in oxytocin concentrations (Spearman's $\rho = 0.414$, $p = 0.035$). Correlation coefficients for the entire cohort are presented in Table 2.

Table 2. Correlations Between Changes in Depressive Symptom Severity and Plasma Biomarker Levels

Variable Pair	Spearman's ρ	p-value
Change in HAMD – Change in BDNF	−0.554	0.003
Change in HAMD – Change in Oxytocin	0.414	0.035

(HAMD, Hamilton Depression Rating Scale; BDNF, brain-derived neurotrophic factor)

Subgroup analyses stratified by antidepressant class revealed heterogeneous correlation patterns, although most did not reach statistical significance, likely due to limited statistical power associated with small subgroup sizes (Table 3). These subgroup findings should therefore be interpreted cautiously. Overall, four weeks of antidepressant treatment were associated with significant clinical improvement accompanied by significant modulation of both BDNF and oxytocin levels, with the strongest association observed between reduction in depressive symptom severity and increase in BDNF levels.

Table 3. Exploratory Correlations Stratified by Antidepressant Class

Antidepressant Class	N	ρ (HAMD–BDNF)	p-value	ρ (HAMD–Oxytocin)	p-value
SSRI	10	−0.674	0.033	0.809	0.005
SNRI	9	−0.378	0.316	0.334	0.380
SMS	4	−0.738	0.262	0.500	0.500
TCA	3	0.866	0.333	0.000	1.000

(SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SMS, serotonin modulator and stimulator; TCA, tricyclic antidepressant)

4. Discussions

The present longitudinal study examined peripheral neurobiological dynamics during the early phase of antidepressant treatment in patients with unipolar major depressive disorder, focusing on brain-derived neurotrophic factor (BDNF) and oxytocin (OXT) in relation to changes in depressive symptom severity. Rather than reiterating the statistical findings, the broader implications of the results lies in their alignment with established neurobiological models of depression. A substantial body of evidence supports the neurotrophic hypothesis, which posits that

reduced BDNF signalling contributes to impaired neuroplasticity in major depressive disorder and that effective antidepressant treatment is associated with restoration of BDNF levels (Sen, Duman, & Sanacora, 2008; Polyakova et al., 2015). Meta-analytic data have consistently demonstrated lower peripheral BDNF concentrations in patients with depression compared to healthy controls, with subsequent increases following antidepressant therapy (Sen, Duman, & Sanacora, 2008; Zhou et al., 2017). Within this theoretical framework, the observed association between symptomatic improvement and BDNF modulation in the present cohort reinforces the interpretation of BDNF as a state-sensitive marker linked to treatment response rather than merely a static vulnerability indicator. Importantly, plasma BDNF measurements are known to be methodologically sensitive, particularly with regard to platelet activation and pre-analytical handling, and plasma values may not fully mirror central nervous system concentrations (Polyakova et al., 2015). Therefore, the findings are best interpreted as reflecting peripheral correlates of neuroplastic adaptation during early treatment rather than direct evidence of central synaptic remodelling.

The oxytocin findings add a complementary yet more complex dimension. The oxytocin system has been implicated in stress regulation, social bonding, and emotional processing, all of which are domains frequently disrupted in depression (Scantamburlo et al., 2007; Cochran et al., 2013). However, the literature on peripheral oxytocin levels in major depressive disorder remains heterogeneous. Some studies have reported reduced oxytocin concentrations in individuals with depression compared to healthy controls (Yuen et al., 2014), whereas others have identified elevated levels or sex-specific alterations (Parker et al., 2010; Ozsoy, Esel, & Kula, 2009). Systematic reviews have emphasised that oxytocin alterations in depression are influenced by contextual factors, including sex, attachment patterns, stress exposure, and methodological variability in assay procedures (Massey, Backes, & Schuette, 2016). Within this context of inconsistency, the present findings suggest that oxytocin dynamics may be treatment-sensitive and related to clinical evolution over time, although mechanistic directionality remains uncertain. It is plausible that oxytocin modulation during antidepressant treatment reflects adaptive recalibration of stress-response systems rather than a direct antidepressant-specific molecular target.

The absence of significant differences between antidepressant classes in clinical or biomarker changes should be interpreted with particular caution. Although contemporary models of antidepressant action propose that diverse pharmacological agents may converge on shared downstream pathways, including neuroplasticity-related signalling cascades, even if their primary neurotransmitter targets differ (Zhou et al., 2017), the subgroup analyses in the present study should be considered exploratory and based on relatively small sample sizes. Accordingly, the lack of statistically significant between-class differences should not be interpreted as evidence of equivalence between antidepressant classes, but rather as a preliminary observation that requires confirmation in larger, adequately powered samples. At the same time, the heterogeneous correlation patterns observed across treatment subclasses may still provide clinically relevant indications to be examined in future studies designed specifically for class-level comparisons.

Several methodological considerations further contextualise the findings. The within-subject longitudinal design reduces interindividual variability and strengthens inference regarding temporal associations between symptom change and biomarker modulation. However, the relatively small sample size limits the stability of correlation estimates and increases susceptibility to both type I and type II errors. The four-week follow-up interval captures early treatment response rather than sustained remission, and longer-term trajectories of BDNF and oxytocin remain to be elucidated. Moreover, peripheral biomarkers cannot be assumed to directly reflect central neurobiological processes, particularly in the case of BDNF, where serum and plasma measurements may differ substantially due to platelet contributions (Polyakova et al., 2015). Baseline biomarker levels were not examined as predictors of treatment response in the present study and should be investigated in future large-scale studies. A further limitation is the predominance of female participants in the present sample, which may affect the generalisability of the findings and did not allow a reliable exploration of potential sex-related differences in biomarker dynamics or antidepressant response.

Future studies incorporating standardised pre-analytical protocols, larger sample sizes, and potentially multimodal approaches combining peripheral markers with neuroimaging or cognitive endpoints would help clarify the clinical utility of these measures.

In addition to their biological significance, longitudinal changes in biomarkers such as BDNF and oxytocin may also be relevant to future efforts to predict antidepressant response. In major depressive disorder, recent studies have increasingly combined clinical and biological information to improve treatment stratification at the individual level. Within this context, repeated peripheral biomarker assessments may help clarify symptom-related changes over time and may also become useful as part of broader datasets that integrate clinical features with other sources of information, including cognitive and neuroimaging findings. Although the present sample is too small to support predictive modelling directly, the association observed here between biomarker dynamics and early clinical improvement suggests that such longitudinal data may be informative for future artificial intelligence–based approaches to treatment response. Recent studies indicate that predictive performance may improve when biological measures are considered together with symptom trajectories and other patient-level characteristics (Poirot et al., 2024; Corrivetti et al., 2024). From this perspective, the present findings may contribute to the development of biologically informed datasets for future treatment-response stratification models.

From a clinical perspective, these findings may be relevant to current efforts to identify biomarkers that could support early treatment decisions in major depressive disorder. If confirmed in larger longitudinal studies, early changes in peripheral markers such as BDNF and oxytocin may help identify patients who are more likely to improve during the initial phase of antidepressant treatment. Although the present results are preliminary and do not support clinical use at this stage, they suggest that longitudinal biomarker assessment may have future value for treatment monitoring and response prediction.

5. Conclusions

In summary, the findings support the notion that early antidepressant response is accompanied by coordinated changes in peripheral neurotrophic and neuropeptidergic systems. The association between improvement in depressive symptom severity and BDNF modulation aligns with established neuroplasticity-based models of depression, while the oxytocin findings suggest additional involvement of stress-regulatory mechanisms. Although preliminary, these results contribute to the growing body of literature examining biologically informed markers of treatment response in major depressive disorder and underscore the need for larger longitudinal studies to determine their predictive and mechanistic relevance.

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