

## BDNF AND ALOX12 DURING ANTIDEPRESSANT TREATMENT IN MAJOR DEPRESSION: A LONGITUDINAL STUDY

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BDNF AND ALOX12 DURING ANTIDEPRESSANT TREATMENT IN MAJOR DEPRESSION: A LONGITUDINAL STUDY (Abstract): This study investigated the longitudinal dynamics of brain-derived neurotrophic factor (BDNF) and arachidonate 12-lipoxygenase (ALOX12) during antidepressant treatment in patients with major depression. **Materials and methods:** Twenty-six patients were assessed at baseline, 4 weeks, and 8 weeks. Depressive and anxiety symptoms were measured using HAM-D and HAM-A, and plasma BDNF and ALOX12 levels were quantified using ELISA. **Results:** HAM-D decreased from 31.0 to 23.0 and HAM-A from 28.0 to 18.0. BDNF increased from 0.87 to 5.33, while ALOX12 decreased from 1.39 to 0.22 ( $p < 0.001$ ), with the largest change between weeks 4 and 8; ALOX12 at 8 weeks correlated inversely with HAM-D ( $r = -0.416$ ; adjusted  $r = -0.515$ ). **Conclusions:** BDNF and ALOX12 showed distinct temporal patterns. BDNF increase and ALOX12 reduction occurred without significant associations between their changes. **Keywords:** MAJOR DEPRESSION; BDNF; ALOX12; BIOMARKERS.

### INTRODUCTION

Major depression is a clinical condition defined by persistent low mood, anhedonia, cognitive impairment, and somatic symptoms that impair daily functioning (1). The clinical presentation varies across individuals, with differences in symptom profiles, illness trajectory, and comorbidity patterns. This variability also extends to treatment response. A substantial proportion of patients fail to achieve full remission despite adequate pharmacological intervention. Data from the STAR\*D study indicate remission rates of approximately 28–33%

following first-line treatment, highlighting the limited effectiveness of standard approaches in a large segment of patients (2).

The disorder lacks a single identifiable biological mechanism. Structural and functional alterations have been described in corticolimbic circuits, including the prefrontal cortex, hippocampus, amygdala, and striatum (3). Cellular findings include reduced synaptic density, dendritic retraction, and altered excitatory and inhibitory neurotransmission (4, 5). Inflammatory activation and oxidative stress have been consistently reported, with increased circulating

cytokines and elevated markers of oxidative damage (6-8). These findings indicate a disorder involving multiple interacting biological systems rather than a unitary pathophysiological process.

Numerous biomarkers have been investigated in psychiatric disorders, particularly in depression. These include inflammatory markers, oxidative stress indicators, neurotrophic factors, and metabolic parameters. Nonetheless, no biomarker has demonstrated sufficient sensitivity and specificity for routine clinical use. Findings remain inconsistent across studies, influenced by methodological variability, heterogeneity of patient populations, and differences in biological sampling. Current research has shifted toward examining dynamic biological changes and interactions between systems rather than relying on single-marker approaches (9-12).

Brain-derived neurotrophic factor is one of the most extensively studied molecules in depression. It is involved in neuronal survival, synaptic plasticity, and activity-dependent signaling. BDNF is widely expressed in corticolimbic regions implicated in mood regulation. Its signaling includes functionally distinct isoforms, with mature BDNF promoting synaptic strengthening through TrkB receptors and proBDNF associated with synaptic weakening via p75 receptors (13, 14). Experimental studies have shown reduced BDNF expression following stress exposure and restoration after antidepressant treatment (13-15). Clinical studies report lower peripheral BDNF levels in depression and increases following treatment, although effect sizes are moderate and variability is high (16-18).

Peripheral BDNF reflects both central and systemic sources. Transport across the

blood-brain barrier has been demonstrated, although circulating levels are influenced by platelet release and peripheral production (19). Associations with symptom severity are inconsistent. Changes over time appear more informative than baseline levels, particularly in relation to treatment response. These characteristics position BDNF as a marker of neuroplastic processes rather than a diagnostic indicator.

Lipid-mediated pathways represent another component of cellular stress response. Polyunsaturated fatty acids, including arachidonic acid, are integral to neuronal membranes and serve as precursors for bioactive lipid mediators (20). Enzymatic pathways involving cyclooxygenases and lipoxygenases generate molecules that regulate inflammation, oxidative balance, and intracellular signaling (21). Lipoxygenases catalyze the formation of oxidized lipid derivatives that influence membrane integrity and cellular responses to stress (22).

Arachidonate 12-lipoxygenase, encoded by the ALOX12 gene, converts arachidonic acid into 12-hydroxyeicosatetraenoic acid and related metabolites (23). Experimental data show activation of this pathway under conditions of oxidative stress, leading to lipid peroxidation, calcium dysregulation, and neuronal injury (24). Increased expression has been observed in models of cerebral ischemia, with reduced damage following enzyme inhibition (25). This suggests involvement in redox-sensitive cellular processes.

Clinical evidence linking ALOX12 to psychiatric disorders remains limited. Genetic association studies report relationships with bipolar disorder (26). Neuroimaging and genetic analyses suggest associations with cortical structural changes in

stress-related conditions (27). Experimental models demonstrate modulation of lipoxygenase-derived metabolites under chronic stress, particularly in reward-related brain regions (28). Direct clinical data on major depression are scarce, which limits interpretation but highlights the need for longitudinal investigation of this pathway.

Inflammatory, oxidative, and neurotrophic systems interact at multiple levels. Cytokines influence neurotransmitter systems and reduce neurotrophic support, with documented effects on monoaminergic transmission and BDNF expression (29, 30). Oxidative stress affects membrane integrity, mitochondrial function, and intracellular signaling pathways, contributing to neuronal dysfunction (6, 8). These processes converge on mechanisms regulating synaptic plasticity and neuronal adaptation, with inflammation and oxidative stress both implicated in impaired neurogenesis and synaptic remodeling (31, 32). BDNF and lipid-mediated pathways may represent distinct components of these interactions, reflecting different aspects of the biological response to stress and cellular injury (20, 22).

The present study investigates the dynamics of BDNF and ALOX12 during antidepressant treatment in patients with major depression. Biological assessments are performed at baseline, before treatment initiation, and at subsequent time points during treatment. Clinical evaluation is conducted using standardized measures of depressive and anxiety symptom severity, allowing examination of associations between biomarker changes and symptom trajectories.

### **MATERIALS AND METHODS**

This study was designed as a prospec-

tive, longitudinal observational investigation conducted between January and June 2025 at the Socola Institute of Psychiatry in Iasi, Romania. The study was approved by the Ethics Committee of Grigore T. Popa University of Medicine and Pharmacy, in Iasi, Romania and the Socola Institute of Psychiatry. All participants provided written informed consent before inclusion.

Participants were evaluated at three predefined time points: baseline (T0), before initiation of pharmacological treatment, 4 weeks after treatment initiation (T1), and 8 weeks after treatment initiation (T2). All assessments were performed under standardized conditions.

A total of 26 patients aged between 24 and 63 years were included in this study. Participants were recruited from inpatient admissions and subsequently monitored in an outpatient setting, with rehospitalization when clinically indicated. Inclusion criteria comprised age between 18 and 65 years, a diagnosis of severe depressive episode or recurrent depressive disorder, and absence of psychiatric medication in the two weeks preceding baseline evaluation. Exclusion criteria included bipolar disorder, psychotic disorders, significant cognitive impairment, chronic alcohol or substance use, pregnancy or breastfeeding, severe untreated medical comorbidities, positive serology for hepatitis B, hepatitis C or HIV, known hypersensitivity to prescribed medications, poor compliance, and the presence of active suicidal ideation or aggressive behavior at baseline.

Clinical evaluation was performed by the same clinician at all time points and included both a general medical examination and a structured psychiatric assessment. Depressive symptom severity was measured using the 17-item Hamilton De-

pression Rating Scale, while anxiety symptoms were assessed using the Hamilton Anxiety Rating Scale. Anthropometric measurements were obtained for the calculation of body mass index (BMI), and relevant demographic and clinical variables, including smoking status and alcohol consumption, were recorded due to their potential influence on inflammatory and metabolic processes.

Venous blood samples were collected at each time point between 08:00 and 09:00 following an overnight fast of at least 8 hours in order to minimize circadian and metabolic variability. Samples were drawn into EDTA tubes and processed within 30 minutes. Platelet-poor plasma was obtained using a two-step centrifugation protocol, aliquoted into polypropylene tubes, and stored at  $-80^{\circ}\text{C}$  until analysis. Samples from the same participant were analyzed within the same experimental run to reduce inter-assay variability, and repeated freeze-thaw cycles were avoided.

Plasma concentrations of brain-derived neurotrophic factor were determined using a commercially available sandwich ELISA kit (IBL International GmbH/Tecan, catalogue number RB59041), following the manufacturer's instructions. All samples and standards were analysed in duplicate. The same applies to plasma levels of arachidonate 12-lipoxygenase, which were measured in duplicate using a commercially available ELISA kit specific for human ALOX12 (FineTest, catalogue number EH1980) according to the manufacturer's protocol.

Pharmacological treatment was initiated after baseline assessment and was prescribed individually by the treating psychiatrist in accordance with current clinical guidelines. The study followed a naturalistic design,

with no intervention from the investigators in treatment selection or dosing.

Statistical analyses were performed using IBM SPSS Statistics v28.0. Data distribution was assessed using the Shapiro–Wilk test. As the data were not normally distributed, non-parametric tests were applied. Changes across the three time points were analyzed using the Friedman test, with pairwise comparisons performed using the Wilcoxon signed-rank test. Associations between biomarker levels and clinical measures were evaluated using Spearman's rank correlation coefficient. Statistical significance was set at  $p < 0.05$  (two-tailed).

## RESULTS

### Clinical and biomarker evolution

At baseline, patients presented with high levels of depressive and anxiety symptoms, with median HAM-D and HAM-A scores of 31.0 and 28.0, respectively, indicating moderate-to-severe symptomatology. After 8 weeks of treatment, both measures showed a clear reduction, with median values decreasing to 23.0 for HAM-D and 18.0 for HAM-A (tab. I).

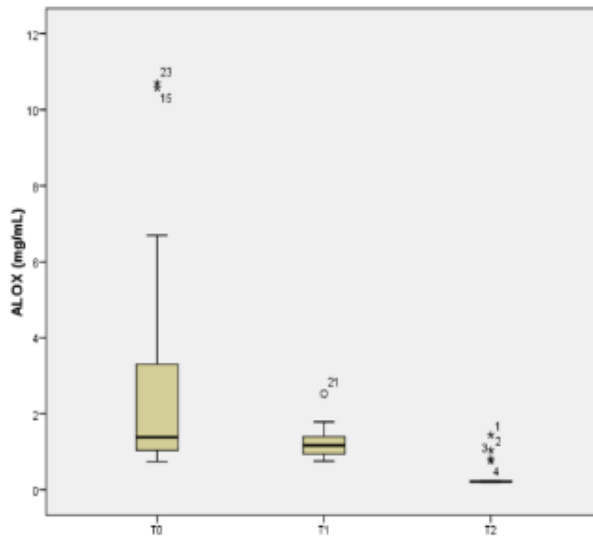
In parallel, biological markers showed distinct temporal patterns. Serum BDNF levels increased markedly over the course of treatment, from a median of 0.87 at baseline to 5.33 at 8 weeks. In contrast, ALOX levels showed a progressive decrease, from a median of 1.39 at baseline to 0.22 at 8 weeks (tab. I).

These temporal changes are illustrated in figure 1, which shows a progressive reduction in ALOX values over time, with the most pronounced decrease observed at 8 weeks. The distribution also indicates greater variability at baseline, followed by a reduction in dispersion at subsequent time points.

**TABLE I.**

**Descriptive statistics of clinical variables and biomarkers across time points**

Variable	T0 Median (IQR)	T1 Median (IQR)	T2 Median (IQR)
ALOX	1.39 (1.04–3.41)	1.17 (0.94–1.41)	0.22 (0.21–0.23)
HAM-D	31.0 (29.75–32.0)	30.0 (28.0–31.25)	23.0 (17.5–24.25)
HAM-A	28.0 (26.0–30.0)	24.0 (22.0–26.0)	18.0 (18.0–20.0)
BDNF	0.87 (0.54–1.43)	5.11 (2.53–8.89)	5.33 (3.15–9.42)



**Fig. 1.** Evolution of ALOX levels at T0, T1, and T2 during treatment

Given the non-normal distribution of most variables, non-parametric analyses were applied. The Friedman test revealed a significant overall effect of time on ALOX levels ( $\chi^2(2) = 34.462, p < 0.001$ ). Mean ranks decreased progressively from T0 (2.62) to T1 (2.31) and T2 (1.08), indicating a consistent downward trajectory.

Post-hoc pairwise comparisons showed that the reduction between baseline and 4 weeks did not reach statistical significance after Bonferroni correction ( $p = 0.027$ ). In contrast, differences between baseline and 8 weeks, as well as between 4 and 8 weeks, were statistically significant (both

$p < 0.001$ ), indicating that the main change in ALOX occurred during the later phase of treatment. Stratified analyses across antidepressant classes showed similar temporal patterns of ALOX reduction across all groups (tab. II). Baseline values were numerically higher in the tricyclic antidepressant group, although interpretation is limited due to the small subgroup sizes. No statistically significant differences between classes were observed (Kruskal–Wallis  $\chi^2(3) = 6.769, p = 0.080$ ), although the highest mean rank change was noted in the multimodal serotonergic group.

TABLE II.  
Descriptive statistics stratified by antidepressant class

Variable	Time	SMS (n=4)	SNRI (n=9)	SSRI (n=10)	TCA (n=3)
HAM-D	T0	30.5 (30.0–31.5)	32.0 (31.0–32.0)	32.0 (30.0–32.0)	29.0 (28.5–29.0)
	T1	30.0 (29.0–30.0)	30.0 (30.0–32.0)	30.5 (28.0–32.0)	–
	T2	21.0 (16.5–24.0)	24.0 (20.0–25.0)	21.0 (16.0–24.0)	24.0 (20.0–25.0)
HAM-A	T0	28.0 (27.0–29.0)	28.0 (28.0–30.0)	26.0 (26.0–30.0)	24.0 (24.0–26.0)
	T1	25.0 (22.0–27.0)	26.0 (22.0–26.0)	23.5 (20.0–26.0)	22.0 (22.0–24.0)
	T2	19.0 (17.0–21.0)	20.0 (18.0–20.0)	18.0 (16.0–20.0)	20.0 (19.0–20.0)
BDNF	T0	0.50 (0.40–0.86)	0.86 (0.63–1.33)	0.98 (0.73–1.55)	0.72 (0.59–1.25)
	T1	9.09 (2.52–18.70)	5.39 (4.17–5.88)	3.67 (2.33–11.25)	5.46 (3.90–6.04)
	T2	9.81 (2.84–20.70)	5.65 (4.29–6.25)	4.15 (3.23–11.44)	5.41 (4.12–6.05)
ALOX	T0	1.10 (0.87–1.32)	1.21 (0.91–2.59)	1.60 (1.06–3.71)	3.31 (2.19–5.00)
	T1	1.37 (1.28–1.58)	1.07 (0.91–1.56)	1.15 (0.94–1.37)	1.15 (1.07–1.33)
	T2	0.52 (0.22–0.93)	0.22 (0.21–0.22)	0.22 (0.22–0.24)	0.23 (0.22–0.23)

\*The symbol “–” indicates that the interquartile range (IQR) could not be calculated due to the small subgroup size (particularly TCA, n=3) and insufficient variability in the data at that time point.

#### Associations between biomarkers and clinical outcomes

Correlation analyses at 8 weeks revealed a significant negative association between ALOX levels and depressive symptom severity. Higher ALOX levels were associated with lower HAM-D scores

in both zero-order analysis ( $r = -0.416$ ,  $p = 0.035$ ) and after adjustment for age and body mass index (partial  $r = -0.515$ ,  $p = 0.010$ ) (tab. III).

This relationship is illustrated in figure 2, which shows an inverse relationship between ALOX and HAM-D scores.

TABLE III.  
Spearman and partial correlations at 8 weeks

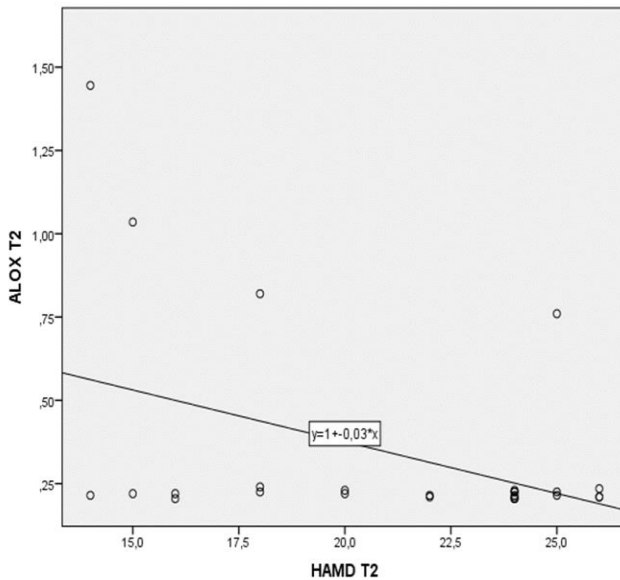
Variable pair	r (zero-order)	p (zero-order)	r (partial)	p (partial)	Significant
HAM-D T2 vs ALOX T2	-0.416	0.035	-0.515	0.010	Yes
HAM-D T2 vs BDNF T2	-0.400	0.043	-0.402	0.052	Trend
HAM-D T2 vs Age	+0.501	0.009	–	–	Yes
HAM-D T2 vs BMI	+0.391	0.048	–	–	Yes
HAM-A T2 vs ALOX T2	-0.211	0.301	-0.240	0.259	No
HAM-A T2 vs BDNF T2	-0.250	0.218	-0.338	0.106	No
BDNF T2 vs ALOX T2	+0.282	0.163	+0.285	0.178	No
Age vs. BMI	+0.701	<0.001	–	–	Yes

In contrast, no significant associations were observed between ALOX levels and anxiety symptoms (HAM-A) at 8 weeks, either before or after adjustment (tab. III), suggesting the specificity of this relationship for depressive symptomatology.

BDNF levels at 8 weeks showed a negative association with HAM-D scores in zero-order analysis ( $r = -0.400$ ,  $p = 0.043$ ), which remained at a trend level after adjustment (partial  $r = -0.402$ ,  $p = 0.052$ ). The magni-

tude of this association remained stable after controlling for demographic variables.

No significant correlations were identified between changes in ALOX and changes in clinical scores or BDNF levels (all  $p > 0.05$ ). A strong negative correlation was observed between baseline ALOX and its change over time ( $r_s = -0.833$ ,  $p < 0.001$ ), although this finding is influenced by mathematical coupling and should be interpreted cautiously.



**Fig. 2.** Association between depressive symptom severity at 8 weeks and ALOX levels at T2

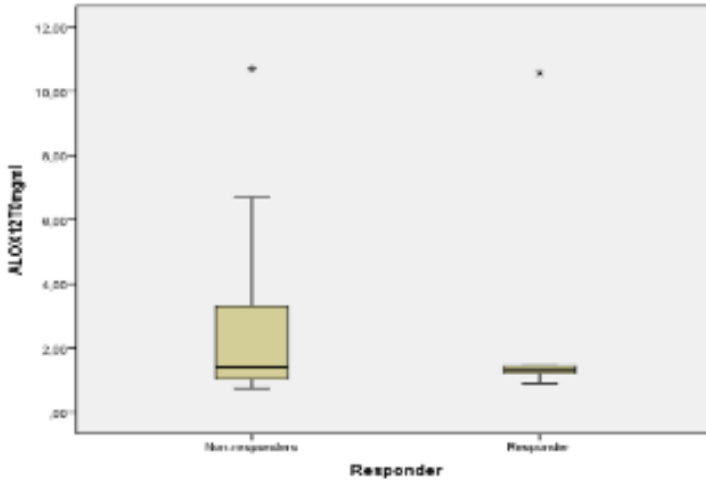
Age and body mass index were both positively associated with HAM-D scores at 8 weeks ( $r = +0.501$ ,  $p = 0.009$  and  $r = +0.391$ ,  $p = 0.048$ , respectively). These variables were strongly correlated with each other ( $r = +0.701$ ,  $p < 0.001$ ), supporting their inclusion as covariates in adjusted analyses.

**Exploratory subgroup and predictive analyses**

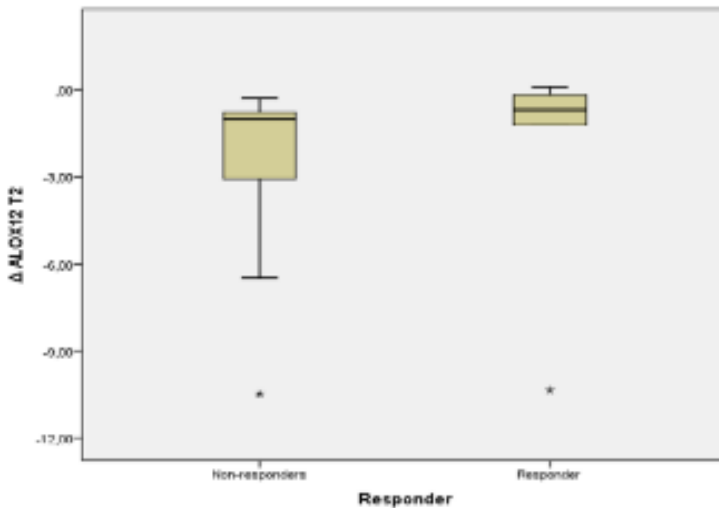
No statistically significant differences

in ALOX change were observed between responders and non-responders after 8 weeks of treatment (Mann–Whitney  $U = 35.5$ ,  $p = 0.269$ ), although responders showed higher mean ranks, suggesting a tendency toward greater reduction.

The distribution of ALOX values across these groups is shown in fig. 3 and fig. 4. Responders exhibited more homogeneous changes, whereas non-responders showed greater variability.



**Fig. 3.** Comparative boxplot of baseline serum ALOX levels in responders and non-responders



**Fig. 4.** Change in ALOX levels between T0 and T2 in responders and non-responders

Receiver operating characteristic analysis did not demonstrate predictive value of baseline ALOX levels for treatment response (AUC = 0.510,  $p = 0.948$ ; 95% CI: 0.232–0.787).

Exploratory analyses of demographic and lifestyle factors did not identify significant associations with ALOX change (all  $p$

$> 0.05$ ) (tab. IV). The closest trend toward statistical significance was observed for smoking status ( $p = 0.143$ ), with smokers showing higher mean ranks compared to non-smokers, which may indicate a more pronounced change in ALOX in this subgroup. In the absence of statistical significance, this observation remains exploratory.

**TABLE IV.**  
**Exploratory subgroup analyses of ALOX change**

Variable	Group	N	Mean Rank	Mann-Whitney U	Z	p-value
Sex	Female	20	13.03	50.500	-0.578	0.563
	Male	6	15.08			
Residence	Rural	15	14.30	70.500	-0.623	0.533
	Urban	11	12.41			
Marital status	In a relationship	18	14.19	59.500	-0.695	0.487
	Not in a relationship	8	11.94			
Smoking	Smoker	12	15.88	55.500	-1.466	0.143
	Non-smoker	14	11.46			
Physical activity	Moderate	12	14.29	74.500	-0.489	0.625
	Low	14	12.82			
Alcohol use	Occasional use	15	15.00	60.000	-1.168	0.243
	No use	11	11.45			
Occupation status	Employed	12	13.33	82.000	-0.103	0.918
	Unemployed	14	13.64			

**DISCUSSION**

This study identified three principal observations: a reduction in depressive and anxiety symptom severity over 8 weeks, a marked increase in BDNF levels, and a progressive decrease in ALOX levels. The reduction in depressive severity was accompanied by an increase in BDNF and a decrease in ALOX, although these biological changes followed distinct temporal patterns and showed limited direct correlation with each other.

The absence of significant correlations between changes in ALOX and changes in clinical scores suggests that these markers capture partially independent biological processes. This dissociation is consistent with previous evidence indicating that biological markers in depression often reflect heterogeneous mechanisms rather than a unified pathophysiological pathway (33).

Depressive and anxiety symptoms

showed a progressive reduction over the 8-week treatment period, with the most substantial improvement observed at the final time point. This temporal pattern aligns with clinical data indicating that antidepressant effects accumulate over several weeks rather than emerging immediately (34, 35). The magnitude of symptom reduction observed in this study is consistent with large clinical datasets showing partial response rather than full remission in most patients during early treatment phases (35). Previous studies have shown that early symptom reduction does not necessarily correspond to full biological normalization, supporting the interpretation of clinical improvement as a gradual and multidimensional process (36).

BDNF levels increased significantly over the course of treatment, consistent with the neurotrophic hypothesis of depression. This increase is in line with meta-

analytic findings reporting elevated peripheral BDNF following antidepressant treatment (16, 18). However, the lack of strong correlations between BDNF changes and symptom improvement in this study reflects the variability described in the literature. Several longitudinal analyses have reported weak or absent associations between peripheral BDNF changes and clinical outcomes, suggesting that BDNF does not function as a direct proxy for symptom severity (16, 17, 33).

The negative association between BDNF and depressive severity at endpoint, although modest, is consistent with evidence that reduced neurotrophic support is linked to impaired synaptic plasticity (4, 13). Some studies indicate that inflammatory processes can suppress BDNF expression, while BDNF itself may regulate neuroinflammatory activity, supporting a bidirectional relationship between these systems (30, 31).

ALOX levels showed a progressive and statistically significant decrease over time, with the most pronounced reduction occurring between weeks 4 and 8. This delayed dynamic suggests that ALOX-related pathways may reflect biological processes evolving later in treatment. The absence of significant correlations between ALOX changes and symptom improvement suggests that this marker does not directly reflect clinical response. However, the significant inverse association between ALOX levels and depressive severity at the endpoint indicates a more complex relationship. Higher ALOX levels at 8 weeks were associated with lower depressive severity, a finding that does not align with a simple pro-inflammatory or neurotoxic interpretation. This pattern may reflect compensatory or regulatory mechanisms within lipid signaling pathways. Lipid mediators derived from arachidonic acid

metabolism participate in both pro-inflammatory and resolution processes, and their functional role may depend on context, timing, and cellular environment (20, 37).

The findings indicate that BDNF and ALOX reflect different aspects of biological response during antidepressant treatment. BDNF appears to capture processes related to neuroplastic adaptation, while ALOX may reflect changes in lipid-mediated oxidative pathways that evolve later in treatment. The absence of predictive value of baseline ALOX for treatment response suggests that this marker is more relevant for monitoring biological changes over time rather than predicting outcomes. The variability observed in non-responders further supports the presence of biological heterogeneity within depressive disorders (38, 39).

The relatively small sample size limits statistical power and may reduce the ability to detect subtle associations. The use of peripheral biomarkers introduces uncertainty regarding their relationship to central nervous system processes, particularly for BDNF, where peripheral levels may not directly reflect brain concentrations (17). The naturalistic design introduces variability related to treatment heterogeneity, although it enhances ecological validity. The absence of a control group limits causal interpretation of observed changes.

## CONCLUSIONS

The study demonstrates that antidepressant treatment is associated with increased BDNF and decreased ALOX levels over time, alongside clinical improvement. These markers show distinct temporal patterns and limited direct association with each other.

BDNF appears to reflect neuroplastic processes associated with treatment, while ALOX may represent a separate biological

pathway related to oxidative and lipid-mediated mechanisms. Their combined assessment provides a broader perspective on biological changes occurring on treatment.

Longitudinal evaluation of multiple biomarkers may offer a more accurate representation of the biological processes under-

lying treatment response in major depression.

### CONFLICT OF INTERESTS AND FUNDING

The authors declare no conflict of interest and they received no financial support was received for perfecting this article.

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