

## **BRAIN DERIVED NEUROTROPHIC FACTOR LEVELS AND HIPPOCAMPAL VOLUME IN DEPRESSED PATIENTS TREATED WITH ESCITALOPRAM**

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### **Abstract**

Recent studies suggest the important roles of brain derived neurotrophic factor (BDNF) and hippocampal volume in the etiopathogenesis of the depressive disorder and also in the mechanisms of action of some antidepressants. The aim of this study was to find possible correlations between serum levels of BDNF, hippocampal volume and clinical symptoms in patients with major depressive disorder (MDD), before, during and after 6 months treatment with escitalopram. Forty female subjects were included: 20 women diagnosed with MDD and 20 aged-matched healthy female controls (without medication). Complete data for statistical analysis were obtained for 8 patients and 16 controls. The patients received escitalopram 10-15mg/day. BDNF serum levels were measured at inclusion in the study, at week 4, week 12 and week 24. Hippocampal volumes were assessed using magnetic resonance imaging at inclusion and at week 24. Low serum levels of BDNF and small left hippocampal volumes were associated with MDD. In women with MDD, escitalopram had a positive effect on BDNF serum levels, as well as on hippocampal volume. The study suggests that changes in the BDNF serum levels and in hippocampal volume in women with MDD might be associated with the treatment with escitalopram. The positive changes in the BDNF serum levels and hippocampal volume seem to be clinically correlated with good patient outcomes. Further research upon association of BDNF serum levels and hippocampal volume with MDD and antidepressant treatment is needed.

### **Rezumat**

Studii recente sugerează ca atât factorul neurotrofic derivat din creier (FNDC) cât și volumul hipocampusului intervin în etiopatogenia tulburării depresive și de asemenea în mecanismele de acțiune ale unor antidepressive. Scopul acestui studiu a fost de a găsi posibile corelații între nivelurile serice ale FNDC, volumul hipocampusului și simptomele clinice ale pacienților cu tulburare depresivă majoră (TDM), înainte, în timpul și după 6 luni de tratament cu escitalopram. Au fost incluși patruzeci de subiecți de sex feminin: 20 de femei diagnosticate cu TDM și 20 de femei sănătoase de aproximativ aceeași vârstă, acesta fiind lotul de control (fără medicație). Date complete pentru analiza statistică au fost obținute de la 8 paciente și 16 subiecți de control. Pacientele au primit escitalopram 10 – 15 mg/zi. Nivelurile FNDC plasmatic au fost măsurate la momentul începerii studiului, în a patra săptămână, în a douăsprezecea și în a douăzeci și patra. Volumul hipocampusului a fost determinat folosind imagistica prin rezonanță magnetică la începutul studiului și în a

douăzeci și patra săptămână. Niveluri reduse ale FNDC plasmatic și volume mici ale hipocampusului stâng au fost asociate cu prezența TDM. La femeile cu TDM, escitalopramul a avut un efect pozitiv asupra nivelurilor FNDC plasmatic, precum și asupra volumului hipocampusului. Studiul sugerează că modificările nivelurilor FNDC plasmatic și ale volumului hipocampusului la femei cu TDM poate fi asociată cu tratamentul cu escitalopram. Schimbările pozitive în ceea ce privește atât nivelurile FNDC plasmatic cât și a volumului hipocampusului par a fi corelate cu rezultatele clinice bune obținute de la pacienți. Sunt necesare cercetări suplimentare în ceea ce privește asocierea nivelurilor FNDC plasmatic și a volumului hipocampusului cu TDM și medicația antidepresivă.

**Keywords:** brain derived neurotrophic factor (BDNF), escitalopram, major depression disorder (MDD), hippocampus

### Introduction

Data from literature suggest that Brain Derived Neurotrophic Factor (BDNF) may play an important role in the etiopathogenesis of major depressive disorder (MDD) and may also be involved in the mechanism of action of antidepressants. The reference level of BDNF is not established yet, but BDNF is known to vary according to race, gender, age and level of stress [11,15]. There is growing evidence that serum levels of BDNF are decreased in patients with MDD and that these levels may be increased by antidepressant medication. An association between the severity of MDD and BDNF serum levels was demonstrated [3,20,21]. They also found that BDNF serum levels are influenced by the antidepressant medication, implying an important role of BDNF in the pathogenesis of depression.

It was shown that escitalopram may increase BDNF serum levels in women with MDD [1]. In another study, it was suggested that sertraline and venlafaxine induce an increase in the BDNF levels, while escitalopram has no effect on BDNF levels in patients with MDD [14]. All three substances had similar efficacy in treating depressive symptoms. Numerous Magnetic Resonance Imaging (MRI) studies show that the volume of the hippocampus is smaller in patients with MDD, but may return to previous size parameters, as a result of neural plasticity processes following antidepressant treatment, suggesting the important role of the hippocampus in the etiopathogenesis of MDD [7,8,9,12]. The changes are positively correlated with a favourable clinical outcome for the patients.

It was demonstrated that chronic antidepressant treatment in rats influences the BDNF gene expression and neurogenesis in hippocampal structures [2,13]. Further studies on human patients have confirmed the influence of antidepressants in the neurogenesis processes in hippocampal structures through BDNF gene expression increase [4,5,6].

The aim of the study was to correlate serum levels of BDNF, hippocampal volume and clinical symptoms in women with MDD before, during and after 6 months treatment with escitalopram.

## **Materials and Methods**

### ***Subjects***

This study included 20 caucasian women aged between 18 and 50 years, diagnosed with MDD, according to the Diagnostic and Statistical Manual of Mental Disorder Fourth Edition Text Revision (DSM-IV-TR) criteria, together with 20 aged-matched female controls. Female subjects within a specific frame of age were selected because BDNF is known to vary by gender and age [11,15]. Control subjects were healthy female volunteers, which did not receive any medication. All participants in the study provided a written consent. All study procedures were approved by the Romanian National Medical Ethics Committee and the National Agency for Medicines and Medical Devices.

At inclusion visit, patients were required to have a Montgomery-Åsberg Depression Rating Scale (MADRS) score of 26 or higher [16]. The patients had to have been drug free for at least 3 months prior to participation in the study. Neither patients nor the controls were allowed to take oral contraceptives during the study, since the level of serum BDNF can be affected by these drugs [19]. Patients were required to have no suicidal ideation and no contraindications for escitalopram. Previous diagnosis of Axis I mental disorders, neurological disorders and head injuries, pregnancy or contraindications for MRI were exclusion criteria. Inclusion criteria for the control group were good physical health, no history of mental disorders and no treatment during the past 3 months.

The patients received escitalopram in variable doses according to the clinician is judgment starting from 10 mg per day to 15 mg per day. The psychiatric and physical status of the subjects (patients and controls) was assessed at admission and during the study by a trained physician.

### ***BDNF assessment:***

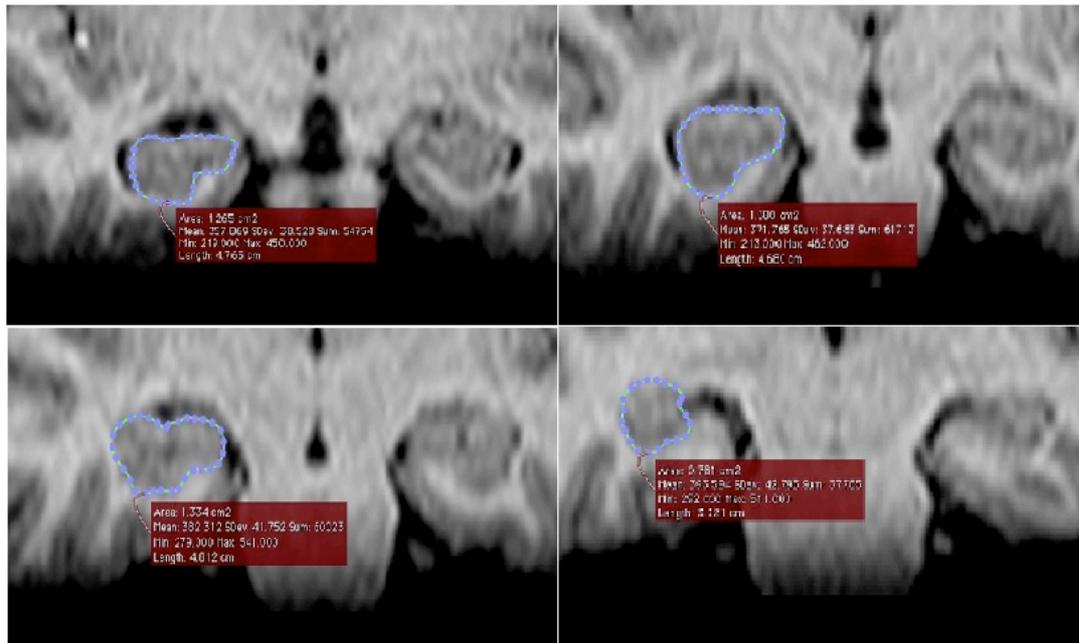
Serum level of BDNF is correlated with the level of cerebral BDNF [10]. The evaluation of BDNF serum level was done by obtaining 5mL of blood from the antecubital vein between 8 and 10 a.m. The blood was collected in anticoagulant-free tubes from all subjects included in the study at inclusion, week 4, week 12, and week 24. Blood samples were kept at room temperature for 1 hour, followed by 1 hour at 4°C, and then

centrifuged at 4000g x 15 minutes at 4°C. Serum was collected and kept at -20°C before assaying BDNF. The BDNF assay was performed in ≤30 days using a solid-phase, sandwich, two-site, enzyme-linked immunoassay (ELISA), (BDNF Human ELISA Kit from Phoenix Pharmaceuticals), according to the manufacturer's instructions. All samples were tested twice and the mean was calculated.

#### ***Hippocampal volume assessment:***

The scans were performed on a Siemens Magnetom Avanto 1.5 Tesla device, with a system of gradients of 33 mT, using a 12-channel head coil. T2-weighted acquisitions were executed in sagittal and coronal planes in order to exclude associated pathologies together with (3D) T1-weighted volumetric acquisitions with a gradient-echo in transverse acquisition (T1-weighted three-dimensional spoiled gradient-echo MR sections). Hippocampus delimitation was performed manually on the images reconstructed in a coronal plane. Volumetric acquisitions with high spatial resolution, intended for post-processing for hippocampal volume measurements: T1 - weighted 3D MP-RAGE ISO - acquisition in axial plane, T1 - weighted 3D MP-RAGE ISO - reconstruction in coronal plane. Acquired sequences for the exclusion of associated pathologies were: T2 SPC ISO in sagittal plane; T2-Weighted TSE (turbo spin-echo) in coronal; T2 FLAIR – acquisition in coronal plane; T1-Weighted SE in sagittal plane.

Image processing was performed by a single neuroimaging specialist and was blinded, meaning that he did not know whether the subject was a patient or a control. Image processing was performed using the program Osirix-32 bits, version 3.8. The images obtained from the 3D isotropic MP-RAGE T1-weighted acquisitions were used in transverse plane with a thickness of 1 mm per slice (FOV: 250, TR: 1650, TE: 2.95 ms, slice thickness: 1 mm, n=80, matrix: 192 x 256). Images were reconstructed in coronal and sagittal planes and the hippocampus was manually marked, using the mammillary bodies as anterior landmark, the posterior commissure as posterior landmark, the choroidal fissure as superior landmark, the subarachnoid structures as medial landmark, the temporal horn of the lateral ventricle as lateral landmark and the white matter of the parahippocampal gyrus as inferior limit of the region of interest. After the manual identification of the hippocampus in all successive sections, bilaterally, where the region of interest was visible, the computer calculated the volume in cubic centimetres (cm<sup>3</sup>) based on the number of present voxels within the delimited regions (Figure 1).



**Figure 1**  
Hippocampal volume measurement using MRI.

### *The evaluation of depression severity*

The severity of depression was assessed using the MADRS, which was administered by a qualified psychiatrist at inclusion, 4 weeks, 12 weeks and 24 weeks.

### *Statistical analysis*

The statistical analysis was performed only for the observed cases (8 patients and 16 controls). Most variables in the study are continuous and therefore are described as means and standard deviations (SDs). For the same variable, differences from one moment of measurement to another of the same group were analysed using paired t-tests. Correlations between variables were used to assess the condition of subjects at each measurement moment, and across measurements. We considered  $p \leq 0.05$  as statistically significant. All statistical calculations were performed using Statistical Package for the Social Sciences (SPSS) statistical software.

### **Results and Discussion**

Of the 20 patients included in the study, only 8 had all the data for the statistical analysis. For 12 patients there was incomplete data [withdrawn

due to adverse events (n=1), demyelinating lesions observed at the MRI (n=1), withdrawal of informed consent (n=6), missed a study visit (n=4)]. At the end of the study, from these 8 patients, 2 patients received 15 mg and 6 received 10 mg of escitalopram per day.

Of the 20 healthy controls included, only 16 had all the data to enter the statistical analysis (2 subjects withdrew informed consent, and 2 missed week 4 visit).

For depressed patients (n=8) the mean age was 40 ( $\pm 8.7$ ) and the mean number of depressive episodes was 1.3 ( $\pm 0.5$ ); for controls (n=16) the mean age was 33 ( $\pm 5.9$ ). (Table I).

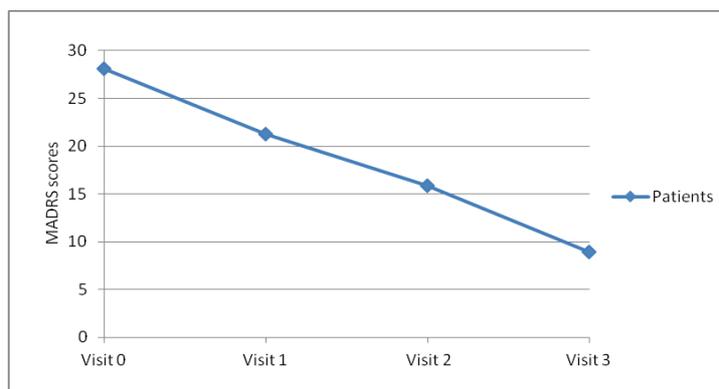
**Table I**  
Clinical features of depressed patients and control subjects

	Depressed patients				Control subjects			
Subjects included (n)	20				20			
Subjects analysed (n)	8				16			
Age (years)*	40 $\pm$ 8.7				33 $\pm$ 5.9			
Depressive episodes (n)	1.3 $\pm$ 0.5				No			
MADRS score at inclusion	28 $\pm$ 2.4				No			
MADRS score at study end	9 $\pm$ 2.9				No			
	<b>Visit 0</b>	<b>Visit 1</b>	<b>Visit 2</b>	<b>Visit 3</b>	<b>Visit 0</b>	<b>Visit 1</b>	<b>Visit 2</b>	<b>Visit 3</b>
BDNF serum level (ng/mL)	33.9 $\pm$ 10.8	33.3 $\pm$ 9.3	40.0 $\pm$ 16.9	35.2 $\pm$ 10.7	38.4 $\pm$ 19.4	25.7 $\pm$ 6.4	29.5 $\pm$ 10.8	31.1 $\pm$ 5.1
Hippocampal volume (cm <sup>3</sup> )	<b>Visit 0</b>		<b>Visit 3</b>		<b>Visit 0</b>		<b>Visit 3</b>	
Total	3.21 $\pm$ 0.48		3.32 $\pm$ 0.70		3.46 $\pm$ 0.51		3.26 $\pm$ 0.54	
Left	1.52 $\pm$ 0.24		1.61 $\pm$ 0.39		1.74 $\pm$ 0.26		1.61 $\pm$ 0.23	
Right	1.69 $\pm$ 0.25		1.70 $\pm$ 0.32		1.71 $\pm$ 0.26		1.65 $\pm$ 0.32	

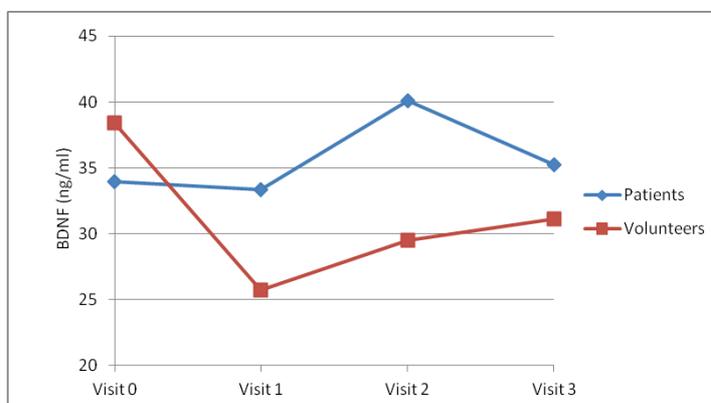
\*Age, Number of depressive episodes, MADRS total score, BDNF level are shown as mean  $\pm$  SD  
BDNF serum level, Total Hippocampal Volume, Left Hippocampal Volume, Right Hippocampal Volume are shown as mean  $\pm$  SD  
MADRS, Montgomery-Åsberg Depression Rating Scale; BDNF, Brain Derived Neurotrophic Factor  
Visit 0, inclusion visit; Visit 1, 4 weeks from inclusion; Visit 2, 12 weeks from inclusion; Visit 3, 24 weeks from inclusion

For the patients included in statistical analysis, the MADRS total mean score at inclusion was 28.13 (n=8, SD=2.4) and at week 24 was 8.8 (n=8, SD=2.9) (Figure 2). The mean BDNF serum values for the patients

included in statistical analysis are shown in Table 1. After the inclusion visit, the BDNF value decreased at week 4 and then increased at week 12 and again decreased at week 24 (Figure 3). The mean change from inclusion to week 4 in BDNF level (0.64; 2-tailed  $t=0.150$ ,  $p=0.885$ ), from inclusion to week 12 (-6.11, 2-tailed  $t=-0.695$ ,  $p=0.10$ ) and from inclusion to week 24 (-1.29, 2-tailed  $t=-0.298$ ,  $p=0.774$ ) showed a quantitative variation, but was not statistically significant, probably due to the small number of patients. The mean change in BDNF level in the healthy control group from inclusion to week 4 was 12.69 (2-tailed  $t=2.937$ ,  $p=0.010$ ), from inclusion to week 12 was 8.92 (2-tailed  $t=1.466$ ,  $p=0.163$ ) and from inclusion to week 24 was 7.29 (2-tailed  $t=1.429$ ,  $p=0.174$ ) (Table I). Although there was an increase in the mean BDNF values after week 4, the healthy control group level did not reach the mean BDNF level at inclusion.



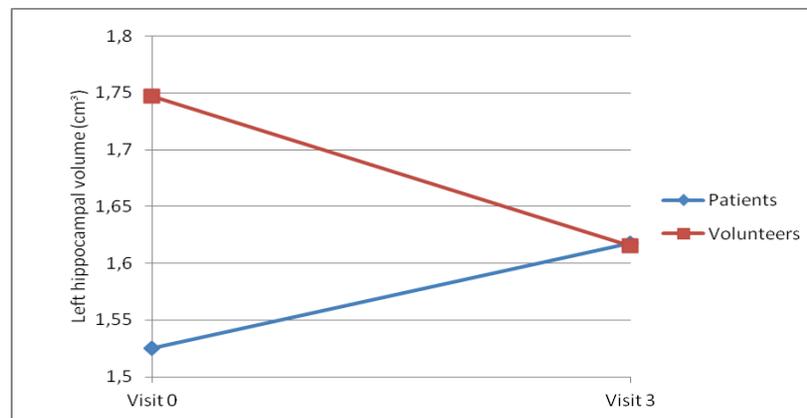
**Figure 2**  
MADRS mean total score in patients



**Figure 3**  
Mean BDNF values in patients and control

The hippocampal volumes were analysed separately (left and right) and then the total volume was calculated as the sum of the left and right hippocampal volumes. In the patient group, the mean left hippocampal volume increased to 1.61 cm<sup>3</sup> (n=8, SD=0.39), after 24 weeks, but was not statistically significant (-0.092 cm<sup>3</sup>, 2-tailed t =-1.127, p=0.297), while the right hippocampal volume increased to 1.70 cm<sup>3</sup> (n=8, SD=0.32). The increase of the mean left hippocampal volume in the patient group paralleled the clinical response of the patients, as well as the increase in mean BDNF values. The change in the mean total hippocampal volume (0.10 cm<sup>3</sup>, 2-tailed t =0.847, p = 0.425) was not statistically significant.

In the healthy control group, mean hippocampal volume showed the same descending trend as the change in mean BDNF levels (Figure 4). The mean left hippocampal volume decreased by 0.13 cm<sup>3</sup> (2-tailed t =2.599, p=0.020) and the total hippocampal decrease was 0.198 (2-tailed t=1.952, p=0.070) from inclusion to week 24.



**Figure 4**

The left hippocampal volumes (mean) change in patients and healthy controls.

This study included only women in order to reduce the variability for the BDNF assessment. On the other hand, hippocampal volumes are considered age and sex independent [17]. The drop-out rate was high (12 out of 20 patients), probably due to the long study period. In a similar study, a drop-out rate of approximately 50% during a 1-year follow-up was reported [18].

The patients had a good clinical response to antidepressant treatment, as illustrated by the MADRS scores. Response (decrease of MADRS score with 50%) was obtained for 3 patients at week 12. At the end of the study

remission ( $\text{MADRS} \leq 10$ ) was obtained for 6 patients, while the other 2 had a response to escitalopram.

The mean BDNF serum levels at inclusion were lower in the patient group (33.96 ng/mL) than in the control group (38.42 ng/mL), confirming the data from previous studies [21]. BDNF serum levels in the patient group decreased in the first 4 weeks, probably due to latency in the synthesis processes [5,6].

In the patient group, at the end of the study, the mean BDNF value was higher than the mean value from inclusion visit. The favourable clinical evolution of the patients, under treatment, as shown by the mean MADRS scores, could be associated with the variation of BDNF. We observed that the BDNF serum levels were positively correlated with response to treatment and it did not seem to be dose dependent, similar to other studies [21].

In the healthy control group, no differences were observed in changes in the volume between the left and right hippocampal volumes, as previously shown in other studies [7]. In the patient group, we observed a smaller left hippocampal volume at baseline. A similar finding was described in male patients with a first episode of MDD [7].

In the patient group, after 24 weeks of treatment with escitalopram, the evaluations showed an increase of the left hippocampal volume. Both the left hippocampal volume and the BDNF serum level in the patient group increase and the mean values at the end of the study are higher than the baseline ones. This increase in the left hippocampal volume shows the same trend as the increase in the BDNF serum level and clinically correlates, although not statistically significant, with the decrease of MADRS mean total score.

An analysis of total hippocampal volumes at baseline shows that the control group mean is higher than that of the patient group. The localization of the BDNF and his receptor TrkB in the hippocampal structures could play both a protector and a trophic role [21].

### **Conclusions**

Our study suggests that changes in the BDNF serum levels might be associated with an increase of left hippocampal volume, for depressed patients treated with escitalopram, although the correlation had no statistical significance. The small study population does not allow us to generalize the results, but they may constitute an important objective for further research.

This clinical trial has been audited by the Romanian National Agency for Medicines and Medical Devices in September 2011.

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