

BRAIN DERIVED NEUROTROPHIC FACTOR (BDNF) LEVELS IN DEPRESSED WOMEN TREATED WITH OPEN-LABEL ESCITALOPRAM

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SUMMARY

Background: Recent studies suggest the important role of brain derived neurotrophic factor (BDNF) in the etiopathogenesis of major depressive disorder (MDD) and the mechanism of action of antidepressants. This study aimed to correlate serum levels of BDNF and clinical symptoms in patients with MDD before and after 6 months treatment with escitalopram.

Subjects and methods: Twenty women diagnosed with MDD and 20 aged-matched healthy female controls were recruited. The patients received escitalopram 10-20 mg/day. BDNF serum levels were measured at inclusion, week 4, week 12 and week 24. The Montgomery-Åsberg Depression Rating Scale (MADRS) was used to assess the severity of depressive symptoms and the clinical evolution of patients. Statistical analysis was performed using both observed cases and last observation carried forward.

Results: At baseline, low serum levels of BDNF were associated with MDD. In women with MDD, escitalopram seems to have a positive effect on BDNF serum levels in parallel with the clinical response.

Conclusions: This study suggests that a good clinical evolution under treatment with escitalopram might be associated with increases of BDNF levels in female patients.

Key words: brain derived neurotrophic factor – BDNF – depression - escitalopram

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INTRODUCTION

Brain derived neurotrophic factor (BDNF) is an important member of the neurotrophin family that is present in both the central and peripheral nervous system. Its effects on neuronal outgrowth, differentiation, synaptic connectivity, and neuronal repair and survival have been demonstrated (Karege et al. 2005). The literature suggests its role in stress and in the pathophysiology of major depression (Brunoni et al. 2008, Sen et al. 2008). There is growing evidence that serum levels of BDNF are low in patients with major depressive disorder (MDD) (Shimizu et al. 2003, Molendijk et al. 2011, Kimpton 2012, Karlović et al. 2013) and that there is an association between the severity of MDD and BDNF serum levels (Shimizu et al. 2003, Gonul et al. 2005, Kurita et al. 2012), although the latter finding is not ubiquitous (Jevtovic et al. 2011, Molendijk et al. 2011).

Although the standard level of BDNF is not established, BDNF is known to vary according to race, gender, and age (Lommatzsch et al. 2005, Mitoma et al. 2008). BDNF serum levels are also influenced by the antidepressant medication (Aydemir et al. 2005). The neurotrophin hypothesis of depression suggests that central BDNF deficiency underlies depression, and that antidepressants work via restoration of central BDNF levels (Wolkowitz et al. 2011). The neurotrophin hypothesis is further supported by the fact that intra-cerebroventricular and intra-hippocampal injection of BDNF produces antidepressant-like effects in animal models of depression (Hoshaw et al. 2005). Other

studies showed that BDNF could be involved in the mechanism of action of some antidepressants. Aydemir et al. (2005) has shown that escitalopram may increase BDNF serum levels in women with MDD. Matrisciano et al. (2009) suggested that sertraline and venlafaxine induce an increase in the BDNF levels, while escitalopram had no effect on BDNF levels in patients with MDD, although all three antidepressants had similar efficacy in treating depressive symptoms.

SUBJECTS AND METHODS

Subjects

In this study, 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, were included together with 20 aged-matched healthy female controls. Only women were included in the study in order to limit the variability of the BDNF assessment. All participants in the study provided written consent before any study procedure was performed. All study procedures were approved by the Romanian National Medical Ethics Committee and the National Agency for Medicines and Medical Devices.

BDNF evaluation

The evaluation of BDNF was made four times during 6 months: at inclusion, at week 4, week 12, and week 24. At each study visit, depression severity was assessed using Montgomery-Åsberg Depression Rating

Scale (MADRS) and blood samples were collected for the determination of BDNF serum levels. At inclusion, patients were required to have a MADRS total score of 26 or higher. The patients had to have been free of any antidepressant medication 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 may be affected by these drugs. Included patients were required to have no suicidal ideation and no contraindications for receiving escitalopram. Other exclusion criteria for patients were: a previous diagnosis of an Axis I mental disorders, neurological disorders and head injuries or pregnancy. Inclusion criteria for the control group were good physical health, no history of mental disorders and no treatment of any kind during the previous 3 months.

The patients received escitalopram in flexible dose according to the clinician's judgment, starting at 10 mg per day with the possibility to increase the dose up to 15 or 20 mg per day. Rescue medication permitted in the study was lorazepam (maximum dose 2 mg per day) for anxiety and zolpidem (maximum dose 10 mg per day) for insomnia. Rescue medication was allowed to be used when needed during the study. The psychiatric and physical status of the subjects (patients and controls) was assessed at admission and during the study by a trained physician.

BDNF laboratory assessment

Serum BDNF is correlated with the level of cerebral BDNF (Karege et al. 2005). 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 for 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, CA, USA), according to the manufacturer's instructions. All samples were assayed in duplicate and the mean was calculated.

The evaluation of depression severity

The severity of depression was assessed using the MADRS, which was administered at inclusion, 4 weeks, 12 weeks and 24 weeks. The evaluation was made by a qualified psychiatrist. A backup rater was available during the study period.

Statistical analysis

The statistical analysis was first performed using observed cases (OC): 8 patients and 16 controls as well as last observation carried forward (LOCF) for 20

patients and 20 controls. LOCF involves completing missing values with the last available measurement. The OC group includes subjects with all the study visits completed and with all the data needed for the statistical analysis. Most variables in the study are continuous variables 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 analyzed using paired t-tests. Correlations between variables were used to assess the condition of subjects at each measurement moment and across measurements. All statistical calculations were performed using SPSS statistical software. We considered $p \leq 0.05$ as statistically significant.

RESULTS

Table 1 shows the subjects characteristics and the mean BDNF serum levels at each study visit.

At the end of the study, in the OC group 2 patients received 15 mg and 6 received 10 mg of escitalopram per day. None of the patients received 20mg/day of escitalopram.

The mean MADRS value at inclusion was 29.6 (n=20, SD= 2.3). For the 8 patients included in the OC statistical analysis, the MADRS total mean score at visit 0 was 28.1 (n=8, SD=2.4) and at the final visit (after 3 months) was 8.8 (n=8, SD=2.9). Remission (MADRS ≤ 10) was achieved by 6 patients, while the other 2 had responded to treatment (decrease of MADRS score by $\geq 50\%$).

At the last assessment, the mean MADRS value for the patients included in the LOCF statistical analysis was 15.4 (n=20, SD=11.3) (Figure 2).

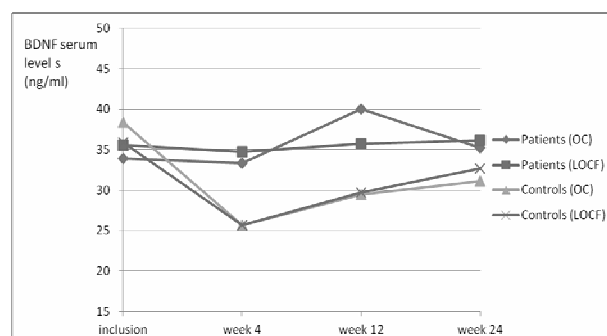


Figure 1. Mean BDNF values in patients and controls

In the OC group of patients the mean BDNF serum levels showed no statistical variation from visit 0 to visit 3, although a quantitative variation could be observed: the mean change from visit 0 to visit 1 in BDNF level (0.64; 2-tailed $t=0.150$, $p=0.885$), from visit 0 to visit 2 (-6.11, 2-tailed $t=-0.695$, $p=0.10$) and from visit 0 to visit 3 (-1.29, 2-tailed $t=-0.298$, $p=0.774$). After the first visit, the mean BDNF value decreased at visit 1 and then increased at visit 2 and again decreased at visit 3 as shown in figure 1.

Table 1. Clinical features of depressed patients and control subjects

	Depressed patients				Control subjects			
	Visit 0	Visit 1	Visit 2	Visit 3	Visit 0	Visit 1	Visit 2	Visit 3
Subjects included (n)	20				20			
Subjects analysed (n)	8(OC)	20 (LOCF)			16(OC)	20 (LOCF)		
Age (years)*	40±8.7	36.6±8.1			33±5.9	32.9±5.5		
Depressive episodes (n)	1.3±0.5	1.4±0.5			No			
MADRS score at inclusion	28.1±2.4	29.6±2.3			No			
MADRS score at study end	8.8±2.9	15.4±11.3			No			
BDNF serum level (ng/ml) (OC)	33.9±10.8	33.3±9.3	40.0±16.9	35.2±10.7	38.4±19.4	25.7±6.4	29.5±10.8	31.1±5.1
BDNF serum level (ng/ml) (LOCF)	35.6±12.7	34.7±11.8	35.7±13.2	36.1±10.5	35.9±18.6	25.7±7.3	29.7±10.1	32.7±5.6

*Age, Number of depressive episodes; MADRS total score; BDNF level are shown as mean ± SD; BDNF serum level is shown as mean ± SD; MADRS, Montgomery-Åsberg Depression Rating Scale; BDNF, Brain Derived Neurotrophic Factor; OC, Observed cases; LOCF, Last observation carried forward; Visit 0, inclusion visit; Visit 1, 4 weeks from inclusion; Visit 2, 12 weeks from inclusion; Visit 3, 24 weeks from inclusion

Table 2. Correlation between MADRS scores and BDNF variations

		BDNF variation week4-inclusion	BDNF variation week12-inclusion	BDNF variation week24-inclusion
MADRS variation week4-inclusion	Pearson Correlation	0.870	0.619	0.537
	Sig. (2-tailed)	0.005	0.102	0.170
	N	8	8	8
MADRS variation week12-inclusion	Pearson Correlation	0.597	0.666	0.388
	Sig. (2-tailed)	0.118	0.071	0.343
	N	8	8	8
MADRS variation week24-inclusion	Pearson Correlation	0.395	0.014	0.286
	Sig. (2-tailed)	0.333	0.973	0.493
	N	8	8	8

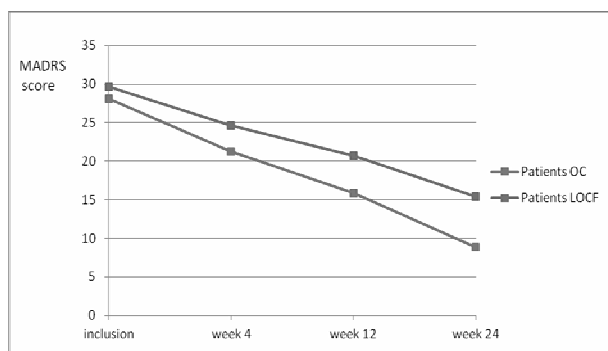


Figure 2. Mean MADRS scores

In the LOCF analysis the variations are smaller and after a decrease from visit 0 to visit 1 the mean BDNF increases all the way to visit 3. The mean change from visit 0 to visit 1 in BDNF level (0.87; 2-tailed $t=0.515$, $p=0.613$), from visit 0 to visit 2 (-0.04, 2-tailed $t=-0.01$, $p=0.992$) and from visit 0 to visit 3 (-0.46, 2-tailed $t=-0.151$, $p=0.882$) showed a quantitative variation, but was not statistically significant. In the control group, the OC analysis of the mean change in BDNF level from visit 0 to visit 1 was 12.69 (2-tailed $t=2.937$, $p=0.010$), from visit 0 to visit 2 was 8.92 (2-tailed $t=1.466$, $p=0.163$) and from visit 0 to visit 3 was 7.29 (2-tailed $t=1.429$, $p=0.174$). Although there was an increase in the mean BDNF values after visit 1, the control group level did not reach the mean BDNF level from visit 0.

In the LOCF analysis for the control group the mean BDNF changes keep the same trend like the mean changes in the OC analysis, but the value at visit 3 is closer to the value from visit 0.

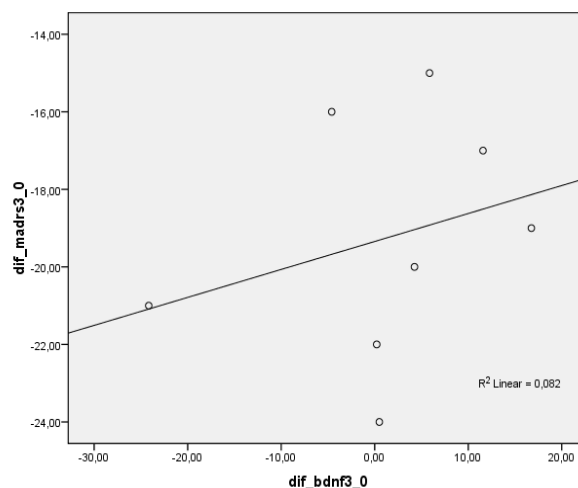


Figure 3. Correlations between MADRS and BDNF variations (week 24-inclusion)

In the LOCF analysis for the control group the mean BDNF changes keep the same trend like the mean changes in the OC analysis, but the value at visit 3 is closer to the value from visit 0.

In the OC analysis the variations in the MADRS scores and BDNF levels from inclusion to week 4, 12 and 24 were analyzed using Pearson's correlation (Table 2). A relevant correlation was observed between inclusion and week 4 (Pearson's=0.87, Sig.2-tailed=0.005). No statistically relevant correlation in the variation from inclusion to the end of the study of MADRS score and BDNF level was observed (Figure 3).

DISCUSSION

In order to reduce the variability of the serum BDNF assessment, this study included only women, aged between 18 and 50 years. BDNF is known to vary according race, gender, and age and is also influenced by some medication including the antidepressant medication.

The drop-out rate of the study was high 7 out of 20 patients, but similar with other studies (Piccinni et al. 2008), taking into account the relatively long duration of the study (6 months).

We had 13 patients and 19 controls as study completers, but only 8 patients and 16 controls entered the OC statistical analysis meaning that not all study completers had all the data available at the end of the study. From these completers 5 patients and 3 controls missed the week 4 (4 patients and 2 controls) or week 12 visits (1 patient and 1 control). At the end of the study, the completers received 15 mg of escitalopram per day (3 patients) or 10 mg of escitalopram per day (10 patients). None of the patients in the study received 20mg/day of escitalopram. Rescue medication was used for 5 patients. Three patients received lorazepam for anxiety for 4 weeks (1 received 2mg per day and 2 received 1mg per day). Two patients received zolpidem 10mg per day for insomnia (one for 4 weeks and the other for 12 weeks).

All the patients who completed the study had a good clinical response to treatment as shown by the MADRS scores evolution. Response (decrease of MADRS score by $\geq 50\%$) was obtained for 3 patients at week 12. At the end of the study remission for the OC group (MADRS ≤ 10) was achieved by 6 patients, while the other 2 responded to escitalopram.

Patients with MDD had lower levels of serum BDNF at inclusion, similar to other studies (Shimizu et al. 2003, Molendijk et al. 2011, Karlović et al. 2013). After the first study visit all the subjects had a lower value of the BDNF level. In the patient group this decrease is smaller. A possible explanation could be a protective effect of escitalopram. We may presume that the decrease in the BDNF serum levels, in patients, from the first month could be due to the latency in the synthesis processes (Duman 2004). In the patients group, at the end of the study the mean BDNF value was higher than the inclusion value as observed both with OC and LOCF statistical methods (OC: 33.9ng/ml versus 35.2ng/ml; LOCF: 35.6ng/ml versus 36.1ng/ml).

The increase of the mean BDNF values in the patient group is clinically correlated with the treatment response as shown by variation of the MADRS scores and it was not dose dependent, similar to other research (Shimizu et al. 2003). In the healthy control group, there was a decrease in the mean BDNF serum level from baseline to the end of the study. The decrease was found with both analyses: using OC and LOCF statistical methods respectively. Another finding of this study was that the mean level of the BDNF in the control group at the end was lower than the baseline value. We could presume that this decrease might be explained by some psychological stress, as other studies suggest (Mitoma et al. 2008), but we have no data concerning this issue, in our subjects.

CONCLUSIONS

This pilot research, with a small study population does not allow us to generalize the results, but they could be useful references for further studies. Low serum levels of BDNF were associated with MDD in women. A good clinical response to escitalopram seemed to be associated with an increase of BDNF levels. BDNF serum level could be useful as a depression marker and might be associated with the efficacy of antidepressant therapy as other researchers suggest (Wolkowitz et al. 2011).

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Conflict of interest: None to declare.

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