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Effects of fluoxetine and venlafaxine on serum brain derived neurotrophic factor levels in depressed patients

Ayse Devrim Başterzi [a,*], Kemal Yazici [a], Eda Aslan [a], Nuran Delialioğlu [b], Bahar Taşdelen [c], Şenel Tot Acar [a], Aylin Yazici [a]

[a] Department of Psychiatry, Mersin University Faculty of Medicine, Zeytinlibahçe Cad., 33079-Mersin, Turkey
[b] Department of Microbiology, Mersin University Faculty of Medicine, Zeytinlibahçe Cad., 33079-Mersin, Turkey
[c] Department of Biostatistics, Mersin University Faculty of Medicine, Zeytinlibahçe Cad., 33079-Mersin, Turkey

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ABSTRACT

Background: Several studies demonstrated that depressed patients had low serum BDNF levels which correlated with the severity of their depression, and antidepressant treatment increases levels of serum BDNF in depressed patients. It was speculated that agents acting on both noradrenergic and serotonergic transporters might have a greater influence on BDNF levels. The aim of our study was to determine effects of venlafaxine vs. fluoxetine on serum BDNF levels in depressive patients.
Methods: Forty-three patients diagnosed as major depressive disorder according to DSM-IV are included in the study. Forty-three patients were randomized to take fluoxetine (22 cases) or venlafaxine (21 cases). Serum levels of BDNF were measured by ELISA at baseline and 6 weeks after the start of treatment.
Results: Baseline levels of BDNF were not significantly different between the patient group and the controls. But male patients and the male controls showed statistical differences with respect to baseline BDNF levels. BDNF levels of the patient group did not change with treatment. Yet, the increase of BDNF levels was close to statistically significant in the fluoxetine group, whereas not significant in the venlafaxine group. There were no significant differences in baseline and 6th week BDNF levels between the responders and the non-responders.
Conclusion: Further studies controlling for a wide variety of confounding variables are needed, which may help to reach a clear conclusion about the potential of BDNF as a biomarker for depression or as a predictor of antidepressant efficacy.

1. Introduction

Depression is a widespread, debilitating psychiatric illness with significant economic and humanistic consequences. Biological markers for depression are of great interest to aid in elucidating the causes of major depression (Mössner et al., 2007). However, there is no a sufficiently specific biological marker to contribute to the diagnosis of major depression, yet.

Brain derived neurotrophic factor (BDNF) obviously has a role in survival of neurons during hippocampal development, which may relate to its putative role in depression (Alcantara et al., 1997). BDNF has been implicated in development, neural regeneration, synaptic transmission, synaptic plasticity and neurogenesis in the brain (Thoenen, 1995; Zigova et al., 1998; Schinder and Poo, 2000; Pencea et al., 2001) and also thought to be involved in long-term potentiation, a cellular mechanism of learning and memory (Korte et al., 1995).

Pre-clinical studies suggest that BDNF exhibits antidepressant activity on its own, as infusion of BDNF into the midbrain or hippocampus in rats induces antidepressant effects (Shirayama et al., 2002; Siuciak et al., 1997). Different classes of antidepressant drugs had been proved to increase BDNF messenger ribonucleic acid and protein levels in animal studies (Russo-Neustadt et al., 2001; Altar et al., 2003). Animal studies have demonstrated that BDNF crosses the blood-brain barrier (Poduslo and Curran, 1996; Pan et al., 1998). Karege et al. reported a high positive correlation (r=0.81) between serum and cortical BDNF concentrations for rats (Karege et al., 2002b).

Several studies demonstrated that serum BDNF, which is likely reflective of BDNF levels in the brain, was significantly decreased in depressed patients (Karege et al., 2002a; Shimizu et al., 2003). Increased BDNF levels were observed in post-mortem hippocampal tissue of patients treated with antidepressants (Chen et al., 2001). Several clinical studies reported that depressed patients had low serum BDNF that correlated with the severity of their depression and antidepressant treatment increased serum BDNF levels of depressed patients (Aydemir et al., 2005; Gonul et al., 2005; Karege et al., 2002a, b; Shimizu et al., 2003; Aydemir et al., 2006; Gervasoni et al., 2005, Lee

Abbreviations: BDNF, Brain-derived neurotrophic factor; FLX, Fluoxetine; VEN, Venlafaxine.

* Corresponding author. Tel.: +90 324 3374300x1179; fax: +90 324 3368098.
E-mail address: adcingi@yahoo.com (A.D. Başterzi).

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et al., 2007). BDNF plasma levels were increased significantly in depressed patients receiving ECT for major depression and were accompanied by a significant decrease in depressive symptoms (Marano et al., 2007).

Venlafaxine (VEN) and other SNRIs have improved clinical response and remission rates in depressive patients and have a faster clinical onset of action as compared to other antidepressants (Golden and Nicholas, 2000; Rosenzweig-Lipson et al., 2006; Tran et al., 2003), nevertheless, the clinical evidence is not consistent (Montgomery et al., 2007). Larsen et al. (2008) demonstrated that VEN and imipramine, but not fluoxetine (FLX), induce neuroplastic effects in the hippocampus through stimulation of BDNF mRNA expression, and that the effect on BDNF is not directly translated into regulation of synaptophysin and growth associated protein 43 (GAP-43) mRNA in the rat brain. Several studies reported no effect on BDNF mRNA expression in the hippocampus after fluoxetine treatment (Altieri et al., 2004; Conti et al., 2002; Dias et al., 2003; Miro et al., 2002). Gonul et al. (2005) found no difference between the serum BDNF levels of patients receiving SSRIs or VEN. Yoshimura et al. (2007) demonstrated that paroxetine and milnacipran equally increase serum BDNF levels, especially in responders to these drugs. On the other hand, Hellweg et al. (2008) recently showed that amitriptyline, but not paroxetine, led to an increase in serum concentrations of BDNF independent of clinical response.

Although it was speculated that agents acting on both noradrenergic and serotonergic transporters may have a greater influence on BDNF levels (Larsen et al., 2008), results of the clinical studies conducted so far remain controversial. To investigate the possible differential influence of the two different classes of antidepressant drugs on serum BDNF levels, we administered FLX, an SSRI, or VEN, an SNRI, to patients with major depressive disorder (MD), and investigated the effects of these drugs on serum BDNF levels.

2. Subjects and methods

Patients diagnosed with MD or MD-recurrent according to DSM-IV criteria, were included in the study. An expert clinician interviewed patients and healthy controls with SCID (First et al., 1997). Informed consent was obtained from all patients. Local ethic committee approved the study. These patients were part of a larger scale study of proinflammatory vs. inhibitory cytokines in depression, which is still ongoing in our department.

Exclusion criteria were presence of any additional axis I or axis II DSM-IV diagnosis, current pregnancy, acute or chronic infections within the past month, autoimmune, allergic, neoplastic or endocrine diseases and other acute physical disorders, including surgery or infarction of the heart or brain within the past 6 months. These illnesses were ruled out by clinical interview, physical examination and comprehensive laboratory work-up focusing on parameters indicative of inflammation. Patients exposed to any drug including antidepressants, non-steroidal anti-inflammatory drugs and oral contraceptives in the past 4 weeks were also excluded.

Healthy volunteers were also interviewed with SCID-1 also, and in addition to the above exclusion criteria, those with no lifetime or current diagnosis of any psychiatric disorders were included as the control group.

Patients were consequently randomized to either FLX or VEN treatment. After the index evaluation with Hamilton Rating Scale for Depression (HAM-D) and the collection of blood for serum BDNF levels, treatment with VEN 75 mg/day or FLX 20 mg/day was initiated. If the improvement in the follow-up assessments was not adequate according to the clinician's judgment, the dose of venlafaxine was raised to 150 mg/day; fluoxetine was raised to 40 mg/day. At week 6 of the treatment period, the patients were reassessed with HAM-D and "follow-up" blood samples were drawn.

2.1. Instruments

The severity of depression was evaluated with HAM-D (Williams, 1978). It was adapted into Turkish and was shown to be reliable and valid (Akdemir et al., 1996). The severity of anxiety was evaluated by Hamilton anxiety scale (HAM-A). It was adapted into Turkish and was shown to be reliable and valid (Yazıcı et al., 1998). HAM-A and HAM-D were administered at the beginning of treatment and at the end of the 6th week. Response was defined as a 50% reduction in the index total HAM-D score.

2.2. Laboratory methods

15 ml of venous blood was drawn from each subject between 08.00 and 10.00 A.M. Samples were centrifuged at 4 °C (3000 rpm, for 15 min using a refrigerated centrifuge) and the sera transferred to a new set of polypropylene tubes. All sera samples were stored at −80 °C before use. BDNF concentrations in the sera were determined by the sandwich enzyme immunoassay method, using BDNF Human ELISA kit (R&D systems, Quantikine, Lot: 256830, Catalog No: DBD00, Minneapolis MN 55413). All samples were tested in the same run, which also included a set of standards that were measured in duplicate. The amount of BDNF in each sample was calculated using the standard curve. A monoclonal antibody specific for the BDNF had been precoated onto a micro-plate. Standards and samples were then pipetted into the wells and any BDNF present was bound by the immobilized antibody. An enzyme linked to the monoclonal antibody specific for the BDNF was added to the wells. Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution was added to the wells, and color developed in proportion to the amount of the BDNF bound in initial step. After the color development was stopped, its intensity was measured. The minimum detectable dose of BDNF, typically less than 20 pg/ml, was determined by adding two standard deviations to the mean optical density value of 20 zero standard replicates and calculating the corresponding concentration. BDNF levels are given as pg/ml.

2.3. Statistical methods

Statistical analysis was carried out using a computerized statistical package (SPSS for Windows). Kolmogorov–Smirnov test was used to control normal distribution assumption of parametric tests. The means of BDNF measurements were compared by using independent *t*-test when there are two groups and oneway ANOVA when there are more than two groups. Dependencies between two categorical variables such as (gender-group, response to treatment-group) were

Table 1
Demographic and clinical variables for the groups

	Female (*n*)	Male (*n*)	Mean age	Mean HAM-D		Previous depressive episodes present	Family history of depression positive
				Baseline	Post-treatment		
Fluoxetine	16	6	32±11	25.7±3.5	12.1±8.1	13	8
Venlafaxine	14	7	31±14	26.5±4.9	11.2±8.1	11	5
Control	9	6	36±10	–	–	0	4
p value	0.719		0.219	0.572	0.769	0.658	0.370

evaluated by using chi-square test. Pairwise comparisons of pre- and post-treatment BDNF levels were performed by using paired *t*-test. Spearman's rank correlation analysis was used to assess correlations between BDNF, HAM-D, and HAM-A. All tests were two-tailed with a significance level of α=0.05.

3. Results

A total of 43 patients and 15 controls were included in the study. Twenty-two patients were assigned to FLX and 21 patients were assigned to VEN treatment group. By the 6th week of treatment, 7 patients in the FLX group and 7 in the VEN group had dropped out due to adverse effects or use of anti-inflammatory drugs. Thus, 29 patients completed the study. The data regarding age and sex distribution, mean HAM-D scores, and personal and family history of depression across the groups are shown in Table 1.

Baseline levels of BDNF were not significantly different between the patient group (42,005±12,630 pg/ml) and the controls (47,727±7698 pg/ml) (p=0.105), and across the FLX (n=22, 41,502±13,486 pg/ml), the VEN (n=21, 42,532±11,978 pg/ml) and the control groups (n=15, 47,727±7698 pg/ml) (p=0.262) (Fig. 1).

In the patient group, BDNF levels increased after 6 weeks of treatment, but the difference did not reach statistical significance (BDNF-1: 41,738±12,985 pg/ml, BDNF-2: 47,868±13,028 pg/ml, p=0.115). Increment of BDNF levels in the FLX group was almost significant (41,264±12,548 pg/ml vs. 50,461±12,954 pg/ml, p=0.056), whereas change in BDNF level was less apparent in the VEN group (42,246±13,894 pg/ml vs. 45,090±12,992 pg/ml, p=0.656) (Fig. 2).

Of the 29 patients who completed the study, 17 (62%) were classified as treatment responders and 12 (38%) as non-responders based on HAM-D scores. No statistically significant differences were found either in baseline (43,280±13,932 vs. 39,214±11,439 pg/ml, p=0.262) or 6th week (50,011±12,060 vs. 44,362±14,369 pg/ml, p=0.265) BDNF levels between the responders and the non-responders. Likewise, percent change in BDNF was also not significant between the responders (10.2%) and the non-responders (9.8%) (p=0.785), and between the FLX (11.2%) and the VEN (9%) groups (p=0.621).

The comparisons between the male (39,172±8619 pg/ml) and the female patients (43,232±13,969 pg/ml) (p=0.253); the female patients (43,232±13,969 pg/ml) and the female controls (47,520±8615 pg/ml) (p=0.391) did not show statistical differences with respect to baseline BDNF levels. But the male patients showed significantly lower BDNF levels at baseline (39,172±8619 pg/ml) compared to the male controls (48,037±6855 pg/ml) (p=0.041). The change in BDNF levels after treatment period was not statistically significant in female (p=0.241), or male patients (p=0.275) (Fig. 3).

Baseline level of anxiety was not correlated with baseline BDNF levels (r=0.138, p=−0.197). Age (p=0.491) and HAM-D score of depression (p=0.513) were not found to be correlated with BDNF levels.

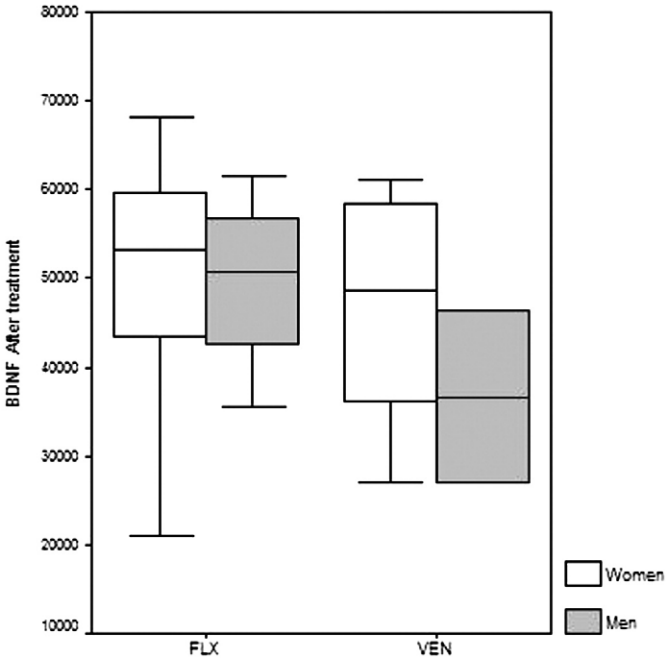

Fig. 2. After treatment BDNF levels in men and women in FLX and VEN groups.

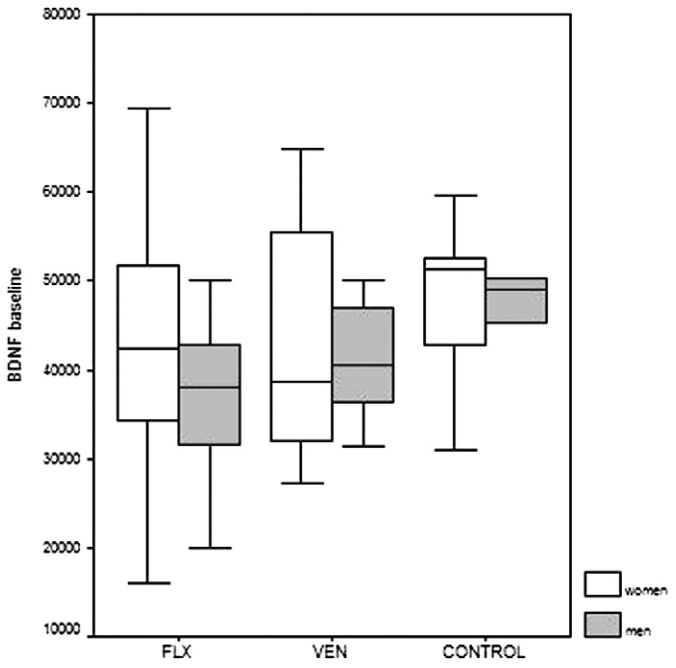

Fig. 1. BDNF levels at baseline in men and women across study groups.

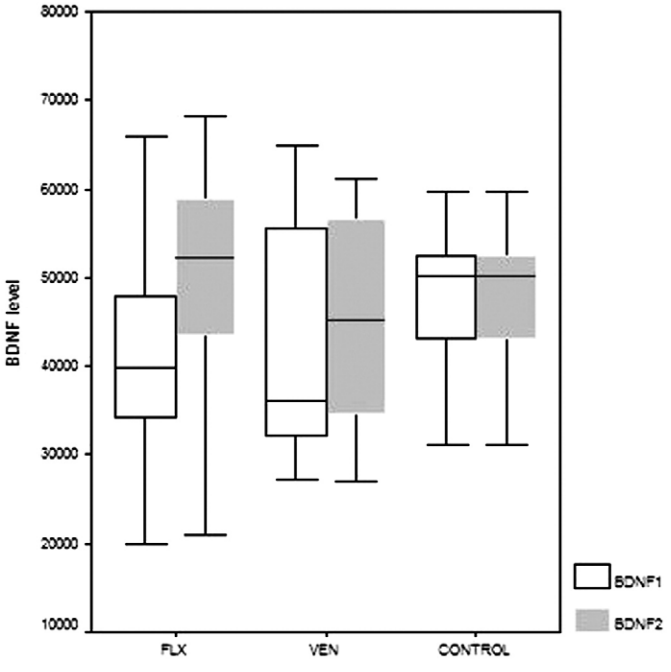

Fig. 3. BDNF levels before and after treatment.

4. Discussion

The main finding of this study was that prior to treatment the serum BDNF levels of depressed patients did not show any significant differences than healthy controls. First time Karege (2002a), showed the low serum BDNF level in patients with major depressive disorder when compared to control subjects. After that several studies reported that depressed patients had lower serum BDNF levels than healthy subjects (Aydemir et al., 2005; Gonul et al., 2005; Shimizu et al., 2003; Gervasoni et al., 2005; Aydemir et al., 2006; Deveci et al., 2007; Lee et al., 2007). More recently, Sen et al. (2008) conducted a meta-analysis of 11 studies examining serum BDNF levels between depressed and non-depressed patients (366 patients and 382 controls) and showed that BDNF levels were lower in depressed subjects than healthy control subjects. We have a small size healthy controls and there was a difference between patients (42,005± 12,630 pg/ml) and the controls (47,727±7698 pg/ml), but it did not reach statistical significance. More recently Lee et al. (2008) mean plasma BDNF level was lower in the depressive patients (n=42) than in the control subjects (n=50), although the difference was not statistically significant. Similar to our finding, Ziegenhorn et al. (2007) demonstrated in a large population that there were no significant differences of BDNF levels between non-depressed elderly subjects and depressed elderly subjects. In a group of 140 subjects, Lommatzsch et al. (2005) reported that BDNF levels were likely to decrease as the age increases. However, Trajkovska et al. (2007) found no relationship between BDNF levels and age in a study of 206 subjects and they also reported that storage at −20 °C of serum, but not whole blood, was associated with a significant decrease in BDNF concentration. Serum was stored at −20 °C or below in some of the BDNF studies (Gervasoni et al., 2005; Aydemir et al., 2005; Gonul et al., 2005; Lee et al., 2007), and storage conditions were not explained in some others (Huang et al., 2008). Clearly, there is need for data how samples for BDNF should be handled and stored.

In addition, an inspection of BDNF levels in previous studies of patients with depression shows considerable variation among serum levels. BDNF level before antidepressant treatment was reported as 9.5±7.8 ng/ml by Yoshimura et al. (2007), 19.3±8.8 ng/ml by Piccinni et al. (2008) and 27.7±13.7 ng/ml by Aydemir et al. (2006). Same is true for BDNF levels after antidepressant treatment, as mean BDNF level was 34.6±7.1 ng/ml in Aydemir et al. (2007) study, 38.6±15.3 ng/ml in Aydemir et al. (2006) study, 17.7±8.1 ng/ml in Yoshimura et al. (2007) study and 12±8.9 ng/ml in Huang et al. (2008) study. Variation of BDNF levels was also evident in control subjects. For example, mean BDNF level of controls was reported 27.7±11.4 ng/ml by Schimizu et al. (2003) and 41.2±15.1 ng/ml by Aydemir et al. (2007).

Furthermore, there are some concerns about association of BDNF with depressive states. Some studies in rodents suggest that impairment of BDNF and its receptor TrkB does not lead to depression or anxiety like behavior but rather a blunted behavioral response to antidepressants (Saarelainen et al., 2003; Monteggia et al., 2004; Chen et al., 2006). These studies implicate that BDNF/TrkB signaling plays a pivotal role in the action of antidepressants, rather than in the development and expression of depression per se.

Parallel to above findings, we found that serum BDNF levels increased after treatment, but the difference did not reach statistical significance. Increment of BDNF levels in the FLX group was greater than that of the VEN group. Multiple clinical studies showed that antidepressant treatment increased serum BDNF levels (Karege et. al., 2002a,b; Shimizu et al., 2003; Gonul et al., 2005; Aydemir et al., 2005; Aydemir et al., 2006; Huang et al., 2008). Animal studies demonstrate different results upon antidepressants class effects. The selective noradrenergic reuptake inhibitor reboxetine is more potent in up-regulating rat hippocampal BDNF transcription than the selective serotonergic reuptake inhibitor citalopram (Russo-Neustadt et al., 2004). Larsen et al. (2008) reported that venlafaxine and imipramine, but not fluoxetine, induced neuroplastic effects in the hippocampus through stimulation of BDNF mRNA expression, and that the effect on BDNF was not directly translated into regulation of synaptophysin and GAP-43 mRNA in the rat brain. Gonul et al. (2005) could not detect any differences between the serum BDNF levels of patients who received SSRI or venlafaxine. Yoshimura et al. (2007) found that both paroxetine and milnacipran equally increase serum BDNF levels. More recently, Matriscioni et al. (in press) followed-up depressive patients for 6 months and demonstrated that only sertraline increased BDNF levels after 5 weeks. Sertraline and venlafaxine increased BDNF levels after 6 months and escitalopram did not affect BDNF levels any time. But all the drugs showed the same treatment response. In this respect, long term monitorization of the effects of antidepressant medications on serum BDNF levels may provide a better understanding of this relationship.

In this study, we have not detected any differences of BDNF levels between treatment responders and non-responders (p=0.262). Shimizu et al. (2003) have demonstrated that decreased serum BDNF levels in antidepressant-naïve patients recovered to normal levels in association with lower HAM-D scores after treatment with antidepressant medication. Lee et al. (2008) reported that plasma BDNF levels were significantly increased after 6 weeks of treatment in the responder group, while there was no statistically significant change in the non-responders. Yoshimura et al. (2007) also found that only responders to paroxetine or milnacipran had increased serum BDNF levels after 8 weeks of treatment, while non-responders to the drugs showed no altered serum BDNF levels from baseline to 8 weeks after the treatment. More recently, Hellweg et al. (2008) showed that amitriptyline, but not paroxetine, led to an increase in serum concentrations of BDNF independent of clinical response.

Another important finding of this study is about gender issue. We found that baseline serum BDNF level in the male patients was significantly lower than the male controls. In contrast, Karege et al. (2002a) found that female patients were more depressed and had lower serum BDNF levels. Huang et al. (2008) detected lower serum BDNF levels in female patients than female controls but there was no difference between male patients and controls. On the other hand, Shimizu et al. (2003) found no sex differences in the groups they studied. In principle, a number of factors like estrogen may affect the levels of BDNF in female patients (Berchtold et al., 2001). Lommatzsch et al. (2005) reported that women in the second half of the menstrual cycle showed higher platelet levels of BDNF than women in the first half of the menstrual cycle or postmenopausal women. More recently in a study of 28 healthy volunteers, Piccinni et al. (2008) reported that they detected a statistically significant diurnal variation in plasma BDNF level in men, with the peak at 08:00 h and nadir at 22:00 h. At this time, the plasma BDNF concentration of men was significantly lower than that of women (p=0.02). However, they found no diurnal variation either in plasma BDNF of women, in either the follicular or luteal phases of the menstrual cycle, or in serum BDNF level in both men and women. These findings underline the need for more strict control of gender related parameters in studies related with BDNF.

Some limitations must be considered when interpreting results of this study. Firstly, the sample size is relatively small. Secondly, the difference was found in serum and is related to the presence of BDNF in platelet cells and not in brain cells. This raises the possibility that BDNF in platelet cells may not be related to BDNF in brain cells. Moreover, recent results suggest that the correlation between serum BDNF and platelet cell BDNF may vary and a decrease in serum BDNF could be more dependent on a decrease in BDNF excretion from platelet cells than on a decrease in BDNF levels inside platelet cells.

In the future, these preliminary results should be confirmed in larger samples of patients. It would also be interesting to test the modification of BDNF plasma levels in relation to specific antidepressant treatments.

We found that serum BDNF levels were not significantly different between patients with depression and healthy controls; BDNF levels increased with antidepressant treatment, especially with FLX, but not to the degree of statistical significance and male patients had significantly lower baseline BDNF levels than male controls. Several factors including age, sex, body weight, platelet count, menstrual phase and storage conditions may potentially influence BDNF level and such confounding factors may account for some of the conflicting findings reported in the literature. Further studies controlling for these variables are needed, which may help to reach a clear conclusion about the potential of BDNF as a biomarker for depression or as a predictor of antidepressant efficacy.

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