

# Changes of Serum Concentrations of Brain-Derived Neurotrophic Factor (BDNF) during Treatment with Venlafaxine and Mirtazapine: Role of Medication and Response to Treatment

## Authors

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## Key words

- brain-derived neurotrophic factor (BDNF)
- depression
- remission
- antidepressant

## Abstract

**Introduction:** Depression, stress and antidepressant treatment have been found to modulate the expression of brain-derived neurotrophic factor (BDNF). Recent research suggests that serum BDNF concentration is reduced in depression and that antidepressant treatment leads to an increase in serum BDNF concentration.

**Methods:** We studied depressed patients receiving a randomized antidepressant treatment with either mirtazapine (n=29) or venlafaxine (n=27) for 28 days in a prospective design. Changes in the concentrations of serum neurotrophins in response to antidepressant treatment were assessed.

**Results:** There was a significant “treatment” by “medication” interaction effect on BDNF serum concentrations that indicated a decline of BDNF in venlafaxine-treated patients ( $7.82 \pm 3.75 - 7.18 \pm 5.64$  ng/mL), while there was an increase in mirtazapine-treated patients ( $7.64 \pm 6.23 - 8.50 \pm 5.37$  ng/mL). There was a trend for a “treatment” by “remission” interaction with a favourable clinical course being related to increasing serum BDNF.

**Discussion:** Changes in BDNF serum concentrations as a result of antidepressant therapy depend on the antidepressant and potentially on the clinical course.

## Introduction

Next to evidence demonstrating that stress decreases the expression of brain-derived neurotrophic factor (BDNF) leading to structural damage in limbic neurons, the BDNF-stimulating effect of antidepressants contributed to the formulation of the “neurotrophin hypothesis of depression” [1,2].

In rodents, chronic electroconvulsive treatment or antidepressant treatment enhanced the expression of hippocampal BDNF and prevented damaging effects of stress [3,4]. BDNF infusion in the hippocampus produced an antidepressant effect in various behavioral models of depression suggesting BDNF to be involved in the therapeutic action of antidepressants [5]. Most antidepressants, including venlafaxine [6,7] and mirtazapine [8], may increase the hippocampal expression of BDNF, while others did not (fluoxetine [9,10]; tranlycypromine, fluoxetine, desipramine [11]; citalopram [12]; escitalopram [13]).

In line with a recent meta-analysis [14], an epidemiological study (n=962) found serum BDNF to be low in currently depressed subjects and to be normalized in remission, while antidepressants were differentially related to serum BDNF (St. John's wort > SSRI > venlafaxine > TCA > mirtazapine) [15]. Thus, antidepressants may differ in their ability to induce BDNF. A small case series showed sertraline having early, venlafaxine late and some antidepressants, like escitalopram, no effect on serum BDNF [16]. Negative findings with regard to venlafaxine [17] emerged in other studies, while mirtazapine's effects on serum BDNF have never been studied. Most treatment studies did not specifically consider treatment response as a potential factor for BDNF regulation or studied only treatment responders [18–21], while others found increasing serum BDNF in female responders to antidepressant treatment only [22] or no association with treatment response at all [17,23]. Taken together, the effect of antidepressants on serum BDNF is undisputed, while it is unclear whether all classes of antidepressants affect

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BDNF equally and whether the effect is confined to treatment responders. Therefore, we intended (a) to compare serum BDNF between healthy controls and depressed subjects, (b) to study the effect of antidepressant treatment on serum BDNF, (c) to disentangle the effects of venlafaxine vs. mirtazapine and treatment response on serum BDNF and (d) to test whether serum BDNF is related to platelet numbers or volume.

## Material and Methods

### Patients and healthy controls

We included adult inpatients with a major depressive episode diagnosed according DSM-IV and a score of at least 18 points on the Hamilton depression rating scale (HDRS, 21 items). There were 41 female (age:  $53.2 \pm 17.2$  years; body mass index [BMI]:  $26.0 \pm 6.3$  kg/m<sup>2</sup>; HDRS after wash-out:  $23.2 \pm 4.5$ ) and 14 male patients (age:  $49.4 \pm 12.9$  years; BMI:  $25.2 \pm 4.3$  kg/m<sup>2</sup>; HDRS after wash-out:  $22.1 \pm 3.8$ ). Also, we included 14 healthy controls (13 female/1 male; age:  $56.7 \pm 11.6$  years; BMI:  $25.1 \pm 4.8$  kg/m<sup>2</sup>). Healthy controls were recruited by advertisement. Screening procedures included a psychiatric interview, physical examination, laboratory analyses and brain imaging (patients only). Exclusion criteria were a lifetime diagnosis of schizophrenia, schizoaffective disorder or bipolar disorder, substance dependence and pre-treatment with venlafaxine, mirtazapine, fluoxetine or long-acting antipsychotics during the current episode. Also, we excluded subjects with incomplete or haemolytic samples or baseline BDNF serum concentrations above mean plus 5 SDs (1 patient: male, 52 years). Semi-standardized diagnostic interviews revealed no current and lifetime axis I disorder, especially affective disorders, in healthy controls. All subjects provided written informed consent and the study was approved by the local ethics committee.

### Study design

Patients were kept off psychiatric medication for a period of at least 6 days (week -1), after which they received randomized (pre-defined allocation list), although open label treatment with either venlafaxine (final dosage:  $203 \pm 47$  mg) or mirtazapine (final dosage:  $46 \pm 9$  mg) in flexible dosages for 4 weeks. With the exception of lorazepam (33/55 patients; mean total dosage  $5.1 \pm 8.7$  mg) and zolpidem (11/55 patients; mean total dosage  $44.4 \pm 86.4$  mg), no additional psychotropic medication was allowed throughout the study. Compliance during inpatient treatment was assured by ward staff.

Psychopathology was assessed by the treating psychiatrist (MG, BS) once a week by means of the HDRS. Both clinicians were experienced and blind with regard to BDNF measures. However, there was no formal HDRS training. Patients with less than 18 points at the end of the drug-free run-in period or a drop of  $\geq 10$  points during that period (week -1) were excluded from the study as responders during washout. Remission was defined as a final HDRS score of  $\leq 7$  [24].

### Laboratory methods

On the mornings of day -1 and day 28 blood was drawn, centrifuged (800×g for 15 min) and serum samples stored at  $-80^\circ\text{C}$  until BDNF concentrations were determined. BDNF serum concentrations were quantified by a modified ELISA (Promega Co., Madison, WI, USA) as described in detail previously [25,26]. Endogenous BDNF levels were measured in the rethawed serum

samples using commercial ELISA kits according to the manufacturer's instructions (Promega Inc., USA) but adapted to a fluorometric technique. Briefly, microtiter plates (Thermoscientific; microfluor2Black, 96-well, flat-bottom) were coated with 100 µL/well of primary monoclonal anti-BDNF antibody diluted 1:1 000 in carbonate buffer (pH 9.6). After an overnight incubation at  $4^\circ\text{C}$  the plates were washed once with washing buffer (Tris-buffered saline with 0.05% NP-40). As a blocking step, 200 µL of Block & Sample Buffer 1× (Promega) were added into each well and incubated for 1 h in the dark at room temperature. After washing the plates 5 times with washing buffer, 100 µL of the samples (diluted 1:200 in Block & Sample Buffer 1×), recoveries [serum added with a known concentration of hBDNF (Alo-mone Labs)] and standards were added. The samples were measured in triplicate, the standards in duplicate and the recoveries in monuplicate. After an incubation step of 2 h in the dark at room temperature, the plates were washed 5 times with washing buffer. 100 µL of the secondary anti-BDNF polyclonal antibody (Promega) diluted 1:500 in Block & Sample Buffer 1× were added into each well, followed by an incubation step of 2 h in the dark at room temperature. After washing 5 times with washing buffer again, 100 µL of anti-chicken IgY alkaline phosphatase conjugate (Abcam) diluted 1:2 000 in Block & Sample Buffer 1× were added into each well and incubated for 1.5 h in the dark at room temperature. This incubation is followed by washing 5 times with washing buffer and 2 times with substrate buffer (0.1 M sodium phosphate at pH 8.7; 1 mM MgCl<sub>2</sub>). Enzyme reaction was started by adding 50 µL AttoPhos Substrate Set (Roche Diagnostics GmbH) into each well, incubating over night in the dark in a moist chamber at room temperature. The reaction was stopped by adding 200 µL Stop Solution (0.15 M glycine; pH 10.5) into each well. The emission was measured with a fluorescence photometer (excitation wavelength 485 nm, emission wavelength 538 nm). This assay has a detection limit of 0.7 pg/mL serum BDNF, the coefficients of inter- and intra-assay variation are 34.1% and 6.7%, respectively [23]. Since the intra-assay variation is much less than the inter-assay variation, the corresponding pre- and post-treatment samples of patients were always measured in the same BDNF assay.

### Statistics

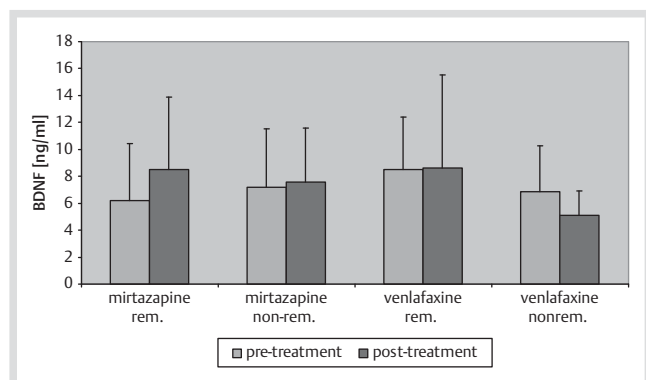
Univariate and analysis of variance with repeated measures (ANOVA-rm) using treatment (pre vs. post), medication (mirtazapine vs. venlafaxine) and outcome (remission vs. nonremission; relative change of HDRS score) as independent variables as well as Pearson's correlations were used as appropriate. Post-hoc tests were performed with a 2-tailed significance value set to 0.05. Data are reported as means  $\pm$  standard deviations.

### Results

Healthy controls and depressed patients did not differ with regard to age (controls vs. patients:  $56.7 \pm 11.6$  vs.  $52.2 \pm 16.2$  years, n.s.) or body mass index (controls vs. patients:  $25.1 \pm 4.8$  vs.  $25.8 \pm 5.8$  kg/m<sup>2</sup>, n.s.). There was a difference in sex distribution (1 m/14 f vs. 13 m/41 f,  $\chi^2=22.0$ ,  $p<0.001$ ; see **Table 1**). Healthy controls and depressed patients did not differ in BDNF serum concentrations ( $6.64 \pm 2.11$  vs.  $7.29 \pm 4.00$  ng/mL, n.s.). Sex and age had no significant effect on BDNF serum concentrations. In depressed patients, severity of depression at baseline as

**Table 1** Clinical characteristics, platelets and serum BDNF in depressed patients being treated with mirtazapine vs. venlafaxine.

	Mirtazapine treatment		Venlafaxine treatment		Unpaired t-test, $\chi^2$ -test, ANOVA repeated measures	
gender (f/m)	22/7		19/8		n.s.	
age (years)	50.5 ± 18.0		54.1 ± 13.8		n.s.	
age of onset	42.0 ± 16.4		42.9 ± 16.9		n.s.	
recurrent/single	18/11		22/5		p < 0.01	
nr. of episodes	3.9 ± 5.9		3.1 ± 2.6		n.s.	
duration episode (weeks)	15 ± 12		18 ± 15		n.s.	
pre-treatment (last 4 weeks)	14 none, 3 SSRI, 3 TCA, 4 other antidepressants, 2 combinations, 1 mood stabilizer, 1 atypical antipsychotic, 1 unclear		12 none, 3 SSRI, 3 TCA, 1 MAOI, 2 other antidepressants, 4 combinations, 1 mood stabilizer+antidepressant, 1 low potent antipsychotic			
	before treatment	after treatment	before treatment	after treatment	effect: "treatment"	interaction effect: "treatment" × "medication"
HDRS rating	22.7 ± 4.2	8.9 ± 6.0	23.0 ± 4.5	7.4 ± 5.3	$F_{1,54} = 42.1$ ; p = 0.001	n.s.
BMI [kg/m <sup>2</sup> ]	25.2 ± 6.2	25.6 ± 6.3	26.4 ± 4.2	26.3 ± 4.3	n.s.	$F_{1,49} = 6.58$ ; p = 0.02
BDNF [ng/mL]	7.64 ± 6.23	8.50 ± 5.37	7.82 ± 3.75	7.18 ± 5.64	n.s.	$F_{1,51} = 5.04$ ; p = 0.029
platelet number [1 000/mL]	275 ± 97	295 ± 115	273 ± 81	284 ± 90	$F_{1,31} = 4.51$ ; p = 0.041	n.s.
platelet volume [fl]	8.34 ± 0.90	8.12 ± 0.76	8.04 ± 0.85	8.10 ± 0.98	n.s.	n.s.

**Fig. 1** Serum BDNF before and after treatment with mirtazapine and venlafaxine.

measured by HDRS was not related to BDNF serum concentrations ( $r = -0.15$ , n.s.).

Before treatment, mirtazapine- and venlafaxine-treated patients did not differ with regard to age ( $50.4 \pm 18.3$  vs.  $54.1 \pm 13.8$  years, n.s.) and body mass index ( $24.4 \pm 5.9$  vs.  $27.2 \pm 5.6$  kg/m<sup>2</sup>,  $p = 0.074$ ). Patients were well-matched according to clinical features, except that in the venlafaxine group less patients had major depression, single episode. After treatment, 11/25 mirtazapine- and 14/24 venlafaxine-treated patients were in remission. The final HDRS score was normally distributed (Kolmogorov-Smirnov) with a mean score of  $8.18 \pm 5.66$  (range 0–22). There was no difference in total usage of lorazepam between the group treated with mirtazapine ( $6.0 \pm 9.1$  mg) and the group treated with venlafaxine ( $5.3 \pm 12.3$  mg).

ANOVA-rm revealed a significant interaction effect of "treatment" × "medication" (Wilk's lambda = 0.910,  $F_{1,51} = 5.04$ ,  $p = 0.029$ ) and a trend effect of borderline significance for a "treatment" × "outcome" interaction (Wilk's lambda = 0.928,  $F_{1,51} = 3.93$ ,  $p = 0.053$ ) on serum BDNF. There was no effect of "treatment" (repeated measures) and no significant "treatment" × "outcome" × "medication" interaction. BDNF serum concentrations increased in patients remitting during treatment with mirtazapine ( $6.21 \pm 4.22$ – $8.50 \pm 5.40$  ng/mL, paired  $T = -2.81$ ,

$p = 0.017$ ), but not venlafaxine ( $8.50 \pm 3.91$ – $8.61 \pm 6.91$  ng/mL, n.s.). In non-remitting patients, there was no change of serum BDNF in mirtazapine-treated patients ( $7.20 \pm 4.33$ – $7.55 \pm 4.05$  ng/mL, n.s.), while BDNF serum concentrations significantly declined in venlafaxine-treated patients ( $6.83 \pm 3.42$ – $5.11 \pm 1.80$  ng/mL, paired  $T = 2.439$ ,  $p = 0.035$ ) (see ◉ Fig. 1). Controlling for age or sex did not change the findings (◉ Fig. 1). Accordingly, the relative change of serum BDNF ( $t_{28} - t_{-1}/t_{-1}$ ) depended on "medication" ( $F_{1,51} = 11.2$ ,  $p < 0.001$ ) and relative change of HDRS rating ( $F_{1,51} = 4.4$ ,  $p = 0.04$ ).

Platelet number at the time of sampling for BDNF (available in 37 patients) slightly increased over time (pre vs. post:  $270.351 \pm 84.280$  vs.  $284.838 \pm 103.523$  n/mL, Wilk's lambda = 0.880,  $F_{1,31} = 4.51$ ,  $p = 0.041$ ), while ANOVA-rm did not reveal significant effects of "treatment" × "medication" or "treatment" × "outcome" interactions (all  $F < 0.6$ , n.s.). Platelet volume (available in 37 patients) did not change during treatment (pre vs. post:  $8.0 \pm 0.86$  vs.  $8.1 \pm 0.89$  fl, n.s.) and there was no effect of "medication" or "outcome" (all  $F < 1.7$ , n.s.). Neither platelet number nor volume at baseline were related to BDNF serum concentrations ( $r = 0.195$ ,  $r = 0.028$ ; both n.s.).

## Discussion



In our study, serum BDNF did not differ between depressed patients and healthy controls and, in contrast to earlier findings [27], within the group of patients serum BDNF was not related to severity of depression. Of course, we cannot exclude that this negative finding is due to the small healthy control sample size, the moderate severity of depression or carry-over effects of antidepressant pre-treatment.

While the small sample size and uneven gender distribution may have not allowed us to adequately assess the effects of diagnosis and gender, the sample size was considered sufficient to analyze treatment effects. During antidepressant treatment, the change of serum BDNF depended on medication (mirtazapine > venlafaxine) and clinical outcome (remission > non-remission). Antidepressants are thought to up-regulate the expression of cerebral BDNF and its receptor trkB [28] and to increase adult

neurogenesis [29,30] which might be at the core of antidepressant activity. Recent studies in animal models of depression demonstrated that antidepressant classes differ in their potential to induce hippocampal BDNF mRNA changes [9–13]. While there is evidence that different classes of antidepressants differentially influence hypothalamus-pituitary-adrenal (HPA) axis parameters in humans [31,32], there is only limited information on changes in BDNF serum concentrations after administration of different antidepressants. Both, cross-sectional epidemiological [15] as well as longitudinal studies support the hypothesis that antidepressants have heterogeneous effects on serum BDNF [16,17,23]. Only few studies considered response to treatment to play a role in antidepressants' effects on serum BDNF. Our data support the notion that both, choice of medication and, with borderline significance, treatment response are relevant for the effects on serum BDNF. Interestingly, the effect of outcome differed between both drugs. We found increasing serum BDNF only in mirtazapine remitters, no change in mirtazapine non-remitters and venlafaxine remitters, but a decline of serum BDNF in venlafaxine non-remitters. To the best of our knowledge, this is the first report of declining serum BDNF during antidepressant treatment with a specific drug. Of course, most of our patients were not drug-naïve. Thus, declining serum BDNF concentrations during unsuccessful treatment with venlafaxine may be due to a weaker effect of venlafaxine on serum BDNF when compared to pre-treatment.

The source and significance of serum BDNF is not fully understood. Serum BDNF may be independent from platelet reactivity [33] and there is evidence that cerebral and peripheral BDNF are related [4,34]. BDNF has been shown to cross the blood-brain barrier by a high-capacity, saturable transport system [35,36]. However, it remains unclear whether serum BDNF reflects or contributes to brain BDNF.

A mirtazapine-mediated increase of BDNF seems feasible as also animal studies suggest an increase of BDNF during chronic mirtazapine treatment, at least in the hippocampus and the prefrontal cortex of rats [8,36].

Differential effects of mirtazapine [37], which decreases platelet activity and venlafaxine [38], which increases platelet activity, might explain our current observation. In this context we might miss the BDNF redistribution between platelets and plasma, which has been described during SSRI treatment [39] as we only studied serum concentrations.

In contrast to most recent studies, we did not find depressed patients and males to have lower BDNF serum concentrations when compared to controls and females [40], respectively. This might be due to small sample size and uneven gender distribution. Apart from the obvious limitation due to the small sample size, our results should be interpreted with caution in view of the short drug-free interval before the start of the study, short duration of the antidepressant trial, the small group of healthy controls as well as the unusually high rate of patients being in remission after inpatient antidepressant treatment. These limitations may limit generalizability of our findings. However, this is the first randomized study comparing the effects of 2 antidepressants on serum BDNF and considering the clinical course as a potential factor. In humans, a polymorphism in the BDNF gene has been associated with depression-related personality traits, i.e., neuroticism [41]. Regrettably, the BDNF genotype was not analyzed, but could have contributed to both the negative finding with regard to diagnosis as well as the treatment effects. A subgroup of patients, but not controls, were given lorazepam

and zolpidem in low dosages. So far, it is assumed that benzodiazepines do not affect BDNF levels [42], except in the case of withdrawal or catatonia.

Taken together, our data give evidence to the assumption that antidepressants may have different effects on serum BDNF. The clinical course should be considered in future studies.

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## Conflict of Interest

Yes: Dr. Deuschle has received speaker fees from Otsuka and Bristol Myers Squibb.

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