Published in final edited form as:
Prog Neuropsychopharmacol Biol Psychiatry. 2011 August 15; 35(7): 1623–1630. doi:10.1016/j.pnpbp.2011.06.013.

Serum BDNF Levels Before Treatment Predict SSRI Response in Depression

Owen M. Wolkowitz, MD[1,3], **Jessica Wolf, MA**[1], **Wendy Shelly, MD**[2], **Rebecca Rosser, BA**[1], **Heather Burke, PhD**[1], **George K. Lerner, MD**[1], **Victor I. Reus, MD**[1], **J. Craig Nelson, MD**[1], **Elissa S. Epel, PhD**[1], and **Synthia H. Mellon, PhD**[2]

[1]Department of Psychiatry, University of California, San Francisco (UCSF) School of Medicine, San Francisco, CA 94143

[2]Department of Obstetrics, Gynecology and Reproductive Sciences, UCSF School of Medicine, San Francisco, CA 94143

Abstract

OBJECTIVES—The "neurotrophin hypothesis" of depression posits a role of brain-derived neurotrophic factor (BDNF) in depression, although it is unknown whether BDNF is more involved in the etiology of depression or in the mechanism of action of antidepressants. . It is also unknown whether pre-treatment serum BDNF levels predict antidepressant response.

METHODS—Thirty un-medicated depressed subjects were treated with escitalopram (N=16) or sertraline (N=14) for eight weeks. Twenty-five of the depressed subjects completed 8 weeks of antidepressant treatment and had analyzable data. Twenty-eight healthy controls were also studied. Serum for BDNF assay was obtained at baseline in all subjects and after 8 weeks of treatment in the depressed subjects. Depression ratings were obtained at baseline and after 8 weeks of treatment in the depressed subjects.

RESULTS—Pre-treatment BDNF levels were lower in the depressed subjects than the controls ($p = 0.001$) but were not significantly correlated with pre-treatment depression severity. Depression ratings improved with SSRI treatment ($p < 0.001$), and BDNF levels increased with treatment ($p = 0.005$). Changes in BDNF levels were not significantly correlated with changes in depression ratings. However, pre-treatment BDNF levels were directly correlated with antidepressant responses ($p<0.01$), and "Responders" to treatment (≥ 50% improvement in depression ratings) had higher pre-treatment BDNF levels than did "Non-responders" ($p < 0.05$).

[3]To Whom Correspondence Should be Sent: 401 Parnassus Avenue, Box F-0984, San Francisco, CA 94143-0984, USA, Tel: 1-(415) 476-7433, FAX: 1-(415) 502-2661, Owen.Wolkowitz@ucsf.edu.

Clinical Trials Registration: *Registry name:* ClinicalTrials.gov. *URL:* http://ClinicalTrials.gov

STATEMENT OF INTEREST

Drs. Mellon and Wolkowitz received an investigator-initiated grant award from Forest Labs, which markets escitalopram. No other authors have financial ties to these or any other pharmaceutical companies. None of the granting agencies had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Ethics Statement:

This work was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the Uniform Requirements for manuscripts submitted to Biomedical Journals.

CONCLUSIONS—These results confirm low serum BDNF levels in unmedicated depressed subjects and confirm antidepressant-induced increases in BDNF levels, but they suggest that antidepressants do not work simply by correcting BDNF insufficiency. Rather, these findings are consistent with a permissive or facilitatory role of BDNF in the mechanism of action of antidepressants.

Keywords

Depression; brain-derived neurotrophic factor (BDNF); neurotrophin; antidepressant; SSRI

1. INTRODUCTION

Brain-derived neurotrophic factor (BDNF) is an important regulatory protein in neurodevelopment, in synaptogenesis and neurogenesis and in protecting the viability of newly differentiated neurons (Duman R. S. and Monteggia 2006); it also has multiple non-CNS effects (Wolkowitz et al. 2011). The “neurotrophin hypothesis of depression” posits that certain central BDNF deficiencies underlie depression, and that antidepressants work via restoration of central BDNF activity (Duman R. S. and Monteggia 2006). Several studies have found that hippocampal and serum BDNF levels are low in un-medicated depressed patients, and that these levels increase with antidepressant treatment (Bocchio-Chiavetto et al., Brunoni et al. 2008, Duman R. S. and Monteggia 2006, Gass and Hellweg 2010, Hashimoto 2010, Sen et al. 2008). The neurotrophin hypothesis is further supported by findings that intra-cerebroventricular and intra-hippocampal injection of BDNF produces antidepressant-like effects in animal models of depression (Hoshaw et al. 2005, Shirayama et al. 2002). Conversely, experimentally lowering brain BDNF (or lowering expression of its high affinity receptor, tyrosine kinase TrkB, in neural progenitor cells in the hippocampus) or inhibiting neurogenesis diminishes antidepressant efficacy in animal models (Adachi et al. 2008, Li et al. 2008, Santarelli et al. 2003). Still other studies suggest that region-specific expression of BDNF results in different behavioral consequences, as expression of BDNF in the meso-accumbens dopamine system is pro-depressive (Govindarajan et al. 2006, Krishnan and Nestler 2008) and local knockdown of BDNF in the ventral tegmental area ameliorates the adverse effects of social defeat (Berton et al. 2006, Krishnan et al. 2007). This raises the possibility that brain region-specific BDNF deficiency (especially in areas of the brain such as the subgranular zone of the dentate gyrus of the hippocampus) may underlie the development of depression in humans, and/or that treatment-associated increases in BDNF are important in the mechanism of action of antidepressants. While intriguing, not all data are consistent with the neurotrophin hypothesis (Castren and Rantamaki 2008, Castren et al. 2007, Groves 2007). BDNF’s role in the etiology of depression may be separate from its role in the mechanism of action of antidepressants (Groves 2007, Martinowich et al. 2007), and evidence is more consistent with BDNF involvement in certain antidepressant actions than in causing depression (Groves 2007, Henn F. A. and Vollmayr 2004a, Henn F.A. and Vollmayr 2004b, Larsen et al. 2010, Li et al. 2008, Sahay and Hen 2007). For example, elimination of hippocampal neurogenesis has no effect on mouse sensitivity to unpredictable chronic mild stress, suggesting that reduced neurogenesis is not a cause of stress-related behavioral deficits (Surget et al. 2008). However, elimination of hippocampal neurogenesis does diminish the antidepressant-like effects of imipramine and fluoxetine, suggesting involvement of BDNF in antidepressant actions (Surget et al. 2008). In another study, heterozygous BDNF knockout mice (+/−), compared to wild-type (+/+) mice, failed to show increased vulnerability to chronic unpredictable mild stress exposure but did show dampened antidepressant effects in several behaviors (Ibarguen-Vargas et al. 2009). In contrast, however, heterozygous BDNF knockout rats did show increased sensitivity to social isolation stress compared to wild-type rats (Duman C. H. et al. 2007), and BDNF knockdown in the dentate gyrus induced

depression-like behaviors in rats (Taliaz et al. 2010). These observations highlight the complexity of BDNF's role in affective regulation, and may suggest that region-specific regulation of BDNF also underlies its behavioral effects. As further evidence of BDNF's role in certain antidepressant actions, BDNF potentiates the effect of paroxetine on hippocampal extracellular serotonin levels in mice, and this effect is blocked by antagonism of BDNF's high affinity TrkB receptor (Deltheil et al. 2008).

In this study, we sought to determine whether serum BDNF levels are low in un-medicated depressed subjects compared to matched healthy controls, whether serum BDNF levels increase in response to antidepressant treatment, and whether baseline serum BDNF levels and treatment-associated changes in serum BDNF levels are related to concurrent depression ratings. These findings would add to an already large body of evidence regarding serum BDNF levels in depression, and our major goal was not to replicate prior findings of diminished BDNF levels in depression and of BDNF increases with treatment, but to determine whether pre-treatment serum levels of BDNF predict antidepressant response. Finding that higher pre-treatment BDNF levels predict better antidepressant response would argue against a BDNF "deficiency-correcting" effect of antidepressants, and would support a permissive or facilitatory role of BDNF in the mechanism of action of antidepressants.

2. METHODS AND MATERIALS

2.1 Subjects

Thirty subjects with unipolar Major Depressive Disorder (MDD) (DSM-IV) (AmericanPsychiatricAssociation 2000), with a minimum score of 17 on the 17-item Hamilton Depression Rating Scale (HDRS-17) (Hamilton 1967), who were medication-free for at least 6 weeks before entry into the study, were enrolled. Depressed subjects were recruited from outpatient psychiatric clinics, physician referral, posted fliers and newspaper and internet advertisements (e.g., craigslist.com). The average baseline HDRS-17 rating was 26.1 ± 8.3. Individuals with co-morbid panic disorder were excluded, since they may poorly tolerate typical starting doses of antidepressants (Louie et al. 1993), and individuals with co-morbid post-traumatic stress disorder were excluded, since they may have neuroendocrine regulatory responses different from those of depressed subjects without PTSD (Yehuda 2006). Other comorbid anxiety diagnoses were allowed if the MDD diagnosis was considered primary. Twenty-eight matched healthy controls with no history of psychiatric illness were also enrolled. Controls were recruited by posted fliers and newspaper and internet advertisements (e.g., craigslist.com). Demographics, including age, BMI, gender distribution and menopausal status, are presented in Table 1. Exclusion criteria for both groups included recent (within 6 months) alcohol or drug abuse as defined by DSM-IV criteria, concurrent psychotherapeutic interventions, poor medical health or abnormal clinical labs, active suicidality, and use of medications that could interfere with the study. All subjects were screened for medical illness by complete medical review of systems, cardiopulmonary and physical examination by a Board-certified physician and laboratory testing (combined blood count [CBC], electrolytes, renal function, hepatic enzymes, thyroid stimulating hormone). At the time of testing, subjects were also required to pass urine toxicology screens (assessing the presence of drugs of abuse), and women of child-bearing capacity were required to test negative for pregnancy.

2.2 Procedure

The study was approved by the UCSF Committee on Human Research, and all participants gave written informed consent. Depressed subjects were studied in two separate studies, one involving the serotonin selective reuptake inhibitor (SSRI), escitalopram, and the other, the SSRI, sertraline. Because the study methodologies were similar, (although see below for

differences in study designs) data were pooled to increase statistical power. Secondary analyses examining the results of each group separately are also presented here. In the escitalopram group, 16 depressed subjects (all male) began treatment with placebo for one week, followed by escitalopram for eight weeks (10 mg per day × 4 weeks, followed by 20 mg per day × 4 weeks, as tolerated) in a single-blind, fixed-order, within-subject cross-over manner. Only two subjects did not tolerate the increase to 20 mg per day and were kept on lower doses. The depressed subjects and the psychiatric rater were unaware of the study design and the sequence and duration of treatments. Subjects and the rater were informed only that the subjects would be receiving escitalopram and placebo at various times during the study. Subjects received a fixed number (two) of identically-appearing medication capsules each day of the study, so they would not know when medication changes or adjustments were being made. A study physician who had no role in the psychiatric ratings was responsible for adjusting escitalopram doses based on study protocol, clinical tolerability and response. Depressed subjects showing a greater than 20% improvement in depression ratings during the placebo week were discontinued from the study. One subject met this criterion, leaving 15 escitalopram-treated depressed subjects for analysis. Each of these completed all eight weeks of active escitalopram treatment. In the sertraline group, 14 depressed subjects (nine female, five male) were treated with sertraline, prescribed in an open-label manner (beginning with 50 mg per day, and the dose was increased to a maximum of 200 mg per day, as tolerated and as warranted by clinical response). In two cases, the beginning dose was initially lowered to 25 mg per day due to initial transient side effects. Two depressed subjects dropped out of the study before completion for non-study-related reasons (one for school/ work commitments and one due to geographical relocation). Twelve depressed subjects completed all 8 weeks of treatment. Serum samples for Week 8 BDNF assays were unavailable for two of these subjects, leaving 10 sertraline-treated depressed subjects with compete sets of data. In all, 27 depressed subjects completed 8 weeks of SSRI treatment and 25 had all blood data available (Table 1). Medication compliance was monitored by pill counts and by plasma antidepressant levels (described below) at Week 8 of treatment for both drugs.

At baseline (pre-treatment for the depressed subjects), all subjects underwent venipuncture to obtain blood for BDNF assays. The controls underwent venipuncture once, and the depressed subjects underwent venipuncture just prior to beginning active antidepressant treatment and again after 8 weeks of antidepressant treatment. In the escitalopram group, the baseline sample for BDNF was drawn after the placebo week but just before the beginning of active drug treatment. Depressed subjects had blood drawn at the same time of day on both occasions (Baseline and Week 8) to facilitate interpretation of within-subject BDNF changes with treatment. In the escitalopram cohort, blood was drawn in the morning (1000 hrs) or afternoon (1400 hrs), and in the sertraline cohort, blood was always drawn at 1000 hrs. The matched control for each depressed subject had blood drawn at the same time of day as the depressed subject to facilitate between-group comparisons.

2.3 Behavioral Ratings

Depression severity was assessed in all depressed subjects at Baseline and at the end of Week 8 of antidepressant treatment with the HDRS-17, which was our principal dependent variable. In the escitalopram group only, general clinical improvement was also assessed with the Clinical Global Impression-Severity (CGI-S) scale (Guy 1976), which was a secondary dependent variable in that group. This latter is a 7-point scale that assesses global severity of illness ranging from “1”= “normal, not at all ill” to “4”= “moderately ill” to “7”= “among the most extremely ill patients.”

2.4 Blood Processing and Assay Methods

Blood for BDNF was collected into serum separator tubes (Vacutainer; BD, Franklin Lakes, NJ). After sitting at room temperature for one hour to allow clotting, followed by one hour at 4° C for platelet activation (Karege et al. 2002), blood was centrifuged at 2000 × g for 20 min, and serum was separated and stored at −80° C until assay. Serum was assayed for BDNF in duplicate, using a commercial BDNF ELISA assay kit (R&D Systems, Minneapolis, MN, USA). Sera were diluted 1:60 with diluent supplied by the kit manufacturer, to obtain BDNF concentrations within the linear range of the standard curve. To evaluate inter-assay variability, an internal control consisting of serum obtained from a single individual, frozen in multiple aliquots, was run on each plate processed. BDNF concentrations of this control sample were measured on several different days and multiple 96-well plates. The R&D Systems Human BDNF Quantikine ELISA Kit was found to have an acceptable 8–14% inter-assay variability of this control sample, when measured on each plate run with human MDD and control subject samples. Intra-assay CV was <10%, or samples were re-assayed. Depressed subjects' baseline and week 8 samples, and samples from their matched controls, were run in the same assay batch. Blood for assay of antidepressant and metabolite levels was collected into EDTA (powder) coated tubes. Plasma citalopram and two metabolites, desmethyl- and didesmethyl-citalopram, were measured using a published liquid chromatographic method (Oyehaug et al. 1982). Plasma sertraline and its metabolite, N-desmethylsertraline, were measured using high-performance liquid chromatography with fluorescence detection, as previously described (Serebruany et al. 2005). Assays were performed by Thomas B. Cooper (Analytical Psychopharmacology Laboratory, Nathan Kline Institute, Orangeburg, NY 10962).

2.5 Statistics

Differences in serum BDNF levels between groups, and changes within subjects, were assessed with independent sample and paired t-tests (or by Mann-Whitney U tests for non-normal distributions), respectively, and correlations between BDNF levels and clinical ratings were assessed with Spearman correlation coefficients. As described above, four subjects had baseline serum BDNF levels but did not have Week 8 levels. This was handled as follows, and depended upon the statistical question being asked in each analysis. To compare baseline serum BDNF levels between depressed individuals and healthy controls, all subjects with baseline data were included (29 depressed and 28 controls). For all analyses that depended upon treatment condition or upon Week 8 biochemical data, only depressed subjects with Week 8 BDNF data were included (25 depressed individuals). Accordingly all within-subject data analyses only included the 25 depressed individuals with both baseline and Week 8 BDNF data. As neither age nor sex was significantly correlated with serum BDNF levels or with HDRS ratings (at baseline or during treatment), analyses were not co-varied for age or sex, although co-varying for these variables did not substantially alter the results. Alpha was set at 0.05 for two-tailed tests.

3. RESULTS

Pre-treatment serum BDNF levels were significantly lower in the 29 depressed subjects who had baseline BDNF values than in the healthy controls (mean ± S.D.= 14.88 ± 5.41 ng/ml vs 20.91 ± 7.07 ng/ml., respectively) ($t= 3.58$, $p= 0.001$; Fig. 1). This difference remained statistically significant when only the 25 depressed subjects who had both baseline and Week 8 BDNF data were included ($t= 3.09$, $p= 0.003$). Baseline BDNF levels were not significantly different in men vs. women ($t= -0.28$, ns). The difference between depressed and control individuals was statistically significant in both females ($t= 2.65$, $p<0.02$) and in males ($t= 2.42$, $p= 0.02$). Mean pre-treatment serum BDNF levels did not differ between the escitalopram- and the sertraline-treated subjects ($t= 0.06$, ns). Also, the mean the serum

BDNF levels did not differ in morning blood samples vs. afternoon blood samples in the escitalopram cohort (t= 0.00, ns). Further, baseline serum BDNF levels (across groups) were not significantly correlated with age (r= −0.05, ns) or body-mass index (r= −0.32, ns).. Baseline serum BDNF levels were not significantly correlated with platelet counts within the depressed sample (r= −0.09, ns) or within the entire group of subjects (r=0.27, ns) but tended to be positively correlated within the control group (r=0.53, p< 0.10). Pre-treatment serum BDNF levels were not significantly correlated with pre-treatment HDRS-17 depression severity ratings (r= 0.21, ns) or with pre-treatment CGI-S ratings (r= 0.04, ns) in the depressed sample.

As expected, HDRS-17 depression ratings significantly improved with antidepressant treatment (Baseline = 26.1 ± 8.3, Week 8 = 13.2 ± 8.9) (t= 6.35, p< 0.001). The escitalopram- and the sertraline-treated subjects had significantly different pre-treatment HDRS-17 ratings (Table 1; t= 5.76, p< 0.001), but treatment-related improvement in depression ratings was statistically significant within each drug treatment group (escitalopram: t= 6.08, p< 0.001; sertraline: t= 4.25, p= 0.02). CGI-S global ratings also significantly improved (Baseline= 3.80 + 0.68, Week 8 = 2.00 ± 1.07) (t= 5.78, p< 0.001). The mean plasma (escitalopram + citalopram) level at Week 8 was 47.5 ± 26.4 ng/ml; range: 4– 94 ng/ml, and the mean plasma (sertraline + N-desmethylsertraline) level at Week 8 was 66.8 + 36.5 ng/ml; range: 10–146 ng/ml. All individuals had plasma concentrations within the range of published steady state concentrations for these drugs at therapeutic doses (Mauri et al. 2002, Rao 2007), indicating good compliance with medication treatment.

Serum BDNF levels significantly increased with treatment (from 15.07 ± 5.41 ng/ml at the pre-treatment point to 18.75 ± 6.97 ng/ml at Week 8; t= 3.12, p= 0.005; Fig. 1). (Note these baseline BDNF values are slightly different than those used to compare MDD subjects with controls at baseline [a between-groups comparison], since the present within-subject analyses only include MDD subjects with BDNF values both at baseline and at Week 8.) This increase was statistically significant within each individual drug treatment group (escitalopram: t= 2.17, p< 0.05; sertraline: t= 2.60, p< 0.05). Escitalopram and sertraline-associated increases in serum BDNF levels did not significantly differ (t= 1.57, ns). By Week 8 of treatment, serum BDNF levels in the depressed subjects were statistically indistinguishable from those in the controls (18.75 ± 6.97 ng/ml, vs 20.91 ± 7.07 ng/ml) (t= 1.13, p= 0.26). Changes in serum BDNF levels from pre-treatment to Week 8 were not significantly correlated with concurrent changes in HDRS-17 depression ratings (rs= 0.36, ns) or in CGI-S ratings (r= 0.30, ns). BDNF data with the two different SSRI's are presented in Table 1.

Although pre-treatment serum BDNF levels were not significantly correlated with pre-treatment HDRS-17 depression ratings or with pre-treatment CGI-S ratings, pre-treatment serum BDNF levels were significantly correlated with improvements in HDRS-17 depression ratings (r= −0.53, p< 0.01; Fig. 2) and CGI-S ratings (r= −0.60, df= 12, p <0.03). Specifically, depressed subjects with relatively higher pre-treatment serum BDNF levels showed larger antidepressant responses (decreases in HDRS ratings) and overall clinical improvement with antidepressant treatment. Further, pre-treatment serum BDNF levels were significantly higher in the "Responders" (improvement in depression ratings of ≥50%) than in the "Non-Responders" (16.88 ± 5.81 ng/ml vs. 12.70 ± 4.50 ng/ml, respectively) (t= 2.11, p< 0.05) (Fig. 3). The pre-treatment serum BDNF level in the "Responders" tended to be lower than that in the controls, but this was not statistically significant ("Responders": 16.88 ± 1.50 vs. Controls: 20.91 ± 1.34; t= 1.89, p= 0.07). The relationship between pre-treatment serum BDNF levels and change in depression ratings remained significant after controlling for time of blood draw (morning vs. afternoon) (r= −0.68, df= 12, p= 0.007). Considering the two treatment groups separately, baseline serum BDNF levels significantly

predicted antidepressant response (change in HDRS-17 ratings) in the escitalopram group ($r = -0.67$, $p < 0.01$) and tended to predict it in the sertraline group ($r = -0.60$, $p = 0.07$) (Fig. 2).

4. DISCUSSION

Many studies have already examined serum BDNF levels in un-medicated depressed subjects, and nearly all have found decreased BDNF levels in un-medicated depressed subjects compared to controls (Bocchio-Chiavetto et al., Brunoni et al. 2008, Groves 2007, Sen et al. 2008). However, low serum BDNF levels are seen in several other conditions and are not specific to major depression (Gass and Hellweg 2010, Ikeda et al. 2008, Joe et al. 2007, Mitoma et al. 2008). Our current findings are in accord with these prior reports in showing low serum BDNF levels in un-medicated MDD subjects. We also found that serum BDNF levels increased over the course of antidepressant treatment, again in accord with most prior studies (Brunoni et al. 2008, Groves 2007, Sen et al. 2008). We did not, however, find that baseline serum BDNF levels were significantly correlated with baseline depression ratings, nor did we find that the change in serum BDNF levels with antidepressant treatment was significantly correlated with the change in depression ratings. These findings are consistent with some studies (Hellweg et al. 2008, Lang et al. 2006, Lee B. H. et al. 2007, Molendijk et al. 2010, Monteleone et al. 2008, Piccinni et al. 2009) but not with others (Gervasoni et al. 2005, Gonul et al. 2005, Huang et al. 2008, Karege et al. 2002, Lee H. Y. and Kim 2008, Matrisciano et al. 2009, Shimizu et al. 2003, Yoshimura et al. 2007).

Increases in hippocampal and serum BDNF levels with antidepressant treatment have been reported in multiple human and preclinical studies (Bocchio-Chiavetto et al., Brunoni et al. 2008, Duman R. S. and Monteggia 2006, Groves 2007, Hashimoto et al. 2004, Sen et al. 2008), yet the mechanistic and therapeutic significance of this is uncertain. Our data, which showed significant increases in serum BDNF levels with antidepressant treatment, but no significant relationship between the changes in serum BDNF levels and changes in depression ratings, suggest that serum BDNF increases *per se* are not necessarily involved in the therapeutic action of these drugs. Our findings do suggest that BDNF activity (as reflected in serum BDNF levels) is involved in major depression, but not in a simple linear manner regarding the severity of depression across patients. Despite considerable evidence supporting the neurotrophin hypothesis of depression, questions remain as to the extent to which BDNF activity is relevant to the pathogenesis of depression, to the mechanism of action of antidepressants, or to both. For example, there is little convincing evidence that inhibition of BDNF signaling leads to depression (Martinowich et al. 2007) (although see (Taliaz et al. 2010)). In contrast, considerable preclinical evidence suggests that BDNF signaling, as well as neurogenesis capacity, are necessary for antidepressant-like effects to occur (Li et al. 2008, Martinowich et al. 2007, Saarelainen et al. 2003, Santarelli et al. 2003). However, this effect may be region-specific (hippocampal), since other pre-clinical animal studies suggest that BDNF knockout in the accumbens is anti-depressive (Berton et al. 2006, Govindarajan et al. 2006, Krishnan and Nestler 2008, Krishnan et al. 2007). Thus, BDNF's role in depression and its role in antidepressant activity may be separable (Martinowich et al. 2007) and region-specific, with greater evidence of a role in antidepressant actions in the hippocampus.. Specifically, BDNF may be a target of antidepressant action or it may facilitate antidepressant action, but it may not be integrally involved in the development or maintenance of depression itself (Martinowich et al. 2007).

The predictive utility of pre-treatment (baseline) serum BDNF levels for subsequent response to antidepressants has rarely been examined. One study found a non-significant trend ($p = 0.10$) toward *lower* pre-treatment serum BDNF levels predicting better response to sertraline (Umene-Nakano et al. 2009). In another study, baseline plasma BDNF levels did

not significantly differentiate responders vs. non-responders to SSRI or SNRI medications (Yoshimura et al. 2009). Reasons for the apparent discrepancies with our findings are not immediately clear. However, other studies, utilizing non-pharmacologic treatments, did find that higher baseline BDNF levels were associated with larger antidepressant responses. In panic disorder patients receiving ten weeks of Cognitive-Behavioral Therapy (CBT), higher pre-treatment serum levels of BDNF predicted better responses to CBT (Kobayashi et al. 2005). Further, depressed patients (who were non-remitters to antidepressants alone) who had relatively higher baseline serum or plasma BDNF levels responded significantly better to ECT (Piccinni et al. 2009) and to exercise (Toups et al. 2011) augmentation of antidepressants. The latter investigators hypothesized that baseline BDNF may function as an "augmentation moderator," and that treatments that raise baseline BDNF levels may improve the efficacy of augmentation strategies.

Our finding that subjects with initially higher serum BDNF levels showed larger antidepressant responses to sertraline or escitalopram after eight weeks of treatment is interesting in light of findings that depression is characterized by low serum BDNF levels. It is possible that subjects with relatively higher pre-treatment serum BDNF levels may be less depressed or may already be nearing an incipient remission, e.g., their BDNF expression is already nearing that of the healthy controls, and this presages earlier clinical improvement. This explanation is not supported by our data, however, since we found no significant relationship between pre-treatment serum BDNF levels and pre-treatment depressive severity. Alternatively, higher pre-treatment serum BDNF levels may indicate more intrinsic "restorative" capacity and a greater ability of ambient BDNF to synergize with the actions of antidepressants to alleviate depression (Mattson M.P. et al. 2004a, Mattson M. P. et al. 2004b). It has been suggested, for example, that adequate BDNF concentrations during antidepressant treatment are essential in mediating the therapeutic effects of antidepressants by augmenting activity-dependent neuronal plasticity, restoring mood-related network functioning, facilitating neural adaptations to the environment (Castren and Rantamaki 2010, Kozisek et al. 2008) and increasing antidepressant effects on hippocampal serotonin levels (Deltheil et al. 2008). Also, relatively higher brain BDNF activity may provide greater neurotrophic support for those neurons being acted upon by antidepressants (D'Sa and Duman 2002, Groves 2007, Hashimoto et al. 2004, Mattson M. P. et al. 2004b), especially serotonin neurons (Mamounas et al. 1995, Mamounas et al. 2000, Mattson M. P. et al. 2004b, Siuciak et al. 1996). Lastly, BDNF exerts other effects in an animal model of spinal cord injury (Joosten and Houweling 2004). It is possible that such effects of BDNF could synergize with certain of antidepressants (Wolkowitz et al. 2011). Regardless of the explanation, our finding that relatively higher pre-treatment serum BDNF levels predict enhanced response to SSRI antidepressants suggests that these antidepressants do not work simply by correcting baseline states of BDNF insufficiency.

Strengths of the present study include a minimum 6-week medication-free period before baseline, an 8-week period of antidepressant treatment verified by plasma antidepressant assays, the use of matched healthy control subjects and the use of an in-house verified BDNF assay kit. Limitations include the use of a relatively small sample, the use of only two single time-point blood samples to characterize BDNF levels and the assessment of antidepressant response only at Week 8. It is possible that earlier or later assessments of antidepressant response could show different relationships with serum BDNF levels. Also, we studied only two SSRI antidepressant drugs, and some studies have noted different BDNF responses to different classes of antidepressants and even to different antidepressants within the same class (Hellweg et al. 2008, Larsen et al. 2008, Matrisciano et al. 2009, Molendijk et al. 2010) as well as differences in brain regions acted upon (Balu et al. 2008). The present study was not powered to detect differences between escitalopram and sertraline, although our findings with the two drugs were generally similar. Another

limitation is the lack of a double-blind design. It is unlikely, but possible, that non-specific "placebo effects" yielded the observed BDNF-clinical outcome correlations. For example, it is conceivable that individuals with higher pre-treatment serum BDNF levels are more likely to be "placebo responders." Also, there are several non-specific confounds that may affect serum BDNF levels, such as non-fasting status, later measurement, longer sample storage, binge drinking, smoking, exercise, urbanicity and menstrual phase (The latter has been found to affect plasma BDNF levels but has not yet [to our knowledge] been studied in serum) (Bus et al. 2011, Lommatzsch et al. 2005, Seifert et al., Zoladz et al. 2008). In our study, females were studied in follicular as well as luteal menstrual phases, and the sample sizes were to small to evaluate the effect of menstrual phase on our findings. In our study, non-fasting status, time of blood draw and smoking history did not affect BDNF levels. Binge drinking was associated with higher BDNF levels in our sample (in contrast to Bus et al., who found binge drinking to be associated with lower BDNF levels (Bus et al. 2011)), but the rate of binge drinking in our study was nearly identical in the depressed and control groups ($p= 0.80$), and individuals with recent diagnoses of alcohol abuse were excluded from participation. Although some studies have noted increased BDNF levels following chronic exercise training in humans (Seifert et al. 2010, Zoladz et al. 2008), we noted no significant relationship between self-reported exercise levels and serum BDNF levels in our sample. We also observed no significant relationship between current tobacco consumption and serum BDNF levels. Finally, the relationship between serum BDNF levels and BDNF levels in the brain is unknown, and nothing in our data directly addresses the relationship between brain BDNF levels and clinical response. Whereas the origin of serum BDNF remains uncertain, it likely derives from platelet stores and vascular endothelial cells as well as from the brain (Guo et al. 2008, Karege et al. 2005, Pandey et al., Serra-Millas et al.). Nonetheless, BDNF appears to cross the blood-brain barrier (Gass and Hellweg 2010, Klein et al., Sartorius et al. 2009), and serum BDNF levels in healthy volunteers are positively correlated with anterior cingulate cortex concentrations of N-acetylaspartate (NAA), a marker of neuronal integrity (Lang et al. 2007). Further, even peripherally administered BDNF diminishes depressive and anxiety-like behaviors and increases hippocampal neurogenesis in mice, suggesting that serum BDNF concentrations are functionally significant for brain function (Schmidt and Duman 2010)..

5. Conclusion

The present findings, especially the novel finding that pre-treatment serum BDNF levels predict antidepressant response, require replication. If confirmed, these findings raise the possibility that serum BDNF is a peripheral marker for antidepressant mechanisms of action. In turn, these findings may lead to better predictive tests and a better understanding of both the biology of depression and the factors conducive to better antidepressant response.

Acknowledgments

The authors gratefully acknowledge the assistance of Steven Hamilton, MD, PhD, who assisted in evaluating the depressed subjects, of Alanie Lazaro and Genevieve Manalo, who assisted in study procedures, laboratory collections and assays, Thomas B. Cooper of the Analytical Psychopharmacology Laboratory at the Nathan Kline Institute (Orangeburg, NY) for assaying plasma antidepressant concentrations, and the nursing and other staff of the UCSF CTSI's Clinical Research Center. This study was funded by a grant from NIMH (1 R01 MH083784), the O'Shaughnessy Foundation and grants from the UCSF Academic Senate and the UCSF Research Evaluation and Allocation Committee (REAC). This project was also supported by NIH/ NCRR UCSF-CTSI Grant Number UL1 RR024131. The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. This study was also partially supported by Forest Labs (which provided partial funding and escitalopram and matching placebo capsules, but which had no role in study design, implementation, analysis or reporting) and Pfizer Pharmaceuticals (which provided sertraline tablets, but which provided no funding and which had no role in study design, implementation, analysis or reporting).

LIST OF ABBREVIATIONS USED

BDNF	Brain-Derived Neurotrophic Factor
BMI	Body Mass Index
CGI	Clinical Global Impression
DSM	Diagnostic and Statistical Manual
EDTA	Ethylenediaminetetraacetic Acid
ELISA	Enzyme-Linked Immunosorbent Assay
HDRS	Hamilton Depression Rating Scale
MDD	Major Depressive Disorder
PTSD	Post-Traumatic Stress Disorder
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
SSRI	Serotonin Selective Reuptake Inhibitor
UCSF	University of California, San Francisco

References

Adachi M, Barrot M, Autry AE, Theobald D, Monteggia LM. Selective loss of brain-derived neurotrophic factor in the dentate gyrus attenuates antidepressant efficacy. Biol Psychiatry. 2008; 63:642–649. [PubMed: 17981266]

AmericanPsychiatricAssociation. Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR. 4. Washington, DC: American Psychiatric Association; 2000. (Text Revision)

Balu DT, Hoshaw BA, Malberg JE, Rosenzweig-Lipson S, Schechter LE, Lucki I. Differential regulation of central BDNF protein levels by antidepressant and non-antidepressant drug treatments. Brain Res. 2008; 1211:37–43. [PubMed: 18433734]

Berton O, et al. Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress. Science. 2006; 311:864–868. [PubMed: 16469931]

Bocchio-Chiavetto L, et al. Serum and plasma BDNF levels in major depression: a replication study and meta-analyses. World J Biol Psychiatry. 11:763–773. [PubMed: 20334574]

Brunoni AR, Lopes M, Fregni F. A systematic review and meta-analysis of clinical studies on major depression and BDNF levels: implications for the role of neuroplasticity in depression. Int J Neuropsychopharmacol. 2008; 11:1169–1180. [PubMed: 18752720]

Bus BA, Molendijk ML, Penninx BJ, Buitelaar JK, Kenis G, Prickaerts J, Elzinga BM, Voshaar RC. Determinants of serum brain-derived neurotrophic factor. Psychoneuroendocrinology. 2011; 36:228–239. [PubMed: 20702043]

Castren E, Rantamaki T. Neurotrophins in depression and antidepressant effects. Novartis Found Symp. 2008; 289:43–52. discussion 53–49, 87–93. [PubMed: 18497094]

Castren E, Rantamaki T. Role of brain-derived neurotrophic factor in the aetiology of depression: implications for pharmacological treatment. CNS Drugs. 2010; 24:1–7. [PubMed: 20030415]

Castren E, Voikar V, Rantamaki T. Role of neurotrophic factors in depression. Curr Opin Pharmacol. 2007; 7:18–21. [PubMed: 17049922]

D'Sa C, Duman RS. Antidepressants and neuroplasticity. Bipolar Disord. 2002; 4:183–194. [PubMed: 12180273]

Deltheil T, Guiard BP, Cerdan J, David DJ, Tanaka KF, Reperant C, Guilloux JP, Coudore F, Hen R, Gardier AM. Behavioral and serotonergic consequences of decreasing or increasing hippocampus brain-derived neurotrophic factor protein levels in mice. Neuropharmacology. 2008; 55:1006–1014. [PubMed: 18761360]

Duman CH, Schlesinger L, Kodama M, Russell DS, Duman RS. A role for MAP kinase signaling in behavioral models of depression and antidepressant treatment. Biol Psychiatry. 2007; 61:661–670. [PubMed: 16945347]

Duman RS, Monteggia LM. A neurotrophic model for stress-related mood disorders. Biol Psychiatry. 2006; 59:1116–1127. [PubMed: 16631126]

Gass P, Hellweg R. Peripheral brain-derived neurotrophic factor (BDNF) as a biomarker for affective disorders? Int J Neuropsychopharmacol. 2010; 13:1–4. [PubMed: 19995480]

Gervasoni N, Aubry JM, Bondolfi G, Osiek C, Schwald M, Bertschy G, Karege F. Partial normalization of serum brain-derived neurotrophic factor in remitted patients after a major depressive episode. Neuropsychobiology. 2005; 51:234–238. [PubMed: 15897674]

Gonul AS, Akdeniz F, Taneli F, Donat O, Eker C, Vahip S. Effect of treatment on serum brain-derived neurotrophic factor levels in depressed patients. Eur Arch Psychiatry Clin Neurosci. 2005; 255:381–386. Epub 2005 Apr 2006. [PubMed: 15809771]

Govindarajan A, Rao BS, Nair D, Trinh M, Mawjee N, Tonegawa S, Chattarji S. Transgenic brain-derived neurotrophic factor expression causes both anxiogenic and antidepressant effects. Proc Natl Acad Sci U S A. 2006; 103:13208–13213. [PubMed: 16924103]

Groves JO. Is it time to reassess the BDNF hypothesis of depression? Mol Psychiatry. 2007; 12:1079–1088. [PubMed: 17700574]

Guo S, Kim WJ, Lok J, Lee SR, Besancon E, Luo BH, Stins MF, Wang X, Dedhar S, Lo EH. Neuroprotection via matrix-trophic coupling between cerebral endothelial cells and neurons. Proc Natl Acad Sci U S A. 2008; 105:7582–7587. [PubMed: 18495934]

Guy, W. Clinical Global Impression (CGI). ECDEU Assessment Manual for Psychopharmacology. Guy, W., editor. Rockville, MD: U.S. Department of Health, Education and Welfare; 1976.

Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol. 1967; 6:278–296. [PubMed: 6080235]

Hashimoto K. Brain-derived neurotrophic factor as a biomarker for mood disorders: an historical overview and future directions. Psychiatry Clin Neurosci. 2010; 64:341–357. [PubMed: 20653908]

Hashimoto K, Shimizu E, Iyo M. Critical role of brain-derived neurotrophic factor in mood disorders. Brain Res Brain Res Rev. 2004; 45:104–114. [PubMed: 15145621]

Hellweg R, Ziegenhorn A, Heuser I, Deuschle M. Serum concentrations of nerve growth factor and brain-derived neurotrophic factor in depressed patients before and after antidepressant treatment. Pharmacopsychiatry. 2008; 41:66–71. [PubMed: 18311687]

Henn FA, Vollmayr B. Basic pathophysiological mechanisms in depression: what are they and how might they affect the course of the illness? Pharmacopsychiatry. 2004a; 37(Suppl 2):S152–156. [PubMed: 15546068]

Henn FA, Vollmayr B. Neurogenesis and depression: etiology or epiphenomenon? Biol Psychiatry. 2004b; 56:146–150. [PubMed: 15271582]

Hoshaw BA, Malberg JE, Lucki I. Central administration of IGF-I and BDNF leads to long-lasting antidepressant-like effects. Brain Res. 2005; 1037:204–208. [PubMed: 15777771]

Huang TL, Lee CT, Liu YL. Serum brain-derived neurotrophic factor levels in patients with major depression: effects of antidepressants. J Psychiatr Res. 2008; 42:521–525. [PubMed: 17585940]

Ibarguen-Vargas Y, Surget A, Vourc'h P, Leman S, Andres CR, Gardier AM, Belzung C. Deficit in BDNF does not increase vulnerability to stress but dampens antidepressant-like effects in the unpredictable chronic mild stress. Behav Brain Res. 2009; 202:245–251. [PubMed: 19463708]

Ikeda Y, Yahata N, Ito I, Nagano M, Toyota T, Yoshikawa T, Okubo Y, Suzuki H. Low serum levels of brain-derived neurotrophic factor and epidermal growth factor in patients with chronic schizophrenia. Schizophr Res. 2008; 101:58–66. [PubMed: 18289832]

Joe KH, Kim YK, Kim TS, Roh SW, Choi SW, Kim YB, Lee HJ, Kim DJ. Decreased plasma brain-derived neurotrophic factor levels in patients with alcohol dependence. Alcohol Clin Exp Res. 2007; 31:1833–1838. [PubMed: 17850220]

Joosten EA, Houweling DA. Local acute application of BDNF in the lesioned spinal cord anti-inflammatory and anti-oxidant effects. Neuroreport. 2004; 15:1163–1166. [PubMed: 15129166]

Karege F, Perret G, Bondolfi G, Schwald M, Bertschy G, Aubry J-M. Decreased brain-derived neurotrophic factor levels in major depressed patients. Psychiatry Res. 2002; 109:143–148. [PubMed: 11927139]

Karege F, Bondolfi G, Gervasoni N, Schwald M, Aubry JM, Bertschy G. Low brain-derived neurotrophic factor (BDNF) levels in serum of depressed patients probably results from lowered platelet BDNF release unrelated to platelet reactivity. Biol Psychiatry. 2005; 57:1068–1072. [PubMed: 15860348]

Klein AB, Williamson R, Santini MA, Clemmensen C, Ettrup A, Rios M, Knudsen GM, Aznar S. Blood BDNF concentrations reflect brain-tissue BDNF levels across species. Int J Neuropsychopharmacol. 14:347–353. [PubMed: 20604989]

Kobayashi K, et al. Serum brain-derived neurotrophic factor (BDNF) levels in patients with panic disorder: as a biological predictor of response to group cognitive behavioral therapy. Prog Neuropsychopharmacol Biol Psychiatry. 2005; 29:658–663. [PubMed: 15905010]

Kozisek ME, Middlemas D, Bylund DB. Brain-derived neurotrophic factor and its receptor tropomyosin-related kinase B in the mechanism of action of antidepressant therapies. Pharmacol Ther. 2008; 117:30–51. [PubMed: 17949819]

Krishnan V, Nestler EJ. The molecular neurobiology of depression. Nature. 2008; 455:894–902. [PubMed: 18923511]

Krishnan V, et al. Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions. Cell. 2007; 131:391–404. [PubMed: 17956738]

Lang UE, Bajbouj M, Gallinat J, Hellweg R. Brain-derived neurotrophic factor serum concentrations in depressive patients during vagus nerve stimulation and repetitive transcranial magnetic stimulation. Psychopharmacology (Berl). 2006; 187:56–59. [PubMed: 16767416]

Lang UE, Hellweg R, Seifert F, Schubert F, Gallinat J. Correlation between serum brain-derived neurotrophic factor level and an in vivo marker of cortical integrity. Biol Psychiatry. 2007; 62:530–535. [PubMed: 17560556]

Larsen MH, Hay-Schmidt A, Ronn LC, Mikkelsen JD. Temporal expression of brain-derived neurotrophic factor (BDNF) mRNA in the rat hippocampus after treatment with selective and mixed monoaminergic antidepressants. Eur J Pharmacol. 2008; 578:114–122. [PubMed: 17950272]

Larsen MH, Mikkelsen JD, Hay-Schmidt A, Sandi C. Regulation of brain-derived neurotrophic factor (BDNF) in the chronic unpredictable stress rat model and the effects of chronic antidepressant treatment. J Psychiatr Res. 2010; 44:808–816. [PubMed: 20172535]

Lee BH, Kim H, Park SH, Kim YK. Decreased plasma BDNF level in depressive patients. J Affect Disord. 2007; 101:239–244. [PubMed: 17173978]

Lee HY, Kim YK. Plasma brain-derived neurotrophic factor as a peripheral marker for the action mechanism of antidepressants. Neuropsychobiology. 2008; 57:194–199. [PubMed: 18679038]

Li Y, Luikart BW, Birnbaum S, Chen J, Kwon CH, Kernie SG, Bassel-Duby R, Parada LF. TrkB regulates hippocampal neurogenesis and governs sensitivity to antidepressive treatment. Neuron. 2008; 59:399–412. [PubMed: 18701066]

Lommatzsch M, Zingler D, Schuhbaeck K, Schloetcke K, Zingler C, Schuff-Werner P, Virchow JC. The impact of age, weight and gender on BDNF levels in human platelets and plasma. Neurobiol Aging. 2005; 26:115–123. [PubMed: 15585351]

Louie AK, Lewis TB, Lannon RA. Use of low-dose fluoxetine in major depression and panic disorder. J Clin Psychiatry. 1993; 54:435–438. [PubMed: 8270588]

Mamounas LA, Blue ME, Siuciak JA, Altar CA. Brain-derived neurotrophic factor promotes the survival and sprouting of serotonergic axons in rat brain. J Neurosci. 1995; 15:7929–7939. [PubMed: 8613731]

Mamounas LA, Altar CA, Blue ME, Kaplan DR, Tessarollo L, Lyons WE. BDNF promotes the regenerative sprouting, but not survival, of injured serotonergic axons in the adult rat brain. J Neurosci. 2000; 20:771–782. [PubMed: 10632606]

Martinowich K, Manji H, Lu B. New insights into BDNF function in depression and anxiety. Nat Neurosci. 2007; 10:1089–1093. [PubMed: 17726474]

Matrisciano F, et al. Changes in BDNF serum levels in patients with major depression disorder (MDD) after 6 months treatment with sertraline, escitalopram, or venlafaxine. J Psychiatr Res. 2009; 43:247–254. [PubMed: 18511076]

Mattson MP, Maudsley S, Martin B. A neural signaling triumvirate that influences ageing and age-related disease: insulin/IGF-1, BDNF and serotonin. Ageing Res Rev. 2004a; 3:445–464. [PubMed: 15541711]

Mattson MP, Maudsley S, Martin B. BDNF and 5-HT: a dynamic duo in age-related neuronal plasticity and neurodegenerative disorders. Trends Neurosci. 2004b; 27:589–594. [PubMed: 15374669]

Mauri MC, Laini V, Cerveri G, Scalvini ME, Volonteri LS, Regispani F, Malvini L, Manfre S, Boscati L, Panza G. Clinical outcome and tolerability of sertraline in major depression: a study with plasma levels. Prog Neuropsychopharmacol Biol Psychiatry. 2002; 26:597–601. [PubMed: 11999914]

Mitoma M, Yoshimura R, Sugita A, Umene W, Hori H, Nakano H, Ueda N, Nakamura J. Stress at work alters serum brain-derived neurotrophic factor (BDNF) levels and plasma 3-methoxy-4-hydroxyphenylglycol (MHPG) levels in healthy volunteers: BDNF and MHPG as possible biological markers of mental stress? Prog Neuropsychopharmacol Biol Psychiatry. 2008; 32:679–685. [PubMed: 18160197]

Molendijk ML, Bus BA, Spinhoven P, Penninx BW, Kenis G, Prickaerts J, Voshaar RO, Elzinga BM. Serum levels of brain-derived neurotrophic factor in major depressive disorder: state-trait issues, clinical features and pharmacological treatment. Mol Psychiatry. 2010 epub ahead of print: 21 September 2010.

Monteleone P, Serritella C, Martiadis V, Maj M. Decreased levels of serum brain-derived neurotrophic factor in both depressed and euthymic patients with unipolar depression and in euthymic patients with bipolar I and II disorders. Bipolar Disord. 2008; 10:95–100. [PubMed: 18199246]

Oyehaug E, Ostensen ET, Salvesen B. Determination of the antidepressant agent citalopram and metabolites in plasma by liquid chromatography with fluorescence detection. J Chromatogr. 1982; 227:129–135. [PubMed: 6948816]

Pandey GN, Dwivedi Y, Rizavi HS, Ren X, Zhang H, Pavuluri MN. Brain-derived neurotrophic factor gene and protein expression in pediatric and adult depressed subjects. Prog Neuropsychopharmacol Biol Psychiatry. 34:645–651. [PubMed: 20227453]

Piccinni A, et al. Plasma Brain-Derived Neurotrophic Factor in treatment-resistant depressed patients receiving electroconvulsive therapy. Eur Neuropsychopharmacol. 2009; 19:349–355. [PubMed: 19223156]

Rao N. The clinical pharmacokinetics of escitalopram. Clin Pharmacokinet. 2007; 46:281–290. [PubMed: 17375980]

Saarelainen T, et al. Activation of the TrkB neurotrophin receptor is induced by antidepressant drugs and is required for antidepressant-induced behavioral effects. J Neurosci. 2003; 23:349–357. [PubMed: 12514234]

Sahay A, Hen R. Adult hippocampal neurogenesis in depression. Nat Neurosci. 2007; 10:1110–1115. [PubMed: 17726477]

Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S. Requirement of hippocampal neurogenisis for the behavioral effects of antidepressants. Science. 2003; 301:805–809. [PubMed: 12907793]

Sartorius A, Hellweg R, Litzke J, Vogt M, Dormann C, Vollmayr B, Danker-Hopfe H, Gass P. Correlations and discrepancies between serum and brain tissue levels of neurotrophins after electroconvulsive treatment in rats. Pharmacopsychiatry. 2009; 42:270–276. [PubMed: 19924587]

Schmidt HD, Duman RS. Peripheral BDNF produces antidepressant-like effects in cellular and behavioral models. Neuropsychopharmacology. 2010; 35:2378–2391. [PubMed: 20686454]

Seifert T, et al. Endurance training enhances BDNF release from the human brain. Am J Physiol Regul Integr Comp Physiol. 2010; 298:R372–377. [PubMed: 19923361]

Sen S, Duman R, Sanacora G. Serum brain-derived neurotrophic factor, depression, and antidepressant medications: meta-analyses and implications. Biol Psychiatry. 2008; 64:527–532. [PubMed: 18571629]

Serebruany VL, Suckow RF, Cooper TB, O'Connor CM, Malinin AI, Krishnan KR, van Zyl LT, Lekht V, Glassman AH. Relationship between release of platelet/endothelial biomarkers and plasma levels of sertraline and N-desmethylsertraline in acute coronary syndrome patients receiving SSRI treatment for depression. Am J Psychiatry. 2005; 162:1165–1170. [PubMed: 15932816]

Serra-Millas M, Lopez-Vilchez I, Navarro V, Galan AM, Escolar G, Penades R, Catalan R, Fananas L, Arias B, Gasto C. Changes in plasma and platelet BDNF levels induced by S-citalopram in major depression. Psychopharmacology (Berl).

Shimizu E, et al. Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. Biol Psychiatry. 2003; 54:70–75. [PubMed: 12842310]

Shirayama Y, Chen AC, Nakagawa S, Russell DS, Duman RS. Brain-derived neurotrophic factor produces antidepressant effects in behavioral models of depression. J Neurosci. 2002; 22:3251–3261. [PubMed: 11943826]

Siuciak JA, Lewis DR, Wiegand SJ, Lindsay RM. Antidepressant-like effect of brain-derived neurotrophic factor. Pharmacol Biochem Behav. 1996; 56:131–137. [PubMed: 8981620]

Surget A, Saxe M, Leman S, Ibarguen-Vargas Y, Chalon S, Griebel G, Hen R, Belzung C. Drug-dependent requirement of hippocampal neurogenesis in a model of depression and of antidepressant reversal. Biol Psychiatry. 2008; 64:293–301. [PubMed: 18406399]

Taliaz D, Stall N, Dar DE, Zangen A. Knockdown of brain-derived neurotrophic factor in specific brain sites precipitates behaviors associated with depression and reduces neurogenesis. Mol Psychiatry. 2010; 15:80–92. [PubMed: 19621014]

Toups MS, Greer TL, Kurian BT, Grannemann BD, Carmody TJ, Huebinger R, Rethorst C, Trivedi MH. Effects of serum Brain Derived Neurotrophic Factor on exercise augmentation treatment of depression. J Psychiatr Res. 2011 in press.

Umene-Nakano W, Yoshimura R, Ueda N, Suzuki A, Ikenouchi-Sugita A, Hori H, Otani K, Nakamura J. Predictive factors for responding to sertraline treatment: views from plasma catecholamine metabolites and serotonin transporter polymorphism. J Psychopharmacol. 2009; 24:1764–1771. [PubMed: 19825907]

Wolkowitz OM, Reus VI, Mellon SH. Of sound mind and body: depression, disease, and accelerated aging. Dialogues Clin Neurosci. 2011; 13:25–39. [PubMed: 21485744]

Yehuda R. Advances in understanding neuroendocrine alterations in PTSD and their therapeutic implications. Ann N Y Acad Sci. 2006; 1071:137–166. [PubMed: 16891568]

Yoshimura R, Hori H, Ikenouchi-Sugita A, Umene-Nakano W, Ueda N, Nakamura J. Higher plasma interleukin-6 (IL-6) level is associated with SSRI- or SNRI-refractory depression. Prog Neuropsychopharmacol Biol Psychiatry. 2009; 33:722–726. [PubMed: 19332097]

Yoshimura R, Mitoma M, Sugita A, Hori H, Okamoto T, Umene W, Ueda N, Nakamura J. Effects of paroxetine or milnacipran on serum brain-derived neurotrophic factor in depressed patients. Prog Neuropsychopharmacol Biol Psychiatry. 2007; 31:1034–1037. [PubMed: 17459550]

Zoladz JA, Pilc A, Majerczak J, Grandys M, Zapart-Bukowska J, Duda K. Endurance training increases plasma brain-derived neurotrophic factor concentration in young healthy men. J Physiol Pharmacol. 2008; 59(Suppl 7):119–132. [PubMed: 19258661]

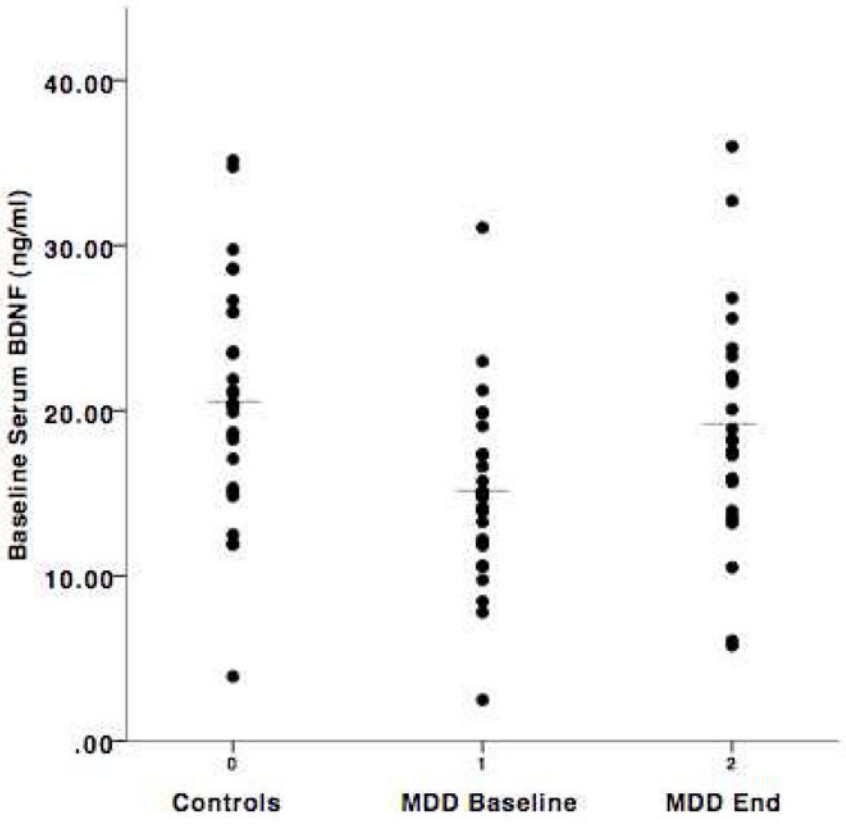

Figure 1.
Baseline serum BDNF levels in un-medicated depressed subjects ("MDD-Baseline"), depressed subjects after 8 weeks of SSRI treatment ("MDD-Treated") and healthy controls ("Controls"). Univariate ANOVA: F= 6.08, p= 0.004. Horizontal lines represent group means.

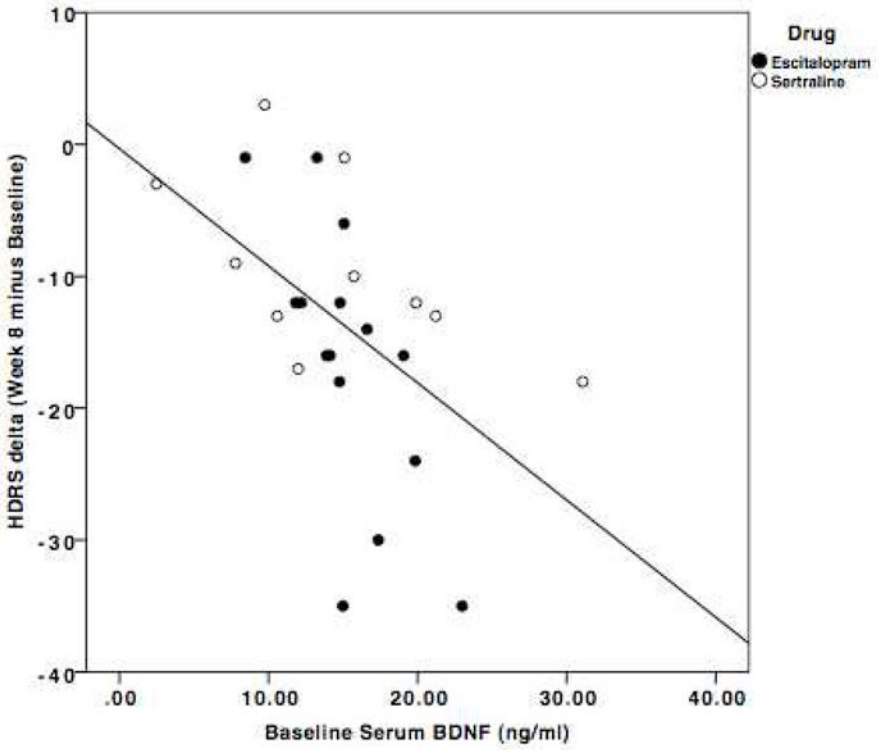

Figure 2.

Correlation between baseline serum BDNF levels and change in Hamilton Depression Rating Scale (HDRS-17) ratings, where "HDRS delta" = Week 8 rating minus baseline rating. ($r = -0.53$, $p < 0.01$). Black circles represent escitalopram-treated subjects ($r = -0.67$, $p < 0.01$), and open circles represent sertraline-treated subjects ($r = -0.60$, $p = 0.07$).

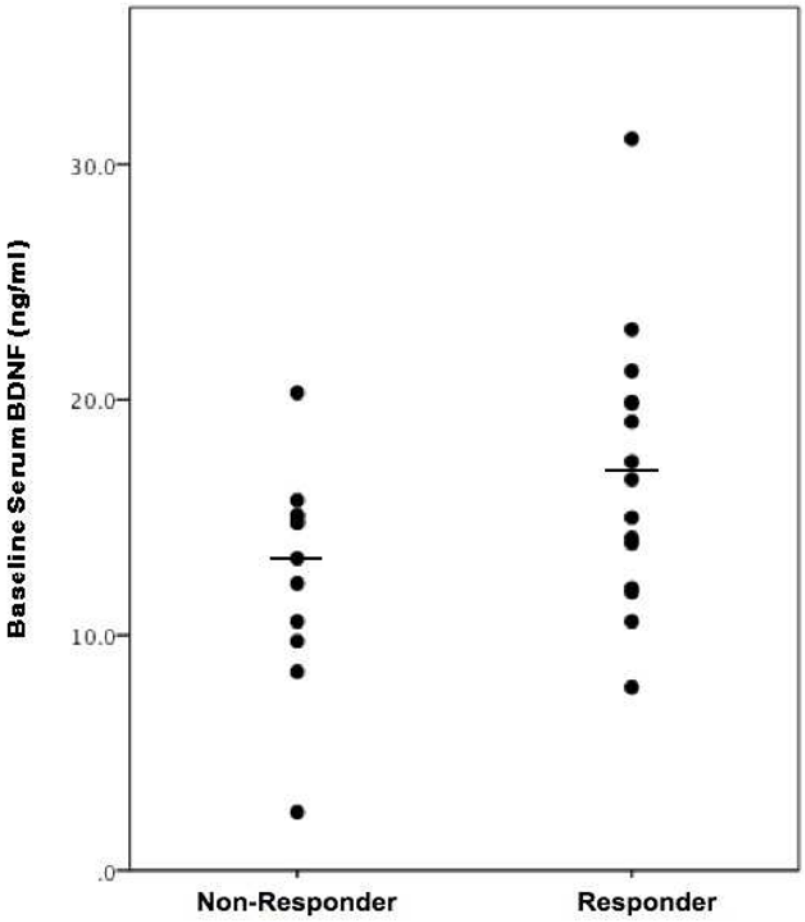

Figure 3.
Baseline serum BDNF levels in "Responders" vs. "Non-responders" to antidepressant treatment, where "response" is defined as a ≥ 50% decrease in HDRS-17 depression ratings from Baseline to Week 8. Horizontal lines represent group means. ($t = 2.11$, $p < 0.05$).

Prog Neuropsychopharmacol Biol Psychiatry. Author manuscript; available in PMC 2012 August 15.

Table 1

	All Subjects Combined			Escitalopram Group			Sertraline Group		
	Controls	**MDD-Baseline**[3]	**MDD-Treated (Week 8)**[4]	**Controls**	**MDD-Baseline**	**MDD-Treated (Week 8)**	**Controls**	**MDD-Baseline**	**MDD-Treated (Week 8)**
N	28	29	27[5]	15	15	15	13	14	12[8]
Age	39.0 ± 10.3	39.1 ± 10.0	39.0 ± 10.1	41.4 ± 8.8	41.4 ± 8.6	41.4 ± 8.8	36.6 ± 11.8	36.8 ± 10.5	36.7 ± 10.2
Sex (%F)	36%	36%	32%	0%	0%	0%	64%	64%	
Menopausal (Pre, Peri or Post) (%)[6]	69%, 30%	69%, 30%	67%, 33%	--	--	--	69%, 30%	69%, 30%	67%, 33%
BMI[7]	24.8 ± 3.7	26.6 ± 5.9	26.9 ± 6.2	N/A	N/A	N/A	24.8 ± 3.7	26.6 ± 5.9	26.9 ± 6.2
HDRS-17	--	26.1 ± 8.3	13.2 ± 8.9***	--	31.2 ± 7.9	14.5 ± 11.2***	--	19.2 ± 4.0	9.7 ± 4.9**
Serum BDNF (ng/ml)	20.91 ± 7.07***	14.88 ± 5.41	18.75 ± 6.97**	20.63 ± 4.81**	15.28 ± 3.55	17.46 ± 3.96*	21.24 ± 9.23*	14.43 ± 7.12	20.77 ± 10.15*

[3] "MDD- Baseline" excludes the one early placebo responder who was excluded from analysis

[4] "MDD- Treated" comparisons between baseline and Week 8 include data only from those subjects who completed 8 weeks of treatment and had all data available.

[5] Twenty-five of the 27 combined subjects had Week 8 BDNF data available.

[6] Based on sertraline group data only.

[7] Based on sertraline group data only. BMI data not available for the escitalopram group.

[8] Ten of the 12 MDD subjects treated with sertraline had Week 8 BDNF data available.

* Different from "MDD-Baseline": p< 0.05

** Different from "MDD-Baseline": p< 0.01

*** Different from "MDD-Baseline": p<0.001