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Comparison of efficacy, safety and brain derived neurotrophic factor (BDNF) levels in patients of major depressive disorder, treated with fluoxetine and desvenlafaxine

R. Ghosh [a], R. Gupta [a,*], M.S. Bhatia [b], A.K. Tripathi [c], L.K. Gupta [d]

[a] Department of Pharmacology, University College of Medical Sciences & Guru Teg Bahadur Hospital, New Delhi 110095, India
[b] Department of Psychiatry, University College of Medical Sciences & Guru Teg Bahadur Hospital, New Delhi 110095, India
[c] Department of Biochemistry, University College of Medical Sciences & Guru Teg Bahadur Hospital, New Delhi 110095, India
[d] Department of Pharmacology, Lady Hardinge Medical College & Smt. S.K. Hospital, New Delhi, India

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ABSTRACT

This randomized, open label, prospective, observational study compared clinical efficacy, safety alongwith plasma BDNF levels in outpatients of depression treated with fluoxetine and desvenlafaxine. Patients (aged 18–60 years) with moderate to severe major depressive disorder (MDD) diagnosed by DSM-IV criteria, and Hamilton Rating Scale for Depression (HAM-D) score ≥14, who were prescribed fluoxetine or desvenlafaxine were included ($n = 30$ in each group). Patients were followed up for 12 weeks for evaluation of clinical efficacy, safety along with BDNF levels. In the fluoxetine group, HAM-D scores at the start of treatment was 19 ± 4.09 which significantly ($p < 0.05$) reduced to 9.24 ± 3.98 at 12 weeks. In the desvenlafaxine group, HAM-D scores at the start of treatment was 18 ± 3.75 which significantly ($p < 0.05$) reduced to 10 ± 3.75 at 12 weeks. The BDNF levels in the fluoxetine group were 775.32 ± 30.38 pg/ml at the start of treatment which significantly ($p < 0.05$) increased to 850.3 ± 24.92 pg/ml at 12 weeks. The BDNF levels in the desvenlafaxine group were 760.5 ± 28.53 pg/ml at the start of treatment which significantly ($p < 0.05$) increased to 845.8 ± 32.82 pg/ml at 12 weeks. Both the antidepressants were found to be safe and well tolerated. The efficacy and the safety profile of desvenlafaxine is comparable to fluoxetine in patients of MDD. BDNF levels were significantly increased post-treatment with both the antidepressive agents. Whether BDNF may have a prognostic value in predicting treatment response to antidepressant drugs needs to be investigated in a larger patient population.

1. Introduction

Major depressive disorder (MDD) is a prevalent, chronic illness and one of the leading causes of disability worldwide (Schatzberg, 2007).

Over the past years, increasing evidence has implicated the role of neurotrophic factors in the pathophysiology of depression (Duman et al., 1997), among which brain derived neurotrophic factor (BDNF) has been most extensively studied. BDNF is a member of the neurotrophin family involved in proliferation, differentiation, survival and death of neuronal and non-neuronal cells in the developing and adult central nervous system (Lewin and Barde, 1996). 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). Various studies have reported that serum/plasma BDNF levels in depressed patients are lower than healthy controls reflecting a failure of neuronal plasticity in depression (Karege et al., 2005).

Increases in hippocampal and serum BDNF levels with antidepressant treatment have been reported in multiple human and preclinical studies (Bocchio-Chiavetto et al., 2010; Brunoni et al., 2008; Duman and Monteggia, 2006; Groves, 2007; Hashimoto et al., 2004; Nibuya et al., 1995; Sen et al., 2008), yet the mechanistic and therapeutic significance of this is uncertain. However, inconsistent results with the neurotropin hypothesis have also been reported. Some studies did not detect alterations in BDNF levels in depressed persons or in the course of treatment with antidepressant drugs (Basterzi et al., 2009; Matrisciano et al.,

* Corresponding author. Tel.: +91 11 22582972-74; fax: +91 11 22590495.
E-mail address: drrachna1@rediffmail.com (R. Gupta).

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2009; Ziegenhorn et al., 2007); and others did not find any significant relationship between the changes in serum BDNF levels and changes in depression rating (Wolkowitz et al., 2011). A recent study showed that baseline levels of BDNF did not significantly predict response to antidepressant drug treatment at week 12 (Ninan et al., 2014).

Furthermore, emergence of many newer antidepressants makes it difficult to select an optimum therapy. Recent studies suggest that the treatment of MDD with newer antidepressant drugs i.e. selective norepinephrine reuptake inhibitors (SNRIs) that simultaneously enhance norepinephrine and serotonin neurotransmission, might result in higher response and remission rates than the selective serotonin reuptake inhibitors (SSRIs) (Papakostas et al., 2007). Desvenlafaxine (administered as desvenlafaxine succinate), the major active metabolite of venlafaxine, is a novel SNRI approved for the treatment of MDD (DeMartinis et al., 2007; Septien-Velez et al., 2007).

Amongst SSRIs, fluoxetine has been the most commonly prescribed drug on account of well established efficacy and patient acceptability. However, data comparing the clinical efficacies of fluoxetine and desvenlafaxine with BDNF levels is lacking. Therefore, this study was carried out to compare and correlate the clinical efficacy, safety profiles and plasma BDNF levels in patients of MDD treated with fluoxetine and desvenlafaxine.

2. Material and methods

This was a randomized, open label, prospective, observational study. The patients aged 18–60 years, of either sex attending psychiatry outpatient department (OPD) of Guru Teg Bahadur (GTB) Hospital, New Delhi, with a diagnosis of moderate to severe MDD by DSM-IV criteria (American Psychiatric Association, 2000), single or recurrent episode, aged 18–60 years and complying with Hamilton Rating Scale for Depression (HAM-D) score $\geq$14, were included in the study. The exclusion criteria for the patients were acute suicidal risk, lifetime DSM-IV diagnosis of dementia, schizophrenia, bipolar disorder, post traumatic stress disorder, obsessive compulsive disorder, patient on any antidepressant for the last 3 months, substance dependence, depression due to organic brain disease, pregnant & lactating women and any significant medical illness epilepsy, diabetes mellitus, chronic kidney disease, chronic liver disease, hypothyroidism.

Patients were randomly allocated to fluoxetine and desvenlafaxine treatment (n = 30 in each group). Fluoxetine and desvenlafaxine were prescribed in the doses of 20 mg and 50 mg respectively, orally once daily. If the improvement in the follow-up assessments was not adequate according to the psychiatrist's judgment, the dose of either drug could be raised. In both the groups safety was evaluated by changes in vital signs and adverse events reported by the patient and/or observed by the psychiatrist.

The study protocol was approved by the Institutional Ethical Clearance Committee (human research) of University College of Medical Sciences and written informed consent was obtained from all patients.

2.1. Clinical evaluation

The Hamilton's 21 item depression rating scale (HAM-D) was used to clinically evaluate depression (Hamilton, 1960). The evaluations consisted of patient characteristics and their medical and psychiatric history for the purpose of establishing DSM-IV criteria diagnosis All patients of each drug group were evaluated (HAM-D criteria) on day 1 and henceforth on 6th and 12th week after the start of drug treatment. HAM-D score of $\leq$7 or >50% reduction in the score in the patients was considered as positive response to the drug and hence was the criteria for responders.

2.2. Blood sample collection

Blood samples (4 ml) from the patients were drawn from their antecubital veins in the morning following overnight fast, and collected in 5 ml EDTA containing tubes.The samples were centrifuged at 2000 rpm for 10 min at 4 °C to separate plasma. The contents were put into microtubes/aliquots and stored at −80 °C until analysis. Blood samples were drawn twice from each patient, one on the initial day and other after the completion of study (at 12th week) for BDNF assay.

2.3. BDNF analysis

Plasma BDNF levels was evaluated by using human BDNF ELISA kit (Weldon biotech-Cat No:EIA-5106®). The immunoplate in the kit was precoated with Anti-Human BDNF Capture Antibody and the nonspecific binding sites were blocked. Human BDNF standard, positive control and plasma samples were added 100 μl/well in the 96-well plate and incubated at room temperature (20–23 °C) for 2 h. Then the immunoplate was washed 4 times with 350 μl/well assay buffer. After washing procedure, the biotinylated anti-human BDNF Detection Antibody (100 μl/well) which would bind to the Human BDNF trapped in the wells was added and then the immunoplate was incubated for 2 h. After washing, the Streptavidin-Horseradish Peroxidase (SA-HRP) (100 μl/well) which catalyzes the substrate solution (TMB) was added. After incubation for 30 min and washing 4 times, 100 μl/well of substrate solution was added. After further incubation for 20–30 min, the enzyme-substrate reaction was terminated by the addition of a stop solution (2 N HCl). The optical density of the color reaction in the wells was read using a micro-plate reader set (Biotek Synergy H4 Hybrid Microplate Reader®) for 450 nm. The intensity of the color was directly proportional to the amount of Human IFGBP-1 in the standard solutions or samples. A standard curve of Human BDNF with known concentration was established accordingly. The Human BDNF with unknown concentration in samples was determined by extrapolation to this standard curve. All assays were performed in duplicate using the manufacturer's recommended buffers, diluents, and substrates.

3. Statistical analysis

A compromise power analysis performed (using GPOWER version 2.0) keeping an equal sample size of 30 in the two groups, an effect size of 1 and β/α ratio equal to 2, returned an alpha value of 0.0278 and power 0.9443, which was acceptable. Results are presented as mean ± standard deviation (mean ± SD). Baseline HAM-D scores and BDNF levels in the treatment groups were compared using Mann–Whitney test and independent samples t-test, respectively. The primary efficacy endpoint i.e. the change from baseline in HAM-D score at week 12 was analyzed using ANCOVA taking gender, baseline BDNF level, BDNF level at week 12 and HAM-D score at the start of treatment as covariates. Paired 't' test was used to compare pre and post treatment BDNF values. $p < 0.05$ is considered as significant. The analysis was carried out using SPSS 14.0 software package.

4. Results

Our study enrolled 60 patients in two groups who were given fluoxetine and desvenlafaxine and followed up for 12 weeks. Demographic data of the patients is shown in Table 1. There were no statistical differences in the treatment groups with respect to baseline HAM-D scores and BDNF levels.

In flouxetine group, there were 19 subjects with moderate depression (HAM-D score 15–20) and 11 with severe depression