RESEARCH PAPER

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Effect of milnacipran on brain-derived neurotrophic factor and oxidative stress biomarkers in patients of major depressive disorder

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Emerging hypotheses in the pathophysiology of major depressive disorder (MDD) suggest important role of neurotrophic factors and oxidative stress. This study assessed the effect of milnacipran (a dual serotonin-noradrenaline reuptake inhibitor) on brain-derived neurotrophic factor (BDNF) and oxidative stress biomarkers i.e., malondialdehyde (MDA), glutathione-S-transferase (GST) and glutathione reductase (GR) in patients of MDD. Thirty patients (aged 18 to 60 years) with MDD diagnosed by DSM-IV criteria, with Hamilton Depression Rating scale (HAM-D) score ≥ 14 were included in the study. Patients were given milnacipran in the doses of 50-100 mg once daily. Patients were followed up for 12 weeks. HAM-D score at the start of treatment was 17.8±1.7 which significantly reduced to 8.9±3.1 at 12 weeks of treatment. In responders, the plasma BDNF levels increased significantly at 12 weeks post treatment. There was no significant change in the pre- and post-treatment values of oxidative stress parameters (MDA, GST and GR) after 12 week treatment. Milnacipran is effective and well tolerated in MDD patients, and its therapeutic response is associated with an increase in plasma BDNF levels. However, milnacipran did not affect oxidative stress biomarkers.

Key words: BDNF, milnacipran, depression, oxidative stress

INTRODUCTION

Pharmacotherapy with antidepressant drugs (ADD) has been an integral part of management of major depressive disorder (MDD). ADD include tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs) and serotonin norepinephrine reuptake inhibitors (SNRIs).

Despite the availability of a number of drugs, the management of MDD remains a challenge as many patients achieve only partial remission. Further, due to excessive non-specificity in the clinical symptoms of MDD and the inability to measure the true drug response, the need for a biomarker has been on. The identification of a biomarker could lead to the development of effective personalized antidepressant treatment in MDD (Polyakova et al., 2015). Convincing evidence has implicated the importance of neurotrophic factors in the pathophysiology of depression, among which brain derived neurotrophic factor (BDNF) has been most extensively studied (Duman et al., 1997; Hoshaw et al., 2005). BDNF is involved in proliferation, differentiation, survival of neuronal and non-neuronal cells in the CNS (Hashimoto et al., 2004).

Animal and human studies have shown that depression is associated with decreased BDNF levels and loss of neurotrophic support causes atrophic structural changes in the hippocampus and anterior cingulate

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(Castrén et al., 2010; Sen et al., 2008). ADD have shown to increase BDNF levels and may be associated with an increase in hippocampus volume in some patients (Gervasoni et al., 2005; Gonul et al., 2005; Hellweg et al., 2008; Gupta et al., 2017) whereas some studies have failed to do so (Basterzi et al., 2009). These studies suggest that antidepressants may differ in their ability to induce BDNF, which could also be related to time-course of treatment.

In addition, multiple lines of evidence suggest derangement of oxidant and antioxidant defense systems in depression followed by oxidative stress (Gałecki et al., 2009; Liu et al., 2015). Oxidative stress develops from an imbalance between reactive oxygen species (ROS), and reduced antioxidant defenses, favoring more production of ROS (Halliwell, 2007). Oxidative stress leads to the damage of several biomolecules (e.g., lipid membrane, proteins and DNA). The brain appears to be more susceptible to the ROS on account of the high content of unsaturated fatty acids, more oxygen consumption per unit weight, high amount of key ingredients of lipid peroxidation (LP) and fewer antioxidant defense systems (Finkel and Holbrook, 2000). Clinical studies have demonstrated that patients with MDD have lower serum/plasma total antioxidant potentials (Cumurcu et al., 2009) and reduced brain GSH levels as compared to healthy controls (Gawryluk et al., 2011). Preclinical and clinical studies have reported the antioxidant effect of antidepressant drugs (Abdel-Wahab et al., 2011; Bilici et al., 2011). However, results of the studies showing the effect of antidepressant drugs on oxidative stress markers are insufficient and inconclusive. Also, potential of SNRIs has not been much explored in this regard.

Milnacipran is a dual SNRI, which enhances noradrenergic and serotonergic neurotransmission in the central nervous system (Nakagawa et al., 2009). Randomized clinical trials have reported that milnacipran has an antidepressant efficacy similar to other antidepressants, such as TCAs and SSRIs (Guelfi et al., 1998; Van Amerongen et al., 2002; Sechter et al., 2004). Bioavailability of milnacipran is about 85-90% following oral administration, maximum concentrations are reached within 2-4 hours after oral dosing, half-life is approximately 6-8 hours and steady-state levels are achieved by 36-48 hours (Puozzo et al., 2002). The mean volume of distribution of milnacipran following a single intravenous dose to healthy subjects is approximately 400 L; it is eliminated primarily by renal excretion (Li et al., 2012). Our study has evaluated the clinical efficacy of milnacipran, a SNRI, in patients of MDD and its effect on plasma levels of BDNF and oxidative stress parameters [MDA, glutathione-S-transferase (GST), glutathione reductase (GR)] after 12 weeks of treatment.

METHODS

The patients of either sex attending psychiatry outpatient department of Guru Teg Bahadur Hospital, New Delhi, with a diagnosis of MDD by DSM-IV criteria (American Psychiatric Association; 2000), single or recurrent episode, aged 18-60 years, and complying with Hamilton 21 item Rating Scale for Depression (HAM-D) score ≥ 14, were included. The exclusion criteria were acute suicidal risk, lifetime DSM-IV diagnosis of dementia, schizophrenia, bipolar disorder, post-traumatic stress disorder, obsessive compulsive disorder, use of any antidepressant during the last 3 months, substance dependence, depression due to organic brain disease, pregnant and lactating women and any significant medical illness.

Thirty patients receiving milnacipran in (50 mg/day) were selected. If the improvement in the follow-up assessments was not adequate according to the psychiatrist's judgment, the dose of milnacipran was raised to 100 mg/day. Safety was evaluated by changes in vital signs and adverse events reported by the patient 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.

Outcome measures: HAM-D was used to clinically evaluate depression (Hamilton, 1960). The evaluations consisted of patient characteristics and their medical and psychiatric history. All patients were evaluated (HAM-D criteria) on day 1 and on 6^{th} and 12^{th} week after the start of milnacipran. HAM-D score of ≤7 or >50% reduction in the score was considered as positive response and hence was the criteria for responders. Significant changes in plasma BDNF, MDA, GST and GR levels after treatment were also used as outcome measures.

Blood sample collection: Blood sample from each patient was taken between 10 am-12 pm every time and collected in a 5 ml EDTA containing tube on the initial day (before treatment), at 6 weeks and 12 weeks after treatment. The samples were centrifuged at 2000 revolutions/min for 10 min at 4°C to separate plasma. The contents were put into microtubes/aliquots and stored at -80°C until analysis.

BDNF analysis

Plasma BDNF level was evaluated by using human BDNF ELISA kit (Weldon biotech-Cat No: EIA-5106®) twice in the study, before treatment and after completing 12 weeks of treatment. Assay was performed as per manufacturer's recommendations.

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. A standard curve of human BDNF with known concentration was made. The human BDNF with unknown concentration in samples was determined by extrapolation to this standard curve.

Analysis of oxidative stress parameters: MDA, GST and GR

The above parameters were evaluated thrice during the study, before and after 6 and 12 weeks of treatment by using standard spectrophotometric methods. Malondialdehyde (MDA)-Lipid peroxidation product-was analyzed by thiobarbituric acid method (Girotti et al., 1991). Plasma levels of lipid peroxides were determined as thiobarbituric acid reactive substances (TBARS) and calculated as MDA. The absorbance was measured at 532 nm spectrophotometrically and the concentrations expressed as nmol MDA/mL.

Glutathione-S-transferase (GST) was analyzed by complexing it with 1-chloro-2,4-di-nitro benzene (CDNB) (Habig et al., 1974). The reaction mixture consisted of 1.425 ml of phosphate buffer (0.1 M, pH 6.5), 0.2 ml reduced glutathione (1 mM), 0.025 ml CDNB (1 mM), and 0.3 ml PMS (10% w/v) in a total volume of 2 ml. The change in absorbance was recorded at 340 nm. GST values were expressed as n moles CDNB conjugate formed/min/ml.

Glutathione reductase (GR): GR activity was assayed using reagents phosphate buffer (0.067 M) pH 6.6,1% sodium bicarbonate, 0.006 M NADPH in 1% sodium bicarbonate and 7.5×10^{-3} M oxidized glutathione (GSSG) (Brunoni et al., 2008). GR catalyzes the reduction of GSSG in the presence of NADPH, which is oxidized to $NADP^+$. The change in absorbance was measured at 340 nm and the activity of GR is expressed in nmol/min/ml.

Statistical analysis

Results are presented as box plots – median and first and third quartiles of distribution are used in constructing the boxes. Unpaired and paired 't' test was used to compare data of responders and non-responders and pre- and post-treatment BDNF. Repeated measure analysis of variance (ANOVA) followed by Dunnett's test was used to compare oxidative parameters. $P<0.05$ was considered as significant. The analysis was carried out using SPSS 14.0 software package.

RESULTS

Our study included 30 patients who were given milnacipran and were followed up for 12 weeks. The age of patients was 29.6±9.36 years, male:female ratio was 1:1, 53.3% of patients were married and 86.7% of patients were educated (>7th class). Milnacipran was started at a dose of 50 mg twice daily but was increased to 100 mg twice daily in 18 out of 30 patients. HAM-D scores at the start of treatment was 17.8±1.7 which significantly reduced to 13.7±2.4 at 6 weeks post-treatment ($P<0.05$) and reduced further to 8.9±3.1 at 12 weeks post-treatment ($P<0.05$). There was a reduction in the HAM-D scores at week 6 and week 12 compared to the baseline score in 24 out of 30 patients. Thus, 80% patients showed a positive response (responders) to milnacipran.

''Responders'' to treatment had higher pre-treatment BDNF levels than did ''nonresponders''. Further, in responders, the plasma BDNF levels increased significantly ($P<0.05$) from 762.3±14.6 pg/ml to 857.0±16.3 pg/ml at 12 weeks post treatment (Fig. 1).

There was no significant change in pre- and post-treatment values of oxidative stress parameters after 12-week treatment (Table 1).

In our study the most common adverse effects of milnacipran were dry mouth (63%), anorexia (60%), headache (60%), sweating (57%), constipation (53%), nausea (47%), dizziness (47%) and in male patients, dysuria (67%). Others were insomnia (30%), somnolence (43%), agitation (40%), anxiety (43%) and tachycardia (30%). None of the patients discontinued the treatment on account of adverse events.

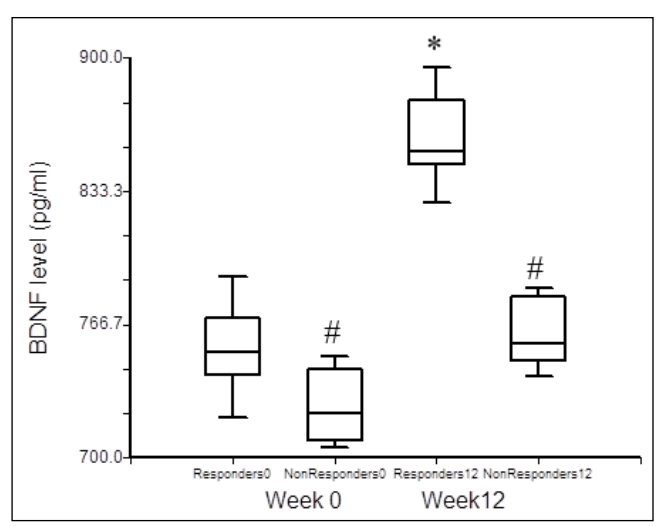

Fig. 1. Serum BDNF levels at 0 and 12 weeks following milnacipran treatment in patients with major depressive disorder (n=30) in responders (n=24) and non-responders (n=6). Values compared using Student's *t* test; *: P<0.05 significant in comparison to before treatment; #: P<0.05 significant in comparison to responders at week 12.

Table 1. Effect of milnacipran treatment on oxidative stress parameters – malonaldehyde (MDA), glutathione-S-transferase (GST) and glutathione reductase (GR) in patients with major depressive disorder (n=30).

	Biochemical parameters in nmol/min/ml (mean±sd)		
No. of weeks	MDA	GST	GR
0	1.75±0.42	1.302±0.26	1.04±0.28
6	1.63±0.38	1.296±0.34	1.02±0.36
12	1.58±0.36	1.187±0.38	0.98±0.32

DISCUSSION

Evidence has suggested prime roles of neurotropic factors and oxidative stress in pathophysiology of MDD. Many clinical studies have evaluated the changes of plasma or serum BDNF levels before and after antidepressant treatments among MDD patients and found inconsistent results. Studies have shown that SSRI and SNRI treatments, for eight weeks or more increased serum BDNF levels in MDD patients (Aydemir et al., 2005; Gervasoni et al., 2005). However, another study reported that SSRI agents but not SNRIs increased serum BDNF levels after six months of treatment (Gonul et al., 2005).

In our study, milnacipran caused significant reduction in HAM-D scores at 6 and 12 weeks post treatment. This is in line with one study which compared milnacipran with placebo and found milnacipran to be efficacious in reducing HAM-D scores significantly (Rouillon et al., 2000).

Our study found significant increase in plasma BDNF levels after 12 weeks treatment with milnacipran, in responders. Our results are in agreement with previous studies. One preclinical study has shown that milnacipran (10 mg/kg, 14 days) increased the levels of BDNF protein and mRNA in the cerebral cortex of mice (Ikenouchi-Sugita et al., 2009). Also, a study done in animals found correlation between cortical and serum BDNF, across species (Klein et al., 2011). Another study found that serum BDNF levels were significantly increased after 8 weeks treatment with paroxetine (n=21) or milnacipran (n=21) in responders (Yoshimura et al., 2007). Other SNRIs such as venlafaxine have also shown increase in BDNF levels in depressed patients (Aydemir et al., 2005). In another study, SSRI (fluoxetine) and SNRI (desvenlafaxine) treatment for 12 weeks resulted in increased plasma BDNF levels in MDD patients (Ghosh et al., 2015).

Next finding of our study is that oxidative stress parameters (MDA, GST, GR) levels did not change significantly after 12 weeks of milnacipran treatment. Very few studies have been conducted with newer antidepressant classes to elucidate their potential against oxidative stress. Moreover, results are contradictory. One study evaluated the effects of long-term antidepressant treatment on oxidative/antioxidant parameters in 50 MDD subjects. MDD patients were administered venlafaxine (125±43.3 mg/day, n=21), milnacipran (100 mg/day, n=2), paroxetine (25±7.6mg/day, n=8), escitalopram (16.3±5.2 mg/day, n=8), sertraline (80±27.4 mg/day, n=5), citalopram (33.3±11.5 mg/day, n=3), fluoxetine (20 mg/day, n=1), tianeptine 37.5 mg/day and moclobemide 600 mg/day for 24 weeks. These drugs decreased MDA levels after 24-weeks of treatment. Plasma MDA was increased in MDD patients before treatment, and positively correlated with the severity of MDD (Kotan et al., 2011). Similarly another study reported increased oxidative stress in major depressive patients (n=32), indexed by higher antioxidant enzyme activities [erythrocyte superoxide dismutase (SOD), glutathione peroxidase and plasma GR] and MDA levels (erythrocyte and plasma) (Bilici et al., 2001). After treatment with four different SSRI drugs (fluoxetine 20 mg/day, n=7; sertraline 50 mg/day, n=13; fluvoxamine 100 mg/day, n=5; or citalopram 20 mg/day, n=5), for 12 weeks, antioxidant enzyme activities (plasma glutathione peroxidase) and MDA levels (plasma and erythrocyte) were restored to control levels. Plasma GR and erythrocyte SOD were also significantly decreased in MDD patients after 12-week antidepressant treatment. In contrast, a study showed that although MDD was accompanied by increased peripheral oxidative stress, however, short-term antidepressant treatment with venlafaxine (SNRI) 75-150 mg/day, sertraline (SSRI) 50 mg/day, or reboxetine 4–8 mg/day for 6 weeks did not alter oxidative stress parameters (MDA) in MDD patients (n=96) (Sarandol et al., 2007). Similarly, another study also showed that MDD is accompanied by disturbances in the balance between pro- and anti-oxidative processes; however, these disturbances did not improve in patients in remission after three months of fluoxetine therapy (Gałecki et al., 2009).

Therefore, it seems that change in oxidative parameters might depend upon various factors including class of antidepressant drug, duration of therapy and the type of oxidative parameters studied. Our study has some limitations such as small sample size, open label design and absence of any control or placebo/comparative group.

To sum up, the results of our study suggest that milnacipran is effective and well tolerated in patients of MDD and, its therapeutic efficacy is accompanied by increased plasma BDNF levels. Therefore, it seems that clinical effect of milnacipran could be on account of

its potential to increase BDNF levels in addition to enhancing effect on serotonergic and noradrenergic neurotransmission. However, milnacipran therapy had no effect on oxidative stress biomarkers (MDA, GST, GR).

Further controlled comparative studies with larger number of patients investigating the role of BDNF and oxidative stress biomarkers in MDD may lead to an improved understanding of the multifactorial pathophysiology of depression and predict response to antidepressant drug treatment.

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