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Brief report

A randomized double-blind comparison of fluoxetine augmentation by high and low dosage folic acid in patients with depressive episodes

Ramakrishnan Venkatasubramanian, Channaveerachari Naveen Kumar*, Ravi Shankar Pandey

National Institute of Mental Health and Neurosciences, Bangalore, Karnataka, India

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ABSTRACT

Background: Though encouraging evidence exists for the use of folic acid as an augmenting agent to antidepressants, evidence regarding its optimal dosage is lacking.
Methods: Forty-two female out-patients with moderate (with or without somatic syndrome) or severe depressive episodes (without psychotic symptoms) diagnosed as per ICD-10 criteria, were randomized in a double-blind fashion to receive either 20 mg fluoxetine and a relatively low dose folic acid (1.5 mg/day; $n=23$; Group I) or 20 mg fluoxetine and high dose folic acid (5 mg/day; $n=19$; Group II). Primary outcome measures were weekly changes of scores on Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventory (BDI) for 6 weeks.
Results: Group II patients showed greater improvement in both HDRS [Mean (SD) baseline HDRS score=21 (2.3) for group I and 20.0 (1.4) for group-II; time X group interaction effect: $p=0.01$] and BDI [Mean (SD) baseline BDI score=25.1 (5.2) for group-1 and 23.1 (2.7) for group-II; time X group interaction effect: $p=0.01$]. With regard to HDRS, 7 (36.8%) group II patients remitted compared to 2 (8.7%) group I patients ($p=0.03$); 9 (47.4%) patients of group II responded when compared to 6 (26.1%) from group I ($p=0.15$). When BDI was considered, 5 (26.3%) group II patients remitted when compared to 2 (8.7%) from group I ($p=0.13$); 10 patients (52.6%) from group II responded when compared to 5 (21.7%) from group I ($p=0.04$). No adverse effects were noted in either group.
Limitations: Lack of a placebo arm and small sample size.
Conclusion: Compared to folic acid 1.5 mg/day, augmentation with 5 mg/day may be more beneficial in female patients with depressive episodes taking fluoxetine 20 mg/day.

1. Introduction

Encouraging evidence exists for the use of omega-3 fatty acids, S-Adenosyl methionine, folic acid and L-tryptophan adjuvant with antidepressants to enhance response and improve efficacy (Sarris et al., 2010). Folic acid in its various forms (folic acid, methyl-folate and folinic acid) (Fava and Mischoulon, 2009) has been found useful as an augmenting agent to antidepressant medications. For example, Godfrey et al. (1990) randomized patients with DSM III diagnosis of major depression as well as schizophrenia to receive either methyl folate ($n=22$ inclusive of both patients in the active treatment arm) or placebo ($n=19$ in this placebo arm) in addition to the psychotropic that they were getting. The trial went on for 6 months. Among both depressed and schizophrenia patients, methyl folate significantly improved clinical and social recovery. In addition, the differences in outcomes became greater with time.

Coppen and Bailey (2000) randomized 127 patients with DSM III R major depression to receive either folic acid (500 mcg/day) or placebo in addition to fluoxetine 20 mg/day. Results showed that overall patients receiving folate showed a significant increase in plasma folate. Statistically significant magnitude of improvement was noted for the fluoxetine plus folic acid group only in women. This result held true among both responders as well as remitters. Passeri et al. (1993) in a randomized double-blind study involving patients with organic depression showed that folate improved the HDRS scores better than Trazadone. Another trial involving 27 depressed subjects found that 20 mg of fluoxetine combined with 10 mg of folic acid was more effective in reducing Hamilton Depression Rating Scale (HDRS) scores compared to augmentation with placebo (final HDRS scores 7.43 ± 1.65 vs. 11.43 ± 1.31, respectively; $p=0.04$). A significant reduction of homocysteine was also observed in the folic acid group, compared to placebo (Resler et al., 2008). However, more information about its optimal dosage is required (Fava and Mischoulon, 2009). The dosage of folic acid or its equivalent has

* Correspondence to: Department of Psychiatry, National Institute of Mental Health and Neurosciences, Hosur Road, Bangalore 560029, India.
Tel.: +91 80 26995254; fax: +91 80 26564830.
E-mail addresses: naveen.nimhans@gmail.com, cnkumar1974@gmail.com, drnkumarc@aol.in (C.N. Kumar).

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widely ranged between 0.2 mg and 105 mg in various studies (Coppen and Bailey, 2000; Godfrey et al., 1990) if we consider that 1 mg of methyl-folate is equivalent to 7 mg of folic acid (Willems et al., 2004). In view of such wide range, it has been suggested without adequate experimental work that 2 mg of folic acid may be given for augmentation of antidepressant response (Abou-Saleh and Coppen, 2006). Since we could not come across any study which has compared the add-on effect of the relatively low (1.5 mg/day) versus high (5 mg/day) dose folic acid, we conducted this study with the aim of comparing the add-on effect of these two doses of folic acid in patients suffering from depressive episodes.

2. Methods

This study comprised consecutive 42 female out-patients who consulted National Institute of Mental Health and Neurosciences, Bangalore, a state funded tertiary care neuropsychiatric centre between May 2006 and May 2007. The study was approved by the Institutional Ethics Committee. Patients currently satisfied ICD-10 (WHO, 1992) criteria for the diagnosis of: (a) moderate depressive episode with or without somatic symptoms or (b) severe depressive episode without psychotic symptoms. Patients with first episode of depression and also those with recurrent episodes were included. For inclusion in this study, the patient had to satisfy the following additional inclusion criteria. Bipolar depression was an exclusion criteria.

1. Aged between 16 and 45 years
2. Provision of written informed consent
3. Scores of at least 18 on Hamilton depression rating scale
4. Absence of symptoms necessitating alternate treatment like suicidal ideation (score of at least three on item no 3 of HDRS), stupor
5. Haemoglobin level of >10 g%, mean corpuscular volume not exceeding 100 fl, normal peripheral smear
6. Drug free state for 8 weeks. For the purpose of this study, a patient who had received antidepressants, benzodiazepines or neuroleptics (non-depot) for four days or more during the past 8 weeks was considered as drug free
7. No contraindication to fluoxetine therapy: e.g., history of acute gastritis, duodenal ulcer, severe reflux oesophagitis or intolerance/allergy to fluoxetine in previous episodes of depression or history of non-response to fluoxetine in previous depressive episodes
8. Absence of any psychiatric comorbidity as assessed by detailed clinical interview
9. Absence of any physical comorbidity as assessed by history/physical examination

Here, we would like to note that none of the patients had any neurological deficits. Moreover macrocytic anaemia was ruled out by estimating haemoglobin and mean corpuscular volume whose normalcy substantially excludes clinically significant vitamin B12 deficiency. In the latter case, addition of folic acid without vitamin B12 is not desirable as is well known.

Diagnosis of depressive disorders was done by clinical interviewing. The 17 item version of the HDRS (Hamilton, 1960) and Beck Depression Inventory (BDI) (Beck et al., 1961) were used to assess change in depression scores over 6 weeks of treatment period. With regard to HDRS, response was defined as 50% reduction in HDRS scores from the baseline (Lam and Kennedy, 2004) and remission was defined as a score <8 (Kelsey, 2002). With regard to BDI, a score of less than nine from baseline was defined as remission (Keller, 2003) and 50% reduction of symptom score was considered as response (Vergouwen et al., 2007). These response and remission criteria were apriori decided. In this dose-response study, assessments were carried out at baseline and weekly intervals. These 42 patients were randomly assigned to one of the two treatment groups: low dose folic acid group (Group I; fluoxetine 20 mg/day $+1.5$ mg folic acid/day) and high dose folic acid group (Group II; fluoxetine 20 mg/day $+5$ mg folic acid/day). Folic acid or pteroylglutamic acid (PGA) was prepared as identical looking capsules in two dosage forms as 1.5 mg and 5 mg. British Pharmacopoeia preparation of folic acid was used for this study. Neither the rater (RV) nor the patients knew the group status. One of the authors (RSP) labelled the vials containing study medications using random numbers from a computer generated random number table and kept the key. The folic acid tablets were identical looking. The rater was not aware of the allocation sequence. After data collection was completed, this key was used to ascertain the group status of patients. In this way, allocation concealment was also ensured. Same rater evaluated the patients from beginning till the end.

3. Statistical analysis

Continuous variables were analysed using the independent sample t-test; discrete variables were analysed using the χ^2 test. Repeated measures analysis of variance was used to analyse the trends of change of depression scores on HDRS and BDI. Analysis was done using the last observation carried forward method.

4. Results

Table 1 shows the socio-demographic and clinical details of the sample. Both groups were comparable except that group-I had

Table 1
Socio-demographic and clinical details.

Variables	Group-I ($n=23$)	Group-II ($n=19$)	t/χ^2	p-value
Mean age (SD) in years	31.7 (7.2)	34.6 (5.7)	−1.46	0.15
Mean duration of education (SD) in years	4.70 (5.0)	6.6 (5.3)	−1.21	0.23
Marital status [n(%)]				
Married	15 (65.2)	14 (73.7)	1.47	0.69
Unmarried	8 (34.8)	5 (26.3)		
Employment				
Employed	20 (87.0)	17 (89.5)	0.06	0.8
Unemployed	3 (13.0)	2 (10.5)		
Mean duration (SD) of current episode (in weeks)	9.9 (7.7)	11.8 (8.7)	−0.76	0.45
Mean haemoglobin (SD) level in gm%	12.87 (0.6)	12.6 (1.1)	0.90	0.37
Mean of the mean corpuscular volume (SD; cubic microns)	90.0 (3.9)	88.2 (4.6)	1.43	0.16
Recurrent depressive episodes [(n)%]	7 (30.4)	1 (5.3)	4.3	0.04
Mean total baseline HDRS (SD)	21 (2.3)	20.0 (1.4)	1.73	0.09
Mean total baseline BDI (SD)	25.1 (5.2)	23.1 (2.7)	1.55	0.13