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Acid Folic Supplementation in Major Depressive Disorder Treatment: A Double-Blind Randomized Clinical Trial

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Abstract

Background: Augmentation therapy involves the addition of a second drug, such as mood stabilizers, antipsychotics, and nutritional supplements, to a primary antidepressant treatment. Studies on adding folic acid to a preexisting antidepressive regimen as a form of augmentation therapy have had different and even controversial results.
Objectives: This study aimed to determine the effects that adding folic acid to a pharmaceutical diet with citalopram has on the treatment of depression.
Methods: This double-blind randomized clinical trial was conducted in Kashan, Iran on 90 patients who suffered from depression. Patients were allocated to study groups using random permuted blocks. One group (n = 45) received a dosage of 20 mg citalopram in combination with 2.5 mg folic acid on a daily basis, and the other group (n = 45) received the same daily dose of citalopram with a placebo for eight weeks. To measure the severity of each patient's depression, the Beck depression inventory II (BDI-II) questionnaire was used prior to starting the antidepressant therapy and was repeated four, six, and eight weeks after beginning the treatment. A reduction from the original BDI-II scores that was greater than 50% was considered to be a response to treatment.
Results: The average depression scores before treatment were 30.11 ± 10.41 in the intervention group and 31.24 ± 10.26 in the control group (P = 0.6). At the end of the study, the depression scores in the intervention and the control groups were 13.31 ± 6.57 and 19.11 ± 8.59, respectively (P < 0.001). A reduction in the average depression scores of the intervention group was statistically significant after six and eight weeks (P = 0.01 and P = 0.001, respectively). At the end of the study, the frequency of response to treatment was 73.3% in the intervention group and 40.0% in the control group (P < 0.001).
Conclusions: Folic acid, when used as a complementary therapy, can improve a patient's response to antidepressants used for the treatment of major depression.

Keywords: Major Depressive Disorder, Citalopram, Folic Acid, Augmentation Therapy

1. Background

Major depressive disorder (MDD) is a chronic mental disorder with an estimated lifetime prevalence of 13% - 17% in the United States (1, 2). Depression is the leading cause of disability in developed countries and has been predicted to become the most significant cause of disability worldwide by 2020 (3). MDD causes a huge economic burden for health systems, with the imposed burden in European countries reaching €118 billion, most of which is related to indirect costs, such as absence from work (4, 5).

Although new therapeutic options have emerged in recent years, there are still many patients who do not respond to first-line antidepressants (6, 7). Several strategies have been proposed for patients with refractory depression, including increasing the dosage of the antidepressant, switching the patient to new-generation medications, and adding another antidepressant medication to the patient's current treatment. However, these methods are not always successful because of unpleasant side effects. Therefore, developing safer and more effective methods for the treatment of refractory depression would be advantageous (8).

Previous studies have investigated the role of nutritional factors in treating neuropsychiatric disorders (9-11). These studies have shown that a considerable portion of patients with psychiatric disorders, including MDD, have been reported as having low levels of different vitamins, especially folate (12, 13). Augmentation therapy using folate, vitamin B12, omega-3 fatty acids, and zinc supplementation are new methods that have been suggested to improve depression and a patient's response to a therapeutic regimen with fewer side effects (14-16).

Few studies have examined the effects of folic acid supplementation as an augmentation of the treatment of major depression, and the results achieved by the few studies that exist are not univocal. Additionally, the concurrent

use of citalopram with folic acid in treating MDD has not yet been evaluated.

2. Objectives

Considering the existing controversies, in this study, we evaluated the effects of the concurrent administration of citalopram and folate in the treatment of MDD.

3. Methods

3.1. Study Participants

This double-blind randomized clinical trial was conducted on 90 patients who were referred to the psychiatric clinic of Kashan University of Medical Sciences in Iran. The study site was a psychiatric clinic affiliated with the government that is the main referral center in the area. This clinic provides outpatient psychiatric and psychological services to children and adults.

The calculation to determine the required sample size for this study was based on the results of a study performed by Venkatasubramanian et al. who evaluated the effects of the coadministration of fluoxetine and a different dosage of folic acid (17). In their study, the frequency of response to treatment was reported to be 52.6% in patients who received high doses of folic acid and 21.7% in those receiving low-dose folic acid. With a power of 80% and Z1-α/2 = 1.96 and with the use of the following equation, we concluded that the required sample size of each group in our study was 39. To allow for a 10% loss of participants, the sample size was adjusted to 45 in each study group (Equation 1).

$$n = \frac{\left(z_1 - \frac{\alpha}{2} + z_{1-\beta}\right)^2 \overline{pq}}{\left(p_1 - p_2\right)^2} \quad (1)$$

Participants were recruited via convenience sampling from those referred to our outpatient psychiatric clinic who were depressed according to the Diagnostic and Statistical Manual of Mental Disorders IV Text Revision. For this purpose, all patients who met the inclusion and exclusion criteria were enrolled until completion of the required sample size (n = 90). All patients were residents of Kashan city.

The inclusion criteria were an age of 20 - 50 years and a Beck depression inventory score greater than 12. The exclusion criteria were the use of antidepressants within the last four weeks, signs of psychosis, mental retardation, a history of manic episodes, a history of taking psychotropic drugs, and certain medical problems (anemia, pregnancy, chronic diseases, etc.). Patients experiencing severe drug reactions at any stage were excluded from the survey. The total number of recruited cases was 100. However, five cases were omitted because of antidepressant usage within the last four weeks, three cases had psychosis, and two cases were put aside because of a history of manic episodes. Thus, the final sample size of the study was 90 cases (Figure 1).

The demographic and clinical data of the patients, such as age, sex, education level, marital status, history of depression, treatment with SSRIs, and history of anxiety disorders, were recorded in a predesigned checklist.

The patients were divided into two equal groups, an intervention group and a control group, using the permuted block randomization method. For this purpose, 15 blocks with a block size of six were used, and the blocks were classified by order of numbers. Both patients and researchers were blind to the treatment allocation. The only person who knew the allocation was the nurse who was in charge of delivering the medications.

All ethical principles were respected in accordance with Resolution 196/96 on research involving human subjects. The ethics committee of Kashan University of Medical Sciences approved the study and supervised all its stages (approval code: p/29/5/1/458). This study was also recorded in the Iran Center of Clinical Trials Registration database (IRCT2014082518922N1). After being informed of the study objectives, all participants signed a written consent form.

3.2. Clinical Assessments

All study participants were visited by a psychiatrist at the beginning of the study and at two-week intervals. In every visit, patients were checked for exclusion criteria, treatment adherence, and possible side effects.

To measure the severity of each patient's depression and anxiety, all participants were asked to complete the second version of the Beck Depression Inventory questionnaire (BDI-II) and the Hamilton anxiety rating scale questionnaire (HAM-A) prior to group allocation. The BDI-II was completed again four, six and eight weeks after the onset of the study. The HAM-A was also completed by all patients at the end of the treatment (the eighth week). Lower BDI-II scores were considered to be the result of the study. Patients were divided according to their BDI-II scores into mild (14 - 19), moderate (20 - 28), and severe (29 - 63) depression categories. A decrease more of than 50% in a patient's primary BDI-II score was reported as a response to treatment.

A developed checklist was used for collecting data. The checklist consisted of two parts. The first part gathered the subjects' demographic data, such as age, sex, height, weight, marital status, education level, and history of MDD

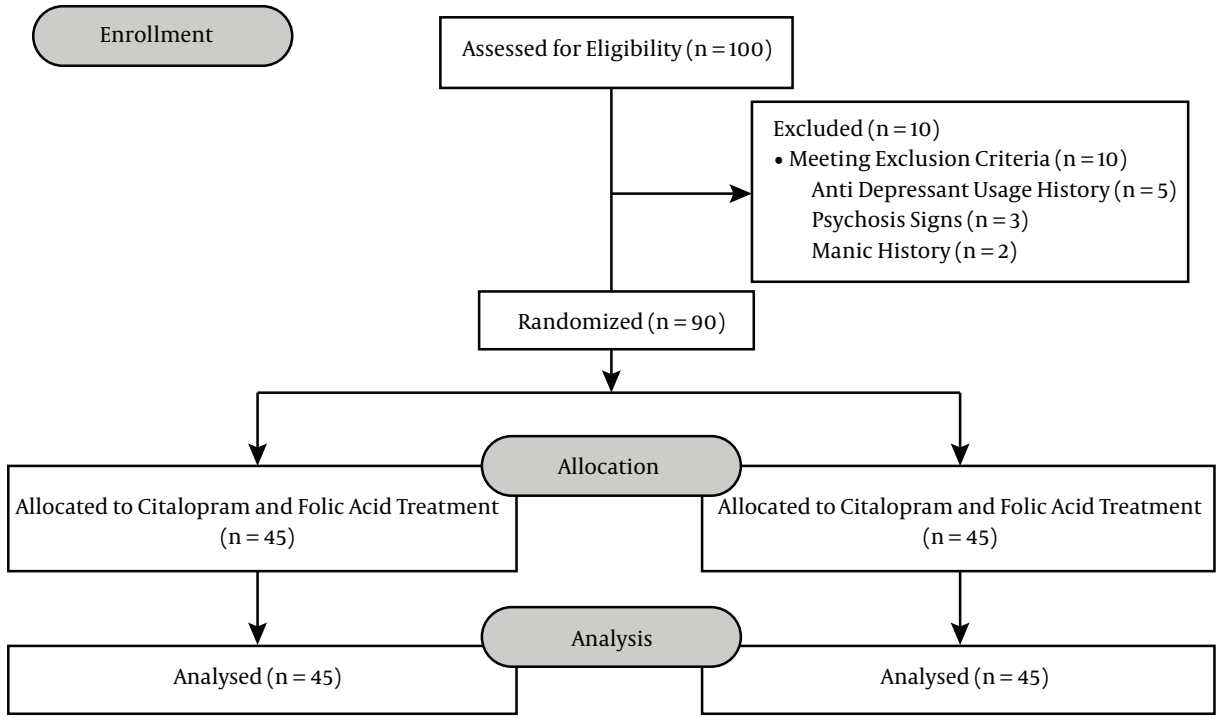

Figure 1. Study Flow Chart

and anxiety disorders. The second part contained clinical information, including BDI-II scores (which were obtained prior to the onset of the study and four, six, and eight weeks into the treatment) and HAM-A (which were obtained before and after the treatment). The content validity of the checklist was approved by four psychiatry and psychology experts. The checklist's reliability was determined using the interobserver method: In an initial pilot study, the questionnaire was completed for five patients in each group by three researchers not involved in creating the checklist. Then, the degree and significance of agreement between observers was calculated (r = 0.87).

3.3. Medications

All patients received 20 mg citalopram tablets (Sobhan Pharmaceutical Company, Iran) per day for eight weeks. The patients in the intervention group also received 2.5 mg folic acid (Sobhan Pharmaceutical Company, Iran) per day, and patients in the control group were given an identical-looking placebo in addition to the citalopram. The drugs were given once every two weeks at the time of the psychiatrist's visit. Patient adherence to treatment and side effects were looked for at each appointment.

3.4. Statistical Analysis

The data were analyzed using SPSS software version 16 for Windows. The descriptive part of the analysis was reported as absolute and relative frequency. The results of the quantitative data analysis were expressed as mean $\pm$ standard deviation. The Kolmogorov-Smirnov test was applied to assess the data distribution. A chi-squared test, an independent t-test, a paired t-test, and a repeated measures ANOVA were used for data analysis. Before analyzing the data using the repeated measures ANOVA, assumptions, including the type of data, randomness, normality, and sphericity, were checked. Since Mauchly's Test of Sphericity indicated that the assumption of sphericity had been violated ($P < 0.001$), the Huynh-Feldt correction was applied. All tests were two-tailed. The level of significance for all tests was considered to be $P < 0.05$.

4. Results

In this study, 90 patients in two groups were surveyed, and all patients completed the treatment course. Of the 90 patients, 56 (62.2%) patients were female. The average age of the patients was 35.73 $\pm$ 9.57 years; the minimum age was 20 years old and the maximum was 50 years old.

The demographic and clinical characteristics of the patients are shown according to treatment group in Table 1. The baseline clinical characteristics of the patients are also shown in Table 1. The average depression scores of the patients before treatment was 30.11 ± 10.41 in the intervention group and 31.24 ± 10.26 in the placebo group (P = 0.6). The mean HAM-A anxiety score before treatment was 34.24 ± 9.09 in the intervention group and 35.82 ± 9.57 in the placebo group. This difference between the scores of the two groups before intervention was not statistically significant (P = 0.42). The treatment outcomes are shown in Table 2. The repeated measures ANOVA showed that the reduction in depression scores were different between the groups (P < 0.001) (Figure 2).

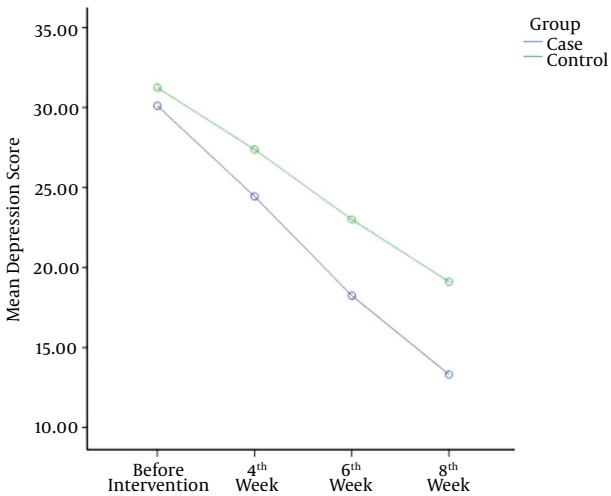

Figure 2. Repeated Measures Analysis of Depression Scores

Table 1. Patient Demographics and Clinical Characteristics[a]

Variable	Group		P Value
	Acid Folic	Placebo	
Age	35.11 ± 8.62	36.35 ± 10.49	0.54
Sex			0.38
Male	19 (42.2)	15 (33.3)	
Female	26 (57.8)	30 (66.7)	
Marital status			0.9
Single	12 (26.7)	10 (22.2)	
Married	27 (60)	29 (64.4)	
Divorced	3 (6.7)	2 (4.4)	
Widow	3 (6.7)	4 (8.9)	
Education			0.69
Primary school	12 (26.7)	11 (24.4)	
Middle School	15 (33.3)	13 (28.9)	
High school diploma	12 (26.7)	17 (37.8)	
Academic degree	6 (13.3)	4 (8.9)	
MDD history			0.16
No	29 (64.4)	35 (77.8)	
Yes	16 (35.6)	10 (22.2)	
Anxiety disorders			0.38
No	27 (60)	31 (68.9)	
Yes	18 (40)	14 (31.1)	
Depression severity			0.96
Mild	9 (20.0)	8 (17.8)	
Moderate	10 (22.2)	10 (22.2)	
Severe	26 (57.8)	27 (60.0)	
BDI-II score	30.11 ± 10.41	31.24 ± 10.26	0.6
Hamilton score	34.24 ± 9.01	35.82 ± 9.57	0.42

[a]Values are expressed as mean ± standard deviation or No. (%).

5. Discussion

The present study was designed to investigate the effects of the coadministration of folic acid and citalopram in patients with MDD. Prescribing 2.5 mg of folic acid as a supplement increased the antidepressant action of citalopram.

Previous studies have investigated the potential effect of folate augmentation of antidepressants. Passeri et al. compared folate with trazodone added to standard medication for the treatment of depression in patients with dementia (18). Another survey confirmed that folic acid greatly improved the effect of fluoxetine in the treatment of major depression (19). Similar results that are consistent with our findings have been reported in other studies as well (20-22). Papakostas et al. confirmed that L-methyl folate is an effective adjunctive therapy in the treatment of patients with MDD that is resistant to SSRIs (23).

Other studies have reported opposite findings. Christensen et al. disagree with the idea of the potentiation of antidepressants with folate + B12 supplementation (24).

One review study addressed the effects of supplements on the improvement of the therapeutic effects of antidepressant drugs. This study did not find sufficient evidence to support the positive effects of folic acid (25). These contradictions may be caused by the differences in prescribed folic acid doses, the treatment duration, and the methods used to measure the patients' clinical response.

Our study indicated that the response to treatment was

Table 2. Treatment Outcomes[a]

Variables	Groups		P Value
	Folic Acid	Placebo	
BDI-II score			
4th week	24.44 ± 9.19	27.38 ± 9.57	0.14
6th week	18.24 ± 7.97	23.0 ± 9.08	0.01
8th week	13.31 ± 6.57	19.11 ± 8.59	0.001
Response frequency			
4th week	0	0	-
6th week	10 (22.2)	5 (11.1)	0.16
8th week	33 (73.3)	18 (40.0)	0.001
Depression scores reduction			
4th week	5.67 ± 3.62	3.87 ± 4.07	0.03
6th week	11.87 ± 4.88	8.24 ± 5.87	0.002
8th week	16.8 ± 5.77	12.13 ± 6.55	0.001
Final depression severity			0.04
Mild	13 (61.9)	10 (30.3)	
Moderate	7 (33.3)	15 (45.5)	
Severe	1 (4.8)	8 (24.2)	
Final Hamilton score	21.93 ± 9.41	27.18 ± 11.16	0.02

[a] Values are expressed as mean ± standard deviation or No. (%).

significantly higher in both men and women in the folic acid and citalopram group compared with the placebo group. To our knowledge, only one study has mentioned the effect of gender on the response to the augmentation of treatment with folic acid. Coppen et al. reported that men need relatively higher doses of folic acid to achieve the positive effects (19). The role of gender was noticed by other studies that surveyed the relationship between folic acid and depression. Sanchez-Villegas et al. pointed out that an inverse association exists between the amount of folic acid intake and the prevalence of depression among men, especially smokers, but no similar relationship was found among women (26). In another study, Astorg et al. observed a strong correlation between high levels of folic acid and reduced incidence of depressive episodes among men, but this association was not seen in women (27). Similar results have been reported by Murakami et al. (28). On the other hand, two other studies stated that the relationship between folic acid intake and occurrence of depressive symptoms was observed only in women (29, 30).

Another study evaluating the effects of two different doses of folic acid on the efficiency of fluoxetine for the treatment of depression showed that both men and women would benefit from treatment augmentation with folate but that higher doses were reported to be more effective in women than in men (17).

Currently, there is no valid reason for explaining these differences, but psychosocial factors, genetics, individual differences in drug metabolism and pharmacokinetics, and food and drug habits may play a role.

We found that there were statistically significant differences between the two groups in the responses of patients of both genders who were less than 35 years old to the treatment, but of the patients who were older than 35 years old, a similar response was observed only in male patients. This aspect of study has not previously received attention (31). Since folic acid deficiency is more common in the older population, elderly people would rationally benefit more from receiving folic acid than younger people. Alternatively, age-related reductions in intestinal folic acid absorption might be the reason for these results (32). However, since our study subjects were not selected from an older population, this possibility seems less likely.

According to current studies, the effects of the coadministration of folate on improving the treatment of depression are noticeable and well proved. Folic acid is essential for various functions of the human body, including processes related to the nervous system. Studies conducted over the last few decades have shown that patients with folic acid deficiency revealed psychological symptoms, such as depression and cognitive impairment (33, 34).

Folate level is thought to be associated with various mood disorders. Previous studies have shown lower plasma and red blood cell folate in patients with depression. Lower levels of folic acid have also been related to longer and more severe depressive phases in bipolar patients (15, 35). In a group of studies that evaluated folic acid levels in depressed patients, individuals with depression had the lowest serum levels of all patients studied, and only individuals with alcohol dependence had similar folic acid levels (36). Folic acid levels are thought to fluctuate depending on the type of mood disorder. For example, the percentage of individuals with low folic acid levels was higher among patients with melancholic depression compared to those with nonmelancholic depression (37).

There have been very few studies conducted on the levels of folate and depression in the general population. Tolmunen et al. examined 2682 Finnish men between 42 and 60 years old. The participants were divided into three categories depending on dietary folate intake (38). After controlling for confounding variables, such as smoking, alcohol consumption, body mass index, and socioeconomic status, people who had low levels of folate in their diet were found to be more likely to be affected by depression 67% higher compared to those who had higher levels of folate

intake (38).

Another study conducted by Morris et al. in the United States involved 3010 individuals selected from the general population who were between 15 and 39 years old. Following an adjustment for confounding factors, people with depression were determined to have significantly lower levels of serum folate. Additionally, people with dysthymia showed lower levels of folate serum than the normal population (39). The consistent results of these two studies, which targeted two different age ranges, demonstrates a causal relationship between folic acid and depression.

Whether poor nutrition is a symptom of depression causes folate deficiency or primary folate deficiency produces depression, folate prescription would be beneficial and folic acid supplementation would improve the treatment process of depression even in patients without folic acid deficiency (34, 37, 39, 40).

Although the pre- and posttreatment serum levels of folic acid were not measured in our study, favorable clinical responses were observed after the coadministration of folic acid with the standard treatment of depression. Based on previous surveys, high doses of folic acid (15 mg) might cause side effects, including sleep disturbances, fatigue, restlessness, and hyperactivity, in healthy volunteers. Large doses of folate have been reported to be associated with low levels of serotonin in the brain within animal models. Therefore, ascertaining the effective and safe therapeutic doses of folic acid and its interactions with a variety of antidepressant treatment regimens is crucial.

Hypotheses have been proposed to explain the role of folate deficiency in pathogenesis of mood disorders, especially MDD, but the exact mechanism of this vitamin in the development and treatment of depression is not yet fully understood. Folate assists in the formation of the cofactor for tyrosine hydroxylase and tryptophan hydroxylase, which are important enzymes in the synthesis of monoamines that are related to depression, including dopamine, serotonin, and epinephrine (41). Another possible pathway that explains the role of folate in pathogenesis of MDD involves homocysteine metabolism. Homocysteine is a nonprotein amino acid that is produced as a result of a one-carbon metabolism pathway. Several enzymes are involved in the catabolism of homocysteine, such as methylenetetrahydrofolate reductase. This enzyme requires sufficient amounts of folic acid in order to function properly (42). Folic acid deficiency results in elevated homocysteine levels, the presence of which has been associated with different psychological disorders, such as schizophrenia, bipolar disorder, and MDD (42-44). Folic acid supplementation in patients with MDD may enhance their response to treatment through the reduction of homocysteine serum levels. There is also evidence to indicate that oxidative stress and reduced antioxidant function play a role in depression (45). Previous studies have well demonstrated that folic acid increases the total antioxidant capacity in the body. Thus, it can be hypothesized that folic acid acts via modifying and reducing oxidative stress to enhance the treatment of patients with MDD (46, 47).

To best of our knowledge, ours is the first study to address the effects of adding folic acid to citalopram for the treatment of depression. One advantage of our study is that it investigated depression and anxiety disorders simultaneously.

Not measuring the folic acid levels in serum and in red blood cells is one of the limitations of this study. Other limitations include not measuring the levels of oxidants and the total antioxidant capacity before and after the folate prescription, which made it impossible to evaluate the effect of folate on oxidant and antioxidant status, and lack of a long-term follow-up period to determine the relapse rate in the study groups.

Further studies are needed to enable more confident conclusions about the mechanism via measuring the exact levels of folic acid. Additionally, more work is required to compare different antidepressant regimens with or without folic acid and also to ascertain the optimum therapeutic dose of folate.

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Footnotes

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