THERAPEUTIC EFFICACY OF COMBINATION THERAPY OF L-METHYLFOLATE AND ESCITALOPRAM IN DEPRESSION

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ABSTRACT

Objective: To evaluate the efficacy of L-Methylfolate in combination with Escitalopram compared to Escitalopram monotherapy in depression.

Study Design: Randomized controlled trial.

Place and Duration of Study: Armed Forces Institute of Mental Health (AFIMH) Rawalpindi, six months, from Jan 2015 to Jun 2015.

Material and Methods: A total of 260 patients having a primary diagnosis of Major Depression with a score of more than 14 on the HAM-D (Hamilton rating scale for depression) scale were selected in this Randomized Controlled Trial. These patients were divided into two groups. Group A received Escitalopram 10mg with a placebo whereas group B received Escitalopram 10mg with L-Methylfolate in a dose of 15mg. Both were reassessed after one month and HAM-D scores were measured again.

Results: Out of the total 260 patients, response was present in 184 (70.8%) and 76 (29.2%) did not respond to the treatment. Out of 130 patients that were treated with SSRI alone, 82 (63.1%) showed response to treatment while 48 (36.9%) did not respsond. Out of 130 patients that were treated with Escitalopram and L-Methylfolate, 102 (78.5%) showed response to treatment while 28 (21.5%) did not respond. The *p*-value with a confidence interval of 95% was found to be 0.006 showing that the difference in the two treatments was statistically significant.

Conclusion: We concluded that a combination of SSRI and L-Methyfolate in depression may prove to be more effective than Escitalopram monotherapy.

Keywords: Escitalopram, L-Methyfolate, Major depressive disorder.

INTRODUCTION

Global Burden of Disease 2010 identified depressive disorders as the second leading cause of disability[1]. Major Depressive Disorder accounted for 8.2% of global burden of disease[1]. Despite advances in the understanding of the psychopharmacology and the introduction of several classes of antidepressants, only 60%-70% of patients with depression respond to antidepressant therapy alone[2]. Beyond first-line treatment, current guidelines recommend either augmentation or switching of the initial antidepressant[3]. A novel strategy to enhance therapeutic efficacy of antidepressants is emerging by combining multiple simultaneous pharmacologic mechanisms from the initiation of antidepressant treatment rather than waiting until several treatments fail[4]. This strategy has lead to the introduction of nutraceuticals including L-Methylfolate, S-Adenosyl Methionine, Vitamin E and Omega 3 Fatty acid[5]. Studies have found low serum folate levels or low RBC folate concentrations in depressed patients. Other studies suggested that low folate levels are associated with reduced response to anti-depressants, which in turn suggested that folic acid might be used to augment antidepressants[6]. There is evidence that combination of L-methylfolate with antidepressants from the initiation of treatment enhances antidepressant efficacy, attains higher remission rates and lowers relapse rates[7]. The potential advantage of augmenting a traditional antidepressant with methylfolate is its low liability for side effects[8].

L-Methylfolate modulates the synthesis of monoamines, including serotonin,

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norepinephrine, and dopamine. As a consequence, L-Methylfolate is a trimonoamine modulator (TMM) and indirect regulator of trimonoamine neurotransmitter synthesis and monoamine concentrations[6]. Repletion of L-Methylfolate levels would theoretically boost monoamine synthesis and this would potentially boost the efficacy of anti depressants[6]. In a study it was seen that adding L-Methylfolate to selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) when starting pharmacotherapy leads to greater reduction of depressive symptoms in a shorter time compared with SSRI or SNRI mono-therapy[9]. According to the study the efficacy of L-Methylfolate and SSRI was 18.5% as compared to 7.04% efficacy of SSRI or SNRI monotherapy[9].

The rationale of this study is based on the fact that 30% of depressed patients do not respond to antidepressants alone[10] and keeping in view the above mentioned studies L-Methylfolate is a promising augmenting agent to antidepressants but the effect of this drug needs to be evaluated in patients of our population as well. This study would be the first study in Pakistan to look into the effects of L-Methylfolate in depression.

MATERIAL AND METHODS

The study was conducted at Armed Forces Institute of Mental Health (AFIMH) from Jan 2015 to Jun 2015. A total of 260 subjects having a primary diagnosis of Major Depressive Disorder (single or recurrent) with a score of more than 14 on the HAM-D scale were selected in a Randomized Control Trial. They were enrolled into the study after informed consent of the patient and ethical approval from the ethical committee of AFIMH. These patients were 18 to 60 years of age and received their respective therapies from the initiation of treatment at Armed Forces Institute of Mental Health, Rawalpindi between 1st January 2015 and 30th June 2015. Criteria that excluded patients from the study included non consenting patients, presence of psychotic features in the current episode or a history of psychotic features; any bipolar disorder (current or past) or any psychotic disorder (current or past), any comorbidity including diabetes mellitus and hypertension, pregnancy, breastfeeding mothers, children and adolescents, patients with serious suicidal risk and patients taking Lithium, anticonvulsants, psychostimulants, antipsychotics or oral contraceptives. The sample size was calculated by WHO sample size calculator using following values[9]:

Level of significance	: 5%
Power of test	: 80%
Anticipated population group A	: 18.5%[9]
Anticipated population group B	: 7.04%[9]

Sampling technique used was consecutive sampling. Patients were divided into two groups by random number tables. Patients who ful-filled the ICD-10 criteria were diagnosed with depression after detailed history. Hamilton rating scale for depression (HAM-D) was administered to these patients. All patients having a score of 14 or more were enrolled into the study. These patients were then divided into control group A which were given SSRI (Escitalopram) only along with a placebo and intervention group B which was given SSRI (Escitalopram) and L- Methyfolate. Patients were allocated to any of the two groups by lottery method. These groups were reviewed after 1 month. HAM-D was used to determine the improvement in depressive symptoms. An uplifting in the mood was determined by a change in the HAM-D (Hamilton rating scale for depression) score from moderate and severe to mild score i.e. 8 to 13 or normal i.e. less than 8. Confounding variables were identified and excluded by exclusion criteria. Data was analyzed using SPSS 19.0. Mean and standard deviation were calculated for quantitative variables like age of the patient. Frequency and percentages were calculated for qualitative variables like gender and efficacy of the patient. Independent sample t-test was used to compare the scores between the 2 groups. Effect modifiers like age, gender, education,

occupation and marital status were controlled by stratification. Post stratification chi-square test was applied and *p*-value less than 0.05 was considered significant.

RESULTS

Patient baseline characteristics are summarized in table-I. There were 260 patients (mean age 36.9 ± 9.6 years) in which female subjects were 139 (53.5%) and male subjects were 121 (46.5%). A total of 212 (81.5%) of the patients were married whereas 36 (13.8%) were single and 12 (4.6%) were divorced/widowed. Occupationally 113 (43.4%) patients were employed, 103 (39.6%) were housewives and 43 (16.5%) were unemployed. One hundred and seventy (65.4%) of the patients were educated and 90 (34.6%) were uneducated. In the HAM-D scores on first interview 157 (60.4%) were in the moderately depressed range i.e. 14-18 followed by those in severe range i.e. 19-23 which were 93 (35.7%) and 10 (3.8%) were in the very severely depressed range i.e. >23. The mean ± SD for HAM-D on first interview was 18.06 ± 2.20. Wheras the post treatment HAM-D score showed mean ± SD of 11.53 ± 2.67 with scores coming down to the mild range in 173 (66.5%) patients.

Table-I: Baseline patient characteristics.

Patient characteristics	SSRI Only (n=130)	SSRI & L-Methylfolate (n=130)	*p*-value
Gender			
Male	58	63	0.532
Female	72	67	
Age			
20-40 years	88	92	
41-60 years	42	38	0.590
SD ± Mean	37.4 ± 10.4	36.5 ± 8.7	
Marital status			
Married	103	109	
Single	20	16	0.623
Divorced/widow	07	05	
Occupational status			
Employed	50	63	
Unemployed	24	19	0.087
House wife	56	48	
Educational status			
Educated	82	88	0.149
Uneducated	48	42	
Severity of Depression			
Moderate	76	81	0.527
Severe	54	49	
HAM-D Score 1st interview SD ± Mean	18.24 ± 2.42	17.88 ± 1.95	0.188
HAM-D Score post treatment SD ± Mean	12.21 ± 2.77	10.85 ± 2.39	0.001

Out of the total 260 patients, response i.e. an uplifting in the mood determined by change in the HAM-D (Hamilton rating scale for depression) score from moderate and severe to mild score i.e. 8 to 13 or normal i.e. less than 8, was present in 184 patients. This means that in the trial 70.8% patients responded overall while 76 patients i.e. 29.2% did not respond to the treatment.

Out of 130 patients that were treated with Escitalopram, 82 showed response to treatment while 48 did not respond. This means that 63.1% patients had an uplifting in the mood while 36.9% did not show adequate response.

Out of 130 patients that were treated with Escitalopram and L- Methylfolate, 102 showed response to treatment while 28 did not respond.

Table-II: Cross tabulatedtreatment response.

Treatment Group	Efficacy		*p*-value
	Yes	No	
SSRIs (Group A)	82 63.1%	48 36.9%	0.006
SSRIs ± L-methyl folate (Group B)	102 78.5%	28 21.5%	
Total	184 70.8%	76 29.2%	

This means that 78.5% patients had an uplifting in the mood while 21.5% did not show adequate response. Chi square test was used to determine the difference in the response of the two treatments. After the application of the test, the *p*-value was found to be 0.006 which was less than 0.05 as shown in table-II. This showed that the difference in the two treatments was statistically significant. Hence it showed that combination of Escitalopram and L-Methylfolate was more effective than Escitalopram alone in treatment of moderate to severe depression.

DISCUSSION

The goal of treatment in major depression is remission. Response is typically defined as a clinically meaningful reduction in symptoms. However, response that falls short of remission is suboptimal because it is associated with continued disabling symptoms, higher rates of relapse and recurrence, poorer work productivity, more impaired psychosocial functioning, higher levels of health care use, and potentially higher risk for suicide. Despite advances in the understanding of the psychopharmacology and the introduction of several classes of antidepressants, only 60%-70% of patients with depression respond to antidepressant therapy alone[2]. Beyond first-line treatment, current guidelines recommend either augmentation or switching of the initial anti-depressant[3]. The effect of this drug needs to be evaluated in patients of our population as well. In this regard this study helped us ascertain the effects of L-Methylfolate in depressed patients in Pakistan.

The findings in this study show that SSRIs, adjunctive L-Methylfolate, 15 mg/day, produced greater response rates compared with SSRIs plus placebo. In another study it was seen that adding L-Methylfolate to selective serotonin reuptake inhibitors (SSRIs) or serotonin–norepinephrine reuptake inhibitors (SNRIs) when starting pharmacotherapy leads to greater reduction of depressive symptoms in a shorter time compared with SSRI or SNRI monotherapy[8].According to the study the efficacy of L-Methylfolate and SSRI was 18.5% as compared to 7.04% efficacy of SSRI or SNRI monotherapy[9] showing a difference in response of 11.5% Papakostas et all showed that adjunctive L-methylfolate at 15mg/day showed significantly greater efficacy compared with continued SSRI therapy plus placebo on both primary outcome measures (response rate and degree of change in depression symptom score)

and two secondary outcome measures of symptom severity[10]. The number needed to treat for response was approximately six in favor of adjunctive L-methylfolate at 15mg/day. L-Methylfolate was well tolerated, with rates of adverse events no different from those reported with placebo[11]. Trials of both monotherapy and adjunctive L-Methylfolate have been reported. Four monotherapy trials (reviewed elsewhere[10]), suggested the same efficacy. Two were open trials and two were double-blind trials comparing L-Methylfolate with antidepressants. The first adjunctive trial was a double-blind placebo-controlled trial in 24 patients with major depression who had deficient RBC folate levels. L-Methylfolate at 15 mg/day was added to ongoing antidepressant treatment. At 3 months and at 6 months, patients receiving adjunctive L-Methylfolate exhibited greater improvement than those in the placebo group. In a study based on using vitamins as adjunctive agents it was seen that B vitamins did not increase the 12-week efficacy of antidepressant treatment, but enhanced and sustained antidepressant response over 1 year[12]. A study of seventy-five patients showed that certain biological markers like BMI, C-reactive protein (CRP) and lows-adenosylmethionine levels predicted a better response to L-methylfolate[13]. In another study looking into the long term effects of L-Methylfolate over a period of 12 months it was found that of 68 subjects who met criteria for the 12-month open-label phase, 38% (n = 26) achieved full recovery, and none experienced a recurrence of MDD. For subjects entering the open-label phase in remission (n = 11), 91% (n = 10) achieved full recovery with l-methylfolate 15 mg, and none experienced a relapse or recurrence. Among 57 subjects who entered the open-label phase as nonremitted, 61% (n=35) achieved remission. Of subjects who entered the open-label phase with a response without remission (n=4), 50% (n=2) had full recovery, and of subjects entering the open-label phase with no response (n=53), 26% (n=14) met recovery criteria. This study has tried to lay a foundation to look into the effect of L-Methylfolate in patients in Pakistan however there were limitations. The duration of the study could have been increased to look for long term effects. Side effects could have been elaborated. Furthermore, this trial excluded certain populations of patients (children and adolescents; patients with bipolar disorder, psychotic major depression, active substance use disorders, or comorbid illness) who can be included in a future study.

In summary, this study is the first such study in Pakistan which suggests that L-Methylfolate is a useful adjunctive treatment for depression. Previous studies of folic acid, folinic acid, and L-Methylfolate support this contention. L-Methylfolate was well tolerated and may be preferred by patients for that reason. The efficacy of L-Methylfolate in resistant depression has not been compared with that of other adjunctive agents, nor has long-term use of the agent been reported in major depression. The potential value of long-term administration of L-Methylfolate in individuals with recurrent depression is particularly intriguing. Another important aspect to look into is if there are cases of severe depression, as this study shows it is possible to get a rather better response on initiating the treatment with a combination of SSRI and L-Methylfolate as compared to SSRI alone. However this aspect needs further studies to confirm the benefits of using augmentative strategy from the start and following it through in long term maintenance treatment a major limitation is the short duration of this study which may be enhanced in future trials for long term analysis of the effects of L-Methylfolate.

CONCLUSION

L-Methylfolate and SSRI have been found more efficacious than SSRI in patients of depression at least in the short term. Future studies on comparing the two interventions over the entire length of recommended duration of treatment (at least 6 months) need to be undertaken.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

REFERENCES

1. Ferrari AJ, Somerville AJ, Baxter AJ, Norman R, Patten SB, et al. Global variation in the prevalence and incidence of major depressive disorder: a systematic review of the epidemiological literature. Psycho Med 2013; 43: 471–81.
2. Al-Harbi KS. Treatment-resistant depression: therapeutic trends, challenges, and future directions. Patient Prefer Adherence 2012; 6: 369–88.
3. Connolly KR, Thase ME. If at first you don't succeed: A review of the evidence for antidepressant augmentation, combination and switching strategies. Drugs 2011; 71(1): 43-64.
4. Millan M. Dual and triple acting agents for treating core and comorbid symptoms of major depression: novel concepts, new drugs. Neurotherapeutics 2009; 6: 53-77.
5. Sarris J. Adjunctive Nutraceuticals for Depression: A Systematic Review and Meta-Analyses. Am J Clin Psychiatry 2016; 173(6): 575-87.
6. Nelson JC. The evolving story of folate in depression and the therapeutic potential of L-Methylfolate. Am J Clin Psychiatry 2012; 169(12): 1223-25.
7. Stahl SM. Combining antidepressant therapies from the initiation of treatment: a paradigm shift for major depression. J Clin Psychiatry 2009; 70: 1493-94.
8. Freeman M, Fava M, Mischoulon D, Papakostas G, Shelton R. The use of complimentary and alternative medicines to achieve remission in major depressive disorder. J Clin Psychiatry 2009; 70 (suppl-5): 1-27.
9. Ginsberg LD, Oubre AY, Daoud YA. L-methylfolate plus SSRI or SNRI from treatment initiation compared to SSRI or SNRI monotherapy in a major depressive episode. Innov Clin Neurosci 2011; 8(1): 19-28.
10. Papakostas GI, Cassiello CF, Iovieno N: Folates and S-adenosylmethionine for major depressive disorder. Can J Psychiatry 2012; 57: 406-13.
11. Papakostas GI, Shelton RC, Zajecka JM, Etemad B, Rickels K, Clain A. L-methylfolate as adjunctive therapy for SSRI-resistant major depression: results of two randomized, double-blind, parallel-sequential trials. Am J Psychiatry 2012; 169: 1267–74.
12. Almeida OP, Ford AH, Hirani V, Singh V, VanBockxmeer FM, McCaul K, et al. B vitamins to enhance treatment response to antidepressants in middle-aged and older adults: results from the B-VITAGE randomised, double-blind, placebo-controlled trial. Br J Psychiatry 2014; 205(6): 450-57.
13. Papakostas GI, Shelton RC, Zajecka JM, Bottiglieri T, Roffman J, Cassiello C, et al. Effect of adjunctive L-methylfolate 15mg among inadequate responders to SSRIs in depressed patoents who were stratified by biomarker levels and genotype; results from a randomized trial. J Clin Psychiatry 2014; 75(8): 855-63.
14. Zajecka JM, Fava M, Shelton RC, Barrentine LW, Young P, Papakostas GI. Long-Term Efficacy, Safety, and Tolerability of L-Methylfolate Calcium 15 mg as Adjunctive Therapy With Selective Serotonin Reuptake Inhibitors: A 12-Month, Open-Label Study Following a Placebo-Controlled Acute Study; J Clin Psychiatry 2016; 77(5): 654–60.