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EFFECTS OF COMBINATION THERAPY OF ESCITALOPRAM AND L-METHYLFOLATE IN COMPARISON TO USAGE OF MONOTHERAPY

[1]Muhammad Muneeb Amjad, [1]Awais Ahmed, [2]Shumaila Qasim
[1]House Officer in Allied Hospital Faisalabad
[2]Woman Medical Officer (WMO) in THQ Hospital, 90SB, Sargodha

Abstract:
Objective: *Our objective in this research was the assessment and evaluation of L-Methyl folate efficacy in the combine form along with the escitalopram in comparison to the escitalopram monotherapy in the depression.*
Place and Duration of Study: *The study was carried out from Jan, 18 to Jun, 18 in 6 months at Mayo Hospital Lahore.*
Material and Methods: *The number of patients was 260 which were having Major Depression's primary diagnosis along with score above fourteen on depression (Hamilton rating scale) i.e. HAM-D & they were selected in this study of Randomized Controlled Trial. The patients were classified in two groups & then Group-A was given ten milligram (Escitalopram) in addition to placebo while group B was given ten milligram (Escitalopram) in addition to L-Methyl folate in the form of a dose of 15 mg. Group-A and Group-B were assessed again after 1 month & the scores of HAM-D were measured.*
Results: *In the total number of 260 patients, the response was there in 70.8 percent i.e. 184 & 29.2 percent i.e. 76 never responded to the treatment. The patients were 82 at 63.1 percent which have shown response to treatment but 48 patients at 36.9 percent never responded and these patients were total 130 which were treated along with SSRI. In total 130 patients which were treated with escitalopram & L-Methyl folate, 28 at 21.5 percent never responded and 102 at 78.5 percent showed response to treatment. With a confidence interval of 95 percent, the P-value was observed as (0.006) which showed that primary difference of both interventions was statistically significant.*
Conclusion: *Our final result was that a combination of L-Methyl folate & SSRI in depression may prove to be more efficient as compared to the Escitalopram monotherapy.*
Keywords: *Major depressive disorder, Escitalopram, L-Methyl folate.*

Corresponding author:
Muhammad Muneeb Amjad,
House Officer in Allied Hospital,
Faisalabad.

QR code

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INTRODUCTION:

Depressive disorders were identified as the 2nd leading cause of disability by Global Burden of Disease, 2010. Moreover, Major Depressive Disorder was made responsible for 8.2 percent of global burden of disease. In spite of the development in the level of understanding of the introduction of several classes of antidepressants and psychopharmacology, it was found that just 60 percent to 70 percent of patients with depression responded to the antidepressant therapy alone. It was beyond the first line cure, and the present guidelines approved either switching of the initial antidepressant or augmentation. A new technique to increase the antidepressants therapeutic efficacy is developing with the combination of multiple concurrent pharmacologic procedures from anti-depressant treatment initiation instead of delay until and unless numerous interventions fail. The technique has given rise to the introduction of nutraceuticals in which Omega 3 Fatty acid, L-Methyl folate, S-Adenosyl Methionine & Vitamin E are included [1].

In the depressed patients, research have found low RBC folate concentrations or low serum folate levels. Many other researches have recommended that low folate levels are linked along with minimized response to antidepressants that may suggest that folic acid could be used in any way to augment antidepressants. The evidence is that the combination of both Methyl folate and antidepressants from start of treatment increases the antidepressant efficacy, lowers relapse rates & attains higher remission rates. The major benefit of augmenting a traditional antidepressant along with methyl folate is that it has low liability for all types of side effects. The L-Methyl folate modulates mixture of monoamines in which dopamine, serotonin & norepinephrine are included. To take it as an outcome, the L-Methyl folate is a (TTM) i.e. trimonoamine modulator & indirect regulator of monoamine concentrations & trimonoamine neurotransmitter synthesis [2].

The theoretical boost of monoamine synthesis will be achieved by repletion of L-Methyl folate levels & this will also enhance the efficiency of anti-depressants. During a research, it was observed that the addition of L-Methyl folate to (SSRIs) that is a selective serotonin reuptake inhibitor or (SNRIs) that is serotonin-norepinephrine reuptake inhibitors when taking start of pharmacotherapy results in the greater reduction of depressive symptoms in lesser time duration as compared to with SNRI or SSRI monotherapy. In connection with the research, efficacy of the L-Methyl folate & SSRI was observed 18.5 percent in comparison to 7.04 percent efficacy of SNRI or SSRI monotherapy [3]. The logical significance of this research depends on the fact that thirty percent of the patients who are depressed do not respond to antidepressants alone. According to the above-mentioned research, the L-Methyl folate is the most promising augmenting agent to antidepressants while the result of this medicine needs also to be assessed in the patients from our population. The present research will be the very 1st study in Pakistan which has looked into the deep effects of L-Methyl folate in depression.

MATERIAL AND METHODS:

This research was carried out at Mayo Hospital Lahore in the duration from Jan, 18 to Jun, 18. The number of patients were 260 which were having a Major Depressive Disorder primary diagnosis both single and recurrent. They all were along with a score of greater than fourteen on HAM-D scale, selected in Randomized Control Trial. After informed consent, they were registered in the study & ethical approval was taken from ethical committee of (AFIMH). The age was ranging between 18 to 60 years & they have underwent their therapeutic interventions from initiation of the treatment.

The following was the criteria which excluded patients from this research: oral contraceptives , antipsychotics, anticonvulsants, psycho stimulants, patients along with serious suicidal risk & also patients taking Lithium, children and adolescents, breastfeeding mothers, non-consenting patients, the presence of psychotic features in current episode or history of psychotic characteristics, any bipolar disorder both at present or previously, any psychotic complexity at present or previous, any deformity or complications such as diabetes mellitus (DM), pregnancy, hypertension or antipsychotics.

By using the following values, sample size was measured by W.H.O sample size calculator: five percent Power of the test, level of significance, eighty percent anticipated population, in group A, 8.5 percent Anticipated population and in group B, 7.04 percent. Consecutive sampling was the sampling technique used in this study & patients were divided into 2 groups by using random number tables. All the patients who were up to ICD-10 criteria were identified with depression after taking history in detail. (HAM.D) i.e. Hamilton Rating Scale for the depression was used for all these under study patients. The patients who were having a score of fourteen or greater were registered in this research. Two groups were made then including: 1- Control group-A which were given SSRI i.e. Escitalopram

Table-I: Baseline patient characteristics

RESULTS:

Patient characteristics	SSRI Only (130)	SSRI & L-Methyl folate (130)	*p*-value
Gender Male Female	58 72	63 67	0.532
Age 20-40 years 41-60 years SD ± Mean	 88 42 37.4 ± 10.4	 92 38 36.5 ± 8.7	0.590
Marital status Married Single Divorced/widow	 103 20 07	 109 16 05	0.623
Occupational status Employed Unemployed House wife	 50 24 56	 63 19 48	0.087
Educational status Educated Uneducated	 82 48	 88 42	0.149
Severity of Depression Moderate Severe	 76 54	 81 49	0.527
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

just with a placebo. 2- The intervention group-B that was given L- Methyl folate & SSRI (Escitalopram).

The lottery technique was used to allocate patients to any of the 2 groups. Both the groups reviewed right after a period of one month. To know the improvement in depressive symptoms, (HAM-D) was effectively used. All the confounding variables were diagnosed & were not included by applying the above-mentioned exclusion criteria. SPSS 19.0 was used to analyse the data. Standard deviation & mean were measured for the quantitative variables for example age of a patient. Percentages & frequency were measured for the qualitative variables e.g. efficacy of a patient or gender.

To compare the scores among two groups, independent sample t-test was used. By stratification, effect modifiers e.g. gender, age, occupation, education, & status of the marital were controlled. Then we used Chi-square test (P-value < 0.05).

All the patient's characteristics have been depicted in Table – I. The total number of patients was 260 and Mean age was ranging between 36.9 ± 9.6 years. The female patients were 139 at the rate of 53.5 percent & male patients were 121 at the rate of 46.5 percent. The number of married patients was 212 i.e. 81.5 percent. Remaining thirty-six at 13.8 percent were single & twelve at 4.6 percent were widowed or divorced. In terms of occupation, 103 i.e. 39.6 percent were housewives, 113 at 43.4 percent were employed & 43 at 16.5 percent were counted un-employed. The number of educated patients was 170 at 65.4 percent & ninety at 34.6 percent were found un-educated. On 1st interview, in HAM-D scores the total of 157 i.e. 60.4 percent were in moderately depressed range which was fourteen to eighteen followed by those in severe range ranging between 19 to 23. These were 93 at 35.7 percent & ten at 3.8 percent were in quite severely depressed range observed greater than twenty-three. The mean of ± SD for (HAM-D) on the day of 1st interview was

found ranging between 18.06 ± 2.20. But after the treatment (HAM-D) score has demonstrated the mean ± SD of ranging between 11.53 ± 2.67 along with scores coming down to mild range in total of 173 i.e. 66.5 patients. In total 260 patients the response which was an uplifting into the mood measured by the change in (HAM-D). It was found present in total of 184 patients. It implies that in this trial a total of 70.8 percent patients responded as a whole and 76 patients at the rate of 29.2 percent never responded to this process of treatment.

Table-II: Cross tabulated treatment 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%	

In total of 130 patients which were treated along with Escitalopram, 48 did not respond while 82 have shown their response. It implies that 63.1 percent patients have an uplifting in their mood and mean while 36.9 percent never showed any sort of proper response. In total 130 patients which were treated along with L- Methyl folate & Escitalopram, 28 did not response and 102 have shown their response to treatment.

It implies that 78.5 percent patients have shown an uplifting in mood and mean while only 21.5 percent never showed any suitable response. In order to determine the main difference in the response of both the treatments, Chi square test was utilized. Right after application of test (P-value = 0.006) which was below (0.05) (Table – II). It means that variation in both treatments was significant and clear. It was proved about the combination of L-Methyl folate & Escitalopram was more efficient as compare to Escitalopram alone in the treatment of moderate towards severe depression.

DISCUSSION:

Remission is the aim of the treatment in major depression. The response to treatment is specifically defined as a big clinically meaningful reduction in all the symptoms. Meanwhile the response which never falls in the category of remission is a suboptimal due to the reason that it is linked along with potentially higher risk for suicide, higher levels of health care use, more impaired psychosocial functioning, continued disabling symptoms, higher rates of relapse & recurrence and poorer work productivity [4]. In spite of the improvements in the introduction of many classes of antidepressants & psychopharmacology, just 60 percent to 70 percent of the patients along with depression respond to antidepressant therapy alone. Other than first-line cure, the present guidelines approved either switching of the initial antidepressant or augmentation [5].

The after effects of this medicine must be assessed in the patients of our population also. In this way the research helped us to ensure the effects of L-Methyl folate in the depressed patients in our country. The results of this study declare that adjunctive L-Methyl folate and SSRIs at 15 mg per day have created bigger response rates in the patients as compared to with SSRIs plus placebo [6]. Another study showed that by adding L-Methyl folate to selective serotonin reuptake inhibitors i.e. SSRIs or serotonin–norepinephrine reuptake inhibitors I.e [7]. SNRIs whenever starting pharmacotherapy can result in much bigger reduction of depressive symptoms in much lesser time duration as compared to with SNRI or SSRI monotherapy. This research shows that the efficacy of SSRI & L-Methyl folate was found 18.5 percent as compared to only 7.04 percent efficacy of SNRI or SSRI monotherapy which clearly shows a main difference in the response of 11.5 percent [8]. The Papa Kostas et all have shown that adjunctive L-methyl folate at 15 mg per day has made clearly bigger efficacy as compared to continued SSRI therapy plus placebo on the primary result measures which is both degree of change in depression symptom score & response rate and also 2 secondary outcome measures of the symptom with severity [9]. The number which was required to treat for the response was almost 6 in the favour of adjunctive L-methyl folate at the rate of 15 mg per day. The L-Methyl folate was very well tolerated along with the

rates of hostile events & no different from those reported along with placebo. The trials of both the adjunctive L-Methyl folate & monotherapy have been reported in this study [10]. Furthermore, 4 monotherapy trials reviewed somewhere else, suggested almost the same efficacy. Out of them 2 were open trials & 2 were double-blind trials comparing L-Methyl folate along with antidepressants. The very 1st adjunctive trial was the double-blind placebo-controlled trial in twenty-four patients with the main depression who had lesser (RBC) folate levels. The L-Methyl folate at fifteen mg per day was in addition to the ongoing antidepressant cure. At the intervals of three months & six months the patients who were receiving adjunctive L-Methyl folate showed a big improvement as compare to those in placebo group [11].

A research based on making use of vitamins as adjunctive agents and it was observed that Vitamins B never increased twelve-week efficacy of antidepressant cure while they increased & sustained antidepressant response over the period of one year. A research conducted on 75 patients proved that certain biological markers as C-reactive protein i.e [12]. (CRP), BRP & lows adenosylmethionine levels predicted a quite improved response to the L-methyl folate. Another research conducted to look into long term effects of L-Methyl folate over the period of twelve months. It was observed that out of sixty-eight patients who met the criteria for the twelve months open label phase which was 38 percent at n = 26 and achieved complete recovery & non-experienced a recurrence of (MDD). For all those patients entering into the open label phase in remission at n=1 and 91 percent at n=10 also attained complete recovery along with l-methyl folate at fifteen mg & non-experienced recurrence or a relapse. Out of fifty-seven patients who were entered in open label phase as non-remitted were 61 percent at n=35 also attained remission. Of all those patients who were entered in open label phase along with a response without any remission at n=4, and 50 percent at n=2 had complete recovery. Those patients who were entering in open label phase without any response at n=53 and were 26 percent at n=14 also met all the recovery requirements [13].

The research has struggled to provide a basis to look into the effect of L-Methyl folate in all the patients in Pakistan but even then, there were some drawbacks. The time duration of research could have been enhanced to attain long term effects. Moreover, side effects could also have been described. This trial also never included some populations of the patients like children & adolescents, comorbid illness, patients along with bipolar disorder, active substance use disorders and psychotic major depression and these can be made part of future researches [14].

In short, this research is the very 1st such type of study in Pakistan which shows that L-Methyl folate is an effective adjunctive cure for the patients of depression. Past researches about folic acid, folic acid & L-Methyl folate also favour this contention. The L-Methyl folate was very well tolerated & can be chosen by patients for that very cause. The effectiveness of L-Methyl folate in the resistant depression has never been compared along with that of many other adjunctive agents. It also has no long-term use of agent that has been reported in any main depression [15].

The main value of long term usage of the L-Methyl folate in patients along with recurrent depression is especially intriguing. A more significant aspect to look into it is either there are some cases of severe depression as is shown in this research is possible to get a rather much better response on starting treatment along with a combination of L-Methyl folate & SSRI as comparing it to SSRI alone [16]. While this aspect of treatment needs more research to ensure all the benefits of using augmentative technique from the beginning & following this procedure through in the long-term maintenance treatment. The main limitation is short term duration of this research that can be increased in future trials for a long-term analysis of all the effects of using L-Methyl folate.

CONCLUSION:

SSRI and L-Methyl folate have been found more effective as compare to SSRI in the patients of depression at least in the duration of short term. The upcoming researches for comparing the 2 interventions over entire length of approved time duration of treatment must be undertaken which is minimum six months' period.

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