ROLE OF L: METHYLFOLATE WITH ESCITALOPRAM FROM TREATMENT INITIATION IN DEPRESSION

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ABSTRACT: BACKGROUND: Patients suffering from depressive episode show incomplete response despite proper use of anti-depressants. This could be due to variety of factors. One factor of utmost importance is low CNS and serum folate levels.

AIMS: Evaluate the efficacy of L-methylfolate in combination with Escitalopram compared to Escitalopram monotherapy in moderate to severe depressive patients.

SETTINGS AND DESIGN: Observational study of L-methylfolate plus Escitalopram at treatment initiation (n=30) and Escitalopram monotherapy (n=30) at outdoor patient department.

METHODS AND MATERIAL: 30 patients of moderate to severe depressive episode were enrolled in each group. All the patients were evaluated for response and side effects on 14, 21, 45, 60 days on Hamilton depression rating scale and adverse drug reaction proforma.

STATISTICAL ANALYSIS: Mann Whitney test.

RESULTS: Major improvement was experienced by 96.7% of L-methylfolate plus Escitalopram group compared to 46.7% of Escitalopram monotherapy group. Response as early as 14 days were reported by 20% patients in combination group. There was no significant differences between groups in adverse events. Conclusion: L-methylfolate plus Escitalopram at treatment onset was more effective, well tolerated in improving depressive symptoms.

KEYWORDS: L-methylfolate (L-MTF), Escitalopram, Depression.

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INTRODUCTION: Major depressive disorder (MDD) currently ranks fourth leading disease burden world-wide and is expected to become second global disease burden in 2020.¹ Though it is viewed as one of the most treatable conditions, it tends to be recurrent.² The sequenced treatment alternatives to relieve depression (STAR*D) study demonstrated disappointing remission rates (30%) for initial antidepressant monotherapy and disappointing rates of not maintaining remission (>70%) attained by the first agent.^{3,4,5} Administering combination or adjunctive agents at the initiation of treatment in lieu of sequenced treatment trials represents a major paradigm shift in the treatment of MDD.⁶ Six clinical trials suggest that combinations from the start of treatment may lead to more rapid clinical outcomes, higher remission rates and lower relapse rates when compared with sequentially administered single antidepressants.⁷⁻¹²

Evidence from the open and blinded studies have demonstrated the efficacy of Methyl-tetrahydrofolate in combination with anti-depressants at the initiation of therapy or as monotherapy in depressed patients with normal and low folate levels.^{10,13-15}

L-Methylfolate (L-MTF), the bioavailable form of folate is required in the central nervous system to aid in the synthesis of monoamines.¹⁶

Suboptimal serum, red blood cell folate levels and C.N.S. folate status have been associated with more severe symptoms of depression, poorer response to antidepressant drugs, longer duration of illness, later onset of clinical improvement and greater treatment resistance.¹⁷⁻²⁴ Depressive episodes are also linked with the common inborn error of metabolism associated with reduced L-MTF. This inborn error is the Methyltetrahydrofolate reductase (MTHFR) polymorphism.²⁵⁻²⁶

To see the effect of L-MTF it must be used with an antidepressant. The present observational study was done on Escitalopram, an antidepressant widely used, easily available, safe and class (SSRI) representative. The study assesses the clinical outcome and tolerability in patients receiving combination of L-MTF plus Escitalopram at the initiation of treatment compared with Escitalopram monotherapy.

MATERIAL & METHODS: Sample – The study included the patients attending the psychiatry outpatient clinic at M.Y.H. Hospital – M.G.M. Medical college Indore.

INCLUSION & EXCLUSION CRITERIA: The patients aged 18-60 years, newly diagnosed as Depression, having moderate to severe severity as per ICD-10 criteria.²⁷ were taken for the study after informed consent. Patients taking supplemental folic acid, having current or a history of psychotic episodes, history of bipolar disorder, patient with suicidal tendencies or the patients having significant physical and neurological illness were excluded from the study.

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Method of Study: The patients who full filled the selection criteria were included in the study. Semi structured proforma and HDRS (Hamilton depression rating scale) was administered.

Patients were divided in two groups based on the observation, one group was of L-MTF plus Escitalopram and other was of Escitalopram alone. The score was calculated for both the groups. The assessment on HDRS was done again in the follow up at 14, 21, 45 & 60 days. 50% or more reduction in HDRS was considered as response. Adverse drug reaction were noted as per the proforma.

Statistical Analysis:
Mann Whitney's Test:

RESULT: The sample consisted of 60 patients, 30 in each group; with the mean age of 37 years in Escitalopram group and 32.23 years in combination group. No significant sex differentiation was observed in two groups. The average duration of illness was comparable in both groups. The dosages of Escitalopram used in both the groups were similar.

DISCUSSION: The present study demonstrated that by adding L-MTF to Escitalopram at the initiation of treatment led to greater number of responders comparison to Escitalopram monotherapy. This number was almost twice more than the Escitalopram group.

The finding of significant greater response was replicated in six controlled studies but they have used combination of two anti-depressants rather than combination of Escitalopram and L methylfolate used in the present study.⁷⁻¹² Coopen A et al found similar results using Fluoxetine with folic acid.²⁸

Our study has used L-MTF, biologically active form of folate and the only form that crosses blood brain barrier. Study by Lawrence D et al also demonstrated major improvement in depressive symptoms and functions in L-MTF plus SSRI or SNRI from treatment initiation, compared to SSRI or SNRI monotherapy.²⁹

However our observation is only on Escitalopram making it more class specific (Only SSRI) and even no intraclass variation among SSRIs could have affected the result.

Additionally 20% patients on L-MTF plus Escitalopram had response as early as 2 weeks. The findings were similar to Lawrence D et al who found time for major improvement in combination group was 23% shorter than monotherapy.²⁹ the reason for rapid improvement could be the synergistic action of Escitalopram and L-MTF. L-MTF may facilitate a more rapid response to reuptake inhibitors by regulating upstream synthesis of serotonin, nor epinephrine and dopamine sufficiently to help achieve and maintain 'Downstream' response of reuptake inhibition.³⁰

Another reason could be because 70% of the patients with the MTHFR polymorphism may have reduced CNS L-MTF level.²⁶ thus the patient given L-MTF from the initiation of therapy achieved better results. All adverse events in both groups were mild and tolerable. No drop outs were reported in both the groups due to adverse events.

LIMITATIONS: The present study is limited by being open label and non-randomized. Only Escitalopram is being used in present study. More studies with other SSRI's and other classes are required to validate the findings. Folate levels at base line could have given more definite results.

CONCLUSIONS: The study shows improvement and rapid response when L-MTF was added to Escitalopram from initiation.

It paves way for further research in the quest to achieve early response and full remission in depressed patients.

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Time duration	Escitalopram		L-methylfolate plus Escitalopram	
	n=30		n=30	
	No. of responders	% of responders	No. of responders	% of responders
0 day	0	0	0	0
14 day	1	3.3	6	20
21 day	5	16.7	11	36.7
45 day	14	46.7	29	96.7
60 day	14	46.7	29	96.7

Table 1: Percentage improvement during the course of study

(Parameter evaluated: HDRS > 50% reduction in scores from day 0)

Time	Escitalopram (HDRS)	L-Methylfolate + Escitalopram (HDRS)	Mann-Whitney U value	(% of difference) Inc. in no. of Responders compared to escitalopram group
0 day	23.03±0.73	24.68±1.20	596.00	0
14 day	19.60±0.92	18.90±1.33	414.50	16.7
21 day	15.33±1.05	8.87±0.76*	146.50	20
45 day	12.93±1.02	3.43±0.67*	55.00	50
60 day	7.50±0.67	3.43±0.67*	146.50	50

Table 2: Hamilton Depression Rating Score, Through the Course of Study

Mann Whitney's test.

Values are mean±SEM, n=30 in each group.

*P<0.001 as compared to escitalopram group.

Tables shows that L-MTF plus Escitalopram did not demonstrate any significant decrease in HDRS on day 14, but 20% (n=6) receiving this combination demonstrated response (50% reduction in HDRS) vs. 3.3% (n=1) of Escitalopram group.

Further, L-MTF plus Escitalopram group demonstrated significant decrease in HDRS ($p<0.001$) at 21,45 and 60 days with 36.7%(n=11), 96.7%(n=29) and 96.7%(n=29) responders (50% reduction in HDRS) compared with Escitalopram monotherapy group 16.7 (n=5), 46.7% (n=14),46.7%(n=14) respectively.

Adverse Events	Escitalopram (n=30)	L-methylfolate plus Escitalopram (n=30)
Gastrointestinal disorders		
Nausea	1(3.33%)	3(10%)
Constipation	1(3.33)	3(10%)
CNS disorder		
Somnolence	1(3.33%)	3(10%)
Dizziness	3(10%)	1(3.33%)
Agitation	3(10%)	None
Table 3: Frequency of overall Adverse Events Observed		

As per table nausea, constipation & somnolence were reported more in combination group while dizziness, agitation in Escitalopram group.