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Original Research Article

Role of Adjunctive L-Methylfolate with Selective Serotonin Reuptake Inhibitor in Depressed Patients at a Tertiary Care Centre

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ABSTRACT

Background: Present study was aimed to determine clinical outcome and tolerability in patients receiving combination of L-MTF plus Escitalopram at the initiation of treatment compared with Escitalopram monotherapy.

Methods: Patients aged 21- 60 years, newly diagnosed as Depression, having moderate to severe severity as per ICD-10 criteria were taken for the study after informed consent.[31] 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 significiant physical and neurological illness were excluded from 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 2,4,6,8 weeks. 50% or more reduction in HDRS was considered as response.

Results: The sample consisted of 70 patients, 35 in each group. No significant sex differentiation was observed as well as average duration of illness was comparable in both groups. 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. L-MTF plus Escitalopram did not demonstrate any significant decrease in HDRS on 2 weeks. Further, L-MTF plus Escitalopram group demonstrated significant decrease in HDRS ($p<0.001$) at 4,6,8 weeks compared with Escitalopram monotherapy group. As per table 3 nausea, constipation & somnolence were reported more in combination group while dizziness, agitation in Escitalopram group.

Conclusions: Greater efficacy was observed with l-methylfolate when used as an adjunct to Escitalopram from initiation. Our present analyses establishes the relative superiority of l-methylfolate plus Escitalopram versus Escitalopram alone in MDD patients during initiation of treatment. More studies with other SSRI's and other classes are required to validate the findings.

Key words: Depression, Escitalopram, L-methylfolate (L-MTF).

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INTRODUCTION

Major depressive disorder (MDD) is a common, one of the most treatable condition yet highly recurrent and potentially fatal illness.[1] Patients with MDD have increased rates of morbidity and mortality, functional impairment, reduced quality of life, and increased risk of suicide.[2] Studies have shown that despite a wide range of options for treating MDD, up to 40% of patients fail to respond to treatment, even after fourth-line therapy.[3]

Patients who do not respond to antidepressants consume a disproportionally larger share of health care resources and have lower work productivity than patients that respond to treat-ment.[4] As even sequential monotherapy with antidepressants fails to produce an adequate response to treatment for a large proportion of patients, augmentation of antidepressant therapy with a second antidepressant, atypical antipsychotics, lithium salts, or other agents has been suggested as a solution when traditional therapy fails. Evidence is accumulating showing that combination therapy in treatment of MDD may produce higher remission rates and lower relapse rates than traditional monotherapy, either as an initial treatment plan or as a strategy for nonresponse to initial treatment.[5-7]

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 Previous researchers suggested that combinations from the initiation of treatment may lead to more rapid clinical outcomes, higher remission rates and lower relapse rates when compared with sequentially administered single anti- depressants.[8-11] Few studies in past have demonstrated the efficacy of Methyl-tetrahydrofolate as adjunctive with anti-depressants at the initiation of therapy or as monotherapy in depressed patients with normal and low folate levels.[12-14]

An association has been observed between folate deficiency, metabolic dysregulation, and inflammation.[15-18] The benefits of folic acid and its biologically active form, l-methylfolate, for treating

MDD have been recognized; also recently recognized are links between folate deficiency and an increased risk for MDD, reduced antidepressant effectiveness, and a more chronic course of illness.[19-21]

The folate cycle plays a central role in the production of catecholamine neurotransmitters, and increasing the synaptic concentration of these transmitters are believed to be one mechanism of action for many antidepressants.[22] Rather than blocking catecholamine reuptake as with the SSRI/SNRI class of compounds, folate works at the presynaptic level to support catecholamine production.[23] Folic acid must undergo enzymatic reduction by methyltetrahydrofolate reductase (MTHFR) to become biologically active. The heterozygous polymorphism of MTHFR has been found in 47%of the normal population and the homozygous polymorphism in 11% of the population. These polymorphisms are known to cause a reduction in MTHFR activity of 34% and 71%, respectively.[24-27] Folate deficiency can also be caused by drugs (such as anticonvulsants, antibiotics, and oral contraceptives), malabsorption syndromes, chronic diseases, and alcohol use.[28] Depression is often associated with weight fluctuation, including anorexia and weight loss, which suggests that low folate levels could be both a cause and a consequence of depression. Low folate blood levels have been associated with poorer or slower response to fluoxetine for MDD, and higher folate levels have been associated with better response to antidepressants.[21,29,30] L-methylfolate is the primary biologically active isomer of folate, does not require MTHFR for biological activity, and is the form of folate that is transported across the blood-brain barrier.[23]

Subotimal 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.[21-26]

The present study was conducted on Escitalopram, an antidepressant widely used, easily available, safe and class (SSRI) representative. Present study was aimed to determine clinical outcome and tolerability in patients receiving combination of L-MTF plus Escitalopram at the initiation of treatment compared with Escitalopram monotherapy.

Table 1: Percentage improvement during study

Time duration	Escitalopram n=35		L-methylfolate plus Escitalopram n=35	
	No. of responders	% of responders	No. of responders	% of responders
0 day	0	0	0	0
2 weeks	2	5.7	8	22.86
4 weeks	6	17.1	17	48.6
6 weeks	15	42.9	31	88.6
8 weeks	17	48.6	32	91.4

Table 2: Assessment on HDRS (Parameter evaluated: HDRS>50% reduction in scores from day 0)

Time	Escitalopram (HDRS)	L-Methylfolate + Escitalopram (HDRS)	(% of difference) Inc. in no. of Responders compared to Escitalopram group
0 day	24.53±0.62	24.02±1.04	0
2 weeks	20.04±0.87	19.87±1.13	17.1
4 weeks	14.89±1.13	9.34±0.49*	31.5
6 weeks	12.78±1.17	3.94±0.98*	45.7
8 weeks	7.84±0.78	3.36±0.63*	42.8

*P<0.001 as compared to escitalopram group.

Table 3: Frequency of overall Adverse Events Observed

Adverse Events	Escitalopram (n=35)	L-methylfolate plus Escitalopram (n=35)
Gastrointestinal disorders		
Nausea, Vomitting	1(2.9%)	2(5.7%)
Constipation	2(5.7%)	3(8.6%)
CNS disorder		
Somnolence	2(5.7%)	3(8.6%)
Dizziness	4(11.4%)	3(8.6%)
Agitation	3(8.6%)	1(2.9%)

MATERIALS & METHODS

Present study was conducted in department of psychiatry, Rama Medical College Hospital & Research Centre, Hapur, UP, India. Patients aged 21- 60 years, newly diagnosed as Depression, having moderate to severe severity as per ICD-10 criteria were taken for the study after informed consent.[31] 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 significiant physical and neurological illness were excluded from 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 2,4,6,8 weeks. 50% or more reduction in HDRS was considered as response. Adverse drug reaction were noted as per the proforma.[32] The dosages of Escitalopram used in both the groups were similar.

OBSERVATIONS & DISCUSSION

The sample consisted of 70 patients, 35 in each group; with the mean age of 35.9 years in Escitalopram group and 33.7 years in combination group. No significant sex differentiation was observed as well as average duration of illness was comparable in both groups.

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.

Tables 2 shows that L-MTF plus Escitalopram did not demonstrate any significant decrease in HDRS on 2 weeks. Further, L-MTF plus Escitalopram group demonstrated significant decrease in HDRS ($p<0.001$) at 4,6,8 weeks compared with Escitalopram monotherapy group. As per table 3 nausea, constipation & somnolence were reported more in combination group while dizziness, agitation in Escitalopram group.

The finding of significant greater response was replicated in previous studies but they have used combination of two anti-depressants rather than combination of Escitalopram and L methylfolate used in the present study.[8-11]

In present study, L-MTF, a biologically active form of folate and the only form that crosses blood brain barrier was used. 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.[33]

Additionally 22.86% patients on L-MTF plus Escitalopram had response as early as 2 weeks. The findings were similar to Pali Rastogi et al[32] and Lawrence D et al[33] who found time for major improvement in combination group was shorter than monotherapy. 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.[32]

Few researchers in past had investigated genetic markers related to folate metabolism to find for their association with MDD.[34-36] The results from these analyses provide further support for the benefits of l-methylfolate as adjunctive treatment for patients not responding adequately to SSRIs and suggest additional avenues for identifying those individuals most likely to respond to this treatment. These results could lead to an opportunity for individualizing treatment approaches for depressed patients unresponsive to initial antidepressant therapy.

CONCLUSIONS

Greater efficacy was observed with l-methylfolate when used as an adjunct to Escitalopram from initiation. Our present analyses establishes the relative superiority of l-methylfolate plus Escitalopram versus Escitalopram alone in MDD patients during initiation of treatment. More studies with other SSRI's and other classes are required to validate the findings.

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