Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v31i2.4350

# EFFICACY OF SERTRALINE WITH L. METHYL FOLATE AND WITHOUT L. METHYL FOLATE IN THE TREATMENT OF MAJOR DEPRESSIVE DISORDER: A COMPARATIVE STUDY

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**Abstract**

**Background:** The objective of this study was to compare the efficacy of Sertraline with L-Methyl folate and without L-Methyl folate in patients with major depressive disorder.

**Methods:** Total of 160 diagnosed of Major Depressive Disorder of either gender patients were included. All patients were examined clinically, and their demographic and medical history was recorded. The patients were divided into two groups with 80 patients. All the patients were treated with Sertraline with L. methyl folate and without L. methyl folate for 2 months.

**Result:** The independent t test indicated that antidepressants resulted in a highly significant difference (p-value <0.00001) in the age of patients in Group B (Sertraline 50 mg/day with L. methyl folate 75 mg/day) as compared to Group A: (Sertraline 50 mg/day) (42.25±11.54 vs 38.27±11.48). The chi-square test indicated that "sleep disturbance" improved significantly in treatment groups ($p<0.05$) for all antidepressant medications at 90 days. The "Weight gain" improved significantly in treatment groups ($p<0.05$) for all antidepressant medications at 90 days. Percentage 37.5 of symptom "Weight gain" reduction was higher for antidepressant Group A: (Sertraline 50 mg/day).

**Conclusion:** It was concluded that L-methyl folate with Sertraline was more successful in relieving depression symptoms and function than mono-therapy group led to substantial symptomatic improvement faster and better tolerated than single drug.

**Keywords:** Sertraline, L. methyl folate, major depressive disorder.

## INTRODUCTION

Major Depressive Disorder (MDD) is a cognitive disorder remaining the different symptoms such as per lack of interest in routine activities, sleep disturbance, poor concentration, lack of appetite and feeling a sense of worthlessness along with suicidal thoughts[1]. Depression and anxiety disorders are individual illnesses coexisting. Patients suffering from both disorders have prone to more psychological, physical, and social impairment than do those suffering from either illness alone.[2] Depression has been associated to a worse quality of life, an increased risk of cardiovascular disease, and an increased chance of mortality[3]. Mental illness and depression in particular has a significant impact on people's capacity to function, their productivity at work, and their mortality[4]. Lifetime prevalence varies, 3% in Japan and 17% in the U.S as twice more common in women than men with a 15% death rate following suicide attempts[5]. Men have a 5% to 12% lifetime risk of depression, whereas women have a 10% to 25% lifetime risk. It is believed that 15% of people suffering from severe depression episodes commit suicide[6]. It's common for depression to begin between the ages of 20 to 45 although it can develop at any time. Previous research in Thailand found that 24.1% of the elderly were depressed, whereas 32.8% of people with cognitive impairment were depressed[7]. Lifetime prevalence varies, 3% in Japan and 17% in the U.S as twice more common in women than men with a 15% death rate following suicide attempts[8]. Pakistan is a South Asian developing country with a mostly Muslim population of almost more than 200 million people. It is the world's sixth most populated country with highest prevalence of depression due to many factors. There was a 47% prevalence of depression among Karachi residents [9]. The total of 33.62 % of men and women had the disease, with the point prevalence ranging from 28.8 % to 66 % for women, and from 10% to 33% for men[10]. When it comes to treating the MDD, patients must make fundamental decisions about their treatment, according to clinical practice guidelines developed by the Depression Guideline Panel of the Agency for Health Care Policy and Research (AHCPR) and the American Psychiatric Association (APA)[11]. In Pakistan, there is the highest depression ratio to multiple factors 47% prevalence of depression among the people of Karachi.[12] Overall mean prevalence in men or women is 33.62%, and 45.5% respectively with a 10-15% suicidal ratio among the Pakistani population.[11]. So it is the best option for psychiatrists to suggest the combination of Sertraline or Paroxetine with L. methyl folate drugs for an immediate response within a short time the decrease the high risk of suicide with a low cost of money and cheap therapy for the major depressive disorder patients. This is the first study in Pakistan to introduce the combination of Sertraline& Paroxetine with L. methyl folate for patients with MDD with a high risk of suicide.One possible mechanism for depression is inflammation, which may reduce monoamines (such as serotonin) synthesis and increase the formation of harmful tryptophan catabolizes in the brain. Interleukin (IL-6) and acute phase C-reactive protein (CRP) levels were considerably greater in depressed patients compared to healthy controls, according to a meta-analysis[13].

The pathophysiology of Major Depressive Disorder may be influenced by the serotonergic system (MDD). The Serotonin Transporter (SERT) in particular may play a significant role as a major site of antidepressant medication activity. After 4 weeks of therapy with paroxetine, several postmortem investigations reported a drop in the density of SERT sites in depressed patients' brains, as well as an 80% reduction in SERT binding in MDD patients[14]. By interacting with the cholinergic, glutaminergic, dopaminergic, or GABAnergic systems, the serotonergic system plays a crucial role in learning and memory[15]. Paroxetine is a powerful and highly selective inhibitor of neuronal serotonin reuptake, with only minor effects on norepinephrine and dopamine neuronal reuptake, and

negligible effect on muscarinic, alpha-1, alpha-2, beta-adrenergic, dopamine ($D_2$),5-HT1,5-$HT_2$, and histamine ($H_1$) receptors[16].Folic acid's active metabolite is 5-Methyl Tetra Hydro Folate (5-MTHF), also known as L-Methyl Folate (LMF). Vasodilation was improved by 5-MTHF, which supports a role for 5-MTHF in increasing the status of Nitric Oxide (NO), an essential vasodilator, as well as endothelial function[17].In adults, depression has been connected to some dietary and physiological factors, including a deficiency in folate and B-12 and an increase in Total Homo Cysteine (tHcy) [18]. Folic acid, 5-Methyltetrahydrofolate (5-MTHF; also known as methyl folate and methyl folate), and folinic acid are three commercially available forms of folate that can be used in conjunction with antidepressants and may help with major depressive disorder[19].

## MATERIALS AND METHODS

Institutional Review Board (IRB) of the Basic Medical Sciences Institute, JPMC, Karachi approved the ethical review of the current study. This prospective research was conducted in collaboration with the Department of Psychiatry OPD, Jinnah Postgraduate Medical Center, Karachi, at the Department of Pharmacology and Therapeutics of the Basic Medical Sciences Institute Jinnah Postgraduate Medical Centre. Inclusion criteria were patients aged 20 years and above of either sex, diagnosed Major Depressive Disorder patients forat least one month and not receiving antidepressant drugs. Exclusion criteria were the patients with psychosis and a high risk of suicide, myocardial infarction, pregnancy and lactation, alcohol dependence, presence of bipolar disorder, medication-induced psychosis or mental illness, anychronic illness, hepatic or renal disease and refused to give consent.

Data Collection Procedure:
Laboratory investigations include:
The level of Oxidative Stress marker like; Interleukin-6 (IL-6) was measured in each group by colorimetric method using commercially available kits Sample collection and measurements: An anticoagulant solution was put into a test tube containing 10 ml of venous blood, which was collected at baseline and at 90 days. There was no evidence of inflammation or oxidative stress in the subjects at baseline, as all subjects were somatically healthy.
Grouping of patients: A total of 160 male and female patients were taken from the psychiatry department and divided into two groups, each group consisted of 80 patients for 2 months. All patients were examined clinically, and their demographic and medical history was recorded.

Group-A was treated with Sertraline 50 mg and Group-B was treated with Sertraline 50 mg and L. methyl folate 75 mg per day.

Statistical Analysis: Data were entered and analyzed using SPSS version 22.0. The independent "t" test was used to compare the means among the different age groups, while numerical factors like age (in years) were provided as Mean + Standard deviation. An interval of 95% was used to calculate all the data. It was considered significant if the P-value was greater than 0.05.

## RESULTS

A total of 160 diagnosed major depressive disorder patients were selected for this study. The independent t test indicated that antidepressants resulted in a highly significant difference (p-value <0.00001) in the age of patients in Group B (Sertraline 50 mg/day with L. methyl folate 75 mg/day) as compared to Group A: (Sertraline 50 mg/day) (42.25±11.54 vs 38.27±11.48).

**Table 1.0** Distribution of patients according to comparison of mean age (in groups) values between the treatment groups (n = 160)

| Gender | Group A: (n=80) | Group B: (n=80) | Total |
|---|---|---|---|
| Male | 35(43.75%) | 32(40.0%) | 67(41.87%) |
| Female | 45 (56.25%) | 48(60.0%) | 93(58.12%) |
| Age in groups | - | - | - |
| 20 to 30 years | 29(36.2%) | 8(10.0%) | 37(23.12%) |
| 31 to 40 years | 16(20.0%) | 30(37.5%) | 46(28. 75%) |
| 41 to 50 years | 22(27.5%) | 23(28.8%) | 45(28.1%) |
| 51 to 60 years | 9(11.2%) | 7(8.8%) | 16(10%) |
| > 60 years | 4(5.0%) | 12(15.0%) | 16(10%) |

In this table distribution of patients according to comparison of mean age (in groups) values between the treatment groups (n = 160) are given. In terms of efficacy, treatment with Group A: (Sertraline 50 mg/day), and Group B: (Sertraline 50 mg/day with L. methyl folate 75 mg/day) did not show any effect with regard to the age of patients. In treatment groups female were found to be in higher percentage as compared in males i.e. 58%) vs 42% respectively. No significant difference in the cure rate was noticed among treatment groups in females as compared to males (p=0.812).

**Table 2.0** Distribution of patients according to the comparison of sleep disturbance at different follow-up periods between the treatment groups(n=160)

| Symptom | Treatment Group | Follow up visit | | | | Percentage decreased 0 – 90 days | P-value |
|---|---|---|---|---|---|---|---|
| | | Dayi0 | Dayi30 | Dayi60 | Dayi90 | | |
| Sleep Disturbance | Group A: (Sertraline 50 mg/day) (n=80) | 80 (100%) | 62 (77.5%) | 55 (68.75%) | 45 (56.25%) | 43.25%* | 0.007 |
| | Group B: (Sertraline 50 mg/day with L. methyl folate 75 mg/day), (n=80) | 80 (100%) | 60 (75%) | 52 (65%) | 32 (40.0%) | 60.0%* | 0.001 |

* P-value <0.05 is statistically significant

The chi-square test indicated that "sleep disturbance" improved significantly in treatment groups ($p<0.05$) for all antidepressant medications at 90 days, this improvement was slightly but significantly larger for all antidepressant medications. Percentage 60.0 of "sleep disturbance" reduction was higher for antidepressant Group B: (Sertraline 50 mg/day with L. methyl folate 75 mg/day) than 43.25% for Group A: (Sertraline 50 mg/day) Table 2. However, the findings of this study indicated that antidepressants Group B:(Sertraline 50 mg/day with L. methyl folate 75 mg/day) resulted in a significantly great reduction in symptom "sleep disturbance" than Group A (Sertraline 50 mg/day) at 90 days of follow-up visits.

**Table 3.0** Distribution of patients according to the comparison of weight gain at different follow-up periods between the treatment groups(n = 160)

| Symptom | Treatment Groups | Follow up visit at | | | | Percentage decreased 0 – 90 days | P-value |
|---|---|---|---|---|---|---|---|
| | | Day 0 | Day 30 | Day 60 | Day 90 | | |
| Weight gain | Group A: (Sertraline 50 mg/day) (n=80) | 80 (100%) | 80 (100%) | 65 (81.25%) | 60 (75.0%) | 25.0% | <0.0001 |
| | Group B: (Sertraline 50 mg/day with L. methyl folate 75 mg/day), (n=80) | 80 (100%) | 80 (100%) | 62 (77.5%) | 50 (62.5%) | 37.5% | <0.0001 |

* P-value > 0.05 is statistically significant

By applying the chi-square test, the "Weight gain" improved significantly among treatment groups ($p<0.05$) for all antidepressant medications at 90 days Table 3. Percentage 37.5 of "Weight gain" reduction was higher for antidepressant Group B: (Sertraline 50 mg/day with L. methyl folate 75 mg/day) than 25.0% Group A (Sertraline 50 mg/day) Table 3. However, the findings of this study indicated that antidepressants Group B (Sertraline 50 mg/day with L. methyl folate 75 mg/day) resulted in a significantly great reduction (p-value > 0.05) in "Weight gain" than Group A at 90 days of follow-up visits.

**Table 4.0** Distribution of patients according to the comparison of mean values of different Interleukins (IL-6) between the treatment groups (n =160)

| Treatment Groups | Interleukin-6 (IL-6) | | Percentage decreased 0 – 90 days | P-value |
|---|---|---|---|---|
| | IL6-0 | IL6-90 | | |
| Group A: (n=80) | 14.06±1.97 | 14.58±1.29 | 52.0% | > 0.05 |
| Group B: (n=80) | 12.99±2.08 | 14.55±1.32 | 1.56% | > 0.05 |

The independent t test indicated that antidepressants resulted in a highly significant difference (p-value <0.00001) in the Interleukin (IL6-0) of patients in Group B (Sertraline 50 mg/day with L. methyl folate 75 mg/day) as compared to Group A (Sertraline 50 mg/day) (12.99±2.08 vs 14.06±1.97) respectively. In terms of efficacy, treatment with Group A did not show any effect with regards to the Interleukin (IL6-0) of patients as shown in Table 4. On the other hand in resulted no significant difference (p-value > 0.05) in the Interleukin (IL6-90) of patients in Group B (Sertraline 50 mg/day with L. methyl folate 75 mg/day) as compared to Group A (Sertraline 50 mg/day) (14.55±1.32 vs 14.58±1.29) respectively. In terms of efficacy, treatment with Group A did not show any effect with regards to the Interleukin (IL6-90) of patients as shown in Table 4.

## DISCUSSION

In the United States, Depression affects about 16% of people at some point in their lives, making it one of the most common mental illnesses there[20] even though the disease is widespread and severe, its exact mechanism is still a mystery. There is a need for a wide range of therapy choices for depression because of its complex neurobiology and genetics. No clinically meaningful indicators exist to aid in the selection of an appropriate course of therapy[21]. In patients with MDD who had not responded to SSRIs[22] found that 7.5 mg of L methylfolate was no better than placebo as an augmentation drug, however, 15 mg of L. methyl folate per day was substantially different from the placebo. Uncertainty exists over L. methyl folate dosage and efficacy as well as possible side effects. We also observed that patients receiving adjunctive L-methyl folate showed a lower overall and depression-specific cost of treatment than did the group receiving an adjunctive Second-Generation atypical Antipsychotic (SGA). The difference in cost of treatment was not simply attributable to the higher overall prescription costs in the SGA group compared with the L-methyl folate group, since the medical cost categories were also found to be higher in the Second-Generation atypical Antipsychotic (SGA) group for all-cause as well as depression-related costs. The adverse effects of Second Generation atypical Antipsychotics (SGAs) such as sedation, sexual dysfunction, glucose abnormalities, and weight gain which are not associated with L-methyl folate, may have contributed to the additional medical utilization in the SGA group. It is noteworthy that the majority of patients who received L-methyl folate utilized 7.5 mg/day, a dose that has not been shown to have significant adjunctive efficacy in randomized controlled trials. Since a recent trial has shown that 15 mg/ day of L-methyl folate for adjunctive therapy of difficult-to-treat MDD is effective, the findings of the current analysis may underestimate the potential utility of this strategy[23]. A prospective study is being conducted to compare the effectiveness of two study drugs containing L-Methyl folate and without L-Methyl folate in patients with major depressive disorder. The results of this trial showed that a larger proportion of individuals with severe depressive disorder were able to reduce their symptoms after beginning treatment with L-methyl folate.

Compared to Sertraline 50 mg/day, the combination of L-methyl folate and Sertraline 50 mg/day at the beginning of treatment led to a more fast progress in depression symptoms and functions. With L methyl folate plus Sertraline 50 mg/day from the start of treatment, a considerable improvement in depression symptoms and function was achieved more quickly than with starting Sertraline 50 mg/day alone, according to this study Patients in the L-methyl folate plus Sertraline 50 mg/day group improved significantly more than those in the Sertraline 50 mg/day mono-therapy group by more than two and a half times. A similar impact was seen in individuals with mild to moderate functional impairment as well as those with severe functional impairment. Several controlled studies have confirmed these results, which indicate that patients treated initially with two antidepressants experienced significantly higher remission rates than those treated with a single drug [24-27]. A study conducted by Angela Hardin in 2020 at the National University of Natural Medicine (NUNM) Health Centers, Portland, Oregon revealed that fatigue and depression often coexist, however, the presence of both is not always related. The main strength of his case study is the drastic improvement in the patient's mood and energy, which can likely be attributed to high-dose L-methyl folate therapy. In fact, in his study, the treatment was so effective in increasing energy level that the patient had to decrease the dosage at one point to avoid sleep disturbance, fatigue and depression remained until she increased her L-methyl folate dose to 10 mg. Patients receiving L-methyl folate plus Sertraline 50 mg/day had a median time to major improvement of 23 % shorter (90 days) than those taking Sertraline 50 mg/day mono-therapy. After starting L-methyl folate plus Sertraline 50 mg/day, individuals with greater functional impairment experienced a notable improvement in symptoms 43 % faster (60 days sooner) than when taking Sertraline 50 mg/day alone. Adverse events were not substantially different between the two treatment groups; however, L-methyl folate Sertraline 50 mg/day combination therapy had a considerably lower rate of dropouts due to adverse events than the other treatment group. To help patients who are less motivated or pessimistic about their chances of recovery, reduce the severity or incidence of unpleasant symptoms and obtain fast beneficial outcomes of therapy. Supplemental L-Methyl folate was found to be more effective than SSRIs in this trial. When commencing medication, L-Methyl folate can lead to a bigger reduction in depression symptoms in a shorter period than SSRI mono-therapy, according to another study SSRI mono-therapy, on the other hand, is ineffective [28,29]. The effectiveness of L-Methyl folate plus SSRI was found to be 18.5%, whereas the effectiveness of SSRI or SNRI monotherapy was found to be 7.04%, indicating a difference in response of 11.5%. (Ginsberg et al., 2011a) L-methylfolate (15mg/day) was shown to be significantly more effective than SSRI therapy plus placebo in Papakostas and colleagues' studies, both in terms of response rate and degree of change in depression symptom score, as well as in two secondary outcome measurements of the severity of symptoms[30].To summarize, this is the first research in Pakistan to show that L-Methyl folate is an effective therapy for depression when used in conjunction with other medications. Folic acid, folinic acid, and L-Methyl folate have all been studied in the past, and the results confirm this claim. Additionally, if any one suffers from severe depression, this study demonstrates that starting therapy with a combination of SSRI and L-Methyl folate is superior to starting treatment with SSRI alone because of the improved response. However, greater research is needed to prove the benefits of employing strategy from the beginning and following it through in long-term maintenance therapy. An important weakness is the short study period, which should be improved in future studies to examine the effects of L-Methyl folate over the long term. Adipocytes have been shown to produce and secrete many cytokines, including leptin, tumor necrosis factor (TNFá), and interleukin-6 (IL-6). IL-6 is a cytokine that mediates inflammatory reactions and is produced by a variety of cell types, including immunological and adipose tissue cells. IL-6 is unique among cytokines in that its principal effects occur at locations far from its source. As a result, IL-6 has earned the moniker "endocrine cytokine." IL-6 levels in the blood are a substantial proatherogenic cytokine[31].

## CONCLUSION

It was concluded that, within 90 days, Sertraline with L-methyl folate and was more successful in relieving depression symptoms and function than other single Sertraline group, led to substantial symptomatic improvement faster than mono-therapy. Combining an antidepressant with L-methylfolate resulted in more fast improvement in both symptomatology and function compared to antidepressant mono-therapy.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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