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RESEARCH ARTICLE

The Effect of Adjuvant Therapy with Folic Acid and Methylcobalamin on Clinical Improvement and Interleukin-6 Levels in Patients with Depression Receiving Fluoxetine

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ABSTRACT

Depression is a multifactorial psychiatric disorder associated with neurotransmitter imbalance and neuroinflammatory processes involving elevated interleukin-6 (IL-6) levels. Despite the efficacy of selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, treatment response varies, partly due to folate and vitamin B12 deficiencies that impair neurotransmitter synthesis and methylation pathways. Folic acid and methylcobalamin supplementation may enhance antidepressant efficacy through neurochemical modulation and anti-inflammatory effects. Objective: This study aimed to evaluate the effect of adjuvant therapy with folic acid and methylcobalamin on depressive symptoms and serum IL-6 levels in patients with depression receiving fluoxetine. Methods: A randomized, pretest–posttest control group design was conducted involving 44 patients diagnosed with depression based on the Pedoman Penggolongan dan Diagnosis Gangguan Jiwa (PPDGJ) III. Participants were assigned to a treatment group (fluoxetine plus folic acid 1 mg/day and methylcobalamin 500 µg/day) or a control group (fluoxetine alone) for six weeks. Depression severity was assessed using the 17-item Hamilton Depression Rating Scale (HDRS-17), and IL-6 levels were measured by enzyme-linked immunosorbent assay (ELISA). Statistical analyses were performed using paired and independent t-tests. Results: Both groups showed significant reductions in HDRS-17 scores and IL-6 levels after six weeks ($p < 0.001$). The treatment group demonstrated a greater reduction in HDRS-17 scores than the control group ($p < 0.001$), while changes in IL-6 levels were not significantly different between groups ($p > 0.05$). Conclusion: Adjuvant therapy with folic acid and methylcobalamin significantly enhanced the antidepressant effect of fluoxetine, likely through neurochemical mechanisms rather than modulation of IL-6–mediated inflammation. This combination may serve as a safe and effective adjunctive strategy to improve clinical outcomes in patients with depression.

INTRODUCTION

Depression is a psychiatric disorder characterized by persistent mood changes, loss of interest in daily activities, cognitive disturbances, altered sleep and appetite patterns, feelings of worthlessness, and suicidal ideation (Zakaria, Samhani, & Mustafa, 2022). Globally, more than 350 million people across various age groups suffer from depression, with a prevalence of approximately 1 in 17 individuals (Jesulola, Micalos, & Baguley, 2018). In Indonesia, the prevalence of depression among individuals aged over 15 years is 6.1%, equivalent to around 14 million people, and approximately 8% in South Sulawesi (Litbang Kementerian Kesehatan RI, 2018). These figures indicate that depression is a serious public health concern with broad impacts on quality of life and suicide risk (Moreno-Agostino et al., 2021).Pathophysiologically, depression is associated with immune system dysregulation and increased inflammatory activity, characterized by elevated levels of proinflammatory cytokines such as interleukin-6 (IL-6) (Yu et al., 2023). IL-6 is produced

by mononuclear cells and macrophages in response to immunologic stimuli, subsequently triggering systemic inflammation. This cytokine can cross the blood–brain barrier and influence central nervous system function. Studies have shown that plasma IL-6 levels are higher in patients with major depressive disorder compared to healthy individuals (Elgellaie et al., 2023), suggesting a close relationship between inflammation and depressive symptoms.

Pharmacological treatment for depression commonly involves selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, which act by increasing serotonin levels at neuronal synapses. Although fluoxetine is widely prescribed, treatment response varies, with only about 40% of patients achieving significant clinical improvement (Erensoy, 2020). This low response rate is believed to be linked to folate and methylcobalamin deficiencies, which play essential roles in neurotransmitter synthesis. Deficiencies in these vitamins may lead to reduced serotonin and norepinephrine levels and elevated neurotoxic homocysteine levels through the generation of reactive oxygen species (ROS) and activation of N-methyl-D-aspartate (NMDA) receptors (Bharti et al., 2023).

Folic acid and methylcobalamin are crucial in the methylation cycle, contributing to DNA synthesis, gene expression, and neurotransmitter metabolism. Both nutrients help reduce homocysteine levels and enhance neurotrophic factors such as brain-derived neurotrophic factor (BDNF), which supports neuronal function (Maladkar, Awatramani, & Samel, 2016). Previous studies have shown that supplementation with folic acid and methylcobalamin can alleviate depressive symptoms by increasing BDNF levels and normalizing neuronal methylation processes (Roberts et al., 2007). Moreover, Lashari et al. (2023) reported that the combination of both agents as adjuvant therapy for eight weeks in schizophrenia patients receiving risperidone improved clinical symptoms and increased serum BDNF levels.

Based on these findings, the use of folic acid and methylcobalamin as adjuvant therapy with fluoxetine is expected to enhance antidepressant efficacy through two mechanisms: reducing inflammatory processes by lowering IL-6 levels and improving neurotransmitter function through optimized methylation pathways. To date, studies investigating the effects of adjuvant folic acid and methylcobalamin on IL-6 levels and clinical symptoms in depressive patients receiving fluoxetine remain limited. Therefore, this study aims to analyze the effects of adjuvant folic acid and methylcobalamin therapy on clinical improvement and serum interleukin-6 (IL-6) levels in depressive patients treated with fluoxetine.

MATERIALS AND METHODS

Study Design

This research employed an experimental design with a pretest–posttest control group approach. Subjects were divided into two groups: treatment and control. Variables were measured before and after intervention to assess changes in depressive symptoms and interleukin-6 (IL-6) levels.

Study Location and Duration

The study was conducted at three sites: Dadi Provincial Mental Hospital of South Sulawesi, Wahidin Sudirohusodo Hospital Makassar, and the Teaching Hospital of Hasanuddin University. The research was carried out after obtaining ethical clearance from the Biomedical Research Ethics Committee involving Human Subjects, Faculty of Medicine, Hasanuddin University, and continued until the required sample size was achieved.

Population and Sample

The study population comprised all patients diagnosed with depression who attended outpatient clinics at the three hospitals. Sampling was conducted using a consecutive sampling technique, enrolling all eligible participants until the minimum required number was reached.

Sample size was determined using the comparative numerical paired two-group formula (Jazayeri et al., 2008), with a significance level (α) of 0.05 and statistical power ($1-\beta$) of 0.90. Based on calculations, a minimum of 44 subjects was required, consisting of 22 patients in the treatment group and 22 in the control group.

Inclusion and Exclusion Criteria

Inclusion criteria included patients diagnosed with depression according to the Indonesian Classification of Mental Disorders (PPDGJ) III, aged between 20 and 65 years, and currently receiving fluoxetine therapy. All participants signed an informed consent form after receiving an explanation regarding the study objectives and procedures. Specifically, subjects in the treatment group also agreed to receive adjuvant therapy with folic acid and methylcobalamin.

Exclusion criteria comprised patients with depression due to organic causes, those with a history of narcotic, psychotropic, or addictive substance (NAPZA) use within the past year, and individuals receiving anti-inflammatory or antibiotic drugs during the study period. Subjects were considered dropouts if they were noncompliant with fluoxetine or adjuvant therapy, withdrew consent, or died during the study period.

Data and Research Instruments

Primary data were collected directly from participants through interviews, questionnaires, and laboratory examinations. Research instruments included informed consent forms, the PPDGJ III diagnostic guideline for depression, the Hamilton Depression Rating Scale (HDRS) for assessing depressive symptom severity, and an enzyme-linked immunosorbent assay (ELISA) kit for measuring serum IL-6 levels. The intervention protocol involved administration of fluoxetine, folic acid, and methylcobalamin according to the established research protocol.

RESEARCH PROCEDURE

Eligible participants were randomly assigned to two groups. The treatment group received fluoxetine 10–20 mg per day combined with folic acid 1 mg per day and methylcobalamin 500 µg per day, all administered orally for six weeks. The control group received fluoxetine 20 mg per day without adjuvant supplementation.

Medication adherence was monitored weekly to ensure compliance and identify any adverse effects. Assessment of depressive symptoms using HDRS and measurement of serum IL-6 levels were performed at baseline (week 0) and after six weeks of intervention (week 6). All measurements were documented and processed according to the study variables.

Variables and Operational Definitions

The independent variable in this study was adjuvant therapy with folic acid and methylcobalamin. The dependent variables were depressive symptoms (HDRS scores) and serum IL-6 levels. Confounding variables controlled in this study included age, sex, educational level, and disease onset, while controlled variables included smoking habits, family history of depression, and personality factors.

Adjuvant therapy was operationally defined as the administration of a combination of folic acid 1 mg/day and methylcobalamin 500 µg/day alongside fluoxetine 20 mg/day for six weeks. Depressive symptoms were measured using the 17-item HDRS, categorized as follows: 0–7 (normal), 8–16 (mild), 17–23 (moderate), and ≥24 (severe). Serum IL-6 concentration (ng/mL) was measured using the ELISA method.

DATA ANALYSIS

Data analysis was performed using standard statistical software. The Shapiro–Wilk test was applied to assess data normality. Paired t-tests were used to evaluate within-group differences before and after intervention, while independent t-tests compared results between groups. Pearson's correlation test was used to analyze the relationship between serum IL-6 levels and HDRS scores. A p-value of <0.05 was considered statistically significant.

RESULTS

Participant Characteristics

Table 1 presents the demographic characteristics of respondents in both groups. The Chi-square test showed no significant differences between the control and treatment groups ($p > 0.05$), indicating that both groups were comparable at baseline.

Table 1. Participant Characteristics by Study Group (n = 44)

Variable	Group		Total n (%)	*p-value*
	Control n (%)	Treatment n (%)		
Sex				0.517
Male	8 (36.4)	6 (27.3)	14 (31.8)	
Female	14 (63.6)	16 (72.7)	30 (68.2)	
Age (years)				0.429
15–24	2 (9.1)	4 (18.2)	6 (13.6)	
25–44	19 (86.4)	18 (81.8)	37 (84.1)	
45–64	1 (4.5)	0 (0.0)	1 (2.3)	
Marital Status				0.763
Married	11 (50.0)	10 (45.5)	21 (47.7)	
Unmarried	11 (50.0)	12 (54.5)	23 (52.3)	
Occupation				0.699
Civil servant / Military / Police	5 (22.7)	3 (13.6)	8 (18.2)	
Private employee	1 (4.5)	0 (0.0)	1 (2.3)	
Entrepreneur	5 (22.7)	5 (22.7)	10 (22.7)	
Contract employee	2 (9.1)	4 (18.2)	6 (13.6)	
Housewife	4 (18.2)	2 (9.1)	6 (13.6)	
Student	3 (13.6)	6 (27.3)	9 (20.5)	
Unemployed	2 (9.1)	2 (9.1)	4 (9.1)	
Education				0.540
Secondary	10 (45.5)	8 (36.4)	18 (40.9)	
Higher	12 (54.5)	14 (63.6)	26 (59.1)	

***Note**: p-values obtained from Chi-square test.*

The Chi-square analysis indicated no statistically significant difference between groups ($p > 0.05$).

Descriptive Statistics of HDRS Scores and IL-6 Levels

Table 2 presents the descriptive statistics of HDRS scores and IL-6 serum levels before and after treatment in both groups.

Table 2. Descriptive Statistics Before and After Treatment

Variable	Group	Before (Mean ± SD)	After (Mean ± SD)
HDRS-17	Control	22.45 ± 1.87	17.68 ± 2.34
	Treatment	22.77 ± 1.88	15.82 ± 2.04
IL-6 (pg/mL)	Control	161.36 ± 38.88	1.37 ± 0.29
	Treatment	161.49 ± 34.48	1.21 ± 0.29

***Note**: HDRS-17 = 17-item Hamilton Depression Rating Scale; IL-6 = interleukin-6; SD = standard deviation.*

Both groups demonstrated reductions in HDRS scores and IL-6 levels after the intervention, with a greater decrease in HDRS scores observed in the treatment group. The Shapiro–Wilk test indicated that all variables were normally distributed ($p > 0.05$); therefore, parametric statistical analyses were applied.

Within-Group Changes

Table 3 summarizes the results of paired t-tests for HDRS scores and IL-6 levels within each group.

Table 3. Within-Group Changes in HDRS and IL-6 (Paired t-test)

Variable	Group	Before (Mean ± SD)	After (Mean ± SD)	t	p-value
HDRS	Control	22.45 ± 1.87	17.68 ± 2.34	−14.528	<0.001
	Treatment	22.77 ± 1.88	15.82 ± 2.04	−26.868	<0.001
IL-6 (pg/mL)	Control	161.36 ± 38.88	1.37 ± 0.29	−19.332	<0.001
	Treatment	161.49 ± 34.48	1.21 ± 0.29	−21.809	<0.001

***Note**: HDRS = Hamilton Depression Rating Scale; IL-6 = interleukin-6; SD = standard deviation.*

There were significant reductions in both HDRS scores and IL-6 levels in both groups ($p < 0.001$).

Between-Group Comparison

The independent t-test was used to compare mean changes (post–pre) between groups, as presented in Table 4.

Table 4. Between-Group Comparison of Mean Changes (Independent t-test)

Variabel	Mean Difference (Mean ± SD)		95% CI	t (df)	p-value
	Kontrol	Perlakuan			
HDRS (Post–Pre)	−4.77 ± 1.54	−6.95 ± 1.21	1.34 – 3.03	5.217 (42)	<0.001
IL-6 (Post–Pre)	−159.99 ± 38.82	−160.27 ± 34.47	−22.05 – 22.62	0.026 (42)	0.980

***Note**: HDRS = Hamilton Depression Rating Scale; IL-6 = interleukin-6; SD = standard deviation; CI = confidence interval.*

The results showed a significant difference in HDRS score reduction between groups ($p < 0.001$), whereas no significant difference was observed in IL-6 levels ($p > 0.05$).

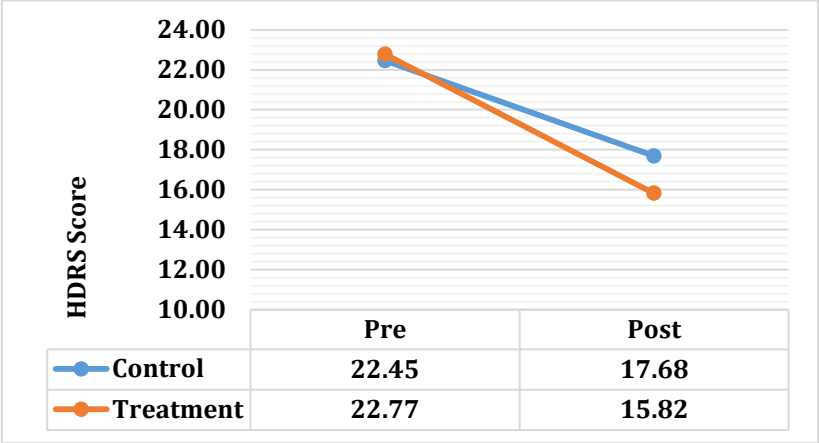

Figure 1

Figure 1 illustrates the pre–post HDRS score changes between groups, demonstrating a more pronounced reduction in the treatment group (−6.95) compared to the control group (−4.77).

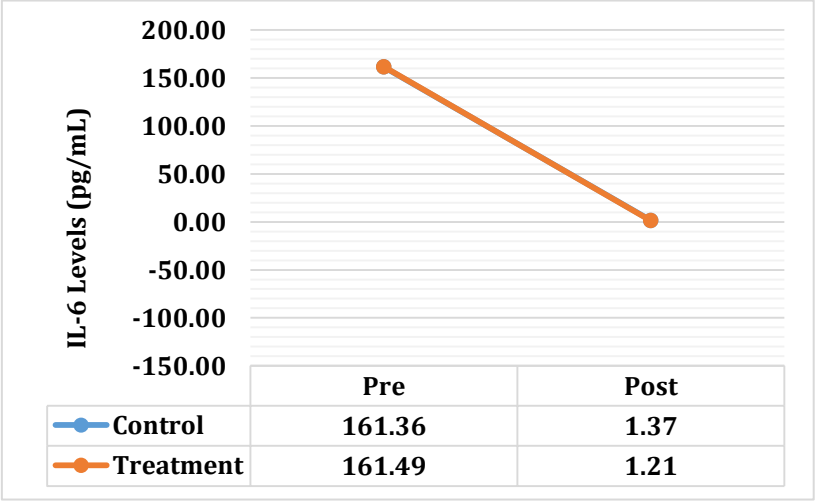

Figure 2

Figure 2 shows the pre–post changes in IL-6 levels, indicating a similar downward trend in both groups without a statistically significant difference.

Overall, these findings indicate that adjuvant therapy with folic acid and methylcobalamin significantly improved depressive symptoms but had no significant effect on IL-6 levels compared to fluoxetine monotherapy.

DISCUSSION

The present study investigated the effect of adjuvant therapy with folic acid and methylcobalamin on clinical symptoms and interleukin-6 (IL-6) levels in patients with depression receiving fluoxetine. The findings demonstrated a significant reduction in Hamilton Depression Rating Scale (HDRS-17) scores in both groups, with a greater decrease observed in the group receiving adjuvant therapy. These results indicate that supplementation with folic acid and methylcobalamin can potentiate the antidepressant effects of fluoxetine.

This finding is consistent with previous research showing that supplementation with folate and vitamin B12 enhances antidepressant response by improving methylation activity and increasing the availability of monoamine neurotransmitters (Yassine et al., 2024; Gao et al., 2024). Thus, combining fluoxetine with these nutrients provides additional benefits for clinical symptom improvement, although it did not show a significant effect on the inflammatory biomarker IL-6.

Effect of Adjuvant Therapy on Clinical Symptoms of Depression

The combination of folic acid and methylcobalamin with fluoxetine resulted in a greater reduction in HDRS-17 scores compared with fluoxetine alone. This supports the hypothesis that folate and vitamin B12 deficiency is associated with a poor antidepressant response (Koubas et al., 2024; Alzahrani, 2024). Both vitamins play a key role in one-carbon metabolism, which produces S-adenosylmethionine (SAMe), a primary methyl donor required for the synthesis of serotonin, dopamine, and norepinephrine (Jha et al., 2021).

Several clinical studies have also shown that patients with low folate levels demonstrate enhanced antidepressant response after supplementation with folate or vitamin B12 (Khosravi et al., 2020; Tan et al., 2023). A recent meta-analysis confirmed the effectiveness of folate as an adjunctive therapy in reducing depressive symptoms (Gao et al., 2024). Clinically, such adjuvant therapy may serve as a valuable strategy to enhance treatment efficacy, particularly in individuals with nutritional deficiencies (Esnafoğlu, 2023; Jamil et al., 2025).

Although baseline folate and vitamin B12 status were not directly assessed, the present findings underscore the importance of nutritional balance in maintaining neurocognitive function. Vitamin B12 deficiency has been associated with neuropsychiatric disorders and cognitive decline (Sahni, 2021). Therefore, integrating nutritional aspects into depression management is increasingly relevant in modern clinical practice.

Effect of Adjuvant Therapy on Interleukin-6 Levels

This study found that the addition of folic acid and methylcobalamin did not significantly affect IL-6 levels compared with fluoxetine alone, although both groups exhibited decreased IL-6 levels after treatment. This suggests that the therapeutic effect of the combination is more dominant in neurochemical mechanisms rather than immune modulation.

Fluoxetine, as a selective serotonin reuptake inhibitor (SSRI), is known to exert anti-inflammatory effects by inhibiting microglial activation and suppressing the NF-κB signaling pathway (Carr et al., 2023; Wang et al., 2022). This mechanism may be sufficiently potent to reduce IL-6 levels, thereby diminishing the additional impact of vitamin B supplementation. Previous studies have also reported inconsistent findings regarding the influence of B vitamins on inflammatory cytokines (Du et al., 2020; Bargieł et al., 2021).

IL-6 is a proinflammatory cytokine involved in the pathogenesis of depression through mechanisms related to oxidative stress and neurotransmitter dysregulation (Koole et al., 2021). However, clinical improvement does not always correspond with changes in inflammatory biomarkers (Asbaghi et al., 2020). Therefore, depression should be understood as a multifactorial

disorder involving complex interactions between the nervous, immune, and endocrine systems rather than a single biochemical response.

Relationship between Clinical Symptoms and Inflammatory Biomarkers

The decrease in HDRS-17 scores without a corresponding significant reduction in IL-6 levels suggests that improvement in depressive symptoms does not necessarily parallel changes in inflammatory biomarkers. This phenomenon has been observed in several studies (Yang et al., 2021; Han et al., 2023), indicating that neurochemical and immunological mechanisms operate in parallel but not always in direct correlation.

Depression is a multifactorial condition involving neurotransmitter imbalance, neuroendocrine dysregulation, and inflammatory responses (Remes et al., 2021; Arias et al., 2021). Fluoxetine increases serotonin levels by inhibiting reuptake, whereas folate and methylcobalamin support methylation processes essential for neurotransmitter synthesis (Zhou et al., 2020; Ma, 2024). However, not all biological alterations are directly reflected in biomarkers such as IL-6 due to the complexity of systemic interactions (Düsedau et al., 2021).

Hence, depression management should not focus solely on biomarker modulation but rather integrate clinical, psychological, and social dimensions to achieve optimal therapeutic outcomes and improve patients' quality of life (Stopińska et al., 2021; Park et al., 2024).

Limitations

Several limitations should be acknowledged. First, this study measured only one inflammatory biomarker (IL-6), while depression involves other mediators such as TNF-α, CRP, and IL-1β. Second, baseline folate and vitamin B12 levels were not assessed, which may influence the magnitude of the adjuvant effect, particularly among individuals with nutritional deficiencies. Third, the intervention period of six weeks may be too short to capture long-term effects.

Despite these limitations, this study provides important insights by showing that the combination of fluoxetine with folic acid and methylcobalamin can accelerate clinical improvement, even though it does not significantly affect IL-6. Further research with larger samples, longer duration, and broader biomarker assessments is needed to clarify the mechanistic and clinical roles of this adjuvant therapy in depression.

CONCLUSION

The administration of adjuvant therapy with folic acid and methylcobalamin alongside fluoxetine produced a significantly greater improvement in depressive symptoms compared with fluoxetine alone. This combination enhances antidepressant efficacy through support of methylation processes and neurotransmitter synthesis, particularly serotonin, dopamine, and norepinephrine.

However, no significant difference was observed in IL-6 levels, suggesting that the therapeutic effects are predominantly neurochemical rather than anti-inflammatory. Overall, folic acid and methylcobalamin supplementation may be considered a safe and promising adjunctive strategy for improving treatment response in depression, especially among patients at risk for nutritional deficiencies.

Further studies with extended treatment duration and comprehensive biomarker analysis are warranted to strengthen the mechanistic and clinical evidence supporting this combination therapy.

Ethics and Disclosure Statements

This study received ethical approval from the Health Research Ethics Committee, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia (approval number: 205/UN4.6.4.5.31/PP36/2025). All participants were informed about the study objectives, procedures, benefits, and potential risks, and provided written informed consent prior to data collection.

The authors declare no financial or non-financial conflicts of interest that could have influenced the results or interpretation of this study. All findings are presented objectively, based solely on the obtained data without external intervention.

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Author Contributions

All authors contributed substantially to the conception and design of the study.

1. Study conception and design: YRR, EL, WT, AAZ, SS, STL
2. Data collection: YRR, EL, WT, AAZ
3. Data analysis and interpretation: RR, EL, WT, AAZ
4. Drafting of manuscript: YRR
5. Critical revision of manuscript: EL, WT, AAZ, SS, STL

All authors reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable and justified request.

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