



## ARTICLE

### THE EFFECT OF FOLIC ACID SUPPLEMENTATION ON LIVER FUNCTION IN CHRONIC SCHIZOPHRENIA PATIENTS

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#### ABSTRACT

Oxidative stress caused by free radicals and long-term antipsychotic use in chronic schizophrenic patients may result in liver cell damage and impaired liver function. Folic acid is an exogenous antioxidant that can boost the antioxidant defense mechanism (Glutathione Reductase), lowering free radicals and improving liver function. Determine the correlation between adjuvant folic acid and liver function in chronic schizophrenic patients. This was a placebo-controlled, double-blinded randomized control trial. The study sample included 36 patients in the control group and 36 patients in the treatment group. Subjects were patients who had suffered from schizophrenia for at least 2 years and received antipsychotics. Research subjects in the treatment group received folic acid supplementation. The intervention was conducted for 21 days during hospitalization. The level of AST (U/L) and ALT (U/L) was measured before and after supplementation. Following folic acid supplementation, AST levels were significantly improved (26.950 U/L compared to prior to treatment 33.09 U/L,  $p < 0.001$ ). ALT levels after treatment were increased but there was no significant difference observed ( $p = 0.835$ ). Folic acid supplementation improves AST levels significantly.

**Keywords:** antipsychotic agents, aspartate aminotransferase, schizophrenia, folic acid, liver function

#### АБСТРАКТ

Окислительный стресс, вызванный свободными радикалами, и длительное применение антипсихотиков у больных хронической шизофренией могут привести к повреждению клеток печени и нарушению ее функции. Фолиевая кислота является экзогенным антиоксидантом, способным усиливать механизм антиоксидантной защиты (глутатионредуктазу), снижая уровень свободных радикалов и улучшая функцию печени. Определить корреляцию между приемом фолиевой кислоты и функцией печени у больных хронической шизофренией. Это было плацебо-контролируемое двойное слепое рандомизированное контрольное исследование. Выборка исследования включала 36 пациентов в контрольной группе и 36 пациентов в лечебной группе. Испытуемыми были пациенты, страдающие шизофренией не менее 2 лет и получающие антипсихотики. Испытуемые в группе лечения получали добавки фолиевой кислоты. Вмешательство проводилось в течение 21 дня во время госпитализации. Уровень АСТ (Ед/л) и АЛТ (Ед/л) измерялся до и после приема добавки. После приема фолиевой кислоты уровень АСТ значительно повысился (26,950 Ед/л по сравнению с 33,09 Ед/л до лечения,  $p < 0,001$ ). Уровень АЛТ после лечения повысился, но существенной разницы не наблюдалось ( $p = 0,835$ ). Прием фолиевой кислоты значительно повышает уровень АСТ.

**Ключевые слова:** антипсихотические средства, аспаратаминотрансфераза, шизофрения, фолиевая кислота, функция печен

## INTRODUCTION

Schizophrenia is a complex mental disorder, marked by cognitive impairment (ie, concrete thinking, disturbances in responding to information).<sup>1</sup> In addition to the poor course of the disease, those suffering from schizophrenia have a significantly reduced life expectancy. The mortality rate is quite high, owing primarily to unnatural death at a young age. Schizophrenia is more common in men, usually begins at the age of 15-25 years old in men and 25-35 years old in women. Males typically have a poorer prognosis.<sup>2</sup> According to World Health Organization (2019), approximately 20 million people worldwide were diagnosed with schizophrenia. Based on the basic health research (RISKESDAS) from the Indonesian Ministry of Health in 2018, the estimated prevalence of people with psychosis in Indonesia is 1.8 per 1000 population.<sup>3</sup> Despite having a low prevalence rate, schizophrenia was ranked 12th out of 310 diseases and injuries worldwide in 2016.<sup>4</sup>

Main pharmacological treatment for schizophrenia is antipsychotics. Antipsychotics are divided into two groups; typical antipsychotics (for example haloperidol), and atypical antipsychotics (for example risperidone). Antipsychotic administration is associated with drug-induced liver injury (DILI) since most of antipsychotic drugs are metabolized in the liver before being excreted through the kidneys.<sup>5-8</sup> The transaminase enzymes, aspartate transaminase (AST) and alanine transaminase (ALT) can be used as a biomarker of liver cell damage (hepatocellular injury), caused by numerous underlying etiologies including DILI.<sup>9,10</sup>

Increased levels of free radicals/ROS (Reactive Oxygen Species) eventually cause hepatocytes damage, characterized by increased levels of AST and ALT.<sup>10</sup> Studies have reported an alteration in antioxidant status in schizophrenic patients.<sup>11</sup> Low antioxidant enzymes can be used as a marker of high levels of ROS. The glutathione (GSH) redox system is important for reducing oxidative stress. Glutathione is present in cells

in the form of a reduced antioxidant known as GSH, and in an oxidized form known as Glutathione Disulfide (GSSG). Therefore, GSH/GSSG ratio is a sensitive marker for oxidative stress. Glutathione peroxidase (GPx) catalyze the reduction of lipid hydroperoxides to alcohol, and hydrogen peroxide to water. As catalysis occur, disulfide bonds of 2 GSH will bind to form oxidized glutathione (GSSG), while the enzyme glutathione reductase (GR) plays a role in recycling GSSG back into GSH by oxidizing NADPH. Therefore, Glutathione Reductase plays a very important role as defense mechanism against free radicals. In addition to GSH levels, GPx and GR levels were found to be significantly lower in schizophrenic group compared to control group without psychiatric disorders.<sup>12</sup>

Folic acid is one of the B complex vitamins, plays a key role as a neuroprotective agent, against central nervous system (CNS) disorders, promotes nerve growth and repair by changing the one-carbon compounds (C1) metabolism.<sup>13</sup> Changes in folic acid metabolism can directly affect the CNS. Studies have shown an important relationship between folic acid metabolism and schizophrenia.<sup>14</sup> These findings support the hypothesis that deficiency of this vitamin is an important risk factor in the development of schizophrenia.<sup>14</sup> Furthermore folic acid increase GSH and total antioxidant capacity.<sup>(15)</sup> Studies revealed that folic acid supplementation will be peaked at the third week in a healthy population.<sup>14</sup> The study aims to determine the correlation of adjuvant folic acid in chronic schizophrenic patients to liver function, by assessing AST and ALT levels.

## MATERIAL AND METHODS

### *Patients*

The study design employed in this research is a randomised, placebo-controlled, double-blind methodology. The study sample consisted of individuals who were recruited from the pool of inpatients at Dr. Amino Gondohutomo Mental Health Hospital. Inclusion criteria were applied to determine eligibility for participation in the study, and

individuals were included if they met the specified criteria. 1) The study included individuals within the age range of 20 to 50 years. 2) The diagnosis of schizophrenia was made by a psychiatrist based on the criteria outlined in the International Classification of Diseases, 10th edition (ICD-10). 3) The participants had been diagnosed with schizophrenia for a minimum duration of two years. 4) The participants were undergoing normal hospital treatment, which involved the administration of psychotropic medications, either with or without supplementary anticholinergic drugs. The exclusion criteria encompassed those with a medical history of comorbidities such as heart disease, hypertension, anemia, liver diseases, cardiovascular disease, and diabetes, as well as those who reported alcohol usage and use of other additives.

#### *Biochemical analysis*

The assessment of liver function involved the measurement of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels both before and after the administration of the supplement. During the patient's initial admission to the emergency unit, venous blood was obtained. A study was conducted at the National Diponegoro Hospital to test liver function using an autoanalyzer. The standard range for aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values were found to be 7-40 U/L and 7-41 U/L, respectively.

The process of randomization is a fundamental technique used in research studies to assign participants to different

The study employed a random assignment method to allocate patients into two groups: one group received a daily oral supplementation of 2 mg folic acid (n=36), while the other group received a placebo (n=36). Both groups were concurrently administered antipsychotic medication for a duration of 21 days. The inpatient pharmacy department was provided with a set of distinct

codes, which were assigned depending on the content (either folic acid or placebo) of the trial, by a third party who was uninformed of the study concept. This process ensured randomization and blindness in the study. The distinct code was documented in the medical record of the individual. On a daily basis, prescriptions were administered to nurses by researchers in accordance with the established code of practice. Regular monitoring was conducted on a daily basis in order to observe and document any potential adverse effects resulting from the intervention.

#### *Data analysis*

The statistical analysis was performed using version 23.0 of the Statistical Package for the Social Sciences (SPSS) software. The data is presented in the form of mean  $\pm$  standard deviation (SD) and median [interquartile range (IQR)]. The analysis of potential differences between treatment groups was conducted using either an independent t-test or a Mann-Whitney test, depending on the appropriateness of each method. The Wilcoxon test and paired t-test were employed to ascertain any significant differences between the pre-treatment and post-treatment results. Statistical significance was determined by using p-values less than 0.05.

#### *Ethical statement*

All patients signed an informed consent for their participation in this study. The procedures related to this study were reviewed and approved by the institutional review board.

## **RESULT**

During the period of study, a total of 220 patients were diagnosed with chronic schizophrenia. Of these patients, 72 patients fulfilled the inclusion criteria which divided into two groups of folic acid (n= 36) and placebo-treated (n=36) groups. The demographic characteristics of the study subjects are shown in Table 1.

**Table 1.** Demographic data

Characteristics	n	%	Mean± SD	Median (IQR)
Age (years)			33.78 ± 7.70	34 (21 – 50)
Gender (%)				
Male	50	69.4		
Female	22	30.6		
Employment status (%)				
Employed	28	38.9		
Unemployed	44	61.1		
Marital status (%)				
Single	36	50.0		
Married	26	36.1		
Widowed	10	13.9		
Educational background (%)				
Elementary school	18	25.0		
Junior high	23	31.9		
Senior high	22	30.6		
Diploma	3	4.2		
Bachelor	6	8.3		
Duration of illness (years)			4.67 ± 2.97	4 (2 – 21)
Family history of schizophrenia (%)				
Present	10	13.9		
Absent	62	86.1		
Body mass index (%)				
Underweight	7	9.7		
Normal	54	75.0		
Overweight	6	8.3		
Obese	5	6.9		
Smoking (%)				
Yes	50	69.4		
No	22	30.6		
Number of admissions			3.40 ± 1.96	3 (1 – 10)

Among the entire sample size of fifty persons, it was observed that males constituted 69.4% of the participants. The mean age of the participants was determined to be 33.78 ± 7.70 years. The prevalence of schizophrenia was found to be significantly higher among those who were unemployed in comparison to those who were

employed. The smoking behavior of a significant proportion of the patients (69.4%) was recorded. The patient characteristics between the therapy groups did not show any significant variations, save for educational background as indicated in Table 2.

**Table 2.** Demographic data

Variables	Treatment		P-value
	Folic acid (n=36)	Placebo (n=36)	
Age	32.78 ± 6.89	34.78 ± 8.42	0.281§
Gender			
Male	26 (72.2)	24 (66.7)	0.609¥
Female	10 (27.8)	12 (33.3)	
	Employment status		
Employed	15 (41.7)	13 (36.1)	0.629¥
Unemployed	21 (58.3)	23 (63.9)	
	Marital Status		
Single	18 (50)	18 (50)	1.000¥
Married	13 (36.1)	13 (36.1)	
Widowed	5 (13.9)	5 (13.9)	
	Educational background		
Elementary school	7 (19.4)	11 (30.6)	0.026¥*
Junior high	13 (36.1)	10 (27.8)	
Senior high	13 (36.1)	9 (25)	
Diploma	3 (8.3)	0 (0)	
Bachelor	0 (0)	6 (16.7)	
Duration of illness	4.58 ± 3.45	4.75 ± 2.44	0.322‡
Family history of schizophrenia			
Present	6 (16.7)	4 (11.1)	0.496¥
Absent	30 (83.3)	32 (88.9)	
	Body mass index		
Underweight	4 (11.1)	3 (8.3)	0.781¥
Normal	26 (72.2)	28 (77.8)	
Overweight	4 (11.1)	2 (5.6)	
Obese	2 (5.6)	3 (8.3)	
	Smoking		
Yes	26 (72.2)	24 (66.7)	0.609¥
No	10 (27.8)	12 (33.3)	
Number of admission	3.47 ± 2.13	3.33 ± 1.81	0.735‡

Liver enzymes were measured prior and after treatment (Table 3). Following folic acid supplementation, AST and ALT levels were 24.206 U/L and 38.628 U/L, respectively. AST levels were significantly improved (p = <0,001) when compared to the baseline value prior to supplementation. In contrast, ALT levels were increased following folic acid supplementation. To assess potential bias, we compare the drug type and duration of treatment between the placebo and folic acid groups. There was no significant difference between treatment groups in terms of drug type (p = 0.413) or treatment duration (p = 0.158).

**Table 3.** Liver enzymes value in folic acid groups

	Pre-treatment (n=36)	Post-treatment (n=36)	p¥
AST levels (mean ± SD)	31.531 ± 12.7924	24.206± 6.9111	<0.001*
ALT levels (mean ± SD)	29.475± 14.5433	38.628± 65.7009	0.756

\* Significant (p < 0.05). ¥ Wilcoxon ranks test. AST: Aspartate transaminase, ALT: Alanin Transaminase

## DISCUSSION

Based on demographic result in our studies, schizophrenic patients were predominantly male (69.4%), with unemployment status (61.1%), and smoking habits (69.4%). These findings are in accordance with previous studies. Our results were concordant with previous studies which states that males have a higher prevalence of schizophrenia than females, with disease onset occurred ranging from 15 to 25 years old, whilst females experience schizophrenia with onset ranging from 25 to 35 years old.<sup>1,2</sup> High rates of unemployment also correlated with schizophrenia.<sup>(16)</sup> Those individuals with schizophrenia also showed difficulties in daily activities that leads to significant disability and unemployment. A study of daily activities assessment using the Lawton instrumental activities of daily living (LIADL) revealed that those with schizophrenia had difficulties in: handling medication (86%), preparing food (85%), shopping (78%), managing finances (61%), handling household (47%), using public transportation (32%) and using telephones (5%).<sup>17</sup> Schizophrenia diagnosis also associated with over six times higher risk of having neither secondary nor higher education. Education level are markedly related to LIADL score of daily activities.<sup>17</sup> Smoking and schizophrenia has well established relationship. A meta-analysis revealed that the odds ratio of individuals with schizophrenia to smoke was 5.3 times higher than normal population<sup>18</sup> and those with schizophrenia had tendency to be a heavy smoker and lower smoking cessation rates.<sup>19</sup> Smoking is at least related to increased brain dopamine activity by inducing dopamine release and inhibiting its degradation process.<sup>20</sup> Duration of illness in our study was  $4.67 \pm 2.97$  years. Long term antipsychotics administration has been correlated with drug induced liver injury (DILI) and one year treatment of antipsychotic resulted in elevated AST and ALT levels. Liver dysfunction also found in 20% in those who received long-term treatment with haloperidol.<sup>5</sup>

There was no significant difference in patients characteristic between placebo and folic acid groups, except in education background, particularly in the number of patients with elementary school background.

A meta-analysis study from Wang and colleagues revealed that reduced serum folic acid levels are related to the development of schizophrenia.<sup>14</sup> Increased activities of nicotinamide adenine dinucleotide phosphate oxidase enzymes (NADPHo) has been correlated with elevated levels of ROS in liver and kidney. Meanwhile, as an antioxidant, folic acid is critical in reducing NADPHo activities and regenerate GSH via homocysteine trans-sulfuration pathway (TSP). Therefore, folic acid deficiency resulted in increased reactive oxygen species (ROS), which elicits cellular oxidative damage. Increasing oxidative stress has been known to contribute in the development of schizophrenia.

### *AST levels following folic acid supplementation*

A significant difference ( $p < 0.05$ ) was observed between AST levels prior to and following folic acid supplementation. These findings supported the notion of a previous study that the liver is the main organ affected by ROS accumulation. Kupffer cells, stellate cells and endothelial cells are highly sensitive to oxidative stress, and during this condition numerous cytokines such as TNF- $\alpha$  is produced by Kupffer cell which leads to cell apoptosis and inflammation. As a consequence of liver cell death, AST serum levels are increased. Previous studies suggested that high levels of ROS following long term antipsychotic administration induce liver cell damage and liver dysfunction. According to Baeza<sup>(5)</sup> and Telles-Coreia<sup>9</sup>, antipsychotic are known to correlate with DILI. In other study, approximately 20% patients with long term treatment of haloperidol were reported with liver dysfunction. Increased levels of AST and ALT were observed in 3% of patient within a year of antipsychotics treatment.<sup>5</sup> A study by Morlan-Coarasa revealed that the risk of non-alcoholic fatty liver disease are increased following three year of antipsychotic



treatment.<sup>8</sup> In our study AST levels were significantly increased ( $p < 0.001$ ) after folic acid supplementation, suggesting that folic acid supplementation alleviate liver cell dysfunction and improve AST levels.

#### *ALT levels following folic acid supplementation.*

Based on our results, there are no significant differences of ALT and GR levels in the patients before and after oral folic acid administration. These results suggest the benefits of folic acid might be interfered by antipsychotic metabolism effect in which in this research the patient selection criteria including at least two years of antipsychotic medication was given to the patient.

#### **CONCLUSION**

In conclusion, this study revealed that folic supplementation improves AST levels in chronic schizophrenic patient. However, there were several limitations to this study. The antipsychotic drugs administered in the hospital were in accordance with the individualized treatment for schizophrenia, and there was no drug uniformity between individuals.

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#### **DECLARATIONS**

Author contribution. The contribution of this research is as follows:

“Conceptualization, Alifiati, Inawati, Hang, Julianata; methodology, Alifiati, Inawati, Hang; software, Julianata; validation, Alifiati,

Inawati, Hang, Julianata; formal analysis, Alifiati, Inawati; investigation, Alifiati, Hang; resources, Julianata; data accuracy, Julianata; writing - preparation of the original draft, Julianata; writing - reviewing and editing, Julianata, visualization, Julianata; supervision, Alifiati, Inawati, Hang; project administration, Alifiati, Inawati; fund acquisition, Inawati.

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