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The Effect of Adjuvant Therapy on Metabolic Syndrome in Schizophrenia Patients at Madani Hospital

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ABSTRACT

Background: Schizophrenia is a mental disorder that impacts behavior, emotions, and communication. In recent years, atypical antipsychotics have been increasingly prescribed because they significantly reduce both positive and negative symptoms. However, the long-term effects of atypical can cause metabolic syndrome. Additional therapy is provided to maximize the primary therapy and reduce the side effects.
Method: This study used a quasi-experimental design with a single-blind, pretest-posttest approach. Patients who had been using atypical antipsychotics, either monotherapy or combination therapy, for more than 3 were examined pretest to determine metabolic syndrome levels. Group A received adjuvant therapy, while Group B did not receive adjuvant therapy. Based on this data, an analysis of the reduction in metabolic syndrome categories was conducted.
Result: The percentage of schizophrenia patients by gender was dominated by males (60%). By age, the majority were adults (87%). In Group A, the incidence of metabolic syndrome decreased from 53% in the pretest to 40% in the posttest after being given vitamin A, B, and folic acid therapy. The most commonly used other medication was THP (38%).
Conclusion: The administration of adjuvant therapy with vitamins A, B, E, and folic acid can reduce the value of one or two of the five metabolic syndrome criteria for schizophrenia patients (p = 0.052) compared to the group of patients who did not receive vitamins A, B, E, and folic acid adjuvant therapy. Future research should use a longer duration to observe the effects of vitamins A, B, E, and folic acid and evaluate their therapeutic doses. Additionally, it should narrow down the criteria for medication use, focusing solely on the atypical antipsychotic's clozapine or olanzapine.

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INTRODUCTION

Schizophrenia is a mental disorder that impacts behaviour, emotions, and communication. Schizophrenia affects around 24 million people or 1 in 300 people (0.32%) worldwide, of which 1 in 222 people (0.45%) occurs among adults. Indonesia's health profile presented in the 2023 Indonesian Health Survey (SKI) shows that the prevalence of serious mental disorders such as schizophrenia reached 315,621 incidents in Indonesia. This figure is spread across all provinces in Indonesia, with the highest figure in D.I. Yogyakarta province at 9.3%, followed by Central Java province at 6.5% and West Sulawesi at 5.9% (1).

The standard treatment for schizophrenia involves the use of either typical or atypical antipsychotics. However, the use of atypical antipsychotics is more recommended due to the side effects associated with them (2).

Long-term use of atypical antipsychotics can lead to metabolic side effects, including weight gain, insulin resistance, and hyperglycaemia (3). Research conducted by Carli et al. concluded that the use of antipsychotics can cause metabolic syndrome (MetS) such as weight gain, dyslipidemia, type 2 diabetes (T2D), and high blood pressure, which results in a reduced life expectancy (4). Metabolic syndrome is defined by the presence of metabolic abnormalities, such as large waist circumference, dyslipidemia, fasting hyperglycemia, and high blood pressure. Schizophrenia patients have higher morbidity and mortality compared to the general population, with cardiovascular problems being the leading cause of these deaths and an estimated life expectancy decrease of 10-20 years (5).

Antipsychotics are often combined with other therapies to achieve a better therapeutic response while minimizing side effects (6). Although several nonpharmacological and pharmacological interventions (e.g., metformin) are recommended for the management of physical health conditions related to metabolic syndrome in schizophrenia patients, the results are not satisfactory (7). Adjuvant therapy, known as additional or enhancement therapy, is provided to maximize the primary therapy and minimize the risk of side effects (8).

Several previous studies support this, including the addition of Berberine administration is effective in reducing weight gain and antipsychotic-related metabolic syndrome (9). In line with this study, the addition of probiotics showed improvement in clinical symptoms and decreased levels of Inter Leukin (IL)-6 in schizophrenia patients (10). IL-6 plays a role in weight regulation and regulates the metabolic system, which is characteristic of metabolic syndrome (11).

Other studies related to the addition of fish oil as adjuvant therapy in schizophrenia patients have shown a decrease in Positive and Negative Syndrome Scale (PANSS) scores (12). In addition to fish oil, the addition of folic acid has been found effective in influencing the social function of chronic schizophrenia patients (13). Research on clinical trials shows folate supplementation, its derivatives especially ketomycolic acid or 5-methylfolate can improve clinical outcomes for certain psychiatric illnesses, especially as adjunctive therapy with minimal side effects (14).

Research involving clinical trials is still very limited on the use of vitamins A, B, E, and folic acid, especially in schizophrenia patients. Analysis of adjuvant therapy to improve the metabolic syndrome side effect from the use of atypical antipsychotics using vitamins A, B, E and folic acid has not been widely carried out, so the accuracy of dose selection, as well as the duration of vitamin use, needs to be studied more deeply. Based on this, the authors are interested in researching the administration of adjuvant therapy (vitamins A, B, E, and folic acid) to improve metabolic syndrome.

METHOD

Study Design

This quasi-experimental study employed a single-blind, pretest-post-test design, which is experimental research carried out on one group only without any comparison group or control group.

Pretest design, patients receiving atypical antipsychotic mono and combination therapy for > 3 months were examined for metabolic syndrome.

Post-tests design, patients with incident metabolic syndrome were divided into 2 groups. Group A received adjuvant therapy (4000 IU vitamin A, 3 mg vitamin B1, 10 mg vitamin E, and 1 mg folic acid) for 1 week, and Group B without adjuvant therapy.

Metabolic syndrome was determined if at least three out of five criteria were met, and pre-metabolic syndrome was determined if two out of the following five criteria were met:

BMI > 30 kg/m^2,

Blood pressure ≥ 130/85,

Triglycerides ≥ 150 mg/dl,

HDL ≤ 40 mg/dl, dan

Fasting blood glucose ≥ 110 mg/dl.

Measurement of metabolic syndrome reduction, if there is a decrease in the value of 1 or 2 of the 3 metabolic syndrome criteria

Subjects and Study Location

The subjects of this study were outpatient schizophrenia patients. The study was conducted at Madani Hospital, Central Sulawesi Province, with data collection taking place from June 2024 to August 2024.

Inclusion and Exclusion Criteria

Inclusion

Adult patients aged 18-65 years as defined by WHO, diagnosed with schizophrenia.

Family members willing and signing the informed consent.

Outpatients who had been using atypical antipsychotics (clozapine, olanzapine, and risperidone) monotherapy and combination therapy for more than 3 months.

Exclusion

Patients who changed medications.

Family members or patients who refused or did not sign the informed consent.

Subjects who died during the study.

Subjects who experienced a relapse and were hospitalized.

Patients uncooperative during blood collection.

Research Implementation Flow

Research permission at Madani Hospital, Central Sulawesi Province. Data collection from all study subjects meeting the inclusion criteria, including: 1) Patient characteristics data covering name, age, gender, educational status, and medical record number with the last number obscured. 2) Study subjects diagnosed with schizophrenia receiving atypical antipsychotic therapy (clozapine, olanzapine, and risperidone) either as monotherapy or in combination for at least three months.

Data Collection Method

Patients receiving atypical antipsychotics (clozapine, olanzapine, and risperidone) monotherapy, and combination therapy experiencing metabolic syndrome were divided into two groups. Group A received adjuvant therapy, while Group B did not. Data were analysed for BMI, triglycerides, blood pressure (systolic and diastolic), HDL, and fasting glucose levels before and after therapy and compared for reductions.

Data Analysis

All the obtained data is recorded and tabulated. The data were analyzed using one-way ANOVA to determine significant differences. Significance is determined based on a p-value < 0.05

The p-value is a proportion that indicates the extent to which the data supports or rejects the hypothesis. A p-value smaller than 0.05 indicates the less likely that a statistical value can cause the observed result. Therefore, a higher p-value corresponds to a more convincing hypothesis.

Ethical Considerations

The study was conducted after obtaining approval from the Ethics Committee of the Faculty of Medicine, Tadulako University, with approval number 120/UN28.1.30/KL/2024.

RESULTS

Based on the study results, categories of patients were established based on distribution, assessment of adjuvant therapy, and patient treatment.

Table 1. Distribution of Schizophrenia Patients

No	Category	Frequency	%
1	**Gender**		
2	Male	18	60
3	Female	12	40
	TOTAL	**30**	**100**
4	**Age (years)**		
5	Adolescent (10-18)	1	3
6	Adult (19-59)	26	87
7	Elderly (>60)	3	10
	TOTAL	**30**	**100**
9	**Education**		
10	None	4	13
11	Elementary School	5	17
12	Junior High School	2	7
13	High School	13	43
14	Bachelor's Degree	2	7
15	College Student	1	3
16	Private Sector	1	3
17	Military	1	3
18	Retired	1	3
	TOTAL	**30**	**100**

As shown in Table 1, the distribution of patients by gender was dominated by males (60%) and females (40%). The age category was predominantly adults (87%), and the education category was dominated by those with a high school education (43%). The use of atypical antipsychotic medications is presented in Table 2.

Table 2. Use of Atypical Antipsychotics

Antipsychotic	Frequency	%
Clozapine	22	47%
Risperidone	19	30%
Olanzapine	6	13%
TOTAL	**47**	**100%**

In Table 2, the most frequently used atypical antipsychotic was clozapine (47%), followed by risperidone (30%), and olanzapine (13%). The results of the effect of adjuvant therapy administration are shown in Table 3 below.

Table 3. Pre and Post Results for Group a Receiving Adjuvant Therapy

Category	Pre		Post		*p*
	n	%	n	%	
Blood Glucose Level					
Normal	1	7%	6	40%	0.606
High	14	93%	9	60%	
Triglycerides					
Normal	3	20%	3	20%	0.032
High	12	80%	12	80%	
HDL Levels					
Normal	15	100%	15	100%	0.094

High	0		0		
Blood Pressure					
Normal	5	33%	9	60%	0.326
High	10	67%	6	40%	
Body Mass Index					
Normal	12	80%	12	80%	0.315
Obesity	3	20%	3	20%	
Metabolic Syndrome	8	53%	6	40%	0.052
Pre-metabolic Syndrome	7	47%	6	40%	
Non-metabolic Syndrome	0	0%	3	20%	

In Table 3 for Group A adjuvant therapy, the pre and post-examination categories of metabolic syndrome incidence are shown. Glucose value 0.606 > 0.05 no significant difference. HDL value 0.094 > 0.05 no significant difference. Blood pressure value 0.326 > 0.05 no significant difference and BMI value 0.315 > 0.05 no significant difference. While the value of triglycerides is 0.032 < 0.05 which means there is a significant difference. The results for the control group without adjuvant therapy are shown in the table below:

Table 4. Pre and Post Results for Group B Without Adjuvant Therapy

Category	**Pre**		**Post**		***P***
	n	**%**	**n**	**%**	
Blood Glucose Level					
Normal	0	0%	4	27%	0.90
High	15	100%	11	73%	
Triglycerides					
Normal	9	60%	9	60%	0.491
High	6	40%	6	40%	
HDL Levels					
Normal	10	67%	11	73%	0.100
Low	5	33%	4	27%	
Blood Pressure					
Normal	8	53%	8	53%	0.063
High	7	47%	7	47%	
Body Mass Index					
Normal	13	87%	13	87%	0.100
Obesity	2	13%	2	13%	
Metabolic Syndrome	5	33%	2	13%	0.078
Pre-metabolic Syndrome	10	67%	11	73%	
Non-metabolic Syndrome	0	0%	2	13%	

In Table 4 for Group B without adjuvant therapy, pre, and post values show that none of the five measurements indicated a significant difference. The results for metabolic syndrome, pre-metabolic syndrome, and non-metabolic syndrome reveal no significant changes. The use of other drugs is outlined in Table 5 below:

Table 5. Use of Other Drugs

Group	Medicine	n	%
Antimuscarinic	THP	20	38
Typical Antipsychotic	CPZ	1	2
	Haloperidol	2	4
Proton Pump Inhibitor	Omeprazole	1	2
	Lansoprazole	1	2
Beta Blocker	Propranolol	1	2
Benzodiazepine	Diazepam	6	11
	Lorazepam	1	2
	Clobazam	2	4
	Merlopam	3	6
	Alprazolam	1	2
Mucolytic	Acetylcysteine	1	2
Vitamin	Vitamin B6	2	4
	Curcuma	1	2
Analgesic	Sodium diclofenac	1	2
Antidepressant	Fluoxetine	1	2
	Sertraline	1	2
Anticonvulsant	Depakote	3	6
TOTAL		**53**	**100**

In Table 5, the antimuscarinic drug trihexyphenidyl (THP) is the most dominantly used drug, followed by the benzodiazepine diazepam.

DISCUSSION

The data assessment began by evaluating the characteristics of the subjects in terms of gender, age, and educational level. The study on schizophrenia patients, based on patient characteristics, revealed that males (60%) were more prevalent than females (40%). This finding aligns with research conducted by Dewi et al., where the characteristic prevalence of male schizophrenia patients was higher than that of females. This difference is influenced by the hormone estrogen, particularly estradiol-17β, which has a protective mechanism that delays the development and exacerbation of schizophrenia symptoms. This protection includes mitigating excitotoxicity, oxidative stress, inflammation, and apoptosis (15). Additionally, males are more susceptible to mental disorders, partly because they are often the primary breadwinners in households, thus experiencing higher life stresses compared to females (16).

Regarding age distribution, the incidence of schizophrenia was more common in the adult age group (48%). This concurs with the findings of Puig et al., where the adult group was more prevalent (n = 58) compared to the adolescent group (n = 26) (17). This is related to the signs and symptoms necessary for diagnosing schizophrenia predominantly appearing in this age group (18).

In terms of educational level, most individuals had completed high school education. This is consistent with the research conducted by Agustaria Ginting, where the highest educational attainment among patients was primarily high school (42%). This correlation is due to the onset of schizophrenia (19), where initial symptoms typically appear in late adolescence or early adulthood, around 18 years of age, limiting most individuals to achieving only a high school level education as the disease begins to impact the patients (20).

In Table 2, Clozapine was the most frequently prescribed medication, accounting for 47% of the prescriptions. This aligns with research by Sahni et al., where Clozapine was used more extensively (n = 28) compared to Risperidone (n = 27) (21). In terms of the spectrum of atypicality, Clozapine is considered level III, the most

atypical. Thus, it significantly impacts the side effects related to metabolic syndrome, affecting receptors such as H1, α2, BDNF, M1, and GlyT activity (4).

The mechanism of action of Clozapine involves antagonizing both dopamine and serotonin receptors. This drug binds to dopamine receptors D1–5, with a higher affinity for D4 over D2. Both the D4 antagonism and 5-HT2A actions contribute to reducing negative symptoms and producing lower extrapyramidal side effects (22)

In alignment with Table 2, the outcomes of the side effects are presented in Table 3, where the incidence of metabolic syndrome was 5% and pre-metabolic syndrome 47%. This indicates that the long-term use of atypical antipsychotic drugs can lead to both metabolic syndrome and pre-metabolic syndrome. To determine the improvement of metabolic syndrome values, metabolic syndrome levels were examined after receiving adjuvant therapy. In this study, patients took vitamins within 7 days of the initial examination. In contrast to research conducted by Araki, where the provision of additional therapy for 24 weeks can significantly reduce triglyceride levels by 45% (23). This could be the reason that the reduction in metabolic syndrome carried out in this study did not significantly decrease. Therefore, a longer study duration is needed to monitor in depth the effects of adjuvant therapy of vitamin A 4000 IU, 3 mg vitamin B1, 10 mg vitamin E and 1 mg folic acid. In addition to the duration of vitamin use, a proper dosage assessment is needed in vitamin administration to enhance personalized therapy outcomes.

Conversely, the use of Risperidone, when administered up to high therapeutic doses, results in a loss of its atypicality/becomes less atypical (24). Within the spectrum of atypicality, Risperidone is categorized as level 1, implying that its side effects are not correlated with the incidence of metabolic syndrome.

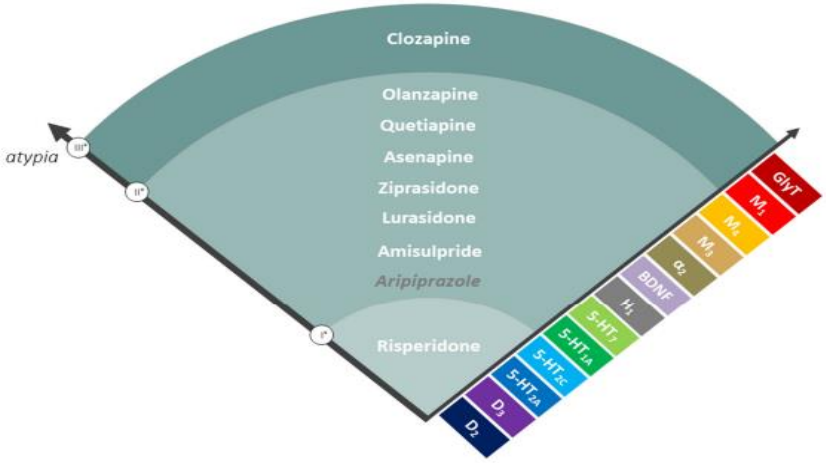

Figure 1. Atypicality Spectrum

Consistent with Clozapine, Risperidone also belongs to the atypical class, with a mechanism that blocks serotonin (particularly 5-HT2A) and dopamine D2 receptors and also binds to α1 and α2 adrenergic receptors (25). Generally, Risperidone is effective for negative symptoms and is well-tolerated depending on the dosage administered to schizophrenia patients (26).

Meanwhile, the mechanism of action of Olanzapine involves blocking both dopamine and serotonin receptors. Olanzapine has antimuscarinic effects, including dry mouth, constipation, and urinary retention. It presents lower extrapyramidal symptoms and epileptogenic effects compared to other antipsychotics. However, this medication causes metabolic side effects, including diabetes, hyperlipidaemia, and weight gain (27).

The administration of adjuvant therapy (vitamins A, B, E, and folic acid) in Group A resulted in a decrease in metabolic syndrome values, but not completely. There are 2 or 1 criteria of metabolic syndrome that have decreased. This is in line with the research conducted by Ashok et al., where the administration of folate and vitamin B12 supplementation still needs to be re-evaluated, particularly regarding how much and how long vitamin supplementation affects each occurrence of metabolic syndrome (28).

Folic acid, vitamin B6, and vitamin B12 facilitate nucleic acid synthesis and methyl group formation when these essential nutrients are available (29). Folic acid, whether from food or supplements, contributes carbon groups to homocysteine, which can be methylated to methionine or degraded to cysteine, with these vitamins acting as essential coenzymes (30). A deficiency in these vitamins can lead to obesity, dyslipidemia, vascular endothelial dysfunction, glucose intolerance, and insulin resistance, which are also pathogenetic mechanisms in metabolic syndrome (31) (32).

Supplementation with folic acid alone or combined with vitamins B6 and B12 has been shown to lower blood pressure, improve insulin resistance, and enhance lipid metabolic profiles (33). Therefore, adequate intake of folic acid, vitamin B6, and vitamin B12 is recommended as a preventative measure against metabolic syndrome (34). This study suggests that further investigation is needed to determine how long vitamins A, B, E, and folic acid are required to produce beneficial effects, as well as the recommended dosages for the improvement of metabolic syndrome.

In Table 5, the most frequently used supportive medications were antimuscarinics, specifically trihexyphenidyl (THP) (38%), and the benzodiazepine, diazepam (11%). This is consistent with research by Musdalifah on the combination of risperidone – clozapine – THP (35). The administration of combination therapy likely depends on the severity of schizophrenia symptoms. THP is intended as prophylaxis to prevent the onset of extrapyramidal side effects syndrome (36).

Future research should use a longer duration to observe the effects of vitamins A, B, E, and folic acid and evaluate their therapeutic doses. Additionally, it should narrow down the criteria for medication use, focusing solely on the atypical antipsychotics clozapine or olanzapine

CONCLUSION

The administration of adjuvant therapy with vitamins A, B, E, and folic acid can reduce several parameters of metabolic syndrome compared to group B, which did not receive adjuvant therapy with vitamins A, B, E, and folic acid.

CONFLICTS OF INTEREST

The authors declare no conflict of interest in this research

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