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RESEARCH ARTICLES

Comparison Of The Use Of Single Atypical Antipsychotics And Combination Atypical Antipsychotics Against LDL Levels In Schizophrenic Patients

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Abstract: Schizophrenia is a collection of psychotic disorders with irregularities in the thought process, which have the feeling that they are controlled by external forces, delusions, perceptual disorders and abnormal effects integrated with real situations or reality. The use of antipsychotics in schizophrenic patients is the treatment of this disease, especially the most commonly used atypical antipsychotic users. This study aims to compare LDL (low-density lipoprotein) levels in schizophrenia patients who use single atypical antipsychotics and combination atypical antipsychotics at Madani Hospital Medan, North Sumatra. This type of research is descriptive analytical using a *cross-sectional* method that takes data on variable-free bound variables at one time, which is housed at the Upt Health Laboratory. North Sumatra Provincial Health Office. The results of the Independent T-Test of the use of single antipsychotics and a combination of atypical antipsychotics on LDL levels in schizophrenia patients were p=0.001 (P≤0.05). There was a significant difference between the administration of a single atypical antipsychotic and a combination of atypical antipsychotics to LDL levels in patients with schizophrenia.

Keywords: Schizophrenia, Antipsychotic Atypical, LDL

INTRODUCTION

Previous research found that the use of antipsychotics in schizophrenic patients at Grhasia Hospital Yogyakarta for the period from January to December 2017 was found to be the largest regimen, namely 88.66. Previous studies have shown that clozapine has a low extrapyramidal effect, a high risk of orthostatic hypotension and tachycardia, a low risk of heart abnormalities, a high risk of anticholinergic effects, a high risk of weight gain and

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metabolic abnormalities.[1]

Research conducted in 2019 at Grhasia Hospital Yogyakarta showed that the most widely used combination of antipsychotics was the combination of risperidone and clozapine as much as 43.3%. Klozapine is the most commonly prescribed atypical antipsychotic by doctors with a dose of 25-50 mg/day (26.94%) and risperidone is also one of the most commonly prescribed atypical antipsychotics with the most commonly prescribed dose of 4 mg/day (27.39%).[2]

The high prevalence of schizophrenia requires the use of appropriate therapeutic management for schizophrenic patients. In the treatment of schizophrenia, there are two treatment patterns, namely single and combination treatment. Guidelines recommend that combination antipsychotics be used only in certain circumstances, but in clinical practice combining two or more antipsychotics is very common, ranging from 10-30%. 5 Another study said that antipsychotic combinations were recommended to patients who failed with the administration of monotherapy antipsychotics. [3]

LDL (low-density lipoprotein) or often also called bad fats is a lipoprotein that transports cholesterol to the body's cells that need it, which if the level is too high, it will certainly have a bad effect on health. The more fat that enters, the more LDL accumulates. This is because LDL is a saturated fat that is not easily soluble.[4] A Singapore Med study in 2012 comparing LDL levels after 8 weeks of use of the atypical antipsychotic risperidone found a result of 111.80 ± 3.26 mg/dL.[4]

Based on the description above, the author wants to know about the comparison of the use of combination atypical antipsychotics and single antipsychotics to LDL (low-density lipoprotein) levels in schizophrenia patients.

METHODS

This type of research is descriptive analytical using a *cross-sectional* method that takes data on variable-free bound variables at one time, which is housed at the Upt Health Laboratory. North Sumatra Provincial Health Office. The sample technique was obtained by first looking for a standard deviation, based on differences in LDL cholesterol levels. [5]

Inclusion Criteria

1. Patients diagnosed with schizophrenia
2. Patients who have been on atypical antipsychotics for at least 4 months
3. Outpatients, Antipsotics in respondents using single and combination antipsychotics
4. Ages 15-55
5. Patients willing to be sampled

Exclusin Criteria

1. Patients have chronic diseases such as, thyroid, HIV, TB, Hepatitis, COVID-19, and other infectious diseases.
2. Patients are not taking antilipidemia drugs
3. Patients with an obese state
4. Patients taking antipsychotics other than Risperidone and Klozapin

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RESULTS

This research was conducted at the Madani Hospital in Medan North Sumatra, located on Jl. Arief Rahman Hakim No. 168, Sukaramai I, Medan Area District, Medan City, North Sumatra, has received a research ethics permit, with no. 698KEPK/FKUMSU/2021. The sample in this study was 30 patients, with 15 respondents using a single atypical antipsychotic and 15 respondents using combination antipsychotics. This study performed venous blood draws on respondents who used single and combination antipsychotics to see LDL levels.

Table 1. Distribution of Schizophrenia Patient Data

Skizofrenia		
Patient Data	**Frequency (n)**	**Percentage (%)**
Gender		
Men	18	60
Women	12	40
Age		
18-27	5	17.7
28-37	13	43.3
38-47	8	26.7
48-57	2	6.7
58-63	2	6.7
Types of Drugs		
Single	15	50
Combination	15	50
Total	**30**	**100%**

Table 1. can be seen from the demographics of schizophrenic patients in the hospital. Madani, it was found that the male gender was more with a total of 18 people and women as many as 12 people. Based on the age range, the age group of 28-37 years is 13 people and there are a few people at the age of 48-57 years and 58-63 which each amount to 2 people.

Table 2. Gender Data of Patients With Schizophrenia Who Used Single and Combination Antipsychotics

Gender	Antipsychotics				Total	N
	Risperidon		Klozapin			
	N	%	N	%		
Man	7	23.3	11	36.7	60	18
Women	8	26.7	4	13.3	40	12
Total	**15**	**50**	**15**	**50**	**100**	**30**

Based on table 2. The most gender was found in patients with schizophrenia who used antipsychotics, 7 people (23.3%) and 11 people (36.7%) who used a single antipsychotic. Meanwhile, the female gender who used a single antipsychotic was 8 people (26.7%) and a combination antipsychotic was 4 people (13.3%).

Table 3. Characteristics of LDL Levels by Gender

LDL Level						
Gender	**N**	**Percentage (%)**	**Highest Single (mg/dL)**	**Lowest Single (mg/dL)**	**Highest Combination (mg/dL)**	**Kombinasi Lowest (mg/dL)**
Men	**18**	**60**	**144**	**32**	**292**	**103**
Women	**12**	**40**	**125**	**44**	**234**	**15**

The results of table 3, above in male patients who used a single antipsychotic with the highest LDL level was 144 mg/dl and the lowest with a value of 32 mg/dl, while the highest value combination antipsychotic was 292 mg/dl and the lowest

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was 103 mg/dl. In female patients who used a single antipsychotic, the highest LDL level was found to be 125 mg/dl and the lowest with a value of 44, while in patients who used combination antipsychotics the highest value was found to be 234 mg/dl and the lowest value was 15 mg/dl.

Table 4. Age Data of Patients With Schizophenia Using Single and Combination Antipsychotics

Age	Antipsychotics				Total (%)	Total (N)
	Single (Risperidon)		Combination (Klozapin)			
	N	%	N	%		
18-27	1	3.3	4	13.3	16.7	5
28-37	6	20	7	23.3	43.3	13
38-47	6	20	2	6.7	26.7	8
48-57	1	3.3	1	3.3	6.7	2
58-63	1	3.3	1	3.3	6.7	2
Total	**15**	**50**	**15**	**50**	**100**	**30**

The results of table 4 above are the age of patients with schizophrenia who use antipsychotics, at the age of 18-27 years who use antipsychotics, at the age of 18-27 years who use a single antipsychotic as much as 1 person (3.3%) and combination antipsychotics as many as 4 people (13.3%), age 28-37 years who use a single antipsychotic as many as 6 people (20%) and anpsychotics as many as 7 people (23.3%), 38-47 years old who used a single antipsychotic as many as 6 people (20%) and a combination anipsychotic as many as 2 people (6.7%), aged 48-57 years who used a single antipsychotic as many as 1 person (3.3%) and a combination anipsychotic as many as 1 person (3.3%), and aged 58-63 years who used a single antipsychotic as many as 1 person (3.3%) and a combination anipsychotic as many as 1 person (3.3%).

Table 5. LDL Character Levels by Age

Age	N	%	LDL Level			
			Antipsychotics Single		Antipsychotics Kombinasi	
			Highest	Lowest	Highest	Lowest
18-27	5	16.7	172	4	205	151
28-37	13	43.3	144	32	234	103
38-47	8	26.7	111	37	292	201
48-57	2	6.7	-	51	168	-
58-63	2	6.7	-	51	204	-
Total	**30**	**100**				

Based on the results of table 5. At the age of 18-27 years, LDL levels were obtained with the highest combination antipsychotic levels of 205 mg/dl, and the lowest of 151 mg/dl. Meanwhile, in the use of a single antipsychotic, it was found that the highest LDL level was 172 mg/dl, and the lowest was 44 mg/dL. In the age group of 38-47 years, LDL levels with a single antipsychotic were 111 mg/dl and the lowest was 37 mg/dl, while in the combination the highest was found to be 292 mg/dl and the highest was 201 mg/dl. In the age group of 48-57 years, LDL levels with a single antipsychotic were the lowest at 51mg/dl. Meanwhile, in combination antipsychotics, the highest results were found at 168mg/dl. In the age group of 58-63 years, LDL levels with a single antipsychotic were lowest at 51 mg/dl and

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at the highest combination were 204 mg/dl.

Table 6. Normality Test

Antipsychotics	N	P Value
Single	15	0.884
Combination	15	
Total	30	

Results of table 6. The normality test was given a value of p=0.884 (P>0.05) so that the data was distributed normally and met the requirements to conduct the Independent T-Test

Table 7. Results of Independent T-Test Data Analysis

LDL Level	Antipsychotics				Total	P
	Single (Risperidon)		Combination (Klozapin)			
	N	%	N	%		
Low	2	6.7	0	0	6.7	0.001
Normal	10	33.3	3	10	43.4	
Height	3	10	12	40	50	
Total	**15**	**50**	**15**	**50**	**100**	

Based on table 7. Above were obtained patients with low LDL levels who used a single antipsychotic as many as 2 people (6.7%), normal LDL with a single antipsychotic as many as 10 people (33.3%) and a combination antipsychotic as many as 3 people (10%), and High LDL who used a single antipsychotic as many as 3 people (10%) and antipsychotics a combination of 12 people (40%).

The results of *the Independent T-Test* on the use of single and combination antipsychotics on the LDL levels of schizophrenic patients were obtained p=0.001 (P≤0.05) so that there was a significant difference between the administration of antipsychotics and the LDL levels of schizophrenia patients.

DISCUSSION

The results of this study found that patients with schizophrenia suffered the most from men as many as 18 people (60%) and women as many as 12 people (40%), male respondents with schizophrenia who used single antipsychotics as many as 7 people (23.3%) and combination antipsychotics as many as 11 people (36.7%), while female respondents who used single antipsychotics as many as 8 people (26.7%) and combination antipsychotics as many as 4 people (13.3%). The results of this study are in accordance with a study conducted by Lee et al., in Singapore where the results of 36.5% of people with schizophrenia who take antipsychotics are dominated by 40.8% men and 32.2% women. The number of patients with schizophrenia in this study is in accordance with previous studies where men tend to have a higher prevalence of schizophrenia than women, due to the antidopaminergic effect of estrogen in women. Estrogen has an effect on dopamine activity in the acumbent nucleus by inhibiting the release of dopamine. Based on research conducted by Kaplan, it was found that women have good social functions compared to men which causes men to tend to suffer from schizophrenia more easily. [6]

The results of the study based on age in patients with schizophrenia, it was found that the most patients with schizophrenia were at the age of 28-37 years, namely 13

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people (43.3%), with patients who used single antipsychotics as many as 6 people (20.0%) and 7 combination antipsychotics (23.3%), this is in accordance with the results of the previous study which showed that the most age group was 36-45 years old as many as 16 people (34.3%) who received combination antipsychotic treatment and who received single antipsychotic treatment aged 36-45 years as many as 17 people (36.9%). The results of this study are in accordance with the theory conveyed by Kaplan, that 90% of patients in the treatment of schizophrenia are between the ages of 15-55 years.[7]

The results of this study showed that there was a significant difference between the administration of single and combination antipsychotics in schizophrenic patients with LDL levels with a value of p=0.001 (p<0.05). In this study, high LDL levels were found in schizophrenic patients who used combination atypical antipsychotics when compared to patients who used single atypical antipsychotics, this is because the combination atypical antipsychotic mechanism works as an adregiergic α1 antagonist by blocking the adrenergic α1 receptor which can cause sedation so that there is a decrease in physical activity so that it can increase LDL levels. In accordance with research conducted in North Sumatra, where LDL levels between the group that received atypical combination antipsychotics compared to the control group found patients who received atypical antipsychotic treatment, one of which was risperidon, statistically significant differences were found. In this study, it appears that atypical antipsychotic combinations cause an increase in LDL levels in patients with schizophrenia. Based on previous research, it is stated that klozapine and olanzapine are atypical antipsychotics that are most closely related to increased LDL levels, but all antipsychotics have an effect in increasing LDL levels due to the different actions of serotonergic, dopaaminergic, cholinergic, histaminergic and other neurotransmitter systems. In accordance with previous studies comparing the effects of clozapine and risridone on the lipid profile of patients with schizophrenia, there was a significant increase in serum LDL, TG and a significant decrease in HDL. This can lead to dyslipidemia in patients with schizophrenia disorder. [8,9]

The results of this study are in line with a study conducted by Omamuomu, et al. which found significant changes in lipid profiles (increases in TC, TG, LDL, and total cholesterol) at the end of 12 weeks on the use of combination antipsychotics. These findings are similar to studies in the United States that compared the effects of atypical antipsychotics clozapin, risperidone, quetiapin, and olanzapine with typical antipsychotics haloperidol and fluphenazin on lipid profiles. In 212 patients reviewed 2.5 years before and after initiation of antipsychotic treatment, the group using combination atypical antipsychotics experienced a significant improvement in lipid profile. In a previous study conducted by Syahputra I and Nuralita SN, in North Sumatra in 2020, a

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significant difference was found between the use of the atypical antipsychotic drug risperidone and the single typical antipsychotic drug haloperidol on cholesterol levels. Based on the results obtained from the use of antipsychotics, it was found that the increase in cholesterol levels, especially in the use of risperidone, was higher compared to haloperidol with the average total cholesterol level using risperidone was 192.4 mg/dl and the average total cholesterol level in the use of haloperidol was 139.7. The increase in cholesterol levels in the use of risperidone is due to the effect of atypical antipsychotics that induce the change from *Acetyl-CoA* to cholesterol. There are about 20 enzymes that play a role in converting *Acetyl-CoA* into cholesterol, one of the antipsychotic pathways in converting *Acetyl-CoA* into cholesterol is the lanosterol pathway, *7-dehydrocholesterol reductase* (DHCR7) has 2 roles in the formation of cholesterol, the first is DHRC7 is able to convert *7-dehydrocholesterol* into cholesterol and the second is DHRC7 is able to convert *7-dehydrocholesterol* become demosterol, which will later turn into cholesterol. [10,11]

The results of previous research in accordance with this study found a significant increase in LDL in patients with schizophrenia who used combination atypical antipsychotics compared to single antipsychotics. This can be caused by blockade of dopamine D2 and D3 receptors which are other potential mechanisms for the effect of antipsychotic-induced LDL enhancement, for example blockade of D2 receptor has a strong effect on eating behavior. With respect to antipsychotics, changes in lipid metabolism associated with the three-ring structure of dibenzodiazepine derivatives (klozapine, quetiapin, and olanzapine) give rise to a configuration space involved in side effects in lipid metabolism disorders. [12]

Increased LDL levels in schizophrenia patients also need to be traced further into the patient's history regarding lifestyle patterns, behavioral patterns such as smoking, poor patient diet, and genetic factors. Some genetic data also show the role of *G-protein signaling*, *leptin signaling*, and leptin *receptor activity, promelanin-concentrating hormone signaling*, and cannabinoid receptor activity on antipsychotic drugs that induce lipid levels. Some studies have also shown that antipsychotic drugs are associated with dysregulation of hepatic lipid metabolism which is the result of inhibition of the activity of AMP *(activated protein kinase).* [13]

CONCLUSION

Based on research that has been conducted on schizophrenia patients at the hospital. Madani, which amounted to 30 outpatient schizophrenia patients, with 15 patients each using single and combination atypical antipsychotic drugs, can be concluded as follows:

The gender of male patients with schizophrenia who are undergoing outpatient treatment at the hospital. Madani is more than 18 respondents (60%) compared to the female gender.

The age of the most schizophrenic

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patients was 28-37 years old, which was 13 people (43.3%).

LDL levels were found to be higher in respondents who used combination antipsychotics, namely 12 respondents (40%) compared to the use of a single antipsychotic.

There was a significant difference between patients using combination antipsychotics and single antipsychotics where there was an increase in LDL levels in schizophrenic patients who used combination antipsychotics.

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