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The Difference of Fasting Blood Sugar of Male Patients with Schizophrenia Treated with Flexible Dose between Aripiprazole and Risperidone in Medan, Indonesia

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Keywords: Schizophrenia; Aripiprazole; Risperidone; Fasting blood sugar level; Flexible dose

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Abstract

BACKGROUND: Life expectancy among schizophrenic patients is 20% shorter than the general population. Currently, long-term use of antipsychotic drugs can induce metabolic symptoms, including weight gain, glucose intolerance, high blood glucose.

AIM: This research aimed to investigate the fasting blood sugar level of a male patient with schizophrenia treated with flexible dose.

METHODS: This research is an experimental study, unpaired numerical comparative analytic with non-probability consecutive sampling by recruiting 50 research subjects of men with male patients with schizophrenia. Every 25 people were treated with aripiprazole, and another 25 subjects were treated with risperidone. The flexible dose on how doses are equated with bioequivalent doses between aripiprazole and risperidone was applied. Sampling was carried out in the inpatient and outpatient clinic of the psychiatric hospital Prof. Dr M. Ildrem Medan, North Sumatra, Indonesia, in a span of 6 months from January 2018 to July 2018. The diagnostic test used a Mini structured interview system International Statistical Classification of Diseases-10 (Mini-ICD 10) and the statistical analysis was involving Mann Whitney U Test.

RESULTS: This research showed the mean of fasting blood sugar level in week 8 in the group receiving treatment with aripiprazole was 88.96 with a standard deviation of 4.33 and in the group receiving risperidone treatment was 102.80 with a standard deviation of 2.92. The results of the analysis using unpaired t-test in the two groups showed a significant difference in fasting blood sugar levels for men with schizophrenia in the group receiving aripiprazole treatment and the group receiving risperidone treatment in week 8 with a value of $p < 0.001$ ($p < 0.05$).

CONCLUSION: This research revealed that based on the equivalence of risperidone and aripiprazole dosage given to the male patients with schizophrenia, the treatment using risperidone can significantly increase the fasting blood sugar level compared to the aripiprazole treatment in week 8.

Introduction

The best treatment option for schizophrenia is the use of long-term antipsychotic drugs. It is currently documented that long-term use of antipsychotic drugs can induce metabolic symptoms, such as body weight, glucose intolerance, high blood glucose, and unhealthy blood lipid profiles, which are closely related to cardiovascular disease and diabetes [1].

Atypical antipsychotics are the most commonly prescribed class of schizophrenia drugs. The published evidence shows that these agents provide antipsychotic properties with a lower risk of extrapyramidal symptoms than other specific antipsychotic drugs. However, concerns about Extra Pyramidal Symptoms (EPS) have been replaced by other side effects, such as weight gain, glucose deregulation and dyslipidemia [2].

Glucose is a sugar contained in the blood formed from carbohydrates contained in food and stored as glycogen in the liver and skeletal muscles [3]. The presence of blood glucose in the body has a function to be used as fuel for metabolic processes and the most important energy source in the brain. Glucose in the blood can also be used as a parameter to determine the presence of diabetes mellitus [4].

A study also explained that about gender, it

was found that when compared with men, women with normal glucose tolerance have better levels of insulin sensitivity and cell-β function, but could be damaged by the level of injury. As well as sex-related, it is also said to be associated with using the glucose oral tolerance test that women have a higher impaired glucose tolerance level, while the disturbed fasting glucose level is higher in men. This is in addition to the influence of hormones and fat distribution also due to slower glucose absorption in women [5].

The right mechanism for diabetes mellitus which is associated with antipsychotics and various possible factors to increase levels of free fatty acids (FFAs) has been found to cause insulin resistance in skeletal muscle in vivo through reducing stimulation of insulin synthesis in muscle glycogen and glucose oxidation, which causes a decrease in glucose transport activity [6].

Atypical antipsychotic drugs are the first limit that can be given to almost all patients with psychotic disorders that have low side effects for metabolism. In some literature, there is still a potential relationship with the administration of risperidone to have a risk of weight gain, diabetes, hyperglycemia, lipid dysregulation [7]. One study showed that risperidone had lower levels of hyperglycemia and diabetes mellitus compared to other antipsychotic drugs, especially olanzapine. However, several other studies also concluded that risperidone has a risk of diabetes that is comparable to First Generation Antipsychotic (FGA_S) [8].

Aripiprazole is different from most other antipsychotics due to partial agonists at D_2 receptors and not antagonists. Aripiprazole does not have the pharmacological properties that usually associated with sedation, namely the cholinergic M_1 (muscarinic cholinergic) and H_1 (Histamine) and is therefore generally not soothing. Furthermore, there is little association of aripiprazole with dyslipidemia, increased fasting triglycerides, or insulin retention. The pharmacological properties that make aripiprazole different in their low metabolic risk are unknown but can be explained if aripiprazole cannot bind postulated receptors which mediate insulin resistance and hypertriglyceridemia [9].

A study conducted by Marusita and colleagues in 2007 in Japan using the first schizophrenia group which treated with monotherapy of risperidone and the control group. The metabolic changes in people with schizophrenia compared to the control group where among metabolic parameters showed that only fasting blood glucose which has significantly higher levels in the risperidone monotherapy schizophrenia group [7].

A study conducted by Robinson et al. (2015) that looked at a randomised comparison of aripiprazole and risperidone in the treatment of acute schizophrenia in the first three-month schizophrenic patients in this study found results in improved symptom relief on aripiprazole. However, the side effects of each drug were different, which is found to be more severe akathisia on aripiprazole compared with risperidone. Moreover, aripiprazole is also associated with better results for fasting glucose [10].

This research aimed to investigate the fasting blood sugar level of a male patient with schizophrenia treated with flexible dose.

Methods

Population and Demographics

This study is an experimental study with non-randomized pre-test and post-test design, and consecutive sampling method. The sampling was conducted in mental hospitals Prof. Dr Ildrem Medan, namely patients who come to the clinic and emergency department with inpatient status and fulfilling the inclusion and exclusion criteria [11]. Group I, is consisted of 25 men with schizophrenia who received treatment with aripiprazole, while group II consists of 25 men with schizophrenia who received risperidone treatment. The retrieval of the number of subjects in this study has been adjusted in advance with a large sample formula for the unpaired numerical scale group, according to the literature used in Indonesia [12].

In this study, the subject was obtained from a mental hospital Prof. dr. M. Ildrem Medan, North Sumatra, Indonesia, where this study lasted for 6 months, from January 2018 to June 2018. Subjects were diagnosed with schizophrenia using diagnostic criteria and interviews structured using Mini ICD 10.

Inclusion criteria

Male schizophrenic patients aged 20-45 years old, the first patient affected by schizophrenia or schizophrenic patients who have already dropped out of treatment for 7 days, with a long illness below 5 years, and having an ideal weight scale (body mass index) = 18.5-24.99, with a total PANSS 80-120 and PANSS-EC scores (Excited PANSS Component Scale = ≤ 15) with regard to each agitation score symptom being P4, P7, G4, G8, G14 = ≤ 4.

Exclusion criteria

Male subjects with schizophrenia who have other comorbid medical illnesses, organic mental disorders, or other psychiatric disorders, comorbid subjects with chronic and metabolic diseases and have a family history of DM, obesity, dyslipidemia, heart disease and other metabolic disorders, he found history of use of prohibited substances and

hypersensitive subjects to aripiprazole and risperidone.

Procedure

In this study, both groups of subjects in both men with schizophrenia who received aripiprazole treatment and groups of subjects in men with schizophrenia who received risperidone were given a flexible dose by first using equivalents between aripiprazole and risperidone. Schizophrenia found that the equivalent of aripiprazole with 1 mg olanzapine was 1.4 and the equivalent of risperidone with olanzapine was 0.4. Therefore, it can be concluded that 14 mg of aripiprazole is equivalent to 4 mg risperidone [13]. The dose increase in the aripiprazole group is carried out every 2 weeks, and risperidone is increased per 2-3 days, each group will stop if the dose has responded to PANSS totalling 50% and at week 8 the average dose for each subject group will be made. The aripiprazole subject group was the subject of Aripiprazole treatment and started with a dose of 10 mg/day, then the PANSS score will be measured the following week, if the PANSS score has not yet reached a response, the dose of Aripiprazole will be increased by 5 mg/day every two weeks until the response occurs. Maximum dose of 30mg. The risperidone group was subjects who received risperidone therapy.

For men with schizophrenia in the first attack, the dose of risperidone will be raised titration, which begins with a dose of 2 mg/day and PANSS score will be measured every day and the dose of risperidone will be increased 1 mg/day until a response occurs. Especially for male subjects with schizophrenia who were not the first attack or discontinued the drug, then the dose of risperidone given was the last dose that responded. If the occurrence of side effects such as Parkinsonism during treatment is given trihexyphenidyl anticholinergic therapy at a dose of 6 mg/day/oral in divided doses, a maximum of 15 mg. If there are acathic side effects, the subject will be given lorazepam 2 mg in divided doses, a maximum of 6 mg in divided doses, and if the drug is still not able to overcome these side effects, the subject will be dropped and given other class of drugs as indicated for the benefit of the subject.

This study was treatment analysis so that if a drop out occurs, the subject will be replaced with a new one. The drop out criteria was subjects who have not succeeded in completing treatment for 8 weeks, as well as unresolved drug side effects.

Fasting blood glucose sampling on all subjects was collected starting from baseline (week 0, i.e. before administration of the drug), and every week until the 8th week. Blood samples were taken at 6:00 a.m. to 8:00 p.m., where previous patients fasted at least 10-12 hour.

Table 1: Sample distribution on demographic characteristics of research subjects

	Male patients with schizophrenia who were treated with aripiprazole, n = 25	Male patients with schizophrenia who were treated with Risperidone, n = 25	*p*
Age (Mean ± SD)	33.520 ± 4.718	33.120 ± 4.969	0.772[a]
Educational Background	11 (44.0%)	8 (32.0%)	0.561[b]
Elementary-Junior High School	14 (56.0%)	17 (68.0%)	
Senior High School			
Marital Status			0.1000[b]
Married	7 (28.0%)	7 (28.0%)	
Single	18 (72.0%)	18 (72.0%)	
Job Status			0.762[b]
Work	9 (36.0%)	7 (28.0%)	
Unemployed	16 (64.0%)	18 (72.0%)	
Illness Duration Median (minimum-maximum)	3.000 (1.00-4.00)	3.000 (1.00-4.00)	0.844-0.422[c]
Hospitalisation History (year)			0.1000[b]
≤ 3	13 (52.0%)	13 (52.0%)	
> 3	12 (48.0 %)	12 (42.0%)	
Onset Age (Mean±SD)	30.84 ± 4.259	33.60 ± 4.481	0.847[a]
Fasting Blood Sugar Levels (week 0) Median (minimum-maximum)	76.00(70.00-86.00)	74.00 (70.00-86.00)	0.310-0.155[c]
Body Mass Index Week 0 (Mean ± SD)	21.719 ± 1.563	21.367 ± 1.140	0.368[a]
8th week (Mean ± SD)	22.018 ± 1.714	21.960 ± 1.355	0.896[a]
PANSS Score (week 0) (Mean ± SD)	104.200 ± 6.745	103.840 ± 6.920	0.853[a]
PANSS Score (8th week) Median (minimum-maximum)	37.00 (36.00-40.00)	37.00 (35.00-41.00)	0.537-0.269[c]

[a] Unpaired t-test Tidak Berpasangan; [b] *chi-square test;* [c] *Mann Whitney U test.*

Statistical Analysis

Data were analysed using SPSS version 21 statistical test. Normality tests were conducted on the data of each group using the Saphiro-will test because the number of subjects in each group is smaller than 50. For unpaired numerical comparative groups two groups, if the distribution of data is normally distributed so that the unpaired T-test is carried out. If the distribution of data is not normally distributed then the data transformation is carried out, after that the normality test is conducted again, if the data is not normally distributed then the analysis carried out is the Mann-Whitney U test, [12] while for the comparative numerical group the two groups are paired, if the distribution of data is normally distributed then a paired T-test will be carried out. If the distribution of data is not normally distributed, then data transformation will be carried out. After that the normality test was finished; if the data is still not normally distributed then the analysis carried out is the Wilcoxon test [12].

Results

This research was the first study ever conducted in Indonesia regarding fasting blood sugar levels at week 8 in male patients with schizophrenia who recruited 50 subjects, namely subjects with treatment for aripiprazole and risperidone treatment with 25 subjects each and with flexible dose by first paying attention to the dose bioequivalence in both

drug groups. And during this study, there were no subjects who dropped out and experienced side effects from the administration of aripiprazole and risperidone.

Demographic data in both groups of subjects are described in Table 1. It is found that there were no differences in demographic characteristics in the two groups of subjects with the majority value (p > 0.05).

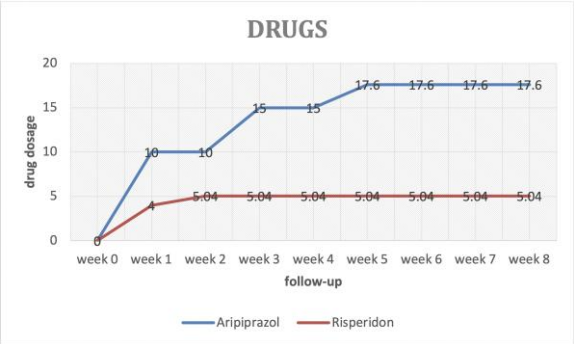

Figure 1: The line chart of the average subject group dosage for treatment with aripiprazole and risperidone

Based on Figure 1, the average dosage in the group of men with aripiprazole is 17.6 while in the group of men with risperidone is 5.04. This is equivalent to 17.5 aripiprazole is comparable to 5 mg risperidone.

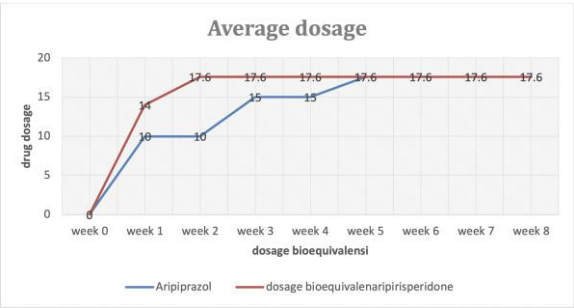

Figure 2: The line chart of the average of bio-equivalence dosage of the risperidone treatment group to the aripiprazole treatment group

Figure 2 shows the average of risperidone dosage is started to be equivalent to aripiprazole at week 5. Moreover, Figure 1 and Figure 2 shows equivalence for both treatment groups which can be seen at week 5. This is due to differences in half-life in both drugs and titration properties from different aripiprazole and risperidone.

Table 2: The normality test result of fasting blood sugar level in male patients with schizophrenia who were treated with aripiprazole between week 0 and week 8

Aripiprazole Treatment	Subjects (n)	*p*
Blood Sugar Level-week 0	25	0.251*
Blood Sugar Level-8th week	25	0.997*
Blood Sugar Level Difference between a 1st week and 8th week	25	0.940*

**Shapiro-Wilk p* > 0.05.

Based on Table 2 above, the data are normally distributed, so that, a paired t-test can be performed.

Table 3: The result of complete paired t-test for aripiprazole

	Mean ± SD	Difference ± SD	IK 95%	*p*
Blood Sugar Level-week 0 (n = 25)	76.24 ± 4.48	12.72 ± 3.40	11.31-14.12	< 0.001*
Blood Sugar Level-8th week (n = 25)	88.96 ± 4.33			

**Paired t-test, p < 0.05.*

Table 3 shows that the average fasting blood sugar level at week 0 that received treatment for aripiprazole was 76.24 ± 4.48 and the mean fasting blood sugar level at week 8 receiving treatment with aripiprazole was 88.96 ± 4.33. The differences in mean fasting blood sugar levels of week 0 and week 8 are 11.31 to 14.12. The results of the analysis using paired t showed a significant difference in fasting blood sugar levels in men with schizophrenia who received aripiprazole treatment at week 0 and week 8 with p values < 0.001 (p < 0.05).

Table 4: The normality test result of fasting blood sugar level in male patients with schizophrenia who were treated with risperidone between week 0 and week 8

Risperidone Treatment	Subjects (n)	*p*
Blood Sugar Level-week 0	25	0.002*
Blood Sugar Level-8th week	25	0.311*
Blood Sugar Level Difference between week 0 and 8th week	25	0.142*

**Shapiro-Wilk p* > 0.05.

Based on Table 4 above, the data are normally distributed, so that, a paired t-test can be performed.

Table 5: The result of complete paired t-test for risperidone treatment

	Mean ± SD	Difference ± SD	IK 95%	*p*
Blood Sugar Level-week 0 (n = 25)	74.84 ± 5.11	27.96 ± 4.11	26.26 – 29.66	< 0.001*
Blood Sugar Level-8th week (n = 25)	102.80 ± 2.91			

**Paired t-test, p < 0.05.*

In Table 5 shows that the average fasting blood sugar level at week 0 who received risperidone treatment was 74.84 ± 5.11 and the mean fasting blood sugar level at week who received risperidone treatment was 102.80 ± 2.91 difference in mean fasting blood sugar levels of week 0 and week 8 26.26 to 29.66.

The results of the analysis using paired t showed a significant difference in fasting blood sugar levels in men with schizophrenia who received risperidone treatment at Week 0 and Week 8 with p values < 0.001 (p < 0.05).

Table 6: The normality test result of fasting blood sugar level between the group treated with aripiprazole and risperidone on week 8

	Treatment	Subjects (n)	*p*
Blood Sugar Level-8th week	Aripiprazole	25	0.977*
	Risperidone	25	0.311*

**Shapiro-Wilk p*>0.05.

Based on the result above, the data are normally distributed (p > 0.05). Therefore, an unpaired t-test can be performed.

Table 7: The difference of fasting blood sugar level between the group treated with aripiprazole and risperidone on week 8

Treatment	Mean ± SD	Mean Difference (IK 95%)	*p*
Aripiprazole	88.96 ± 4.33	-13.84 (11.74-15.94)	< 0.001*
Risperidone	102.80 ± 2.92		

**Unpaired t-test, p < 0.05.*

Table 7 shows the mean of fasting blood sugar level on week 8 in the group receiving treatment with aripiprazole is 88.96 with a standard deviation of 4.33 and in the group that received treatment for risperidone is 102.80 with a standard deviation of 2.92. The results of the analysis using unpaired t-test in the two groups showed a significant difference in fasting blood sugar levels for men with schizophrenia in the group receiving aripiprazole treatment and the group receiving risperidone treatment on week 8 with a value of p < 0.001 (p < 0.05).

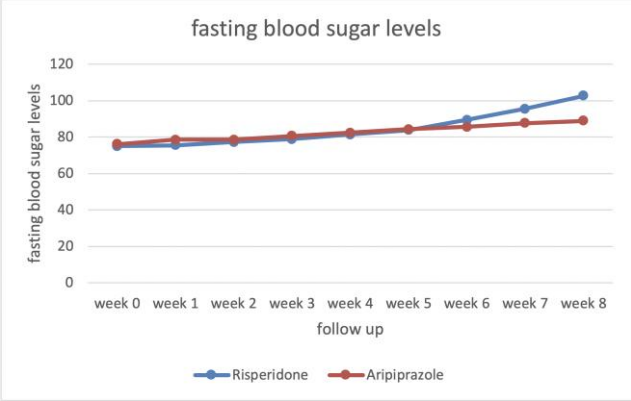

Figure 3: The line chart of the mean of fasting blood sugar level between groups treated with aripiprazole and risperidone

Based on Figure 3 above, it shows that there was no increase in fasting blood sugar levels in the initial week. However, at week 8 the increase in fasting blood sugar levels showed a significant difference in both groups. Where fasting blood sugar levels in the group of men with schizophrenia who received risperidone treatment experienced an increase compared to the group of men with schizophrenia who received treatment for aripiprazole.

Moreover, by using a flexible dose of bioequivalent doses, the development of the PANSS score is a benchmark in increasing doses and to pay attention to the level of development of treatment. As well as stopping the increase in dosage on the PANSSS score which reaches a 50% decrease in change, as a sign that the maximum response has occurred. In other words, this study also puts a concern to the treatment response too.

In Figure 4, the PANSS score in both groups of subjects achieved a 50% loss in the PANSS score faster in subjects of the group of men with schizophrenia who received risperidone treatment.

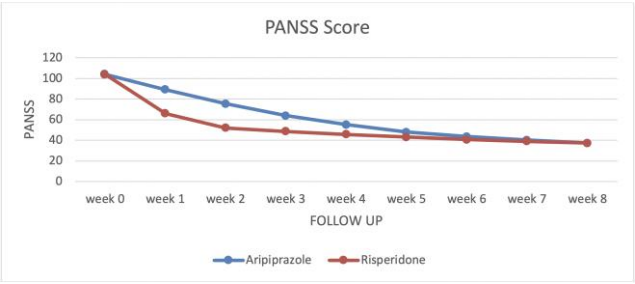

Figure 4: The PANSS Score between the group treated with aripiprazole and risperidone

Furthermore, a subgroup test was also carried out between blood sugar levels and the dose of the drug as a secondary outcome which is an additional or supportive outcome, intended only for whether there are additional effects due to the intervention studied in addition to the main effects. But this is only an illustration and cannot be drawn as a conclusion (Table 8) [14].

Table 8: The difference in fasting blood sugar level based on dosages

Treatment	Dosages	Blood Sugar Level (Mean ± SD)	*p*
Aripipazole	15 mg (n = 12)	88.417 ± 3.423	0.558
	20 mg (n = 13)	89.462 ± 5.125	
Risperidone	4 mg (n = 11)	103.090 ± 2.773	0.668
	6 mg (n = 14)	102.571 ± 3.106	

From Table 8 above, it can be seen that the average fasting blood sugar level based on the dose of aripiprazole with a dose of 15 mg obtained was 88.417 ± 3.423, whereas fasting blood sugar levels at a dose of 20 mg obtained was 89.462 ± 5.125. The fasting blood sugar level of the risperidone group with a dosage of 4 mg was 103.090 ± 2.773, while the average fasting blood sugar level at a dose of 6 mg obtained was 102.57 ± 3.106. Since the p-value was more than 0.05, it can be inferred that the dose does not provide a significant difference in fasting blood sugar levels.

Discussion

Table 1 shows the demographic characteristics of each group. The mean based on age in the group that received treatment for aripiprazole is 33.520 years with a standard deviation of 4.718 years. For that receiving risperidone treatment, the mean based on age was 33.120 years with a standard deviation of 4.969 years. The highest education level in the treatment group that received Aripiprazole and risperidone was Senior High School and Higher Education with the number of 14 subjects (56.0%) in the aripiprazole group and 17 subjects (68.0%) in the risperidone group respectively. The

most marital status in each group was not married with 17 (72%) in the aripiprazole and risperidone groups. The highest occupational history in the treatment group that received aripiprazole and risperidone was unemployed, each of 16 subjects (64.0%) in the aripiprazole group and 18 subjects (72.0%) in the risperidone group. The duration of illness in the treatment group of aripiprazole and risperidone is that they have a median value of 3.000 with the same minimum-maximum limit in the two groups of 1.00-4.00. The fasting blood sugar level at week 0 baseline or before administration of therapy of the aripiprazole and risperidone treatment groups were having an equal median value of 76.00 with the same minimum-maximum limit in the 70.00-86.00 groups. The mean BMI-Week 0 (Baseline) in the group receiving aripiprazole treatment was 21.719 ± 1.563 and in the group receiving risperidone treatment was 21.367 ± 1.140. The mean pass score of 0 (before therapy) in the aripiprazole group was 104.200 with a standard deviation of 6.745 and the mean in the 103.840 group with a standard deviation of 6.920. The results of the analysis using unpaired t-test in the two groups showed a significant difference in fasting blood sugar levels for men with schizophrenia in the group receiving aripiprazole treatment and the group receiving risperidone treatment on Week 8 with a value of $p < 0.001$ ($p < 0.05$). Where in the 8th week, fasting blood sugar levels in the group of men with schizophrenia who took risperidone treatment were higher than in the group of men who used the treatment of aripiprazole. It's by Wani, et al., (2015), discovered that the use of aripiprazole and risperidone increase the fasting blood sugar. However, the significant difference between aripiprazole and risperidone usage was observed at week 14 [15].

In conclusion, this study showed that based on flexible dose with equalising of bio-equivalent doses between the dosage of aripiprazole and risperidone in men with male schizophrenia who were treated with risperidone is tend to experience more a significant increase in fasting blood sugar levels compared with people receiving treatment for aripiprazole at week 8.

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Ethical Aspects

Authors state that the research follows the ethical aspect as regulated by the ethical committee of the University of Sumatera Utara, Indonesia.

References

1. Zhang S, Lan G. Prospective 8-week trial on the effect of olanzapine, quetiapine, and aripiprazole on blood glucose and lipid among individuals with first- onset Schizophrenia. Shanghai Archives of Psychiatry. 2014; 26:339-346.

2. Nasrallah HA. Atypical antipsychotic-induced metabolic side effects: insights from receptor- binding profiles. Molecular Psychiatry. 2008; 13:27-35. https://doi.org/10.1038/sj.mp.4002066 PMid:17848919

3. Lestari DD, Purwanto DS, Kaligis SHM. Gambaran kadar glukosa darah puasa pada mahasiswa angkatan 2011 Fakultas kedokteran Universitas Sam Ratulangi dengan indeks masa tubuh 18,55-22,9 kg/m2. Jurnal e-Biomedik (eBae). 2013; 1:991-996.

4. Subiyono, Martsiningsih MA, Gabrela D. Gambaran kadar glukosa darah metode GOD-PAP (Glucose Oxsidase-Peroxidase Aminoantypirin)Sampel Serum dan Plasma EDTA(Ethylen Diamin Terta Acetat). Jurnal Tekhnologi laboratorium. 2016; 5:45-48.

5. Kautzky-Willer A, Kosi L, Lin J, Mihaljevic R. Gender-based differences in glycaemic control and hypoglycaemia prevalence in patients with type 2 diabetes: results from patient-level pooled data of six randomised controlled trials. Diabetes, Obesity and Metabolism. 2015; 17(6):533-40. https://doi.org/10.1111/dom.12449 PMid:25678212

6. Buchholz S, Marrow AF, Coleman PL. Atypical antipsychotic-Induced diabetes mellitus; An Uptade on epidemiology and postulated mechanisms. Internal Medicine Journal. 2008; 38(7):602-606. https://doi.org/10.1111/j.1445-5994.2008.01712.x PMid:18715305

7. Murashita M, Inoue T, Kusumi I, Nakagawa S, Itoh K, et all. Glucose and lipid metabolism of long-term risperidone monotherapy in patiens withschizopherenia. Psychiatry and Clinical Neurosciences. 2007; 61:61-64. https://doi.org/10.1111/j.1440-1819.2007.01610.x PMid:17239039

8. Marder SR. Davis MC, Second- generation Antipsychotic in: Sadock BJ, Sadock VA, Ruiz. Kaplan & Sadock's Comphrenhensive textbook of psychiatry. vol. 1, 10thed Philadelphia: Lippincott William & Wilkins, 2017:8125-8132.

9. Stahl SM. Antipsychotic agent In Stahl's Essential Psychopharmacology; Neuroscientific Basis and Practical Application. 4th ed. Cambridge; Cambridge University Press, 2013:238-347.

10. Robinson DG, Gallego JA, Jhon M, Petrides G, Hassoun Y, et al. A randomized comparison of aripiprazole and risperidon for the acute treatment of first-episode schizophrenia and related disorders: 3-month out comes. Schizophrenia Bulletin. 2015; 6:1227-1236. https://doi.org/10.1093/schbul/sbv125 PMid:26338693 PMCid:PMC4601722

11. Sastromoro S, Ismail S. Dasar-dasar metode penelitian klinis. Edisi Ketiga. Jakarta: Sagung Seto, 2008.

12. Dahlan MS. Uji hipotesis komparatif numerik berpasangan. Dalam Statistik untuk kedokteran dan kesehatan, deskriptif, bivariate, dan multivariate dilengkapi aplikasi SPSS. Edisi 6. Jakarta: Epidemiologi Indonesia, 2015.

13. Leucht S, Samara M, Heres S, Patel MX, Furukawa T, Cipriani A, et al. Dose equivalents for second-generation antipsychotic drugs; the classical mean dose method. Schizophrenia Bulletin. 2015; (41):1397-1340. https://doi.org/10.1093/schbul/sbv037 PMid:25841041 PMCid:PMC4601707

14. Sastroasmoro S, Setiabudy R, Setyawati A, Taher A, Harimurti K, Idris N S. Uji klinis landasan teori dan paduan praktis. Jakarta: Sagung Seto; 2017.

15. Wani RA, Dar MA, MArgood MA, Rather YH, Hag I, Shah MS. Diabetes mellitus and impaired glucose tolerance in patient with schizophrenia, before and after antipsychotic treatment. Journal of Neurosciences in Rural Practices. 2015; 6(1):17-22. https://doi.org/10.4103/0976-3147.143182 PMid:25552846 PMCid:PMC4244781