Evaluation of Clinical Outcome of Antipsychotic Therapy in Schizophrenic Patients in Palu – Indonesia

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Info Article	ABSTRACT
	Schizophrenia is a severe mental disorder characterized by psychotic episodes. The first line of treatment for schizophrenia is the use of antipsychotics that is still subjective. There is still a need for research related to the use of antipsychotics to achieve an effective treatment. This study aimed to compare the effectiveness of First-Generation Antipsychotics (FGAs) such as haloperidol, trifluoperazine, and risperidone as Second-Generation Antipsychotics (SGAs) based on symptom reduction using the Positive and Negative Syndrome Scale-Excited Component (PANSS-EC) method in patients with acute schizophrenia and relapse hospitalization. This research used a quantitative analysis with a prospective approach where the sampling was conducted using total sampling and the data obtained were analyzed using independent t-test and linear regression analysis. There were 40 out of 120 patients who met the inclusion criteria, consisting of patients in groups of haloperidol, trifluoperazine, and risperidone therapies with a therapeutic duration of 3–10 days. The results showed that the average PANSS-EC score of haloperidol medication of 15.35 was greater than that of trifluoperazine medication of 14.42 and the p-value showed no significant difference between the use of two FGAs, namely haloperidol and trifluoperazine with $p = 0.190$ ($p > 0.05$). The average PANSS-EC score of the haloperidol medication (FGA) of 15.35 was greater than that of risperidone (SGA) of 13.6 and the p-value showed that there was a significant difference between haloperidol and risperidone with $p = 0.027$ ($p < 0.05$). The multivariate analysis showed $p = 0.022$ ($p < 0.05$), which means haloperidol showed the greatest symptom reduction among the three antipsychotic medications. The conclusion showed that haloperidol is better in improving the symptoms in schizophrenic patients than trifluoperazine and risperidone. **Keywords:** Haloperidol, Risperidone, Trifluoperazine, PANSS-EC, Schizophrenia

INTRODUCTION

Schizophrenia is the most complex psychiatric disorder that represents psychosocial dysfunctions. Schizophrenia can occur in early adulthood but it rarely appears before adolescence and after the age of 40 years. Based on the American Psychiatric Association in 2013, the prevalence of schizophrenia was in the range of 0.3 to 0.7%, almost the same in every country in the world (DiPiro *et al*., 2017). Based on the results of the 2018 Basic Health Research, the highest prevalence of schizophrenia in Indonesia was found in Bali, while Central Sulawesi ranked the 10th (Basic Health Research, 2018). The main

therapy in schizophrenic patients is the administration of antipsychotic medications.

Antipsychotic therapy is divided into two groups; both of which are used as a therapy for schizophrenia and show the ability to produce antipsychotic effects with or without extrapyramidal symptoms (DiPiro *et al*., 2017). First-Generation Antipsychotics (FGAs) are competitive inhibitors of various receptors, but their antipsychotic effects reflect the blocking of competitive D2 dopamine receptors. First-Generation Antipsychotics (FGAs) are associated with movement disorders, especially for medications that are closely linked to dopamine

neuroreceptors such as haloperidol. Second-Generation Antipsychotics (SGAs) have less extrapyramidal symptoms (EPS) than First-Generation Antipsychotics (FGAs) and have activities to block serotonin and dopamine receptors (Clark *et al.*, 2012). In clinical research, a series of instruments is used to quickly assess the level of anxiety and aggression in schizophrenic patients. The measurement chosen in modern research is the positive and negative syndrome scale. This research used the Positive and Negative Syndrome Scale-Excited Component (PANSS-EC) which is a validated sub-scale of PANSS to measure agitation symptoms, and assess 5 (five) symptoms, namely poor impulse control, tension, hostility, and uncooperative and noisy anxiety. PANSS-EC is one of the simplest but most intuitive scales used to assess patients with anxiety disorders (Montoya *et al.*, 2011).

In a recent study related to the effect of antipsychotics on a decrease in the Positive and Negative Syndrome Scale-Excited Component (PANSS-EC) score, the selection of antipsychotics had an effect on decreasing the severity of schizophrenia with a percentage of 73.80% (Purwandityo *et al.*, 2018). Haloperidol and trifluoperazine are First-Generation Antipsychotics (FGAs) of high potential groups that have a high affinity as D2 receptor antagonists that cause extrapyramidal side effects. In addition, antipsychotic therapy could reduce symptoms, prevent side effects, and improve psychosocial functions and productivity. Based on the results of a meta-analytic research, 6 out of 9 experiments showed that patients with chronic schizophrenia who were given risperidone therapy were associated with significantly higher response rates in decreasing the prescription of anticholinergic medications (Davies *et al.*, 1998). This research aimed to compare the effectiveness of the use of single antipsychotics of haloperidol and trifluoperazine as well as haloperidol and risperidone in reducing the symptoms of schizophrenia measured using the PANSS-EC score differences. In this study, it was known the value of the symptom reduction to facilitate the selection of antipsychotics was according to the characteristics and conditions of the patients.

MATERIAL AND METHODS
Ethics statement
This research had been approved by the Research Ethics Committee of the Faculty of Medicine and Health, Tadulako University, with a letter number 4755/UN28.1.30/KL/2018 and 4746/UN 28.1.30/KL/2018.

Subject
The subjects of this research were schizophrenic patients hospitalized at Madani Hospital Palu - Indonesia, who received haloperidol, trifluoperazine and risperidone therapies and met the inclusion criteria, namely Schizophrenic patients who were 15-65 years old and met the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) and International Classification of Diseases (ICD 11) in the acute phase and relapses who were hospitalized without any concomitant diseases. The exclusion criteria were patients who were pregnant, patients with concomitant diseases, and patients using other antipsychotic therapies.

Method and analysis
This was a quantitative analysis using a prospective approach by using the data from the average PANSS-EC (Positive and Negative Syndrome Scale - Excited Component) score differences where the therapeutic duration was 3–10 days in patients with acute phase of schizophrenia and relapses who had signed an informed consent. PANSS-EC was assessed in the patients with acute episodes of schizophrenia and relapse who received haloperidol, trifluoperazine, and risperidone therapy. The patients with acute episodes were schizophrenic patients who never received antipsychotic therapy, while the relapsed patients were schizophrenic patients who had been previously treated with antipsychotics. Assessment was done by giving a score on the PANSS-EC sheet which had 5-point scales to rate symptoms, where a scale of 1 was given when the patients did not meet the definition of symptoms and a scale of 7 was given when the patient was almost totally withdrawn, uncommunicative, and neglectful of personal needs due to a profound lack of interest and emotional commitment. The PANSS-EC score data were divided into 2, namely the scores before and after the antipsychotic interventions. The initial data were taken when the patients were admitted to the hospital after drug administration and the patients were re-assessed after showing improvement in symptoms, and the second data were taken. Next, the researchers calculated the score differences between the two data.

Table I. Demographic characteristics of hospitalized schizophrenia patients

Characteristics	Number of schizophrenic patients (n=120)	Percentage (%)
Gender		
Male	83	69.16
Female	37	30.83
Age		
15-24	38	31,7
25-44	55	45.8
45-65	27	22.5
Marital Status		
Unmarried	68	56.66
Married	44	36.66
Widow/Widower	8	6.66
Education		
Low	60	50
Moderate	57	47.5
High	3	2.5
Occupation		
Unemployed	70	58.33
Farmer	23	19.16
Housewife	12	10
Entrepreneur	11	9.16
Fisherman	2	1.66
Labor	2	1.66

The data analysis was conducted by collecting secondary data obtained from the measurement results in the form of an average PANSS-EC score difference, then the data were analyzed using independent t-test and linear regression analysis to see significant differences in the antipsychotics.

RESULT AND DISCUSSION
Demographic characteristics

Out of the 120 patients with schizophrenia, there were 83 male patients (69.2%) and 37 female patients (30.8%) (Table I). In terms of age group, the majority of the patients with schizophrenia were 25–44 years old, with a total of 55 patients (45.8%), followed by the age group of 15–24 years old with a total of 38 patients (31.7%) and the age group of 45–65 years old with a total of 27 patients (22.5%). In terms of the marital status of these schizophrenic patients, most of them (56.7%) were unmarried, while the married ones were 36.7%. In terms of education, this research divided the respondents into Low education level category (No School, Elementary School, Junior High School), Moderate level (High School), and High level (Bachelor Degree). The highest percentage was found in the Low category (50%). Finally, in terms of employment, the majority of the respondents in this research were unemployed (58.3%).

In this research, there was a difference in the incidence of schizophrenia between male and female patients. Schizophrenia and acute psychosis are less common in women than in men. In women, it seems that the prognosis of psychiatric disorders, social functioning, and response to treatment is better. Women show a later age of onset than men, which allows them to adjust better. The estrogen hypothesis tries to explain why women have a lower age of onset for psychotic disorders. According to this hypothesis, some therapeutic treatments related to estrogen can be useful to improve symptoms and cognition. In addition, women need more risk factors to develop schizophrenia than men (more family risk, more emotional involvement in life events) (Ochoa *et al.*, 2012). Based on previous research on the rationality of using antipsychotics, there are more men with schizophrenia hospitalized than women because men usually have very high aggressiveness so it is difficult to handle if they are only treated at home, while aggressiveness in women with schizophrenia can still be handled by families at home so they tend to be treated at home (Fahrul, *et al.*, 2014).

Table II. Clinical manifestations of hospitalized schizophrenic patients

Symptoms	Number of schizophrenic patients	Percentage (%)
Hallucinations	109	19.7
Restless	96	17.3
Insomnia	68	12.3
Blunted Affect	57	10.3
Anxiety	37	7.1
Alogia	31	5.6
Delusion	30	5.4
Unstable Emotion	29	5.2
Hostility	27	4.8
Disorganized speech	22	3.9
Echopraxia	16	2.8
Anhedonia	16	2.8
Mania	14	2.5
Total	552	100

Schizophrenia is a chronic disorder characterized by an increased social disability that begins at the end of adolescence, namely at the age of 15 years or early adulthood at the age of 35 years, and tends to continue throughout life (Williams and Debattista 2017). This age is an age where a person can experience various conflicts in life, not only conflicts between individuals but also conflicts with themselves, for example, having desires that cannot be achieved. In schizophrenic patients, there is an inability to face reality. In fact, 90% of patients who receive treatment for schizophrenia are 15–55 years old in which there is no difference between men and women if they have a family history. However, it is different in terms of the age of onset that seems to depend on the presence or absence of family history (Sianturi 2010).

In this research, most of the schizophrenic patients were unmarried. If a patient has been exposed to schizophrenia, especially chronic schizophrenia, then the patient is not likely to get married but s/he needs treatment for the mental disorder, thus disturbing her/his social life and ability to build a good relationship (for example, marriage) (Sira 2013).

Educational characteristics are related to the cognitive function of schizophrenic patients. Common cognitive functions are genetically correlated with health and neuropsychiatric disorders. In particular, a lower cognitive function is consistently correlated with the risk of schizophrenia. Current treatment strategies largely fail to improve the cognitive impairment in schizophrenia (Ohi *et al.*, 2018).

People with schizophrenia have decreased productivity and ability to perform certain jobs. In addition to a lack of self-motivation due to the underlying negative symptoms, stigmatization and discrimination against people with mental disorders prevent them from community integration because they often get ridiculed and face social and economic isolation. Therefore, this factor limits those with schizophrenia from the right to freedoom of opinion and the right to a decent job (Saperstein, *et al.*, 2011).

Clinical characteristics
Clinical manifestation

The clinical manifestations of hallucinations (19.7%), restless (17.3%), insomnia (12.3%), blunted affect (10.3%), and anxiety (7.1%) (Table II).

The most often found clinical manifestation in this study was hallucinations. The most common hallucinations were in the form of auditory hallucinations such as hearing voices or criticisms that seemed real to the schizophrenic patients. Perceiving sound when there is no external stimulus is a general phenomenon and it belongs to a positive psychosis symptom which tends to decrease over time (Tracy and Shergill 2013). The next most common clinical manifestation was nervous anxiety (17.3%), where this symptom appears as a manifestation of psychotic symptoms felt by patients. The third most common clinical manifestation was insomnia (12.3%).

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Table III. Diagnosis of hospitalized schizophrenic patients

Diagnosis	Number of schizophrenic patients (n=120)	Percentage (%)
Undifferentiated schizophrenia	80	66.6
Unspecified schizophrenia	32	26.6
Hebephrenic schizophrenia	4	3.3
Paranoid schizophrenia	4	3.3

Table IV. Medication Profile of hospitalized schizophrenic patients

Pharmacology therapy	Number of schizophrenic patients (n=120)	Percentage (%)
Diazepam	85	48.85
Trihexyphenidyl	65	37.35
Sodium Divalproate	14	8.04
Lorazepam	10	5.74
Total	174	100

The relationship between antipsychotic therapy and sleep disorders is still unclear. Recent pilot studies showed that even though patients with schizophrenia report sleep disorders, they do not feel sleepy during the day (Bosch *et al.*, 2018). There were 37 schizophrenic patients (10.3%) whose clinical manifestation was blunted affect. Affection is an expression of feelings that appear in schizophrenic patients including unchanging facial expressions, decreased spontaneous motion, minimal eye contact, and monotonous intonation. In addition, 33 schizophrenic patients (7.1%) had anxiety symptoms. Anxiety in schizophrenia is not pure anxiety. In addition, people with paranoid schizophrenia often have symptoms that include unfocused anxiety, anger, hospitality or debating, and acts of violence (Ibrahim 2010).

Diagnosis

The most commonly found type of schizophrenia was undifferentiated schizophrenia (66.7%) (Table III). Meanwhile, unspecified schizophrenia had a percentage of 26.7%, while both paranoid and hebephrenic schizophrenia had a percentage of 3.3%.

The most common type of schizophrenia in this study was undifferentiated schizophrenia with a percentage of 66.6%. This type has positive symptoms that stand out or meet the criteria of schizophrenia but cannot be classified into other types of schizophrenia. The second type (26.6%) was an unspecified schizophrenia of which the symptoms are difficult to classify into certain types of schizophrenia (Fahrul, *et al.,* 2014). Another type of schizophrenia shown from the results of this research was paranoid schizophrenia (3.3%) in which the main feature of paranoid schizophrenia is the presence of irrational beliefs or auditory hallucinations in the context of the presence of cognitive and affective functions that are relatively maintained. The least common type of schizophrenia was hebephrenic schizophrenia (3.3%) with a prominent main feature of disorganized speech and behavior and blunted affect (Ibrahim 2010).

Medication profile

The other therapies combined with antipsychotics were diazepam (48.85%) and trihexyphenidyl (37.35%) (Table IV). There was also a small percentage combined with lorazepam and sodium divalproate.

Haloperidol and trifluoperazine in the treatment of schizophrenia are usually combined with trihexyphenidyl as prophylaxis for the onset of symptoms of Parkinsonism due to the use of a First-Generation Antipsychotic (FGA) medication of haloperidol. This medication works by reducing the effects of excessive central cholinergic due to the presence of dopamine deficiency in the extrapyramidal system such as symptoms of Parkinsonism. Parkinsonism that occurs in patients with schizophrenia is characterized by bradykinesia, stiffness, irregular tremors, reduced arm swing, mask or flat face, and slowness of movement. In addition to being combined with first-generation anti-psychotics, it can also be combined with second-generation antipsychotics, namely risperidone, as prophylaxis of extrapyramidal effects.

Table V. Independent T-Test analysis of the PANSS-EC score differences based on the duration of antipsychotic therapy of hospitalized schizophrenic patients

Variable	Antipsychotics	Total	Average	*p*-Value
	Haloperidol			
	Days 1-3	20	14.45	0.055
	Days 1-7	20	16.25	
	Trifluoperazine			
PANSS-EC	Days 1-3	20	14.4	0.962
	Days 1-7	20	14.45	
	Risperidone			
	Days 1-7	20	14.8	0.049
	Days 1-10	20	12.4	

Risperidone has been known to induce extrapyramidal effects but in the low category, whereas haloperidol falls in the quite high category. Other medications subsequently combined with antipsychotics are benzodiazepines, namely diazepam, and lorazepam. Benzodiazepines are prescribed to treat anxiety and insomnia symptoms in people with schizophrenia as a manifestation of the positive symptoms of schizophrenia because they work by sedation, hypnosis, anti-anxiety, and muscle relaxation effects (Hardman and Limbird 2014). Sodium divalproate is a mood stabilizer medication used as an adjunct therapy combined with antipsychotics which, in this study, was used by 5 patients (4.23%) to treat the maniac symptoms that tend to occur less frequently in patients with schizophrenia (Pramudianto and Evaria 2016). The maniac symptoms that occur in schizophrenic patients are characterized by excessive pleasure, pressure in speaking, sensitivity, irritability, and decreased sleep needs. Sodium divalproate can be used separately or in combination with antipsychotics for the treatment or therapy of severe mania. The mood stabilizer does not increase the antipsychotic effect but improves the lability and restless behavior in certain patients (DiPiro *et al.,.* 2011).

Evaluation of clinical outcome of antipsychotic therapy
Evaluation of duration of antipsychotic therapy
Results of the post-measurement on days 3 and 7 using haloperidol where $p = 0.055$ ($p < 0.05$), trifluoperazine where $p = 0.962$ ($p > 0.05$) and risperidone where $p = 0.049$ ($p> 0.05$) (Table V).

Based on the Independent samples t test related to the duration of therapy, there was no difference in terms of symptom improvement in

the post-operative measurements on days 3 and 7 in the Haloperidol group with $p = 0.055$ ($p > 0.05$). However, as seen from the average score, the result on day-7 post measurement was better than that on day-3. Likewise, in the trifluoperazine group, there was also no difference in the symptom improvement of the post-measurement on days 3 and 7 with $p = 0.962$ ($p > 0.05$) but the average results showed that the post-measurement on day-7 was better than that on day-3. However, in the Risperidone group, there was a significant difference in the symptom improvement on the post-measurement on day-7 and day-10 with $p = 0.049$ ($p< 0.05$) in which the result on day-7 was better than that on day-10 as seen from the average results. The post-measurements of the PANSS-EC scores on day-3 and day-7 in the haloperidol and trifluoperazine groups, and on day-7 and day-10 in the risperidone group were performed based on the symptom improvement which was firstly seen after the administration of the antipsychotic therapy. This is in accordance with the goal of antipsychotic treatment in the acute phase where in the first 7 days it should result in a reduction in the symptoms of agitation, hostility, aggressiveness, anxiety, and tension, as well as normalization of sleep and eating (DiPiro *et al.*, 2011).

First-Generation Antipsychotics (Haloperidol and Trifluoperazine)
Te average PANSS-EC score difference of haloperidol was 15.35, greater than that of trifluoperazine (14.42) with $p = 0.190$ ($p> 0.05$) (Table VI).

The results of the analysis of the independent samples t test of the haloperidol and trifluoperazine therapy, with $p = 0.190$ ($p> 0.05$),

Table VI. Independent T-Test Analysis of the PANSS-EC Score Differences of Haloperidol and Trifluoperazine Therapy in Hospitalized Schizophrenic Patients

Variable	Pharmacology therapy	Total	Average	*p*-Value
PANSS-EC	Haloperidol	40	15.35	0.190
	Trifluoperazine	40	14.42	

Table VII. Independent T-Test Analysis of the PANSS-EC Score Differences of Haloperidol and Risperidone Therapy in Hospitalized Schizophrenic Patients

Variable	Pharmacology therapy	Total	Average	*p*-Value
PANSS-EC	Haloperidol	40	15.35	0.027
	Risperidone	40	13.6	

Table VIII. Linear Regression Analysis of the PANSS-EC Score Differences of Haloperidol, Trifluoperazine, and Risperidone Therapy in Hospitalized Schizophrenic Patients

Variable	Pharmacology therapy	Total	Average	*p*-Value
PANSS-EC	Haloperidol	40	15.35	0.022
	Trifluoperazine	40	14.42	
	Risperidone	40	13.6	

showed that there were no significant differences between these two groups. The reason is that both therapy groups are high-potential First-Generation Antipsychotics (FGA) that have a similar mechanism. Although it was found that the average difference of haloperidol was slightly greater, i.e., 15.35 compared to that of trifluoperazine, i.e., 14.42, both medications could not be compared. Based on a study on Haloperidol versus first-generation antipsychotics for the treatment of schizophrenia, related to efficacy, there was no clear evidence of the difference between haloperidol and other medications, especially for the high-potential first-generation antipsychotics (Dold *et al.,* 2015).

First-Generation Antipsychotics and Second-Generation Antipsychotics (Haloperidol and Risperidone)

The average PANSS-EC score difference of haloperidol was 15.35, greater than that of risperidone (13.6) with *p* = 0.027 (*p*<0.05) (Table VII).

Based on the results of the Independent samples t test related to the PANSS-EC score on the difference between Haloperidol and Risperidone, it was shown that there were significant differences in the improvement of schizophrenia symptoms. Based on the results of the average PANSS-EC score difference, the use of haloperidol showed a better result in improving the symptoms in schizophrenic patients than risperidone. However, there was no difference in the effectiveness of a therapy which combined haloperidol and risperidone in the acute phase of schizophrenia using the first 7 days PANSS-EC measurement parameters (Ranti, *et al.*, 2015).

First-Generation Antipsychotics and Second-Generation Antipsychotic (Haloperidol, Trifluoperazine, and Risperidone)

The average PANSS-EC score difference of haloperidol was 15.35, greater than that of trifluoperazine which was 14.42 and that of risperidone which was 13.6 with *p* = 0.022 (*p*<0.05) (Table VIII).

This research showed that haloperidol was a better treatment choice in improving the symptoms of schizophrenia because hospitalized patients had positive symptoms or severe agitation with the pre-PANSS-EC score ≥ 20, characterized by nervous anxiety, hallucinations, labile emotional expressions that could disturb others or hurt themselves, so they needed rapid handling using antipsychotics, in this case, haloperidol. It is known that haloperidol is more beneficial than risperidone because it can significantly decrease agitation, delusion, and hallucinations in schizophrenic patients (Marder *et al.*, 2003). However, the administration of haloperidol can bring side effects

in the form of an extrapyramidal effect while risperidone cannot (Hardman and Limbird 2014).

CONCLUSION

Among the three therapies, consisting of two First-Generation Antipsychotics (FGAs) namely haloperidol and trifluoperazine, as well as Second-Generation Antipsychotic (SGA) namely risperidone, haloperidol showed a better result in improving the symptoms of schizophrenic patients than trifluoperazine and risperidone.

ACKNOWLEDGEMENTS

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