

## Study of adverse effects of extrapyramidal syndrome use of combination of antipsychotics antidepressants in outpatient schizophrenia patients in RSUP Fatmawati for the period 2016-2020

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### ABSTRACT

Schizophrenia disorder is a serious mental disorder and chronic symptoms that have mixed of schizophrenia and mood symptoms. Schizophrenia affects the individual concerned. Schizophrenia has several symptoms that can cause social and occupational dysfunction, such as disruption of work or activities, lack of interpersonal relationships, decreased self-care skills, and mortality. This study was an observational study with a cross-sectional study design using secondary data in the form of medical records. The population of this study is 449 patients, and 126 patients met the inclusion criteria. The number of patients with age 20-35 years is 47.6%, 54% male gender, 96.8% take the drug by oral. The most common diagnosis of the patient with schizophrenia was paranoid schizophrenia 100 (79.4%), and got the most common extrapyramidal adverse effect in acute dystonia is 32.5%. The type of drug that may cause extrapyramidal adverse effects are the Risperidone antipsychotic in 90 (17.9%). The results of the study showed that there was no significant relationship between the type of drug combination use and the incidence of adverse effects from extrapyramidal syndrome with a sig.  $0.966 > 0.05$ . Meanwhile, the number of drugs consumed by the patients did not have a significant relationship with the sig value.  $0.119 > 0.05$ . The Gender, patient age, method of administration, and diagnosis of schizophrenia did not affect the adverse effects of extrapyramidal syndrome with sig values of each gender ( $p=0.881$ ), patient age ( $p=0.665$ ), method of administration ( $p=0.920$ ), and diagnosis of schizophrenia ( $p=0.908$ ).

**Keywords:** Schizophrenia, antipsychotics, antidepressants, extrapyramidal adverse effects

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## INTRODUCTION

Schizophrenia is a serious and chronic mental disorder that has mixed symptoms of schizophrenia and mood symptoms. According to the International Classification of Assessed (ICD-10), schizophrenia disorders are divided into several types, i.e., the manic type, the depressive type, and the mixed type. Depressive type mental disorder is a mental state when symptoms of depression and schizophrenia are prominent in one episode. Manic-type mental disorder is a mental disorder with symptoms of mood changes usually appearing in the form of elation followed by changes in self-confidence, and mixed type mental disorder such as periods of pain without interruption of affective disorder (major depression/manic) together with the main symptom criteria, namely schizophrenia.

According to the results of the National Comorbidity Survey Replication survey, 16.2% of Americans experience depression during their lifetime, and over the last 12 months, more than 6.6% of them have depression (Teter et al., 2009). According to the Indonesian Ministry of Health, in 2016, around 21 million people worldwide are affected by schizophrenia. It is estimated that 75% of patients with this disease can occur at the age of 16-25 years (Kementerian Kesehatan Republik Indonesia, 2016). The mortality rate of people with psychotic disorders is higher than the general population (Reininghaus et al., 2015). Suicide is a common cause of death among people with schizophrenia (Ventriglio et al., 2016). Although patients usually experience a remission of positive symptoms within the first few months of treatment, however, the long-term outcome is poor, it is because 80% of patients have experienced a relapse within 5 years. In addition, negative symptoms are largely unresponsive to antipsychotic treatment (Firth et al., 2017).

According to research conducted by (Redayani et al, 2015), the main therapy given to schizophrenia patients is an antipsychotic combination of antidepressants. This combination therapy is useful not only to treat the positive and negative symptoms that occur in schizophrenia patients but also to improve the quality of life of schizophrenia patients. Based on Rianti's research (2015), at RSJ, Dr. Suharto Heerdjan Schizophrenia patients received combination drug therapy which is often used a combination of Risperidone with Fluoxetine which is a class of antipsychotic drugs combined with antidepressants which is indicated to relieve extrapyramidal symptoms. According to research conducted by (Puspitasari & Angeline, 2019), the type of antidepressant drug that was most widely prescribed for outpatient BPJS schizophrenia patients at RSJ Dr. Suharto Heerdjan in 2016 was an SSRI antidepressant, namely Fluoxetine. The combination of Fluoxetine and Risperidone is the most commonly prescribed combination.

In this study, the authors wanted to evaluate the adverse effects of extrapyramidal syndrome in the use of an antidepressant combination of antipsychotics for outpatient schizophrenia in Fatmawati Hospital within the period of 2017-2019. Since there is a previous supporting theory that states the administration of antipsychotics is able to cause the adverse effects of extrapyramidal syndrome to higher and by giving antipsychotic drugs combined with antidepressants may able to reduce extrapyramidal effects and detect which therapy is able to reduce adverse effects in schizophrenia patients.

## MATERIALS AND METHOD

The study was conducted in Fatmawati Hospital, Cilandak South Jakarta, within the period of June to August 2020, with the ethical recommendation no. 30/KPP/VI/2020 dated on 24 June 2020.

### Research design

This study is a descriptive retrospective cross-sectional design that is only observing the phenomenon at one time. The Sampling was taken by obtaining medical record data based on inclusion and exclusion criteria in out-patient schizophrenia with adverse effects of extrapyramidal syndrome who received antipsychotic antidepressant drugs in Fatmawati Hospital within the period 2016 - 2020.

### Population and sample

The population in this study was all medical record data of the outpatient diagnosed schizophrenia who received the antipsychotic combination of antidepressants within the period 2016 - 2020 and had met the inclusion criteria. Here are the inclusion and exclusion criteria that use in this study. The inclusion criteria: the outpatient who was diagnosed with schizophrenia and got the extrapyramidal symptom as an adverse effect in Fatmawati Hospital, the outpatient in Fatmawati Hospital within the period 2016 – 2020, the outpatient aged more than 20 years, the schizophrenia patient who got the antipsychotic drug combination of antidepressant treatment. And the exclusion criteria: the schizophrenia patient who was pregnant and breastfeeding, incomplete and illegible medical records, the patient with comorbidities or complications.

The sample of this study was patients aged 20-60 years and over 60 years who were diagnosed with schizophrenia and the outpatient who received antipsychotic antidepressant combinations in Fatmawati Hospital within the period 2016-2020.

### Sampling technique

The sampling technique in this study was purposive sampling which, based on the population results, the samples of the study were found that met the inclusion criteria. Then, the medical records of the samples were determined and collected. The required data were transferred from all types of sample medical records to the data collection sheet. The data collected were from the outpatient schizophrenia with extrapyramidal adverse effects who received antipsychotic combination antidepressant drugs in Fatmawati Hospital within the period of 2016-2020.

### Sample size

The sample size of the study is to measure the proportion with a degree of accuracy at a statistically significant level (significance) using a simple formula (Notoatmodjo, 2010). The sampling technique is the process of taking the number of samples that meet the inclusion criteria. The sample size of this study was calculated based on Slovin's formula.

$n$  = number of samples

$N$  = number of populations

$e$  = Critical score (limit of accuracy), i.e., 0.1

Based on the formula and the population, the sample size for this study was 90 patients with schizophrenia.

### The process of study

For all data that have been collected, the next process will be processed for editing, coding, entering or data processing, cleaning, and tabulating. Then, the data will be analyzed in univariate analysis, Chi-square analysis, and also the multiple regression analysis.

## RESULT AND DISCUSSION

This study was conducted on outpatient schizophrenia who got a combination therapy of antidepressant antipsychotic therapy in Fatmawati Hospital Jakarta for a period of 2016-2020. Based on [Table 1](#), the population of this study was 449 patients.. However, the number of patients who met the inclusion criteria in this study was 126 patients.

## The outpatient characteristics

**Table 1. The Outpatient characteristics of Schizophrenia with adverse effects of extrapyramidal syndrome in Fatmawati Hospital for a period of 2016-2020**

Patient Characteristics	Patient (n=126)	
	amount	Percentage
<b>Gender</b>		
Men	68	54%
Women	58	46%
<b>Age</b>		
20 – 35 years old	60	47.6%
36 – 45 years old	40	31.7%
46 – 60 years old	25	19.8%
> 60 years old	1	0.8%
<b>Administration Route</b>		
Oral	122	96.8%
Combination oral injection	4	3.2%
<b>Number of Schizophrenia Drug Use</b>		
1 – 5	115	91.3%
More than 5	11	8.7%

### The patient characteristics by gender

The data showed that the schizophrenia patients with adverse effects of extrapyramidal syndrome who got the combination therapy of antipsychotic drugs combined with antidepressants were 126 patients, 54% male patients and 46% female patients. The results of this study are supported by another research conducted in Atma Husada Mahakam Regional Psychiatric Hospital Samarinda which states that patients with male sex are found to be more common, which is about 6.02 – 15.66% for each type of schizophrenia compared to female patients (Nisa et al., 2014). Likewise, the study by (Cardoso et al., 2005) found that male patients are more difficult to accept pressure than women.

### The patient characteristics by age

Based on the data, the highest incidence of schizophrenia occurred in the age interval of 20-35 years as 60 patients (47.6%). This was due to the fact that this age range is the productive age range, in which one of the triggers of schizophrenia is the stresses of various problems, i.e., family problems, work, and even economic problems. The National Institute of Mental Health (NIMH) statistics reported that schizophrenia is typically diagnosed in the late teens years to early thirties and tends to emerge earlier in males (late adolescence – early twenties) than females (early twenties – early thirties).

### The patient characteristics based on drug administration routes

The most widely used drug is by oral route, with 122 patients (96.8%). The rational selection of drugs is based on the considerations of safety and efficacy (World Health Organization, 2014). Besides that, the drug should be having a therapeutic effect in accordance with the disease (Kementerian Kesehatan Republik Indonesia, 2008). In drug administration, there are several ways to give drugs to patients or usually called the drug administration route. Generally, drug administration routes are divided into 2, i.e., oral and non-oral. However, the parental or non-oral route is often associated with drug administration by injection (Puspitasari & Angeline, 2019).

The patient's compliance with taking the medicines that prescribed by a doctor at the right time and at the right dose will be effective if the patient obeys the regimen of the drugs (Kaunang et al., 2015). Based on the study data, schizophrenia patients who did not continue taking oral or non-oral drugs one

to two years after the first episode will cause relapse. However, it does not trigger a severe relapse if the patient does not take the drug after taking treatment for a long time period (Emsley et al., 2013).

### The patient characteristics based on the number of schizophrenia drug

The results of the study obtained that patients received therapy of 1 – 5 drugs and more than 5. The highest number of drugs used during the therapy is 1 – 5 drugs, i.e., 115 patients (91.3%). Based on the research by (Stuart, 2005), there were patients who received treatment by 1-5 drug use since the patients were included in the acute schizophrenia category, which requires a combination of drugs to support the therapy successfully by adding anticholinergic drugs or vitamins. The number of drugs prescribed to the patient was based on the recurrence of predominant and uncontrolled symptoms.

### The patient characteristics based on the diagnosis of Schizophrenia

Most of the schizophrenia patients in Fatmawati Hospital as describe on Table 2 were diagnosed with paranoid schizophrenia, i.e., 100 patients (79.4%). In line with the research conducted by (Fahrul & Mukaddas, 2014) in the Madani Regional Hospital, Central Sulawesi, the highest number of schizophrenia was the paranoid type of schizophrenia (40.5%) compared to other types of schizophrenia. This study is in accordance with the International Classification of Diseases (ICD-10), which, based on epidemiology data, the most common type of schizophrenia found in the world is the paranoid type (Puspitasari & Angeline, 2019). It can be caused by the positive symptoms that are often seen in patients with paranoid schizophrenia (F20), such as hallucinations in sight or sound or delusions. Patients with paranoid type also tend to have an aggressive attitude and are difficult to treat as outpatients, so they need to be hospitalized (Tarigas & Untari, 2018).

One of the symptoms of schizophrenia patients is suicidal ideation, and it is a common cause of death among schizophrenic patients (Ventriglio et al., 2016). The lifetime rate of suicidal ideation among schizophrenic patients is estimated from 4% to 10% (Teraishi et al., 2014). Meanwhile, according to Siti Zahnia and Dyah Wulan Sumekar's research 2016 (Zahnia and Sumekar, 2016), based on diagnosis and the type of schizophrenia, the most common subtype is schizophrenia with the paranoid type (48%) followed by Schizophrenia residual (39.4%). Paranoid schizophrenia is considered the most common subtype of this chronic disorder. The paranoid type is characterized by the presence of delusions and hallucinations but no disturbance of thought, disorganized behavior, and flat responses.

**Table 2. The type of Schizophrenia in outpatients of Fatmawati Hospital for the period 2016-2020**

Types of Schizophrenia	Number of Patients (n=126)	
	Amount	Percentage
Paranoid	100	79.4%
Hebephrenic	13	10.3%
Catatonic	1	0.8%
Not Detailed	6	4.8%
Residual	5	4%
Post-schizophrenic depression	1	0.8%
<b>Total</b>	<b>126</b>	<b>100%</b>

Source: Medical record data of schizophrenic patients

### The characteristics of other drugs that used by the outpatient Schizophrenia

Based on the result of this study that describe on Table 3, the most prescribed drugs other than antipsychotics and antidepressants are anticholinergic. Trihexyphenidyl (hexamer, THD) is the most prescribed drug for outpatient treatment of schizophrenia in Fatmawati Hospital i.e.101 patients (80.2%). Since the most common adverse effect of the anti-schizophrenia drug is extrapyramidal

syndrome so a number of other types of drugs that are common to be prescribed is the THD.

**Table 3. The Number of other types of drug therapy used by the outpatient Schizophrenia in Fatmawati Hospital for a period of 2016-2020**

Drug Use	Patient (n=126)	
	Amount	Percentage
Anticholinergic	101	80.2%
Anticonvulsants	25	19.2%
Vitamin	13	10.3%

Source: Medical record data of schizophrenic patients

Whereas the other type of drugs that are used as adjuvants therapy are diazepam and alprazolam as anticonvulsants. In addition, diazepam and alprazolam are included as tranquilizer drugs that are added to treat acute episodes in patients with schizophrenia. They are able to give a sedative effect that makes the patient calm (Wiffen et al., 2007). The process of schizophrenia therapy should be based on the patient's needs to avoid adverse reactions, other psychiatric disorders, or other medical conditions and also based on the patient or family history (Redayani et al, 2015). Based on the data of this study, the number of 126 patients got a difference in the number of drugs in their prescriptions. It is because the therapy of schizophrenia is a long-term therapy and has several stages depending on the current condition.

#### The description of the use of combination drugs in schizophrenia patients

Based on the Table 4 below it showed that antipsychotics, antidepressants, and anticholinergics were the 3 drugs that were common use for the combination and prescribed by doctors, i.e., as many as 76 patients (60.3%).

The data obtained show that antipsychotic is the most common drug to be used in the therapy. It is because the use of antipsychotics is recommended based on the therapeutic algorithm and is included in several stages of therapy. The use of a combination of two antipsychotics will result in a greater variety of receptor targets and maintains the efficacy by additively increasing the blocking dopaminergic D2 receptor and reducing the dose-related adverse effects (Roh et al., 2014).

The combination of antipsychotic drugs (Haloperidol, Risperidone) with antidepressants (Fluoxetine, Amitriptyline) and anticholinergics (Hexymer) was most frequently used in 76 patients (60.3%). While anticholinergic (Hexymer) added to the treatment of psychosis is intended to reduce dose-related adverse effects of antipsychotics, especially the extrapyramidal symptoms, anticholinergic, sedative effects, and undesirable cardiovascular effects are lower than other groups.

Since there is research that states that schizophrenia patients are often found to have vitamin and mineral deficiencies, in this study, there were some patients who got the drug combination of vitamins with antipsychotic combination antidepressant therapy. Therefore, the additional therapy of benzodiazepine as an anticonvulsant drug aimed to reduce the effects of fear and anxiety on antipsychotic drugs (Hariyani et al., 2016).

In this study, the class drug that is most used for therapy of outpatient schizophrenia in Fatmawati Hospital is antipsychotic antidepressants in combination with other classes of drugs. The most widely used antipsychotic is Risperidone, i.e., 90 drugs (17.9%). Hence, Risperidone is a low-potential class of drug to treat patients with dominant symptoms of agitation, anxiety, hyperactivity, and insomnia (Wells et al., 2015).

In this study, haloperidol is widely used in a dose of 0.5 - 2.5 mg/day, i.e., 49 (9.8%). Haloperidol is recommended for chronic schizophrenic psychosis to treat negative symptoms (Tjay, 2015), and haloperidol has a half-life of 24 hours (Dharmono, 2011). Then in the third, Trifluoperazine and Clozapine, which are 31 drugs (6.2%), each drug is included in the typical antipsychotic class. The typical antipsychotic class works by blocking dopamine strongly to the other drugs; one of the drugs is trifluoperazine.

**Table 4. The distribution of Schizophrenia patients on combination drug use in Fatmawati Hospital period 2016-2020**

Drug combination	Patient (n=126)	
	Amount	Percentage
<b>Combination of Two Drugs</b>		
Antipsychotics, Antidepressants	15	11.9%
<b>Combination of Three Drugs</b>		
Antipsychotics, Antidepressants, Anticholinergics	76	60.3%
Antipsychotics, Antidepressants, Anticonvulsants	7	4.8%
Antipsychotics, Antidepressants, Vitamin	1	0.8%
<b>Combination of Four Drugs</b>		
Antipsychotics, Antidepressants, Anticholinergics, Anticonvulsants	16	12.7%
Antipsychotics, Antidepressants, Anticonvulsants, Vitamin	3	2.4%
Antipsychotics, Antidepressants, Anticholinergics, Vitamin	8	6.3%
<b>Combination of Five Drugs</b>		
Antipsychotics, Antidepressants, Antimuscarinic, Anticholinergics, Vitamin	1	0,8%
<b>Total</b>	<b>126</b>	<b>100%</b>

Source: Medical record data of schizophrenic patients

**Table 5. The pattern of Schizophrenia drug administration in Fatmawati Hospital period 2016-2020**

Drug combination	Patient (n=126)	
	Amount	Percentage
Antipsychotic	235	46.9 %
Antidepressants	128	25.5 %
Anticholinergic	101	20.0 %
Anticonvulsants	25	5.0 %
Vitamin	13	2.60%
<b>Total</b>	<b>446</b>	<b>100 %</b>

Source: Medical record data of schizophrenic patients

From the data obtained, another drug that is most widely used is clozapine with a dose of 25-50 mg/day i.e., 31 (6.2%). In order to get the sedative effect, the range of dos for clozapine is 25-50 mg (Natari et al., 2012). For antidepressants, the most widely used drug is fluoxetine, i.e., 113 drugs (22.5%), which include in the class of Selective Serotonin Reuptake Inhibitors (SSRI). This drug was chosen as a first-line antidepressant because of its safety and high tolerance. The maximum dose of fluoxetine is 10 mg - 20 mg/day. According to research by (Teter et al., 2009), the initial dose for the use of fluoxetine is 20 mg, and the range of usual dose is 20-6 mg/day. It is aligned with the research data that the amount is 22.7%.

In the treatment of schizophrenia as describe in Table 5, there were several patients who received a combination of anticholinergics (Hexymer), i.e., 101 drugs (20.0%). The mechanism of action of Hexymer works through an inhibitory effect on the parasympathetic nervous system. Muscarinic receptors are acetylcholine receptors in the parasympathetic nervous system (Baradero et al., 2016). In addition, the use of anticholinergics (Hexymer) is able to reduce the adverse effects of drugs due to the extrapyramidal symptoms of Parkinsonism (Wijono et al., 2013).

The last drug which also prescribe is vitamins. The functions of the vitamins are as active co-

enzymes in metabolism and formation energy formation. Vitamins also use as an alternative therapy to give a good effect and relieve the symptoms of depression and schizophrenia (Tjay & Rahardja, 2007).

### The characteristics of the extrapyramidal syndrome adverse effects

The incidence of Extrapyramidal Syndrome (EPS) may appear since the beginning of the antipsychotic administration. When using a combination of antidepressants, the incidence of Extrapyramidal Syndrome in schizophrenia patients is more controlled or suppressed.

**Table 6. The characteristics of the extrapyramidal syndrome adverse effect of Schizophrenia drugs**

The Adverse Effects	Patient (n=126)	
	Amount	Percentage
Akathisia	36	28.5%
Acute dystonia	40	32%
Tardif dyskinesia	29	23%
Parkinsonism	21	16.5%
<b>Total</b>	<b>126</b>	<b>100%</b>

Research results show that the use of antipsychotics has a risk of extrapyramidal adverse effects. However, the combination of antipsychotics with antidepressants may be able to decrease the occurrence of extrapyramidal adverse effects. The acute extrapyramidal syndrome often occurs start from the beginning of drug treatment or when the dose is increased. In addition, the subsequent extrapyramidal syndrome usually occurs after long-term treatment (Divac et al., 2014).

Based on data in Table 6, the acute extrapyramidal syndrome that often happens is acute dystonia, i.e., 40 patients (32%). For example, the outpatient schizophrenia with a medical record number of 875700 in Fatmawati Hospital, Jakarta. The patient got antipsychotic drugs in combination with antidepressants; during the therapy, the patient felt the acute dystonia as a manifestation of the extrapyramidal syndrome.

The adverse effect of acute dystonia occurs shortly after the administration of antipsychotics in combination with antidepressants. The main trigger of the occurrence is by increasing the dose, especially when it uses by oral and parenteral injection of combination drugs. There are several hypotheses on the pathomechanism of extrapyramidal adverse effects, even though it is still uncertain for the cause of acute dystonia. However, it may involve a drug action process that results in higher sensitivity to dopamine signaling then, followed by higher cholinergic activity and increased sensitivity of muscarinic acetylcholine receptors (Burkhard, 2014). The therapy using clozapine as a second-generation antipsychotic which has the mechanism of action by occupying the D2 receptor, only induce about 38-47% of the adverse effect. Even at doses as high as 900 mg daily that less than 50%, clozapine has a superior efficacy in reducing suicidal behavior and is effective in treating both positive and negative symptoms in patients with refractory schizophrenia (Bruno et al., 2015).

The Adverse effects that occur may be influenced by several factors, including individual differences in tolerating the adverse effects of each drug, and the more combinations used of drugs may induce, the greater the risk of adverse effects. The adverse effects that occur are based on the strength of the affinity for each receptor occupied by each drug combined. The antidepressant and antipsychotic drugs may combine with other drugs in the treatment of schizophrenia, so there is a possibility that adverse effects may be induced by other drugs and/or increase the potential of adverse effects.

### The relationship between the extrapyramidal adverse effects with the number of drugs in Schizophrenic patients

The extrapyramidal syndrome is a common adverse effect in schizophrenia patients who get

antipsychotic treatment in combination with antidepressants and also with other drugs. The results of the analysis relationship between the number of drugs and the incidence of adverse effects as informed in Table 7 were obtained with a p-value of 0.973. So, it showed that the factor of the number of drugs that used in antipsychotic with antidepressant combinations was not associated with the incidence of drug adverse effects. These results align with research conducted by (Nag et al., 2011), which states that there is no significant relationship between adverse drug effects and the number of drugs prescribed. However, this may be due to the increasing number of drugs prescribed, the potential for drug adverse effects will be increased (Dasopang et al., 2015).

**Table 7. The relationship between the incidence of extrapyramidal syndrome and the number of drugs of Schizophrenia patients in Fatmawati Hospital for period 2016-2020**

Adverse effects	Number of Drug Therapy		p-value
	1-5	>5	
Akathisia	26.2%	2.4%	0.973
Acute dystonia	28.6%	3.2%	
Tardif dyskinesia	21.4%	1.6%	
Parkinsonism	15.1%	1.6%	
<b>Total</b>	<b>91.3%</b>	<b>8.7%</b>	

#### **The relationship between the patterns of antipsychotic combination antidepressants and the adverse effects of extrapyramidal syndrome**

In this study, the relationship between the use of combination drugs in schizophrenia patients and the incidence of the drug's adverse effects on the extrapyramidal syndrome is able to see in Table 8. The highest percentage of adverse effects of using schizophrenia drugs is extrapyramidal syndrome in the combination of three drugs for schizophrenia in as many as 85 patients (67.5%). The chi-square test the results obtained sig 0.966 ( $p > 0.05$ ).

Thus, it can be concluded that there is no significant relationship between the use of drug therapy and the incidence of adverse effects of extrapyramidal syndrome in schizophrenia patients.

**Table 8. The relationship between the use of schizophrenia drugs and the incidence of outpatient extrapyramidal syndrome in Fatmawati Hospital**

Adverse effects	Extrapyramidal Syndrome		p-value
	Amount	%	
Combination of Two Drugs	14	11.1%	0.966
Combination of Three Drugs	85	67.5%	
Combination of Four Drugs	25	19.8%	
Combination of Five Drugs	2	1.6%	
<b>Total</b>	<b>126</b>	<b>100%</b>	

#### **The relationship between confounding factors and adverse effects of treatment**

The results of the analysis show that all variables have a p = value of more than 0.05. Thus, it can be concluded that the variables of gender, patient age, route of administration, and diagnosis of schizophrenia do not have a significant effect on the adverse effects of extrapyramidal syndrome while using antipsychotic combination antidepressants in schizophrenia patients. Schizophrenia is treated using combination drug therapy or polypharmacy so that it is able to increase the risk of drug adverse effects. Combinations or polypharmacy can significantly increase the risk of drug interactions that cause adverse effects (Dasopang et al., 2015).

The Analysis result of the relationship between sex and extrapyramidal adverse effects on the use of antipsychotic combination antidepressant therapy obtained p value = 0.881. It means that gender does not have any correlation with extrapyramidal adverse effects. This result is aligned with the

research that conducted by (Sari, 2015), which shows that there is no relationship between gender and the potential adverse effects of drugs. It may be due to there being no differences in the class of drugs given between males and females.

**Table 9. The relationship between confounding factors on drug adverse effects**

Variable	<i>p-value</i>
Gender	0.881
Patient Age	0.665
Administration Route	0.920
Schizophrenia Diagnosis	0.595

Since this research was conducted in the retrospective design and used medical records as the main source of the data. So there is some data that may be incomplete or unclear, and it maybe impacts the results of this study and also able to be less than optimal.

## CONCLUSION

In conclusion the most adverse events extrapyramidal syndrome is akathisia; there was no correlation between the incidence of adverse effects from extrapyramidal syndrome with the number of drugs consumed by the patients, and sociodemographic patients ( $p > 0.05$ ).

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