The Adverse Drug Reactions on Antipsychotic Use in Residual Schizophrenia Outpatients at Hospital in Purworejo, Central Java, Indonesia

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Abstract. Residual schizophrenia is a type of schizophrenia with a record of at least one psychotic episode, followed by symptoms that are more prominently negative. Antipsychotic use is the primary therapy, but long-term antipsychotic use affects problems such as Adverse Drug Reactions, resulting in reduced adherence, relapse, and poorer quality of life. This study aims to identify the cases of adverse drug reactions using antipsychotics in Residual Schizophrenia patients in the Outpatient Installation of Purworejo Hospital, Central Java, Indonesia. This study is a non-experimental study with descriptive analysis with prospective data collection from October to November 2020. Data were collected through direct interviews employing the Naranjo Scale instrument to assess symptoms and medical record data to observe laboratory values. Data analysis used univariate analysis with the descriptive test on the SPSS programmed version 16.0. The sample of this study was schizophrenic patients aged ≥ 18 years and receiving antipsychotic therapy for at least one month, while the exclusion criteria were patients with low adherence levels, and patients receiving metoclopramide therapy. This study obtained a sample of 97 patients. Most of the patients received treatment with Haloperidol + Clozapine 37.1%, Risperidone + Clozapine 10.3%, and Clozapine 10.3%. The highest cases of adverse reactions were in the use of Haloperidol with tremor 36 (24.66%), rigidity 16 (10.96%), akathisia 15 (10.27%), and bradykinesia 6 (4.411%), weight gain 11 (7.53%), dyskinesia tardive 2 (1.37%), acute dystonia 2 (1.37%), and erectile dysfunction 1 (0.68%). Studies related to the side effects of antipsychotic use in patients with residual schizophrenia mostly occur with haloperidol with various effects, one of which is an extrapyramidal syndrome, weight gain, and erectile dysfunction. Thus, the role of pharmacists is very much needed in monitoring antipsychotic drug therapy related to side effects to achieve drug effectiveness in the success of therapy.

Keywords: Antipsychotics · Adverse Drug Reaction · Residual Schizophrenia

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1 Introduction

According to Riskesdas data in 2013, one to two patients out of 1000 residents experience severe mental disorders (1). The prevalence of schizophrenia in Central Java, which was 0.23% of the total population, exceeded the national percentage of 0.17% (2). Residual schizophrenia is one of five schizophrenia types (3). Residual schizophrenia is a category that is considered free from schizophrenia but still shows residual symptoms, such as negative beliefs, or may still have inappropriate ideas (3). One antipsychotic therapy spends minimally two to six weeks (4).

Antipsychotic therapy is divided into the first generation of antipsychotics and the second generation of antipsychotics. The antipsychotic use for the first-generation has a higher adverse reaction in the form of an extrapyramidal syndrome than the use of second-generation antipsychotics (4). Antipsychotic therapy can cause a poor patient response, including extrapyramidal symptoms, metabolic syndrome, and weight gain. The emergence of antipsychotic effects can occur at the beginning of the administration, depending on the dose prescribed (5). As a result, practitioners often switch to ineffective therapies based on trial and error (6,7). The most common side effects of extrapyramidal symptoms were the first-generation antipsychotics, namely Haloperidol and Chlorpromazine (8–10). According to Oommen et al. (2019), the use of second-generation antipsychotics, such as Olanzapine and Risperidone, commonly causes adverse reactions, including weight gain, sedation, tremors, Parkinson's, and menstrual cycle disorders.

The selection of a hospital in the Purworejo area, Central Java, Indonesia as a research site was because the residual disease of schizophrenia is included in the top ten cases in outpatients with a total of 4,849 cases. The high number of residual cases of schizophrenia has prompted researchers to identify a description of the incidence of adverse events in the use of antipsychotic therapy. The results of the study are expected to be used to select effective antipsychotic therapy to minimize the risk of side effects.

2 Research Method

This research has received a code of ethics from the Research Ethics Committee at a Purworejo hospital with the number 060/KEPK/25/IX/2020.

2.1 Research Design

This type of research is non-experimental research with descriptive data analysis. Data were taken prospectively by direct interview method implementing Naranjo Scale Instrument and medical record data.

2.2 Place and Time of Research

The research was conducted at a hospital in Purworejo, Central Java from October to November 2020 on residual schizophrenia patients in outpatient installations.

2.3 Research Population

The population of this study was taken in patients with residual schizophrenia at the outpatient installation of a hospital in Purworejo, Central Java from October to November 2020. Inclusion criteria were patients diagnosed with residual schizophrenia (F.20.5), aged $\geq$ 18 years, received at least one month of antipsychotic therapy, and adhered to treatment. Meanwhile, the exclusion criteria were incomplete medical record data, non-adherence during treatment, received metoclopramide therapy for one month, used high doses of antipsychotics, and had a stroke, hypertension, diabetes mellitus, or post-fall record.

2.4 Research Sample

The estimated residual schizophrenia patient population was 53.4%. The data were then calculated using the formula for the proportion from Lameshow *et al.* (1997).

$$\frac{NZ^2 1 - {}^{a}/2pq}{d^2(N-1) + Z^2 1 - {}^{a}/2pq} \tag{1}$$

From the above formula, the minimum sample that must be met was 79.78 patients. The sample of this study was 97 patients. Hence, it met the specified number of samples.

2.5 Research Instrument

The Naranjo scale instrument was used to determine potential adverse reactions. This instrument is an official scale and has been examined for validity and reliability on patients. The Naranjo algorithm was developed in 1991 by Naranjo *et al.*, from the University of T.oronto and is often referred to as the Naranjo Scale. The Naranjo instrument was chosen because it can measure the potential for side effects through questions on a certain scale and can analyze the incidence of side effects quantitatively and qualitatively (12).

This instrument has ten questions with a scoring system assessment based on complaints experienced by patients. The Naranjo scale instrument has three categories. The possible score category, score 1–4, shows that the patient's complaint is an adverse drug reaction case. The probable score category, 5–8, indicates the patient's complaint has a high probability of experiencing a suspected adverse drug reaction. The definite score category, 9, indicates the patient's complaint is the suspected adverse drug reaction (13).

2.6 Research Procedure

The sampling procedure was selected by consecutive sampling. The patients who meet the requirements are reviewed from sociodemographic data, antipsychotic therapy, and the adverse drug reaction cases with the Naranjo Instrument. Then, collected data were analyzed using statistical analysis. Primary data collection was taken by direct interviews, and discussions with doctors and other health care professionals, while the secondary data were collected from medical record data.

2.7 Data Analysis

The data obtained were analyzed using SPSS version 16.0.0. Then, the results were examined by univariate analysis with descriptive tests to determine the description of patient characteristics, use of antipsychotics, and adverse reaction of each drug presented in the form of frequency and percentage tables.

3 Results and Discussion

3.1 Characteristics of Residual Schizophrenic Patients

In this study, the number of outpatients diagnosed with residual schizophrenia at a hospital in Purworejo, Central Java from October to November 2020 was 97 patients (Table 1).

The prevalence of males at 60 (61.9%) was more significant than females at 37 (38.1%). The percentage of males is two times greater than females. It is influenced by a female's antidopaminergic hormone (14). The most frequent age distribution was 18–45 years, with a percentage of 70.1%. Most cases of Schizophrenia occur in late adolescence and early adulthood (15). According to Handayani *et al.*, (2018), the adult age category (26–45 years), about 55.7%, still dominated the occurrence of mental disorders with schizophrenia.

The most educational background was at the senior high school level by 30 (30.9%) patients, and the least was at the academic or college education level by 5 (5.2%) patients.

Table 1. Characteristics of Residual Schizophrenia Patients Outpatient Installation at a hospital in Purworejo, Central Java.

Patient Characteristics	Classification	Total	Percentage (%)
Gender	Male	60	61,9
	Female	37	38,1
Age	18–45	68	70,1
	45–49	9	9,3
	50–60	20	20,6
Education	Did not finish elementary school	14	14,4
	Elementary School	22	22,7
	Junior High School	26	26,8
	Senior High School	30	30,9
	S-1	5	5,2
Employment Status	Employed	50	51,5
	Unemployed	47	48,5
Rehabilitation status	Ever	90	92,8
	Never	7	7,2

According to Gracianita *et al*., (2020), there is no relationship between low and high levels of education on the case of schizophrenia so that it can occur at all levels of educational background. Nevertheless, the background of the problem of schizophrenia mainly occurs at low levels of education (18).

The most employment status was 50 (51.5%) patients in the employed category. This result is different from Erlina *et al*., in 2010, who revealed that the percentage who unemployed was a 6.2 times greater risk of suffering from schizophrenia than those employed. Unemployed individuals would be more easily stressed, which was associated with high levels of stress hormones (catecholamines) and led to helplessness (18).

Most of the rehabilitation status were in the category of ever undergoing rehabilitation 90 (92.8%). Rehabilitation combines medication and education to achieve proper functional abilities (19). According to Zuraida in 2017, schizophrenia patients given rehabilitation interventions were less likely to relapse.

3.2 Characteristics of Antipsychotic Drug Use

The results of the study in Table 2 obtained that the most antipsychotic use was a combination of first-generation (typical) and second-generation (atypical) antipsychotics, namely Clozapine-Haloperidol 36 (37.1%). This study is almost the same as Yulianty *et al*., in 2017 the most use occurred in two combinations of Clozapine-Haloperidol. Followed by the use of a combination of Clozapine – Risperidone 10 (10.3%), and the use of a single antipsychotic Clozapine 10 (10.3%).

Based on the American Psychiatric Association (APA) schizophrenia treatment algorithm, if a patient has a poor response to clozapine therapy, the patient will respond less to other monotherapy antipsychotics (21). Therefore, the antipsychotic Clozapine is often added, with other antipsychotics, both first and second-generation antipsychotics (22). This is also adjusted for clinical response history of previous drug use. Clozapine is often used alone or in combination, this is because clozapine acts on the D2 receptor 38%-48% and can treat positive and negative symptoms without causing extrapyramidal effects, does not increase prolactin levels, and tardive dyskinesia with long-term use (15,23). In contrast to Purwandityo et al., in 2018, the most combination was Risperidone-Clozapine 20.62%, followed by Haloperidol-Clozapine 13.4%. The average use of atypical antipsychotic polypharmacy in Asian countries was 42.2% ± 12.0%, with details of the most frequently used being Risperidone (36.9%), Olanzapine (20.5%), and Clozapine (18.5). %)(25).

3.3 The Side Effect Cases on the Use of Antipsychotic Drugs

This study classified the types of ADRs based on the antipsychotic group used. There are two groups: the first/typical antipsychotic (AGP) and the second/atypical (AGK) generation of antipsychotics. The cases of side effects from these two drug generations based on the causality of ADRs were in the possible category and the probable category.

Table 2. Characteristics of Drug Use for Residual Schizophrenia Patients in Outpatient Installation at a hospital in Purworejo, Central Java.

Drug	Frequency of use	Percentage (%)
Haloperidol	4	4.1
Clozapine	10	10.3
Risperidone	3	3,1
Olanzapine	2	2.1
Chlorpromazine-Haloperidol	1	1.0
Haloperidol-Trifluoperazine	1	1.0
Clozapine-Risperidone	10	10.3
Clozapine-Olanzapine	1	1.0
Clozapine-Quetiapine	1	1.0
Risperidone-Olanzapine	2	2,1
Haloperidol-Clozapine	36	37,1
Haloperidol-Olanzapine	5	5.2
Haloperidol-Risperidone	3	3.1
Chlorpromazine-Clozapine	3	3.1
Trifluoperazine-Clozapine	2	2.1
Haloperidol-Clozapine-Risperidone	4	4.1
Haloperidol- Chlorpromazine- Clozapine	4	4,1
Haloperidol-Clozapine-Olanzapine	1	1.0
Chlorpromazine -haloperidol-risperidone	1	1.0
Chlorpromazine-clozapine-risperidone	1	1.0
Quetiapine-Clozapine-Olanzapine	2	2,1
Total	97	100%

3.3.1 The Side Effect Cases on the Use of Typical Antipsychotic Drugs

Based on the first generation of antipsychotics users presented in Table 3, it was found that the use of Chlorpromazine drugs caused the cases of ADRs in the form of extrapyramidal syndrome effects, including tremor 8 (5.48%), rigidity 5 (3.42%), akathisia 1 (0.68%), bradykinesia 2(1.37%). Chlorpromazine works by binding to 70% of dopamine D2 receptors in the brain, suppressing the release of hypo(15). Hence, the first generation of antipsy thalamic and pituitary hormones chotic treatment frequently causes an adverse reaction in the greater extrapyramidal syndrome (14). Another adverse reaction in using chlorpromazine was orthostatic hypotension by 8 (5.48%). The orthostatic hypotensive effect arises because of the inhibition of reflex vasoconstriction when ascending to a sitting or standing position (26,27).

Table 3. The cases of ADRs in Typical Antipsychotics of Residual Schizophrenia Patients in the Outpatient Installation at a hospital in Purworejo, Central Java.

Medi cine Name	Type of ADRs	Causality Category		Number of occurren ces of ADRs (%)
		Possible	*Probable*	
CPZ*	Tremor	2	6	8 (5,48)
	Rigidity	1	4	5 (3,42)
	Akathisia	1	-	1 (0,68)
	Bradykinesia	-	2	2 (1,37)
	Hypotension Orthostatic	3	5	8 (5,48)
HLP*	Tremor	3	33	36 (24,66)
	Hypersalivation	1	1	2 (1,37)
	Rigidity	8	8	16 (10,96)
	Bradykinesia	1	5	6 (4,41)
	Dyskinesia Tardive	2	-	2 (1,37)
	Dystonia	-	2	2 (1,37)
	Akathisia	5	10	15 (10,27)
	Weight gain	7	4	11 (7,53)
	Erectile Dysfunction	-	1	1 (0,68)
TFZ*	Tremor	-	2	2 (1,37)
	Rigidity	-	1	1 (0,68)
	Akathisia	-	1	1 (0,68)
	Dry Mouth	-	1	1 (0,68)
	Rash/Itching	-	1	1 (0,68)

Description: *CPZ: Chlorpromazine, *HLP: Haloperidol, *TFZ: Trifluoperazine.

The use of Haloperidol drug caused ADRs to occur in symptoms of extrapyramidal effects of syndromes, including tremor 36(24.66%), hypersalivation 2(1.37%), rigidity 16(10.96%), bradykinesia 6(4.41%), dyskinesia tardive 2(1.37%), acute dystonia 2(1.37%), and akathisia 15(10.27%). Haloperidol binds 90% of D2 receptors in the mesolimbic pathway, regulating memory, attitudes, awareness, and stimulus processing (15). The extrapyramidal effect occurs because of the stronger D2 receptor binding in the nigrostriatal capable of influencing the occurrence of extrapyramidal symptoms (27,28). The case of ADRs such as erectile dysfunction occurred in haloperidol 1 (0.68%). It is because antipsychotic drugs can block D2 receptors in the mesolimbic and mesocortical regions, resulting in inhibition of D2 receptors on lactotroph cells, causing hyperprolactinemia and the release of prolactin in the anterior pituitary gland(29).

Trifluoperazine side effects that appeared were tremor 2 (1.37%), rigidity 1 (0.68%), akathisia 1 (0.68%), dry mouth 1 (0.68%), rash/itching 1 (0.68%), and dizziness 1 (0.68%). According to Chawla & Kumar (2017), the side effects of Trifluoperazine

caused tremors, extrapyramidal syndrome, and hypersalivation. It is because the mechanism of action is almost similar to Chlorpromazine, namely binding to the D2 receptor; the side effects that appear are more extrapyramidal syndromes (15).

3.3.2 The Side Effect Cases on the Use of Atypical Antipsychotic Drugs

The cases of Adverse Drug Reactions (ADRs) on the use of second-generation/atypical antipsychotics are presented in Table 4. The most common side effects in using Clozapine were sedation, 38 (30.65%), and Weight gain 23 (18.55%). According to Indriani et al.(2020), Clozapine in the range of 25–50 mg/day has a higher sedative side effect than other antipsychotics. Furthermore, Casey et al. (2004) explained that Clozapine has a more significant potential for weight gain. Other side effects such as hypersalivation also appeared the most 4 (3.23%). Meanwhile, Yoshida & Takeuchi (2021) discovered that sialorrhea may occur with other antipsychotics but is more common with clozapine.

The incidence of ADR using Olanzapine is an increase in cholesterol levels. Then, based on the causality category, there were 2 possible cases and 2 probable cases with a total ADR incidence of 4 (3.23%) cases. This is because the no-adrenergic H-1,5-HT2C, M1, and α-1 nor-adrenergic receptors may be capable to regulate the incidence

Table 4. The cases of ADRs in Atypical Antipsychotics of Schizophrenic Residual Patients in the Outpatient Installation at a hospital in Purworejo, Central Java.

Medicine name	Type of ADRs	Causality Category		Number of ADRs occurrence (%)
		Possible	*Probable*	
Second class antipsychotics (atypical)				
CLZ*	Hypersalivation	4	-	4 (3,23)
	Dizziness	6	-	6 (4,48)
	Sedation	37	1	38(30,65)
	Weight gain	23	-	23 (18,55)
OLZ*	Dizziness	2	1	3 (2,42)
	Sedation	2	-	2 (1,61)
	Weak	4	-	4 (3,23)
	Increase in Cholesterol	2	2	4 (3,23)
RSP*	Tremor	2	8	10 (8,06)
	Dizziness	8	-	8 (6,45)
	Weak	2	-	2 (1,61)
	Insomnia	-	3	3 (2,42)
QTP*	Dry Mouth	1	-	1 (0,81)
	Dizziness	1	-	1 (0,81)
	Pain	1	-	1 (0,81)

Description: *CLZ: Clozapine, *OLZ: Olanzapine, *RSP: Risperidone, *QTP: Quetiapine.

of food intake, causing weight gain (15). According to McEvoy et al., (2013) prescribing atypical antipsychotics, especially Olanzapine for one year, can significantly increase lipid levels.

Next is the use of the drug Risperidone. The most side effect was tremor 10 (8.06%). Risperidone works by blocking dopamine D2 and 5HT2 receptors. The side effect profile is almost identical to the first generation of antipsychotics, especially in motor symptoms and hyperprolactinemia (14). This effect appears depending on the dose (15). Research conducted by Saharuddin *et al.* in 2021revealed that Risperidone administration causes extrapyramidal symptoms, especially tremor symptoms, higher than other atypical antipsychotics. The effects of an extrapyramidal syndrome may be increased when used with Haloperidol or Chlorpromazine (15).

Quetiapine effects were mostly dry mouth 1 (0.81%), dizziness or headache 1 (0.81%), pain 1 (0.81%). This characteristic of antipsychotics has a lower risk for extrapyramidal effects (34). Quetiapine also triggers a relatively strong affinity for histaminergic and -1 adrenergic receptors, which can cause effects, including drowsiness, weakness, dry mouth, constipation, orthostatic hypotension, and dyspepsia. (24).

Manifestations of side effects on each drug are varied. It is due to sociodemographic, social, and drug influence factors (35). In addition, the considerable potential for side effects to occur with the use of antipsychotics in both the first and second generations is almost similar (36,37). According to research studies, using the second generation of antipsychotic PANSS-EC instruments from the severity level did not reduce acute psychopathology and the severity of the patients (24). In certain clinical situations, it is stated that the combination of antipsychotics, both first and second generations, can make therapy more effective than single-use. It is due to the failure of less effective monotherapy (38). So, that in the selection of antipsychotic treatment, clinical considerations need to be seen from the benefits and risks.

Pharmacists must contribute pharmacists in monitoring treatment, both from adherence to drug use, in patients or families. In addition, pharmacists need to educate patients and families when side effects occur. In addition, pharmacists need to review and review the treatment of residual schizophrenic patients related to dosage and interactions in both acute and chronic conditions.

However, it should be re-observed that schizophrenia is a multi-etiological disorder. Several patients with psychotic symptoms want or do not want to be prescribed antipsychotic drugs, or maybe they have been given drugs without responding to them so that other approaches are needed (38).

The limitation of this study is that it was only conducted on outpatients, so it did not see how long the ADRs occurred. Second, the use of antipsychotics here can change over time, depending on the patient's response to therapy, so there is no therapeutic basis for this treatment.

4 Conclusion

The cases of Adverse Drug Reaction occur most frequently in the use of Haloperidol with tremor 36 (24.66%), rigidity 16 (10.96%), akathisia 15 (10.27%), and bradykinesia 6 (4.41%), weight gain 11 (7.53%), dyskinesia tardive 2 (1.37%), acute dystonia 2 (1.37%),

and erectile dysfunction 1 (0.68%). The influence of the study can provide considerations regarding the choice of treatment therapy, either polypharmacy or monotherapy, in residual schizophrenia patients perceived from the effectiveness and side effects that arise to achieve therapeutic success.

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