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Effectiveness and Safety Comparison of Clozapine-Haloperidol with Clozapine-Risperidon Regimen in Schizophrenia Inpatients at Prof. Dr. Soerojo Magelang Mental Hospital

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ABSTRACT

Background: Schizophrenia treatment uses drugs from the antipsychotic group. Antipsychotics combination of clozapine-haloperidol and clozapine-risperidone are widely used in schizophrenia inpatients. Clozapine is often used in combination with haloperidol and risperidone (high-potency antipsychotic) to enhance the blockade of D2 receptors.

Objectives: To compare the effectiveness and safety of the clozapine-haloperidol regimen with clozapine-risperidone used by schizophrenia inpatients.

Methods: The research design was retrospective cohort observational. Data collection based on medical records of inpatients diagnosed with schizophrenia at Prof. Dr. Soerojo Magelang Mental Hospital in January 2021 - June 2023. The subjects were 142 people (71 people in both groups). Effectiveness was assessed by the difference in pre and post-PANSS-EC scores, as well as clinical improvement through the final PANSS-EC score. Meanwhile, safety was evaluated based on the incidence of drug side effects. The data was then analyzed statistically.

Results: The average PANSS-EC score decrease was 10 ± 5.53 in the clozapine-haloperidol group and 11 ± 5.70 in clozapine-risperidone group. Nonetheless, there was no meaningful contrast between them in terms of PANSS-EC difference (p=0.326), or improvement in clinical condition by the final PANSS-EC score (p=0.111). Also, there was no meaningful distinction in the incidence of adverse drug events (p=0.422). However, extrapyramidal syndrome, the most frequent side effect (18 out of 40 cases), had a significant difference with the clozapine-haloperidol group having the most cases (p=0.044).

Conclusion: Both regimens are interchangeable in clinical practice. But clozapine-risperidone is better tolerated regarding extrapyramidal side effects.

Keywords: Antipsychotic combination; safety; schizophrenia; therapeutic effectiveness.

INTRODUCTION

Schizophrenia is a psychiatric disorder featuring the presence of psychotic symptoms and negative symptoms and is a severe and chronic mental disorder.[1,2] Schizophrenia is among the most prevalent mental diseases, affecting an estimated 23.6 million people worldwide in 2019, with a prevalence in Indonesia of 6.7 per 1,000 households.[3,4] Schizophrenia is considered a life-shortening condition, with a life span 15-20 years shorter than ordinary people, and it has a 2.4 times higher chance of death compared to ordinary people due to the presence of symptoms of delusions and hallucinations.[2,5]

People with schizophrenia use antipsychotic drugs for therapy.[6] Although antipsychotic monotherapy is more recommended in clinical practice treatment guidelines, antipsychotic combinations are often widely used.[7] Research on inpatient schizophrenia patients at Prof.Dr. Soerojo Magelang Mental Hospital showed that the most widely used combination antipsychotic regimens were Clozapine-Risperidon and Clozapine-Haloperidol.[8] Clozapine was chosen as the basis for the combination because clozapine is the first atypical antipsychotic that has high effectiveness and low extrapyramidal side effects.[9] In combination therapy, clozapine requires other antipsychotic drugs with high potency to enhance blockade at the D_2 receptor such as haloperidol and risperidone.[10,11] Even though haloperidol and risperidone are both high-potency antipsychotics, they come from different types of antipsychotics. Haloperidol belongs to the first-generation (typical) antipsychotics, while risperidone belongs to the second-generation (atypical) antipsychotics which same as clozapine. This difference may lead to differences in the mechanism of action that can affect their occupancy at the D2 receptor while used in combination with clozapine.[6,10] In addition, these drugs are readily available in health facilities and are highly adequate due to their low price, so they are commonly used as combination therapy options.[12,13]

Research related to the effectiveness and safety of antipsychotic combinations has been conducted previously, but there has been no study that directly compares the efficacy and safety of clozapine-haloperidol with clozapine-risperidone.[14–16] Previous studies have indicated that there is no notable contrast relating the efficacy of clozapine-haloperidol and clozapine-aripiprazole regimens, although there was a noteworthy difference in safety where the clozapine-aripiprazole combination was better tolerated.[16] In addition, there are no *real-world* and observational studies comparing the effectiveness and safety of clozapine combination use.[17] Therefore, it is important to determine whether there are similarities or differences in the efficacy of clozapine-haloperidol and clozapine-risperidone regimens that are often used as combination therapy. By knowing the effectiveness and safety of clozapine-haloperidol and clozapine-risperidone regimens during inpatient treatment, it is hoped that the use of both regimens can be optimal and replace each other if one regimen cannot be used due to contraindications for patients.

METHODS

Study design

This study used an analytic observational design with a retrospective cohort research design. Data collection has been done retrospectively utilizing medical record data. The study used The Positive and Negative Syndrome Scale-Excited Componen (PANSS-EC) *pre-post* difference and clinical condition improvement assessed built upon PANSS-EC post score, to assess the efficacy comparison. The PANSS-EC pre-score was measured at the time of admission, while the PANSS-EC post-score was measured before discharge or before the regimen was discontinued and replaced with another antipsychotic regimen. Patients are said to have improved clinical condition if the post-PANSS-EC score is ≤15 so that patients can be admitted to the quiet ward or discharged for further therapy. As for safety, it is assessed based on the incidence of side effects that occur, and its probability is measured by Naranjo's algorithm.

Population and samples

The subjects of this study were patients who were admitted to the hospital in the period January 2021 - June 2023, with a diagnosis of schizophrenia, and met the inclusion and exclusion requirement. The inclusion were patients aged >18 years who received clozapine-risperidone or clozapine-haloperidol combination antipsychotic therapy during inpatient treatment. The exclusion were patients with incomplete medical record data, pregnant, who were discharged at their request, having severe systemic disease and stroke, and those who received electroconvulsive *therapy* during hospitalization. The total population of inpatients with schizophrenia in January 2021 - June 2023 at Prof.Dr. Soerojo Magelang Mental Hospital was 1.732 people. By the calculation, the sample size minimum was 71 people. The sampling method was carried out using consecutive sampling techniques collected from the withdrawal of medical record data of schizophrenia patients through the Hospital Management Information System (SIMRS).

Study instruments

The instruments used were data collection forms and Naranjo algorithm forms. Data filled in the data collection blank included a general recording of patient characteristics data (patient initials, medical record number, date of birth, age, gender, type of schizophrenia, type of comorbid disease, history of drug use) and recording of patient treatment data (antipsychotic therapy regimen (main therapy) received by the patient,

additional therapy, and pre and post-PANSS-EC scores). The Naranjo algorithm form was used to evaluate the probability of side effect incidence. It takes the form of a 10-question questionnaire, aimed at deciding the probability of whether an adverse drug event is caused by the drug instead of other variables. The presence or absence of side effects is known from the information of the doctor or nurse, which is written in the medical record. The probability of side effect is given through a score called doubtful with a Naranjo score of 0, possible with a Naranjo score of 1-4, probable with a Naranjo score of 5-9, and definite/highly probable with a Naranjo score of more than 9.

Data collection

The data collected were patient demographic data, pre and post-PANSS-EC scores which were measured by a psychiatrist and/or nurse who had received a PANSS-EC training certificate, and the incidence of side effects that had been evaluated with the Naranjo scale instrument. The researcher maintained the confidentiality of patient identity by not displaying patient identity data and marking patients using numbering. After the data was collected, the data was analyzed.

Data Analysis

Patient data was processed descriptively to obtain a description of basic sociodemographic data characterizing patients with schizophrenia as research subjects. One of the important data used in this study is the PANSS-EC score. It score measurement was conducted by a psychiatrist and/or nurse who has received a PANSS-EC training certificate. The score ranged from 5-35, with the interpretation that a score > 30 is a patient who has clinical symptoms of agitation that are so severe that they need to be admitted to the intensive ward, a score ≥20 is a patient who has clinical symptoms of agitation that are quite severe, and a score ≤15 is symptoms that have improved and the patient can be transferred to a quiet ward or discharged for further therapy.

All data related to determining effectiveness and safety were analyzed statistically. Wilcoxon test was used to see the significance of PANSS-EC score reduction. We used Mann-Whitney test analysis to compare the contrast in PANSS-EC scores of clozapine-risperidone or clozapine-haloperidol regimens. Meanwhile, chi-square analysis was used to contrast the improvement of clinical condition and safety of the two therapy regimens. In addition, an analysis was also conducted between confounding variables with effectiveness using the general linear model test and safety using the multiple logistic regression test. The confounding variables studied included patient factors such as age, gender, and recurrence of schizophrenia episodes, drug factors such as dosage, and disease factors such as disease severity. Disease severity was how severe the patient's symptoms were, especially at the time of initial admission. The severity of schizophrenia patients can be assessed using the PANSS-EC instrument.

RESULTS AND DISCUSSION

Based on the results of reviewing medical record data for the period January 2021-June 2023, as well as selection retrieved from predetermined inclusion and exclusion requirements, we obtained 142 patients, divided into two groups, namely 71 subjects in the clozapine-haloperidol regimen group and 71 subjects in the clozapine-risperidone regimen group. Patient characteristics data are presented in Table I.

Comparative effectiveness of clozapine-haloperidol and clozapine-risperidone antipsychotic regimens

Comparison of PANSS-EC score reduction

The success of antipsychotic therapy can be assessed from the decrease in the patient's PANSS-EC score obtained from the reduction of PANSS-EC scores before and after therapy. The mean initial PANSS-EC score of both groups was 22 (p=0.776). Nevertheless, there was a distinction in the final PANSS-EC score's mean between the two groups, which was 12 for the clozapine-haloperidol side and 11 for the clozapine-risperidone side. The distinction was not statistically meaningful (p=0.107). The decrease in PANSS-EC score analyzed statistically showed significant results in both groups (p=0.000). Nonetheless, there was no meaningful distinction in PANSS-EC difference with a significance of *p>0.05* (p=0.326). The same thing was also found in the study of the combination of haloperidol and combination of risperidone. The study revealed no meaningful difference regarding the effectiveness between them based on PANSS-EC difference with p=0.711.[14]

Table I. Characteristics of schizophrenia patients using clozapine-haloperidol and clozapine-risperidone antipsychotic regimens at Prof.Dr.Soerojo Magelang Mental Hospital

Subject Characteristics	Regimen Clozapine-Haloperidol n = 71	Regimen Clozapine-Risperidone n = 71	Total n=142	P-value
Age mean ± SD	42 ± 14,42	43 ± 13,56		
Adults (19-60 years old)	62 (87%)	63 (89%)	125 (88%)	0,796
Elderly (>60 years old)	9 (13%)	8 (11%)	17 (12%)	
Gender				
Men	48 (68%)	47 (66%)	95 (67%)	0,858
Women	23 (32%)	24 (34%)	47 (33%)	
Types of Schizophrenia				
Paranoid schizophrenia(F20.0)	33 (46%)	27 (38%)	60 (42%)	
Catatonic schizophrenia(F20.2)	6 (8%)	3 (4%)	9 (6%)	
Undifferentiated schizophrenia(F20.3)	32 (45%)	38 (54%)	70 (49%)	0,164
Post-schizophrenic depression(F20.4)	0 (0%)	3 (4%)	3 (2%)	
Relapse during diagnosis of schizophrenia				
History >10 times	11 (15%)	6 (8%)	17 (12%)	
History 6-10 times	11 (15%)	10 (14%)	21 (15%)	0,083
History 1-5 times	42 (59%)	37 (52%)	79 (56%)	
New/first-time patient	7 (7%)	18 (25%)	25 (18%)	
Severity means ± SD	21 ± 4,48	21 ± 4,39		
>30	4 (6%)	2 (3%)	6 (4%)	0,561
21-30	34 (48%)	31 (44%)	65 (46%)	
<21	33 (46%)	38 (54%)	71 (50%)	
Comorbidities				
Yes	58 (82%)	59 (83%)	117 (82%)	0,826
No	13 (18%)	12 (17%)	25 (18%)	
Antipsychotic dose per day				
Clozapine dosage				
Clozapine <50 mg	14 (20%)	34 (48%)	48 (34%)	0,001*
Clozapine >100 mg	22 (31%)	9 (13%)	31 (22%)	
Clozapine 50-100 mg	35 (49%)	28 (39%)	63 (44%)	

Notes: [a]Chi-square analysis; *Statistically meaningful results (p<0.05); SD: Standard deviation; initial PANSS-EC score at hospital admission (>30: very severe symptoms, 21-30: moderate to severe symptoms, <21:mild symptoms)

Table II. Comparison of the effectiveness of antipsychotic regimens based on PANSS-EC score difference

PANSS-EC Score	Regimen Clozapine-Haloperidol n = 71	Regimen Clozapine-Risperidone n = 71	P-value
Pre	22 ± 4,48	22 ± 4,36	0,776
Post	12 ± 3,82	11 ± 3,52	0,107
Δ PANSS-EC	10 ± 5,53	11 ± 5,70	0,326
Paired p values	0.000 *[b]	0.000 *[b]	

Notes: [a]Comparison of PANSS-EC scores between clozapine-haloperidol and clozapine risperidone regimen groups using Mann-Whitney U analysis;[b] Comparison of PANSS-EC scores between pre and post using Wilcoxon analysis; *Statistically significant results (p<0.05)

Table III. Comparison of effectiveness of antipsychotic regimens based on improvement in clinical condition

Improvement of clinical condition	Regimen Clozapine-Haloperidol n = 71	Regimen Clozapine-Risperidone n = 71	Total n =142	P-value
Final PANSS-EC score				
≤15	60 (47,6%)	66 (52,4%)	126 (88,7%)	0,111[a]
>15	11 (68,8%)	5 (31,3%)	16 (11,3%)	

Notes: [a]Comparison of clinical improvement between clozapine-haloperidol and clozapine-risperidone regimen groups using Chi-square analysis, significant if p-value <0.05.

Table IV. Safety comparison of antipsychotic regimens

Drug side effects	Regimen Clozapine-Haloperidol n = 71	Regimen Clozapine-Risperidone n = 71	Total n =142	P-value
Experiencing drug side effects				
Yes	18 (25,4%)	14 (19,7%)	32 (22,5%)	0,442
No	53 (74,6%)	57 (80,3%)	110 (77,5%)	
Extrapyramidal side effect				
Yes	13 (18,3%)	5 (7,0%)	18 (12,7%)	0,044*
No	58 (81,7%)	66 (93,0%)	124 (87,3%)	

Notes:[a] Comparison between clozapine-haloperidol and clozapine-risperidone regimen groups using *Chi-square* analysis*;* *Statistically significant results (p<0.05)

Table V. Types of adverse events in schizophrenia patients using clozapine-haloperidol and clozapine-risperidone antipsychotic regimens

Types of drug side effects	Group Clozapine-Haloperidol	Group Clozapine-Risperidone	Total cases
Extrapyramidal Syndrome	13 (56,5%)	5 (29,4%)	18 (45,0%)
Hypotension	2 (8,7%)	2 (11,8%)	4 (10,0%)
Parkinson	2 (8,7%)	1 (5,9%)	3 (7, 5%)
Sedation	2 (8,7%)	0 (0,0%)	2 (5,0%)
CK enhancement	1 (4,3%)	0 (0,0%)	1 (2,5%)
Seizures	0 (0,0%)	1 (5,9%)	1 (2,5%)
Suspicious of SNM	0 (0,0%)	1 (5,9%)	1 (2,5%)
Confusion	1 (4,3%)	0 (0,0%)	1 (2,5%)
Orthostatic hypotension	0 (0,0%)	1 (5,9%)	1 (2,5%)
Hypertension	0 (0,0%)	1 (5,9%)	1 (2,5%)
Cardiogenic shock	1 (4,3%)	0 (0,0%)	1 (2,5%)
Bradikardi	0 (0,0%)	1 (5,9%)	1 (2,5%)
Diarrhea	1 (4,3%)	0 (0,0%)	1 (2,5%)
Constipation	0 (0,0%)	1 (5,9%)	1 (2,5%)
Anorexia	0 (0,0%)	1 (5,9%)	1 (2,5%)
Nausea vomiting	0 (0,0%)	1 (5,9%)	1 (2,5%)
Dyspepsia	0 (0,0%)	1 (5,9%)	1 (2,5%)
Total	23	17	40

Comparison of clinical condition improvement

In addition to the decrease in initial and final PANSS-EC scores, the success of therapy can also be assessed based on the response to therapy which can be assessed from the final PANSS-EC score. A person is said to respond if they show signs of symptom reduction or symptom improvement.[18] The clozapine-haloperidol group showed 60 patients had improved clinical conditions with a final PANSS-EC score ≤ 15. Meanwhile, in the clozapine-risperidone group, 66 patients had a final PANSS-EC score ≤ 15. However, the statistical test results revealed no meaningful difference between the two (p=0.111). This result is similar to the PANSS-EC difference results as mentioned earlier. So it can be concluded that there is no critical distinction in effectiveness, both based on PANSS-EC difference and clinical condition improvement.

Differences or similarities in the effectiveness of antipsychotic regimens can be caused by several factors, one of which is the pharmacodynamics of drugs related to drug occupancy at receptors. Clozapine-haloperidol and clozapine-risperidone combination both have high occupancy at the D_2 receptor, so the two combinations have almost the same effectiveness.[11]

Safety comparison of clozapine-haloperidol and clozapine risperidone antipsychotic regimens

This study uses the Naranjo algorithm as the basis for determining whether the signs and symptoms that arise are side effects of drugs or not. Based on a total of 142 patients, 32 patients showed adverse drug events, 18 patients from the clozapine-haloperidol group, and 14 patients from the clozapine-risperidone group. In this study, patients who had side effects fell into the possible and probable naranjo categories. There were no patients in the doubtful and definite/highly probable categories. The possible category has been considered as an adverse drug event because the adverse effect occurred after drug administration and several factors may affect it so that the score results still show doubt. The types of side effects in the study subjects that fall into the probable criteria include extrapyramidal syndrome (8 patients), increased creatinine kinase value (1 patient), parkinsonism (1 patient), hypotension (2 patients), cardiogenic shock (1 patient), sedation (1 patient), seizure (1 patient). As for other types of side effects, they are included in the possible criteria.

Statistical analysis showed no meaningful distinction in the occurrence of adverse effects between the clozapine-haloperidol and clozapine-risperidone groups (p=0.442). The safety-related results in this study differed from previous studies, which showed there were differences in the safety of combined antipsychotic regimens.[16] However, the previous study examined the combination regiment of clozapine-haloperidol and clozapine-aripiprazole, where aripiprazole is an atypical antipsychotic that encompasses minimal chance of adverse effects in contrast to other atypical.[19] Although there was no distinction in safety or general side effects, this study revealed a noteworthy difference in extrapyramidal side effects (p=0.044). This result illustrates that the clozapine-risperidone group was safer or better tolerated in terms of EPS than the clozapine-haloperidol group.

The types of side effects that occurred in patients are shown in Table 5. Some patients experienced more than one side effect, resulting in a total of 40 cases of side effects. Of the 32 patients, 7 of them experienced more than one type of side effect. The rest only experienced one type of side effect.

The most common side effect in both groups in this study was extrapyramidal syndrome (EPS) (TABLE 5). Of the total 18 patients who developed extrapyramidal syndrome, 13 patients were from the clozapine-haloperidol group, while 5 patients were from the clozapine-risperidone group. Based on the statistical analysis in Table 4, there was a meaningful difference in the side effects of EPS (p=0.044).

Haloperidol monotherapy does have a high chance of extrapyramidal adverse events. The utilization of clozapine-haloperidol can increase drug occupancy at D receptors$_2$, so it can increment the chance of extrapyramidal side effects as well.[20,21] Second-generation or atypical antipsychotics tend to cause metabolic and cardiovascular-related side effects, so the clozapine-risperidone combination group in this study experienced more cardiovascular and gastrointestinal-related side effects.[22]

Confounding factors and limitations of the study

In this study, basic patient characteristics or confounding variables were analyzed. Based on the analysis, there was a meaningful influence of gender (p=0,001) and severity characteristics (p=0,012) on the effectiveness of antipsychotic regimens. As for safety, the clozapine dose per day parameter had a significant influence as a confounding variable (p=0,008). These results are similar to previous studies, namely gender and severity can affect the effectiveness of antipsychotic drugs, and there is an influence of antipsychotic doses on drug side effects.[23–25]

This study has several limitations, including the absence of dose standardization which could be a confounding variable related to safety in this study, and no measurement of the severity of drug adverse effects. In addition, the patient's baseline severity and comorbidities differed substantially, which could be a confounding variable for the effectiveness of antipsychotic regimens. In this study, there was no standardization of the measurement intervals of the initial and final PANSS-EC scores that were the same in all patients, which may cause bias in the analysis of drug effectiveness. The effectiveness assessment in this study was limited to the measurement results of the PANSS-EC instrument and did not assess based on the signs and symptoms that appeared in the patient. The *setting in* this study was an inpatient installation, so the side effects found and studied were limited to side effects with rapid onset.

Aspects of regimen selection for use in clinical practice

In determining therapy regimens for patients, consideration of various aspects is needed. This study examines the drug aspect, specifically related to effectiveness and safety. However from this study, there was no meaningful contrast between the two regimens studied in terms of effectiveness and safety. Thus, in the selection and determination of antipsychotic combination regimens between clozapine-haloperidol and clozapine-risperidone, aspects other than drug effectiveness and safety can be considered. One aspect or factor that can be taken into consideration is pharmacoeconomics, where the cost-effectiveness of the haloperidol combination regimen is greater than the risperidone combination regimen.[14,26] Therefore, in choosing between clozapine-haloperidol and clozapine-risperidone combination regimens, pharmacoeconomic aspects can be taken into consideration. For aspects other than drugs, aspects of the patient can also be considered, such as the presence or absence of a history of side effects, as well as the presence or absence of comorbidities that may affect the risk of side effects and the severity of the patient's comorbidities.

CONCLUSION

From this study, it can be determined that there is no substantial distinction in terms of the effectiveness or safety of clozapine-haloperidol and clozapine-risperidone antipsychotic regimens used in schizophrenia patients at the Inpatient Unit of Prof.Dr.Soerojo Magelang Mental Hospital. Thus, clozapine-haloperidol and clozapine-risperidone antipsychotic regimens can replace each other in clinical practice. In addition, clozapine-risperidone is better tolerated regarding extrapyramidal side effects.

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STATEMENT OF ETHICS

This research met the ethical requirements of research Number DP.04.03/D.XXXVI.12/42/2023, issued by Prof.Dr.Soerojo Magelang Mental Hospital on July 7, 2023.

REFERENCES

1. Marder SR, Cannon TD. Schizophrenia. *New England Journal of Medicine*. 2019;381(18):1753-1761. doi:10.1056/nejmra1808803
2. Peritogiannis V, Ninou A, Samakouri M. Mortality in Schizophrenia-Spectrum Disorders: Recent Advances in Understanding and Management. *Healthcare (Switzerland)*. 2022;10(12). doi:10.3390/healthcare10122366
3. GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Psychiatry*. 2022;9(2):137-150. doi:10.1016/S2215-0366(21)00395-3
4. Kementerian Kesehatan RI. *InfoDATIN: Situasi Kesehatan Jiwa Di Indonesia*.; 2019.
5. Kim W, Jang SY, Chun SY, Lee TH, Han KT, Park EC. Mortality in schizophrenia and other psychoses: Data from the south korea national health insurance cohort, 2002-2013. *J Korean Med Sci*. 2017;32(5):835-842. doi:10.3346/jkms.2017.32.5.835
6. DiPiro JT, Yee GC, Posey LM, Haines ST, Nolin TD, Ellingrod V. *Pharmacotherapy: A Pathophysiologic Approach*. 11th Edition. McGraw Hill; 2020.

7. Lähteenvuo M, Tiihonen J. Antipsychotic Polypharmacy for the Management of Schizophrenia: Evidence and Recommendations. *Drugs*. 2021;81(11):1273-1284. doi:10.1007/s40265-021-01556-4
8. Purwandityo AG, Febrianti Y, Sari CP, Ningrum VDA, Sugiyarto OP. Pengaruh Antipsikotik terhadap Penurunan Skor The Positive and Negative Syndrome Scale-Excited Component. *Jurnal Farmasi Klinik Indonesia*. 2018;7(1):19-29. doi:10.15416/ijcp.2018.7.1.19
9. Nucifora FC, Mihaljevic M, Lee BJ, Sawa A. Clozapine as a Model for Antipsychotic Development. *Neurotherapeutics*. 2017;14(3):750-761. doi:10.1007/s13311-017-0552-9
10. Freudenreich O, Goff DC. Antipsychotic combination therapy in schizophrenia. A review of efficacy and risks of current combinations. *Acta Psychiatr Scand*. 2002;106:323-330. doi:10.1034/j.1600-0447.2002.01331.x
11. Kapur S, Roy P, Daskalakis J, Remington G, Zipursky R. Increased Dopamine D2 Receptor Occupancy and Elevated Prolactin Level Associated With Addition of Haloperidol to Clozapine. *Am J Psychiatry*. 2001;158(2):311-314. doi:10.1176/appi.ajp.158.2.311
12. Styawan Y, Suprapti S, Utami AW. Pola Penggunaan Obat Antipsikotik pada Pasien Skizofrenia di Seluruh Puskesmas Kota Yogyakarta. *INPHARNMED Journal (Indonesian Pharmacy and Natural Medicine Journal)*. 2022;6(1):10-17. doi:10.21927/inpharnmed.v6i1.2244
13. Meilina NA, Cahaya N, Putra AMP. Analisis Trend Peresepan Golongan Antipsikotika Tipikal dan Atipikal di Tiga Puskesmas di Kota Banjarmasin Periode 2019-2021. *Jurnal Sains dan Kesehatan*. 2022;4(4):393-400. doi:10.25026/jsk.v4i4.1269
14. Ranti I, Octaviany AF, Kinanti S. Analisis Efektivitas Terapi dan Biaya antara Haloperidol Kombinasi dengan Risperidon Kombinasi pada Terapi Skizofrenia Fase Akut. *Mutiara Medika*. 2015;15(1):57-64.
15. Kuwilsky A, Krumm B, Englisch S, Dressing H, Zink M. Long-term efficacy and tolerability of clozapine combined with ziprasidone or risperidone. *Pharmacopsychiatry*. 2010;43(6):216-220. doi:10.1055/s-0030-1254089
16. Cipriani A, Accordini S, Nosè M, et al. Aripiprazole versus haloperidol in combination with clozapine for treatment-resistant schizophrenia: A 12-month, randomized, naturalistic trial. *J Clin Psychopharmacol*. 2013;33(4):533-537. doi:10.1097/JCP.0b013e318296884f
17. Barber S, Olotu U, Corsi M, Cipriani A. Clozapine combined with different antipsychotic drugs for treatment-resistant schizophrenia. *Cochrane Database of Systematic Reviews*. 2017;2017(3). doi:10.1002/14651858.CD006324.pub3
18. Sadock BJ., Sadock VA., Ruiz Pedro. *Kaplan & Sadock's Synopsis of Psychiatry : Behavioral Sciences/Clinical Psychiatry*. Eleventh Edition. Wolters Kluwer; 2015.
19. Khanna P, Suo T, Komossa K, et al. Aripiprazole versus other atypical antipsychotics for schizophrenia. *Cochrane Database of Systematic Reviews*. 2014;(1). doi:10.1002/14651858.CD006569.pub5
20. Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: A multiple-treatments meta-analysis. *The Lancet*. 2013;382(9896):951-962. doi:10.1016/S0140-6736(13)60733-3
21. Huhn M, Nikolakopoulou A, Schneider-Thoma J, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *The Lancet*. 2019;394(10202):939-951. doi:10.1016/S0140-6736(19)31135-3
22. Solmi M, Murru A, Pacchiarotti I, et al. Safety, tolerability, and risks associated with first-and second-generation antipsychotics: A state-of-the-art clinical review. *Ther Clin Risk Manag*. 2017;13:757-777. doi:10.2147/TCRM.S117321
23. Seeman M V. Men and women respond differently to antipsychotic drugs. *Neuropharmacology*. 2020;163:1-10. doi:10.1016/j.neuropharm.2019.05.008
24. Furukawa TA, Levine SZ, Tanaka S, et al. Initial Severity of Schizophrenia and Efficacy of Antipsychotics: Participant-level meta-analysis of 6 placebo-controlled studies. *JAMA Psychiatry*. 2015;72(1):14-21. doi:10.1001/jamapsychiatry.2014.2127
25. Yoshida K, Takeuchi H. Dose-dependent effects of antipsychotics on efficacy and adverse effects in schizophrenia. *Behavioural Brain Research*. 2021;402(113098). doi:10.1016/j.bbr.2020.113098
26. Abdulah R, Siregar RF, Alfian SD. Analisis Efektivitas Biaya Penggunaan Kombinasi Antipsikotik pada Pasien Rawat Inap Skizofrenia. *Jurnal Farmasi Klinik Indonesia*. 2017;6(1):61-66. doi:10.15416/ijcp.2017.6.1.61