



Potential Analysis of Drug Interactions in Schizophrenia Cases at One of the Bandung District Pharmacy, Indonesia

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Abstract

Schizophrenia is a heterogeneous syndrome of thought disturbances, delusions, hallucinations, emotional disturbances, decreased cognitive function and disturbed psychosocial functions. Treatment of schizophrenia aims to prevent hospitalization, ensure the patient's symptoms are stable and independent such as work or school. The purpose of this study was to determine the potential for drug interactions in schizophrenia cases based on their mechanism of action and severity. This research method is a descriptive study using data collected retrospectively on prescription drug data sheets in the pharmacy. The collected data were analyzed quantitatively and qualitatively. The results of the study from a total of 133 prescriptions found potential drug interactions in 509 cases. Drug interactions based on the mechanism of action, pharmacodynamics were found in 494 cases and 15 cases of pharmacokinetic. Based on the level of severity, there were interactions with 15 cases of mild severity, 287 cases of moderate severity and 217 cases of severe severity.

Keywords: Schizophrenia, drug interactions, pharmacodynamics, pharmacokinetics, polypharmacy.

1. Introduction

The prevalence of schizophrenia in Indonesia based on the 2018 Riskesdas is 6.7%, where the highest prevalence is in Bali (11.1%), DI Yogyakarta (10.4%), West Nusa Tenggara (9.6%), and West Java (5.0%). Schizophrenia tends to be higher in men and tends to be higher in people who live in rural areas (Ri, 2013). Research by Agung Wahyudi and Arulita Ika (2016) shows that many factors can increase the risk of schizophrenia, namely gender, residential area, personality type, marital status, employment status, socio-economic status. While the factors that are not related to the incidence of schizophrenia are the level of education and heredity (Wahyudi and Fibriana 2016).

Treatment of schizophrenia aims to the goals in treating schizophrenia include targeting symptoms, preventing relapse, and increasing adaptive functioning so that the patient can be integrated back into the community (Dwi Aulia et al., 2018). Management of schizophrenia is divided into pharmacological and psychosocial or non pharmacological treatments. Pharmacological treatment can control the signs and symptoms of schizophrenia. In pharmacological treatment, many drugs are combined so that the patient reaches a stable state (Dyer et al., 2018; Farook et al., 2021). This combination of drugs often causes problems including drug interactions. Drug interactions are changes in effect of a drug due to the presence of other drugs when given together so that the effectiveness or toxicity of other drugs will change.

Research conducted by Dwi a Ramdini et al in 2018 at a psychiatric hospital in the city of Bandung showed that the prevalence of potential drug interactions in schizophrenic patients was 92.54%, with the majority falling into the category of significant interactions (78.24%). While research on paranoid schizophrenic patient prescriptions showed potential for antipsychotic drug interactions based on the severity of 373 cases, namely serious 1.5%, significant 94.5%, minor 4% (Paula et al, 2021). This high percentage is due to the large number of drugs prescribed to schizophrenic patients. The use of drugs other than antipsychotics, including anticholinergics, anticonvulsants and antidepressants is also widely administered to patients with schizophrenia. The number of drugs prescribed and adherence to therapy have a significant relationship with the potential for drug interactions (Dwi Aulia et al., 2018).

Polypharmacy with antipsychotic medications is defined as the simultaneous use of two or more antipsychotic medications. The chronic clinical course of schizophrenia, resistance to treatment, drug side effects, different

responses of negative and cognitive symptom clusters to anti-psychotic medications with different receptor profiles may require combination therapy and thus antipsychotic polypharmacy (Ayani, 2021).

The potential for drug interactions is generally found in schizophrenic patients with combination therapy which becomes drug-related problems for patients. The occurrence of this drug interaction is very closely related to the emergence of adverse drug reactions that affect patient compliance. Regarding to this finding, we aimed to determine the potential drug interactions in schizophrenia cases based on their mechanism of action and severity level in community pharmacy

2. Methods

This research was a descriptive retrospective study that conducted at one of Bandung District Pharmacy. The data were shown in tables. Inclusions criteria was the prescription with schizophrenia diagnosed (Kishimoto et al., 2018). Whereas, exclusion criteria was incomplete prescription. Samples were all the prescriptions with schizophrenia diagnosed that entered to the pharmacy during December 2021. Research object was data taken from prescription, including drug name, number of cases, and drug-drug (DDI) interaction. DDI was analysed by interactions checker on medscape.com and was accessed on <http://reference.medscape.com/druginteractionchecker> and using Stockley's drug interactions 9th ed.2010 textbook (Baxter and Preston 2010). Quantitative analysis includes the number of drug interaction cases, the number of drug interaction cases based on the mechanism of action and severity. Qualitative analysis includes an analysis of the mechanism of action and the severity of drug interactions

3. Result and Discussion

There were 133 prescriptions with schizophrenia diagnosed during December 2021. We categorized the number of patient by age. The result is shown in Table 1.

Table 1: Age Criteria

Age (year)	Number
Late teenager 17-25	14
Early adult 26-35	40
Late adult 36-45	47
Early elderly 46-55	26
Late elderly 56-65	2
Senior over 65	4
Total	133

Schizophrenia can occur at any age, the average age tends to be in the late teens to early 20s for men, and the late 20s to early 30s for women (NAMI) (Shah and Prabu 2020; Krishnakumar and Kethar 2023). In this study, Schizophrenia most in the age of late adult. Of the 133 prescriptions, there 509 cases of potential DDI. Drug interaction is the effect of a drug that is caused when two or more drugs interact and affect the body's response in the form of increasing or decreasing effects that can affect the outcome of patient therapy. Number of potential DDI was briefly explain in the Table 2 and Table 3.

Table 2: DDI Based on mechanism

Interacting drugs	n	Type of DDI	
		Pharmacokinetic	Pharmacodynamic
Alprazolam X Risperidon	23		23
Alprazolam X Amitriptilin	4		4
Alprazolam X Clozapin	25		25
Alprazolam X Haloperidol	3		3
Alprazolam X Quetiapine	1		1
Amitirptilin X clozapine	31		31
Amitriptilin X Risperidon	27		27
Amitriptilin X Trihexiphenydl	11		11
Clozapin X Haloperidol	30		30
Clozapin X Risperidon	79		79
Clozapin X Trihexiphenydl	33		33
Divalproex Sodium X Amitriptilin	5	5	
Divalproex Sodium X Risperidon	5	5	

Flouxetin X Amitiptylin	12		12
Flouxetin X clozapine	17		17
Fluoxetin X Alprazolam	5		5
Fluoxetin X Haloperidol	11		11
Fluoxetin X Risperidon	24		24
Fluoxetin X Trihexiphenydil	11		11
Haloperidol X Risperidon	4		4
Haloperidol X Trihexiphenydil	4		4
Olanzapine X Amitriptilin	4		4
Olanzapine X Fluoxetin	4		4
Risperidon X Trihexiphenydil	40		40
Sertralin X Clozapin	2		2
Sertralin X Risperidon	2		2
Sertralin X Trihexiphenydil	2		2
Sertralin X Fluoxetin	1		1
Quetiapine X Risperidon	1		1
Quetiapine X Amitriptilin	3		3
Quetiapine X Trihexiphenydil	3		3
Trihexiphenydil X Alprazolam	14		14
Trifluferazin X Clozapin	21		21
Trifluferazin X Haloperidol	12		12
Trifluferazin X Risperidon	9		9
Trifluferazin X Trihexiphenydil	21		21
Divalproex Sodium X Clozapin	5	5	
Total	509	15	494

Based on the mechanism of action, the most common are pharmacodynamic interactions where there is synergism between two types of drugs with different mechanisms of action but leading to the same effect. The most potential pharmacodynamic interactions were combination of clozapine and risperidone with a total of 79 cases. The use of both clozapine and risperidone can increase the antidopaminergic effect and increase sedation, so the use of both drugs needs to be monitored closely. Potential pharmacokinetic interactions were found in the use of Divalproex and Clozapine. Valproate can increase or decrease clozapine levels which affect the metabolic rate, while in other studies state that the use of divalproex sodium and clozapine has no significant effect.

Table 3: DDI Based on severity level

Interacting Drugs	n	Severity level		
		minor	moderate	severe
Alparazolam X Risperidon	23		24	
Alprazolam X Amitriptilin	4		4	
Alprazolam X Clozapin	25			25
Alprazolam X Haloperidol	3		3	
Alprazolam X Quetiapine	1		1	
Amitirptilin X clozapin	31			31
Amitriptilin X Risperidon	27		27	
Amitriptilin X Trihexiphenydil	11		11	
Clozapin X Haloperidol	30			30
Clozapin X Risperidon	79			79
Clozapin X Trihexiphenydil	33		33	
Divalproex Sodium X Amitriptilin	5		5	
Divalproex Sodium X Risperidon	5		5	
Flouxetin X Amitiptylin	12			12
Flouxetin X clozapin	17		17	
Fluoxetin X Alprazolam	5		5	
Fluoxetin X Haloperidol	11		11	

Fluoxetine X Risperidon	24		24	
Fluoxetine X Trihexiphenydil	11		11	
Haloperidol X Risperidon	4			4
Haloperidol X Trihexiphenydil	4		4	
Olanzapine X Amitriptilin	4		4	
Olanzapine X Fluoxetine	4		4	
Risperidon X Trihexiphenydil	40		40	
Sertralin X Clozapin	2			2
Sertralin X Risperidon	2		2	
Sertralin X Trihexiphenydil	2		2	
Sertralin X Fluoxetine	1			1
Quetiapine X Risperidon	1		1	
Quetiapine X Risperidon	1		1	
Quetiapine X Amitriptilin	3		3	
Quetiapine X Trihexiphenydil	3		3	
Trihexiphenydil X Alprazolam	14		14	
Trifluoperazin X Clozapin	21			21
Trifluoperazin X Haloperidol	12			12
Trifluoperazin X Risperidon	9		9	
Trifluoperazin X Trihexiphenydil	21		21	
Divalproex Sodium X Clozapin	5	5		
Total	509	5	287	217

The most frequent potential drug interactions were interactions with moderate severity in 287 cases, then severe in 217 cases and mild severity in 5 cases. From the results of the analysis above, there were many interactions that occur which will cause a decrease or increase in the effect of the drug on the patient. Risperidone with Trihexiphenydil was found to be the most common with moderate severity, namely 40 cases. Risperidone can increase the effects of trihexiphenydil with pharmacodynamic synergism, the combination of risperidone with trihexiphenydil has the potential to produce additive anticholinergic effects. Management of patients who are prescribed this combination that patient should be advised to inform the doctor immediately if experiencing potential symptoms of anticholinergic poisoning such as abdominal pain, fever, blurred vision, confusion and hallucinations (Drug.com).

A lot of potential drug interactions with severe severity were found in 217 cases, the most frequently found were the use of clozapine with risperidone in 79 cases. Interaction management is recommended when clozapine is started in patients receiving other antipsychotic drugs. Vital signs should be monitored closely. In addition, the potential for additive effects on the QT interval and increased arrhythmias must be considered (Drugs.com). Special attention is needed because the effects are quite severe. Efforts need to be made to prevent adverse effect on schizophrenia patients. Doctors and pharmacist should collaborate together through good communication. The pharmacist should give special counselling to patient with such combinations.

4. Conclusion

The number of cases of potential drug interactions in schizophrenia cases is as many as 509 potential drug interactions. Based on the mechanism, there were 494 pharmacodynamic interactions and 15 pharmacokinetic interactions. And based on the level of severity, there were interactions with mild severity in 15 cases, moderate severity in 287 cases and severe severity in 217 cases.

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References

Ayani, N., Morimoto, T., Sakuma, M., Kikuchi, T., Watanabe, K., & Narumoto, J. (2021). Antipsychotic polypharmacy is associated with adverse drug events in psychiatric inpatients: the Japan Adverse Drug Events study. *Journal of clinical*

psychopharmacology, 41(4), 397.

Baxter, K., & Preston, C. L. (Eds.). (2010). *Stockley's drug interactions* (Vol. 495). London: Pharmaceutical Press.

Dwi Aulia, R., Sri Adi, S., Melisa Intan, B., Dika Pramita, D., & Ice Laila, N. (2018). Potensi Interaksi Obat pada Pasien Skizofrenia di Salah Satu Rumah Sakit Jiwa di Provinsi Jawa Barat. *Potensi Interaksi Obat pada Pasien Skizofrenia di Salah Satu Rumah Sakit Jiwa di Provinsi Jawa Barat*, 7(4), 280-293.

Dyer, S. M., Harrison, S. L., Laver, K., Whitehead, C., & Crotty, M. (2018). An overview of systematic reviews of pharmacological and non-pharmacological interventions for the treatment of behavioral and psychological symptoms of dementia. *International psychogeriatrics*, 30(3), 295-309.

Farooq, S., Tunmore, J., & Comber, R. (2021). Pharmacological or non-pharmacological interventions for treatment of common mental disorders associated with Tuberculosis: A systematic review. *Chronic Respiratory Disease*, 18, 14799731211003937.

Kishimoto, T., Hagi, K., Nitta, M., Leucht, S., Olfson, M., Kane, J. M., & Correll, C. U. (2018). Effectiveness of long-acting injectable vs oral antipsychotics in patients with schizophrenia: a meta-analysis of prospective and retrospective cohort studies. *Schizophrenia Bulletin*, 44(3), 603-619.

Krishnakumar, S., & Kethar, J. (2023). Efficacy of virtual reality treatment with NIBS for Schizophrenia. *Journal of Student Research*, 12(1).

Ri, K (2013). *Badan Penelitian dan Pengembangan Kesehatan. Riset Kesehatan Dasar (RISKESDAS) 2018*. Laporan Nasional 2013. 2018: 1–384.

Shah, T. D., & Prabhu, S. (2020). Correlation between Physical Activity and Quality of Life in Schizophrenic Patients. *Journal of Exercise Science & Physiotherapy Vol*, 16(2).

Wahyudi, A., & Fibriana, A. I. (2016). Faktor resiko terjadinya Skizofrenia (studi kasus di Wilayah Kerja Puskesmas Pati II). *Public Health Perspective Journal*, 1(1).