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POTENTIAL DRUG-DRUG INTERACTION AND ASSOCIATED FACTOR AMONG GERIATRIC OUTPATIENT

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Abstract

Drug interactions are changes that occur in the pharmacological activity of a drug due to its concomitant use with other drugs, herbal medicines, food or beverages. The drugs most commonly involved in potential drug interactions are those that are used on a daily basis in the clinical management of geriatric patients. The purpose of this study is to evaluate the incidence profile of drug-drug interactions with prescribed drugs in outpatient geriatric patients at Ummi Bengkulu General Hospital in 2022. This research method uses a cross sectional research design and retrospective data collection using a research sample of 100 geriatric patients. The potential drug interaction was analyzed using medscape and drugs.com and the predictor factors of drug interaction potential were analyzed using the chi-square test. The results showed that out of 100 geriatric patients, 76 patients (76%) experienced drug interactions, with a total of 204 interaction events. Based on the mechanism of interaction, it was found that there were 104 (51%) pharmacodynamic interactions and 100 (49%) pharmacokinetic interactions. Based on the severity, it was found that the moderate category was 155 (76%), minor as many as 30 (14.7%), and major as many as 19 (9.3%). The conclusion of this study is that most of the drug-drug interactions are seen in the prescriptions of geriatric patients. Comorbidities and polypharmacy were identified as predictors of potential drug interactions with a value of ($p<0.05$).

Keywords:Drug Interaction, Geriatric, Polypharmacy, Comorbid Disease

INTRODUCTION

Geriatric age is very susceptible to drug interactions because at that age the physiological anatomy of the body's organs has decreased in function so that it tends to have comorbidities (comorbidities).

Therefore, the frequency of drug therapy and the average number of drugs used are increasing with age, and have the potential to cause polypharmacy. The incidence of polypharmacy can increase the risk of drug interactions in geriatric patients (Salwe et al., 2016). Increasing age and polypharmacy are identified as predictors of potential drug interactions (Maulida and Puspitasari, 2021). The drugs most commonly involved in potential interactions are those used in the day-to-day clinical management of geriatric patients (Shetty et al., 2018).

A study on polypharmacy and drug interactions in geriatric patients conducted in Mexico involving 385 geriatric patients found 1,458 interactions. Based on the severity, there were 518 minor drug interactions, 847 moderate ones, and 72 major drug interactions. Only 50 (12.9%) patients did not show any type of drug interaction (Ramirez et al., 2018). One of the potential occurrences of Drug Related Problems (DRP) is drug interactions (Sihombing et al., 2021). In a study conducted at the Sukabumi City Government Hospital, 108 potential interactions between drugs were found with a percentage of 48.86% of 48 outpatient prescriptions. Drug interactions in the minor category were 5, moderate as many as 90, and major as many as 13 (Irawan and Wilar, 2022).

A study conducted at Haji Adam Malik Hospital in Medan found that 259 medical records experienced drug interactions (78.96%) out of a total of 328 medical records (Dasopang et al., 2015). In the Maindoka study (2017) reported that out of 100 inpatient geriatric patients at Prof. Dr. R. D. Kandou Manado Hospital, 146 drug interaction events were found with a percentage of 44%. The prevalence of drug interactions found in this study is quite high. In the research of Herdaningsih et al., (2016) out of 197 recipes, there were 121 recipes that interacted with a percentage of 34.38% in each recipe sheet obtained. The total potential interactions that occurred were 194 interactions. Potential interactions were major as many as 25, moderate as many as 134, and minor as many as 35. The most drug interactions were in the moderate category. Drug interactions in the moderate category mean that the administration of this drug combination has a clinically significant effect.

Based on the description above, it shows that the prevalence of drug interaction events in geriatric patients in Indonesia is still high and currently there are no studies on the incidence of drug interactions in geriatric patients in the city of Bengkulu, so this study intends to study and evaluate drug interactions in outpatient geriatric patients at Ummi Bengkulu General Hospital in 2022

MATERIALS AND METHODS

The type of research used is an analytical descriptive research with a cross sectional research design and retrospective data collection based on medical record data from Outpatients of Ummi Bengkulu General Hospital for the January-December 2022 period. The population used in this study was geriatric

patients who received outpatient therapy at Ummi Bengkulu General Hospital during the January-December 2022 period which amounted to 10,200 patients. The sample in this study was outpatient geriatric patients at Ummi Bengkulu General Hospital in January-December 2022 who met the inclusion criteria. The number of samples was calculated using the Slovin formula, which is 100 patients.

The inclusion criteria for the sample of cases in this study are:

1. Age range ≥ 60 years
2. Patients who receive two or more medications at the same time
3. Complete medical record data
4. Outpatient in the period of January - December 2022.

Drug interaction will be evaluated using Medcape dan Drugs.com application and the relationship between drug interaction and patient characteristics and drug interaction with polypharmacy was analyzed using SPSS using the Chi square correlation test method. Based on the Chi Square test, it can be decided if a P-value of < 0.05 is obtained, it means that there is a relationship between patient characteristics and the occurrence of drug interactions. On the other hand, if a P-value of > 0.05 is obtained, it means that there is no relationship between patient characteristics and the occurrence of drug interactions in geriatric patients

Ethical Approvals

This research has received an Ethical Clearance from the Health Research Ethics Commission of the University of Jember with No.1876/UN25.8/KEPK/DL/2023 and has obtained a research permit from the Ummi Bengkulu General Hospital, so that research can be carried out in accordance with applicable procedures

RESULTS AND DISCUSSION

The number of research samples of outpatient geriatric patients at Ummi Bengkulu General Hospital is 100 patients. The frequency distribution of characteristic outpatient geriatric patients at Ummi Bengkulu General Hospital for the January-December 2022 period can be seen in the Table 1.

Table 1: Patient Characteristics

No.	Patient Characteristics	N	(%)
1	**Gender**		
	Male	48	48%
	Female	52	52%
	Total	100	100%

2	**Age**		
	60-74 years	83	83%
	75-90 years	17	17%
	Total	100	100%
3	**Comorbid**		
	With comorbid	70	70%
	Without comorbid	30	30%
	Total	100	100%

It can be seen that out of 100 outpatient geriatric patients at Ummi Bengkulu General Hospital, the number of female geriatric patients is more, namely 52 patients (52%) and male geriatric patients amounting to 48 patients (48%). The same thing was also shown in previous studies that the number of female geriatric patients was more than that of men (Supraptia et al., 2014). Polypharmacy acceptance is strongly associated with increasing age and is more common in female patients (Guthrie et al., 2015). Based on age, in this study, the most geriatric patients were 83 patients (83%) with an age range of 60-74 years and 17 patients (17%) with an age range of 75-90 years. The results of this study are in line with previous research that the highest age of geriatric patients who visit is 60-74 years old, which is 529 patients (85.61%) and 75 years and older as many as 89 patients (14.39%) (Zulkarnaini and Martini, 2019).

Based on comorbidities, it was shown that the majority of geriatric patients had comorbidities, namely 70 patients (70%) and 30 patients (30%) without comorbidities. The same thing was also shown in the previous study that the majority of geriatric patients had comorbidities, namely as many as 170 patients (85%) had comorbidities and 30 patients (15%) had no comorbidities. The number of patients with a diagnosis of more than one disease is related to complications experienced due to chronic diseases suffered by patients (Arini et al., 2016). Diagnosing patients with comorbidities will increase the number of drugs given for therapy for patients. This will increase the potential for drug interactions in the therapy (Erviana, 2018).

In this study, it was found that the 5 most common diseases in geriatric patients were hypertension as many as 57 patients (32%), followed by type II diabetes mellitus as many as 27 patients (15%), ischemic heart disease as many as 17 patients (10%), dyspepsia syndrome as many as 17 patients (10%), and chronic kidney disease as many as 4 patients (2%). In previous studies reported that the most common diseases found in geriatric patients were hypertension, type II diabetes mellitus, ischemic heart disease and chronic obstructive pulmonary disease. Cardiovascular drugs are the most commonly prescribed in geriatric patients (Patel et al., 2014). The risk of cardiovascular disease increases with age and cardiovascular disorders are the most common diseases in geriatric patients (Shakeel et al., 2018)

The potential drug-drug interaction in outpatient geriatric patients at Ummi Bengkulu General Hospital for the January-December 2022 period can be seen in Table 2 as follows.

Table 2: The Potential Drug-Drug Interaction

No.	Drug-Drug Interaction (DDI)	Frequency (n=100)	(%)
1.	With DDI	76	76 %
2.	Without DDI	24	24 %
Total		**100**	**100 %**

Based on Table 2 above, it shows that as many as 76 patients (76%) experienced drug interactions and 24 patients (24%) did not experience drug interactions. From these results, it can be seen that the majority of patients experience drug interaction events. Similar results were reported in previous studies that the potential for drug interactions in geriatric patients was quite high, as many as 271 out of a total of 300 patients showed the potential for drug interactions with a prevalence of 90.3% with a total of 4,797 drug interaction events. The high prevalence of drug interactions in geriatric patients is caused by chronic diseases suffered by patients, so it requires combination therapy that causes an increase in drug interactions in patients (Suthar et al., 2021)

The distribution of drug interactions based on severity in outpatient geriatric patients at Ummi Bengkulu General Hospital can be seen in Table 3 below.

Table 3: Distribution of Drug Interaction Based on Severity

No.	Drug-Drug Interaction	Frequency (n=100)	(%)
1.	*Major*	19	9,3 %
2.	*Moderate*	155	76 %
3.	*Minor*	30	14,7 %
Total		**204**	**100 %**

Based on Table 3, it is shown that drug interactions that occur a lot based on severity, namely in the moderate category as many as 155 (76%) events, minor as many as 30 (14.7%) events, and major as many as 19 (9.3%) drug interaction events. The results of this study are in line with the research of Herdaningsih et al., (2016) stated that the most potential drug interactions occurred were the moderate category 134 (69.07%), then the minor category as much as 35 (18.04%), and the major category as much as 25 (12.89%). The highest potential drug interaction occurred in the moderate category with a percentage of 76.8% (Salwe et al., 2016). Moderate interactions rarely lead to life-threatening complications. However, the interactions that occur must be monitored to prevent harmful interactions

and reduce the prevalence of drug interactions (Kapp et al., 2013). The most common occurrence of drug interactions based on severity can be seen in Table 4 as follows.

Table 4: Potential Drug-Drug Interaction (DDI) severity

Severity level	DDI	N	Effect
Major	Spironolacton + Candesartan	5	Increase level of potassium in the blood
	Spironolacton + Ramipril	3	Increase risk of hyperkalemia
	Clopidogrel + Omeprazol	2	Decrease the effectivity of clopidogrek
Moderate	Metformin + Glimepirid	15	Increase risk of hypoglichemia
	Amlodipin + Bisoprolol	6	Increase the risk of hypotension
	Amlodipin + Metformin	6	Amlodipin decrease the effect of metformin
Minor	Digoxin + Spironolakton	5	Spironolacton can decrease tubular secretion of digoxin
	Amlodipin + Ramipril	3	Hypotension
	Glimepirid + Clopidogrel	3	Increase level and toxicity of clopidogrel

Based on Table 4, it shows that the interaction of major category drugs with the most incidences, namely spironolactone and candesartan as many as 5 events with pharmacodynamic mechanisms. Major level interactions between spironolactone and candesartan were found to cause hyperkalemia with an increase in plasma potassium levels from 5.2 to 6 mEq/L. Patients developed hyperkalemia after 1 to 6 days after administration of the combination drug. The use of angiotensin converting enzyme inhibitors (ACEIs) such as captopril or angiotensin II receptor blockers (ARBs) such as losartan, candesartan, telmisartan leads to a decrease in aldosterone, which can lead to potassium retention. As a result, hyperkalemia often occurs in patients who use medications simultaneously (Wulandari et al., 2018). In certain conditions, such as patients with heart failure, the elderly, and patients with type II diabetes mellitus cause severe hyperkalemia (Diaconu et al., 2021).

Major category drug interactions with the next most common events, namely clopidogrel and omeprazole, were 2 events with pharmacokinetic mechanisms. The Food and Drug Administration (FDA) in 2011 issued a third warning that there is an interaction between clopidogrel and omeprazole

of the proton pump inhibitor (PPI) class on metabolic disorders of cytochrome P4502C19 (CYP2C19) enzymes. Concomitant use of clopidogrel with omeprazole can significantly reduce the antiplatelet activity of clopidogrel. The biotransformation of clopidogrel requires CYP2C19 to become an active metabolite. The use of clopidogrel and PPIs resulted in a 40% - 53% increase in the incidence of myocardial infarction in a number of patients. This is because clopidogrel's efficacy can be reduced in concomitant use with PPIs that inhibit clopidogrel activator enzymes (Guérin et al., 2016).

Based on Table 4, it shows that the most common moderate category drug interactions are the interactions between metformin and glimepirids, which are as many as 15 events with pharmacodynamic mechanisms. The combination of glimepiride and metformin is a commonly used combination because glimepiride will stimulate pancreatic secretion which can provide an opportunity for metformin to work effectively, so that it has a mutually supportive effect and will be more optimal in suppressing hyperglycemia and the risk of cardiovascular disorders. However, metformin and glimepyride both have the effect of lowering high blood sugar levels (hyperglycemia), so the combination of these two drugs can increase the risk of hypoglycemia or excessive blood sugar drop (Hassan and Abd-Allah, 2015). The next most common moderate category drug interaction was amlodipine with metformin as many as 6 events with a pharmacodynamic mechanism. Metformin when given at the same time as amlodipine can reduce the effect of metformin with pharmacodynamic antagonism. (Tuladhar et al., 2021). The interaction of amlodipine with metformin does not affect blood pressure, but amlodipine inhibits the action of metformin by preventing metformin from binding to receptors by weakening or releasing metformin from the receptor system so that the hypoglycemic effect of metformin decreases (Wahyuni et al., 2022).

The next most common moderate category drug interaction was amlodipine with bisoprolol as many as 6 events with pharmacodynamic mechanisms. The combination of bisoprolol and amlodipine can be a treatment option for hypertensive patients. However, the combination of the two substances increases the risk of drug-drug interactions, namely increasing the risk of low blood pressure. The mechanism of drug interaction that occurs is pharmacodynamic interaction, where both drugs have the effect of lowering blood pressure so as to increase the risk of hypotension in patients who receive polypharmacy (Gillessen et al., 2019).

Based on Table 4, it shows that the most common minor category drug interactions are digoxin with spironolactone as many as 5 events with pharmacokinetic mechanisms, where spironolactone can reduce tubular secretion from digoxin. Spironolactone increases plasma concentrations of digoxin by up to 25% and can interfere with plasma concentrations of digoxin, as well as increase levels of free digoxin (Carone et al., 2017). Spironolactone can cause digoxin toxicity which is manifested by nausea,

vomiting, and abnormalities in heart rhythm. When using this combination, clinical response, plasma concentration of digoxin and dosage should be monitored (Ismail et al., 2012).

The next most common minor category drug interaction is amlodipine with ramipril as many as 3 events with pharmacodynamic mechanisms. Based on the Drug Interaction Checker application, the results were obtained that the use of a combination of amlodipine (CCB) and ramipril (ACE Inhibitor) drugs at the same time has the potential for hypotension. This happens because these two groups of drugs lower blood pressure by lowering peripheral resistance. Although the use of a combination of these two drugs is relatively safe, systemic blood pressure monitoring should still be carried out, especially during the first one to three weeks of therapy (Phillip and Ward, 2010).

The next most common minor category drug interaction is clopidogrel with glimepirid as many as 3 events with pharmacokinetic mechanisms. The simultaneous use of sulfonylurea (glimepirid) and clopidogrel can enhance the effects of glimepirid and cause hypoglycemia. There is a potential interaction mediated by the CYP2C9 enzyme, i.e. competitive inhibition between clopidogrel and glimepirid. The interaction may not only reduce the efficacy of clopidogrel but may also enhance the glimepiride effect and increase the risk of hypoglycemic events in patients with type II diabetes mellitus when prescribed together (Ruiz et al., 2022).

The relationship between drug interaction and patient characteristics was analyzed using Chi Square. The characteristics of the patients in this study are gender, age, and comorbidities. The results of the statistical test of the relationship between drug interactions and the characteristics of outpatient geriatric patients at Ummi Bengkulu General Hospital for the January-December 2022 period can be seen in Table 5 as follows.

Table 5: The relationship between drug interaction and patient characteristics

Variable	**DDI**		**Total n=100**	**P Value**
	With	Without		
Gender				
Male	36	12	48	0,822
Female	40	12	52	
Total (n)	76	24	100	
Age				
60-74	62	21	83	0,501
75-90	14	3	17	
Total (n)	76	24	100	
Comorbid				
With	55	15	70	0,025*
Without	21	9	30	
Total (n)	76	24	100	

Based on bivariate analysis using Chi Square, a P value of 0.0250 (<0.05) was obtained, indicating that there was a significant relationship between drug interactions and comorbidities in geriatric patients. The results of this study are in line with previous research that the prevalence of drug-drug interactions has a significant relationship related to polypharmacy and polymorbidity (comorbidities). Polypharmacy incidence and increased risk of potential drug-drug interactions are higher in elderly patients with comorbidities. This is because the more diseases suffered by patients, the more drugs will be consumed so that the potential for drug interactions also increases. Diseases in the elderly population differ in their journey and appearance from those found in other populations, where diseases are multipathological, degenerative, interrelated, and chronic (Assefa et al., 2020).

There were 59 geriatric patients with polypharmacy prescriptions (≥5 drugs), where 52 patients (88.2%) experienced drug interactions and 7 patients (11.8%) did not experience drug interactions. While patients with prescriptions of 2-4 drugs were 41 patients, where 24 patients (58.5%) who received the prescription experienced drug interactions while 17 patients (41.5%) did not experience drug interactions. Based on bivariate analysis using Chi Square, a P value of 0.001 (<0.05) was obtained, indicating that there was a significant relationship between drug interactions with polypharmacy. In this study, it was known that patients with polypharmacy prescription (≥5 drugs) had a higher potential to experience drug interactions than patients with 2-4 drug prescriptions. Previous studies reported that there was a strong association between polypharmacy and negative clinical consequences in the elderly population. There are many negative consequences associated with polypharmacy.

Table 6: The Relationship polypharmacy and Drug Interaction

Variable	**DDI**		**Total n=100**	**P *Value***
	With	**Without**		
2-4 drugs	24	17	41	
≥ 5 (polypharmacy)	52	7	59	0,001*
Total (n)	76	24	100	

This study identifies potential drug interactions using drug interaction checkers to predict the likelihood of drug interactions on patient prescriptions, so that drug interactions will not necessarily occur in patients. However, by checking the possibility of drug interactions, this can be a preventive measure and minimize the risk of drug interactions in patients. There are many factors that can affect drug interactions, especially in geriatric patients who tend to get polypharmacy prescriptions and have comirbids. Identifying potential drug-drug interactions can help suggest effective treatment therapies and preventive policies to avoid the occurrence of drug interactions in geriatric patients (Annisa and Abdulah, 2012).

CONCLUSION

Of the 100 geriatric patients, 76 patients (76%) experienced drug interactions, with a total of 204 interaction events. Based on the mechanism, drug interactions occurred in pharmacodynamics, namely as many as 104 events (51%). Based on severity, the highest drug interactions occurred in the moderate category, which was 155 events (76%). The characteristics of patients that have a significant relationship with drug interactions are comorbidities. There is a significant relationship between drug interactions with polypharmacy.

Declaration of Interest Statement

The authors declare that they have no conflict of interests.

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