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Pharmacist intervention can reduce the potential use of inappropriate drugs medications in Indonesian geriatric patients

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ABSTRACT

Intervention study design by pharmacists to doctors using face-to-face interviews conducted in this study aims to analyze potentially inappropriate medications (PIMs) with prospective data collection in the geriatric ward of Regional General Hospital Dr.M. M. Dunda Gorontalo, Indonesia in the period from January to March 2018. The sampling technique was a total sampling design and obtained by the end of the study were 123 patients. Results of analysis with Beers and screening tool of older people's prescriptions (STOPP) from 123 patients found 54 PIMs in 48 patients (39.0%) based on Beers criteria and 6 patients (6.3%) based on STOPP criteria. Bivariate analysis showed that there was a significant relationship between the incidence of adverse drug events (ADEs), with unresolved PIMs with a relative risk value at 1.55 (95% CI 1.26:1.91), $p = 0.007$ and a correlation coefficient (r) of 0.332. Based on the results of univariate and bivariate statistical analysis, it can be concluded that there are still many PIMs occurring in the prescription of geriatric patients based on Beers and STOPP criteria and pharmacists have a large enough role to reduce the incidence of PIMs so that the prevalence of ADEs due to inappropriate use of the drug can be minimized at Regional General Hospital Dr. M. M. Dunda Gorontalo, Indonesia.

INTRODUCTION

Indonesia is a developing country with significant population growth. Globally, Indonesia has the fifth largest elderly population in the world (Central Bureau of Statistics, 2010). The population of the elderly in 2020–2050 is estimated at 11.34%–19.2% of the total population (HelpAge International, 2012). The increasing proportion of the elderly population requires special attention and treatment in health care so that the quality of life of the elderly or geriatric in Indonesia will improve. One way from the pharmaceutical side is to reduce the use of drugs in geriatrics that are classified as potentially inappropriate medications (PIMs) because they can increase the risk of adverse drug events (ADEs) (Alhawassi *et al.*, 2019; Holt *et al.*, 2010).

The pattern of major diseases in geriatrics is dominated by multiple morbidities whose prevalence will increase with age, especially in the elderly (Mahwati, 2014). Various pathological conditions, polypharmacy, or the use of multiple medications to treat a patient, decreased organ function and disease manifestations that are not unique to the geriatric disease, making handling in this group a separate challenge (Abdulah *et al.*, 2018; Negara *et al.*, 2016). Physiological changes related to aging causes changes in the pharmacokinetics and pharmacodynamics of the drug in geriatric patients.

In geriatric patients, it is not uncommon to find more than one chronic disease (multiple morbidities) by administering drugs that are classified as polypharmacy (Fialová *et al.*, 2005). The research in Ireland, Europe, and America shows that more than 40% of geriatric patients with chronic diseases receive more than five types of drugs simultaneously and more than is medically indicated (Naughton *et al.*, 2006). In Indonesia, based on the research on 100 elderly patients hospitalized in two hospitals in Yogyakarta, Indonesia in 2006–2007 showed 63% of prescriptions

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classified as polypharmacy and costs total unnecessary drug therapy is equivalent to The Indonesian rupiah 12.553.349, 00 (the US $ 1,046, 11), the polypharmacy is closely related to improper drug use (Rahmawati *et al.*, 2009). Therefore, the role of pharmacists in paying attention to the pharmacokinetics and pharmacodynamics of drugs in the elderly because at that age has four times the risk of experiencing ADEs due to improper treatment (Fauziah *et al.*, 2017; Primejdie *et al.*, 2016; Santos *et al.*, 2019).

Handling of potentially inappropriate medication incidents in geriatrics is needed to prevent ADEs, non-compliance, increased risk of cognitive impairment, increased risk of morbidities, hospitalization, and mortality. Some criteria that could be used explicitly in identifying the potential improper use of the drugs in geriatric patients include Beers and screening tool of older people's prescriptions (STOPP) criteria (Momin *et al.*, 2013). In this study, the analysis of PIMs will use these instruments because they both have the most common criteria used in the identification of the potential improper use of drugs in geriatric patients. In addition, the application is simple, easy to follow, the data obtained are reproducible, have strong evidence, are inexpensive, and can clearly identify potential inaccuracies in the drug use (Rumore and Vaidean, 2012).

This study aims to determine problems related to inappropriate use of drugs based on Beers criteria and STOPP criteria, to find out whether PIMs found based on Beers and STOPP criteria are followed up by the doctors responsible for medication-related, as well as the relationship between ADEs and PIMs found. Conducting this research is expected to reduce adverse events and drug interactions so that it can cause significant morbidities and mortality, especially in geriatric patients at Regional General Hospital Dr. M. M. Dunda Gorontalo.

MATERIALS AND METHODS

Study design and setting

The design in this study is an intervention study design by pharmacists to doctors using face-to-face interviews (Demik *et al.*, 2013; Francis *et al.*, 2014; Riordan *et al.*, 2016; Santos *et al.*, 2019). This research was conducted at the geriatric ward of Regional General Hospital Dr. M. M. Dunda Gorontalo, Indonesia from January to March 2018.

Sample size and sampling methods

The sampling technique was conducted in addition to the sum total of 123 subjects who are running the geriatric patients hospitalized in Regional General Hospital Dr. M. M. Dunda Gorontalo. The inclusion criteria are research subjects hospitalized patients with age more than 65 years, willing to participate in the research with the signed informed consent, and patients with doctors responsible for medication-related specialists in internal medicine. The design and procedure will be explained more about this research in Figure 1.

Data collection

Collecting data prospectively from January to March 2018. The study was conducted by taking the patient's medical record data according to the inclusion criteria, then the researcher conducted interviews with patients and/or patients' families who voluntarily agreed to participate in this study, as well as directly monitoring the patient's condition and treatment. The interventions given were carried out using face-to-face interviews by researchers (pharmacists) to doctors responsible for medication-related to discuss the existence of PIMs in the treatment of patients in this study.

Instrument

The health assessment sheet that includes data on patient age, sex, medical history, and history of previous drug use. Data is taken from the time the patient is admitted to the hospital, which is since the patient was moved from the emergency room to the inpatient unit for internal medicine until the patient was discharged by the doctor responsible for medication-related. Integrated patient development record sheet, patient medication record sheet, and pharmacy education in accordance with the standards in the Regional Hospital Dr. M. M. Dunda Gorontalo.

Ethical approval

This study has received ethics approval from the Ahmad Dahlan University Research Ethics Committee in Yogyakarta, which is proven by the issuance of an ethics-worthy certificate number 011710144.

Data analysis

Data analysis of research results was carried out univariate and bivariate. Univariate analysis was performed to determine the socio-demographic frequency distribution of subjects and the incidence of PIMs. The results of the identification of PIMs based on the 2015 Beers criteria and 2016 STOPP criteria, a bivariate analysis of ADEs that has been monitored during the inpatient at Dr. M. M. Dunda Gorontalo General Hospital. The statistical analysis used is the Chi-square test or Fisher's exact test (if the results of the 2×2 data table do not meet the Chi-squre rules), the aim is to determine the relationship between the PIMs events based on Beers criteria and STOPP criteria with ADEs events.

While the Spearman correlation analysis is used to know the direction of the correlation between the risk of ADEs and unresolved PIMs. Risk ratio (RR) analysis in this study was conducted with a confidence level of 95% to find out how effective the role of pharmacists and doctors in dealing with the incidence of PIMs in the prevention of ADEs in geriatric patients who were undergoing hospitalization in the internal medicine ward in Dr. M. M. Dunda Gorontalo General Hospital. If the RR = 1 indicates the same risk of ADEs if PIMs are resolved with PIMs that are not resolved, RR > 1 means the risk of experiencing ADEs is higher in the PIMs group that is not resolved, and if RR < 1 means the risk of ADEs incidence is lower in the group resolved PIMs.

RESULTS AND DISCUSSION

Socio-demographic characteristics of subjects

The total sample of 123 research subjects, namely, geriatric patients hospitalized in the ward in the General Hospital of Dr. M. M. Dunda Gorontalo who met the inclusion criteria became the study sample. Based on univariate descriptive statistical analysis of socio-demographic characteristics of research subjects in Table 1, most of the research subjects were female
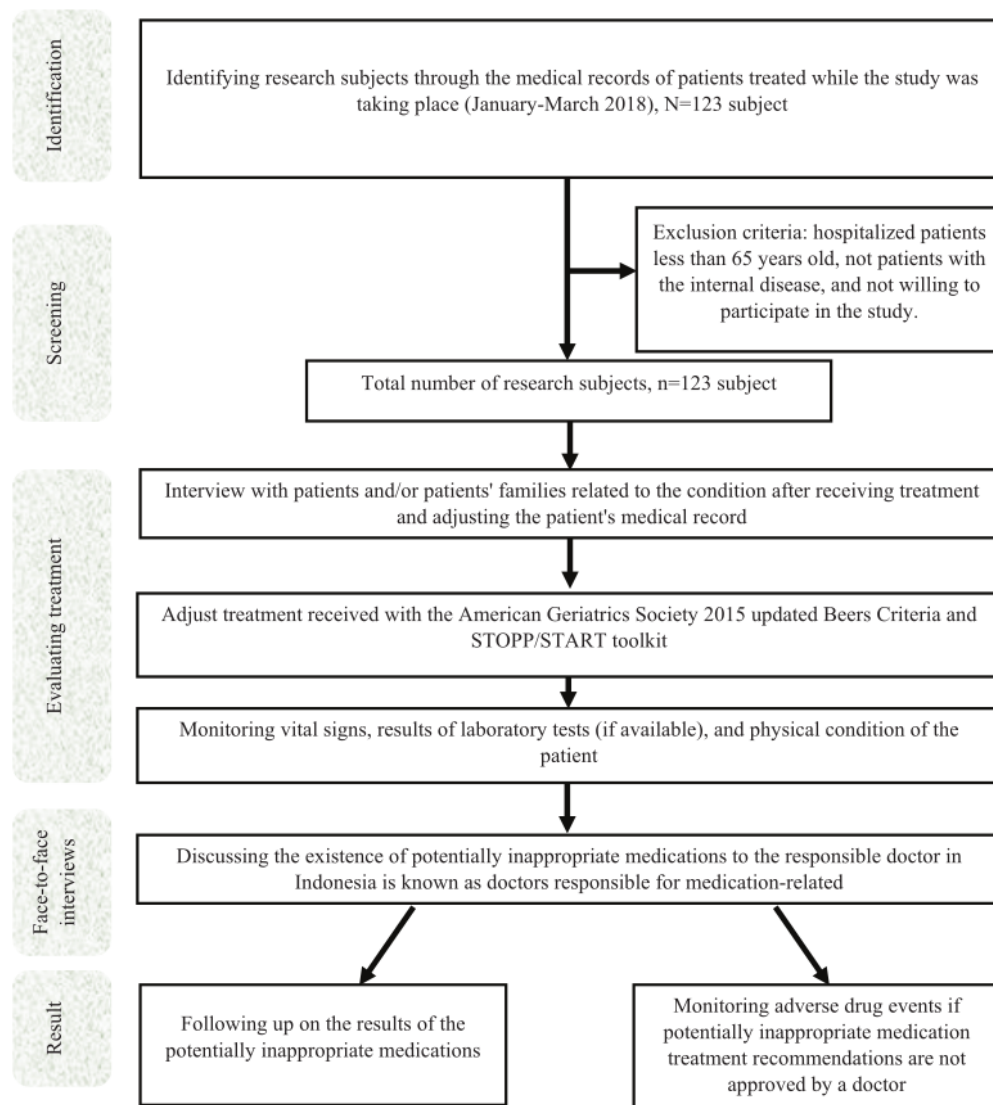
Figure 1. Research design and procedure concerning pharmacist intervention on PIMs in Indonesian geriatrics patients.

(54%), most age categories (84%) in the range of 65–74 years [X^- = 60.05, standard deviation (SD) = 6.65], and most subjects have a diagnosis of one until three diseases (57%). The length of stay for most subjects (85%) was 1–7 days (X^- = 5.44, SD = 2.79). The results of descriptive statistical analysis of the socio-demographic characteristics of research subjects can be seen fully in Table 1.

The highest prevalence of a geriatric disease in male patients is inseparable from poor lifestyles, such as smoking, consuming alcohol, eating patterns with unbalanced nutrition, obesity, and psychological factors. These risk factors occur twice as many in male patients, making it easier to trigger multiple morbidities in older men (Handajani *et al.*, 2010). Unlike the case

with multicenter and retrospective research results in Aragon and Catalonia, which show that gender differences in the prevalence and patterns of multiple morbidities in men and women over 65 years will have different characteristics. As many as 67.5% of the elderly population suffer from two or more chronic diseases, with details of 45.3% of women having one specific pattern of multiple morbidities, namely, diseases related to mechanics, whereas in men associated with cardiometabolic disease. The prevalence will affect age, life expectancy, and adequate health services (Abad-Díez *et al.*, 2014).

Similarly, with the results of the research in China indicates that vascular risk factors by age and patterns of gender distribution will give different results, elderly women will have

a higher prevalence of diabetes mellitus and hypertension were higher, while men are associated with heart disease and atrial fibrillation (Yao *et al.*, 2012). Therefore, prevention strategies for geriatric multiple morbidities in health services must emphasize the control of various risk factors based on age and sex. The optimization of health services in Indonesia has been pursued by the government with the existence of government health insurance issued by the Social Security Organizing Agency.

The Social Security Organizing Agency is the most dominant health insurance owned by the people of Indonesia, especially at the age of geriatrics. This is in line with data released by the Social Security Organizing Agency stating that as of May 18, 2018, around 75% (197.644.315 people) of Indonesia's population had been served by the National Health Insurance by the Social Security Organizing Agency. The Government of Indonesia through the Ministry of Health targets universal health coverage in Indonesia in 2019 to reach 95% or around 257.5 million people (Social Insurance Administration Organization, 2018). These conditions are expected to increase life expectancy and health quality, especially in geriatrics.

Tabel 1. Demographic characteristics of geriatric hospitalized patients at a government hospital in Indonesia, January–March 2018.

Characteristics	Frequency, Total subject n = 123
Sex, *n* (%)	
Male	67 (54%)
Female	56 (46%)
Age, *n* (%)	
65–74 years old	103 (84%)
75–90 years old	19 (15%)
>90 years old	1 (1%)
Number of diagnoses, *n* (%)	
1–3	70 (57%)
4–6	53 (43%)
Treatment duration, *n* (%)	
1–7 days	105 (85%)
>7 days	18 (15%)

PIMs based on Beers criteria (2015) and STOPP criteria (2016). Elderly or geriatric patients are not uncommon with more than one chronic disease (multiple morbidities). This situation has been prevalent in the population group of elderly patients, considering that in the course of their lives they can suffer from a disease that will tend to be chronic and be followed by other diseases, and so on. These conditions cause the risk of potential improper drug use. Therefore, it is a necessary collaboration of health workers to overcome this, especially in terms of pharmacy which plays a role related to the success of therapy.

The incidence of PIMs in geriatric patients hospitalized in the Regional General Hospital of MM Dunda Gorontalo identified the treatments received by subjects using Beers criteria and STOPP criteria. Drugs included in PIMs based on Beers Criteria results of this study can be seen further in Table 2 and Figure 1. Most of the PIMs identified based on Beers criteria in 2015 were the use of Non-steroidal Anti-inflammatory Drugs (NSAIDs) class and followed by the use of ranitidine injection in research subjects with decreased kidney function (GFR 10–50 ml per minute per 1.73 m^2.

The incidence of PIMs if based on STOPP criteria (Fig. 2) and (Table 2) found as much as 50% in the use of colchicine, which is one of the NSAIDs class to reduce pain in geriatric patients who experience gout. The use of colchicine in geriatric patients with chronic gout for more than 3 months is not recommended, especially in geriatric patients with decreased kidney function its use can be stopped. In addition to the use of NSAIDs, into PIMs based on STOPP criteria, it turns out that the use of hypertension drugs calcium channel blockers (CCB) and diuretics are still widely used in test subjects who incidentally are elderly, with a percentage of 16.67% each. Especially, the use of diltiazem in elderly patients with heart failure may worsen heart failure. The use of furosemide as a loop diuretic belongs to PIMs with a percentage of 16.67%; the condition is given to subjects with concurrent urinary incontinence. This can cause, exacerbate incontinence so that it is classified as PIMs.

Based on Table 2, medications that work on the central nervous system must also be used with extreme caution. This study still found the use of alprazolam which is a group of benzodiazepines with short-acting and diazepam (benzodiazepine

Table 2. List of PIMs based on Beers criteria & STOPP criteria and the pharmacist recommendations suggested to the physician.

| PIMs	Criteria	Pharmacist recommendation to physician
Ketorolac injection	Beers	Treatment is discontinued, recommending to replace with other analgesics such as metamizole injection.
Ranitidine injection	Beers	Therapy can be continued, but a dose adjustment is recommended to be 50 mg i.v daily.
Alprazolam tablet (oral)	Beers	Therapy can be continued, it is recommended to choose non-pharmacological therapy to treat insomnia.
Aspirin tablet (oral)	Beers	Therapy can be continued for primary protection against cardiovascular disease. Use it carefully while monitoring possible side effects such as bleeding and risk of gastrointestinal pain.
Diazepam tablet (oral)	Beers	Therapy can be continued, it is recommended to choose non-pharmacological therapy to treat insomnia.
Colchicine tablet (oral)	STOPP	Treatment is discontinued, recommending to replace with allopurinol if the results of the uric acid examination more than 8.5 mg/dl in elderly men and more than 8 mg/dl for older women.
Diltiazem tablet (oral)	STOPP	Treatment is discontinued in elderly patients with heart failure, this use may worsen heart failure.
Furosemide tablet (oral)	STOPP	Treatment is discontinued in elderly patients if used as monotherapy to treat hypertension and concurrent urinary incontinence. Excessive diuresis induced by furosemide may result in dehydration and reduction of blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients.
Loperamide tablet (oral)	STOPP	Therapy can be continued, geriatric patients who use two or more drugs with potential for anticholinergic adverse effects (ACB score greater than or equal to 4) (risk of increased anticholinergic toxicity). It also can cause gastrointestinal perforation.
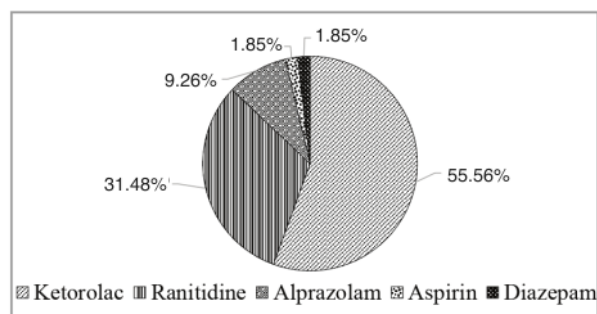
Figure 2. PIM based on Beers criteria.

Figure 3. PIM based on STOPP criteria.

long-acting). Based on Beers criteria in 2015, the use of these classes of drugs has been banned with the quality of evidence included in the moderate category. Giving benzodiazepines to geriatrics can increase the risk of cognitive impairment, delirium, falls, fractures, motor vehicles, eye cracks, and rapid eye movement sleep disorder in the use of long-acting benzodiazepines (American Geriatrics Society, 2015).

Besides the use of benzodiazepines, the use of anticholinergic drug burden (ACB) with a score of two, such as loperamide for geriatrics, is still found in some cases (16.67%). The use of ACB with the number of two or more ACB drugs simultaneously (score greater than or equal to four can lead to an increased risk of anticholinergic toxicity), therefore uses on the elderly must be very careful. The findings of PIMs based on Beers criteria and STOPP criteria, the researchers continued to monitor the incidence of ADEs on subjects that have been intervened by researchers to doctors responsible for medication-related to follow up on recommendations for strengthening PIMs that have been submitted verbal and written.

Adverse drug events due to potentially inappropriate medications

The results of monitoring of ADEs based on the administration of drugs classified as PIMs according to Beers and STOPP criteria (Fig. 3), it is known that ADEs that occur a lot and are not handled is from the administration of H2 receptor antagonists (ranitidine injection) which occurs in 64.29% of subjects. The use of ranitidine (H_2 receptor antagonists/H_2RAs) is commonly found in geriatric hospitalized patients, this use is not prohibited, but it must be noted that ranitidine is an ACB which can cause an increased risk of geriatrics in geriatric hospitalization. It is not prohibited, but it must be noted that ranitidine is an ACB which can cause an increased risk of anticholinergic toxicity in geriatrics when used together with ABC with a total score of greater than or equal to four, such as in conjunction with the use of antidepressants, atypical antipsychotics, incontinence drugs (oxybutynin), which have a score of three or concomitant administration with codeine, benzodiazepines, diuretics with an ACB score of one (National Health System, 2016).

The symptoms of central adverse effects of anticholinergic drugs may be delirium and mild alterations in memory skills. This condition is caused by the fact that ABC
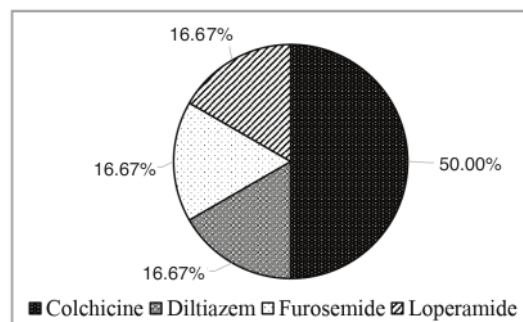
drugs are distributed to the brain and bind affinities to the cerebral muscarinic receptors. These drugs will easily cross the blood-brain barrier (BBB) by affecting the permeability of the BBB, causing adverse central effects (Kersten and Wyller, 2014). In addition, the effects can increase dementia due to the long-term use of anticholinergics drugs. The central nervous system, especially in the age of geriatrics, will be very sensitive to anticholinergic side effects because there has been a substantial decrease in cholinergic neurons or receptors contained in the brain (Arseneau and Braden, 2015). The adjustment of the dosage of H_2RAs in geriatric patients with decreased renal function is often overlooked, studies, a systematic review showed that the decrease in GFR would cause a significant increase area under the curve (AUC) and elimination half-life ($t_{1/2}$) of the serum drug concentration of H_2RAs (Anderson, 2019).

In this case, based on Figure 4 administration of ranitidine injection was given to subjects with glomerular filtration rate (GFR) 10–50 ml/minute/1.73 m^2 and some with GFR < 10 ml/minute/1.73 m^2, ADEs that occur are an increase in serum creatinine and blood urea nitrogen until the subject is declared able to be discharged from the hospital. Further examination is needed relating to the incidence of ADEs that can affect the decline in kidney function in geriatric patients who have experienced kidney failure during ranitidine injection. The condition is caused because the administration of ranitidine can give false results to an increase in serum creatinine. Further examination is needed relating to the symptoms and signs of hyperkalemia and monitor potassium levels. Patients with a GFR rate of 30 ml/minute/1.73 m^2 had an increase in AUC of 200%, and 300% when the GFR rate of 20 ml/minute/1.73 m^2 when compared with patients who had a GFR rate of more than 80 ml/minute/1.73 m^2. This condition is associated with decreased H_2RAs protection in the digestive tract (Manlucu, 2005). Therefore, dose adjustment is needed in patients with a decreased GFR rate to prevent adverse events. Giving 75% of dosage is needed in patients with a GFR rate of more than 50 ml/minute/1.73 m^2, 50% of doses in patients with a GFR rate of 10–50 ml/minute/1.73 m^2, and administration of 25% of doses in patients with kidney failure (GFR <10 ml/minute/1.73 m^2) (Baumgarten, 2011).

In addition to the use of ranitidine injection in geriatric patients with decreased kidney function, the administration of NSAIDs in this study with unaddressed PIMs caused ADEs in

28.57% of subjects and 7.14% of subjects experienced ADEs due to the administration of CCB-related PIMs that were not resolved in geriatric patients with heart failure. The use of NSAIDs includes aspirin with warfarin is not recommended for the geriatric age. Percentage of patients experiencing ADEs in DR. MM. Dunda Gorontalo Public Hospital due to the non-handling of PIMs can be seen in Figure 4. The use of acetaminophen, NSAIDs, or weak episodes can be administered with a low dose and short time, according to the pain severity and patient condition (McCarberg, 2013; National Health System, 2016). In this study, the most widely used is colchicine for the management of gout pain, the use of colchicine for 3 months in geriatrics is recommended to be stopped based on STOPP criteria, if geriatric patients do not have contraindications to the use of allopurinol as an alternative treatment to reduce levels of uric acid in the blood, with initial dose of 100 mg per day and monitoring of GFR (Bell *et al.*, 2013; National Health System, 2016).

Based on the 2015 Beers criteria and STOPP criteria of 2016, the use of NSAIDs, especially geriatrics with age more than 75 years can increase the risk of gastrointestinal bleeding or peptic ulcer, cardiovascular side effects, and induced nephrotoxicity (American Geriatrics Society, 2015; National Health System, 2016; Wongrakpanich *et al.*, 2017). Upper gastrointestinal ulcers, gross bleeding, or perforation can occur after administration of 3 until 6 months to 1 year (the long term used), except for concomitant use with parenteral corticosteroids, anticoagulants, or antiplatelet agents (American Geriatrics Society, 2015).

Effect of pharmacist intervention on PIMs in geriatric patients

The relationship between PIMs interventions by pharmacists that are received or not received by the doctors in the incidence of ADEs will be explained in Figure 3. The results show a significant relationship from the results of Fisher's exact test analysis between ADEs and PIMs based on Beers criteria (p-value = 0.024), with a positive correlation direction, meaning that if PIMs events based on Beers criteria are increasing or not resolved it will cause increased incidence of ADEs in geriatric patients ($r = 0.309$), with a RR value of 1.57 (95% CI 1.26: 1.97) which shows a clinically significant difference. The results of the analysis of the relationship between collaborative health professionals and the incidence of PIMs will be explained further in Table 3.

Table 4 shows no significant relationship between the incidence of PIMs based on STOPP criteria that are resolved or unresolved with ADEs on subjects in the internal ward of the Regional General Hospital Dr. M. M. Dunda Gorontalo. The results of the bivariate statistical analysis with Fisher's exact test showed an RR value of 1.33 (95% CI 0.76: 2.35, $p > 0.050$) which showed no significant relationship between the two variables.
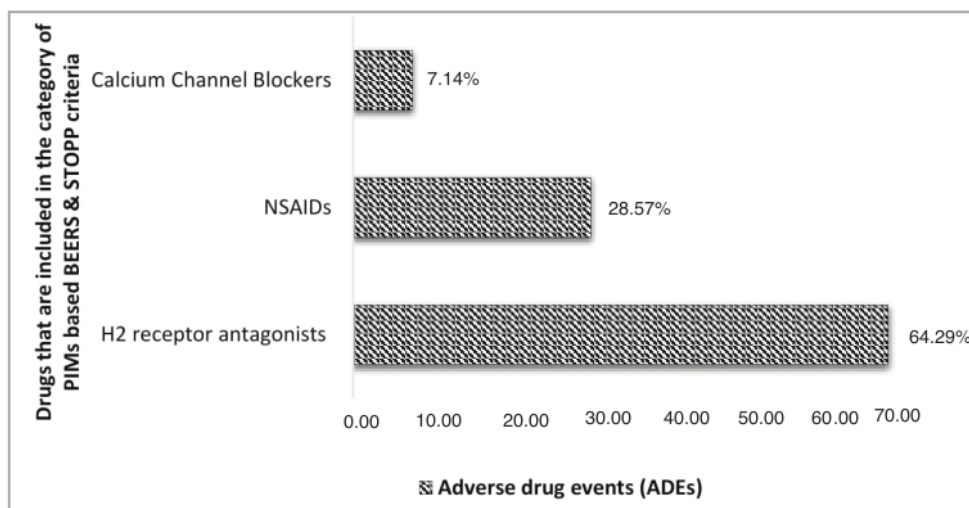

Figure 4. ADEs due to PIMs that are not resolved.

Tabel 3. The relationship between pharmacist interventions acceptance by physician and output monitoring of PIMs based on BEERs criteria.

ADEs	Result of PIMs ($n = 54$)		Statistical analyzes			
	Interventions not acceptance	Interventions acceptance	RR value	95% CI		p-value
				Lower	Upper	
Yes	10 (18.5%)	0 (0.0%)	1.57	1.26	1.97	0.024*
No	28 (51.9%)	16 (29.6%)				

n = number of samples undergo PIMs, RR = relative risk ratio, a = bivariate analysis results with Fisher's exact test, * = shows that there is a significant relationship between ADEs and recommendations for the occurrence of PIMs that are unresolved (p <0.050), ADEs = adverse drug event caused by unresolved potentially inappropriate medications.

Table 4. The relationship between pharmacist interventions acceptance by a physician and output monitoring of PIMs based on STOPP criteria.

ADEs	Result of PIMs (*n* = 54)		Statistical analyzes		
	Interventions not acceptance	Interventions acceptance	RR value	95% CI	
				Lower	Upper
Yes	4 (50.0%)	0 (0.0%)	1.33	0.76	2.35
No	3 (37.5%)	1 (12.5%)			

n = number of samples undergo PIMs, RR = relative risk ratio, *a* = result of bivariate analysis with Fisher's exact test, ADEs = adverse drug event caused by unresolved PIMs.

Based on the results of this study it can be seen that there are still many drug users that are classified as potentially inappropriate drugs in geriatric patients at the Regional General Hospital Dr. M. M. Dunda Gorontalo. This condition can cause ADE that must be prevented by collaboration between doctors and pharmacists. Therefore, education is needed for doctors and pharmacists at the undergraduate, graduate, and continuing education levels related to pharmacotherapy and pharmacodynamics in geriatrics with an emphasis on appropriate prescribes and is able to recognize PIMs. In addition, the pharmacist's task of delivering information on the drug and the patient's family or elderly patients (geriatrics) also informed of PIMs and risks that may arise. Open communication between patients, prescribers, and pharmacists are the key to success in the prevention and early detection of PIMs, so that the potential occurrence of ADE diversions due to the neglect of PIMs that causes an increase in mortality and morbidities in geriatric patients in health services can be suppressed as much as possible.

Limitations

This research still has some shortcomings that are expected to be used as suggestions or input for further research. The results of this study were not able to describe the ADE caused by the non-handling of PIMs through the identification of laboratory examination results, besides the lack of collaboration between health workers in overcoming the incidence of PIMs. The condition is caused due to the lack of information dissemination about the importance of identifying and addressing the use of drugs belonging mainly to geriatric PIMs.

CONCLUSION

The highest prescribing of geriatrics in the Regional General Hospital Dr. M. M. Dunda Gorontalo detected in the PIMs category based on Beers and STOPP criteria is the use of NSAIDs and H$_2$ receptor antagonists. In addition, the results of this study indicate that there is a significant relationship between ADEs with unresolved PIMs. The incidence of ADEs due to PIMs in hospitalized internal diseases, specifically for geriatric can be reduced by having face-to-face joint discussions based on the PIMs findings and the patient's condition between pharmacists and doctors (doctors responsible for medication-related) to decide on handling and preventing the occurrence of PIMs.

DATA AVAILABILITY

The datasets generated during or analyzed during the current study are available from the corresponding author or reasonable request.

CONFLICT OF INTEREST

The authors declared that they have no conflict of interests.

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