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| RESEARCH ARTICLE

Identification of Potential Drug Interactions in Osteoarthritis Patients at X Hospital, South Tangerang, 2019

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| ABSTRACT
Osteoarthritis (OA) is a degenerative joint disease characterized by progressive damage to joint cartilage and diarthrodial joint structures. In Indonesia, OA is the most common rheumatic disease. The causes of OA are multifactorial, such as obesity and genetic and racial factors, the risk of which rises at the age of 50 years. This study aimed to assess the therapeutic use of OA and drug interactions that occur in patients with osteoarthritis. This study used a cross-sectional design with prospective data collection through medical records of 60 OA patients in 2019 who met the inclusion and exclusion criteria. The Results showed that 87 drug interactions occurred in OA patients in this study; the other results were found to be a relationship between comorbidities and significant drug interactions (P value <0.05). The drug most widely interacted is ketorolac (45.71%), the interaction between paracetamol with ranitidine (15.71%), the interaction of ketorolac with ranitidine (12.86%), and ketorolac with metformin (11.43%). The most common mechanism of interaction is in pharmacodynamic (66.67%), and the pharmacokinetic interaction mechanism is 25.29%. The highest severity of interactions was found to be major (58.62%), and moderate severity was 25.3%. In conclusion, it was found that 87 drug interactions occurred in OA patients in this study. Other results were found to be a relationship between comorbidities and significant drug interactions. The drug most widely interacted with is Ketorolac, the interaction between par. The most interaction mechanism is pharmacodynamically. The most severe of interactions were found to be at the major severity level of paracetamol with ranitidine, the interaction of ketorolac with ranitidine, and ketorolac with metformin.

| KEYWORDS

Osteoarthritis, NSAID drugs, Drug interactions

| ARTICLE INFORMATION

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1. Introduction

Osteoarthritis (OA) is the most common musculoskeletal disorder and a primary cause of disability affecting diarthrodial joints. It is characterized by cartilage degradation and is accompanied by local inflammation and changes in the subchondral bone. Aging, excessive injuries, genetic predisposition, and obesity are crucial risk factors for the development and progression of OA (Chakraborty et al., 2022) (Goldring, 2012). OA is a degenerative joint disorder frequently observed in elderly patients, characterized by the degeneration of joint cartilage and surface hypertrophy, accompanied by stiffness after prolonged activities. Weight-bearing joints, such as the hips and knees, are commonly affected by osteoarthritis (Chakraborty et al., 2022) (Goldring, 2012).

Osteoarthritis poses a significant health concern with increasing life expectancy. According to WHO, in 1997, approximately 80% of OA patients experienced movement limitations, and 25% were unable to perform daily activities. The 2013 Riskesdas study indicates the highest prevalence of joint diseases, based on health professional diagnoses, occurring in Bali (19,3%), followed by Aceh (18,3%), West Java (17,5%), and Papua (15,4%). Meanwhile, the highest prevalence of joint diseases based on symptoms

occurs in East Nusa Tenggara (33,1%), followed by West Java (32,1%) and Bali (30%) (National Institute of Health Research and Development, 2013). The multifactorial nature of OA's causes increases its risk at the age of 50. Paracetamol is the first-line pharmacological therapy for OA patients, while topical analgesics are recommended for patients over 75 years old, with oral NSAIDs used if the effects are inadequate (Epstein, 2008; (Ganvir & Zambare, 2013) (Hochberg et al., 2012).

The treatment of OA aims to educate patients, reduce pain and stiffness, maintain cartilage function, improve joint mobility, and enhance the quality of life (Cao et al., 2020). Elderly OA patients often have comorbidities, leading them to receive multiple medications simultaneously (polypharmacy). Additionally, physiological changes in the elderly affect the pharmacokinetics and pharmacodynamics of drugs, increasing the likelihood of unwanted drug-related problems that may interfere with the expected healing outcomes (Mansjoer et al., 2000).

Studies in Central Java show a prevalence of knee osteoarthritis reaching 12,7% in males and 15,5% in females. Research in Southern Estonia in 2008 revealed that the most common OA scale found was scale 1 at 55,6%, while scale 2 was at 7,5%, and scale 3 was at 0,6% (Tamm et al., 2008). Another study in Surakarta in 2009 indicated that overweight seniors have a 4.9 times greater risk of osteoarthritis compared to non-overweight seniors, whether unilateral or bilateral (Mutiwara et al., 2016). Previous studies on OA in the elderly with various comorbidities imply the use of various medications, posing risks of drug interactions and side effects. This needs to be investigated through a study on Drug-Related Problems (DRPs), focusing on drug interactions in OA patients with diverse comorbidities. The aim of this research is to determine the impact of Drug-Related Problems (DRPs) on the treatment of Osteoarthritis concerning drug interactions at X Hospital in South Tangerang.

2. Method

This research was conducted at X Hospital in South Tangerang in 2019, using a cross-sectional design, and data collection was done prospectively. The sample in this study consisted of 60 OA patients who met the inclusion and exclusion criteria.

The inclusion criteria for this study were:

1. OA patients treated at X Hospital in South Tangerang,
2. Age >35 years, patients with complete medical records and patient status,
3. Patients using OA medications.

The exclusion criteria for this study were pregnant patients and patients with forced discharge status. Data analysis was performed using SPSS 20.

3. Result and Discussion

Table 1. Distribution of OA Patient Characteristics Based on Gender, Age, Osteoarthritis Scale, Comorbidities, and Medication Use at X Hospital in South Tangerang in 2019

No.	Patient Characteristics	Frek (n = 60)	(%)
	Gender		
1.	Male	25	42
	Female	35	58
	Age (Year)		
2.	35-59	54	90
	≥60	6	10
	Scale Osteoarthritis		
	Scale 2 (light)	5	8,34
3.	Scale 3 (currently)	29	48,33
	Scale 4 (heavy)	26	43,33
	Concomitant Diseases		
4.	< 5 Comorbidities	26	43,33
	≥ 5 Concomitant Diseases	34	56,67
	Drug use		
5.	**< 5 Drug**	23	38,67
	≥ 5 Drug	37	61.33

The table above presents the characteristics of osteoarthritis (OA) patients receiving outpatient care at X Hospital in South Tangerang in 2017. The majority of patients were female (58%). The research findings indicate that osteoarthritis (OA) occurs more frequently in female patients. This aligns with the results of the study by Price SA Wilson LM (2006), which found that OA is more prevalent in women than in men, particularly in women aged >50 years. OA is considered a normal aging process, as its incidence increases with age. The study by Srikanth VK et al. (2005) suggested that women are at a higher risk, attributing OA to estrogen levels. Srikanth VK also reported that women experience an increase in cartilage volume after the age of 50, indicating the potential influence of hormonal mediators. The increased prevalence of OA in postmenopausal women, associated with the presence of estrogen receptors (ER) in joint tissues, suggests a link between OA and ovarian function loss. This finding is consistent with the research conducted by Roman-Blas JA, Castaneda S, Largo R, Herrero B, and Gabriel (2009).

The majority of patients were aged between 35-59 years (90%), followed by those aged >60 years. Overall, below the age of 45, the frequency of osteoarthritis patients between males and females is relatively similar. However, after the age of 50 (post-menopause), the frequency of osteoarthritis is higher in females than in males. This indicates a hormonal role in osteoarthritis pathogenesis, consistent with the results of the study by Tjokroprawir (2015). The study by Sumual et al. (2013) showed that the prevalence of osteoarthritis in patients aged 61 years and above is 65%, indicating that elderly patients are more vulnerable to osteoarthritis due to physiological declines in organ function and the frequent occurrence of joint cartilage loss in the elderly.

Another characteristic of OA patients in this study is the presence of comorbidities in approximately 43% of patients, suggesting that nearly half of the OA patients in this study have comorbidities. This aligns with the findings of the research conducted by Rahmawati E et al. (2013) and a study in Puerto Rico (2014), which stated that OA patients are more likely to have comorbidities. From this research, the most prevalent comorbidity is Diabetes Mellitus, with complaints of OA in the hands and knees. This is due to glucose metabolism disorders that can affect OA, as chondrocytes in OA patients cannot adjust to GLUT-1, resulting in the accumulation of glucose and higher reactive oxygen species production (Mutiwara et al., 2016). Epidemiological studies indicate a positive correlation between OA and conditions affecting glucose metabolism, such as glucose imbalance, metabolic dysfunction, and diabetes mellitus (DM) (Hart et al., 1995). The relationship between DM and OA has been suggested in early epidemiological studies showing a higher incidence of radiographic OA, early onset, and more severe manifestations in diabetic patients (Courties & Sellam, 2016). The second most common comorbidity is hypertension, attributed to the elderly population suffering from OA, where reduced blood vessel elasticity at this age increases total peripheral resistance, leading to elevated blood pressure (Tjokroprawiro, 2015). OA patients generally experience stressors from OA-related pain complaints. The connection between stress and primary hypertension is suspected through sympathetic nerve activity via catecholamines and renin, which can intermittently increase blood pressure. Prolonged stress may lead to high blood pressure (Lestari, 2014).

Another characteristic is the pain scale, with the research findings showing that a moderate pain scale is the most prevalent in OA patients (48.3%), followed by a severe pain scale at 43.3%. According to Kellgren and Lawrence, OA assessment is divided into four scales: (1) doubtful, (2) mild, (3) moderate, and (4) severe. This study indicates that the most prevalent OA scale is scale 3 (moderate), followed by scale 4 (severe), aligning with the findings of the study by Lukum EM et al. (2012). In this study, most patients have OA with scales 3 and 4, indicating the progression of OA and perceived functional impairment in joints. When OA is at scale 1, the development is still in the early stages, and the perceived pain is very mild. Thus, with an early diagnosis, patients can treat OA at an earlier stage (Tamm et al., 2008).

Table 2. Frequency Distribution of Medication Use in Osteoarthritis Patients at X Hospital in South Tangerang in 2019

No.	Type of Medicine	Frekuensi	%
1.	Paracetamol (analgesic) NSAIDs	46	40,00
2.	Ketorolac	31	27,00
3.	Mefenamic acid	13	11,30
4.	Meloxicam	13	11,30
5.	Natrium Diklofenak	12	10.40
	Total	115	100

Table 2 above shows that the most commonly used medication is paracetamol (an analgesic). The management of OA therapy should be based on the severity of pain experienced by the patient. According to the ACR (American College of Rheumatology) guidelines, paracetamol therapy (maximum 4g/day) can be given for Osteoarthritis with mild to moderate symptoms. In this study, the most widely used therapy is paracetamol (first-line therapy) in OA patients. Its mechanism of action inhibits prostaglandin biosynthesis, addressing mild to moderate joint pain without causing gastric irritation (d'Arqom et al., 2022). Currently, paracetamol

therapy for OA is rarely used due to its low effectiveness and numerous side effects, including hepatotoxicity and kidney dysfunction.

Next, the NSAIDs group widely used in OA patients is ketorolac (27%), in addition to mefenamic acid, meloxicam, and sodium diclofenac. The Italian Journal of Medicine (2011) stated that NSAIDs selective to cyclooxygenase-2 (COX-2) enzymes pose a higher risk of causing hypertension. This can occur because COX-2 enzyme inhibition is associated with reduced prostaglandin E2 production. The lack of prostaglandin E2 can lead to a decrease in daily sodium excretion by 30-50%. In patients with normal kidney function, kidney adaptation will increase sodium excretion, maintaining sodium homeostasis in the body. However, in patients with chronic kidney disease, the adaptation process is disrupted. Within 1-2 weeks of NSAID consumption, water, and salt retention occurs in significant amounts, leading to edema, hypertension, and even heart failure in severe cases (Dong et al., 2018). The use of NSAIDs in hypertensive patients should be extremely careful as it can reduce the effectiveness of antihypertensive drugs, causing uncontrolled blood pressure. If NSAID use cannot be avoided, non-interacting antihypertensive drugs such as Calcium Channel Blockers are preferred, allowing NSAID used to be considered in patients (Zahra & Carolia, 2017).

The second most widely used OA therapy in this study is ketorolac (27%). Ketorolac's mechanism of action inhibits cyclooxygenase-1 and 2 enzymes (COX-1 and COX-2) needed in prostaglandin synthesis, which is a pain mediator in inflammation. Ketorolac has anti-inflammatory effects at doses used as analgesics. Prostaglandins produced by COX-1 act as gastric protectors by reducing hydrochloric acid secretion and increasing mucus production as a gastric barrier. They regulate platelet function and vascular rhythm. Prostaglandins produced by COX-2 (involved in inflammatory response) cause vasodilation of blood vessels, increased capillary permeability, white blood cell activation, edema, and pain stimulation. Ketorolac inhibits the production of prostaglandins produced by both COX-1 and COX-2, thus inhibiting pain. Additionally, side effects such as inflammation caused by its use can lead to gastric irritation, ulceration, and bleeding (Department of Health RI, 2014).

The third most widely used OA therapy in this study is mefenamic acid (11%). Some studies indicate that mefenamic acid is similar to other NSAIDs for chronic osteoarthritis, including the elderly, with the usual dose being 500 mg three times a day (Department of Health RI, 2014). Mefenamic acid more inhibits COX-1 than COX-2. COX-1 is an enzyme involved in the production of gastroprotective prostaglandins that promote blood flow to the stomach and produce bicarbonate, where inhibition of COX-1 can trigger gastrointestinal ulcers and increase the risk of bleeding. The use of mefenamic acid in elderly patients has a risk of more than 5 times the occurrence of gastrointestinal disorders, including damage to the gastrointestinal mucosa, inhibition of endogenous protective prostaglandins, increased bleeding time, and increased drug concentration in the blood. This can cause side effects such as impaired kidney function, leading to changes in glomerular filtration and blood pressure, ventricular dysfunction, and an increased risk of congestive heart failure. Therefore, the use of mefenamic acid, especially in the elderly, is not recommended (Loza, 2008).

Other NSAIDs used for OA therapy in this study include meloxicam (11%). Meloxicam's mechanism of action inhibits prostaglandin synthesis, a mediator of inflammation. Meloxicam also inhibits COX-2 ten times more than COX-1. Since OA patients require long-term therapy, meloxicam is chosen as a safer option with the hope of suppressing gastrointestinal disturbances (Waranugraha et al., 2010).

Another NSAID used for OA therapy in this study is sodium diclofenac. Its mechanism of action as a pain reliever is almost the same as other NSAIDs. However, it has more side effects than meloxicam. Diclofenac is used less frequently because it can accumulate well in synovial fluid and has a longer therapeutic effect duration in synovial fluid compared to its plasma half-life (Amrulloh & Utami, 2016).

Table 3. Distribution of Potential Gastrointestinal Drug Interactions Based on Interaction Mechanism and Severity Level in Osteoarthritis Patients at X Hospital in South Tangerang in 2019

No.	Osteoarthritis Medicine	Interacting drugs	Interaction Mechanisms	Severity Level	Frequency Interaction	Effects of Makanism
1.	Ketorolac	Ranitidine	Farmakokinetik	Minor	9	Changing the disposition of NSAIDs may increase plasma concentrations. Inhibits metabolism, changes gastric PH, reduces absorption & reduces urine elimination.

2.	Ketorolak	Dexametason	Farmakodinamik	Moderate	1	Increases potential for gastrointestinal toxicity. Swelling, bleeding, ulceration, perforation
3.	Ketorolak	Asam mefenamat	Farmakodinamik	Mayor	2	Gastrointestinal inflammation, bleeding, and perforation. Increases toxicity and impaired kidney function
4.	Ketorolac	Diclofenac	Farmakodinamik	Mayor	2	Gastrointestinal inflammation, bleeding, and perforation. Impaired kidney function
5.	Ketorolac	Meloxicam	Farmakodinamik	Mayor	2	Gastrointestinal toxicity, nausea, vomiting, abdominal pain, reduced urine elimination
6.	As. Mefenamat	Ranitidine	Farmakokinetik	Minor	6	Inhibits metabolism, changes gastric PH, reduces absorption & reduces urine elimination.
7.	Diclofenac	Ranitidine	Farmakokinetik	Minor	2	Inhibits metabolism, changes gastric PH, reduces absorption & reduces urine elimination.
	Total				24	

Table 3 above shows there are 24 potential gastrointestinal drug interactions in OA, with the most frequent interaction mechanism being pharmacokinetic, occurring 17 times (70.83%) among potential gastrointestinal interactions, with a severity level of 25% among those with potential gastrointestinal effects. The most common drug interaction is between Ketorolac and Ranitidine (37.5%), followed by Mefenamic Acid and Ranitidine (25%). The interaction between Ketorolac and the Ranitidine group (H2 receptor antagonist) occurs because ranitidine inhibits gastric acid secretion by competing with histamine to bind to the H2 receptors located on the parietal cell's vasolateral membrane; this binding is reversible.

The use of NSAIDs in OA patients leads to gastropathy through two mechanisms: local and systemic. The systemic mechanism occurs through the inhibition of prostaglandin synthesis, while the local mechanism results from topical disturbances by NSAIDs. This topical disturbance causes a series of changes to the mucosal surface, leading to H+ and pepsin ions damaging the epithelium (Del Valle, 2005). Meanwhile, H2 receptor antagonists have a therapeutic effect by inhibiting gastric acid secretion, reducing the amount of damaging substances in the lumen, and reducing topical disturbances in the stomach (Valle, 2005).

Interactions between Ketorolac and Ranitidine, Mefenamic Acid, and Ranitidine and Diclofenac with Ranitidine, Ketorolac, Mefenamic Acid, and Diclofenac are NSAID drugs whose mechanism of action causes disturbances in the stomach and increases gastric acid. To reduce this gastric acid in OA patients, ranitidine is given, which works by reducing excess gastric acid. When given concurrently with ketorolac, mefenamic acid, or diclofenac, the therapeutic effect of mefenamic acid or diclofenac as an analgesic may be disrupted.

Administration of ketorolac with diclofenac, ketorolac with mefenamic acid, and ketorolac with meloxicam in OA patients will further increase gastrointestinal disturbances. In OA patients, if ketorolac is given with dexamethasone, it can cause gastrointestinal toxicity, ulcers, and even perforation.

Table 4. Distribution of Potential Nephrotoxic Drug Interactions and Kidney Function Impairments Based on Interaction Mechanism and Severity Level in Osteoarthritis Patients at X Hospital in South Tangerang in 2019

No.	Osteoarthritis Medicine	Interacting drugs	Interaction Mechanisms	Severity of interaction	Frequency. Interaction	Effects of Makanism interaction
1.	Ketorolac	Metformin	Farmakodinamik	Major	4	Increases lactic acidosis and causes impaired kidney function (decreased kidney function).
2.	Ketorolak	Diclopenac	Farmakodinamik	Major	3	Increased serious side effects of NSAIDs include kidney failure, inflammation, bleeding, ulceration and gastro intestinal perforation.
3.	Ketorolak	Mefenamic acid	Farmakodinamik	Major	1	Increases toxicity and results in kidney failure
4.	Ketorolac	Spironolacton	Unknown	Moderate	1	Increases serum potassium, which affects kidney function, causing sodium and water retention, which results in an increased risk of congestive heart failure
5.	Ketorolac	Amlodipin	Unknown	Moderate	4	Ketorolac inhibits cyclooxygenase and, reduces the antihypertensive effect of amlodipine and worsens renal function (Medscape 2018)
6.	Ketorolac	Captopril	Unknown	Moderate	4	Ketorolac inhibits cyclooxygenase and reduces the antihypertensive effect of captopril and worsens renal function.
7.	Ketorolac	Gentamicin	Unknown	Moderate	4	Can cause nephrotoxic effects and cause kidney damage, gentamicin inhibits the action of ketorolac.
6.	Gentamicin	Cepoferazon	Unknown	Moderate	1	Increasing the risk of nephrotoxicity can cause kidney damage, especially in the elderly
		Cefotaxim	Unknown	Moderate	3	Increasing the risk of nephrotoxicity can

						cause kidney damage, especially in the elderly.
		Seftriakson	Unknown	Moderate	2	Increasing the risk of nephrotoxicity can cause kidney damage, especially in the elderly.
	Total				27	

Table 4 above indicates there are 27 potential nephrotoxic drug interactions and kidney function impairments in OA, with the pharmacodynamic mechanism occurring 8 times (29.62%) and the severity level of major interactions being 29.62%. The research results show that the interaction of ketorolac, both with other NSAIDs (mefenamic acid and diclofenac) and with antihypertensive drugs (amlodipine, captopril, and spironolactone), as well as with OAD (antidiabetic drugs) such as metformin when used concurrently, can have detrimental effects on patients, causing kidney function impairment. Interactions between NSAIDs and OADs, like metformin, occur through the mechanism of protein binding displacement. NSAIDs and OADs are metabolized through CYP2C9; because they are metabolized by the same cytochrome, NSAIDs have a higher affinity for CYP2C9, leading to an increase in the concentration of OADs (metformin, glibenclamide, glimepiride, and gliclazide) in free conditions (not bound to plasma proteins). This drug interaction occurs through an additive mechanism and has the potential to cause hypoglycemia. The interaction between NSAIDs and metformin can lead to the formation of lactic acidosis, which can cause kidney function impairment (Permana Sari et al., 2008).

Ketorolac belongs to the NSAID drug class with a mechanism of inhibiting prostacyclin synthesis, causing vasoconstriction of the afferent arterioles of the kidneys and blocking prostaglandin synthesis by inhibiting the enzymes COX-1 and COX-2. In the kidneys, prostaglandin and COX-1 can dilate the afferent arterioles, maintaining intraglomerular pressure and glomerular filtration rate. When renal blood flow is reduced, and renal prostaglandins are inhibited by NSAIDs, blood flow is disrupted, leading to impaired kidney function (Cao et al., 2020).

Ketorolac with captopril, a drug belonging to the Angiotensin Converting Enzyme Inhibitor (ACE-I) class, works by inhibiting Angiotensin I into Angiotensin II, causing dilation of the afferent arterioles and reducing aldosterone secretion in the adrenal cortex. This vasodilation causes a hemodynamic decrease in the glomerular filtration rate, leading to reduced blood pressure ultimately affecting kidney function (Lapi et al., 2013). The research results indicate that when NSAIDs and ACEIs are used together, it causes an interaction leading to afferent stimulation becoming vasoconstriction, posing a risk of kidney impairment, as stated in the Stokley drug interaction (van Mil, 2016).

Table 4 above shows interactions between NSAIDs (ketorolac) and diuretics (spironolactone), consistent with previous research. A meta-analysis indicates that NSAIDs can increase blood pressure by an average of 3.3 mmHg and 5 mmHg in hypertensive patients. In hypertensive patients taking antihypertensive drugs and NSAIDs, the mean arterial pressure may increase by 6 mmHg. This suggests that administering NSAIDs to hypertensive patients will decrease the effectiveness of the antihypertensive drugs consumed (Fanelli et al., 2017). Other side effects include hyponatremia and hyperkalemia, especially in elderly patients (Fournier et al., 2014).

Interactions between Ketorolac, Diclofenac, and Ketorolac with Mefenamic Acid occur because these drugs belong to the NSAID class, causing an increase in serious NSAID side effects, including kidney failure, inflammation, bleeding, gastrointestinal ulceration, and perforation.

Another drug interaction occurring in this study is the administration of gentamicin with cephalosporins (Cepoferazon, Cefotaxim, and Seftriakson), which can lead to nephrotoxicity and kidney damage, especially in the elderly.

Table 5. Distribution of Other OA Drug Interactions Based on Interaction Mechanism and Severity Level in Osteoarthritis Patients at X Hospital in South Tangerang in 2019

No	Osteoarthritis Medicine	Interacting drugs	Interaction Mechanisms	Severity Level	Frequency Interaction	Effects of Makanism
1.	Diclopenac	Glimepirid	Unknown	Moderate	5	Increases the effect of glimepiride at risk of hypoglycemia.

						It is necessary to monitor blood glucose levels.
2.	Diclopenac	Spironolacton	Farmako dinamik	Moderate	1	Inhibition of prostaglandins causes uncontrolled pressor activity, which risks increasing blood pressure. Blood pressure monitoring is necessary.
3.	Paracetamol	Ranitidin	Unknown	Minor	11	Potentially hepatotoxic. Liver function monitoring is necessary.
4.	Mefenamic acid	Metformin	Unknown	Moderate	5	Increases the effect of metformin at risk of hypoglycemia. It is necessary to monitor blood glucose levels.
5.	Mefenamic acid	Glibenclamid	Unknown	Moderate	6	Increases the effect of glibenclamide, risk of hypoglycemia. It is necessary to monitor blood glucose levels.
6.	Metformin	Inssulin Aspart	Farmakodinamik	Moderate	2	Potential for hypoglycemia It is necessary to monitor blood glucose levels.
7.	Spironolacton	Captopril	Farmakodinamik	Major	4	Increasing the risk of hyperkalemia, ACE inhibition causes aldosterone secretion to decrease, which will lower blood pressure. Need to monitor blood pressure.
	Total				34	

From Table 5 above, there is an interaction between NSAIDs (mefenamic acid) and Metformin, as well as Glibenclamide. NSAIDs work by inhibiting prostaglandins through the inhibition of the cyclooxygenase enzyme, while Metformin and Glibenclamide work by coating the stomach, pepsin, and bile. The use of Metformin and Glibenclamide can cause a decrease in the effectiveness of NSAIDs because it can inhibit the absorption of NSAIDs. This result is consistent with previous research findings (Permana Sari et al., 2008).

Table 6. Distribution of Drug Interactions in Osteoarthritis Patients based on Interaction Mechanisms at X Hospital in South Tangerang in 2019

No.	Interaction Mechanisms	Frequency	%
1.	Pharmacodynamics	22	25,89
2.	Pharmacokinetics	17	20,00
3.	Unknown	46	54,11
	Total	85	100.00

From Table 6 above, it can be seen that out of 85 drug interaction incidents, 25.89% involve pharmacodynamic mechanisms, and nearly 20.00% involve pharmacokinetic mechanisms. Pharmacodynamic interactions occur between drugs that affect the same receptor system, site of action, or physiological system, resulting in additive, synergistic, or antagonistic effects without changes in drug plasma levels. Meanwhile, pharmacokinetic drug interactions occur when ≥ 2 types of drugs interact, causing an increase or decrease in plasma levels of both drugs, leading to increased toxicity or decreased effectiveness of the drug.

Table 7. Distribution of Drug Interactions in Osteoarthritis Patients based on the Severity Level of Drug Interactions at X Hospital in South Tangerang in 2019

No.	Severity Level	Frekuency	%
1.	Minor (Light)	28	32,94
2.	Moderate (Currently)	39	45,88
3.	Major (Heavy)	18	21,18
	Total	85	100.00

Based on Tables 3, 4, and 5, it is concluded in Table 6 that the severity level of drug interactions in osteoarthritis patients at X Hospital in South Tangerang in 2019 shows that the most common severity level is moderate (58.62%), followed by minor severity (32.94%).

In terms of the severity level of drug interactions, according to the research results, the most frequent severity level is moderate/moderate (45.88%). Moderate severity is a level of interaction that is sought to be prevented and addressed. If the drug interaction produced is more dangerous than its benefits, it is advisable to use alternative drugs. The next most frequent severity level in this study is the major severity level at approximately 21.18%. This severity level needs to be prevented and addressed because its potential effects can endanger life or cause permanent damage/disability. To improve the quality of osteoarthritis patient treatment, the use of drugs that may result in major and moderate interactions should be avoided when used simultaneously. This is to prevent the risk of harmful interactions for patients and to minimize unwanted drug interactions so that therapy goals can be achieved.

Based on the results of bivariate analysis, there is a relationship between comorbidities and drug interactions, as indicated by the obtained P-value (significant) of P=0.000, which is less than 0.05 (P<0.05), indicating a significant relationship between comorbidities and drug interactions.

4. Conclusion

From the research results, the following conclusions can be drawn:

1. A total of 85 drug interactions were found in OA patients at X Hospital in South Jakarta in 2019. The most interacting drug was Ketorolac (45.71%), followed by interactions between paracetamol and ranitidine (15.71%), interactions between ketorolac and ranitidine (12.86%), and ketorolac with metformin (11.43%).
2. The mechanism of interaction is 25.89% pharmacodynamic and 20.00% pharmacokinetic.
3. There is a significant relationship between comorbidities and drug interactions, indicated by a P-value <0.05.
4. A moderate severity level was found in 45.88%, and the major severity level was 21.18%.

Drug interactions potentially causing nephrotoxicity and kidney dysfunction occurred 27 times (31.76%). Drug interactions potentially causing gastrointestinal problems occurred 24 times (28.23%).

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