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Patterns Of Drug Use In Patients With Knee Osteoarthritis At The Bina Sehat Jember Hospital

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ABSTRACT

Osteoarthritis is a degenerative disease characterized by progressive damage to joint cartilage. The prevalence of osteoarthritis will continue to increase and continue as the population and age increase. Cases of knee osteoarthritis are more common than other types of osteoarthritis. The high prevalence of osteoarthritis will have implications for the high treatment regimen given to patients. Irrational use of drugs can lead to drug-related problems (DRPs). This study used a descriptive design. The sample in this study were knee osteoarthritis patients at the Bina Sehat Jember Hospital. The sampling technique used is purposive sampling. The data in this study used secondary data from patient medical records for the period January 2020 - April 2021. A total of 3 knee osteoarthritis patients have the potential to experience drug-related problems in the drug interaction category.

Keywords: drug interaction, drug-related problems, knee osteoarthritis, pharmacological therapy.

INTRODUCTION

Osteoarthritis is a degenerative disease characterized by progressive damage to joint cartilage and is the most common joint disorder. Osteoarthritis can affect the knees, hips, hands, spine, and feet. Conditions caused by this disease are joint stiffness, deformity, and pain which are often complained of by patients with osteoarthritis because it causes a very uncomfortable feeling when used to move (Setiati et al., 2014). The number of symptoms and bone or joint damage in osteoarthritis makes this disease very important to pay attention to, especially in the elderly. Osteoarthritis generally occurs after 40-50 years (Palazzo et al., 2016). Based on national data from the Research and Development Agency of the Ministry of Health of the Republic of Indonesia in

Basic Health Research in 2013, the prevalence of osteoarthritis in Indonesia is 24.7%. The prevalence of osteoarthritis in East Java is higher, at 26.9% (Riskesdas, 2013). The prevalence of osteoarthritis will continue to increase and continue with population and age (Wittenauer et al., 2013). Cases of knee osteoarthritis are more common than other types of osteoarthritis (Wijaya, 2018).

The high prevalence of osteoarthritis will have implications for the high treatment regimen given to patients. Management of osteoarthritis is divided into non-pharmacological therapy, pharmacological therapy, and surgical therapy. Non-pharmacological therapy includes education, physical therapy, rehabilitation, and weight loss. At the same time, pharmacological therapy is a therapy that uses drugs such as non-opioid oral analgesics, topical analgesics, NSAIDs, and others (Soeroso et al., 2014). Doctors can do surgical therapy if pharmacological therapy has been given but does not reduce symptoms (Alwi et al., 2016). Management carried out on osteoarthritis patients is primarily palliative, which focuses on relieving pain symptoms so that pain relievers play a significant role (Gupta et al., 2018). One of the pain relievers often used in osteoarthritis patients is NSAIDs. Giving NSAIDs therapy in the long term in osteoarthritis patients can cause many side effects (Lovell & Ernst, 2017).

Generally, therapy for osteoarthritis patients is not monotherapy but uses several types of drugs, including acetaminophen, NSAIDs, to opioid derivatives. The use of an antiulcer such as pantoprazole can also be combined with NSAIDs to avoid the side effects of NSAIDs that can cause problems in the gastrointestinal system. One of the NSAIDs, namely the COX-2 group, is often used to prevent side effects on the gastrointestinal system, but this group has side effects on the cardiovascular system. Because of the various ways of use and the impact of administering these multiple drugs, it is necessary to monitor the pattern of drug use from time to time to rationalize drug use (Gupta et al., 2018).

Irrational use of drugs can lead to drug-related problems (DRPs). Drug-related problems are related to drug selection patterns, drug dosing discrepancies, duration of drug use, many medications prescribed, inappropriate drug combinations, and drug use behavior in patients (Pharmaceutical Care Network Europe Association, 2019). Comorbidities in the patient can also cause drug-related problems (Fathnin et al., 2020). The more treatment regimens are given, the more side effects and the possibility of drug interactions will be pretty high. In addition, the treatment time given is also not in a short time but over a long period, years, and even a lifetime.

The results of previous studies showed that treatment in knee osteoarthritis patients has the potential for drug-related problems, namely drug interactions (Khotib et al., 2019). Similar research results were also obtained from research conducted by Muslim et al. (2018) that there are also incidents of drug-related problems, namely inappropriate doses and side effects of drugs (Muslim et al., 2018). Based on a preliminary study conducted at the Bina Sehat Jember Hospital, the number of patients with knee osteoarthritis has continued to increase in the last five years. This study aims to determine the demographic characteristics of knee osteoarthritis patients, the treatment given to knee osteoarthritis patients, and the potential for drug-related problems in knee osteoarthritis patients at

the Internal Medicine Clinic, Orthopedic Clinic, and Neurology Clinic at the Bina Sehat Jember Hospital.

METHODS

This study used a descriptive design. This research was conducted in June – July 2021 at the Bina Sehat Jember Hospital. The population in this study was all medical records of knee osteoarthritis patients at the Internal Medicine Clinic, Orthopedic Clinic, and Neurology Clinic at the Bina Sehat Jember Hospital, for the period January 2020 - April 2021. The sample in this study amounted to 97 patients. This research was conducted after obtaining ethical approval number 1517/H25.1.11/KE/2021 from the Health Research Ethics Committee from the Faculty of Medicine, University of Jember.

RESULTS AND DISCUSSION

Knee osteoarthritis patients who met the inclusion and exclusion criteria from research conducted at the Internal Medicine Clinic, Orthopedic Clinic, and Neurology Clinic at Bina Sehat Jember Hospital for January 2020 - April 2021 were taken as many as possible 97 patients. Characteristics of knee osteoarthritis patients in this study are shown in Table 1.

Table 1. Characteristics of knee osteoarthritis patients at the Bina Sehat Jember Hospital

Patient Characteristics	Category	Frequency and Percentage
Sex	Male	24 (24,7%)
	Female	73 (75,3%)
Age in years	<40	3 (3,1%)
	40-50	19 (19,6%)
	51-60	39 (40,2%)
	>60	36 (37,1%)
Comorbidities	Yes	5 (5,2%)
	No	92 (94,8%)

In this study, the number of knee osteoarthritis patients at the Bina Sehat Jember Hospital was mostly female, with 73 patients (75.3%). The age of most knee osteoarthritis patients in this study was the age range of 51-60 years. The mean age of knee osteoarthritis patients in this study was 57 years. The age distribution diagram of knee osteoarthritis patients in this study can be seen in Figure 1.

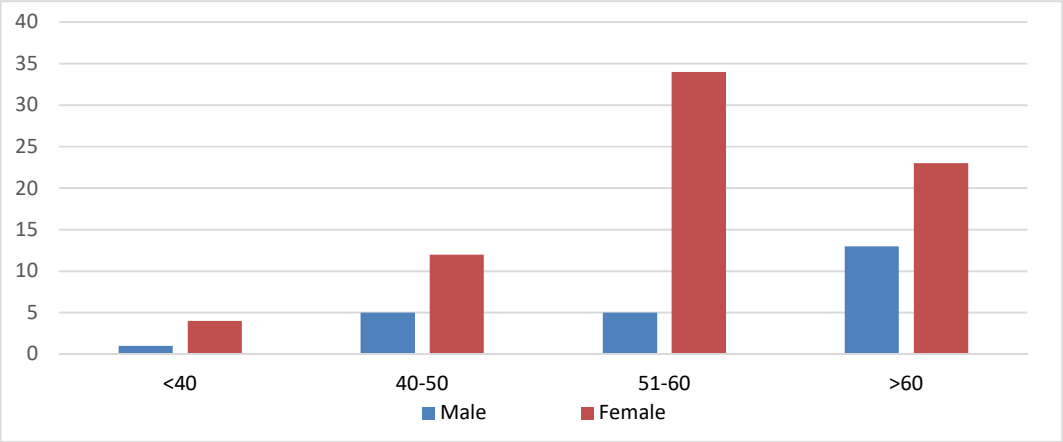

Figure 1. Age distribution diagram of knee osteoarthritis patients

Knee osteoarthritis patients who did not have comorbidities were 92 patients. The number of osteoarthritis patients who had comorbidities was five patients. A total of three knee osteoarthritis patients had one comorbidity, namely diabetes mellitus, hypertensive heart disease, and chronic kidney failure. Two knee osteoarthritis patients had two comorbidities. The first patient had comorbidities of diabetes mellitus and hypertensive heart disease, while the second patient had comorbidities of dyslipidemia and cholelithiasis.

The drug dosage regimen given to knee osteoarthritis patients in this study was adjusted to the existing reference, namely the MIMS Drug Reference. Administration of drug therapy to knee osteoarthritis patients at Internal Medicine Clinic, Orthopedic Clinic, and Neurology Clinic in Bina Sehat Jember Hospital period January 2020 – April 2021 in this study are presented in Table 2. The route of drug administration to all knee osteoarthritis patients in this study was oral. The most widely used drug group was NSAIDs in 90 patients (50.9%). In addition to NSAIDs, there was also quite a lot of drug use, namely Symptomatic Slow Acting Drugs for Osteoarthritis (SYSADOA), as many as 62 patients (34.9%). In addition to NSAIDs and SYSADOA, three patients (1.7%), GABA analogs (6.2%), and vitamin D analogs were found in 11 patients (6.2%).

The administration of therapy based on the number of drugs given in this study was divided into monotherapy and combination therapy, as shown in Table 3. Patients who received this type of combination therapy were 75 patients (77.4%), while the kind of monotherapy was much less, namely 22 patients (22.6%). Combination therapy between meloxicam and glucosamine sulfate is the most commonly used combination therapy for other drugs. Knee osteoarthritis patients generally receive more than one drug regimen. The more drug regimens are given, the greater the risk of drug-related

problems. Drug-related problems in this study are included in the category of interactions between drugs. In this study, drug interactions occurred in patients receiving therapy other than drugs for osteoarthritis, namely glimepiride, candesartan, and valsartan. The incidence of drug interactions in this study is listed in Table 4.

The highest distribution of knee osteoarthritis patients by gender in this study was female, with as many as 73 patients (75.3%). The number of male patients was much less, namely as many as 24 patients (24.7%). The number of female patients in this study increased dramatically in the age range of 51-60 years. This is in line with the existing data that the prevalence of osteoarthritis at the age of more than 50 years is increasing in women (Suyasa & Setiawan, 2016). The increasing incidence of osteoarthritis in women occurs around the time of menopause. Several studies suspect that the role of the hormone estrogen is closely related to the incidence of osteoarthritis in women (Contartese et al., 2020).

The highest number of knee osteoarthritis patients by age is in the range of 51-60 years. This is in line with the existing data that the prevalence of osteoarthritis will increase at the age of 40-60 years (Wijaya, 2018). At the time of aging, chondrocytes become wider, lysosomal enzyme activity increases, and are no longer produced. Proteoglycans decreased in mass and size. In addition, the concentration of chondroitin sulfate decreases, and the concentration of keratin sulfate increases. Then there was also an increase in protein content and a reduction in water content. These changes can result in a decrease in the solubility and flexibility of cartilage. Osteoarthritis can result in macro and micro changes. Macro changes include softening, fibrillation, and erosion, while micro-changes include cartilage degradation and failure to repair (Sherman et al., 2012).

The number of knee osteoarthritis patients who did not have comorbidities was 92, while the number of patients with comorbidities was five. Osteoarthritis patients generally have comorbidities, but only a small number of patients had comorbidities in this study. This happens because patients with these comorbidities do not meet the inclusion and exclusion criteria. In this study, comorbidities suffered by knee osteoarthritis patients were diabetes mellitus, hypertensive heart disease, dyslipidemia, chronic kidney failure, and cholelithiasis. Diabetes, hypertension, and dyslipidemia are metabolic diseases that can be risk factors for osteoarthritis (Piva et al., 2015). There is no relationship between cholelithiasis and chronic kidney failure with osteoarthritis. However, treatment in every osteoarthritis patient should be assessed and considered, especially if certain conditions such as chronic kidney disease, cardiovascular disease, risk of gastrointestinal bleeding, or other comorbidities that may impact the risk of side effects from certain pharmacological agents (Kolasinski et al., 2020).

Diabetes mellitus is caused by disturbances in glucose metabolism in the body, leading to the progression of osteoarthritis. Normal chondrocytes can adapt to variations in extracellular glucose concentrations or modulate glucose transporter-1. In contrast, chondrocytes in osteoarthritis patients

cannot regulate glucose transporter-1, resulting in glucose accumulation and producing higher amounts of ROS and other free radicals. These pathogenic mechanisms can lead to the development of osteoarthritis (Nieves-Plaza et al., 2013). Hypertension can influence the development of osteoarthritis through constriction of blood vessels and subchondral ischemia, which will initiate cartilage degradation (Piva et al., 2015). Hypertension can cause blood vessels to become narrowed and obstruct blood circulation. Therefore, the blockage of the supply of blood and nutrients to the cartilage can be the beginning of cartilage damage. If this problem is left long enough, it will cause osteoarthritis (Verma et al., 2017). Research conducted by Jianping et al. (2020) proved a relationship between dyslipidemia and osteoarthritis. The reduction of high-density lipoprotein cholesterol plays a vital role in the pathogenesis of osteoarthritis. High LDL levels can stimulate synovial inflammation. Low-density lipoproteins may be involved in the development of osteoarthritis through stimulation of synovial cells and chondrocytes (Xiong et al., 2020).

Based on the medical records that the researchers took, all data on drug administration to knee osteoarthritis patients at the Bina Sehat Jember Hospital were in accordance with the indications. The drug dosage regimen given to knee osteoarthritis patients at the Bina Sehat Jember Hospital was in accordance with the existing literature, namely the MIMS Drug Reference (MIMS, 2019). In this study, the management of knee osteoarthritis patients consisted of two types, namely combination therapy and monotherapy. Combination therapy was used more than monotherapy. The combination of meloxicam and glucosamine sulfate is the most common drug combination compared to other drug combination therapies.

The combination of meloxicam with glucosamine sulfate effectively treats osteoarthritis. Meloxicam is an NSAID that can inhibit prostaglandin biosynthesis by blocking COX-2. Glucosamine sulfate can slow down bone degradation and promote cartilage regeneration. Glucosamine sulfate also inhibits the collagenase and phospholipase A2 enzymes that damage cartilage and prevent the production of superoxide free radicals in injured cells. The combination of meloxicam and glucosamine sulfate effectively reduced the serum concentrations of CTX-I, CTX-II, COMP, and MMP-3. The combination of these two drugs can reduce clinical symptoms such as joint pain, swelling, and joint stiffness in osteoarthritis patients. In addition, there were no serious drug side effects with the combined use of meloxicam and glucosamine sulfate (Zhijun et al., 2019).

In this study, the class of drugs most widely used in patients with knee osteoarthritis at the Bina Sehat Jember Hospital was NSAIDs. The use of non-steroidal anti-inflammatory drugs is the most because the treatment for osteoarthritis patients is mostly palliative (Gupta et al., 2018). The most widely used type of NSAIDs in this study was meloxicam. Meloxicam has an anti-inflammatory effect that can be the drug of choice for osteoarthritis (Zhijun et al., 2019). Meloxicam inhibits COX-2 rather than COX-1, so this drug causes fewer gastrointestinal symptoms and side effects than diclofenac (Katzung et al., 2014). In addition to NSAIDs, many Symptomatic Slow Acting Drugs for

Osteoarthritis (SYSADOA) were used, namely glucosamine sulfate, in 62 patients (34.9%). According to guidelines from the Europe Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO), using SYSADOA drugs is the first step before using NSAIDs in knee osteoarthritis patients (Bruyère et al., 2019). Glucosamine is one of the most abundant monosaccharides. in the body and is also available in dietary supplements. Glucosamine affects cytokine-mediated pathways that regulate inflammation, cartilage degradation, and immune responses. Glucosamine has immunomodulatory activity through inhibition of interleukin-1, which can reduce inflammation and cartilage degradation and stimulate proteoglycan synthesis. Glucosamine is also a glycosaminoglycan precursor, a major cartilage component. Therefore, glucosamine supplementation can help increase glycosaminoglycan synthesis or reduce cartilage degradation (Sherman et al., 2012).

The use of acetaminophen in this study was classified as the least used drug. The analgesic efficacy of acetaminophen is lower than that of other NSAIDs in osteoarthritis (Gupta et al., 2018). Acetaminophen is helpful in mild to moderate pain. However, this drug is less effective in inflammatory diseases because of its weak anti-inflammatory effect (Katzung et al., 2014). The activity of acetaminophen is low when high levels of arachidonic acid and peroxide are present. Therefore, acetaminophen cannot inhibit the inflammatory process (Gunawan et al., 2016).

In addition to NSAIDs, SYSADOA, and acetaminophen, this study also found the use of gabapentin and calcitriol drugs. Gabapentin is not included in the ESCEO osteoarthritis management guidelines. However, research conducted by Enteshari-Moghaddam et al. (2019) showed that gabapentin has fairly high efficacy in treating knee osteoarthritis. Gabapentin has an acceptable effect in reducing pain and improving functional status in patients with knee osteoarthritis at the end of the third month of treatment (Enteshari-moghaddam et al., 2019). The mechanism of action of the gabapentin class of drugs is to suppress the excitability of nerve cells through their interaction with the a2d1 subunit of the calcium channel, stimulate descending inhibition, inhibit the facilitation of serotonergic neurotransmitters, inhibit inflammatory mediators, and affect the propagation component from pain (Chincholkar, 2018). Calcitriol, a vitamin D analog, has also been effective for administering knee osteoarthritis patients. Based on research conducted by Garfinkel et al. (2017), the use of calcitriol affects osteoarthritis patients. Patients with sufficient vitamin D have a lower risk of developing osteoarthritis, and adequate vitamin D can reduce radiographic degeneration of articular cartilage (Garfinkel et al., 2017). Calcitriol works by binding to vitamin D receptors in the kidneys, parathyroid glands, intestines, and bone to increase blood calcium levels by increasing absorption in the intestine, tubular reabsorption in the kidneys, and the release of calcium from bones. Calcitriol functions as a transcription factor for encoding calcium-binding proteins, which simultaneously transport calcium and phosphate ions across intestinal epithelial cells. With parathyroid hormone, calcitriol stimulates bone resorption by activating osteoclasts by releasing

nuclear factor kappa-B ligand-receptor activator (RANKL) from osteoblasts (Lung et al., 2021). Vitamin D administration is a safe method for treating and preventing osteoarthritis. However, there is currently no general consensus on the effect of vitamin D on osteoarthritis. Therefore, future research on calcitriol in osteoarthritis is needed to determine the specific pathway and its effectiveness (Garfinkel et al., 2017).

Many drug administration to patients can cause drug-related problems (DRPs). A total of 3 knee osteoarthritis patients in this study had the potential to experience drug-related problems in the category of a drug interaction. The first drug interaction is between NSAIDs (diclofenac) and antihypertensive drugs of the angiotensin II receptor blocker class (valsartan and candesartan). Nonsteroidal anti-inflammatory drugs (NSAIDs) can decrease the response to antihypertensive drugs (Katzung et al., 2014). This mechanism is the inhibition of NSAID-induced renal prostaglandin synthesis, which results in unopposed suppressive activity that produces hypertension. In addition, NSAIDs can cause fluid retention, which also affects blood pressure. Concomitant use of NSAIDs and angiotensin II receptor antagonists can also cause decreased renal function, especially in elderly patients (Drugs.com, 2021).

The second drug interaction is between NSAIDs (diclofenac and meloxicam) with sulfonylurea antidiabetic drugs (glimepiride). Coadministration of insulin secretagogues with NSAIDs can increase the hypoglycemic effect of these drugs. These nonsteroidal anti-inflammatory drugs can increase the risk of hypoglycemia by stimulating insulin secretion. The interaction between these two drugs can also increase the plasma concentration of insulin secretagogue by removing it from the plasma protein binding site or inhibiting its metabolism (Drugs.com, 2021).

Table 2. Dosage regimen for knee osteoarthritis patient

Osteoarthritis Therapy	Administration Route	Dosage Regimen	Daily Maximum Dose	Suitability	Frequency and Percentage
Diclofenac	Oral	50 mg (2x1)	150 mg	Yes	16 (9%)
		50 mg (3x1)		Yes	2 (1,1%)
		50 mg (1x1)		Yes	1 (0,6%)
Dexketoprofen	Oral	25 mg (2x1)	75 mg	Yes	3 (1,7%)
Etoricoxib	Oral	90 mg (1x1)	120 mg	Yes	9 (5,1%)
		60 mg (1x1)		Yes	5 (2,8%)
		60 mg (2x1)		Yes	2 (1,1%)
Gabapentin	Oral	300 mg (1x1)	3600 mg	Yes	3 (1,7%)
		300 mg (2x1)		Yes	3 (1,7%)
		150 mg (2x1)		Yes	2 (1,1%)
		100 mg (1x1)		Yes	1 (0,6%)
		100 mg (2x1)		Yes	1 (0,6%)
		100 mg (3x1)		Yes	1 (0,6%)
Glucosamine sulfate	Oral	500 mg (2x1)	1500 mg	Yes	56 (31,6%)
		500 mg (1x1)		Yes	6 (3,3%)
Calcitriol	Oral	0,25 mcg (1x1)	1 mcg	Yes	9 (5,1%)
		0,25 mcg (2x1)		Yes	2 (1,1%)
Ketoprofen	Oral	100 mg (2x1)	200 mg	Yes	4 (2,3%)
Meloxicam	Oral	15 mg (1x1)	15 mg	Yes	44 (24,9%)
		7,5 mg (2x1)		Yes	4 (2,3%)
Acetaminophen	Oral	500 mg (3x1)	4000 mg	Yes	3 (1,7%)

Table 3. Type of therapy based on the amount of drug given

Osteoarthritis Therapy	Types of Therapy	Frequency and Percentage
Diclofenac	Monotherapy	4 (4,1%)
Diclofenac and calcitriol	Combination Therapy	1 (1%)
Diclofenac and gabapentin	Combination Therapy	1 (1%)
Diclofenac and glucosamine sulfate	Combination Therapy	13 (13,4%)
Dexketoprofen and glucosamine sulfate	Combination Therapy	3 (3,1%)
Etoricoxib	Monotherapy	7 (7,2%)
Etoricoxib and calcitriol	Combination Therapy	2 (2,1%)
Etoricoxib dan glucosamine sulfate	Combination Therapy	7 (7,2%)
Glucosamine sulfate	Monotherapy	6 (6,2%)
Ketoprofen	Monotherapy	1 (1%)
Ketoprofen and gabapentin	Combination Therapy	1 (1%)
Ketoprofen and glucosamine sulfate	Combination Therapy	2 (2,1%)
Meloxicam	Monotherapy	4 (4,1%)
Meloxicam, acetaminophen, and gabapentin	Combination Therapy	2 (2,1%)
Meloxicam and calcitriol	Combination Therapy	8 (8,2%)
Meloxicam and gabapentin	Combination Therapy	3 (3,1%)
Meloxicam, gabapentin, and glucosamine sulfate	Combination Therapy	3 (3,1%)
Meloxicam and glucosamine sulfate	Combination Therapy	28 (28,9%)
Acetaminophen and gabapentin	Combination Therapy	1 (1%)

Table 4. Drug-related problems in the drug interaction category

Osteoarthritis drugs	Interaction with	Information	Frequency and Percentage
NSAIDs (diclofenac)	Antihypertensive drug (candesartan)	Attenuates the effects of antihypertensive drugs	1 (1,033%)
NSAIDs (diclofenac)	Antihypertensive drug (valsartan)	Attenuates the effects of antihypertensive drugs	1 (1,033%)
	Antidiabetic drug (glimepiride)	There is a hypoglycemic effect	
NSAIDs (meloxicam)	Antidiabetic drug (glimepiride)	There is a hypoglycemic effect	1 (1,033%)

CONCLUSION

Based on the results of the analysis and discussion that the researcher has described, conclusions can be drawn as follows: The pattern of drug use used in patients with knee osteoarthritis in this study were non-steroidal anti-inflammatory drugs (meloxicam, diclofenac, etoricoxib, ketoprofen, dexketoprofen, and acetaminophen) as many as 90 patients, symptomatic slow-acting drugs for osteoarthritis (glucosamine sulfate) as many as 62 patients, acetaminophen in 3 patients, gamma-aminobutyric acid (gabapentin) analogs in 11 patients, and vitamin D analogs (calcitriol) in 11 patients. The highest number of knee osteoarthritis patients by gender in this study was female, with as many as 73 patients. The number of male patients was much less, namely as many as 24 patients. The mean age of knee osteoarthritis patients in this study was 57 years. A total of 3 knee osteoarthritis patients have the potential to experience drug-related problems in the drug interaction category.

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