THE MAJOR OF DRUG-RELATED PROBLEMS IN CHRONIC KIDNEY DISEASE WERE CLASSIFIED BY PHARMACEUTICAL CARE NETWORK EUROPE

Sophia Shany Anasthasya, *Widya Kardela, Sri Oktavia
Department of Pharmacology and Clinical Pharmacy, School of Pharmaceutical Sciences STIFARM Padang, West Sumatera, Indonesia, 25147
*Correspondence: Phone: +62 85376136691
Email: widyakardela@gmail.com

ABSTRACT: *The treatment and control of comorbidities and complications that occur in patients with CKD required an increase in the number of drugs used, thus causing them vulnerable to the incidence of DRPs. This article aimed to review the frequency, risk factors, and types of DRPs and to become useful literature for preventing the occurrence of DRPs in CKD patients were classified by PCNE. A literature search was carried out systematically using 4 databases including PubMed, Google Scholar, 1library, and e-journal. The keywords used were ((("drug-related problems" AND "chronic kidney disease")). A total of 344 articles regarding DRPs have been identified by the final analysis of 9 articles. It was found the incidence of DRPs with the most common problem category was adverse drug reactions followed by drug interactions, while the most common cause category was drug/dose selection followed by drug use process. The role of pharmacists is very important to identifying, overcoming, and preventing drug-related problems. Therefore, it is necessary to optimize drug therapy by health professionals particularly pharmacists to improve the quality of life of patients with CKD.*

Keywords: Drug-Related Problems, Chronic Kidney Disease, PCNE, Adverse Drug Reaction, Drug Choice Problem

INTRODUCTION

The kidney is one of the important organs in the urinary system which has functions such as excreting metabolic waste products containing urea, ammonia and removing foreign substances in the urine, and producing several hormones (e.g. calcitriol and erythropoietin)[1]. Kidneys can be impaired if there is a progressive decline in kidney function over a long period and cannot recover as usual, which is known as Chronic Kidney Disease. Chronic kidney disease (CKD) is a clinical condition that leads to kidney damage, characterized by abnormal albumin excretion for three months or more. To assess kidney function, a Glomerular Filtration Rate (GFR) test can be performed, which is the average rate of blood filtering in the glomerulus [2].

Table 1.Stages of CKD are based on GFR [3]

Stage	Description	GFR (mL/min/ 1.73 m^2)
	At increased risk	≥ 90 (with CKD risk factors)
1	Kidney damage with normal or ↑ GFR	≥90
2	Kidney damage with mild ↓ GFR	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29
5	Kidney failure	<15 (or dialysis)

According to the Global Burden of Disease Study in 2010, explained that the prevalence of Chronic Kidney Disease, a significant improvement based on the previous findings in 1990 was observed where CKD conditions increased from rank 27th to 18th which caused death in various countries. The sharp increase in prevalence is accompanied by increased lifespan[4]. Based on the Kidney Disease Outcome Quality Initiative (K / DOQI), Chronic kidney disease (CKD) can be classified based on the GFR value, stage 1 (normal/elevated Glomerular Filtration Rate) to stage 5 (End-Stage Renal Disease/ESRD). As the CKD stage increases, the GFR value decreases [3]. Chronic kidney disease (CKD) can be characterized by decreased kidney function. Decreased kidney function can cause the alteration of drug pharmacokinetics such as drug bioavailability and absorption, distribution, metabolism, and drug elimination [5]. Therefore, appropriate and effective drug dosage adjustments are needed to reduce the worsening condition of CKD patients. The worsening of the condition in CKD patients can trigger complications such as anemia, hyperlipidemia, osteodystrophy, and cardiovascular risk. Treating and controlling comorbidities and complications that occur in patients with CKD, required an increase in the number of drugs used, causing them vulnerable to the incidence of drug-related problems (DRPs)[6].

The Pharmaceutical Care Network Europe (PCNE) defined Drug-Related Problems (DRPs) as an event or circumstance associated with drug therapy that occurs in actual and potential that can interfere with the desired therapeutic outcome[7]. There are 14 types of drug-related problems classification systems that have been published in various

literature in international journals, which have different definitions and categories of drug-related problems used[8]. The classification system is useful for assisting healthcare professionals in documenting drug-related problems. From the various existing drug-related problem classification systems, The Pharmaceutical Care Network Europe (PCNE) classification system is used as the right choice to identifying Drug-Related Problems in CKD patients. The DRPs classification system of Pharmaceutical Care Network Europe (PCNE) was established in 1999, which is officially recognized internationally as DRPs classification systems, the PCNE classification system is often involved in review studies related to comprehensive treatment problems, the classification system is continuously improved and updated through a clinical approach to producing a better classification system[9], it has a hierarchical structure that is divided into clear and easy-to-understand categories and sub-categories [7], where the information above is some of the reasons why choosing PCNE classification system to identify DRPs.

Health care professionals especially pharmacists, play an important role in the pharmaceutical care process including optimizing treatment therapy, thereby improving the patient's health status, especially in providing consultation, information, and education related to the therapy provided. This underlines the importance of knowledge about Drug-Related Problems (DRPs) thus the expected results can treat and control the actual DRPs and prevent potential DRPs. Consequently, this article is needed to review the frequency, risk factors, and types of DRPs that occur in CKD patients in reducing morbidity and mortality rates and become useful literature for preventing the occurrence of DRPs in CKD patients were classified by Pharmaceutical Care Network Europe.

METHODS

Literature Search Strategy

The literature search was carried out systematically using 4 databases including PubMed, Google Scholar, 1library, an e-Journal. Based on the title of this review, the keywords used in the PubMed database to find relevant articles were (("drug-related problems " AND "chronic kidney disease")) published in the last 10 years. Google Scholar and 1library were also searched using the following keywords (("drug-related problems" AND "chronic kidney disease")), while e-journals used the same keywords but with Indonesian. Boolean logic such as 'AND' is used to increase the accuracy of the literature search thus the results obtained include both keywords used.

Study Selection

The inclusion criteria have the following characteristics: drug-related problems in CKD patients that occur in hospitals, using the PCNE classification system. The exclusion criteria are case studies, articles that do not use English/Indonesian, and paid articles. The process and stages of the systematic review using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) diagram as documentation of the process of searching, filtering and selecting articles to obtain relevant articles that can be used. The PRISMA diagram can be seen in Figure 1. Quality assessment is to exclude and include articles that will be included based on quality. The assessment quality of the articles used was based on Title, abstract, research design, inclusion, and exclusion criteria. For further analysis, when the screening process has been passed, data extraction is carried out to know the articles have been screened already qualified. Data extraction is developed, tested, and filtered.

RESULTS

It can be seen in Figure 1, the first stage was identification. A total of 344 articles were retrieved through four databases used (PubMed, Google scholar, 1library, e-journals) based on the keywords in accordance with this review. Then further identification was carried out to eliminate 344 articles based on duplication. A total of 256 articles were retrieved and of these 88 were removed. In the screening stage based on the title of the articles, a total of 195 articles were removed due to several reasons such as the title does not correspond to the topic, not the original articles, case studies, and articles that used a language other than English / Indonesian. From the title screening, 61 articles were obtained and then re-screened based on the abstract. 29 articles were relevant and 32 articles were removed because they did not describe the parameters of the DRP used, patients with other diseases, and no clear research results. Additionally, an assessment was conducted based on the full text and eligibility criteria, it was found that 14 articles were included and 15 articles were excluded. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) diagram is used as evidence and documentation of the steps taken by the author in identifying, screening until the articles comply the eligibility criteria and can be used.

The last stage was obtained 9 suitable articles and further review was conducted by making a data extraction consisting of the title, method, DRP parameters used, results, and conclusions can be seen in Table 2 below.

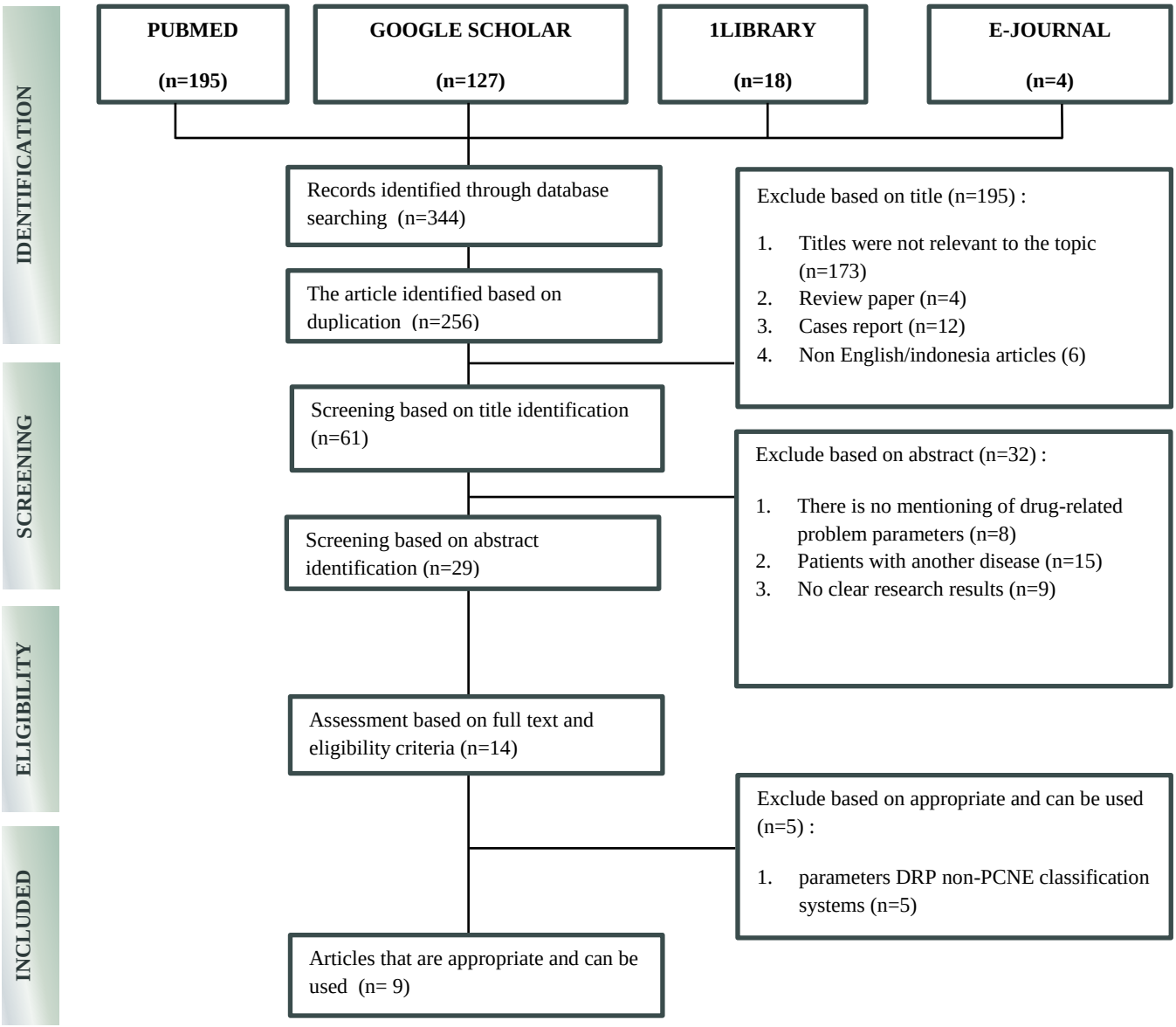

Figure 1: PRISMA diagram

Table 2: Data extraction

REF	METHODS	VERSION	RESULT	CONCLUSION
[10]	A prospective cross sectional study	V 5.01	Problems : 1. P1 ADR 4 (1.19%) 2. P2 Drug Choice Problem • P2.1 Inappropriate drug 4 (1.19%) • P2.3 Drug duplication 4 (1.19%) • P2.4 Contraindications 11 (3.26%) • P2.5 Drug without indication 3 (0.89%) • P2.6 Indication without drug 38 (11.28%) 3. P3.2 Too high dose 14 (4.15%) 4. Dose adjustment 10 (2.97%) 5. Frequency error 39 (11.57%) 6. P5 Drug interactions 202 (59.94%) 7. P6 others • P6.2 Insufficient awareness 4 (1.19%) • P6.5 Worries about ADR 4 (1.19%)	The most common DRP were drug interactions (59.94%), followed by frequency error (11.57%) and indication without drug (11.28%).
[11]	A prospective study	V 6.2	Problems were mostly related to : 1. P1 Treatment effectiveness 1134 (95.13%) 2. P2 Adverse reaction 18 (1.51%)	The most frequent DRPs were untreated indication 27.18% (324) and incorrect dose – too low

			3. P3 Treatment cost 5 (0.42%) 4. P4 Others 35 (2.94%) causes in the PCNE system : 1. C1 Drug selection (n=677; 56.80%) 2. C2.1 Inappropriate dosage form (n=16; 1.34%) 3. C3 Dose selection (n=459; 38.51%) 4. C4 Treatment duration (n=21; 1.76%) 5. C5 Drug administration process (n=6; 0.50%) 6. C6 Logistics (n=12; 1.01%) 7. C7 patient (n=1; 0.08%)	20.81% (248).
[12]	A prospective observational study	V 6.2	Problems : 1. P1 Treatment effectiveness 483 (47.1%) 2. P2 Adverse reactions 476 (46.4%) 3. P3 Treatment costs 67 (6.5%) Causes : 1. C1 Drug selection 682 (66.5%) 2. C2 Drug form 2 (0.2%) 3. C3 Dose selection 387 (37. %) 4. C4 Treatment duration 47 (4.6%) 5. C5 Drug use process 214 (20.9%) 6. C6 Logistics 148 (14.4%) 7. C7 Patient 17 (1.7%) 8. C8 Other 107 (10.4%)	Treatment effectiveness and adverse reaction domains contributed to the majority of DRP's primary domains for problems. Drug selection contributed to the predominant cause of DRPs
[13]	A prospective descriptive study	V 5.01	Identified drug therapy problem : 1. P2 Drug Choice Problem 38.46% 2. P3 Dosing problem 20.08% 3. P3 Drug use problem 4.7% 4. P5 Interactions 36.75%	Inappropriate drug selection and drug interactions were the commonest drug therapy problems.
[14]	A prospective cohort study	V 7.0	The problems : 1. P1 Treatment effectiveness • P1.2 effect of drug treatment not optimal 12 (28.6%) • P1.3 unnecessary drug-treatment 2 (4.8%) • P1.4 untreated indication 5 (11.9%) The causes : 1. C1 Drug selection 11 (26.2%) 2. C3 Dose selection 2 (4.8%) 3. C6 Drug use process 11 (26.2%)	drug-related problems for the problem category that occurs is the treatment effectiveness 19 (45.2%). As for the category of causes that occur are drug selection 11 (26.2%), drug use process 26.2%) and dose selection 2 (4.8%).
[15]	A Prospective observational study	V 5.01	Identified Drug Therapy Problems : 1. P1 adverse reaction 23 (29.11%) 2. P2 drug choice problem 9 (11.39%) 3. P3 Dosing problem 8 (10.12%) 4. P4 drug use problem (0%) 5. P5 drug interaction 38 (48.10%) 6. P6 Others 1 (1.26%)	Drug interactions (48.10%) and adverse drug reactions (29.11%) were found the major of DRPs.
[16]	A prospective observational study	V 8.02	The problems : 1. P1 Treatment effectiveness • P1.1 no effect of drug treatment 18 (2.48%) • P1.2 Effect of drug treatment not optimal 39 (5.39%) • P1.3Untreated symptoms or indication 84 (11.61%) 2. P2 Treatment safety • P2.1 Adverse drug event (possibly) occurring 578 (79.94%) 3. P3 Others • P3.2 Unnecessary drug treatment 6 (0.82%) The causes : 1. C1 Drug selection 641 (88.65%) 2. C3 Dose selection 12 (1.65%) 3. C5 Dispensing 2 (0.27%) 4. C7 patient related 7 (0.96%) 5. C8 others 58 (8.022%)	The most common category of DRP identified was Adverse drug events possibly occurring (79.94%) and the most frequent cause was drug selection (88.65%).

[17]	A prospective observational study	V 6.2	The problems : 1. P2 adverse reaction (68.39%) • P2.1 adverse drug event non-allergic (61.29%) • P2.3 toxic adverse drug event (7.10%) 2. Treatment costs (3.87%) 3. Others (1.29%) The causes : 1. C1 Drug selection (18.99%) 2. C3 Dose selection (38.55%)	The most common DRPs were adverse drug reactions 68.39% and the most common causes were related to dose selection 38.55%.
[18]	Descriptive analytic study with Prospectively approach	V 6.2	The problems : 1. P1 treatment effectiveness • P1.2 effect of drug treatment not optimal 61 (62.24%) 2. P2 adverse reaction • P2.1 adverse drug event (non-allergic) 20 (20.41%) • P2.3 toxic adverse drug event 17 (17.35%)	Drug-related problems identified were the effect of drug treatment not optimal 62.24%, adverse drug event non-allergic 20.41%, and toxic adverse drug event 17.35%.

DISCUSSION

Conducted on nine articles that have different versions used, so required a good comprehension and knowledge to reconcile the differences which is essentially have the similar interpretation, intent, and purpose. The PCNE versions used in these 9 studies were V5.01, V6.02, V7.0, and V8.02. The PCNE classification system has the function of documenting the incidence of drug-related problems by classifying it into several categories. This is expected to improve counseling competence, increase rational drug use and increase awareness about DRPs events for healthcare professionals, particularly pharmacists. The PCNE classification system divides problems and causes using separate codes with different numbers of primary domains and sub-domains. In this discussion was used primary domains of V5.01 consisting of P1 adverse drug reaction, P2 drug choice problem, P3 dosing problem, P4 drug use problem, P5 interactions, P6 other for problems and for causes were C1 drug/dose selection, C2 drug uses process, C3 information, C4 patient/ psychological, C5 logistics and C6 other. There are 21 grouped sub-domains for problems and 33 grouped subdomains for causes. V5.01 was the oldest version in these 9 articles, which was published in 2006 so it has often been involved in previous studies even until now. Hence, V5.01 was used to interpret the type, risk factors, and frequency of DRP events in CKD patients. Drug-related problems in CKD patients with the highest incidence were in adult and elderly patients. This may happen while the number of age is increasing, the risk of chronic kidney disease increased[10], adult and elderly patients are prone to the incidence of DRPs because they consume five or more drugs to treat CKD, where we know that the incidence of DRP increased with an increasing number of drugs taken[19].

Problem

Adverse drug reaction

Adverse drug reactions in patients with chronic kidney disease including hypoglycemia, indigestion, cough, muscle aches and cramps, dizziness with a low percentage of 1.19%[10]. Similar to an article[11], adverse drug reactions were in a low percentage of 1.51%. Adverse drug reactions were in high percentages 46.4%, 29.1%, 79.94% and 61,29% respectively with subdomain problems that occur are side effects (non-allergic)[12, 15, 16, 17]. It was explained the incidence of adverse drug reactions was mostly caused by bleeding / gastrointestinal disorders, potassium imbalance, and diarrhea. Three main drug groups for nonallergic events: antiplatelet, phosphate binders, laxatives[12]. The problem involved in non-allergic adverse drug reactions is the occurrence of side effects of diarrhea due to the use of colchicine[17].ADR events can occur in patients with GFR <10 ml/min given aspilet 1x80 mg, whereas the use of aspirin is avoided in patients with GFR <10 ml/min because it can worsen kidney function and cause Na and water retention. Several risk factors have the potential to increase the occurrence of adverse drug reactions such as age, gender, the number of disease diagnoses, duration of drugs taken[20], alcohol consumption, pregnancy, kidney problems, breastfeeding mothers, and the frequency of the number of drugs taken by the patient contribute to the increased incidence of ADR disproportionately, the more amount of drug the more vulnerable of ADR[21]. There are 2 articles that did not experience ADR events[13,14].

Drug choice problem

The presence of drug choice problems occurred in 8 articles with different sub-domains problems. It is dominated by the subdomains of 'drugs not prescribed but clear indications. A total of 7 articles [10-16] with the respective percentages of 11.28%, 27.8%, 8.6%, 2.99%, 11.9%, 11.39% and 11.61%. Drug-related problems with the subdomain P2.6 'drugs not prescribed but clear indications' can occur, one of the reasons is due to the absence of clear symptoms and signs in some complications/ comorbidities[10], drug therapy is minimized before transplantation thus allowing untreated indications[11]. Another study report explains that most of the symptoms/signs are not treated because there is no good communication between patients and health professionals[22]. Indications that were not treated in this study were aspirin (antiplatelet) preventive therapy was not given to patients with chronic kidney disease with comorbid conditions of diabetes[17]. Then the second most problem is the subdomain P2.5 'administration of drugs with unclear indications' [10,12-16] with percentages of 0.89%, 3.4%, 2.56%, 4.8%, 8.86% and 0.82% respectively. Drug administration problems with unclear indications can be

interpreted as unnecessary drug therapy. It was found that one of the causes of unnecessary drug therapy problems is the patient's condition which is better treated with non-drug therapy, a condition where multiple drugs are given while only requiring a single dose, taking drugs to treat unwanted reactions and patient health problems (related to alcohol consumption, smoking)[23]. A case example is a patient diagnosed with ESRD and hypertension, receiving therapy with captopril 25 mg 1x1 and valsartan 80 mg 1x1. The use of this drug is considered inappropriate because according to JNC VII in Chobanian[24] these two drugs cannot be combined because they have a higher mortality rate than the use of monotherapy.

Dosing problem

A dosing problem is an event where patients received a dose that is less or more than the amount they need. It is divided into 4 subdomains with the highest incidence is 'drug dose too high/dosing regimen too frequent' subdomain with an average of 4.15%, 13.25%, and 6.32% respectively [10,13,15]. Drug dose too high is the dose of the drug given is too high so that an unexpected effect is produced, this incident can be caused by several things, including the concentration of the drug in the blood is above the therapeutic range, the patient's drug dose increases too quickly and the frequency is not right[23]. The second most common problem is 'drug dose too low/dosing regimen not frequent enough' with an average of 3.85%, 2.53% [13,15]. Drug dose is too low/dosing regimen not frequent enough is the dose of the drug given is too low to produce the desired response so that the drug effect is not optimal, this can be caused by improper storage of the drug, drug concentration in the blood is below the therapeutic range and there is a change in dose or route or inappropriate formulation[23].

Drug Use Problem

Only 1 article had a drug use problem, namely the 'drug not taken/administered at all' subdomain with a percentage of 4.7%[13]. The problem of drug use is where the drug is not taken or uses the wrong drug. This may happen because the patient himself, where the drug is not taken is accompanied by an error in taking the drug. Several factors cause this to happen such as lack of knowledge about the drugs to be taken, stopping taking drugs immediately when symptoms disappear, and the poverty factor. In fact, some patients have language barriers so that they cannot communicate well with health workers regarding the use of drugs which leads to the wrong drug being taken[25].

Interactions

Drug interactions are events that can produce harmful treatment outcomes for patients such as drug toxicity which is caused by changes in drug effects that are influenced by other drugs. There were 3 articles that experienced drug interactions[10,13,15]with percentages of 59.94%, 36.75%, and 48.18% respectively. Drug interactions are divided into 2, namely actual and potential. Actual is a drug-related problem that is currently happening to the patient while the potential is a drug-related problem that will occur/potentially affect the patient's treatment outcome[26]. Several risk factors for potential DDI are age under 60 years, hypertension, number of drugs prescribed $\geq$ 5, and long hospital stay[27]. The occurrence of drug interaction can have a negative impact on morbidity, mortality, hospitalization time, treatment costs, and patient quality of life[28]. Preventive treatment can be operated by health workers in controlling drug interactions such as early identification of the use of harmful drug combinations, rational use of prescription drugs, and appropriate monitoring of drug therapy[29].

Others

Out of 9 existing articles, only 3 experienced in this domain. P6 Other problems are divided into 4 subdomains including patients dissatisfied with therapy, insufficient awareness of health and disease, unclear complaints, and therapy failure. Most events occurred in the therapy failure subdomain[12,15, 16].The incidence of therapy failure can be caused by the patients not carrying out regular physical activity, routine blood monitoring, and follow-up medication. It can also lead to insufficient awareness of health and disease[25].

Causes

After the process of identifying problems that occur in drug-related problems, the pharmacist then identifies the causes of drug-related problems. There are 6 primary domains of cause drug-related problems, with the highest incidence was the drug/dose selection domain[11,12,14,16,17] followed by the drug use process[11,12,16]. The drug/dose selection domain is a cause related to the drug/dose selection schedule[7], this indicates the importance of the pharmacist's role in ensuring the selection of the right drug and dosage in order to achieve efficacy in treatment. While the drug use process is cause-related to how the patient uses/consumes the drug regardless of the exact dosage instructions on the label[7], This demonstrated that pharmacists must provide information and knowledge about the appropriate medicines use to patients when administering the medications, thereby increasing patient compliance and reducing medication errors.

CONCLUSION

It can be concluded that the incidence of drug-related problems with the most common problem category is adverse drug reactions followed by drug interactions, while the most common cause category is drug/dose selection and followed by the drug use process. The incidence of drug-related problems has an impact on mortality and morbidity of the disease as well as the outcome of therapy. Pharmacists play an important role in identifying, overcoming, and preventing drug-related problems, both actual and potential. Therefore, it is necessary to optimize drug therapy by health care professionals, especially pharmacists, to improve the quality of life of patients with chronic kidney disease.

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