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Assessment of drug-drug interactions in patients with chronic kidney disease

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Abstract
Chronic kidney disease (CKD) changes the pharmacodynamics and pharmacokinetics of the various drugs excreted through the kidneys which increases the risk of DDIs. In CKD patients' prescriptions, polypharmacy is the common cause of occurring DDIs. DDIs alters the effects of one another drug by decreasing or diminishing the pharmacokinetics, pharmacodynamics, and other mechanism of the drugs in the body. The aim of this study is to assess the DDIs in the prescriptions of CKD patients. Ambi-directional observational study was conducted for six months among the CKD patients admitted to the in-patient nephrology ward of Mahavir Hospital and research center in Hyderabad. The DDIs of the prescribed drugs were classified as per Clinirex. A total of 101 prescriptions were included. A total of 742 drug interactions were reported. Around 73.18% were monitored closely, 17.12% were unclassified, 4.99% adjust dosing, 3.50% generally avoid and 1.21% were contraindicated. The average number of DDI per prescription was 7.35 thus results indicated that it was more. The DDIs may show immediate adverse outcomes or delayed adverse outcomes thus follow-up for a longer duration is necessary for predicting clinically important outcomes of these DDIs. Early detection of DDIs is necessary in the prescriptions of patients with CKD as it can lead to serious adverse outcomes. Thus, it is necessary for a clinical pharmacist to collaborate with the nephrologist and develop strategies for appropriate and continuous follow-up and monitoring of patients with CKD for a longer duration.

Keywords: Clinical pharmacists, collaboration, nephrologists, adverse effects, monitoring

Introduction
CKD is a persistent systemic and functional deformity for a prolonged period of time [Sridhar Srimath Tirumals Konduru *et al.* 2018] [10]. Major risk factors of CKD are hypertension, diabetes mellitus, cardiovascular disorders, excessive smoking, obesity, excessive salt intake. By the assessment of glomerular filtration rate (GFR) kidney function can be determined. Early stages of CKD are asymptomatic. Hence, it is usually detected at advanced stages. Patients suffering from higher stages of CKD with co-morbidities are at higher risk of developing complications. CKD is a major medical issue worldwide.
With increase in number of patients of CKD and end stage renal disease [ESRD] providing medical care to them becomes a difficult job due to their wide spread, co-morbidities and risk factors. CKD patients should be assessed with proper care and optimal treatment should be given to improve their quality of life. Deterioration of kidney can be slowed down by providing required treatment. The treatment depends upon kidneys residual functions, stages of CKD and GFR. However, end stage renal disease can only be treated by two procedures; they are renal transplantation and renal replacement therapy [Sridhar Srimath Tirumals Konduru *et al.* 2018] [10].
DDIs is a phenomenon in which it decreases or deminished the effect of other drugs by pharmacodynamic, pharmacokinectics and from other mechanisms. DDIs are one of the biggest therapeutic challenges for treating the inpatients who are suffering from CKD. Such studies are only carried out in a particular clinical setting where pharmaceutical service department is well developed and clinical pharmacists should perform their job effectively to overcome any serious DDIs [Ahsan Saleem, Imran Masood *et al.*2017] [1].

Staging and identification of CKD: Staging of CKD solely depends upon the rate of GFR [Christina Pothen. 2019] [2]. Early stages of CKD are asymptomatic, hence it is usually detected at higher stages [Anina Anil, *et al*, 2020].

Christina Pothen conducted study to deepen insight of drug usage and also to estimate particular drugs exposed to patients with CKD for a period of time [Christina Pothen *et al*, 2019] [2]. There are limited studies on the CKD medication profile in Hyderabad, India, therefore medical audits help to achieve a rational use of drugs. Drug-related problems [DRPs], such as DDIs, are one of the major leading therapeutic challenges for the treatment of inpatients, especially for those who are suffering from CKD, due to its complicated nature. Multiple medications are essentially required to control co-morbid conditions which may often lead to drug interactions with undesired outcomes.

There is a need to conduct study to avoid drug related risk factors in CKD patients. Poly-pharmacy is most common in patients with kidney disorders. With medically unstable nature of the disease and restricted life styles, these patients are at higher risk for developing drug related problems. Non-compliance of drugs may increase the risk of severe complications and can cause complications in hemodialysis patients those are on multiple medicines. Early detection of drug interactions is necessary to minimize the risk of adverse effects [Janet Mary Oommen *et al*, 2019] [15].

In prescriptions of CKD patient's poly-pharmacy is prevalent. Detecting potential DDI by assessing prescription pattern of drugs can help to reduce adverse drug reactions. Monitoring and identifying probable DDIs improve the rationality of prescription [Mylapuram Rama, *et al*, 2012] [7]. Minimum of ten to twelve drugs are consumed by CKD patients on daily basis which includes drugs for co-morbid conditions. These drugs frequently require adjustments to minimize adverse effects and DDIs [Anina Anil, *et al*, 2020]. As there are many numbers of drugs prescribed in CKD there is a high risk of DDIs. Hence, fixed dose combinations should be avoided [Maxwell Ogochukwu Adibe, *et al*, 2017] [8]. Pharmacist plays vital role to assess DDI and in turn prevent or minimize risk of adverse effects and reduce the length of hospital stay, health care utilization and costs. Thus, there is a need to assess and deepen insight of drug usage and also to estimate particular drugs exposed to patients with CKD.

Aim

The aim of this study is to assess the DDIs in the prescriptions of CKD patients.

Methodology

Study was conducted in the nephrology in-patient department at Mahavir hospital and research center, Hyderabad. This present study was conducted for 6 months from November 2021 to April 2022. Ethical committee approval was obtained from Mahavir hospital and Research center. Inclusion criteria: Patients of equal to or more than 18 years and below 90 years, patients with CKD with or without dialysis, patients of either gender. Exclusion criteria: Patients below 18 years, special population including pregnant and lactating women. Eligible patients as per inclusion criteria those admitted in the nephrology inpatient department were explained about this present study. Then these patients were invited to participate in this study. Verbal consent was obtained and included in the study. Drug Utilization review was carried out as per K.Seiyadu Ibrahim *et al*. Study design was ambidirectional observational study.

Source of data utilized for this present study was the patient's medical records obtained from the inpatient nephrology department and also from medical records department in Mahavir hospital. Data collection form (DCF) was specially designed for the purpose of the present study [Kaunain Fatima *et al.* 2023] [6]. The DCF comprised of the following parameters demographics: age, gender, inpatient number, unit, date of admission, complaints on admission, date of discharge, medication history, patient history. Final diagnosis and treatment chart details comprised of drugs names, dosage form, frequency, route of administration, treatment duration and details of DDIs. Data was collected and documented in DCF. Collected data was entered in excel sheet and descriptive statistical analysis was done.

Degree of poly-pharmacy was calculated with following formula: total number of drugs prescribed was divided with number of encounters included in this study [http://apps.who.int, Handle PDF selected drug use indicators-WHO, accessed on 26/4/22]. Poly-pharmacy was defined as use of five or more medications at a time for patients with CKD [Chandel Ritesh Kumar *et al*, 2019] [12]. GFR was calculated as per Kaunain Fatima *et al* [Kaunain Fatima *et al.* 2023] [6]. Clinirex was used to identify DDIs [www.clinirex.com]. Categorization of DDIs was based on clinirex such as generally avoid, contraindicated, monitor closely, additional contraception, adjust dosing and unclassified interactions [www.clinirex.com].

Results and Discussion

Total 130 patient's medical records were screened and it was noticed that 101 patients medical record data was complete. Total 101 patients with CKD were enrolled in this present study.

Gender wise distribution

Table 1: Gender wise distribution (N=101)

S. No.	Gender	Number (N)	Percentage (%)
1.	Male	62	61.39
2.	Female	39	38.61
	Total	101	100.00

Data related to it is represented in Table No.1. Roja Rani K, *et al.* and Chander Ritesh Kumar, *et al.* reported that majority of patients were males [Roja Rani, *et al.* 2020 [9], Chander Ritesh Kumar, *et al.* 2019] [12]. This present study results were similar to results of Roja Rani K, *et al.* and Chander Ritesh Kumar, *et al.* [Roja Rani, *et al*, 2020 [9], Chander Ritesh Kumar, *et al*, 2019] [12].

Age wise distribution

Table 2: Age wise distribution (N=101)

S. No.	Age group (in years)	Number (N)	Percentage (%)
1.	21-30	7	6.93
2.	31-40	7	6.93
3.	41-50	21	20.79
4.	51-60	28	27.72
5.	61-70	25	24.75
6.	71-80	12	11.88
7.	81-90	1	0.99
	Total	101	100

Data related to it is represented in Table No.2. Roja Rani K., *et al.* and Vikram Raja *et al.* reported that the majority of patients were in age category 51-60 years followed by age category 61-70 years. This present study results were similar to results of Roja Rani K. *et al*. and Vikram Raja *et al*. [Roja Rani *et al.* 2020, Vikram Raja *et al*, 2020] [9].

Distribution of CKD stages

Table 3: Distribution of CKD stages (N=101)

S. No	CKD Stages	eGFR (ml/min/1.73m^2)	Number (N)	Percentage (%)
1.	Stage 1	>90	0	0
2.	Stage 2	60-89	1	0.99
3.	Stage 3a	45-59	4	3.96
4.	Stage 3b	30-44	3	2.97
5.	Stage 4	15-29	19	18.81
6.	Stage 5	<15	74	73.27
		Total	101	100.00

Data related to it is represented in Table No.3. Stephin V Mathew, *et al.* and Kamanth L. *et al.* reported that majority of the patients were in stage 5 of CKD. This present study results were similar to it [Stephin V Mathew *et al.* 2021, Kamanth L. *et al.* 2019] [13, 14].

Co-morbidities status among patients with CKD

Table 4: Co-morbidities status among patients with CKD (N= 101)

S. No.	Co-morbidities	Number (N)	Percentage (%)
1.	Diabetes mellitus	69	31.65
2.	Hypertension	91	41.74
3.	Diabetic nephropathy	1	0.46
4.	Diabetic neuropathy	1	0.46
5.	Diabetic retinopathy	1	0.46
6.	Hypothyroidism	14	6.42
7.	Coronary artery disease	18	8.26
8.	Retro-viral disease	3	1.38
9.	COVID	2	0.92

Table 4: Co-morbidities status among patients with CKD (Continued)

S. No.	Co-morbidities	Number (N)	Percentage (%)
10	Urosepsis	8	3.67
11	Urinary Incontinence	3	1.38
12	Seizures	1	0.46
13	Bell's palsy	1	0.46
14	Chronic obstructive pulmonary disease (COPD)	1	0.46
15	Alzheimer's	1	0.46
16	Asthma	2	0.92
17	Anemia	1	0.46
	Total	218	100.00

Data related to co-morbidities status is represented in Table No.4. Stephin V Mathew *et al.* and Kamanth L. *et al.* results shown that hypertension was the co-morbidity found in 75% of the patients with CKD, followed by anemia. Results of this present study was not similar to it [Stephin V Mathew *et al.* 2021, Kamanth L. *et al.* 2019] [13, 14].

Details of DDIs categories

Data related to DDIs categories is represented in the Table No.5. Roja Rani *et al.* results shown that 282 DDIs were identified from 125 prescriptions. Out of it 48.90% and 41.40% DDIs were from category of major and moderate DDIs respectively. Results of this present study was not similar to it [Roja Rani *et al.* 2020] [9].

Table 5: Details of DDIs categories

S. No.	DDI category	Number (N)	Percentage (%)
1.	Contraindicated	9	1.21
2.	Generally avoid	26	3.50
3.	Monitor closely	543	73.18
4.	Adjust dosing	37	4.99
5.	Unclassified	127	17.12
	Total	742	100.00

Details of DDIs from contraindicated category

Table 6: Details of DDIs from contraindicated category

S. No	Name of the contraindicated DDI	Number (N)	Percentage (%)
1.	Ceftriaxone + Calcium gluconate	6	0.81
2.	Amiodrone + Levofloxacin	1	0.13
3.	Tramadol + Linezolid	1	0.13
4.	Potassium chloride + Glycopyrrolate	1	0.13
	Total	9	1.21

Data related to it is represented in the Table No. 6.

Details of generally avoid DDIs

Table 7: Details of generally avoid DDIs

S. No.	Name of generally avoid DDI	Number (N)	Percentage (%)
1.	Aspirin + Heparin	6	0.81
2.	Amiodarone + Ondansetron	3	0.40
3.	Doxycycline + Penicillin	2	0.27
4.	Amiodarone + Ondansetron	1	0.13
5.	Amiodarone + Trazodone	1	0.13
6.	Aspirin + Dalteparin	1	0.13
7.	Cefuroxime + Pantoprazole	1	0.13
8.	Clopidogrel + Fondaparinux	1	0.13
9.	Clopidogrel + Rabeprazole	1	0.13
10.	Doxycycline + Piperacillin	2	0.27

Table 7: Details of generally avoid DDIs (continued)

S. No.	Name of generally avoid DDI	Number (N)	Percentage (%)
11	Magnesium hydroxide + Calcitriol	1	0.13
12	Ofloxacin + Sodium bicarbonate	1	0.13
13	Omeprazole + Clopidogrel	1	0.13
14	Carvedilol + Valsartan	1	0.13
15	Fluconazole + Clopidogrel	1	0.13
16	Heparin + Diclofenac	1	0.13
17	Sodium bicarbonate + Levofloxacin	1	0.13
	Total	26	3.50

Data related to it is represented in the Table No.7.

Conclusion

The number of medicines prescribed was more in each prescription among these patients as co-morbid conditions was more. However, 742 DDIs were identified. The average number of DDI per prescription was 7.35 thus results indicated that it was more. The majority of DDIs were from the category to be monitored closely. Such studies need to involve pharmacists along with nephrologists to identify and report DDIs. Thus, adverse drug reactions due to DDIs can be reduced and prevented and promote rational drug prescribing. The DDIs may show immediate adverse

outcomes or delayed adverse outcomes thus follow-up for a longer duration is necessary for predicting clinically important outcomes of these DDIs. Early detection of DDIs is necessary for the prescriptions of patients with CKD as it can lead to serious adverse outcomes. Thus, it is necessary for a clinical pharmacist to collaborate with a nephrologist and develop strategies for appropriate and continuous follow-up and monitoring of patients with CKD for a longer duration.

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