WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 6, 144-155. Review Article ISSN 2277– 7105

A REVIEW ON DRUG-DRUG INTERACTIONS IN RENAL IMPAIRMENT PATIENTS

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Article Received on
23 Feb. 2023,

Revised on 14 March 2023,
Accepted on 04 April 2023

DOI: 10.20959/wjpr20236-27726

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ABSTRACT

Chronic kidney disease (CKD) involves a gradual deterioration of kidney function and it is typically present with other comorbidities, such as diabetes mellitus and cardiovascular conditions like hypertension, heart failure, and stroke. Globally, the prevalence of CKD is increasing, with estimates ranging from 11 to 13%. Several medications are used by them as a result of coexisting diseases and declining renal function. Drug interactions and adverse drug reactions (ADRs) in polypharmacy might arise as a result of different pathological and physiological changes caused by renal impairment. Use online or electronic calculators to calculate the dosages of medications cleared by the kidneys by the creatinine clearance or glomerular filtration rate. Reduced doses, longer intervals between doses, or a combination of the two are suggested maintenance dosage modifications. Although not all patients who take interacting medications experience negative side effects, it is nonetheless essential to take reasonable care to prevent accidents in all circumstances where interactions are conceivable. In observational studies conducted globally about drug-drug interaction, the prevalence of moderate to minor drug interactions is more than the major interactions. Drug interactions

and ADRs affect the health and quality of life of patients by raising healthcare costs, and hospital stays. It has been demonstrated that drug-related clinical decision support raises patient care standards and lowers ADE rates. Using drug interaction software, together with a general knowledge of typical DDI processes and cooperation with pharmacists, doctors can prevent clinically severe DDIs and maximise drug safety.

KEYWORDS: CKD, ADRs, Drug interactions, Polypharmacy.

INTRODUCTION

Drug interactions are modifications in a drug's effects brought on by the recent or concurrent use of another drug or drugs, ingesting food (drug-nutrient interactions), or ingesting dietary supplements (dietary supplement-drug interactions) and diseases (drug-condition interactions). It involves pharmacokinetic (PK) and pharmacodynamic (PD) interactions (MSD 2022; FDA, 2013).

A condition known as chronic kidney disease (CKD) is characterised by decreased kidney function, as measured by glomerular filtration rate (GFR) of less than 60 ml/min per 1.73 m2 or by markers of kidney damage, or both, for a period of at least three months. The cause of kidney disease, the degree of albuminuria, and the level of GFR must also be known. GFR readings show CKD is divided into five phases of increasing severity. Dialysis or kidney transplantation is the only available treatment for end-stage kidney disease (ESKD) (Levey A.S *et al*; 2003; K/clinical practice, 2021). The most common comorbidities seen in CKD are hypertension, diabetes mellitus, cardiovascular diseases, anaemia, and electrolyte abnormalities; Comorbid conditions must be properly managed to slow the progression of CKD and lower mortality (Simon D. S. Fraser *et al*; 2015; NKF 2022).

When CKD and comorbidities coexist, patients are exposed to polypharmacy and require numerous drugs, leading to drug-drug interactions (DDIs) and adverse drug reactions (ADRs). Patients with CKD have an increased risk of morbidity and death, longer hospital stays, and lower quality of life (Tasneem M. Shouqair *et al*; 2022).

Although the exact incidence and prevalence rates are not available, it is estimated that one out of 10,000 people suffer from CKD in India and around one lakh new patients develop ESRD in India annually. In addition to this, a higher number of patients are requiring renal replacement therapies such as dialysis and renal transplantation. (Rama M et al; 2012).

According to estimates, between 56.9% and 89.1% of CKD patients have DDIs because of polypharmacy (Bianca Papotti *et al*; 2021).

The kidneys are crucial for handling drugs, especially for excreting them. Patients with renal impairment experience variations in pharmacodynamic (PD) and pharmacokinetic (PK) parameters, which exacerbates this pathological condition. CKD is linked to several physiological changes that may affect extra-renal PK processes, such as drug absorption, distribution, and metabolism, raising the possibility of toxicity. Pharmacodynamics is concerned with how medicine interacts with the body, including how it affects its target and has downstream metabolic effects (Lea-Henry *et al*; 2018). Even though resources of data are limited on CKD, the current brief review outlines the existing body of evidence about potential DDIs in CKD patients receiving polytherapy.

DISCUSSION

Various studies conducted globally on drug-drug interactions in CKD patients out of those few studies are discussed here.

Potential drug interactions were widely seen in CKD patients because of polypharmacy. Drug-drug interactions (DDIs) happen when one medication increases or reduces the effects of another medication (i.e., a pharmacodynamic interaction) or when one medication affects the absorption, distribution, metabolism, or excretion of another medication (i.e., pharmacokinetic interaction). CYP450 enzymes alter the drug metabolism and cause drug-drug interactions in CKD patients. The majority of Phase I drug metabolism is carried out by CYP enzymes, which are primarily expressed in the liver and intestine but also the kidney (McQuade BM *et al*; 2021).

Online software like Lexi Comp, Thomson Reuters Micromedex, Drug Reax, or Medscape drug reference database system, which provides information about the type, the risk of DDI, and its mechanisms, if known, as well as suggestions on how to manage DDI, can be used to identify and categorise potential DDIs. Based on their level of clinical significance, software like Medscape divides DDI into 5 categories:

Type A: No interactions

Type B: Minor

Type C: Moderate

Type D: Major or Severe

Type X: Contraindicated

S. No.	Author and year	Country	Study title	Method	Results							Conclusion
					No. of patients	Mean age (± SD)	Average drugs per prescription (±SD)	No. of DIs	Prevalence of DDIs	Common DDIs	Severe DDIs	
1	Shrijana kumari C *et al*; 2021	India	Polypharmacy and potential drug-drug interactions among medications prescribed to chronic kidney disease patients	Cross-sectional observational study	143	54.38 ± 16.43	6.1	206	78.3%	Amlodipine + Calcium carbonate Amlodipine + Calcium acetate Calcium Carbonate + Calcitriol	Linagliptin + Torsemide	Prevalence of drug-drug interactions is high in CKD patients it is essential for regular monitoring of the medication chart.
2	Priyadharshini. P. *et al*; 2021	India	Drug-Drug Interactions among Chronic Kidney Disease patients in a tertiary hospital	Cross-sectional observational study	80	47.24 ± 14.37	7.55 ± 2.73.	387	92.5%	Amlodipine + Calcium carbonate Amlodipine + Prazosin Calcium carbonate + Nifedipine	Metoprolol + Clonidine Iron + Calcium carbonate Iron + Sodium Bicarbonate Glyceryl Trinitrate + Sildenafil Chlorpheniramine + Ipratropium Bromide (Avoid combination)	Recognizing potential DDIs and important drug combinations helps prevent situations in which treatment fails or reduces drug toxicity.
3	Marquito AB *et al*; 2014	Brazil	Identifying potential drug interactions in chronic kidney disease patients	Cross-sectional observational study	558	Male (54.7%); elderly (69.4%) (NA)	5.6 ± 3.2	1,364	74.9%	Furosemide + Acetylsalicylic acid Enalapril + Furosemide	Carbamazepine + Nifedipine Nifedipine + Phenytoin sodium Nifedipine + Phenobarbital Enalapril maleate + Losartan Allopurinol + Captopril	CCBs show more serious interactions with centrally-acting drugs because of the CYP enzyme.

CCBs- Calcium channel blockers; DDIs - Drug-drug interactions; SD- Standard deviation

4	Hammoud *et al*;2022	UAE	Evaluation of potential drug-drug interactions and adverse drug reactions among chronic kidney disease patients: An experience from the United Arab Emirates	Prospective observational study	150	63.3 ± 14.0	16.9 ± 6.1	811	85.3%	Aspirin + Insulin Aspirin + Bisoprolol Atorvastatin + Clopidogrel Aspirin + Calcium salt	Amlodipine + Clopidogrel Clopidogrel + Enoxaparin Budesonide + Levofloxacin	The clinical pharmacist plays a prominent role in managing DDIs and their effects combined with other healthcare teams.
5	Farnouda M *et al*; 2020	Iran	Evaluation of Drug-Drug Interactions in Chronic Kidney Disease Patients: A Single-Center Experience	Descriptive-analytical study	173	41-50 years	NA	NA	93.64%	Atorvastatin + Pantoprazole Ferrous Sulfate + Pantoprazole	Ferrous sulfate + CaCO3 Prednisolone + CaCO3 Atorvastatin + Cyclosporine (Avoid combination)	Improve the health of the patient by identifying common DDIs and their various causes of them.
6	Rama, M *et al;* 2012	India	Assessment of Drug-Drug Interactions among Renal Failure Patients of Nephrology Ward in a South Indian Tertiary Care Hospital	Prospective, observational study	205	48.58 ± 16.23	12.08± 6.30	474	76.09%	Ascorbic acid + Cyanocobalamine Clonidine + Metoprolol Amlodipine + Metoprolol Insulin + Metoprolol	NA	In CKD patients most frequently used drugs are CCBs, Beta-blockers, cardiovascular drugs, anti-diabetic drugs and others through monitoring to reduce DDIs.
CKD- Chronic kidney disease; NA- Not available												
7	Saleem A *et al*; 2017	Pakistan	Clinical relevancy and determinants of potential drug-drug interactions in chronic kidney disease patients: results from a retrospective analysis	Retrospective study	209	38.34 ± 16.82	NA	541	78.5%	Ferrous sulfate + Omeprazole Calcium/ vitamin D + ciprofloxacin Captopril + furosemide	Ciprofloxacin + Metronidazole Lisinopril + Spironolactone Amlodipine + Carbamazepine Calcium gluconate + Ceftriaxone Calcium acetate + Ceftriaxone (**Contraindicated**)	The greater frequency of potential DDIs in our study setting reflects the value of clinical pharmacy staff who can assist in managing and lowering

												potential DDIs in CKD.
8	Adanne OE *et al*; 2017	Nigeria	Evaluation of Drug-Drug Interactions Among Chronic Kidney Disease Patients of Nephrology Unit in the University of Nigeria Teaching Hospital, Ituku-Ozalla, Enugu State	Retrospective	169	51.03 ± 14.89	6.11 ± 2.03	898	NA	Lisinopril + Furosemide; Furosemide + Calcium carbonate Lisinopril + Calcium carbonate	Metoclopramide + Methyldopa (**Serious**)	Patients with CKD, who were primarily in stages 4 or 5 of renal disease, were most frequently given furosemide and lisinopril as medications. Drug interactions largely tended to be significant.
9	Shahzadi A. *et al*; 2022	Turkey	The Prevalence of Potential Drug-Drug Interactions in CKD-A Retrospective Observational Study of Cerrahpasa Nephrology Unit	Retrospective observational study	96	53	6.25	149	69.7%	Iron + Electrolytes Calcium channel blockers + β-blockers Aspirin + Electrolytes β-blockers + NSAIDs	NA	Patients with end-stage chronic kidney disease had a statistically significant correlation between potential DDIs and polypharmacy
10	Olumuyiwa JF, *et al*; 2017	Nigeria	Prevalence and Pattern of Potential Drug-Drug Interactions among Chronic Kidney Disease Patients in South-Western Nigeria	Descriptive retrospective study	123	53.81 ± 16.03	10.06 ± 3.97	1851	95.9%	Calcium Carbonate + Ferrous Sulfate Folic Acid + Furosemide Calcium Carbonate + α-Calcidol Vitamin E + Ferrous Sulfate	calcium gluconate (IV) + Ceftriaxone (IV) (Avoid combination)	The majority of these interactions have a moderate severity and a delayed onset, it is important to monitor these patients after drug prescription to lower associated morbidity and

												mortality.
11	Al-Ramahi *et al*; 2016	Palestine	Evaluation of potential drug-drug interactions among Palestinian haemodialysis patients	Observational-retrospective cohort study	275	50.67 ± 15.93	7.87 ± 2.44	930	89.1%	Calcium carbonate + Amlodipine Aspirin + Calcium carbonate Aspirin + Furosemide Aspirin + Enoxaparin	Amlodipine + Atenolol Amlodipine + Enalapril	Potential drug-drug interactions are very common among haemodialysis patients. Before prescribing, check for potential interactions and conduct routine monitoring to enhance the quality of the prescription.
12	Shireen I Hijazeen *et al*; 2020	India	Drug-Drug Interactions among haemodialysis Patients	Descriptive cross-sectional study	300	53.6 ± 16.8	5.16 ± 3.21	932	96.3%	Calcium carbonate + Nifedipine Aspirin + Calcium carbonate	Gemfibrozil + Simvastatin Atenolol + Telmisartan Gemfibrozil + Glimepiride	To manage medical care for HD patients, each HD unit should have a clinical pharmacist.
HD- Haemodialysis												
13	Santos-Díaz *et al*; 2020	Spain	Prevalence of Potential Drug-Drug Interaction Risk among Chronic Kidney Disease Patients in a Spanish Hospital	Observational cross-sectional study	112	77.1 ± 10.4	8.6 ± 3.4	928	91%	Acenocoumarol + Omeprazole Ferrous Sulfate + Omeprazole Metformin + Acetylsalicylic Acid	Acenocoumarol + Allopurinol Levothyroxine + Ferrous Sulfate Tramadol + Trazodone	The use of software in healthcare settings decreases the occurrence of Drug interactions.
14	Busari AA *et al*; 2019	Nigeria	High Risk of Drug-drug interactions among Hospitalized Patients with kidney Diseases at a Nigerian Teaching Hospital: A Call for Action	Prospective observational study	61	53.8 ± 17.5	NA	508	93.8%	Lisinopril + Losartan, Lisinopril + Furosemide Lisinopril + Metformin, Furosemide + Aspirin, Calcium carbonate + Atenolol, Calcium carbonate + Ferrous gluconate,	NA	Several technologies can be used to reduce DDIs caused by the polypharmacy exhibited in CKD patients' prevalence of various

										Ferrous gluconate + calcitriol, Ferrous gluconate + levofloxacin		comorbidities.
15	Shouqair T M *et al*; 2022	UAE	Evaluation of Drug-Related Problems in Chronic Kidney Disease Patients	Prospective cross-sectional study	130	61-70 years	11.1 ± 3.8	708	89.2%	Aspirin + Enoxaparin Insulin + Linagliptin Moxonidine + bisoprolol Clopidogrel + Enoxaparin Linagliptin + Gliclazide Aspirin + Urokinase	Carvedilol + Cinacalcet Loratadine + ipratropium bromide	Better clinical outcomes can be attained through drug optimization by preventing, identifying, and resolving certain Issues.

The studies conducted on DDI in CKD patients show that most are type C interactions, and severe interactions are rare. According to studies observed in this literature, the mean prevalence is 80.21%. The highest prevalence observed is 96.3% (Shireen I Hijazeen *et al*., 2020) which is conducted in India on haemodialysis patients. The majority of interactions are seen in end-stage renal disease (ESRD) patients because of polypharmacy.

The most common classes of DDIs seen in Calcium salts, Iron substances CCBs, β-blockers, ACE inhibitors, Antibiotics, anti-platelets, anti-diabetic drugs and Diuretics.

The most common DDIs are Calcium channel blockers (CCBs) and Calcium salts which is a pharmacodynamic interaction, the vasodilatory effect of CCBs on the small arteries is blocked and decreased by calcium salts, which lessens their antihypertensive effect. (Shrijana kumari. C. *et al*; 2021; Priyadharshini P. *et al*; 2021; Al-Ramahi *et al*; 2016; Shireen I Hijazeen *et al*., 2020). Calcium salts and Iron substances (Calcium carbonate and Ferrous sulfate) CaCO3 will decrease intestinal absorption of Ferrous sulfate by raising GIT pH, and vice versa (Priyadharshini. P. *et al*, 2021; Hammoud *et al*, 2022; Farnouda M *et al*, 2020; Adanne O E.*et al*, 2017; Shahzadi A. *et al*, 2022; Olumuyiwa JF, *et al*, 2017; Busari A *et al*, 2019). Furosemide with ACE inhibitors interaction seen in some studies causes' postural hypertension. Drugs metabolised through CYP enzymes and excreted through the renal route show more drug interactions.

X-type interactions are Chlorpheniramine + Ipratropium Bromide; Nifedipine with Carbamazepine, Phenytoin sodium and Phenobarbital; Atorvastatin + Cyclosporine; Metoclopramide + Methyldopa; Calcium acetate + Ceftriaxone; Calcium gluconate (IV) + Ceftriaxone (IV) observed in 6 studies (Priyadharshini P *et al*, 2021; Marquito AB *et al*, 2014; Farnouda M *et al*, 2020; Adanne OE *et al*, 2017; Saleem A *et al*, 2017; Olumuyiwa JF, *et al*, 2017).

Medications that cause nephrotoxicity: Analgesics, antidepressants, antimicrobials, cardiovascular agents, antiretrovirals, chemotherapeutics, diuretics, benzodiazepines, herbals and others. Medications that change intraglomerular hemodynamics are ACE inhibitors, ARBs, NSAIDs, cyclosporine and tacrolimus; drugs linked to toxicity in tubular cells are aminoglycosides, amphotericin-B; chronic interstitial nephropathy caused by acetaminophen. Aspirin, lithium, NSAIDs; crystal nephropathy by acyclovir, methotrexate, sulphur antibiotics and others (Naughton CA 2008). Dose adjustments are needed in renal impairment patients based on creatinine clearance and glomerular filtration rate (GFR) values by using various methods like the Cockcroft- Gault formula, and the Modification of Diet in Renal Disease (Lea-Henry *et al*, 2018; Myrna Y. Munar *et al*, 2007.

It is necessary to know about the medication, the degree of the patient's altered physiology, and the pharmacokinetic factors that affect the design of dose regimens when prescribing to patients with kidney disease. Drug clearance and volume of distribution altered in renal disease patients, understanding the pharmacokinetic principles and designing of drug dosing regimen may decrease drug interactions and promote rational therapy in patients. Drug

interactions detected by using software be beneficial. The role of the clinical pharmacist is crucial in the healthcare sector to decrease various drug-related problems. Although all studies show more moderate to minor interactions some patients show serious drug interactions which can be monitored and corrected by collaboration between physicians and clinical pharmacists to improve patient outcomes.

CONCLUSION

Kidney disease can alter the pharmacokinetics in any patient, leading to drug concentrations being sub-therapeutic or toxic, which can lead to the occurrence of potential drug-related problems. Polypharmacy in patients also results in various DDIs, which may result in serious medical issues which cannot be avoided because of the disease conditions, but they can be reduced by prescription reconciliation by a Clinical Pharmacist. These DDIs can be minimised by doing small changes in the following standard approaches in drug dosing regimens without altering the whole therapy to promote rational therapy by having most of the benefit from the drugs and reducing the risk. The use of software, drug banks and medical databases to detect drug interactions even before the treatment is prescribed to the patient will help get good results and avoid DDIs. The inclusion of Clinical Pharmacists in a healthcare setting promotes individualized rational therapy.

Acknowledgements

We, authors, convey our heartfelt gratitude to the management of Vijaya Institute of Pharmaceutical Sciences for women for providing the necessary support and our sincere thanks to our guide for skilfully guiding us, constantly encouraging us, patiently correcting our drafts and thereby helping us in the due course of this review.

Conflicts of interest

The authors confirm that this article's conflict has no conflict of interest.

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