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ASSESSMENT OF POLYPHARMACY PRESCRIPTIONS OF PATIENTS WITH CHRONIC KIDNEY DISEASE FOR DRUG-DRUG INTERACTIONS

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ABSTRACT

Kidney function gradually declines with chronic kidney disease (CKD). Because diabetes mellitus and hypertension are more common, More people are being diagnosed with chronic kidney disease (CKD) with time. Research shows that polypharmacy is very prevalent in patients with chronic kidney disease (CKD), with prevalence rates frequently above 80%. A cross-sectional study was conducted on 348 subjects receiving polypharmacy prescription for Chronic Kidney Disease. Data were collected from Nephrology Department, Government Medical College Hospital, Kozhikode in the duration of 3 months. The electronic DDI checking platform UpToDate was used to evaluate patient medication regimens. This software identifies and classify DDIs into five types according to the degree of clinical significance. Type A: No known interaction, Type B: No action needed, Type C: Monitor therapy. Type D: Consider therapy modification, and Type X: Avoid combination. Among 348 patients enrolled into the study 333 prescriptions showed drug interaction and 15 prescriptions did not show any interaction. In these 348 prescriptions, 2268 DDIs were identified. 524 interacting pairs were identified, out of which 91 were mild, 365 were moderate, 53 were major and 14 were contraindicated DDIs.

KEYWORDS: Chronic Kidney Disease (CKD); Drug-drug interaction (DDI); Interacting pairs; Potential Drug-Drug Interactions (pDDIs); Polypharmacy prescriptions.

INTRODUCTION

Chronic kidney disease (CKD) is defined as a state of impaired kidney function characterised by a glomerular filtration rate (GFR) of less than 60 millilitres per minute per 1.73 meters, or indicators of kidney damage, or both, for a minimum of three months.[1] Albuminuria, abnormalities in urine sediment, electrolyte or other abnormalities resulting from tubular disorders, and abnormalities in histological structure were all indicators of kidney injury.[2] GFR levels are used to categorise CKD into five stages of increasing severity.[3] CKD is a long-term illness that is frequently accompanied by diabetes mellitus and cardiovascular disorders such as hypertension, heart failure, and stroke.[4] Numerous risk factors are associated with chronic kidney disease (CKD). Modifiable risk factors include metabolic factors, hypertension, and proteinuria; non-modifiable risk factors include age, gender, ethnicity, diabetes, and genetic causes.[5,6]

Nephron loss and compensatory hyperfiltration in the remaining nephrons are the first steps in the pathophysiology of chronic kidney disease (CKD). This leads to glomerular hypertension, sclerosis, and more nephron damage.[7] A decrease in GFR, waste product buildup, fluid and electrolyte imbalances, hormonal abnormalities including anemia, and systemic consequences like cardiovascular disease and bone-mineral disorders are all signs of the disease's progression.[8,9]

The pharmacotherapy guidelines for CKD involve controlling blood pressure using ACE inhibitors or ARBs, and managing blood glucose in diabetic patients with agents like SGLT2 inhibitors.[10] It also includes correcting anemia with erythropoiesis-stimulating agents

and iron supplements, and managing mineral and bone disorders with phosphate binders, vitamin D analogs, and calcimimetics.[11,12] Using diuretics for fluid overload, treating metabolic acidosis with sodium bicarbonate if needed, and addressing cardiovascular risk factors with statins and antiplatelet agents when appropriate.[13] The only available treatment for end-stage kidney disease (ESKD) is kidney replacement therapy, which includes dialysis or kidney transplantation.[14]

AIM: Assessment of polypharmacy prescriptions of patients with chronic kidney disease for drug-drug interactions.

OBJECTIVE

To assess the drug-drug interactions in patients receiving polypharmacy prescription for chronic kidney disease.

METHODOLOGY

STUDY DESIGN: Cross-sectional study

STUDY SITE: Nephrology Department, Government Medical College Hospital, Kozhikode.

SELECTION CRITERIA

Inclusion criteria

- CKD patients receiving polypharmacy prescription for chronic kidney disease.

Exclusion criteria

- Pregnant and lactating women
- Patients on treatment with alternative medicine Ayurveda, siddha, unani, homeopathy etc.

SAMPLE SIZE

The study should contain a minimum of 348 subjects

ETHICAL CONSIDERATION

The study protocol was approved by both the Institutional Research Committee (IRC) and the Ethics Committee (IEC). An informed consent form approved by the Human Ethical Committee were signed by all patients and this process was in accordance with Good Clinical Practice.

Table 1: Drug Interaction.

DRUG INTERACTION	FREQUENCY	PERCENTAGE
YES	333	95.68
NO	15	4.31
TOTAL NUMBER OF PRESCRIPTIONS	348	100

STUDY PROCEDURE

- Based on inclusion and exclusion criteria, 348 patients were enrolled during the study period.
- A data collection form prepared according to the study objectives to include the name, age, sex, duration of therapy, co morbidities and medications.
- Data collection form prepared in English.
- Obtaining patient consent by giving information on study.

DATA ENTRY FORMAT

A specially designed data entry format will be used to enter all patient details like name, age, sex, duration of therapy, past medical history, medical history, comorbidities, drugs prescribed and drug interactions involved.

STATISTICAL ANALYSIS

A cross-sectional study will be carried for a period of 3 months. Prescription will be noted down and uploaded in up-to-date software and drug- drug interactions report will be obtained. The data will be tabulated and statistically analysed using SPSS Software based upon normal/ non normal distribution of data obtained (ANOVA/ Kruskal-Wallis/ paired t-test/ Mann- Whitney U test etc) to find relation with their socio demographic variables.

RESULTS

Among 348 patients enrolled into the study 333 prescriptions showed drug interaction and 15 prescriptions does not show any drug interaction. In these 348 prescriptions, 2256 DDIs were identified. 524 interacting pairs were identified, out of which 91 were mild, 356 were moderate and 53 were major DDIs.

Drug Interaction

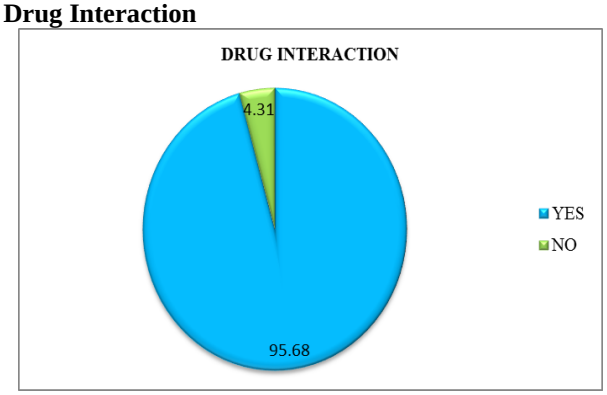

Figure 1: Drug Interaction.

Figure 3 and table 2 show presence of DIs in the prescriptions. Among 348 patients enrolled into the study 333 prescriptions showed drug interaction and 15 prescriptions does not show any drug interaction.

Age Wise Distribution

Table 2: Association of Drug Interaction Frequency with Age.

SL.NO	AGE	DRUG INTERACTION		TOTAL
		PRESENT	ABSENT	
1	20-29	6	1	7
2	30-39	25	0	25
3	40-49	60	5	65
4	50-59	69	5	74
5	60-69	115	1	116
6	70-79	54	3	57
7	80-89	4	0	4

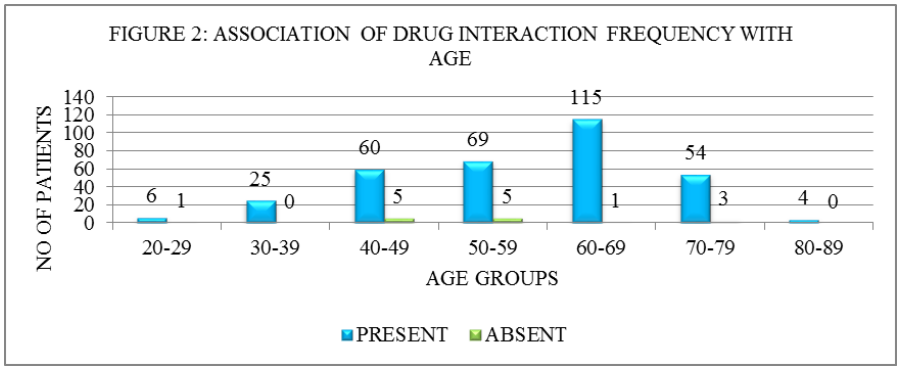

Table 3 and figure 4 show association of drug interaction frequency with age. Out of the total 348 patients enrolled, the majority of patients having drug-drug interactions (33.33%) were under the age of 60-69 and the least number of patients having drug-drug interactions (1.14%) were under the age of 80-89.

Table 2: Association of Drug Interaction Frequency With Gender.

SL.NO	SEX	DRUG INTERACTION		TOTAL
		PRESENT	ABSENT	
1	Female	91	3	94
2	Male	242	12	254

Gender Wise Distribution

Table 4: Association of Drug Interaction Frequency with Gender.

INTERACTING PAIRS	FREQUENCY	SEVERITY	RISK RATING
Furosemide + Cilnidipine	40	C	Moderate
Furosemide + Insulin	26	C	Moderate
Prazosin + Clonidine	22	C	Moderate
Prazosin + Cilnidipine	27	C	Moderate
Prazosin + Torsemide	18	C	Moderate
Torsemide + Cilnidipine	41	C	Moderate
Torsemide + Clonidine	20	C	Moderate
Torsemide + Insulin	33	C	Moderate
Torsemide + Telmisartan	11	C	Moderate
Torsemide + Aspirin	34	C	Moderate
Torsemide + Spironolactone	27	C	Moderate
Torsemide + Dapagliflozin	11	C	Moderate
Torsemide + Metoprolol	14	C	Moderate
Glimepiride + Dapagliflozin	15	D	Major
Glimepiride + Sodium Bicarbonate	32	B	Mild
Glimepiride + Metformin	27	C	Moderate
Glimepiride + Aspirin	16	C	Moderate
Glimepiride + Insulin	18	C	Moderate
Aspirin + Calcium	18	B	Mild
Aspirin + Sodium Bicarbonate	68	B	Mild
Aspirin + Clopidogrel	30	C	Moderate

Aspirin + Insulin	39	C	Moderate
Calcium + Vitamin D3	32	C	Moderate
Calcium + Calcitriol	17	C	Moderate
Calcitriol + Sevelamer	27	C	Moderate
Calcitriol + Calcium Carbonate	15	C	Moderate
Carvedilol + Isosorbide Dinitrate	15	C	Moderate
Isosorbide Dinitrate + Hydralazine	25	C	Moderate
Rosuvastatin + Sodium Bicarbonate	22	C	Moderate
Metoprolol + Insulin	23	C	Moderate
Insulin + Dapagliflozin	15	D	Major
Sodium Bicarbonate + Ferrous Fumarate	20	D	Major
Atorvastatin + Clopidogrel	37	B	Mild
Telmisartan + Spironolactone	16	C	Moderate
Clopidogrel + Cilnidipine	22	B	Mild
Acetaminophen + Tramadol	15	B	Mild

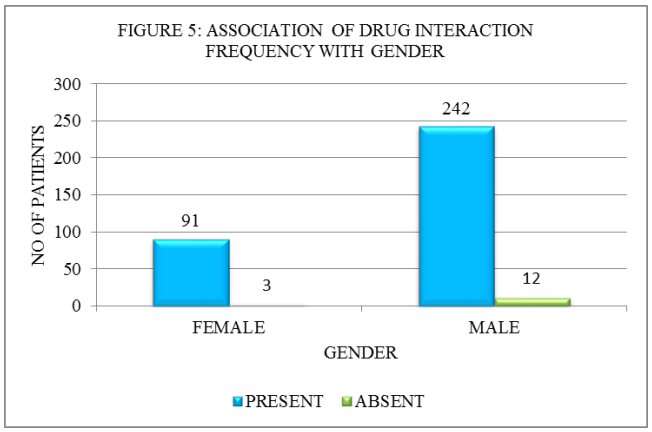

Table 4 and figure 5: Association of drug interaction frequency with gender. The numbers of male patients were greater than female patients. It was found that 94 (27.01%) patients were female and 254 (72.98%) patients were male. Out of 94 prescriptions of female patients, 91 (96.80%) prescriptions had drug interaction. Out of 254 prescriptions of male patients, 242 (95.27%) prescriptions had drug interaction.

Severity of DI

Table 6: Classification Based on Severity of di.

SEVERITY	RISK RATING	FREQUENCY	PERCENTAGE
Mild	B	91	17.36
Moderate	C	365	69.65
Major	D	53	10.11
Contraindicated	X	14	2.67
TOTAL		524	100

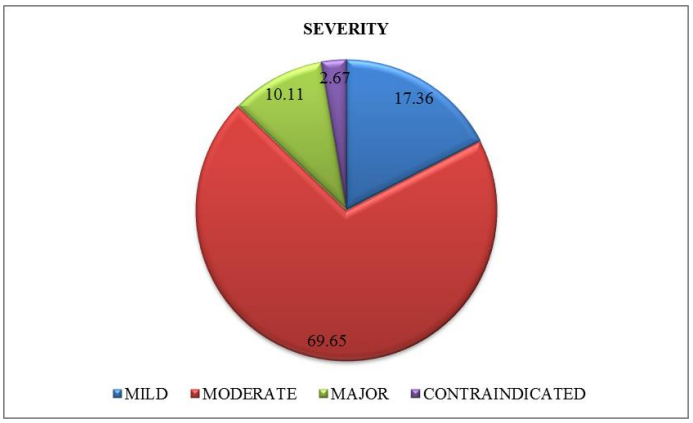

Figure 6: Severity Of Di.

Table 7 and figure 6 shows classification on the basis of severity, drug interaction can be divided into mild, moderate, major and contraindicated. Out of 524 interacting pairs, 91 were mild (17.36%), 365 were moderate (69.65%), 53 were major (10.11%) and 14 were contraindicated (2.67%) drug interaction.

DISCUSSION

Since CKD patients often have several co-morbid conditions, including underlying diseases and harmful effects from reduced kidney function, they typically require multiple medications. A large number of CKD drugs are available in the market. Drug interactions between the CKD agents can lead to many health complications. This study provides a summary and critical analysis of the current understanding of the most common drug interactions in CKD patients receiving multiple medications, highlighting the key underlying mechanisms and the clinical importance of the potential drug-drug interactions.[15]

The data collected were organised, tabulated, analysed and described with the help of tables and graphs.

Drug Interaction

Among 348 patients enrolled in the study. 333 prescriptions (95.68%) showed drug interaction, and 15 prescriptions (4.31%) did not show any interaction. A similar study conducted by Papotti B, Marchi C, Adorni MP and Poti F, using Medscape detected pDDIs in 52% of patients with CKD.[15]

Age Wise Distribution

Out of the total 348 patients enrolled, the majority (33.33%) were under the age group of 60-69, and the least number of patients (1.14%) were under the age group of 80-89. A study was conducted by Papotti B, Marchi C, Adorni MP and Poti F, had a majority of patients between the ages of 60-69.[15]

Gender

It was found that 94 (27.01%) patients were female and 254 (72.98%) patients were male. Out of 94 female patients, 91(96.80%) female had drug interactions. Out of 254 male patients, 242 (95.27%) had drug interactions. The number of male patients was greater than female patients. A study conducted by Papotti B, Marchi C, Adorni MP and Poti F had the majority of patients showed similar pattern where the number of male patients was greater than female patients.[15]

Drug-Drug Interactions

Among 348 patients enrolled in the study, 333 prescriptions showed drug interaction, and 15 prescriptions did not show any interaction. 524 interacting pairs were identified.

In 524 interacting pairs, 14 were contraindicated, 53 were major, 356 were moderate and 91 were mild DDIs. Among 14 contraindicated DDIs, the interacting pairs are **prazosin + Silodosin, prazosin + tamsulosin, calcium + calcium acetate, calcium acetate + calcium gluconate, Calcitriol + vitamin D3, Carvedilol + terbutaline, Metoprolol + etofylline, clopidogrel + omeprazole, levofloxacin + domperidone , nebivolol + etofylline, azithromycin + domperidone, domperidone + olanzapine, domperidone + ondansetron, Tiotropium + ipratropium.**

These findings highlight the critical importance of regular medication review and the implementation of clinical decision support systems to mitigate the risk of potential DDIs in CKD patients. Therefore, continuous pharmacovigilance, appropriate dose adjustments, and alternative drug selections play a key role in minimizing the risk of harmful drug interactions in polypharmacy cases.

It was found that the most frequent interacting pairs in our study were Aspirin + Sodium Bicarbonate, Torsemide + Cilnidipine, Furosemide + Cilnidipine, Calcium + Calcitriol & Aspirin + Insulin. A study conducted by Papotti B, Marchi C, Adorni MP and Poti F found the most frequent pDDI were Calcium carbonate + Ferrous sulphate, Furosemide + Aspirin, Furosemide + Captopril, and Furosemide + Lisinopril.[1]

The most frequent Interacting pairs include Aspirin + Sodium bicarbonate (2.99%), Torsemide + Cilnidipine (1.80%), Furosemide + Cilnidipine (1.76%), Calcium + Calcitriol (1.74%), Aspirin + Insulin (1.71%), Atorvastatin + Clopidogrel (1.63%), Torsemide + Aspirin (1.49 %), Torsemide + Insulin (1.45 %), Glimepiride + Sodium

Bicarbonate (1.41%), Calcium + Vitamin D3 (1.41%), Aspirin + Clopidogrel (1.32%), Prazosin + Cilnidipine (1.19%), Torsemide + Spironolactone (1.19%), Calcitriol + Sevelamer (1.19%), Glimepiride + Metformin (1.19%), Furosemide + Insulin (1.14%), Isosorbide Dinitrate + Hydralazine (1.10%), Metoprolol + Insulin (1.01%), Clopidogrel + Cilnidipine (0.97%), Prazosin + Clonidine (0.97%), Rosuvastatin + Sodium Bicarbonate (0.97%), Torsemide + Clonidine (0.88%), Sodium Bicarbonate + Ferrous Fumarate (0.88%), Aspirin + Calcium (0.79%), Glimepiride + Insulin (0.79%), Prazosin + Torsemide (0.79 %), Furosemide + Clonidine (0.74%), Furosemide + Tamsulosin (0.74%), Glimepiride + Aspirin (0.70%), Telmisartan + Spironolactone (0.70%), Calcium + Ferrous Fumarate (0.69%), Acetaminophen + Tramadol (0.66%), Furosemide + Dapagliflozin (0.66%), Furosemide + Aspirin (0.66 %), Glimepiride + Dapagliflozin (0.66%), Insulin + Dapagliflozin (0.66%), Calcitriol +Calcium Carbonate (0.66%), Carvedilol + Isosorbidedinitrate (0.66%), Torsemide + Metoprolol (0.61%), Metformin + Telmisartan (0.61%), Aspirin + Metformin (0.57%), Aspirin + Omega-3 Fatty Acid (0.57%), Calcium + Cilnidipine (0.57%), Furosemide + Glimepiride (0.57%), Prasocin + Telmisartan (0.57%), Sodium Bicarbonate + Iron Supplement (0.57%),

Torsemide + Isosorbidedinitrate (0.52%), Aspirin + Spironolactone (0.52%), Furosemide + Telmisartan (0.52%), Insulin + Prednisolone (0.52%), Cilnidipine + Tamsulosin (0.52%), Torsemide + Telmisartan (0.48%), Torsemide + Dapagliflozin (0.48%), Glimepiride + Calcium (0.48%), Metformin + Insulin (0.48%), Rosuvastatin + Clopidogrel (0.48%), Prasocin + Nifedipine (0.48%), Torsemide + Hydralazine (0.48%), Sodium Bicarbonate + Ranitidine (0.44%), Metoprolol + Clonidine (0.44%), Torsemide + Glimeperide (0.44%), Glimeperide + Teneligliptin (0.39%), Insulin + Linagliptin (0.39%), Calcitriol + Vitamin D 3 (0.39%), Rosuvastatin + Febuxostat (0.26%), Clonidine + Nebivolol (0.26%), Carvedilol + Clonidine (0.26%), Sodium Bicarbonate + Prednisolone (0.22%), Pantoprazole + Cefuroxime (0.22%), Glimepiride + Linagliptin (0.22%), Calcium + Calcium Acetate (0.17%), Insulin + Teneligliptin (0.17%), Aspirin + Ticagrelor (0.17%), Calcium Carbonate + Prednisolone (0.17%), Levofloxacin + Magnesium Hydroxide (0.17%), Clonidine + Tramadol (0.17%), Prazosin + Tamsulosin (0.13%),

Levofloxacin + Ferrous Fumarate (0.13%), Calcium + Levofloxacin (0.13%), Sodium Bicarbonate + Ferrous Gluconate (0.13%), Levofloxacin + Domperidone (0.08%), Nebivolol + Etofylline (0.08%), Furosemide + Sucralfate (0.08%), Glimeperide + Pioglitazone (0.08%), Calcium + Prednisolone (0.08%), Levofloxacin + Aluminium Hydroxide (0.08%), Calcium Carbonate + Ferrous Fumarate (0.08%), Domperidone + Ondansetron (0.08%), Calcitriol + Aluminium Hydroxide (0.08%), Aluminium Hydroxide + Ethambutol (0.08%), Insulin + Pioglitazone (0.08%), Sodium Bicarbonate + Deflazacort (0.08%), Sodium Bicarbonate + Cefuroxime (0.08%), Teneligliptin + Gliclazide (0.08%), Escitalopram + Quetiapine (0.08%), Tramadol + Gabapentin (0.04%), Tramadol + Chlordiazepoxide (0.04%), Levofloxazin + Aluminium Hydroxide (0.04%), Ferrous Fumarate + Aluminium Hydroxide (0.04%), Ferrous Fumarate + Magnesium Hydroxide (0.04%), Rabeprazole + Ferrous Gluconate (0.04%), Phenylephrine + Chlordiazepoxide (0.04%), Magnesium Hydroxide + Cefuroxime (0.04%), Calcium + Meselamine (0.04%), Calcium + Iron Supplement (0.04%), Calcium Carbonate + Iron Supplement (0.04%), Calcium + Cefuroxime (0.04%), Calcitriol + Magnesium Hydroxide (0.04%), Aluminium Hydroxide + Cefuroxime (0.04%), Metformin + Dapagliflozin (0.04%), Teneligliptin + Glipizide (0.04%), Clonidine + Propranolol (0.04%), Clonidine + Cetrizine (0.04%), Clopidogrel + Rifampicin (0.04%), Clopidogrel + Fluconazole (0.04%), Prazosin + Silodosin (0.04%), Calcium Acetate + Calcium Gluconate (0.04%), Carvedilol + Terbutaline (0.04%), Metoprolol + Etofylline (0.04%), Clopidogrel + Omeprazole (0.04%), Azithromycin + Domperidone (0.04%), Domperidone + Olanzapine (0.04%), Tiotropium + Ipratropium (0.04%).

CONCLUSION

The cross-sectional study titled "Assessment of polypharmacy prescriptions of patients with chronic kidney disease for drug-drug interactions" was conducted with the objective of assessing potential drug-drug interactions (pDDIs) in CKD patients of nephrolology department, Govt. Medical College, Kozhikode. This can help raise awareness about the potential burden of DDIs in clinical practice and highlights the importance of routinely reviewing prescriptions for CKD patients to identify any drug-related issues.

Chronic kidney disease (CKD) is more prevalent among the elderly, who often present with multiple age-related co morbidities. This increases the need for multiple medications, resulting in polypharmacy, which in turn elevates the risk of potential drug-drug interactions (DDIs).

A total of 348 patients with chronic kidney disease were enrolled in the study. Data was collected from the subjects after receiving their consent and result were analyzed for drug-drug interaction possibilities using UpToDate software. Out of total 348 patients enrolled, 333 prescriptions showed drug interaction and 15 prescriptions did not show any interaction.

Among 348 patients, the majority of patients having drug-drug interactions (33.33%) were under the age group of 60-69 and the least number of patients having drug-drug interactions (1.14%) were under the age group of 80-89.

In 333 prescriptions 524 interacting pairs were identified. Out of 524 interacting pairs, 14 were contraindicated, 53 were major, 356 were moderate and 91 were mild DDIs. Among 14 contraindicated DDIs, the interacting pairs are **Prazosin + Silodosin, Prazosin + Tamsulosin, Calcium + Calcium Acetate, Calcium Acetate + Calcium Gluconate, Calcitriol + Vitamin D3, Carvedilol + Terbutaline, Metoprolol + Etofylline, Clopidogrel + Omeprazole, Levofloxacin + Domperidone, Nebivolol + Etofylline, Azithromycin + Domperidone, Domperidone + Olanzapine, Domperidone + Ondansetron, Tiotropium + Ipratropium.** The most frequent interacting pairs include Aspirin + Sodium Bicarbonate, Torsemide + Cilnidipine, Furosemide + Cilnidipine, Calcium + Calcitriol & Aspirin + Insulin. Also, in the 348 prescriptions, a total of 2268 DDIs were identified.

Early detection and avoidance of negative outcomes are made possible by understanding of medication interactions. In order to avoid them, it is crucial that everyone working in the medical field understands possible medication interactions. Additionally, a concerted effort is needed to reduce the issues of medicine and food interactions. Drug interactions are frequent in clinical practice and are linked to a number of conditions, including aging, polypharmacy, hepatic

metabolism, and impaired renal function. Because they typically need several different types of medications, people with chronic kidney disease (CKD) are frequently more likely to develop Drug interactions.

The quantity and dosage of medications should be appropriately managed to lower the risk of drug-drug interactions. A pharmacist is a vital element of the multidisciplinary team and has many chances to enhance the patient's overall treatment. Potential drug-drug interactions can also be decreased by educating patients about how to take their medications. The likelihood of interactions can be decreased by choosing a medication that has little to no interaction with the medication being taken with it.

Patients with chronic kidney disease are often managed by different physicians including but not limited to nephrologists, cardiologists, endocrinologists and general physicians. This increases the chances of drug interaction between medications prescribed by multiple specialists. A multidisciplinary approach is essential in minimizing the risk of possible drug interaction in CKD patients which may not be feasible in government settings where the no.of OPD patients with CKD patients are numerous often nearly greater than 200 patients per day.

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