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A Study on Drug Utilization Review and Potential Drug - Drug Interactions in Chronic Kidney Disease Patients

By Monika K. A., K. S. Charitha, M. Ramana Reddy, K. Vaishnavi,
Ramakrishna Prudhivi & Jyothi
Dayananada Sagar University

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Objectives: The aim of the present study is to evaluate the Drug Utilization Review (DUR) and to assess the potential drug-drug interaction in CKD patients.

Methods: This was a prospective observational & analytical study conducted in Sagar Hospitals, Bengaluru. The information collected in the patient profile form, the prescribing pattern was assessed and potential drug-drug interactions were evaluated by using Micromedex, clinirex and drugs.com.

Results: This study reveals that the males were more prone to CKD (63%) than females (37%) and the highest percentage of patients in the age group 61-75 years with the average of 66.40 ± 3.92 years. Among all medications the major class of drugs prescribed were anti-hypertensives & the least were drugs acting on thyroid. A total of 547 potential DDIs were observed of which moderate DDI (64.71%) were highest followed by minor (21.75%) & major (13.34%).

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Conclusion: The use of polypharmacy for the treatment of multiple co-morbid conditions has been proved to be as one of the most important factors in patients with CKD. Polypharmacy can predispose to drug interactions which results in the failure of the drug therapy and increase in the length of hospital stay. The active participation of clinical pharmacist in clinical activities can help in minimizing the risk and improving the patient care.

Keywords: chronic kidney disease (CKD), drug-drug interactions (DDIs), drug utilization review (DUR).

Author $\alpha \sigma \rho \omega$: Department of Pharmacy Practice, Dayananda Sagar College of Pharmacy, Bengaluru, India. e-mails: monikaamarnath@gmail.com, charita.kodumagulla@gmail.com, ramanareddymadathala@gmail.com, vaishnavi.kulkarni71@gmail.com

Author ¥: M. Pharm., (Ph. D), Asst. Professor, Department of Pharmacy Practice, Faculty of Pharmacy, Dayananda Sagar University, Bengaluru, India. e-mail: ramakrishna.prudhivi@gmail.com

Author §: Department of Nephrology, Senior Resident, Sagar Hospitals, Kumaraswamy Layout & Tilaknagar, Bengaluru, India. e-mail: rkjpty6pho945@gmail.com

1. INTRODUCTION

Chronic kidney disease (CKD) is defined as a reduction in the Glomerular Filtration Rate (GFR) and/or urinary abnormalities or structural abnormalities of the renal tract.¹ One in ten people have chronic kidney disease and about 175,000 new people have chronic kidney disease (stage V CKD) every year in India, requiring dialysis and/or kidney transplantation.² India has been encountering the major problem of the rising incidence of CKD which may lead to difficulties in health care and economy in future. Indeed, it has been recently estimated that the age-adjusted incidence rate of End Stage Renal Disease (ESRD) in India to be 229 per million population (pmp)³ and >100,000 new patients enter renal replacement programs annually in India.⁴ The highest prevalence of CKD was observed in Visakhapatnam, Andhra Pradesh (46.8%), Kanpur, Uttar Pradesh (41.7%) and Delhi (41%). The lowest prevalence was observed in Mysore and Bangalore in Karnataka state.^{5, 6}

Patients with CKD have interrelated co-morbidities with shared risk factors, including hypertension, atherosclerosis, glucose intolerance or diabetes, and lipid disorders, that can worsen renal and cardiovascular outcomes.⁷ The most common cause in the adult population is DM, accounting for approximately 40% of patients on renal replacement therapy. HTN is the second most common cause, accounting for one third of patients on renal replacement therapy.⁸

Elderly patients often face with polypharmacy when they have multiple disease processes. Declining organ function, as part of the normal aging process, adds to the problem of adverse drug effects in this population. To minimize polypharmacy, prescribers aim to treat multiple disease conditions with a single agent in cases where there is a possibility.⁹ CKD patients are medically complex to treat and have high risk of adverse reactions. Noncompliance to medication is also a great concern in CKD patients.¹⁰ A recent research study suggested that CKD patients have higher prevalence of inappropriate medication prescriptions, mostly antihypertensive and antibiotics.¹¹

Drug use evaluation, sometimes referred to as drug utilization review, is a system of continuous,

systematic, criteria-based drug evaluation that ensures the appropriate use of drugs. It is a method of obtaining information to identify problems related to drug use and if properly developed, it also provides a means of correcting the problem and thereby contributes to rational drug therapy.¹² Drug utilization studies in CKD patients help to understand and build evidence for the drug use. CKD patients need to take medicines lifelong, which makes it is very important to study the prescribing trend on a regular basis.

Drug-drug interactions (DDI) can be defined as an appreciably harmful or beneficial process whereby the pharmacological effect of a drug is directly or indirectly influenced and modified by the presence of another drug, which can result in either treatment failure (antagonistic interaction) or drug-induced toxicity (synergistic/additive interaction).¹³

DDIs are major clinical problem; accounting for 2–6% of all hospital admissions with estimated annual cost to the National Health Service of £500 million in the UK.¹⁴ Monitoring the drug-drug interactions may improve the quality of prescribing and dispensing.¹⁵ The present study aimed at assessing the drug utilization review and identifying drug-drug interactions.

II. METHODOLOGY

a) Study Design and Type

This study was a prospective, observational and analytical study carried out at Nephrology Unit of Sagar Hospitals at Tilaknagar and Kumarswamy layout, Bangalore.

b) Inclusion and Exclusion Criteria

A total of 110 patients were being consented for the study and is carried out for a period of 6 months from September 2017 to February 2018. The patients aged below 18 years, patients with Acute Kidney Injury (AKI), and those who continued to take further treatment in some other hospital were excluded from the study.

c) Study Procedure

The medical case records of all the adult CKD patients were retrieved after a verbal informed consent was obtained from each of them, and the following information was extracted using a pro forma: socio-demographic data, stage of CKD, number and list of medications at the time of last clinic visit for outpatients and at the time of discharge for those who received in-patient care, number and list of co-morbidities.

The estimated glomerular filtration rate (eGFR) was measured using MDRD formula, and CKD staging was done using eGFR as follows: stage 1 (eGFR of ≥ 90 mL/min with evidence of kidney damage), stage 2 (eGFR of 60–89 mL/min with or without evidence of kidney damage), stage 3 (eGFR of 30–59 mL/min with or without evidence of kidney damage), stage 4 (eGFR of 15–29 mL/min with or without evidence of kidney

damage), and stage 5 (eGFR < 15 mL/min with or without evidence of kidney damage).¹⁶

The prescriptions were individually screened to assess the drug utilization and drug-drug interactions in CKD patients. The diagnosis and the drugs prescribed along with dosage schedule, duration were analyzed using Micromedex 2.0 and CIMS. The drug interactions were assessed and checked which were divided into major, moderate and minor using www.drugs.com, Medscape, Clinirex and Micromedex2.0. The interactions checked here were even classified into pharmacokinetic, pharmacodynamics and non-specific type.

d) Data Analysis

In this study the results were analyzed using student's t-test (unpaired) for comparing two groups and one-way ANOVA for finding the statistical differences among more than two groups. Results were expressed in the form of mean \pm SD. A p -value < 0.05 was considered statistically significant.

e) Ethical Clearance

Ethical clearance for the study was obtained from the Institutional Human Ethics committee, Dayananda Sagar College of Pharmacy, Bengaluru.

III. RESULTS

A total of 110 patients were reviewed among which 100 patients completed the study, 10 patients continued to take further treatment at different hospital. Our results were based on 100 patients out of which 63% of the patients were male and 37% were female. Most of the patients (54%) were elderly. Major number of patients was diagnosed with end stage renal failure i.e. G5 and the least number are diagnosed with G1. On analysis of type of co morbidities among study population, it was noted that 81% were affected with Hypertension followed by 66% with Diabetes Mellitus, 51% with Anemia, 19% with IHD, 12% with Hypothyroidism, 9% affected with various others diseases such as COPD, Spondylitis, BPH, UTI & LRTI. Maximum number of patients (44%) were appeared with two co-morbidities and 93% of patients had at least one co-morbidity. It was also observed that > 15 prescribed drugs were received by 43% of patients and the average number of drugs prescribed per patient was about 13.4 ± 1.6 drugs. As per the analysis it was reported that the duration of the hospital stay 6-10 days consisted of 43% patients and mean hospital durations was 7.2 ± 2.2 days. The demographic data with clinical variables was shown in Table1.

The major class of drugs prescribed among patients were antihypertensive drugs constituting 16.48% followed by GIT drugs (14.07%), nutritional supplements (10.88%), chemotherapeutic agents (10.80%), respiratory drugs (8.08%), antidiabetic drugs

(6.29%), analgesics & antipyretics (5.83%), hematinics (4.97%), anti - thrombotics (4.66%), CNS drugs (4.51%), drugs acting on acid-base disorders (4.43%), anti - hyperlipidemics (3.65%), immunosuppressants (1.94%), drugs acting on thyroid are (1.01%) and other drugs (2.33%) as shown in Figure 1.

Among 212 antihypertensive drugs, the most widely prescribed antihypertensive drugs were diuretics (26.41%), followed by CCBs (25.47%), and β blockers (12.26%). Patients having DM as a co-morbidity, received insulin injectables with 64.19%. Anticoagulants occupied 80% of all anti thrombotic drugs. Out of drugs acting on GIT, 46.40% of the prescriptions were prescribed with Proton Pump Inhibitors (PPIs), followed by 24.86% with anti-emetics. The least preferred drugs in this category are H2 antagonists. Anti-depressants were seen in 21 prescriptions. Levothyroxine (13%) is the only drug prescribed for treatment of thyroid. The highest number of antibiotics prescribed as combinations with 30.21% followed by 10.79% with carbapenems, 10.07% with macrolide antibiotics, 7.91% with cephalosporins, 7.19% with Anti-TB, 6.47% with Fluoroquinolones, 5.03% with Anti-amoebic, 3.59% with Anti-fungal and 0.71% with Amino glycosides. Of 64 hematinic drugs 56.24% of the prescriptions were Iron, 34.37% Erythropoietin, 9.37% Vit-B12, and 3.12 % of the prescriptions were prescribed with Combinations. Among nutritional supplements, most of the drugs were prescribed as combinations (60%) and 14.28% prescriptions were with calcium carbonate followed by 12.85% with protein powder. Majority of drugs for acid base disorders were sodium bicarbonate (52.63%) and analgesics & antipyretics were seen in 39 prescriptions. The drug utilization pattern was shown in Table 2.

As shown in Figure 2 there were 547 interactions with an average of 5.4 ± 0.9 interactions per each patient in 100 patients, of which major was pharmacokinetic type of interaction accounts for about more than 50% of interactions followed by pharmacodynamic interactions and non-specific. The drug interactions are classified into major, minor & moderate among which moderatedrug interactions accounts for 64.71% followed by minor(21.75%) and major(13.34%).

The interaction between Clarithromycin and budesonide (29.62%) was the most commonly seen major DDI. The list of drugs involved in major DDI was shown in Figure 3. The interaction between levothyroxine and basalog was responsible for 12.06% of moderate DDI and most prevalent interaction seen in minor DDI was between aspirin and pantaprazole (23.72%).

There was no significant difference between male and female in occurrences of drug interactions but there was a statistical significant difference ($p=0.035^{**}$) among different age groups. The maximum numbers of interactions were found in age group of 46-60years. Patients with 2 co-morbidities were experienced

predominant number of DDI (43.14%). As there was increase in number of drugs in the prescription chart more number of DDI were noticed. However there was no co-relation between duration of hospital stay and occurrence of DDI (Table 3).

IV. DISCUSSION

In this study, an attempt was made to reveal the prescribing pattern of drugs and potential drug-drug interactions in study population of about 100 patients diagnosed with CKD and who satisfied the inclusion and exclusion criteria for a period of 6 months in Sagar Hospitals, Kumaraswamy layout and Tilaknagar, Bengaluru.

Among 100 patients who were involved in the study, total number of male patients were 63 (63%) and females were 37 (37%), showing that the males were predominant for the development of CKD which was compared and found similar to the study conducted by Rachana PR et al.¹⁷ In our study CKD was seen most commonly in the age group above 60 years but it was in contrast to the study conducted by Tamilselvan.et.al, in which age group between 50-60 years age –group were most affected.¹⁸ It was observed that, most of the patients admitted to the hospital belonged to G5 stage (48%) and least belonged to G1 stage. Here the staging was done based on GFR rate i.e., by calculating glomerular filtration rate and compared to the study carried out by Anand N et.al, which matched with the study results i.e. here the patients diagnosed with CKD mostly belonged to G5 stage (87.8%).¹⁹ Co morbidity is one of the common conditions seen with CKD which leads to the increased rate of morbidity and mortality. In the present study, Hypertension(81%) was the most seen co morbid condition, followed by DM (66%), Anemia(51%), IHD(19%), Hypothyroidism(12%) was inconsistent to the study conducted by Fraser SD et.al. showing that the major common co morbid condition was HTN (88%) followed by anemia (23%).²⁰ 44% of study population had 2 co-morbid conditions and only 1% of the population with 5 co-morbid conditions was found homogeneous to Pranavi Dasari et.al study.²¹

In patients who were diagnosed with CKD, there were several co morbid conditions present. So, wide class of drugs are prescribed for their treatment, of which the most prescribed were anti-hypertensive drugs (16.48%), followed by GIT drugs (14.07%), nutritional supplements (10.08%), respiratory drugs(8.08%) and the least prescribed class was drugs acting on thyroid which was not agreed to the study in which drugs acting on CVS(31%) was major followed by nutritional supplements (15%), hematinics (11%).¹⁹ Among the Anti-HTN drugs prescribed in this study the majority of the drugs were diuretics (26.41%), followed by CCB (25.4%), β -blockers (12.26%) and the least prescribed was ACE-I which was compared to the study organized

by Amit Ranjan et.al, showed that the most prescribed drugs in anti-HTN class were Diuretics (78%), followed by α -blockers (40%), CCB (38%) and the least was combination therapy of α -blockers with CCB.²² Among 66 patients diagnosed with DM, there were 81 numbers of prescriptions for anti-diabetic drugs. In this study insulin preparations were most preferred to treat DM than oral hypoglycemic agents. These results were correlated with the study done by Devi DP, George.²³ Among all the class of drugs prescribed, analgesic and antipyretic drugs were 5.83%. The most common reason for using this was bone-joint pain, headache, and pain. This was found dissimilarity with Zibgniew et.al study, showing 35% use of NSAID class of drugs.²⁴ Antibiotics were prescribed to minimize the infectious conditions. Combination therapy was most preferred to monotherapy. Other than combination therapy, carbapenems, macrolides, cephalosporins were prescribed respectively and were not found in correlation with the study conducted by Sowmya santra et.al, which demonstrated high prescription of Cefoperazone, metronidazole respectively.²⁵ In spite of high prevalence of anemia (51%), the hematanics class of drugs which include Iron supplements (53.12%), erythropoietin (34.37%), vitamin B-12(9.37%) and oral elemental iron (3.12%) were accounted as the major medications for treating anemia in CKD patients subsequently reducing the requirement of blood transfusion. However, in other studies, conducted by Joshi AD et.al showed erythropoietin was the major prescribed drugs. By this comparison it was concluded that the use erythropoietin would be safer in CKD patients, as it reduces the risk of blood transfusion.²⁶

A total of 547 DDI observed in the study were classified based on their severity assessment and type of interactions. Pharmacokinetic drug interactions (55.39%) were more predominantly seen when compared to pharmacodynamic drug interactions (19.37%). Based on severity DDI were categorized into major, moderate and minor interactions. In which moderate DDI were more commonly seen followed by minor and major which was seen in agreement with the study done by Mr. Sibi C Chacko et.al, which showed that moderate interactions contributed to highest than minor and major.²⁷ Our study reveals that majority of the drug interactions were due to interaction between levothyroxine and basalog which is in divergence with the other studies.^{27, 28}

The factors significantly correlated with the occurrence of DDI were elderly, number of co-morbidities and number of drugs prescribed.

V. CONCLUSION

Drug utilization evaluation and identification of the potential drug-drug interactions play a key role in providing better patient care. The use of Polypharmacy

for the treatment of multiple co-morbid conditions has been proved to be as one of the most important factors in patients with CKD. Polypharmacy can predispose to drug interactions which result in the failure of the drug therapy and increase in the length of hospital stay. The active participation of clinical pharmacist in clinical activities can help in minimizing the risk and improving the patient care.

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Abbreviations

CCBs: Calcium Channel Blockers.
CKD: Chronic Kidney Disease.
DDIs: Drug-Drug Interactions.
DUR: Drug Utilization Review.
IHD: Ischemic Heart Disease.
PPIs: Proton Pump Inhibitors.

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Competing Interests

The authors declare that they have no competing interests.

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Table 1: Demographic Data with Clinical Variables

Variable	No. of Patients	Percentage (%)
Gender		
Male	63	63
Female	37	37
Age		
16-30	4	4
31-45	12	12
46-60	30	30
61-75	44	44
76-90	10	10
CKD Classification (Based on GFR)		
G1	2	2
G2	4	4
G3a	2	2
G3b	6	6
G4	22	22
G5	48	48
No. of Comorbidities		
0	7	7
1	21	21
2	44	44
3	19	19
4	8	8
5	1	1
No. of Drugs Prescribed		
≤ 5	2	2
6-10	22	22
11-15	36	36
>15	43	43
Duration of Hospital Stay		
≤5	35	35
6-10	43	43
11-15	16	16
>15	6	6

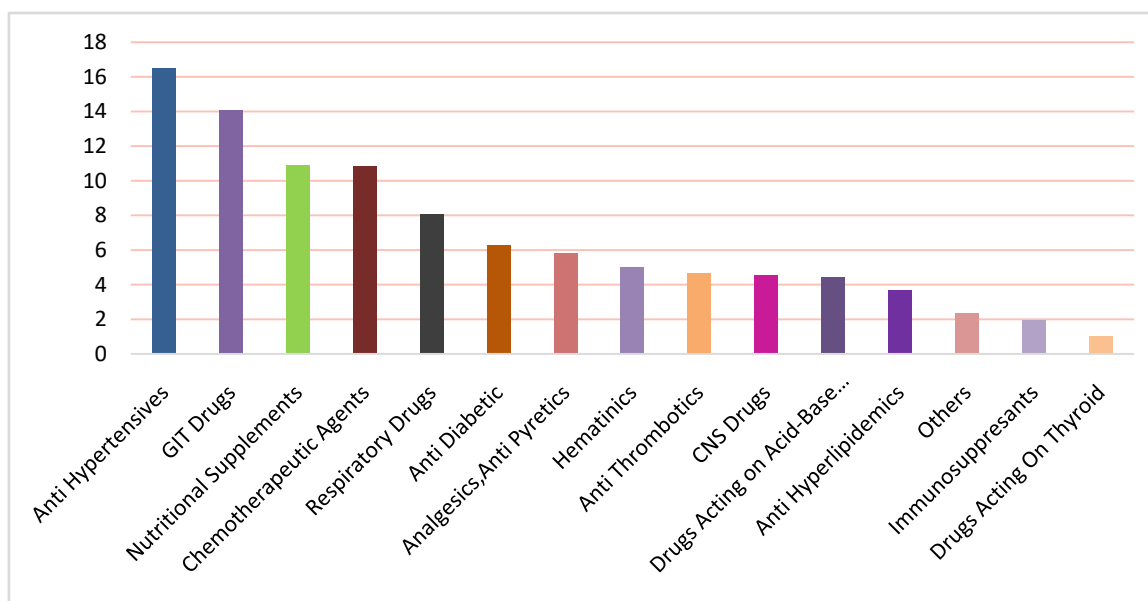


Fig. 1: Classification of Drugs Prescribed

Table 2: Pattern of Various Classes of Drugs Prescribed

Class of Drug	No. of Prescriptions	Percentage (%)
Pattern of Anti-Hypertensive Drugs		
Diuretics	56	26.41
Ccbs	54	25.47
B Blockers	26	12.26
A Blockers	20	9.43
A Agonists	13	6.13
Anti-Anginal	13	6.13
A + B Blockers	9	4.24
Combinations	8	3.77
Centrally Acting Sympatholytics	7	3.30
Anti-Arrhythmic	3	1.41
Arbs	2	0.94
ACE-I	1	0.47
Pattern of Anti-Diabetic Drugs		
Insulin (Injectables)	52	64.19
Gliptins	13	16.04
Sulphonylureas	8	9.87
Combination	5	6.17
A Glucosidase Inhibitor	2	2.46
Biguanides	1	1.23
Pattern of Antibiotics		
Combinations	42	30.21
Others	25	17.98
Carbapenems	15	10.79
Macrolide Antibiotics	14	10.07
Cephalosporins	11	7.91
Anti-TB	10	7.19
Fluoroquinolones	9	6.47
Anti-Amoebics	7	5.03
Antifungals	5	3.59
Aminoglycosides	1	0.71
Pattern of Hematinic Class of Drugs		
Iron Preparations	36	56.24
Erythropoietin	22	34.37
Vit-B12	6	9.37
Pattern of Drugs for Acid-Base Disorders		
Sodium Bicarbonate	30	52.63
Phosphate Binders	22	38.59
Combinations	4	7.01
Calcium Acetate	1	1.75
Pattern of Analgesics & Antipyretic Drugs Usage		
Analgesic & Antipyretic	39	52
Drugs For Gout	18	24
Drugs For Arthritis	10	13.33
Combinations	7	9.33
Antispasmodics	1	1.33
Pattern of Nutritional Supplements Usage		
Combinations	84	60
Ca- Carbonate	20	14.28
Protein Powder	18	12.85
Saline	6	4.28
Vit-E	4	2.85
Others	6	4.28
Vit-D	1	0.71
Folic Acid	1	0.71

CLASSIFICATION OF DDI

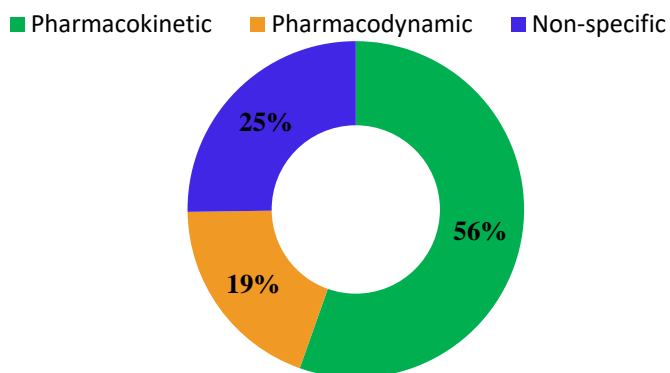


Fig. 2: Classification of DDI

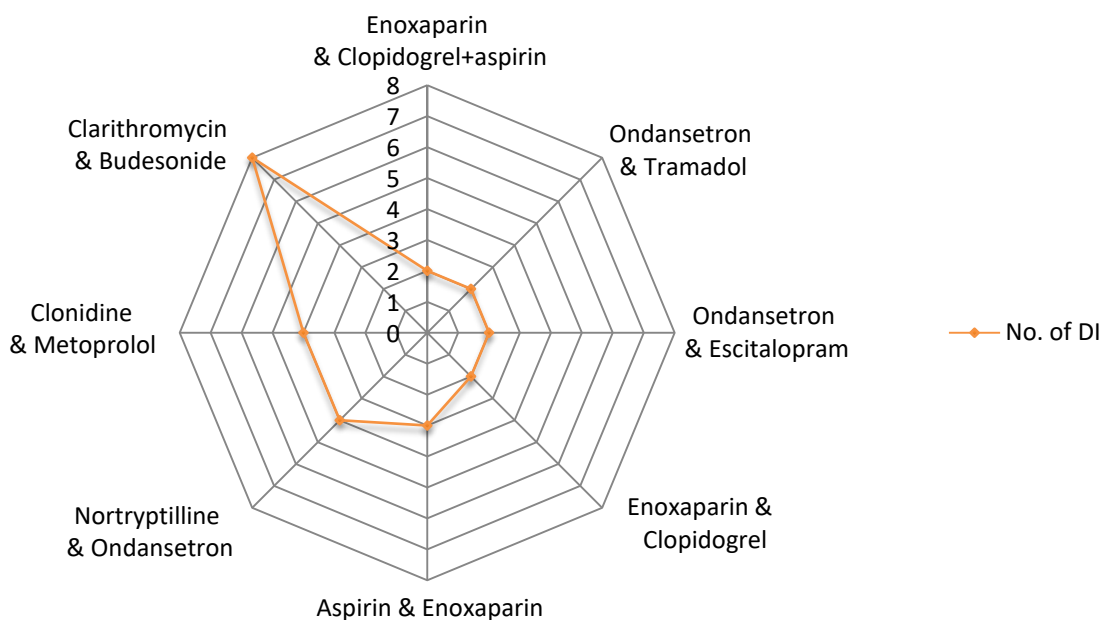


Fig. 3: Description of Major Drug-Drug Interactions

Table 3: Integration of Results

Variable	No. of Patients	Frequency of DDI	P - value
Gender			
Male	63	337 (61.6)	0.69
Female	37	210 (38.3)	
Age			
16-30	4	11 (2.41)	
31-45	12	67 (14.69)	
46-60	30	112 (24.56)	0.035**
61-75	40	192 (42.1)	
76-90	10	74 (16.22)	
No. of Comorbidities			
0	7	22 (4.2)	
1	21	118 (21.57)	
2	44	236 (43.14)	0.0019**
3	19	123 (22.48)	
4	8	43 (7.86)	
5	1	5 (0.91)	
No. of Drugs Prescribed			
≤5	3	3 (0.54)	
6-10	22	83 (15.17)	<0.0001***
11-15	37	198 (36.19)	
≥16	36	263 (48.08)	
Duration of Hospital Stay			
≤5	35	202 (36.9)	
6-10	43	214 (39.12)	0.8053
11-15	16	89 (16.27)	
>15	6	42 (7.67)	