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IDENTIFICATION, EVALUATION AND ANALYSIS OF DRUG-DRUG INTERACTIONS IN THE EMERGENCY DEPARTMENT OF A TERTIARY CARE TEACHING HOSPITAL

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Abstract:
Background: *Drug- Drug interactions (DDIs) occur when the administration of one drug alters the therapeutic effects of another. These effects may be an increase or decrease in the action of either substance or it may be an adverse effect that is not normally associated with either drug. Data was collected from the patients who were admitted in the Emergency Department. The objectives were to identify, evaluate and analyse the drug-drug interactions in the emergency department of a tertiary care teaching hospital by using different information tools like Drug interaction form, Medscape drug interaction checker, Lexicomp, Stockley's drug interaction and Drugs.com.*
Methods: *The study was prospective observational study conducted for the period of six months starting from October 2018 to March 2020 in emergency department of Tertiary care teaching Hospital, Davanagere, Karnataka.*
Results: *The overall data of 121 patients were enrolled in the study. In our study, a total of 230 interactions were seen in 121 patients, out of 230 DDIs, a total of 67 (29.14%) were pharmacokinetics DDIS and a total of 163 pharmacodynamics DDIS were observed of which 28 (12.18%) were major, 166(72.17%) were moderate and 36(15.65%) were minor. Out of 230 DDIs, the age 50-59 years had total of 57 (24.78%) drug interactions which includes 4 major, 44 moderate and 9 minor interactions. The most commonly involved classes of drugs were antibiotics 60 (17.64%), diuretics 35 (10.29%), antihypertensive 34 (10%), H_2 blockers 25 (7.35%), antiemetic's 24 (7.05%), antiasthamatics 22 (6.47%) whereas antipyretics, antiepileptic's and antiplatelet were 17 (05%) in each.*
Conclusion: *In our study, out of 230 DDIs, most frequently occurring major DDIs were Ondansetron + Tramadol. Majority of the patients received polypharmacy in emergency department which is the major cause for the DDIs. In a conclusion, the results of this study emphasized the active role of clinical pharmacist in detecting and managing different types of DDIs.*
Key Words: *Drug-drug interactions, Pharmacokinetic, Pharmacodynamics, Emergency Department, Polypharmacy.*

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INTRODUCTION:

Drug-Drug Interaction (DDI) is defined as a modification of the effect of a drug when it is administered with another drug. These effects may be an increase or decrease in the action of drugs or it may be an adverse effect that is not normally associated with either drug [1]. When the interactions present in the prescription are theoretically evaluated through databases and not by their actual occurrence, they are considered Potential Drug-Drug Interactions (PDDIs) [2].

Drug-drug interactions (DDIs) in patients receiving multi-drug therapy are of wide concern [3]. The majority of the patients is treated with more than one drug simultaneously. Reason for the treatment with multiple drugs includes the treatment of co-morbid conditions in the same patient or the use of multiple drugs for same ailment. With the increasing median age of the population and the now known effectiveness of multiple therapy regimens for viral, cancer, cardiovascular diseases and infectious disease, so the exposure of a patient to multiple drugs is common rather than occurrence [4].

According to severity potential DDIs are classified as:

- **Major:** The effects are potentially life threatening or capable of causing permanent damage.
- **Moderate:** The effects may cause deterioration in patients' health condition and additional treatment or extension of hospital stay.
- **Minor:** The effects are usually not serious and are mild [5].

Some drugs interact together in totally unique ways, but there are certain mechanisms of interaction that are encountered time and time again. Many drugs that interact do so, not by a single mechanism, but often by two or more mechanisms. For convenience, the mechanisms of interactions can be subdivided into pharmacokinetics interactions and pharmacodynamics interactions [6]. Drug interactions can occur both in-vivo and in-vitro. Pharmacokinetic interactions are those that can affect the processes by which drugs are absorbed, distributed, metabolised and excreted (the so called ADME interactions) [6]. These changes are basically modification in the concentration of drugs whereas Pharmacodynamics interactions are those where the effects of one drug are changed by the presence of another drug at its site of action. Sometimes the drugs directly compete for particular receptors (e.g. Beta-2 agonists, such as salbutamol, and beta blockers, such as propranolol) but often the reaction is more indirect and involves interference with physiological mechanisms. These interactions are much less easy to classify neatly than those of a pharmacokinetic type [6]. Regardless of the type of interaction, DIs may compromise treatment efficacy or increase drug toxicity, with serious clinical consequences; they result under-/ over dosing, the pharmacological effect can be boosted, or the drugs can become completely ineffective.

Steps to manage DDIs

- Avoid the combination.
- Adjust the dose.
- Monitor the patient.
- Continue the medication if, the interaction is not clinically significant [3].

There are three possible outcomes during drug-drug interactions;

1. One (drug) may intensify the effects of other.
2. One may reduce the effects of other.
3. The combination may produce but not seen when either of the drug is given alone [3].

Drug-drug interactions may produce beneficial or desirable or undesirable or harmful effects. The beneficial effect is those whose purpose is to treat concomitant disease, enhancing the effectiveness, reducing adverse event (AE) and allowing to reduce the dose while the undesirable effect may reduce the drug effectiveness and may produce unwanted noxious and even life-threatening effects in the body, along with the increased cost [7].

MATERIALS AND METHODS:

STUDY SITE:

The study was conducted in the emergency department of Chigateri General Hospital, Davangere. (Tertiary care teaching hospital).

STUDY DESIGN:

The study was a Prospective, observational study.

SAMPLE SIZE:

121 patients

STUDY DURATION:

The study was conducted for a period of 6 months.

SOURCE OF DATA:

Data was collected from case sheets of in-patients from the emergency department of a tertiary care teaching hospital.

STUDY CRITERIA:
Study was carried out by considering the following inclusion and exclusion criteria.

Inclusion criteria:
- All the patients admitted in emergency department.
- Prescriptions with minimum of 4 drugs.
- Patients with at least 24 hours stay in hospital.
- Patients with age above 18 years.

Exclusion criteria:
Out patients.
Poisoning related cases.atients with missing and insufficient data.
Prescriptions involving Ayurvedic formulations.
Paediatric and pregnant women.
Illegible prescriptions.

ETHICAL CONSIDERATION:
The ethical clearance for the study was obtained from the Institutional Ethical Committee of SCS College of Pharmacy.

MATERIALS USED:
Patient data collection form Drug interaction form
Medscape drug interaction checker
Lexicomp
Stockley's drug interaction
Drugs.com

PHASES OF STUDY
The proposed work is designed as mentioned below:

PHASE 1
Review of literature.
Obtaining institutional ethical committee clearance.
Obtaining permission from the emergency department of hospital.
Designing the data collection form.

PHASE 2
- Collection of data from identified in-patients as per the inclusion criteria.

PHASE 3
- To identify the prevalence of DDIs based on gender and age.
- To categorize and analyze the severity of DDIs.
- To identify the type of DDIs.
- To categorize the drugs, associated with
- DDIs accrding to pharmacological classification.
- Analysing the results.

STUDY POCEDURE
- The investigator will attend the ward rounds on daily basis in emergency department of the hospital and the data will be collected from the patient's medicine case sheets.
- The patient details will be obtained along with co-morbidities, current medication and relevant previous medical and medication histories.
- The collected data will be recorded using specifically designed data collection format by reviewing patient medication charts.
- The pooled data will be analysed for further investigation on drug-drug interactions by using lexicomp, drugs.com and medscape interaction checker.
- The cases only having drug-drug interactions are collected and documented for analysing results.
-

STATISTICAL METHOD
Data will be represented graphically and analyzed using statistical method like computer software MS Excel (percentage analysis).

RESULTS:

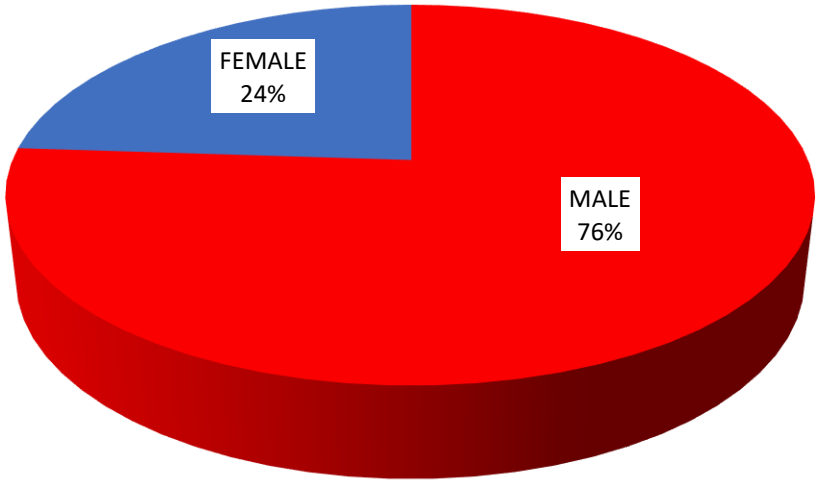
Gender wise distribution of patients

A total of 121 cases were collected, out of which 92 (76.03%) were males and 29 (23.96%) were female.

Table 1: Gender wise distribution of patients

Gender	Number of patients (n=121)	Percentage (%)
Male	92	76.03
Female	29	23.96
Total	**121**	**100**

Figure 1: Gender wise distribution of patients.



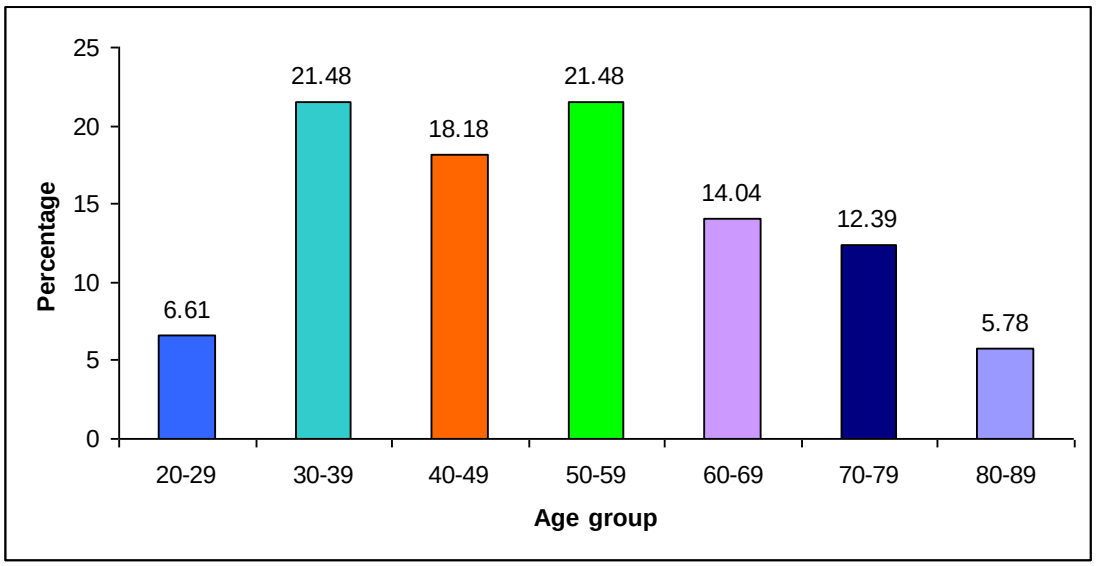
Distribution of patients based on age

Among 121 subjects, majority of population enrolled were in the age group of both 30-39 yrs (21.48%) and 50-59 yrs (21.48%) followed by 40-49 yrs (18.18%), 60-69 yrs (14.04%), 70-79 yrs (12.39%), 20-29 yrs (6.61%) and 80-89 yrs (5.78%).

Table 2: Distribution of patients based on age

Age group	Number of patients (n=121)	Percentage (%)
20-29	8	6.61
30-39	26	21.48
40-49	22	18.18
50-59	26	21.48
60-69	17	14.04
70-79	15	12.39
80-89	7	5.78
Total	**121**	**100**

Figure 2: Distribution of patients based on age



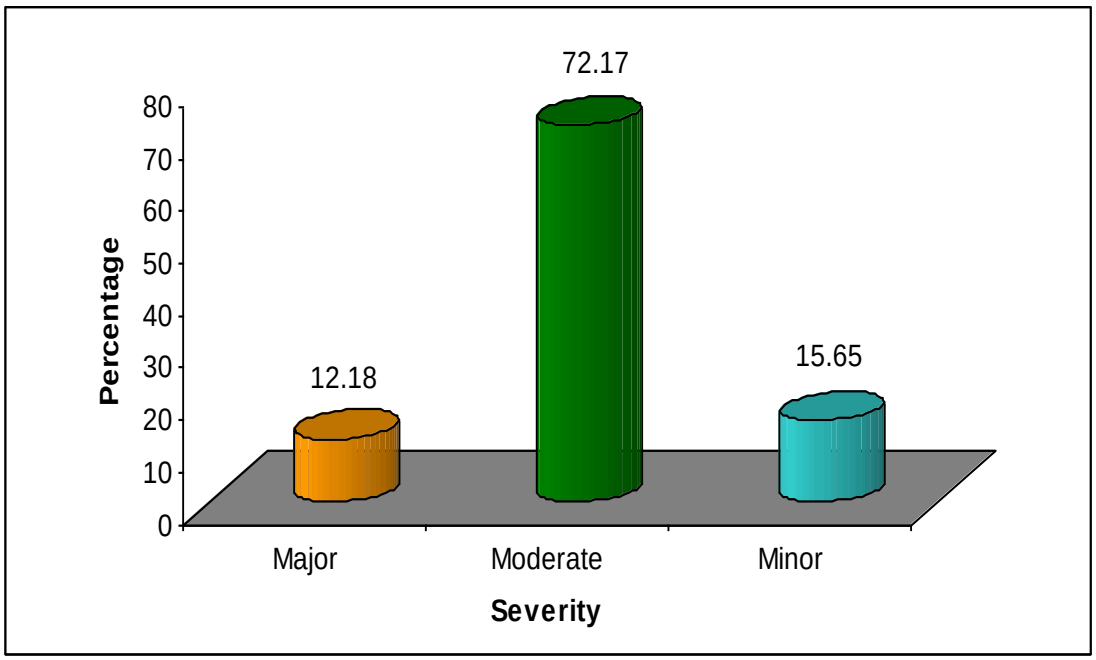
Distribution of DDIs based on severity

Out of 121 prescriptions a total of 230 drug-drug interactions were found which includes major, moderate and minor interactions. Among these, moderate 166 (72.17%) followed by minor 36 (15.65%) and major 28 (12.18%).

Table 3: Distribution of DDIs based on severity

Severity	**Number of DDIs (n=230)**	**Percentage (%)**
Major	28	12.18
Moderate	166	72.17
Minor	36	15.65
Total	**230**	**100**

Figure 3: Distribution of DDIs based on severity



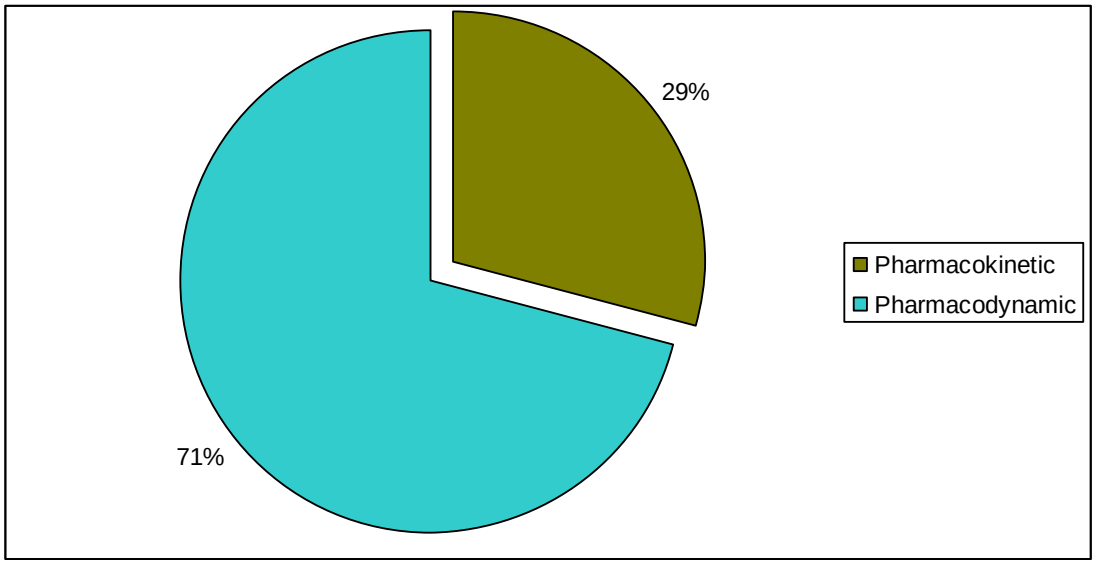
Distribution of DDIs based on its types

A total of 230 DDIs were found, which involve pharmacokinetic and pharmacodynamic interactions. Among these, majority of interactions were Pharmacodynamic 163 (70.86%) followed by pharmacokinetic 67 (29.14%).

Table 4: Distribution of DDIs based on its types

Types of DDI	Number of DDIs (n=230)	Percentage (%)
Pharmacokinetic	67	29.14
Pharmacodynamic	163	70.86
Total	**230**	**100**

Figure 4: Distribution of DDIs based on its types.



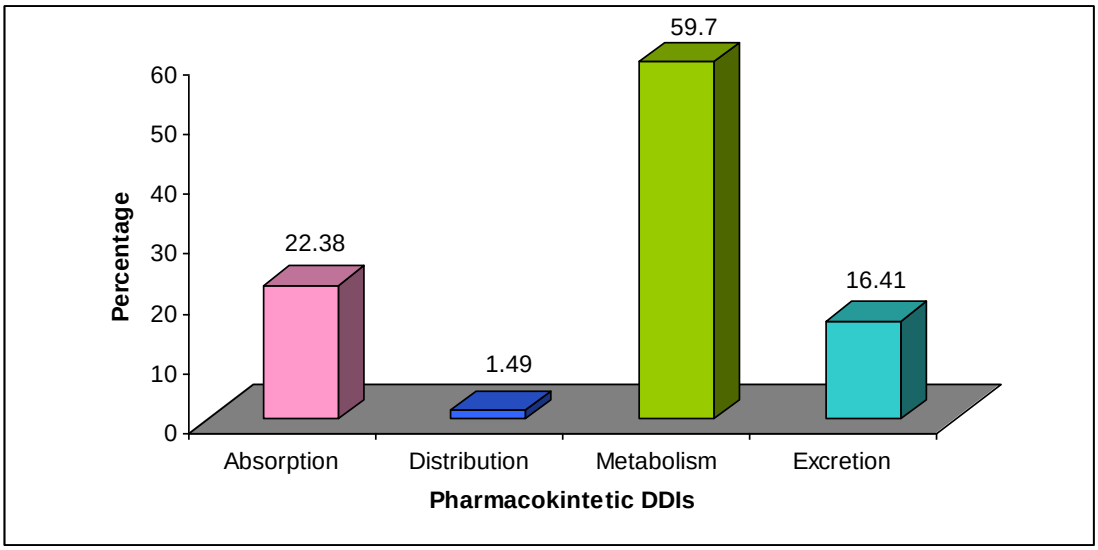
Distribution of DDIs based on pharmacokinetic interactions

Out of 230 DDIs, a total of 67 pharmacokinetic DDIs were found which includes absorption, distribution, metabolism and excretion interactions. Among these, metabolism 40 (59.70%) followed by absorption 15 (22.38%), excretion 11 (16.41%) and distribution 1 (1.49%).

Table 5: Distribution of DDIs based on pharmacokinetic interactions

Pharmacokinetic DDIs	Number of DDIs (n=67)	Percentage (%)
Absorption	15	22.38
Distribution	1	1.49
Metabolism	40	59.70
Excretion	11	16.41
Total	**67**	**100**

Figure 5: Distribution of DDIs based on pharmacokinetic interactions.



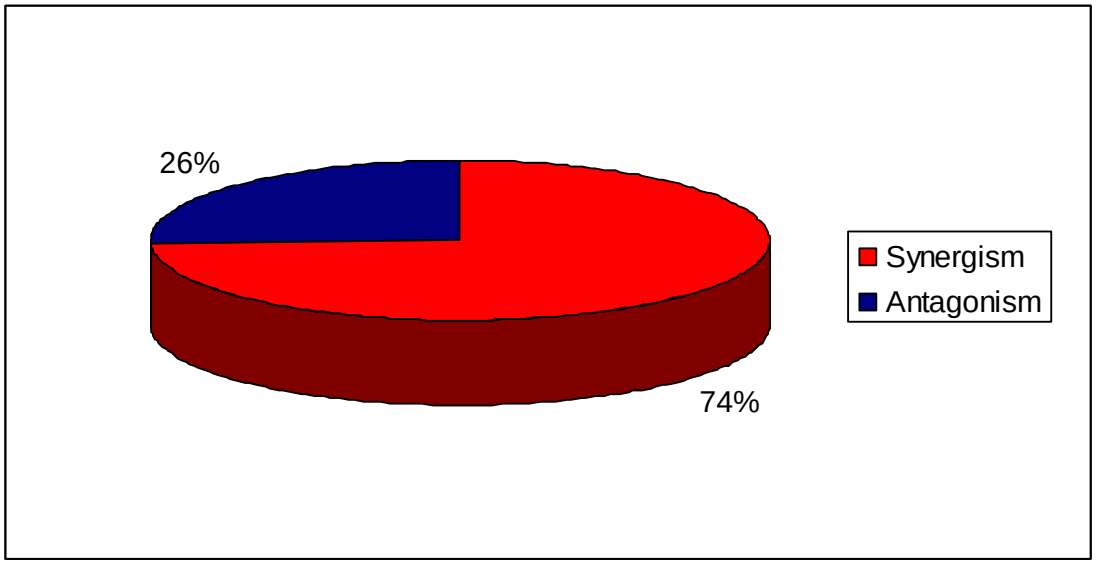
Distribution of DDIs based on pharmacodynamic interactions

Out of 230 DDIs, a total of 163 pharmacodynamic DDIs were found which includes synergistic and antagonistic interactions. Among these, synergistic 121 (74.23%) followed by antagonistic 42 (25.77%) interactions.

Table 6: Distribution of DDIs based on pharmacodynamic interactions

Pharmacodynamic DDIs	**Number of DDIs (n=163)**	**Percentage (%)**
Synergism	121	74.23
Antagonism	42	25.77
Total	**163**	**100**

Figure 6: of DDIs based on pharmacodynamic interactions.



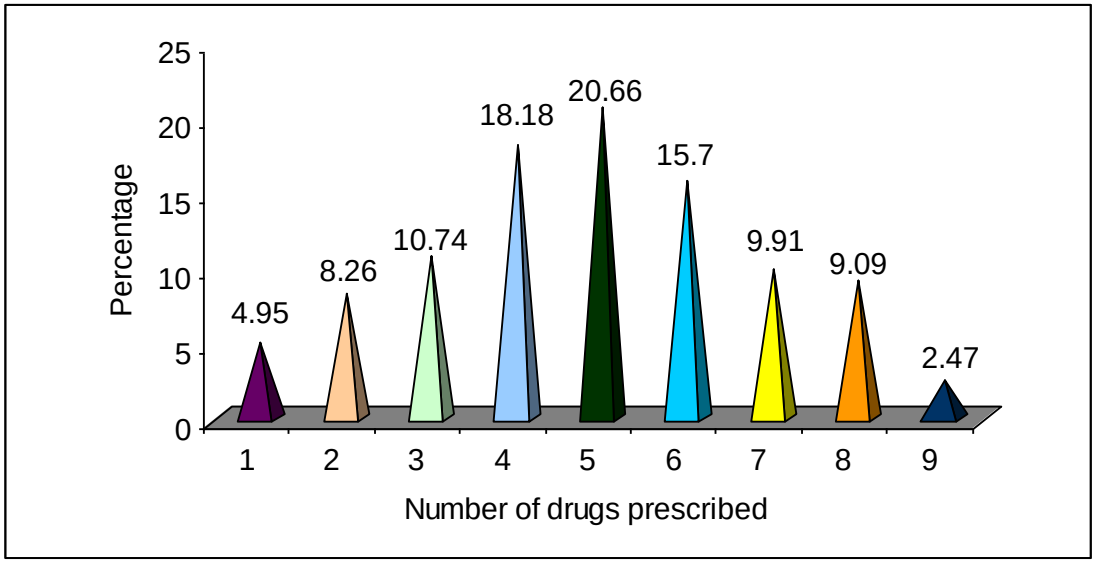
Distribution of DDIs based on number of drugs prescribed.

Out of 121 prescriptions, 25 (20.66%) prescriptions had 8 drugs followed by 22 (18.18%) prescriptions had 7 drugs, 19 (15.70%) prescriptions had 9 drugs, 12 (9.91%) prescriptions had 10 drugs, 13 (10.74%) prescriptions had 6 drugs, 11 (9.09%) prescriptions had 11 drugs, 10 (8.26%) prescriptions had 5 drugs, 6 (4.95%) prescriptions had 4 drugs and 3 (2.47%) prescriptions had 12 drugs.

Table 7: Distribution of DDIs based on number of drugs prescribed.

Number of drugs prescribed	Number of cases (Frequency) (n= 121)	Percentage (%)
4	6	4.95
5	10	8.26
6	13	10.74
7	22	18.18
8	25	20.66
9	19	15.70
10	12	9.91
11	11	9.09
12	3	2.47
Total	**121**	**100**

Figures 7: Distribution of DDIs based on number of drugs prescribed



Distribution of DDIs in different age group

Out of 230 DDIs, the age group 50-59 years had total of 57 (24.78%) DDIs which includes 4 major, 44 moderate and 9 minor interactions followed by 30-39 years had total of 52 (22.60%) DDIs which includes 7 major, 39 moderate and 6 minor interactions, 40-49 years had total of 36 (15.65%) DDIs which includes 5 major, 23 moderate and 8 minor interactions, 60-69 years had total of 31 (13.47%) DDIs which includes 4 major, 24 moderate and 3 minor interactions, 70-79 years had total of 24 (10.43%) DDIs which includes 4 major, 15 moderate and 5 minor interactions, 20-29 years had total of 18 (7.82%) DDIs which includes 2 major, 12 moderate and 4 minor interactions and 80-82 years had total of 12 (5.21%) DDIs which includes 2 major, 9 moderate and 1 minor interactions.

Table 8: Distribution of DDIs in different age group

Age	Severity			Total	Percentage (%)
	Major	Moderate	Minor		
20-29	2	12	4	18	7.82
30-39	7	39	6	52	22.60
40-49	5	23	8	36	15.65
50-59	4	44	9	57	24.78
60-69	4	24	3	31	13.47
70-79	4	15	5	24	10.43
80-89	2	9	1	12	5.21
Total	**28**	**166**	**36**	**230**	**100**

Figure 8: Distribution of DDIs in different age group

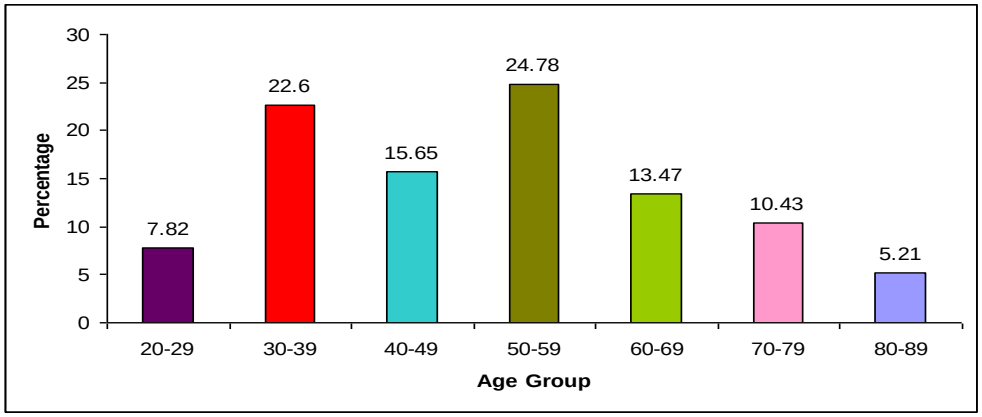


Table 09: A relation between number of drugs prescribed and number of DDIs encountered

Number of drugs	Number of cases	Number of DDIs
04	06	10
05	10	16
06	13	24
07	22	37
08	25	43
09	19	40
10	12	31
11	11	23
12	03	06
Total	**121**	**230**

Table 10: Distribution of drugs causing DDIs based on pharmacological classification

Classes	Frequency of drugs used	Percentage (%)
Antibiotics	60	17.64
Diuretics	35	10.29
Anti-hypertensive	34	10
H_2-blockers	25	7.35
Anti-emetics	24	7.05
Anti-asthmatic	22	6.47
Anti-pyretic	17	05
Anti-epileptic	17	05
Anti-platelets	17	05
Opioid-analgesic	14	4.11
Anti-tubercular	11	3.23
Anti-diabetic	11	3.23
Proton pump inhibitors (PPIs)	09	2.64
Anti-coagulant	07	2.05
NSAIDs	05	1.47
Anti-hyperlipidemic	04	1.17
Anti-histamine	04	1.17
Anti-Parkinson	03	0.88
Anti-arrhythmic	02	0.58
Sedatives and hypnotics	02	0.58
Others	17	4.98
Total	**340**	**100**

Table 11: List of most frequently occurring DDIs based on it's severity.

Drug-drug interactions	Severity	Occurrence
Ondansetron + Tramadol	Major	7
Warfarin + Enoxaparin	Major	3
Meropenam + Valproic acid	Major	2
Ofloxacin + Ondansetron	Moderate	11
Ceftriaxone + Furosemide	Moderate	10
Ceftriaxone + Amikacin	Moderate	5
Spironolactone + Propranolol	Moderate	5
Propranolol + Furosemide	Moderate	4
Cefotaxime + Furosemide	Moderate	4
Phenytoin + Ranitidine	Moderate	4
Theophylline + Hydrocortisone	Moderate	3
Aspirin + Ramipril	Moderate	3
Atorvastatin + Clopidogrel	Moderate	3
Levothyroxine + Metformin	Moderate	2
Clonidine + Nifedipine	Moderate	2
Furosemide + Hydrocortisone	Moderate	2
Aspirin + Heparin	Moderate	2
Aspirin + Clopidogrel	Moderate	2
Warfarin + Tramadol	Moderate	2
Acetaminophen + Phenytoin	Moderate	2
Ethambutol + Isoniazid	Moderate	2
Aspirin + Telmisartan	Moderate	2
Ferrous sulfate + Pantoprazole	Moderate	2
Ferrous sulfate + Iron sucrose	Moderate	2
Phenytoin + Lorazepam	Moderate	2
Ranitidine + Acetaminophen	Minor	14
Metronidazole + Ondansetron	Minor	3

DISCUSSION:

In the present study, 121 subjects were reviewed and had an experience of 230 drug-drug interactions. The DDIs were classified as mild, moderate and severe according to their severity and undesirable effects. DDIs limit the clinical effects. Mild interaction may not need any change in the treatment plan, whereas moderate DDIs may result in exacerbations of the disease of the patient and/or a change in the therapy. The severe DDIs are life threatening and/or they may require medical treatment or an intervention to minimize or to prevent the severe adverse effects.

During the six-month study period, 121 patient cases were collected and studied as follows.

The overall data of 121 patients who were admitted in the emergency department of a tertiary care teaching hospital were collected. In our study, male preponderance was seen 92 (76.03%) whereas female patient was 29 (23.96%). Similar to the study conducted by Bhavana Chowdary M et al [4] collected a total of 202 prescriptions. According to the gender classification there were 131(64.8%) males and 71(35.1%) females.

Patients of age 18 and above were taken into the study and majority of the patients enrolled were of the age group 30-39yrs and 50-59yrs, both age group consist of 26 (21.48%) patients in each group. Similar results were observed in the study conducted by Bhavana Chowdary M et al [4] and N. Vanitha Jyothi et al [8]. In their study, subjects at the age group 51-65years are more prone to DDIs and similarly the age group between 51–60 years are more prone to DDIs. Subjects at the age group 51–60 years were developed a higher rate of DDIs respectively.

In our study, a total of 230 interactions were seen in 121 patients, out of which 28 (12.18%) were major, 166 (72.17%) were moderate and 36 (15.65%) were minor. Identical results were seen in the study conducted by Meiry Fernanda Pinto Okuno et al [9]. In their study, out of 526 PDDIs majority of the interactions were moderate 354 (66.53%).

Out of 230 DDIs, a total of 67 (29.14%) PK DDIs were found which includes absorption 15 (22.38%), distribution 1 (1.49%), metabolism 40 (59.70%) and excretion 11 (16.41%) and a total of 163 (70.86) PD DDIs were found which includes synergistic 121 (74.23%) and antagonistic 42 (25.77%) interactions. Similar results were observed in the study conducted by Jigar Kapadia et al [10]. where they included a total of 1077 cases, 615 (57.10) were PD and 462 (42.90) were PK DDIs.

In our study, out of 121 prescriptions, 25 (20.66%) prescriptions had 8 drugs which were having 43 DDIs. These findings are similar to the study conducted by Biradar S.M. et al [3]. where out of 150 prescriptions, 9 (6%) prescriptions had 15 drugs which were having 35 DDIs.

Out of 230 DDIs, the age 50-59 yrs had a total of 57 (24.78%) DDIs which includes 4 major, 44 moderate and 9 minor interactions. Similar results were observed in the study conducted by Biradar S.M et al [3]. where the age above 60 years had a total of 51(22.46%) DDIs which includes 13 major, 32 moderate and 6 minor interactions.

A total of 121 patients enrolled in our study, the most commonly involved classes of drugs were antibiotics 60 (17.64%), diuretics 35 (10.29%), antihypertensives 34 (10%), H_2 blockers 25 (7.35%), antiemetics 24 (7.05%), antiasthamatics 22 (6.47%) whereas antipyretics, antiepileptics and antiplatelets were 17 (05%) in each. Similar results were observed in the study conducted by Preksha A Barot et al [11] where they included the most common involved drug groups in interactions were antimicrobials (8.74%), antiplatelets (4.19%), and steroids (4.19%).

Out of 230 DDIs most frequently occurring major DDIs were ondansetron + tramadol (7), warfarin + enoxaparin (3) and meropenam + valporic acid (2) whereas moderate DDIs were ofloxacin + ondansetron (11), ceftriaxone + furosemide (10), ceftriaxone + amikacin (5), spironolactone and propranolol (5) and minor DDIs were ranitidine + acetaminophen (14) and metronidazole + ondansetron (3)

CONCLUSION:

The use of multiple drugs in a patient has been a routine practice for the treatment of the illness. However, there are also reports of irrational prescribing of multiple drugs, which may lead to the DDIs depending upon its severity. DDIs has been a global problem causing a substantial economic burden on healthcare system. Identification, evaluation and analysis of DDIs is important to avoid multiple adverse events, treatment failure, non-compliance and increase in the cost of treatment.
Prescription analysis shows the way towards identification of DDIs. DDIs could also leads to ineffective, unsafe treatment, prolongation of illness, additional illness, distress and even life threatening to patients.

In our study, a total of 121 cases were collected and from that we conclude the most commonly occurring DDIs in ED is moderate (72.17%) in severity followed by minor (15.65%) and major (12.18%) interactions.

Based on our study we would like to place on the record that, the prescriptions should be screened at least for major and moderate DDIs and drugs that are commonly involved in major and moderate DDIs, should be analysed by a clinical pharmacist prior to drug dispensing. Patient should also be closely monitored for possible DDIs.

Thus we conclude that, the incidence rate of DDIs is high at the study site. Majority of the patients received polypharmacy in ED which is the major cause for DDIs. Hence, it is important to develop systemic approach to minimize the possible DDIs. Clinical prevalence of certain DDIs might be because of their pharmacological actions. The clinical pharmacist is of prime importance to provide information for a better decision on therapy, improve quality of treatment and reduce risks in the patients.

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Conflict of interest: None declare

Ethical approval:The study was approved by Institutional ethics committee of SCS College of Pharmacy,Harapanahalli,Karnataka,India

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