Research Article

Evaluation and Management of Drug-Drug Interactions in Ambulatory Patients

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ABSTRACT

Aim: To identify, monitor and manage Drug-drug interactions (DDI's). **Objective:** The main objective of the study is to identify DDIs in out-patients and to categorize the severity, onset and MOA of drug interactions and to provide guidance regarding therapeutic management. **Methods:** The study is a Prospective Observational study done for a period of 12 months from December 2013 to December 2014 at the Pharmacist Patient Counselling Department of Rohini Super Speciality Hospital. Patients who visited the hospital with different diseases were reviewed; demographic details are collected, documented and analyzed for DDIs in Micromedex, and Lexicomp. **Results:** A total of 360 prescriptions were reviewed, enrolled 153 (42.5%) Prescriptions which met the study criteria and a total of 328 DDI's were found. Male shows higher DDI's i.e. 200 (60.97%) DDI's. Based on severity moderate shows higher, i.e. 178 (54.26%) and not specified onset shows higher, i.e. 150 (45.73%) of DDIs. When DDI's categorized based on MOA, PK interactions were 256 (78.04%). In managing DDI's the methods to be followed were 114 (34.75%) Avoid combination for long term use and specific lab parameters must be monitored. Most common DDI's were associated with NSAIDS 182, antidepressants 120 and H2-receptor antagonists 95. **Conclusion:** On evaluation, the majority of DDIs found to have not specified onset and moderate severity. An Increase in the number of drugs in prescription showed an increase in the number of DDIs and managing them by avoiding combination for long term use has shown greater impact in improving health related quality of life.

Keywords: Drug-drug interaction, onset, severity, therapeutic management

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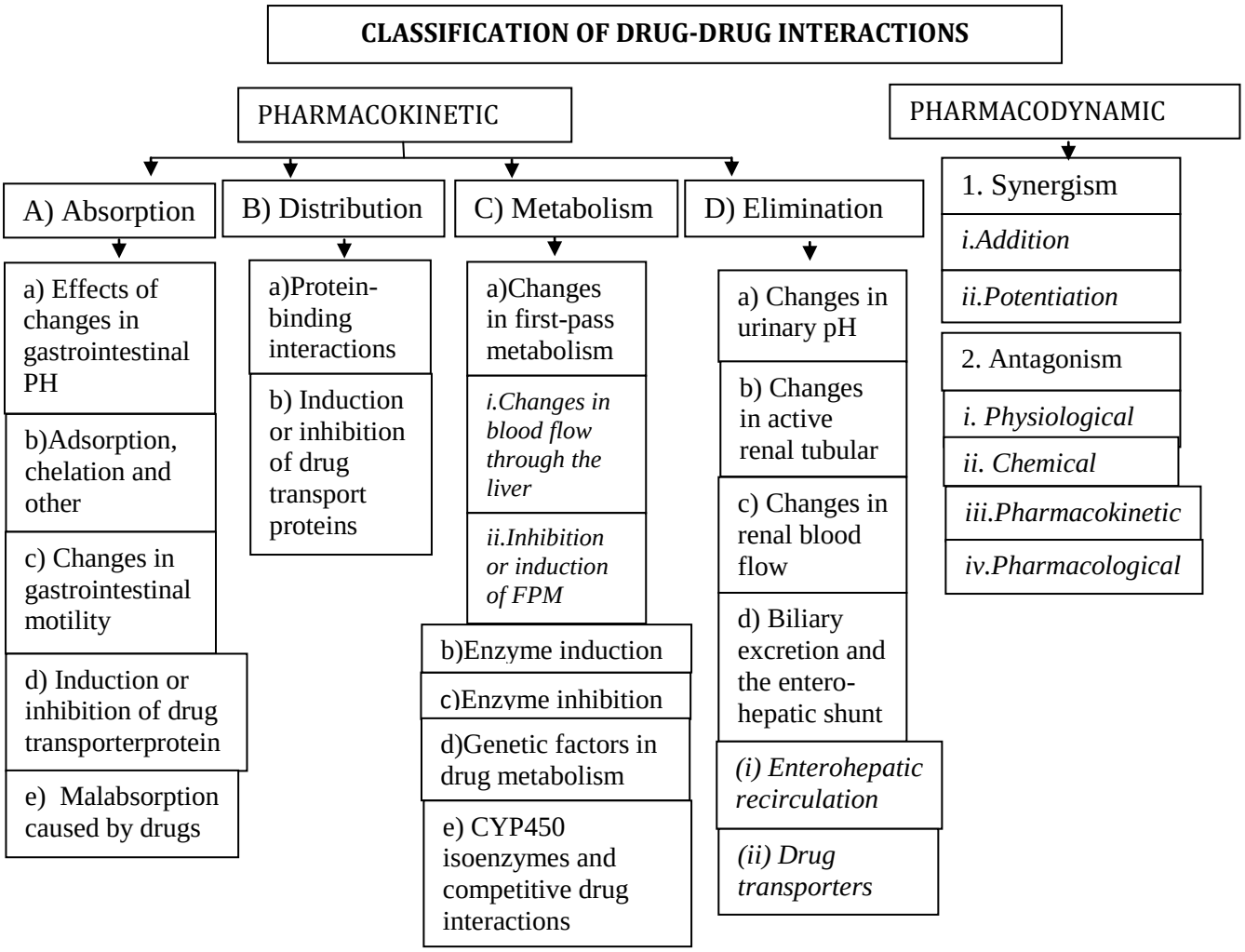
INTRODUCTION

Drug interactions are defined as the pharmacological activity modulation of a given drug by concomitant administration of another drug or previous drug that may cause increased or reduced effect. Drug interactions may compromise the patient safety or treatment efficacy, which may increase hospital stay and hospital costs, affect the patient's quality of life [1]. An interaction is said to occur when the effects of one drug are changed by the presence of another drug, herbal medicine, food, drink or by environmental chemical agent [2]. Drug-drug interaction (DDI) is a pharmacologic response to the administration of a drug combination, different from the known effects of the two agents when given alone [3].

FACTORS CONTRIBUTING TO THE DRUG INTERACTIONS: Some of the important risk factors that lead to drug interactions include administration of multiple drug therapy, using multiple prescribers, due to multiple pharmacological effects of the drug, Poor patient compliance, Advancing age of patient and Drug related factors include Interactions between drugs that have potent effects [1].

COMPLICATIONS OF DRUG-DRUG INTERACTIONS: Consequences of drug interactions may be Major leads to life threatening, Moderate cause deterioration of the patient's status and Minor are bothersome or have little effect [4].



EPIDEMOLOGY:

Drug interactions are important in clinical practice and estimated to account for 6-30% of all adverse drug reactions (ADR's). The incidence of drug interactions has been estimated to be 2.2 to 30% of hospitalized patients and between 9.2 and 70.3% of ambulatory patients [5].

OBJETIVE OF THE STUDY:

The main goal of the study is to assess the prevalence of drug-drug interactions in out-patients based on age, gender and to categorize the severity, onset, MOA of drug interactions and to study the pattern of DDI's caused by drugs. To provide guidance regarding monitoring and therapeutic management of patients with various drug-drug interactions.

MATERIALS AND METHODS

A Prospective Observational study done for a period of 12months from December 2013 to December 2014 at the Pharmacist Patient Counselling Department of Rohini Super Speciality Hospital. Study topic is selected as Drug-Drug Interactions in Ambulatory patients at Super Speciality Hospital, Literature review is done, study design, study criteria are determined. Data collection forms and drug interaction forms are designed. Data is collected from patient's medical chart, clinical data by interviewing patient or patient's care taker, and many other relevant sources. The collected data includes demographics and the clinical information like names of drugs prescribed, laboratory reports. The obtained data were systematically analyzed and potential drug interactions were identified using Micromedex and Lexicomp to promote greater sensitivity in our study. All Drug-drug interactions were classified on the basis of potential clinical outcome and relevance of supporting clinical and pharmacological documentation. The significant information is provided to patient through patient counselling. In our research study, we have not taken any samples from humans, so we have not

obtained permission from the relevant ethics committee.

RESULTS

During the study period a total of 360 prescriptions reviewed, of which 153 (42%) prescriptions found to have at-least one drug-drug interactions. A total of 328 drug-drug interactions were identified in which 200 (60.97%) were found in males and 128 (39.03%) were found in females. Based on Age (**Figure 1**), the highest percentage of drug-drug interactions were observed in the age group of 50-59 years of 87 (26.52%).

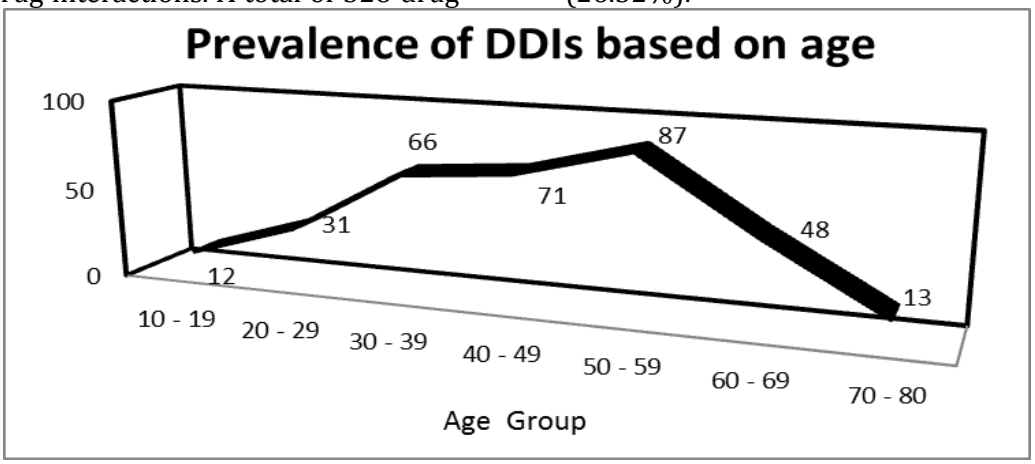


Figure 1: Age Wise Distribution of Prescriptions

When the data was distributed based on mechanism of action and severity (**Table 1**) moderate severity interactions were higher, i.e. 178 (54%) while 84 (26%) were major and followed by 66 (20%) minor.

Table 1: Pattern Of Ddis Based On Probable Mechanism And Severity

Probable mechanisms[a]	**No. of DDIs (328 (%)**	**Major[b] 84 (%)**	**Moderate[b] 178 (%)**	**Minor[b] 66 (%)**
PK DDIs	256 (78.04)			
ABSORPTION	**86 (33.59)**			
Effects of changes in gastrointestinal PH	67 (77.90)	17 (25.37)	30 (44.78)	20 (29.85)
Adsorption, chelation and complexion mechanisms	12 (13.95)		07 (58.33)	05 (41.67)
Changes in gastrointestinal motility, Malabsorption	07 (08.15)		04 (57.14)	03 (42.86)
DISTRIBUTION	**20 (07.81)**			
Induction or inhibition of drug transport proteins	20 (100)	04 (20)	12 (60)	04 (20)
METABOLISM	**93 (36.33)**			
Changes in FPM & blood flow through the liver	23 (23.73)	04 (17.39)	13 (56.52)	06 (26.09)
Enzyme induction	34 (36.56)	10 (29.41)	20 (58.82)	04 (11.77)
Enzyme inhibition	36 (38.71)	05 (13.89)	23 (63.89)	08 (22.22)
ELIMINATION	**57 (22.27)**			
Changes in urinary pH & active renal excretion	14 (24.56)	03 (21.43)	11 (78.57)	
Changes in renal blood flow & Biliary excretion	43 (75.44)	15 (34.88)	23 (53.49)	05 (11.63)
PD DDIs	**57 (17.37)**			

Synergism: Addition	57 (100)	21(36.84)	28(49.13)	08(14.03)
OTHER DDIs	**15 (04.57)**			
Unknown mechanism	15 (100)	05(33.33)	07(46.67)	03(20)

a Karen Baxter.2008 [3], b Micromedex Version 2.0. [4]

Based on the probable mechanism (**Table 1**) pharmacokinetic interactions in absorption due to Effects of changes in gastrointestinal PH were 67 (77.90%), due to Adsorption, chelation and complexation mechanisms were 12 (13.95%), changes in gastrointestinal motility and Malabsorption 07 (08.15%) interactions were found. In distribution due to Induction or inhibition of drug transport proteins 20 (6.09%) interactions were found. In Metabolism due to Changes in first-pass metabolism & blood flow through the liver 23 (23.73%), due to Enzyme induction 34 (36.56%) and Enzyme inhibition 36 (38.71%) interactions were found. In elimination due to Changes in urinary pH & active renal excretion 14 (24.56%) and changes in renal blood flow & Biliary excretion 43 (75.44%) interactions were found. In pharmacodynamic interactions due to Synergistic Addition interactions were 57 (17.37%) and other DDIs due to unknown mechanism were 15 (04.57%) [3, 4, 7].

Table 2: drug categories vs. Number of DDIS

Drug Categories[a, b]	ATC Code[a]	656Drugs (%)
ACE inhibitors [C09A], Angiotensin II receptor antagonists	[C09C]	18 (02.74)
Anticoagulant	[D01]	08 (01.21)
Anticonvulsant [NO3], Antidepressant [N06AA], Benzodiazepine	[N05CD]	120 (18.29)
Antitubercular drugs	[JO4]	19 (02.89)
B- blockers [C07], Calcium channel blockers	[C08]	79 (12.04)
Benzoxazolones [MO3BB], NSAIDS	[G02CC]	182(27.74)
Cephalosporin's [JO1E], Fluoroquinolones	[JO1MA]	32 (04.87)
Corticosteroids [DO7], Multivitamin	[A11B]	25 (03.81)
Hypoglycemic agents	[A10B]	29 (04.42)
H2-receptor antagonists [A02BA], Proton pump inhibitors	[AO2BC]	95 (14.48)
Loop diuretic [CO3C], Thiazide [C03A], Statins	[C10A]	36 (05.48)
Others		13 (01.98)

a. Hanne Strom, et al [6]
b.www.lexi.com [7]

When drug interactions were categorized based on drugs involved in interaction with their ATC coding[6] (**Table 2**) the number of drug interactions due to Angiotensin II receptor antagonists and ACE inhibitors were 18, anticoagulant were 08, anticonvulsant, benzodiazepines and tricyclic antidepressant were 120, Antitubercular drugs were19, calcium channel blockers and beta-adrenergic receptor blockers were 79, nonsteroidal anti-inflammatory drugs and benzoxazolones were 182, cephalosporin's and fluoroquinolones were 32, corticosteroids and multivitamin were 25, hypoglycemia agents were 29, H2-receptor

antagonists and proton pump inhibitors were 95, loop diuretics, thiazide, statins were 36 and other drugs were 13 [4,6,7].

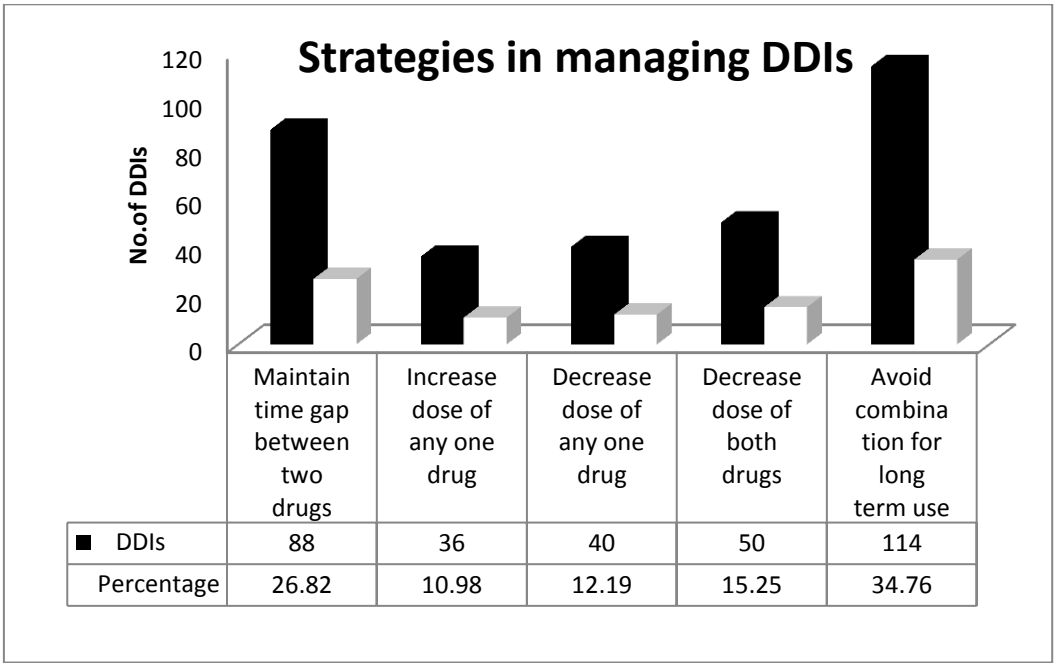


Figure 2: Management Strategies To Overcome Drug Interaction

Necessary managing methods of drug-drug interactions to be followed 114 (35%) were Avoid combination for long term use, 88 (27%) were Maintain time gap between two drugs administration , 50 (15%) Decrease dose of both drugs, 40 (12%) were Decrease dose of any one drug and 36 (11%) were Increased dose of any one drug [4] are detailed in (**Figure 2**).

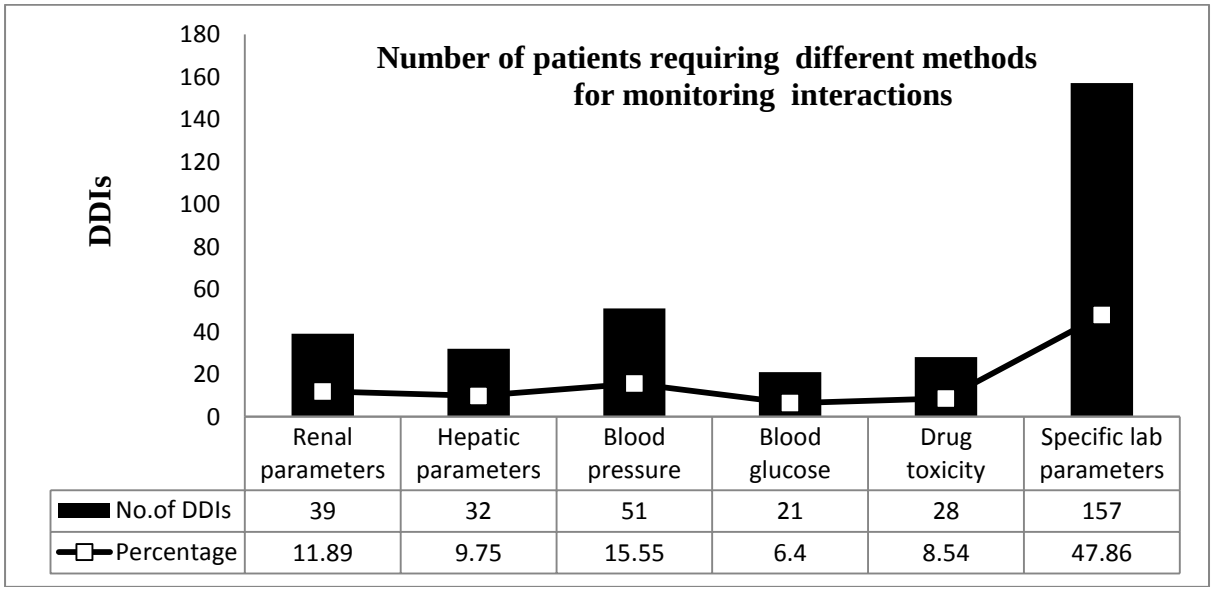


Figure 3: Monitoring Parameters for Drug-Drug Interactions

Various parameters considered in the monitoring of drug-drug interactions (**Figure 3**) were, specific lab parameters in 157 (48%) interactions, Blood pressure in 51 (16%) interactions, Renal parameters in 39 (12%) interactions, Hepatic parameters in 32 (10%) interactions, Drug toxicity in 28 (08%) interactions and blood glucose levels in 21 (06%) interactions [4,7].

DISCUSSION

A total of 360 prescriptions were reviewed in out-patients in a Super Specialty Hospital during one year study period and 153 prescriptions with 328 Drug-drug interactions were identified. In this study, 60.97% of DDIs were found in males and 39.03% were found in female patients, which is similar to study done by Paulo Roué Obreli, *et al* [8] in which males (52.6%) were higher than females (47.4%). In our study prescriptions with 1DDI (52.3%) were higher followed by 9DDIs (1.3%) per prescription. Our findings are similar to the study conducted by Carina Duarte D, *et al* [9] in which prescriptions with 1 DDI (81.8%) were higher than 4DDIs (18.2%) per prescription.

In this study based on the onset of interaction not specified shows higher, i.e. 150 (45.73%) while 134 (40.85%) delayed and 44 (13.41%) were rapid which was similar to the study done by Leão DF, *et al* [10] in which not specified frequency (48.6%) of interactions were more, followed by delayed and rapid interactions. In this study, based on severity (**Table 1**); moderate were higher, i.e. 178 (54.26%) while 84 (25.6%) were major and followed by 66 (20.12%) minor this was similar to study done by Leão DF, *et al* [10] in which moderate severity DDIs (74.8%) were higher and study done by Carina Duarte D, *et al* [9] in which two-thirds of drug-drug interactions were moderate.

In this study, based on probable mechanism (**Table 1**) among 328 interactions, Pharmacokinetic (78.04%) were higher, followed by unknown mechanisms (04.57%). In pharmacokinetic interactions, metabolism interactions were higher 36.33%, this is similar to studies done by Christina Teeter Doligalski, *et al* [11] and S-M Huang, *et al* [12] in which metabolism contributes for more number of DDIs in Pharmacokinetic mechanism. In our study out of 656 drugs involved in interactions (**Table 2**), NSAIDS were 182, antidepressants were 120 and H2-receptor antagonists were 95, this is similar to study done by Carina Duarte D, *et al* [9] in which most of DDIs involved NSAIDS, loop and thiazide diuretics, and β-blockers.

According to our study results the management strategies of drug interactions is of 5 types (**Figure 2**), Maintain time gap between two drugs administration and avoid combination for long term use were shown in most of the drug interaction. Our study is similar to study done by Bhaskhar H Vaidhun, *et al* [13] which has concluded that limited use of multiple drug regimens may decrease the number of Drug Interactions.

CONCLUSION

In this study, we discussed about the DDIs in 360 prescriptions, including both male and female patients with age of 10-80 years in a Super Specialty Hospital. An increase in the number of drugs in prescription showed an increase in the number of DDIs. According to their severity, the Moderate type of Drug-drug interactions were found to be more and Based on onset of action, the not specified drug-drug interactions were found to be higher. Based on their mechanism of action, the Drug-drug interactions with Pharmacokinetic mechanisms are more in which metabolism showed a major contribution. Out of 5 management methods, Maintain time gap between two drugs administration and avoid combination for long term use were shown to be major. In monitoring drug-drug interactions the parameters that must be considered are Renal, Hepatic, Blood pressure, Blood glucose, Drug toxicity and specific lab parameters. Clinical pharmacist plays a major role in identifying the Drug-drug interactions and it has a greater impact on decreasing the Adverse Drug Reactions especially in Ambulatory patients. Hence this study is conducted to increase the Health Related Quality of Life in Ambulatory patients.

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