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Study on polypharmacy and potential drug – drug interactions in drug therapy of elderly patients at a tertiary care teaching hospital

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ABSTRACT

The administration of many drugs at the same time or the administration of an excessive number of drugs can cause the potentially serious drug-drug interactions and adverse drug events. Adverse drug events and serious harms occurs at all ages, although they are more commoner in older people, who are more vulnerable to drug toxicity because of age related physiologic changes and increased risk of disease associated with aging and because of polypharmacy. The objective of this study was to identify the degree of polypharmacy and the frequency of potential drug- drug interactions in the medication regimen of elderly patients. This is a cross – sectional observational study conducted in the general medicine department of a tertiary care teaching hospital over a period of 6 months. Sample size of 150 cases of elderly patients was collected from general medicine ward and was reviewed for polypharmacy and potential drug-drug interactions. From among the 150 cases collected, 65(43%) cases were identified with polypharmacy out of which 23(35%) were male and 42(65%) were female. The average number of drug prescribed per patient was 6.05. Among 150 cases, 71(47%) cases were identified with 152 potential drug-drug interactions out of which 8 cases (11%) were with clinically observed adverse drug reaction due to drug interactions. Majority of the potential drug-drug interactions were pharmacodynamic in nature (67%). It was observed that out of 152 pDDIs identified,17(11%) were major, 110(72%) were moderate and 25(16%) were minor in severity.

Key Words: Polypharmacy, potential drug-drug interactions (pDDI), elderly patients, pharmacodynamic drug Interaction, pharmacokinetic of drug Interaction, severity of potential drug-drug interactions, adverse drug reactions.

INTRODUCTION

Polypharmacy, defined by WHO (2004) as "The administration of many drugs at the same time or the administration of an excessive number of drugs."[1].Polypharmacy is the use of more medications than a medically necessary.[2] Polypharmacy is consistently associated with higher rates of potentially serious drug-drug interactions and adverse drug events.[3] Adverse drug events and serious harms occurs at all ages, although they are more commoner in older people, who are more vulnerable to drug toxicity because of age related physiologic changes and increased risk of disease

associated with aging and because of polypharmacy.[4] Among older people taking multiple drugs, there is often evidence of simultaneous over and under treatment, with prescriber and patients often struggling to balance benefit and harm in the face of complexity and uncertainty.[5] Various studies have examined the issues of polypharmacy in the hospitalized elderly. In a study of older hospitalized adult taking 5 or more medications, the prevalence of potential hepatic cytochrome enzyme mediated drug-drug interaction was 80%. The probability of a drug-drug interaction increased with the number of medications, specifically, a patient taking 5-9 medications had a 50% probability whereas the risk increased to 100% when a patient was found to be taking 20 or more medications.[6] In a study of community-dwelling elderly adults, almost 50% of patients had potential drug-drug interaction due to polypharmacy.[7] Another study in Italy found that on admission 51.9% of patients were on greater than 5 medications.[8] Risk of drug-drug interaction and adverse drug reaction has been to increase markedly with the number of concomitant medications, which may also increase risks of impaired treatment efficacy and increased drug related toxicity. Clinicians, administrator, and policymakers have become interested in the system factor that contributes to adverse drug reactions and how prescribing pattern can be improved. In a study done in united states, rates of adverse drug reactions due to drug-drug interaction ranges from 2% to 50%.[9][10] Taking multiple drugs for multiple health conditions increases the risk of drug interaction and ADRs, especially in older adults. Elderly patients often present with multiple medical conditions, and treating all of those conditions often necessitates polypharmacy. As the number of medications being taken by a given patient increases, the risk of drug interactions in that patient also increases. The risk of drug interaction can increases from approximately 6% in patient taking only two medications to 50% in those taking five medications and 100% in those taking ten medications[11]. Here the study aimed to identify the extent of polypharmacy, occurrence and associated factors for the occurrence of potential drug-drug interactions in the drug therapy of elderly patient in the general medicine department.

OBJECTIVES: The objective of this study was to identify the degree of polypharmacy and the frequency of potential drug- drug interactions in the medication regimen of elderly in-patients.

METHODS:

A prospective cross-sectional study was conducted over a period of 6 months in the general medicine ward of MVJ medical college and research hospital, Bangalore. All elderly in-patients (60 or greater than 60years old) receiving drug therapy in general medicine ward was included in the study.

The patients who were not willing to participate or not co-operating for the study was excluded from the study. The study was conducted on gaining approval from the institutional ethical committee. All patients who meet the inclusion criteria were enrolled in the study after taking Informed Consent (IC) before commencing the study. The entire elderly in-patients medication chart who was admitted in general medicine ward of study was reviewed. The basic demographics, number of medications prescribed and laboratory investigation values were collected by the researchers personally using the Case Report Form (CRF). The patient charts were screened and because of lack of consistency with the use of term "polypharmacy" we applied two of the most commonly cited ones to our dataset, specifically

1) Use of five or more concomitant drugs [12].
2) Use of potentially inappropriate drugs [13].

All the cases included in the study were assessed for the potential drug-drug interactions using drug database MICROMEDEX. Based on severity, the potential drug-drug interactions were classified into three main types:

a) Major: such interactions may have risk of death or may result in some serious negative outcomes.
b) Moderate: it may have harmful effects on patient's condition and can require change in the prescription.
c) Mild: it may have mild effects and can be minimized with alternative drug. The cases with polypharmacy and /or Drug- Drug Interactions were monitored for any Adverse Drug Reactions.

RESULTS:

Under demographic Data, firstly, Gender categorization was done in which out of 150 medication chart analyzed, 95(63%) were males and 55(37%) were females. Secondly age categorization was done in which majority of study subjects who participated in the study, belonged to the age group of 60-70 years [93 (63%)]. Above 53(35%) were in age group of 70-80 years and 2(1%) were of 80-90 age group. Then under social history, firstly all 150 patients participated in the study were seen for alcohol consumption, in which, 33(22%) were found to be alcoholic and 117(78%) were non-alcoholic. Secondly, smoking history of all 150 patients were seen in which 38(25%) patients were found to be smoker and 112(75%) were non-smoker. The average number of drugs prescribed per patient was found to be 6.053. In case of polypharmacy, out

of 150 cases, 65(43%) prescriptions showed cases with polypharmacy and 95(57%) showed cases with non-polypharmacy. Out of all polypharmacy cases i.e. 65 cases, 42 were seen in male and 23 were seen in female, which makes 65% in males and 35% in females. Out of 150 cases reviewed for drug interactions, 71(47%) cases were found to have Potential Drug-Drug Interaction (pDDI) and 79(53%) cases were with no interactions. And drug-drug interaction found (71 cases) were classified according to the gender, 61% (44) were male whereas 38%(27) were females. The total number of PDDI accounted for 152 among which, major interactions were found to be 17(11%), moderate interactions accounted for 110(72%) and minor interactions showed 25(16%) of total potential drug-drug interactions. Then the potential PDDIs were classified based on mechanism as pharmacodynamics and pharmacokinetics. Among 127(major and moderate) drug interactions, 42(33%) were pharmacokinetics in nature and 85(67%) were pharmacodynamics in nature. And some of the most prevalent drug-drug interaction found were Furosemide and Pantoprazole (9), Theophylline and Pantoprazole (5), Insulin and Metformin (4), Ceftriazone and Furosemide (4), Aspirin and Glipizide , Norfloxacin and Ondansetron, Furosemide and Ramipril, Ofloxacin and Ondansetron, Azithromycin and Theophylline and Fluconazole and Atorvastatin. The adverse drug reaction were observed which is caused due to drug drug interactions, in which out of 71 cases (150) with pDDI, 8(11%) cases were seen with adverse drug reactions clinically significant due to pDDIs and 63(89%) were with only theoretically significant ADRs. Some of the clinically observed ADRs were, ADR:- change in BP caused due to interaction between dextromethorphan and ondansetron, ADR:- anemia was experienced due to interaction between aspirin + methotrexate and diclofenac + methotrexate, ADR:- vomiting was experienced due to interaction between drugs like Ceftriaxone + Furosemide , ADR:- weakness was due to interaction between drugs like Norfloxacin + Glipizide and Insulin + telmisartan, ADR:- tachycardia was seen due to interaction between Lorazepam + Tamsulosin, ADR:- decrease in appetite was seen when MTX + Diclofenac were taken together and ADR:- nausea was seen due to interaction between Theophylline and Pantoprazole.

DISCUSSION:

Drug drug interactions are becoming serious issues with complex drug therapy. They are attributed to polypharmacy, non-compliance of patients & deterioration because of illness or secondary infection. The present study revealed the prevalence of polypharmacy and potential drug-drug interaction in elderly patients in General Medicine Ward. Majority of study subjects who participated in our study were belonged to the age group of 60-70 years [93 (63%)]. Above 53(35%) were in age group of 70-80 years and 2(1%) were of 80-90 age group. In our study, the prevalence of polypharmacy was found to be 43%. It is shown in the study that elderly males were exposed to polypharamcy more than elderly females in the same age group. These finding is supported by Mubarak N. Al. A.[14] However some study from literatures had shown there is no association between polypharmacy and gender. The average number of drugs prescribed per patient was 6.05 in our study which was higher in comparison with a study having 4.4 by Nilesh B C in South Gujarat Region.[15] The prevalence of pDDI's in our study was 47% which was low compared to other studies which encountered potential drug-drug interaction of 58%, 78% and 52%. It was observed that male 61% (44, N=71) were more susceptible to potential drug -drug interaction than female 38% (27, N=71). From 152 potential drug - drug interaction detected in our study, majority of pDDIs were moderate (72%) followed by minor (16%) and major (11%). Whereas in one study, 1.65% pDDIs were major, 75% were moderate and 22% were major in severity[16] and in another study, 24%, 36% and 12% of major, moderate and minor pDDIs respectively were reported.[17] From 152 pDDIs detected in our study, the majority were pharmacodynamics (pD) (67%) in nature followed by pharmacokinetic (pK) (33%) interactions . these finding is supported by a study conducted in South Gujarat Region, who reported 58% of pharmacodynamics potential drug-drug interactions and 38% of pharmacokinetic potential drug-drug interactions. Whereas these finding are in contrast to the study reported by Vonbach et al .[18] and Aparasu et al, [19] who reported 76% of pK and 22% of pD interactions. In our study, the most common pDDI reported major interactions was seen between Acebrophylline and Theophylline because both together causes CNS stimulation. Other common major interaction reported was between Methotrexate and Diclofenac where Diclofenac increases the blood levels and also increases the side effects of Methotrexate, leading to Methotrexate toxicity especially patients with kidney disease. The mechanism of major interaction with Domperidone + Ondansetron and Domperidone + Azithromycin was that both interactions cause QT Prolongation. Other major interaction seen between Methotrexate and Esomeprazole was the increase in serum concentration of Methotrexate. Another one major interaction seen was between Theophylline and Tramadol where Tramadol may rarely cause seizures

and if given with Theophylline risk of seizures may increase. The most commonly reported moderate pDDIs was between Furosemide and Pantoprazole (9) and the mechanism involved in the interaction was additive lowering of levels of magnesium in blood causing hypomagnesaemia. The second most occurring moderate pDDI was Theophylline and Pantoprazole (5) causing increased effects of Theophylline with symptoms like nausea, vomiting, insomnia, tremors and seizures. Next most commonly occurring moderate pDDI were Insulin and Metformin (4) causing increased insulin effects causing hypoglycemic condition and interaction between Ceftriaxone and Furosemide (4) causing kidney damage. Other some commonly occurring moderate interactions are

a) Aspirin+ Glipizide
b) Norfloxacin + Ondansetron
c) Furosemide + Ramipril
d) Ofloxacin + Ondansetron
e) Azithromycin + Theophylline
f) Fluconazole + Atorvastatin

Among 71 potential drug-drug interactions, only 8 patients experienced ADRs induced due to drug-drug interaction which were clinically observed such as change in BP caused due to interaction between dextromethorphan and ondansetron, anemia was experienced due to interaction between aspirin + methotrexate and diclofenac + methotrexate, vomiting was experienced due to interaction between drugs like Ceftriaxone + Furosemide , weakness was due to interaction between drugs like Norfloxacin + Glipizide and Insulin + telmisartan, tachycardia was seen due to interaction between Lorazepam + Tamsulosin, decrease in appetite was seen when MTX + Diclofenac were taken together and nausea as an adverse drug reaction was seen due to interaction between Theophylline and Pantoprazole.

CONCLUSION:

Drug-Drug Interactions are becoming serious issues particularly in geriatric patients with polypharmacy and with complex drug therapy. It was observed that the number of pDDI increased linearly with the number of drugs. Therefore, a step wise approach should be developed in all hospitals to decrease the exposure of elderly patients to polypharmacy. Thus, inclusive educational programs targeting primary care physicians, other healthcare professionals and elderly patients should be developed. The use of medicine in a disease condition is necessary, but unnecessary load of drugs to patient will increase the safety problems. Polypharmacy can be avoided by sharing treatment goals and plans. This will ensure safe, effective and appropriate use of medications in this specific population. Strategies should also be defined to closely monitor elderly who are more likely to be exposed to polypharamacy and drug-drug interactions to increase the awareness of the magnitude of polypharamacy phenomenon, improve drug therapy and minimize drug intake in elderly patients.

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Table 1: Number of drugs prescribed per patient (N=150)

Number of drugs	Number of patients (%)
2	1
3	6
4	12
5	20
6	22
7	21
8	26
9	14
10	11
11	5
12	1
13	6

14	1
15	1
17	3

Table 2: Most prevalent Drug-Drug Interactions

S.no	Drug combination	No. of cases	Severity	Effects
1	Methotrexate+Esomeprazole	1	Major	Methotrexate toxicity
2	Methotrexate + Diclofenac	2	Major	Methotrexate toxicity
3	Theophylline + Tramadol	1	Major	Seizures
4	Acebrophylline+Theophylline	3	Major	CNS Stimulation
5	Domperidone + Ondansetron	2	Major	QT Prolongation
6	Dextromethophan+Escitalopram	1	Major	Serotonin syndrome
7	Furosemide + Pantoprazole	9	Moderate	Hypomagnesemia
8	Theophylline+Pantoprazole	5	Moderate	↑ces effect of Theophylline
9	Insulin + Metformin	4	Moderate	Hypoglycemia
10	Ceftriaxone + Furosemide	4	Moderate	Kidney damage
11	Aspirin + Glimipiride	3	Moderate	↑ces effect of Glimepiride
12	Norfloxacin + Ondansetron	2	Moderate	↑ces QT Interval
13	Metronidazole+Atorvastatin	1	Minor	Nerve damage
14	Budesonide + Metformin	1	Minor	↓ces effect ofMetformin

Table 3: Drug-drug interaction with clinically significant ADRs

S.no	Drug combination	Severity	Effects	ADR due to pDDI
1	Aspirin + MTX	Major	MTX Toxicity	Anemia
2	Diclofenac + MTX	Major	MTX Toxicity	Anemia
3	Dextromethorphan + Escitalopram	Major	Serotonin Syndrome	Irregular BP
4	MTX + Diclofenac	Major	MTX Toxicity	Decreased Appetite
5	Dextromethorphan + Ondansetron	Major	Serotonin Syndrome	Change in BP and Nausea
6	Theophylline + Pantaprazole	Moderate	↑ced effects of Theophylline	Nausea
7	Lorazepam + Tamsulosin	Moderate	Hypotensive agents	Tachycardia
8	Insulin + Telmisartan	Moderate	↑ced risk of Hypogylcemia	Weakness
9	Ceftriaxone + Furosemide	Moderate	Kidney damage	Vomiting
10	Norfloxacin + Glipizide	Moderate	Interferes with blood glucose interference	Weakness
11	Enalpril + Aspirin	Moderate	Hypotension	Hypotension

Figure 1: Gender Categorization (N=150)

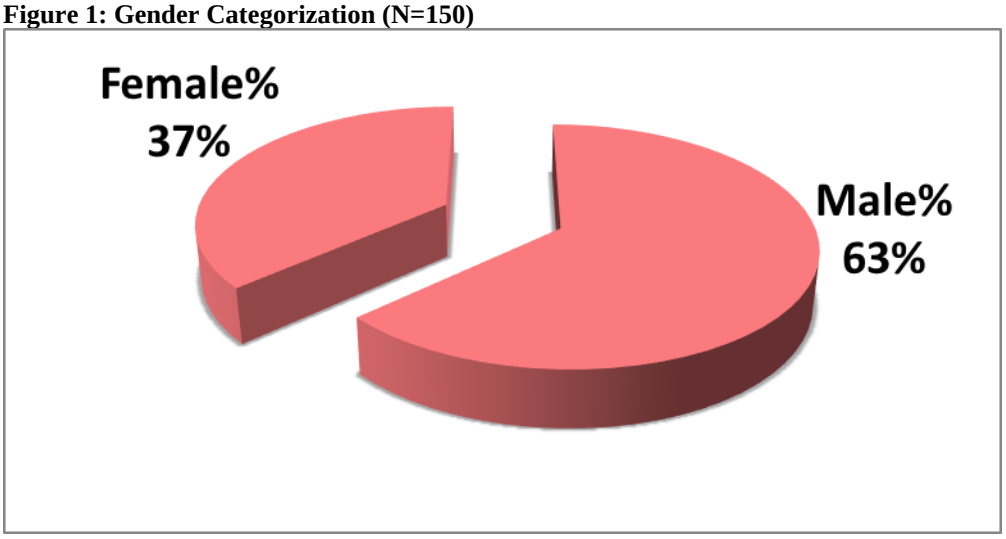


Figure 2: Age categorization (N=150)

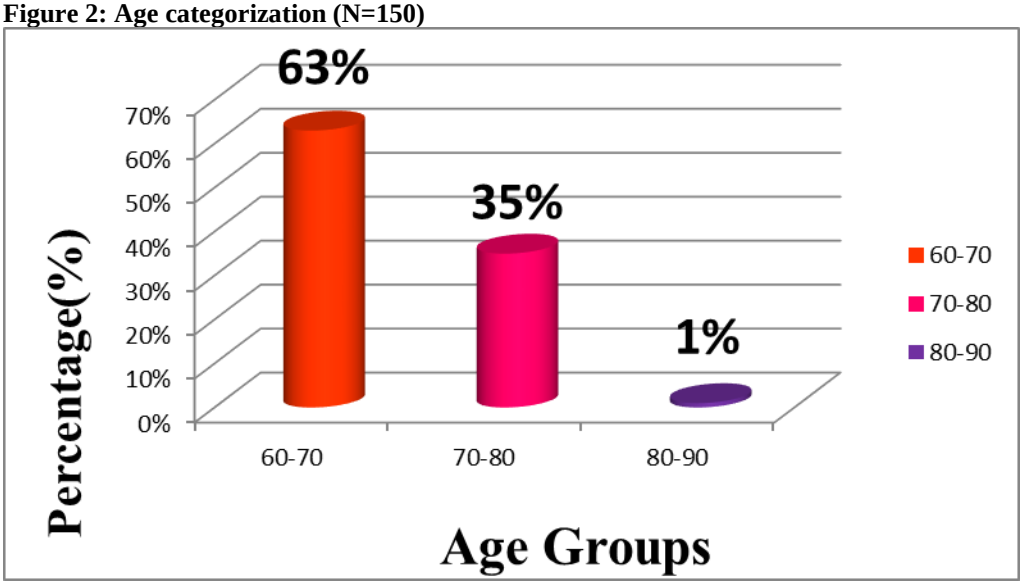


Figure 3: Polypharmacy (N=150)

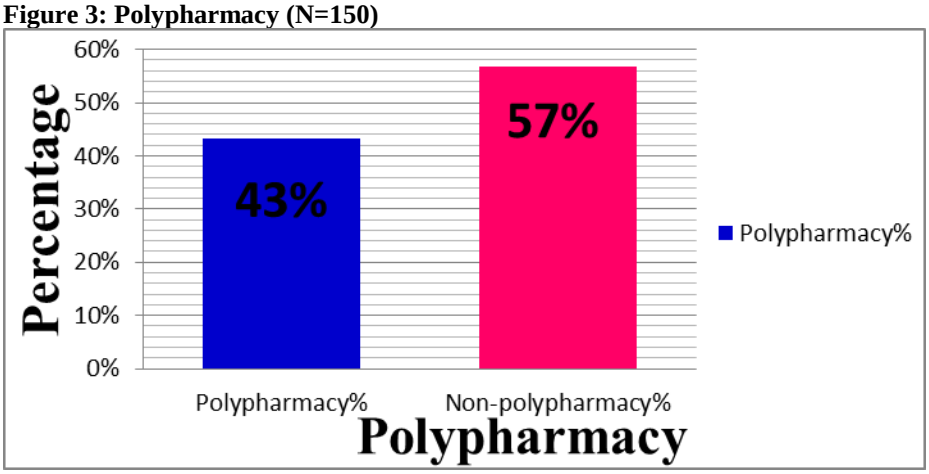


Figure 4: Occurrence of Polypharmacy in male and female (N=65)

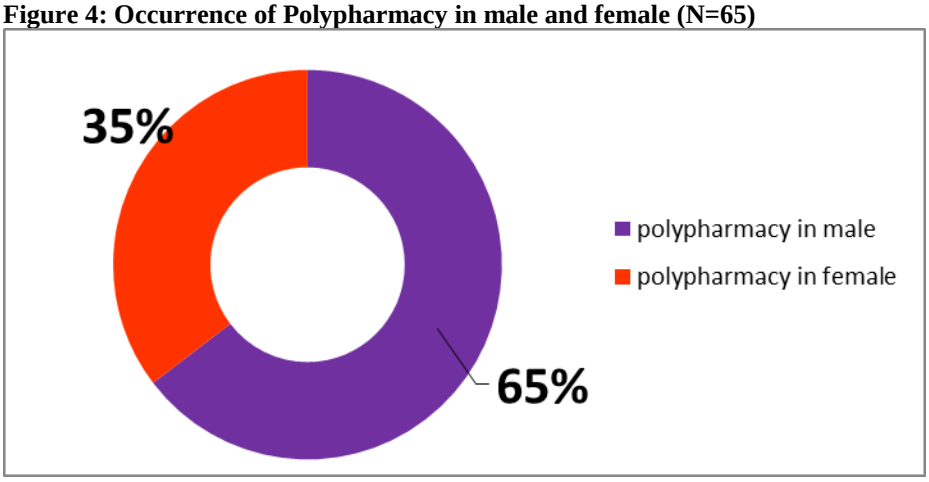


Figure 5: Potential drug-drug interactions(pDDI) (N=150)

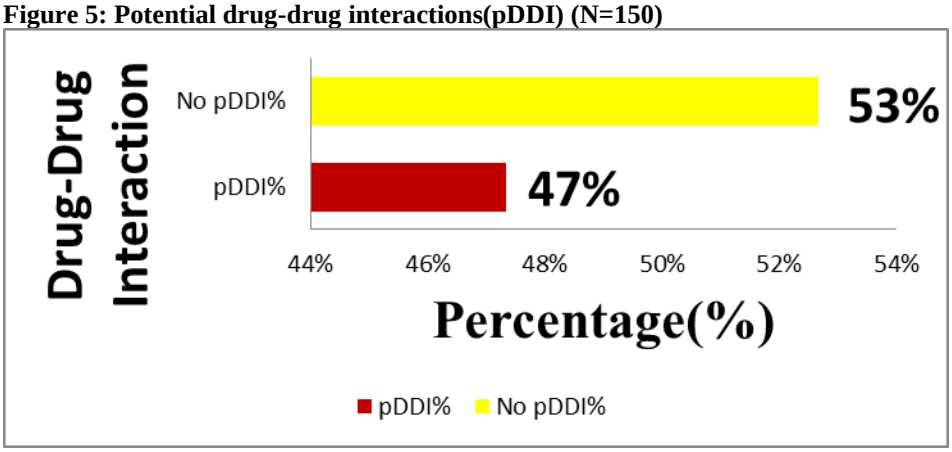


Figure 6: Potential drug-drug interactions based on severity (N=152)

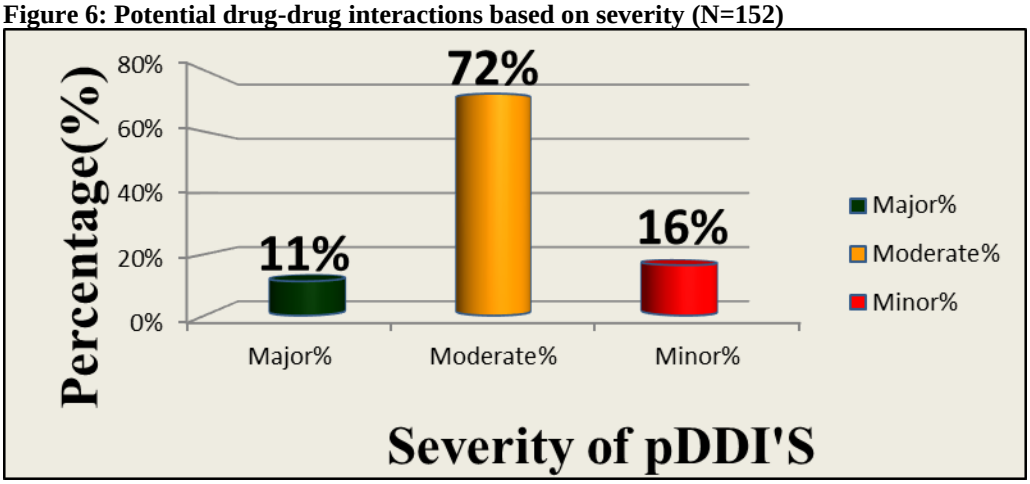


Figure 7: Potential drug-drug interactions based on mechanism (N=127)

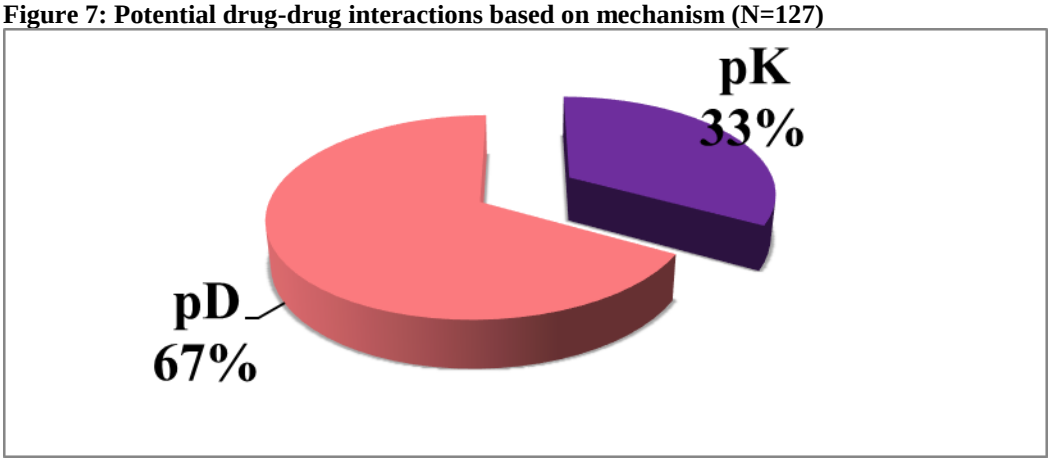
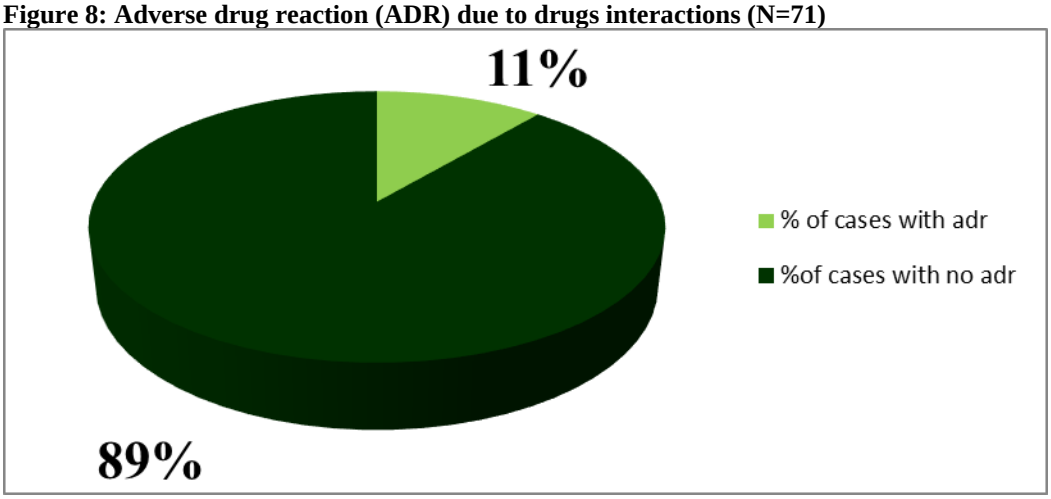


Figure 8: Adverse drug reaction (ADR) due to drugs interactions (N=71)



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