Original Research Article

Evaluation of potential drug-drug interactions in prescription in outpatient department of tertiary care hospital

ABSTRACT

Aims: To evaluate potential drug- drug interactions in prescriptions generated in outpatient department.

Study design: A cross sectional, observational study.

Place and Duration of Study: Pharmacy store, Government Medical College & Hospital, Nagpur, between July 2022 to September 2022.

Methodology: We included 382 patients (Male : Female 1.41 : 1.0 ; Mean Age 33.67 ± 23.18). Patients visiting the outpatient department during July 2022 to September 2022 were included randomly. All the patients whose medication profile contains at least two drugswere included in the study. In this study, data was collected from prescription given to patients in outpatient department. Data wasanalysed for potential drug- drug interactions using Rx list drug interaction checker Online, an online software to check drug-drug interactions (https://www.rxlist.com/drug-interaction-checker.htm) available on the website.

Results: Of the 382 prescriptions analysed for potential DDIs , 55 prescription were found to have potential DDIs. In those 55 prescriptions, 73 potential DDIs were identified.

Conclusion: Incidence of pDDIs was found to be 14.39% in these study

Keywords: pDDIs, prescription, Rx list drug interaction checker, Aspirin

1. INTRODUCTION

Adverse drug events (ADEs) in recent decades have become a major area of concern in the health care system because of their greater impact on medical and societal issues[1-2].ADEs carries a significant burden of outpatient hospital care, many of which develop serious illness and leads to increased loss of life.

Drug-drug interactions (DDIs) have shown to be a significant cause for adverse drug events (ADEs) [3-6].Alteration in the efficacy or toxicity of one drug due to the presence of another simultaneously administered drug is termed as drug-drug interactions (DDIs).This alteration is mostly quantitative, i.e., the response to a drug is either increased or decreased in intensity. DDIs may occur due to pharmacokinetic processes, i.e. the delivery of a drug to its site of action is altered by a second drug or

due to pharmacodynamic processes, i.e., when the two drugs act on same or interrelated target resulting in synergistic or antagonistic activity.

The estimates of hospital admissions caused by DDIs vary from 0.1% to 2.6% [7-9]. ADEs related to drug-drug interactions increase the length of stay in the hospital, add costs, and result in adverse consequences for patients [10]. Many drugs have even been withdrawn from the market due to their potential to cause fatal drug-drug interactions [11-12]. A significant percentage of ADEs are preventable if adequate emphasis is given and detected early [13-15]. Potential Drug–Drug Interactions (pDDIs) constitute one of the often preventable Causes of ADEs [16-17]. The frequency of adverse drug events (ADEs) associated with DDIs has not been extensively studied in the outpatient setting. DDIs occur in 9–70% of patients in community and ambulatory care settings, depending on the population studied and the methods used [18].

Drug therapy is an integral part of patient management. Though the use of multiple drugs may be required either to manage a single disease or comorbidities, harmful interactions may occur between these drugs [19]. The enthusiasm to use new drugs may lead to DDIs that are yet to be identified [19]. Adverse drug reactions may occur as the consequence of DDIs and clinicians may be unaware of the clinical risks of some drug combinations [19]. The drugs most commonly implicated in major potential interactions are those used in the day-to-day clinical management [19]. Most of the existing studies on DDI incidence focus on interactions in hospitalized patients [20-21], with fewer concerning the incidence of DDIs in primary care outpatients [22]. Many studies have focused on certain patient groups, e.g., aged people , cancer patients or on certain medicine groups, such as HIV drugs [22].

A previous study done by Yugandhar Bethi et al showed 46% prevalence of DDIs in the prescription [23]. Study done by Ahmad et al showed that prevalence of DDIs in Indian patients was 19% ,whereas another study done by Pankti S. Patel et al showed very high prevalence of 83% [24]. Also we could not find a published article that studied association between potential DDIs and experience of prescriber. In general there is great deal of variability regarding the prevalence of potential DDIs so therefore, this study aims to measure the prevalence, clinical significance and associated factors (age, gender, polypharmacy, designation of prescriber, number of comorbidities) of potential DDIs in the outpatient department of tertiary care hospital.

2. MATERIAL AND METHODS

2.1 Aim - To evaluate potential drug- drug interactions in prescriptions generated in outpatient department.

2.2 Objectives -

2.2.1 Primary objective

1. To measure the prevalence of potential drug - drug interactions in the generated prescriptions of outpatient department.

2.2.2 Secondary objective

1. To identify high risk medications involved in potential drug drug interaction in outpatient department.

2. To find the association between potential DDIs and age, numbers of drug prescribed, numbers of comorbid condition and designation of prescriber.

2.3 Methodology-

This was an cross-sectional study of prescription generated in outpatient department of a tertiary care teaching hospital, intended to evaluate the potential DDIs likely to occur due to co-prescriptions of medicine. This study was performed after the approval from the Institutional Ethics Committee and was carried out as per the GCP guidelines. Patients visiting the outpatient department from July 2022 to September 2022 were included randomly. All those patients whose medication profile contained at least two drugswere included in the study. In this study, data was collected from the prescription given to patients in outpatient department. Information like demographic characteristics, diagnosed main disorder, and other comorbidities, and number and type of prescribed drugs were collected from the prescription. All the co-prescribed drugs were checked for potential DDIs.

Data was analysed for potential drug- drug interactions using Rx list drug interaction checker Online, an online software to check drug-drug interactions (https://www.rxlist.com/drug-interaction-checker.htm) available on the website. This software categorises drug-drug interaction into contraindicated, serious, significant, minor and gives the summary of drug-drug interactions.

A total of 382 patients were included considering confidence interval of 95% and absolute precision of 5 % and the prevalence of DDIs was taken as 46% from previous studies [23].

2.4 Statistical analysis

Age, number of male and female patients were expressed as mean±SD. Association of patients' age, number of drugs prescribed, number of comorbid conditions and designation of prescriber with pDDI was done using the odds ratio. Potential DDI was the dependent variable in the model (0=absent, 1=present). Variables included in the analysis were age (1=<60 years of age, 2=≥60 years of age), gender (male=1, female=2), number of drugs prescribed per prescription (1=<5 drugs, 2=≥5 drugs), number of comorbid conditions (1=>1 comorbidities 2= ≤ 1 comorbidities). Descriptive statistics was done using Microsoft Excel 2019 and graph pad prism version 9.4.0.

3. RESULTS AND DISCUSSION

3.1 RESULTS :-

382 random OPD prescriptions from July 2022 to September 2022 from various departments of the hospital wereanalysed. In those 382 prescriptions, male patients were more in number (M:F; 1.41:1.00) , mean age was33.67 ± 23.18 (Table 1).Incidence of pDDIs was found to be 14.39% in these study (Figure 1). Of the 382 prescriptions analysed for potential DDIs , 55 prescription were found to have pDDIs. In those 55 prescriptions 73 pDDIs were identified. Aspirin & Ferrous Sulphate were the most commonly involved drug involved in pDDIs(Table 2). Most of the pDDIswe encountered were classified in the Major category by the Rx list drug interaction checker Online software (Table 3).The prescriptions we analysed randomly were not homogenous in nature pertaining to the Experience/Seniority of the prescriber (Table 4) & majority of the prescription which showed pDDIs belong to the junior doctors.Association between pDDIs& level of prescriber was analysed using Fischer exact test ,*P value* came out to be < *0.0001* which was significant (Table 5).Of the 73 pDDIs majority were single in occurrence, as in, one patient were

reported to have only single pDDIs in their prescription& only 14 patients had multiple (>1) pDDIs in their prescription (Table 6).

Most common Drugs involved :-

1. Aspirin 18 times&Ferrous Sulphate 18 times
2. Diclofenac 13 times
3. Pantoprazole 12 times
4. Glimepiride 9 times&Folic Acid 9 times

Most common pDDIsencountered :-

1. Ferrous Sulphate + Pantoprazole :-11times
2. Diclofenac + Amoxyclav:- 7 times
3. Folic Acid + Metformin :-4 times
4. Aspirin + Enalapril :- 4 times
5. Aspirin + Glimepiride :- 3 times

Table 1 :- Demographic Data :-

Age	33.67 ± 23.18
Sex (Male : Female)	1.41 : 1.0

Figure 1 :- Incidence of pDDIs

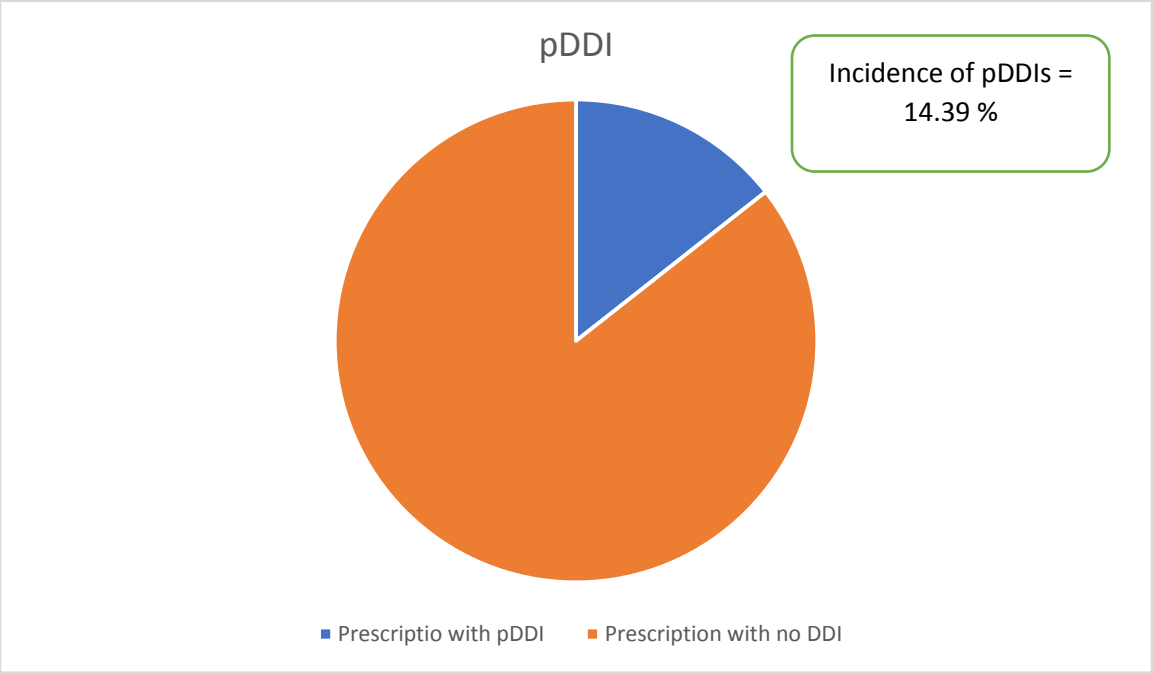

Table 2 :- Analysis Of Prescriptions

Total No of Prescription assessed for pDDIs	382
Total No of Prescription with pDDIs	55
Total pDDIs encountered	73
Most common Drug Involved	Aspirin Ferrous Sulphate (18 times each)
Most common Interaction encountered	FSFA with Pantoprazole (11 times)

Table 3 :- Severity of pDDIs

Severity	**Number n = 55 (%)**	**Most common Combination Involved**
Minor	20 (27.39%)	Folic Acid with Metformin
Major	52 (71.23%)	FSFA with Pantoprazole
Significant	1 (1.36%)	FSFA with Doxycycline
Contraindicated	0 (0%)	-

Table 4 :- Association of pDDIs& Level Of Prescriber

	Total Prescription (%)	Prescription with pDDIs (%)	Incidence	Odds Ratio (95 % CI)	*P Value*
Professor	02 (0.52 %)	01 (1.81 %)	50 %	6.037 (0.31 – 114.9)	.26
Associate Professor	08 (2.09 %)	02 (3.63 %)	25 %	2.019 (0.40 – 8.34)	.32
Lecturer	16 (4.18 %)	01 (1.81 %)	6.25 %	0.3852 (0.03 – 2.38)	.48
Senior Resident	27 (7.06 %)	0 (0%)	0 %	0.000 (0.00 – 0.70)	.02
Junior Resident	192 (50.26 %)	44 (80.00 %)	22.91 %	4.838 (2.39 – 9.65)	< 0.0001*
Not Mentioned	137 (35.86 %)	07 (12.72 %)	5.10%	0.2210 (0.09 – 0.50)	< 0.0001*

Table no 5 :- Comparison of Age & No of Drugs prescribed in Prescriptions having pDDIs& No pDDIs

Parameter	Prescription with pDDIs (n= 55)	Prescription with no pDDIs (n = 327)	*P value*
Age	47.13 ± 20.69	31.41 ± 22.84	< 0.0001 *
No of Drugs Prescribed	4.85 ± 1.33	3.36 ± 0.90	< 0.0001 *

Table 6 :- Number of pDDIs seen in Patients

No Of Drug Interaction	Patients
0	327
1	41
2	10
3	4
>3	0

3.2 Discussion

Result from these study demonstrated that incidence of pDDIs in a tertiary care teaching hospital in central India is 14.39 % , most common drug involved in these pDDIs were Aspirin & Ferrous Sulphate (18 times each), most common interaction involved was FSFA with Pantoprazole (11/73) , majority of these 73 interaction were of minor severity. Increasing age & more number of drugs prescribed were found to be an important determinant in detection of these pDDIs. Also knowledge & experience of the prescriber , were important factor associated with occurence of pDDIs

The study aimed at assessing the incidence of pDDIs in OPD setting.382 OPD patients prescriptions were evaluated for pDDIs. 55 prescription containing 73 pDDIs were found out to have pDDIs, which showed that the incidence of pDDIs was 14.39%. These result are in accordance with a study done by Mateti UV et al, where they found out the prevalence of pDDIs was 14.66%, although there study was done in In-patients department of Cardiology department [26]. Similar study was done by Yugandhar Bethi et al, again in, In-Patients department of medicine ward , they found the prevalence to be 46%. Their mean age of patient was 44.15 ± 16.9 as compared to our study which was 33.67 ± 23.18 &also their number of drug prescription was greater with 27.3% patients prescribed with > 7 drugs & only 12% were given <3 drugs, our mean consumption of drugs was 4.105 ± 1.11 [23]. As also we have found in our study , increasing age &more number of drugs consumed are contributing factors for pDDIs. With increasing age the likeliness of encountering a co-morbid condition increases as seen with hypertensive & diabetic patients also for them multivitamins are prescribed more often, as more number of drugs are prescribed the likelihood of encountering these pDDIs also increases.

Though the drugs & combination involved in pDDIs would vary with the hospital in which study is being conducted, according to the availability of medicines , type of patients which are encountered , site of hospital (country in which study is conducted) as the nature of disease may vary geographically. Aspirin & FSFA were the most commonly involved drug in pDDIs in our study. Aspirin was involved most commonly with Enalapril & Glimepiride. NSAIDs are known to attenuate the effects the hypotensive actions of ACE inhibitors by retaining salt and water. Incidence of renal failures have also been reported when NSAIDs have been given with diuretic especially in elderly population. Sulfonylureas like Glimepiride have increased chances of potentiating its action of lowering blood glucose level when given with salicyclates, salicyclates have the tendencies to displace sulfonylureas from its protein binding state thereby increasing the levels of free drug in plasma. Ferrous Sulphate was most commonly involved in pDDIs with Pantoprazole & these was the most common pDDIs we found in our study. PPIs like pantoprazole are used to lower the gastric acidity & for absorption of FSFA (especially the iron part) it requires acidic environment , so the absorption of FSFA is hampered when given with antacids. Patients should be advised to keep a gap of 1-2 hours between consumption of these drugs otherwise it could lead to therapeutic failure. The second most common combination of pDDIs we encountered was between Diclofenac &Amoxiclav ,either drug increases levels of the other by reducing drug clearance through the kidneys. Ahmad et al, also found similar findings , in their study , paracetamol (19.4%) & pantoprazole (19.4%) were the most common involved drugs in pDDIs.Also the most combination of drugs involved in pDDIs was Paracetamol with Pantoprazole & Furosemide(diuretic) with Aspirin(NSAID) [26]. Similar findings are reported by Pankti Patel et al , the most common combination they found out was between aspirin with Losartan &Aspirin with Glimepiride. As stated earlier , the drugs commonly involved in pDDIs or the combinations involved in pDDIs will vary from hospital to hospital according to the availability of medicines , type of patients which are encountered , site of hospital (country in which study is conducted) as the nature of disease may vary geographically.

Incidence of minor pDDIs was 20 (27.39%) , significant 52 (71.23%) , serious 1 (1.36%) , Contraindicated was 0. Minor pDDIs are the one in which the risk of interaction is unlikely , minor or non significant. Significant pDDIs are the one which in which there is potential for interaction & monitoring by treating physician is required. Serious pDDIs have the potential for serious interaction & regular monitoring is required or alternative medication should be tried. Contraindicated combinations should never be used

because of high risk for dangerous interaction. In our study most of the interaction were of minor nature , there was no combination prescribed which was contraindicated. The only serious pDDIs we encountered was Doxycycline with FSFA. Doxycycline decreases levels of ferrous sulphate by reducing drug absorption from the stomach and intestine. It is known that Milk, iron preparations, nonsystemic antacids and sucralfate reduce absorption of tetracyclines. Administration of these substances and tetracyclines should be staggered, if they cannot be avoided altogether. This co-prescription of Doxycycline & FSFA is touted as serious by the Rx list drug interaction checker Online, the online software we used for checking these pDDIs. Doxycycline is one the broad spectrum antibiotic , when originally introduced it acted against all pathogenic organism except fungi & viruses. Over the years due to injudicious use resistant organism have been developed , though it is still used as one the major antibiotics for infection. So when a patient is suspected to have infection or is diagnosed as one & if patient concurrently also has anemia , these two drugs are co-prescribed. As seen with few of these pDDIs , these interactions could be avoided by simply taking the two medicines few hours apart , so the need for proper counselling of the patient by treating physician & the pharmacist could play an important role in actual occurrence of DDIs. As we can't say when & how patients could have taken their medicine, whether with food or not , whether they took all medicines together or in intervals. So we cannot comment whether these pDDIs will actually lead to occurrence of DDI

There were not many studies we could find out showing the association between the number of pDDIs& the knowledge/seniority/experience of the prescriber. Association between pDDIs& level of prescriber was analysed using Fischer exact test , p value came out to be < 0.0001 which was significant. As seen from our result most of the prescription showing pDDIs were from junior resident doctors which was 80% of total pDDIs encountered, which signifies the importance of more thorough scrutiny, by the senior doctors of the respective department, of the final prescription which patients receive. Also Junior resident doctors should be made aware of their prescription error & the need for it to avoid in future practices as these pDDIs even though they are just a potential risk can still lead to potential failure of therapy , can prove to be an economic burden to patient as well as the government and the most important factor being the welfare & health of patient being at risk. As only a few prescriptions were signed by senior physicians , it is important to study these aspect of association of experience of prescriber &pDDIs with further studies, having more number of homogeneous prescription, before these findings of our study can be generalised

3.3Limitations

1) More number of prescription of senior doctors are needed for appropriate comparison
2) Co-morbid conditions could not be studied as planned earlier as not all prescription mentioned about the past history of patients
3) Being a cross sectional study , patient were not followed up , hence how many of the pDDIs noted in the prescriptions actually occurred could not be evaluated

4. CONCLUSION

Incidence of pDDIs was found to be 14.39%. Aspirin & Ferrous Sulphate were the most commonly involved drug in pDDIs. Experience, increasing age of patients, more number of drugs in prescription were important factors seems to be associated with pDDIs

Ethical approval – Study was conducted after obtaining permission from Institutional Ethics Committee

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