Journal of Pharmaceutical Research International

Volume 35, Issue 28, Page 28-35, 2023; Article no.JPRI.108207
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Evaluation of Potential Drug-drug Interactions in Prescription in Outpatient Department of Tertiary Care Hospital

Sunil M. Mahakalkar [a++], Akhil Giradkar [a#], Rahul Gholse [a†], Umesh Rathod [a‡*] and Divya Raj [a‡]

[a] Department of Pharmacology, GMCH, Nagpur, India.

sAuthors' contributions

This work was carried out in collaboration among all authors. Author SMM designed the study, wrote the protocol. Authors AG and RG managed the analyses of the study, performed the statistical analysis, literature searches. Author UR managed the data acquisition, wrote the first draft of the manuscript. Author DR assisted in reviewing relevant literature to support the discussion section of the paper. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2023/v35i287447

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/108207

Original Research Article

Received: 19/08/2023
Accepted: 27/10/2023
Published: 01/11/2023

ABSTRACT

Aims: To evaluate potential drug- drug interactions (pDDIs) 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.

[++] Professor & Head;
[#] Assistant Professor;
[†] Senior Resident;
[‡] Junior Resident-3;
**Corresponding author: E-mail: ummu8598@gmail.com;*

Methodology: Cross Sectional study performed in outpatient department from July 2022 to September 2022 analysed 382 patient prescriptions (Male : Female 1.41 : 1.0 ; Mean Age 33.67 ± 23.18) to evaluate for potential DDIs. Precription with atleast 2 drugs were included in the analysis. 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. Descriptive statistics were performed using MS Excel 2019.
Results: Of the 382 (Male: Female 1.41 : 1.0 ; Mean Age 33.67 ± 23.18)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 potential drug- drug interactions was found to be 14.39% in these study.

Keywords: Potential drug- drug interactions; prescription; Rx list drug interaction checker; Aspirin.

1. INTRODUCTION

In recent decades, Adverse Drug Events (ADEs) have emerged as a significant concern within the healthcare system, exerting a profound influence on both medical and societal domains [1-2]. ADEs impose a substantial burden on outpatient hospital care, often resulting in severe illnesses and an increased loss of lives.

One major contributor to ADEs is Drug-Drug Interactions (DDIs) [3-6], a phenomenon characterized by changes in the efficacy or toxicity of one drug when co-administered with another. These alterations are generally quantitative, either augmenting or diminishing the drug's effects. DDIs can occur through pharmacokinetic processes, where the delivery of a drug to its target site is influenced by another drug, or through pharmacodynamic processes, where both drugs act on the same or related targets, leading to synergistic or antagonistic effects.

Estimates of hospital admissions stemming from DDIs range from 0.1% to 2.6% [7-9]. ADEs linked to DDIs result in prolonged hospital stays, increased costs, and adverse outcomes for patients [10]. Some drugs have even been withdrawn from the market due to their potential to cause fatal DDIs [11-12]. A significant proportion of ADEs can be prevented with greater awareness and early detection [13-15]. Potential Drug-Drug Interactions (pDDIs) represent one of the often avoidable causes of ADEs [16-17]. However, the frequency of ADEs associated with DDIs in outpatient settings has not received extensive study. DDIs have been observed in 9-70% of patients in community and ambulatory care, with the rate varying based on the population studied and the methodology employed [18].

Drug therapy plays a pivotal role in patient management, but the use of multiple drugs to treat a single condition or comorbidities can lead to harmful interactions [19]. The eagerness to adopt new drugs may result in unidentified DDIs [19]. Adverse drug reactions can ensue due to DDIs, and clinicians might be unaware of the associated risks [19]. Often, the drugs most commonly implicated in major potential interactions are those commonly used in everyday clinical practice [19]. Existing studies on DDI incidence have primarily centered on interactions within hospitalized patients [20-21], with relatively fewer investigations into DDIs in primary care outpatient settings [22]. Additionally, many studies have focused on specific patient groups, such as the elderly, cancer patients, or particular medication categories like HIV drugs [22].

Previous research conducted by Yugandhar Bethi et al. revealed a 46% prevalence of DDIs in prescriptions [23]. Ahmad et al. found a 19% prevalence of DDIs among Indian patients, while Pankti S. Patel et al. reported a considerably higher prevalence of 83% [24]. Interestingly, we were unable to locate a published article exploring the link between potential DDIs and the prescriber's experience. Consequently, given the substantial variability in potential DDI prevalence, this study seeks to assess the prevalence, clinical significance, and associated factors (such as age, gender, polypharmacy, prescriber designation, and the number of comorbidities) of potential DDIs in the outpatient department of a tertiary care hospital.

2. MATERIALS 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 drugs were 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 were analysed. In those 382 prescriptions, male patients were more in number (M:F; 1.41 : 1.00) , mean age was 33.67 ± 23.18 (Table 1). Incidence of pDDIs was found to be 14.39% in these study (Fig. 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 pDDIs we 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).

3.1.1 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

3.1.2 Most common pDDIs encountered

1. Ferrous Sulphate + Pantoprazole :- 11 times
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

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 [25-26]. 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.

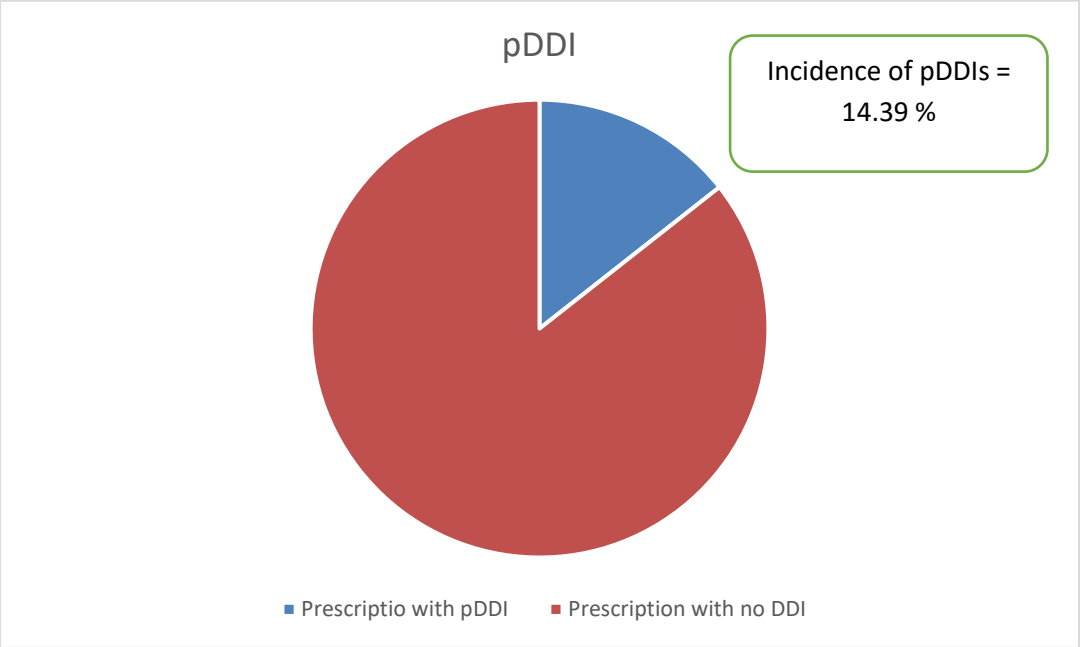

Fig.1. Incidence of pDDIs

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 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

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

3.3 Limitations

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

CONSENT

It is not applicable.

ETHICAL APPROVAL

Study was conducted after obtaining permission from Institutional Ethics Committee.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
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