

Study of potential drug–drug interaction between prescribed drugs in patients attending outpatient department of medicine at tertiary-care hospital in south Gujarat region

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ABSTRACT

Background: Drug–drug interactions (DDIs) are very common and responsible for 6%–30% of the adverse drug events that will increase healthcare cost and patient outcome. Polypharmacy significantly contributes to DDIs. **Aims and Objective:** To assess the DDIs in the outpatients in the medicine department in a tertiary-care hospital. **Materials and Methods:** The prescription of patients attending OPD of medicine department were analyzed for demography of patients and potential drug–drug interaction (pDDI). pDDI were checked by freely available drug interaction checker on Internet. pDDI were classified major, moderate, and minor according to severity and, by its mechanism, as pharmacokinetic, pharmacodynamic, or pharmacokinetic + pharmacodynamic. Statistical analysis was done using appropriate statistical software (MS Excel, Epi info, etc.). **Results:** Of the 300 patients who attended the medicine OPD during the study period, 253 patients were included in our study. From these, 128 (50.59%) were men and 125 (49.41%) women. Among these 253 patients, 147 (58.27%) patients had at least one pDDI and 106 (41.9%) patients had no pDDIs. The incidence of pDDI per patient was 1.68 ± 2.68 in our study. Average number of drugs prescribed per patient was 4.4 ± 1.48 in our study. A direct correlation was observed between the age of the patients and the number of pDDIs ($r = 0.35$, $P < 0.01$), between the age of the patients and the number of the drugs prescribed ($r = 0.18$, $P < 0.01$), and between the number of drugs prescribed and the number of pDDIs ($r = 0.69$, $P < 0.01$). Among 423 pDDIs, 215 (50.83%) were pharmacodynamic drug interactions, 163 (38.53%) pharmacokinetic, and 45 (10.64%) showed both kinds of mechanisms. Interactions with major severity accounted for seven (1.65%) of the total pDDIs, while those with moderate and minor severity accounted for 321 (75.87%) and 95 (22.46%), respectively. **Conclusions:** In our study, we found that most common pDDIs were pharmacodynamic in nature and of moderate severity. The number of pDDI increased with increase in the age of patients and the number of drugs prescribed.

KEY WORDS: Potential Drug–Drug Interaction (pDDI); Pharmacokinetic Drug Interaction; Pharmacodynamic Drug Interaction; Severity of Drug Interaction

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INTRODUCTION

Rational drug prescribing without drug–drug interactions (DDIs) is becoming very difficult with polypharmacy and complex drug therapies. Adverse drug reactions (ADRs) include adverse effects, drug interactions, idiosyncratic reactions, and hypersensitivity reactions.^[1]

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A drug interaction is defined as a modification of the effect of a drug when it is administered with another drug. The effect may be an increase or a decrease in the action of either drug, or it may be an adverse effect that is not normally associated with either drug. This definition applies to the interactions of drugs with other drugs (DDIs) and those of drugs with food (drug–food interactions) and other substances.

Adverse DDIs are a major cause of morbidity and mortality. In the Harvard Medical Practice Study of adverse events, 20% of such events were drug related. Of this, 8% were considered to be because of DDIs.^[2] In another study, DDIs were responsible for 6%–30% of adverse drug events. These DDIs will significantly increase risk to patient's health and increase the burden of health care system.^[3]

The factors that are significantly associated with DDIs includes polypharmacy, increasing age more than 60 years, and comorbid conditions such as cardiovascular diseases.^[4] DDI happens because of pharmacokinetic or pharmacodynamic mechanisms. In pharmacokinetics, they may interact by affecting absorption, distribution, metabolism, or excretion. In pharmacodynamic, it may interact by acting synergistically or antagonistically. Most of the drugs are metabolised by various microzomal enzymes, and the most common microzomal enzyme involved in drug metabolism is cytochrome P (CYP) 450 (the most common subtype involved are CYP3A4). Drugs affecting function of this microzomal enzyme also responsible for important DDI. Hence, DDIs are important hazards to the health of millions of patients, they have to be tackled, and it is the need of the hour.

Aims and Objectives

Although drug interactions are reported to be common in OPD in medicine department, there is no published report of the prevalence of such interactions in South Gujarat region. The aim of this study was to analyze potential DDIs (pDDIs) between the prescribed drugs among patients visiting out-patients department (OPD) of medicine department of a tertiary-care hospital.

MATERIALS AND METHODS

This cross-sectional observation study was performed on the OPD of the medicine department of a tertiary-care teaching hospital. This study was started after obtaining ethical clearance from the institutional ethical committee. The study period was 6 months (July 2013–December 2013), during which the data were collected.

The investigator visited the medicine OPD daily. Patients visiting medicine OPD for treatment were included in the study. Prescriptions with two or more drugs prescribed were selected for the study. Only one prescription from each patient during his/her visit in the OPD during the study period was included. Written informed consent from patients participating in study

was taken. Patients who refused to give consent were excluded from the study. Prescriptions with one drug were excluded from study.

Information about patient's demographic profile, diagnosis and information about prescribed drugs were collected. The data were analyzed by using the online freely available drug interaction checker.^[5] This computer program will give information about pDDI. It also informs about its severity, management, and monitoring parameters with scientific references. Statistical analysis was done using appropriate statistical software (MS Excel, Epi info, etc.).

Classification of Potential Drug–Drug Interaction

On the basis of the profile of medications prescribed, the pDDIs were identified and classified.

1. According to the mechanism, pDDIs were classified as: (a) pharmacokinetic, (b) pharmacodynamic, and (c) pharmacokinetic + pharmacodynamic.
2. According to severity, pDDIs were classified as: (1) major, the effects are potentially life threatening or capable of causing permanent damage; (2) moderate, the effects may cause deterioration in patients' clinical status and additional treatment or extension of hospital stay; and (3) minor, the effects are usually mild. Consequences may be bothersome or unnoticeable but should not significantly affect the therapeutic outcome.
3. Pharmacokinetic pDDIs were further classified as either increase/decrease in: (a) absorption, (b) distribution, (c) metabolism, and (d) excretion.
4. Pharmacodynamic pDDIs were further classified as: (a) synergistic or (b) antagonistic.

RESULTS

From the patients attending medicine OPD in the study period, 300 patient's prescriptions were analyzed. Among them, 253 patients were included in the study. From these 253 patients, 128 (50.59%) were men and 125 (49.41%) women. Among these 253 patients, 147 (58.27%) patients

Table 1: Frequency of number of drugs prescribed per patient

Number of drugs	Number of patients (%)
2	13 (5.14)
3	47 (18.58)
4	96 (37.94)
5	60 (23.72)
6	20 (7.91)
7	6 (2.37)
8	5 (1.98)
9	2 (0.79)
10	3 (1.19)
12	1 (0.40)

Table 2: Frequency of number of pDDIs per patient

Number of pDDIs	Number of patients (%)
0	106
1	56 (38.10)
2	36 (24.49)
3	25 (17.01)
4	7 (4.76)
5	4 (2.72)
6	5 (3.40)
7	4 (2.72)
8	4 (2.72)
9	1 (0.68)
10	1 (0.68)
11	1 (0.68)
12	1 (0.68)
15	1 (0.68)
24	1 (0.68)

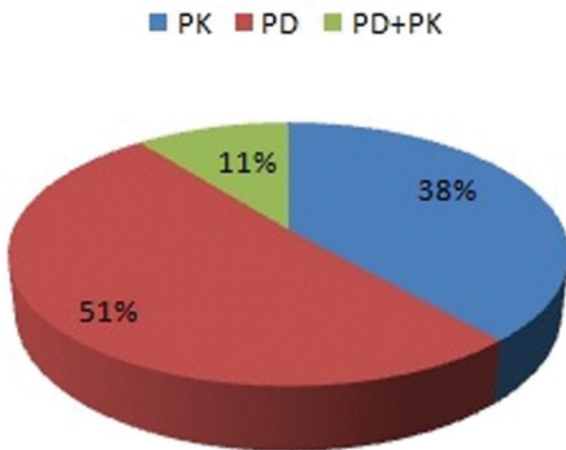


Figure 1: Classification of pDDIs (according to mechanism).

showed at least one pDDI and 106 (41.9%) patients no pDDIs. The mean age of patient was 43.50 ± 15.63 years. The most common diagnosis of patients of the study was hypertension (19.41%), followed by upper respiratory tract infection (14.29%) and diabetes (11.36%).

Potential Drug-Drug Interactions

On evaluation, the number of drugs prescribed to the individual patient was 4.4 ± 1.48 (range, 2-12). The frequency of pDDIs per patient was 1.68 ± 2.68 (range, 1-24). Of the 253 patients, 147 (58.1%) had at least one interaction. The results are represented in Tables 1 and 2.

A direct correlation was observed between the age of the patient and the number of pDDIs ($r = 0.35, P < 0.01$), between the age of the patient and the number of drugs prescribed ($r = 0.18, P < 0.01$), and between the number of drugs prescribed and the number of pDDIs ($r = 0.69, P < 0.01$).

MAJOR MINOR MODERATE

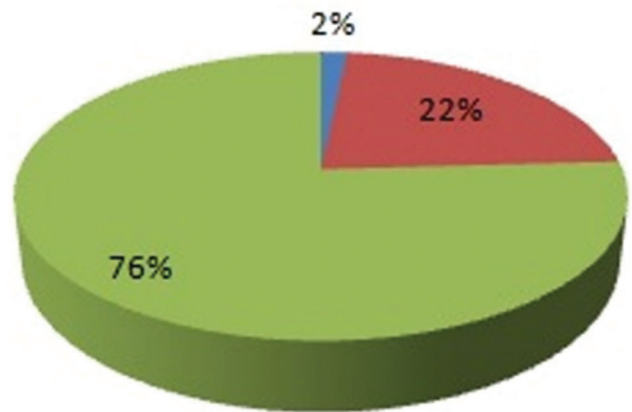


Figure 2: Classification of pDDIs (according to severity).

Table 3: Commonly observed pDDIs

S. no.	Drug-drug interaction	Total
1	Tab. atenolol (50 mg)-tab. deriphyllin (300 mg)	1
2	Tab. domperidone (10 mg)-cap. tramadol (50 mg)	1
3	Tab. enalapril (10 mg)-tab. spironolactone (25 mg)	1
4	Tab. methotrexate (2.5 mg)-cap. omeprazole (20 mg)	1
5	Tab. ofloxacin (200 mg)-tab. lumefantrine (480 mg)	1
6	Cap. omeprazole (20 mg)-tab. clopidogrel (75 mg)	1
7	Tab. spironolactone (25 mg)-tab. losartan (50 mg)	1
8	Tab. atenolol (50 mg)-tab. amlodipine (5 mg)	22
9	Tab. alprazolam (0.5 mg)-cap. omeprazole (20 mg)	15
10	Cap. omeprazole (20 mg)-tab. Iron (200 mg)	15
11	Tab. aspirin (75 mg)-tab. amlodipine (5 mg)	11
12	Tab. atenolol (50 mg)-tab. calcium (600 mg)	10
13	Tab. atenolol (50 mg)-tab. aspirin (75 mg)	10

Classification of pDDIs

The pDDIs were classified based on their mechanism such as pharmacodynamic, pharmacokinetic, or both. Among 423 pDDIs, 215 (50.83%) were pharmacodynamic drug interactions, 163 (38.53%) pharmacokinetic, and 45 (10.64%) showing both kind of mechanisms (Figure 1).

The severity of pDDIs was classified as major, moderate, and minor. Of the 423 pDDIs, the majority were of moderate severity. Interactions with major severity accounted for seven (1.65%) of the total pDDIs, while those with moderate and minor severity accounted for 321(75.87%) and 95 (22.46%), respectively (Figure 2).

Few commonly observed major, moderate, and minor pDDIs in our study were shown in Table 3.

Pharmacokinetic interaction: Of the 163 pharmacokinetic pDDIs found, two (1.23%) were major, 99 (60.74%) moderate, and 62 (38.04%) minor severities. From these 163 pharmacokinetic pDDIs, 45.41% were affecting absorption (11.59% increase and

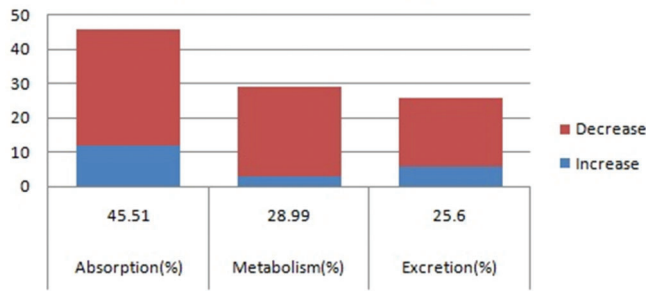


Figure 3: Classification of pharmacokinetic pDDIs.

33.82% decrease in absorption), 28.99% were affecting metabolism (2.90% increase and 26.09% decrease in metabolism), and 25.60% were affecting excretion (5.80% increase and 19.81% decrease in excretion) (Figure 3).

The most common CYP450 enzyme involved in pDDI in our study was CYP3A4, and the most common drugs involved were alprazolam–omeprazole in 15 patients. Other enzymes involved in pDDI are shown in Table 4.

Pharmacodynamic interactions: Among these 215 pharmacodynamic pDDIs, four (1.86%) were major, 188 (87.44%) moderate, and 23 (12.56%) minor severities. On the basis of action, of these 215 pharmacodynamic pDDIs, 145 (67.44%) were synergistic, 66 (30.70%) antagonistic, and four (1.86%) unknown in nature (Figure 4).

Pharmacokinetic + pharmacodynamic interactions: Among these 45 pharmacokinetic + pharmacodynamic pDDIs, one (2.22%) was major, 34 (75.56%) were moderate, and 10 (22.22%) were of minor significance. On the basis of action, 28.06% were affecting absorption (23.91% increase and 2.17% decrease in absorption), 69.57% were affecting metabolism (0% increase and 69.57% decrease in metabolism), and 4.35% were affecting excretion (2.17% increase and 2.17% decrease in excretion). From these 45 pharmacokinetic +

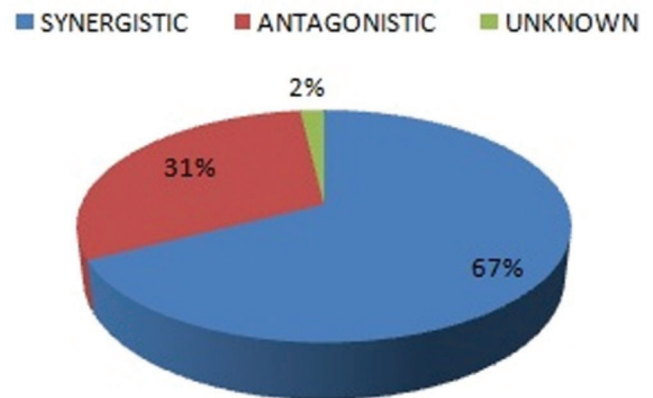


Figure 4: Type of pharmacodynamic pDDIs.

pharmacodynamic pDDIs 31 (68.89%) were synergistic and 14 (31.11%) antagonistic in nature (Figure 5a,b).

DISCUSSION

DDIs are becoming serious issue with complex drug therapies. DDIs can result in anything from minor morbidities up to fatal consequences. Studies have shown that up to 11% of outpatients experience symptoms associated with DDIs and DDIs are responsible for up to 2.8% of hospital admissions.^[6] DDIs cause 4.8% of the hospitalizations in the elderly people.^[7] They are attributed to polypharmacy, noncompliance of the patients, and deterioration because of illnesses or secondary infections.^[8]

The incidence of the pDDIs in our study patient population was 58.27%. In other studies, incidence of pDDIs were quiet variable from 44% to 80%.^[1,9,10] The incidence of pDDI per patient was 1.67 in our study. The average number of drugs prescribed per

Table 4: CYP450 enzymes subtypes involved in pDDIs

S. no.	Enzyme	Interacting drug	No. of patients	Total
1	CYP 3A4	Tab. alprazolam (0.5 mg)–cap. omeprazole (20 mg)	15	28
		Tab. atorvastatin (20 mg)–tab. clopidogrel (75 mg)	4	
		Tab. famotidine (20 mg)–Tab. glipizide (5 mg)	3	
		Tab. ranitidine (150 mg)–tab. metformin (500 mg)	2	
		Tab. azithromycin (500 mg)–tab. atorvastatin (20 mg)	1	
		Tab. carbamazepine (200 mg)–tab. phenytoin (100 mg)	1	
		Tab. ciprofloxacin (500 mg)–tab. amlodipine (5 mg)	1	
		Tab. famotidine (20 mg)–tab. deriphyllin (300 mg)	1	
2	CYP2C19	Tab. glipizide (5 mg)–cap. omeprazole (20 mg)	3	4
		Cap. omeprazole (20 mg)–tab. clopidogrel (75 mg)	1	
3	CYP2C9	Tab. diclofenac (50 mg)–tab. clopidogrel (75 mg)	1	2
		Tab. naproxen (500 mg)–tab. clopidogrel (75 mg)	1	
4	CYP3A5	Tab. azithromycin (500 mg)–tab. deriphyllin (300 mg)	4	5
		Cap. omeprazole (20 mg)–tab. atorvastatin (20 mg)	1	
5	CYP3A6	Cap. omeprazole (20 mg)–tab. atorvastatin (20 mg)	4	4

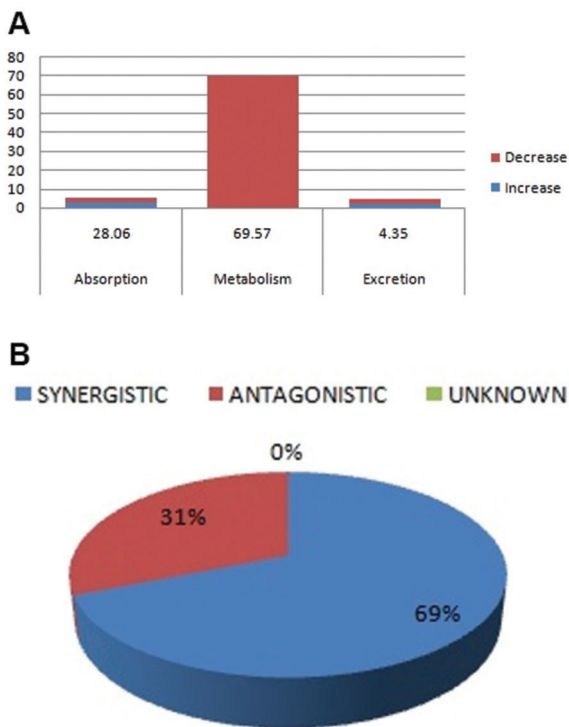


Figure 5: Types of pharmacokinetic + pharmacodynamic pDDI by a) pharmacokinetic b) pharmacodynamic mechanisms.

patient was 4.4 in our study, which was lower in comparison with other study, which showed 7.8 and 5.9 pDDI per patient.^[1,9]

A direct correlation was observed between the age of the patients and the number of pDDIs ($r = 0.35$, $P < 0.01$). Similar findings were seen in other studies; so, the elderly patients are at increased risk of PDDIs.^[10–14] A direct correlation was also observed between the age of the patient and the number of drugs prescribed ($r = 0.18$, $P < 0.01$) and between the number of drugs prescribed and the number of pDDIs ($r = 0.69$, $P < 0.01$); similar findings seen in other studies too.^[10,12,15] So, with increase in patient's age, more number of drugs will be prescribed, and it will increase the chances of having more number of pDDIs. In elderly patients, kidney and liver functions are compromised, which will also increase the chances of pDDIs.

From pDDIs detected, the majority were of pharmacodynamic (58.83%) in nature, followed by pharmacokinetic (38.53%) interactions. These findings are in contrast to the study reported by Vonbach et al.^[16] and Aparasu et al.,^[6] who reported 76% of pharmacokinetic and 22% of pharmacodynamic interactions.

In our study, we found that the majority of pDDIs was moderate (75.87%), followed by minor (22.46%) and major (1.65%) significance. In one study, 33% PDDIs were of major severity, 32% PDDIs moderate severity, and 35% PDDIs minor severity.^[10]

In our study, the most common pDDI was atenolol–amlodipine, which was of moderate severity and mechanism

of interaction was additive slowing of atrioventricular (AV) conduction, reduced cardiac contractility secondary to beta blockage, and decreased peripheral vascular resistance secondary to calcium channel blockage. Slowing of AV conduction mainly seen when verapamil was used with beta blocker, but with high doses, it can be seen amlodipine.^[17,18] The second most common moderate pDDI was alprazolam–omeprazole, and the mechanism was omeprazole inhibits hepatic enzymes and leads to secondary increase in benzodiazepine level in blood; so, the dosage of benzodiazepine should be reduced.^[19,20] The interaction between omeprazole and iron was of moderate severity, and the mechanism was omeprazole decreases iron absorption, which requires acidic medium.^[21] Recently, major interaction was seen between atenolol–deriphyllin because pharmacological effect of both are opposite and selectivity of atenolol will be lost at high doses and produce severe bronchospasm.^[22] Major interaction also seen between domperidone and tramadol, where domperidone reduced seizure threshold in elderly people, history of epilepsy, and other risk factor for seizures.^[23,24] The mechanism of major interaction with enalapril–spironolactone and losartan–spironolactone was that both drugs can cause hyperkalemia.^[25,26] One major interaction seen in methotrexate–omeprazole was that proton pump inhibitor reduces active tubular secretion of methotrexate in kidney and increases plasma methotrexate level and toxicity.^[27,28] Major interaction between ofloxacin and lumefantrine was because both the drugs prolong QT interval and produce arrhythmia.^[29] Major interaction seen between omeprazole and clopidogrel was because proton pump inhibitor inhibits hepatic CYP2C19-mediated bioactivation of clopidogrel by enzyme inhibition and blocks clopidogrel antiplatelet effect.^[30–32]

In our study, from 163 pharmacokinetic pDDIs, majority of pDDIs were affecting absorption (45.51%), followed by metabolism (28.99%) and excretion (25.6%) processes. In one study, 431 significant potential pharmacokinetic DDIs were detected of which majority [186 (43.16%)] affected the metabolism, followed by 154 (35.73%) affecting absorption, 57 (13.23%) excretion, and 21 (4.87%) distribution of the drugs.^[33]

Among 215 pharmacodynamic pDDIs, majority of pDDIs were synergistic (67.44%), followed by antagonistic (30.70%) and unknown (1.86%) in nature. In one study, 523 significant potential pharmacodynamic DDIs were detected, of which majority [298 (56.98%)] were synergistic, followed by 209 (39.96%) showing a potential for antagonism.^[33] Among 45 pharmacokinetic + pharmacodynamic pDDIs majority affected metabolism (69.57%) and of synergistic (68.89%) in nature.

In our study, the most common subtype of CYP450 enzyme involved in pDDIs were CYP3A4, followed by CYP3A5, CYP2C19, CYP3A6, and CYP2C9. The most common drugs affecting CYP3A4 were alprazolam–omeprazole. In another study, the common enzyme involved in pDDIs was CYP3A4, followed by CYP2C9/10, CYP1A2, CYP2C19, and CYP2E1.^[33]

The limitation of our study was cross-sectional observational study in nature, and further study can be planned with

prospective study design in which pDDIs will be followed up and studied in detail with more sample size. We used a freely available DDI checker on Internet, and further study will be planned with the use of more than one drug interaction checker; then, it will produce more refined results.

CONCLUSION

This study showed that the overall incidence of pDDIs was 58.27%. It was observed that the number of pDDIs increased linearly with the number of drugs and age. The majority of interactions was pharmacodynamic in mechanism and showed moderate severity. This study provided a reference data for the surveillance of pDDIs in medicine department OPD patients of a tertiary-care hospital in South Gujarat region. Development of similar data base of other departments might help to evaluate the economic, clinical, and humanistic outcomes of clinically important DDIs in the South Gujarat region.

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