Original Article

Assessment of drug-related problems among diabetes and cardiovascular disease patients in a tertiary care teaching hospital

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How to cite this article:
Sharma A, Baldi A, Sharma DK. Assessment of drug-related problems among diabetes and cardiovascular disease patients in a tertiary care teaching hospital. Pharmaspire 2018;10(1):7-12.

Source of Support: Nil,
Conflict of Interest: None declared.

ABSTRACT

Drug-related problems (DRPs) are common in hospitalized patients and may lead to increase hospital stay, health-care cost, and augment the risk of morbidity and mortality. The aim of this study was to assess the prevalence of DRP and associated factors among medical ward patients in three different tertiary care teaching hospitals in Punjab, India. This study shows the evaluation of current prescribing pattern to identify different adverse drug reactions, specific drug-drug, drug-food interactions, and medication errors. The study was conducted at the Department of Medicine in three different hospitals setting in the Moga, District of Punjab, India. Based on the inclusion and exclusion criteria, the patient's after signing the informed consent form data was collected from the patient case file, case reports, and laboratory reports. A total of 1230 cases were followed and reviewed in the medicine department during the study. Of the cases reviewed, 353 (78.27%) DRPs were identified from 451 patients. Of 451 patients, 256 (56.76%) were male and 195 (43.23%) were female. In this study, it was found that DRPs were identified in 451 patients. In which, drug interactions were maximum 252 (55.88%) followed by adverse reactions 106 (23.50%). The present study highlights the fact that clinical pharmacist can play a very important role in the health-care management by rationalizing and optimizing the drug therapy to achieving better quality of life.

Keywords: Adverse drug reactions, drug interactions, drug-related problems, drug use evaluation, inappropriate prescribing, medication error

INTRODUCTION

Even though medications play a major role in the cure, palliation, and inhibition of disease, they also expose patients to drug-related problems (DRPs).[1] According to Pharmaceutical Care Network Europe (PCNE) classification volume 6.2, DRPs are "an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes," and it is classified them as dosing problems, adverse drug reaction (ADR), drug-drug interaction (DI), inappropriate prescription, and patient adherence to the drug.[2]

Access this article online	
Website: www.isfcppharmaspire.com	**P-ISSN:** 2321-4732 **E-ISSN:** XXXX-XXXX

Previous studies reported that majority of hospitalized patients have some kind of DRPs. In many instances, DRPs are a major safety issue for hospitalized patients, and it may lead to reduced quality of life, increased hospital stay, increased overall health-care cost, and even increases risk of morbidity and mortality.[3]

There are a number of consequences associated with DRPs which include hospitalizations, long-term care admissions, emergency department visits, additional physician office visits, and additional prescriptions. In addition to these, substantial costs are also associated with DRPs. For example, the economic burden arising from drug-related morbidity and mortality in the United State of America was $177.4 billion annually.[4] Whereas, £100707 was reported in the Australian study. Therefore, DRPs are major area concern of the patient's physical, psychological, and economic burden to the patients

as well as to the whole society. Hence, improving drug therapy by preventing DRPs may have an important effect on the patient's health, treatment-related costs, potentially save lives, and enhance patient's quality of life.[5]

Increased number of medications, complexity of drug regimens, and availability of new drug therapies potentially increase the risks of patient for iatrogenic adverse drug events in hospitals. This can lead to prolonged hospital stay and increased health-care costs.[6] Hence, the injury or death that may occur as a result of DRPs has to be evaluated so as to reduce the occurrence of similar events in future.[1]

DRPs may arise at all stages of the medication process from prescription to follow-up of treatment. Most of the problem usually occurs on administration, dispensing, and during the patient's use of a medicinal product, but lack of proper follow-up and reassessment of medical treatment by the physician is also a major problem.[7] DRPs occur more frequently in hospitalized patients where multiple changes are being made in patient's medication regimens and lack of continuity of care may be accompanied. The most common problems associated with drug use are many and includes inappropriate medication prescribing, discrepancies between prescribed and actual regimens, poor adherence, DIs, inappropriate use, patients monitoring, and inadequate surveillance for adverse effects. DRPs lead to substantial morbidity, mortality, as well as increased health-care expenditure which in turn affects the patient's quality of life. The goal of pharmaceutical care is to improve an individual patient's quality of life through the achievement of definite (predefined), medication-related therapeutic outcomes.[8]

Cardiovascular disease (CVD) and diabetes are a major public health problem and one of the leading causes of premature death throughout the world and contributes substantially to increased health-care costs.[9] The most common underlying pathology expected to cause CVDs is atherosclerosis. Cardiovascular patients usually get exposed to multiple comorbid conditions like diabetes and are prescribed with multiple drugs.[10] Hence, the chances of occurring DRPs are more in such kind of patients. Hence, to identify the DRPs in such patients with CVDs mainly diabetes, the study has been conducted.[11]

METHODS

The study was conducted on after obtaining approval and clearance from the Institutional Ethics Committee. The study was conducted at the Department of Medicine in three different hospitals setting in the Moga, District of Punjab, India. Based on the inclusion and exclusion criteria, the patient's after signing the informed consent form data was collected from the patient case file, case reports, and laboratory reports. The sample size is calculated through Software "Statcalc Epi info" which is designed by the US Department of Health and Social Services Centre for Disease Control and Prevention for prospective observational studies.[12] The collected data were code, cleared, and checked for completeness and entered analyzed using software SPSS version 24.[13] The population size of the study was found to be = 1613254 as per census (2011). Sample of the study was found to be = 1230 patients. The study was conducted for 1 year. Descriptive statistics were used to characterize DRPs. Results of the study were organized in the form of frequencies and percentages. The data were summarized and described using tables and figures. Micromedex DI checker was used to identify drug-DI. Identified DRPs were recorded and classified using DRP registration format which was taken from pharmaceutical care practice: The clinician's guide.[14]

Objective

The general objective of this study is to identify the prevalence, pattern, and risk factor of drug therapy problems and their risk factors among diabetes and CVD patients in a tertiary care teaching hospital.

RESULTS AND DISCUSSION

A total of 1230 cases were followed and reviewed in the medicine department during the study. Of the cases reviewed, 353 (78.27%) DRPs were identified from 451 patients. Of 451 patients, 256 (56.76%) were male and 195 (43.23%) were female. The majority of the DRPs occurred in the age group of 51–70 years 320 (70.95%) patients [Table 1].

The PCNE classification that was used in this study has been critically appraised as the most appropriate classification that reflects outcomes, and the results are reproducible.[15,16] The classification tool has been validated and was used in many other published studies to assess DRP occurrence.[17,18]

In this study, it was found that DRPs were identified in 451 patients. In which, DIs were maximum 252 (55.88%) followed by adverse reactions 106 (23.50%) as shown in Table 2. Other causes include inappropriate route, costly drug prescribed, drug overuse, inappropriate timing of administration and/or dosing intervals, patient dissatisfied with therapy, despite taking drug(s) correctly, insufficient awareness of health and diseases (possibly leading to future problems), unclear complaints, therapy failure (reason unknown), and the cases were further clarification were found necessary.

The study reveals that 66 (62.26 % of) ADRs were from non-allergic, whereas 40 (37.74%) of ADRs belongs to allergic class as mentioned in Table 3. Potential drug-DIs were detected in 252 (55.87%) patients out of the 451. This frequency is lower than Figure 1 reported in a Mexican study, where almost 80% of patients presented potential pharmacologic interactions. This difference could be associated with the Mexican study's inclusion criteria, namely, patients older than 50 years, with the non-malignant syndrome. It is noteworthy that the prevalence of hypertensive and diabetic patients was higher in the present study (67.3% and 29.5%, respectively), as were the predominant interactions, generally associated to medications used to treat these pathologies Dubova *et al.*,[19] the most common DI was found to be enalapril maleate + furosemide causing postural hypotension.[20]

We found that patients older than 50 years of age were at high risk of experiencing DDIs. In general, elderly patients are at higher risk for DDIs. It is because they are likely to have multiple diseases that

usually occur with an increased duration of diabetes. Because they have comorbidities, polypharmacy is common in these patients. In this study, the average number of drugs per prescription was 4.76. In high-risk patients, the number was higher (5.54 drugs per prescription). Thus, it was evident that polypharmacy is a predisposing factor for DDIs. The documentation status of most of the potential DDIs was good, suggesting that these DDIs may be prevented by an evidence-based approach. One of the better approaches is to obtain data on drugs from a Drug Information Centre during the process of prescribing, thus ideally avoiding DDIs in these patients. In this study, cardiovascular drugs posed the maximum risk for potential DDIs, followed by antidiabetic drugs as shown in Table 4. It is well documented in the literature that the incidence of DDIs is higher in patients with multiple diseases.[21-23] Among the various drugs implicated for potential DDIs, enalapril maleate, and furosemide ranked first [Figures 2 and 3, Table 5and 6].

Table 1: Demographic and clinical characteristic of the patients (*n*=451)

Characteristics	Number of patients (%)
Total patients followed and reviewed	1230
Drug-related problems were identified in patients	451 (36.66)
Total drug-related problems identified	353 (78.27)
Sex	
Male	256 (56.76)
Age (51–70) years	320 (70.95)
Duration of hospital stay	
Not more than 7 days	238 (52.77)
8–14 days	129 (28.60)
More than 15 days	84 (18.62)
Duration of type 2 diabetes mellitus	
Not more than 10 years	186 (41.24)
11–20 years	153 (33.92)
Unknown duration	112 (24.83)
HBA1c	
Achieved target (<6.5)	148 (32.81)
Did not achieve target (≥6.5)	167 (37.02)
Unknown	136 (30.15)
Diabetic complications	
Diabetic retinopathy	151 (33.48)
Diabetic foot ulcer	57 (12.63)
Diabetic neuropathy	36 (7.98)
Comorbidities	
Renal impairment	56 (12.41)
Cardiovascular disease	111 (24.61)
Gastrointestinal disease	36 (7.98)
Stroke	59 (13.08)
Bronchial asthma	48 (10.64)
Dyslipidemia	67 (14.86)
Benign prostatic hyperplasia	56 (12.42)
Gouty arthritis	32 (7.10)
Liver impairment	87 (19.29)
Osteoarthritis	56 (12.42)
Chronic kidney disease	41 (9.09)

HBA1c: Hemoglobin A1c

Table 2: DRP distribution among study participants

DRP type	N (%)
Adverse reactions	106 (23.50)
Drug interactions	252 (55.88)
Drug choice problem	25 (5.54)
Dosing problem	43 (9.53)
Other	25 (5.54)

DRP: Drug-related problem

Factors that were significantly associated with drug-related problems

Gender

In this study, a significant statistical difference was detected between gender and the occurrence of DRP. Male patients had a higher chance (56.7%) of having DRPs compared to female patients (43.2%). To date, there is a lack of studies focusing on the association of DRP with gender. However, a study by Babwah *et al.*, in 2006, reported that women who are unemployed have more time to attend clinic appointments and tend to be more compliant in terms of diet and medication when compared to men.[24] On the other hand, men who work and practice unhealthy habits, such as drinking alcohol and smoking, have a higher probability of having DRPs.[25,26] To

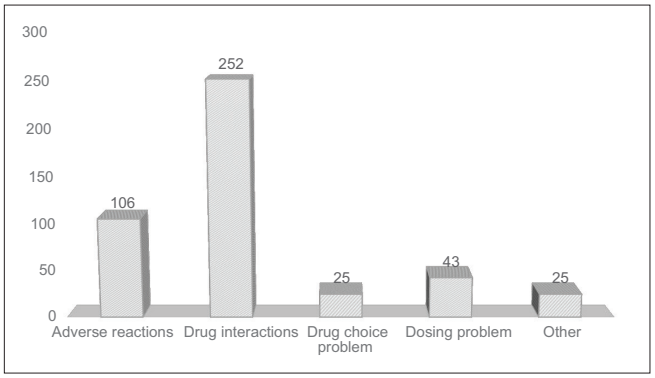

Figure 1: Drug-related problem distribution among study participants

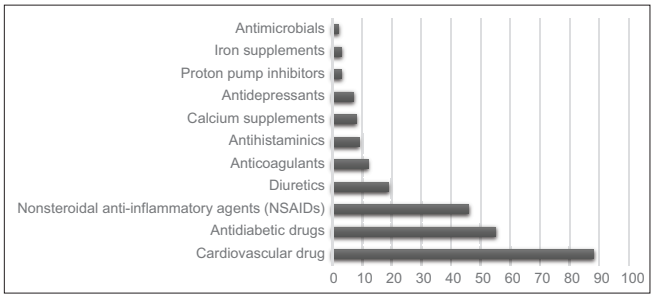

Figure 2: Class of drugs associated with a high risk of drug-drug interactions

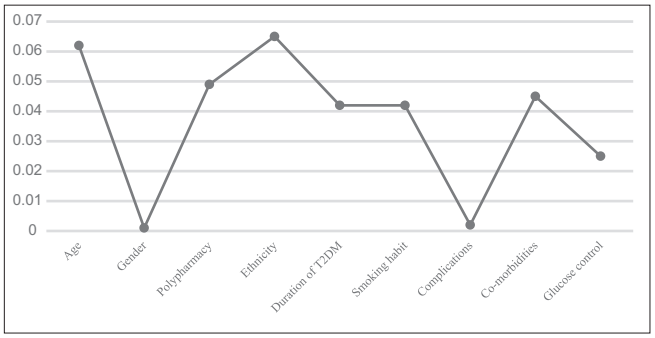

Figure 3: Parameters significantly associated with drug-related problem

date, there is a lack of evidence to suggest that biological factors associated with gender may affect the pharmacological treatment. Besides, in this study, the higher proportion of males compared to female patients may lead to the random chance of males having at least one DRP.[27]

Polypharmacy

The issue of polypharmacy is commonly reported as a risk factor that contributes to the occurrence of DRPs in different study subjects.[28] In agreement with a few studies, polypharmacy was shown to be significantly associated with DRP in type 2 diabetes mellitus (T2DM) patients with dyslipidemia, in which about 95% of patients with four to five drugs had at least one DRP.[29] Polypharmacy has been associated with problems such as poor medication adherence, potential drug-DIs, and side effects of drugs.[30] Patients with multiple drug classes of medicines often have a complex drug schedule. The frequent daily drug administration and different pill numbers for each medication may contribute to the poor medication adherence problem in these patients. A recent study showed that DRPs secondary to polypharmacy will lead to the increased cost of treatment and hospitalization.[4] However, the undertreatment of disease by reducing the number of drugs may cause more serious consequences, especially in T2DM patients with dyslipidemia.[31] Hence, pharmacists play an important role in the optimization of drug treatment for the patient's benefit.

Other parameters such as ethnicity, duration of T2DM, smoking habit, complications, comorbidities, and glucose control were also found significant and associated with DRPs. The results of our study were similar to study conducted by others [Table 7].[32,33]

In most of the ADR cases, immediately drug responsible for the causes of reaction was stopped and management therapy was initiated as per guidance and guidelines. Type A reactions accounted for most of the ADRs. Using the Naranjo algorithm, (61.19%) ADRs were assessed as "probable," whereas 37.86% were assessed as "possible," and 3 (1%) were classified as "definite" in relation to the suspected drug similar results were found in study conducted by Sharma *et al.* Gastrointestinal system was the most common organ system affected.[34] Sign and symptoms related to gastrointestinal system were vomiting, diarrhea, constipation, nausea, gastritis, peptic ulcer, and gastric pain.[35] When organ systems affected were studied, gastrointestinal system was the organ system most commonly affected by the ADRs with vomiting as the most common individual reaction. This study showed the level of gastric intolerance of patients to this class of drugs. These findings substantiate previously reported studies on gastric ADRs. In most of the ADRs cases drug were withdrawn instead of dose alteration or alternative therapy. The present study showed that females experienced a higher incidence of ADRs when compared to males which are similar to the results of Sharma *et al.*, cardiovascular drugs were the second most common drug class with furosemide being the most commonly implicated drug.[27] These findings are consistent with the findings of Lampert *et al*. During the study, it was found that percentage of the reactions was severe in nature and mostly skin reactions accounted for that. Preventable ADRs were less in this study compared to available reports.

Table 3: PCNE classification of DRP (*n*=451)

DRP detailed classification	*n* (%)
Adverse reactions	106 (23.50)
Side effect suffered (non-allergic)	66 (62.26)
Side effect suffered (allergic)	40 (37.74)
Drug interactions	252 (55.88)
Potential interaction	252 (55.88)
Drug choice problem	25 (5.54)
Inappropriate drug (not most appropriate for indication	8 (32.00)
Inappropriate drug form (not most appropriate for indication	7 (28.00)
Inappropriate duplication of therapeutic group or active ingredient	4 (16.00)
Contraindication for drug (incl. Pregnancy/breastfeeding)	3 (12.00)
No clear indication for drug use	2 (8.00)
No drug prescribed but clear indication	1 (4.00)
Dosing problem	43 (9.53)
Drug dose too low or dosage regime not frequent enough	17 (39.53)
Drug dose too high or dosage regime too frequent	11 (25.58)
Duration of treatment too short	9 (20.93)
Duration of treatment too long	6 (13.95)
Other	25 (5.54)
Patient dissatisfied with therapy despite taking drug (s) correctly	7 (28.00)
Insufficient awareness of health and diseases (possibly leading to future problems)	9 (36.00)
Unclear complaints. Further clarification necessary	5 (20.00)
Therapy failure (reason unknown)	4 (16.00)

DRP: Drug-related problem, Pharmaceutical Care Network Europe

CONCLUSION

The present study indicated that DRPs are common among medical ward patients. Non-compliance and unnecessary drug

Table 4: Most frequent potential drug-drug interactions and their clinical effects

Drugs	*n* (%)	Clinical effect
Acetylsalicylic acid+enalapril maleate	33 (7.32)	Decreased antihypertensive effect
Glibenclamide+hydrochlorothiazide	31 (6.87)	Decreased antihypertensive effect; worse glucose tolerance
Acetylsalicylic acid+glibenclamide	5 (1.11)	Reinforced hypoglycemic effect
Enalapril maleate+furosemide	42 (9.31)	Postural hypotension
Acetylsalicylic acid+captopril	23 (5.10)	Decreased antihypertensive effect
Spironolactone+enalapril maleate	25 (5.54)	Hyperkalemia
Digoxin+spironolactone	21 (4.66)	Digoxin toxicity symptoms (anorexia, nauseas, vomits, headache, fatigue, disorientation, hallucination, and arrhythmia)
Digoxin+hydrochlorothiazide	26 (5.76)	Digoxin toxicity symptoms (anorexia, nauseas, vomits, headache, fatigue, disorientation, hallucination, and arrhythmia)
Digoxin+lovastatin	12 (2.66)	Increased rhabdomyolysis risk
Captopril+furosemide	16 (3.55)	Postural hypotension
Propranolol hydrochloride+Glibenclamide	18 (3.99)	Decreased responses to insulin and sulphonylureas; potentially increased frequency and severity of hypoglycemia episodes

therapy were the top and the least prevalent DRPs, respectively. It is concluded that, there is an alarming rate of prevalence and incident of DIs which is much higher in patients receiving combinations of drugs or polypharmacy or suffered from comorbidity of diseases such as diabetes, hypertension, peptic ulcer, fungal infections, and neurodegenerative disorders, which require prolonging and multi treatments and the risk of DI will increase as they are treated with multitherapies. It is well reported that diabetic patients are suffering due to higher risk of DI as they receive a combination of therapies for diabetic complications as well, and hence, the rate of occurrence of DI is rapidly increased. As medication experts, pharmacists are a vital part of the treatment team, especially when an ADR occurs. Treating an ADR consists mainly of supportive therapy with symptom management. Furthermore, additional steps should be taken to determine the cause of the patient's symptoms and whether they can be attributed to the use of a drug. Review of the patient's drug therapy by a clinical pharmacist can positively influence the patient outcomes and quality of care. The present study highlights the fact that clinical pharmacist can play a very important role in the health-care management by rationalizing and optimizing the drug therapy to achieving the better quality of life.

Table 5: Classification of drugs associated with a high risk of drug-drug interactions (*n*=252)

Therapeutic category	*n* (%)
Cardiovascular drug	88 (34.92)
Antidiabetic drugs	55 (21.83)
Non-steroidal anti-inflammatory agents (NSAIDs)	46 (18.25)
Diuretics	19 (7.54)
Anticoagulants	12 (4.76)
Antihistaminics	9 (3.57)
Calcium supplements	8 (3.17)
Antidepressants	7 (2.78)
Proton pump inhibitors	3 (1.19)
Iron supplements	3 (1.19)
Antimicrobials	2 (0.79)

Table 6: Parameters that were associated and significantly associated with DRP

Characteristic	*P* value
Age	0.062
Gender	0.001
Polypharmacy	0.049
Ethnicity	0.065
Duration of T2DM	0.042
Smoking habit	0.042
Complications	0.002
Comorbidities	0.045
Glucose control	0.025

DRP: Drug-related problem, T2DM: Type 2 diabetes mellitus

Limitations of the study

DRPs related to medication administration were not addressed in the study. The result of the study may not be generalized to all hospitals because it was only three hospitals study conducted in a hospital serving referred patients who have severe illnesses and more comorbidities.

Finally, further, research is warranted to determine the most commonly implicated drugs and risk factors associated with drug-related hospitalizations in other hospitalized populations, patients living in the community, and nursing home residents.

ACKNOWLEDGMENTS

We thank Mr. Parveen Garg, Chairman, and Department of Pharmacy Practice, ISF College of Pharmacy, for providing support of Micromedex software for this study.

Abbreviation

ACEI: Angiotensin-converting enzyme inhibitor, AF: Atrial fibrillation, AT-receptor antagonist: Angiotensin receptor antagonist, CCB: Calcium channel blocker, CHF: Congestive heart failure, GTN: Glyceryl trinitrate.

Table 7: ADRs reported during study

Brand name	Drug	Effect on patients	Action taken
Injection emeset	Ondansetron	Vomiting, itching over face, and rashes	Immediately drug stopped and management therapy (i.e., injection hydrocortisone, injection avil, and Injection rantac) initiated as per guidance
Injection metrogyl	Metronidazole	Difficulty in breathing and vomiting	Immediately drug stopped and management therapy (i.e., injection Hydrocortisone and injection avil) initiated as per guidance
Injection taxel	Ranitidine	Diarrhea and vomiting	Immediately drug stopped and management therapy (i.e., injection octreotide) initiated as per guidance
Injection monocef	Ceftriaxone	Vomiting, nausea, rashes, and redness	Immediately drug stopped and management therapy initiated as per guidance
Injection dynapar	Diclofenac	Rashes all over body	Immediately drug stopped and management therapy (i.e., injection hydrocortisone, injection avil, and injection rantac) initiated as per guidance
Injection rantac	Ranitidine	Rashes all over body	Immediately drug stopped and management therapy initiated as per guidance
Injection drotin	Drotaverine	Redness and itching all over body	Immediately drug stopped and management therapy (i.e., injection Hydrocortisone and injection avil) initiated as per guidance
Injection supacef	Cefuroxime	Itching and urticarial rashes	Immediately drug stopped and management therapy initiated as per guidance
Capsule citrol	(Vit. D) Vitamin supplements	Cough, vomiting difficulty in swallowing and dizziness	Immediately drug stopped and management therapy initiated as per guidance
Tablet livogen	Folic acid and ferrous fumarate	Amenorrhea, fatigue and headache, vomiting	Immediately drug stopped and management therapy initiated as per guidance

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