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EVALUATION OF ADVERSE EFFECTS DUE TO ANTIDIABETIC AND CARDIOVASCULAR DRUGS IN A TERTIARY CARE HOSPITAL IN KOLKATA, WEST BENGAL, INDIA

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ABSTRACT: Purpose: Diabetes mellitus is a significant burden to the present society, associated with various co-morbid conditions like hypertension, cardiovascular diseases, etc. A number of drugs are available to handle these health problems successfully. However, therapeutic success of such diseases is limited due to adverse effects of drugs or medicines. The aim of the present study was to evaluate the cases of adverse events due to these medications. **Methods:** An observational study on patients attending the Out Patient Department (OPD) of R.G. Kar Medical College, Kolkata, West Bengal, India, for a period of 8 months (September 2014- April 2015). Adverse drug events due to the use of anti-diabetic and cardiovascular drugs were collected and evaluated. **Result:** Present study revealed that, out of the total 48 adverse event reports collected in patients using anti-diabetic and cardiovascular drugs, 66.7% may be due to anti-diabetic drugs and 31.25% may be due to cardiovascular drugs. The prevalence of adverse effects due to antidiabetics was more in female (62.5%) as compared to male (37.5%). 40.63% of the patients suffering from adverse effects predicted due to antidiabetics, were in the age group of 36-45 years. Metformin was the most common antidiabetic drug, may be responsible for 87.5% of the adverse events. Antihypertensives may be associated with 93.33% of the cases of adverse effects in cardiovascular disease, causing mostly gastrointestinal problems. **Conclusion:** It may be concluded that it is essential to investigate the adverse effects of these drugs, to identify the causative agent, to ensure safe therapy.

INTRODUCTION: Diabetes Mellitus (DM) is a disease of improper metabolism of carbohydrates, proteins, lipids, due to lack of insulin hormone or insensitivity of cells to insulin, causing increased blood sugar level [1].

A study performed with different countries across the world revealed 382 million people affected with DM in 2013 and this number is expected to increase to 592 million by 2035 [2]. Among all the continents, 60% of the diabetic population is contributed by Asia, mainly India and China [3, 4]. Diabetes is associated with various co-morbid conditions like hypertension and cardiovascular diseases.

Hypertension or elevated blood arterial pressure affects about 40% of the adult population of the world as estimated in 2008 [5]. Globally, 70% of

diabetic patients are reported to be affected with hypertension and the risk of development of hypertension is twice for diabetic patients as compared to euglycemic subjects [6]. Hypertension is one of the major causes of cardiovascular disorders. Moreover patients suffering from both diabetes and hypertension are at a greater risk of cardiovascular disease. Cardiovascular diseases (CVD) have also contributed significantly to the leading causes of death throughout the world. About 80% of the diabetic patients die due to cardiovascular problems[7].

To combat these complicated medical conditions often physicians are compelled to prescribe a dozen of drugs or medicines to the patients. However, apart from beneficial effects, drugs are found to have various adverse effects on the health. Adverse drug event (ADE) is defined to be "any untoward medical occurrence that may present during treatment with a medicine, but which does not necessarily have a causal relationship with the treatment" [8]. Adverse drug events (ADE) associated with the use of multiple drugs are not an uncommon phenomenon in therapeutics. These negative consequences of drugs are therefore major drawbacks. Research in European countries illustrated that adverse effects of drugs is responsible for 5% of the hospitalized incidents and 197,000 deaths annually [9].

Various factors contribute to the adverse effects of drugs, like type of the disease, age and gender of the patient, lifestyle, race, genetics, even polypharmacy (i.e., use of multiple medications by a single patient), etc. Thus detection and assessment of these adverse effects gained importance for safer therapeutics.

Pharmacovigilance is an approach to ensure safe use of medicines.

It is the pharmacological science relating to the collection, detection, assessment, monitoring and prevention of adverse effects of pharmaceutical products. It identifies the risk associated with a marketed drug and minimizes the chance of ill effects [10]. Present study aim to evaluate the prevalence of adverse drug events associated with antidiabetic drugs and cardiovascular drugs in a Tertiary Care hospital, in Kolkata, India.

MATERIALS AND METHODS:
This was an observational study conducted on the reports collected from patients, attending different outdoor departments of R.G. Kar Medical College, Kolkata, West Bengal, India. Prior permission was obtained from Institutional Ethics Committee (IEC). Study duration was 8 months, from September 2014-April 2015. Patients of both sexes and all ages who suffered from Adverse Drug Events (ADE) due to antidiabetics and/or cardiovascular drugs were included in the study.

RESULT:
During the 8 months of study, a total of 466 cases indicating adverse drug events were reported at the Adverse Drug Reaction (ADR) Monitoring Centre of R.G. Kar Medical College, Kolkata, West Bengal, India. Out of these, 48 reports based on adverse events due to antidiabetics and cardiovascular drugs were selectively screened and evaluated. Detailed study revealed, majority (32, 66.7%) of these events were attributed to antidiabetic drugs (**Table 1**).

TABLE 1: DISTRIBUTION OF ADVERSE DRUG EVENTS (ADE) DUE TO ANTIDIABETICS, CARDIOVASCULAR OR BOTH IN STUDY POPULATION

Sl. No.	Parameters	Total Number of Cases (n= 48)	Percentage (%)
	Distribution of Reports on Adverse Drug Events:		
a.	Adverse Drug Events due to anti-diabetic drugs	32	66.7
b.	Adverse Drug Events due to cardiovascular drugs	15	31.25
c.	Adverse Drug Events due to both anti-diabetic and cardiovascular drugs	1	2.05

The distribution of male and female patients that experienced adverse effects due to these drugs was evaluated. Out of the 32 patients who experienced

adverse events due to antidiabetic drugs, 12 (37.5%) were males whereas 20 (62.5%) were females. On the other hand, out of the 15 patients

suffering from adverse effects due to cardiovascular drugs, 9 (60%) were males whereas 6 (40%) were females. This indicated majority of the patients who experienced adverse events due to antidiabetics were females, however, that due to cardiovascular drugs were mostly males.

Age is one of the factors that determine the effect of drug on an individual. The age of the study population ranged from 25 years to 75 years, with mean 43.2 years. It was observed that most of the adverse events were prevalent among the elderly age groups. Among the 32 patients complaining of ADE due to antidiabetics, 40.63% (13) belong to the age group 36-45 years. However, out of the 15 reports on adverse effects due to cardiovascular drugs, 40% (6) of the reported cases included patients within age group 56-65 years.
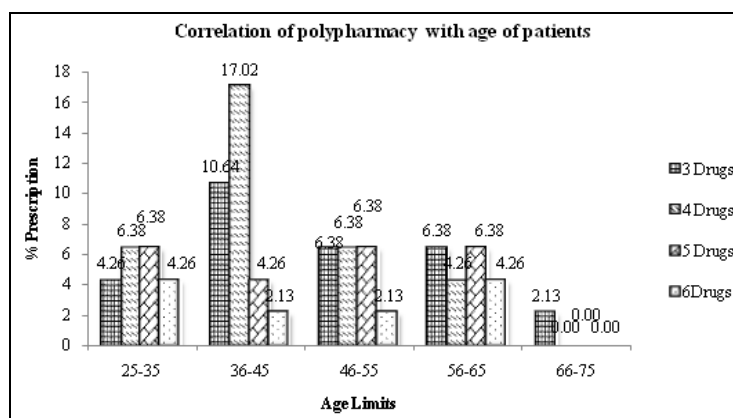

FIG. 1: CORRELATION OF POLYPHARMACY WITH AGE OF PATIENTS IN THE STUDY POPULATION

A single patient suffering from multiple disorders is a common observation in the world of medicine, recently. 20.83% (10) of the reported cases documented comorbid conditions of diabetes and hypertension. Average number of drugs prescribed per prescription for these 48 reports was 4.2. With the aim to find the correlation between polypharmacy and the age of the patients, the numbers of drugs used per prescription were classified based on the age groups (**Fig. 1**). Interestingly, it was observed that the use of 5 or 6 drug combinations in a single prescription was mostly prevalent among the older age group of 46-65 years.

TABLE 2: DRUG PRESCRIBING PATTERN OF ANTIDIABETIC AND CARDIOVASCULAR DRUGS BASED ON ANATOMICAL THERAPEUTIC CHEMICAL (ATC) CLASSIFICATION SYSTEM [11]

Sl. No.	Parameters	ATC Code	Total Number of Cases	Percentage (%)
A.	**Anti-diabetic Drugs:**		**n= 32**	
I.	Biguanides	A10BA	31	96.875
II.	Sulfonylureas	A10BB	29	90.625
III.	Dipeptidyl peptidase 4 (DPP-4) inhibitors	A10BH	11	34.375
IV.	Thiazolidinediones	A10BG	10	31.25
V.	Insulin	A10AB	2	6.25
VI.	Alpha glucosidase inhibitors	A10BF	2	6.25
B.	**Cardiovascular Drugs:**		**n= 15**	
I.	Calcium Channel Blocker	C08CA	8	53.33
II.	Analgesic	N02B	2	13.33
III.	Sulfonamides	C03BA	2	13.33
IV.	Angiotensin II Antagonist	C09CA	2	13.33
V.	Angiotensin-Converting-Enzyme (ACE) Inhibitor	C09AA	2	13.33
VI.	HMG CoA reductase inhibitors	C10BA	2	13.33
VII.	Antithrombotic	B01A	1	6.67
VIII.	Aldosterone antagonists	C03DA	1	6.67
IX.	Beta blocking agents	C07A	1	6.67

The drug prescription pattern was evaluated on the 32 reports collected on ADE due to anti-diabetic drugs. Several prescriptions contained a combination of anti-diabetic drugs. In 40.6% cases, a combination of two antidiabetic drugs was prescribed. Biguanide or Metformin was the most commonly prescribed (31, 96.9%) antidiabetic drugs, followed by Sulfonylureas (29, 90.4%) (**Table 2**). Biguanide (Metformin) was responsible for 87.5% (28) of the ADEs reported, whereas, Sulfonylureas accounted for 15.63% (5) of the cases. Among the cardiovascular drugs, antihypertensives were the most commonly prescribed (93.33%) and were responsible for 60% of the ADR (**Table 2**). Among the antihypertensives, Calcium channel blocker, amlodipine, accounted for 55.6% of the prescriptions.

Complains of ADE observed in these reports were classified according to MedDRA system [12]. MedDRA (the Medical Dictionary for Regulatory Activities Terminology) is the vocabulary used as medical coding scheme in pharmaceutical companies or for reporting adverse events. It deals with the symptoms, therapeutic indications, the method and result of investigations and the medical history of the patients [12]. In the present study, most common symptom for adverse effects due to antidiabetics was musculoskeletal disorder (16, 50%) i.e., joint and muscle pain. However, in case of cardiovascular drugs, the most prevalent symptom reported was gastrointestinal disorder (6, 40%).

DISCUSSION: Objective of the study was to document the adverse events due to the use of antidiabetics and cardiovascular drugs. This study was conducted on patients attending different outdoor departments of R.G. Kar Medical College, Kolkata. ADE reports were collected over a period of 8 months. About 10.3% (48) of the total 466 reports documented on adverse drug events were associated with antidiabetics and cardiovascular drugs. Out of these 48 cases reported, 66.7% (32) may be associated with antidiabetic drugs, 31.25% (15) for cardiovascular drugs and 2.08% (1) may be due to both these groups of drugs. The incidence of ADE due to antidiabetics was almost half among the male (37.5%) as compared to the female (62.5%). A study on adverse drug reaction (ADR) conducted at the same tertiary care hospital on 2013 observed comparable results, 29.87% male patients whereas 70.12% female patients [13]. However, in case of adverse events due to cardiovascular drugs, prevalence was observed in male (60%) as compared to female (40%). Similar observation was reported in a study in India (69.5% male, 30.5% female) [14]. However, a study on ADR due to antihypertensives conducted in Australia and Germany, found 47% were female and 53% male, which were almost similar with the present study [15].

The age (mean ± SD) of the patients experiencing adverse effects due to antidiabetics was 43.2 ± 9.55 years which was much lower, compared to other studies in India (51.5 ± 12.3 years) [16, 17], Hongkong (56.5 ± 12.6 years) [18] and West Indies (58.9 ± 3.4 years) [19]. Present study highlighted that 40.63% of these adverse drug events were reported in patients of age group of 36-45 years. In case of adverse effects due to cardiovascular drugs, the age (mean ± SD) of the patients were 51.2 ± 11.26 years, which was less compared to previous studies in India, Germany and Australia [14, 15]. The incidence of ADE was highest (40%) in the age group of 56-65 years, similar to that observed in the study of Germany and Australia [15].

Biguanide or Metformin (96.875%), followed by Sulfonylureas or Glimepiride (87.375%) were the most commonly prescribed drugs for antidiabetics, as observed in this present study. Studies in India, Malaysia also suggested biguanides and sulfonylureas were the most commonly used oral antidiabetics [17, 20]. Metformin was responsible for 87.5% of the ADE cases in the present study. Among the cardiovascular drugs, the most commonly prescribed were antihypertensives, 93.33% and it was responsible for 60% of the events. Among the antihypertensives, Calcium channel blocker was responsible for 55.6% of the ADE cases, comparable with other studies conducted in Brazil [21].

Average number of drugs per prescription was 4.2 in present study that were much higher as compared to other studies in India, reporting an average of 2.27 drugs per prescription [16]. In this present study a combination of two antidiabetics

were mostly (40.625%) prescribed. The combination of biguanide and sulfonylureas was prescribed in 32.26% of the cases, which is similar to an observation among indoor patients of a tertiary care hospital at South India [17]. Use of multiple drugs, i.e., polypharmacy is a common practice among the elderly patients. This study also reported prescriptions containing 5 or 6 drugs, which was more prevalent among elder patient of age group 46-65 years. Therefore this indicates that more drugs were prescribed to the elderly patients, thereby complicating the therapeutic regimen and increasing the chance of adverse events. Literature1. also supports the fact that polypharmacy is a regular practice among the elderly patients in different countries including Indonesia (average 4), Ghana (average 4.5), Pakistan (average 4.51), Nepal (average 2.5), US (average 5) [22-24].

Musculoskeletal disorder (50%) was the most common adverse effects due to antidiabetic drugs in the present study, which include muscle pain, joint pain and fatigue, followed by gastrointestinal problem (31.25%). However, a study conducted in this tertiary care hospital, in 2013, revealed 61.03% were due to gastrointestinal problems [13]. On the other hand, in case of the cardiovascular drugs, majority (40%) of the ADE comprised of gastrointestinal problems.

CONCLUSION: The prevalence of Diabetes and various comorbid conditions is a frequent observation that compels the clinicians to prescribe multiple drugs. Use of multiple drugs enhances the chance of adverse reactions. Various other factors like age, gender, lifestyle of the patients are also responsible for the development of adverse reactions. These adverse consequences are therefore a limitation for the therapeutic success. Thus, it becomes essential to identify the responsible drugs to avoid adverse effects to ensure safe and efficient therapeutics. Detection and prevention of these adverse reactions is essential to reduce patient suffering. Future studies on adverse drug events will help the therapy and ensure the use of safe medicine.

CONFLICTS OF INTEREST: Nil

REFERENCES:

1. Anonymous American Diabetes Association: Diagnosis and classification of diabetes mellitus. Diabetes Care 2010; 33(Suppl 1):S62–9.
2. Guariguata L, Whiting D, Hambleton I, Beagley J, Linnenkamp U, et al.: Global estimates of diabetes prevalence for 2013 and projections for 2035 for the IDF Diabetes Atlas. Diabetes Research and Clinical Practice 2013.
3. Ramachandran A, Snehalatha C, Shetty AS and Nanditha A: Trends in prevalence of diabetes in Asian countries. World Journal of Diabetes 2012; 3:110-117.
4. Ma RC and Chan JC: Type 2 diabetes in East Asians: similarities and differences with populations in Europe and the United States. Annals of the New York Academy of Sciences 2013; 1281:64-91.
5. Park JB, Kario K and Wang JG: Systolic hypertension: an increasing clinical challenge in Asia. Hypertension Research 2015; 38:227–36.
6. Purohit P: A cross-sectional study of type -2 diabetic females at a higher CVD risk owing to a strong correlation of Systolic hypertension to CVD risk factors. Int J Biol Med Res. 2012; 3:1905-1909.
7. Cade WT: Diabetes-Related Microvascular and Macrovascular Diseases in the Physical Therapy Setting. Physical Therapy 2008; 88:1322-1335.
8. Tripathi KD: Essentials of Medical Pharmacology. Jaypee Brothers Medical Publishers (P) Ltd., New Delhi, Edition 6, 2008: 78.
9. Bouvy JC, De Bruin ML and Koopmanschap MA: Epidemiology of Adverse Drug Reactions in Europe: A Review of Recent Observational Studies. Drug Safety 2015; 38:437-53.
10. Shuka SS, Gidwani B, Pandey R, Rao SP, Singh V and Vyas A: Importance of Pharmacovigilance in Indian Pharmaceutical Industry. Asian J. Res. Pharm. Sci. 2012; 2:04-08.
11. Retrieved from: http://www.whocc.no/ on: 10.06.2015
12. Reston VA: MedDRA Maintenance and Support Services Organization. Introductory Guide, MedDRA Version 10.1. International Federation of Pharmaceutical Manufacturers and Associations.2007
13. Adhikari A, Bhowal T, Ray M, Chatterjee S, Mukherjee AK, Das AK, et al: Investigation Of Adverse Drug Reactions Related To Metformin Use In Patients Of Type 2 Diabetes Mellitus In A Tertiary Care Hospital In Kolkata, West Bengal, India. Explor. Anim. Med. Res. 2013; 3:117-22.
14. Kaur S, Kapoor V, Mahajan R, Lal M and Gupta S: Monitoring of incidence, severity, and causality of adverse

drug reactions in hospitalized patients with cardiovascular disease. Indian J Pharmacol. 2011; 43:22–6.

15. Bramlage P, Fronk EM, Wolf WP, Smolnik R, Sutton G and Schmieder RE: Safety and effectiveness of a fixed-dose combination of olmesartan, amlodipine, and hydrochlorothiazide in clinical practice. Vasc Health Risk Manag. 2014; 11:1-8.

16. Sultana G, Kapur P, Aqil M, Alam MS and Pillai KK: Drug utilization of oral hypoglycemic agents in a university teaching hospital in India. J Clin Pharm Ther. 2010; 35:267–77.

17. Abdi SAH, Churi S and Kumar YSR: Study of drug utilization pattern of antihyperglycemic agents in a South Indian tertiary care teaching hospital. Indian J Pharmacol. 2012; 44:210–4.

18. Wu SY, Lung BC, Chang S, Lee SC, Critchley JA and Chan JC: Evaluation of drug usage and expenditure in a hospital diabetes clinic. J Clin Pharm Ther. 1998; 23:49–56.

19. Gossell-Williams M, Williams-Johnson J and Francis L: Hypoglycaemic complications with diabetes mellitus management: the predominant adverse drug reaction presenting to the Accident and Emergency Department of The University Hospital of the West Indies. West Indian Med J. 2010; 59:555-60.

20. Huri HZ and Wee HF: Drug related problems in type 2 diabetes patients with hypertension: a cross-sectional retrospective study. BMC Endocrine Disorders 2013; 13:2.

21. Goncalves CBC, Moreira LB, Gus M and Fuchs FD: Adverse events of blood pressure-lowering drugs: evidence of high incidence in a clinical setting. Eur J Clin Pharmacol. 2007; 63:973–8.

22. Rambhade S, Chakarborty A, Shrivastava A, Patil UK and Rambhade A: A survey on polypharmacy and use of inappropriate medications. Toxicol. Int. 2012; 19:68–73.

23. Ghimire S, Nepal S, Bhandari S, Nepal P and Palaian S: A prospective surveillance of drug prescribing and dispensing in a teaching hospital in Western Nepal. Journal of Pakistan Medical Association 2009; 59:726-31.

24. Das N, Baloch H, Badini ZA and Parkash J: Prescribing Practices of Consultants at Karachi, Pakistan. Journal of Pakistan Medical Association 2009; 51(74).