www.jmscr.igmpublication.org
Impact Factor 5.84
Index Copernicus Value: 83.27
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v5i5.30

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

# A Study of Drug Use in Type 2 Diabetes Mellitus with and Without Co-Morbidities in Patients Visiting A Tertiary Care Hospital

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**ABSTRACT**

**Background:** *A good number of diabetes patients suffer from co-morbidities such as hypertension, hyperlipidaemia and ischemic heart disease. Owing to the presence of co-morbid conditions, geriatric patients usually receive more than one drug. Objective of the study is to evaluate the drug use in type 2 diabetes mellitus (DM) with and without co-morbidities in patients visiting a tertiary care hospital.*

**Methods:** *Prospective, observational study was carried out at diabetic OPD of B. J. Government Medical College and Sassoon General hospital, Pune, where Consecutive 400 prescriptions from diabetic OPD were positioned into a case record form and antidiabetic drug utilization pattern was analyzed.*

**Results:** *In the present study, 43% patients had DM without co-morbidities while 57% patients had co-morbidities. Majority of Type 2 DM was found to be most prevalent in the age group of 61-75 years, with Hypertension was the most prevalent co-morbidity (60.52%). In DM without co-morbidities there were change in anti-diabetic prescription seen in (29.06%) and in DM with co-morbidity there were change in anti-diabetic prescription seen in (25.87%) patients. DM without co-morbidities at 0 day and at 3 months 56.97%, 63.95% prescription had Drug-Drug Interactions (DDIs) and in DM with co-morbidities at 0 day and at 3 months 76.31%, 74.12% prescription had DDIs.*

**Conclusions:** *Prescription after 3 months was changed in some patients due to uncontrolled diabetes mellitus. Hypertension was the most common co-morbid condition present while Tablet Metformin was most commonly prescribed drug in diabetes mellitus without co-morbidity and with co-morbidities patients respectively.*

**Keywords**-*Anti-diabetic drugs, Co-morbidity, Generic name, Drug interactions.*

## Introduction

Diabetes is a complex, chronic illness requiring continuous medical care with multifactorial risk-reduction strategies beyond glycaemic control. Ongoing patient self-management education and support are critical to preventing acute complications and reducing the risk of long-term complications. Significant evidence exists that supports a range of interventions to improve diabetes outcomes[1]. A good number of diabetes patients suffer from cardiovascular disease such as hypertension, hyperlipidaemia and ischemic heart disease[2]. Owing to the presence of comorbid conditions, geriatric patients are usually on more than one drug (polypharmacy). Several problems in drug use patterns have been reported. This includes use of irrational

combinations, excessive prescription of multi-vitamins, and use of antibiotics in viral infections, adverse drug reaction, drug interactions, and etc[3]. Moreover irrational prescribing can lead to an increase in the cost of drug therapy. Often, the chronically ill patients like the diabetic patients suffer from multiple diseases and hence are prescribed multiple drugs [4]. Drug utilization is defined as the marketing, distribution, prescr-iption, and use of drugs in a society, with emphasis on the resulting medical and social consequences [5]. Drug utilization studies create a sound sociomedical and health economic basis for healthcare decision-making. They help to ascertain the role of drugs in a society [6]. The ultimate aim of drug utilization research must be to assess whether drug therapy is rational or not [7]. Drug utilisation studies in the diabetes with and without co-morbidities, especially in our country, are few. Hence the current study was undertaken to gain an overview of the prescribing pattern in diabetes with and without co-morbidities patients visiting diabetic OPD at a tertiary care hospital.

## Materials and Methods

This study was a prospective, observational, 1 year (10 December 2014 to 10 December 2015) duration. The study protocol was approved by the Institutional Ethics committee. The study was conducted in B. J. Government Medical College and Sassoon general hospital, Pune, where total 400 patients aged 18 to 75 years, attending the diabetic outpatient department (OPD) were recruited. Diagnosed patients of diabetes mellitus without co-morbidities and with co-morbidities like hypertension, epilepsy and asthma were included in the study. While pregnant patients, breast feeding women, type 1 diabetes and psychiatric patients were excluded. Consecutive 400 prescriptions from diabetic OPD were collected and put into a specially designed case record forms (CRFs). Each enrolled patient were followed after 3 months, to note if any change in the anti-diabetic drug/s or dose has been made meanwhile. The detailed data was entered into the Microsoft excel sheet and subsequently analyzed statistically by using Microsoft excel 2013 and Vassarstat.net [8]. Chi square test was used to compare between two categories. A p value of $< 0.05$ was considered significant.

Comparisons were made between the patients with DM with various co-morbidities. Frequency of potential drug- drug interactions in the above prescriptions was ascertained using online database Medscape drug interaction checker [9].

## Results

A total of 400 prescriptions were included in study during 1 year data collection period. Amongst them 228 (57%) were diabetes with co-morbidities and 172 (43%) were diabetes without co-morbidities (Fig 1).

**Figure 1:** Distribution of diabetes mellitus 2 patients without and with co-morbidities

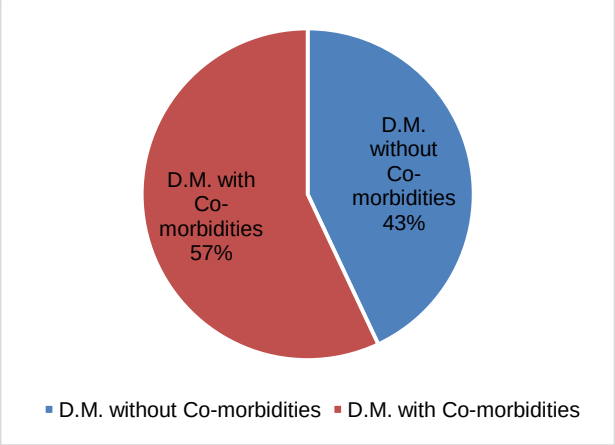



**Table 1:** Gender distribution of diabetes mellitus 2 patients without and with co-morbidities

| CATEGORY / GENDER | D.M. without co-morbidity | D.M. with co-morbidity | Total | p Value |
|---|---|---|---|---|
| Male | 105 (61.04%) | 117 (51.31%) | 222 (55.5%) | 0.0525 |
| Female | 67 (38.95%) | 111 (48.68%) | 178 (44.5%) | 0.0525 |
| Total | 172 (100.00%) | 228 (100.00%) | 400 (100%) | - |

Z test, *p<0.05 as significant

Table 1 shows gender distribution among patients in diabetes mellitus without co-morbidities and with co-morbidities. Out of total 400

prescriptions observed 222 (55.5%) patients are males and 178 (44.5%) patients are females. Out of 172 patients without co-morbidity 105 (61.04%) are males and 67(38.95%) are females. Out of 228 patients with co-morbidity 117 (51.31%) are males and 111(48.68%) are females. This table also shows that Sex distribution in diabetes mellitus without co-morbidities and with co-morbidities is not statistically different.

**Table 2:** Age Distribution among diabetes mellitus 2 patients without and with co-morbidities

| Category / Age group | D.M. without co-morbidity | D.M. with co-morbidity | Total | p value | Z ratio |
|---|---|---|---|---|---|
| 18-30 years | 1 (0.58%) | 3 (1.31% ) | 4 | NC* | NC* |
| 31-45 years | 27 (15.69%) | 28 (12.28%) | 55 | 0.32 | 0.982 |
| 46-60 years | 66 (38.37% ) | 61 (26.75%) | 127 | 0.01* | 2.47 |
| 61-75 years | 78 (45.34% ) | 136 (59.64%) | 214 | 0.00* | -2.83 |

*P<0.05 as significant, *NC: Not Calculated

Age wise distribution of diabetes patients without co-morbidities shows. 0.58% patients are of the age group 18-30 years, 15.69% patients are of the age group 31-45 years, 38.37% patients are of the age group 46-60 years, and 45.34% patients are of the age group 61-75 years.

Age wise distribution of diabetes patients with co-morbidities shows. 1.31% patients are of the age group 18-30 years, 12.28% patients are of the age group 31-45 years, 26.75% patients are of the age group 46-60 years, and 59.64% patients are of the age group 61-75 years.

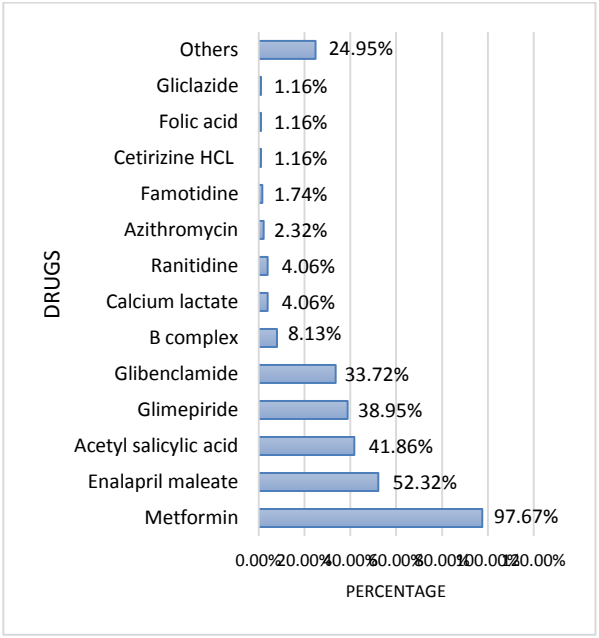
**Co-morbidity**

**Table 3:** Distribution of co-morbidities in Diabetes Mellitus 2 patients

| Diagnosis | Total Number (%) of patients |
|---|---|
| Common co-morbidities | |
| Hypertension | 138 (60.52%) |
| Epilepsy | 44 (19.29%) |
| Asthma | 26 (11.40%) |
| Occasional co-morbidities | |
| Nephropathy | 8 (3.50%) |
| IHD | 6 (2.63%) |
| Obesity | 3 (1.31%) |
| Rareco-morbidities | |
| Hypothyroidism | 1 (0.43%) |
| Hyperthyroidism | 1 (0.43%) |
| Dyslipidemia | 1 (0.43%) |
| Total | 228 (100%) |

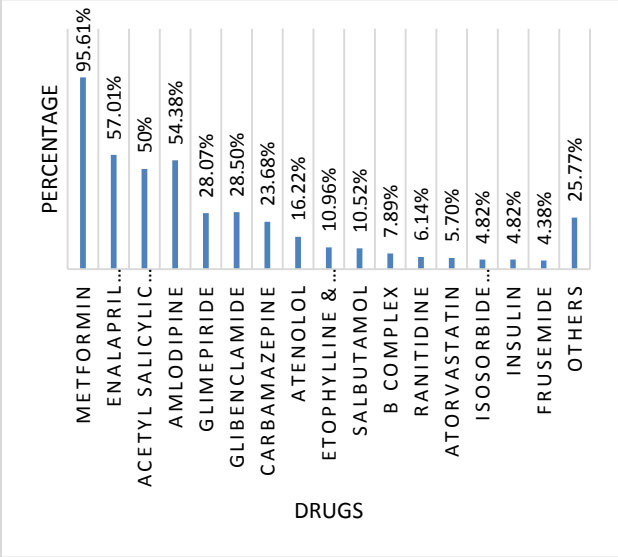
Diagnoses written on the prescription were classified. More of the enrolled diabetics had co-morbidity 228 (57%), as compare to only diabetics 172 (43%). Hypertension was the most prevalent co-morbidity (60.52%), followed by Epilepsy (19.29%) and Asthma (11.40%). Occasional co-morbidities include Nephropathy (3.50%), Ischaemic heart disease (2.63%) and Obesity. Obesity is present in very few patients as a co-morbidity (1.31%). Remaining rare co-morbidities include Hypothyroidism (0.43%), Hyperthyroidism (0.43%), and Dyslipidaemia (0.43%). As presented in Table.

**Figure 2:** Drugs prescribed in diabetes mellitus 2 patients without co-morbidities



The most commonly medication prescribed is Metformin (>95%), other commonly prescribed drugs are Enalapril maleate, Acetyl salicylic acid, Glimepiride and Glibenclamide (>30% - 95%), occasionally used drugs are B-complex, Calcium lactate, Ranitidine, Azithromycin (2-30%), rarely used drugs are Acarbose, Dextromethorphan, Diclofenac sodium, Metronidazole, Paracetamol (<2%) as presented in Fig. 2

**Figure 3:** Drugs prescribed in diabetes mellitus 2 patients with co-morbidities




The most commonly medication prescribed is Metformin (>95%), other commonly prescribed drugs are Enalapril maleate,Acetyl salicylic acid, Amlodipine, Gimepiride, Glibenclamide, Carba-mazepine, Atenolol, Salbutamol, Etophylline& Theophylline (>10% - 95%), occasionally used drugs are B-complex, Ranitidine, Atorvastatin, Isosorbidedinitrate, Insulin, Frusemide (4-10%), others rarely used drugs are Rosuvastatin, Acarbose, Dextromethorphan, Diclofenac sodium, Diphenhydramine, Cetirizine HCL, Gliclazide, Phenytoin sodium, Amoxycilin, Prazocin hydrochloride, Carbimazole, Folic acid, Olmesartan, Pantoprazole, Paracetamol, Prednisolone, Thyroxine, Voglibose (<4%). as presented in Fig.3

**Table 4:** Reason for change in anti-diabetic prescription after 3 months in diabetes mellitus 2 patients without and with co-morbidities

| Reason | D.M. without co-morbidities n=172 | D.M. with Co-morbidities n=228 | p Value | Z ratio |
|---|---|---|---|---|
| Uncontrolled diabetes mellitus | 50 (29.06%) | 59 (25.87%) | 0.47 | 0.71 |
| Non compliance | 1 (0.58%) | 3 (1.31%) | 0.46 | -0.73 |
| Toxicity | 1 (0.58%) | 1 (0.43%) | 0.84 | 0.20 |

p<0.05 as significant

Table 4 shows that the reasons for change in anti-diabetic prescriptions in both the categories i.e. with and without co-morbidities are more or less similar.

In diabetes mellitus without co-morbidities there were 50 (29.06%) patients shown change in anti-diabetic prescription after 3 months follow-up due to uncontrolled diabetes mellitus i.e. change in frequency of drug administration (27.01%) & alteration of drug (2.05%), non-compliance to medication 1 (0.58%) and toxicity to anti-diabetic drug 1 (0.58%).

In diabetes mellitus with co-morbidities there were 59 (25.87%), patients shown change in anti-diabetic prescription after 3 months follow-up due to Uncontrolled diabetes mellitus i.e. change in frequency of drug administration (24.31%) & alteration of drug (1.56%), non-compliance to medication 3 (1.31%) and toxicity to anti-diabetic drug 1 (0.43%). This information is shown in Table 4

**Table 5:** Potential drug-drug interactions among diabetes Mellitus 2 patients without co-morbidities

| Potential drug-drug interactions | D.M. without co-morbidity at 0day | D.M. without co-morbidity at 3 months |
|---|---|---|
| Yes | 98 (56.97%) | 110 (63.95%) |
| No | 74 (43.02%) | 62 (36.04%) |
| Total | 172 (100%) | 172 (100%) |

Chi-square= 1.751
P= 0.4166

Table 5 shows that the distribution of diabetes mellitus patients without co-morbidity, potential drug-drug interactions at 0 day and in 3 months are more or less similar.

Out of 172 prescriptions, 98 (56.97%) prescr-iption shows frequency of drug-drug interactions in diabetes mellitus without co-morbidities at 0 day. Out of 172 prescriptions, 110 (63.95%) show frequency of drug-drug interactions in diabetes mellitus without co-morbidities at 3 months. This information is shown in Table 5

**Table 6:** Potential Drug-drug interactions in diabetes Mellitus 2 patients with co-morbidities

| Potential drug-drug interactions | DM with co-morbidity at 0 day | DM with co-morbidity at 3 months |
|---|---|---|
| Yes | 174 (76.31%) | 169 (74.12%) |
| No | 54 (23.68%) | 59 (25.87%) |
| Total | 228 (100%) | 228 (100%) |

Chi-square test = 0.2941
P = 0.8632

Table 6 shows that the distribution of diabetes mellitus patients with co-morbidity, potential drug-drug interactions at 0 day and in 3 months are more or less similar.

Out of 228 prescriptions, 174 (76.31%) prescr-iption shows frequency of drug-drug interactions in diabetes mellitus with co-morbidities at 0 day. Out of 228 prescriptions, 169 (74.12%) prescription shows frequency of drug-drug interactions in diabetes mellitus with co-morbidities at 3 months. This information is shown in Table 6

Phenytoin is one of the most widely-prescribed antiepileptic drugs in

## Discussion

Type-2 diabetes is a chronic disease requiring lifelong treatment. Although lifestyle modifica-tions play an important role in diabetes management, drugs become necessary in many patients. This prescription based study is considered to be one of the most effective methods to assess and estimate drug utilization of medication. Prescription by the clinician may be taken as a reflection of his/her attitude to the disease and role of the drug in its treatment. It also provides insight into the nature of healthcare delivery system. This study analysed the drug utilization pattern in type-2 diabetes patients with and without co-morbidities.

In the present study, 43% patients of Diabetes Mellitus without co-morbidities and 57% patients had co-morbidities. Thus more than half of study population was found to be co-morbid with various conditions, which is similar with result of various studies carried out in India. M. S. Alam et al10, in his study found that out of 200 diabetic patients, 117 patients (58.5%) had comorbidities. k. Suresh Kumar et al[11], found that out of 120 diabetics, 57 (47.5%) had co-morbidities which is slightly lower than our study.

In the present study, among male patients, 61.04% were without co-morbidities and 51.31% were with co-morbidities. Among female patients, 38.95% were without co-morbidities and 48.68% were with co-morbidities, indicating that men predominance over women in group without co-morbidities. This may be assigned to difference between life style, dietary habit and stress, physical activity.

In the present study, 55% were males and 45% were females. Males predominated in the study population which is in agreement with the observations of various other studies in India. (Vengurlekar S et al [12]) and in United States. (Willey CJ et al [13]). This reflects a higher number of male patients visiting the hospital. Also, the gender profile changes in the country from region to region. These findings also corroborate with the findings of a cohort study conducted in the U.S. which also reported a male preponderance for DM. (Bocuzzi JS et al) [14].

Type 2 diabetes mellitus was found to be most prevalent (45.34%) in the age group of 61-75 years (mean±SEM age 67.44 ± 0.42 years) in diabetics without co-morbidities and in (mean±SEM age 68.29 ± 0.33 years) in diabetics with co-morbidities. The above figures indicate that type 2 diabetes is more prevalent in Geriatric patients. More number of cases next to middle

age patients indicates that the risk of Type 2DM and co-morbidities increases after the age of 60 years. The (mean±SD) age of the patients was 57.28 ± 17.22 years with a range between 18 and 75 years. It was higher than that reported in studies carried out in India (51.5 ± 12.3 years) by Sultana G et al [15]. A study from Netherland had reported that diabetic population investigated has an average age of 67 years [16].

Diabetes is significantly associated with a wide spectrum of co-morbidities. A total 228 patients suffered from co-morbid conditions such as hypertension, epilepsy, asthma, nephropathy, ischaemic heart disease, obesity, hypothyroidism, hyperthyroidism, dyslipidaemia. In this study Hypertension accounted for 60.52% of the total co-morbidity condition which was lower than in the study reported in Nepal (Hypertension accounted for 70.62% of the total co-morbidity) [8]. Our study findings are also similar to the study conducted by Arauz-Pacheco et al., in Texas medical centre that hypertension is more common co-morbidity affecting 20-60% of people with diabetes[17]. These findings are significantly alarming, as hypertension is a predictor of cardiovascular disease.

The study showed an average number of drugs used as 2.91 and 4.35 per prescription in diabetes mellitus without and with co-morbidities. higher than the value, 2.6 reported 3.3 by Adibe et al (2009), in south-east Nigeria [18], Jimoh et al (2011) in north-west Nigeria [19] and similar to 4 drugs reported by Bnouham et al (2006) in south-west Nigeria [20]. The WHO recommended 2-3 drugs per prescription for developing countries [21], suggesting a tendency for poly-pharmacy in this study. Many of the prescriptions recorded up to 5 to 6 drugs per prescription, thereby increasing the risks of drug related problems and reduced quality of life of patients. This indicates the need for improved rational use of drugs for the patients in view of the lifelong therapy in diabetes. The use of fewer drugs reduces side effects, drug interactions and minimizes cost [22]. However the relatively higher average number of drugs in this study can be attributed to the extent of co-morbidity associated with diabetes and hence the need to manage such conditions. Consequently, it was not surprising that anti-hypertensive drugs were the most co-prescribed non-diabetic medication considering the predominance of hypertension as the most common co-morbidity in the study, findings similar to previous studies in Nigeria and other settings [20], [23].

In the present study, in diabetes without co-morbidities Metformin (biguanide) use was high (97.67%), followed by Enalapril maleate (52.32%), Acetyl salicylic acid (41.86%), Glimepiride (38.95%) and Glibenclamide (33.72%) were the most commonly prescribed drugs. Das et al., reported biguanides (24.5%) and sulphonylureas (19.9%) as the most commonly prescribed oral hypoglycemic agents (OHAs) [24]. Metformin is the therapy of choice for overweight and obese patients with type 2 diabetes[25]. Metformin acts as a peripheral sensitizer of insulin and also has beneficial effects on insulin resistance, an important factor in the pathogenesis of type 2 diabetes. It reduces cardiovascular-related mortality rates more than sulfonylurea[26]. Metformin is unlikely to cause severe hypoglycaemia, because it does not stimulate insulin release. So the physicians prefer metformin over other OHAs. It is recommended that only WHO approved fixed dose combination products should be prescribed. The use of hospital formulary as approved by a competent pharmacy and therapeutic committee (PTC) is also recommended for rational use of medicines. Furthermore lifestyle modifications, inclusive of dietary modification, regular physical activity and weight reduction are indicated for prevention and treatment of type 2 diabetes[27]. In diabetes mellitus with co-morbidities, Metformin (95.61%), Enalapril maleate (57.01%), Amlo-dipine (54.38%), Acetyl salicylic acid (50%), Glibenclamide (28.50%), Glimepiride (28.07%), Carbamazepine (23.68%), Atenolol (16.22%), Salbutamol (10.52%), Etophylline& Theophy-

lline (10.96%) were most commonly used drugs. This correlates with the finding that Hypertension, epilepsy and asthma were the most common presenting co-morbidities at the OPD.

In this study, each enrolled patient was followed after three months, to note meanwhile change in the prescription of anti-diabetic drug or dose. Most common cause for such a change was uncontrolled diabetes mellitus. In diabetes mellitus without co-morbidities there were change in anti-diabetic prescription seen in (29.06%) and in diabetics with co-morbidity there were change in anti-diabetic prescription seen in (25.87%) patients. This lack of control may be due to inadequate dose or unhealthy life style. Change of dose and frequency was found to be an uncommon practice, which is remarkably lower than the findings of Baccuzzi et al., who reported 15% -30% upward dosage changes [28]. As would be expected, need for dosage titration was justified with increasing duration of therapy, reinforcing issues related to agent efficiency or progression of the disease process. The change in frequency was found to be high, which may not be useful as it decreases patient compliance. This supported by previous finding that compliance is better with once daily preparation[29]. This study found that diabetes without co-morbidities at 0 day and at 3 months 56.97%, 63.95% prescription had Drug-Drug Interactions (DDIs) and in diabetes with co-morbidities at 0 day and at 3 months 76.31%, 74.12% prescription had DDIs, suggesting more common DDIs in diabetics with co-morbidities. Manjusha S at el study reported 40% patients found to be exposed to potential DDIs.

Most common minor interaction was found to be between Metformin and Famotidine or Ranitidine, Metformin and B complex. Ranitidine or Famotidine increase the level and effect of metformin by decreasing renal clearance. Hence the two should be used with caution.

Most common moderate interaction was found to be between Aspirin and Glibenclamide, Aspirin and Enalapril maleate. Aspirin increases the effect of Glibenclamide by unknown mechanism, adding to the risk of hypoglycaemia. On the other hand Aspirin decreases effects of Enalapril by pharmacodynamic antagonism. Hence the two should be used with caution and monitor closely.

Most common serious interaction was found to be between Carbamazepine and Atorvastatin. Carbamazepine will decrease the level or effect of atorvastatin by affecting hepatic/intestinal enzyme CYP3A4 metabolism.

**Conclusion**

In the present study there was change in anti-diabetic prescription after 3 months follow-up in diabetes mellitus without co-morbidity (29.06%), and diabetes mellitus with co-morbidity (25.87%), due to uncontrolled diabetes mellitus and this is due to change in frequency of drug administration & alteration of drug.

The study highlights the commonly occurring potential Drug-Drug Interactions (DDIs) at the diabetic OPD at tertiary care hospital. Like minor interactions were found to be between Metformin and Famotidine or Ranitidine, Metformin and B complex. Moderate interactions were found to be between Aspirin and Glibenclamide, Aspirin and Enalapril maleate. Serious interaction was found to be between Carbamazepine and Atorvastatin. Drug-drug interactions were not monitored for their clinical manifestations in the present study, which stands as a major limitation in the study. The study indicated a significant compliance to treatment guidelines in the management of type 2 diabetes in the teaching hospital. Utilization pattern of antidiabetic medications shows no significance difference in both the genders.

**Acknowledgement**: Nil

**Conflict of Interest:** The authors declare that they have no conflict of interest

**Source of support –** Nil

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