A STUDY ON DRUG UTILIZATION PATTERN IN PATIENTS OF TYPE II DIABETES MELLITUS ATTENDING REFERRAL DIABETIC CLINIC AT A TERTIARY CARE TEACHING HOSPITAL IN RURAL BENGAL

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ABSTRACT

Introduction: Type II DM is a pandemic metabolic disorder with great burden of complications. Intensive glycemic control often needs several anti-diabetic drugs with substantial cost. It is crucial to monitor prescriptions periodically for promoting rational pharmacotherapy and improving patient compliance. **Aims & Objectives:** To assess the prescription pattern of anti-diabetic drugs in patients of Type II DM along with the drugs needed for the treatment of co-morbidities. **Methodology:** It was a cross-sectional, institutional based, observational study done at diabetic OPD at B.S. Medical College for a duration of three months. At the exit point, information was collected in pre-structured case report form including socio-demographic profile, histories of diabetes, co-morbidities if any, relevant investigations and details of medications after obtaining written consent. **Result:** Among 202 patients majority were males. Three forth of patients suffered from DM for less than 5 years of duration. Two third of them had one or more co-morbidities. A total of 726 drugs were prescribed of which nearly half were anti-diabetic drugs. Metformin was the leading used anti-diabetic drug given to 77.2% of patients. Newer OHAs were used only as part of combination therapy. Only 14 patients received Insulin. Statin and anti-hypertensive were used in good percentage. Average cost of prescription per day per patient was 26.33 INR. **Conclusion:** Number of drugs prescribed was less than contemporary drug utilization studies. It was a very short duration study incorporating only 202 patients. In future we plan to undertake this with larger number of patients in multiple centers.

KEYWORDS: Type II Diabetes Mellitus, Drug utilization study.

INTRODUCTION

Diabetes mellitus refers to a group of metabolic disorder sharing a common phenotype of hyperglycemia resulting in inadequate insulin secretion or its action on peripheral tissues or both.[1] On long term; it brings about a number of vascular and non-vascular complications including cardiovascular diseases, neuropathies, nephropathy and retinal damages. It is estimated that in 2013, about 382 million people were diabetic worldwide and with this trend, as projected by International Diabetes Federation that about 592 million people will have diabetes by the year 2035.[2] India stands second following only China in respect to harbor maximum number of diabetic persons (65.1 million).[2] In 2013, it was estimated that 11% of total health care expenditures worldwide were spent on individuals with

diabetes which approximates nearly $548 billion.[2] Type II DM is the most prevalent form of Diabetes mellitus, with features of Beta cell failure and Insulin resistance. Pharmacotherapy of Type II DM is very crucial with a great medical, social and economic impact. It is based on administration of Oral Hypoglycemic Agents (OHA) and/or Insulin. Metformin is the standard first line drug for Type II DM patients.[3] Other preferred alternatives are Sulfonylureas (2nd generation), Di-Peptidyl Peptidase 4(DPP4) inhibitors, Thiazolindinediones, Alfa-glucosidase inhibitors. Irrational prescriptions in Type II DM are found frequently especially regarding prescription of antibiotics or multivitamins. Hence it is very important to perform regular prescription monitoring study both at public and private sectors for

rational pharmacotherapy and improved patient compliance in Type II DM patients.

World Health Organization has defined Drug utilization (1977) as "Marketing, distribution, prescription and use of drugs in society, with special emphasis on medical, social and economic consequences".[4] Drug utilization studies (DUS) are very important tool in the evaluation of healthcare systems as well as to find irrational prescriptions and for logical healthcare planning. Irrational prescriptions cause adverse effects, potential drug interactions, increased cost of treatment, drug redundancy and poor drug compliance.[5] Though a number of drug utilization studies have been performed on Type II DM patients[6-13], a periodic review of pattern of drug utilization is necessary to ensure safe and effective treatment. Not only that, pattern of use can guide the extent and profiles of drug use and its trend, quality of use audits by comparing the use with national, regional and local guidelines or formularies. In United States drug utilization research is a part of local health programs, but in India, it is not done routinely. Type II DM is associated with a number of co-morbidities like hypertension, dyslipidemia, obesity, ischemic heart disease, renal disease etc which also need specific treatment. We decided to perform this study on drug utilization among Type II DM patients in referral diabetic OPD at Bankura Sammilani Medical College which have a large catchment area with a great proportion of patients belonging to low socio-economic status.

AIMS & OBJECTIVES
1. To assess the prescription pattern of anti-diabetic drugs in patients of Type II Diabetes Mellitus
2. To assess the prescription pattern of drugs for treatment of co-morbidities.
3. To find out the WHO core drug use indicators in the prescriptions[4, 5]

METHODOLOGY
It was a cross-sectional, institutional based, observational study done at the referral diabetic OPD at B.S. Medical College for a duration of three months starting from 1st October 2015 to 31st December 2015. Approval from Institutional Ethics Committee was taken prior to study. All patients Type II DM irrespective of age and sex, who were prescribed at least one anti-diabetic medication(OHA/Insulin) were included whereas patients with Type I DM, patients suffering from any malignancies, patients with moderate to severe known hepatic/renal/cardiac diseases, diabetic coma, repeat attendance and those not willing to give consent were excluded from the study. Patients were interviewed at the exit point as they depart after consulting the physician. Information was collected in pre-structured case report form including socio-demographic profile, Histories of diabetes, co-morbidities if any, relevant investigation reports and details of medications prescribed after obtaining written consent from the patients or their legal representatives. Photographs of the prescriptions were also taken with due permission. All data were entered into SPSS version 22 software and checked for accuracy. Descriptive statistics were presented using appropriate tables, figures and diagrams suitably.

RESULT
Out of 247 patients screened, 202 patients were enrolled according to inclusion and exclusion criteria. Among them 57.4% were males. We found that 14.3% of cases were newly diagnosed cases of Type II DM. The different age group distribution sex wise is given in Figure 1. Information on BMI, Glycemic status, history of diabetes is given in Table No 1. It is evident from the table that most of the patients were suffering from Type II DM for less than 5 years of durations. Interestingly co-morbidities were found to be common with Type II DM where 60.9% of patients were suffering from one or more co-morbidities. The co-morbidities are presented in Figure No 2 according to different organ system involved. However the most common five co-morbidities were Hypertension(92), Dyslipidimia(72), Peripheral neuropathy(42), Infection(26) and Hypothyroidism(20). All together we found 302 co-morbidities in 123 patients with 2.46 co-morbidities per patients.

All 202 patients were prescribed with anti-hyperglycemic medications and all patients with co-morbidities(123) were given the medications for respective diseases in addition to their management of Type II DM. A total of 726 drugs were used out of which 344 were drugs for Type II DM, (1.70 drug/patient). Out of them, 330 were oral medications and rest 14 were were insulin preparations. A single medication was prescribed to 98 patients whereas rest of them(104) received two or more drugs. Figure 3 shows the different anti-diabetic drug use in 202 patients

So it is evident from the figure that Biguanide was most commonly used anti-diabetic drug given to 77.2% of patients and accounting for 45.3% of total anti-diabetic drugs, followed by Sulfonylureas.Table 2 shows in detail different OHA according to different classes. Out of 14 Insulin preparations 8 were mixed Insulin(30% soluble/ 70% isophane Insulin) whereas rest were regular soluble Insulin. Mixed Insulins were given both as monotherapy as well as with Metformin, while regular Insulin were preferred only as a part of three drugs regimen. A total of 72 patient received two anti-diabetic drugs(OHA/OHA or OHA/Insulin), while 26 patient were given three drugs and rest 6 patient received four drugs. The most frequently observed drug combinations are presented in Table no 3. As the patients were diagnosed to be suffering from a number of co-morbidities(60.9%) apart from Type-II DM, a significant number of drugs (382) not pertaining to

DM management were prescribed. Use of such different drugs has been presented in the Figure 4 as follows. However, Statins were the commonest drug class prescribed(70), followed by ACE inhibitors(46), Anti-microbials(42), Gabapentinoids(39), Angiotensin Receptor Blockers(28), Methyl Cobalamin(27), Beta Blockers(26) and L-Thyroxin(20). 92% of all the drugs, both Anti-DM drugs and other drugs, were prescribed by generic name. It was seen that 72.1% of anti-DM drugs & 46.3% of other drugs were from National List of Essential Medicine (NLEM-2015).

Table No 1:

Parameter	Value
BMI (Kg/m^2)	Mean= 26.183 SD=2.645 Range=19-31.5
Socio-economic status	Monthly income ➢ 2000-5000 INR- 27.7% ➢ 5000-10000 INR-24.7% ➢ 10000-20000 INR-18.8% ➢ >20000 INR- 28.7%
FBG	Mean= 141.3mg/dl SD=39.2mg/dl Range=88-278mg/dl
PPBG	Mean= 224.2mg/dl SD=67.3mg/dl Range=98-402mg/dl
HBA1C	Mean=8.6 SD=1.1 Range=7.1-10.7
Duration of DM	Newly diagnosed=14.3% 1day-1yr= 31.3% 1yr-5yr=27.2% 5-10yrs=23.1% >10yrs=4.1%
Co-morbidities	Yes= 123(60.9%) No=79(39.1%)

Table 2: Different OHA according to classes.

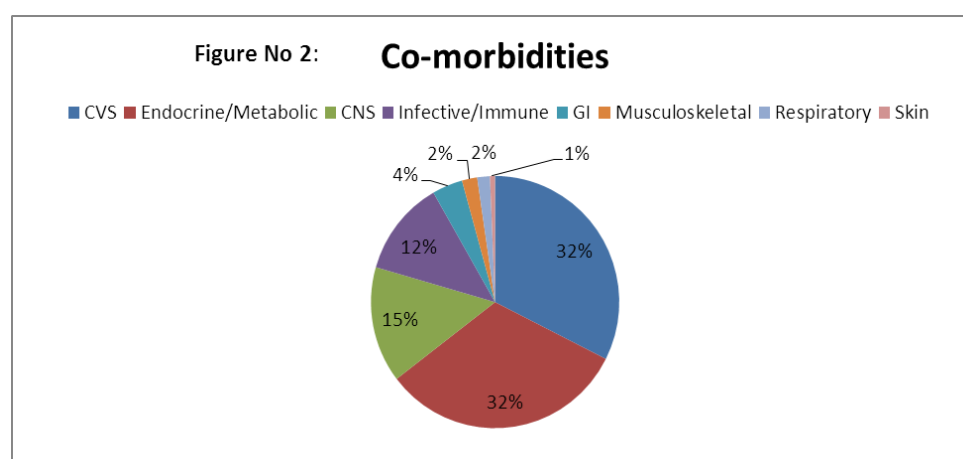| Class	Drugs	Number of use
Biguanides	Metformin	156
Sulfonylureas	Glimepiride	78
	Glipizide	18
	Gliburide	2
Thiazolidinediones	Pioglitazone	22
DPP-4 inhibitors	Sitagliptin	14
	Vildagliptin	4
	Linagliptin	2
α Glucosidase inhibitors	Voglibose	26
	Acarbose	4

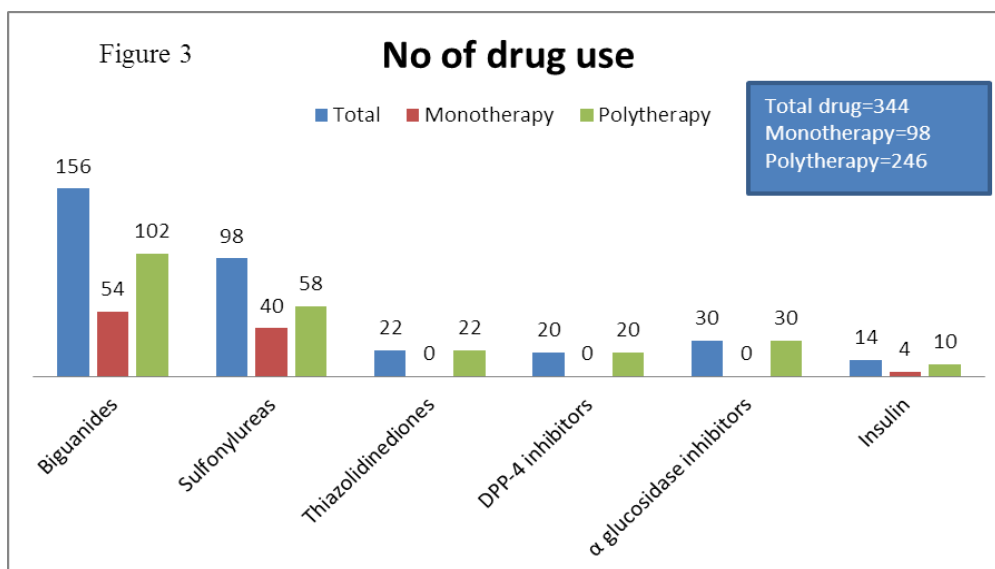**Table no 3: Frequenly observed drug combinations**

Drug combinations	Number of patients
Metformin+Glimepiride	18
Metformin+Voglibose	16
Metformin+ Pioglitazone	10
Metformin+Glimepiride+Pioglitazone	8
Metformin+ Sitagliptin	6
Metformin+Glipiizide	6
Metformin+ Glimepiride+ Voglibose	6
Metformin+ Glimepiride+ Sitagliptin	6
Metformin+ Glimepiride+Insulin(Mixed)	6

Metformin+Vildagliptin	4
Metformin+Glimepiride+Voglibose+Pioglitazone	4
Metformin+Insulin(Mixed)	4
Metformin+Acarbose	4
Metformin+Linagliptin	2
Metformin+Vildagliptin	2
Metformin+ Glimepiride+ Sitagliptin+Pioglitazone	2
Total	104

Table No 4: WHO core drug use indicators

Class	Indicators	Value
Prescribing Indicators	Average number of drugs per encounter	3.59/ encounter
	Percentage of drugs prescribed by generic name	92%
	Percentage of encounters with an antibiotic prescribed	15.84%
	Percentage of encounters with an injections prescribed	6.93%
	Percentage of drugs prescribed from essential drug list(NLEM 2015)	58.52%
Patient Care indicators	Average consulting time	4 min
	Average dispensing time	Not determined
	Percentage of drugs actually dispensed	Not determined
	Patient's knowledge of correct dosage	69%
Facility indicators	Availability of copy of EDL(NLEM 2015)	Yes
	Availability of Key drugs	Yes
Complementary indicators	Percentage of patients treated without drugs	Nil
	Average drug cost per encounter	26.33 INR/day/patient(based on price list from CIMS 2016)
	Percentage of drug costs spent on injection	2.85%

Figure 1: Age/ Sex distribution of cases

Figure No 2: Co-morbidities

Figure 3 — No of drug use

Figure 4 — Drug use-system wise
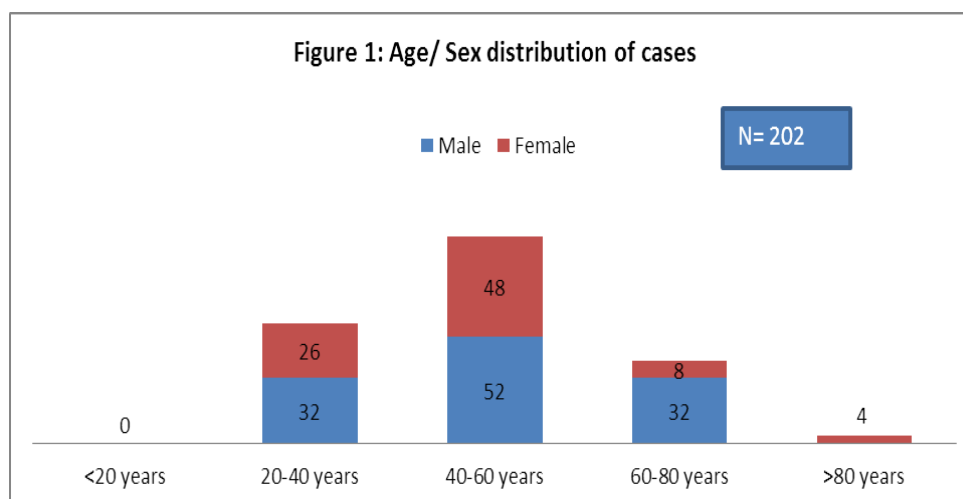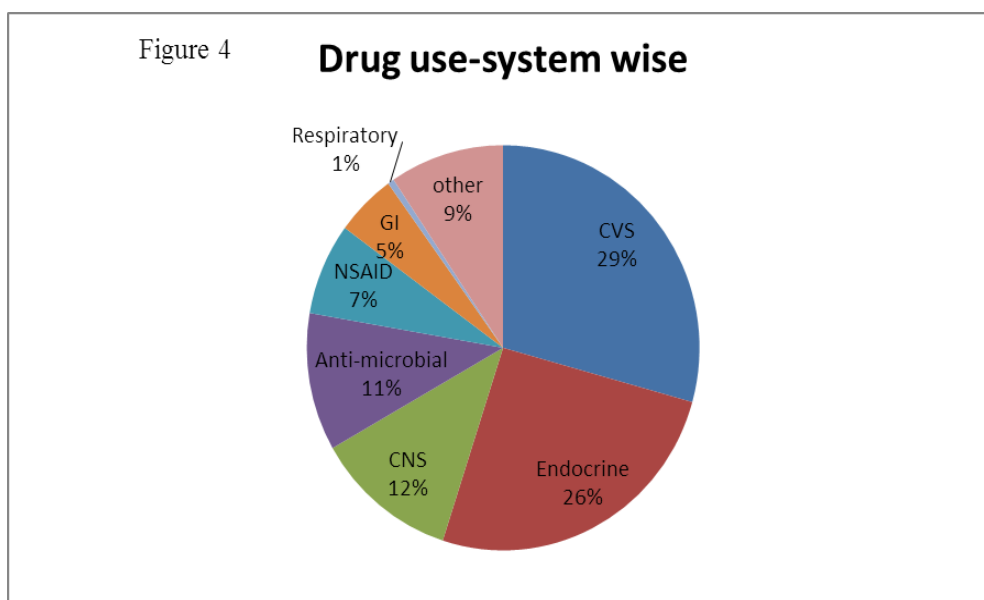
DISCUSSION

Diabetes Mellitus is now become a pandemic with a rising trend in both morbidity and mortality. Management of Type II DM is based on control of hyperglycemia and also preventing the complications. Duration of Type II DM influence its management to a great extent. Whereas Diabetes for less than 5 years of duration can be managed by one or two anti-diabetic drugs, it becomes usually necessary to use more than two drugs which may include Insulin for management of DM of 5 or more years of duration. Associated co-morbidities and complications of DM also have a great impact on selecting the suitable anti-diabetic regimen. Other factors are age, cost of therapy and convenience. It is necessary to achieve intensive glycemic control from beginning for retarding disease progression as well as to prevent complications, especially microvascular and macrovascular complications. Several drug utilization stuides have been performed to assess irrational prescribing practice and to improve pharmacotherapy for better patient compliance.

In our studies, males outnumbered females to a slight extent. Similar results were found in Nepal(Upadhay et al)[6], Kerala(Alex et al)[7], Tamilnadu(Shivasankari et al)[8] where males were found to be predominant than females., though globally there is no internationally accepted data of preponderence of either sex in Type II DM. Majority of patients (49.5%) were among 40-60 years of age whereas a significant number of patients(28.7%) were from 20-40 years. It is noteworthy that Type II DM is becoming prevalent under the age of forty. Mean age of the patients were 49.2, years which was lower than that found in Rajkot[9], Ahmedabad[10], Nepal, Andhra Pradesh.[11] According to BMI, most of the patients were overweight/ obese which is in accordance to global data. Highest percentage of patients(28.7%) had the monthly family income of >20,000/ though almost equal percentage of

patients(27.7%) had income of 2000-5000/month. A recent study in Tamilnadu showed that 77.1% of their included patients belonged to low socioeconomic status.[8]

Regarding the glycemic status and history of DM, we noticed that almost three forth of the patients had history of DM of less than 5 years out of which 14.3% were newly diagnosed case of DM. Upadhyay et al in Nepal found similar result where 70.3% of patients had a H/O DM of less than 5 years, but studies in Rajkot, Kerala, Ahmedabad, Mumbai[12] found that half of the patients had H/O DM of more than 5 years. Mean FBG & PPBG was 141.3±39.2mg/dl and 224±67.3mg/dl respectively which is somehow lower than that of earlier studies. Mean HBA$_1$C was 8.6±1.1%.

We found that two third of the patients had at least one co-morbidites. This percentage was found to be higher in studies in Kerala(87.3%), UAE(84.1%),[13] Nepal(74.7%) and lower in Andhra Pradesh(47.4%) and Tamilanadu(28.2%). Hypertension and Dyslipidimia was most commonly associated with Type II DM, but a significant percentage(12.9%) of patient were suffering from a number of infections.

A total of 726 drugs were used out which almost half were anti diabetic drugs. The number of anti-diabetic drugs was 1.70/patient, which is higher than that of found in Mumbai(1.40/patient), but lower than that in Kerala(1.81/patient), UAE(3.2/patient). High pill burden is associated with increased cost of therapy, unwanted drug interaction and adverse drugs reactions. Oral hypoglycemic agents were preferred to Insulin in our study both as monotherapy as well as in combination. Metformin was the leading used drug in both category(monotherapy/ Polytherapy). Its low cost, less propensity to cause hypoglycemia, weight reducing role and also ability to prevent macrovascular complications has made it to be the drug of choice to start with in Type II DM. second genaration Sulfonylureas, especially Glimepiride came out to be just next to Metformin in order of preferrence. Glimepiride can be given once daily, for which it is more convenient than Glipizide or Glyburide. Pioglitazone, DPP4 inhibitors, α Glucosidase inhibitors all were used as part of combination , but none as monotherapy. Metformin plus Glimepiride was the most preferred regimen. In studies done in Kerala, Nepal, Andhra Pradesh, Ahmedabad, UAE, Mumbai Metformin was seen to be the most commonly used anti-diabetic regimen. Only one study in Rajkot showed preferrence of Glipizide over Metformin as monotherapy. Three or more drugs have been prescribed only to 15.8% of patients which clearly less than earlier studies. Use of Insulin was remarkably low in our study, probably because majority of the patient population had history of DM of less than five years. In earlier studies ,Alex et al showed that in 42.1% of patients Insulin were used.
In accordance to high percentage of co morbidities, the number of other drugs were remarkably high. Statins were given only to those having elevated lipid profile, but according ADA guidelines 2016, moderate or high intensity statin should be prescribed to all DM patients with ASCVD risk factors.[14] Antihypertensives were used in 28% of patients, with ACE inhibitors or Angiotensin Receptor Blockers being most preferred regimen, which comply with standard guidelines. Antibiotics were used frequently, without obivious sign of bacterial infection in most cases. In peripheral neuropathies gabapentoids were used most. According to USFDA, only two drugs are approved for neuropathic pain in Painful Diabetic Polyneuropathy(PDPN), Duloxetine and Pregabalin.[15] In earlier studies, also showed similar results.

LIMITATION
First, it was short duration study including only 202 patients. Secondly, the patient population had relatively shorter history of DM and most of them had good glycemic control, which does not represent the actual universe of DM patients. Thirdly, we did the study only at OPD. If we would have performed that in pharmacy, it would incorporate more information , especially the WHO facility indicators.

CONCLUSION
However, Drug utilization studies are an important mirror of pattern of use of drugs in community in actual practice, reflecting not only preference of doctors in drug selection and their prescription, but also cost of therapy, convenient regimen and their impact on medical, social and economic factors. It is a dynamic process, hence is to be undertaken time by time on different places, on different patient population with different socio economic background. It is noteworthy that DPP4 inhibitors have used more commonly in comparison to earlier studies which reflect its popularity owing to its unique Incretin based " Glucose dependant insulinotrpic action". In future it will be more extensively used as anti-diabetic regimen without risk of hypoglycemia. We planned to extend the study to incorporate more patients in future and also to monitor their compliance to drugs for longer duration.

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