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A SINGLE CENTRIC, PROSPECTIVE, OBSERVATIONAL DRUG UTILISATION STUDY OF ORAL HYPOGLYCAEMIC AGENTS AND INSULIN BEING PRESCRIBED TO THE PATIENTS OF TYPE 2 DIABETES MELLITUS, IN THE DIABETES CLINIC OF A TERTIARY CARE HOSPITAL

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ABSTRACT

Introduction: Type 2 Diabetes Mellitus (T2DM) is a chronic disease which is allied with significant morbidity and complications, especially when it is associated with poor glycaemic control. Hence, meticulous management of diabetes mellitus is very essential. The treatment options for T2DM and prescription of anti-diabetic drugs have increased over the recent years. Appropriate selection of these drugs is therefore extremely important. The main objective of this study was to highlight the current prescribing patterns in T2DM patients with and without other co-morbid conditions. **Materials and Methods:** A prospective observational descriptive study was carried out for a period of 18 months between June 2018 to November 2019. Patients with type 2 Diabetes Mellitus visiting the outpatient department of medicine, of a tertiary care hospital were included in this study. Demographic data and prescription details of the included patients were obtained and were recorded in the structured case record form. The cost of drug therapy for each patient was also calculated. **Results:** A total of 600 patients were enrolled in the study with their mean age being 56.16 ± 12.59 years. Out of the 600 patients, 321 (53.5%) were male and 279 (46.5%) were female. A total of 3385 drugs were prescribed to our study population with the mean of 5.44 ± 0.94 drugs being prescribed per patient. Out of these 3385 drugs, 1381 (40.80%) drugs were anti-diabetic drugs with the mean of 2.10 ± 0.58 drugs per patient. As far as monotherapy is concerned, out of the total 1381 antidiabetic drugs, Metformin was most commonly prescribed {588(42.58%)} followed by Glibenclamide {360 (26.07%)}. On the other hand, the combination of Glimepiride and Metformin was the most frequently prescribed antidiabetic fixed-dose combination. This combination was prescribed in 37 (38.54%) patients out of the 96 who received various antidiabetic fixed-dose combinations. Most commonly prescribed drugs other than antidiabetics were gastro protective drugs 509 (15.04%) and anti-hypertensive drugs 312 (9.22%). The average cost per prescription was 278.95 INR. **Conclusion:** The most commonly prescribed single anti-diabetic drug was Metformin followed by Glibenclamide. The combination of Metformin and Glimepiride was the most frequent fixed-dose drug combination prescribed. Majority of the prescriptions followed standard guidelines.

KEYWORD: Diabetes mellitus, Anti-diabetic drugs, Prescription, Fixed drug combinations.

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) 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 for prevention of acute complications and reducing the risk of long-term complications. Significant evidence exists in support of wide range of interventions to improve the short-term and long-term outcomes of type 2 diabetes mellitus.[1]

The dynamics of the Diabetes Mellitus (DM) epidemic are changing rapidly. Once a disease of the western world, T2DM can now be considered a pandemic disease which is prevalent in every country of the world. Once considered as a "disease of the affluent," it is now commonly seen even amongst the poor. WHO has estimated that, in 2000, 31.7 million individuals were affected by diabetes in India and these figures are expected to rise to 79.4 million by the year 2030.[2]

Apart from being a huge burden on the healthcare sector, DM is an equally rankling ailment for the affected individual. This can partly be attributed to the numerous life-threatening complications associated with DM and partly to the fact that the therapy of DM is almost a life-

long process. The development of new classes of blood glucose-lowering medications to supplement the older therapies, such as insulin, sulfonylurea, and metformin, has increased the number of treatment options available, especially for T2DM. Conversely though, this increased number of available choices has heightened uncertainty regarding the most appropriate means of treating this widespread disease among clinical health care practitioners. Although, numerous reviews on the management of DM have been published in recent years, clinical practitioners are often left without a clear pathway or protocol of therapy to follow.[3]

Then there is always the perennial issue of patient compliance. The treatment strategy of DM, on a routine basis, calls for active involvement of the patient, as the patient is supposed to self-administer his/her medication daily. Additionally, various other adjuvant management strategies like exercise and diet control will be useless without a co-operative patient. Therefore, people with diabetes mellitus should receive diabetes self-management education (DSME) that apprises them with the necessary knowledge, skill, and ability pertaining to diabetes self-care.[4] DSME is associated with improved patient compliance towards therapy, improved self-care and thus, improved clinical outcomes such as lower glycosylated haemoglobin (HbA1c), lower self-reported weight (kgs) and overall, improved quality of life. This ultimately also lowers the total cost of anti-diabetic therapy.[4,5]

A good number of diabetes patients suffer from cardiovascular diseases such as hypertension, hyperlipidaemia, and coronary artery disease.[6] Owing to the presence of such co-morbid conditions, geriatric patients are usually on more than one drug (polypharmacy) for the same. Additionally, several problems in drug prescription patterns have been reported. This includes use of irrational combinations, excessive prescription of multivitamins, use of antibiotics in viral infections, adverse drug reaction, drug-drug interactions, etc.[7] Moreover, irrational prescription can lead to an increase in the cost of drug therapy. As previously mentioned, the chronically ill patients like the diabetic patients suffer from multiple diseases and hence are prescribed multiple drugs.[8]

Drug utilization is defined as the marketing, distribution, prescription, and use of drugs in a society, with emphasis on the resulting medical and social consequences.[9] 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.[10] The ultimate aim of drug utilization research must be to assess whether drug therapy is rational or not.[11]

Hence the current study was undertaken to gain an overview of the prescribing pattern in diabetes patients visiting diabetes OPD of a tertiary care hospital.

METHODOLOGY

A prospective, non-interventional, observational study was conducted in 600 patients of type 2 diabetes mellitus attending Medicine outpatient department of a tertiary care hospital. This study was conducted only after obtaining an approval from the institutional ethics committee. All the participants included in the study were explained clearly about the purpose and nature of the study in the language they understood and were included in the study only after obtaining a written informed consent on the Informed Consent Form (ICF).

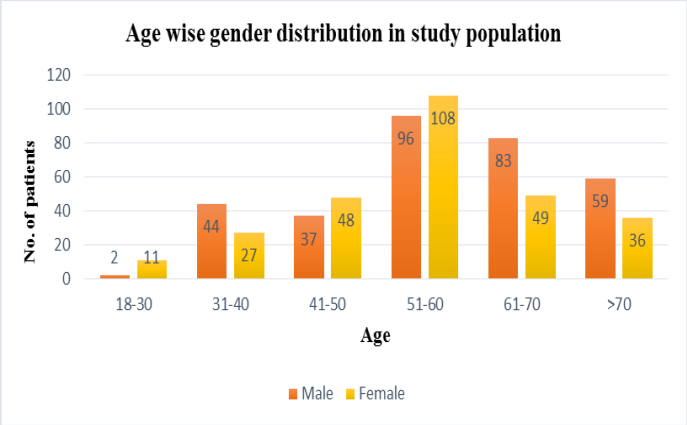
All individuals of either sex, aged above 18 years of age, diagnosed with type 2 diabetes mellitus and willing to participate in the study by giving a written consent were included in the study, while those diagnosed as type 1 diabetes mellitus along with pregnant and lactating females were excluded from the study. The detailed information of the participants pertaining to age, sex, occupation, relevant medical history, past history and drug therapy administered were obtained from their case files and were documented in the Case Record Form (CRF). Details regarding the treatment of diabetes such as the drugs used, the dose, duration and frequency of administration, type of dosage form used etc. were also documented.

Statistical analysis

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements have been presented on Mean ± SD (Min-Max) and results on categorical measurements have been presented in Number (%). The gathered data has been expressed in the percentile form.

RESULTS

1. Among a total of 600 participants diagnosed with type 2 DM, 321 (53.5%) of them were male and 279 (46.5%) were female. It was observed to be highest 294 (34%) in the age group 51-60 years followed by 132 (22%) in the age group 61-70 years and 95 (15.83%) in more than 70 years. While studying the religion-wise distribution of study population it was found that the majority of the study population were Hindu 349 (58.17%) followed by Muslims 234 (39%) followed by other religions 17 (2.83%).



2. Among the 600 prescriptions studied there were total of 515 prescriptions associated with comorbid conditions such as Hypertension (HTN), Coronary Artery Disease (CHD), Chronic Obstructive Pulmonary Disease (COPD), Asthma, Hypothyroidism. Diabetes mellitus (DM) alone was observed in 85 (14.17%) prescriptions of the study population whereas hypertension was found to be the most commonly associated comorbid condition with diabetes mellitus seen in 191 (31.83%) prescriptions of the population studied, followed by hypertension with CHD combination having 167 (27.83%) prescriptions out of the 600 studied prescriptions.

Table 1: Distribution of diabetes mellitus with Co-morbidities in study population (n= 600)

Associated comorbidities	Total No.	Percentage (%)
DM (No comorbidities)	85	14.17
DM with HTN	191	31.83
DM with CHD	63	10.5
DM with HTN & CHD	167	27.83
DM with COPD	3	0.5
DM with HTN & COPD	4	0.67
DM with Asthma	10	1.67
DM with Hypothyroidism	2	0.33
DM with HTN & Hypothyroidism	8	1.33
Others *	67	11.17
Total	600	100

Others * include epilepsy, psychiatric disorders etc.

3. During the study period, the average number of drugs prescribed per prescription in our study population was 5.44 with a standard deviation of 0.94 whereas the average number of antidiabetic drugs prescribed per prescription was 2.10 with a standard deviation of 0.58.

Table 2: Average number of drugs prescribed in the study population (n=600).

Parameter	Number
The average number of drugs prescribed per prescription	5.44 ± 0.94
The average number of antidiabetic drugs prescribed per prescription	2.10 ± 0.58

4. Out of 1381 prescribed anti-diabetic drugs, oral hypoglycaemic agents (OHA) were 1285 (93.05%) and 96 (6.95%) was insulin.

Table 3: Number of various classes of antidiabetic drugs prescribed in the study population (n=1381).

Drug class	Number	Percentage (%)
Biguanides	588	42.58
Sulfonylureas	496	35.92
Dipeptidyl peptidase-4 (DPP-4) inhibitor	112	8.25
Thiazolidinedione (TZD)	64	4.63
Alpha-glucosidase inhibitor	25	1.81
Insulin	96	6.95
Total	1381	100

5. In this study, OHA's were the more common class of anti- diabetic drugs prescribed. 1164 (92.38%) were prescribed single-drug OHA formulations and 96 (7.62%) were prescribed combination therapy. Out of prescribed OHAs, biguanides (42.58%) were the most commonly prescribed class followed by the sulfonylureas (35.92%) and combination of these 2 OHAs as fixed dose combination (FDC) was 38.54%.

Metformin (Biguanide) as an individual OHA, was the most commonly prescribed OHA and accounted for 42.58%. Other commonly prescribed OHAs were Glibenclamide (sulfonylurea) 26.07% and the FDC of Glimepiride plus metformin 38.54%.

Table 4: Number of different individual antidiabetic drugs in the study population (n=1381).

Antidiabetic drugs	Number of drugs prescribes	Percentage (%)
Metformin	588	42.58
Glibenclamide	360	26.07
Glimepiride	124	8.98
Gliclazide	10	0.72
Voglibose	25	1.81
Sitagliptin	16	1.16
Teneligliptin	98	7.10
Pioglitazone	64	4.63
Insulin	96	6.95
Total	1381	100

Table 5: Number of antidiabetic drugs prescribed as formulations with fixed dose. (FDC) (n= 96).

Combination	Drugs	No. Of drugs prescribed	Percentage %
Two drugs combinations			
Biguanides + sulfonylureas	Metformin + glimepiride	37	38.54
Biguanides + dipeptidyl peptidase-4 (dpp-4) inhibitor	Metformin + teneligliptin	25	26.04
Biguanides + dipeptidyl peptidase-4 (dpp-4) inhibitor	Metformin + sitagliptin	9	9.38
Three drugs combinations			
Biguanides + sulfonylureas + alpha-glucosidase inhibitor	Metformin + glimepiride+ voglibose	25	26.04
Total		96	100

6. The average cost per prescription in the present study was 278.95 INR. The cost borne by hospital was 17.26% of the average cost and that by the participant was 82.74 %.

Table 6: WHO/INRUD drug use indicator.

Average number of drugs per encounter	5.44±0.94
Percentage of drug prescribed by generic name	61.69%
Percentage of encounter with an antibiotic prescribed	1.45%
Percentage of encounter with injection prescribed	6.95%
Percentage of drug prescribed from Hospital formulary	68.65%
Percentage of drug prescribed from National essential drug list (NLEM, 2015)	51.56%
Percentage of drug prescribed from WHO essential drug list (WHOEML,2017)	50.25%

DISCUSSION

Type 2 Diabetes Mellitus (T2DM) is the most common endocrine disorder worldwide and has emerged as a major public healthcare problem in both developed and developing countries. It is a chronic endocrine disorder that requires life-long management through multifaceted strategies. Although lifestyle modifications play an important role in diabetes management, especially in early course of the disease, drugs eventually become unavoidable in almost all of the patients. Oral hypoglycaemic agents (OHA) and insulin are therefore the mainstay of treatment of T2DM with respect to management of its acute emergency conditions as well as prevention of long term vascular and neural complications.

Polypharmacy is also seen very commonly with T2DM. This is because of several reasons. Firstly, the incidence of diabetes mellitus is highest in the 6th and 7th decade of life, where patients are prone to suffer from chronic

degenerative disorders.[12] Such patients are already on one or more drugs for the same.[13,14,15] Secondly, other cardiovascular disorders like hypertension, congestive heart failure, coronary artery disease, hyperlipidaemia etc. are also commonly seen in patients with DM.[6] Additionally chronic complications of DM in a person suffering from the disease for many years also mandate treatment with additional drugs for its treatment. Therefore, studies focusing on various aspects of DM and its management are of paramount importance. Several anti-diabetic prescription studies have been published in the healthcare settings from various parts of world and have facilitated rational drug use in patients with diabetes.

A prescription-based study / Drug utilisation study (DUS) is considered to be one of the most effective methods to assess and evaluate drug utilization of medication. Prescription by the physician 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.[12] Therefore, drug utilization research plays a crucial role in understanding role of various anti-diabetic drugs in different clinical scenarios with respect to the physician's point of view. This insight can help form amendments in the drug dispensing policies at local and national levels. The ultimate goal of such research is to facilitate "appropriate drug use". Also, since it can help in developing strategies to utilize health resources in the most efficient manner, it is particularly needed in a developing economy like India where 72% of all health care burden is borne by the patients.[16]

To summarise, a prescription pattern research study will help in improvement of drug usage. Selecting proper cost-effective medications will help in cost reduction, proper dose selection, and better health outcome. This study is therefore aimed at determining the pattern of drug prescription among the diabetic patients so as to evaluate the degree of physician's compliance to current evidence and clinical guidelines, and analyse prescriptions according to the WHO core drug prescribing indicators.

In our study, a total of 600 prescriptions were studied. The most common age group from study population was 51-60 years (34%). The mean age of the study population was observed to be 56.16 years with a standard deviation of 12.59. A similar finding was also observed in study carried out by Soumya Mary Alex et al, where the most common age group in the study population was 51-60 years (39.6%).[17] Also, a high proportion of diabetic patients in our study were represented by males (53.5%). This may be attributed to their social habits and lifestyle changes. The slight male preponderance in the diabetic study population was also noticed in similar studies carried out by Soumya Mary Alex et al. (50.3%),[17] Kaushali G. Acharya et al. (50.4%)[18] and Sasisekar T.V.D. et al. (56%).[19] On the contrary, a higher proportion of diabetic patients in the study represented by females was observed in a similar study carried out by Bela Patel et al.[20]

Co-morbidity has been shown to intensify health care utilization and increase medical care costs for patients with diabetes. In our study, co-morbid conditions were found in 515 patients (85.83%) out of 600 patients. The most common co-morbidity observed was hypertension (61.66%). A similar study conducted by Sayed Aliul Hasan Abdi et al also reported that hypertension, which contributed to 51.95% of all co-morbid conditions, was the most common co-morbidity in patients with diabetes mellitus.[21] A similar result was obtained in a study conducted by Rataboli P et al., (2007). The study states that among all diabetic complications, cardiovascular complications, especially hypertension pose a major threat.[22]

As far as polypharmacy is concerned, the average number of drugs per prescription in our study was observed to be 5.44 with a standard deviation of 0.94 drugs per prescription. This finding is a little high when compared to the study of Soumya Mary Alex et al in which the average number of drugs per prescription was 4.76.[17] On the other hand, the average number of drugs per prescription in the study by Bela Patel et al., was comparatively higher at 7.58.[20]

Also, the average number of antidiabetic drugs encountered per prescription in our study was 2.10. This finding is less when compared to the results of the studies by Upadhyay DK et al., (3.76 anti-diabetic drugs per prescription)[23] and V. Karthikeyan et al., (4.83 anti-diabetic drugs per prescription).[24] However, the same finding is more when compared to that reported by Das Priya et al., (1.83 anti-diabetic drugs per prescription)[25] and Kannan et al., (1.4 anti-diabetic drugs per prescription).[26]

The drugs prescribed from national essential drug lists were 51.56%. This was reported to be more in the study conducted by V. Karthikeyan et.al. (74.30%)[24] but less (31.36%) in the study conducted by Kumar Raj et.al.[27]

Among the total number of anti-diabetic drugs prescribed in the 600 prescriptions of our study, it was found that, Metformin was the most commonly prescribed anti-diabetic drug (either alone or in combination with other anti-diabetic drugs), and constituted for 42.48% of all anti-diabetic drugs. This finding is in line with and similar to a number of studies carried out by Upadhyay et al (51.27%),[23] Johnson et al, 2006,[28] Yurgin N et al, 2007;[29] and Sultana G et al, 2010[30] who also reported metformin as the most commonly prescribed anti-diabetic drug in their respective studies. In contrast to this, studies conducted by R Ramesh et al, 2011,[31] Chiang CW et al, 2006;[32] and Al Khaja KA et al, 2001;[33] had sulphonylureas as the most commonly prescribed anti-diabetic drugs in their respective studies.

Metformin and Glibenclamide was most commonly prescribed polytherapy for diabetes in our study which is in accordance with the study by Abdi SA et al.[21] On the other hand, Metformin and Glimepiride was the most common polytherapy observed in study by Patel B et al.[20] whereas Metformin and Sitagliptin was the most common polytherapy observed by Soumya Mary Alex et al in her study.[17] Metformin is considered a cost effective and safe drug. Metformin was the first choice in many studies (as mentioned) among all the oral anti-diabetic drugs, especially during the onset. The fact that Metformin was the most prescribed OHA in our study as well as many others, reinforces its preference as the initial oral anti-diabetic of choice, as per current clinical guidelines laid down by important organisations like American association of clinical endocrinologists (AACE) and American diabetes association (ADA) 2019.[34]

In our study, 61.69% prescriptions had drugs prescribed with their generic names. Patients were advised monotherapy as an initial therapy along with dietary restrictions, exercise and lifestyle modifications. Routine eye examination, cardiovascular and neurological check-up were advised, which is in adherence with ADA guideline.[34]

All the Antidiabetic drugs prescribed in our study were classified according to the Anatomical Therapeutic Chemical (ATC) – Defined Daily Dose (DDD) classification. The ATC classification system divides drugs into different groups according to the organ or system on which they act and their chemical, pharmacological and therapeutic properties.[35] The 'DDD' concept was developed to overcome the objections against the traditional units of measurement of drug consumption and to ensure comparability between the drug utilization studies which were carried out at different locations and at different time periods. It is important to remember that the DDD is the assumed average maintenance dose per day for a drug which is used for its main indication in adults.[35] The prescribed daily dose (PDD) is defined as the average dose prescribed according to a representative sample of prescriptions. When there is a substantial discrepancy between the PDD and the DDD, it is important to take this difference into consideration when evaluating and comparing drug utilization figures.[36] When the PDD/DDD ratio is either less than or greater than 1, it may indicate that there is either under or overutilization of drugs. Having said that, it is important to note that, PDD can vary according to both, the illness treated and national therapeutic practices. The PDDs may also vary substantially between different countries, for example, PDDs are often lower in Asians than in Caucasian populations. Because of this, it may seem as if there is an underutilization of a particular drug as per the PDD/DDD ratio in the Asian population.[35,36] In our study, Glibenclamide & Pioglitazone had a PDD/DDD ratio equal to 1. The PDD/DDD ratio was more than 1 with Insulin whereas Metformin, Sitagliptin and Glimepiride had PDD/DDD ratios which were less than 1. Glimepiride had lowest PDD/DDD amongst all anti-diabetic drugs included in our study.

Finally, the average cost per prescription was 278.95 INR out of which, the cost borne by the hospital was 17.26% and the cost that was borne by the patient was 82.74%. Studies in India estimate that for a low-income Indian family with an adult having diabetes, as much as 25% of the family's income may be devoted to diabetes care.[37] For families in the USA, with a child who has diabetes, the corresponding figure is 10%. The cost of diabetes care affects everyone everywhere, but it's not just a financial problem. Intangible costs (pain, anxiety, inconvenience and generally lower quality of life, etc.) also have a great impact on the lives of the patients and their families and are the most difficult to quantify.[37] That's why cost of diabetes treatment is an important aspect in health economics which should be considered and assessed by every practicing physician for each individual patient separately. To conclude, cost of drugs, plays a crucial role in patient care especially in developing countries like India and constitutes an essential part of rational drug prescription.[38]

CONCLUSION

The study entitled "A single centric, prospective, observational drug utilisation study of oral hypoglycaemic agents and insulin being prescribed to the patients of type 2 Diabetes Mellitus, in the diabetes clinic of a tertiary care hospital" was a study conducted in department of Pharmacology in collaboration with department of Medicine in a tertiary care hospital after obtaining permission from the Institutional Ethics Committee.

In this study, prescriptions of 600 with Type 2 Diabetes Mellitus were analysed and the following conclusions can be made.

1. According to the study, the incidence of T2DM was found to be more in males than females.
2. Diabetes mellitus was most common in the age group of 51-60 years.
3. The most common co-morbidity associated with diabetes mellitus was hypertension.
4. Oral dosage form was the most commonly used dosage form to increase patient compliance in T2DM. This is a good prescribing habit.
5. The majority of drugs were prescribed by their generic names.
6. The most commonly prescribed single dose and combination dose drugs were, Metformin and Metformin + Glibenclamide, respectively.
7. Overall, the principles of rational prescribing were followed according to the various drug use indicators mentioned by WHO.
8. A major part of the total cost per prescription was borne by the patient. Cost is a major factor for non-compliance among diabetic patients. Some of the

drugs which were prescribed by generic name were dispensed from the hospital pharmacy, thus reducing the burden to some extent.

9. Incidence of poly-pharmacy was relatively high, but poly pharmacy is quite relevant in diabetic patients because diabetes is associated with various co-morbidities and complications.
10. As per our study, the following recommendations can be made, to improve pharmacotherapy of type 2 Diabetes Mellitus, thereby also improving its outcome in patients.

- The economic burden of diabetes mellitus on patients suffering from it is high and is a major reason for non-compliance. Newer antidiabetic agents with lesser costs and equal or better efficacy should be included in the hospital pharmacy to reduce this economic burden.
- The drug therapy has to be individualised as per each patient as uniform response to anti-diabetic therapy may not be seen. The doses may vary, depending on the severity of the condition, medication, and the person's overall health.
- Studies on the utilization pattern of antidiabetic drugs in the population appear to be lacking in our country. This study provides baseline data regarding the prescribing pattern in diabetic patients and urges strongly for further research in this area.

Abbreviations

- AACE: American association of clinical endocrinologists
- ADA: American diabetes association
- CAD: Coronary artery disease
- COPD: Chronic obstructive pulmonary disease
- CRF: Case record form
- DM: Diabetes Mellitus
- HTN: Hypertension
- ICF: Informed consent form
- OHA: Oral hypoglycemic agents
- T2DM: Type 2 Diabetes Mellitus

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