Drug Utilisation Study of Antidiabetic Agents in Patients Attending Medicine Outdoor Patients Department of a Tertiary Care Teaching Hospital

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Abstract: _Background: Diabetes mellitus (DM) is a chronic disorder emerging as major health problem which increases the rate of morbidity and mortality. For treatment of diabetes mellitus recently many guidelines published, but there is substantial variation in treatment of diabetes mellitus in different countries. Aims and objectives: To identify Antidiabetic prescribing pattern in diabetic patients ,to know the correlation of BMI pattern among diabetic patient and to provide some useful recommendations, if any. Materials and Methods: A prospective, observational study was conducted by department of pharmacology in a tertiary care teaching hospital over period of 12 months. The line of treatment to be given was decided by the physician in charge of the department of medicine. Results: Out of 610 patients, 53.11% were female and 46.88 % were male. Maximum patients belonged to age group of 46-60 years(46.48%).Hypertension (57.21%) was most common associated disease with diabetes. About half of the patients had received one antidiabetic drug (55.40%), followed by two (39.40%) and three (28%).Metformin was most commonly prescribed antidiabetic drug (77.57%). Conclusion: Incidence of poly-pharmacy is relatively high, but poly-pharmacy is quite relevant in diabetic patients because diabetes is associated with various concurrent diseases and its complications that also increases cost burden to patient._

Keywords: Diabetes mellitus (DM), Drug utilization pattern, Antidiabetic agents, metformin, Antihypertensive

1. Introduction

Drug utilization studies are powerful exploratory tools to ascertain the role of drugs in society. They create a sound sociomedical and health economic basis for healthcare decision making.[1] Diabetes mellitus (DM) is a chronic disorder emerging as major health problem which increases the rate of morbidity and mortality. It is associated with abnormal carbohydrate, protein and lipid metabolism.[2] Diabetes mellitus is affecting nearly 6% of the world population.[3] With changing life style in developing countries like India, diabetes mellitus has enormously increased the statistical figures. As per World Health Organization, around 31.7 million individuals in India were affected by diabetes during the year 2000 which may further rise to 79.4 million by the year 2030.[4] According to the Chennai Urban Population Study the prevalence of diabetes between the ages of 45 to 60 years was nearly 25%, which was similar to that seen among individuals above the age of 65 years in developing countries.[5] Although the prevalence of type 1 diabetes is also increasing, type 2 diabetes accounts for more than 90% of all the diabetes cases.[6] The management of type-1 diabetes mellitus depends mainly on insulin, whereas the management of type-2 diabetes mellitus is mainly managed using oral hypoglycaemic agents (OHAs).[7] [ ] The chronic complications of diabetes mellitus make it necessary to prescribe drugs for these patients lifelong. Moreover, a good number of diabetes patients suffer from cardiovascular disease such as hypertension, hyperlipidaemia and ischaemic heart disease.[9] This further necessitates polypharmacy in these patients. Therefore, appropriate drug therapy is necessary for diabetic patients to achieve adequate glycaemic control.

2. Methods

The present study was a prospective cross sectional conducted by Dept of Pharmacology in association with Department of Medicine of a tertiary care hospital. The study was performed over a period of 12 months from January 2020 to December 2020 after approval from Institutional Ethics Committee.

1) Protocol Development
An appropriate study protocol and proforma were developed and discussed with teaching staff members of the pharmacology department and head of Medicine department.

2) Selection Criteria of Patients

Inclusion Criteria:
- Patients above 12 years and either sex attending diabetic clinic and   medicine OPD with confirmed diagnosis of diabetes
- Patients referred from other department who are taking antidiabetic drugs.

Exclusion Criteria:
- Indoor diabetic patients
- Diagnosis is yet to confirm
- Paediatric patients (age <12 years)
- If written informed consent is not given by patient.

Sample Size:
WHO recommendation on sample size is that there should be at least 600 encounters in a cross-sectional survey describing current treatment practices. [10]

Collection of Data:
1) Data of patients matching inclusion criteria was recorded.
2) Before including in the study, patients were explained about the aspects of research work. Patient's informed written consent was taken before including him or her into the study. (Appendix II, III, IV)
3) Once the consultation by the physician was over, the prescriptions were copied and patients were interviewed.
4) Data like name, age, sex, weight, height, duration of diabetes, concurrent diseases, and ongoing treatment was recorded from patient's case. These data were recorded in previously predesigned and pretested case record forms. (Appendix V) Total 610cases were collected. The study was carried out for 12 months duration from January 2020 to december 2020.
5) Finally, all the data was compiled and subjected to descriptive statistical analysis.

Data Analysis
Data would be analyzed using general parameters like demographic profile of patient, type of diabetes, Daily Defined Dose for each antidiabetic drug and some of the WHO indicators as mentioned below.
1) Age & Sex distribution
2) Distribution of patients depends on duration of diabetes
3) Concurrent medical illness associated with diabetes
4) Distribution pattern of BMI
Body Mass Index was calculated by dividing the weight of patient in kilogram (kg) by square of height in meter (m). BMI was categorized in National Heart, Lung, and Blood Institute Obesity Education Initiative, 2000.[11]
5) Total number of antidiabetic drugs prescribed per encounter
6) Total number of drugs prescribed per encounter
7) Average number of drugs per encounter
8) Duration of diabetes and total no of drugs prescribed per encounter
9) Commonly used drug groups in study subjects
10) Utilization pattern of different Antidiabetic drugs
11) Percentage of antidiabetic drugs prescribed by generic name
12) Percentage of encounters with an injection prescribed
13) Percentage of drugs prescribed by essential medicine list
14) Average drug cost per encounter
15) ATC[12], Prescribed Daily Dose (PDD)and Defined Daily Dose (DDD)[13] of antidiabetic drugs

3. Results

Out of 610 patients, 324(53.11%) were female and 286 (46.88%) were male.Prevalence was slightly higher in females compared to male. Maximum patients 286 (46.88%) belonged to the age group of 46-60 years followed by 187 (30.65%) in >60 yearsand 107 (17.54%) in 31- 45 years.

Mean age in study subject was 51.74±12.51 years. Out of 610 patients, 115 (18.85%) patients had type I diabetes and 495 (81.14%) had type II diabetes.

Majority of the patients (57.21%) were suffering from concurrent hypertension. Other commonly associated conditions were IHD (9.01%), cataract (1.47%), asthma (0.49%).

In this study, about half of the patients had received one antidiabetic drug (55.40%), followed by two (39.18%), three (28%) antidiabetic drugs and four (0.81%) antidiabetic drugs (**Table 1**). The average number of antidiabetic drugs per encounter was 1.50±0.7 with range of 1 to 4.

Table 1: Number of antidiabetic drugs prescribed per encounter

No. of drugs	Total no. of patients (%)
1	338 (55.40%)
2	239 (39.18%)
3	28 (4.59%)
4	5 (0.81%)
Total	610(100%)

In this study 56.86% patients were receiving 3 or more drugs. (**Table 2**)

Table 2: Number of drugs prescribed per encounter

No. of drugs	No. of patients (%)
1	90 (14.75%)
2	173 (28.36%)
3	128 (20.98%)
4	93 (15.25%)
5	63 (10.32%)
6	26 (4.26%)
7	23 (3.77%)
8	11 (1.80%)
9	1 (0.16%)
10	2 (0.32%)

The average number of antidiabetic drugs per encounter was 1.51 in present study with range of 1 to 4.

Table 3: Average number of antidiabetic drug per encounter

| Total no. of antidiabetic drugs prescribed	Total no. of encounters	Average no. of drugs per encounter ($\pm$ SD)
921	610	1.50±0.7

Among the Antidiabetic drugs, Metformin was the commonest drug prescribed 473(77.54%) followed by H. Mixtard 135(22.13%) glipizide 106 (17.37%), Basalog 84(13.77%), glimipride 32(5.24%) (**Table 4, Figure 1**)

Table 4: Commonly used drug groups in study subjects

Drugs	No. of patients
Antidiabetic drugs	
Metformin (Biguanides)	**473 (77.54%)**
Sulphonylureas	**151 (24.75%)**
Glibenclamide	13 (2.13%)
Glimepiride	32 (5.24%)
Glipizide	106 (17.37%)
Insulin	
Plain insulin	16(2.62%)
H.mixtard	135(22.13%)
Humalog mix	27(4.42%)

Basalog	84(13.77%)
Pioglitazone (Thiazolidinediones)	**0 (0.0%)**
α glucosidase Inhibitors	**20 (3.27%)**
Acarbose	**0 (0.0%)**
Voglibose	20 (3.27%)
Cardiovascular drugs	
Antihypertensive drugs	
ACE inhibitor & ARB	286 (46..88%)
Beta blocker	98 (16.06%)
Calcium channel blocker	80 (13.11%)
Diuretic	33 (5.40%)

Antiplatelet drugs	
Aspirin	79 (12.95%)
Clopidogrel	33 (5.40%)
Hypolipidemic drugs	
Atorvastatins	66 (10.8%)
Others	
Amitryptiline	8(1.31%)
B complex & Folic acid	130 (21.31%)

Figure 1: Commonly used antidiabetic drug groups in study subjects
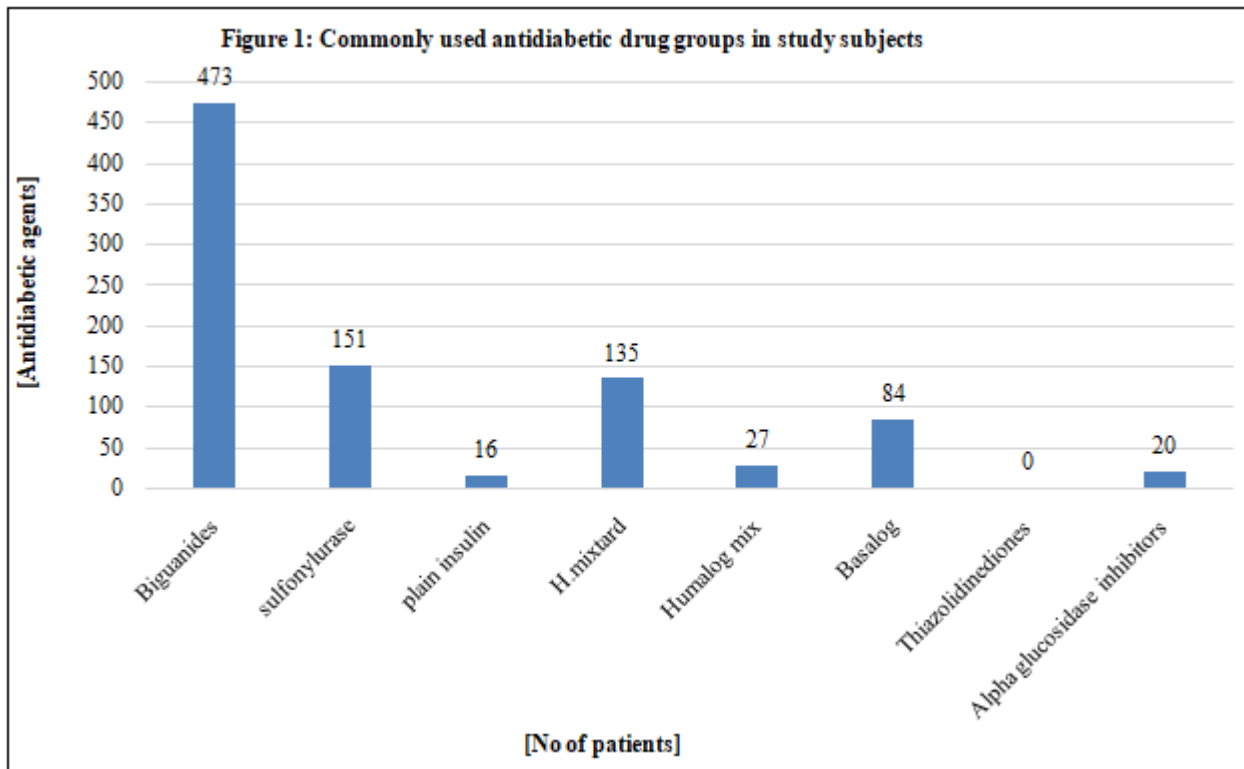
In this study among 610 patients, Antihypertensive drugs were prescribed to 497 (81.47%) of patients. ACE inhibitor & ARB was the most commonly prescribed drug 286 (46.88%) followed by beta blocker 98 (16.06%), CCB 80 (13.11%), diuretic 33 (5.40%). Antiplatelets (aspirin and clopidogrel) were prescribed to 112 (18.35%) of patients. Amitryptiline were prescribed to a small proportion of patients 8 (1.31%). Other drugs prescribed were vitamins- B complex and folic acid 131 (21.31%) and Atorvastatin (10.8%). (**Table 4**)

In present study, 669 drugs were prescribed by generic name and 253 drugs were given by brand name. So,72.63 % drugs were given by generic name and 27.47% were given by brand name. (**Table 5**)

Table 5: Percentage of antidiabetic drugs prescribed by generic name

Drug nomenclature	No of drugs	Percentage (%)
Generic name	669	72.63%
Brand name	253	27.47%
Total	921	100%

In present study at each encounter antidiabetic drugs were prescribed for 30 days. Average cost of antidiabetic drugs per encounter was 229.97₹. The cost was calculated according to minimum price of that drug in CIMS (Current Index Of Medical Specialities) Apr – July 2022. (**Table 6**)

Table 6: Average cost of antidiabetic drugs per encounter

	Total Cost (₹)	Total number of encounters	Average drug cost per encounter (₹)
Antidiabetic drugs	140283.6	610	229.97

In present study prescribed daily dose of Insulin (33.12 IU), Metformin (1.34 gm), Glibenclamide (11.53 mg), Glimepiride (2.34 mg), Glipizide (9.28 mg), voglibose (0.55 gm) was observed. PDD:DDD ratio was ranged between 0.670-1.83 with voglibose having maximum ratio (1.83) followed by Glibenclamide(1.153), Glipizide (0.928),Insulin (0.753), and Metformin (0.670). (**Table 7**)

Table 7: ATC, PDD and DDD of antidiabetic drugs

Drug	ATC code	PDD	DDD	PDD:DDD ratio
Insulin	A10AD30	30.12 IU	40 IU	0.753
Metformin	A10BA02	1.34 gm	2 gm	0.67

Glibenclamide	A10BB01	11.53 mg	10 mg	1.153
Glimepiride	A10BB12	2.34 mg	2 mg	1.17
Glipizide	A10BB07	9.28 mg	10 mg	0.928
voglibose	A10BF01	0.55 gm	0.3 gm	1.83

4. Discussion

Diabetes is a chronic disease requiring lifelong treatment. Although lifestyle modifications play an important role in diabetes management, drugs become unavoidable in many patients. This study analyzed the prescription pattern in diabetic patients attending the diabetic clinic and medicine outpatient department of a tertiary care hospital.

We have collected data of 610 patientsmatching inclusion criteria. Data of patients like age, sex, weight, concurrent diseases, drug utilization pattern and cost of drug treatment were analyzed.

1) Age & Sex distribution
Most common age group involved in our study was 46-60 years (46.88%) followed by >60 years (30.65%) &31-45 years (17.54%). Study by M Ashok Kumaret al also found most common age group 41-60 years (55.63%), followed by 61–80 years (28.87%) and 21-40 years (11.26 %).[14]In general, elderly patients are at greater risk of developing type II diabetes mellitus (DM). This study reported sex distribution of patients as seen in other studies. In our study, 324(53.11%) were female and 286 (46.88%) were male.Study conducted by M Ashok Kumar et alreported 51.4% were females and 48.6% were male.[14] Similar finding also found in study conducted by P Das et al 52.6% were females and 47.4% were males. [15]

In present study, mean age of study subjects were 51.74 ± 12.51 years. Study by Patel KP et alhas found mean age in study subject 56.8 ± 10.5 years. [16]

2) Concurrent diseases
Patients with chronic diseases like diabetes usually suffer from other associated conditions. In present study,Majority of the patients (57.21%) were suffering from concurrent hypertension.Other commonly associated conditions were IHD (9.01%), hypothyroidism (0.65%), and asthma (0.49%). Abdul Gafar et al also reported Hypertension (43.9%) as the most frequent co-morbidity.[17] Such patients are at greater risk of developing complications. Among the various complications, cardiovascular complications pose a major threat. Multiple drugs are required for their management.

3) Total number of drugs prescribed per encounter
In present study, the average number of antidiabetic drugs per encounter was 1.50 ± 0.7 with range of 1 to 4. Study conducted by Kannan et al has reported 1.4 antidiabetic drugs per encounter.[18] Also study by Acharya KG et alin 2012 has reported 2.18 ± 0.96 antidiabetic drugs per encounter. [19]

The observed difference might be because of different demographic profile of study patients, different prescribing practices and availability of drugs. Because diabetes is associated with various concurrent diseases and its complications, polypharmacy is quite prevalent.

The duration of diabetes plays an important role in diabetes management. In patients with longer duration of diabetes, chances of complications are high. So, tight glycaemic control is needed. In present study, more than half of the patients had a diabetic history of 5 or more than 5 years.In this study the mean duration of diabetes is 6.78 ± 4.29 years. A study by Patel KP et al reported the mean duration of diabetes as 8.3 ± 9.4 years.[16] The comparatively lower duration of diabetes in present study may be due to lack of early diagnosis, as many of the so called freshly detected cases are suffering from the disease from long time but are not aware of it.

4) Distribution pattern of BMI
Obesity is a well-recognized risk factor for type 2 diabetes and increase in diabetes incidence is associated with increased risk for morbidity and mortality.[20]Thus, an attempt was made to study the pattern of BMI among diabetic patients in present study. In present study, about 60% patients had BMI more than normal and obese or morbidly obese.

5) Duration of Diabetes and total no. of drugs prescribed per encounter
Diabetes is a progressive disease. As the disease progresses, it is difficult to control the blood sugar and this requires combination of drugs. In this study, the number of drugs prescribed to patients is more for those who had longer duration of diabetes. In this study 56.85% patients were receiving 3 or more drugs.74.26% of patients who had more than 5 years of duration of diabetes have taken 3 or more different drugs as compared to 38.8% of patients who had less than 5 years of duration of diabetes have taken 3 or more drugs.

6) Commonly used drug groups in study subjects.
Among the antidiabetics, Biguanides were the most commonly prescribed drugs followed by insulin. The results comply with study done by Patel KP et al [16] & Gholamreza Yusefzadeh et al.[21] Majority of the drugs were prescribed in oral dosage form. Metformin was the commonest drug prescribed (91.31%) followed by Glibenclaimide (32.79%), Insulin (24.43%), Pioglitazone (14.26%), Glimepiride (10.82%), Glipizide (10.82%). A study by Ashok Kumar et al reported Sulfonylureas as the most common drug class followed by Insulin. [14]This difference can be due to physician's choice with relation to type of patients, their concurrent illness, as well as the availability of medicines.

Also, Antihypertensive drugs were prescribed to 81.47% of patients. ACE inhibitor & ARB was the most commonly prescribed drug (46.88%) followed by Beta blocker (16.06%), CCB (13.11%), Diuretic (5.40%). As per HOPES study, the role of ACE inhibitors in the reduction of cardiovascular associated morbidity and mortality is well established (The Heart Outcomes Prevention Evaluation Study Investigators, 2000).[22]Antiplatelats (Aspirin and Clopidogrel) were prescribed to 18..36% of patients.

7) Combination pattern of different antidiabetics drugs

The present study observed that single drug therapy (55.72%) was more common than multiple drug therapy (44.28%).

In this study, about half of the patients had received antidiabetic single drugs (55.72%), followed by two (39.18%) antidiabetic drugs and three drug (4.59%) regimen In study by Patel KP reported monotherapy (81.58%) as most commonly prescribed pattern followed by two (65.78%) and three drug (7.02%) regimen. [16]

Present study found Metformin + Glipizide (15.40%) was the most commonly prescribed combination of two antidiabetic agents, followed by H.mixtard + Basalog (7.70%). Guidoni CM et al also found Metformin + Glibenclamide (28.06%) was the most commonly prescribed combination of two antidiabetic agents followed by Insulin + Metformin (6.9%).[23] Patel KP et alfound Metformin + Glimepiride (50%) was the most commonly prescribed combination of two antidiabetic agents followed by Metformin + Voglibose (7.02%).[16]

This study found Metformin+ Glipizide + voglibose (1.63%) as most commonly prescribed three drug combinations (8%) followed by Metformin+Basalog+ H.Mixtard (1.14%). Abdulgafar O Et al also found Metformin + Glibenclamide + Pioglitazone (10.6%) as most commonly prescribed three drug combinations followed by Insulin + Metformin + Glibenclamide (5.2%).[17] Patel KP et al found Metformin + Glimepiride + Pioglitazone (7.02%) as most commonly prescribed three drug combinations.[16] Findings of present study is in accordance with algorithm. [24]

8) Average drug cost per encounter
In present study at each encounter antidiabetic drugs were prescribed for 30 days. Average cost of antidiabetic drugs per encounter was 229.97₹. The cost was calculated according to minimum price of that drug in CIMS (Current Index Of Medical Specialities) Apr – July 2020. (**Table 6**) Study by Acharya KG et al found mean cost for antidiabetic drugs was 354.60 INR. [55] The higher cost in these studies is due to more drugs were prescribed by brand name as compared to generic name. Cost of prescription is important in chronic disease like diabetes. One of the better approaches to decrease the prescription cost is to prescribe cheaper brands. Since diabetes is a long term disease and drug has to be continued for life time, there is a reasonable scope in reducing the prescription cost by prescribing cheaper alternatives.

9) Prescribed Daily Dose (PDD)and Defined Daily Dose (DDD)[36] [intro DUS] of antidiabetic drugs
In present study prescribed daily dose of Insulin (30.12 IU), Metformin (1.34 gm), Glibenclamide (11.53 mg), Glimepiride (2.34 mg), Glipizide (9.28 mg), and voglibose (0.55 gm) was observed. PDD: DDD ratio was ranged between 0.670-1.83 with voglibose having maximum ratio (1.83) followed by Glimepride (1.170), Glibenclamide (1.153), Glipizide (0.928), Insulin (0.753), Metformin (0.670). Present study result concluded that PDD: DDD While ratio of voglibose (1.82) suggest overutilization of this antidiabetic drug. Predicting that the PDD:DDD ratio depends on patient related factors-irrespective of indication

or severity of the disease or sociodemographic factors like age or gender-the ratio should not change with a change of the drug. However, factors such as the severity of the hypertension or the doctor's dissatisfaction with the efficacy of a drug may lead to a change of drugs or change of dose-seem to be responsible for alteration of PDD: DDD ratio.

5. Limitations

Present study had a few limitations:
1) The cost of treatment taken in account was only drugs price but not the other factors like cost of travelling, cost in treating the complications, economic cost due to loss of days etc. So future studies on pharmacoeconomics can be done by taking in account all these factors.
2) Present study was cross sectional study with short duration. Hence, longitudinal studies of longer duration are needed to confirm our findings.

6. Conclusion

Studies on utilization pattern of antidiabetic drugs appear to be less in this part of the country. Thus, this study provided a baseline data regarding the prescribing pattern in diabetic patients that showed overall prescribing pattern of ADA is rational. Since diabetes is a common lifelong disorder, prescription cost is one of the major reasons for non-adherence to drug therapy. There is a need to prescribe cheaper alternatives for these types of patients for good glycemic control. This study has provided a scope for further research in this area.

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