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Original Research Article

The observational, cross-sectional study of drug utilization 90% and use of dipeptidyl peptidase-4 inhibitor in the patients with type 2 diabetes mellitus

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ABSTRACT

Background: Diabetes is a chronic metabolic disease which affects the quality of life. It leads to multiple complications due to metabolic involvement. Out of multiple drugs used to treat diabetes, dipeptidyl peptidase 4 (DPP-4) inhibitors are comparatively new drugs used for type-2-diabetes mellitus (DM) treatment. This study aimed to find out the drug utilization (DU) 90% and use of DPP-4 inhibitors in patients with type-2-DM.

Methods: A prospective, cross-sectional, observational study was conducted at a private healthcare clinic of an endocrinologist in Nashik. Type-2-DM patients of both sexes were selected and a total of 199 patients were enrolled in the study. The consented patients were interviewed and prescription copies were collected. After studying them; statistical analysis was done and results and conclusions were drawn.

Results: Out of total prescribed drugs, 58.77% of drugs were anti-diabetics. It was observed that the biguanides were most frequently (25.32%) prescribed while the least prescribed drugs were meglitinide analogues (0.08%). Most commonly utilized anti-diabetic found to be metformin. Vildagliptin 50 mg is the most commonly prescribed drug from DPP-4 inhibitors. Most of the drugs from the DPP-4 inhibitor group came under DU90%.

Conclusions: DPP-4 inhibitors are showing wide acceptability by endocrinologists for type-2-DM management, according to this study. Performing repetitive drug utilization pattern study and circulation of standard treatment guidelines to practising physicians can be required. To emphasize the point on generic prescription, more awareness should be created. So that these can responses to further cost-effective and rational prescribing practices.

Keywords: Diabetes, DPP-4 inhibitors, Drug utilization study, Daily defined dose, DU 90%

INTRODUCTION

The irrational use of drugs is a major problem of a present-day medical practice and its consequences include ineffective treatment, unnecessary prescription of drugs, development of resistance to antibiotics, adverse effects and economic burden on patients and society. In spite of extensive programs on the rational use of drugs and the essential drug list (EDL) of World Health Organization (WHO), which are being promoted by various national and international agencies working on the health sector, an irrational prescription is still a common practice. There is a need for mass awareness amongst physicians and consumers about the concept of essential medicines, advantages of generic drug prescription and use of rational combinations.[1] Drug utilization (DU) research was defined by WHO in 1997 as "The marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social, and economic consequences".[2]

DU 90% segment reflects the number of drugs that account for 90% of drug prescriptions and adherence to the local or national prescription guidelines to obtain a

rough estimate of the quality of prescribing. DU 90% calculated for the description of the drug use patterns. The rationale behind the development of DU 90% rest on an assumption that a low number of products prescribed is associated with the more rational prescribing practice. DU 90% study provides a basis for areas needs to be analysed in detail for assessing the quality of prescribing.[2]

Diabetes is a chronic metabolic disease which affects the quality of life. It leads to multiple complications due to metabolic involvement. Diabetes has become one of the major cause of death. Out of two forms of diabetes, one is the 'non-insulin dependent diabetes mellitus' i.e. type-2-diabetes mellitus (DM). Oral hypoglycaemic agents i.e. anti-diabetic drugs acting through different pharmacological pathway are majorly used in the management of type-2-DM. This study involves a drug utilization analysis for them.

Sulfonylurea, biaguanides, meglitinide derivatives, thiazolidinedione, dipeptidyl peptidase 4 (DPP-4) inhibitors, and alpha-glucosidase inhibitors, etc. are the group of drugs used to treat type-2-DM as said above. Out of which DPP-4 inhibitors are comparatively new drugs.[3,4] DPP-4 is an enzyme which is accountable for degradation of incretins like glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Food intake responses to glucose release which leads to the secretion of the incretins. These incretins stimulate the pancreas and more insulin will be secreted. So, it leads to blood sugar level control.[5]

Possibility of sudden hypoglycaemia is low with DPP-4 inhibitors. In one way they are safer in developing hypoglycaemia because their effect starts after incretins secretion in response to a rise in blood glucose. DPP-4 inhibitor is one of the important and comparatively new in type-2-DM management. It was also noted in many multicentre studies that they are safe and effective in a real-world population.[6,7] This research aims to study DU 90% and drug use pattern in type-2-DM patients with specific reference to the role of DPP-4 inhibitors. This will be helpful to formulate the role of DPP-4 inhibitors in type-2-DM management and promote rational use by calculating DU90%.

METHODS

A prospective, cross-sectional, observational study was conducted at the outpatient department (OPD) of Dr. Buva's Hormocare Clinic (the private healthcare clinic of an endocrinologist) in Nashik from December 2017 to February 2018, after approval from the local ethics committee and permission at the study site. The study was conducted in compliance with ICH-GCP guidelines, schedule Y, WHO guidelines and Indian Council of Medical Research (ICMR) guidelines. Considering the prevalence rate of 15% for type-2-DM, the total sample

size calculated was 196. The convenient sampling technique was used in this study.

The patient enrolment was done as per the inclusion and exclusion criteria. Patients of 18 years old and above of either sex with type-2-DM who received anti-diabetic medicine at the OPD were selected. Patients in the inpatient department (IPD), patients those who were unable to comply due to mental retardation and those who were not willing to give informed consent were excluded. Before enrolment signed, dated and written informed consent was taken from the patients after providing information about the study with proper explanation. Thereafter the patients were interviewed and prescription copies were collected. These prescriptions were studied; defined daily dose (DDD)% and DU90% were calculated. After statistical analysis; results and conclusions were drawn.

Data analysis

The Statistical Package for Social Sciences (IBM SPSS Statistics for window, NY: IBM Corp.) and Microsoft Excel 2010 were used for the analysis of data. Drug utilization parameters were analyzed as follows;

- DDD/1000/day = [Total no. of dosage units prescribed ×Strength of each dose unit ×1000]/ [DDD (ATC) × Duration of study in weeks ×Total sample size]
- DDD% = [DDD/1000/day of particular drug x 100]/ [Sum of DDD/1000/day total drugs]
- DU 90% was calculated by addition of DDD percentages of the drugs involved.

Descriptive statistics such as percentages were also measured. Tabulation, graph, and diagrams were used to present the data.

RESULTS

According to the statistical calculation of sample size, a minimum of 196 patients of type-2-DM could be taken. In the pre-screening, the number of potentially eligible patients were 233 whereas the number of confirmed eligible patients included in the study was 199. Out of which 104 (52.26%) were male while 95 (47.74%) were female. Out of total prescribed drugs, 58.77% were anti-diabetic drugs. Some of the other demographic parameters and the prescription indices are mentioned in Table 1 and Table 2.

From all the anti-diabetic group of drugs, Biguanides were highly prescribed (25.32%). DPP-4 inhibitor was the third highly prescribed anti-diabetic group of drugs followed by sulfonylureas (12.78%) and then DPP-4 inhibitors (9.78%). The least prescribed drugs were from the meglitinide analogues group (0.08%) (Figure 2).

Table 1: Details of demographic parameters.

Demographic profile	No. of patients
Total sample size	199
Male	104
Female	95
Patients with type 2 DM only	111
Patients with type 2 DM and cardiovascular diseases	45
Patients with type 2 DM and thyroid disorders	28
Patients with type 2 DM, cardiovascular diseases and thyroid disorders	15

Table 2: Details of prescription indices.

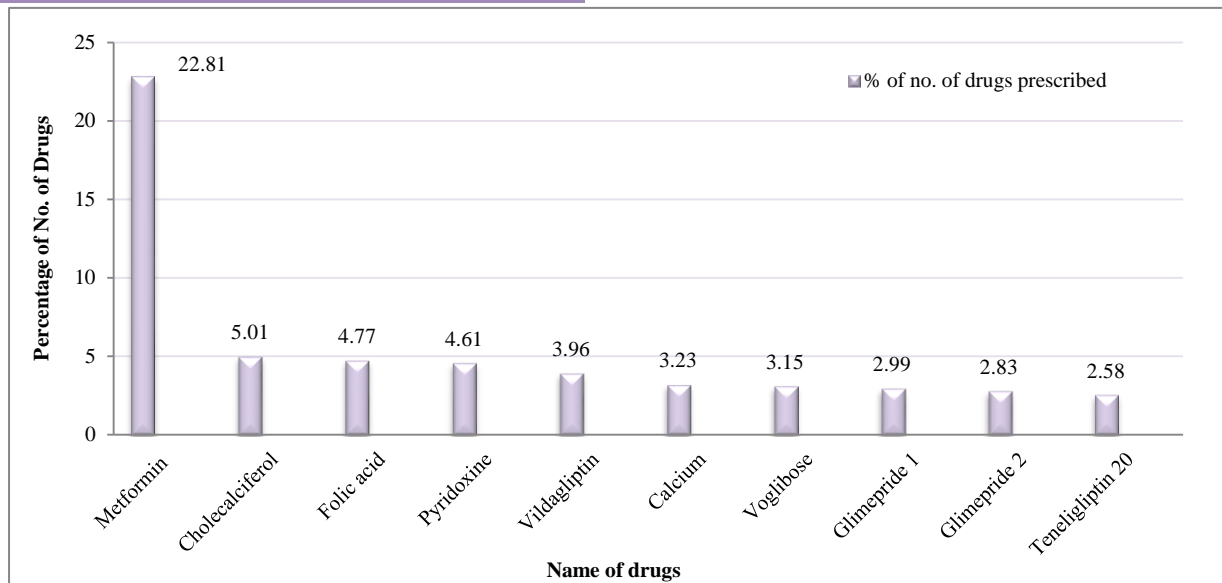| Prescription indices	No. of drugs
Total number of drugs prescribed	93
Drugs prescribed for type-2-DM	54
Drugs prescribed for co-morbid conditions	39
Total number of dosages prescribed	1236
Number of dosages per prescription (average)	6.21
Total number of combinations prescribed	814 (average 4.09)

Figure 1: Percentage distribution of top 10 prescribed drugs in type-2-DM.
All coloured bars indicate the percentage number of drugs prescribed. X-axis: Name of drugs; Y-axis: Percentage number of drugs.
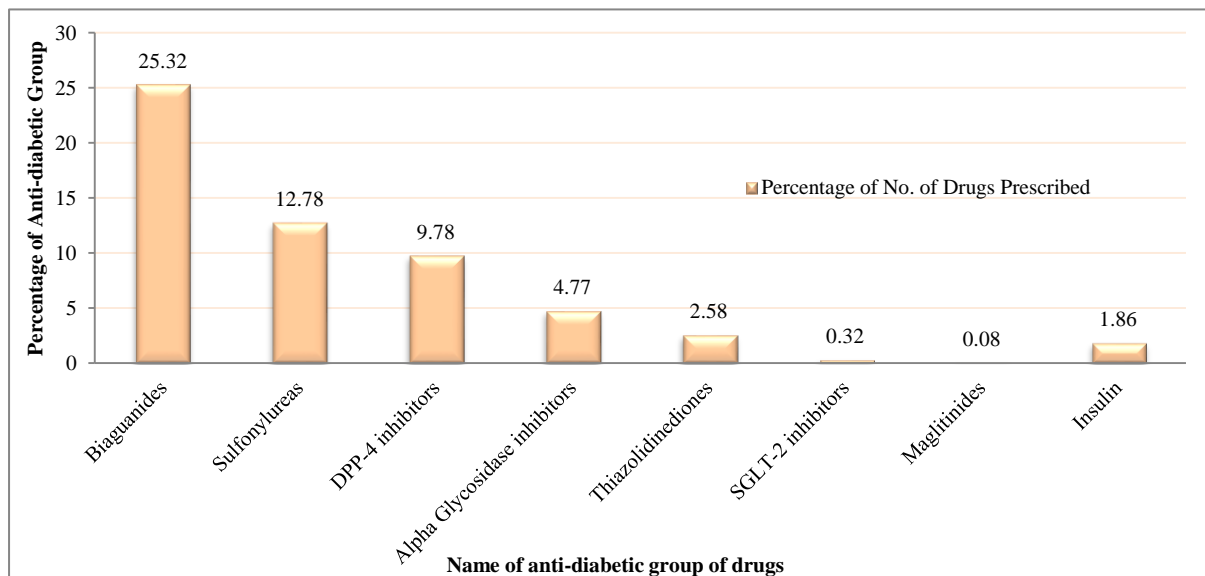

Figure 2: Percentage distribution of groups of anti-diabetic drugs.
All coloured bars indicate the Percentage of a group of antidiabetic drugs prescribed. X-axis: Name of an anti-diabetic group of drugs; Y-axis: Percentage of anti-diabetic group.
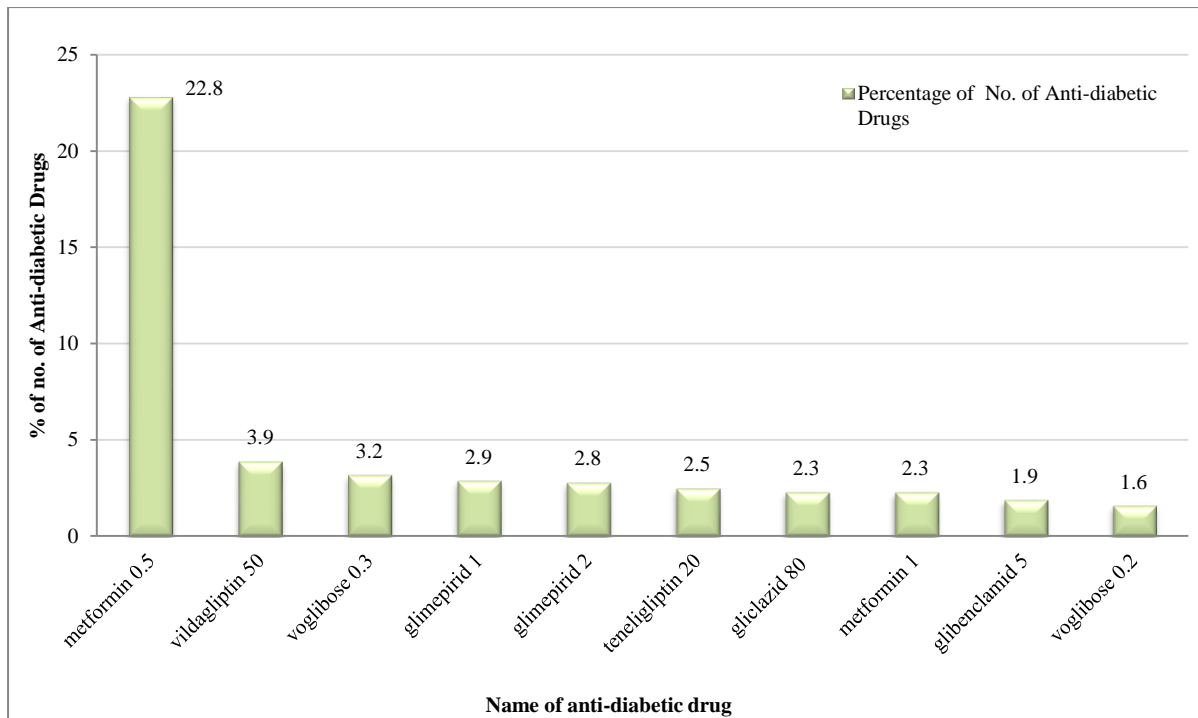
Figure 3: Percentage distribution of top 10 prescribed anti-diabetic drugs.

All coloured bars indicate the percentage of top 10 anti-diabetic drugs prescribed. X-axis: Name of anti-diabetic drug; Y-axis: Percentage of anti-diabetic drugs.
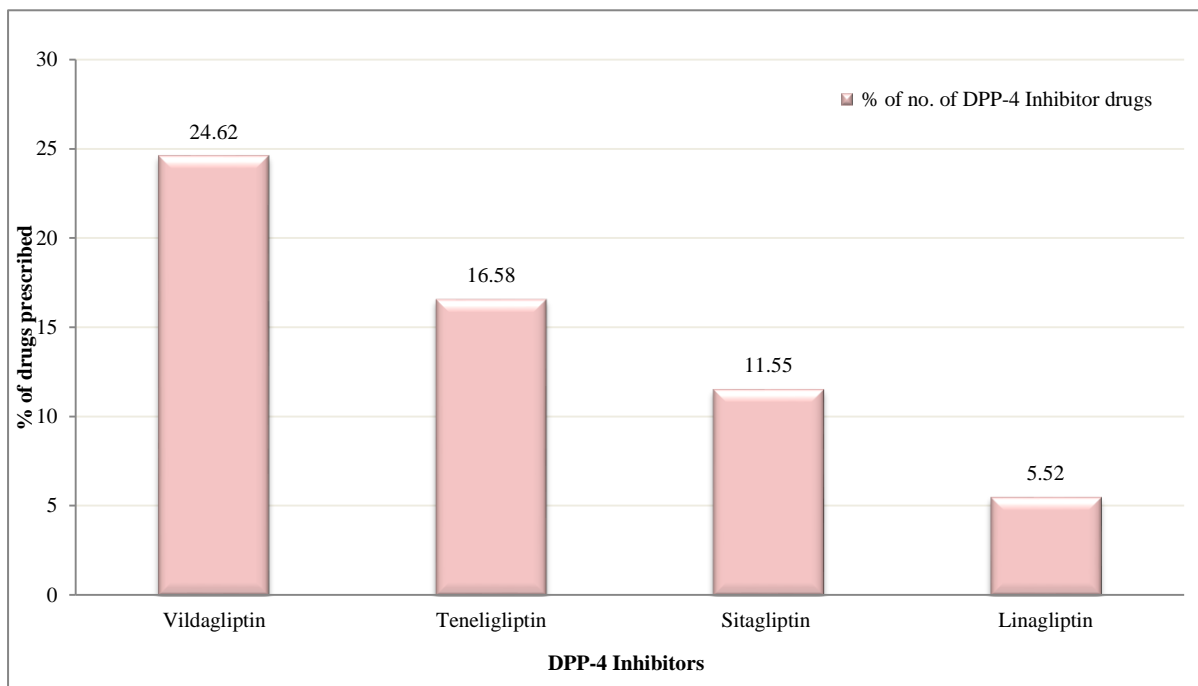

Figure 4: Percentage distribution of different DPP-4 inhibitors prescribed in type-2-DM.

All coloured bars indicate the percentage of different DPP-4 Inhibitor drugs prescribed. X-axis: DPP-4 Inhibitors; Y-axis: Percentage of drugs prescribed.

Metformin 0.5 (22.8%) was highly prescribed the oral hypoglycaemic drug. Vildagliptin 50 (3.9) was the second most prescribed while teneligliptin 20 (2.5) was the sixth most prescribed anti-diabetics from DPP-4 inhibitors class (Figure 3).

'Vildagliptin 50' was the most prescribed DPP-4 inhibitor drug. (24.62%) vildagliptin was prescribed to 49 patients amongst all while teneligliptin, sitagliptin, and linagliptin were prescribed to 33, 23 and 11 patients respectively (Figure 4).

Table 3: Details of drug utilization parameters and DU90% for drugs used in type-2-DM management.

Sr.no.	Drug	ATC Code	Total no. of dosage units prescribed	DDD/1000/Day	DDD%
1	Cholecalciferol 1000	A11CC05	62	48.68090452	9.785241383
2	Metformin 0.5	A10BA02	282	44.2839196	8.901413129
3	Insulin human	A10AB01	8	30.65326633	6.161545542
4	Calcium	A12AA20	40	25.12562814	5.050447165
5	Gliclazid 80	A10BB09	29	24.2881072	4.882098926
6	Glimepirid 2	A10BB12	35	21.98492462	4.41914127
7	Cholecalciferol 2000	A11CC05	13	20.41457286	4.103488322
8	Rabeprazole	A02BC04	16	20.10050251	4.040357732
9	Tenegliptin 20	NA	32	20.10050251	4.040357732
10	Talmisartan 40	C09CA07	26	16.33165829	3.282790657
11	Vildagliptin 50	A10BH02	49	15.38944724	3.093398889
12	Voglibose 0.3	A10BF03	39	12.24874372	2.462092993
13	Glimepirid 1	A10BB12	37	11.62060302	2.335831814
14	Insulin mixtard	A10AE56	6	9.422110553	1.893917687
15	Metformin 1	A10BA02	28	8.793969849	1.767656508
16	Amlodipin 5	C08CA01	13	8.165829146	1.641395329
17	Domperidome	A03FA03	13	8.165829146	1.641395329
18	Insulin lispro	A10AB04	5	7.851758794	1.578264739
19	Glibenclamid 5	A10BB01	24	7.537688442	1.51513415
20	L methyl folate	B03BB51	12	7.537688442	1.51513415
21	Mecobalamin	B03BA05	12	7.537688442	1.51513415
22	Atorvastatin 10	C10AA05	21	6.595477387	1.325742381
23	Sitagliptin 50	A10BH01	20	6.281407035	1.262611791
24	Rosuvastatin 10	C10AA07	9	5.653266332	1.136350612
25	Pyridoxin	A11HA02	57	5.594378141	1.124513627
26	Folic acid	B03BB01	59	5.559045226	1.117411435
27	Insulin glargine	A10AE04	4	5.464824121	1.098472258
28	Pioglitazon 15	A10BG03	16	5.025125628	1.010089433
29	Voglibose 0.2	A10BF03	20	4.18760469	0.841741194
30	Cilinidipin 10	C08CA14	6	3.768844221	0.757567075
31	Gliclazid 40	A10BB09	9	3.768844221	0.757567075
32	Empagliflozin	A10BK03	4	3.589375449	0.721492452
33	Linagliptin 2.5	A10BH05	11	3.454773869	0.694436485
34	Linagliptin 5	A10BH05	5	3.140703518	0.631305896
35	Nabivolol 5	C07AB12	5	3.140703518	0.631305896
36	Glimepirid 3	A10BB12	3	2.826633166	0.568175306
37	Rosuvastatin 5	C10AA07	9	2.826633166	0.568175306
38	Atorvastatin 80	C10AA05	1	2.512562814	0.505044717
					(DU 90%) 90.37824054

ATC code: Anatomical therapeutic chemical code.

Not a single drug was prescribed by generic name; all the drugs were prescribed by brand name only. 20.43% of drugs were prescribed from the essential drug list (EDL). Total 93 drugs were studied in drug utilization study for type-2-DM management. DDD/1000/day and DDD% were calculated for all these drugs. We achieved DU90% with 38 drugs out of them (Table 3). Vildagliptin, tenegliptin, sitagliptin, and linagliptin are the DPP-4 inhibitor drugs and all of them with certain doses were the part of DU90% as mentioned in Table 3. Sitagliptin 100

mg and tenegliptin 10 mg were least prescribed and did not come under the DU 90% of type-2-diabetes.

DISCUSSION

Rational drug utilization and efficient drug control system are demanded everywhere in health system without exception to any rule. ATC/DDD is the international standards classification system. Along with the ATC/DDD methodology introduction, it is important that

its proper use, awareness with timely exploitations inevitably includes an essential step.[2] With this realization and based on available resources; a small scale, basic observational study was conducted on 199 type-2-DM patients. In the pre-screening, the high number of patients (233) was potentially eligible but the reason for non-participation for some of the patients was no willingness to share the prescription, not willing to sign the ICD & not having much time for conversation.

The drugs like dutasteride and iron ascorbate are neither having DDD and nor having ATC code. They are prescribed to only one patient each and are not included in DDD calculations. DPP-4 inhibitor like teneligliptin 20, which is very new and isn't allotted ATC code and DDD, it is prescribed frequently and is included in analysis. For such frequently prescribed drugs, the DDD should be taken.[8]

After metformin the second most commonly prescribed drug was cholecalciferol i.e. of vitamin D. There is a hypothesis to suggest an association of vitamin D deficiency and diabetes. The destruction of beta cells in the endocrine pancreas is associated with a high level of circulating immune markers, vitamin D act as important immunosuppressive drug hence may take better care of beta cells.[9] Secondly, vitamin D is related to calcium absorption. In the deficiency of vitamin D, low levels of calcium are observed. Calcium is very important ion for the release of insulin from the beta cell of the pancreas. There are many independent studies to suggest the role of vitamin D in diabetes. The role is related to good glycaemic control and to reduce insulin resistance. On the other hand, many isolated studies are contradictory to this finding. This hypothesis should be rejected as a meta-analysis of the clinical trial-related to vitamin D and diabetes clearly state that there is insufficient evidence to support the hypothesis. Clinical usefulness of vitamin D in terms of glycaemic control or insulin resistance is questioned.[10]

Amongst anti-diabetic drugs, biguanides thereafter sulfonylurea and DPP-4 inhibitors are highly prescribed drugs. It shows a close similarity of already published data related to the treatment of diabetes, especially in type-2-DM.[11] Vildagliptin 50 mg a DDP-4 inhibitor is comparatively more prescribed than the Glimepiride 1mg which is from sulfonylurea group. Clinical trials and some systematic review and meta-analysis also suggest the benefit of use of this drug from the new group in diabetes management with low adverse drug reaction profile.[12,13] Here it is important to note that vildagliptin in short-acting hence in many patients were prescribed twice whereas linagliptin is long-acting, the once-daily dose is sufficient. Acceptability of DPP-4 inhibitors is very good with very small adverse drug reaction profile.[14] Teneligliptin is also found to be safe and effective in a large study known as TREAT-INDIA study.[15]

Folic acid and pyridoxine are also prescribed in good amount, this is related to the prevention and treatment of diabetic neuropathy which is common complication observed in diabetic patients.[16] It was noted that patients receiving only anti-diabetics were 57.77%, co-prescription of antidiabetics with cardiovascular drugs were noted in 22.6% cases. This co-morbidity of diabetes with cardiovascular diseases is well established and reported by many.[17] Also from the prescribing indices, fewer drugs from essential drug list and less generic prescriptions were observed in many drug use pattern study.[18]

Limitations

This study included patients from the single site only; that was the private healthcare clinic of an endocrinologist. So, available patients of type-2-DM having comorbidity conditions of cardiovascular diseases and thyroid disorders only. The results generalization to larger or certain kind of population may not much justify.

CONCLUSION

DPP-4 Inhibitors are the part of drug utilization DU90% in type-2-DM. This study suggests DPP-4 Inhibitors are having wide acceptability by endocrinologists for type-2-DM management. The study concludes that a large number of drugs is in the DU90% segment with less prescribed drugs from EDL and lack of generic prescriptions. Therefore performing repetitive drug utilization pattern study and circulation of standard treatment guidelines to practising physicians can be required. To emphasize the point on generic prescription, more awareness should be created. So that these can responses to further cost-effective and rational prescribing practices.

ACKNOWLEDGEMENTS

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