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Original Research Article

Drug Utilization pattern of Antidiabetic Drug at Tertiary Care Teaching Hospital

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Abstract: *Background:* Diabetes is an opportunistic killer. Approximately 77 million people in India suffer from diabetes. A person develops diabetes due to genetic predisposition, family history, obesity, lack of physical activity, diet low in fruits and vegetables. Modification of life style and pharmacotherapy of diabetes are often indicated to control diabetes and emergence of complications. Therefore, the present study was undertaken to evaluate the prescription pattern of anti diabetic drugs among indoor patient with adherence to WHO core prescribing indicator. *Material and Method:* This was a prospective observational study. All the relevant data were collected and drug utilization pattern of AHA was determined. Direct cost associated with the use of ant hyperglycemic medicines was calculated and consumption of the ant hyperglycemic medicines was measured as defined daily dose (DDD)/100 bed-days. The adverse drug reactions (ADRs) related to anti-diabetic medicines was monitored. *Results:* In the present study, 99 (50.3%) of the 197 diabetic patients were males. Majority of patients were in the age group of 51-60 years (39.6%) and most of the patients (36.5%) had a diabetic history of <5 years. Metformin was the most commonly prescribed drug (68%), followed by sulfonylurea class of drugs (49.7%). Nearly, 42% patients were using insulin preparations with 30.4% using biphasic isophane human insulin. Majority of the patients (58.4%) were on multidrug therapy with two drug therapies being received by nearly 40%. Metformin was the most commonly prescribed drug in monotherapy (18.8%) and glimepiride + metformin was the most common two drug therapy (13.2%). Co-morbid condition was found in 172 patients (87.3%) with hypertension (68.5%) being the most common co-morbid condition. 17 ADRs were observed with hypoglycemia being the most common ADR reported. *Conclusion:* To conclude, the study reveals that Metformin continues to be the choice of oral hypoglycemic agents with least adverse effects and insulin was used to treat uncontrolled state, where physicians have greatly considered the socio-economic status while prescribing which is obvious with least use of costly insulin preparations.
Keywords: Drug Utilization pattern, Antidiabetic Drug, Metformin.

INTRODUCTION

The term diabetes mellitus is described as metabolic cum vascular syndrome of multiple etiology, characterized by chronic hyperglycemia with disturbances of carbohydrate, lipid and protein metabolism, resulting from defects in insulin secretion, action or both leading to changes in both small blood vessels (microangiopathy) and large blood vessels (macroangiopathy; 1). [1]

According to the 9th edition of the International Diabetes Federation (IDF) atlas 2019, there are about 463 million adults, of which one third is people older than 65 years of age, estimated to have diabetes globally. India ranks 2nd with 77 million people with diabetes, while China leads the chart with 116.4 million people diabetes population. [2]

The reasons for the explosive increase in the prevalence of diabetes in India have been the subject of much study. While a high level of genetic predisposition does play a role, it is unlikely that the genetic makeup of the population has changed so drastically in the past 30 years as to account for the alarming increase in the prevalence of diabetes. More likely, increasing prosperity and urbanization have led to wholesale changes in lifestyle which causes diabetes to manifest in individuals who already have a genetic predisposition to the disease [3,4].

Risk factors for diabetes mellitus are overweight, obesity, sedentary life habits, hypertension, low levels of high density lipoprotein (HDL-C) cholesterol, elevated triglycerides (insulin resistance), smoking and dietary indiscretion. Lifestyle changes are aimed to achieve and maintain normal body weight. It can be achieved by physical exercise for 30-40 minutes and dietary regulation which includes reduction in fat intake, increased fruit & vegetable consumption [5].

The management of diabetes is complex often requiring poly pharmacy. The existence of other co morbidities further increases the economic burden on patients. This often leads to non-adherence to ant diabetic therapy by most of the patients which further leads to various complications. Drug utilization studies provide information about the existing prescribing practice among the physicians and economic impact of the therapy in terms of cost of medications and loss of work and wages.

The objective of this study was to evaluate the prescribing pattern of ant diabetic drugs in indoor diabetic patients and adherence to WHO core prescribing indicators.

METHODS
This was a prospective observational study conducted for a period of 150 days after approval by Institutional Ethics Committee of Tertiary care teaching Hospital. Informed consent was obtained from all the patients before conducting the study.

Inclusion Criteria
Newly diagnosed and known cases of DM with other co morbidities that were receiving ant hyperglycemic medicines and admitted as inpatients were included. Inpatients of either sex or age group of 18 years and above were included.

Exclusion Criteria
Patients with gestational diabetes were excluded from the study.

Assessment of Cost of Therapy
Total cost per patient for ant diabetic medicine was calculated. The results were expressed as mean ± standard deviation.

Measurement of Drugs Consumption in Medicine Wards in DDD/100 Bed-days
Drug consumption in medicine wards were measured in DDD/100 bed days. The medicines were classified according to the Anatomical Therapeutic Chemical (ATC) classification system. As per ATC classification system, the medicines are divided into different groups according to the organ or system on which they act and as per their chemical, pharmacological and therapeutic properties. [4] The DDD/100 bed-days were calculated using the following formula:

$$DDD/100 \text{ bed-days} = \frac{\text{Drug consumption in study period (mg)} \times 100}{DDD\,(mg) \times \text{period of study} \times \text{bed strength} \times \text{average occupancy}}$$

The average occupancy was calculated by dividing the number of occupied beds by the total number of beds in the medicine wards.

ADR Monitoring
The ADRs related to ant diabetic medicines were monitored and documented in suitably designed ADR documentation form after initial notification of the suspected ADR by physicians. Additional details were collected by review of the patient case records and interview with patients. Severity and causality of the ADRs were assessed by using Modified Hartwig and Seigel [5] scale and Naranjo's Algorithm, [6] respectively. The Modified Hartwig and Siegel scale grades ADRs as Mild (Level 1 and Level 2), Moderate (Level 3, Level 4 (a) and Level 4(b)) and Severe (Level 5, Level 6 and Level 7). Naranjo's Algorithm scale grades causality of ADRs as Definite, Probable, Possible and Unlikely.

Statistical Analysis
To evaluate the pattern of drugs used in this study, data were subjected to Chi square test ($\chi2$) and percentage value. The level of significance (*P* value) was set at 0.05. Patient's demographic data were presented as mean ± standard deviation (SD). The data were analyzed using SPSS version 12.0 and Microsoft excel.

RESULT
Diabetes mellitus is a chronic lifelong disease affecting a large spectrum of population in the developing countries including India. In the initial stages, single oral agents can be used to control the glucose level, but in later stages combination therapy may be needed for better glycemic control and prevention of micro and macro vascular complications. Hence, the present study aimed to evaluate the prescription trend of anti-diabetic drugs in diabetic outpatients.

A total of 240 diabetic patients were evaluated during the study period. In the present study, neither male nor female preponderance was seen (males 50.3%; females 49.7%) (Table1).

Table 1: Gender wise distribution of patients

Gender	Number of patients	Percentage
Male	120	50.3
Female	120	49.7

Table 2: Age wise distribution of patients

Age (years)	Number of patients	Percentage
18-30	5	2.0
31-40	9	3.6
41-50	36	15.2
51-60	95	39.6
61-70	76	31.5
71-80	19	8.1

Majority of our patients were in the age group of 51-60 years (39.6%). The mean age of the patients in the present study was 57.6 years (age range: 18-79 years) the age distribution of patients is presented in Table 2.

In the present study, 230 patients had Type 2 diabetes mellitus, whereas three patients suffered from Type 1 diabetes mellitus. Among the Type 2 diabetic patients, 120 patients had a family history of diabetes, 78 patients had no family history while the details for 32 patients was not available. Among the three Type 1 diabetic patients, two had a positive family history.

Duration of diabetes has a significant role in its management. Patients who have diabetes for <5 years could usually be managed with single drug therapy while combination therapy is required in patients having diabetes for more than this period. In the present study, most of the patients (36.5%) had a diabetic history of <5 years.

Co-morbidity has been shown to intensify health care utilization and to increase medical care costs for patients with diabetes. In the present study, co-morbid condition was found in 210 patients (87.3%). 54 patients (22.3%) were suffering from a single co-morbid condition, and 156 (65%) were suffering from more than one co-morbid condition.

Majority of the patients (30.4%) were suffering from two co-morbid conditions. Twenty-five patients had no other diseases apart from diabetes. Hypertension (68.5%) was the most common co-morbid condition, followed by dyslipidemia (39.6%). The combination of hypertension and diabetes is clinically important since it magnifies the risk of diabetic complications. Diabetic neuropathy, nephropathy, and retinopathy were found in 41 patients (17.2%), 23 patients (9.6%) and 18 patients (7.6%), respectively. Diabetic foot complication was present in only one patient.

As diabetes progresses, functional decline in beta cells is usually apparent, and the need for combination therapy is unavoidable. Therefore, combination modalities have become an integral part of diabetes management. The basic rationale for combination therapy is to provide additive effects with different mechanisms of action and to allow lower doses for disease management. Consistent with the same, in the present study, majority (58.4%) of the patients were on combination therapy with two drug therapies being received by nearly 40% patients.

Table 3: Drug utilization pattern of anti-diabetic drugs

Class	Drug	Number of Patients (%)
Biguanides	Metformin	163 (68.0)
Sulfonylureas	Glimepiride	78 (32.5)
	Glibenclamide	22 (9.1)
	Glipizide	15 (6.1)
	Gliclazide	5 (2.0)
	Total	119 (49.7)
Insulin	Insulin	101 (42.1)
α-glucosidase inhibitors	Voglibose	18 (56)
	Acarbose	10 (4.1)
	Total	23 (9.6)
DPP-4 inhibitors	Sitagliptin	9 (3.6)
	Vildagliptin	6 (2.5)
	Linagliptin	1 (0.5)
	Total	16 (6.6)

Thiazolidinediones	Pioglitazone	10 (4.1)
	Rosiglitazone	1 (0.5)
	Total	11 (4.6)
Glucagon like peptide 1 agonist	Exenatide	1 (0.5)

DDP-4: Dipeptidyl peptidase-4

Unlike sulfonylureas, thiazolidinediones, and insulin, metformin is weight neutral, which makes it an attractive choice for obese patients. Furthermore, the management of Type 2 diabetes can be complicated by hypoglycemia, which can seriously limit the pursuit of glycemic control. Here, too, metformin has advantages over insulin and some types of insulin secretagogues; by decreasing excess hepatic gluconeogenesis without raising insulin levels, it rarely leads to significant hypoglycemia when used as a monotherapy. As a result, metformin is widely considered an ideal first-line agent for the treatment of Type 2 diabetes. In addition, the cost of metformin is very low, thus making it affordable by the patients in economically weak countries like India. Our study also supported the same conclusion; 68% of patients studied received metformin alone and/or in combination followed by sulfonylureas (49.7%). Among the sulfonylureas, glimepiride was the most frequently prescribed (32.5%) followed by glibenclamide (9.1%) (Table 3).

Eighty of the 230 Type 2 diabetic patients were on insulin therapy. Among these, nearly 50% had a diabetic history of more than 10 years and the majority of the patients were above the age of 50 years. Among the 101 patients on insulin treatment, 79 patients were using only one insulin formulation while the remaining were using two insulin formulations. Majority of the patients (30.4%) were using biphasic isophane human insulin followed by human neutral soluble insulin (8.1%), insulin glargine and isophane human insulin (4.6% each).

In the present study, the most commonly used anti-diabetic medications in monotherapy were metformin (18.8%) followed by insulin (14.2%), glimepiride (3.6%) and glibenclamide (2.5%). Among two drug combination therapy, glimepiride + metformin (13.2%) was the most commonly prescribed followed by metformin + insulin (12.2%). However, the most prescribed three drug combination was insulin + glimepiride + metformin (8.3%) which is consistent with our results. Four and five drug combination therapy was received by 4.6% and 0.5% patients, respectively. Sulfonylureas and metformin were part of majority of the four and five drug combinations. Two patients were not on anti-diabetic drugs.

Table 4: ADRs

ADR	Number of patients	Percentage
Hypoglycemia	10	4.1
Nausea	4	1.5
Gastric irritation	4	1.5
Diarrhea	2	1.0
Abdominal discomfort	1	0.5

17 ADRs were reported during the study (Table 4). Hypoglycemia was the most common ADR observed in eight patients (moderate intensity in seven patients and mild in one patient). Seven hypoglycemic episodes were probably related to the study medication.

DISCUSSION

India is the diabetes capital of the world with 41 million Indians having diabetes; every fifth diabetic in the world is an Indian. It also leads in prevalence of metabolic syndrome as well as obesity. 20 million Indians are either obese or abdominally obese with children being the prime targets and by 2025; the expected number is 68 million.[7] Therefore, the prevalence of diabetes in India is increasing at an alarming rate, which needs to increase the awareness among people about causative factors for diabetes and its consequences.[8]

Diabetes being chronic debilitating disease requires lifelong management. The sedentary stressful life lack of exercise, irregular food habits all these environmental factors along with the predominant genetic inheritance increase the risk of type II diabetes mellitus.[9] style, although diet and exercise along with life style modifications remains the mainstay of diabetes management, regular treatment with the drugs is essential to delay the anticipated long term complications of diabetes.[10]

The research on drug utilization studies for the ant diabetic agents conducted by Sudha V et al. (2008), Boccuzzi SJ et al. (2004), Johnson et al. (2001), Yurgin N et al. (2007) show that there occurs male preponderance in the prevalence of diabetes, [11-14] while in contrast to these studies several other studies conducted by Lisha et al. (2012), Saiyad et al. (2012), R. Ramesh et al. (2011) have reported a high proportion of diabetes in female patients. [3,15] However, our

study findings are also in concurrence with the earlier studies which show male preponderance in prevalence of DM with the male: female ratio being 2:1.

As described in National Institute for Clinical Excellence (NICE) guidelines for diabetes, routine monitoring of glycemic control is an important part of diabetes management. It was observed in our study that patients were investigated and monitored for glycemic control.[16] Thus it was evident that all the physicians made a good effort to follow the NICE guidelines to achieve good glycemic control in the admitted patients. Considering this, of all the oral hypoglycemic agents, metformin was the preferred drug as it was considered to be safe in regards to the hypoglycemic episodes & it was less expensive as well, thus making it affordable to the economically weak patients in our hospital. This observation makes it clear that socio-economic status of patient was definitely taken into consideration while prescribing the ant diabetic medications.

Biguanides were found to be the preferred class of OHA in our set up, of which Metformin was commonly prescribed ant diabetic drug either alone or in combination with other ant diabetic agents. This observation in our study was in concurrence with many other similar studies. [2,10,13,14,17] similarly, some studies have shown sulfonylurea group as a commonly prescribed ant diabetic agents, whereas several other studies show that metformin is a prescribed in combination along with glimepiride or glibenclamide or sitagliptin.[18-20] However, most commonly prescribed combination was metformin+ glimiperide.[17]

It was however found to be difficult to obtain a good glycaemic control as per NICE guidelines in the diabetic individuals who were included in our studies, probably because of either improper & irregular medications or the existing comorbid conditions. In those patients who were not achieving targeted glycaemic control insulin preparations were preferred either alone or in combination with oral hypoglycaemic agents. Regular insulin (30) was the most commonly prescribed while, Lantus (5) was least prescribed. This helped in achieving a good glycaemic control and in good prognosis.

Polypharmacy was observed to be practiced in the management of the diabetes where in selection of the individual agents was made on the basis of their glucose lowering effectiveness and other characteristics suitable to the patients 'conditions.[19] However, when adding second and potentially third ant hyperglycemic Medications, the synergy of particular combinations and other interactions were considered. Insulin plus metformin [21] and insulin plus a thiazolidinediones (TZD) [22] are particularly effective by means of lowering hyperglycemia but the increased risk of fluid retention with the latter combination must be considered. (TZD in combination with insulin is not currently approved in the European Union.) Although both TZDs and metformin effectively increase sensitivity to insulin, they have different target organs and have been shown to have modest additive effects, with addition of TZD to metformin lowering HbA1C by 0.3-0.8%. [23,24] In our study it was found that patients who were prescribed insulin in management of diabetes and had HbA1C assessments available before and following therapy achieved a substantial benefit from initiation of insulin. Although few patients did not meet target blood glucose levels, however clinical improvement was noticed for which they were admitted.

CONCLUSION

To conclude with the available wide range of oral hypoglycemic agents, metformin (Biguanides) was the most preferred oral hypoglycemic agents which could achieve good glycemic control when used either alone or in combination with other oral hypoglycemic agents / insulin preparations. This study reveals a rational use of medications although the prescriptions with generic names were about 15%. However, the prescription pattern was observed to be largely in compliance with the NICE guidelines. Despite of polypharmacy practice by the physicians no adverse drug event was reported among the treated participants.

Limitations of the study

As it was a short term research project, the restricted sample size restricts the generalization of findings therefore, similar studies can be conducted in larger number of populations to confirm our findings.

REFERENCES

1. Ramachandran, A., Snehalatha, C., Nanditha, A. Classification and Diagnosis of Diabetes. Textbook of Diabetes. Holt RIG, Cockram CS, Flyberg A, Goldstein BJ, editors. 5th Edition. Wiley Blackwell, New Delhi; 2018: 23- 28.
2. Global Picture (Chapter 3). IDF Diabetes Atlas. 9th edition 2019.
3. Mohan, V., Unnikrishnan, R., Anjana, R. M. Introduction to diabetes mellitus. Dr Mohan's Handbook of Diabetes Mellitus. 4th edition, Madras Diabetes research Foundation, Chennai; 2011: 1-2.
4. Sridhar, G. R. Prevention of Diabetes Mellitus. Seshadri KG, Prasanna Kumar KM, Sridhar GR, Sasale A, editors. Clinicians Handbook of Diabetes.2nd edition. Macmillan Medical Communication, 2015: 9-14.
5. Ramachandran, G., Rohit, V., Topno, I. Evaluation of prescribing pattern of anti-diabetic drugs using WHO prescribing indicators in a tertiary care hospital in Puducherry: A cross-sectional study. The Pharma Innovation Journal 2015; 4(5): 76-80.

6. Venkateswaramurthy, N., Md. Shajeem, S., Sambathkumar, R. Prescription pattern of ant diabetic drugs in type-2 diabetic patients. Int J Pharm Sci Res 2016; 7(11): 4550- 4555.
7. Mahmood, M., Reddy, R. C., Lahari, S.J.R., Fatima, S., Shindhe, P., Reddy, S. A., et *al*. Prescription Pattern Analysis of Ant diabetic Drugs in Diabetes Mellitus and Associated Comorbidities. Clin. Invest. (Lond.). 2017; 8(1): 5-12.
8. Dutta, S., Beg, M. A., Anjoom, M., Varma, A., Bawa, S. Study of prescribing pattern in diabetes mellitus patients in a tertiary care teaching hospital in Dehradun, Uttarakhand. Int J Med Sci Public Health. 2014; 3: 1351-1354.
9. Tripathy, R., Lenka, B., Pradhan, M. R. Prescribing activities at district health care centers of Western Odisha. Int J Basic Clin Pharmacol 2015; 4: 419-421.
10. Ashar, S. M., Hanif, A., Jadoon, A., Rehman, M., Ullah, N., Kamal, Z., *et al*. Assessment of Drug Use Pattern Using WHO Prescribing Indicators in the Medication Therapy of Indoor Diabetic Patients. International Journal of Basic Medical Sciences and Pharmacy. 2016; 6(1): 16-20.
11. Ragam, A. S., Acharya, S., Holla, R. Assessment of drug use pattern using World Health Organization prescribing indicators in a tertiary care hospital in Mangalore: A cross- sectional study. Natl J Physiol Pharm Pharmacol. 2017; 7(10): 1026-1030.
12. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2012; 35 Suppl 1:64-71.
13. IDF Diabetes Atlas. 6th ed. International Diabetes Federation, 2013.
14. El-Kaissi S, Sherbeeni S. Pharmacological management of type 2 diabetes mellitus: An update. Curr Diabetes Rev 2011; 7(6):392-405.
15. Jimoh AO, Sabir AA, Chika A, Sani Z. Pattern of antidiabetic drugs use in a diabetic outpatient clinic of a tertiary health institution in Sokoto, North-western Nigeria. J Med Sci 2011; 11:241-5.
16. John LJ, Arifulla M, Sreedharan J, Muttappallymyalil J, Das R, John J, *et al*. Age and gender-based utilisation pattern of antidiabetic drugs in Ajman, United Arab Emirates. Malay J Pharm Sci 2012; 10:79-85.
17. Kannan, Arshad, Kumar S. A study on drug utilization of oral hypoglycemic agents in type-2 diabetic patients. Asian J Pharm Clin Res 2011; 4:60-4.
18. Shamna M, Karthikeyan M. Prescription pattern of antidiabetic drugs in the outpatient departments of hospitals in Malappuram district, Kerala. J Basic Clin Physiol Pharmacol 2011; 22(4):141-3.
19. Dave DJ, Dikshit RK, Gandhi AM. Utilization of some newer oral antidiabetic agents in a tertiary care hospital. Natl J Physiol Pharm Pharmacol 2012; 2(2):146-51.
20. Kumar KS, Sreeramya G, Krishna KM, Nalini K, Kiranmai N, Vasavi P. Drug use pattern study of antidiabetics in type 2 diabetes mellitus at a tertiary care hospital in Tenali, Andhra Pradesh. Int J Inv Pharm Sci 2013; 1:162-6.
21. Patel B, Oza B, Patel KP, Malhotra SD, Patel VJ. Pattern of antidiabetic drugs use in type 2 diabetic patients in a medicine outpatient clinic of a tertiary care teaching hospital. Int J Basic Clin Pharmacol 2013; 2:485-91.
22. Sivasankari V, Manivannan E, Priyadarsini SP. Drug utilization pattern of anti-diabetic drugs in a rural area of Tamil Nadu, South India - A prospective, observational study. Int J Pharm Bio Sci 2013; 4:514-9.
23. Alam MS, Aqil M, Qadry SA, Kapur P, Pillai KK. Utilization pattern of oral hypoglycemic agents for diabetes mellitus type 2 patients attending out-patient department at a University hospital in New Delhi. Pharmacol Pharm 2014; 5:636-45.
24. R. Ramesh, Subash Vijaya Kumar, S. Gopinath, B. Gavaskar, G. Gandhiji. Diabetic knowledge of rural community and drug utilization pattern in a tertiary care hospital. Int J Pharm Life Sci. 2011; 2(1):531-5.