A STUDY ON DRUG UTILIZATION EVALUATION AND POTENTIAL DRUG RELATED PROBLEMS IN TYPE-2 DIABETES MELLITUS PATIENTS WITH CO-MORBIDITIES IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Objective: The objective of this study is to evaluate prescribing pattern, analyze drug-related problems, identify co-morbidities and complications in Type 2 Diabetes Mellitus patients and also to perform cost analysis of Biguanides, Sulphonylureas, Dipeptidyl Peptidase Inhibitors

Methods: A Prospective observational study was done in General Medicine and Endocrinology Departments of PSG Hospitals. A total of 200 study subjects, including both inpatients and outpatients, above 18 y of age, prescribed with OHAs (Biguanides, Sulphonylureas and DPP4 inhibitors) were included in the study.

Results: Diabetes was more prevalent among males. OHAs were most prescribed in the age group of 51-60 y. Hypertension (71%) was the most common comorbidity and Diabetic neuropathy (23%) was the most common complication found in the patients. Multidrug therapy (72.5%) was most prescribed in diabetic patients, followed by Biguanides. Hypoglycemia was the most prevalent ADR. Cost analysis showed that T. Linagliptin was of high cost and T. Glimepride being the low cost. Using WHO core indicators prescribing patterns were assessed. Feedback was collected and results were reported to the physicians which showed rational utilization of drugs.

Conclusion: The study on drug utilization conducted in a tertiary care hospital helped us to find out that prescribing trends seems to be progressing towards combination therapy, predominately two-drug therapy

Keywords: Antidiabetic drugs, Drug utilization evaluation, Naranjo adverse drug reaction scale, WHO core indicators, Prescribing patterns

INTRODUCTION

The term Diabetes describes a metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbances of carbohydrates, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both [1, 2]. Diabetes mellitus is a leading cause of morbidity and mortality because of its associated complications viz: Neuropathy, Nephropathy, Retinopathy, and cardiovascular disorders. The prevalence of type 2 Diabetes mellitus has been increasing worldwide as a result of excess body weight and physical inactivity.

According to 2019 International Diabetes Federation survey of India, among 997 million population, 88 million (8.8%) people were reported to have Type 2 Diabetes Mellitus [3]. Indians are more prone to diabetes because of obesity and change in lifestyle pattern. The symptoms of Type-2 diabetes are similar to Type-1 diabetes but are often less marked. Consequently, the disease may be diagnosed several years after onset, once complications have become apparent. The lack of compliance towards diabetes could lead to chronic complications, including macrovascular and microvascular [4]. Most of the diabetic patients have relatively poor glycaemic control and are presented with multiple co-morbidities like Hypertension, Dyslipidemia, Coronary artery disease, etc.

Diabetes Mellitus mainly occurs in the older age group though incidence is now increasing in younger population [5]. As elderly diabetic patients have more co-morbid conditions and complications, they are prescribed with multidrug regimen making them more prone to drug-related problems (DRPs). Therefore polypharmacy should be monitored among patients with diabetes as it increases the probability of adverse drug events, drug-drug interactions, which escalates the drug costs and health care costs leading to poor compliance to medications. Administrative databases seem to be useful in analyzing trends in the prescribing pattern and cost analysis.

Hence the drug utilization evaluation (DUE) studies have become one of the potential tools in the evaluation of the health system and it also suggests modifications in the current prescribing practices to the prescribers to encourage rational use of drugs. Therefore, this study focuses on evaluating the prescribing pattern, analyzing drug related problems, identifying co-morbidities and complications in Type 2 Diabetes Mellitus patients and also performing cost analysis of Biguanides, Sulphonylureas, Dipeptidyl peptidase-4 inhibitors which is one of the components of the Drug utilization metrics

MATERIALS AND METHODS

Study site
The study was conducted at PSG Hospitals, Peelamedu, Coimbatore.

Study approval
This study was approved by the Institution Human Ethics Committee (IHEC, PSG IMSR) of the hospital. The protocol was approved on 08/02/2019, Proposal number: 19/033.

Study design
A prospective observational Drug Utilization Evaluation study.

Study period
The study was conducted for a period of 6 mo.

Study subjects
All T2DM patients who were attending Endocrinology and General Medicine departments with co-morbidities were included in this
study. Patients of either gender who were above 18 y of age and prescribed with Biguanides, Sulphonylureas, DPP4 Inhibitors for Type 2 Diabetes Mellitus were included. Diabetic patients who were pregnant, lactating, patients taking Insulin analogues and those who were not willing to participate in this study were excluded.

Data collection
Patients were approached in the respected departments based on the inclusion and exclusion criteria. After explaining about the study in a regional language, the consent form was collected from the patients prior to data collection. Data regarding the socio-demographic and clinical characteristics of the patients were obtained through interviews and past medical records. From the drug chart review, current medications along with dosage, frequency, route of administration and duration of therapy have been recorded and assessed for drug interactions, adverse drug reactions, polypharmacy, prescribing patterns and also for cost analysis.

Statistics
The statistical analysis was done using SPSS version 25 and the odds ratio

RESULTS
In this study, a total of 200 patients were included from the departments of Endocrinology and General Medicine of PSG Hospitals, Coimbatore. Both Inpatients and Outpatients were included. Baseline characteristics such as social habits and gender of the patient were summarized in table 1.

| Characteristics | No of prescriptions | Percentage |
|-----------------|---------------------|------------|
| **Gender**      |                     |            |
| Male            | 110                 | 55         |
| Female          | 90                  | 45         |
| **Social habits** |                   |            |
| Smoker          | 55                  | 50         |
| Alcoholic       | 58                  | 52.7       |
| Both            | 49                  | 44.5       |

The age wise distribution of patients with co-morbidities was summarized in fig 1 in which most prevalent co-morbid conditions were found in the age group of 51-60 y. Diabetic complications were most prevalent in the age group of 51-60 y and patients with a diabetic history of 5-10 y were more prone to diabetic complications which were summarized in table 2 and table 3. Diabetic complications were observed more in smokers therefore, there is an association between smoking and diabetic complications (p=0.000).

![Fig. 1: Age wise distribution of patients with co-morbidities](image)

Table 1: Baseline characteristics

![Table 2: Age wise distribution of patients with diabetic complications](image)

Table 2: Age wise distribution of patients with diabetic complications

| Age group | 18-30y | 31-40y | 41-50y | 51-60y | 61-70y | 71-80y | 81-90y |
|-----------|--------|--------|--------|--------|--------|--------|--------|
| Retinopathy | 0      | 1      | 4      | 12     | 10     | 2      | 0      |
| Neuropathy  | 0      | 3      | 14     | 14     | 10     | 5      | 0      |
| Nephropathy | 0      | 0      | 2      | 3      | 1      | 1      | 0      |
| Foot Ulcer  | 0      | 2      | 3      | 1      | 0      | 1      | 0      |
| Total       | 0      | 6      | 23     | 30     | 21     | 9      | 0      |

Table 3: Diabetic duration wise distribution of complications

| Diabetic duration | Complications | Percentage |
|------------------|---------------|------------|
| <5y              | 18            | 26         |
| 5-10years        | 34            | 49         |
| 11-15years       | 12            | 17.3       |
| 16-20years       | 4             | 5.7        |
| >20years         | 1             | 1.4        |
Fig. 2: Drug class wise distribution of OHAs. The drug classes included in this study were Biguanides, Sulfonyl ureas and DPP4 Inhibitors which were summarized in fig. 2.

Table 4: Age wise distribution

| Age group | Biguanides | Sulfonyl ureas | DPP-4 inhibitors | Combination S. U+BG | DPP4+BG |
|-----------|------------|----------------|------------------|---------------------|---------|
| 18-30     | 0          | 0              | 0                | 0                   | 0       |
| 31-40     | 4          | 3              | 0                | 0                   | 3       |
| 41-50     | 25         | 12             | 4                | 31                  | 8       |
| 51-60     | 34         | 8              | 0                | 46                  | 19      |
| 61-70     | 26         | 11             | 2                | 37                  | 7       |
| 71-80     | 5          | 2              | 5                | 9                   | 1       |
| 81-90     | 1          | 0              | 0                | 2                   | 0       |
| Total (n) | 95         | 36             | 11               | 135                 | 38      |
| Percentage (%) | 47.5     | 18             | 5.5              | 67.5                | 19%     |

Biguanides were more prescribed in the age group of 51-60 y (n=34, 17%); Sulfonylureas in the age group of 41-50 y (n=12, 6%) and its combination in the age group of 51-60 y (n=46, 23%); DPP-4 Inhibitors in the age group of 71-80 y (n=5, 2.5%) and its combination in the age group of 51-60 y (n=19, 9.5%) which are illustrated in table 4.

According to dose wise distribution, the most prescribed doses among the OHAs were:

Biguanides-Metformin 500 mg (n=51, 25.5%); Sulfonyl ureas-Glimepiride 1 mg (n=6, 3%) and Gliclazide 40 mg (n=6, 3%); DPP4 Inhibitors-Stagliptin 25 mg (n=3, 1.5%); Sulfonyl ureas Combination-Glimepiride+Metformin 0.5/500 mg (n=22, 11%); DPP4 Inhibitors Combination-Vildagliptin+Metformin 50/500 mg (n=16, 8%).

Fig. 3 shows the distribution of the number of Oral Hypoglycemics prescribed among patients according to their diabetic history in years.

Out of 200 prescription encounters, Biguanides had 69 plain, 10 Extended-Release and 12 Sustained Release preparations, Sulfonylureas had 7 plain and 2 Extended-Release preparations and its combination had 1 plain and 1 Extended Release, DPP4 Inhibitors and its combination had only plain formulation.

Fig. 3: Distribution of OHAs according to diabetic duration
Distribution of OHAs according to diabetic duration was summarized by fig. 3.

Out of 200 prescriptions, polypharmacy was seen in 35 (17.5%) prescriptions, hyperpolypharmacy in 16 (8%) prescriptions and it was high in patients with the age group of 51-60 y.

Micromedex and Medscape were used to assess drug-drug interaction based on its severity and significance. In this study 72 patients had drug interactions in which 17 were minor, 31 were moderate and 28 were major which were clinically significant. As more drugs were prescribed in a prescription, more drug interactions were encountered. So, there was an association between Polypharmacy and DI (p=0.000).

Out of 200 Diabetic patients, 15 developed ADR in which 10 were caused by Metformin, which shows that there is an association between drug use and ADR (p=0.017); table 5 depicts the Adverse Drug Reaction assessed by using Naranjo’s scale.

### Table 5: Adverse drug reaction

| S. No. | Suspected drug | Reaction observed | Causality assessment (Naranjo scale) | No of patients |
|--------|----------------|-------------------|-------------------------------------|----------------|
| 1      | Glimepiride    | weight gain       | Probable                            | 1              |
| 2      | Glimepiride    | weight gain       | Possible                            | 2              |
| 3      | Metformin      | hypoglycemia      | Probable                            | 3              |
| 4      | Metformin      | hypoglycemia      | Possible                            | 5              |
| 5      | Metformin      | GI disturbance    | Possible                            | 1              |
| 6      | Metformin      | Dyspepsia         | Definite                            | 2              |
| 7      | Vildagliptin    | burning sensation in feet | Possible | 1              |

The prescriptions were analyzed for WHO core indicators in table 6.

### Table 6: Prescribing pattern

| Prescribing Indicators                              | Total drugs/Encounters | Average percentage (%) | WHO Ideal values |
|------------------------------------------------------|-------------------------|-------------------------|------------------|
| Average number of drugs per encounter                | 997                     | 4.98                    | 1.6-1.8          |
| Percentage of drugs prescribed by Generic Name       | 79                      | 7.92                    | 20.6-26.8%       |
| Percentage of drug encounters with Antibiotics       | 33                      | 3.3                     | 13.4-24.1%       |
| Percentage of drug encounters with Injections        | 77                      | 7.7                     | 100%             |
| Percentage of drugs prescribed from EML/Formulary    | 997                     | 100%                    | 100%             |

Cost analysis was done for the selected classes of OHAs which showed that combination of DPP-4 Inhibitors (Teneligliptin+Metformin) was cheaper when compared to other prescribed brands of DPP-4 Inhibitors (Sitagliptin). It was also found that the most expensive brands of DPP-4 Inhibitors (Linagliptin) was less prescribed. Metformin was the most prescribed brand and also one of the cheapest drugs among OHAs. Cost analysis showed that among Sulphonylureas, Glimepiride was the cheapest, but more often, Sulphonylureas and Biguanide combinations (Glimepiride+Metformin) were prescribed with reasonable prices.

### DISCUSSION

In this study, the prevalence of T2DM were more in males 110 (55%) compared to females 90 (45%), which was in contrast to the previous study in which the prevalence of T2DM were more in females when compared to males [6]. Hypertension (71%) and Dyslipidemia (42.5%) were the most prevalent co morbidity conditions in the age group of 51-60 y. This was similar to the study conducted in 2017 in which hypertension was the most common comorbidity observed [7, 8]. Patients with diabetic duration of 5-10 y showed a significant effect on the prevalence of Diabetic neuropathy. In this study the association between duration of diabetes and risk of neuropathy is strong which was in concordance to the previous study in which diabetic neuropathy is present mainly in patients after 5 y of diabetes history [9,10]. Multidrug Therapy (72.5%) was most prescribed among the OHAs followed by Biguanides (33%). The most prevalent multidrug therapy was a two-drug combination Glimepiride+Metformin (45.5%). This was similar to the previous study in which two-drug therapy–Glimepiride+Metformin was most prescribed [11]. During this study, 15 ADRs (7.5%) were recorded in which the most common were hypoglycaemia (n=8), dyspepsia (n=2) and GI disturbances (n=1). This was in concordance with the previous study in which hypoglycaemia was the most common ADR found [12, 13].

Polypharmacy (17.5%) and Hyperpolypharmacy (8%) were observed. The maximum level of polypharmacy was observed in the age group of 51-60 y followed by patients with the age group of 61-70 y and 41-50 y. This was in contrast to the previous study in which the level of polypharmacy increased with age of patients [13]. The Prescribing patterns were evaluated using WHO Core Indicators. The average number of drugs per prescription was 4.98%, which was higher when compared to WHO Ideal Value (1.6-1.8%), showing high degree of polypharmacy. Similarly, the average number of drugs per prescription was also higher than the findings of the studies conducted in Ayder Referral Hospital of Northern Ethiopia: 2.61 [14]. Percentage of drugs prescribed by generic name (7.92%) was lesser than WHO ideal values (100%), which shows less tendency of the prescribers to prescribe drugs by generic names. Percentage of injection and antibiotics were 7.7% and 3.3%, respectively, which was lesser when compared with WHO Ideal Values. This showed less tendency of over usage and prescribing expensive drugs. However, the percentage of injection and antibiotics were lower when compared to other reports from studies conducted in Northern Ethiopia [15]. The percentage of drugs prescribed from EML/Formulary was found to be 100%, this shows prescribing was based on national essential drug/formulary. Among the prescribed brands, DPP4 Inhibitors were of high cost and Biguanides were found to be cheaper. Cost analysis also showed that Sulphonyl urea-Biguanide combinations and Biguanides were the most prescribed and economical. This was in concordance with the previous study in which Biguanides and Sulfonyl urea-Biguanide combination were most prescribed. Both of these therapies were economical and DPP-4 Inhibitors were costlier [16]. The limitation of the study was the synthesis of data sources regarding pharmacoeconomic evaluation was impossible due to the shorter duration of the study.

### CONCLUSION

This study helped us to find out the current prescribing patterns of oral antidiabetic drugs in Type 2 Diabetes Mellitus patients. The prescribing trends seems to be progressing towards combination therapy predominantly two-drug therapy. Economic burden should not affect the treatment regimen of the patient therefore it is the physician's responsibility to be aware of the inter-brand price.
variations and to prescribe drugs of cheaper prices. Rational drug use is a significant factor to be checked for the ideal benefit of drug therapy inpatient care.

AUTHORS CONTRIBUTIONS

Conceived and designed the study: Prudence A. Rodrigues, Naresh Kumar, M, Dawn Teslin Damien, Mary Cecil, K. T and Reshma. S. S. Performed the study: Naresh Kumar, M, Dawn Teslin Damien, Mary Cecil, K. T and Reshma. S. S. Contributed materials/analysis tool: Prudence. A. Rodrigues. Manuscript preparation and correction and Correspondence: Dawn Teslin Damien, Mary Cecil, K. T and Reshma. S. S. Peer support: Susan Varghese Paul.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

REFERENCES

1. WHO, Consultation, Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications, Geneva, Switzerland: World Health Organization; 1999. p. 31-3.
2. Ranjodh Jeet Singh, Ashwani Kumar Gupta, Kanika Kohli. Diabetes mellitus: a review with edge of SGLT2 inhibitors. Int J Curr Pharm Res 2018;10:1-2.
3. International Diabetes Federation-IDF Diabetes Atlas 9th Edition; 2019. p. 74-75.
4. Ilin Presetiawati, Retnosari Andrajati, Rani Sauriasari. Effectiveness of a medication booklet and counseling on treatment adherence in type 2 diabetes mellitus patient. Int J Appl Pharm 2017;9:27-30.
5. Afroz Abidi, Dilshad Ali Rizvi, Ali Ahmad. Pharmacoeconomic and drug utilization study of antidiabetic therapy in a tertiary care teaching hospital of Northern India. Asian J Pharm Clin Res 2016;9:371-5.
6. Deepika Perumilla, Divya Gopini, Venkatapathi Raju, R Chaitanya Deepthi, Ranganayakulu D. A prospective study on co-morbidities and drug utilization evaluation in the diabetic patient in a tertiary care hospital. Inventi Impact: Pharmacy Practice 2018;3:136-43.
7. Geetha P, Shanmugasundharam P. Drug utilization evaluation of antidiabetic drugs among type 2 diabetes patients of Tamil Nadu. Asian J Pharm Clin Res 2017;10:202-5.
8. Kenneth Ekorua, Ayo Doumateya, Amy R Bentleya, Guanje Chena, Jie Zhoua, Daniel Shriner. Type 2 diabetes complications and comorbidity in Sub-Saharan Africans. E Clin Med 2019;16:30-41.
9. Pradeep Battula, S Afreen, E Meena, S Swa Ram Reddy, G Sujatha. Prevalence of peripheral sensory neuropathy in diabetic patients at diabetes care centre: a cross-sectional study. Int J Res Med Sci 2017;5:4066-71.
10. Eva L Feldman, MJ Stevens, DA Greene. A practical two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy. Diabetes Care 1994;17:1281-9.
11. G Sultana, P Kapur, M Aqil, MS Alam, KK Pillai. Drug utilization of oral hypoglycemic agents in a university teaching hospital in India. J Clin Pharm Ther 2010;35:267-77.
12. Shanthi M, Madhavrao C. Study of adverse drug reaction and causality assessment of antidiabetic drugs. Int J Basic Clin Pharmacol 2019;8:56-60.
13. Soumya Mary Alex, Sreedekshmi BS, Smitha S. Drug utilization pattern of anti-diabetic drugs among diabetic outpatients in a tertiary care hospital. Asian J Pharm Clin Res 2015;8:144-6.
14. Rania Indu, Anjan Adhikari, Indira Maisnam, Polypharmacy and comorbidity status in the treatment of type 2 diabetic patients attending a tertiary care hospital: an observational and questionnaire-based study. Perspectives Clin Res 2018;9:139-44.
15. Birhanu Demoke, Tigist Asfe, Fantahun Molla, Admassu Assen. Evaluation of drugs utilization pattern using who prescribing indicators in ayder referral hospital, Northern Ethiopia. Int J Pharma Sci Res 2015;6:343-7.
16. Pardeep Kumar Goyal, Shalini Arora, Bharti Mahajan, Sandeep Kaushal. Prescribing pattern and pharmacoeconomic analysis of antidiabetic drugs. Int J Basic Clin Pharmacol 2019;8:1844-9.