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PREDICTORS OF POLYPHARMACY PRESCRIPTION IN TYPE 2 DIABETES MELLITUS PATIENTS: A CROSS-SECTIONAL SURVEY

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ABSTRACT: Polypharmacy is defined as the “prescription, administration, or use of more medications than are clinically indicated. It can lead to drug-drug interactions and result in adverse drug events. Therefore, this study aimed to determine the prevalence of polypharmacy and factors that independently predict polypharmacy prescription. 200 Type 2 Diabetes Mellitus (T2DM) patients were enrolled and analyzed. The overall prevalence of polypharmacy was 51%, with the average number of drugs prescribed being 4.68 ± 3.18 . The odds of polypharmacy prescription increased with the duration of T2DM, with comorbid conditions, and were higher in patients with uncontrolled glycaemic status. At the same time, the other factors, gender, smoking, and alcohol habits, did not reveal any significant association with polypharmacy prescription. Thus the most common predictors of polypharmacy prescription found were duration of T2DM, comorbid conditions, and glycaemic status of the patient. The findings of this study would be helpful in Government programs in developing, evaluating, and implementing interventions for supporting medicines optimization and deprescribing in India.

INTRODUCTION: The word "polypharmacy" has been used in the medical field for many years. It is defined as "Prescription, administration, or usage of more medications than are clinically recommended, or when a medical regimen contains at least one unneeded medication". Most frequently, it is acknowledged that polypharmacy is similar to "the use of 5 or more medicines per day"¹. Multiple drug therapy has become the norm for treating most chronic illnesses, including Diabetes Mellitus, and polypharmacy may yet be unavoidable². Hypertension, dyslipidemia, depression, and coagulopathies are typical comorbidities of diabetes, and each of these conditions may need one or more medications for effective management³.

There is a progressive increase in type 2 diabetes mellitus (T2DM) globally and among Indians. Adverse drug events and drug-drug interactions can emerge from polypharmacy⁴. The T2DM patient, their family, the healthcare system, and the economy may all suffer as a result. It can have a negative impact on a patient's ability to take their medications as prescribed, their quality of life, and how long they will live. It can also result in subpar blood glucose control, hospital admissions, a higher chance of developing severe hypoglycemia, and higher medical expenses⁵. The number of drugs taken at first, patient age, presence of illnesses like diabetes or coronary ischemic disease, and the usage of drugs without obvious indications is all polypharmacy predictors⁶.

Only a small amount of study has been done up to this point to investigate the causes of polypharmacy. Therefore, this study aimed to identify the prevalence of polypharmacy and the variables that can be used to predict polypharmacy prescriptions. Understanding these variables will be useful for government initiatives to create, assess

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and implement strategies to promote the optimization of pharmaceuticals in India.

MATERIAL AND METHODS:

Study Design and Setting: A cross-sectional observational study was conducted in an outpatient clinic of the medicine department of a tertiary care teaching hospital. This study was an extension of our previous study⁷. Approval of the research project was obtained from the scientific review committee and Institutional Ethics Committee. (Ref. no. HREC/4973/18 dated 28-02-2018)

Study Population, Inclusion and Exclusion Criteria: All adult patients (≥ 18 years of age) of either sex diagnosed with type 2 DM taking anti-diabetic drug therapy for more than six months and prescribed at least two drugs were included in the study. The study excluded severely disabled diabetics who cannot be interviewed, cognitive deficit patients and patients not willing to give informed consent.

Sample size, Study Period and Data Collection:

A total of 200 patients who met the study criteria were enrolled for four months from April 2018 to July 2018. Informed consent was obtained from the study participants after explaining the study details. A suitably designed data collection form was used to collect all the necessary data, including patient Socio-demographic details, current anti-diabetic

drug therapy, details of the duration of treatment, associated co-morbidities, glycaemic status of patient, and number of medications in each prescription.

Statistical Analysis: Data were expressed in actual number, Mean \pm standard deviation (SD), and percentage. The odds ratio and its associated 95% confidence intervals were calculated (CIs). A multiple logistic regression model was used to explore the relationship between independent variables and polypharmacy prescription. A P-value less than 0.05 was considered statistically significant. IBM SPSS Statistics Version 20.0 for Windows was used for data analysis.

RESULTS: Socio-demographic characteristics of the study population from our previous study⁹ are summarized in **Table 1**. A total of 200 T2DM patients were enrolled and analyzed. The mean age of the patients was 56 (± 7.8) years, with a female predominance (56.5%). 35 patients were smokers and 26 patients had a history of alcohol drinking.

Among the T2DM patients, co-morbidities were found in the majority (76%) in which hypertension (49%) was most common, followed by hyperlipidaemia (39%). We found that 37% had controlled blood glucose, whereas 63% had uncontrolled blood glucose despite being on drug therapy.

TABLE 1: SOCIO-DEMOGRAPHIC CHARACTERISTICS OF THE STUDY POPULATION

Patient characteristics		Value (Mean \pm SD OR n=200(%))
Patients with Type 2 Diabetes (T2DM)		200
Age in years		56 \pm 7.8
Gender	Male	87 (43.5)
	Female	113 (56.5)
Smoking	Yes	35 (17.5)
Alcohol drinking	Yes	26 (13)
Comorbidity	Present	152 (76)
	Absent	48 (24)
Duration of treatment in years		9.6 \pm 5.7
Number of medications		4.68 \pm 3.18
Mean blood glucose (mg/dl)	Fasting	156 \pm 55
	Postprandial	220 \pm 65
Glycaemic status	Controlled level	74 (37)
	Uncontrolled level	126 (63)

TABLE 2: PREVALENCE OF POLYPHARMACY IN STUDY PATIENTS

Number of drugs	Frequency (n)	Percentage (%)
< 5 drugs	98	49
≥ 5 drugs	102	51
Total	200	100

The prevalence of polypharmacy is tabulated in **Table 2**. In the present Study, We considered polypharmacy as a prescription containing 5 or more than five drugs. The overall prevalence of polypharmacy in our study was 51%, with the average number of drugs prescribed being 4.68 ± 3.18 .

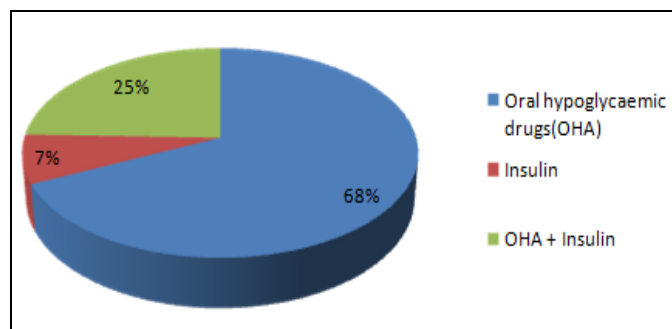


FIG. 1: PATTERN OF USE OF ANTI-DIABETIC DRUGS

Fig. 1 shows the pattern of use of anti-diabetics agents prescribed in our study. 68% of T2DM patients were on oral hypoglycaemic drugs, 7%

were on insulin alone, and 25% were receiving both.

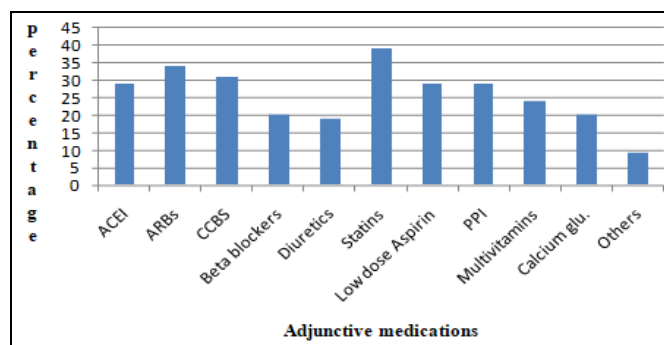


FIG. 2: ADJUNCTIVE MEDICATIONS PRESCRIBED

In our study, the most common drug classes prescribed other than anti-diabetic drugs were statins, ACE inhibitors and angiotensin receptor blockers (ARBs), Calcium channel blockers (CCBs), low-dose aspirin, proton pump inhibitors (PPI), multivitamins, calcium tablets, diuretics, beta-blockers *etc.* **Fig. 2.**

TABLE 3: MULTIPLE LOGISTIC REGRESSION ANALYSES TO DETERMINE FACTORS INDEPENDENTLY ASSOCIATED WITH POLYPHARMACY

Independent variables	Adjusted OR (95% CI)
Duration of T2DM in years	
≤1	1
>1-5	1.69 (1.40,2.03)
>5-10	2.04 (1.41,2.94)
>10	2.99(2.24,3.99)
Comorbidity	
No	1
Yes	3.04 (2.42,3.82)
Gender	
Female versus Male	1.01 (0.83-1.22)
Smoking	
No	1
Yes	1.14 (0.89,1.47)
Alcohol	
No	1
Yes	1.12 (0.78,1.61)
Glycaemic status	
Controlled	1
Uncontrolled	2.24 (1.76,2.85)

The adjusted ORs (AORs) and 95% CIs from multiple logistic regressions on polypharmacy were shown in **Table 3**. Previous studies identified several factors: duration of T2DM, comorbid conditions, gender, smoking, alcohol consumption, and glycaemic status. The odds of polypharmacy prescription increased with the duration of T2DM, with comorbid conditions, and were higher in

patients with uncontrolled glycaemic status, while the other factors, gender, smoking, and alcohol habits, did not reveal any significant association with polypharmacy prescription.

DISCUSSION: We found polypharmacy in more than 50% of study patients. The fact that the patients admitted to our hospital were elderly

patients with numerous co-morbidities can be attributed to the greater number. These results were corroborated by Srivatsa *et al.*⁸, who found that 74% of patients aged between 61 to 70 years were of polypharmacy. Age-related increases in polypharmacy may be brought about by the prevalence of comorbid diseases in elderly patients. Moreover, in our study 66.7 % of patients had poor medication adherence who received 5 or more 5 drugs⁷.

We found that 68% of patients were on oral hypoglycaemic agents, while only 7% were on insulin and 25% were receiving both. We have noticed that adherence score was poor in T2DM patients prescribed insulin in combination with oral anti-diabetic agents. Combination therapy has become popular in recent years for the treatment of diabetes, but it also increases the risk of polypharmacy and unfavourable drug reactions because many doctors would rather prescribe an additional medication than switch the class of anti-diabetic drugs. In a different study conducted in China, Jialin *et al.*⁹ reported that a significant percentage of T2DM patients were provided oral anti-diabetic drugs (80%) and insulin (75%). All of these factors may make managing T2DM more difficult and add to the cost of medications. In the current study, statins were prescribed to 39% of patients, followed by ARBs (38%), CCBs (34%), low-dose aspirin (34%), and ACE inhibitors (32%), among other medications. Myopathy is one of the serious side effects of statins, which are metabolized by the enzyme cytochrome P4503A4 (CYP3A4). Calcium channel blockers like amlodipine inhibit CYP3A4. Amlodipine may raise plasma levels of statin when these two medications are taken together, which may raise the risk of myopathy^{10, 11}. Medication reconciliation and deprescribing among T2DM patients are thus urgently needed.

According to our research, the likelihood of a polypharmacy prescription rises with the duration of T2DM. Similarly, a study among Italian T2DM patients found that polypharmacy was linked to 5-year T2DM duration (1.93, 1.38–2.70)¹². In yet another study including diabetic patients in Brazil, polypharmacy was discovered to be connected to T2DM duration of 10 years (1.64, 1.36–1.98)¹³. The function and mass of β -cells increasingly

deteriorate as T2DM worsens. Patients with T2DM require numerous anti-diabetic medications as the condition worsens since single anti-diabetic medications, such as metformin, sulfonylureas, or thiazolidinediones, cannot manage their blood glucose levels for an extended period. Additionally, the length of T2DM raises the risk of vascular problems, necessitating additional medications as part of the management plan.

We discovered that people with low blood glucose levels were more likely to have polypharmacy. Another study conducted in the USA among T2DM patients showed that more anti-diabetic medications are required in T2DM patients with low blood glucose levels¹⁴. It should be noted that comorbidities may contribute to low blood glucose levels (*e.g.*, other metabolic disorders). Those with comorbidities such as endocrine, nutritional, metabolic illnesses (like hyperlipidemia) and circulatory system diseases (such as hypertension and T2DM macro-vascular complications like coronary heart diseases) had a higher likelihood of being prescribed multiple medications. Polypharmacy was found to be associated with cardiovascular diseases (2.89, 2.54–3.29), respiratory diseases (2.42, 1.92–3.03) and musculoskeletal diseases (3.16, 2.31–4.30 in a different study conducted among diabetic patients in Saudi Arabia)¹⁵. Most T2DM patients have at least one comorbidity, and 40% have three or more^{16, 17}. The results of this study confirm that patients with diabetes who also had multiple chronic diseases were more likely to have polypharmacy.

It was impossible to determine the causal association between various variables and polypharmacy prescription because the study was cross-sectional. A population-based study might present a different picture of the problem, as ours was a hospital-based study. The causes could be due to many population traits, such as the diseases' severity and how they seek medical attention.

CONCLUSION: More than 50% of study patients were of polypharmacy, and the most common predictors identified were the duration of T2DM, comorbid conditions, and glycaemic status of the patient. There are various steps to decrease polypharmacy which every clinician should adapt with the help of a clinical pharmacologist like

medication reconciliation, deprescribing, SAIL (Simplify, Adverse effects, Indication, List), and TIDE (Time, Individualize, Drug interactions, Educate) techniques, *etc.*^{18, 19}.

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