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ORIGINAL ARTICLE

A Study on Complications of Polypharmacy in Diabetic Geriatric Patients

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ABSTRACT

Objectives: To evaluate medication adherence, drug-drug interactions, adverse drug reactions (ADRs), and the incidence of falls among geriatric patients with diabetes.

Methods: This observational, prospective study included 100 geriatric patients with diabetes on polypharmacy (> 4 drugs) over 6 months. Patients were monitored for ADRs, with causality and severity assessed using the Naranjo Scale and Modified Hartwig & Siegel Scale, respectively. Medication adherence was evaluated using the Morisky Medication Adherence Scale. Potential drug-drug interactions were checked via the Lexicomp online database, and falls were tracked through telephonic follow-ups over one month. Data were analysed using descriptive statistics.

Findings: The average number of drugs per prescription was 8.6. Among the 100 patients, 81% had at least one comorbid condition. Medication adherence rates were 41%, 17%, and 32%, respectively. A total of 108 potential drug-drug interactions were identified: 6 major, 59 moderate, and 42 minor, involving drugs such as enalapril, diclofenac, metformin, glimepiride, aspirin, ondansetron, and norfloxacin. Six ADRs were reported: one moderate and five mild, with metformin-induced hypoglycaemia (50%), glimepiride-induced dyspepsia (33.33%), and metformin-induced diarrhoea (16.66%). Six falls were observed among the patients during the study.

Novelty: Polypharmacy among geriatric patients with diabetes is a significant concern, requiring combined efforts from healthcare professionals to address issues of medication adherence, drug interactions, and cognitive impairment.

Keywords: Polypharmacy; Diabetes; Medication adherence; Drugdrug interaction

INTRODUCTION

Polypharmacy is consistently associated with higher rates of potentially serious drug-drug interactions and adverse drug events[1–3]. Adverse drug events and serious harm occur at all ages, although they are common in older people, who are more vulnerable to drug toxicity because of age-related physiological changes and increased risk of disease associated with aging and polypharmacy[4]. In this context, interactions between multiple drugs and diseases can lead to more challenging management and control of chronic conditions. Among the most prevalent chronic diseases in older people, diabetes mellitus can affect up to 19.3% of individuals aged 65 years or older (135.6 million people worldwide)[5]. Although polypharmacy is an important topic in clinical practice, studies on this topic have increased only over the last 10–15 years, and the available evidence in terms of prevalence, related outcomes, and contrasting interventions is highly heterogeneous[6,7]. Unlike middle-aged diabetics, elderly individuals are characterized by some chronic medical conditions typical of the disorder (such as hypertension, obesity, metabolic syndrome, dyslipidaemia, and renal failure) as well as a higher prevalence of serious geriatric conditions such as cognitive impairment, depression, falls, and disability[8]. According to a recent study, middle-aged and older diabetics take a mean of nine drugs daily, corresponding to approximately 12 administrations daily[9,10]. Globally, approximately 50% of people have diabetes mellitus (DM). Patients with diabetes are more likely to take multiple medications to tackle these complications, and as the patient ages, he or she develops various chronic conditions and uses multiple drugs as a result[11]. According to California research, 41.5% of patients with diabetes receive at least one antihypertensive

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medication[12]. People with diabetes are at a high risk of developing polypharmacy[13]. A cross-sectional study in Italy revealed that 57% of diabetic patients use five or more medications[14,15].

The present study was conducted to ensure the safe and effective treatment of diabetic patients; it is crucial to check for potential drug-drug interactions among the medications prescribed. Additionally, evaluating adverse drug reaction outcomes due to polypharmacy is important because the use of multiple medications can increase the risk of harmful side effects. Determining medication nonadherence is vital for understanding and addressing issues that may lead to poor disease management and adverse health outcomes. Furthermore, assessing episodes of falls in elderly patients with diabetes is essential, as falls can result in serious injuries and are often linked to both the disease itself and the medications used for its treatment.

METHODOLOGY

This prospective observational study was conducted over a period of six months at the Department of General Medicine at MVJ Medical College and Research Hospital in Bangalore, South India. This study included 100 inpatients and provided a comprehensive dataset to investigate the specified research objectives. Ethical clearance for conducting the study was obtained from the Human Ethical Committee of the MVJ Medical College and Research Hospital on 24.10.2018. Certificate No: MVJMC&RH/Adm/ECM/2017-18. The data sources included multiple forms and scales to ensure comprehensive data collection. These sources included the informed consent form, patient case report form, drug interaction form, causality of adverse drug reactions assessed using Naranjo's scale, and severity of adverse drug reactions evaluated using the Modified Hartwig & Siegel scale. The Morisky Medication Adherence Scale was used to determine medication adherence among study patients.

Study Criteria

Inclusion Criteria

The study included inpatients aged 60 years and above of either sex who were suffering from type II diabetes mellitus, with or without comorbid conditions. This study specifically targeted inpatients who had been prescribed four or more medications to thoroughly investigate the effects of polypharmacy in these patients.

Exclusion Criteria

The study excluded inpatients with diabetes mellitus who were admitted to the intensive care unit. Additionally, inpatients who do not provide informed consent will not be included in the study

Procedure

Demographic, medication, clinical, and laboratory data were collected using a modified case-report form. Potential drug-drug interactions, adverse drug reactions, medication adherence, and episodes of falls were identified and documented. The prevalence, type, mechanism, and consequences of potential drug-drug interactions were assessed using the Lexicomp database, categorizing interactions as severe, moderate, or minor. Pharmacists intervened to manage potential drug-drug interactions in collaboration with physicians, with assessments and management occurring from the first day following the identification of polypharmacy. Adverse drug reactions, particularly hypoglycaemia due to polypharmacy, were assessed by observing signs and symptoms, such as loss of consciousness, sweating, hunger, and anxiety. Various parameters, such as age distribution, gender, diabetes duration, number of drugs per prescription, therapeutic class of drugs, type of insulin used, dosage form, prescribing indicators, and laboratory data (including blood glucose levels during the first seven days), were used in the assessment. Blood glucose levels below 70 mg/dl were classified as hypoglycaemic. The causality and severity of adverse drug reactions were assessed using the Naranjo and modified Hartwig and Siegel scales, respectively. Medication adherence to polypharmacy was evaluated using the Morisky Medication Adherence Scale. Episodes of falls due to polypharmacy were documented over a one-month period through telephonic follow-up, with falls assessed by enquiring about the type of fall experienced by the patient or their relatives.

Naranjo's ADR probability scale

The Naranjo Scale was used to standardize the assessment of causality for all adverse drug reactions. The ADR Probability Scale consists of 10 questions that are answered as either yes, no, or do not know. Different point values (-1, 0, +1, or +2) were assigned to each answer. Total scores range from -4 to +13; the reaction is considered definite if the score is 9 or higher, probable if it is 5 to 8, possible if it is 1 to 4, and doubtful if it is 0 or less.

Hartwig's And Siegal Scale

The term severity was used to describe the intensity of a medical event, as in grading mild, moderate, and severe. The severity assessment categorizes ADRs as mild, moderate, or severe based on the steps taken for the management of ADRs. Hartwig and Siegal categorized ADRs into seven levels according to their severity. Levels 1 and 2 fall under the mild category, levels 3 and 4 under the moderate category, and levels 5, 6, and 7 under the severe category.

Morisky Medication Adherence Scale (Mmas-8

The Morisky Medication Adherence Scale (MMAS-8) was used to assess patient adherence. The patients were asked eight questions to assess their medication use behaviour. Score is given as every correct answer is given —0‖ and wrong answer as —1‖. The scale categorizes adherence as high adherence (0), medium adherence (1-2) and low adherence (3-8) based on the scores.

MANOVA

Multiple analysis of variance (MANOVA) was used to analyze the variance, with two or more dependent variables which measured different aspects of some cohesive themes, including several different reductions in BP (for example. DAY0, DAY3 & DAY6).

NIPALS

The NIPALS Algorithm ("Nonlinear Iterative Partial Least Squares") was used for calculating the principal components of a data set which gives more numerically accurate results when compared with the singular value decomposition (SVD) of the covariance matrix, but is slower to calculate.

Statistical analysis

Descriptive analysis was conducted for demographic data. The correlation between blood glucose levels and falls was analyzed using a Multivariate Analysis of Variables (MANOVA). Various factors such as polypharmacy, age, gender, and other factors that might correlate with falls and adverse drug reactions (ADRs) were assessed using the statistical method of Nonlinear Iterative Partial Least Squares (NIPALS) at a significance level of $P<0.000$.

RESULTS

This study was carried out to assess medication adherence, drug-drug interactions, adverse drug reactions, and falls in geriatric patients with diabetes.

Demographic Data

Gender Distribution

Of the 100 patients enrolled in the study, 55 (55%) were males, and 45 (45%) were females (Table 1).

Age distribution

The majority (71%) of the patients were aged between 60 and 69 years, 19% belonged to the 70-79 category, and 10% were older than 80 years. (Table 1).

Duration of diabetes

The patients were divided into groups depending on the number of years they had been suffering from diabetes. 34 patients were diagnosed with diabetes within the past 1-5 years. 44 patients were diagnosed with diabetes for 6-10 years. Sixteen individuals belonged to the group aged 11-15 years and five patients had diabetes for 16-20 years and one individual had diabetes for more than 20 years (Table 1).

Social habits

The distribution of the study patients based on their social habits revealed that 33% of them were alcoholics and 34% were smokers (Table 1).

Polypharmacy

Polypharmacy was divided into prescriptions containing four, 5-7 drugs, to 8-10 drugs and more than ten drugs consumed by 10%, 33%, 45%, and 12%, respectively (Table 1).

Utilization pattern of number of anti-diabetic drugs

The drugs utilized by the patients were categorized based on whether they were administered single or combination therapy. Among all patients, 59 (59%) were on monotherapy and 41 (41%) were on combination therapy; 38 patients were consuming two drugs and three drugs were consumed by three drugs (3%) (Table 1).

Utilization pattern of various anti diabetic drugs

The utilization pattern of anti-diabetic drugs among the study patients indicates that insulin was the most frequently used medication, administered 62 times. Among the oral anti-diabetic drugs, metformin, a biguanide, was used 27 times. Sulfonylureas were less commonly used, with glimepiride administered 2 times and glipizide 1 time. The alpha-glucosidase inhibitor voglibose was used 3 times (Table 1).

Monotherapy utilized

Among 100 patients, insulin alone was utilized 62 times as a single drug therapy, followed by metformin (27 times), glimepiride (2 times), glipizide (1 time), and voglibose (3 times) (Table 1).

Combination therapy utilized

Among the 100 patients, a combination of Glimepiride + Metformin was utilized 40 times, Metformin + Glibenclamide was utilized once, Vildagliptin + Metformin was used once, Metformin + Pioglitazone was utilized once, and triple therapy was administered three times, that is, Glimepiride + Voglibose + Metformin (Table 1).

Table 1: Demographic distribution among patients

Gender distribution among study population		
Gender	**n=100**	**%**
Males	55	55 %
Females	45	45%
Age distribution among study population		
Age in years	**n=100**	**%**
60-69	71	71%
70-79	19	19%
80+	10	10%
Duration of diabetes mellitus in years		
Duration of Disease (in years)	**n=100**	**%**
1-5 years	34	34%
+6-10years	44	44%
11-15years	16	16%
16-20 years	5	5%
More than 20 years	1	1%
Distribution of population based on their social habits		
Social habits	**Yes**	**No**
Alcoholic (n=100)	33%	67%
Smoker(n=100)	34%	66%
Polypharmacy among study population		
No. of drugs	**n=100**	**%**
4 drugs	10	10%
5-7drugs	33	33%
8-10 drugs	45	45%
More than 10 drugs	12	12%
Utilization pattern of number of anti- diabetic drugs among study population		
No. of drugs	**n=100**	**%**
Mono therapy(1drug)	59	59%
2 drugs	38	38%
3 drugs	3	3%
Utilization pattern of anti-diabetic drug		
Class	**Drug**	**No. of times**
-	Insulin	62
Biguanides	Metformin	27
Sulfonyl urea	Glimepiride	2
	Glipizide	1
Alpha glucoside inhibitors	Voglibose	3
Monotherapy utilized among patients		
Utilized as single medication	**No. of times given in all prescriptions**	
Insulin	62	
Metformin	27	
Glimepiride	2	
Glipizide	1	
Voglibose	3	
Combination therapy among patients		
Double therapy	**No. of times**	
Glimepiride + metformin	40	
Metformin + glimenclamide	1	
Vildagliptin +metformin	1	
Metformin + pioglitazone	1	
Triple therapy	**No. of times**	
Glimepiride + voglibose + metformin	3	

Comorbid conditions

The study included 100 patients with various comorbid conditions, and 19% of them had diabetes alone. The most common combination was diabetes with hypertension (15%) and diabetes with COPD (13%). Other notable combinations included diabetes with peripheral neuropathy (10%), diabetes with hypertension and COPD (9%), and diabetes with gastroenteritis (4%). There were also instances of diabetes with hemiparesis, rheumatoid arthritis, benign prostatic hyperplasia, blood disorders, alcoholic liver disease, hyperlipidaemia with COPD, and hypertension with cerebrovascular accidents, each affecting 1% of the patients. Additionally, some patients had more complex conditions, such as diabetes with hypertension, ischaemic heart disease, and COPD (4%), diabetes with hypertension and ischaemic heart disease (2%), and diabetes with Alzheimer's disease and lower respiratory tract infection (2%). Other combinations, such as diabetes with asthma, polyarthralgia, lower respiratory tract infection, and urinary tract infection with anaemia and hypothyroidism, were present in smaller percentages (Table 2).

Medication adherence

The level of medication adherence of study patients was assessed using the Morisky Adherence Scale for patients on polypharmacy before admission to the hospital. We found that 10 patients were not on polypharmacy before admission, 17 patients were found to be highly adherent, 41 were medium adherent, and 32 patients were low adherent (Table 2).

Drug Interactions

It was found that, there are 6 major drug interactions, 59 moderate drug interactions, 42 minor drug interactions. We identified 42 minor interactions which were found to be less significant. (Table 2).

Adverse drug reactions

ADRs were observed in 6% of study patients. The observed ADRs were metformin-induced hypoglycaemia in three patients (3%), metformin-induced diarrhea in1 patient (1%), and glimepiride-induced dyspepsia in two patients (2%) (Table 2).

ADR Causality

In present study, it was found that the probability of ADR was possible (2), probable (2), and doubtful (2). Among the observed ADRs, 33.33% were possible, 33.33% probable, and 33.33% doubtful (Table 3).

Severity of ADR

The severity of ADRs was assessed using the Modified Hartwig and Siegal scale. This study found out one moderate and five mild ADRs. 83.33 Of the ADRs, 83.33% were mild, and 16.66% were minor. No severe ADRs were observed (Table 3).

Episodes of falls in patients

In our study, we noticed six episodes of falls. Various factors such as polypharmacy, age, adherence, severity of adverse drug reactions, and drug-drug interactions (major, moderate, minor) correlate with falls and ADR type. It shows strong significance, and some are moderately significant for the various factors. This was performed using NIPALS (Figure 1).

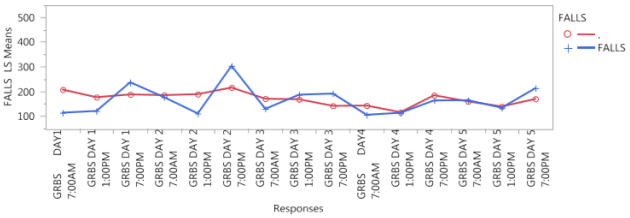

Fig. 1: Correlation between blood glucose levels and falls

DISCUSSION

The study was conducted among geriatric patients with diabetes (aged > 60 years) who were on polypharmacy for a period of 6 months. One hundred patients were enrolled from the MVJ Medical College and Research Hospital, Hoskote. It is a general assumption that gender does not play a role in influencing the risk of being affected by type 2 DM; however, in the last half century, the disorder had a predominant effect on men as compared to women. According to our current sample of patients, we had a higher number of male representatives (55%) than female representatives (45%). Many other studies have also reported a higher incidence of diabetes in males. This could be due to the higher number of associated risk factors present in males[16], which suggests a gender difference in type 2 diabetes, with a higher prevalence and increased risk in males.

Of the 100 T2DM patients studied, the majority of patients were found in the category of 60 69, 71 patients belonged to 60-69 years, while 19 patients were between the age of 70-79 followed by 10 patients above 80 years of age, with a mean age of 66.89. According to WHO estimates of the global prevalence of diabetes, the majority of patients are in the range of 45-68 years thus, our study showed a similar trend in age-wise distribution[17].

Among the 100 patients in the study, 33 (33%) had a habit of drinking alcohol and 34 (34%) were smokers. This

Table 2: Comorbidities, medical adherence, drug interactions observed among patients

Comorbid conditions		
Co-morbid condition	**n=100**	**%**
Diabetes Alone	19	19%
DM+HTN	15	15%
DM+HTN+COPD	9	9%
DM+ Peripheral Neuropathy	10	10%
DM+COPD	13	13%
DM+ Hemiparesis	1	1%
DM+ Peripheral Neuropathy + Bronchitis	2	2%
DM+RA	1	1%
DM+BPH	1	1%
DM+ Blood Disorder	1	1%
DM+ Gastroenteritis	4	4%
DM+ALD	1	1%
DM+ Nephropathy	3	3%
DM+ Asthma	2	2%
DM+HTN+IHD+COPD	4	4%
DM+HTN+IHD	2	2%
DM+ Hyperlipidaemia +COPD	1	1%
DM+ Polyarthralgia	2	2%
DM+HTN+LRTI	4	4%
DM+UTI+ Anaemia + Hypothyroid ISM	1	1%
DM+ADS+LRTI	2	2%
DM+HTN+CVA	1	1%

Medical adherence among patients		
Adherence	**n=100**	**%**
High	17	17%
Medium	41	41%
Low	32	32%
Adherence not taken	10	10%

Drug interactions among patients	
Type of drug interaction	**No. of times observed**
Major drug interactions	6
Moderate drug interactions	59
Minor drug interactions	42

Major drug interactions among patients		
Drug-drug interaction	**Effect/ mechanism**	**Management**
Ciprofloxacin + ondansetron	Increase QT interval	ECG monitoring
Diclofenac + Enalapril	Decrease in renal function	Ability of NSAIDS to reduce the synthesis of vasodilating renal prostaglandins, dosage adjustment
Enalapril+ Pregabalin	Increases toxicity of others like angioedema of face, mouth and neck	Adjust the dose
Azithromycin + Ondansetron	Increases qt interval	ECG monitoring
Dosulepin + Phenylephrine	Increase or decreases effect of sympathomimetic, blocking reuptake of ne	Dosage adjustment
Escitalopram + Amitriptyline	Both increases serotonin levels	Monitor closely

Table 3: Adverse drug reaction among patients

Adverse type	**n=100**	**%**
Metformin induced hypoglycaemia	3	3%
Metformin induced diarrhoea	1	1%
Glimepiride induced dyspepsia	2	2%
ADR probability of study subjects		
Causality of ADR	**n=100**	**%**
Possible	2	33.33%
Probable	2	33.33%
Doubtful	2	33.33%
Severity of ADR		
Severity of ADR	**n=100**	**%**
Severe	0	0%
Moderate	1	16.66%
Mild	5	83.33%

result was similar to a study which found that men who drank >14 drinks of spirits per week should be advised of the increased risk of diabetes associated with heavy alcohol consumption[18]. Smoking increases the incidence of diabetes, aggravates glucose homeostasis, and causes chronic diabetic complications. Among microvascular complications, the onset and progression of diabetic nephropathy are highly associated with smoking. However, smoking prevention and cessation may not be sufficiently emphasized in diabetic clinics. Thus, educating patients on the importance of not smoking and engaging in smoking cessation programs is an important strategy for diabetes management[19].

Adherence was calculated among the patients using the Morisky medication adherence scale; high adherence was found in 17 patients (17%), medium adherence in 41 patients (41%), and low adherence in 32 patients (32%). There was no medication adherence for 10 patients since they were not on polypharmacy before admission. A cohort study, conducted on 128 randomly selected patients with type 2 diabetes from a community health centre, responded to a questionnaire regarding medication use. Survey data were linked to clinical data available from electronic medical records. They found that among patients on three or more medications, 70% sub-optimal adherence was perfectly adherent to all but one medicine and of 29 medications causing side effects, 24 interfered with adherence for more than one month, and only seven were reported to the physician. The present study showed that medication adherence rates that were too high, regardless of the number of medications used and patients on multiple medications, showed suboptimal and unreported side effects, lack of confidence, and were significant predictors of suboptimal adherence. Physicians should not feel deterred from prescribing multiple agents to achieve adequate control of hyperglycaemia, hypertension and hyperlipidemia[20].

Potential drug-drug interactions were found; major interactions were found in 7 (7%), moderate drug-drug interactions were found in 59 (59%), and minor drug–drug interactions were found in 42 (42%) patients, similar to the results of other studies which were conducted on polypharmacy and potential drug-drug interactions among elderly patients. Polypharmacy was observed on the basis of admission and discharge prescriptions. Frequently occurring drug-drug interactions were assessed using online checks. The results were found to be more than half of the patients have received 5-9 number of drugs and severe drug interactions were 6.8% and moderate drug interactions were 76.8% and minor drug interactions were 16.4%. Appropriate prescriptions are important to improve drug safety in high-risk patients[21]

In the present study, most patients had comorbidities. The majority of patients had DM alone (19%), hypertension (15%), DM + COPD (13%), DM + Peripheral neuropathy (10%), DM + HTN + COPD (8%), and other comorbidities (56%). Polypharmacy was divided into prescriptions containing 4 medicines, ae 10 individuals (10%), 5-7 medicines were 33 individuals (33%) and 8-10 medicines are 45 individuals (45%), more than 10 medicines were 12 individuals (12%). Our study results are similar to those reported by Richard et al.[20]. Our study found that six episodes of falls were not due to antidiabetic drugs which is consistent with a previous study[22] .

In our study, insulin alone was prescribed in 62 patients, metformin in 27, sulfonylureas in 3, and alpha-glucosidase inhibitors in 3. Sulfonylureas were the most commonly prescribed class, whereas metformin (biguanide) was the most commonly prescribed individual drug among oral hypoglycaemic agent (OHA). A fixed-dose combination of biguanide and sulfonylurea is commonly prescribed. Monotherapy was dominant over polytherapy, and there was a higher percentage of insulin use in patients with type 2 dia-

betes. Only 41% of the patients receiving antidiabetic therapy had optimal glycaemic control. The association between antidiabetic therapy, lifestyle modification, and glycaemic control was statistically significant[23]. The study observed metformin-induced hypoglycaemia in three patients (3%), metformin-induced diarrhoea in one patient (1%), and glimepiride-induced dyspepsia in two patients (2%) which is in accordance with the study by Deb et al.[16].

CONCLUSION

Geriatric patients with type-2 diabetes often face complications due to polypharmacy, primarily due to increased age and comorbid conditions. Understanding these issues can improve the quality of life of geriatric patients with diabetes, who often require multiple medications to treat their diabetes and comorbidities.

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