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Original Article

A COMPREHENSIVE ANALYSIS OF ANTIDIABETIC DRUG INTERACTIONS IN GERIATRIC NON-INSULIN DEPENDENT DIABETES MELLITUS PATIENTS

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ABSTRACT

Objective: Type 2 diabetes mellitus (DM) is a disease that is the leading cause of blindness, heart disease, and kidney failure. Geriatric patients with type 2 DM and complications require multiple medications (polypharmacy), contributing to drug-drug interactions (DDIs). DDIs can affect the clinical outcome of patients. This study aims to analyze potential drug-drug interactions based on the mechanism and severity, determine the relationship between the number of medications and potential drug interaction, and determine the relationship between polypharmacy and the severity of clinical outcomes.

Methods: This was an analytical observational with retrospective data collection through patient medical records of hospitalized patients treated with an antidiabetic and one or more other drugs that met the inclusion criteria, involving 81 patients using total sampling.

Results: The result showed that out of 81 patients, there were 59 patients who potentially experienced drug-drug interactions (72.8%) with a total of 162 cases of drug interactions, and the most prevalent interaction mechanism was pharmacodynamic (84.0%) with a moderate severity level (57.4%). There was a significant relationship between the number of medications and potential drug-drug interactions ($p<0.05$). At the same time, there was no meaningful relationship between polypharmacy and the severity of drug interactions with clinical outcomes ($p>0.05$).

Conclusion: An increase in the number of drugs is a predictor of drug interactions. Although drug interactions may theoretically occur, not all interactions will significantly affect patients.

Keywords: Potential drug interactions, Type 2 DM, Geriatrics, Antidiabetic

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INTRODUCTION

One of the degenerative diseases that has garnered global attention is diabetes mellitus (DM). Out % of all DM cases, 90% of them are type 2 diabetes. Apart from being a leading cause of premature death worldwide, this disease is also a primary cause of kidney failure, blindness, and heart disease [1]. The International Diabetes Federation (IDF) estimated that in 2021, there would be 537 million diabetes patients aged 20-79 worldwide. This number is projected to rise to 643 million by 2030 and 783 million by 2045 [2, 3]. Based on Basic Health Research for West Sumatra Province, Padang holds the third-highest prevalence after Pariaman and Padang Panjang, at 1.79% [4]. In 2017, as many as 62.5% of type 2 DM patients at Dr. M. Djamil Hospital in Padang had uncontrolled blood sugar levels. In 2020, Type 2 DM ranked 8th out of that hospital's top 10 most admitted diseases [5].

The elderly tend to have multiple diseases, especially degenerative ones related to age, such as hypertension, hyperlipidemia, diabetes mellitus, stroke, rheumatism, and osteoporosis. This leads to polypharmacy, where the elderly consume multiple medications [6]. Polypharmacy is often associated with adverse outcomes such as death, adverse drug reactions (ADR), prolonged hospital stays, and increased risk of drug interactions [7–9]. Around 3-26% of all ADRs requiring hospitalization are caused by drug interactions [10, 11].

Based on the research by Sankar *et al.* (2015), out of 50 prescriptions for diabetes patients, 35 (70%) of them had at least one drug-drug interaction [12]. The most significant interactions were between antidiabetic drugs and heart medications (92%), analgesics (66%), antibiotics (52%), other antidiabetic drugs (26%), diuretics (26%), and antipsychotic drugs (24%) [12]. Seeing this high number, a comprehensive study was conducted to assess the potential for drug iteration among geriatric DM patients.

MATERIALS AND METHODS

Research design

This study was conducted at the Medical Records Installation of Dr. M. Djamil Hospital in Padang from February to April 2023. This research is an analytical observational study with retrospective data, which involves collecting data from patient medical records throughout 2021 using total sampling.

Patient criteria

Data were included if inpatients were prescribed an antidiabetic with one or more other drugs (including other antidiabetic), were aged ≥60 y, were diagnosed with type 2 DM with complications, and had random blood sugar test data. We excluded any data for Elderly patients diagnosed with type 2 diabetes mellitus with incomplete and unreadable treatment data in the medical record.

Data analysis

After the data were collected, the data was analyzed for potential interactions using references such as Stockley's Drug Interactions 9th edition textbook [6, 13], Drug Interaction Facts textbook, the Medscape application, and the Drug Interaction Checker database (www. drugs. com) developed by Wolters Kluwer Health, the American Society of Health-System Pharmacists, Cerner Multum [14], and Micromedex from Truven Health. Subsequently, Bivariate analysis was used to examine the relationship between the average daily drug usage and the potential for drug interactions and the relationship between the average daily drug usage, polypharmacy, and clinical outcomes. These factors were then hypothetically tested using IBM SPSS for Windows, Version 26 (IBM Corp., Armonk, NY, USA). To see the relationship between sociodemographic variables (categorical) and type of interaction, the number of interactions (categorical) and clinical outcome (categorical) will be analyzed using chi-square analysis. The relationship between all numerical and categorical variables will be analyzed using the T-test (parametric) or Mann-Whitney (non-parametric). To determine the data distribution, normality analysis will be done using Kolmogorov Smirnov (data more than 50) [15, 16]. A value of $p<0.05$ indicated that there was a relationship between the two variables.

Ethical approval

This research received ethical approval from the Health Research Ethics Committee of Dr. M. Djamil Padang Hospital with approval No. LB.02.02/5.7/125/2023.

RESULTS

In this study, a description of patient characteristics of geriatric T2DM patients can be seen in table 1. The distribution of geriatric patients suffering from type 2 diabetes mellitus is highest in the age group of 60-69, with a percentage of 81.5%.

Table 1: Patient characteristic

Patient characteristics	n	Percentage (%)
Age		
Elderly (60-69 y)	66	81.5
High-risk elderly (≥70 y)	15	18.5
Gender		
Man	38	46.9
Women	43	53.1

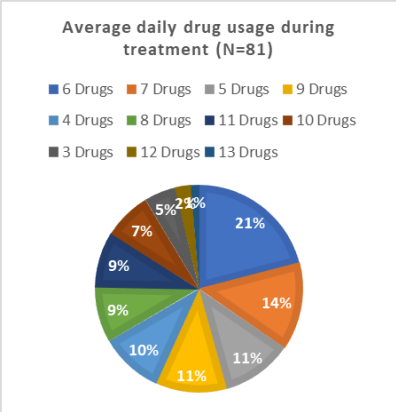

Fig. 1: Average daily drug usage during treatment

Fig. 1 shows the average daily drug usage during treatment. The average daily dose during treatment ranges from 3-13 drugs, with the most common average being six (21.1%). The average daily drug usage of diabetes mellitus medications is determined based on the number of drugs patients consume daily during their hospitalization.

Among 125 instances of antidiabetic drug use in Dr. M. Djamil Padang Hospital in 2021 that met the inclusion criteria, the most commonly used antidiabetic drug was Novorapid 47.2%, followed by Levemir 26.4%, and Gliquidone 13.6% (fig. 2). According to fig. 3, it was found that 59 patients (72.8%) potentially experienced interactions.

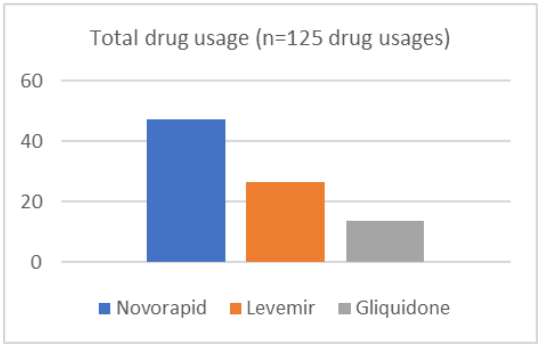

Fig. 2: Profile of antidiabetic drug usage

There were 162 cases of drug interactions in 59 patients who used antidiabetic drugs. These DDI cases were identified based on the type of interactions, with the most common interaction mechanism being pharmacodynamic at 136 incidents (84%), followed by pharmacokinetic interactions at two incidents (1.2%), and there were also unknown types of interactions at 24 incidents (14.8%). For the severity of DDIs, moderate level severity had the highest value, namely 93 incidents (57.4%), followed by major interactions with 56 (34.6%0 and minor interactions with 13 (8.0%).

The results of the Mann-Whitney test for the relationship between the average number of drugs and the potential for drug interactions that can be seen in table 2 yielded a p-value of 0.005, which means p<0.05.

Table 2: Mann-Whitney test result of the relationship between average daily number of drugs and potential drug interactions

Potential drug-drug interactions	n	Average daily number of drugs					*P-value*
		mean±SD	95% CI		Min.	Max.	
			Lower	Upper			
Yes	59	7.627±2.525	6.969	8.285	3.00	13.00	0.005
No	22	5.863±1.726	5.098	6.629	3.00	10.00	

Examining table 3, it's evident that the p-value stands at 0.730, signifying that P>0.05. This suggests there is no notable association between Polypharmacy and the clinical outcome of Random Blood Glucose (RBS). When observing the average values of patients, those with minor Polypharmacy saw a reduction in RBS levels, while patients with major Polypharmacy showed an increase in RBS.

Table 3: Mann-Whitney test result of the relationship between polypharmacy with clinical outcomes

Average daily number of drugs	n	% Random blood sugar difference					*P-value*
		mean±SD	95% CI		Min.	Max.	
			Lower	Upper			
1-4 Drugs (Minor Polypharmacy)	12	15.639±35.769	-7.088	38.365	-62.04	53.13	0.730
≥ 5 Drugs (Major Polypharmacy)	69	-14.678±121.413	-43.844	14.489	-590.3	75.31	

Meanwhile, based on table 4, the obtained p-value is 0.527, which means P>0.05, indicating no significant relationship between the severity level of drug interactions and clinical outcome (RBS).

Table 4: Mann-Whitney test result of the relationship between severity with clinical outcomes

Interaction severity	n	% Random blood sugar difference					*P-value*
		mean±SD	95% CI		Min.	Max.	
			Lower	Upper			
Minor and Moderate	24	-17.414±105.529	-61.976	27.147	-443.3	60.18	0.527
Major	35	-3.521±103.381	-39.034	31.992	-525.4	73.94	

DISCUSSION

The American Diabetes Association (ADA) states that advancing age increases the risk of type 2 diabetes mellitus [17]. This is based on the accumulation of body fat, particularly in the abdominal area, in older individuals, leading to central obesity. Central obesity, in turn, triggers insulin resistance, which is the initial process of developing type 2 diabetes mellitus [1, 18, 19]. Similarly, a study by Fitria *et al.* indicates that the highest prevalence of type 2 diabetes mellitus is among the elderly (60+years) [20, 21]. Table 1 shows that the distribution of patients by gender reveals that the percentage of geriatric patients with type 2 diabetes mellitus is higher among females, accounting for 53.1% [22]. This corresponds to the research, which indicates that more females suffer from type 2 diabetes mellitus compared to males, at 55.56 % [23]. During menopause, the response to insulin decreases due to low levels of estrogen and progesterone, hormones that play a role in improving insulin responsiveness. Another factor is that many females have less than ideal body weight, which can reduce insulin sensitivity. These factors contribute to females being at a higher risk of developing diabetes than males [24].

Medication use in geriatric patients with type 2 diabetes aims to control the patient's blood sugar levels and manage several complications that arise in individuals with type 2 diabetes. This often leads to unavoidable polypharmacy [25]. The degenerative (aging) process results in the loss of tissue's ability to repair itself, maintain its structure, and function normally[26]. Older individuals generally suffer from more than one chronic disease that requires specific therapy. This is consistent with the previous research, which showed that most elderly diabetes patients receive Polypharmacy treatment, with the most common cases involving five drugs, six drugs, seven drugs, and nine drugs [27, 28].

Novorapid and Levemir belong to antidiabetic drugs and are typically administrated to T2DM patients with complications. According to PERKENI, insulin therapy for inpatients with diabetes is indicated for (1) DM patients with critical illness: hyperglycemic crisis, and (2) DM patients with non-critical illness: uncontrolled with oral hypoglycemic agents (OHA), corticosteroid use, surgical preparation, gestational diabetes, and specific conditions causing insulin metabolism disorders [29]. This study is in line with Gunawan *et al.* (2019), which showed that the most commonly used antidiabetic drugs for type 2 DM patients with complications were Novorapid (48.89%) and Levemir (15.56%) [29]. According to Azemi *et al.*, insulin is used when dietary efforts and oral hypoglycemic drugs cannot control blood sugar levels close to normal. Insulin use aims to achieve and maintain blood sugar levels close to normal limits to prevent and delay long-term complications [30].

Analysis of antidiabetic drug interactions in geriatric patients with type 2 diabetes in the inpatient ward is based on interaction mechanisms divided into two categories: pharmacodynamic and pharmacokinetic. A pharmacodynamic drug interaction occurs when a combination of two or more drugs changes the effect of one of the drugs (this interaction can be synergistic if the effect increases or antagonistic if the effect decreases). On the other hand, pharmacokinetic interactions involve changes in a drug's absorption, distribution, metabolism, and excretion, which can affect the drug's blood concentration.

The use of multiple drugs is one of the contributing factors to drug interactions, which subsequently affect the effects of drugs in the body, thus influencing the success of patient therapy (clinical outcomes). However, based on the average percentage change in initial and final RBS values for patients, the group with major severity level interactions did not experience a higher increase in RBS compared to the groups with minor and moderate severity levels. This is because interactions do not always lead to an increase in RBS (hyperglycemia); they can also lead to a decrease (hypoglycemia). For example, the most common major interaction between insulin and levofloxacin can lead to either hyperglycemia or hypoglycemia. However, the exact effects cannot be determined as the final RBS values were not measured immediately after a possible interaction, which is a study limitation.

The RBS is influenced not only by the drugs consumed by patients but also by various factors such as stress, common in hospitalized patients, other foods consumed by patients besides those provided by the hospital, and the lack of physical activity during hospitalization. Furthermore, another contributing factor is that patients experiencing drug interactions may not have just one case of interaction at the minor, moderate, or major severity level; many have more than two, even up to ten drug interactions with the same or different severity levels.

Several factors influence the diverse alterations in the potential effects of drug interactions on individuals. These include the dosage of the drug, the concentration of the drug in the bloodstream, the method of drug administration, how the drug is metabolized in the body, the length of time the therapy is administered, and individual patient attributes such as age, gender, genetic predispositions, and specific health conditions. Notably, patients with liver and kidney disorders, which can disrupt the metabolism and elimination of drugs, may experience particularly pronounced effects [31]. Although drug interactions may theoretically occur, not all interactions will significantly affect patients. Nevertheless, pharmacists should always remain vigilant about the harmful effects of these drug interactions to prevent patient morbidity or even mortality as early as possible [32].

Strengths and limitations of the study

The study thoroughly analyzes potential drug-drug interactions (DDIs) in geriatric patients with type 2 diabetes mellitus (DM) and complications. It covers various aspects, including mechanism, severity, and relationship with medication count and polypharmacy. The research relies on retrospective data collected from actual patient medical records. This enhances the study's applicability to clinical practice and reflects real-life scenarios. The study encompasses a sizable sample of 81 patients, utilizing total sampling. This increases the robustness and generalizability of the findings. The study employs statistical analysis, including p-values, to assess the significance of relationships between variables. This adds a quantitative dimension to the results. However, there are still several limitations to this research, including retrospective data being subject to biases, incomplete records, and potential confounding variables, which could impact the accuracy and reliability of the results. Apart from that, this research is still a Single-Center Study: If the study is conducted in a single healthcare facility, it may limit the diversity of patient demographics and treatment approaches, potentially affecting the generalizability of the findings. Overall, while the study provides valuable insights into potential DDIs in geriatric patients with type 2 DM, it is important to consider these strengths and limitations when interpreting the findings and applying them to clinical practice.

CONCLUSION

In this study involving 81 patients, a substantial 72.8% (59 individuals) were found to have potentially experienced drug-drug interactions, resulting in 162 recorded cases of such interactions. Among these interactions, the predominant mechanism observed was pharmacodynamic, accounting for a notable 84.0%, often manifesting at a moderate severity level of 57.4%. The research also revealed a statistically significant correlation between the quantity of medications taken and the likelihood of encountering drug-drug interactions ($p<0.05$). However, intriguingly, no substantial connection was established between polypharmacy and the severity of drug interactions concerning clinical outcomes ($p>0.05$). This emphasizes that an increase in the number of prescribed drugs predicts drug interactions. It's important to acknowledge that while drug interactions are theoretically possible, not all interactions will inevitably produce discernible effects on patients.

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AUTHORS CONTRIBUTIONS

RY: Conceptualization, Supervision, Writing–Original Draft; NF: Supervision, Resources, Review and Editing; and ES: Data Collection, Writing–Original Draft. All authors approved the final version of the manuscript.

CONFLICT OF INTERESTS

There is no conflict of interest from all the authors

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