

Analysis of Antidiabetic Adverse Drug Reaction (ADR) at Puskesmas X Wonogiri Regency

Analisis *Adverse Drug Reaction* (ADR) Antidiabetes di Puskesmas X Kabupaten Wonogiri

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ABSTRACT

Antidiabetic drugs are used in the long term and have the potential for side effects or Adverse Drug Reaction (ADR), but how their prevalence and probability have not been widely studied. The purpose of this study was to determine the incidence rate of ADR, especially glibenclamide, metformin and insulin in primary care and how the probability is.

The type of research is an observational, descriptive non-analytic study, prospective data collection using questionnaires that have been tested for validity and reality. The number of samples used in this study was 120 respondents. The data were analyzed univariately by percentage of ADR events, and probability analysis was performed using the Naranjo algorithm.

The results showed that as many as 46 (38.3%) respondents experienced ADR. The types of ADR events in the form of nausea, drowsiness, dizziness, weakness, and tremor were 32.6%, 30.4%, 17.4%, 15.2%, and 3.3%. Glibenclamide causes manifestations of tremor, weakness, nausea, drowsiness in the categories of probable, doubtful, probable, probable. The use of metformin manifestations in the form of weakness, nausea, drowsiness, and dizziness in the categories of doubtful, possible, probable, and probable. The combination of Glibenclamide and Metformin manifests in the form of weakness, nausea, drowsiness, and dizziness in the categories of possible, probable, probable, and probable. Insulin manifestations in the form of weakness in the probable category.

Keywords: Adverse Drug Reaction; Diabetes Mellitus; Antidiabetic Mellitus Drugs

ABSTRAK

Obat antidiabetes digunakan dalam jangka panjang dan memiliki potensi efek samping atau Adverse Drug Reaction (ADR), namun bagaimana prevalensi maupun probabilitasnya belum banyak diteliti. Tujuan penelitian ini untuk mengetahui angka kejadian ADR terutama glibenklamid, metformin dan insulin di layanan primer dan bagaimana probabilitasnya

Jenis penelitian adalah studi observasional, deskriptif non analitik, pengambilan data secara prospektif menggunakan kuesioner yang telah diuji validitas dan realibilitas. Jumlah sampel yang digunakan dalam penelitian ini yaitu 120 responden. Data dianalisis secara univariat dengan mempersentasekan kejadian ADR, dan analisis probabilitas dilakukan menggunakan algoritme Naranjo.

Hasil penelitian menunjukkan sebanyak 46 (38,3%) responden mengalami ADR. Jenis kejadian ADR berupa mual, mengantuk, pusing, lemas, dan tremor sebesar 32,6%, 30,4%, 17,4%, 15,2%, dan 3,3%. Glibenklamid menimbulkan manifestasi tremor, lemas, mual, mengantuk pada kategori *probable, doubtful, probable, probable*. Penggunaan metformin manifestasi berupa lemas, mual, mengantuk, dan pusing pada kategori *doubtful, possible, probable, dan probable*. Kombinasi Glibenklamid dan Metformin manifestasi berupa lemas, mual, mengantuk, dan pusing pada kategori *possible, probable, probable, dan probable*. Manifestasi Insulin berupa lemas pada kategori *probable*.

Kata kunci: *Adverse Drug Reaction*; Diabetes Melitus; Obat Antidiabetes Melitus

1. INTRODUCTION

Diabetes Mellitus is a condition when a person has high blood sugar levels due to abnormalities in insulin secretion. Diabetes is divided into several groups, among others, Insulin dependent diabetes mellitus (IDDM) is often referred to as type 1 DM,

Non-insulin dependent diabetes mellitus (NIDDM) or type 2 diabetes and gestational diabetes, type 2 diabetes is included in diseases encountered by a percentage of 95% of patients worldwide (1). WHO (World Health Organization) states that in 2015, Indonesia was ranked 7th among China, India, the United States, Brazil, Russia and Mexico as the highest diabetic sufferers in the world [2]. DM cases in Wonogiri city in 2015 based on data from the Wonogiri Regency Health Office, as many as 2143 cases and 1954 cases of which were type 2 DM sufferers [3]

The therapy used in DM sufferers is antidiabetic mellitus drugs, one of the antidiabetic drugs used is oral antidiabetic, the administration of these drugs is given based on the severity and condition of the patient. The use of oral antidiabetic drugs (ADO) in patients with diabetes mellitus using one or more combinations of drugs [1].

Another therapy in the treatment of DM is using insulin therapy, insulin therapy is given subcutaneously by injection or with an insulin pump. This therapy is commonly used in patients with type 1 diabetes, because patients are unable to produce insulin according to the body's needs caused by damage to pancreatic β cells [4]. Therapy given to diabetes mellitus patients must be given optimally to get maximum results, one of the forms of therapy implementation is pharmaceutical care by conducting a study of Drug Related Problems (DRP's) from therapy given to pasi [5], one form of DRP is ADR [6].

A study states that 77.1% of ADR arising after the use of oral antidiabetes mellitus drugs experienced by men and 22.86% ADR experienced by women [7] Research related to DM is more focused on the management of treatment and lifestyle changes in DM patients, but for the assessment of side effects of the use of antidiabetes mellitus drugs is still rarely done [8]. Various kinds of research related to the use of antidiabetic drugs, say that the side effects of antidiabetes mellitus drugs are a serious problem that should be overcome [9], Therefore, this research is important to do as an effort to prevent unwanted drug reactions for patients.

METHOD

2.1. RESEARCH DESIGN

The observational, descriptive non-analytical research study aimed to determine the percentage and drugs suspected of causing ADR in 120 respondents of DM patients at Puskesmas X Wonogiri Regency. This research has received an ethical approval letter from the Health Research Ethics Commission of Dr. Moewardi Hospital Surakarta City with number 1,228 / IX / HREC / 2022. The inclusion criteria of this study were outpatient DM patients at Puskesmas X Wonogiri Regency, and/or without complications, those aged over 20-79 years who wished to fill out questionnaires, with complete medical record data, and patients undergoing routine therapy. Exclusion criteria in this study were diabetes mellitus patients with lost, damaged, and incomplete medical record data, and patients did not fully receive therapy or patients stopped forcibly before recovering.

2.2 RESEARCH MATERIALS AND TOOLS

The tools used in this study were questionnaires that had passed validity and reliability tests, laptops contained in the SPSS program, as well as pharmacovigilance module literature, Meyler's Side Effect of Drugs Interaction, and supporting journals that assisted in the preparation of research.

2.3 SUBJECT

The inclusion criteria in this study were patients aged ≥ 18 years with a diagnosis of DM with or without comorbidities, patients who received painkillers either using

monotherapy or combination therapy, patients who had a complete medical record including patient identity, diagnosis, treatment given, and duration or time of drug use (date therapy was given). The exclusion criteria in this study were patients with complications of other diseases such as impaired heart, kidney, and liver function, as well as patients with complaints of pain unrelated to diabetic neuropathy.

2.4 ANALYSIS

Data analysis was carried out univariately by percentages of observed parameters, calculated from the total respondents multiplied by 100%. To conduct a qualitative analysis of the probability of ADR events, the Naranjo scale is used as follows:

Tabel 1. Naranjo Algorithm

No	Questions	Yes	No	Not Know	How to determine the score
1	Are there reports of similar side effects?	1	0	0	Find evidence of research/case reports using an article search
2	Do side effects occur after drug administration?	1	0	0	Based on respondents' answers (using questionnaires)
3	Do side effects of the drug improve after the drug is stopped or given antagonistic drugs?	2	1	0	Based on respondents' answers (using questionnaires)
4	Whether side effects of the drug recur after the medicine is re-administered	2	1	0	Based on respondents' answers (using questionnaires)
5	Are there alternative causes of possible side effects?	1	2	0	Based on respondents' answers (using questionnaires)
6	Do side effects occur when a placebo is given?	1	1	0	Answered don't know (score 0)
7	Is the suspected drug detected in blood or other body fluids in toxic concentrations?	1	0	0	Answered don't know (score 0)
8	Do side effects get worse when the dose is increased and decrease when the dose is lowered?	1	0	0	Answered don't know (score 0)
9	Whether the patient has experienced the same side effects or with similar medications before	1	0	0	Based on respondents' answers (using questionnaires)
10	Can side effects be confirmed with objective evidence?	1	0	0	Based on medical report data

Score conclusion :

- 9+ : highly probably
- 5-8 : probably
- 1-4 : possible
- 0 : doubtful

3. RESULTS AND DISCUSSION

3.1 RESPONDEN CHARACTERISTIC

Table 1 shows that the age range of 56-65 years shows the highest frequency with a percentage of 40% of the total respondent, and the range of 26-35 years has the lowest frequency of 1.7%. These results are in line with research conducted by Ramdini et al, 2020 that the distribution of elderly respondents with a range of 46-65 years has the highest frequency, this shows that the higher the age of diabetes mellitus risk factors also increase. [10]. Age has a close relationship with the increase in blood sugar levels so the older you increase, the risk of developing diabetes mellitus and its complications is even greater. Increasing age, the state of a person's body will experience a decrease in the function of organs in absorption, distribution, metabolism, and excretion.

Tabel 2. Distribution of Characteristics of Respondents Users of Antidiabetes Mellitus Drugs

Characteristic		Frequency	Percentage (%)
Age (years)	26-35	2	1,7
	36-45	3	2,5
	46-55	25	30
	56-65	55	45,8
	>65	24	20
	Total	120	100
Gender	female	75	71
	male	32	29
	Total	129	100
Type of Diabetes Mellitus	DM Tipe 1	4	3,3
	DM Tipe 2	116	96,7
	Total	120	100
Long of sufering	<6 years	11	9,2
	6-10 years	12	10
	11-15 years	67	55,8
	>16 years	30	25
	Total	120	100
comorbidity	Yes	63	52,5
	No	57	47,5
	Total	120	100

Source : primary data processed in 2022

This study also shows that the frequency of female respondents has a percentage of 71% of the total respondents, in line with research conducted by Millita et al in 2021 which stated that 55.5% of Diabetes mellitus respondents were women [10][11], this shows that women have a greater risk of developing diabetes mellitus, possibly caused by differences in daily activities and lifestyles, and also hormonal influences.

3.2 Adverse Drug Reaction (ADR) events

The incidence of Adverse Drug Reaction (ADR) experienced by outpatients using anti-diabetes mellitus drugs at Puskesmas X Wonogiri Regency from 120 respondents, 46 respondents (38%) of whom experienced ADR from the use of the drug. The frequency distribution of ADR can be seen in the following diagram:



Figure 1. Diagram of the incidence of ADR on the use of DM drugs in 120 respondents

Figures 1 explains that as many as 62% of respondents felt an undesirable effect. This is different from other studies which state that a small percentage of respondents experience ADR, which is 8.1% [1]. Research by Isnaini and Mulyani (2018) also explained that the use of antidiabetic drugs impacted ADR in a small percentage of respondents, namely 31.57%, with drugs suspected of causing the following:

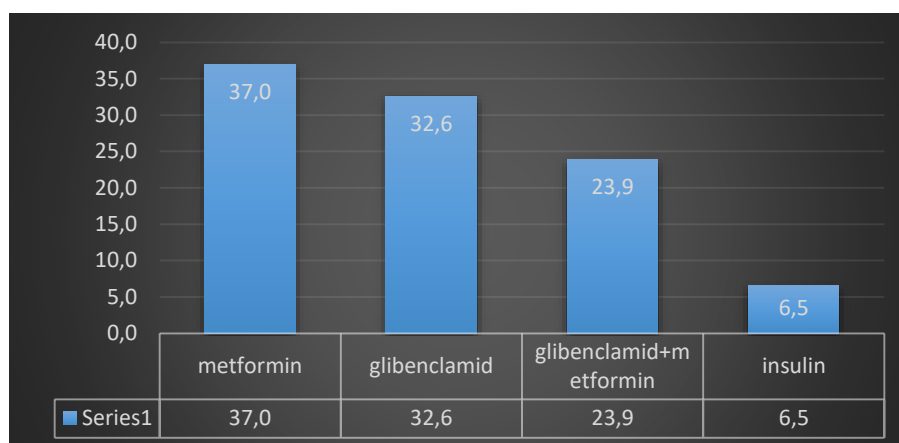


Figure 2. Types of drugs suspected of causing side effects

Based on the study result, figure 2 shows that metformin drug users have the highest percentage of ADR at 37%, while the lowest ADR cause is insulin at 6.5%. In line with research by Putra, et al in 2017 which stated that the cause of ADR among other antidiabetics is metformin [12].

3.3 Probability ADR Analysis with Naranjo algorithm

Tabel 2. Frequency Distribution of Adverse Drug Reaction (ADR) Events based on Diabetes Mellitus Drugs

Drug used	ADR Tremor		ADR weak fatigue		ADR Nausea		ADR Sleepy		ADR dizziness	
	N	Scale	N	Scale	N	Scale	N	Scale	N	Scale
Glibenclamid	1	Probable	1	Doubtful	3	Probable	6	Possible	-	-
	2	Possible	-	-	-	-	1	Probable	-	-
	-	-	-	-	-	-	1	Doubtful	-	-
Metformin	-	-	1	Doubtful	4	Possible	1	Doubtful	2	Possible
	-	-	-	-	2	Probable	1	Possible	3	Probable
	-	-	-	-	2	Doubtful	1	Probable	1	Doubtful
Combination Glibenclamid and Metformin	-	-	2	Possible	4	Probable	1	Probable	2	Probable
Insulin	-	-	1	Possible	-	-	-	-	-	-

It can be known that there are manifestations of ADR due to the use of anti-diabetes mellitus drugs. The Glibenclamide drug used has an impact on the incidence of tremors as many as 1 respondent in the Probable category which means that it is likely that the glibenclamide drug causes dizziness for its users. While two respondents in the possible category which means the incidence of ADR is caused by the use of Glibenclamide drugs. Furthermore, in the manifestation of ADR in the form of weakness caused by the drug Glibenclamide, as many as one respondent was in the doubtful category which means that the drug has no impact or doubtfully gives side effects of weakness. In the manifestation of ADR nausea as many as 3 respondents in the probable category which means that the drug Glibenclamide is likely to cause nausea in its use. In the manifestation of sleepy ADR as many as 6 respondents in the possible category where this means that the drug Glibenclamide may cause drowsiness for its users.

The metformin drug used had an impact on the incidence of ADR in the form of weakness as much as one respondent in the Doubtful category, which means that the drug has a dubious impact on the weakness experienced by metformin drug users. Meanwhile, four respondents who were in the Possible category, which means that they are likely to experience ADR manifestations in the form of nausea. In line with research [12] mentions that both metformin and glibenclamide give side effects of nausea. In the manifestation

of sleepy ADR, there was one respondent in the doubtful category, which means that the drug has doubtfully had an impact on sleepiness for users. However, there was one respondent who was in the probable and possible categories which means that the drug metformin may and is likely to cause drowsiness. Finally, in the manifestation of dizziness, three respondents were in the probable category and two respondents in the possible category, which means that the drug metformin may and is likely to cause dizziness.

Users of the combination drug Glibenclamide and Metformin had an impact on the incidence of ADR in the form of weakness in as many as two respondents in the possible category which means that the drug might cause users to become weak. In the manifestation of ADR in the form of nausea as many as four respondents in the probable category which means that it is likely that the drug causes nausea for its users. In the manifestation of ADR in the form of drowsiness as many as one respondent in the probable category which means that it is likely that the drug causes drowsiness for its users. Finally, in the manifestation of ADR in the form of dizziness as many as two respondents in the probable category which means that it is likely that the drug causes dizziness for its users.

A similar study related to ADR entitled Pharmacological Study of Antidiabetic Drugs in Type II Diabetes Mellitus Outpatients at Dr.H.Moch.Ansari Saleh Hospital Banjarmasin, showed the results of the study of the incidence of ADR with a total score of 1-4 categories "quite likely" had the largest percentage value of 31.57% and the use of combination drugs that produced the most ADR was 22.1% for the category quite likely [14]. Insulin users have an impact on the incidence of ADR in the form of weakness, where one respondent is in the possible category and one other respondent is in the probable category. This means that Novomix Insulin may and is likely to cause dizziness for its users.

4. CONCLUSION

The results showed that as many as 46 respondents (38.3%) experienced ADR. The types of ADR events in the form of nausea, drowsiness, dizziness, weakness, and tremor were 32.6%, 30.4%, 17.4%, 15.2%, and 3.3%. Glibenclamide causes events with manifestations of tremor, weakness, nausea, and drowsiness in the categories of probable, doubtful, probable, and probable. The use of metformin manifestations in the form of weakness, nausea, drowsiness, and dizziness in the categories of doubtful, possible, probable, and probable. The combination of Glibenclamide and Metformin manifests in the form of weakness, nausea, drowsiness, and dizziness in the categories of possible, probable, probable, and probable. Insulin manifestations in the form of weakness in the probable category.

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