Jurnal Manajemen dan Pelayanan Farmasi (JMPF)
(Journal of Management and Pharmacy Practice)
ISSN-p : 2088-8139 | ISSN-e : 2443-2946
JMPF Vol 15(1) 2025: 15-22

Pharmacovigilance Study of Antidiabetic Drugs in Diabetes Mellitus Patients in Three Pharmacies in Yogyakarta

Qarriy 'Aina Urfiyya[1*], Ratu Aimeesadra Kamilabanat[1], Rahma Febita Solekhah[1]
[1] Academy of Pharmacy Indonesia Yogyakarta, Indonesia

ARTICLE INFO
Submitted : 12-09-2023
Revised : 29-06-2024
Accepted : 03-03-2025
Published : 31-03-2025

Corresponding Author:
Qarriy 'Aina Urfiyya

Corresponding Author Email:

ABSTRACT

Background: Diabetes mellitus has become a global health problem. Indonesia has the third highest number of diabetes mellitus cases in the Southeast Asia region, with a prevalence of 11.3%. The high prevalence of diabetes mellitus increases the risk of Adverse Drug Reaction (ADR). Pharmacovigilance studies are important to detect possible adverse drug reaction of antidiabetic drugs.

Objective: This study aimed to describe and analyze the adverse drug reaction of using antidiabetic drugs at three pharmacies in Yogyakarta City.

Methods: This study used an analytic observational with a cross-sectional study design. Data were collected at three pharmacies in Yogyakarta City from 59 patients with diabetes mellitus who met the inclusion and exclusion criteria. The instrument used was an interview guide that refers to the Naranjo form. Data analysis included the incidence of adverse drug reaction according to patient characteristics, type of therapy, and description of antidiabetic adverse drug reaction based on causality.

Results: The results showed that antidiabetic ADRs occurred in 19 patients (32%). The incidence of ADRs was 68% in men and 32% in women. The incidence of adverse drug reaction was most prevalent at the age of 56-65 years (47%). The most common adverse drug reaction of antidiabetic metformin were flatulence, drowsiness, decreased appetite and dyspepsia, diarrhea, weight loss and nausea and vomiting.

Conclusion: This study concluded that the most common ADRs of antidiabetics was the probable and possible category (42%). The most common cause of ADRs was metformin (53%)

Keywords: Adverse Drug Reactions; Antidiabetic; Diabetes mellitus; Pharmacovigilance; Side effect

INTRODUCTION

Diabetes mellitus is a chronic metabolic disease characterized by hyperglycemia. Diabetes mellitus over a long period can cause damage to many organs. Indonesia ranks third in terms of the number of cases of diabetes mellitus in Southeast Asia.[1] Based on the 2018 Riskesdas data, there was an increase in the prevalence of diabetes mellitus from 2013 (6.9%) to 2018 (8.5%),[2] in addition to the death rate from diabetes mellitus in poor and developing countries doubling by 2030.[3] The high prevalence of diabetes mellitus will lead to increased use of antidiabetic drugs[4] and increased risks of drug ADRs. Drug ADRs can decrease patients' quality of life, increase the frequency of physician visits, increase the length of patient care, and increase the risk of mortality.[5] Every medication can cause adverse drug reaction or side effects, so it is necessary to pay attention to the safety of treatment and the potential ADRs of antidiabetics. In addition, awareness of drug ADRs is also included in the indicators of rational drug use assessment.[6]

Data suggest that there are 44,000 to 98,000 deaths each year due to medical errors, of which 7000 are due to adverse drug events. A previous study in the US estimated that 6.7% of hospitalized patients experienced serious adverse drug events, with a mortality rate of 0.32%.[7] Several studies have revealed the potential ADRs of antidiabetics. Research conducted at Bendan Pekalongan Hospital showed that the incidence of antidiabetic

ADRs was 12.5% in the highly probable category and 28.1% in the possible category.[8] Another study showed potential ADRs of nausea due to metformin at 18.53% (highly probable) and Glimepiride at 13.33% (highly probable). Glibenclamide can also cause hypoglycemia adverse drug reaction by 15.79% (highly probable).[9] Another study showed that there was a nausea effect due to the use of metformin and flatulence due to acarbose, with a causality assessment of 5.4% in the probable category and 2.7% in the possible category.[10]

One way to reduce the risk of adverse drug reactions is by conducting pharmacovigilance studies. Pharmacovigilance studies are conducted to improve patient safety and security related to the drugs obtained. Based on the above background, it is considered necessary to assess ADRs, especially in patients with chronic diseases, such as diabetes mellitus. Several previous studies have observed ADRs of antidiabetics limited to oral preparations or single therapy. In this study, ADRs observations were made on oral and insulin antidiabetics as well as single therapy and combination therapy. In addition, the incidence of ADRs was also observed based on patient characteristics, which is expected to improve the safety of patient treatment.

METHODS

Study design

The study used an analytic observational design. The research conducted at three Yogyakarta City pharmacies: Ramadhan Pharmacy, Medikatama Pharmacy, and Perdana Pharmacy. Selection of pharmacies based on criteria, namely non-franchise pharmacies, collaboration with physician practices, and willingness to be used as research locations.

Population and samples

The population in this study comprised all patients who filled prescriptions containing antidiabetics at Ramadhan Pharmacy, Medikatama Pharmacy and Perdana Pharmacy. The sampel calculation was done using method based on Malhotra's theory. The minimum sample size can be determined by multiplying the number of variables or the number of questions by 5[11], with the calculation method, the minimum sample was 50 patients. In this study, there were 59 patients who met the inclusion criteria. The inclusion criteria were patients who redeemed their antidiabetic prescriptions, took antidiabetics, had diabetes without complications, were willing to become respondents, and could communicate well. The exclusion criteria were the patient's who are pregnant and breastfeeding, and respondents who did not complete the form fully.

Study instruments

The Naranjo form is an instrument to assess and measure the risk of adverse drug reactions. The Naranjo form consists of 10 questions with 3 answer options (yes, no, and unknown).[12] Each answer choice has a score. Adverse event data were analyzed based on patient characteristics (age and gender), type of therapy, and description of antidiabetic ADRs based on causality (doubtful, possible, probable, and highly probable). Adverse drug ractions were analyzed by calculating the Naranjo score and categorizing the level of causality. The causality category based on Naranjo uses a score of doubtful/doubtful (score 0), quite possible/possible (1-4), possible/probable (5-8), and highly probable (>9).[12]

Data collection

This research was conducted from February to June 2023. Data collection was conducted through structured interviews with patients for primary data (Adverse Drug Reactions) and observations on prescriptions for secondary data (patient characteristics), then recording on data collection forms.

Data Analysis

The chi-square test was conducted to determine the effect of patient characteristics (age and gender) and type of therapy on the incidence of antidiabetic ADRs. The characteristics of the patients affected the incidence of adverse drug reactions if the significance value or p-value was <0.05.

RESULTS AND DISCUSSION

Pharmacovigilance studies are conducted to ensure the safety of drugs used by patients by assessing Adverse drug Reactions (ADRs) or side effects of drugs. Adverse drug reactions are all adverse or unwanted effects that occur at therapeutic doses.[13] The results of the observation of the incidence of antidiabetic ADRs are shown in Table I.

Table I. Distribution of Adverse Drug Reactions (ADRs) of Antidiabetic Drugs

Occurrence of ADRs	Number of Patients (%)
ADRs occurred	19 (32)
No ADRs occurred	40 (68)
Total	**59 (100)**

Notes: ADRs= Adverse Drug Reactions

Based on the results presented in Table I, the proportion of patients with diabetes mellitus who did not experience ADRs (68%) was higher than that of patients who experienced ADRs (32%). This result is consistent with several previous studies that have reported that not many patients experienced were affected by adverse drug reactions (ADRs) associated with antidiabetic drug. Research conducted at the Pekalongan Regional Hospital showed that more patients did not experience ADRs (52%).[8] Research in Padang Hospital also mentioned that the incidence of ADRs due to antidiabetics was not much, which amounted to 8.1%.[10] The distribution of adverse drug reactions based on patient characteristics and the results of the chi-square test of the effect of patient characteristics and type of therapy on the incidence of ADRS are presented in Table II.

The results of the study in Table II show that most patients with diabetes mellitus are aged 55–65 years (41%), which represents the late elderly category. These results are in accordance with data from the Indonesian Ministry of Health in 2018, which reported that the incidence of diabetes mellitus was highest in the age category 55–64 years (19.6%).[2] With increasing age, the body will experience various changes, especially changes in kidney function and structure. Decreased kidney function will affect the body's ability to manage blood glucose, increasing the risk of developing diabetes mellitus.[14] Table II also shows that the incidence of antidiabetic drug ADRs in patients with diabetes mellitus is mostly at the age of 56–65 (47%). Older patients experience changes in drug pharmacokinetics, including changes in the volume of distribution, metabolism, and elimination of drugs. These changes can extend the half-life of the drug, increase the risk of toxicity, and increase the likelihood of drug ADR.[15] However, in this study, patients aged >65 years had a lower incidence of ADRs than those aged 56-65 years. This may be due to older patients tend to get more attention in managing their medication, so as to minimize the risk of ADRs, for example by adjusting the dosage.[16] This study showed that age did not significantly affect the risk of antidiabetic ADRs (p 0.548). This result is similar to another study reporting that age was not significantly correlated with adverse drug reactions (p 0.173).[17] The meta-analysis study also showed that antidiabetic ADRs can be experienced by many patients without specific age restrictions.[18]

Based on gender, women (53%) suffer from diabetes mellitus more than men (47%). The risk of diabetes mellitus in women is 3–7 times higher, while in men it is 2–3 times.[8] This is because, physically, women have a greater chance of increasing Body Mass Index.[10] In addition, women also experience menstruation and post-menopausal conditions that affect the distribution of fat in the body, making it easier to accumulate.[19] Based on the results in Table II, ADRs due to antidiabetics occurred more in men (68%) compared to women (32%). The high incidence of drug ADRs in men may be due to differences in the pharmacokinetic and pharmacodynamic profile of a drug.[20] This study also found that gender differences significantly affect the risk of ADRs (p 0.049). This result is similar to a previous study which stated that men (32.8%) experienced more ADRs from oral antidiabetics than women (29.3%). The other study also found that gender was associated with the incidence of ADRs due to antidiabetics (p 0.008).[19] Gender affects ADRs because it creates differences in the pharmacokinetics and pharmacodynamics of a drug, which means the effects that a drug can have.[19]

In this study, combination antidiabetic therapy (63%) was more common than antidiabetic monotherapy (37%). Combination antidiabetic therapy is given if monotherapy does not provide good blood glucose control or HbA1c > 7.5.[20] These results agree with previous studies showing that combination therapy (63%) was more widely used compared to monotherapy (37%) in patients with diabetes mellitus.[21] Table II shows that ADRs in patients using combined antidiabetic therapy (53%) was higher than monotherapy (47%), but this type of therapy did not significantly affect the risk of drug ADRs (p 0.270). This result is similar to a previous study, where the incidence of ADRs in patients who received a combination of antidiabetics (57.02%) was higher than that in patients who received monotherapy (40.98%).[22] Another study also mentioned that there was no significant difference in the incidence of ADRs in either single or combination antidiabetic therapy (p 0.493).[19] The type of antidiabetic therapy (single and combined) does not affect the incidence of ADRs, this may be due to the similarity of the mechanism of antidiabetic drugs used alone or in combination.[23] So that the difference in the

Table II. Distribution of Adverse Drug Reactions by Patient Characteristics

Category	Number of Patients (%)		p value*
	Number of Diabetes Mellitus Patients	ADRs Incidence	
Age (years)			
26-35	2 (3)	2 (11)	
36-45	4 (7)	1 (5)	0,548
46-55	20 (33)	3 (16)	
56-65	25 (41)	9 (47)	
> 65	10 (16)	4 (21)	
Gender			
Male	28 (47)	13 (68)	0,049
Female	31 (53)	6 (32)	
Type of Therapy			
Monotherapy	21 (36)	8 (42)	0,564
Combination therapy	38 (64)	11 (58)	
Total	**59 (100)**	**19 (100)**	

Notes: * result of chi square test. If p value <0.05, there is a significant effect on the incidence of antidiabetic ADRs; ADRs: Adverse Drug Reaction

type of therapy does not have a significant effect on the incidence of adverse drug reactions. The distribution of antidiabetic ADRs by causative drug is shown in table III.

Drug interactions, particularly in the use of combination therapy are a significant factor in adverse drug reactions.[24,25] For instance, a study in Romania reported that 6% of adverse drug reactions in hospitalized patients were caused by drug interactions. Most of these ADRs were serious but preventable.[26] However, in this study, none of the combination therapies had the potential for drug interactions that could lead to ADRs. It may be due to the overlapping ADRs of antidiabetic combinations. The Different types of antidiabetics have different mechanisms of action, but the side effects often overlap.[23] For example, the use of a combination of glimepiride and metformin causes hypoglycemia. Although metformin is known to lower blood glucose levels without causing hypoglycemia[27], but in some cases metformin shows hypoglycemic risk at therapeutic doses.[28]

Table III shows that the incidence of ADRs was mostly caused by metformin (53%), followed by insulin novorapid (21%). The antidiabetic group that caused the most ADRs was biguanid (53%), followed by insulin (26%). These results are almost similar to previous studies, where the incidence of antidiabetic ADRs was mostly due to metformin (47.6%).[21] Another study also obtained the same results, namely that the incidence of side effects was mostly due to metformin (51.64%)[28]. Metformin is a widely used first-line antidiabetic in diabetic type 2 patients[29] compared to other antidiabetics, which may be the reason for the many reports of metformin ADRs. The distribution of ADRs based on causality is shown in Table IV.

Based on causality, the results of the study in Table IV show that the most ADRs are in the probable category (42%), and there is no highly probable category. Probable indicates that the patient's complaint is likely to be an ADRs of the drug, possible indicates that it is likely that the patient's complaint is a side effect of the suspected drug, and doubtful indicates the complaint is not a side effect, but can be due to other factors or causes other than the suspected drug.[12] The data suggests that for most patients, the link between the drug and the adverse reaction is either "probable" or "possible," indicating a significant but not definitive connection. The absence of "highly probable" cases means that none of the reactions were deemed almost certain to be caused by the drug. The small percentage of "doubtful" cases shows that in a few instances, the drug was likely not the cause of the ADRs. In summary, the table shows that while there is some likelihood that the drug caused ADR in many of the patients, the evidence is not strong enough to be conclusive in most cases.

The results of the study in Table V show the most antidiabetic ADRs due to metformin, which occurred in 10 patients. Systematic reviews show the greatest risk of gastrointestinal side effects occurs with the use of metformin compared to other antidiabetics [30]. In this study, the probable ADR of metformin were diarrhea, decreased appetite and dyspeptic symptoms, weight loss, and flatulence. Based on the drug information handbook, metformin has the risk of causing several ADR, including diarrhea (>10%), dyspepsia (1–5%), and flatulence (1–5%)[32]. The results of this study are similar to previous studies, which showed that ADRs of gastrointestinal effects were most common in the use of metformin, including dyspepsia (14.2%), diarrhea

Table III. Distribution of Antidiabetic Adverse Drug Reaction by Causative Drug

Antidiabetic Group	ADRs Number of patients (%)	Type Antidiabetic	ADRs Number of patients (%)
Monotherapy			
Alpha-glucosidase inhibitor	1(5)	Acarbose	1(5)
Insulin	5(26)	Insulin novorapid	4(21)
		Insulin ryzodeg	1(5)
Biguanid	10(53)	Metformin	10(53)
Combination			
Alpha-glucosidase inhibitor-biguanid-sulfonylurea	1(5)	Acarbose-metformin-gliclazide	1(5)
Sulfonylurea-Biguanid	2(10)	Glimepiride-metformin	1(5)
		Gliquidone-metformin	1(5)

Table IV. Distribution of Adverse Drug Reactions Based on Naranjo Causality

Naranjo Causality Category	Number of Patients (%)
Highly probable	0 (0)
Probable	8 (42)
Possible	8 (42)
Doubtful	3 (16)
Total	**19 (100)**

Table V.Overview of Adverse Drug Reactions Based on Antidiabetic Type

Antidiabetic	Adverse Drug Reactions	Number of Patient	Causality Naranjo
Acarbose	Flatulence	1	Possible
Acarbose-metformin-glicazid	Flatulence	1	Probable
Glikuidone-metformin	Symptom of hypoglycemia	1	Possible
Glimepiride-metformin	Symptom of hypoglycemia (shaking)	1	Possible
	Flatulence	1	Doubtful
Metformin	Decreased appetite, dyspeptic symptoms	1	Probable
	Diarrhea	1	Probable
	Weight loss	1	Probable
	Flatulence	1	Probable
	Flatulence, abdominal pain, nausea	2	Possible
	Drowsiness	1	Doubtful
	Drowsiness	1	Possible
	Nausea, vomiting	1	Doubtful
Insulin Ryzodeg	Symptom of hypoglycemia	1	Probable
Insulin Novorapid	Easy hunger	1	Probable
	swelling (swelling at the injection site)	1	Probable
	Weight gain	2	Possible
Total		**19**	

(7.1%), nausea (2.3%), and gastric irritation (2.3%).[21] Another study also showed that the most common ADR due to metformin were dyspepsia and diarrhea.[30] Metformin can activate selective serotonin type 3 (5-HT 3) receptors that can cause gastrointestinal disorders and have serotonergic effects.[31] In addition, metformin can reduce bile acid absorption, which can cause osmotic diarrhea.[31]

According to the results of the study in Table V, metformin caused weight loss (5%). Previous studies have also shown a weight loss effect due to the long-term use of metformin.[32] This may be due to appetite-reducing

effects, reduced adipose tissue leptin production, reduced carbohydrate absorption from the gut, increased GLP-1 levels, and reduced fat storage in tissues.[33] This weight loss can be an unfavorable ADRs for patients as they become thinner.

The results of the study in Table V show the ADRs of hypoglycemia in the use of the sulfonylurea group are gliquidone and glimepiride. Previous research found that the most common ADRs in the use of glimepiride was hypoglycemia.[21] Other studies also show the same results, sulfonylurea antidiabetics cause metabolic abnormalities such as hypoglycemia.[33] The effect of hypoglycemia can appear in the use of doses >2 mg/day.[30]

Table V shows that the use of acarbose as monotherapy and combination therapy caused flatulence with complaints of frequent farting after taking the drug, which occurred in 2 patients. This result is in line with previous studies, that acarbose causes flatulence with complaints of frequent farting.[8,10,34] This effect occurs in relation to the mechanism of action of acarbose, which inhibits the enzyme alpha-glucosidase, breaking down oligosaccharides into monosaccharides, so that carbohydrates reach the colon more quickly and result in gas production.[35]

The results in Table V also show the effect of weight gain due to novorapid insulin, which occurred in 2 patients. Weight gain is a common side effect of insulin therapy. One of the anabolic effects of insulin is to increase fatty acid absorption into adipose tissue. The amount of weight gain after insulin therapy in patients with type 2 diabetes mellitus is 4 kg.[36]

Differences in adverse drug reactions experienced by patients can be caused by several factors, namely the mechanism of the drug, the place of action of the drug, the period of drug use, drug interactions, the presence of comorbidities, and genetic or other conditions that reduce the body's metabolism.[34] In addition, the incidence of adverse drug reactions can also be influenced by the accuracy of drug use.[37] The limitation of this research is that it was only conducted in three pharmacies in the city of Yogyakarta, so the research results cannot be generalized to the Yogyakarta City area.

CONCLUSION

The most common side effects of antidiabetic drug use in several pharmacies in Yogyakarta City were in the probable and possible category (42%), with the most common cause of side effects being metformin therapy (53%).

ACKNOWLEDGEMENT

We would like to thank the Academy of Pharmacy Indonesia (AFI) Yogyakarta for providing financial assistance for the implementation of this research. Second, we would like to express our deepest gratitude to the pharmacist in charge and the staff of the three pharmacies, namely Medikatama Pharmacy, Ramadhan Pharmacy, and Perdana Pharmacy, for their assistance in completing this research.

STATEMENT OF ETHICS

This study was approved by the Health Research Ethics Commission, Respati University, Yogyakarta (approval number 035.3/FIKES/PL/III/2023).

REFERENCES

1. Kementrian kesehatan republik indonesia (Kemenkes RI). Tetap Produktif, Cegah Dan Atasi Diabetes Mellitus. *pusat data dan informasi kementrian kesehatan RI*.2020
2. Kementrian Kesehatan Republik Indonesia (Kemenkes RI). Hasil Riset Kesehatan Dasar Tahun 2018. *Kementrian Kesehatan RI*. 2018;53(9):1689-1699
3. Jansson SPO. A Longitudinal Study of Diabetes Mellitus : With Special Reference to Incidence and Prevalence, and to Determinants of Macrovascular Complications and Mortality. *Acta Universitatis Upsaliensis*; 2014.
4. Pavlov R, Topličan I, Vrcić Keglević M. Ten-Year Trends in the Morbidity of Diabetes Mellitus and Antidiabetic Drug Utilization in Croatia: A Study Based on Routinely Collected Data. *Int J Family Med*. 2016;2016:1-9. doi:10.1155/2016/9837496
5. Aditya. M., Muhammad, H.A., Feliadewi, R. Reaksi Obat Yang Tidak Dikehendaki (ROTD) Pada Pasien Rawat Jalan Penyakit Ginjal Kronis Tahap Akhir Di Komunitas Pasien Cuci Darah Indonesia Cabang Jawa Timur : Metode Cross Sectional. *BIMFI.*2021

6. Kementrian Kesehatan Republik Indonesia (kemenkes). Modul Penggunaan Obat Rasional Dalam Praktek. *Kementerian Kesehatan Republik Indonesia*. 201;3–4
7. U.S.Food and Drug Administration (FDA). *Preventable Adverse Drug Reactions: A Focus on Drug Interactions*. 2018. https://www.fda.gov/drugs/drug-interactions-labeling/preventable-adverse-drug-reactions-focus-drug-interactions . Diakses 18 Juni 2024
8. Desiani E, Anindhita MA, Rusli Effendi M. Evaluasi Farmakovigilans Obat Antidiabetes Oral Pada Pasien Rawat Jalan Diabetes Mellitus Tipe Ii Di Rsud Bendan Kota Pekalongan. *Cendekia Journal of Pharmacy.* 2020. http://cjp.jurnal.stikescendekiautamakudus.ac.id
9. Joddy Sutama Putra R, Achmad A, Rachma Pramestutie H. Kejadian Efek Samping Potensial Terapi Obat Anti Diabetes Pada Pasien Diabetes Melitus Berdasarkan Algoritme Naranjo. *Pharmaceutical Journal of Indonesia*. 2017;2(2):45-50. doi:10.21776/ub.pji.2017.002.02.3
10. Yosmar R, Putri Inanta N, Yelly D, Sari O. Studi Prospektif Adverse Drug Reactions (ADRS) Obat Hipoglikemik Oral Terhadap Pasien Diabetes Mellitus Tipe 2 di Suatu Rumah Sakit, Padang (A Prospective Study On Adverse Drug Reactions (Adrs) Of Oral Hypoglycemic Agents Among Type 2 Diabetes Patients in A Hospital, Padang). 2018;5(3):169-175. http://jsfk.ffarmasi.unand.ac.id
11. Malhotra NK, Dash S. *Marketing Research: An Applied Orientation*. 7th edition. Pearson Education; 2016.
12. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239-245. doi:10.1038/clpt.1981.154
13. BPOM. Modul farmakovigilans untuk tenaga kesehatan proyek 'ensuring drug and food safety. *BPOM Japan International coorporation agency*.2020.
14. Rahayu S, Jayakarta PKP DKI Jakarta Stik. Hubungan Usia, Jenis Kelamin Dan Indeks Massa Tubuh Dengan Kadar Gula Darah Puasa Pada Pasien Diabetes Melitus Tipe 2 Di Klinik Pratama Rawat Jalan Proklamasi, Depok, Jawa Barat.; *Jurnal Kesehatan Kusuma Husada.* 2020.
15. Davies EA, O'Mahony MS. Adverse drug reactions in special populations - The elderly. *Br J Clin Pharmacol*. 2015;80(4):796-807. doi:10.1111/bcp.12596
16. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. *Expert Opin Drug Saf*. 2014;13(1):57-65. doi:10.1517/14740338.2013.827660
17. Riwu M, Subarnas A, Lestari K. The Correlation of Age Factor, Administration, and Metformin Dose Against Risk of Side Effect on Type 2 Diabetes Mellitus. *Indonesian Journal of Clinical Pharmacy*. 2015;4(3):151-161. doi:10.15416/ijcp.2015.4.3.151
18. Adiputra R. Efek Samping Penggunaan Obat Anti Diabetes Jangka Panjang: Sebuah Meta Analisis. *Jurnal Kesehatan Tambusai*. 4(3).2023
19. Isnani, M., Muliyani. Pengaruh Karakteristik Pasien Dengan Terjadinya Adverse Drug Reaction (ADR) Pada Pasien Diabetes Melitus Tipe 2 Rawat Inap. *Jurnal Mandala Pharmacon Indonesia*. 2018;4. www.jurnal-pharmaconmw.com/jmpi
20. Endokrinologi Indonesia. Pedoman Pengelolaan Dan Pencegahan Diabetes Melitus Tipe P. *Pedoman Pengelolaan Dan Pencegahan Diabetes Melitus Tipe 2 Dewasa Di Indonesia*-2021.2020.Penerbit *PB. PERKENI*.
21. Muthukumar A, Sundaraganapathy R, Mohan S. A Pharmacovigilance Study Of Antidiabetic Drugs In Hypertensive Patients In A Territory Hospital In Coimbatore Zone. *Der Pharmacia Lettre.* 2017. http://scholarsresearchlibrary.com/archive.html]
22. Dey I, Mohanty S, Prasad A, Patnayak C, Palit R. A study on adverse drug reactions of oral anti-diabetic agents in patients with type II diabetes mellitus in Hi-Tech Medical College and Hospital, Bhubneswar, Odisha, India. *Int J Basic Clin Pharmacol*. 2019;8(5):837. doi:10.18203/2319-2003.ijbcp20191566
23. Malik M, Habib A, Ahmad R, Khanna S. Comparison of the Efficacy and Safety of Various Oral Antidiabetic Drug Regimens Used for Type-2 Diabetes Mellitus-in a Tertiary Care Hospital in South Delhi International Journal of Toxicological and Pharmacological Research. *International Journal of Toxicological and Pharmacological Research Original Research Article*. 2023;13(3):155-166. www.ijtpr.com
24. Roy K, Divya S, Nadig P, Prakash B. Monitoring And Analysis Of Adverse Drug Reactions In A Private Tertiary Care Teaching Hospital. 2015;8. http://apps.who.int/medicinedocs/en/d/Jh3009e/.

25. Pizzimenti V, Ientile V, Fava G, Giudice I, Bonfiglo C, Alecci U. *Adverse Reactions with Antidiabetic Drugs: Results from a Prospective Cohort Study in Sicily*. Asian J Pharm Clin Res.8(2):335-7. 2015 www.tcpdf.org
26. Bucşa C., Farcaş, A., Cazacu, I., Leucuta D., Achimas-Cadariu, A., Mogosan, C., Bojita, M. How many potential drug-drug interactions cause adverse drug reactions in hospitalized patients? *Eur J Intern Med*. 2012;24. doi:10.1016/j.ejim.2012.09.011
27. Nur Fahmi K, Urfiyya A. Gambaran Penggunaan Insulin Pada Pasien Diabetes Melitus Tipe 2 Rawat Jalan Di Rsi Hidayatullah Yogyakarta An Overview Insulin Used In Outpatient With Diabetes Mellitus Type 2 At Hidayatullah Islamic Yogyakarta Hospital. Jurnal Inovasi Farmasi Indonesia. 2022;4(1).
28. Barrouq D. Development of Hypoglycemia Associated with Therapeutic Dose of Metformin: a Case Report. *International Journal of Medical Reviews and Case Reports*. 2020;(0):1. doi:10.5455/ijmrcr.hypoglycemia-metformin
29. American Diabetes Association. Standard medical care in diabetes 2018. *The journal of clinical and applied research and education*. 2018;41(January). doi:10.2337/dc18-Sint01
30. Deb T, Chakrabarty A, Ghosh A. Adverse drug reactions in Type 2 diabetes mellitus patients on oral antidiabetic drugs in a diabetes outpatient department of a tertiary care teaching hospital in the Eastern India. *Int J Med Sci Public Health*. 2017;6(3):1. doi:10.5455/ijmsph.2017.0423203102016
31. Nabrdalik K, Skonieczna-Żydecka K, Irlik K, Krzysztof & Hendel, Mirela & Kwiendacz, Hanna & Loniewski, Igor & Januszkiewicz, Kornelia & Gumprecht, Janusz & Lip, Gregory. Gastrointestinal adverse events of metformin treatment in patients with type 2 diabetes mellitus: A systematic review, meta-analysis and meta-regression of randomized controlled trials. *Front Endocrinol (Lausanne)*. 2022;13. doi:10.3389/fendo.2022.975912
32. Subramaniam K, Joseph MP, Babu LA. A Common Drug Causing a Common Side Effect at an Uncommon Time: Metformin-Induced Chronic Diarrhea and Weight Loss after Years of Treatment. *Clinical Diabetes*. 2021;39(2):237-240. doi:10.2337/cd20-0101
33. Malin SK, Kashyap SR. Effects of metformin on weight loss: potential mechanisms. *Curr Opin Endocrinol Diabetes Obes*. 2014;21(5):323-329. doi:10.1097/MED.0000000000000095
34. Aberg JA, LC, AL, GM and LLL. *Drug Information Handbook* . 17th ed. American PharmacistAssociation.; 2014.
35. Sheehan MT. *Current Therapeutic Options in Type 2 Diabetes Mellitus: A Practical Approach*. Vol 1.; 2003. www.mfldclin.edu/clinmedres
36. Donnor T, Sarkar S. insulin- Pharmacology, Therapeutic Regimens and Principles of Intensive Insulin Therapy. https://www.ncbi.nlm.nih.gov/books/NBK278938/.
37. Mahirsyah WT, Andayani TM, Ika PS. *Hubungan Antara Ketepatan Penggunaan Obat Pada Pasien Usia Lanjut Terhadap Efek Samping Dan Lama Perawatan Di Bangsal Rawat Inap RSUP Dr Kariadi Semarang*. Universitas Gadjah Mada; 2016.