Int J Adv Life Sci Res. Volume 7(4) 98-106
https://doi.org/10.31632/ijalsr.2024.v07i04.009

International Journal of Advancement in Life Sciences Research

Online ISSN: 2581-4877

Journal homepage http://ijalsr.org

Original Article

Assessment of Prevalence, Determinants and Management of Potential Antidiabetic Drug Interactions Altering Glycemic Control in Patients with Type II Diabetes Mellitus- A Cross-Sectional Analysis

Vini Pavithran[1*], Balachandran Pandiyan[1], Sajeeth Chadappully Ismail[2], Athiappan Hariharan[3]

[1]Department of Pharmacy, Annamalai University, Annamalai Nagar, Tamil Nadu, India,
[2]Department of Pharmacy Practice, Grace College of Pharmacy, Palakkad, Kerala, India
[3]Department of General Medicine, Karuna Medical College and Hospital, Palakkad, Kerala, India

**Correspondence E-mail:vinipavithran57@gmail.com*

Abstract

Patients diagnosed with type II diabetes mellitus are often prescribed multiple medications to achieve glycemic target and to treat the co-morbidities. In these patients, polypharmacy eventually leads to potential drug-drug interactions (pDDI) and adverse outcomes. The study aimed to assess the prevalence of pDDIs altering glycemic control, its determinants, and its management. A cross-sectional investigation was carried out using the medical records of individuals diagnosed with type II diabetes mellitus. Demographic characteristics, medical history, and medications prescribed were obtained from the patient records. The Lexi-Interact® online database was utilised to identify the pDDI. Out of the 101 diabetic patients included, 68% of patients had at least 1 pDDI. A total of 375 drug-drug interactions and 107 pairs of interacting drugs altering the glycemic control were identified. 71.9% drug-drug interaction could lead to hypoglycemic episodes, and 28% drug-drug interaction could cause hyperglycemia-like symptoms. Most of the interactions were moderate interactions (89%) belonging to category C, followed by minor interactions (11%). The antidiabetic drug with the maximum number of interactions was metformin (51%). Female patients, presence of co-morbidities, duration of hospitalisation, and medication count per patient were found to have significant associations with the occurrence of pDDI. Screening of prescriptions by a clinical pharmacist can guide the physicians on avoiding drug combinations causing adverse outcomes in diabetic patients.

Keywords: antidiabetic drugs, diabetes mellitus, glycemic control, potential drug-drug interactions.

Introduction

Optimal glycemic control is essential for managing diabetes. When glycated haemoglobin (HbA1c) levels exceed 7.0%, the risk of both microvascular and cardiovascular complications significantly increases (Liposombe *et al.,* 2018). The ICMR-INDIAB study provided crucial insights into the substantial impact of diabetes in India, with approximately 101 million people affected. Hypertension and dyslipidaemia are much more common in patients with diabetes than previously thought, further increasing the risk of cardiovascular events (Anjana *et al., 2023*). Given the increasing prevalence of co-morbidities, current guidelines for diabetes treatment justify polypharmacy (Ikäheimo *et al.,* 2019).

Polypharmacy refers to the simultaneous use of five or more drugs, while hyper-polypharmacy specifically involves taking ten or more medications simultaneously (Sheikh-Taha *et al.,* 2021). As the

Received on :11th June 2024; Revised version received on :14thSeptember 2024; Accepted: 19th September 2024

number of medications a patient takes increases, so does the risk of potential drug interactions. Drug-drug interactions occur when the effectiveness or safety of a medication is affected due to its simultaneous use with another drug (Zheng *et al.,*2018). They can be categorised as either real drug interactions, which are observed in medical practice, or potential drug-drug interactions (pDDI), which are theoretical interactions predicted based on pharmacological properties and require vigilance to prevent adverse outcomes (Dagnew *et al.,* 2022; Hamadouk *et al.,* 2023).

Polypharmacy and pDDI resulting in adverse outcomes are quite commonly observed in diabetic patients. Ensuring that the pDDI that may alter the glycemic control is prevented is essential for achieving optimal therapeutic outcomes in diabetic patients. As per the American Diabetes Association guidelines, glycemic control refers to the efforts made to maintain blood sugar levels within the ideal range as safely achievable (American Diabetes Association. 2021). A pharmacist, working alongside other health care providers, tackles medication related problems and optimizes medication therapy through a patient-centered approach. By educating both physicians and patients, they ensure safe, effective and co-ordinated patient care (Pharmacists' Patient Care Process. 2014; American Diabetes Association. 2023)

In India, many studies have reported drug-drug interactions in diabetic patients. But studies specifically addressing drug interactions that impact glycemic control remain scarce. The primary objective of this study is to investigate the prevalence, determinants, and strategies for managing antidiabetic drug interactions that can alter glycemic control in adult diabetic patients, with the goal of increasing awareness among physicians regarding the significant burden faced by diabetic patients.

Material and Methods

Study design: The investigation utilised a cross-sectional study design and was conducted at a tertiary care teaching hospital in rural Kerala from October 2023 to March 2024. The inclusion criteria were inpatients aged above 40 years with type II diabetes mellitus who were prescribed anti-diabetic medications. Patients diagnosed with Type I DM and with incomplete chart records were excluded.

Sample size: A convenient sampling technique was used. Only patients who fulfilled the inclusion criteria were identified and enrolled. The final sample size achieved was 101 patients.

Data collection and analysis: Patient socio-demographics, lab data, and medications prescribed were collected from patient's medical records. The study utilised Lexicomp® drug interaction software (paid version) to examine patient records for pDDIs (Lexi-Drugs/Drug Interaction. 2024). The prescribed medication was entered individually into the interaction checker, and interactions that specifically impacted glycemic control were identified and documented.

Classification of pDDIs: Firstly, each interaction was given a code. The interaction was then categorised based on the severity into minor, moderate, or major interactions. Lexicomp® classified the interaction into 5 categories: Category A indicates no known interactions, category B indicates no action needed, category C indicates to monitor therapy, category D indicates to consider therapy modification, and category X indicates to avoid combination (Lexi-Drugs/Drug Interaction. 2024). Next, these interactions were analysed for their clinical outcome and categorised into hypoglycemia or hyperglycemia-causing interactions. When the blood glucose level drops below 70 mg/dl, it is referred to as Hypoglycemia. Shakiness, sweating, headaches, and palpitations are some common symptoms observed. When the fasting blood sugar is more than 125 mg/dl, hyperglycemia is observed. If left untreated, it can harm nerves, blood vessels, and organs. In severe cases, it may lead to a life-threatening condition known as diabetic ketoacidosis (Good *et al.,* 2002).

Statistical analysis: Descriptive statistics such as frequencies, percentages, mean, and standard deviation were used to present the findings. For categorical variables, the chi-square test was employed. The statistical software utilised was SPSS 22, and statistical significance was determined using a two-sided P value of <0.05.

Ethical consideration: Ethical clearance was granted from the Institutional Human Ethics Committee of Karuna Medical College and Hospital, Palakkad, Kerala, under the study reference number KMC/IHEC/15/2023.

Results

Baseline characteristics

101 patients admitted in the general medicine department who fulfilled the inclusion criteria were utilised for the study. The mean age of the patient was 63.14±11.29 years, and female patients made up 43.5% of the study population. The most frequent co-morbidity diagnosed was hypertension (56.4%), followed by coronary artery disease (23.7%) and chronic kidney disease (12.8%). On average, each patient was taking 9.39±4.22 medication in the hospital, 46% of patients met the definition of polypharmacy, and 40% met the definition of hyper-polypharmacy. Among the prescribed glucose-lowering drugs, metformin was the most commonly used medication for monotherapy (67%) while the combination therapy of biguanides and sulfonylureas (33.6%) was frequently prescribed. Most of the patients (47%) were hospitalised for more than 5 days, and 64.3% had at least one chronic disease. After identifying drug-drug interaction altering the glycemic control using Lexicomp® software, 67% of patients had at least 1 pDDI. The categorisation of the number of pDDI per patient was: 15% of patients had less than 3 interactions, 28% had 3-6, and 24% of patients had more than 7 drug-drug interactions (Table 1).

Table I. Demographic and clinical characteristics of patients included in the study (n =101 patients)

Variable	Percentage of patients (%)
Gender	
Male	56.4
Female	43.5
Age category (years)	
Mean ± S.D	63.14±11.29
Duration of hospitalisation (days)	
<5	31
5-10	47
>10	22
Presence of chronic disease	
Yes	64.3
No	35.6
Types of co-morbidities	
Hypertension	56.4
Coronary artery disease	23.7
Dyslipidemia	6.9
Chronic kidney disease	12.8
Chronic liver disease	2.9
COPD	4.9
BPH	7.9
Number of drugs administered	
<4	14
5-10	46
>10	40
Class of Antidiabetics commonly prescribed	
Biguanides	67
Sulfonylureas	42.5
Alpha glucosidase inhibitor	5
DPP-4 inhibitors	9.9
SGLT-2 inhibitors	35.6
Insulin	49.5
Presence of pDDI	
Yes	67
No	34
Number of pDDI s in patients with pDDI	
>3	15
3-6	28
>7	24

pDDI-potential drug-drug interactions, DPP-4 inhibitors- Dipeptidy peptidase-4 inhibitors, SGLT-2 inhibitors- sodium- glucose cotransporters-2 inhibitors.

pDDI

A total of 370 drug-drug interactions altering the glycemic control were detected, and 107 interacting drug combinations were identified. In terms of severity**,** moderate interaction was most prevalent (88.7%), followed by minor interactions (11.2%). Regarding risk rating, Type C interactions were the most common (88.7%), followed by Type B interactions (11.2%). Hypoglycemia causing drug-drug interactions (71.9%) was more prevalent than hyperglycemia causing drug-drug interactions (25.2%). 3 patients (2.8%) were diagnosed with Diabetic ketoacidosis during their hospital stay (Table 2).

Table 2. Severity, risk rating and adverse outcome of the identified pDDI

Level	Number (%) in 107 interacting drug combination
Severity	
Mild	12 (11.2)
Moderate	95 (88.7)
Risk	
B	12 (11.2)
C	95 (88.7)
Adverse outcome	
Hypoglycemia	77 (71.9)
Hyperglycemia	27 (25.2)
Diabetic ketoacidosis	3 (2.8)

Table 3. Most common pDDI causing Hypoglycemia and its management (n =101 patients)

Drug A (Anti-diabetic agents)	Drug B	Severity of potential interaction	Risk category	N (%)	Management
Metformin	Glimepride	Moderate	C	13 (17)	Monitor patient closely for hypoglycemia
	Aspirin	Moderate	C	8 (10)	Monitor closely for excessive hypoglycemia when salicylate dose is 3grams or more.
	Ondansetron	Moderate	C	15 (19)	Monitor for increased metformin effect/toxicity.
	Pantoprazole	Minor	B	32 (42)	No action needed.
	Bisoprolol	Moderate	C	15(19)	Educate patients regarding risk of masked hypoglycemia symptoms with β blocker.
	Insulin	Moderate	C	10 (13)	Monitor patient closely for hypoglycemia.
Glimepride	Tramadol	Moderate	C	5 (6)	Monitor patient closely for hypoglycemia.
	Diclofenac	Moderate	C	5 (6)	NSAIDS may diminish or enhance hypoglycemic effect of Sulfonylureas.
	Enalapril	Moderate	C	10 (13)	Monitor closely for risk of hypoglycemia and lactic acidosis.
Dapagliflozin	Levofloxacin	Moderate	C	6 (7)	Monitor for evidence of hypo or hyperglycemia.

N indicates number of interactions observed in patients, Category B means no action needed, category C means to monitor therapy

Table 4. Most common pDDI causing Hyperglycemia and its management

Drug A (Anti-diabetic agents)	Drug B	Severity of potential interaction	Risk category	N (%)	Management
Metformin	Telmisartan	Mild	B	14(47)	No action needed.
	Furosemide	Moderate	C	11 (37)	Increase antidiabetic dose or need for additional agents when initiating diuretics.
Glimepride	Hydrochlorthiazide	Moderate	C	10 (33)	Increase monitoring of blood glucose control when starting or stopping a thiazide diuretic.
	Dexamethasone	Moderate	C	3 (10)	Monitor blood glucose frequently when initiating therapy with steroids.
Insulin	Torsemide	Moderate	C	14(47)	Increase antidiabetic dose or need for additional agents when initiating diuretics.
Dapagliflozin	Furosemide	Moderate	C	6 (20)	Increase antidiabetic dose or need for additional agents when initiating diuretics.

N indicates number of interactions observed in patients, Category B means no action needed, category C means to monitor therapy

Tables 3 and 4 represent the most commonly identified interacting drug combinations altering the glycemic control and their management. There were no major drug interactions identified. The most predominant interacting drug combination that may cause hypoglycemia was Metformin with Pantoprazole (n = 32, 42%), followed by Metformin with Ondansetron (n = 15, 19%), and Metformin with Glimepiride (n = 13, 8.13%). The management includes monitoring patients closely for hypoglycemic symptoms. Management of patients prescribed with drug combinations that may lead to hyperglycemia involves increasing the antidiabetic dose, and the most common interacting drug pair identified was antidiabetic drugs with diuretics (40.5%).

Clinical significance of risk factors associated with occurrence of pDDI

The occurrence of pDDIs is significantly associated with several factors, including female gender ($p = 0.041$), duration of hospitalisation ($p = 0.006$), the presence of chronic diseases ($p = 0.0003$), and the number of drugs per patient ($p < 0.0001$). There was no significant association between the occurrence of pDDIs and age (Table 5).

Table 5. Relationship between occurrence of pDDI and associated risk factors (n =101 patients)

Variables	Incidence of Drug interaction		χ^2-value	p-value
	Yes	No		
Gender				
Female	34	10	4.17	0.041
Male	33	24		
Age (years)				
40 - 50	10	3		
50 - 60	8	10	4.94	0.293
60 - 70	28	12		
70 - 80	16	7		
>80	5	2		
Duration of Hospitalisation (days)				
<5	17	14	10.07	0.006
5-10	40	8		
>10	19	3		
Presence of chronic disease				
Patients with chronic disease	53	12	12.56	0.0003
Patients without chronic disease	16	18		
No. of Drugs/patient				
≤ 4	4	9		
5 - 9	28	20	18.63	<0.0001*
10 - 14	19	5		
15+	16	0		

χ^2-value indicates chi-square value calculated to determine the association of risk factors with the occurrence of pDDIs.
P value <0.05 indicates positive association between risk factors and occurrence of pDDIs.

Discussion

Polypharmacy is a common phenomenon in patients with type II diabetes mellitus. Multiple medications not only increase the cost and complexity of the treatment regimen but also increase the likelihood of drug-drug interactions and adverse drug outcomes (Good *et al.,* 2002). The present study focused on the prevalence of pDDI altering the glycemic control in 101 patients diagnosed with type II Diabetes Mellitus who were prescribed antidiabetic drugs. The overall prevalence of pDDI was 67% in our study. Investigations led by Nagpure *et al.* (2021) and Yosmar *et al.* (2024) found the prevalence of pDDI > 50% among diabetic patients. In assessing the severity of pDDI, most of the interactions were of moderate severity (88.7%), followed by minor interactions (11.2%). In terms of risk rating, Type C interactions were prevalent compared to Type B interactions. This is in accordance with research carried out by Kulkarni *et al.* (2013) and Hamadouk *et al.* (2023), where the majority of the pDDI were of moderate severity belonging to Type C, indicating the need to monitor the patient regularly. Metformin was the commonest antidiabetic drug prescribed, with the maximum number of drug-drug interactions (33.6%). Tuladhar *et al.,* 2021, also found that metformin, glibenclamide, and insulin were the medications to have maximum drug-drug interactions with other medications prescribed. Our study revealed that 56.4% and 23.7% of patients with diabetes had hypertension and coronary artery disease, respectively, contributing to polypharmacy. Utami *et al.* (2022) reported that out of 194 patients, 158 had hypertension and 11 had coronary artery disease, indicating a close relationship between diabetes patients and hypertension. Petrie *et al.* (2018) also reported a significant association between hypertension and type II DM. The prevalence of polypharmacy and hyper polypharmacy was 46% and 40%, respectively, in our study. This is in wide contrast to a similar study conducted by Sheik-Taha *et al.* (2021), where the prevalence of polypharmacy and hyperpolypharmacy was 95% and 65%, respectively.

Intensive therapy with insulin or a combination with 2 or more medications is more effective in maintaining glycemic control compared to monotherapy (Koto *et al.,* 2023). In diabetic patients with co-morbidities such as CKD or CVD, newer antidiabetics such as SGLT-2 inhibitors and DPP-4 inhibitors have shown superior glycemic control and cardiovascular protection (Arow *et al.,* 2020). The majority of the pDDIs identified were between hypoglycemic agents, such as metformin and glimepride, and non-hypoglycemic agents prescribed to treat the co-morbidities that occur with diabetes. Frequently occurring drug-drug interactions identified in our study included Glimepride-Enalapril (13%), Metformin-Furosemide (37%), Metformin-Aspirin (10%), and Insulin-Torsemide (47%). Similar pDDIs were reported in studies conducted in Indonesia, Nepal, and India (Tuladhar *et al.,* 2021; Utami *et al.,* 2022; Sankar *et al.,* 2015). SGLT-2 inhibitors (Dapagliflozin, Empagliflozin) and DPP-4 inhibitors (Teneligliptin, Vildagliptin) had low interaction potential when concomitantly prescribed with other hypoglycemic agents or non-hypoglycemic agents. This makes them an ideal treatment choice for patients with co-morbidities. Scheen A J *et al.* (2014) showed similar results.

The adverse outcome of the drug-drug interactions was divided into two categories: hypoglycemia and hyperglycemia-causing interactions. Drug interactions that lead to an increase in FBS were categorised under hyperglycemia-causing interactions, and interactions that decrease the FBS are hypoglycemia-causing interactions. For example, the combination of metformin with glimepride (8.13%) or insulin (6.25%) is proven to cause hypoglycemia. According to R. Koto *et al.* (2023), contributing factors that lead to the occurrence of severe hypoglycemia include treatment with insulin combinations, sulfonylurea combinations, and excessive polypharmacy. Hammad *et al.* (2017) evaluated the hyperglycemic effect of pDDI, which led to UCG in diabetic patients. Most of the pDDI related UCG cases were caused by diuretics (78%), similar to our findings with 40.5%. Magot *et al.* (2018) also identified diuretics as the most common drug implicated in DDI. Our study has concluded with the findings that female gender, presence of chronic disease, duration of hospitalisation, and polypharmacy are significantly associated with the occurrence of pDDI. Liu *et al.,* 2022, also concluded that female gender, length of hospitalisation, and number of drugs are independent risk factors for the severity of ADR.

Clinicians should be able to differentiate between appropriate and inappropriate polypharmacy to minimise pDDIs and mitigate adverse outcomes. Recognising drug interactions is therefore crucial for ensuring safe and effective management in patients with diabetes (Triplitt *et al.,* 2006). According to Patel and Beckett, lexicomp (81.4%) and stockley's drug interactions (81.2%) are recommended resources for understanding the mechanism of interactions. Meanwhile, Micromedex (89.2%) would be useful in identifying the potential outcome (Patel *et al.,* 2017). Clinicians can use these tools to help with prescribing and providing evidence-based information that is reliable and up-to-date. Free online softwares, while easy to use, may lack the same level of rigor in content curation, potentially leading to incomplete or outdated information.

One of the limitations of this study was that although Lexicomp is a popular application, all the interactions were not listed in its database. Also, the study focused on determining the prevalence of drug-drug interaction rather than assessing the actual clinical outcome resulting from these interactions. Also, the exact outcome could not be assessed as the RBS values were not determined immediately after a possible interaction, which is one of the drawbacks of this study.

Another limitation arises when a drug interaction screening program categorises the concomitant administration of two or more antidiabetic agents as a Type C interaction due to an elevated risk of hypoglycemia. However, when patients are diagnosed with uncontrolled glycemia, this drug combination is clinically appropriate.

Conclusion

Managing medications for patients with diabetes presents a unique challenge for clinicians, as drug-drug interactions are inevitable due to the higher prevalence of comorbidities. Our study findings demonstrated a significant occurrence of pDDIs in patients with diabetes. The majority of the pDDI

belonged to moderate severity, with risk category C indicating the need to monitor the patients regularly. Also, there is a significant association between female gender, duration of hospitalisation, presence of chronic disease, and number of medications prescribed with the occurrence of the pDDI. Online software such as Lexicomp can help identify pDDI, allowing health care professionals to prevent them. It is vital for medical institutions to provide these software resources to support evidence-based practices. Additionally, assigning a clinical pharmacist to each clinical department in a hospital would enhance the identification of clinically significant drug-drug interactions, ultimately improving patient therapeutic outcomes.

Acknowledgement

We thank Dr Kiran, Medical Superintendent at Karuna Medical college and Hospital, Palakkad, Kerala, India for their guidance and continuing support. We also thank the Institutional Human Ethics Committee of Karuna Medical College, India for timely approval of the research proposal.

Conflict of Interest

The authors declare no conflict of interest.

References

American Diabetes Association. (2021). 6. Glycemic targets: Standards of medical care in diabetes—2021. *Diabetes Care*, 44(Supplement 1), S73–S84.

American Diabetes Association. (2023). Hyperglycemia (High Blood Glucose). https://diabetes.org/healthy-living/medication-treatments/blood-glucose-testing-and-control/hyperglycemia. Accessed February 3, 2023.

Anjana, R. M., Unnikrishnan, R., Deepa, M., Pradeepa, R., Tandon, N., Das, A. K., ... & Ghosh, S. (2023). Metabolic non-communicable disease health report of India: the ICMR-INDIAB national cross-sectional study (ICMR-INDIAB-17). *The Lancet Diabetes & Endocrinology*, *11*(7), 474-489.

Arow, M., Waldman, M., Yadin, D., Nudelman, V., Shainberg, A., Abraham, N. G., ... & Arad, M. (2020). Sodium–glucose cotransporter 2 inhibitor Dapagliflozin attenuates diabetic cardiomyopathy. *Cardiovascular diabetology*, *19*, 1-12. https://doi.org/10.1186/s12933-019-0980-4

Dagnew, E. M., Ergena, A. E., Wondm, S. A., & Sendekie, A. K. (2022). Potential drug-drug interactions and associated factors among admitted patients with psychiatric disorders at selected hospitals in Northwest Ethiopia. *BMC Pharmacology and Toxicology*, *23*(1), 88. https://doi.org/10.1186/s40360-022-00630-1

Good, C. B. (2002). Polypharmacy in elderly patients with diabetes. *Diabetes Spectrum*, *15*(4), 240-248.

Hamadouk, R. M., Alshareif, E. M., Hamad, H. M., & Yousef, B. A. (2023). The Prevalence and Severity of Potential Drug–Drug Interactions in Internal Medicine Ward at Soba Teaching Hospital. *Drug, Healthcare and Patient Safety*, 149-157.

Hammad, M. A., Tangiisuran, B., Kharshid, A. M., Abdul-Aziz, N., Hassan, Y., Aziz, N. A., & Elsayed, T. M. (2017). Drug-drug interaction-related uncontrolled glycemia. *Journal of Pharmacy and Bioallied Sciences*, *9*(4), 221-228. https://doi.org/10.4103/jpbs.JPBS_26_17

Ikäheimo, I., Karjalainen, M., Tiihonen, M., Haanpää, M., Kautiainen, H., Saltevo, J., & Mäntyselkä, P. (2019). Clinically relevant drug-drug interactions and the risk for drug adverse effects among home-dwelling older persons with and without type 2 diabetes. *Journal of clinical pharmacy and therapeutics*, *44*(5), 735-741. https://doi.org/10.1111/jcpt.12854

Koto, R., Nakajima, A., Miwa, T., & Sugimoto, K. (2023). Multimorbidity, polypharmacy, severe hypoglycemia, and glycemic control in patients using glucose-lowering drugs for type 2 diabetes: a retrospective cohort study using health insurance claims in Japan. *Diabetes Therapy*, *14*(7), 1175-1192. https://doi.org/10.1007/s13300-023-01421-5

Kulkarni, V., Bora, S. S., Sirisha, S., Saji, M., & Sundaran, S. (2013). A study on drug–drug interactions through prescription analysis in a South Indian teaching hospital. *Therapeutic advances in drug safety*, *4*(4), 141-146. https://doi.org/10.1177/2042098613490009

Lipscombe, L., Booth, G., Butalia, S., Dasgupta, K., Eurich, D. T., & Goldenberg, R. (2018). Diabetes Canada 2018 clinical practice guidelines for the prevention and management of diabetes in Canada: pharmacologic glycemic management of type 2 diabetes in adults. *Can J Diabetes*, *42*(Suppl 1), S88-S103.

Liu, Y., Yang, M., Ding, Y., Wang, H., Zhang, H., Wang, D., Zhuang, T., Ji, M., Cui, Y., & Wang, H. (2022). Clinical significance of potential drug–drug interactions in older adults with psychiatric disorders: A retrospective study. *BMC Psychiatry*, 22, 563. https://doi.org/10.1186/s12888-022-04207-4

Magot, A. A., Karimi, P. N., Guantai, E. M., Maru, S. M., & Nyamu, D. G. (2018). Identification and characterization of potential drug interactions in hypertensive patients in a Kenyan tertiary hospital. *African Journal of Pharmacology and Therapeutics*, *7*(1).

Nagpure, S., Kela, K., & Dahiwele, A. C. (2021). Polypharmacy and Drug Interactions Study on Diabetic Patients of Geriatric Age Group at Rural Tertiary Care Hospital. *Int J Cur Res Rev| Vol*, *13*(12), 39–43. http://dx.doi.org/10.31782/IJCRR.2021.131216

Patel, R. I., & Beckett, R. D. (2016). Evaluation of resources for analyzing drug interactions. *Journal of the Medical Library Association: JMLA*, *104*(4), 290.

Petrie, J. R., Guzik, T. J., & Touyz, R. M. (2018). Diabetes, hypertension, and cardiovascular disease: clinical insights and vascular mechanisms. *Canadian Journal of Cardiology*, *34*(5), 575-584. https://doi.org/10.1016/j.cjca.2017.12.005

Joint Commission of Pharmacy Practitioners. (2014). *Pharmacists' patient care process*. Available at https://jcpp.net/wp-content/uploads/2016/03/PatientCareProcess-with-supporting-organizations.pdf

Sankar, V., Saaed, Y., Joseph, R. M., Azizi, H., & Mariyam Thomas, P. (2015). Serious drug-drug interactions in the prescriptions of diabetic patients. *Medical Sciences*, *3*(4), 93-103. https://doi.org/10.3390/medsci3040093

Scheen, A. J. (2014). Drug–drug interactions with sodium-glucose cotransporters type 2 (SGLT2) inhibitors, new oral glucose-lowering agents for the management of type 2 diabetes mellitus. *Clinical pharmacokinetics*, *53*, 295-304. https://doi.org/10.1007/s40262-013-0128-8

Sheikh-Taha, M., & Asmar, M. (2021). Polypharmacy and severe potential drug-drug interactions among older adults with cardiovascular disease in the United States. *BMC geriatrics*, *21*, 1-6. https://doi.org/10.1186/s12877-021-02183-0

Triplitt, C. (2006). Drug interactions of medications commonly used in diabetes. *Diabetes Spectrum*, *19*(4), 202.

Tuladhar, L. R., Shrestha, S. L., Regmi, D., Bimali, S., Bhusal, S., & Khadka, P. (2021). Drug-drug Interactions between Hypoglycemic and Non-hypoglycemic Medication in Diabetic Patients with Comorbidities in a Tertiary Care Center: A Descriptive Cross-sectional Study. *JNMA: Journal of the Nepal Medical Association*, *59*(243), 1125–1130. https://doi.org/10.31729/jnma.7080

UpToDate Inc. (2024). *UpToDate LexiDrug/Drug interactions* (Version 8.4.4) [Mobile app]. Accessed March 28, 2024.

Utami, P. R., & Octavia, D. (2022). Study of potential interactions of oral antidiabetic drugs in patients with type 2 diabetes mellitus with comorbidities: A retrospective study. *Pharmacy Education*, 22(2), 200–206.

Yosmar, R., Shepany, E., & Fitria, N. (2024). A comprehensive analysis of antidiabetic drug interactions in geriatric non-insulin dependent diabetes mellitus patients. *Int J Appl Pharm*, *16*(1), 62-65.

Zheng, W. Y., Richardson, L. C., Li, L., Day, R. O., Westbrook, J. I., & Baysari, M. T. (2018). Drug-drug interactions and their harmful effects in hospitalised patients: a systematic review and meta-analysis. *European journal of clinical pharmacology*, *74*, 15-27. https://doi.org/10.1007/s00228-017-2357-5